HHS Public Access

Author manuscript

Curr Pharmacol Rep. Author manuscript; available in PMC 2020 November 20.

Published in final edited form as:

Curr Pharmacol Rep. 2019 ; 5: 332–344. doi:10.1007/s40495-019-00196-3.

Gut microbiota, dietary phytochemicals and benefits to human health

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Abstract

Purpose of the review—In this review, we discuss the roles of the gut microbiota, dietary phytochemicals in improving human health. Recent studies have reported that the human gut microbiota can be altered by dietary phytochemicals including phenolics, carotenoids, and dietary fibers. In addition, both pathogenic and nonpathogenic bacteria show regulatory effects with phytochemicals, suggesting potential synergistic effects in the improvement of human gut health and prevention of chronic diseases.

Recent findings—Numerous studies have been conducted on gut microbial alterations induced by phytochemicals, such as phenolics and carotenoids. Butyrate, a short-chain fatty acid produced via bacterial fermentation in the colon, also shows a significantly beneficial effect in the maintenance of gut microbial homeostasis. However, the molecular mechanisms underlying the effects of diets and the interactions of the gut microorganisms remain poorly understood. The gut microbiome profile changes have been observed in chronic inflammation-induced diseases including colitis, Crohn's disease, immune dysfunction, colon cancer, obesity and diabetes. The anti-inflammatory effects of dietary phytochemicals against these diseases may be partially mediated by regulation of microbial profiles. Latest advances in biomedical technology such as the next-generation sequencing (NGS), and continuous cost reduction associated with these technologies, enabled researchers to perform ever-increasing number of large-scale, high-

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Compliance with Ethical Standards

Conflict of Interest

The authors declare no conflicts of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

throughput computational analyses to elucidate the potential mechanism of phytochemical-microbiome interactions.

Summary—Information obtained from these studies may provide valuable insights to guide future clinical research for the development of therapeutics, botanicals and drug efficacy testing, many of which will be discussed in this review.

Keywords

Microbiota; Phytochemicals; Chronic diseases; Human Health

Introduction

The term “microbiota” refers to microbial communities [1]. The human gastrointestinal (GI) tract harbors more than 100 trillion total microbes, including bacteria, archaea, microbial eukaryotes and viruses [2, 3]. Although this number varies in individual studies, it remains clear that microbial biological functions are important [4]. The gut microbiota has several beneficial effects on human health, including promoting innate and adaptive immunity [5, 6], maintaining the intestinal epithelial integrity [7, 8], helping the metabolism and synthesis essential nutrients such as vitamins, carbohydrate [9, 10], and resisting pathogens [11, 12]. Currently, scientists can explore the characteristics of the human microbiota from low to high resolution by collecting and analyzing high-throughput sequencing data with computational methods and algorithms [13, 14]. The National institutes of health common fund-supported human microbiome project initiated the profiling of the signature of the human microbiota and interpreted the high-throughput data obtained from 16S rRNA sequencing (relative abundance and diversity) and shotgun sequencing (functions and pathways) [3]. Subsequently, the gut microbiota of healthy subjects and patients with specific diseases has been explored dynamically in the last decade [15–18]. Phytochemicals are bioactive compounds that are abundantly distributed in fruits and vegetables [19–22]. A strong correlation between specific classes of phytochemicals and modification of the responding microbiota was observed [23–25]. However, comprehensive understanding of the interactions among phytochemicals and the gut microbiota remains in the early phase.

In this review, we will cover the roles of several classes of phytochemicals in the modification of the human gut microbiota. We will explore the relationship between the human gut microbiota and chronic diseases, including inflammatory bowel disease (IBD), colorectal cancer (CRC) and obesity. We will also discuss the potential mechanism underlying the triangular regulation of phytochemicals, the gut microbiota and human diseases, along with other significant factors, including dietary patterns, lifestyles and environmental exposure. The purpose of this review is to highlight the importance of interactions between phytochemicals and the gut microbiota and demonstrate the strong potential for the development of multiple platforms of diagnosis and therapies using this information, which will guide future clinical studies.

Phytochemicals in the modification of the gut microbiota

Flavonoids

Flavonoids are a major subgroup of phenolics that contain two phenyl rings and one heterocyclic ring, and are widely distributed in fruits and vegetables such as blueberry and cranberry [26–28]. Evidence suggests that flavonoids and their derivatives influence the profile of the gut microbiota for improvement of host immune function and metabolism [29–31], and the metabolic process reveals that flavonoids have both prebiotic and antibacterial effects [32]. Possible growth enhancement of *Bifidobacterium*, *Lactobacillus*, *Enterococcus* species and inhibition of *Clostridium* and *Bacteroides* species were observed during the coculture with flavonoids, and the changes in the human gut microflora were assessed by fluorescence in situ hybridization [33]. The bacterial species *Eubacterium ramulus* and *Clostridium orbiscindens* were also involved in flavonoid metabolism [34, 35]. Quercetin and its glycoside derivatives are abundant flavonols (subcategorized as flavonoids [36]) that are consumed via regular diets [37, 38]. Study showed that quercetin, not its glycoside derivatives, inhibited the growth of the bacteria *Bacteroides galacturonics*, *Lactobacillus*, *Escherichia coli*, *Enterococcus caccae*, and *Ruminococcus gauvreauii* in a dose-dependent manner [29]. Other flavonoids also showed antimicrobial properties against food-borne pathogens and are widely applied in the food industry [39]. Naringin (a flavanone) and rutin (a flavonol) metabolism have been determined to be microbiota dependent based on results obtained for mixed cultures with the human microflora [40]. All evidence suggest that flavonoid metabolism and the gut microbiota influence each other, and the gut microbiota has a strong impact on flavonoids and the associated metabolites, leading to strong health benefits.

Anthocyanins

Anthocyanins represent a major subgroup of flavonoids that are distributed in the common vegetables and fruits consumed in the US market, such as blueberry, raspberry, purple cauliflower and lettuces [41–44]. Raspberry anthocyanins (glycosides) have been significantly degraded in the presence of the active human microflora during coincubation [45]. Anthocyanins from potato, black rice and malvidin-3-glucoside also exhibited significant impacts on the growth of the gut microbiota, including on the growth of *Bifidobacterium spp.*, *Lactobacillus spp.*, *Staphylococcus aureus* and *Salmonella typhimurium*, during in vitro fermentation [33, 46, 47]. This bidirectional effect between anthocyanins and the gut microbiota was also observed *in vivo*. The catalytic gut bacteria *Eubacterium ramulus* and *Clostridium saccbarogumia* were involved in the deglycosylation of cyanidin-3-glucoside, a major derivative of cyaniding [48]. Black raspberry anthocyanins restored the growth of *Eubacterium rectale*, *Faecalibacterium prausnitzii* and *Lactobacillus spp*. and inhibited the growth of *Desulfovibrio spp*. and *Enterococcus spp*. in C57BL/6J mice [49]. The luminal abundances of *Firmicutes* (*Clostridium spp.*) and *Bacteroidetes* (*Barnesiella spp.*) were significantly altered by raspberry anthocyanins [50]. The relative abundances of *Bacteroides*, *Prevotella*, *Porphyromonas* and *Lactobacillus* significantly increased and those of *Bifidobacterium* and *Clostridium* decreased in rats fed with blackcurrant anthocyanins [51]. Berry anthocyanins suppressed the growth of the proinflammatory bacterium *Bilophila wadsworthia* and increased the abundance of

Gammaproteobacteria in the high-fat diet group [52, 53]. In human clinical trials, subjects fed anthocyanin-rich red wine exhibited increased relative abundances of *Eggerthella lenta*, *Bifidobacterium* and *Enterococcus* at the genus level in feces [54]. An 8-week study with 51 subjects fed anthocyanins and prebiotic fibers showed increased phylum levels of *Bacteroidetes* and reduced levels of *Firmicutes* and *Actinobacteria* [55]. A majority of anthocyanins undergo metabolism in the lower small intestine and colon, which was mediated by the colonic microbiota [56]. Even through large amount of studies and results have been reported, further research of specific bacteria and anthocyanins interaction and their molecular mechanisms are needed to be elucidated.

Hydrolyzable Tannins

Tannins are polyphenolic compounds and are subcategorized into ellagitannins, gallotannins, complex tannins, and condensed tannins [57]. Ellagitannins are hydrolyzable tannins that are present in berries, walnuts, plant seeds and herbs [58–61]. Ellagitannins were hydrolyzed to ellagic acid, and ellagic acid was then gradually metabolized by the colon microbiota to produce urolithin A and urolithin B [62]. In addition, it has been demonstrated that the antioxidants urolithin C and urolithin D were also present at significantly high concentrations in the intestines [63]. Evidently, urolithin metabolites production and tannins metabolism occurs primarily in the human lower GI tract and are microbiota dependent. To identify specific microbes that are involved in ellagitannin metabolism, human clinical studies have reported that species belonging to the genera *Bacteroides*, *Prevotella* and *Ruminococcus* are the dominant gut microbes in subjects that consumed urolithin-enriched walnut and pomegranate extracts, and the family *Coriobacteriaceae* is associated with urolithin metabolites and blood cholesterol levels [64]. Other studies have suggested that the genera *Clostridium*, *Bifidobacterium*, *Lactobacillus* and *Bacteroides* are involved in the production of urolithins [65, 66]. *Bifidobacterium* and *Clostridium* were also involved in pomegranate ellagitannin metabolism in a bacteria species-dependent manner, as determined by measuring the optical density of culture media [67]. Gallotannin is another type of hydrolyzable tannin [68, 69]. A human clinical trial revealed that gallotannins underwent microbe-mediated metabolism and released free gallic acid in the GI tract [70]. Although many studies have suggested that hydrolyzable tannin metabolism is microbiota related, the mechanisms underlying the antioxidant and anti-inflammatory activities of tannin metabolites and urolithins in the improvement of human health remain poorly understood [62].

Carotenoids

Carotenoids are tetraterpenoids, colored pigments that are present in fruits and vegetables [71]. The subgroups include xanthophylls (lutein, zeaxanthin) and carotenes (alpha-carotene, beta-carotene, and astaxanthin), and these compounds exhibit high antioxidant activity in the maintenance of human health [72–75]. Astaxanthin is an oxycarotenoid that is abundant in certain microalgae and marine animals [76, 77, 75]. Dietary astaxanthin (50 mg/kg) altered the relative abundances of the phyla *Bacteroidetes* and *Proteobacteria*; genera *Butyricimonas*, *Bilophila* and *Parabacteroides*; and species from *Verrucomicrobia* and *Akkermansia* in C57BL/6J mice [78]. Astaxanthin (200 mg per kg body weight per day) reduced the bacterial load of gram-negative pathogen *Helicobacter pylori* 119/95p on

Helicobacter pylori infected Balb/cA mice, and reduced the gastric inflammation and *Helicobacter. pylori* specific T-cell cytokine release [79]. A pilot study showed that dietary astaxanthin (0.04%, w/w) modified cecal microbiota at the phylum by both gender and genotype *in vivo* [80]. Astaxanthin application selectively reduced the abundance of cecal *Proteobacteria* and *Bacteroides* in female wide-type and BCO2 knockout mice C57BL/6J mice. In addition, astaxanthin significantly increased the abundance of *Actinobacteria* and *Bifidobacterium* in male wide-type mice only.

Fibers and butyrates

Whole plant foods include vegetables, whole grains and fruits and contain high amounts of fibers. Digestible fibers are among the major bioactive components of whole-food dietary interventions and significantly change the profile of the human gut microbiota [81–83]. Butyrate is a short-chain fatty acid (SCFA) that is commonly produced by bacterial fermentation of dietary fibers in the colon [84, 85]. This fatty acid plays several important biological roles, including as an inhibitor of histone deacetylase, an energy metabolite for the production of ATP, an activator of G protein-coupled receptors, an antioxidant, an anti-inflammatory agent and promoter of brain health [86–92]. Human clinical trials determined that dietary fiber intake was strongly associated with the abundances of specific gut microbes, including those of the bacterial class *Clostridia*, phylum *Actinobacteria* and order *Bifidobacteriales* [93]. Soluble corn fibers (21 grams per day) significantly altered the bacterial phyla *Firmicutes* and *Bacteroidetes* and families *Ruminococcaceae*, *Lachnospiraceae*, *Eubacteriaceae* and *Porphyromonadaceae* in a randomized human clinical study [94]. Furthermore, metabolic pathways, including metabolism of carbohydrates, nucleotides, vitamins, and amino acids, were also induced by dietary fiber consumption. Studies have reported that a high-fiber diet influences the composition of the intestinal microbiome, indicating that the process of fiber fermentation is highly microbiota dependent [95, 96]. Thus, to fully appreciate the benefits to human health and understand the potential underlying mechanisms to guide the improvement of dietary requirements in the future, further research is needed.

From the above discussion, one could see that there is significant interactions between dietary phytochemicals and gut microbiota (summarized in Table 1), that could impact human health, to be discussed below.

Gut microbiota and phytochemical interactions in chronic diseases

The human gut microbiome and chronic diseases have been extensively studied in recent years [97–99]. An increasing number of studies have reported that microbial profiles systematically represent the interactions between the gut microbiota and microbiota-derived metabolites. The signature profiles are variable and highly dependent on the chronic diseases exhibited by the subject. In this review, the microbiota signatures of IBD, colorectal inflammation/CRC, and obesity/metabolic syndrome are discussed.

IBD and gut microbiota

IBDs are induced by severely dysregulated and excessive immune response to commensal microbes, especially pathogens [100, 101]. IBD has been subcategorized to two major types: ulcerative colitis (UC) and crohn's diseases (CD) [102]. With the development of gene sequencing technologies, especially 16s ribosome RNA and metagenomic sequencing and powerful bioinformatic tools, the reliability and accuracy of the description of gut microbial profiles and bacterial functions during intestinal inflammation in IBD have increased [103, 104]. UC is characterized as a continuous inflammation in the colon [102]. Compared with the "normal" gut microbiota, patients with UC suffer from a reduction in bacterial diversity, microbiota instability (over- or under-expression of certain species) and adverse effects of therapies and drugs [100]. Some signature changes have been observed in human clinical trials where UC patients exhibited abnormalities of the gut microbiota, such as total depletion of the phyla *Firmicutes* and *Bacteroidetes* [105]. Other clinical reports have shown that UC patients exhibited increased abundances of the phyla *Actinobacteria* and *Proteobacteria* with decreased bacterial diversity. *In vitro*, *Fusobacterium varium*, *Fusobacterium nucleatum* and *Enterobacteriaceae coli* were isolated from patients with UC and were possibly responsible for induction of chronic inflammation in the colon [106–110]. Unlike UC, CD occurs in the entire GI tract with mixed healthy and inflamed areas [100]. A systematic review and meta-analysis revealed that the abundance of *Mycobacterium avium* subspecies *paratuberculosis* was positively correlated with CD [111]. Reduced abundances of the genera *Faecalibacterium* and *Roseburia*, as well as increased levels of *Enterobacteriaceae coli* and *Ruminococcus gnavus*, were also observed in patients with CD [112]. Currently, the gut microbiota-host interaction-induced mucosal immune response dysfunctions and intestinal chronic inflammation are the major causes of IBD, leading to reduced gut bacterial diversity and microbial dysregulation. To restore the gut microbiota homeostasis and prevent IBD, dietary intervention has become a critical and promising approach.

Phytochemicals show strong anti-inflammatory activity *in vivo* and *in vitro* and might have potential applications in the treatment of IBD [113–116]. In human clinical trials, forty patients with IBD were tested on an anti-inflammatory diet (IBD-AID) treatment [117–119]. The IBD-AID diet contained fish, egg, various fruits and vegetables to improve IBD patients' carbohydrate modification, ingestion of pre- and probiotics, balance of the fatty acids intake and overall dietary pattern. Results showed that over 60% of IBD patients had good or very good response to dietary treatment in clinical assessment. The symptom reduction and life quality improvement was effective. Unfortunately, the underlying mechanism of efficiency was not elucidated. For other phytochemicals, flavonoids and polyphenols played anti-inflammatory roles against IBD through increasing intestinal bacterial diversity, reducing the relative abundance of *Enterobacteriaceae coli* and *Fusobacteria*, and increasing the abundance of *Bacteroidetes* [120, 121]. Flavanols EGCG from green tea, and tannic acids from gelatin tannate also showed strong anti-inflammatory activity *in vitro* by modulating gut microbiota, yet the accurate interaction was not fully understood [122, 123]. With accumulated evidence of gut microbiota interaction with phytochemicals, future human clinical trials of selected dietary supplementation would help developing effective and lower toxic botanical therapies against IBD.

Gut microbiota in colorectal inflammation and CRC

The human colonic mucosa is populated with a wide range of microorganisms, usually in a symbiotic relationship with the host [124]. The imbalance of colon microbiota raises the risk of the colon exposed to metabolic and inflammatory stimuli [125, 126]. This imbalance, or dysbiosis, is a multifactorial issue that has been found to be associated with lifestyle (indicative of dietary habits and sedentary behaviors), DNA mutations, and inflammation and, most recently, changes in microbiota [127–130]. Recent studies have attempted to identify microbial changes that may enhance the process [131–135]. For example, *Proteobacteria* is a phylum that houses more than 200 genera of gram-negative bacteria, including several well-known pathogens as *Enterobacteriaceae coli*, *Salmonella* and *Helicobacter pylori* [136]. Several preclinical and clinical studies have demonstrated that these pathogens were found associated with human colon inflammation and CRC [137–141]. Meta-analyses of human clinical studies revealed that *Helicobacter pylori* infection was associated with nearly 50% significant higher risk of CRC [142, 143]. A case-control study from Germany in 2003 – 2007 showed slightly higher level of *Helicobacter pylori* (around 46.1%) in CRC cases than healthy controls (40.1%). *Firmicutes* comprises mostly gram-positive phylum in human colon [144, 145]. The overall gut mucosa *Firmicutes* accounted 43.46% and 63.46% in healthy individuals and CRC patients respectively[146]. *Staphylococcaceae*, a family class of *Firmicutes*, was found to be more abundant in human CRC patients than in healthy controls [147]. Controversially, another human clinical showed that *Firmicutes* phylum at mucosal tissue of tumor was lower at 37.12% than paired normal mucosa at 44.72% of total mucosal bacteria [148]. *Fusobacterium* is a gram-negative bacteria and shows to be more prevalent in individuals with CRC than in healthy rats and humans [147, 149]. Furthermore, among individuals, those with a high abundance of *Fusobacterium* were apparently more likely to have adenomas than those with a low abundance of this genus [150]. A significant increasing of *Fusobacteria* occurred on the gut microbiota of CRC patients from 0.03% to 10.58% compared with healthy individuals [146]. These findings suggest that such microbiota may accumulate during the colorectal carcinogenesis. Meanwhile, by transplanted fecal microbiota from both CRC patients and healthy individuals into germ-free mice, tumor burden increased was strongly associated with the mice gut genus Bacteriodies abundance [149]. Evidence suggests that inflammatory and metabolic stimuli, along with the microbial community are important for the prognosis of colon carcinogenesis. Investigation of the colon microbiota and the associated modulatory cellular pathways is an area with great potential for research.

Phytochemicals show anticancer and anti-inflammatory activities on various human cancers [151–153]. Phytochemicals also modulate the intestinal microbial ecology, especially the gut microbiota as early as a few days after switching between carefully controlled diets [154–156]. Evidence suggested that dietary polyphenols stimulated the growth of certain *Lactobacillus* strains [157]. Berry phenolics inhibited the growth of both gram-positive and gram-negative pathogenic bacterial strains, but interestingly, the lactic acid bacteria group was hardly affected [158]. *Lactobacillus acidophilus* CECT 362 was resistant to tea phenolic extracts containing caffeine, (−)-epicatechin, (−)-epicatechin gallate, (−)-epigallocatechin, (−)-epigallocatechin gallate, and gallic acid, whereas food-borne bacteria were inhibited [159]. Polyphenolic extracts from green tea, honey, peppers, black currants, raspberry,

cinnamon, and peppermint also exhibited inhibitory activity against *Helicobacter pylori* [160–162]. Polyphenols in olive oil diffused into the gastric juice and exerted a potent bactericidal effect against eight strains of *Helicobacter pylori* at very low concentrations (1.3 μg/mL) [163]. Tea extracted phenolics (epicatechin, catechin, 3-O-Me galic acid, gallic acid and caffeic acid), aromatics and metabolites (3-(4-OH phenyl)propionic acid, 3-phenylpropionic acid, 4-OH phenylacetic acid) showed selective growth effects on human gut microflora and reduce the growth of pathogenic bacteria including *Clostridium perfringens*, *Clostridium difficile* and *Bacteroides spp.* significantly [164]. Despite systemic similarities between rodents and humans, it is important to understand the complexity, exposure-related differences and mechanisms of action of phytochemicals in gut microbial modulation [165]. Phytochemicals contribute to the maintenance of human GI health, largely via modulation of the gut microbial balance with simultaneous inhibition of pathogens and stimulation of beneficial bacteria. Hence, regular consumption of a diet rich in phytochemical contents may beneficially balance the gut microbial ecology, helping prevent GI disorders and thus enhancing host health.

Gut microbiota and obesity, metabolic syndrome

Obesity is commonly defined as body mass index (BMI) values greater than 30 kg/m^2 [166, 167], and widely characterized by the pathophysiology of lipid accumulation in body compartments and excessive secretion of pro-inflammatory adipokines by adipocytes and macrophages [168, 169]. Obesity and insulin resistance can lead to the development of metabolic syndromes, including high blood glucose levels, high blood pressure, high serum triglyceride levels, low high-density lipoprotein levels and large waist circumferences, which increase the risk of heart disease, diabetes mellitus and stroke [170, 171]. Genetic changes in the body may not fully explain the dramatic increase in the occurrence of obesity in the past few decades [172, 173]; instead, environmental factors, such as high-caloric diet and sedentary lifestyle, are among the major driving forces [174]. An increasing number of studies have shown that the gut microbiome diversity and composition are associated with both diet and human diseases such as obesity, metabolic syndromes and type 2 diabetes [175–181]. The gut microbiota transplantation from conventional mice to lean and insulin-sensitive germ-free mice (a process called conventionalization) led to a 60% increase in adiposity and caused insulin resistance [182]. Subsequently, the same laboratory reported that the gut microbial composition in obese (ob/ob) mice showed a 50% reduction in the abundance of *Bacterioidetes* and an increase in the abundance of *Firmicutes* compared to the abundances in lean (ob/+) and wild-type (+/+) mice [183]. To understand the causative role of the gut microbiome in obesity, a landmark study was conducted showing that germ-free mice transplanted with the gut microbiota from obese (ob/ob) mice exhibited substantially increased adiposity compared with mice transplanted with the gut microbiota from lean (ob/+) mice [184]. The mechanism was interpreted based on increased capacity for energy harvest, as demonstrated by the increased acetate and butyrate levels. Similar results were also reported on western diet induced obesity C57BL/6J mice, and microbiota profile was shifted to an increased abundance of *Firmicutes* and a decreased abundance of *Bacteroidetes* [185]. Meanwhile, one bacterial class *Mollicutes* class in the phylum of *Firmicutes* was found significantly up-regulated by diet-induced obese, which increased host energy harvest, as indicated by the enrichment of microbial genes and KEGG pathways involved in the

import and anaerobic fermentation of dietary carbohydrates. The lipopolysaccharides (LPS) are an endotoxin produced at the outer membrane of all gram-negative microbes[186], and cause systemic inflammation to initiate insulin resistance and obesity (a phenomenon called metabolic endotoxemia) [187, 188]. LPS-producing pathogens including family of *Enterobacteriaceae* and *Desulfovibrionaceae* (phylum of *Proteobacteria*) were found enriched in high-fat diet induced obesity mice and rats [189, 190]. A significant decrease in fecal *Enterobacteriaceae* was observed in obese adolescent humans who lost 4–7 kg following a 3-month energy-restricted diet and a physical exercise program [191]. In addition, diurnal oscillations of the microbiota were linked to obesity and metabolic syndromes [192, 193]. Mice fed a high-fat diet with disturbance in circadian rhythm exhibited altered microbial compositions and presented higher weight gains and glucose intolerance than mice fed the same diet with a normal circadian rhythm [192]. Moreover, germ-free mice transplanted with feces from jet-lagged human subjects exhibited dysbiosis, which caused weight gain and glucose intolerance [192].

Cranberry extracts, composed of phenolic acid, flavonols, anthocyanins, and proanthocyanidins, reduced weight gain, visceral adiposity and insulin resistance by reinforcement of antioxidative defense and prevention of intestinal inflammation in obese mice fed a high-fat/high-sucrose diet [194]. In this study, cranberry extracts restored the metabolic homeostasis in a positive correlation with the abundance of *Akkermansia* [194]. Strikingly consistent results were observed in mice fed 1% concord grape polyphenols (high in anthocyanins, flavan-3-ols, and flavonols). Grape polyphenols substantially increased the abundance of *Akkermansia muciniphila*, leading to altered intestinal gene expression. This effect in turn regulated intestinal epithelial integrity and inflammatory marker levels, finally resulting in improved lipid deposition (reduced adiposity and weight gain) and glucose tolerance (decreased glucose absorption and increased insulin secretion) [195]. In cafeteria diet-induced obese rats, a negative correlation was observed between weight gain and enrichment of microbial pathways involved in flavonoid biosynthesis [196]. The results indicated that dysbiosis caused by obesogenic diets could disrupt the biosynthesis of flavonoids, which may lead to decreased host utilization of flavonoids, resulting in an obesity phenotype [196]. The gut microbiota exhibited conversion of flavonoids, which were mainly distributed in the phyla *Actinobacteria*, *Firmicutes*, and the family of *Clostridiaceae*, *Enterococcaceae*, *Eubacteriaceae*, *Erysipelotrichaceae*, *Lactobacillaceae*, *Lachnospiraceae*, *Ruminococcaceae* and *Streptococcaceae* [197]. In addition, glucoraphanin (which can be metabolized to isothiocyanates), which is abundant in cruciferous vegetables such as broccoli, cauliflower, and mustard, could mitigate obesity, insulin resistance and related metabolic disorders by browning white fat, inhibiting metabolic endotoxemia-related chronic inflammation, and decreasing oxidative stress in mice fed a high-fat diet [198]. Glucoraphanin exerted its anti-obesity effect via a decrease in the abundances of the phylum of *Proteobacteria*, many bacteria from which can produce endotoxins [198, 199]. Moreover, *Ganoderma lucidum*, a medicinal mushroom that is used in traditional Chinese medicine, reduced obesity and insulin resistance by suppressing metabolic endotoxemia-related chronic inflammation in mice fed a high-fat diet by decreasing the endotoxin-bearing *Proteobacteria* and *Firmicutes* to *Bacteroidetes* ratios [200]. Fecal transplantation from mice treated with the *Ganoderma lucidum* extracts to mice fed a high-fat diet could effectively

reverse obesity and fat accumulation as well as the dysregulation of proinflammatory cytokines and intestinal tight junctions. These findings indicate that modulation of the gut microbiota is the mechanism for underlying the treatment of obesity.

Current challenges in and applications of human microbiota studies

Some of the challenges on the human microbiota studies are associated with interpretation of the metagenomic data with a lack of standard parameters and references and with the potential biases of technicians and methods during sample preparation. These challenges include, but are not limited to, the following: 1) variations in data process and analysis using different computational tools; 2) difficulty in sample collection of the mucosal and cecal microbes, as well as GI tract tissue under inflammation and oxidative stress; 3) microbiota composition changes during fermentation and degradation and during passage from the rectum to lumen; 4) DNA extraction efficiency for gram-positive and gram-negative bacteria are different, and results also varies in different chemical isolation kit.

Conclusion

There is solid evidence that gut microbes play the key roles in the reduction of the risk of chronic diseases, and phytochemicals are interactive with them. Currently, comprehensive preclinical and clinical studies reveal the gut microbial profiles of both healthy subjects and those suffering from chronic disease such as IBD, CRC and obesity. Dietary intervention seems to be a less aggressive, low risk and effective approach to prevent and treatment such diseases. In future, we will understand the biological functions of the gut microbiota and the interactions with phytochemicals, which contribute to the improvement of health benefits for humans.

Acknowledgments

We thank all members of Dr. Ah-Ng Kong’s lab for helpful discussions and preparation of the manuscript.

Funding

This review was supported by R01 CA200129, from the National Cancer Institute (NCI), and R01 AT009152, from National Center for Complementary and Integrative Health (NCCIH) of the National Institute of Health (NIH) to Dr. Ah-Ng Tony Kong.

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Table 1:

Summary of phytochemical and microbiota interaction

Phytochemical	Altered microbiota	Reference
Flavonoids	*Bacteroides galacturonics, Lactobacillus, Escherichia coli, Enterococcus caccae, Bifidobacterium catenulatum, Ruminococcus gauvreauii*	29
	Bifidobacterium, Lactobacillus, Enterococcus, Clostridium, Bacteriodies	33
	Eubacterium ramulus, Clostridium orbiscindens	34, 35
Anthocyanins	*Bifidobacterium ssp., Lactovacillus ssp., Staphylococcus aureus, Salmonella typhimurium*	33, 46, 47
	Eubacterium ramulus, Clostridium saccbarogumia	48
	Eubacterium rectale, Faecalibacterium prausnitzii, Lactobacillus spp., Desulfovibrio ssp., Enterococcus spp.	49
	Firmicutes (Clostridium spp.). Bacteroidetes (Barnesiella spp.)	50
	Bacterodies, Prevotella, Porphyromonas, Lactobacillus, Bifidobacterium, Clostridium	51
	Bilophila wadsworthia, Gammaproteobacteria	52, 53
	Eggerthella lenta, Bifidobacterium, Enterococcus	54
	Bacteroidetes, Firmicutes, Actinobacteria	55
Hydrolyzable Tannins	*Bacteroides, Prevotella, Ruminococcus, Coriobacteriaceae*	64
	Clostridium, Bifidobacterium, Lactobacillus, Bacteroides	65, 66
	Bifidobacterium, Clostridium	67
Carotenoids	*Bacteroidetes, Proteobacteria; Butyricimonas, Bilophila, Parabacteroides; Verrucomicrobia, Akkermansia*	78
	Helicobacter pylori	79
	Proteobaceria, Bacterioides, Actinobacteria, Bifidobacterium	80
Fibers and butyrates	*Clostridia, Actinobacteria, Bifidobacteriales*	93
	Firmicutes, Bacteroidetes, Ruminococcaceae, Lachnospiraceae, Eubacteriaceae, Porphyromonadaceae	94