Bioscience of Microbiota, Food and Health Vol. 42 (3), 152–171, 2023

Review

Dietary phytochemicals, gut microbiota composition, and health outcomes in human and animal models

Seyedeh Nooshan MIRMOHAMMADALI[1] and Sara K. ROSENKRANZ[2*]

[1]*Department of Food, Nutrition, Dietetics and Health, Kansas State University, 110 Anderson Hall, 919 Mid-Campus Drive North, Manhattan, KS 66506-0110, USA*

[2]*Department of Kinesiology and Nutrition Sciences, University of Nevada Las Vegas, 4505 S. Maryland Pkwy, Las Vegas, NV 89154, USA*

Received December 15, 2022; Accepted April 17, 2023; Published online in J-STAGE April 25, 2023

The role of the composition of the gut microbiota on human health is not well understood. However, during the past decade, an increased emphasis has been placed on the influence of the impact of nutrition on the composition of gut microbiota and how the gut microbiota affects human health. The current review focuses on the role of some of the most studied phytochemicals on the composition of the gut microbiota. First, the review highlights the state of the research evidence regarding dietary phytochemical consumption and gut microbiota composition, including the influence of phytochemicals such as polyphenols, glucosinolates, flavonoids, and sterols that are present in vegetables, nuts, beans, and other foods. Second, the review identifies changes in health outcomes with altered gut microbiota composition, in both animal and human model studies. Third, the review highlights research that includes both associations between dietary phytochemical consumption and gut microbiota composition, and associations between the gut microbiota composition and health outcomes, in order to elucidate the role of the gut microbiota in the relationship between dietary phytochemical consumption and health outcomes in humans and animals. The current review indicated that phytochemicals can beneficially alter gut microbiota composition and decrease the risk for some diseases, such as cancers, and improve some cardiovascular and metabolic risk biomarkers. There is an urgent demand for high-quality studies that determine the relationships between the consumption of phytochemicals and health outcomes, examining gut microbiota as a moderator or mediator.

Key words: gut microbiota, phytochemicals, phenolics, 16S rRNA, bacteria

INTRODUCTION

The associations between health-promoting human dietary patterns, a healthy gut, and chronic disease prevention are well documented [1]. One such health-promoting dietary pattern is a plant-based diet, which has recently gained popularity [2]. Plants, including fruits and vegetables, provide primary and secondary metabolites. Primary metabolites are amino acids, enzymes, coenzymes, and nucleosides [3]. Secondary metabolites, also known as phytochemicals, are the result of several chemical pathways such as the Shikimik Pathway, also known as the phenylpropanoid pathway, and are derived from the transformation of primary metabolites. This transformation process occurs under environmental stresses such as ultraviolet (UV) radiation, microbial infections, mechanical wounding, and chemical stressors such as herbicides [4]. Phytochemicals are essential in defensive roles for plants, such as resistance to diseases (viruses, fungi, bacteria, and insects), herbivores (insects and mammals), plant competitors, and abiotic stress (e.g. UV radiation, heat, tissue damage, etc.) [5].

Phytochemicals are comprised of six main groups which are shown in Fig. 1. The largest group of phytochemicals, phenolics, consists of six subgroups which are flavonoids (comprised of eight subgroups), phenolic acids (for example curcumin), stilbenes (for example resveratrol), catechins, and lignans [6]. Phytochemicals are used for medicinal, nutritive, and cosmetic purposes, and humans can benefit either directly or indirectly from the consumption of phytochemicals found in fruits and vegetables. Examples of indirect uses of phytochemicals include food additives, flavors, medicines, and industrially important medications containing phytochemicals [7].

Since phytochemicals are metabolized by the body as xenobiotics, their bioavailability tends to be low [8]. Following consumption, only 5–10% of phytochemicals are absorbed into the bloodstream through the small intestine and may be further metabolized in the liver. The remaining 90–95% of

*Corresponding author. Sara K. Rosenkranz (E-mail: Sara.Rosenkranz@unlv.edu)

doi: 10.12938/bmfh.2022-078

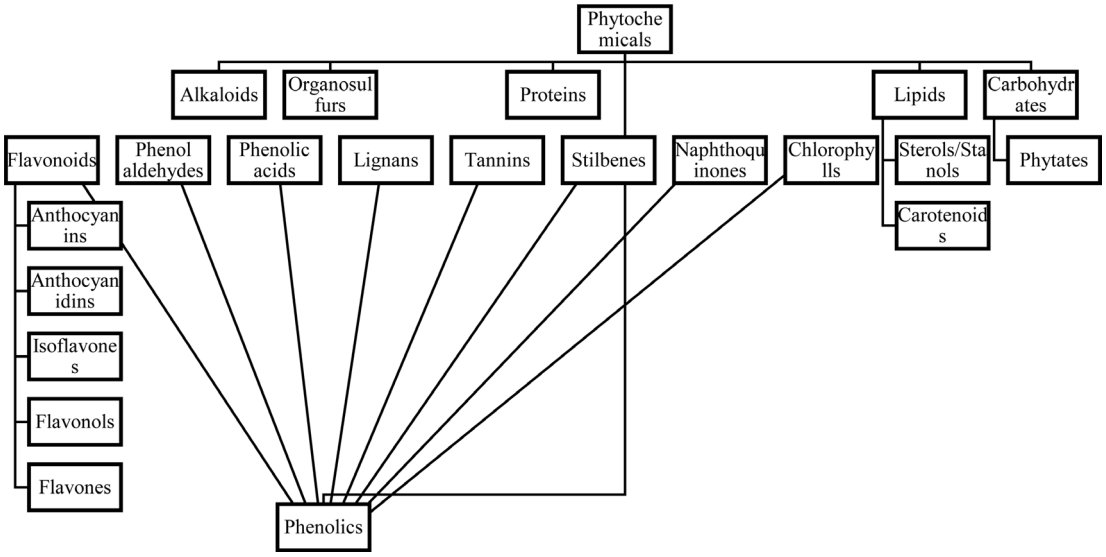

Fig. 1. Organization of phytochemical classifications [91].

these compounds reach the colon, where the colonic microbiota modify the structural composition into absorbable metabolites via hydrolysis, reduction, dihydroxylation, demethylation, decarboxylation, and ring fission [9]. For instance, polyphenols that are not absorbed in the small intestine make it to the colon, where they are significantly structurally altered. The intestinal bacteria actively hydrolyze glycosides into aglycones, and degrade them to simple phenolic acids [10]. Since the intestinal microbiota produces active metabolites, this activity is central to the biological action of polyphenols. As an example, daidzein is transformed in the large intestine to produce the active metabolite equol [11, 12].

Associations between the gut microbiota, dietary intake, and health outcomes need to be elucidated. Gut microbiota composition analysis categorizes diversity into two types, alpha and beta diversity. The alpha type is a measurement of microbiome diversity in a single sample, and the beta type is a measurement of diversity between two communities [13]. Eukaryotic organisms, viruses, bacteria, and archaea make up the human microbiome [14]. The microbiota is a term for the group of bacteria; genes, along with the microbiota, comprise the microbiome [15]. The gut microbiome varies greatly between people, as genetics, diet, physical activity, medical interventions, and other factors affect the diversity and quantity of the microbiome. Some gut bacterial genome diversity has been determined via fecal sampling methods, and in fact, the most used method for analyzing the microbiome is stool sampling, though this method does not fully capture α and β diversity of gut microbiomes, especially in the small intestine [16]. Other than stool sampling, the primary method of analysis is polymerase chain reaction (PCR) [17]. In PCR, 16S rRNA is used to amplify the variants of bacteria in the gut microbiome [18].

In healthy humans, the gut microbiota is likely to be dominated by members of the phyla Bacteroidetes and Firmicutes; in contrast, in those with poor health, the gut microbiota may be dominated by bacterial phyla such as Proteobacteria (which contains *Escherichia coli*), Verrucomicrobia, Actinobacteria, or Fusobacteria. However, the interpretation of a healthy or unhealthy gut is complex, as the composition of bacteria varies within and between individuals [19]. For example, one previous study concluded that the rapid effects of vegan and carnivore diets on gut microbiome composition were evident in both alpha and beta diversity [20].

Continuous imbalance of the microbial composition of the gut is called dysbiosis, which is correlated with obesity and diabetes [15], inflammatory bowel disease [21], alcoholic and nonalcoholic fatty liver disease [22], and hepatocellular carcinoma [23]. Physical and health status can also influence gut microbiota composition, and in addition, the immune system is thought to affect gut microbiota composition. It has become obvious that gut microbiota dysbiosis is linked to a wide range of human diseases and ailments [24]. The complex association between the gut microbiota and the human mucosal immune system helps to attain and maintain immunological homeostasis. This reciprocal system makes determining causality quite challenging. Studies of the relationship between diet and microbiome composition date back more than a century ago [25]. Through technological advances, researchers have observed that diet can affect intestinal gas production and bacterial metabolism [26]. The gut microbiota can break down some dietary indigestible fibers, producing short-chain fatty acids (SFCAs) as a potential energy source, and these SCFAs are associated with decreased risk of some diseases such as colon cancer [27]. All of the associations mentioned thus far have been primarily observed in non-human animals, mainly rodents; however, there is ongoing research in humans [28]. Recent studies have shown that SCFAs produced by gut, might be correlated with diet–gut–brain–behavior interactions, which could prevent or mitigate cravings for unhealthful foods [29]. Moreover, another study showed an association between SCFA produced by intestinal gut microbiota, and blood pressure regulation [30]. With this background in mind, the primary goal of this review was to examine the potential importance of consuming active phytochemicals for beneficially altering gut microbiota composition and to better understand what the state of the current literature regarding whether the gut microbiota serves as an independent health outcome/therapeutic target, or as a

doi: 10.12938/bmfh.2022-078

mediator or moderator in the relationship between phytochemical consumption and subsequent health outcomes. This review explores the observational and clinical studies which have discussed the roles of phytochemical consumption after reaching the large intestine, on gut microbiota composition, and plausible resultant health outcomes. Therefore, this review comprises five parts based on the included categories of phytochemicals. In each category, the associations between phytochemical consumption, changes in gut microbiota composition, and associated health outcomes, both in human and animal studies are included when both are available.

LITERATURE SEARCH

In order to examine the peer-reviewed research available on the interactions between phytochemicals and gut microbiota composition, a comprehensive literature search was conducted in PubMed and SCOPUS until March 2022. The following keywords were used: Gastrointestinal Microbiomes, Microbiome, Gut Microbiotas, Gastrointestinal Flora, Gastrointestinal Microbiota, Gastrointestinal Microbial Community, Gastric Microbiome, Intestinal Microbiome, Intestinal Microbiota, Intestinal Microflora, Enteric Bacteria, Dietary Phytochemical, Plant Bioactive Compound, Plant-Derived Chemical, and Phytonutrient. Boolean Operators "AND", "OR" were used to combine keywords. All observational and experimental studies of human and animal participants that included phytochemical consumption, gut microbiota composition, and measured health-related outcomes, were included. Reviews, editorials, letters, and articles not written in English, were excluded. A PRISMA flow diagram of the study selection process is shown in Fig. 2.

ASSOCIATIONS BETWEEN CONSUMPTION OF FLAVONOIDS, GUT MICROBIOTA COMPOSITION, AND HEALTH OUTCOMES

Flavonoids in general

Human studies

One of the subgroups of polyphenols, flavonoids, which consists of 5 other subgroups, was used to determine associations with gut microbiota changes. Li and Somerset studied adults with cystic fibrosis (CF) using a flavonoid-specific food frequency questionnaire (FFQ) to estimate participants' flavonoid intake. This study showed that flavonoid intake was correlated with an increase in *Actinomyces*, and a reduction in class *Coriobacteriia* [31]. Since the gut microbiota composition of patients with CF comprises more Actinobacteria as compared with patients without CF, it is possible that flavonoids, especially gallocatechin in black tea, might decrease colorectal cancer (CRC) and lung cancer in CF patients by modifying gut microbiota composition (decreased *Coriobacteriia*) [32]. However, considering the small sample size, the study design, and data collection methods, these effects are only speculative and require more investigation in future studies.

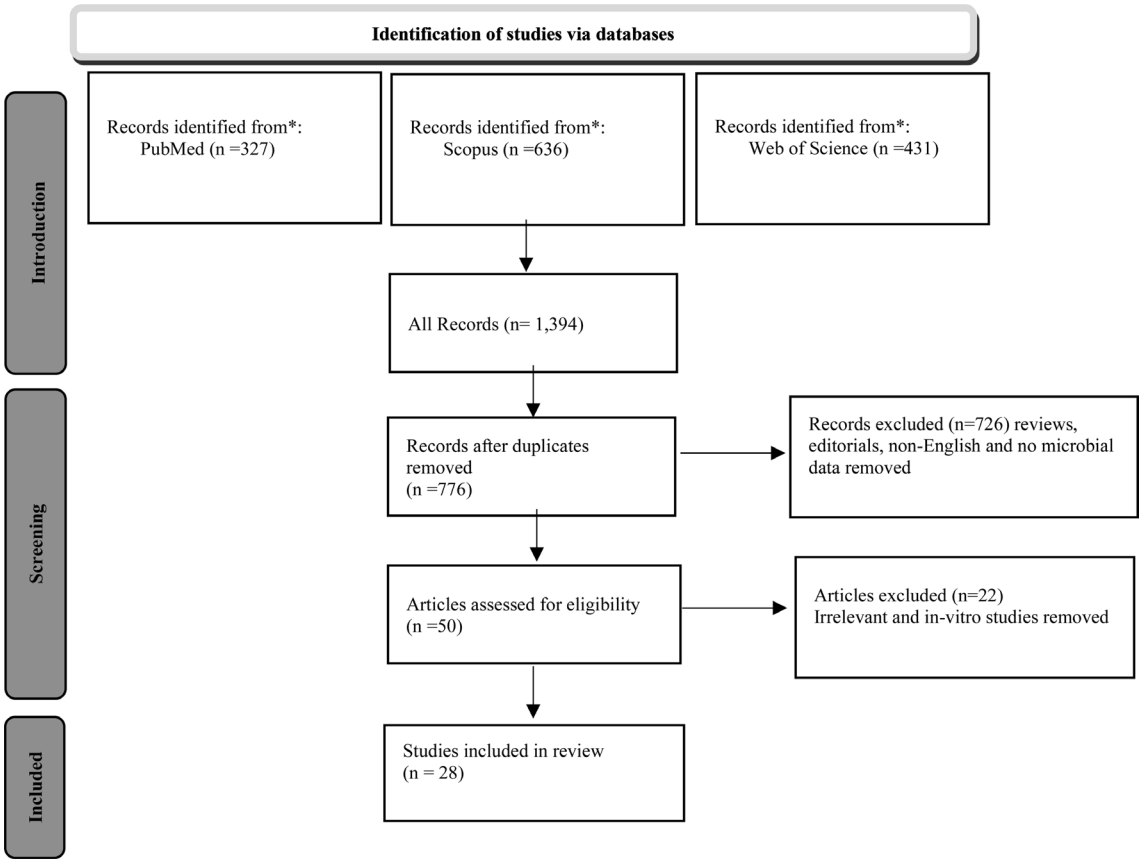

Fig. 2. PRISMA flow diagram of study selection process.

Isoflavones

Human studies

Legumes, soybeans, green beans, and mung beans are abundant in isoflavones including daidzin, the glycoside form of daidzein. Equol, produced by the metabolic conversion of daidzein by the gut bacteria, is an isoflavandiol nonsteroidal estrogen [33]. About one third to one half of humans (depending on the community) can generate equol, as compared with non-human animal species which are all capable of this conversion [34]. Equol production has been reported as 40–70% among Asian populations versus 20–30% Western populations [35]. Phytoestrogens are known to have hormonal effects on animals and cell culture systems. In premenopausal women, where estrogen levels are high, phytoestrogen consumption may reduce endogenous estrogen levels and activity. In postmenopausal women, when estrogen levels are low, phytoestrogens may operate as estrogen agonists. Given the numerous health benefits associated with higher estrogen levels generally, hormonal impacts may account for positive epidemiological associations in populations consuming soy, where a lower risk of chronic diseases and menopausal symptoms have been shown [36–38]. However, whether these health benefits are modulated by the gut microbiome, is unknown. Recently, with the advancement of new research techniques, more studies have been conducted in an attempt to determine the role of the gut microbiome following isoflavonoid consumption. For example, a cross-sectional study demonstrated associations between isoflavonoids (genistein and equol) and changes in lipid profiles as well as gut microbiome composition changes. Results indicated a negative association for *Haemophilus parainfluenzae* and a positive association for *Klebsiella pneumoniae* and *Lachnospiraceae bacterium*-8_1_57FAA with total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and apolipoprotein B (ApoB). Further, a higher relative abundance of *H. parainfluenzae,* and lower levels of *K. pneumoniae* and *Lachnospiraceae bacterium*-8_1_57FAA were shown in participants who were able to produce equol as compared to non-producers. These results suggest that microbial equol synthesis may play a role in the variations in blood lipid levels following consumption of isoflavonoids [39]. In addition, a clinical trial in menopausal women showed a strong positive association between consumption of soy and prevalence of the genus *Bifidobacterium* and *Rothia* in equol producers [40]. However, a 6-month trial in menopausal women showed no associations between equol levels and lipid profiles both in producers and non-producers, despite alterations in gut microbiome composition [41]. Also, a randomized clinical trial has shown that soy isoflavone group had significantly better scores on cognitive tests compared to the placebo group, indicating that soy isoflavones may have a positive effect on cognitive function in patients with Alzheimer's disease [42]. Moreover, a cross-sectional study showed that equol producers had significantly better scores on the Mini-Mental State Examination (MMSE) compared to non-producers, indicating a positive association between equol production and cognitive function in older adults [43].

Genistein

Animal studies

Genistein is the primary isoflavonoid found in soy, which was included in three separate studies. First, it was studied to assess the effects on gut microbiota composition, metabolic endotoxemia, and cognitive performance in mice given a high-fat diet. Genistein altered gut microbiota composition by increasing the genus *Prevotella* and *Akkermansia,* which were associated with lower lipopolysaccharides (LPS), and decreased metabolic endotoxemia. A reduction in LPS and endotoxemia correlated with a decrease in neuroinflammation and improvements in cognitive function [44]. Genistein can stimulate the oxidation of fat in subcutaneous adipose tissue and decrease fat formation through unidentified mechanisms [45]. Moreover, these findings are consistent with earlier research, which showed that a rise in *Akkermansia muciniphila* strengthened the gut barrier by thickening the mucous layer and reducing the influx of LPS. Together, by reducing inflammation, these changes may lessen metabolic abnormalities in lipid and carbohydrate metabolism [46]. Second, genistein was studied to determine effects on gut microbiota alterations and adverse effects of chemotherapy, by transplanting feces to mice from human participants with breast cancer, who were receiving chemotherapy. Patients had their feces collected before and after chemotherapy in order to transplant to mice. Each patient's feces were transplanted to four mice, and the mice were then given a corn oil diet without genistein (control), or a corn oil diet with genistein (intervention). Feces were collected each month and sequencing was performed using 16S rRNA. By transplanting breast cancer patients' feces, researchers were able to successfully humanize germ-free mice. Genistein decreased members of the genus *Paraprevotella, Anaerostipes, and Bacteroides,* and increased members of genus *Lactococcus*, *Akkermansia,* and *Eubacterium* before tumor induction. These alterations, in turn, increased SCFA production. However, after tumor induction, gut bacteria diversity was reduced [47]. Third, genistein was found to exacerbate type 1 diabetes, solely in female offspring. It was hypothesized that in female offspring, genistein could down-regulate some pro-inflammatory genes such as IL-10 and IgM, which are assumed to contribute to gut dysbiosis and increases in Enterobacteriales. The rise in Enterobacteriales were associated with increased inflammation and worsened type 1 diabetes symptoms in female mice. However, in male offspring, genistein had the opposite effect by decreasing inflammation through a reduction in T cells [48].

Flavanols

The most commonly studied flavanols include quercetin and kaempferol.

Quercetins

Human studies

Quercetin is consumed through foods or supplements and has been shown to have beneficial effects on health outcomes. A randomized clinical trial in polycystic ovary syndrome (PCOS) patients showed that quercetin supplementation increased adiponectin while decreasing homeostasis model assessment-estimated insulin resistance (HOMA-IR), testosterone, luteinizing hormone (LH), fasting blood sugar (FBS), and insulin. Therefore, quercetin may be a useful supplement for PCOS, as indicated by these reported effects on adiponectin levels [49]. In healthy males, previous research has indicated that after quercetin supplementation, plasma concentrations of uric acid decreased, without inducing changes in body mass index (BMI) [50]. However, the underlying mechanisms for these beneficial health

doi: 10.12938/bmfh.2022-078

effects in humans require further research, and the role of the gut microbiome needs to be clarified.

Animal studies

Quercetin is transformed to metabolites such as 3,4-dihydroxyphenylacetic acid by *Bacteroides fragilis*, *Clostridium perfringens*, *Eubacterium ramulus*, *Streptococcus* S-2, *Lactobacillus* L-2, *Bifidobacterium* B 9, and *Bacteroides* JY-6 after digestion in the gut [51–53]. These metabolites are shown to prevent cholesterol-induced mitochondrial dysfunction and cholesterol-impaired insulin secretion in pancreatic β-cells [54]. Studies have shown that quercetins alter gut microbiome composition by increasing α diversity, which is an indication of a healthy gut and stable intestinal ecosystem [55]. There was a reduction in the abundance of Verrocomicrobia and an increase in microbiome diversity and the abundances of Actinobacteria, Cyanobacteria, and Firmicutes. Some modifications in gut microbiota composition were associated with health biomarkers. For example, Actinobacteria correlated negatively with intestinal cholesterol and positively with coprostanol. Also, Firmicutes correlated negatively with cholesterol. Together, these findings showed that quercetin affects the pro-inflammatory cytokines production and atherogenic lipid metabolites, which is correlated to a rise in the number of Actinobacteria while a reduction in the number of Firmicutes. Therefore, quercetin might have beneficial effects on atherosclerotic diseases and oxidative stress, which are likely to be due to the modulation of indicators of inflammation like IL-6 and malondialdehyde (MDA) [56]. Quercetin was also studied to determine its effects on nonalcoholic fatty liver disease (NAFLD) development through gut microbiota modulation. Mice were grouped into two different sets of donors and receivers of fecal microbiota transplantation. Gut microbiota donors were selected based on obesity status and NAFLD-related biomarkers, after consuming a high-fat diet and quercetin. Fecal transplantation recipients were selected to show metabolic and variations in phenotype caused by interactions between quercetin, diets, and transplanted microbiota. The details of the within-group categories are listed in Table 1. The findings showed that in the high-fat diet fed receiver groups, the *Akkermansia* genus was found to be positively associated with butyrate production (p-value=0.01) and negatively associated with body weight (p-value=0.001), HOMA-IR (p-value=0.01), NAFLD Activity Score (p-value=0.001), and inflammasome activation (p-value=0.05). There was a notable increase in the

Table 1. Summary of included studies

Phytochemicals	Study	Animal or human participants	Changes in gut microbiota composition	Health outcome assessment	Determination of associations between gut microbiota changes and health outcomes
Phytochemicals	[80]	Human	✓	×	×
Lipid phytochemicals	[83]	Human	✓	✓	×
(Phytosterols)	[85]	Human	×	✓	×
	[86]	Human	✓	✓	×
	[87]	Human	✓	✓	×
Protein phytochemical (Glucosinolate)	[82]	Human	✓	✓	✓
Polyphenols	[71]	Human	✓	✓	✓
Polyphenols (Lignan)	[78]	Human	✓	×	×
Polyphenols (Flavonoids)	[32]	Human	✓	✓	✓
Polyphenols	[49]	Human	✓	✓	×
[Flavonoids (Quercetins)]	[50]	Human	✓	✓	×
Polyphenols (Isoflavonoids)	[39]	Human	✓	✓	✓
	[41]	Human	✓	×	×
	[40]	Human	✓	×	×
Polyphenols + Alkaloids	[79]	Human	✓	×	×
	[81]	Animal	✓	✓	✓
Polyphenols	[56]	Animal	✓	✓	✓
[Flavonoids (Quercetin)]	[57]	Animal	✓	✓	✓
	[59]	Animal	✓	✓	×
Polyphenols [Flavonoids (Quercetin + trans-resveratrol)]	[58]	Animal	✓	✓	✓
Polyphenols [Flavonoids (Kaempferol)]	[60]	Animal	✓	✓	✓
Polyphenols	[65]	Animal	✓	✓	✓
[Flavonoids (Baicalein)]	[67]	Animal	✓	✓	✓
Polyphenols [Flavonoids (Chrysin)]	[68]	Animal	✓	✓	×
Polyphenols	[46]	Animal	✓	✓	✓
[Flavonoids (Genistein)]	[47]	Animal	✓	✓	✓
	[48]	Animal	✓	✓	✓
Polyphenols [Flavonoids (Anthocyanin)]	[70]	Animal	✓	✓	✓

Akkermansia genus when transferring from the donor to the receiver mice in the high-fat diet fed. The *Akkermensia* genus potentially plays a crucial part in developing protective metabolic phenotypes against NAFLD [57]. Moreover, the associations between gut microbiota composition, trans-resveratrol, and quercetin in high-fat, sucrose diet-fed rats, were assessed with the aim of controlling gut microbiota dysbiosis and enhancing gut health. Mainly quercetin was found to alter gut microbiota composition, and these changes are reported in detail in Tables 2, 3. For instance, quercetin increased *Bacteroides vulgatus* and *A. muciniphila,* which are inversely associated with obesity. Quercetin also reduced *Eubacterium cylindroides* and *Bilophila wadsworthia* which are correlated with obesity caused by diet. Quercetin alone or in combination with resveratrol decreased insulin resistance and HOMA-IR. The processes through which these decreases occur are not clear [58]. Quercetin elevated gut microbial diversity when vitamin D levels were low (including *Facklamia* and *Aerococcus*) and decreased Aβ plaques, tau phosphorylation, neuroinflammation, and miR-26a and miR-125b, in the hippocampus and cortex. These alterations may play a role in improving cognition in rats; however, the mechanisms require more research [59].

Kaempferol

Animal studies

Another flavonoid that is common in vegetables and fruit is kaempferol. Kaempferol has been correlated to anti-arthritis effects, which may be due to modulation in gut flora, which was shown to modulate energy production, tryptophan, fatty acid, and secondary bile metabolism [60].

Flavones

Baicalein

Animal studies

Baicalein is another type of flavons, found in *Scutellariae baicalensis* Georgi. It is thought to have antioxidant [61], anti-inflammatory [62], and anti-aging effects [63]. Baicalein may be linked to some factors that reduce oxidative stress, including elevated catalase activity (CAT), elevated glutathione (GSH) levels, and reduced oxidized glutathione (GSSG) levels [64]. In a study, the associations between baicalein, gut microbiota composition, and cognitive function in mice were assessed. Baicalein changed the abundance of five genera in the mice, decreasing *Mucispirillum*, *Parabacteroides*, *Bacteroides*, and *Sutterella*. In contrast, there was an increase in *Christensenellaceae.* According to correlational analysis, the abundances *of Mucispirillum, Bacteroides, and Sutterella* were adversely associated with cognitive function, but *Christensenellaceae* was positively associated with cognition. Additionally, *Christensenellaceae* abundance was negatively associated with IL-6 and TNF-α. *Mucispirillum* and *Bacteroides* were also correlated with IL-6 in the brain cortex. Gut microbiota modification and suppression of cerebral pro-inflammatory cytokines may be associated with improvements in cognitive function in mice [65]. The impact of baicalein on gut microbiota composition and glycemic and lipid markers were assessed in a study of diabetic rats [66]. Results indicated that baicalein changed the gut microbiota composition in rats with diabetes by elevating α diversity, a relative abundance of *Butyricimonas* and *Parabacteroides*, and a relative abundance of *B. fragilis*. With these changes, the gut microbiome composition of diabetic rats resembled healthy rats. Increased ratios of Firmicutes to Bacteroidetes were shown to be positively associated with inflammation, insulin resistance, and increased blood glucose [66]. Since baicalein decreased this ratio, it may improve type 2 diabetes mellitus (T2DM) abnormalities, insulin resistance, and inflammation. Furthermore, baicalein increased SCFA-producing bacteria such as *A. muciniphila,* which increased the fecal SCFA and the thickness of the mucus layer and and beneficially affected gut barrier function, possibly preventing T2DM in diabetic rats [67].

Chrysin

Animal studies

Another flavonoid, chrysin, was studied to determine its effects on gut microbiota composition and metabolic syndrome in rats. Chrysin alone did not influence gut microbiota composition. Therefore, it does not prevent metabolic syndrome through gut microbiota modulation. However, chrysin could reduce GLUT-5 (glucose transporter) mRNA gene expression, which was elevated in fructose-fed mice, and possibly contribute to reductions in metabolic syndrome risk factors [68].

Anthocyanins

Human studies

A study conducted using a mouse model, showed that anthocyanin malvidin 3-glucoside (MV), predominantly occurring in blueberries, modulated gut microbiota composition by decreasing the abundance of Firmicutes, while increasing the abundance of Bacteroidetes so that the Firmicutes:Bacteroidetes (F:B) ratio was reduced. Reductions in the F:B ratio is assumed to have pro-inflammatory effects. Moreover, MV reduced the abundance of *Ruminococcus gnavus*, which is thought to be associated with elevated disease activity in inflammatory bowel disease (IBD) patients. In addition, MV inhibited bacterial outer membrane lipoproteins, oxidative phosphorylation, and LPS production pathways. The development and severity of IBD are both influenced by decreased fecal butyrate content [69]. The genus *Clostridium*, which is known to contain species that produce butyrate, as well as the class Clostridia, were both much more prevalent after MV supplementation [70].

ASSOCIATIONS BETWEEN CONSUMPTION OF OTHER POLYPHENOLS, GUT MICROBIOTA COMPOSITION, AND HEALTH OUTCOMES

Polyphenols

Human studies

Polyphenols consists of 8 subgroups which is shown in Fig. 1. Numerous studies have identified the associations between polyphenols, including their subgroups, with modifications in gut microbiota composition, and health outcomes. However, most human studies have not been conclusive regarding how gut microbiota alterations could affect health status. A recent study

doi: 10.12938/bmfh.2022-078

Table 2. Summary of included studies: human studies

	First authors/ year/ country	Study design	Participant characteristics	Active phytochemicals	Intervention arms		Study duration	Sample collection and tested biomarkers	Changes in gut microbiota composition	Summary points or major findings (p-value <0.05)
					Intervention	Control				
1	[71] USA	RCT	A) Arm 1 • Symptomatic pre-menopausal; overweight/obese females working in healthcare • n=57 • Intervention group n=27 Age: 36.7 ± 7.7 • Control group n=30 Age: 35.1 ± 8.0 B) Arm 2 Total=26 • Intervention group n=14 Age: 36.7 ± 7.7 • Control group n=12 Age: 35.1 ± 8.0	Polyphenols	A) First Arm: 6 FVC capsules per day B) Second Arm: Meal-replacement shake: 13 g plant-based protein (high fiber)	A) Microcrystalline cellulose B) Usual breakfast	A) 16 weeks B) 4 weeks	• Blood • Stool • DEXA Scan	• Reduction in Family Bacteriodaceae and genus *Bacteroides* in fruit vegetable concentration (FVC) supplementation arm after two months • Reduction in *Lactococcus* in high fiber arm	Dried fruit and vegetable supplement, plus a high-fiber meal substitute: • improved glucose clearance • reduced the risk of insulin resistance • no changes in the immune system.
2	[78] USA	RCT	• Healthy, postmenopausal women of African ancestry (AA) and European ancestry (EA) • Age: 59.8 ± 6.1 • n=252 • Intervention n=93 • Control group n=96	Enterolactone (ENL) in Lignans in flaxseed	10 g/d ground flaxseed	Usual Diet	• 2 × 6-week period • 8-week washout	• Fasting Blood draw • Overnight urine • Stool • BIA	• Regardless of ethnicity, genera that were positively related to ENL included genera in Christensenellaceae, Prevotellaceae, Ruminococcaceae, and some Lachnospiraceae	• Not identified in this study
3	[79] Spain	Case Series	• Healthy adults • n=147 • Three groups: non-coffee-consumers (0–3 mL/day), n=49 Age: 58.8 ± 18.62 • Moderate consumers (3–45 mL/day) n=49 Age: 67.57 ± 14.77 • High-coffee consumers (45–500 mL/day) n=49 Age: 47.10 ± 10.86	• Polyphenols • Alkaloids • Caffeine	Different doses of coffee (0–3 mL/day), (3–45 mL/day). (45–500 mL/day)		• 12 weeks	• Stool • Blood • FFQ	• Phenols in coffee increased the *Bacteroides-Prevotella-Porphyromonas* group levels in feces	• Not identified in this study

The Table was organized by date of publication from the most recent to the oldest. All the papers used the 16s rRNA method to amplify the variants of bacteria in the gut microbiome. RCT: Randomized Clinical Trial; CRC: Colorectal Cancer; OGTT: Oral Glucose Tolerance Test; BIA: Bioimpedance Analysis; ENL: enterolactone; PS: Plant Sterol; HFD: High Fat Diet; CF: Cystic Fibrosis; FVC: Fruit and Vegetable Concentrate; MDA: malondialdehyde; TNF: tumor necrosis factor; MCP: monocyte chemoattractant protein; IL-6: interleukin; HFS: High Fat Sucrose; SCFA: Short Chain Fatty Acid.

doi: 10.12938/bmfh.2022-078

Table 2. Continued

	First authors/ year/ country	Study design	Participant characteristics	Active phytochemicals	Intervention arms		Study duration	Sample collection and tested biomarkers	Changes in gut microbiota composition	Summary points or major findings (p-value <0.05)
					Intervention	Control				
4	[82] USA	RCT	• Healthy adults • n=18 • Age: 21–70	Dietary fiber and phytonutrients, such as glucosinolates	200 g of cooked broccoli, 20 g of raw daikon radish per day		American foods, except Brassica vegetables	• 2 × 18 days • 24-day washout	• Decreased the relative abundance of Firmicutes • Elevated the relative abundance of Bacteroidetes • Increased *Bacteroides*	• Enhanced endocrine system pathways, transport, and catabolism pathways, and energy metabolism pathways
5	[83] Spain	RCT	• Postmenopausal women with hypercholesterolemia • n=40 Age: 26–65 • Control group n=20 • Plant Sterol Enriched group n=20	• Beta-cryptoxanthin • Phytosterols	A plant sterol-enriched (2 g PS/ day) milk-based fruit beverage	Skimmed milk-based fruit beverage	• 2 × 6-week period • 4-week washout	• Stool • FFQ	• Not identified in this study	• More cholesterol in feces of plant sterol-enriched group and hypocholesterolemia
6	[85] USA	RCT	• Overweight and obese CRC survivors n=18 • Control group n=10 65.50 ± 3.07 • Navy Bean group n=8 60.9 ± 11.0	• Phytosterols • Vanillin • Nobiletin • Salicylate	35 g of cooked navy bean powder /day	Snacks without navy beans	• 4 weeks	• Stool	• Not identified in this study	• Stool metabolome alteration • Microbial metabolism which is believed to be protective against
7	[32] Australia	Cross-sectional	Cystic fibrosis free-living adults n=16	Flavonoids (gallocatechin)	—-	——	—-	• Stool • Flavonoid specific FFQ	• Increased Actinomyces a • Decreased class Coriobacteriaceae (Actinobacteria)	• Actinomyces *and* Coriobacteriaceae affect the stage of CF lung disease and colorectal cancer • Decrease colorectal cancer and CF
8	[86] The Netherlands	RCT	• Healthy adults • n=13 • Age: 30.3 ± 11.6	Plant sterol	20 g/day margarin which includes 3 g/d plant sterols	Control margarin (No Plant sterol)	• 2 × 3- week • 4-week washout	• Stool • Blood • FFQ	• No change in gut microbiota composition.	• Plasma oxyphytosterol decreased
9	[49] Iran	RCT	• Healthy adults • n=82 Control=40 Treatment=42 • Age: 20–40	Quercetin	1 g quercetin (two 500 mg capsules) daily	Placebo	12 weeks	• Blood	• Not identified in this study	• Favorable effect of quercetin on PCOS by increasing adiponectin levels • Reduced HOMA-IR and slightly improved the hormonal profiles

doi: 10.12938/bmfh.2022-078

Table 2. Continued

	First authors/ year/ country	Study design	Participant characteristics	Active phytochemicals	Intervention arms		Study duration	Sample collection and tested biomarkers	Changes in gut microbiota composition	Summary points or major findings (p-value <0.05)
					Intervention	Control				
10	[41] Spain	CT	• Menopausal women • n=16 • Equol producers (EP) n=4 • Non producers (NP) n=12 Age: 48–61	Isoflavone tablet	80 g/day	———-	6 months	• Stool • Urine	• No change in gut microbiota composition	• Not identified in this study
11	[80] USA	RCT	• Healthy adults n=32 Age: 29–64 • Almond feeding Study n=18 • Pistachio feeding study n=16	Natural Fiber and Phytochemicals	• 1.5 servings/d almond or pistachio • 3 servings/d almond or pistachio	• no nuts	• 3 × 18-day intervention • 2-week washout	• Stool	• Observations were consistent with nuts' potential prebiotic impact by apparent enrichment of butyrate producers	• Not identified in this study
12	[39] Japan	Cross-sectional	• Healthy adults n= 99 Age: 18–65 • Equol producers (EP) n=59 • Non producers (NP) n=40	Isofllavonoids (Genistein and Equol)	1 Capsule per day daidzein, • 0.38 mg daidzein, • 1.07 mg genistin • 0.32 mg genistein • 1.75 mg glycitin, • 0.18 mg glycitein	—-	• 3 days	• Stool • Urine • Blood • FFQ	• Increase in *Adlercreutzia equolifaciens* and *Bifidobacterium bifidum* species in EP	• Negative associations for *Haemophilus parainfluenzae* and positive association for *Klebsiella pneumoniae* and *Lachnospiraceae bacterium*-8_1_57FAA with total cholesterol, LDL-C, and apolipoprotein B (ApoB) • EP showed a higher relative abundance of *H. parainfluenzae* and lower levels of *K. pneumoniae* and *L. bacterium* 8_1_57FAA compared to NP
13	[50] UK	RCT	• Healthy males n=22 Age: 19–65	Quercetin	500 mg quercetin	Placebo containing lactose monohydrate, magnesium stearate and cellulose	12 weeks	• Urine	• Not identified in this study	• Reduced elevated plasma uric acid concentrations
14	[40] USA	RCT	• Healthy White post-menopausal women n=17 • Equol producers (EP) n=4 • Non producers (NP) n=13 Age: 60.2 ± 7.3	Isofllavonoids	1 Soy bar per day: 160 mg of soy isoflavones and 1 g saponin	——	2 × one-week	• Stool • Urine	• Significant increase in one genus, *Bifidobacterium* after soy consumption	• Not identified in this study

doi: 10.12938/bmfh.2022-078

Table 2. Continued

	First authors/ year/ country	Study design	Participant characteristics	Active phytochemicals	Intervention arms		Study duration	Sample collection and tested biomarkers	Changes in gut microbiota composition	Summary points or major findings (p-value <0.05)
					Intervention	Control				
15	[87] India	RCT	• Healthy adults n=24 Age: 36 ± 22.7 • Control group n=12 • Intervention group: n=12	Phytosterol esters	40 g of control margarine, consisting of 8.6 g vegetable oil phytosterols	40 g of the control margarine	Men: 21 days Women: 28 days	• Stool	• No change in gut microbiota composition	• Reduced cholesterol

Table 3. Summary of included studies: animal studies

No.	First authors/ year/ country	Study design	Characteristics of participants	Active phytochemicals studied	Intervention arms		Study duration	Sample collection and tested biomarkers	Change in gut microbiota composition	Summary points or major findings
					Intervention	Control				
1	[60] China	Experimental study	Male DBA/1 J mice Age: 6–7 weeks n=28 2 groups • Injected flavonoid (Kaempferol) • Orally administrated flavonoid (Kaempferol)	• Flavonoid (Kaempferol)	• Orally administrated flavonoid (Kaempferol) (200 mg/kg) • Injected flavonoid (Kaempferol) (20 mg/kg)	————	4 weeks (From day 21 to day 48)	• Stool	• Increased Lachnospiraceae and Staphylococcaceae • Decreased abundance of Bacteroidales, Prevotellaceae, Bacteroidaceae, Erysipelotrichaceae, Alcaligenaceae, and Christensenellaceae at the family level	• In the model mice, the presence of kaempferol at high concentrations had unique anti-arthritis effects and controlled intestinal flora and macrobiotic metabolism
2	[81] Australia	Experimental study	Male Wistar rats Age: 8–9 weeks n=48 4 groups • Corn starch diet-fed rats (C) • Corn starch diet for 8 weeks, supplemented with 5% dried spent coffee grounds for the final 8 weeks (CS) • High carbohydrate, high-fat diet-fed rats (H) • High-carbohydrate, high-fat diet for 8 weeks, supplemented with 5% dried spent coffee grounds for the final 8 weeks (HS)	• Flavonoid and alkaloid • High-carbohydrate, high-fat diet for 8 weeks, supplemented with 5% dried spent coffee grounds for the final 8 weeks (HS)	• Corn starch diet for 8 weeks, supplemented with 5% dried spent coffee grounds for the final 8 weeks	• Corn starch diet-fed • High carbohydrate, high-fat diet-fed rats (H)	16 weeks	• Stool	• Increased Bacteroidetes in supplementation with coffee grounds • Decreased F:B ratio • Increased alpha diversity	• Improvements in obesity, systolic blood pressure, and glucose tolerance

The Table was organized by date of publication from the most recent to the oldest. All the papers used the 16s rRNA method to amplify the variants of bacteria in the gut microbiome. RCT: Randomized Clinical Trial; CRC: Colorectal Cancer; OGTT: Oral Glucose Tolerance Test; BIA: Bioimpedance Analysis; ENL: enterolactone; PS: Plant Sterol; HFD: High Fat Diet; CF: Cystic Fibrosis; FVC: Fruit and Vegetable Concentrate; MDA: malondialdehyde; TNF: tumor necrosis factor; MCP: monocyte chemoattractant protein; IL-6: interleukin; HFS: High Fat Sucrose; SCFA: Short Chain Fatty Acid.

doi: 10.12938/bmfh.2022-078

Table 3. Continued

No.	First authors/ year/ country	Study design	Characteristics of participants	Active phytochemicals studied	Intervention arms		Study duration	Sample collection and tested biomarkers	Change in gut microbiota composition	Summary points or major findings
					Intervention	Control				
3	[56] China	Experimental study	24 C57BL/6 mice n=24 Age: 90 days • Control group n=12 • Intervention group n=12	• Flavonoid (Quercetin)	• Quercetin (100 µg/day)	Regular Chow diet (10% fat, 70% carbohydrate, and 20% protein)	12 weeks	• Urine and serum samples	• Decreased the abundance of Verrocomicrobia • Elevated microbiome diversity and the abundances of Actinobacteria, Cyanobacteria, and Firmicutes	• Quercetin decreased levels of atherogenic lipid metabolites, lipid levels, regions of atherosclerotic lesions, and plaque size • Increased levels of IL-6 and decreased levels of MDA have positive impacts on immunological and inflammatory responses, as well as oxidative stress
4	[57] Spain	Experimental study	C57BL/6 J conventional male mice divided in to gut microbiota donors and receivers Age: 42 days n=54 • Control diet-fed donor [dC] n=6 • Control diet supplemented with quercetin-fed donor [dCQ] n=6 • Responder to the HFD donor [dHFD+] n=6 • Non-responder to HFD donor [dHFD−] n=6 • Higher response to quercetin with HFD [dHFDQ] n=6 • Control: C n=6 • Control + quercetin: CQ n=6 • HFD n=6 • HFD + quercetin: HFDQ n=6	• Flavonoid (Quercetin) • High Fat Diet (HFD) • Flavonoid (Quercetin) + High Fat Diet (HFD) (HFD: 0% energy from fat)	• Quercetin (80 mg/day)	• Normal diet • High Fat Diet (HFD)	16 weeks	• Plasma • Cecal • Stool • Liver tissues • Visceral adipose tissues	• Increased *Akkermansia* genus	• Quercetin has a preventive impact against the development of NAFLD by a combination of its anti-inflammatory, antioxidant, and prebiotic effects

doi: 10.12938/bmfh.2022-078

Table 3. Continued

No.	First authors/ year/ country	Study design	Characteristics of participants	Active phytochemicals studied	Intervention arms		Study duration	Sample collection and tested biomarkers	Change in gut microbiota composition	Summary points or major findings
					Intervention	Control				
5	[68] Portugal	Experimental study	Adult male Sprague-Dawley rats Age: 8 weeks n=24 4 groups • Tap water (CONT) n=6 • Tap water and chrysin (100 mg/ kg per day) (CHRY) n=6 • 10% fructose in tap water (FRUCT) (MVD) n=6 • 10% fructose in tap water and chrysin (100 mg/ kg per day) (FRUCT + CHRY) n=6	• Flavonoid (Chrysin)	• Fructose • Chrysin • Fructose + chrysin	Standard chow diet	18 weeks	• Body weight • Food intake • Glycemia • Blood pressure • Stool	• Chrysin had no effect on gut microbiota composition • Fructose considerably raised the levels of *Lactobacillus* and *E. coli* • Enhanced the Firmicutes to Bacteroidetes ratio while decreased Bacteroidetes	• Chrysin reduced GLUT-5 mRNA levels which were elevated by fructose-fed mice • Reduced metabolic syndrome features
6	[70] USA	Experimental study	C57BL/6 mice Age: 4–5 weeks 3 groups • Normal (N) n=10 • DSS-induced colitis (M) n=10 • DSS colitis mice supplemented with MV (MV) n=9 DSS= dextran sulfate sodium	Anthocyanin (Malvidin 3-glucoside =MV)	• Dextran sulfate sodium • Malvidin 3-glucoside =MV (24 mg kg^{-1})	Standard laboratory rodent diet (AIN-93M)	7 weeks	• Stool • Colon tissue samples • Body weight	• Increase Firmicutes/ Bacteroidetes ratio • Reduce *Ruminococcus gnavus*	• Reduced intestinal inflammation by altering the gut microbiota, colon epithelial integrity, and major inflammatory mediators
7	[59] China	Experimental study	APP/PS1 male transgenic mice Age: 70 days n=28 4 groups • Control group (CON) n=7 • Low-VD-level group (LVD) n=7 • Medium-VD-level group (MVD) n=7 • High-VD-level group n=7	• Flavonoid (Quercetin) • Different dosages of vitamin D	0.08% quercetin or approximately 120 mg /kg per day in modified AIN-93G diet	AIN-93G diet (VD level=1,000 IU/kg diet)	20 weeks	• Body weight • Food intake • Cecal	• Quercetin increased gut microbial diversity when vitamin D levels were low (including *Facklamia* and *Aerococcus*)	• Quercetin enhanced cognitive function

doi: 10.12938/bmfh.2022-078

Table 3. Continued

No.	First authors/ year/ country	Study design	Characteristics of participants	Active phytochemicals studied	Intervention arms		Study duration	Sample collection and tested biomarkers	Change in gut microbiota composition	Summary points or major findings
					Intervention	Control				
8	[65] China	Experimental study	Senescence accelerated mouse prone 8 (SAMP8) for intervention and SAMR 1 mice for control Age: 8 months • SAMR1 Group: intragastrically administered 340 saline solution-0.9% NaCl n=15 • SAMP8 + baicalein group: intragastrically administered baicalein (200 mg/kg/d) n=14 • SAMP8 group (Control) intragastrically administered saline solution-0.9% NaCl n=13	• Flavonoid (Baicalein)	Baicalein (200 mg/kg/d)	Saline solution	8 weeks	• Stool	• Decreased *Mucispirillum*, *Parabacteroides*, *Bacteroides*, and *Sutterella* • Increased Christensenellaceae	Baicalein might improve the aging process and senescence function and cognitive function possible due to pro-inflammatory prohibition and gut microbiota alteration
9	[67] China	Experimental study	Male Wistar rats • Diabetic rats: n=24 1) vehicle-treated (DM) n=6 2) 50 mg/kg/d of baicalein (LB) n=6 3) 150 mg/kg/ d of baicalein (HB) n=6 4) 500 mg/kg/d metformin (Met) (Positive Control) n=6 • Non-diabetic Rats: 4) Normoglycemic (NM) n=6	Flavonoid (Baicalein)	Baicalein (50 and 150 mg/kg/d)	500 mg/kg/d metformin	4 weeks	• Stool • Oral glucose tolerance test (OGTT) • Body weight • Blood sample	• Increased relative abundance of *Butyricimonas* and *Parabacteroides* • Elevated the relative abundance of *Bacteroides fragilis*	Baicalein potentially: • Had a prebiotic effect by modifying the gut microbiota and improved T2DM, insulin resistance, and blood sugar • Reduced lipopolysaccharide and inflammation • Increased fecal SCFA
10	[46] Mexico	Experimental study	C57/BL6 mice Age: 9 weeks n=24 • Control group (C) n=8 • High Fat (HF) n=8 • High Fat +0.2% genistein (HFG) n=8	• Flavonoid (Genistein)	Genistein 3 mg/kg/d	Mainly cornstarch	21 weeks	• Blood • Brain • Sample Adipose tissue	• Increased the genus *Prevotella* and *Akkermansia*	• Genistein was able to manage the gut flora • Lowered metabolic endotoxemia • Decreased the neuroinflammatory response

doi: 10.12938/bmfh.2022-078

Table 3. Continued

No.	First authors/ year/ country	Study design	Characteristics of participants	Active phytochemicals studied	Intervention arms		Study duration	Sample collection and tested biomarkers	Change in gut microbiota composition	Summary points or major findings
					Intervention	Control				
11	[48] Georgia	Experimental study	• Prenatal female mice with T1DM • Vehicle group (VEH) n=12 • Genistein group (GEN) n=12 Offspring mice • Vehicle group (VEH) n=4 • Genistein group (GEN) n=4	• Flavonoid (Genistein)	Genistein 20 mg/kg	Sodium carbonate	90 days	Stool	• Bacteroides/Firmicutes was decreased in female offspring mice • NOD mice that were treated with genistein during pregnancy showed more enterobacterial	• Pro-inflammatory response in female offspring due to the increase in Enterobacteriales • Exacerbated type 1 diabetes in female offspring
12	[47] USA	Experimental study	• Cancer patients' stool n=3 mice for stool transplant • Control group: corn oil diet without genistein patient 1 pre-chemotherapy: n=4 patient 1 post-chemotherapy: n=4 patient 2 pre-chemotherapy: n=4 patient 2 post-chemotherapy: n=4 patient 3 pre-chemotherapy: n=4 patient 3 post-chemotherapy: n=4 • Intervention: corn oil diet with genistein n=24 patient 1 pre-chemotherapy: n=4 patient 1 post-chemotherapy: n=4 patient 2 pre-chemotherapy: n=4 patient 2 post-chemotherapy: n=4 patient 3 pre-chemotherapy: n=4 patient 3 post-chemotherapy: n=4	• Flavonoid (Genistein)	Genistein	Corn oil	4 weeks	Stool	• A decline in the species of *Turicibacteria, Blautia, Anaerostipes, Bacteroides, Paraprevotella* and *Coprobacillus* • A rise in numbers of *Lactococcus, Akkermansia,* and *Eubacterium* genus	• Decreased tumor growth • Decreased tumor size and weight

doi: 10.12938/bmfh.2022-078

Table 3. Continued

No.	First authors/ year/ country	Study design	Characteristics of participants	Active phytochemicals studied	Intervention arms		Study duration	Sample collection and tested biomarkers	Change in gut microbiota composition	Summary points or major findings
					Intervention	Control				
13	[58] Spain	Experimental study	Wistar rats n=23 4 groups • HFS diet; trans-resveratrol group (RSV; n=6) • Quercetin group (Q; n=6) • Trans -resveratrol+ quercetin group (RSV+Q; n= 6) • Control group (HFS; n=5)	• Flavonoid (Quercetin) • Trans-resveratrol	• Quercetin (30 mg/kg BW/day) • Trans-resveratrol (15 mg/kg BW/day)	• High Fat sucrose (HFS)	6 weeks	• Feces • Liver tissue	• Quercetin could lessen gut microbiota dysbiosis induced by HFS diet • Quercetin reduced Firmicutes/Bacteroidetes ratio • Quercetin reduced Erysipelotrichia (classified within the Firmicutes phylum) • Quercetin reduced the levels of the *Bacillus* genus • Quercetin increased *Akkermansia* • The mean relative abundance of various *Clostridium* species, including *Clostridium aldenense, Clostridium hathewayi, Clostridium* sp. C9, and *Clostridium* sp. MLG661, was decreased by trans-resveratrol	• Either separately or in combination, trans-resveratrol and quercetin effectively reduced serum insulin levels and HOMA-IR • There was a tendency for trans-resveratrol and quercetin to inhibit body weight increase brought to the consumption of an HFS diet

doi: 10.12938/bmfh.2022-078

of obese/overweight women showed that supplementation with fruit and vegetable concentrates (FVC) and high fiber plant-based protein shakes with polyphenols, changed gut microbiota composition and significantly reduced Bacteriodaceae and genus *Bacteroides* and genus *Lactococcus*. At the same time, there were improvements in glucose clearance, and the authors speculated that there was a reduction in insulin resistance, which would then be associated with a decreased risk of T2DM. However, the same study indicated no effects on immune markers [71]. This result is in line with findings from earlier research that the *Bacteroides* genus is capable of complex carbohydrate metabolism and may be protective against T2DM [72].

Lignans

Human studies

Lignan has an estrogen like structure, acting as a phytoestrogen in humans [73]. Lignan is found in seeds, vegetables, cereals, legumes, nuts, fruits, and to a lesser extent in beverages like tea and coffee [74]. Dietary lignan is converted to enterodiol and enterolactone by the gut microbiota, and these metabolites have anti-inflammatory, anti-oxidant, estrogenic/anti-estrogenic, and anti-cancer effects which are thought to be health promoting [75, 76]. Several studies have shown that increased dietary lignan consumption is associated with decreased cardiovascular disease (CVD) risk [77]. However, the associations between gut microbiome composition and subsequent health outcomes following lignan consumption, have not been clearly determined. Flaxseed, which is abundant in enterolactone, a type of lignan, was used in a study of postmenopausal women with African American (AA) and European American (EA) ancestry. Results of the study showed that women with different ancestries had different gut microbiota compositions, both at the baseline and after enterolactone intervention. For example, there were significant differences in the abundance of 18 genera among AA participants and 17 genera among EA participants; 12 of these were shared by the two groups. However, following the flaxseed intervention, only 9 genera were shared by participants in the AA group (21 genera) and the EA group (14 genera). There were no associations between lignan, α and β diversity of microbiome composition and the onset of any chronic diseases [78].

PHYTOCHEMICAL COMBINATIONS, GUT MICROBIOTA COMPOSITION, AND HEALTH OUTCOMES

Flavonoids and alkaloids

Human studies

There are not many studies investigating the associations between combinations of phytochemicals and gut microbiota composition. One such clinical study that included 147 participants, assessed the associations between some phenols such as flavonoids and alkaloids combined as the active phytochemicals in coffee, and alterations in gut microbiota composition. Participants were divided into tertiles based on the daily coffee consumption. Flavonoids and alkaloids in the highest tertile of coffee consumption showed a significant elevation in the prevalence of *Bacteroides-Prevotella-Porphyromonas* in feces. However, this study did not aim to determine how gut microbiota changes might affect health outcomes [79]. Likewise, in another clinical trial, the associations between the phytonutrients in pistachios and almonds, and gut microbiota composition, were assessed without determination of associations with health outcomes. Nut consumption increased butyrate and bifidobacterial. Pistachio consumption had a larger effect on butyrate composition than almonds and was connected to a reduction in the lactic acid bacteria. Therefore, nut consumption modifies gut microbiota composition in ways that align with health promotion, but no direct health outcomes have been determined in the studies conducted thus far [80].

Animal studies

The effects of ground coffee consumption, abundant in alkaloids and flavonoids, was studied during a high-carbohydrate, high-fat diet that induced metabolic syndrome and cardiovascular remodeling in male Wistar rats [81]. This 16-week controlled study showed that ground coffee consumption increased Bacteroidetes (p-value=0.05), decreased the F:B ratio (p-value=0.0027), and increased α diversity (p-value=0.0005). In terms of health outcomes, coffee grounds decreased body weight, abdominal fat, total body fat mass, systolic blood pressure, and plasma triglycerides, and non-esterified fatty acid concentrations. Coffee ground consumption also improved glucose tolerance and the structure and function of the heart and liver. The changes in the gut microbiota composition were also significantly associated with improvements in glucose tolerance as well as in adiposity and systolic blood pressure [81].

PROTEIN PHYTOCHEMICALS, GUT MICROBIOTA COMPOSITION, AND HEALTH OUTCOMES

Glucosinolate

Human studies

Broccoli and radish consumption are abundant in glucosinolate. Broccoli increased *Bacteroides*, the relative abundance of Bacteroidetes, and reduced the relative abundance of Firmicutes [82]. Therefore, it altered β diversity. In participants with BMIs <26 kg/m^2, broccoli consumption increased glucosinolate metabolites, which supports the idea that variations in the presence of health-promoting glucosinolate metabolites may relate to alterations in the microbiota. Since the greatest peak in plasma metabolites was positively associated with the difference in Bacteroidetes from baseline to post-intervention with broccoli consumption (r=0.69, p-value=0.04). Firmicutes variation from baseline to post-intervention was likely to be negatively associated (r=0.66, p-value=0.05), but variation in the Bacteroidetes to Firmicutes ratio was likely to be positively associated (r=0.58, p-value=0.1). Following the trial, Phylogenetic Investigation of Communities by Reconstruction of Unobserved States (PICRUST), a predictive software package to infer the metabolic activities of the microbiota by comparing compositions, was used to assess the function of the gut microbiota. Overall, consumption of broccoli increased the number of pathways involved in energy metabolism (p-value=0.01), transport and catabolism (p=0.04), and endocrine system functions (p-value=0.05), while decreasing the number of pathways related to membrane transport (p-value=0.03). Additionally, the protein families involved in transcription control and cellular transportation, were among those anticipated to be elevated in the broccoli group (e.g., RNA polymerase sigma-70 factor) [82].

doi: 10.12938/bmfh.2022-078

LIPID PHYTOCHEMICALS, GUT MICROBIOTA COMPOSITION, AND HEALTH OUTCOMES

Phytosterols

Human studies

Plant phytosterol consumption was studied in a trial where two milk-based fruit beverages were fortified with plant sterols or a placebo without enrichment. Plant phytosterols consumption in the intervention group was shown to decrease cholesterol absorption. As the structure of plant sterols is the same as cholesterol, the amount of cholesterol was measured in feces. Since more cholesterol was in the feces in the intervention group, plant phytosterol consumption was associated with hypocholesterolemia in participants. However, the gut microbiota composition was not studied in this trial. The authors assumed that gut microbiota alterations could be related to the amount of cholesterol in the feces [83]. Another study showed that when colorectal cancer survivors consumed navy beans, which are abundant in sterols, the stool metabolome and microbial metabolism of amino acids, fatty acids, and phytochemicals were altered. For example, there was an increase in anacardic acid, 4-hydroxyphenylacetate, cadaverine, diacetylchitobiose, and 5,6 dihydrothymine. Five metabolites increased and were recognized as navy bean metabolites: ophthalmate, piperidine, adenosine-2′, 3′-cyclic monophosphate, and N-methylpipecolate. Therefore, navy bean consumption may modulate the metabolism of nutrients and metabolic pathways which have been shown previously to be protective against colorectal cancer [84]. However, gut microbiota alterations were not directly studied, and it was only hypothesized that changes in metabolites and feces composition might be correlated with changes in gut microbiota composition [85]. Moreover, another study assessed the associations between plant stanols, and saturated plant sterols, on gut microbiota changes. With 20 g margarine consumption per day, which contains 3 g of plant stanol, plasma oxyphytosterol decreased. However, there were no alterations in gut microbiota composition [86]. These findings are in line with another study that assessed the associations between daily consumption of 40 g margarine in females, sex hormones, and gut microbiota changes. Results indicated no significant effects on gut microbiota composition or sex hormone levels. However, margarine, enriched with phytosterol esters, decreased serum low-density lipoprotein (LDL) cholesterol and total cholesterol. The improvements in health outcomes occurred despite lack of alterations in gut microbiota composition [87]. The primary purpose of the current review was to identify the current state of the published research regarding the consumption of phytochemicals, associations with gut microbiota composition, and related health outcomes in human and non-human animals. Most of the previous gut microbiota research has been conducted in non-human animal models, and clinical studies in humans identifying the roles that gut microbiota plays in disease pathogenesis are still lacking. Based on previous human and non-human animal studies, the phytochemical associations with gut microbiota composition and health outcomes fall into two broad categories; 1) Regular consumption of some active phytochemicals can alter gut microbiota composition in ways that have been shown to be correlated with positive health outcomes. This is particularly true in non-human animals, for example, different types of flavonoids altered gut microbiota composition which was correlated with improved glycemic markers, inflammation, cognitive function, and oxidative stress; 2) Some phytochemicals have been shown to improve markers of disease risk without significant changes in the gut microbiota, for example, phytosterol esters present in navy beans have positive impact on colon health in cancer survivors without changing gut microbiota composition.

DISCUSSION

There is little evidence in the current published research literature that connects phytochemical consumption, gut microbiota alterations, and health outcomes. While many of the published studies offer feasible mechanistic rationale; however, future research that includes all three of these components are needed. For example, antioxidants are beneficial for decreasing the risk for cancer, however, a well-known outcome of this type of research is supplementation with some antioxidants (vitamin C, A, E). Unfortunately, supplementation with vitamin E in smokers, who would be at increased risk for developing cancer, has been shown to increase the risk [88].

There is an urgent need to determine whether microbiome alterations serve as moderators or mediators between phytochemical consumption and non-communicable health outcomes, or whether the gut microbiota is an independent therapeutic target. The limitations of the current published research leave important gaps that make interpretation difficult. This is particularly true given the transient nature and changeability of the gut microbiota composition with acute lifestyle (diet and physical activity) interventions as well as the influence of aging. Previous research suggests distinct differences in the composition of gut microbiota with aging, potentially associated with dietary intake and specific nutrients [89]. These changes include increases in proteolytic bacteria and decreases in saccharolytic bacteria associated with sarcopenia and decreased longevity. Additionally, some research suggests that prebiotics and probiotics may help to mitigate these age-related changes [90]. Future research should investigate the effects of age-related changes on the gut microbiota and the efficacy of consumption of some phytochemicals as potential therapeutic approaches. Most of the initial research on the gut microbiota has been conducted in animal models, based on these studies, there has been a lot of interest generated for research in humans, and substantial new grant funding designated for this type of research. However, little has been published that connects phytochemical consumption, alterations in gut microbiota composition, and non-communicable health outcomes.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST

None.

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