British Journal of Nutrition (2022), 128, 577–591 doi:10.1017/S0007114521003627
© The Author(s), 2021. Published by Cambridge University Press on behalf of The Nutrition Society

Interactions between dietary flavonoids and the gut microbiome: a comprehensive review

Mostafa Hassan Baky[1], Mostafa Elshahed[2], Ludger Wessjohann[3] and Mohamed A. Farag[4,5]*

[1]*Pharmacognosy Department, College of Pharmacy, Egyptian Russian University, Badr City, 11829 Cairo, Egypt*
[2]*Department of Microbiology and Molecular Genetics, Oklahoma State University, 1110 S. Innovation Way, Stillwater, OK, USA*
[3]*Department of Bioorganic Chemistry, Leibniz Institute of Plant Biochemistry, Weinberg 3, 06120 Halle (Saale), Germany*
[4]*Pharmacognosy Department, College of Pharmacy, Cairo University, Kasr el Aini St., P.B. 11562, Cairo, Egypt*
[5]*Chemistry Department, School of Sciences & Engineering, The American University in Cairo, New Cairo 11835, Egypt*

(Submitted 19 April 2021 – Final revision received 24 July 2021 – Accepted 27 August 2021 – First published online 13 September 2021)

Abstract

Flavonoids are natural polyphenol secondary metabolites that are widely produced *in planta*. Flavonoids are ubiquities in human dietary intake and exhibit a myriad of health benefits. Flavonoids-induced biological activities are strongly influenced by their *in situ* availability in the human GI tract, as well as the levels of which are modulated by interaction with the gut bacteria. As such, assessing flavonoids–microbiome interactions is considered a key to understand their physiological activities. Here, we review the interaction between the various classes of dietary flavonoids (flavonols, flavones, flavanones, isoflavones, flavan-3-ols and anthocyanins) and gut microbiota. We aim to provide a holistic overview of the nature and identity of flavonoids on diet and highlight how flavonoids chemical structure, metabolism and impact on humans and their microbiomes are interconnected. Emphasis is placed on how flavonoids and their biotransformation products affect gut microbiota population, influence gut homoeostasis and induce measurable physiological changes and biological benefits.

Key words: **Flavonoids: Gut microbiota: Bioavailability: Polyphenols: Biological activity: Biotransformation**

Microbial populations residing in the human gut play a pivotal role in the host's overall health by providing defence against pathogens, aiding in nutrient processing, lowering serum cholesterol level and improving the host's immune functions (Fig. 1)[1–3]. There are several factors that can lead to inter individual variations in gut microbial composition such as genetic factors, age, diet, the use of antibiotics and consumption of pre- and probiotics which can affect the colonisation of host gut microbiota[4,5]. Such inter individual differences have been shown to affect the metabolism of ingested polyphenols[6]. Dysbiosis in normal gut microbiota population can lead to chronic inflammatory conditions, for example, gastritis, inflammatory bowel syndrome, diarrhoea and colorectal cancer. Further, poor dietary habits, lack of exercise, stress and drugs can induce and sustain dramatic changes in the gut community structure[5]. This can trigger a wide range of non-communicable diseases, including neurodegenerative diseases,CVD and obesity, some of which are combined in the metabolic syndrome[7,8]. The association between specific microbial taxa and specific beneficial or harmful health outcomes continues to be an area of active research[9].

Flavonoids represent a major group of secondary metabolites found in several dietary sources including fruits, vegetables and drinks like coffee, tea and wine[10]. Flavonoids are well recognised for their potential anti-carcinogenic, antioxidant, anti-microbial and anti-inflammation effects[11,12]. Additionally, flavonoids can mitigate against several degenerative diseases such as diabetes, obesity, CVD and neurodegenerative disease, or combinations such as metabolic syndrome[13]. Possible beneficial effects of flavonoids depend mainly on their intrinsic bioavailability and vary between different flavonoids subclasses[14]. Generally, phenolic glycosides are not hydrolysed in the stomach[15]. Although some special aglycone moieties, depending on the structure, can show (other) reactions under the high HCl levels of the stomach, this is a rare case and not the focus of this review. Thus, after stomach passage, flavonoid glycosides are either hydrolysed in the small intestine by specific enzymes (e.g. lactase phlorizin hydrolase or human β-glucosidase[16,17]) or metabolised in the large intestine by the action of intestinal microbiota to yield aglycones, the hydrophobic core of the flavonoid molecule[14,18,19]. Aglycones pass through cell membranes to exert their biological functions *via* passive diffusion[20].

Abbreviations: MIC, minimum inhibitory concentration.

* **Corresponding author:** Mohamed A. Farag, email mohamed.farag@pharma.cu.edu.eg

https://doi.org/10.1017/S0007114521003627 Published online by Cambridge University Press

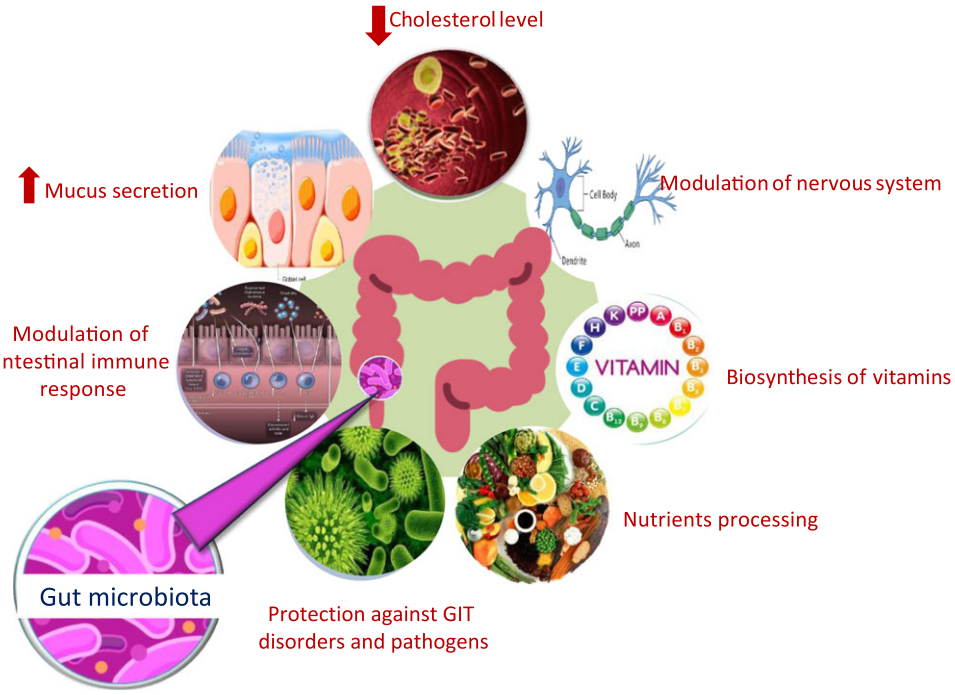

Fig. 1. Role of gut microbiota in affecting host health.

In addition, flavonoid ingestion can also modulate the gut microbial community[21]. As such, dietary flavonoids and commensal gut microbiota exhibit a two-way mutual interaction. Firstly, flavonoids are metabolised by intestinal microbiota that leads to enhancement of their bioavailability, and secondly flavonoids can modulate the intestinal microbial population structure[22,23].

This review aims to provide a holistic overview on the interaction between dietary flavonoids in their different forms or classes and human intestinal microbiota. We start by describing the structure and distribution of the various classes of flavonoids in human diet. We then proceed to examine each major class of flavonoids in detail. Specifically, we examine their metabolic fate, structure activity relationship and role of the gut microbial communities in modulating their structure and activity, their impact on the microbial community structure inside the gut, and their overall impact on the host's physiology.

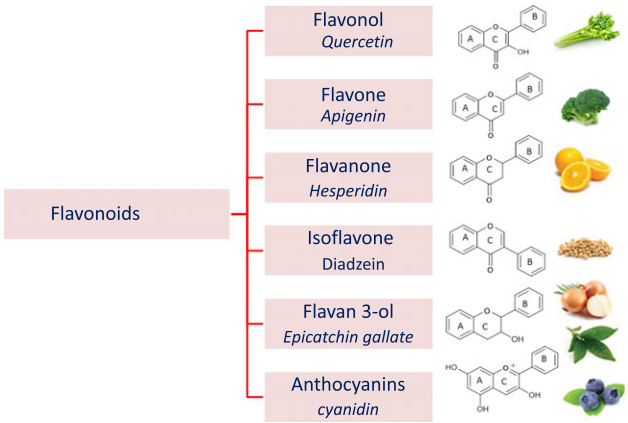

Fig. 2. Flavonoid subclasses (as structures) and example names of a common flavonoid of the respective subgroup.

Flavonoid classes

Flavonoids structure is based on a 15-carbon skeleton consisting of two phenyl rings (A and B) linked *via* a 3-carbon bridge forming a heterocyclic pyrane ring (C)[11,24]. According to the substitution pattern on the central pyran ring, flavonoids are sub-classified into flavonols, flavones, flavanones, flavan-3-ols, isoflavones and anthocyanins, cf. (Fig. 2)[24–26]. Common dietary flavonoids include flavonols in onions, apples, and tea, flavanones in citrus fruits, flavan-3-ols in cocoa, tea, apples, and broad beans, and anthocyanins in berries and roses[27]. Only 5–10 % of the ingested flavonoids are absorbed in the small intestine, with the rest undergoing enzymatic breakdown by the resident microbiota in the large intestine or excretion[28]. Microbial β-glucosidases produced by specific gut microbes such as *Bifidobaterium* spp. and *Lactobacillus* spp. effectively hydrolyse flavonoid glycosides yielding aglycones and glucose units. Indeed, the amount of sugars released from phenolics is considered much lower compared with that from macronutrients such as pectin, etc. Glucose supports bacterial growth and is fermented to SCFA, the production of which triggers a wide range of beneficial physiological effects for the host, see Fig. 3[4,28].

The two-way interaction between flavonoids and intestinal microbiota can be used to modulate the composition and diversity of the intestinal microbiome[21,29,30]. This reciprocal relationship between dietary flavonoids and gut microbiota often enhances the biological activity of flavonoids, since their bioactive metabolites may have greater biological action than their parent compounds[21,31].

British Journal of Nutrition

https://doi.org/10.1017/S0007114521003627 Published online by Cambridge University Press

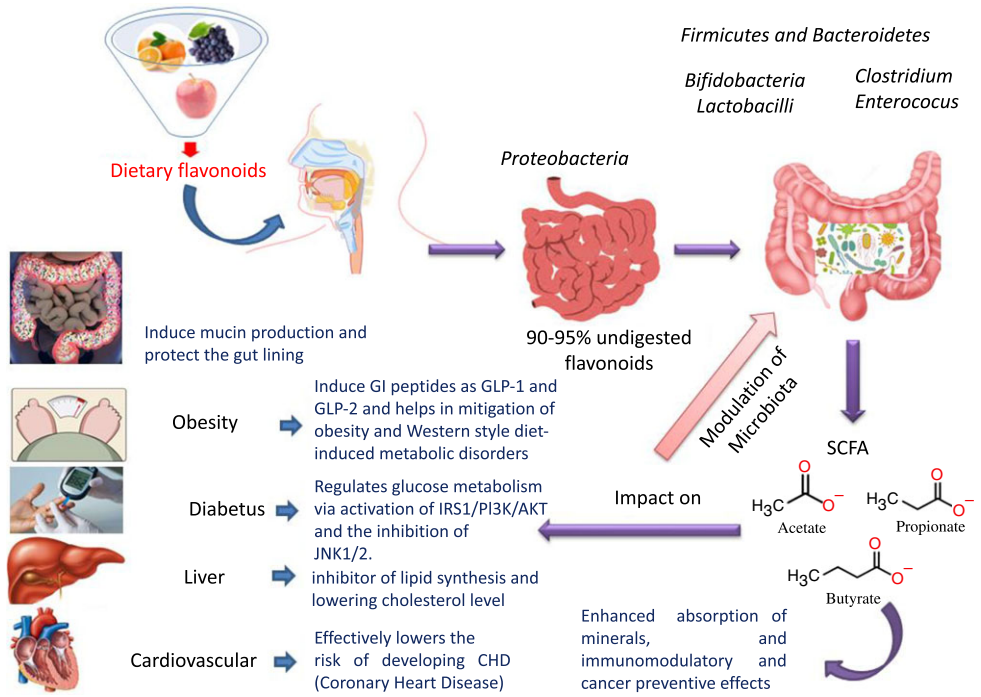

Fig. 3. Dietary flavonoids modulation of gut microbiota, action mechanisms and impact on health.

Flavonoids interaction with the human microbiome

Flavonols

Occurrence and metabolism. Flavonols are composed of a 3-hydroxyflavone base that is hydroxylated at certain positions (Fig. 2)[32]. Flavonols are distributed in several foods, particularly onions, broccoli, tea, apples, tomatoes, grapes, berries, red wine, some fruit varieties and vegetables[32,33]. The most commonly known flavonols include kaempferol, quercetin, myricetin and fisetin[34].

Flavonol glycosides are hydrolysed by microbial *β*-glucosidases to the corresponding aglycones which are then biotransformed by intestinal microbiota through mostly oxidative C-ring cleavage and demethylation, or dehydroxylation reactions to yield simple phenols and benzoates, see Fig. 4. For example, quercetin yields phloroglucinol, dihydrocaffeic acid, 2-(3,4-dihydroxyphenyl)acetic acid, 2-(3-hydroxyphenyl)acetic acid, 3,4-dihydroxybenzoic acid and 3-(3-hydroxyphenyl)propionic acid as major metabolites (Fig. 4). Other metabolites of flavonols include 2,4,6-trihydroxybenzoic acid, 3-(3,4-dihydroxyphenyl) benzoic acid methyl ester, vanillic acid and 3-(*p*-hydroxyphenyl) propionic acid. Additionally, myricetin which contains a trihydroxy ring-B yielded 2-(3-dihydroxyphenyl)acetic acid, 2-(3-hydroxyphenyl) acetic acid and 2-(3,4,5-trihydroxyphenyl) acetic acid. Whereas in the case of kaempferol (bearing a mono hydroxylated ring B), only 2-(4-hydroxyphenyl) acetic acid was produced[35]. Mono-glycosylated flavonols such as quercetin-3-*O*-*β*-D-glucopyranoside showed faster metabolic breakdown by gut bacteria than the more complex di- and trisaccharides[36]. Both the type of sugar and glycosidic bond (α- or *β*- and *C*- or *O*-glycoside) also affect flavonoids stability inside the colon[37], with C-flavonoid glycosides showing slower metabolic rates than *O*-glycosides.

Interactions with the microbial community. The impact of flavonol (or flavonol-rich extracts/foods) on the microbial community structure and diversity in the large intestine has been investigated in multiple studies (Table 1).

In vitro *studies.* The impact of flavonols on model microbial species has been extensively examined *in vitro*. The influence of the flavonol 'rutin' and its aglycone quercetin on the growth of the intestinal bacteria *Enterococcus caccae*, *Bacteroides galacturonicus* (DSM 3978), *Lactobacillus* sp. (DSM 20059), *Ruminococcus gauvreauii* (DSM 19829), *Bifidobacterium catenulatum* (DSM 16992) and *E. coli* (DSM 1116) was investigated at a dose of 20, 100 or 250 μg/ml of rutin and 4, 20 or 50 μg/ml of quercetin[38]. While quercetin inhibited the growth of all examined bacteria, especially *Ruminococcus gauvreauii* (with minimum inhibitory concentration (MIC) 20 μg/ml), *Bacteroides galacturonicus* and *Lactobacillus* (MIC 50 μg/ml) in a dose-dependent manner, no effect was observed in case of rutin. These results suggest that only flavonol aglycones can affect intestinal bacterial growth, such pattern was observed for other flavonoid glycosides such as flavanones, especially naringenin as described below[38]. Moreover, the metabolising capacity of *Bifidobacterium* and *Lactobacillus* on flavonoids and the anti-inflammatory potential of various metabolites on lipopolysaccharide-stimulated RAW264 macrophages was evaluated *in vitro*[39]. Different flavonols were tested in the presence of *B. adolescentis* culture, with galangin, quercetin and fisetin to show significant inhibition of nitric oxide (NO) production induced by lipopolysaccharide and hence anti-inflammatory activity. Additionally, galangin prevented *B. adolescentis* growth by 30–70 % after 1–6 h co-culture, while quercetin and fisetin showed no effect on bacterial growth rate. On the other hand, biotransformation

British Journal of Nutrition

https://doi.org/10.1017/S0007114521003627 Published online by Cambridge University Press

Table 1. Effect of different groups of individual flavonoids and flavonoid extracts on gut microbiota composition and health effects

Flavonoid compound or extract	Subject	Dose and intervention	Impact on microbiota		Health outcomes	Reference
Flavonoids						
Apigenin	*In vitro* batch culture fermentation	100 μg/ml	*Clostridium, Peptostreptococcaceae, Bacteroidetes, Proteobacteria*	+	- ↑Acetate, propionate, and butyrate production - ↑Mucin secretion	Wang, et al, (2017)[54]
			Enterococcus caccae, Firmicutes, E. caccae and B. galacturonicus	–		
Baicalein	Male Wistar rats	50 mg/kg/d	*Bacteroidetes: Firmicutes, Bacteroidales, Bacteroidaceae, Porphyromonadaceae, and Verrucomicrobiaceae*	+	↓ Blood glucose level - Lowers insulin resistance in diabetic rats	Zhang, et al, (2018)[56]
			Streptococcaceae, Deferribacteraceae, and Desulfarculaceae, Ruminococcaceae	–		
Enteromorpha prolifera (EPW) aqueous ethanolic extract and flavonoid-rich fraction containing eriodictyol-*O*-glucuronide and kaempferol	Kunming male ICR mice	150 mg/kg body weight of EPW	*Bacteroidetes, Actinobacteria Proteobacteria, Alistipes, Lachnospiraceae and Odoribacter*	+	↓ Blood glucose level protected against liver and kidney damage ↓Inflammation in diabetic mice	Yan, Yang *et al.* (2019)[41]
			Firmicutes, Akkermansia, Ruminiclostridium	–		
Passion fruit (*Passiflora edulis*), including vitexin, isovitexin and isoorientin	Male Wistar rats	*P. edulis* leaf extract (1·1 mg dry leaves ml–1)	*Bifidobacterium ssp. and Lactobacillus ssp.*	+	↓SOD Activities in liver and brain	da Silva, Cazarin *et al.* (2013)[57]
			Clostridium ssp. and Bacteroides spp.	–		
Cyanidin-3-*O*-glucoside, delphinidin-3-*O*-glucoside, gallic acid, rutin, myricetin and quercetin as the main flavonoids in aqueous extract of berry (*Plinia jaboticaba*)	Male Wistar rats	15, 25 and 50 g/l of of *jaboticaba* extract	*Lactobacillus*, *Bifidobacterium* and Enterobacteriaceae	+	Antioxidant activity	da Silva-Maia, Batista *et al.* (2019)[120]
Flavonoid intake including flavonols, flavones, flavan-3-ols, flavanones, and anthocyanidins	18 adults with stable cystic fibrosis		*Actinomyces* and Actinomycetaceae (Actinobacteria)	+	Immunomodulation activity Anti-inflammatory activity ↓ Risk of lung disease	Li and Somerset (2018)[93]
			Coriobacteriia (Actinobacteria)	–		
Flavonoids of *Moringa oleifera* Lam. leaves containing quercetin-3-*O*-*β*-D-glucoside, 6,8-di-C-glucosylapigenin and catechin	*In vitro* fermentation	5·0 mg/mL (w/v)	Ratio of *Firmicutes* to *Bacteroidetes*, *Cyanobacteria* and *Proteobacteria*	+	Antioxidant activity	Dou, Chen *et al.* (2019)[121]
Mulberry leaf and oat bran combination containing flavonoids like rutin	Old male Kunming mice	6 g/kg of BW mulberry leaf–oat bran mixture	*Firmicutes*, Alistipes and Ruminiclostridium	+	Antidiabetic activity	Hu, Wen *et al.* (2019)[122]
			Bacteroidetes, Ruminococcus, *Anaeroplasma*, *Anaerostipes* and Odoribacter, and *Escherichia-Shigella*	–		
Cranberry powder (anthocyanins and flavonoids)	Eleven healthy subjects (7 males, 4 females	30 g/d cranberry diet	*Bacteroidetes, Lachnospira Anaerostipes, Clostridia*	+	↑Urinary levels of anthocyanins and phenolic acids	Rodríguez-Morató, Matthan *et al.* (2018)[123]
			Firmicutes, Clostridiales Oribacterium	–		
Hesperidin[124] and its aglycone hesperetin	Male Wistar rats	0·40 g and 0·83 g of HT and HD per kg of body weight	*Bifidobacterium, Lactobacillales*	+	↑SCFA production	Unno, Hisada *et al.* (2015)[70]
Hesperidin	Lewis rats	100 or 200 mg/kg hesperidin	*Lactobacillus, Enterococcus, Staphylococcus, StreptococcusBacteroides/Prevotella, Bifidobacterium Escherichia coli*	+	Immunomodulatory actions of hesperidin	Estruel-Amades, *et al.* (2019)[125]
			Clostridium coccoides, Eubacterium rectal, Clostridium subcluster	–		

https://doi.org/10.1017/S0007114521003627 Published online by Cambridge University Press

Table 1. (*Continued*)

Flavonoid compound or extract	Subject	Dose and intervention	Impact on microbiota		Health outcomes	Reference
Isoorientin	5 weeks old BALB/c male mice	15 mg/kg BW	*Acinetobacter, Alistipes, Anaerotruncus, Bifidobacterium, Desulfovibrio Faecalibaculum, Helicobacter, Kurthia, Lachnoclostridium, Lactobacillus, Odoribacter, Oscillibacter, Ruminiclostridium*	–	Antioxidation and anti-inflammation effects	Yuan, Li *et al.* (2018)[60]
			Bacteroides, Enterococcus, Alloprevotella, Enterorhabdus, Mucispirillum, Parabacteroides, Parabacteroides, Parasutterella, Caproiciproducens, Roseburia, Anaeroplasma and Pantoea	+		
Schisandra chinensis bee pollen containing naringenin, rutin and chrysin	Male C57BL/6 mice	7·86 and 15·72 g SCPE/kg BW	*Coriobacteriales, Coriobacteriia, Coriobacteriaceae, and Bifidobacterium, Bifidobacteriales, Bifidobacteriaceae, Lactobacillaceae, and Verrcomicrobiaceae, Actinobacteria, Proteobacteria and Pseudomonas*	+	↓ Fasting blood glucose ↓ Lipid accumulation in serum and liver ↓Oxidative injury and inflammation in obesity mice	Cheng, Chen *et al.* (2019)[126]
			Lactobacillaceae	–		
Fruit, vegetables and flavonoid as flavonols quercetin and rutin	154 subjects male and female		*C. leptum-R. bromii/flavefaciens, Bacteroides/ Prevotella Bifidobacterium, Ruminococcus bromii*	+	Control obesity Protective role against metabolic endotoxemia	Klinder, Shen *et al.* (2016)[127]
			Clostridium histolyticum/Perfringens, Ruminococcus torques, Ruminococcus gnavus and Ruminococcus torques	–		
Flavanol containing green tea extract	Chicken and Pigs	6 tea cups per d for 2 months	*Lactobacillus* (+)	+		Terada, Hara *et al.* (1993)[128]
			Enterobacteriaceae (-)	–		
Tea flavanol polyphenols	Human (8 Japanese subject)	0·4 g 3 timesdaily for 4 weeks	*Bifidobacterium* (+)	+	Microbiota profile restored 2 weeks after discontinuation	Okubo, Ishihara *et al.* (1992)[129]
			Clostridium perfringens (-)	–		
Oolong tea flavonoids (OTP) containing flavanol	Mice (fed on high fat diet)	0·1 % w/w OTP for four weeks	*Firmicutes/Bacteroidetes* ratio	–	↓ Obesity	Cheng, Zhang *et al.* (2018)[130]
The total flavonoids of *Quzhou Fructus Aurantii*. Extract (TFQ) standardised as narirutin, naringin, hesperidin and neohesperidin	8-weeks old male mice	daily dose of 300 mg/kg TFQ	*Akkermansia, Alistipes, Dubosiella, Faecallbaculum and Lactobacillus.*	+	↓ Obesity, inflammation and liver steatosis	Bai, Wang *et al.* (2019)[75]
			Firmicutes to Bacteroidetes ratio	–		
Schisandra chinensis fruit extract total flavonoids standardised as catechin			*Akkermansia, Roseburia, Bacteroides, Prevotell, and Bifidobacterium*	+	↓ Waist circumference ↓ Fat mass	Song, Wang *et al.* (2015)[131]
			Ruminococcus, Firmicutes	–	↓ Fasting bloodglucose ↓ TAG ↓ Aspartate aminotransferase and alanine aminotransferase	

SOD, superoxide dismutase.

https://doi.org/10.1017/S0007114521003627 Published online by Cambridge University Press

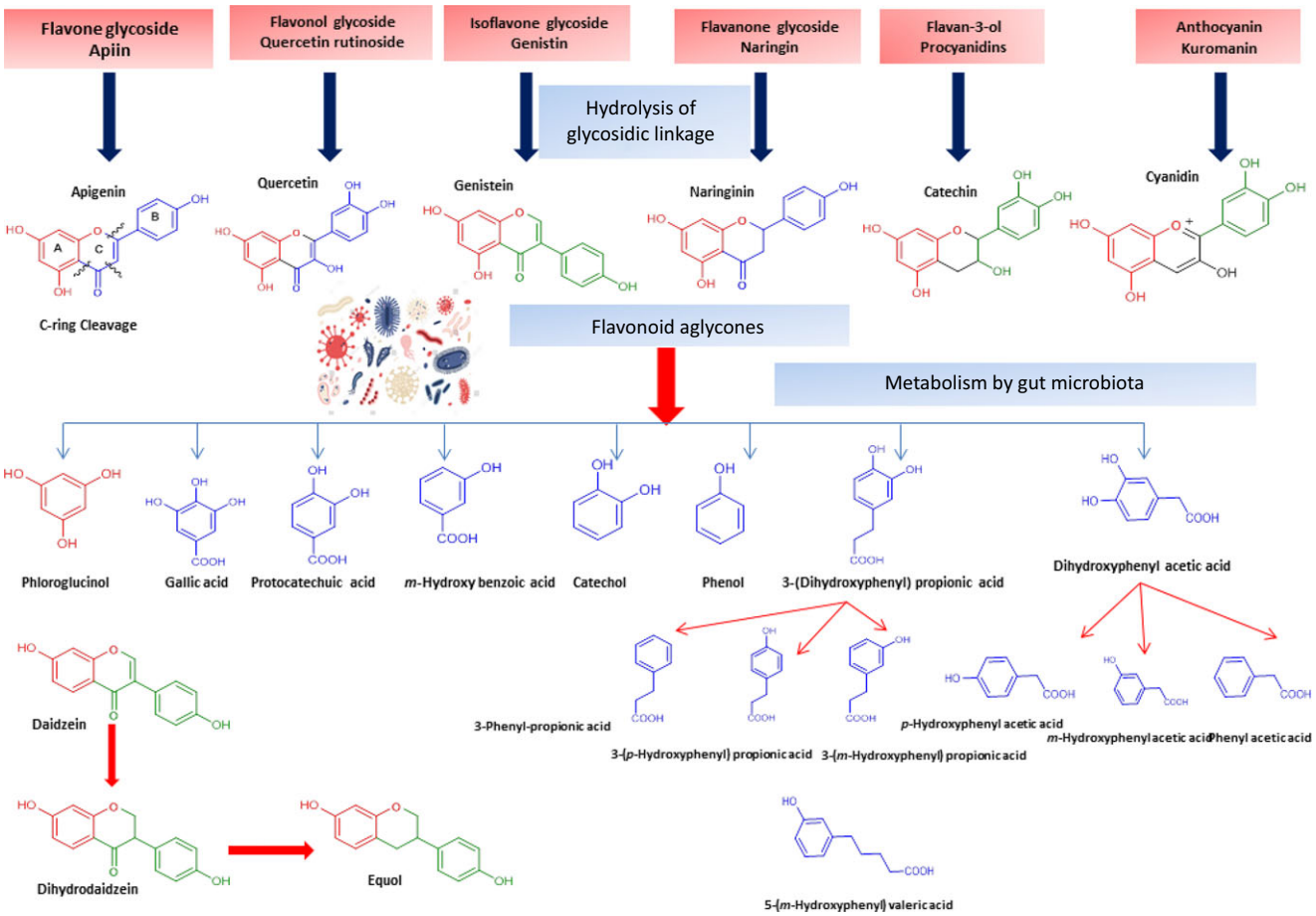

Fig. 4. Schematic representation of microbiota modulation by flavonoids and most common metabolites detected in colon.

products of flavonols detected in the culture media, *viz.* 2–3) hydroxyphenyl)acetic acid, 2-(3,4-dihydroxyphenyl) acetic acid, 3-phenylpropionic acid, 3-(3,4-dihydroxyphenyl)propionic acid, phloroglucinol and resorcinol failed to suppress NO production[39]. Accordingly, these results suggest that flavonols exerted weak modulatory activity against *B. adolescentis,* with only galangin to show inhibition capacity[39].

In vivo/*animal studies.* The impact of quercetin intake on the intestinal microbiota diversity in both fat- and carbohydrate-rich diets in rats was compared by Etxeberria *et al.* (2015). Quercetin consumption (30 mg/kg BW/d) was found to affect the gut microbiota composition by inhibiting the growth of bacterial species associated with diet-induced obesity such as Erysipelotrichaceae, *Bacillus* spp. and *Eubacterium cylindroides,* and to likewise modulate *Firmicutes/Bacteroidetes* ratio towards a higher Bacteroidetes content[40]. In addition, quercetin prevented body weight gain, reduced serum insulin level, insulin resistance and reduced high-fat/carbohydrate-diet-induced gut microbiota dysbiosis[40]. How the well-known antidiabetic potential of flavonols can be modulated by gut microbiota interaction has yet to be reported.

Additional studies investigated the antidiabetic potential of both *Enteromorpha prolifera* (green macroalgae) water–ethanol extract and its flavonoids-rich fraction enriched in kaempferol in diabetic mice[41]. *E. prolifera* flavonols (150 mg/kg b.w.) significantly increased the relative abundance of members of the family *Lachnospiraceae*, as well as the genera *Odoribacter*, and *Alistipes*. Notably, *Alistipes* is one of the most abundant SCFA-producing bacteria[42]. *E. prolifera* flavonols significantly increased *Bacteroidetes*, *Actinobacteria* and *Proteobacteria* populations, concurrent with decreased *Firmicutes, Ruminiclostridium* and *Akkermansia*[41]. The same study also reported that *E. prolifera* flavonols could lower fasting blood glucose level, enhance oral glucose tolerance and prevent liver and kidney damages modulated by its anti-inflammatory action in diabetic mice. Whether biotransformed flavonols exert a more potential anti-inflammatory action inside the colon ought to be examined post their characterisation.

The potential of flavonols for alleviating systemic lupus erythematosus symptoms and severity was investigated[43]. Twenty women subjects suffering from systemic lupus erythematosus were provided with an orange-rich and apple-rich diet standardised to contain 300 mg·d^{-1} of flavonols. The observed increase in the relative abundance of *Lactobacillus* and *Bifidobacterium* populations in systemic lupus erythematosus patients was associated with the flavonol-rich diet. Enhancement of *Bifidobacterium* growth was suggested to benefit systemic lupus erythematosus patients due to the immunomodulatory effect associated with the presence of this

https://doi.org/10.1017/S0007114521003627 Published online by Cambridge University Press

bacterial genus[44]. Specifically, *B. bifidum* promotes the induction of regulatory T cells (T regs), expressing chemokine receptors and potentially favouring mucosal homoeostasis[45,46]. Likewise, enhancement of *Lactobacillus* growth have a beneficial effect for systemic lupus erythematosus patients by modulating the host immune response that leads to improvement of disease symptoms and or severity[47,48].

Various mechanisms have been suggested for the interaction of flavonols with intestinal microbiota[49]. Mechanisms for inhibiting microbial growth could include interference with bacterial cell membrane structure to inhibit growth, modulate growth factors or suppress bacterial nucleic acid biosynthesis[39]. However, such effects do not appear to be universal, since flavonols intake showed negative association with certain bacteria like *Actinobacteria* and *Bifidibacteria*, but positive association with others, for example, *Blautia*[40].

Flavones

Occurrence and metabolism

Flavones are a subgroup of flavonoids characterised by possessing a basic 2-phenyl-benzopyrone nucleus and the absence of hydroxylation at C-3 of ring C (Fig. 2)[32]. Flavones are abundant as *O*-glycosidic forms in various dietary sources, for example, celery, parsley, red peppers, chamomile, mint and *Ginkgo biloba*[21]. Citrus fruits and their peel are the richest source of polymethoxylated flavones such as tageretin, nobiletin and sinensetin[18]. In addition, many of the *C*-glycosylated flavones are widespread in cereal crops[50]. Generally, *O*-glycosides are metabolised to their aglycones in the small intestine by human enzymes such as lactase phlorizin hydrolase and *β*-glucosidase[51]. In contrast, *C*-glycosides reach the colon almost intact[52]. Flavones are metabolised by the action of colonic bacteria *via* C-ring degradation to yield phloretin chalcone, 3-(3,4-dihydroxyphenyl)-propionic acid, 3-(4-hydroxyphenyl)-propionic acid, 3-(3-hydroxyphenyl)-propionic acid and 4-hydroxycinnamic acid as major metabolites (Fig. 4)[53].

Interactions with the microbial community

Several studies have examined the interaction between flavones and gut microbiota and the impact of such interaction on host's physiology (Table 1).

In vitro *studies.* The modulatory activity of apigenin on pure cultures of *Bacteroides galacturonicus*, *Bifidobacterium catenulatum, Lactobacillus rhamnosus* and *Enterococcus caccae*, as well as on the gut microbiota from a donor's faecal inoculum, was tested *in vitro*[54]. Apigenin revealed an effective inhibition activity on both *E. caccae* and *B. galacturonicus* growth (100 µg/ml), while *L. rhamnosus* and *B. catenulatum* were not affected[54]. Apigenin slightly increased the relative abundance of the Bacteroidetes from 0·14 % and 1·07 % in the control to 0·28 % and 1·95 % in apigenin-treated group at 4 h and 12 h, respectively. On the other hand, the relative abundance of Firmicutes decreased within a 48-h incubation period, resulting in an overall decrease in the Firmicutes/Bacteroidetes (F/B) population ratio. SCFA (acetate, propionate and butyrate) production also increased upon apigenin treatment[55] (Fig. 3). SCFA production may originate not only from the colonic microbial fermentation of carbohydrates in the culture medium, but rather from microbial metabolism of polyphenols though with the latter less in levels[19].

In vivo/*animal studies.* The antidiabetic activity and gut microbiota modulation by baicalein (5,6,7-trihydroxyflavone) was examined in streptozotocin and high-fat-diet-induced diabetic rats[56]. The results revealed that the Firmicutes/Bacteroidetes (F/B) ratio significantly increased in the baicalein treatment group due to an increase in the relative abundance of members of the Bacteroidaceae and Porphyromonadaceae, concurrent with a decrease in the relative abundance of members of the families Streptococcaceae, Deferribacteraceae, Ruminococcaceae and Desulfarculaceae. Many of the taxa stimulated by baicalein treatment are SCFA producers, for example, members of the *Bacteroides*, *Alloprevotella*, *Butyricimonas*, *Parabacteroides* and *Bacteroidales*, and the family Prevotellaceae. Such results clearly indicate that the intestinal microbiome can mediate and enhance the antidiabetic action of flavonoids specially flavones, which thus can to be used as natural agent to support a type 2 diabetes preventive or antidiabetic lifestyle.

Another study investigated the antioxidant activity of flavone compounds from passion fruits and leaves (*Passiflora edulis,* maracuja/maracuya) water extract *in vivo*[57]. The antioxidant capacity of such compounds was inferred from a decrease in thiobarbituric acid reactive in the liver by 20 %, increased GSH content in kidneys by 40 %, a two-fold increase of glutathione reductase level, 3·5 times decreased glutathione peroxidase (GPx) abundance in liver, and a 45 % reduction of superoxide dismutase in liver and brain after treatment with *P. edulis* relative to the control group. Additionally, three flavones were found to be abundant in *P. edulis* leaf aqueous extract, identified as vitexin, isovitexin and isoorientin, which led to an increase of bacterial count in feces, especially of *Bifidobacterium*, *Lactobacillus* and total aerobic bacteria. Such a pattern was also observed in a study where rats fed with a diet rich in grape fibres, showing eventually higher levels of *Lactobacillus* and *Bacteroides*[58]. Interestingly, SCFA levels were reduced in groups treated with *P. edulis* leaf extract enriched in flavones, with a significantly lower percentage of acetic and butyric acids (21 and 66 %, respectively). These results contradict the effect of apigenin reported in ref[54] and could indicate differential effects of various flavones on bacterial growth depending on the nature of the administered flavones, although a mechanistic understanding of this process is currently unclear and other options exist, for example,, counteracting effects of other components of the maracuja extract[59].

Finally, the effects of the flavone isoorientin (luteolin 6-*C*-glucoside) on the intestinal microbiota and antioxidation, anti-inflammation and antibiosis of BALB/c mice were investigated *in vivo*[60]. Isoorientin consumption was showed to promote body weight gain and increase the digestibility of crude proteins and the antioxidation capacity in mice. Additionally, isoorientin was shown to inhibit the growth of several bacterial genera such as *Acinetobacter, Anaerotruncus, Bifidobacterium, Desulfovibrio, Faecalibaculum, Kurthia, Lachnoclostridium,*

British Journal of Nutrition

https://doi.org/10.1017/S0007114521003627 Published online by Cambridge University Press

Lactobacillus, Odoribacter and *Ruminiclostridium*. Moreover, isoorientin inhibited the growth of some inflammation-causing pathogenic bacterial genera such as *Alistipes*, *Helicobacter* and *Oscillibacter*[60].

Flavanones

Occurrence and metabolism

Flavanones are an important flavonoid subclass that is widely distributed in all citrus fruits such as orange, grapefruit, lime and lemon[32]. Flavanones possess a 2,3-dihydro-2-phenylchromen-4-one structure, with a saturated C2–C3 bond (Fig. 2)[34]. Hesperitin, naringenin and eriodictyol are examples of these phenolics commonly encountered in citrus fruits[61] and are responsible for their bitter taste and several health effects[61,62]. Flavanones are mostly found as glycosides, either rutinosides (-rhamnosyl-α-1→6-glucosides) or neohesperidosides (-rhamnosyl-α-1→2-glucosides) at C-7 of ring A[62,63]. The flavanone metabolism is similar to that of flavonol and other flavonoid degradation pathways (Fig. 4). For example, naringin (naringenin-7-*O*-rhamnoglucoside) as a flavanone member, if subjected to sugar hydrolysis yields naringenin as the aglycone part (Fig. 4)[21]. The aglycone suffers further breakdown *via* C-ring fission to yield phloroglucinol and 3-(3,4-dihydroxyphenyl) propionic acid as a major metabolite which can be further dehydroxylated to produce 3-(*m*-hydroxyphenyl) propionic acid (Fig. 4). Isoxanthohumol a major prenylflavonoid of hops (*Humulus lupulus* L.) is biotransformed by intestinal bacteria *Eubacterium limosum via* demethylation and formation of a potent bioavailable phyto-oestrogen 8-prenylnaringenin[64,65].

Interaction with the microbial community

Compared with flavonols and flavones, intact flavanones have a higher bioavailability in the human gut, due to the fact that a lower percentage is converted by intestinal microbiota[66]. Therefore, a higher concentration reaches the distal colon and is absorbed by enterocyte cells[66].

In vitro *studies.* The effect of flavanones on microbial growth was also investigated in multiple *in vitro* studies. For instance, the effect of naringenin on the growth of a probiotic (*Lactobacillus rhamnosus*), a commensal (*Escherichia coli)* and two pathogenic bacteria (*Staphylococcus aureus* and *Salmonella typhimurium*) was studied *in vitro*[67]. Naringenin enhanced the growth of *L. rhamnosus* and *E. coli* and inhibited the pathogens *S. aureus* (MIC 62·5 μg/ml), and *S. typhimurium* (MIC 125 μg/ml). Moreover, the growth inhibition effect on *H. pylori* by citrus flavanones, *viz.* hesperetin, naringenin and poncirin has been tested *in vitro*. Among the tested compounds, ponciretin was the most potent one and its MIC was 10–20 μg/ml[68]. In another study[38], the effect of flavanones, *viz.* naringenin, naringin, hesperetin and hesperidin on 6-bacteria, that is, *Bacteroides galacturonicus, Lactobacillus sp., E. caccae, Bifidobacterium catenulatum, Ruminococcus gauvreauii* and *E. coli* was studied, revealing growth inhibition of all monitored species with interestingly aglycones to show higher activity compared with the corresponding glycosides[38]. Such strong inhibitory effect of flavonone aglycones might cause unfavourable changes in the composition of physiological microbiota in the human intestine[38].

The impact of the flavanones naringenin and hesperidin on *Bifidobaterium bifidum* and *B. adolescentis* growth was also tested *in vitro*[69]. Results revealed inhibitory growth effects of hesperidin on the both *Bifidobacterium* species, whereby high doses (100 μg/ml) reduced the growth of *B. bifidum* and *B. adolescentis* by 20 and 50 %, respectively. On the other hand, naringenin (20 and 100 μg/ml) showed a 20 % increase in growth of *B. bifidum* compared with control cultures[69].

In vivo/*animal studies.* The influence of citrus flavanones including hesperidin and its aglycone hesperetin on the composition, diversity and activity of gut microbiota was studied *in vivo* in rat models[70]. The hesperetin-rich diet increased the relative abundance of *Bifidobacterium* and *Lactobacillus* and decreased *Clostridium* subcluster XIVa population in feces. Notably, the *Clostridium* cluster XIVa proportion was increased by feeding a high-fat diet, whereas vegetarians with a fibre-rich diet had a low relative abundance of *Clostridium* cluster XIVa, compared with omnivores[71,72]. Accordingly, alteration of the microbial composition by hesperetin and its derived or induced SCFA resulted in a significant decrease in abdominal adipose tissue accumulation, fatty acid synthesis, fatty acid oxidation and increased lipolysis in the body[73]. Further, rats fed with a daily dose of hesperetin and hesperidin (0·40 g and 0·83 g per kg body weight) had a lower abdominal adipose tissue weight compared with those fed with the control diet. The hesperetin-rich diet showed a significant elevation in caecum content weigh,; whereas hesperidin (corresponding glycoside) fed groups recorded no change when compared with the control group. Hesperetin also elevated SCFA production in the intestine as a result of blocking the action of pancreatic α-amylase which led to an increase in fermentation by gut microbiota in the colon (Fig. 3)[74].

In another study, the impact of flavanones from Quzhou *Fructus Aurantii* (a dried unripe fruit of Rutaceae Citrus changshan-huyou) extract standardised for narirutin, naringin, hesperidin and neohesperidin on gut microbial diversity was studied in high-fat diet fed mice[75]. Results revealed that *Fructus Aurantii* extract significantly reduced body weight, intestinal inflammation and liver steatosis in obese mice. Additionally, *Fructus Aurantii* flavanones extracts decreased the F:B ratio, increased the relative abundance of the genera *Akkermansia* and *Alistipes*, and decreased the relative abundance of the genera *Dubosiella*, *Faecalibaculum* and *Lactobacillus*[75].

Isoflavones

Occurrence and metabolism

Isoflavones exhibit a planar basic ring system with attachment of a benzene ring B at C-3, which differentiate their structure from other flavonoids (Fig. 2). A unique aspect of some isoflavonoids is their ability to bind to oestrogen receptors[32], hence their classification as natural phyto-oestrogens[76,77]. Soya is a rich

British Journal of Nutrition

https://doi.org/10.1017/S0007114521003627 Published online by Cambridge University Press

source of isoflavonoids[76], with genistein, daidzein and glycitein as the major forms. Isoflavones such as genistein and daidzein are commonly utilised as selective oestrogen receptor modulators because of their mild oestrogenic activity *in vivo*[78].

Isoflavones usually pass to the colon unabsorbed. Their bioavailability depends on the hydrolysis of glycosides into their bioactive aglycones such as, daidzein, genistein and glycitein *via* the action of *β*-glucosidase from gut microbiota[79]. Isoflavone aglycones are absorbed completely and taken up into the blood stream[80,81] The soya isoflavones were metabolised by the effect of some intestinal bacteria, such as *Eggerthella* spp., *Enterococcus faecium*, *Adlercreutzia equolifaciens*, *Slackia equolifaciens*, *Lactobacillus mucosae*, *Bifidobacterium* spp. and *Bacteroides ovatu*[38]. For example, genistein is metabolised to *p*-ethylphenol and 4-hydroxyphenyl-2-propionic acid, whereas daidzein is further reduced to *O*-demethylangolensin and equol[76]. Also, the metabolism of daidzein by faecal bacteria from four human individuals were identified as *Lactobacillus mucosae* EPI2, *Enterococcus faecium* EPI1, *Veillonella* sp and *Finegoldia magna* EPI3 was investigated. Dihydrodaidzein, *O*-desmethylangolensi, and equol were detected as major metabolites (Fig. 4)[82]. Due to its nonplanar structure, equol has a good bioavailability and is able to inhibit oxidative damage *in situ*. However, with the high bioavailability of equol, it should be noted that the biotransformation capacity of isoflavones to form equol in humans is much lower than that of animals[76,79]. Additionally, dihydrodaidzein, tetrahydrodaidzein, hydroxydaidzein, 6-hydroxydaidzein, 8-hydroxydaidzein, hydroxyphenylbenzopyran-4,7-diol and 2-dehydro-*O*-DMA have also been reported to be microbial metabolites of daidzein[76].

Interactions with the microbial community

Almost all isoflavones, for example, daidzein, genistein and formononetin, exist as glucosides and are subjected to hydrolysis by intestinal *β*-glucosidases from gut microbiota to yield their corresponding more bioavailable aglycones[79].

The inhibitory effect of genistein and daidzein against the gram-positive *S. aureus*, *S. pasteurianus* and *B. cereus*, as well as the gram-negative bacteria *H. pylori* and *E. coli* was tested *in vitro*[83]. And 100-μM Genistein inhibited growth of all tested gram-positive spp., while in gram-negative only the growth of *H. pylori* was inhibited and *E. coli* growth was not affected. Compared with the structurally related daidzein, genistein was more active due to its ability to inhibit DNA topoisomerase II and tyrosine kinases enzymes[83]. These results support the ability of the isoflavone genistein to inhibit the growth of pathogenic bacteria in the human gut. Additionally, the intestinal metabolism of daidzein by gut microflora yields equol a potent phyto-oestrogen that also exhibit anti-androgenic, anticancer, antioxidant and anti-inflammatory activities[84–86]. Calycosin-7-*O*-*β*-D-glucoside, a glycosylated isoflavone, was shown to promote the growth of beneficial microbiota, *viz*. *Lactobacillus* and *Bifidobacterium* after oral administration to rats (40 mg/kg) which induced its angiogenic effect[87]

Flavan-3-ols or catechins

Occurrence and metabolism

Flavan-3-ols, which commonly feature catechol moieties, include a wide variety of compounds such as catechin, epigallocatechin and epicatechin[32]. Flavan-3-ol structures are characterised by having a B ring attached to C-2, with an absent carbonyl group at C-4 and double bonds between C-2 and C-3[88]. They are abundant in fruits, tea and wine and are considered the primary supply of dietary phenolics. Green tea is considered to be the richest source of catchins as it contains about 30–42 % catechin of total phenols. Major tea catechins include (−)-epigallocatechin gallate which is considered the most abundant one with a share of 50–80 % of the total catchin concentration, along with other catchins such as (−)-epigallocatechin, (−)-epicatechin gallate and (−)-epicatechin[88,89]. Catechins are metabolised in the colon by the action of intestinal microbiota to yield low molecular weight metabolites which may be absorbed or otherwise are excreted in feces[90]. Interestingly, epicatechin when incubated with intestinal bacterial strains *in vitro* yields pyrogallol, 5-(3,4-dihydroxyphenyl) valeric acid, 5-(3-hydroxyphenyl) valeric acid, 3-(3-methoxyphenyl) valeric acid, 3-(3,4-dihydroxyphenyl) propionic acid, 3-(3-hydroxyphenyl)propionic acid and 2,3-dihydroxyphenoxyl 3-(3,4-dihydroxyphenyl) propionic acid as major metabolites[91]. The production of phenylpropionic acids or *p*-hydroxyphenyl acetic acids from flavan-3-ols and procyanidins is a result of C-ring cleavages (Fig. 4). Moreover, the inter individual variations in the human intestinal microbial metabolism was found to affect the metabolism of polyphenolics[6]. An *in vitro* study was conducted to quantify the effect of inter individual variations in gut microbiota on the metabolism (−)-epicatechin by using faecal inoculum from twenty-four healthy donors. Two key metabolites were detected 1-(3′,4′-dihydroxyphenyl)-3-(2″,4″,6″-dihydroxyphenyl)-2-propanol (3,4-diHPP-2-ol) and 5-(3′,4′-dihydroxyphenyl)-*γ*-valerolactone (3,4-diHPV) which were to match *in vivo* metabolism. In addition, the use of such *in vitro* model could be further used to characterise *in vivo* colonic metabolism and related human plasma metabolites as well as to assess inter individual differences in the intestinal microbial metabolism of (−)-epicatechin[6]. Another *in vitro* study was developed to characterise inter individual differences in gut microbial metabolism of (−)-epigallocatechin-3-O-gallate by using anaerobic human faecal incubations. The major metabolites were identified as gallic acid, pyrogallol, phenylpropane-2-ols, phenyl-*γ*-valerolactones and 5-(3′,5′-dihydroxyphenyl)valeric acid with substantial inter individual variations[92]. Moreover, the inter individual differences in intestinal microbial metabolism was found to affect not only (−)-epigallocatechin-3-O-gallate metabolism but rather its health effects[92].

Interactions with the microbial community

Due to its poor bioavailability in the small intestine, large amounts of catechins come in contact with the colon's microbiota[90]. Tea flavonoids, especially catechins, have been shown to inhibit growth of pathogenic and opportunistic

British Journal of Nutrition

https://doi.org/10.1017/S0007114521003627 Published online by Cambridge University Press

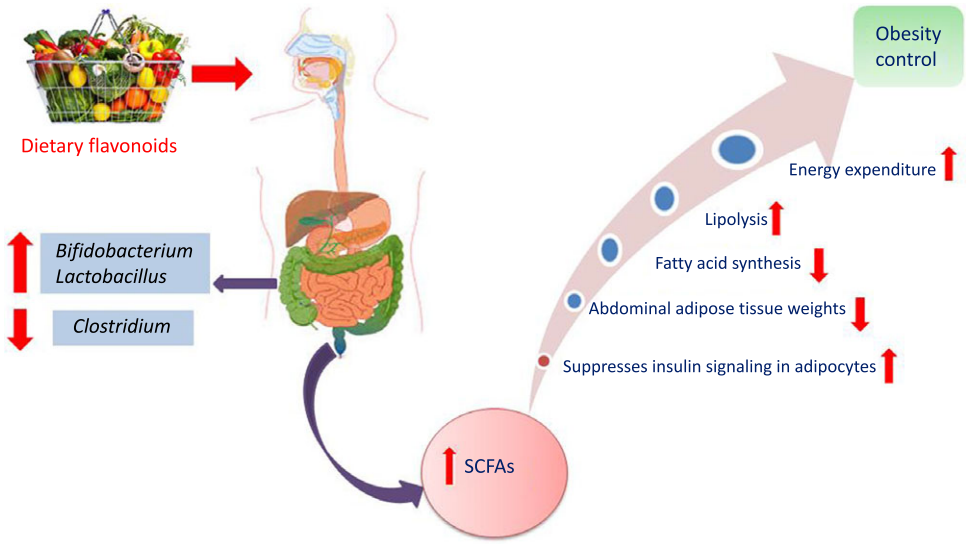

Fig. 5. Mechanism of obesity control by flavonoids mediated *via* modulation of gut microbiota.

micro-organisms such as *S. aureus, E. coli, S. typhimurium, Helicobacter pylori, Listeria monocytogenes* and *Pseudomonas aeruginosa*[9].

The correlations between catechins intake and intestinal microbiota were studied in a group of cystic fibrosis patients[93]. Results showed that gallocatechin consumption positively correlated with the relative abundance of members of the family Actinomycetaceae, specifically the genus *Actinomcyes* (phylum *Actinobacteria*), and negatively correlated with the family Coriobacteriaceae (*Actinobacteria). Actinomcyes* species were reported to play a role in pre-disposing or exacerbating cystic fibrosis and colorectal cancer symptoms. So, supplementation with nutritional recipes including catechin-rich diet could be potentially helpful for the management of cystic fibrosis and colorectal cancers[93].

Another interesting beneficial effect of grape seed extract and black raspberry catechins was demonstrated in ref[94], where the relative abundance of the butyrate producers Lachnospiraceae, Clostridiales and Ruminococcacceae increased in rats and human subjects subjected to a diet rich in oligomeric and polymeric proanthocyanidins. Higher butyrate levels have been shown to be associated withlower obesity[4](Fig. 5), improving bowel functions, preventing the transmission of pro-inflammatory molecules in systemic circulation and preventing metabolic endotoxemia[94]. Butyrate also showed a direct effect on adipose tissue by enhancing adaptive thermogenesis in mice with depleted microbiota[95].

Anthocyanins

Occurrence and metabolism

Anthocyanins are hydrophilic flavonoids that occur in coloured fruits and their peel, for example, cranberries, blueberries, black current, strawberries, red grapes and raspberries to name only a few, as well as in vegetables and grains including black rice, red rice and black soyabeans[96,97]. Anthocyanins are sensitive to degradation and natively occur usually as glycosides due to their higher stability[98]. Cyanidin, delphinidin, malvidin and pelargonidin are the most commonly identified anthocyanins in different plant sources[99]. Although, antioxidant, anti-inflammatory, anti-carcinogenic and cardioprotective activities have been reported for anthocyanins[100,101], their low bioavailability limits such effects[102]. Anthocyanins are metabolised and biotransformed by gut microbiota in the human intestine[103]. For example, cyanidin 3-rutinoside is partially hydrolysed to its related glucoside and then is subsequently hydrolysed to yield the aglycone[104]. The aglycones of anthocyanins are chemically unstable and undergo additional metabolism by the intestinal bacteria to yield small phenolic acids such as protocatechuic acid (3,4-dihydroxybenzoic acid) (Fig. 4)[105,106]. Other bacteria-generated anthocyanin metabolites include syringic acid, vanillic acid, phloroglucinol aldehyde, phloroglucinol acid, gallic acid and 3-*O*-methylgallic acid, depending on the anthocyanins precursor[104,107]. The metabolic fate of (–)-epicatechin, procyanidin B1 and polymeric procyanidin was studied *in vivo* in humans[108]. Blood plasma, urine or feces were collected from seven non-smoking men receiving 1 mg/kg body weight epicatechin and 2 mg/kg body weight procyanidin and polymeric procyanidin. Several *in vitro* identified gut-mediated catabolites were detected in feces including 3-hydroxybenzoic acid, 4-hydroxybenzoic acid, protocatechuic acid, vanillic acid, 3-hydroxyphenyl acetic acid, 4-hydroxyphenyl acetic acid, 3,4-dihydroxyphenyl acetic acid, 3-hydroxyphenyl propanoic acid, 4-hydroxyphenyl propanoic acid, 3,4-dihydroxyphenyl propanoic acid, 4 -hydroxy-5-(3′,4′-dihydroxyphenyl)valeric acid and 5-(3′,4′-dihydroxyphenyl)-valerolactone suggestive that *in vivo* model results parallel that reported from *in vitro* assays of microbial action[108].

Interactions with the microbial community and health outcomes

Multiple studies have revealed that anthocyanins and their metabolites could induce specific changes in human gut

British Journal of Nutrition

https://doi.org/10.1017/S0007114521003627 Published online by Cambridge University Press

microbiota[28]. The daily consumption of anthocyanins in human diet has been estimated at 215 mg/d, with some studies to suggest for an average consumption of 57 – 69 mg/d[109].

In vitro *studies.* *In vitro* incubation of malvidin-3-glucoside with faecal slurry enhanced total bacterial growth, including *Bifidobaterium* spp. and *Lactobacillus* spp.[109], though without change in *Bacteroides* spp. growth. Moreover, malvidin-3-glucoside yielded a synergistic growth promotion effect for *Bifidobaterium* spp. and *Lactobacillus* spp. when mixed with other anthocyanins[109]. In addition, an increase in the growth of *C. coccoides–Eubacterium rectale*, a butyrate production group, was observed after incubation with malvidin-3-glucoside with such shifts in microbial community to present potential benefits to the host[109]. Moreover, anthocyanins-derived gallic acid (Fig. 4) reduced the growth of the potentially harmful *Clostridium histolyticum*, with no significant effect on beneficial bacteria populations[109]. Also, gallic acid significantly decreased *Bacteroides* spp. growth and enhanced *Atopobium* spp.[109].

In vivo/*animal studies.* As described above, anthocyanins are not absorbed in the stomach or small intestine and are metabolised by the colon microbiota. Sánchez-Patán *et al.* observed a decreased level of *Clostridium histolyticum* in human faecal samples incubated with red wine extract, standardised to the anthocyanins malvidin-3-O-glucoside, peonidin and petunidin-3-*O*-glucosides[110]. Such studies were also confirmed *in vivo* in a study using red wine consumption by human volunteers[111]. Another study examined the gut microbiota composition in human volunteers after red wine and dealcoholised red wine consumption. Results showed an increase in relative abundance of Firmicutes and a lower F:B ratio after red wine intake[111]. Additionally, *Bacteroides* and *Prevotellaceae* abundance was lower than those post-anthocyanin consumption periods, whereas the *Clostridium* abundance was high[111]. In addition to changes in microbial composition, a significant decrease in blood pressure and serum TAG, total cholesterol, HDL-cholesterol and C-reactive protein was observed as a consequence of red wine consumption both dealcoholised or not. In another study, 6 weeks ingestion of a prebiotic anthocyanidin-rich wild blueberry drink led to a significant elevation of *Lactobacillus acidophilus* and *Bifidobacterium* spp. populations[112]. Finally, anthocyanin-derived gallic acid was shown to reduce the growth of potentially harmful pathogenic bacteria, such as *Clostridium histolyticum* and *Bacteroides spp.*, without any negative effect on the monitored beneficial bacteria[113].

In another study, supplementation of mice diet with a polyphenol-rich source such as apples resulted in a significant elevation in *Lactobacillus* spp. and *Bifidobacterium* spp.[114]. In a third study, 6 weeks of blueberry (*Vaccinium angustifolium*) drink consumption enriched with the anthocyanins peonidin glucose, malvidin galactose, delphinidin glucose and delphinidin galactose by human volunteers significantly elevated *Bifidobacterium* spp. and *Lactobacillus* spp.[112,115].

The role of habitual anthocyanin intake and association with gut microbiome modulation and visceral abdominal fat accumulation was studied in ref[116]. Collectively, a higher anthocyanin intake was associated with higher microbial diversity and abundance of *Firmicutes, Clostridiales, Ruminococcaceae* and *Roseburia*[116]. The consumption of anthocyanin-rich foods was associated with a decrease in visceral abdominal adipose tissue, high levels of Clostridiales and Ruminococcaceae and lower concentrations of *Clostridium* XIVa. Such anthocyanin activity is mediated via their microbiotically derived metabolites. These are present in the blood stream in significantly higher levels and for a longer time than the unaltered anthocyanins. These catabolites provide more valuable vascular and anti-inflammatory activities than the metabolites produced and absorbed in the small intestine[117,118].

Collectively, the above studies present the anthocyanins as a valuable health promotors *via* modulation of commensal gut microbiota[113], as well as by exhibiting a direct impact through the biological activities of them and from them generated metabolites. Anthocyanin-rich foods hence can be considered valuable prebiotic modulators that can change the gut community towards higher levels of *Lactobacillus spp.* and *Bifidobacterium spp.*[119]

Conclusion and future perspectives

The human diet is readily modifiable variable that can significantly impact the consumers' health, either directly or indirectly via metabolic activity of the host's microbiota action or by alteration of the microbiota composition. A balanced gut microbiota modulates appetite regulation, energy management, obesity, diabetes, immune function, allergy, behavioural disturbance, heart disease and colon cancer. Here, we highlighted the complex interactions between flavonoid intake and the gut microbiota. This review highlights the overall, mostly positive, impacts of flavonoid consumption through enriching potentially beneficial members of the gut microbioata, for example, *Bifidobacterium* and *Lactobacillus*, often occurring at the expense of *Clostridium* spp. We also highlighted other potential benefits associated with flavonoid consumption such as the production of breakdown products believed beneficial to human intestinal cells such as SCFA, that is, acetate, propionate and butyrate. Although our understanding of the correlation between flavonoid consumption, human gut microbiota and biological activities is rapidly expanding, additional research on documenting the impact of various specific flavonoid compounds, various doses and regiments on a wider range of chronic diseases are required. There is a need to identify the crucial drivers and those of the highest general relevance. Studies combining and correlating microbial community analyses not only with certain flavonoid or other dietary compounds intake with direct and accurate measurements of health outcomes are especially needed. A better reproducibility, understanding and assessment of results in such research, and the impact of ethnic, age, health and prevalent diet variations are needed. Only through such assessments, supplements, diet regimes, prebiotics and

British Journal of Nutrition

https://doi.org/10.1017/S0007114521003627 Published online by Cambridge University Press

probiotics can be confidently suggested to fully exploit the health benefits of flavonoids on a wider scale.

Acknowledgements

M. A. F. acknowledges the funding received from the Alexander von Humboldt Foundation, Germany.

CRedit author contributions: M. H. B.: data collection curation and writing – original draft. M. E.: writing – review and editing. L. W.: review and editing. M. A. F.: supervision, conceptualisation, investigation, and writing – review and editing. All authors contribute to the revision of final manuscript.

The authors declare no conflict of interest.

References

1. Flint HJ, Scott KP, Louis P, *et al.* (2012) The role of the gut microbiota in nutrition and health. *Nat Rev Gastroenterol Hepatol* **9**, 577.
2. Bin P, Liu S, Chen S, *et al.* (2017) The effect of aspartate supplementation on the microbial composition and innate immunity on mice. *Amino Acids* **49**, 2045–2051.
3. Gotteland M, Andrews M, Toledo M, *et al.* (2008) Modulation of Helicobacter pylori colonization with cranberry juice and Lactobacillus johnsonii La1 in children. *Nutrition* **24**, 421–426.
4. Aravind SM, Wichienchot S, Tsao R, *et al.* (2021) Role of dietary polyphenols on gut microbiota, their metabolites and health benefits. *Food Res Int* **142**, 110189.
5. Kumar Singh A, Cabral C, Kumar R, *et al.* (2019) Beneficial effects of dietary polyphenols on gut microbiota and strategies to improve delivery efficiency. *Nutrients* **11**, 2216.
6. Liu C, Vervoort J, Beekmann K, *et al.* (2020) Interindividual differences in human intestinal microbial conversion of (−)-epicatechin to bioactive phenolic compounds. *J Agric Food Chem* **68**, 14168–14181.
7. Masumoto S, Terao A, Yamamoto Y, *et al.* (2016) Non-absorbable apple procyanidins prevent obesity associated with gut microbial and metabolomic changes. *Sci Rep* **6**, 31208.
8. Sampson TR, Debelius JW, Thron T, *et al.* (2016) Gut microbiota regulate motor deficits and neuroinflammation in a model of Parkinson's disease. *Cell* **167**, 1469–1480. e1412.
9. Duda-Chodak A, Tarko T, Satora P, *et al.* (2015) Interaction of dietary compounds, especially polyphenols, with the intestinal microbiota: a review. *Eur J Nutr* **54**, 325–341.
10. Vinson JA, Su X, Zubik L, *et al.* (2001) Phenol antioxidant quantity and quality in foods: fruits. *J Agric Food Chem* **49**, 5315–5321.
11. Kumar S & Pandey AK (2013) Chemistry and biological activities of flavonoids: an overview. *Sci World J* **2013**, 162750.
12. Farkas O, Jakus J & Héberger K (2004) Quantitative structure – antioxidant activity relationships of flavonoid compounds. *Molecules* **9**, 1079–1088.
13. Khurana S, Venkataraman K, Hollingsworth A, *et al.* (2013) Polyphenols: benefits to the cardiovascular system in health and in aging. *Nutrients* **5**, 3779–3827.
14. Manach C, Williamson G, Morand C, *et al.* (2005) Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. *Am J Clin Nutr* **81**, 230S–242S.
15. Braune A & Blaut M (2016) Bacterial species involved in the conversion of dietary flavonoids in the human gut. *Gut Microbe* **7**, 216–234.
16. Day AJ, Cañada FJ, Díaz JC, *et al.* (2000) Dietary flavonoid and isoflavone glycosides are hydrolysed by the lactase site of lactase phlorizin hydrolase. *FEBS Lett* **468**, 166–170.
17. Day AJ, DuPont MS, Ridley S, *et al.* (1998) Deglycosylation of flavonoid and isoflavonoid glycosides by human small intestine and liver β-glucosidase activity. *FEBS Lett* **436**, 71–75.
18. Manach C, Scalbert A, Morand C, *et al.* (2004) Polyphenols: food sources and bioavailability. *Am J Clin Nutr* **79**, 727–747.
19. Blaut M, Schoefer L & Braune A (2003) Transformation of flavonoids by intestinal microorganisms. *Int J for Vitamin Nutr Res* **73**, 79–87.
20. Aherne SA & O'Brien NM (2002) Dietary flavonols: chemistry, food content, and metabolism. *Nutrition* **18**, 75–81.
21. Selma MV, Espin JC & Tomas-Barberan FA (2009) Interaction between phenolics and gut microbiota: role in human health. *J Agric Food Chem* **57**, 6485–6501.
22. Lee HC, Jenner AM, Low CS, *et al.* (2006) Effect of tea phenolics and their aromatic fecal bacterial metabolites on intestinal microbiota. *Res Microbiol* **157**, 876–884.
23. Murota K, Nakamura Y & Uehara M (2018) Flavonoid metabolism: the interaction of metabolites and gut microbiota. *Biosci Biotechnol Biochem* **82**, 600–610.
24. Tsao R (2010) Chemistry and biochemistry of dietary polyphenols. *Nutrients* **2**, 1231–1246.
25. Andrés-Lacueva C, Medina-Remon A, Llorach R, *et al.* (2010) *Phenolic Compounds: Chemistry and Occurrence in Fruits and Vegetables*. New York, USA: Wiley Online Library.
26. Lu M-F, Xiao Z-T & Zhang H-Y (2013) Where do health benefits of flavonoids come from? Insights from flavonoid targets and their evolutionary history. *Biochem Biophys Res Commun* **434**, 701–704.
27. Williamson G (2017) The role of polyphenols in modern nutrition. *Nutr Bull* **42**, 226–235.
28. Faria A, Fernandes I, Norberto S, *et al.* (2014) Interplay between anthocyanins and gut microbiota. *J Agric Food Chem* **62**, 6898–6902.
29. Oteiza P, Fraga CG, Mills D, *et al.* (2018) Flavonoids and the gastrointestinal tract: local and systemic effects. *Mol Aspects Med* **61**, 41–49.
30. Tomás-Barberán FA, Selma MV & Espín JC (2016) Interactions of gut microbiota with dietary polyphenols and consequences to human health. *Curr Opin Clin Nutr Metab Care* **19**, 471–476.
31. Ozdal T, Sela DA, Xiao J, *et al.* (2016) The reciprocal interactions between polyphenols and gut microbiota and effects on bioaccessibility. *Nutrients* **8**, 78.
32. Panche A, Diwan A & Chandra S (2016) Flavonoids: an overview. *J Nutr Sci* **5**, e47.
33. Hollman PCH & Katan MB (1999) Dietary flavonoids: intake, health effects and bioavailability. *Food Chem Toxicol* **37**, 937–942.
34. Iwashina T (2013) Flavonoid properties of five families newly incorporated into the order Caryophyllales. *Bull Natl Mus Nat Sci* **39**, 25–51.
35. Rechner AR, Smith MA, Kuhnle G, *et al.* (2004) Colonic metabolism of dietary polyphenols: influence of structure on microbial fermentation products. *Free Radical Biol Med* **36**, 212–225.
36. Simons AL, Renouf M, Hendrich S, *et al.* (2005) Human gut microbial degradation of flavonoids: structure – function relationships. *J Agric Food Chem* **53**, 4258–4263.
37. Hein E-M, Rose K, van't Slot G, *et al.* (2008) Deconjugation and degradation of flavonol glycosides by pig cecal microbiota characterized by fluorescence *in situ* hybridization (FISH). *J Agric Food Chem* **56**, 2281–2290.

British Journal of Nutrition

https://doi.org/10.1017/S0007114521003627 Published online by Cambridge University Press

38. Duda-Chodak A (2012) The inhibitory effect of polyphenols on human gut microbiota. *J Physiol Pharmacol* **63**, 497–503.
39. Kawabata K, Sugiyama Y, Sakano T, *et al.* (2013) Flavonols enhanced production of anti-inflammatory substance (s) by Bifidobacterium adolescentis: prebiotic actions of galangin, quercetin, and fisetin. *Biofactors* **39**, 422–429.
40. Etxeberria U, Arias N, Boqué N, *et al.* (2015) Reshaping faecal gut microbiota composition by the intake of trans-resveratrol and quercetin in high-fat sucrose diet-fed rats. *J Nutr Biochem* **26**, 651–660.
41. Yan X, Yang C, Lin G, *et al.* (2019) Antidiabetic potential of green seaweed Enteromorpha prolifera flavonoids regulating insulin signaling pathway and gut microbiota in type 2 diabetic mice. *J Food Sci* **84**, 165–173.
42. Brown CT, Davis-Richardson AG, Giongo A, *et al.* (2011) Gut microbiome metagenomics analysis suggests a functional model for the development of autoimmunity for type 1 diabetes. *PLoS One* **6**, e25792.
43. Cuervo A, Hevia A, López P, *et al.* (2015) Association of polyphenols from oranges and apples with specific intestinal microorganisms in systemic lupus erythematosus patients. *Nutrients* **7**, 1301–1317.
44. Konieczna P, Akdis CA, Quigley EM, *et al.* (2012) Portrait of an immunoregulatory Bifidobacterium. *Gut Microbe* **3**, 261–266.
45. López Suárez P, González Rodríguez I, Gueimonde Fernández M, *et al.* (2011) Immune response to Bifidobacterium bifidum strains support Treg/Th17 plasticityen. *PLoS ONE* **6**, e24776.
46. López P, González-Rodríguez I, Sánchez B, *et al.* (2012) Interaction of Bifidobacterium bifidum LMG13195 with HT29 cells influences regulatory-T-cell-associated chemokine receptor expression. *Appl Environ Microbiol* **78**, 2850–2857.
47. Daly K, Darby AC, Hall N, *et al.* (2014) Dietary supplementation with lactose or artificial sweetener enhances swine gut Lactobacillus population abundance. *Br J Nutr* **111**, S30–S35.
48. Atarashi K, Tanoue T, Shima T, *et al.* (2011) Induction of colonic regulatory T cells by indigenous Clostridium species. *Science* **331**, 337–341.
49. Cardona F, Andrés-Lacueva C, Tulipani S, *et al.* (2013) Benefits of polyphenols on gut microbiota and implications in human health. *J Nutr Biochem* **24**, 1415–1422.
50. Xiao J (2017) Dietary flavonoid aglycones and their glycosides: which show better biological significance? *Crit Rev Food Sci Nutr* **57**, 1874–1905.
51. Xiao J & Hogger P (2015) Dietary polyphenols and type 2 diabetes: current insights and future perspectives. *Curr Med Chem* **22**, 23–38.
52. Zhang Y, Tie X, Bao B, *et al.* (2007) Metabolism of flavone C-glucosides and p-coumaric acid from antioxidant of bamboo leaves (AOB) in rats. *Br J Nutr* **97**, 484–494.
53. Hanske L, Loh G, Sczesny S, *et al.* (2009) The bioavailability of apigenin-7-glucoside is influenced by human intestinal microbiota in rats. *J Nutr* **139**, 1095–1102.
54. Wang M, Firrman J, Zhang L, *et al.* (2017) Apigenin impacts the growth of the gut microbiota and alters the gene expression of Enterococcus. *Molecule* **22**, 1292.
55. Van Dorsten F, Peters S, Gross G, *et al.* (2012) Gut microbial metabolism of polyphenols from black tea and red wine/grape juice is source-specific and colon-region dependent. *J Agric Food Chem* **60**, 11331–11342.
56. Zhang B, Sun W, Yu N, *et al.* (2018) Anti-diabetic effect of baicalein is associated with the modulation of gut microbiota in streptozotocin and high-fat-diet induced diabetic rats. *J Funct Food* **46**, 256–267.
57. da Silva JK, Cazarin CBB, Colomeu TC, *et al.* (2013) Antioxidant activity of aqueous extract of passion fruit (Passiflora edulis) leaves: *in vitro* and *in vivo* study. *Food Res Int* **53**, 882–890.
58. Pozuelo MJ, Agis-Torres A, Hervert-Hernández D, *et al.* (2012) Grape antioxidant dietary fiber stimulates Lactobacillus growth in rat cecum. *J Food Sci* **77**, H59–H62.
59. Macfarlane GT & Macfarlane S (2012) Bacteria, colonic fermentation, and gastrointestinal health. *J AOAC Int* **95**, 50–60.
60. Yuan L, Li X, He S, *et al.* (2018) Effects of natural flavonoid isoorientin on growth performance and gut microbiota of mice. *J Agric Food Chem* **66**, 9777–9784.
61. Tomás-Barberán FA & Clifford MN (2000) Flavanones, chalcones and dihydrochalcones–nature, occurrence and dietary burden. *J Sci Food Agric* **80**, 1073–1080.
62. Shakour ZTA, Fayek NM & Farag MA (2020) How do biocatalysis and biotransformation affect Citrus dietary flavonoids chemistry and bioactivity? A review. *Crit Rev Biotechnol* **40**, 689–714.
63. Robards K, Li X, Antolovich M, *et al.* (1997) Characterisation of citrus by chromatographic analysis of flavonoids. *J Sci Food Agric* **75**, 87–101.
64. Possemiers S, Heyerick A, Robbens V, *et al.* (2005) Activation of proestrogens from hops (Humulus lupulus L.) by intestinal microbiota; conversion of isoxanthohumol into 8-prenylnaringenin. *J Agric Food Chem* **53**, 6281–6288.
65. Possemiers S, Verstraete W & Van de Wiele T (2009) *Estrogenicity of Beer: the Role of Intestinal Bacteria in the Activation of the Beer Flavonoid Isoxanthohumol. Beer in Health and Disease Prevention*. Netherlands: Elsevier.
66. Marín L, Miguélez EM, Villar CJ, *et al.* (2015) Bioavailability of dietary polyphenols and gut microbiota metabolism: antimicrobial properties. *Biomed Res Int* **2015**, 905215.
67. Parkar SG, Stevenson DE & Skinner MA (2008) The potential influence of fruit polyphenols on colonic microflora and human gut health. *Int J Food Microbiol* **124**, 295–298.
68. Bae E-A, Han MJ & Kim D-H (1999) *In vitro* anti-Helicobacter pylori activity of some flavonoids and their metabolites. *Planta Med* **65**, 442–443.
69. Gwiazdowska D, Ju K, Jasnowska-Małecka J, *et al.* (2015) The impact of polyphenols on Bifidobacterium growth. *Acta Biochim Pol* **62**, 895–901.
70. Unno T, Hisada T & Takahashi S (2015) Hesperetin modifies the composition of fecal microbiota and increases cecal levels of short-chain fatty acids in rats. *J Agric Food Chem* **63**, 7952–7957.
71. Kabeerdoss J, Devi RS, Mary RR, *et al.* (2012) Faecal microbiota composition in vegetarians: comparison with omnivores in a cohort of young women in southern India. *Br J Nutr* **108**, 953–957.
72. Yoshimoto S, Loo TM, Atarashi K, *et al.* (2013) Obesity-induced gut microbial metabolite promotes liver cancer through senescence secretome. *Nature* **499**, 97–101.
73. Den Besten G, van Eunen K, Groen AK, *et al.* (2013) The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism. *J Lipid Res* **54**, 2325–2340.
74. Gibson GR & Roberfroid MB (1995) Dietary modulation of the human colonic microbiota: introducing the concept of prebiotics. *J Nutr* **125**, 1401–1412.
75. Bai Y-F, Wang S-W, Wang X-X, *et al.* (2019) The flavonoid-rich Quzhou Fructus Aurantii extract modulates gut microbiota and prevents obesity in high-fat diet-fed mice. *Nutr Diabetes* **9**, 1–11.

British Journal of Nutrition

https://doi.org/10.1017/S0007114521003627 Published online by Cambridge University Press

76. Yuan JP, Wang JH & Liu X (2007) Metabolism of dietary soy isoflavones to equol by human intestinal microflora–implications for health. *Mol Nutr Food Res* **51**, 765–781.
77. Cornwell T, Cohick W & Raskin I (2004) Dietary phytoestrogens and health. *Phytochem* **65**, 995–1016.
78. Szkudelska K & Nogowski L (2007) Genistein – a dietary compound inducing hormonal and metabolic changes. *J Steroid Biochem Mol Biol* **105**, 37–45.
79. Setchell KD, Brown NM, Zimmer-Nechemias L, *et al.* (2002) Evidence for lack of absorption of soy isoflavone glycosides in humans, supporting the crucial role of intestinal metabolism for bioavailability. *Am J Clin Nutr* **76**, 447–453.
80. Linford NJ & Dorsa DM (2002) 17β-Estradiol and the phytoestrogen genistein attenuate neuronal apoptosis induced by the endoplasmic reticulum calcium-ATPase inhibitor thapsigargin. *Steroids* **67**, 1029–1040.
81. Zubik L & Meydani M (2003) Bioavailability of soybean isoflavones from aglycone and glucoside forms in American women. *Am J Clin Nutr* **77**, 1459–1465.
82. Decroos K, Vanhemmens S, Cattoir S, *et al.* (2005) Isolation and characterisation of an equol-producing mixed microbial culture from a human faecal sample and its activity under gastrointestinal conditions. *Arch Microbiol* **183**, 45–55.
83. Verdrengh M, Collins LV, Bergin P, *et al.* (2004) Phytoestrogen genistein as an anti-staphylococcal agent. *Microbe Infect* **6**, 86–92.
84. Kang NJ, Lee KW, Rogozin EA, *et al.* (2007) Equol, a metabolite of the soybean isoflavone daidzein, inhibits neoplastic cell transformation by targeting the MEK/ERK/p90RSK/activator protein-1 pathway. *J Biol Chem* **282**, 32856–32866.
85. Zheng W, Zhang Y, Ma D, *et al.* (2011) (±) Equol inhibits invasion in prostate cancer DU145 cells possibly via down-regulation of matrix metalloproteinase-9, matrix metalloproteinase-2 and urokinase-type plasminogen activator by antioxidant activity. *J Clin Biochem Nutr* **51**, 61–67.
86. Qin H-D, Shi Y-Q, Liu Z-H, *et al.* (2010) Effect of chlorogenic acid on mast cell-dependent anaphylactic reaction. *Int Immunopharmacol* **10**, 1135–1141.
87. Ruan J-Q, Li S, Li Y-P, *et al.* (2015) The presystemic interplay between gut microbiota and orally administered calycosin-7-O-β-D-glucoside. *Drug Metab Dispos* **43**, 1601–1611.
88. Hackman RM, Polagruto JA, Zhu QY, *et al.* (2008) Flavanols: digestion, absorption and bioactivity. *Phytochem Rev* **7**, 195.
89. Musial C, Kuban-Jankowska A & Gorska-Ponikowska M (2020) Beneficial properties of green tea catechins. *Int J Mol Sci* **21**, 1744.
90. Takagaki A & Nanjo F (2013) Catabolism of (+)-catechin and (−)-epicatechin by rat intestinal microbiota. *J Agric Food Chem* **61**, 4927–4935.
91. Meselhy MR, Nakamura N & Hattori M (1997) Biotransformation of (–)-epicatechin 3-O-gallate by human intestinal bacteria. *Chem Pharm Bull* **45**, 888–893.
92. Liu C, Vervoort J, van den Elzen J, *et al.* (2021) Interindividual differences in human *in vitro* intestinal microbial conversion of green tea (–)-epigallocatechin-3-o-gallate and consequences for activation of nrf2 mediated gene expression. *Mol Nutr Food Res* **65**, 2000934.
93. Li L & Somerset S (2018) Associations between flavonoid intakes and gut microbiota in a group of adults with cystic fibrosis. *Nutrients* **10**, 1264.
94. Peng L, Li Z-R, Green RS, *et al.* (2009) Butyrate enhances the intestinal barrier by facilitating tight junction assembly via activation of AMP-activated protein kinase in Caco-2 cell monolayers. *J Nutr* **139**, 1619–1625.
95. Li B, Li L, Li M, *et al.* (2019) Microbiota depletion impairs thermogenesis of brown adipose tissue and browning of white adipose tissue. *Cell Rep* **26**, 2720–2737. e2725.
96. Sui X, Zhang Y & Zhou W (2016) Bread fortified with anthocyanin-rich extract from black rice as nutraceutical sources: its quality attributes and *in vitro* digestibility. *Food Chem* **196**, 910–916.
97. Wallace T & Giusti M (2015) Anthocyanins. *Adv Nutr* **6**, 620–622.
98. Samadi AK, Bilsland A, Georgakilas AG, *et al.* (2015) A multitargeted approach to suppress tumor-promoting inflammation. *Semin Cancer Biol* **35**, S151–S184.
99. Matsumoto H, Inaba H, Kishi M, *et al.* (2001) Orally administered delphinidin 3-rutinoside and cyanidin 3-rutinoside are directly absorbed in rats and humans and appear in the blood as the intact forms. *J Agric Food Chem* **49**, 1546–1551.
100. Wang H, Nair MG, Strasburg GM, *et al.* (1999) Antioxidant and antiinflammatory activities of anthocyanins and their aglycon, cyanidin, from tart cherries. *J Nat Prod* **62**, 294–296.
101. Hou D-X (2003) Potential mechanisms of cancer chemoprevention by anthocyanins. *Curr Mol Med* **3**, 149–159.
102. Xiao J & Hogger P (2014) Editorial (Thematic issue: advances in the pharmacokinetics of natural bioactive polyphenols). *Curr Drug Metab* **15**, 1–2.
103. Hanske L, Engst W, Loh G, *et al.* (2013) Contribution of gut bacteria to the metabolism of cyanidin 3-glucoside in human microbiota-associated rats. *Br J Nutr* **109**, 1433–1441.
104. Keppler K & Humpf H-U (2005) Metabolism of anthocyanins and their phenolic degradation products by the intestinal microflora. *Bioorg Med Chem* **13**, 5195–5205.
105. Aura A-M (2008) Microbial metabolism of dietary phenolic compounds in the colon. *Phytochem Rev* **7**, 407–429.
106. Vitaglione P, Donnarumma G, Napolitano A, *et al.* (2007) Protocatechuic acid is the major human metabolite of cyanidin-glucosides. *J Nutr* **137**, 2043–2048.
107. Forester SC & Waterhouse AL (2008) Identification of cabernet sauvignon anthocyanin gut microflora metabolites. *J Agric Food Chem* **56**, 9299–9304.
108. Wiese S, Esatbeyoglu T, Winterhalter P, *et al.* (2015) Comparative biokinetics and metabolism of pure monomeric, dimeric, and polymeric flavan-3-ols: a randomized cross-over study in humans. *Mol Nutr Food Res* **59**, 610–621.
109. Hidalgo M, Oruna-Concha MJ, Kolida S, *et al.* (2012) Metabolism of anthocyanins by human gut microflora and their influence on gut bacterial growth. *J Agric Food Chem* **60**, 3882–3890.
110. Sánchez-Patán F, Cueva C, Monagas M, *et al.* (2012) *In vitro* fermentation of a red wine extract by human gut microbiota: changes in microbial groups and formation of phenolic metabolites. *J Agric Food Chem* **60**, 2136–2147.
111. Queipo-Ortuño MI, Boto-Ordóñez M, Murri M, *et al.* (2012) Influence of red wine polyphenols and ethanol on the gut microbiota ecology and biochemical biomarkers. *Am J Clin Nutr* **95**, 1323–1334.
112. Vendrame S, Guglielmetti S, Riso P, *et al.* (2011) Six-week consumption of a wild blueberry powder drink increases bifidobacteria in the human gut. *J Agri Food Chem* **59**, 12815–12820.
113. Parkar SG, Trower TM & Stevenson DE (2013) Fecal microbial metabolism of polyphenols and its effects on human gut microbiota. *Anaerobe* **23**, 12–19.

British Journal of Nutrition

https://doi.org/10.1017/S0007114521003627 Published online by Cambridge University Press

114. Espley RV, Butts CA, Laing WA, *et al.* (2014) Dietary flavonoids from modified apple reduce inflammation markers and modulate gut microbiota in mice. *J Nutr* **144**, 146–154.
115. Molan AL, Lila MA, Mawson J, *et al.* (2009) *In vitro* and *in vivo* evaluation of the prebiotic activity of water-soluble blueberry extracts. *World J Microbiol Biotechnol* **25**, 1243–1249.
116. Jennings A, Koch M, Jensen MK, *et al.* (2020) The role of the gut microbiome in the association between habitual anthocyanin intake and visceral abdominal fat in population-level analysis. *Am J Clin Nutr* **111**, 340–350.
117. Czank C, Cassidy A, Zhang Q, *et al.* (2013) Human metabolism and elimination of the anthocyanin, cyanidin-3-glucoside: a 13C-tracer study. *Am Clin Nutr* **97**, 995–1003.
118. Amin HP, Czank C, Raheem S, *et al.* (2015) Anthocyanins and their physiologically relevant metabolites alter the expression of IL-6 and VCAM-1 in CD40L and oxidized LDL challenged vascular endothelial cells. *Mol Nutr Food Res* **59**, 1095–1106.
119. Bialonska D, Ramnani P, Kasimsetty SG, *et al.* (2010) The influence of pomegranate by-product and punicalagins on selected groups of human intestinal microbiota. *Int J Food Microbiol* **140**, 175–182.
120. da Silva-Maia JK, Batista AG, Correa LC, *et al.* (2019) Aqueous extract of berry (Plinia jaboticaba) byproduct modulates gut microbiota and maintains the balance on antioxidant defense system in rats. *J Food Biochem* **43**, e12705.
121. Dou Z, Chen C & Fu X (2019) Bioaccessibility, antioxidant activity and modulation effect on gut microbiota of bioactive compounds from Moringa oleifera Lam. leaves during digestion and fermentation *in vitro*. *Food Funct* **10**, 5070–5079.
122. Hu T-G, Wen P, Liu J, *et al.* (2019) Combination of mulberry leaf and oat bran possessed greater hypoglycemic effect on diabetic mice than mulberry leaf or oat bran alone. *J Funct Foods* **61**, 103503.
123. Rodríguez-Morató J, Matthan NR, Liu J, *et al.* (2018) Cranberries attenuate animal-based diet-induced changes in microbiota composition and functionality: a randomized crossover controlled feeding trial. *J Nutr Biochem* **62**, 76–86.
124. Gumul D, Korus J & Achremowicz B (2007) The influence of extrusion on the content of ploy phenols and antioxidant/antirdical activity of rye grains (Secale cereal L.). *Acta Sci Pol Technol Aliment* **6**, 103–111.
125. Estruel-Amades S, Massot-Cladera M, Pérez-Cano FJ, *et al.* (2019) Hesperidin effects on gut microbiota and gut-associated lymphoid tissue in healthy rats. *Nutrients* **11**, 324.
126. Cheng N, Chen S, Liu X, *et al.* (2019) Impact of SchisandraChinensis bee pollen on nonalcoholic fatty liver disease and gut microbiota in highfat diet induced obese mice. *Nutrients* **11**, 346.
127. Klinder A, Shen Q, Heppel S, *et al.* (2016) Impact of increasing fruit and vegetables and flavonoid intake on the human gut microbiota. *Food Funct* **7**, 1788–1796.
128. Terada A, Hara H, Nakajyo S, *et al.* (1993) Effect of supplements of tea polyphenols on the caeeal flora and caeeal metabolites of chicks. *Microb Ecol Health Dis* **6**, 3–9.
129. Okubo T, Ishihara N, Oura A, *et al.* (1992) *In vivo* effects of tea polyphenol intake on human intestinal microflora and metabolism. *Biosci Biotechnol Biochem* **56**, 588–591.
130. Cheng M, Zhang X, Zhu J, *et al.* (2018) A metagenomics approach to the intestinal microbiome structure and function in high fat diet-induced obesity mice fed with oolong tea polyphenols. *Food Funct* **9**, 1079–1087.
131. Song M-Y, Wang J-H, Eom T, *et al.* (2015) Schisandra chinensis fruit modulates the gut microbiota composition in association with metabolic markers in obese women: a randomized, double-blind placebo-controlled study. *Nutr Res* **35**, 655–663.

British Journal of Nutrition

https://doi.org/10.1017/S0007114521003627 Published online by Cambridge University Press