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

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Abstract  
Flavonoids are natural polyphenol secondary metabolites that are widely produced in planta. Flavonoids are ubiquitous 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 role in the host microbiome interactions and exhibit a myriad of health benefits. Flavonoids-induced biological activities are strongly influenced by their intrinsic bioavailability and vary between different flavonoids subclasses. Such inter individual differences have been shown to affect the metabolism of ingested polyphenols. 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. This can trigger a wide range of biological effects of flavonoids depend mainly on their intrinsic bioavailability and vary between different flavonoids subclasses. Generally, phenolic glycosides are not hydrolysed in the stomach, whereas 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) or metabolised in the large intestine by the action of intestinal microbiota to yield aglycones, the hydrophobic core of the flavonoid molecule. Aglycones pass through cell membranes to exert their biological functions via passive diffusion.

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 are mainly observed 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) or metabolised in the large intestine by the action of intestinal microbiota to yield aglycones, the hydrophobic core of the flavonoid molecule(14,16,17). Aglycones pass through cell membranes to exert their biological functions via passive diffusion(20).

Abbreviations: MIC, minimum inhibitory concentration.

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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.

### 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 pyran 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 \( \beta \)-glucosidases produced by specific gut microbes such as *Bifidobacterium* 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).
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. Other metabolites of flavonols include 2,4,6-trihydroxybenzoic acid, 3-(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). These metabolites 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 flavonoids 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

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

<table>
<thead>
<tr>
<th>Flavonoid compound or extract</th>
<th>Subject</th>
<th>Dose and intervention</th>
<th>Impact on microbiota</th>
<th>Health outcomes</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Flavonoids</td>
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<tr>
<td>Apigenin</td>
<td>In vitro batch culture fermentation</td>
<td>100 μg/ml</td>
<td>Clostridium, Peptostreptococcaceae, Bacteroidetes, Proteobacteria Enterococcus caccae, Firmicutes, E. caccae and B. galacturonicus</td>
<td>+ Acetate, propionate, and butyrate production</td>
<td>Wang, et al. (2017)(54)</td>
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<td></td>
<td>Male Wistar rats</td>
<td>50 mg/kg/d</td>
<td>Bacteroidetes: Firmicutes, Bacteroidales, Streptococcaceae, Porphyromonadaceae, and Verrucomicrobiaceae</td>
<td>+ Mucin secretion</td>
<td>Zhang, et al. (2018)(56)</td>
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<td>- Blood glucose level</td>
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<td>- Lowers insulin resistance in diabetic rats</td>
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<td></td>
<td>Male Kunming IC rat</td>
<td>150 mg/kg body weight of EPW</td>
<td>Bacteroidetes, Actinobacteria Proteobacteria, Alistipes, Lachnospiraceae and Odoribacter Firmicutes, Klebsiella, Lactobacillus</td>
<td>+ Blood glucose level protected against liver and kidney damage</td>
<td>Yan, Yang et al. (2019)(41)</td>
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<td></td>
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<td>- Inflammation in diabetic mice</td>
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<td></td>
<td>18 adults with stable cystic fibrosis</td>
<td>P. edulis leaf extract (1-1 mg dry leaves ml-1)</td>
<td>Bifidobacterium sp. and Lactobacillus sp. Clostridium and Bacteroides spp.</td>
<td>SOD Activities in liver and brain</td>
<td>da Silva, Cazarin et al. (2013)(53)</td>
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<td></td>
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<td>- Antioxidant activity</td>
<td>da Silva-Maia, Batista et al. (2019)(120)</td>
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<td></td>
<td>Male Kunming IC rat</td>
<td>15, 25 and 50 g of jaboticaba extract</td>
<td>Lactobacillus, Bifidobacterium and Enterobacteriacae</td>
<td>+ Antioxidant activity</td>
<td>da Silva-Maia, Batista et al. (2019)(120)</td>
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<td></td>
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<td>- Antioxidant activity</td>
<td>da Silva-Maia, Batista et al. (2019)(120)</td>
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<td>- Antioxidant activity</td>
<td>da Silva-Maia, Batista et al. (2019)(120)</td>
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<td>- Antioxidant activity</td>
<td>da Silva-Maia, Batista et al. (2019)(120)</td>
</tr>
<tr>
<td>Flavonoid intake including flavonols, flavones, flavan-3-ols, flavanones, and anthocyanidins</td>
<td>18 adults with stable cystic fibrosis</td>
<td>Actinomyces and Actinomycetaceae (Actinobacteria)</td>
<td>+ Immunomodulation activity</td>
<td>Li and Somerset (2018)(93)</td>
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<td></td>
<td>- Anti-inflammatory activity</td>
<td>Li and Somerset (2018)(93)</td>
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<td>- Risk of lung disease</td>
<td>Li and Somerset (2018)(93)</td>
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<tr>
<td>Flavonoids of Moringa oleifera Lam. leaves containing quercetin-3-O-$\beta$-D-glucoside, 6,8-di-C-glucosylapigenin and catechin</td>
<td>In vitro fermentation 5.0 mg/mL (w/v)</td>
<td>Ratio of Firmicutes to Bacteroidetes, Cyanobacteria, and Proteobacteria</td>
<td>+ Antioxidant activity</td>
<td>Dou, Chen et al. (2019)(121)</td>
<td></td>
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<tr>
<td>Mulberry leaf and oat bran combination containing flavonoids like rutin</td>
<td>Old male Kunming mice</td>
<td>6 g/kg of BW mulberry leaf–oat bran mixture</td>
<td>Firmicutes, Alistipes and Ruminococci, Anaerostipes and Odoribacter, and Escherichia-Shigella</td>
<td>+ Antidiabetic activity</td>
<td>Hu, Wen et al. (2019)(122)</td>
</tr>
<tr>
<td>Cranberry powder (anthocyanins and flavonoids)</td>
<td>Eleven healthy subjects (7 males, 4 females)</td>
<td>30 g/d cranberry diet</td>
<td>Bacteroidetes, Lactobacillales, Anaerostipes, Clostridiales and Odoribacter</td>
<td>+ Urinary levels of anthocyanins and phenolic acids</td>
<td>Rodríguez-Morató, Matthan et al. (2018)(123)</td>
</tr>
<tr>
<td>Hesperidin and its aglycone hesperetin</td>
<td>Male Wistar rats</td>
<td>0.4 0 g and 0.83 g of HT and HD per kg of body weight</td>
<td>Bilobacterium, Lactobacillales</td>
<td>+ SCFA production</td>
<td>Unno, Hisada et al. (2015)(79)</td>
</tr>
<tr>
<td>Hesperidin</td>
<td>Lewis rats</td>
<td>100 or 200 mg/kg hesperidin</td>
<td>Lactobacillus, Enterococcus, Staphylococcus, StreptococcusBacteroides/Prevotella, Bilobacterium Escherichia coli Clostridium cocoides, Eubacterium retcal, Clostridium subclust</td>
<td>+ Immunomodulatory actions of hesperidin</td>
<td>Estruel-Amades, et al. (2019)(126)</td>
</tr>
<tr>
<td>Flavonoid compound or extract</td>
<td>Subject</td>
<td>Dose and intervention</td>
<td>Impact on microbiota</td>
<td>Health outcomes</td>
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<tr>
<td>Isoorientin</td>
<td>5 weeks old BALB/c male mice</td>
<td>15 mg/kg BW</td>
<td>Acinetobacter, Alistipes, Anaerotruncus, Bilobobacterium, Desulfovibrio Faecalibaculum, Helicobacter, Kurthia, Lachnoclostridium, Lactobacillus, Odoribacter, Oscillusbacter, Ruminiclostridium Bacteroides, Enterococcus, Alloprevotella, Enterorhabdus, Mucispirillum, Parabacteroides, Parabacteroides, Parasesputella, Caproiciproducens, Roseburia, Anaeroplasma and Pantoaea</td>
<td>- Antioxidation and anti-inflammation effects</td>
<td>Yuan, Li et al. (2018)[60]</td>
</tr>
<tr>
<td>Schisandra chinensis bee pollen containing naringenin, rutin and chrysin</td>
<td>Male C57BL/6 mice</td>
<td>7.86 and 15-72 g SCPE/kg BW</td>
<td>Coriobacteriales, Coriobacteriia, Coriobacteriaceae, and Bilobobacterium, Bilobobacteriales, Bilobobacteriaceae, Lactobacillaceae, and Verrcomicrobiaceae, Actinobacteria, Proteobacteria and Pseudomonas Lactobacillaceae</td>
<td>+</td>
<td>Cheng, Chen et al. (2019)[128]</td>
</tr>
<tr>
<td>Fruit, vegetables and flavonoid as flavonols quercetin and rutin</td>
<td>154 subjects male and female</td>
<td></td>
<td></td>
<td>+</td>
<td>Kinder, Shen et al. (2016)[127]</td>
</tr>
<tr>
<td>Flavanol containing green tea extract</td>
<td>Chicken and Pigs</td>
<td>6 tea cups per d for 2 months</td>
<td>Lactobacillus (-) Enterobacteriaceae (-)</td>
<td>-</td>
<td>Terada, Hara et al. (1993)[128]</td>
</tr>
<tr>
<td>Tea flavanol polyphenols</td>
<td>Human (8 Japanese subject)</td>
<td>0.4 g 3 times daily for 4 weeks</td>
<td>Bilobobacterium (-) Clostridium perfringens (-)</td>
<td>+ Microbiota profile restored 2 weeks after discontinuation</td>
<td>Okubo, Ishihara et al. (1992)[128]</td>
</tr>
<tr>
<td>Oolong tea flavonoids (OTP) containing flavanol</td>
<td>Mice (fed on high fat diet)</td>
<td>0.1 % w/w OTP for 4 weeks</td>
<td>Firmicutes/Bacterioidetes ratio</td>
<td>-</td>
<td>Cheng, Zhang et al. (2018)[130]</td>
</tr>
<tr>
<td>The total flavonoids of Quzhou Fructus Auranti. Extract (TFQ) standardised as narinutin, naringin, hesperidin and neohesperidin</td>
<td>8-weeks old male mice</td>
<td>daily dose of 300 mg/kg TFQ</td>
<td>Akkermansia, Alistipes, Dubosiella, Faecalibaculum and Lactobacillus. Firmicutes to Bacterioidetes ratio</td>
<td>+ Obesity, inflammation and liver steatosis</td>
<td>Bai, Wang et al. (2019)[70]</td>
</tr>
<tr>
<td>Schisandra chinensis fruit extract total flavonoids standardised as catechin</td>
<td></td>
<td></td>
<td>Akkermansia, Roseburia, Bacteroides, Prevotella, and Bilobobacterium Ruminococcus, Firmicutes</td>
<td>+</td>
<td>Song, Wang et al. (2015)[331]</td>
</tr>
</tbody>
</table>

SOO, superoxide dismutase.
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 \(B.\) adolescens, 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 \(Alsties\). Notably, \(Alsties\) 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...
bacterial genus.\(^{(44)}\) Specifically, \(B.\) \(bifidum\) promotes the induction of regulatory T cells (T reg), expressing chemokine receptors and potentially favouring mucosal homoeostasis.\(^{(45,46)}\) Likewise, enhancement of \(Lactobacillus\) growth has 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 flavonoids 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.\(^{(50)}\) However, such effects do not appear to be universal, since flavonoids intake showed negative association with certain bacteria like \(Actinobacteria\) and \(Bifidobacteria\), but positive association with others, for example, \(Blauntia.\)\(^{(40)}\)

**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 tagetetin, nobiletin and sinensetin.\(^{(59)}\) 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 \(\beta\)-glucosidase.\(^{(51)}\) In contrast, \(C\)-glycosides reach the colon almost intact.\(^{(50)}\) 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).\(^{(1)}\)

**In vitro studies.** The modulatory activity of apigenin on pure cultures of \(Bacteroides\) \(gallinarum\), \(Bifidobacterium\) \(catenulatum\), \(Lactobacillus\) \(rhamnosus\) and \(Enterococcus\) \(cassae\), 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 \(E.\) \(cassae\) and \(B.\) \(gallinarum\) growth (100 \(\mu g/ml\)), 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.\(^{(49)}\)

In vivo/animal studies. The anti-diabetic activity and gut microbiota modulation by baicalein (5,6,7-trihydroxyflavone) was examined in streptozotocin and high-fat-diet-induced diabetic rats.\(^{(50)}\) 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 Desulfovulaceae. Many of the taxa stimulated by baicalein treatment are SCFA producers, for example, members of the \(Bacteroides\), \(Alloprevotella\), \(Butyrivibrio\), \(Parabacteroides\) and \(Bacteroidales\), and the family Prevotellaceae. Such results clearly indicate that the intestinal microbiome can mediate and enhance the anti-diabetic action of flavonoids specifically flavones, which thus can be used as natural agent to support a type 2 diabetes preventive or anti-diabetic lifestyle.

Another study investigated the antioxidant activity of flavone compounds from passion fruits and leaves (\(Passiflora\) \(edulis\), maracuja/maracuyá) 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-G-glucoside) on the intestinal microbiota and antioxidation, anti-inflammatory 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 \(Actinobacter\), \(Anaerotruncus\), \(Bifidobacterium\), \(Desulfovibrio\), \(Faecalibaculum\), \(Kurthia\), \(Lachnospirillum\),
Lactobacillus, Odoribacter and Ruminiclostridium. Moreover, isoorientin inhibited the growth of some inflammation-causing pathogenic bacterial genera such as Alistipes, Helicobacter and Oscillibacter.

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 (68). Flavanones possess a 2,3-dihydro-2-phenylchro- men-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 (63) and are responsible for their bitter taste and several health effects (60,62). Flavanones are mostly found as glycosides, either rutinosides (α-rhamnosyl-α-1→6-glucosides) or neohesperidosides (α-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) (23).

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-(3-hydroxyphenyl) propionic acid (Fig. 4). Isoxanthohumol a major prenyllavonoid of hops (Humulus lupulus L.) is biotransformed by intestinal bacteria Enterobacteriaceae via demethylation and formation of a potent bioavailable phyto-oestrogen 8-prenylnaringenin (64,65).

Interaction with the microbial community
Compared with flavonoids and flavones, intact flavanones have 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. hesperidin, naringenin and poncirin has been tested in vitro. Among the tested compounds, poncirin was the most potent one and its MIC was 10–20 μg/ml (68). In another study (69), the effect of flavanones, viz. naringenin, naringenin, hesperidin and hesperidin on 6-bacteria, that is, Bacteroides galacturonicus, Lactobacillus sp., E. coli, 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 (69). Such strong inhibitory effect of flavonone aglycones might cause unfavorable changes in the composition of physiological microflora in the human intestine (70).

The impact of the flavanones naringenin and hesperidin on Bifidobacterium bifidum and B. adolescentes 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. adolescentes 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/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 weight, 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 changshanyou) extract standardized 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, Faecalibacterium 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 (52), hence their classification as natural phyto-oestrogens (76,77). Soya is a rich...
source of isoflavonoids(76), with genistein, daidzein and glyci-
tein as the major forms. Isoflavones such as genistein and
daidzein are commonly utilised as selective oestrogen recep-
tor modulators because of their mild oestrogenic activity
in vivo(78).

Isoflavones usually pass to the colon unabsorbed. Their bio-
availability depends on the hydrolysis of isoflavones into their
bioactive aglycones such as, daidzein, genistein and glycitin
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
equolificiens, Slackia equolificiens, Lactobacillus mucosae,
Bifidobacterium spp. and Bacteroides ovatus(80). For example,
genistein is metabolised to p-ethylphenol and 4-hydroxy-
phenyl-2-propionic acid, whereas daidzein is further reduced
to O-demethylangolensin and equol(70). Also, the metabolism
of daidzein by faecal bacteria from four human individuals were
identified as Slackia equolificiens EPI2, Enterococcus faecium
EPI1, Veillonella sp. and Finegoldia magna. EPI3 was investi-
gated. Dihydroadziein, O-demethylangolensin, 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, dihydroadziein, tetrahydro-
daidzein, hydroxydaidzein, 6-hydroxydaidzein, 8-hydroxydai-
dzein, 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 for-
mononetin, 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 the 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 top-
isoresetase 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-andro-
genic, anticanccer, antioxidiant 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, epigallo-
catechin and epicatechin(88). Flavan-3-ol structures are charac-
terised by having a B ring attached to C-2, with an absent
aryl group at C-4 and double bonds between C-2 and C-3(89).
They are abundant in fruits, tea and wine and are con-
sidered 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 (–)-epigallo-
catechin, (–)-epicatechin gallate and (–)-epicatechin(88,89).
Catechins are metabolised in the colon by the action of intesti-
nal microbiota to yield low molecular weight metabolites
which may be absorbed or otherwise are excreted in feces(90).
Interestingly, epicatechin when incubated with intestinal bac-
terial strains in *vitro* yields pyrogallol, 5-(3,4-dihydroxy-
phenyl) valeric acid, 5-(3-hydroxyphenyl) valeric acid, 3-(3-
methoxyphenyl) valeric acid, 3-(3,4-dihydroxyphenyl) propi-
onic acid, 3-(3-hydroxyphenyl)propionic acid and 2,3-dihy-
droxyphenoxyl 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 intes-
tinal microbial metabolism was found to affect the metabolism
of polyphenolics(91). An *in vitro* study was conducted to quan-
tify 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
identified 1-(3′,4′-dihydroxyphenyl)-3-(2′,4′,6′-dihydroxy-
phenyl)-2-propanol (3,4-diHPV-2-ol) and 5-(3′,4′-dihydroxy-
phenyl)-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 charac-
terise 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-valerolac-
tones 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 micro-
biot(90). Tea flavonoids, especially catechins, have been
shown to inhibit growth of pathogenic and opportunistic
micro-organisms such as *S. aureus*, *E. coli*, *S. typhimurium*, *Helicobacter pylori*, *Listeria monocytogenes* and *Pseudomonas aeruginosa*.

The correlations between catechins intake and intestinal microbiota were studied in a group of cystic fibrosis patients. Results showed that gallocatechin consumption positively correlated with the relative abundance of members of the family Actinomycetaceae, specifically the genus *Actinomycyes* (phylum Actinobacteria), and negatively correlated with the family Coriobacteriaceae (*Actinobacteria*). *Actinomycyes* 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.

Another interesting beneficial effect of grape seed extract and black raspberry catechins was demonstrated in ref. where the relative abundance of the butyrate producers Lachnospiraceae, Clostridiales and Ruminococcaceae 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 with lower obesity (Fig. 5), improving bowel functions, preventing the transmission of pro-inflammatory molecules in systemic circulation and preventing metabolic endotoxemia. Butyrate also showed a direct effect on adipose tissue by enhancing adaptive thermogenesis in mice with depleted microbiota.

**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. Anthocyanins are sensitive to degradation and natively occur usually as glycosides due to their higher stability. Cyanidin, delphinidin, malvidin and pelargonidin are the most commonly identified anthocyanins in different plant sources. Although, antioxidant, anti-inflammatory, anticarcinogenic and cardioprotective activities have been reported for anthocyanins, their low bioavailability limits such effects. Anthocyanins are metabolised and biotransformed by gut microbiota in the human intestine. For example, cyanidin 3-rutinoside is partially hydrolysed to its related glucoside and then is subsequently hydrolysed to yield the aglycone. 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). Other bacteria-generated anthocyanin metabolites include syringic acid, vanillic acid, chlorogenic acid and 3-O-methylgallic acid, depending on the anthocyanins precursor. The metabolic fate of (-)-epicatechin, procyanidin B1 and polymeric procyanidin was studied in *in vitro* in humans. 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, 3,4-dihydroxyphenyl 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 vitro* model results parallel that reported from *in vitro* assays of microbial action.

Interactions with the microbial community and health outcomes

Multiple studies have revealed that anthocyanins and their metabolites could induce specific changes in human gut
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 promoters via modulation of commensal gut microbiota (115), 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 microbiota, 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...
probiotics can be confidently suggested to fully exploit the health benefits of flavonoids on a wider scale.

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