Food & Function

ROYAL SOCIETY OF CHEMISTRY

REVIEW

Cite this: *Food Funct.*, 2020, **11**, 8444

Phytochemicals as modifiers of gut microbial communities

Giulia Dingeo,†[a] Alex Brito, †[b,c] Hanen Samouda,[b] Mohammed Iddir,[b] Michael R. La Frano [d,e] and Torsten Bohn *[b]

Received 7th June 2020,
Accepted 18th September 2020

DOI: 10.1039/d0fo01483d

rsc.li/food-function

A healthy gut microbiota (GM) is paramount for a healthy lifestyle. Alterations of the GM have been involved in the aetiology of several chronic diseases, including obesity and type 2 diabetes, as well as cardiovascular and neurodegenerative diseases. In pathological conditions, the diversity of the GM is commonly reduced or altered, often toward an increased *Firmicutes*/*Bacteroidetes* ratio. The colonic fermentation of dietary fiber has shown to stimulate the fraction of bacteria purported to have beneficial health effects, acting as prebiotics, and to increase the production of short chain fatty acids, *e.g.* propionate and butyrate, while also improving gut epithelium integrity such as tight junction functionality. However, a variety of phytochemicals, often associated with dietary fiber, have also been proposed to modulate the GM. Many phytochemicals possess antioxidant and anti-inflammatory properties that may positively affect the GM, including polyphenols, carotenoids, phytosterols/phytostanols, lignans, alkaloids, glucosinolates and terpenes. Some polyphenols may act as prebiotics, while carotenoids have been shown to alter immunoglobulin A expression, an important factor for bacteria colonization. Other phytochemicals may interact with the mucosa, another important factor for colonization, and prevent its degradation. Certain polyphenols have shown to influence bacterial communication, interacting with quorum sensing. Finally, phytochemicals can be metabolized in the gut into bioactive constituents, *e.g.* equol from daidzein and enterolactone from secoisolariciresinol, while bacteria can use glycosides for energy. In this review, we strive to highlight the potential interactions between prominent phytochemicals and health benefits related to the GM, emphasizing their potential as adjuvant strategies for GM-related diseases.

1. Introduction

Phytochemicals encompass a large number of compounds, often also termed secondary plant compounds. These include various chemical classes with partly diverging properties, including polyphenols, carotenoids, phytosterols/phytostanols, lignans, glucosinolates, alkaloids, to listen the most abundant ones. Major dietary sources include fruits and vegetables, but also wholemeal grain products.[1] It has been well recognized that in addition to macronutrient/macro-constituent dietary patterns (carbohydrates, proteins, fats, and dietary fiber), and the presence of essential micronutrients, *i.e.* minerals and vitamins, these not strictly essential dietary constituents may play an important role for human health. Many epidemiological studies have meanwhile highlighted their important roles in the prevention of chronic diseases including cancer,[2] cardiovascular and respiratory diseases[3] and metabolic diseases such as type 2 diabetes[4] and the metabolic syndrome.[5]

Most commonly, the potential health benefits of secondary plant compounds are ascribed either to their antioxidant function, *i.e.* quenching reactive oxygen species (ROS) such as for *e.g.* polyphenols and carotenoids,[6,7] to their ability to reduce cholesterol (re)absorption such as for phytosterols,[8,9] their ability to interact with hormonal receptors such as lignans or isoflavonoids,[10] or to interact with cellular processes such as transcription factors, influencing gene expression.[11,12] However, there is more recent evidence that at least some phytochemicals can also contribute to health *via* interacting with the gut microbiome (GM), through a number of different path-

[a]*Independent Researcher, Paris, France. E-mail: giulia.dingeo@gmail.com*
[b]*Luxembourg Institute of Health, Population Health Department, Nutrition and Health Research Group, 1A-B, rue Thomas Edison, Strassen L-1445, Luxembourg. E-mail: alexbritophd@gmail.com, mohammed.iddir@lih.lu, hanene.samouda@lih.lu, torsten.bohn@lih.lu; Tel: +352 26970-394*
[c]*Laboratory of Pharmacokinetics and Metabolomic Analysis, Institute of Translational Medicine and Biotechnology, I.M. Sechenov First Moscow Medical University, Moscow, Russia. E-mail: abrito@labworks.ru*
[d]*Department of Food Science and Nutrition, California Polytechnic State University, San Luis Obispo, CA, USA. E-mail: mlafrano@calpoly.edu*
[e]*Center for Health Research, California Polytechnic State University, San Luis Obispo, CA, USA. E-mail: mlafrano@calpoly.edu*
†These authors contributed equally.

ways, for instance acting as prebiotics.[13] In addition, concentrations of phytochemicals are highest in the gut, and their influence on the GM may be independent from limited bioavailability issues, and may act in their native, unmetabolized form.

Though a number of interactions between the GM and phytochemicals have been revealed, especially in *in vitro* trials, the number of studies investigating the interaction *in vivo*, especially in humans, is still very limited. Thus, an important factor influencing GM is much under-recognized and deserves more investigation, especially in sight of the GM recognized relation to numerous chronic diseases.[14,15] In this review, we aim to raise awareness of the potential functional interactions between phytochemicals and the GM, and summarize evidence available for health benefits of phytochemicals related to microbiota changes.

2. A brief overview of gut microbiota and health aspects

2.1. General aspects of the gut microbiota

The GM represents a large, unique and intricate composition of microbes residing in the gastrointestinal tract. Far from being static, it is sensitive to major changes during the life-course.[16] About 4×10^{13} (40 trillions on the short scale) microorganisms reside in the gastrointestinal tract, which is about the same number as human cells.[17] While the intestinal tract mostly hosts bacteria, with about 500–1000 different species, the gut can also accommodate, especially during pathologic conditions, single-cell eukaryotes such as protozoa, parasitic worms such as tapeworms and hookworms, fungi such as yeasts, especially *Candida*, and also viruses, notable noroviruses and rotaviruses.[18–20] Due to the vast amount of metabolic activities of the combined GM, it has also been termed the "neglected organ".[21]

The majority of the GM is present in the colon, with lower numbers in the upper digestive tract. As the stomach is very acidic, only about 10 bacteria per g have been reported, as compared to 1000 g^{-1} in the duodenum, 10 000 g^{-1} in the jejunum, 10 million per g in the ileum, and 10^{12} g^{-1} in the colon.[22] The predominant phyla include *Bacteroidetes*, *Firmicutes*, *Actinobacteria*, *Proteobacteria*, and *Verrucomicrobia*, with the first two accounting for approx. 90% of bacterial species.[23] The main species include *Bacteroides*, *Eubacterium*, *Clostridium*, *Ruminococcus*, *Peptococcus*, *Peptostreptococcus*, *Bifidobacterium* and *Fusobacterum* spp.[23]

2.2. Importance of gut microbiota for host health

While the GM depends on the host, the GM also provides benefits for the host, truly fulfilling the definition of a symbiotic condition. As the bacteria are fermenting non-absorbed dietary constituents, and not all products are used for bacterial growth, the GM also provides some energy to the host (about 10% of the daily required energy), *via* epithelial uptake of bacteria-products such as short-chain fatty acids (SCFAs), namely butyrate, propionate, and acetate.[24] In addition, the GM plays a critical role in overall health, preserving neuroendocrine, metabolic and immune functions.[25] Dysbiosis of the GM has shown to be related with alterations of the gut barrier function, reduced bacterial diversity, altered immune responses and increased risk of inflammatory diseases. This for example includes ulcerative colitis and Crohn's disease, the major inflammatory bowel diseases (IBD).[26,27] Important for intestinal integrity, the gut associated lymphoid tissue (GALT) is an integrative part of the immune system, protecting the body from invading microorganisms. GALT, rich in IgA-producing plasma cells, and also macrophages, is influenced by GM such as *via* toll-like-receptor (TRL) interactions of dendritic cells and IL-10 production and Th17 cell differentiation *via* serum amyloid A protein.[28]

Due to their relation with the immune system and inflammation, the composition and or function of the GM has been correlated with nearly all major risk factors for cardiovascular diseases (CVD), including aging, metabolically unhealthy obesity, sedentary lifestyle, and unhealthy dietary habits such as high simple sugar and fat intake.[27,29–31] A recent meta-analysis has associated GM with 10 major diseases, finding that some diseases were related to 50 genera, though most only correlated with 10–15.[32] Furthermore, the role of the gut-liver axis has been highlighted regarding non-alcoholic fatty liver disease,[33] and the gut-brain axis regarding neurodegenerative diseases such as multiple sclerosis,[34] among others.

2.3. Dietary substrates of GM, SCFAs and health aspects

Some of the substrates used by the GM are secreted or derived by the host, *e.g. via* cell abrasion and the mucus layer, which is a substrate for some specialized bacteria such as *Bacteroides thetaiotaomicron.*[35] However, as the GM derive the majority of their energy from non-absorbed dietary constituents passed on from the small to the large intestine, dietary patterns are a major influential factor that can modify the composition and numbers of the bacterial communities. Especially the macronutrient composition of the diet, such as the carbohydrate and protein amounts, has been highlighted to influence bacterial composition and diversity,[36] with a higher diversity during low protein and carbohydrate intake. Regarding bacterial species, a carbohydrate-based diet has been related to high numbers of *Prevotella* spp. which are reduced during low-carbohydrate intake,[37] while a higher number of *Bacteroides* spp. was associated with a diet rich in proteins and saturated fat, as reviewed by Senghor *et al.*[38]

However, also small molecules can have significant effects on the microbiota and their function and influences on the human host. Especially the relation between the gut microbiota and certain diet-derived metabolites has been shown to be fundamental for the immune system. This has been highlighted for *e.g.* taurine (triggering NOD-like receptor family pyrin domain containing 6 (NLRP6) mediated inflammasome related to NF-κB activity), polyamines (macrophage polarization inhibition), SCFAs (energy source for gut epithelium), *all-trans* retinoic acid (ATRA, interacting with the nuclear

receptor RAR), and aryl-hydrocarbon receptors (AhR) ligands such as indoles (playing a role for lymphoid follicle morphology).[39]

The predominant fraction of non-absorbed dietary constituents passed on to the colon are non-digestible dietary fiber compounds, though also some proteins are resistant to digestion.[40] These are soluble and insoluble dietary fibers, mostly macromolecular polysaccharides such as fructo-oligosaccharides, hemicelluloses, pectins, and resistant starches. Many are fermentable and can foster the growth of health-associated bacteria such as *Bifidobacteriaceae* and other families, producing metabolites such as SCFAs, which have been associated with health benefical effects.[41,42] Some of these polysaccharides have therefore been termed as prebiotics.[43]

Regarding SCFAs, acetic acid (37 mmol kg^{-1}), propionic acid (13 mmol kg^{-1}), *n*-butyric acid (12.4 mmol kg^{-1}), isobutyric acid (2.2 mmol kg^{-1}), iso-valeric acid (3.2 mmol kg^{-1}), *n*-valeric acid (2.4 mmol kg^{-1}) and *n*-caproic acid (0.5 mmol kg^{-1}) were shown to be among the most predominant, based on human feces measurements.[44] Studies indicate that especially butyrate has local and systemic anti-inflammatory properties,[45,46] and also anti-obesogenic effects have been discussed. Somewhat surprisingly, this compound has been reported to be present in high amounts in feces of individuals having obesity, though being accompanied with low phyla microbiota variety, as shown in a recent meta-analysis.[47] However, SCFAs also contribute to energy supply, and perhaps the amounts produced should be related to the body mass index (BMI) for improvements of diagnostics. Also, SCFAs in the bloodstream may be a more appropriate marker. In fact, circulating SCFAs were inversely associated with TG levels, whole-body lipolysis and positively with glucagon-like peptide 1 (GLP-1), related to insulin sensitivity.[48] Furthermore, butyrate is a histone deacetylase inhibitor, effecting gene-expression,[49] improves intestinal barrier integrity,[50] increases the secretion of antimicrobial peptides,[51] down-regulates TLR-expression and the release of pro-inflammatory cytokines.[52] It further exerts anti-inflammatory properties *via* inhibiting granulocyte[53] and lymphocyte activity.[54] Therefore, butyrate-producing bacteria are generally considered beneficial, and their depletion has been associated with type 2 diabetes (T2D), IBD, irritable bowel syndrome and colorectal cancer.[55–57] Among the main butyrate producers in the gut are *Firmicutes*, while *Bacteroidetes* are rather acetate and propionate producers.[58]

Additional important pathways through which the diet and dietary fiber could influence GM and health and disease status include maintaining tight junction integrity[59] and a thick and stable mucus layer,[59] both important to prevent the crossing-over of pathogens or allergens into the circulatory system. Regarding bacteria and their relative proportions that have been shown to change with disease status, *Bacterioides* spp., *Bifidobacterium* spp., *Firmicutes* spp., and *Clostridum* spp., have been among the most investigated (Fig. 1). Obesity and weight gain, though not in a consistent manner, have been frequently associated with a reduced number of *Bacterioides* spp. *vs.* a higher number of *Firmicutes* spp.,[60,61] but lower

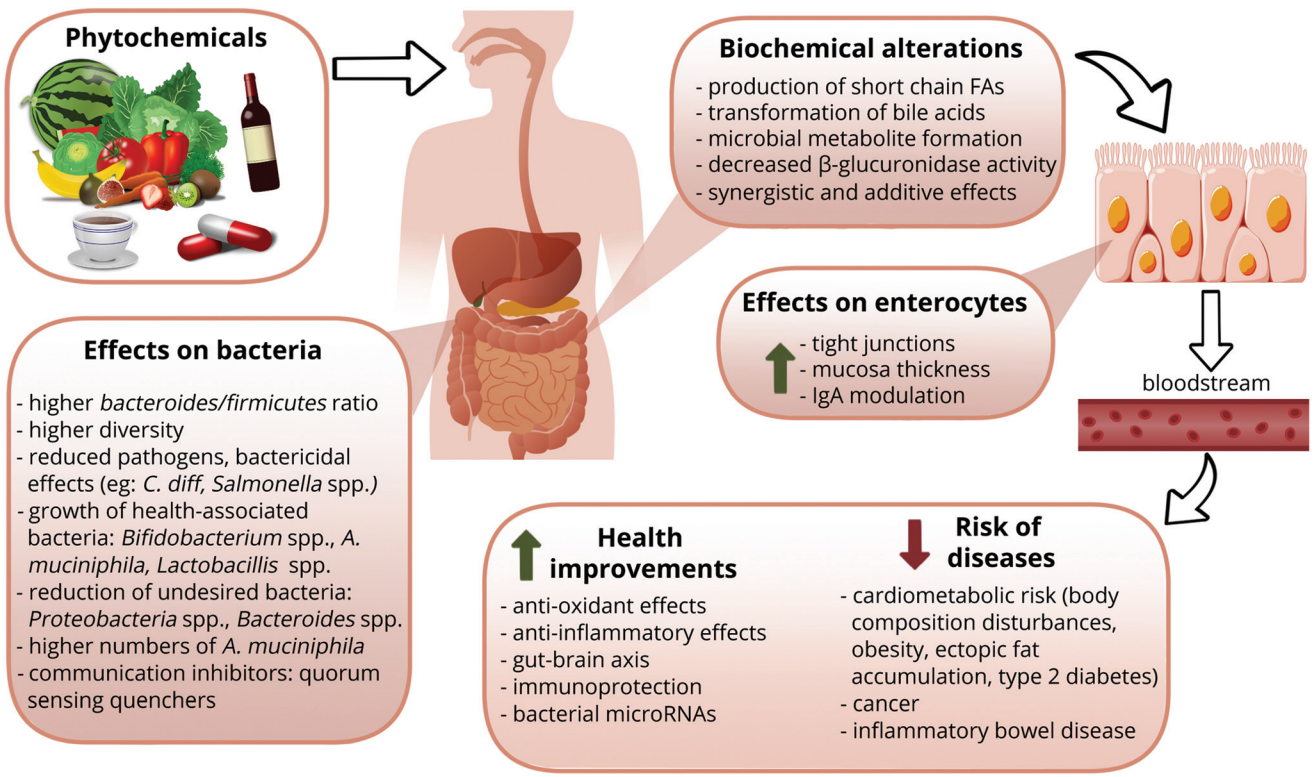

Fig. 1 Phytochemicals and the gut microbiota.

Bifidobacterium spp. as reviewed previously.[60] *Clostridium difficile* as a potential pathogen has been associated with diarrhea.[62] The role of *Akkermansia* spp., especially *A. muciniphila*, a mucus degrader, has also been met with some interest, as a higher number was associated with lower T2D risk, as reviewed by Tomas-Barberan *et al.*[63] and Cani,[64] and it appears that their population increases with dietary fiber and polyphenol intervention. Many more correlations have been reported, such as the decreased abundance of *Prevotellaceace* (SCFA producers) in Alzheimer's patients,[65] but many need to be affirmed.

Taken together, the GM and its composition and diversity have been associated with a number of chronic diseases. As GM is influenced by dietary patterns, these likewise can influence health status, and important pathways include SCFA production, acting as prebiotics, and maintaining barrier function integrity.

3. Phytochemicals and gut microbiota

3.1. Introduction

In addition to dietary fiber, there are other compounds that are poorly absorbed and poorly metabolized in the upper digestive tract, which are consequently passed on the large intestine, and that can also play a role modulating the GM. Among them, phytochemicals or secondary plant metabolites are a broad and varied group of plant-derived constituents, which are frequently consumed within the diet, encompassing, among other, polyphenols, carotenoids and other terpene based compounds, phytosterols/phytostanols, lignans, various alkaloids and sulphur-containing compounds.[66] Phytochemicals are not essential for plants, but they generally have biological activity in the plant host such as controlling its growth and reproduction, and can convey survival benefits, *i.e.* acting against herbivores, competitors, and microorganisms.

Phytochemicals have no known essentiality to humans and are therefore not considered nutrients in a strict sense. As a consequence, no dietary reference sets such as dietary reference intakes (DRIs by the IOM, USA) or dietary reference values (DRVs by EFSA, Europe) include them at present. However, they can significantly contribute to a healthy diet, and their dietary intake has been inversely associated with a lowered risk of several chronic diseases, such as cardiometabolic diseases including T2D[67] and other CVDs,[68] several types of cancer,[69] and to some extent also neurodegenerative diseases,[68] though evidence for the latter is more marginal.

These plant compounds are widely present in fruits, vegetables, grains, nuts, seeds and flowers, as some of these compounds are associated directly with dietary fiber, *i.e.* in part bound to it (covalently or not), such as for polyphenols.[70] In addition, they can be found in certain beverages and products such as coffee, cacao, tea, fruit juices, red wine and cold pressed vegetable oils.[71] Also, they may be consumed within dietary supplements and herbals, as well as within algae and mushrooms. To a lesser extent, some may accumulate in animal derived food items such as carotenoids in egg yolk, cheeses, prawns or salmon.[71]

Though considered minor dietary constituents, the intake of some of these secondary plant metabolites such as polyphenols can reach 1 g d^{-1},[72] though this is still much lower than the RDA of dietary fiber, being 25 and 38 g d^{-1} for men and women, respectively.[73] Many phytochemicals are considered to have bioactive functions, mainly anti-inflammatory and antioxidant activity. In addition to their general association with chronic diseases, some have been related to specific health conditions. For example, the xanthophylls lutein and zeaxanthin in the prevention of age-related macular degeneration,[74] the major cause of vision loss in the elderly, due to their protection from intensive blue-light.

3.2. Bioactive properties of phytochemicals

The majority of phytochemicals, including polyphenols and carotenoids, have been advertised for their general antioxidant properties.[75] This can be achieved either *via* directly quenching reactive oxygen or nitrogen species (RNS, ROS) such as singlet oxygen or lipid peroxides, or interacting with cellular transcription factors such as Nrf-2, important for the body's antioxidant homeostasis *via* the gene expression for antioxidant enzymes such as catalase (CAT), superoxide-dismutase (SOD) and glutathione peroxidase (GPx). Moreover, anti-inflammatory properties, *via* interacting with the transcription factor NF-κB have also been emphasized, related to the formation of pro-inflammatory cytokines such as TNF-α and IL-1β.[11] Other constituents, namely phytosterols, may reduce (re-) absorption of cholesterol and bile acids,[76] improving blood lipids. Lignans and isoflavonoid-derived metabolites such as equol may interact with estrogen receptors and perhaps act upon certain types of cancer.[77]

There is growing evidence that phytochemicals, especially polyphenols, the predominant group consumed within the diet, play a role in modulating the GM.[78,79] Even carotenoids have just recently demonstrated in a human intervention trial with subjects with obesity to influence microbiota composition, related to positive health effects such as improved blood lipids (Table 1).[80] Phytochemicals have the potential to interact with the metabolic activity and composition of colonic bacteria, through dosage, timing and route of administration.[81] Their potential role on the GM depends on their matrix, with whole foods potentially having different effects than extracts,[81] due to certain synergetic effects and altered release kinetics which can influence their bioavailability. They also can have additive or negative effects in terms of their absorption and metabolism.[82] For example, while curcumin alone has low oral bioavailability, the combination with piperine from black pepper can enhance its bioavailability by >2000 fold, possibly due to the reduced phase II metabolism,[83] preventing further glucuronidation and/or sulfation. However, in general, many phytochemicals are poorly absorbed. Absorption is often as low as ~10% such as in the case of the poorly soluble carotene lycopene,[84] and also for many polyphenols, which are in part re-excreted after cellular uptake into

Table 1 Selected studies showing interactions between phytochemicals and the gut microbiota

Classes	Type of study	Type of application	Significant findings	Ref.
Polyphenols				
Supplementation of polyphenol rich food items, *e.g.* apple, tea, wine, coffee, soy and others	*Meta-analysis of human trials*: 27 papers. *In vivo* part (n = 17 studies): 1076 cases in placebo group, and 1095 cases in polyphenol supplemental group, all healthy adults. *In vitro* effects/fermentations were also studied (n = 10 studies)	Variable doses (6.4–2364 mg d^{-1}), between 1.1–18 weeks. For *in vitro* analysis, 0.079–1896 mg L^{-1} were applied, for 1–2 d	Supplementation increased abundance of *Lactobacillus* spp. by 1.22 SMD and *Bifidobacterium* spp. by 0.56 SMD. It had no significant effect on *Eubacterium* abundance. Impacts on abundance of *Bacteriodes* spp. was inconsistent. Tea intake was the most effective to decrease the abundance of *Clostridum* spp., followed by apples. Fruits and vegetables had the greatest effect on stimulating probiotic species. Regarding doses, 400–600 mg d^{-1} appeared to have most significant effects	121
Cacao flavanol supplementation	*Randomized controlled trial*, 22 healthy human subjects	High-cocoa flavanol (HCF) group received *ca.* 500 mg cocoa flavanols per day; low-cocoa flavanol (LCF) group received 23 mg cocoa flavanols per day for 4 weeks	HCF drink enhanced *Bifidobacterium* spp. and *Lactobacillus* spp. numbers and hampered *Clostridium* spp. This alteration was related to lowered plasma TGs and CRP. CRP concentrations were related to *Lactobacillus* spp. numbers	124
Quercetin, rutin, or buckwheat supplementation	*Human randomized controlled intervention trial*: 28 healthy human subjects (aged 22–36 years)	Subjects obtained single dose of flavonoids. Doses: quercetin 14 mg per kg bw. rutin 28 mg per kg bw. (pure or in form of buckwheat) and placebo, on a single occasion	Flavonoids resulted in increased numbers of *Eubacterium ramulus*. Though this outcome was present in all flavonoid group, most predominant increase was registered in those receiving buckwheat, followed by the rutin, quercetin and placebo	123
Blackcurrant polyphenols	*Human randomized controlled trial* with 30 healthy adults, 20–60 years	Supplementation with FL (first leaf: mix of blackcurrant extract, lactoferrin and lutein) at 1500 mg day^{-1} and CAM30 (Cassis Anthomix 30: black currant powder) 672 mg day^{-1}, for 6 weeks	Consumption of FL and CAM30 significantly increased population of *Lactobacilli* and *Bifidobacteria.* The populations of *Clostridium* spp. and *Bacteroides* spp. sign. declined. Moreover, FL and CAM30 decreased β-glucuronidase activity and fecal pH	126
Fruit and vegetable (FV) flavonoids	*Human randomized controlled intervention trial*: 122 subjects, either high flavonoid group (HF), low flavonoid group (LF) or control group, collection of stool samples	Supplementation for 18 weeks total with first 2, then 4, then 6 portions per day high-flavonoid (HF) and low-flavonoid (LF) food intake. Increase in portion number every 6 weeks	Largest effects found for highest FV intakes, *i.e.* week 18, with increases of *Clostidium leptum-Ruminococcus bromii/flavefaciens*, *Bifidobacterium* spp. and *Bacteroides/Prevotella* spp. counts. Marginal effects on microbiota when comparing HF *vs.* LF groups	122
Polyphenols from propolis	*Animal trial*: 24 male Sprague Dawley rats	Rats were given propolis (300 mg per kg bw.), commencing 1 week before DSS exposure for 1 week, then 3 days without DSS (dextran sulfate sodium to induce colitis)	Significant reduction of *Bacteroides* spp., increased diversity and richness with propolis	133
Wine polyphenols	*Human randomized controlled trial*, 10 healthy volunteers	Participants received red wine, the corresponding amount of dealcoholized red wine (both 272 mL d^{-1}), or gin (100 mL d^{-1}) for 20 d each	Intake of red wine polyphenols boosted counts of *Enterococcus*, *Prevotella*, *Bacteroides*, *Bifidobacterium*, *Bacteroides uniformis*, *Eggerthella lenta*, and *Blautia coccoides–Eubacterium rectale*. Slightly weaker trends for dealcoholized red wine but absence of effects in general in gin group. Systolic and diastolic blood pressures and TGs, total-C, HDL-C, and CRP levels were lowered. Changes in total-C and CRP levels were related to changes in *Bifidobacteria*	129

Table 1 *(Contd.)*

Classes	Type of study	Type of application	Significant findings	Ref.
Green tea polyphenols	*In vitro inhibition assay*: AGS cells	Different concentrations of green tea extracts for 30 min	CSI-4 (40% uronic acids, but no catechins) inhibited *E. coli*, *B. stearothermophilus*, *C. thermoaceticum* and *Salmonella typhi.* CSI-4 and CS-F2 did not inhibit *A. actinomycetemcomitans*	255
	In vitro inhibition assay: 56 clinical isolates of *H. pylori*	Serial dilutions of EGCG and/or antibiotics for 4 days	MIC90 of EGCG and ECG against all *H. pylori* was 100 μg ml^{-1}, which was weak compared with the antibiotics tested, including MTZ, CLR and AMX	256
	In vitro inhibition assay: S. aureus ATCC 25923 and *E. coli* ATCC 25922	25, 50 and 100 μg l^{-1} of EGCG for 1 h	Inhibition (MI90 ≥ 800 μg ml^{-1}) against *E. coli*, *K. pneumoniae*, *Salmonella typhi*, *Proteus mirabilis*, *P. aeruginosa*, and *S. marcescens*. Variable susceptibilities of *Staphylococcus* and Gram-negative rods to EGCG was explained with the different affinities of EGCG with parts of the bacterial cell walls	257
Resveratrol	*Animal intervention trial*: BALB/c mice, IL-10 deficient, $n = 9$; GrTP/EGCG and BALB/c mice ($n = 3$), GrTP and DSS colitis model ($n = 9$)	10 days of either 1% green tea polyphenols or EGCG at 0.12–0.5%	GrTP and EGCG improved antioxidant (sulfhydryl, disulfides, GSH, GSSG, cysteine and cystine) levels in plasma and softened severity of colitis similar to sulfasalazine. Blocked NF-κB activation and further IKK activity	115
	Human intervention trial: patients with ulcerative colitis (UC, $n = 8$), Crohn's disease (CD, $n = 6$) and 7 healthy controls	1–3 glasses red wine per day, 7 days (approx. 0.4 g EtOH kg^{-1})	Consuming red wine reduced stool calprotectin in IBD individuals from baseline and enhanced gut permeability as detected by urinary lactulose/mannitol excretion in CD or urinary sucralose secretion in UC	258
	In vitro inhibition assay: *V. choleraeO1* (MCVO9)	Resveratrol 10,15,20,25,30 μg ml^{-1} with cells MCVO9, 1 day	Antimicrobial activity against *V. cholerae*, inhibiting biofilm formation	259
Different types of polyphenols (narigenin, quercetin, rutin, caffeic acid)	*In vitro* inhibition assay: Caco-2 cells (TCC Cat No HTB-37)	Different polyphenols at concentrations of 10, 30 and 100 μg ml^{-1} for 3 h	Naringenin together with quercetin were most potent polyphenols and showed lowest MIC for all bacteria scrutinized. The other polyphenols had the most pronounced effect on *S. aureus*. Naringenin and phloridzin were the compounds with the most pronounced inhibition of *S. typhimurium* adherence to Caco-2 cells, phloridzin and rutin improved adherence of the probiotic *L. rhamnosus*	138
Flavanones naringenin and taxifolin	*In vitro* inhibition assay: *P. aeruginosa* to study quorum-sensing (QS) inhibition	Different polyphenols at 4 mM for 8 and 18 h	Naringenin and taxifolin reduced a number of QS-controlled gene expressions in *P. aeruginosa* PAO1. Naringenin also reduced the production of acyl-homoserine-lactones (AHL) compounds	260
Ginseng extracts	*Animal intervention trial*: 18 male Wistar rats being in a control group (9 rats) or ginseng extract group (GS, 9 rats)	100 mg kg^{-1} of ginseng extracts in drinking water for 34 weeks, other group water	Increased concentrations of IL4, IL10 and IgA in the spleen of the GS group. IL2, IL6, IgG, IgM, and NK were attenuated to some extent in the GS group *vs.* the C group. Ginseng extract reduced TM7, while *Proteobacteria*, *Methylobacteriaceae*, *Parasutterella* spp. abundances were enhanced in GS group. Ginseng extract stimulated *Bifidobacterium* spp, *Lactobacillus*, spp. IL4, IL10, and IgA	261
	Intervention trial: 11 healthy adults and 12 with metabolic syndrome	4-week, pre- and post-treatment with Yangyin Tiluo Decoction (YTD) containing ginseng, blood and feces collected	Intervention increased abundance of *Moraxellaceae*, *Acinetobacter*, species *Acinetobacter incertae sedis* and *Erysipelotrichaceae incertae sedis vs.* controls, reducing *Alphaproteobacteria*, *Rhizobiales*, genus *Bacteroidales incertae sedis* and species *Enterobacteriaceae incertae sedis*. Higher number of lactic acid bacteria and reduced butyric acid-producing bacteria in individuals with the metabolic syndrome	262

Table 1 *(Contd.)*

Classes	Type of study	Type of application	Significant findings	Ref.
Carotenoids				
β-Carotene	*Human observational study* in subjects (n = 16) with cystic fibrosis	Associations tested between faecal microbiota and corresponding micronutrient intakes	Intake of β-carotene (and several other antioxidants) was related to lower *Bacteroides* and higher *Firmicutes*	186
Carotene (and proteins)	*Animal trial*: 32 Duroc pigs, receiving standard protein diet or the same plus carotene, for 1 month	Pigs were fed 2 different diets: a standard protein (SP) diet and carotene-enriched (CE) diet (20% of M37W-Ph3 carotenoid-enriched corn), unspecified amount carotenes	Proteins had a stronger modifying effect than carotenes on the pig gut microbiota patterns. 160 Amplicon Sequences Variants (ASVs) differed between CE and SP	184
Lycopene	*Intervention trial*: humans: 30 adult subjects with obesity, double blinded design	7 or 30 mg for 30 days as supplement	Dose-related improvement in gut microbiota profile with enhanced fractions of, *e.g.*, *Bifidobacterium adolescentis* and *Bifidobacterium longum*. Also related to dose-dependent variation in the blood, liver metabolism, skeletal muscle and skin measures	80
	In vitro inhibition assay: *B. subtilis*	Extraction from tomato paste and tests on *B. subtilis*, 50 μg mL^{-1} lycopene	Inhibition against *B. subtilis*	263
Capsaicin	*Animal trial*: 18 female C57BL/6J WT and B6.129X1-Trpv1tm1Jul/J ($TRPV1^{-/-}$; KO) mice	Mice were randomly placed into three groups (n = 6): standard diet group, a high-fat diet (HFD) group, and an HFD + CAP (capsaicin, 2 mg per kg bw.) group. Treatment was 12 weeks	Compared to the HFD group, the HFD + CAP diet-associated microbiota was of larger abundance of *Bacteroidetes*, *Tenericutes* and *Verrucomicrobia*, and of a lower fraction of *Proteobacteria*, *Actinobacteria*, *Cyanobacteria*, and *Firmicutes*	180
	Animal trial: 12 C57BL/6J male mice	Mice were randomly placed into two groups of 6 and fed with either a HFD or a HFD with 0.01% CAP	Mean proportion of *Acidobacteria*, *Bacteroidetes*, and *Firmicutes* and most notably *Akkermansia muciniphila* increased in the HFD-CAP group. Lower abundance of *Proteobacteria*	181
Fucoxanthin	*Animal trial*: 40 male BALB/c mice	For 4 weeks mice were fed NCD (normal chow diet), NCD + fucoxanthin (NCDF, 125 mg kg^{-1}), HFD + fucoxanthin (HFDF, 125 mg kg^{-1})	No difference between the NCD and NCDF. *Firmicutes* and *Bacteroidetes* increased in the NCDF group (26%). In the HFDF group, it inclined (13%) *vs.* the HFD group, suggesting a positive effect of fucoxanthin. Fucoxanthin decreased abundance of *Verrucomicrobia* phylum	183
β-Carotene and extracts of carotenoids from red paprika, apples, oranges	*In vitro* inhibition assays: HSC-2, HSG and HTLV1	Extracts of carotenoids and β-carotene from red paprika tested on infected cells (*H. pylori* and $HIV\text{-}1_{IIIB}$) for 5 days	Prevention of the development of *H. pylori*-associated disease, MIC_{50} of β-carotene and red paprika extract of >200 μg mL^{-1}, extract from apples showed MIC_{50} of 36 μg mL^{-1}	174
Extracted carotenoids (from shation pummelo *C. grandis*)	*In vitro* inhibition assays: *B. subtilis*, *S. aureus*, *E. coli*, *A. niger*, *A. flavu*, *P. chrysogenum*, *R. oryzae* and *S. cerevisiae*	The extracts were incubated for 24 h with the microorganisms tested	Inhibition against *B. subtilis*, *S. aureus*, *E. coli*, *A. niger*, *A. flavus*, *S. cerevisiae*	264
Tomato powder (TP) rich in carotenoids	*Animal trial*: 18 male $BCO1^{-/-}BCO2^{-/-}$ double KO mice	Mice were fed a HFD with or without dietary TP (42 g kg^{-1} diet) intervention for 24 weeks	The fraction of Gram-positive bacteria was enhanced following TP; the fraction of Gram-negative bacteria was lowered accordingly. TP diminished relative abundance of *Clostridium* and *Mucispirillum* spp.	182

Table 1 *(Contd.)*

Classes	Type of study	Type of application	Significant findings	Ref.
Annatto, carrot, corn and tomato extracts	*In vitro* inhibition assays: *E. coli* and *S. aureus*	Extracts were incubated for 18–24 h with microorganisms tested	Annatto, carrot and tomato extracts exhibited antibacterial property for *S. aureus*. Annatto extract, having the highest total carotenoid content, also exhibited the major MIC for *S. aureus*	176
Phytosterols				
Plant stanol ester	*Human intervention trial*: double blinded study, 13 healthy subjects	Subjects taking for 3 weeks plant stanol ester (3 g d^{-1}), followed by 4 weeks of wash-out period	In spite of decreased plasma oxyphytosterol concentrations, plant stanol consumption did not change composition/diversity of microbiota	197
Phytosterol (PSE) esters	*Animal trial*: 24 six-week-old male Sprague Dawley rats	Divided into 4 groups: a regular chow diet control group (NC, $n = 6$), a high-fat diet group (HFD, $n = 6$), HFD plus a low-dose PSE group (PSEL, $n = 6$) and a high-dose PSE group (PSEH, $n = 6$)	High-dose PSE treatment changed microbial community, which was quite different from those of the HFD group. In the PSEH group there was a high abundance of *Firmicutes* and *Proteobacteria*, which were similar to those in the NC groups	198
Lignans				
Flaxseed supplementation	*Randomized controlled trial*: 42 healthy men and women (20–45 years)	Supplementation of flaxseed lignan (50 mg secoisolariciresinol diglucoside per day) *vs.* placebo	Enterolactone, but not enterodiol, was associated with microbiome composition. 11 bacterial genera and *Methanobrevibacter* (*Archaea*) were associated with enterolactone; 3 were related to enterodiol following lignan intervention	164
	Longitudinal intervention trial: 9 healthy male adult subjects	Subjects ingested 0.3 g kg^{-1} day^{-1} flaxseed for 1 week *vs.* placebo	Enterolactone conc. was related to abundance of *Ruminococcus bromii* and *R. lactaris*. Most abundant species of the order *Bacteroidales* correlated positively with acetic, isovaleric, or isobutyric acid in stool, the latter being negatively related with blood triglyceride levels. The fraction of *Ruminococcaceae* and of *Coprococcus comes* correlated positively with plasma LDL-C and triglycerides, respectively	165
Secoisolarcinresinol diglucoside (seeds of Piper cubeba L.)	*In vitro* inhibition asssay: *E. faecalis*, *S. salivarius*, *S. mitis*, *S. mutans*, *S. sobrinus*, *S. sanguinis* and *C. albicans*	Sub-cultured on blood agar for 24 h	Compounds possessing a lactone ring and bearing two methylendioxyaryl groups displayed significant, antibacterial, anti-inflammatory and analgesic activities. Active against *Streptococcus salivarius S. mitis*, *Enterococcus faecalis*, *Candida albicans*	163
Alkaloids				
Caffeine/coffee	*Human intervention trial*	Comparing effect of 3 cups of coffee per d for 3 weeks in 16 healthy subject	Overall minor changes in main microbiota composition, but increased *Bifidobacterium* spp. compared to study onset	211
Caffeine/coffee	*Human observational study*	Relating GM to frequency of caffeine consumption *via* food-frequency questionnaires	Higher diversity of GM in individuals consuming more coffee, increased *Faecalibacterium* and *Roseburia*, though lower levels of *Erysipelatoclostridium*	210
Sanguinarine	*In vitro* inhibition assay: *S. aureus*, *E. coli*, *E. faecalis*	Incubated for 24 h	Inhibited bacteria adherence on teeth. Perturbation of FtsZ Z-ring (prokaryotic protein needed for cell division) and reduced bacteria induced cytokines, perturbation of SCFAs	102
Piperine and reserpine	*In vitro* inhibition assay: *E. coli* strain CFT073	Overnight culture, extracts at 0.5, 5, 10, 50 mg mL^{-1}	Reduced *E. coli* bacteria mobilities and increased biofilm formation, inhibiting fliC, MotA and MotB	224

Table 1 *(Contd.)*

Classes	Type of study	Type of application	Significant findings	Ref.
Berberine	*In vitro* inhibition assay: *S. oralis*, *S. mutans*, *S. sanguinis A. pleuropneumoniae*, *Listeria monocytogenes*, *S. typhi*	MIC after incubation 24 h	Berberine hampered synthesis of proteins related with the growth and cleavage of bacteria, blocked the division and the development of bacteria. *S. mutans*, *S. sanguinis*, *S. oralis*, *A. pleuropneumoniae*, *L. monocytogenes*, *S. typhi*	265–267
Others (terpenes, aroma active compounds)				
Curcumin	*Randomized placebo controlled study*: a total of 30 adult healthy subjects	Placebo, turmeric, or curcumin tablets for 8 weeks at 6 g d^{-1}	Control group: diminished number of microbiota species by 15% (to an average of 149 species post-treatment). Individuals receiving turmeric: slight increase (7%, up to 167 species). Individuals taking curcumin: species number increase of 69% (to 215). Relative abundance of 89 taxa was lower in the control group, this was mostly due to one individual. Turmeric and curcumin intake caused a reduction in fraction of 71 and 56 taxa, respectively. Turmeric response reflects the breakdown of polysaccharides in the root such as glycosyl hydrolases encoded by *Bacteroides*, *Bifidobacterium*, *Alistipes*, and *Parabacteroides*, which were all increased in responsive individuals	249
		Turmeric tablets were made with 1 g turmeric root (*Curcuma longa*) plus 1.25 mg black pepper-derived extract of piperine. Curcumin tablets contained 1 g of curcumin plus 1.25 mg black pepper piperine		
Ginger	*Animal study*: five-week-old C57BL/6J male mice, n = 48 total	4 groups of: animals fed with a normal chow diet (NCD) or HFD, without or with 500 mg per kg bw. of ginger once daily for 16 weeks	No sign. differences in *Firmicutes* and *Bacteroidetes*. *Actinobacteria* abundance was increased following ginger administration, and lowered by HFD. Abundance of *Proteobacteria* in NCD-fed animals increased with ginger intake. Ginger restored above bacteria abundance to normal. HFD lowered *Erysipelotrichaceae*, *Bifidobacteriaceae* and *Prevotellaceae* but increased *Desulfovibrionaceae*, which were restored (except *Bifidobacteriaceae*) to normal levels in the HFD-G group. Ginger sign. increased *Alloprevotella* in the HFD-fed obese mice, *Bifidobacterium* was higher in the NCD-G group	268
Rosemary extract (carnesol, carnosic acid and terpenes)	*Animal intervention trial*: adult male ICR (Institute of Cancer Research)	21 days treatment, 3 different groups, for the rosemary extract 100 mg kg^{-1}	Modified composition of cecum microbiota. Enhanced SCFAs in obese rats. Reduced SCFAs in lean rats. Attenuation of depression-like behaviour, dysbiosis and inflammation. Extract subdued expression of IL-1β, TNF-α, NF-κB p65 and Iba1 in hippocampus, and enhanced p-AKT/AKT expression	246
Rosmarinus officinals	*Animal intervention trial* (female Zucker rats, obese and lean)	Control group (n = 6 rats) with standard diet and treated group (n = 18 rats) fed with standard diet plus extract (0.5% w/w) for 15 days	Lean group: rosemary extract reduced total bacteria (*Lactobacillus*, *Leuconostoc*, *Pediococcus* and *Clostridium* spp.) and augmented *Bifidobacterium* spp., *Blaudia cocoides* and *Bacteroides* spp.	245
Cruciferous vegetable diet rich in isothiocyanates	*Human intervention trial*	17 healthy human subjects consuming either cruciferous-rich diet or diet low in vegetables, fiber and phytochemicals	Changes in *Eubacterium hallii*, *Phascolarctobacterium faecium*, *Burkholderiales* spp., *Alistipes putredinis*, and *Eggerthella* spp.	233

Table 1 *(Contd.)*

Classes	Type of study	Type of application	Significant findings	Ref.
Allicin (from garlic)	*Mouse intervention study*	6 male mice per group receiving either control chow food, high-fat diet or high fat diet with 100 mg kg^{-1} and day allicin, for 8 weeks	Obese mice treated with allicin showed lowered weight gain and significantly increased numbers of *Akkermansia* spp. while not influencing *Clostridium XIVb* and *Eubacterium spp.* compared to high-fat diet group	241
Allylisothiocyanate, benzylisothiocyanate and 2-phenyl-ethylisothiocyanate	*In vitro* inhibition assay: 18 aerobic bacterial strains [*E. faecalis*, *S. aureus*, *E. coli* (two strains), *P. aeruginosa*, *S. typhi*]	Modification of the disc diffusion method, five different concentrations, 0.015/0.15/0.75/1.50/3 μmol per disc	The antimicrobial activity of individual compounds and dual combinations (streptomycin-phytochemicals) reduced several pathogens, *e.g. E. coli*, *P. aeruginosa*, *Listeria monocytogenes* and *S. aureus*	269

Abbreviations: AHL: acylated homoserine lactone; Bw.: body weight; CRP: c-reactive protein, EGCG: epigallocatechin gallate, AGS: adenocarcinoma gastric cell line, ECg: epicatechin gallate, MTZ, CLR and AMX: susceptibility of H. pylori strains to amoxicillin (AMX), metronidazole (MTZ), clarithromycin (CLR), CSI4 and CS-F2: two different extracts from green tea, MIC: minimum inhibitory concentration, GrTP: green tea polyphenols, BALB/c: mouse strain of albino mice, GSH: glutathione, GSSG: glutathione disulfide, EtOH: ethanol, fliC: flagellar filament protein, HDL-C: high density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol, NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells, IKK: IκB kinase, IBD: inflammatory bowel disease, UC: ulcerative colitis, CD: Crohn's disease, Caco-2: caucasian colon adenocarcinoma, IL-2: interleukin-2, IL-4: interleukin-4, IL-6: interleukin-6, IL-10: interleukin-10, IgG: immunoglobulin-G, IgM: immunoglobulin-M, MotA/MotB: motility protein A/B, NK: natural killer cells, TM7: bacteria from the *Saccharibacteria* phylum, GS: ginseng group, IgA: immunoglobulin-A, HSC-2: squamous carcinoma mouth, HSG: human salivary gland, HTLV1: human T-cell lymphotropic virus type 1, ITF: inulin-type fructans, FtsZ Z-ring: filamenting temperature-sensitive mutant Z, SCFAs: short chain fatty acids, fliC: felagellar gene, MotA and MotB: mobility genes, IL-1β: interleukin-1 β, SMD: standardized mean difference; TGs: triglycerides, total-C: total cholesterol, TNF-α: tumor necrosis factor-α, p65: (or RelA) is one of the five components of NF-κB, Iba1: immunolabeled microglial cells, BDNF: brain-derived neurotrophic factor, p-AKT/AKT: phosphorylated proteins.

the gut lumen.[72] Thus, their majority is passed through to the colon. However, some phytochemicals are macromolecules or bound covalently to dietary fiber and can only be released following fiber fermentation, which is believed to be the case for some non-extractable polyphenols (NEPP[85]), such as complex tannins.

3.3. Energy derived from phytochemicals

The microbiota can perform a large number of metabolic steps with secondary plant compounds, encompassing dihydroxylation, ester cleavage, deglycosylation, decarboxylation, and ring breakage. As non-absorbed carbohydrates such as starches, inulin, pectins and some hemicelluloses *etc*. are the main typical source of energy for the microbiota,[86,87] energy for the microbiota is derived from phytochemicals especially from cleaved glycosides. Some bacteria such as certain *Lactobacilli* spp. were shown to grow well on plant glycosides.[88] For this purpose, the bacteria can take up the phytochemical-glycoside, cleave the sugar moiety intracellularly by glycosidases and secrete the aglycon back to the lumen, while metabolizing the glycoside *via* various pathways, depending on the bacteria species, to butyrate or propionate, as reviewed by Louis *et al.*[86] For example, while *Bacteriodetes* metabolize heptoses and pentoses *via* oxaloacetate and succinate into propionate, the latter is produced by other bacteria such as *Veillonella* spp. *via* pyruvate and lactate, while butyrate is produced *e.g.* by some *Eubacterium* spp. *via* pyruvate and acetyl-CoA. For other phytochemicals such as for carotenoids, to our knowledge, no data is available on their potential metabolism.

In addition to acting as a carbon source for bacteria, some nitrogen-containing phytochemicals can also be metabolized by bacteria, though most phytochemicals do not contain nitrogen. Potential secondary plant compound nitrogen sources include alkaloids and glucosinolates. Many members of the major GM phyla, including *Bacteriodetes*, *Firmicutes*, *Actinomycetes* and *Proteobacteria* were reported to convert glycosinolates.[89] The latter ones are cleaved by bacterial myrosinase to produce thiocyanates and nitriles, as reviewed by Narbad and Rossiter.[89] Many bacteria, especially Gram-positive ones were able to degrade glucosinolates into isothyocyanates and nitriles, including *Streptomyces*, *Bacillus*, *Staphylococcus*, *E. coli*, several *Lactobacillus* spp., among other. Nitriles may be cleaved further by bacteria with nitrilase activity, degrading them *e.g.* into carboxylic acids and ammonia, such as shown for some *Pseudomonas* spp.,[90] but the ammonia is not likely used further but excreted. In fact, nitrogen seems a limiting resource. Nitrogen fixation by several bacteria such as by some *Klebsiella* and *Clostridiales* strains has been reported.[91] Otherwise, non-absorbed amino acids or proteins are likely to be major sources of nitrogen for the GM.[36] However, too high availability of nitrogen has been associated with a less health-associated GM, and diets limiting available GM nitrogen were emphasized as healthy.[36] In this regard, it is interesting that some polyphenols such as tannins may bind protein and make them less available,[92] possibly even for bacteria However, following cleavage of glucosinolates by thioglycosidases, bacteria

harvest energy by the released sugar moiety (glucose). In contrast to glucosinolates, there is evidence that some alkaloids such as purine alkaloids, *e.g.* caffeine, can serve as substrate for GM, yielding various nucleic acids such as xanthine and hypoxanthine, which presumable may act both as nitrogen and energy source.[93]

3.4. Influence of phytochemicals on the GM and health related aspects

Phytochemicals may be involved in a variety of mechanisms related to health aspects in which GM do play a role. These are explained in further detail in the following sections, but in short, these include predominantly:

(a) direct influences on GM composition and numbers, *via* acting as substrates for the GM, acting as prebiotic-like compounds;[94] these seem to include especially polyphenol-glycosides as the bacteria can convert the sugar moiety into energy;

(b) improving gut-health *via* their direct antioxidant effects, which could alter the gut-redox potential, as oxidizing agents have been proposed to increase the risk of *e.g.* antibiotic-related pathogen colonization in the gut;[95]

(c) interactions with the immune-system, especially *via* IgA,[96] playing a role in the degree of colonization, such as reported for some carotenoids;[26,97]

(d) influencing colonization and gut barrier properties *via* their extensive metabolism, such as influencing the mucin layer,[98] in fact vital for the cross-communication between the host and bacterial genome. In this respect, the term "hologenome" has been coined to highlight the interaction of bacteria and the host for mutual health, as reviewed previously;[79]

(e) exhibiting direct bactericidal or bacteriostatic effects,[99,100] reducing *e.g.* pathogenic species such as *Clostridium* spp.[101] by various phenolic compounds and also by some alkaloids, which have shown to influence FtsZ-Z ring formation, important for cell division.[102] In addition the effects of certain sulphur containing compounds such as allicin from garlic are well documented;[103]

(f) acting additively or synergistically with other dietary compounds or bacterial metabolites, such as omega-3 fatty acids and polyphenols acting synergistically as anti-inflammatory agents;[104]

(g) influencing "quorum sensing", *i.e.* bacterial cell communication *via* low weight metabolites, important for *e.g.* differentiation, biofilm formation among others[105] which has been shown to be influenced by certain phytochemicals; and may influence health status *via e.g.* disturbing pathogenic biofilm formation.[106]

However, most often the exact mechanisms of action are unknown, and may even be combinations of several of the above possibilities.

In summary, non-absorbed phytochemicals can, similar as to dietary fiber, influence GM composition and activity. Though their intake *via* fruits, vegetables, cereals, nuts and other plant-based products is rather estimated at around 1–2 g d^{-1}, much lower than dietary fiber, they can be metabolized by the GM and used partly for energy production. Their anti-oxidant, anti-inflammatory properties, directly or *via* acting on transcription factors, together with bactericidal or bacteriostatic effects such as *via* quorum quenching make them interesting molecules for targeting GM related changes associated with certain chronic diseases.

4. Classes of phytochemicals and interactions with the GM

4.1. Polyphenols

4.1.1 Overview of polyphenols and their relation to health outcomes. Polyphenols have been proposed to be able to interact with many diseases *via* their influence on the GM. For instance, the interaction of polyphenols on the gut-brain axis,[107,108] *via* GM metabolites and their potential activity as neurotransmitters following crossing the blood–brain barrier, and thus their potential implication to act on neurodegenerative diseases such as Alzheimer's disease[109] has been emphasized. Due to their concentration being likely highest in the gut, polyphenols have been proposed as adjuvant agents to improve IBD conditions,[110] which are characterized by inflamed tissue in the gut, with increased immune-system activity such as Th1 and Th17 cells, stimulated by bacterial antigens. In addition to the direct prebiotic effects of phenolic compounds, reduced oxidative stress (aggravated by infiltrating neutrophils and macrophages) has been emphasized, and also their anti-inflammatory and antioxidant aspects, *via* acting upon the transcription factors NF-κB and Nrf-2, respectively.[110] Furthermore, polyphenols appear to improve gut epithelial function, *via* reducing barrier permeability through strengthening tight junction functionality.[111]

Indeed, most of the available evidence on interactions between phytochemicals and the GM has been obtained on polyphenols. This is in part due to polyphenols being the most frequently consumed secondary plant metabolites,[112] and their occurrence is associated with many types of dietary fibers.[113] Polyphenols are mostly consumed in the form of fruits, vegetables, cereals, nuts and grains. As polyphenol bioavailability is low, concentrations in the colon may reach highest concentrations in the body, typically in the millimolar range, as reviewed by Cardona *et al.*[78] Many polyphenols are present in the diet in conjugated form, such as with glucose, which can be liberated by GM *via* deglycosylation and provides a substrate and source of energy for bacteria. However, the bacteria may also take part in other reactions with polyphenols, including ring fissions, demethylation, dihydroxylation, hydrolysis of esters, among others.[114]

The two main groups of polyphenols are flavonoids such as isoflavones and anthocyanins and non-flavonoids, including phenolic acids and stilbenes.[72] Research on the interaction of polyphenols with GM has mainly focussed on catechins, flavan-3-ols from green tea including epigallocatechin gallate;[94,115] ellagic acid and ellagitannins, non-flavonoids present *e.g.* in pomegranate, raspberries, blackberries, strawberries and chestnuts;[82,116] ginseng saponins (triterpenoids or

ginsenosides) present in red ginseng roots;[81,117] curcumin from the root of *Curcuma Longa*, a rather apolar polyphenol[118] and resveratrol, a stilbene, prevalent in the skin of raspberries, blueberries, grapes and also of peanuts, among others[119] (Table 1).

4.1.2 Polyphenols as prebiotic-like substances. Most studies on polyphenols and their metabolic products have highlighted their potential to limit the growth of pathogenic bacteria and to foster the increase of beneficial bacteria.[120] As recently reviewed by Singh,[94] microbial modulation studies with co-measured health-outcomes have included testing animals and humans and administering compounds either in isolated form, as extracts, or in food items rich in certain polyphenols. However, only a low number of human studies have been reported, in this latter review,[94] seven studies are summarized. Some of these studies are only observational, thereby precluding causal conclusions. In another recent systematic review and meta-analysis by Ma & Chen,[121] the influence of polyphenol supplementation on GM composition was scrutinized. Sixteen human intervention trials were included in their summary table. A large heterogeneity between the type of polyphenol, dosing and time of intervention was noted. Regarding type and source of polyphenols, cereals, apples, grape pomace, blueberry powder, date fruits, olive oil/thyme red wine and isolated quercetin/rutin were employed. Thus, an analysis of the effect of various polyphenol sources on *Lactobaccilus* spp., *Bifidobacterium* spp., *Bacteriodes* spp. and *Clostridium* spp. was carried out. *In vivo* studies based on different food groups found slightly significant alterations on their abundance (Table 1), enhancing *Lactobaccilus* and *Bifidobacterium* spp. while reducing *Bacteriodes* and *Clostridium.* Of note, all trials except 1 had less than 30 participants and may have been statistically underpowered. As a consequence of their findings, a daily polyphenol dose of 400 mg d^{-1} was promoted, which is achievable with a varied diet rich in plant based food items.

In a large trial conducted by Klinder *et al.*,[122] 3 groups of participants (total n = 122) consumed 2, 4 or 6 additional portions of fruits and vegetables (each for 6 weeks then switching to the next higher dose), either high or low in flavonoids, or continued their normal diet. Differences between high and low flavonoid groups were minimal regarding GM composition. Significant inverse correlations of flavonoids with *Clostridium histolyticum/perfringens*, *Bifidobacterium* spp., *Bacteroides* spp. and *Lactobacillus* spp. were found, but correlation coefficients were below 0.2, perhaps suggesting that still other factors, such as dietary fiber (though also not strongly correlated with GM), played a more important role. The often high number of confounders in trials with whole foods often impede a clear cause-effect interpretation regarding polyphenols.

Simmering *et al.*[123] compared the outcome of a one-time administration of quercetin (14 mg per kg bw.) to rutin (28 mg per kg bw.), both given pure or in form of buckwheat leaves, *versus* a placebo (n = 28). The total number of bacteria and thus fecal flora decreased during the first day of a flavonoid washout diet (61–88%), while increased again in the following intervention, with a drastic increase in the flavonoid metabolizing *Eubacterium ramulus*. However, the reduced bacterial numbers at onset were likely due to the decreased intake of dietary fibers in fruits and vegetables.

In a randomized double blinded placebo controlled trial,[124] with 494 mg *vs.* 23 mg cocoa flavanols (flavan-3-ols) per d consumed by healthy individuals during four weeks, boosted the numbers of *Bifidobacterium* spp. and *Lactobacillus* spp., but reduced pathogenic *Clostridium histolyticum* populations, related to cancer development and also IBD,[125] were found. These effects were accompanied with improvements in triglycerides and C-reactive protein in plasma, with the latter correlating with *Lactobaccillus* spp. counts. The authors proposed that the ability of *Lactobacillus* spp. to garner energy from flavanol oligomers (*i.e.* procyanidins or condensed tannins) or monomers (resulting in the formation of hydroxyphenol-γ-valerolactone metabolites) contributed to this effect, and emphasized that changes observed were comparable to previous interventions with fructo-and galacto-oligosaccharide prebiotics. This is in line with a recent clinical trial, disclosing that consuming a blackcurrant extract (672 mg d^{-1}, for 6 weeks), rich in anthocyanins, raised numbers of *Bifidobacterium* spp. and *Lactobacillus* spp., but hampered *Clostridium* spp. and *Bacteroides* spp. Also, fecal activity of β-glucuronidase (an enzyme believed to constitute a risk factor for colorectal cancer) decreased,[126] therefore proposing prebiotic and anti-cancer properties of the product. The hampering effect of polyphenols on some bacteria, including *Streptococcus* and *Prevotella* spp. has been shown *via* binding of *e.g.* condensed tannins to bacteria, causing growth inhibition and reduced protease activity,[127] and was shown to result in a shift from Gram-positive to Gram-negative, tannin resistant bacteria, at least in ruminants.[128] Gram-negative bacteria have also shown to be more resistant to antibiotics and may be less sensitive also to certain phytochemicals. This may contribute to reduced numbers of *Clostridium*, *Streptococcus*, *Enterococcus* and *Staphylococcus*, but not *Pseudomonas* (which is Gram-negative).

In addition to cocoa, polyphenols from red wine have also received some attention. However, often the effect of alcohol is not taken into account. In a study by Queipo-Ortuo *et al.*, this was considered, and participants received either red wine, alcohol-free red wine, or gin for a period of 20 days.[129] Interestingly, indeed the red wine group exhibited highest numbers of fecal *Proteobacteria*, *Fusobacteria*, *Firmucutes*, and *Bacteroidetes*, with numbers declining in the sequence red wine group > dealcoholized red wine > control > gin, suggesting that indeed red-wine polyphenols, rich in flavon-3-ols, gallic acid and anthocyanins were causing the effects, but also that perhaps alcohol aided in the solubilisation of phenolic compounds.

In addition to effects on *Bifidobacterium* spp. and *Lactobacciluls* spp, the role of *Akkermansia muciniphila* for gut health has been much emphasized in recent years. This bacterium thrives on the mucus layer, and lower numbers of these bacteria have been related to also IBD.[130] Though this may seem at first contradictory, *A. muciniphila* has likewise been

reported to stimulate mucus growth; in addition, its presence may reduce the presence of pathogenic bacteria in this layer.[130] As reviewed recently,[63] *A. muciniphila* has been related to a lower risk of T2D and inflammation, and its abundance, at least in animal models, was shown to be positively influenced by various sources of dietary polyphenols, including grape and cranberry proanthocyanidins, pomegranate ellagitannins, caffeic acid, and others. As the major source of growth for *A. muciniphila* is the mucus, and not exogenous dietary residuals, indirect effects may be the cause for this change in relative abundance. Studies in humans have, to our knowledge, not yet been reported.

Additional evidence on the interaction of polyphenols and the GM is available from animal trials. For instance, in the review by Singh *et al.*,[94] nine animal studies were presented. In these studies, quercetin, pronthocyanidin rich wine extract, coffee and caffeic acid, resveratrol, and polyphenols from algae, fungi, honey and propolis were examined. Benefits regarding GM populations were found, including improvements in the number of health-associated bacteria such as *Bacteroides*, *Lactobacillus* and *Bifidobacterium* spp., and reductions in *Clostridium* spp. In addition, associated parameters such as reduced enzymatic activity of α-glucuronidase mucinase, nitroreductase, β-galactosidase and α-glucosidase were also encountered.

4.1.3 Polyphenols and IBD. Some importance has been placed on models of IBD and improving gut health. Studies with polyphenols from fungi reduced *Firmicutes*/*Bacteriodetes* ratio and restored *Lactobacillus* spp. populations as previously reviewed.[131] The most abundant phenolics in mushrooms are *p*-hydroxybenzoic-, gallic-, vanillic-, protocatechuic-, getisic- and syryngic acids. However, mushrooms are also rich in fiber, including chitin, hemicellulose, α- and β-glucans, mannans, xylans, and galactans. Thus, the effect cannot be solely attributed to polyphenols. Similarly, polyphenols from *Prunella vulgaris* derived honey (5 g per kg bw. with approx. 300 mg per 100 g polyphenol content for 15 days) showed the same effects in rats, as well as improving histopathology.[132] Polyphenols from propolis, given at 300 mg per kg bw. for 10 days to rats reduced namely *Bacteroides* spp., in part increased richness and diversity of the population,[133] and decreased the pro-inflammatory markers MCP-1, IL-1β and IL-6. Similar positive effects were shown for the stilbene resveratrol in an animal model of IBD. Rats receiving 1 mg resveratrol per kg bw. per d for 25 days showed increased *Lactobacillus* spp. and *Bifidobacterium* spp. and reduced *Enterobacteria* spp. Body weight loss was also reduced, as well as PGE-E2, COX-2 and NO levels in the colonic mucosa. A large number of genes in the distal colonic mucosa (>2500) were also differentially regulated following the treatment.[134] Due to their antioxidant and anti-inflammatory properties, both of which are relevant for IBD, polyphenols may be a potential adjuvant candidate for IBD,[11] and their inclusion in enteral or even parenteral nutritional formulas for IBD patients has been recommended.[135]

Colon cancer, which can develop from IBD, has also been studied in animal models in relation to polyphenols and GM. In a rat study, resveratrol (8 mg per kg bw. given for 30 weeks) improved enzymatic activity related to GM dysbiosis, including mucinase, α-glucuronidase and nitroreductase,[136] however GM was not measured directly. A red wine extract rich in proanthocyanidins[137] showed to improve *Bacteroides* and *Lactobacillus* while lowering *Clostridium* spp. However, DNA strand breaks as measured by the COMET assay were not influenced by polyphenols.

Results from *in vitro* analyses are much more difficult to translate to humans, also as typically gastrointestinal digestions, which could change polyphenol composition, are not carried out prior to experiments. The majority of studies are based on inhibition assays such as in petri-dishes. Some studies involving polyphenols have shown a reduction of potential pathogens. For example, it was demonstrated that the flavone narigenin inhibits the growth and adhesion of *Salmonella typhimurium*, a diarrhoea causing bacteria, while enhancing the proliferation of the anti-inflammatory strain *L. rhamnosus* no. 299.[138]

The main bacteria phyla (*Firmicutes*, *Bacteroidetes*, and *Actinobacteria*) and their species have been shown to contain enzymes and genes coding for bile salt hydrolase. Bile salt hydrolase activity may be important for microbial survival and bile detoxification.[139] In a murine-based study, administering a high fat diet together with quercetin, ellagic acid, rutin, catechin, caffeic acid or curcumin minimized secondary bile acid levels in the stool,[140] which was explained by the growth of bacteria capable of efficiently deconjugating bile acids by use of bile salt hydrolase. Microbial metabolism and deconjugation of bile acids makes them less rapidly reabsorbed and more easily excreted into the faeces.[141] In general, bile-acids appear to constitute a decisive role in the homeostasis of the GM,[142] while high levels have been related to chronic diseases such as liver cancer[143] and IBD.[144]

4.1.4 Bacterial communication – quorum sensing. Another important function of polyphenols that has been emphasized is their potential property to act as quorum-sensing regulators or quorum-quenching molecules (QQM), as reviewed previously.[105,106] Such properties were highlighted for a variety of flavonoids, curcumin, and chlorogenic acid, among others. The most highlighted aspect as a result of this blocking of intercellular bacterial communication by small molecules, sometimes termed "bacterial pheromones" is the reduction in biofilm formation, though other factors such as sporulation and virulence factor expression are also known. Given that a critical number of bacteria are present (the quorum), the compounds inducing this sensing are typically acetylated homoserine lactone (AHL) for Gram-negative bacteria, and a variety of secreted peptides for Gram-positive bacteria. Some compounds such as a furanosyl boronated diester (AI-2) and a non-boronated diester (vA1–2) are employed by both Gram-positive and Gram-negatives. Quenching of quorum sensing can occur *via* phytochemicals resembling quorum sensors without being actual inducers, or *via* interfering with the signal receptors.

For instance, pyrogallol and related compounds have shown to have antagonistic effects on AI-2,[145] extracts from

curcuma reduced virulent gene expression in *P. aeruginosa*, and apple extracts were effective as antiquorum sensing agents in a variety of bacteria, which was related to rutin, epicatechin and hydroxycinnamic acids. Also grapefruit and citrus extracts were effective, as reviewed by Nazzaro *et al.*[106] (Table 1). Quercetin, a common polyphenol in apples, onions and grapes, also showed to inhibit biofilm formation in *P. aeruginosa*, as well as virulence factors such as procyanin, elastase and protease, together with a reduced expression of genes encoding for quorum sensing (lasI, lasR, rhlI and rhlR), at concentrations of 8 μg ml^{-1} [146] which is easily reachable in the intestine following consumption of *e.g.* approx. 100 g of apples.[147] However, all these investigations are based on *in vitro* examinations, and more research on these important mechanistic aspects is warranted. A potential specific advantage of phytochemicals acting *via* this pathway would be the ability to not kill bacteria but limiting their growth, which would not result in resistant strains, a problem of many antibiotics.

4.1.5 Further implications of polyphenols for gut health. Finally, interactions between polyphenols and other potential prebiotics have also been discussed. For example, the combination of polyphenols and polyunsaturated fatty acids (PUFAs)[104] has been proposed to promote the growth and metabolism of certain health-related bacteria. Linoleic, α-and γ-linolenic, docosahexaenoic and arachidonic acids can increase the growth and adhesion of a number of strains of *Lactobacillus* spp. and are related to immune functioning.[120] Positive interactions with polyphenols may be related to their antioxidant potential, preventing oxidation of the sensitive PUFA molecules, improving their bioavailability and biological – including intestinal – effects.

In turn, the GM have also shown to modulate bioactive constituents originating from polyphenols. However, the full extent of this modulation is beyond the scope of this review. This "two-way effect" of polyphenols has been highlighted in a review focussing on the interactions of polyphenols, GM and obesity.[148] Examinations in germ-free, human microbiota-associated mice and *in vitro* fermentation studies show that native polyphenols are heavily metabolized by the colonic bacteria, undergoing *e.g.* ring fission, deglycosylation, hydrolysis, deglucuronidation, and demethylation, among other, which can affect their bioactivity.[149] A prominent example for polyphenols are the production of equol out of the isoflavone daidzein,[150] which has been discussed as having superior health benefits than the native parental isoflavone, due to higher affinity for the 17-β-estradiol receptor. However, only about 1/3 of the individuals may be able to produce this metabolite from daidzein. Thus, such inter-individual variabilities in microbial metabolism are expected to result in significant effects regarding polyphenol-related health benefits.[29] For example, in a recent study, GM appeared to influence phenolic acid bioavailability which in turn was associated with cognitive effects in mice.[151]

Taken together, most of the effects of polyphenols may be related to stimulating the abundance of bacteria which have been associated with health beneficial effects, due to *e.g.* the production of SCFAs, including *Bifidobacterium* spp. and *Lactobacillus* spp. This may indirectly reduce potential pathogenic bacteria such as *Clostridium* spp. Additional effects may be related to stimulating *A. muciniphila*, involved in mucus layer integrity, the reduction of α-glucuronidase, increased bile salt excretion and finally on impeding intercellular bacterial communication *via* quorum quenching.

4.2. Lignans

Although broadly classified as polyphenols, lignans have been defined as natural phytoestrogens due to their steroid-like chemical structure. Positive health effects ascribed to lignans entail a decreased risk of heart disease, osteoporosis, menopausal symptoms, and breast cancer.[152] Several studies have shown that the flaxseed lignan secoisolariciresinol diglucoside and the mammalian lignin metabolites enterodiol and enterolactone have antioxidant effects which may contribute to the proposed health benefits.[153] More impressively, higher excretion of urinary enterolactone has been shown to be associated with reduced all-cause mortality in a prospective study based on the US-NHANES cohort including over 6000 adults age 40 or older, pointing out to a protective effect with higher dietary intake of lignans and the ability to convert them.[154]

The major contribution to dietary intake comes from sesame, flax seeds and nuts,[152] though their dietary intake in most western countries may not considerably surpass 1 mg d^{-1}. One study estimated the intake of secoisolariciresinol and matairesinol at approx. 150 μg d^{-1}.[155] In another study, for enterodiol, syringaresinol, enterolactone, medioresinol, pinoresinol, lariciresinol, matairesinol and secoisolariciresinol the average intake was reported at around 1.6 mg d^{-1}.[156]

Diets rich in flaxseed have shown to increase the production of GM-derived enterolignans in a mouse model, leading to increased tissue and plasma levels of sulfate and glucuronide conjugates (the predominant flax-derived lignan metabolites).[157,158] Indeed, these compounds can be heavily metabolized by the GM. For instance, the processing of pinoresinol glucoside to enterolactone requires the successive steps of deglycosylation, demethylation, dehydroxylation and dehydrogenation.[159] Bacteria proposed to be involved in the production of enterolactone included *Peptostreptococcus productus* and *Clostridium coccoides*, as well as bacteria of the *Atopobium* genus such as *Eggertella lenta.*[160] Interestingly, there is evidence that humans able to produce enterolignan show a higher diversity of GM,[161] but it is unknown if such a status can be modified.

In a human study, the microbial metabolite enterolactone (measured in urine) was significantly related to lower incidence of T2D in US women.[162] The enterolignans enterodiol and enterolactone may interact with hormonal receptors such as 17-β-estradiol, potentially having a positive influence on breast cancer risk, especially after menopause.[77] Regarding direct effects on the microbes of the GM, lignans *in vitro* have been shown to be active against certain pathogenic strains,

including *Streptococcus salivarius S. mitis*, *Enterococcus faecalis*, *Candida albicans.*[163]

A randomized clinical trial (RCT) in healthy adults evaluated changes in GM composition following the supplementation of a flaxseed lignan extract (50 mg secoisolariciresinol diglucoside per d). Unexpectedly, the supplementation failed to alter fecal microbial community composition. In contrast, low enterolactone (formed from secoisolariciresinol) secreters showed in biopsies a lower activation of anti-inflammatory pathways in human colonic mucosa, such as growth factor β and IL-10 receptor.[164] In another clinical trial, nine subjects received 0.3 g kg^{-1} d^{-1} for one week of flaxseed. This supplementation increased enterolignan formation but did not considerably change fecal metabolome and prevalent bacterial communities.[165] However, in a recent pilot study involving fecal collections and *in vitro* fermentations with lignans in oilseeds clearly showed alterations of the microbiota, namely of *Clostridiaceae*, and *Klebsiella* and *Collinsella*, with the latter one also proposed to be involved in the production of equol from the isoflavonoid daidzein.[166]

In a mouse experiment, sesamine administration rich in lignans (50 mg per kg bw.) resulted in reduced depression and anxiety, together with reductions in CNS inflammatory processes (IL-6 and TNF-α reductions), and these changes were related to improved gut barrier properties, lower plasma LPS levels, and enhanced the abundance of *Bacteroidales*,[167] possibly highlighting influences on the gut-brain axis.

In conclusion, it is acknowledged that the microbiota plays a vital role in the transformation of lignans and that the intake of the latter are associated with health benefits. However, a strong influence of positive changes of the GM as a causal mechanistic pathway by which lignans exert their health benefits has not yet been clearly demonstrated in humans.

4.3. Carotenoids

Carotenoids are generally tetraterpenoid plant pigments that provide red, orange, and yellow color to plants. A variety of C-30 and C-50 carotenoids of bacterial and fungal origin also exist.[168] Some carotenoids, specifically termed the provitamin A carotenoids, are capable of forming vitamin A following their absorption. Carotenoids have been widely associated with antioxidant capabilities, as they can quench singlet oxygen and aid in the prevention of lipid-peroxidation, offering cell-membrane protection.[169] The most abundant dietary carotenoids include α- and β-carotene, β-cryptoxanthin, lutein, and lycopene.

As fat-soluble bioactive compounds bound within plants, either in crystalline form or dissolved in oil, the bioavailability of carotenoids can be low and variable, depending on food sources and processing (10–40%).[96] Thus, the majority are likely to reach the colon intact and may be fermented by the GM.[170] Common dietary sources include green leafy vegetables (*e.g.* spinach) and red-colored fruits (*e.g.* tomatoes and pink grapefruit). Though their dietary intake is much lower than that of polyphenols, typically in the magnitude of 2–20 mg d^{-1},[171,172] they are the most abundant lipid phytochemicals in the blood plasma, with concentrations of approximately 0.5 to 2 μM.[173] Both their dietary intake and their circulating plasma concentrations have been associated with reduced disease incidence and even total mortality.[6]

Carotenoids have been shown to possess bactericidal properties. For example, an extract rich in violaxanthin, zeaxanthin and lutein reduced *H. pylori* numbers at a minimum inhibitory concentration (MIC_{50}) of 36 μg mL^{-1} (concentrations reachable *in vivo* in the gut following a carotenoid rich meal), similar to the antibiotic metronidazole.[174] Carotenoids extracted from citrus peel (*Shatian pummelo)* showed activity against primarily *E. coli*, but also against *B. subtilis*, *S. aureus*, *Aspergillus niger*, among others (Table 1),[99] with MICs between 19 to 140 μg ml^{-1} representing high but physiological plausible concentrations in the gut. Lycopene in tomato oleorisin (2%) inhibited especially the growth of *P. aeruginosa* (MIC_{50}: 150 μg mL^{-1}), while MICs for other bacteria such as *E. coli* were higher.[175] In another examination, carotenoid-rich extracts (from annatto, carrot, tomato, *ca.* 0.1–1 mg g^{-1} carotenoids) had antibacterial properties against *S. aureus.*[176] However, a truly selective suppression of potential pathogenic bacteria remains to be shown, especially *in vivo*.

Some data is available from animal trials. In a recent review, Lyu *et al.* highlighted potential interactions between carotenoids and the microbiota.[26] Among other, carotenoids may enhance IgA production, preventing gut dysbiosis, *via* its role in recognizing and coating certain bacteria, preventing their infiltration through the epithelial gut barrier. In a study with weanling mice, giving yeast enriched with astaxanthin increased the number of IgA antibody-secreting cells after 7 days, and enhanced mRNA expression of the IgA-C-region in the jejunum and ileum after 14 days[177] (the effect on the colon was not investigated). The effect likely involved vitamin A active compounds binding to the RARβ receptor, which has been shown to play an important role in the intestinal epithelium,[178] promoting IL-17 production and also serum amyloid A, $CD4^+$ T-cell homing and production of IgA.

Capsaicin, a carotenoid found in red pepper, when fed to mice at 2 mg kg^{-1} for 12 weeks (translating to *ca.* 0.16 mg kg^{-1} for humans[179] which is physiological), showed to alter gut microbiota,[180] which was related to anti-obesity effects as transmitted *via* SCFAs. Treated mice had increased numbers of *Akkermansia*, *Prevotella* and *Bacteroides*, and reduced counts of *Escherichia*, related to enhanced acetate and propionate concentrations, combined with reduced weight gain, lower food intake, and lowered blood lipids and glucose/insulin. Similar results for capsaicin were shown by Shen *et al.*[181] Supplementing astaxanthin to mice,[26] at 0.04% in the diet, for 8 weeks, reduced the number of *Proteobacteria* spp. and *Bacteriodes* spp. in BCO2 knock-out mice, while strongly increasing *Actinobacteria* spp. and *Bifidobacterium* spp. in wild-type mice. Also, a study in beta-carotene-15,15′-oxygenase 1 (BCO1) and beta-carotene-9′,10′-oxygenase 2 (BCO2) double knockout mice (in order to prevent rapid formation of carotenoid metabolites) showed a protective effect of lycopene-rich tomato powder feeding for 24 weeks.[182] Supplementation decreased the development of hepatic inflammatory foci and

the expression of pro-inflammatory biomarkers, including inducible NO synthase, monocyte chemoattractant protein-1, IL-12α, IL-6 and IL-1β. The same study revealed that tomato powder administration stimulated bacterial richness and diversity, and reduced the fraction of the genus *Clostridium* and *Mucispirillum*.[182] In a study on fucoxanthin, a carotenoid from see-weed, 14 days of administration decreased cecal *Firmicutes*/*Bacteriodetes* ratio and enhanced *Akkermansia* spp. in mice.[183] In another investigation, pigs on a low-protein diet were fed or not carotenoid fortified corn (20% in the diet, rich in zeaxanthin, total carotenoids *ca.* 10 μg g^{-1}) for 30 days.[184] 16S rRNA sequencing and differential abundance analysis on fecal samples showed that about 160 amplicon sequence variants differed in abundance compared to the control treatment, though proteins more strongly influenced microbiota compared to carotenoids. The effect of astaxanthin, a carotenoid present in algae and seafood, was studied in a mouse model of alcoholic fatty liver disease.[185] In this examination, giving 50 mg of astaxanthin per kg bw. each day for 12 weeks significantly reduced lipid accumulation and serum markers of liver injury, and reduced species of *Bacteroidetes*, *Proteobacteria*, while increasing *Verrucomicrobia* and *Akkermansia*.

Only few human studies exist employing carotenoids. In a study by Li *et al.* in subjects with cystic fibrosis, dietary intake of beta-carotene was related to a higher *Firmicutes*/*Bacteroides* ratio,[186] though whether beta-carotene was merely an indicator for a diet rich in fiber and other antioxidants or had independent effects could not be deduced. In another study, a mixture of blackcurrant powder, lactoferrin and lutein (unspecified amount) significantly increased *Bifidobacteria* and *Lactobacilli* populations while reducing levels of β-glucuronidase producing *Bacteroides* spp. and *Clostridium* spp. (reducing β-glucuronidase activity associated with colonic cancer) in the gut.[126] Most notably, in a recent intervention trial, the effect of lycopene (7 and 30 mg d^{-1}, for 1 month), reachable *via* a diet rich in tomato products or supplements, on the microbiota of 30 subjects with obesity was investigated.[80] Lycopene showed dose-dependent increases of fractions of *Bifodobacterium longum* and *B. adolescentis*. In addition, dose-dependent favourable reductions of LDL-C, LDL-peroxidase, and MDA/thiobarbituric acid reactive substances (TBARS) as oxidative stress markers were seen.

In contrast to the effects of carotenoids on the microbiota, nothing is known regarding the effect of microbiota on carotenoid metabolites.[187] In a recent master dissertation at Ghent University, an association was observed between higher *Bacteroides* spp. numbers and a higher carotenoid release from the food matrix in an *in vitro* fermentation assay,[188] suggesting altered colonic availability of carotenoids. For carotenoids, it is difficult to estimate colonic degradation, and no colonic metabolites have been reported, though surely a certain fraction of carotenoids are broken down.[189,190] Interestingly, even production of carotenoids by the microbiota has been suggested, but remains to be re-confirmed.[191]

In summary, carotenoids have been shown to improve the fraction of *Bifidobacterium* spp. and *Lactobacillus* spp., in addition to decrease the ratio of *Firmucutes*/*Bacteroides*. Additional mechanism may include enhanced *Akkermasia* presence and the reduction of β-glucuronidase and enhanced IgA production, though still very little data is available. An *in silico* examination indicated that zeaxanthin would be an efficient quorum quenching molecule to prevent biofilm formation of *P. aeruginosa*,[192] but this remains to be confirmed by *in vitro* or *in vivo* tests.

4.4. Phytosterols and phytostanols

Phytosterols and phytostanols are bioactive components and due to their lipophilicity present in vegetable oils, nuts, seeds and cereals. They have structural similarity to cholesterol and thus a steroid backbone. Daily consumption of foods rich in phytosterols/phytostanols has shown to decrease total cholesterol and LDL-C,[193] likely in part due to competitive mechanisms for the micellization and/or further absorption of cholesterol.[81] An EFSA-granted health claim exists.[194] Research indicates they may have antioxidant capability as well.[195] Typical dietary intake of these compounds is around 300 mg d^{-1},[117] and their absorption is low (2–3%,[196] thus their majority would also be passed on to the colon. The most common phytosterols/phytostanols present in the human diet are sitosterol, campesterol, sitostanol and campestanol.

To our knowledge, human intervention trials with a focus on GM do not exist, except for the study by Baumgartner *et al.*[197] In their study with 13 healthy subjects receiving 3 g d^{-1} of plant stanols for 3 weeks resulted in no different GM composition or diversity compared to a control group. In a rat intervention study, high doses of phytosterol esters (0.10 g per 100 g bw.) significantly exalted the fraction of *Bacteroidetes* spp. and *Anaerostipes* spp.[198] Consumption of sitostanol was shown to be directly correlated with the quantity of phylum *Bacteroidetes*, while consumption of campestanol has been inversely related with *Eubacterium ventriosum* (phylum *Firmicutes*),[199] a producer of SCFA, especially butyrate.[138] In a study by Huang *et al.*,[200] tempeh administration rich in β-sitosterol reduced insulin resistance, blood glucose, HbA1C, blood lipids and increased SCFA content in the feces of rats fed a HFD.

Fermentation trials *in vitro* have shown that high doses of plant sterols stimulated the fraction of proportion of *Erysipelotrichaceae* spp.[201] This was well-correlated with cholesterol metabolism and earlier found to be involved in human lipid metabolism with high levels in subjects with obesity[202] and increased the abundance *Eubacterium hallii*, a well known butyrate producer.[203] While for cholesterol at least 5 degradation pathways by the GM exist, the further metabolism of phytosterols/phytostanols in the gut is unclear, though some metabolites have been detected in feces which may be of GM origin.[196] It also appears that the GM preferentially metabolizes plant sterols compared to cholesterol, and that the addition of phytosterols to *in vitro* fermentations in the Tim-2 digester enhance SCFA production, associated with increased *Firmicutes* spp.[204]

Overall however, there is still limited evidence on the interaction of phytosterols/phytostanols and GM.

4.5. Alkaloids

Alkaloids are nitrogenous bases synthesized by numerous organisms including plants, fungi, bacteria and animals. The different alkaloids may be categorized into several distinct classes according to their structure: pyrrolizidine alkaloids (*e.g.* jacobine), tropane alkaloids (*e.g.* cocaine, atropine, scopolamine), alkaloid derivatives of lysine such as piperidine alkaloids (*e.g.* coniine), alkaloid derivatives from tyrosine such as isoquinoline alkaloids (*e.g.* papaverine, idrastine), those derived from tryptophan such as indole alkaloids (*e.g.* ergotamine, ergotin, strychnine, and reserpine), polycyclic alkaloids (*e.g.* nicotine), purine alkaloids (*e.g.* caffeine, theophylline, theobromine) and others.[205] Alkaloids have the reputation to be a curse and a blessing at the same time, because they have been associated with health beneficial effects (*e.g.* cinchona bark alkaloids such as the anti-malaria quinine[206]) while others may be extremely poisonous (*e.g.* ergot).[207] Due to their large variety and broad distribution, it is difficult to establish their daily intake. However, caffeine, theobromine, theophylline, piperine (present in peppers) and nicotine may be the most prominent alkaloids consumed, in amounts of up to a few 100 mg d^{-1}, with piperine around 15–30 mg d^{-1}, and possibly around 100 mg d^{-1} methylxanthines such as caffeine.[205]

Some information is present on the effect of caffeine on the GM. In a mouse model of the metabolic syndrome, 16 weeks of coffee intake did not revert damage regarding the Gram positive/negative ratio but altered the abundance of 6 genera including *Prevotella*,[208] associated with increased systemic inflammation in mice and improved SCFA production.[209] It is important to note that coffee also contains polyphenols, which could have contributed to the observed effects. The effects have recently been shown also in humans subjects, in an a small-scale observational study with 34 participants.[210] Caffeine consumption *via* FFQ was associated with larger diversity of GM and increased *Faecalibacterium* spp. and *Roseburia* spp., though decreasing *Erysipelatoclostridium* spp. In a small-scale intervention study with healthy subjects,[211] consuming 3 cups of coffee for 3 weeks, only small overall changes in the microbiota were observed, but included increased abundance of *Bifidobacterium* spp. after this period compared to study onset. As caffeine consumers are also known to have a lower risk for developing T2D[212] than non-consumers, it cannot be excluded that health benefits are in part exerted *via* the GM. However, as similar health benefits were also seen in the same meta-analysis for decaffeinated coffee, the effects may be rather attributable to other ingredients such as polyphenols.

Some alkaloids have shown cardio-protection and anti-tumoral properties, as well as antibacterial and anti-viral effects.[213] Various alkaloids show promising antioxidant potential, with one study indicating it may exceed that of some phenols.[214,215] The alkaloid sanguinarine, found in bloodroot plant and poppy, has been shown to hamper bacterial adherence to the surface of teeth by perturbing the FtsZ Z-ring, a key prokaryote protein present in almost every bacteria and playing a part in cell division, and bacteria-induced cytokines.[216] Another alkaloid, berberine, available as a supplement and obtained from *e.g. Berberis vulgaris* is known to lower blood lipid and glucose levels.[217] This may be due to the production of SCFAs produced in the colon.[218]

Piperine was shown in an animal model of arthritis to possess anti-inflammatory properties, reducing arthritis.[219] Its antimicrobial activities were summarized recently,[220] and included, *in vitro*, at rather high concentrations of 3–100 mg ml^{-1} activity against the fungi *Candida albicans*,[221] while lower concentrations of 0.1–0.6 mg ml^{-1} were active against *P. aeruginosa.*[222] Inhibitions were also shown at concentrations of 2 mg ml^{-1} against the pathogens *S. aureus*, *B. subtilis*, *Salmonella* spp. and *E. coli.*[223] Similarly, piperine (*e.g.* from black pepper) and reserpine (*e.g.* in devil pepper aka *Rauvolfia serpentine*) have shown an action *in vitro* (0.5, 5, 10, 50 mg mL^{-1}) against *E. coli*, being able to decrease bacterial motilities and biofilm formation. Decreased expressions of the flagellar gene (fliC) and motility genes (motA and motB) were demonstrated.[224] Moreover, piperine (*in vitro* 0.5 to 10 μg mL^{-1}) showed an increase in the infiltration of the antibiotics ciprofloxacin and azithromycin into *E. coli* biofilms and thus increased their potential to dissipate existing biofilms, a situation which may also be relevant *in vivo*,[224] and would again suggest quorum sensing inhibition.

However, overall, the role of the diverse alkaloids and any potential influences on the GM are only poorly understood, are often superimposed by confounding factors, and few human-based data exist. In addition, some are rather completely absorbed, such as caffeine and piperine,[225] and their effect is thus not likely to be based on direct metabolism by the GM.

4.6. Other phytochemicals

4.6.1 Glucosinolates and sulphur containing compounds. Glucosinolates are sulphur-containing compounds highly abundant in the *Brassicaceae* family (*e.g.* cabbage, Brussels sprouts, broccoli, cauliflower).[226] Their intake from the diet is hard to gauge due to the large concentration variability of these compounds in their major dietary sources. Their consumption in Europe has been reported to be in the range of 4.7 to 65 mg d^{-1}.[227] Health properties attributed to these compounds include down-regulation of pro-angiogenic molecules and thus anti-tumor effects,[228] with some evidence of antioxidant function.[229]

Among the most significant classes of glucosinolate secondary metabolites (after hydrolysis by plant based myrosinase in the stomach and the small intestine or later by the GM) are isothiocyanates (ITCs). Quite possibly, their most renowned property is their bactericidal effect.[230] Li *et al.* described *in vivo* and *ex vivo* the relation between the composition of gut bacterial community and the metabolism of glucosinolate, following supplementation with broccoli-rich glucosinolates.[231] In this study, it was proposed that degradation of glucosinolates,

effectuating microbiota *ex vivo*, could be related to bacterial metabolism *in vivo*, but they could not establish a direct association with specific bacteria. Liu *et al.*[232] demonstrated in rats that the cecal microbiota changes following broccoli consumption, toward a GM with a higher potential for glucoraphanin (a glucosinolate) hydrolysis to isothiocyanates. Interestingly, this was a reversible phenomena, but demonstrating the adaptability of the GM to metabolize certain phytochemicals.

In human volunteers, consuming a cruciferous-rich diet *vs.* a diet low in fiber and vegetables, changes in a variety of bacteria including *Eubacterium hallii* which were earlier recognized to be related with cruciferous vegetable digestion were noted,[233] though the extent of change due to isothiocyanates remains questionable (Table 1).

Another well-regarded sulphur-containing phytochemical is alliin, a derivative of the amino acid cysteine, present in garlic and onions.[234] This molecule is rapidly processed upon cell damage by alliinase into allicin. The latter has been associated with a number of health benefits, especially for cardiometabolic such as diabetic protection, due to the associated antioxidant and immunomodulatory effects, as reviewed by Salehi *et al.*[235] In a meta-analysis of RCTs, garlic supplements were able to show blood-pressure reduction.[236] Similarly, a meta-analysis of RCTs showed reductions in fasting blood glucose with garlic extracts.[237] In mice, allicin improved gut barrier properties,[238] and also changed the GM toward fewer numbers of *Streptococcus*, *Aeromonas*, *Vibrio*, *Corynebacterium*, *Marinomonas*, among other, was observed, and explained by the anti-microbial activity of allicin. This antimicrobial activity is recognized for some time,[239] including activity against Gram-positive and Gram-negative bacteria, certain fungi such as *C. albicans*, and also anti-parasitic and anti-viral activity. Other *in vitro* trials showed a special resistance of *Lactobacillus* spp. against garlic.[240] However, care should be taken as onions and garlic also contain inulin (and other fructans), a well-known prebiotic. When obese mice were treated with allicin they showed lowered weight gain and significantly increased numbers of *Akkermansia* spp. (Table 1).[241] While not fully understood, the antimicrobial effects of allicin appear to be a combination of oxidative stress *via* the depletion of glutathione, together with enzyme inactivation *via S*-allylmercapto modification of cysteine residues.[242]

4.6.2 Terpenoids, curcumin, and aroma active compounds. Terpenoids are synthesized from isoprene (five-carbon) units. The majority of terpenoids are of multi-cyclic structure, differing in their functional groups and carbon backbones. Evidence supports the ability of terpenoids to provide protection against ROS associated with several chronic diseases.[243] Some volatile oils (*e.g.* anise, caraway, cinnamon bank, juniper and rosemary) are traditionally used against gastrointestinal disorders,[244] but so far there is insufficient evidence confirming interactions between these compounds and the GM.[244] Provisional *in vitro* and clinical data suggests effects of peppermint oil on small intestinal bacterial outgrowth.[244] Furthermore, an *in vivo* study on lean rats showed that administering rosemary extract (highly concentrated in carnosol, carnosic acid and phenolic di-terpenes) modified the composition of cecum microbiota, *i.e.* increasing fecal fiber elimination and suppressing β-glucosidase activity.[245] Employing a similar extract of rosemary leaves (60% carnosic acid),[246] the authors discovered that their supplementation reduced GM dysbiosis and inflammatory reactions in mice, including a decreased diversity of GM (reduction of *Bacteroidetes* spp. and *Proteobacteria* spp., but promoting *Lactobacillus* spp. and *Firmicutes* spp.), also hampering expression of IL-1β, TNF-α and NF-κB in LPS stimulated BV-2 cells.

Other medicinal extracts containing oils rich in sesquiterpenes used to treat GI disorders are *Curcuma longa* and *Curcuma zanthorrhiza*. As curcumin is typically only poorly absorbed, the major fraction is expected to reach the GM.[247] In fact, it has been shown that the metabolism of curcumin by the GM is complex, resulting in a number of metabolites. In one study, 23 metabolites were detected *in vitro* due to fermentation by human GM, following reduction, methylation, demethoxylation, acetylation and hydroxylation reactions.[248]

A double-blinded pilot study performed in healthy human participants showed that extracts modulated the GM.[249] The control group exhibited a generally diminished number of microbiota species (by 15%). Individuals receiving turmeric showed a slight increase of 7%. These changes in the turmeric group seemed to depend on the catabolism of polysaccharide components. An increase of *Bacteroides*, *Bifidobacterium*, *Alistipes*, and *Parabacteroides* spp. (all encoding for glycosyl hydrolases) was noted. Individuals taking curcumin revealed a mean species number increase of 69%. In an interesting small-scale human trial with 8 participants, individuals consumed curry with or without turmeric (*i.e.* curcumin), and breath analysis were conducted in the following 6 h. These showed higher hydrogen concentrations in the turmeric receiving group, suggesting enhanced carbohydrate fermentation.[250] The potential anti-oxidant properties of enhance hydrogen concentrations in the gut were also emphasized. In addition, a smaller small-bowel transit time was found. Ng *et al.*, in a meta-analysis of five clinical trials reported significant positive effects of curcumin-containing products against irritable bowel syndrome. Curcumin alleviated pain and improved quality-of-life in patients with moderate symptoms, explained in part also *via* the antioxidant and anti-inflammatory qualities of curcumin.[251]

Also *Zingiber officinalis* contains sesquiterpenes. A murine-based study showed that ginger administration changed the GM composition, increasing species of the *Bifidobacterium* genus and those producing SCFAs (*Alloprevotella* and *Allobaculum*), also increasing fecal SCFA concentrations.[252]

These examples emphasize that there are a large number of potential plant-derived compounds out there yet to be discovered and utilized for their GM modulating properties. Especially promising first results were obtained by consuming cruciferous vegetables rich in glucosinolates, which are metabolized to isothiocyanates; and curcumin.

5. Conclusions and future directions

There is therapeutic promise that phytochemicals may impact, *via* a variety of different mechanisms, the plasticity of the GM (Fig. 1). These changes of the GM have been related to a variety of cardiometabolic, neurodegenerative and even cancer-related diseases such as IBD. Such GM actions of phytochemicals are a much less investigated route *via* which these compounds could exert their health benefits, in addition to antioxidant and anti-inflammatory properties, acting directly on the host. However, most published articles in this domain are *in vitro*, animal, or human studies with small sample size and reviews thereof. Thus, well-controlled human trials incorporating metagenomic and metabolomic analysis are needed to better characterize the potential metabolic effects of phytochemical administration on the GM. Likewise, for many phytochemicals, their metabolic pathway including changes caused by the GM is very limited. It is therefore difficult to judge which mechanisms are the predominant ones involved in altering GM composition toward a more health-associated one, and this likely depends on the type of secondary plant compound and even concentration related aspects may play a role. For polyphenols, also due to their higher amounts, prebiotic effects may be most important, while for carotenoids influences *via* IgA and perhaps *via* transcription factors and indirect effects on the microbiota may be predominant. For others, such as glucosinolates and allicin, bactericidal properties may shift GM composition.

Consequently, in addition to dietary fiber, phytochemicals may potentially be incorporated in microbiome-based medical approaches as an integral part of precision medicine. However, several areas remain unexplored. For example, so far there are few or no original studies evaluating the effects of phytochemicals on the gut-brain axis.[107] There is also evidence showing improvements on allergy response modulated by the GM,[120] possibly *via* strengthening the gut barrier, however, this has not been tested directly with the use of phytochemicals. Other health conditions deserving investigation of the effects of phytochemicals and the GM include obesity and body composition,[79] cardiometabolic health and associations with chronic diseases such as T2D or hypertension.

The current knowledge concerning the relationship between phyto-therapeutics and the intestinal flora has focused mainly on the study of a few selected polyphenols. However, there remain many more phytochemicals present in the diet which are worthwhile to receive further attention. Due to the potential synergistic effects between various phytochemicals, even between different classes, combinations of phytochemicals should be investigated in order to have a more extensive understanding of their widespread impact on the GM and health. Finally, a much better understanding of the impact of individual bacterial genera and health effects is needed. Toward this end, studying not only the presence of the bacteria and their numbers, but possibly also more function-related aspects such as by metabolomics approaches would likely give novel insights into the interaction of GM and phytochemicals.[253]

In summary, phytochemicals impact the GM through a variety of means, including antioxidant, anti-inflammatory, prebiotic, bactericidal, immunologic, quorum-quenching and proliferative functions. It is evident from the lack of human trials that much is still unknown regarding the different phytochemical types and their specific functions in relation to GM. More long-term and well-designed intervention trials with multi-omics approaches integrating metabolomics, metagenomics and proteomics – both of the host and the GM – and in relation to specific diseases may be promising in revealing further insights into open questions in this domain.[254] The findings included in this review suggest the design of therapeutic adjuvant strategies for phytochemicals in chronic diseases are needed.

Author contributions

The author responsibilities: GD, AB and TB conceptualized the article. GD and AB interpreted information and were in charge of original draft preparation. MI, HS, MRLF and TB provided further input to the manuscript. TB has final responsibility for all parts of this manuscript.

Funding

This research received no external funding.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgements

The authors give special thanks to Hannah Heath, California Polytechnic State University, San Luis Obispo, for assistance with the figure illustration.

References

1 D. Sivakumar, L. Chen and Y. Sultanbawa, A comprehensive review on beneficial dietary phytochemicals in common traditional Southern African leafy vegetables, *Food Sci. Nutr.*, 2018, **6**, 714–727.

2 A. Ranjan, S. Ramachandran, N. Gupta, I. Kaushik, *et al.*, Role of Phytochemicals in Cancer Prevention, *Int. J. Mol. Sci.*, 2019, **20**, 4981.

3 R. M. Pop, A. Popolo, A. P. Trifa and L. A. Stanciu, Phytochemicals in Cardiovascular and Respiratory Diseases: Evidence in Oxidative Stress and Inflammation, *Oxid. Med. Cell. Longev.*, 2018, **2018**, 1603872.

4 M. Bacanli, S. A. Dilsiz, N. Başaran and A. A. Başaran, Effects of phytochemicals against diabetes, *Adv. Food Nutr. Res.*, 2019, **89**, 209–238.

5 F. Francini-Pesenti, P. Spinella and L. A. Calò, Potential role of phytochemicals in metabolic syndrome prevention and therapy, *Diabetes, Metab. Syndr. Obes.: Targets Ther.*, 2019, **12**, 1987–2002.

6 T. Bohn, Carotenoids and markers of oxidative stress in human observational studies and intervention trials – implications for chronic diseases, *Antioxidants*, 2019, **8**, E179.

7 J. Bouayed and T. Bohn, Exogenous antioxidants - Double-edged swords in cellular redox state: Health beneficial effects at physiologic doses versus deleterious effects at high doses, *Oxid. Med. Cell. Longev.*, 2010, **3**, 228–237.

8 T. Bohn, Q. Tian, C. Chitchumroonchokchai, M. L. Failla, *et al.*, Supplementation of test meals with fat-free phytosterol products can reduce cholesterol micellarization during simulated digestion and cholesterol accumulation by Caco-2 cells, *J. Agric. Food Chem.*, 2007, **55**, 267–272.

9 J. H. Dumolt and T. C. Rideout, The Lipid-lowering Effects and Associated Mechanisms of Dietary Phytosterol Supplementation, *Curr. Pharm. Des.*, 2017, **23**, 5077–5085.

10 D. Desmawati and D. Sulastri, Phytoestrogens and Their Health Effect, *Open Access Maced. J. Med. Sci.*, 2019, **7**, 495–499.

11 A. Kaulmann and T. Bohn, Carotenoids, inflammation, and oxidative stress–implications of cellular signaling pathways and relation to chronic disease prevention, *Nutr. Res.*, 2014, **34**, 907–929.

12 A. Kaulmann and T. Bohn, Bioactivity of polyphenols – preventive and adjuvant strategies toward reducing inflammatory bowel diseases – promises, perspectives, and pitfalls, *Oxid. Med. Cell. Longev.*, 2016, **2016**, 9346470.

13 J. Martel, D. M. Ojcius, Y.-F. Ko and J. D. Young, Phytochemicals as Prebiotics and Biological Stress Inducers, *Trends Biochem. Sci.*, 2020, **45**, 462–471.

14 J. Durack and S. V. Lynch, The gut microbiome: Relationships with disease and opportunities for therapy, *J. Exp. Med.*, 2019, **216**, 20–40.

15 C. Ferreira, A. Vieira, M. Vinolo, F. Oliveira, *et al.*, The Central Role of the Gut Microbiota in Chronic Inflammatory Diseases, *J. Immunol. Res.*, 2014, **2014**, 689492.

16 A. Santoro, R. Ostan, M. Candela, E. Biagi, *et al.*, Gut microbiota changes in the extreme decades of human life: a focus on centenarians, *Cell. Mol. Life Sci.*, 2018, **75**, 129–148.

17 R. Sender, S. Fuchs and R. Milo, Revised Estimates for the Number of Human and Bacteria Cells in the Body, *PLoS Biol.*, 2016, **14**, e1002533.

18 M. A. Conlon and A. R. Bird, The impact of diet and lifestyle on gut microbiota and human health, *Nutrients*, 2014, **7**, 17–44.

19 R. Haque, Human intestinal parasites, *J. Health Popul. Nutr.*, 2007, **25**, 387–391.

20 M. Lecuit and M. Eloit, in *The Microbiota in Gastrointestinal Pathophysiology*, ed. M. H. Floch, Y. Ringel and W. Allan Walker, Academic Press, Boston, 2017, pp. 179–183.

21 V. Bocci, The neglected organ: bacterial flora has a crucial immunostimulatory role, *Perspect. Biol. Med.*, 1992, **35**, 251–260.

22 I. Sekirov, S. L. Russell, L. C. Antunes and B. B. Finlay, Gut microbiota in health and disease, *Physiol. Rev.*, 2010, **90**, 859–904.

23 L. Beaugerie and J. C. Petit, Microbial-gut interactions in health and disease. Antibiotic-associated diarrhoea, *Best Pract. Res., Clin. Gastroenterol.*, 2004, **18**, 337–352.

24 E. N. Bergman, Energy contributions of volatile fatty acids from the gastrointestinal tract in various species, *Physiol. Rev.*, 1990, **70**, 567–590.

25 B. Wang, M. Yao, L. Lv, Z. Ling and L. Li, The Human Microbiota in Health and Disease, *Engineering*, 2017, **3**, 71–82.

26 Y. Lyu, L. Wu, F. Wang, X. Shen and D. Lin, Carotenoid supplementation and retinoic acid in immunoglobulin A regulation of the gut microbiota dysbiosis, *Exp. Biol. Med.*, 2018, **243**, 613–620.

27 T. Zuo and S. C. Ng, The Gut Microbiota in the Pathogenesis and Therapeutics of Inflammatory Bowel Disease, *Front. Microbiol.*, 2018, **9**, 2247.

28 K. Atarashi and K. Honda, Microbiota in autoimmunity and tolerance, *Curr. Opin. Immunol.*, 2011, **23**, 761–768.

29 M. L. Battson, D. M. Lee, T. L. Weir and C. L. Gentile, The gut microbiota as a novel regulator of cardiovascular function and disease, *J. Nutr. Biochem.*, 2018, **56**, 1–15.

30 E. A. Murphy, K. T. Velazquez and K. M. Herbert, Influence of high-fat diet on gut microbiota: a driving force for chronic disease risk, *Curr. Opin. Clin. Nutr. Metab. Care*, 2015, **18**, 515–520.

31 S. C. Di Rienzi and R. A. Britton, Adaptation of the Gut Microbiota to Modern Dietary Sugars and Sweeteners, *Adv. Nutr.*, 2019, **11**, 616–629.

32 C. Duvallet, S. Gibbons, T. Gurry, R. Irizarry and E. Alm, Meta analysis of microbiome studies identifies shared and disease-specific patterns, *Nat. Commun.*, 2017, **8**, 1784.

33 Y. Ji, Y. Yin, L. Sun and W. Zhang, The Molecular and Mechanistic Insights Based on Gut-Liver Axis: Nutritional Target for Non-Alcoholic Fatty Liver Disease (NAFLD) Improvement, *Int. J. Mol. Sci.*, 2020, **21**, 2512.

34 P. Riccio and R. Rossano, Diet, Gut Microbiota, and Vitamins D + A in Multiple Sclerosis, *Neurotherapeutics*, 2018, **15**, 75–91.

35 B. O. Schroeder, Fight them or feed them: how the intestinal mucus layer manages the gut microbiota, *Gastroenterol. Rep.*, 2019, **7**, 3–12.

36 A. J. Holmes, Y. V. Chew, F. Colakoglu, J. B. Cliff, *et al.*, Diet-Microbiome Interactions in Health Are Controlled by Intestinal Nitrogen Source Constraints, *Cell Metab.*, 2017, **25**, 140–151.

37 A. Durban, J. J. Abell, A. Latorre and A. Moya, Effect of Dietary Carbohydrate Restriction on an Obesity-Related Prevotella-Dominated Human Fecal Microbiota, *Metagenomics*, 2013, **2**, 235722.

38 B. Senghor, C. Sokhna, R. Ruimy and J.-C. Lagier, Gut microbiota diversity according to dietary habits and geographical provenance, *Hum. Microbiome J.*, 2018, **7–8**, 1–9.

39 M. Levy, C. A. Thaiss and E. Elinav, Metabolites: messengers between the microbiota and the immune system, *Genes Dev.*, 2016, **30**, 1589–1597.

40 P. M. Becker and P. Yu, What makes protein indigestible from tissue-related, cellular, and molecular aspects?, *Mol. Nutr. Food Res.*, 2013, **57**, 1695–1707.

41 T. Cerdó, J. A. García-Santos, M. G. Bermúdez and C. Campoy, The Role of Probiotics and Prebiotics in the Prevention and Treatment of Obesity, *Nutrients*, 2019, **11**, 635.

42 N. Larsen, C. Bussolo de Souza, L. Krych, T. Barbosa Cahú, *et al.*, Potential of Pectins to Beneficially Modulate the Gut Microbiota Depends on Their Structural Properties, *Front. Microbiol.*, 2019, **10**, 223–223.

43 J. L. Carlson, J. M. Erickson, B. B. Lloyd and J. L. Slavin, Health Effects and Sources of Prebiotic Dietary Fiber, *Curr. Dev. Nutr.*, 2018, **2**, nzy005.

44 T. Høverstad, O. Fausa, A. Bjørneklett and T. Bøhmer, Short-chain fatty acids in the normal human feces, *Scand. J. Gastroenterol.*, 1984, **19**, 375–381.

45 P. Louis and H. J. Flint, Formation of propionate and butyrate by the human colonic microbiota, *Environ. Microbiol.*, 2017, **19**, 29–41.

46 J. Li, J. Butcher, D. Mack and A. Stintzi, Functional impacts of the intestinal microbiome in the pathogenesis of inflammatory bowel disease, *Inflamm. Bowel Dis.*, 2015, **21**, 139–153.

47 K. N. Kim, Y. Yao and S. Y. Ju, Short Chain Fatty Acids and Fecal Microbiota Abundance in Humans with Obesity: A Systematic Review and Meta-Analysis, *Nutrients*, 2019, **11**, 2512.

48 M. Muller, M. A. G. Hernandez, G. H. Goossens, D. Reijnders, *et al.*, Circulating but not faecal short-chain fatty acids are related to insulin sensitivity, lipolysis and GLP-1 concentrations in humans, *Sci. Rep.*, 2019, **9**, 12515.

49 L. Sealy and R. Chalkley, The effect of sodium butyrate on histone modification, *Cell*, 1978, **14**, 115–121.

50 A. Geirnaert, M. Calatayud, C. Grootaert, D. Laukens, *et al.*, Butyrate-producing bacteria supplemented in vitro to Crohn's disease patient microbiota increased butyrate production and enhanced intestinal epithelial barrier integrity, *Sci. Rep.*, 2017, **7**, 11450.

51 J. Schauber, C. Svanholm, S. Termen, K. Iffland, *et al.*, Expression of the cathelicidin LL-37 is modulated by short chain fatty acids in colonocytes: relevance of signalling pathways, *Gut*, 2003, **52**, 735–741.

52 S. K. Lee, T. Il Kim, Y. K. Kim, C. H. Choi, *et al.*, Cellular differentiation-induced attenuation of LPS response in HT-29 cells is related to the down-regulation of TLR4 expression, *Biochem. Biophys. Res. Commun.*, 2005, **337**, 457–463.

53 R. Simeoli, G. Mattace Raso, C. Pirozzi, A. Lama, *et al.*, An orally administered butyrate-releasing derivative reduces neutrophil recruitment and inflammation in dextran sulphate sodium-induced murine colitis, *Br. J. Pharmacol.*, 2017, **174**, 1484–1496.

54 C. Nastasi, S. Fredholm, A. Willerslev-Olsen, M. Hansen, *et al.*, Butyrate and propionate inhibit antigen-specific CD8+ T cell activation by suppressing IL-12 production by antigen-presenting cells, *Sci. Rep.*, 2017, **7**, 14516.

55 M. Pozuelo, S. Panda, A. Santiago, S. Mendez, *et al.*, Reduction of butyrate- and methane-producing microorganisms in patients with Irritable Bowel Syndrome, *Sci. Rep.*, 2015, **5**, 12693.

56 J. Qin, Y. Li, Z. Cai, S. Li, *et al.*, A metagenome-wide association study of gut microbiota in type 2 diabetes, *Nature*, 2012, **490**, 55–60.

57 T. Wang, G. Cai, Y. Qiu, N. Fei, *et al.*, Structural segregation of gut microbiota between colorectal cancer patients and healthy volunteers, *ISME J.*, 2012, **6**, 320–329.

58 P. Louis and H. J. Flint, Diversity, metabolism and microbial ecology of butyrate-producing bacteria from the human large intestine, *FEMS Microbiol. Lett.*, 2009, **294**, 1–8.

59 C. A. Kerr, D. M. Grice, C. D. Tran, D. C. Bauer, *et al.*, Early life events influence whole-of-life metabolic health via gut microflora and gut permeability, *Crit. Rev. Microbiol.*, 2015, **41**, 326–340.

60 O. Castaner, A. Goday, Y. M. Park, S. H. Lee, *et al.*, The Gut Microbiome Profile in Obesity: A Systematic Review, *Int. J. Endocrinol.*, 2018, **2018**, 4095789.

61 C. D. Davis, The Gut Microbiome and Its Role in Obesity, *Nutr. Today*, 2016, **51**, 167–174.

62 E. Mylonakis, E. T. Ryan and S. B. Calderwood, Clostridium difficile–Associated diarrhea: A review, *Arch. Intern. Med.*, 2001, **161**, 525–533.

63 F. A. Tomas-Barberan, M. V. Selma and J. C. Espin, Interactions of gut microbiota with dietary polyphenols and consequences to human health, *Curr. Opin. Clin. Nutr. Metab. Care*, 2016, **19**, 471–476.

64 P. D. Cani, Human gut microbiome: hopes, threats and promises, *Gut*, 2018, **67**, 1716–1725.

65 F. Scheperjans, V. Aho, P. A. Pereira, K. Koskinen, *et al.*, Gut microbiota are related to Parkinson's disease and clinical phenotype, *Mov. Disord.*, 2015, **30**, 350–358.

66 J. Xiao and W. Bai, Bioactive phytochemicals, *Crit. Rev. Food Sci. Nutr.*, 2019, **59**, 827–829.

67 J. Rienks, J. Barbaresko, K. Oluwagbemigun, M. Schmid and U. Nothlings, Polyphenol exposure and risk of type 2 diabetes: dose-response meta-analyses and systematic review of prospective cohort studies, *Am. J. Clin. Nutr.*, 2018, **108**, 49–61.

68 F. Poti, D. Santi, G. Spaggiari, F. Zimetti and I. Zanotti, Polyphenol health effects on cardiovascular and neurodegenerative disorders: A review and meta-analysis, *Int. J. Mol. Sci.*, 2019, **20**, 351.

69 G. Grosso, A. Micek, M. Marranzano, A. Mistretta and E. L. Giovannucci, Dietary polyphenols and cancer incidence: a comprehensive meta-analysis: Giuseppe Grosso, *Eur. J. Public Health*, 2015, **25**, ckv175.177.

70 K. E. Bach Knudsen, N. P. Norskov, A. K. Bolvig, M. S. Hedemann and H. N. Laerke, Dietary fibers and associated phytochemicals in cereals, *Mol. Nutr. Food Res.*, 2017, **61**, DOI: 10.1002/mnfr.201600518.

71 USDA, *National Nutrient Database for Standard Reference Release 28*, USDA, 2015. http://ndb.nal.usda.gov/ndb/foods/show. Accessed 05.11.2015.

72 T. Bohn, Dietary factors affecting polyphenol bioavailability, *Nutr. Rev.*, 2014, **72**, 429–452.

73 Institute of Medicine, *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids*, The National Academies Press, Washington, DC, 2005.

74 M. C. Puell, C. Palomo-Alvarez, A. R. Barrio, F. J. Gomez-Sanz and M. J. Perez-Carrasco, Relationship between macular pigment and visual acuity in eyes with early age-related macular degeneration, *Acta Ophthalmol.*, 2013, **91**, e298–e303.

75 K. D. Croft, Dietary polyphenols: Antioxidants or not?, *Arch. Biochem. Biophys.*, 2016, **595**, 120–124.

76 J. Plat, S. Baumgartner, T. Vanmierlo, D. Lutjohann, *et al.*, Plant-based sterols and stanols in health & disease: "Consequences of human development in a plant-based environment?", *Prog. Lipid Res.*, 2019, **74**, 87–102.

77 A. Calado, P. M. Neves, T. Santos and P. Ravasco, The Effect of Flaxseed in Breast Cancer: A Literature Review, *Front. Nutr.*, 2018, **5**, 4–4.

78 F. Cardona, C. Andres-Lacueva, S. Tulipani, F. J. Tinahones and M. I. Queipo-Ortuno, Benefits of polyphenols on gut microbiota and implications in human health, *J. Nutr. Biochem.*, 2013, **24**, 1415–1422.

79 L. Carrera-Quintanar, R. I. Lopez Roa, S. Quintero-Fabian, M. A. Sanchez-Sanchez, *et al.*, Phytochemicals That Influence Gut Microbiota as Prophylactics and for the Treatment of Obesity and Inflammatory Diseases, *Mediators Inflammation*, 2018, **2018**, 9734845.

80 M. Wiese, Y. Bashmakov, N. Chalyk, D. S. Nielsen, *et al.*, Prebiotic Effect of Lycopene and Dark Chocolate on Gut Microbiome with Systemic Changes in Liver Metabolism, Skeletal Muscles and Skin in Moderately Obese Persons, *BioMed. Res. Int.*, 2019, **2019**, 4625279.

81 L. Chen, W. C. S. Tai and W. L. W. Hsiao, Dietary saponins from four popular herbal tea exert prebiotic-like effects on gut microbiota in C57BL/6 mice, *J. Funct. Foods*, 2015, **17**, 892–902.

82 S. M. Henning, P. H. Summanen, R. P. Lee, J. Yang, *et al.*, Pomegranate ellagitannins stimulate the growth of Akkermansia muciniphila in vivo, *Anaerobe*, 2017, **43**, 56–60.

83 G. Shoba, D. Joy, T. Joseph, M. Majeed, *et al.*, Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers, *Planta Med.*, 1998, **64**, 353–356.

84 M. Porrini and P. Riso, What are typical lycopene intakes?, *J. Nutr.*, 2005, **135**, 2042s–2045s.

85 J. Perez-Jimenez, M. E. Diaz-Rubio and F. Saura-Calixto, Non-extractable polyphenols, a major dietary antioxidant: occurrence, metabolic fate and health effects, *Nutr. Res. Rev.*, 2013, **26**, 118–129.

86 P. Louis, G. L. Hold and H. J. Flint, The gut microbiota, bacterial metabolites and colorectal cancer, *Nat. Rev. Microbiol.*, 2014, **12**, 661–672.

87 H. J. Flint, K. P. Scott, S. H. Duncan, P. Louis and E. Forano, Microbial degradation of complex carbohydrates in the gut, *Gut Microbes*, 2012, **3**, 289–306.

88 M. C. Theilmann, Y. J. Goh, K. F. Nielsen, T. R. Klaenhammer, *et al.*, Lactobacillus acidophilus Metabolizes Dietary Plant Glucosides and Externalizes Their Bioactive Phytochemicals, *mBio*, 2017, **8**, e01421-17.

89 A. Narbad and J. T. Rossiter, Gut Glucosinolate Metabolism and Isothiocyanate Production, *Mol. Nutr. Food Res.*, 2018, **62**, e1700991.

90 R. Egelkamp, D. Schneider, R. Hertel and R. Daniel, Nitrile-Degrading Bacteria Isolated from Compost, *Front. Environ. Sci.*, 2017, **5**, 56.

91 K. Igai, M. Itakura, S. Nishijima, H. Tsurumaru, *et al.*, Nitrogen fixation and nifH diversity in human gut microbiota, *Sci. Rep.*, 2016, **6**, 31942.

92 B. Min, T. N. Barry, G. Attwood and W. C. McNabb, The effect of condensed tannins on the nutrition and health of ruminants fed fresh temperate forages: A review, *Anim. Feed Sci. Technol.*, 2003, **106**, 3–19.

93 M. A. Farag, A. Abdelwareth, I. E. Sallam, M. El Shorbagi, *et al.*, Metabolomics reveals impact of seven functional foods on metabolic pathways in a gut microbiota model, *J. Adv. Res.*, 2020, **23**, 47–59.

94 A. K. Singh, C. Cabral, R. Kumar, R. Ganguly, *et al.*, Beneficial Effects of Dietary Polyphenols on Gut Microbiota and Strategies to Improve Delivery Efficiency, *Nutrients*, 2019, **11**, E2216.

95 A. T. Reese, E. H. Cho, B. Klitzman, S. P. Nichols, *et al.*, Antibiotic-induced changes in the microbiota disrupt redox dynamics in the gut, *eLife*, 2018, **7**, e35987.

96 N. W. Palm, M. R. de Zoete, T. W. Cullen, N. A. Barry, *et al.*, Immunoglobulin A coating identifies colitogenic bacteria in inflammatory bowel disease, *Cell*, 2014, **158**, 1000–1010.

97 O. Pabst and E. Slack, IgA and the intestinal microbiota: the importance of being specific, *Mucosal Immunol.*, 2020, **13**, 12–21.

98 R. Puupponen-Pimiä, L. Nohynek, S. Hartmann-Schmidlin, M. Kähkönen, *et al.*, Berry phenolics selectively inhibit the growth of intestinal pathogens, *J. Appl. Microbiol.*, 2005, **98**, 991–1000.

99 N. Tao, Y. Gao, Y. Liu and F. Ge, Carotenoids from the peel of Shatian pummelo (Citrus grandis Osbeck) and its antimicrobial activity, *Am.-Eurasian J. Agric. Environ. Sci.*, 2010, **7**, 110–115.

100 A. M. Elizondo, E. C. Mercado, B. C. Rabinovitz and M. E. Fernandez-Miyakawa, Effect of tannins on the in vitro growth of Clostridium perfringens, *Vet. Microbiol.*, 2010, **145**, 308–314.

101 M. J. Claesson, I. B. Jeffery, S. Conde, S. E. Power, *et al.*, Gut microbiota composition correlates with diet and health in the elderly, *Nature*, 2012, **488**, 178–184.

102 C. Kelley, Y. Zhang, A. Parhi, M. Kaul, *et al.*, 3-Phenyl substituted 6,7-dimethoxyisoquinoline derivatives as FtsZ-targeting antibacterial agents, *Bioorg. Med. Chem.*, 2012, **20**, 7012–7029.

103 R. Barbieri, E. Coppo, A. Marchese, M. Daglia, *et al.*, Phytochemicals for human disease: An update on plant-derived compounds antibacterial activity, *Microbiol. Res.*, 2017, **196**, 44–68.

104 I. Peluso, L. Romanelli and M. Palmery, Interactions between prebiotics, probiotics, polyunsaturated fatty acids and polyphenols: diet or supplementation for metabolic syndrome prevention?, *Int. J. Food Sci. Nutr.*, 2014, **65**, 259–267.

105 M. Pavan Kumar and K. Suman, Modulation of Gut Microbiota through Dietary Phytochemicals as a Novel Anti-infective Strategy, *Curr. Drug Discovery Technol.*, 2019, **16**, 1–9.

106 F. Nazzaro, F. Fratianni and R. Coppola, Quorum sensing and phytochemicals, *Int. J. Mol. Sci.*, 2013, **14**, 12607–12619.

107 S. Filosa, F. Di Meo and S. Crispi, Polyphenols-gut microbiota interplay and brain neuromodulation, *Neural Regener. Res.*, 2018, **13**, 2055–2059.

108 D. Serra, L. M. Almeida and T. C. P. Dinis, Dietary polyphenols: A novel strategy to modulate microbiota-gut-brain axis, *Trends Food Sci. Technol.*, 2018, **78**, 224–233.

109 V. P. Reddy, P. Aryal, S. Robinson, R. Rafiu, *et al.*, Polyphenols in Alzheimer's Disease and in the Gut-Brain Axis, *Microorganisms*, 2020, **8**, 199.

110 A. Kaulmann and T. Bohn, Bioactivity of Polyphenols: Preventive and Adjuvant Strategies toward Reducing Inflammatory Bowel Diseases-Promises, Perspectives, and Pitfalls, *Oxid. Med. Cell. Longev.*, 2016, **2016**, 9346470.

111 G. Yang, S. Bibi, M. Du, T. Suzuki and M. J. Zhu, Regulation of the intestinal tight junction by natural polyphenols: A mechanistic perspective, *Crit. Rev. Food Sci. Nutr.*, 2017, **57**, 3830–3839.

112 H. Palafox-Carlos, J. F. Ayala-Zavala and G. A. González-Aguilar, The role of dietary fiber in the bioaccessibility and bioavailability of fruit and vegetable antioxidants, *J. Food Sci.*, 2011, **76**, R6–R15.

113 J. Perez-Jimenez and J. L. Torres, Analysis of nonextractable phenolic compounds in foods: the current state of the art, *J. Agric. Food Chem.*, 2011, **59**, 12713–12724.

114 S. Pathak, P. Kesavan, A. Banerjee and A. Banerjee, *et al.*, in *Polyphenols: Mechanisms of Action in Human Health and Disease*, ed. R. R. Watson, V. R. Preedy and S. Zibadi, Academic Press, 2nd edn, 2018, pp. 347–359.

115 H. S. Oz, T. Chen and W. J. S. de Villiers, Green Tea Polyphenols and Sulfasalazine have Parallel Anti-Inflammatory Properties in Colitis Models, *Front. Immunol.*, 2013, **4**, 132–132.

116 J. M. Landete, P. Gaya, E. Rodriguez, S. Langa, *et al.*, Probiotic Bacteria for Healthier Aging: Immunomodulation and Metabolism of Phytoestrogens, *BioMed. Res. Int.*, 2017, **2017**, 5939818.

117 Z. Li, S. M. Henning, R. P. Lee, Q. Y. Lu, *et al.*, Pomegranate extract induces ellagitannin metabolite formation and changes stool microbiota in healthy volunteers, *Food Funct.*, 2015, **6**, 2487–2495.

118 F. Di Meo, S. Margarucci, U. Galderisi, S. Crispi and G. Peluso, Curcumin, Gut Microbiota, and Neuroprotection, *Nutrients*, 2019, **11**, 2426.

119 C. Cueva, I. Gil-Sanchez, B. Ayuda-Duran, S. Gonzalez-Manzano, *et al.*, An Integrated View of the Effects of Wine Polyphenols and Their Relevant Metabolites on Gut and Host Health, *Molecules*, 2017, **22**, 99.

120 J. M. Laparra and Y. Sanz, Interactions of gut microbiota with functional food components and nutraceuticals, *Pharmacol. Res.*, 2010, **61**, 219–225.

121 G. Ma and Y. Chen, Polyphenol supplementation benefits human health via gut microbiota: A systematic review via meta-analysis, *J. Funct. Foods*, 2020, **66**, 103829.

122 A. Klinder, Q. Shen, S. Heppel, J. A. Lovegrove, *et al.*, Impact of increasing fruit and vegetables and flavonoid intake on the human gut microbiota, *Food Funct.*, 2016, **7**, 1788–1796.

123 R. Simmering, H. Pforte, G. Jacobasch and M. Blaut, The growth of the flavonoid-degrading intestinal bacterium, Eubacterium ramulus, is stimulated by dietary flavonoids in vivo, *FEMS Microbiol. Ecol.*, 2002, **40**, 243–248.

124 X. Tzounis, A. Rodriguez-Mateos, J. Vulevic, G. R. Gibson, *et al.*, Prebiotic evaluation of cocoa-derived flavanols in healthy humans by using a randomized, controlled, double-blind, crossover intervention study, *Am. J. Clin. Nutr.*, 2011, **93**, 62–72.

125 F. Guarner and J. R. Malagelada, Gut flora in health and disease, *Lancet*, 2003, **361**, 512–519.

126 A. L. Molan, Z. Liu and G. Plimmer, Evaluation of the effect of blackcurrant products on gut microbiota and on markers of risk for colon cancer in humans, *Phytother. Res.*, 2014, **28**, 416–422.

127 G. A. Jones, T. A. McAllister, A. D. Muir and K. J. Cheng, Effects of Sainfoin (Onobrychis viciifolia Scop.) Condensed Tannins on Growth and Proteolysis by Four Strains of Ruminal Bacteria, *Appl. Environ. Microbiol.*, 1994, **60**, 1374–1378.

128 A. H. Smith and R. I. Mackie, Effect of condensed tannins on bacterial diversity and metabolic activity in the rat gastrointestinal tract, *Appl. Environ. Microbiol.*, 2004, **70**, 1104–1115.

129 M. I. Queipo-Ortuno, M. Boto-Ordonez, M. Murri, J. M. Gomez-Zumaquero, *et al.*, Influence of red wine polyphenols and ethanol on the gut microbiota ecology and

biochemical biomarkers, *Am. J. Clin. Nutr.*, 2012, **95**, 1323–1334.
130 M. Derrien, C. Belzer and W. M. de Vos, Akkermansia muciniphila and its role in regulating host functions, *Microb. Pathog.*, 2017, **106**, 171–181.
131 M. Jayachandran, J. Xiao and B. Xu, A Critical Review on Health Promoting Benefits of Edible Mushrooms through Gut Microbiota, *Int. J. Mol. Sci.*, 2017, **18**, 1934.
132 K. Wang, Z. Wan, A. Ou, X. Liang, *et al.*, Monofloral honey from a medical plant, Prunella Vulgaris, protected against dextran sulfate sodium-induced ulcerative colitis via modulating gut microbial populations in rats, *Food Funct.*, 2019, **10**, 3828–3838.
133 K. Wang, X. Jin, Q. Li, A. Sawaya, *et al.*, Propolis from Different Geographic Origins Decreases Intestinal Inflammation and Bacteroides spp. Populations in a Model of DSS-Induced Colitis, *Mol. Nutr. Food Res.*, 2018, **62**, e1800080.
134 M. Larrosa, M. J. Yanez-Gascon, M. V. Selma, A. Gonzalez-Sarrias, *et al.*, Effect of a low dose of dietary resveratrol on colon microbiota, inflammation and tissue damage in a DSS-induced colitis rat model, *J. Agric. Food Chem.*, 2009, **57**, 2211–2220.
135 H. Shapiro, P. Singer, Z. Halpern and R. Bruck, Polyphenols in the treatment of inflammatory bowel disease and acute pancreatitis, *Gut*, 2007, **56**, 426–435.
136 M. Sengottuvelan and N. Nalini, Dietary supplementation of resveratrol suppresses colonic tumour incidence in 1,2-dimethylhydrazine-treated rats by modulating biotransforming enzymes and aberrant crypt foci development, *Br. J. Nutr.*, 2006, **96**, 145–153.
137 P. Dolara, C. Luceri, C. De Filippo, A. P. Femia, *et al.*, Red wine polyphenols influence carcinogenesis, intestinal microflora, oxidative damage and gene expression profiles of colonic mucosa in F344 rats, *Mutat. Res.*, 2005, **591**, 237–246.
138 S. G. Parkar, D. E. Stevenson and M. A. Skinner, The potential influence of fruit polyphenols on colonic microflora and human gut health, *Int. J. Food Microbiol.*, 2008, **124**, 295–298.
139 P. Jarocki, M. Podlesny, P. Glibowski and Z. Targonski, A new insight into the physiological role of bile salt hydrolase among intestinal bacteria from the genus Bifidobacterium, *PLoS One*, 2014, **9**, e114379.
140 Y. Han, T. Haraguchi, S. Iwanaga, H. Tomotake, *et al.*, Consumption of some polyphenols reduces fecal deoxycholic acid and lithocholic acid, the secondary bile acids of risk factors of colon cancer, *J. Agric. Food Chem.*, 2009, **57**, 8587–8590.
141 A. Odermatt, T. Da Cunha, C. A. Penno, C. Chandsawangbhuwana, *et al.*, Hepatic reduction of the secondary bile acid 7-oxolithocholic acid is mediated by 11beta-hydroxysteroid dehydrogenase 1, *Biochem. J.*, 2011, **436**, 621–629.
142 O. Ramirez-Perez, V. Cruz-Ramon, P. Chinchilla-Lopez and N. Mendez-Sanchez, The Role of the Gut Microbiota in Bile Acid Metabolism, *Ann. Hepatol.*, 2017, **16**, s15–s20.
143 X. Wang, X. Fu, C. Van Ness, Z. Meng, *et al.*, Bile Acid Receptors and Liver Cancer, *Curr. Pathobiol. Rep.*, 2013, **1**, 29–35.
144 E. Tiratterra, P. Franco, E. Porru, K. H. Katsanos, *et al.*, Role of bile acids in inflammatory bowel disease, *Ann. Gastroenterol.*, 2018, **31**, 266–272.
145 N. Ni, G. Choudhary, M. Li and B. Wang, Pyrogallol and its analogs can antagonize bacterial quorum sensing in Vibrio harveyi, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 1567–1572.
146 J. Ouyang, F. Sun, W. Feng, Y. Sun, *et al.*, Quercetin is an effective inhibitor of quorum sensing, biofilm formation and virulence factors in Pseudomonas aeruginosa, *J. Appl. Microbiol.*, 2016, **120**, 966–974.
147 J. Bouayed, H. Deusser, L. Hoffmann and T. Bohn, Bioaccessible and dialysable polyphenols in selected apple varieties following in vitro digestion vs. their native patterns, *Food Chem.*, 2012, **131**, 1466–1472.
148 T. A. F. Correa, M. M. Rogero, N. M. A. Hassimotto and F. M. Lajolo, The Two-Way Polyphenols-Microbiota Interactions and Their Effects on Obesity and Related Metabolic Diseases, *Front. Nutr.*, 2019, **6**, 188.
149 W. R. Russell, S. H. Duncan, L. Scobbie, G. Duncan, *et al.*, Major phenylpropanoid-derived metabolites in the human gut can arise from microbial fermentation of protein, *Mol. Nutr. Food Res.*, 2013, **57**, 523–535.
150 B. Mayo, L. Vazquez and A. B. Florez, Equol: A Bacterial Metabolite from The Daidzein Isoflavone and Its Presumed Beneficial Health Effects, *Nutrients*, 2019, **11**, 2231.
151 T. Frolinger, S. Sims, C. Smith, J. Wang, *et al.*, The gut microbiota composition affects dietary polyphenols-mediated cognitive resilience in mice by modulating the bioavailability of phenolic acids, *Sci. Rep.*, 2019, **9**, 3546.
152 C. Rodriguez-Garcia, C. Sanchez-Quesada, E. Toledo, M. Delgado-Rodriguez and J. J. Gaforio, Naturally Lignan-Rich Foods: A Dietary Tool for Health Promotion?, *Molecules*, 2019, **24**, 917.
153 C. Hu, Y. V. Yuan and D. D. Kitts, Antioxidant activities of the flaxseed lignan secoisolariciresinol diglucoside, its aglycone secoisolariciresinol and the mammalian lignans enterodiol and enterolactone in vitro, *Food Chem. Toxicol.*, 2007, **45**, 2219–2227.
154 B. Liu, S. Rong, Y. Sun, R. Wallace, *et al.*, Gut Microbiota Metabolites of Dietary Lignans and Risk of All-Cause and Cause-Specific Mortality in Adults, *Curr. Dev. Nutr.*, 2020, **4**, 1439–1439.
155 P. L. Horn-Ross, S. Barnes, V. S. Lee, C. N. Collins, *et al.*, Reliability and validity of an assessment of usual phytoestrogen consumption (United States), *Cancer Causes Control*, 2006, **17**, 85–93.
156 M. Hedelin, M. Lof, M. Olsson, H. Adlercreutz, *et al.*, Dietary phytoestrogens are not associated with risk of overall breast cancer but diets rich in coumestrol are

inversely associated with risk of estrogen receptor and progesterone receptor negative breast tumors in Swedish women, *J. Nutr.*, 2008, **138**, 938–945.

157 M. C. Marcotullio, M. Curini and J. X. Becerra, An Ethnopharmacological, Phytochemical and Pharmacological Review on Lignans from Mexican Bursera spp, *Molecules*, 2018, **23**, 1976.

158 H. Adlercreutz, Phyto-oestrogens and cancer, *Lancet Oncol.*, 2002, **3**, 364–373.

159 P. Gaya, M. Medina, A. Sanchez-Jimenez and J. M. Landete, Phytoestrogen Metabolism by Adult Human Gut Microbiota, *Molecules*, 2016, **21**, 1034.

160 T. Clavel, G. Henderson, C.-A. Alpert, C. Philippe, *et al.*, Intestinal Bacterial Communities That Produce Active Estrogen-Like Compounds Enterodiol and Enterolactone in Humans, *Appl. Environ. Microbiol.*, 2005, **71**, 6077.

161 M. A. Hullar, S. M. Lancaster, F. Li, E. Tseng, *et al.*, Enterolignan-producing phenotypes are associated with increased gut microbial diversity and altered composition in premenopausal women in the United States, *Cancer Epidemiol. Biomarkers Prev.*, 2015, **24**, 546–554.

162 Q. Sun, N. M. Wedick, A. Pan, M. K. Townsend, *et al.*, Gut microbiota metabolites of dietary lignans and risk of type 2 diabetes: a prospective investigation in two cohorts of U. S. women, *Diabetes Care*, 2014, **37**, 1287–1295.

163 M. L. Silva, H. S. Coimbra, A. C. Pereira, V. A. Almeida, *et al.*, Evaluation of piper cubeba extract, (-)-cubebin and its semi-synthetic derivatives against oral pathogens, *Phytother. Res.*, 2007, **21**, 420–422.

164 J. W. Lampe, E. Kim, L. Levy, L. A. Davidson, *et al.*, Colonic mucosal and exfoliome transcriptomic profiling and fecal microbiome response to a flaxseed lignan extract intervention in humans, *Am. J. Clin. Nutr.*, 2019, **110**, 377–390.

165 I. Lagkouvardos, K. Klaring, S. S. Heinzmann, S. Platz, *et al.*, Gut metabolites and bacterial community networks during a pilot intervention study with flaxseeds in healthy adult men, *Mol. Nutr. Food Res.*, 2015, **59**, 1614–1628.

166 G. Corona, A. Kreimes, M. Barone, S. Turroni, *et al.*, Impact of lignans in oilseed mix on gut microbiome composition and enterolignan production in younger healthy and premenopausal women: an in vitro pilot study, *Microb. Cell Fact.*, 2020, **19**, 82.

167 Q. Wang, M. Jia, Y. Zhao, Y. Hui, *et al.*, Supplementation of Sesamin Alleviates Stress-Induced Behavioral and Psychological Disorders via Reshaping the Gut Microbiota Structure, *J. Agric. Food Chem.*, 2019, **67**, 12441–12451.

168 N. A. Henke, P. Peters-Wendisch, V. F. Wendisch and S. A. E. Heider, C50 Carotenoids: Occurrence, Biosynthesis, Glycosylation, and Metabolic Engineering for their Overproduction, in *Bio–pigmentation and Biotechnological Implementations*, 2017, pp. 107–126.

169 H. E. Khoo, K. N. Prasad, K. W. Kong, Y. Jiang and A. Ismail, Carotenoids and their isomers: color pigments in fruits and vegetables, *Molecules*, 2011, **16**, 1710–1738.

170 A. B. Awad and C. S. Fink, Phytosterols as anticancer dietary components: evidence and mechanism of action, *J. Nutr.*, 2000, **130**, 2127–2130.

171 E. Biehler, A. Alkerwi, L. Hoffmann, E. Krause, *et al.*, Contribution of violaxanthin, neoxanthin, phytoene and phytofluene to total carotenoid intake: Assessment in Luxembourg, *J. Food Compos. Anal.*, 2012, **25**, 56–65.

172 V. Böhm, P. Borel, J. Corte-Real, A. de Lera, *et al.*, From carotenoid intake to carotenoid blood and tissue concentrations – implications for dietary intake recommendations, *Nutr. Rev.*, 2019, DOI: 10.1093/nutrit/nuaa1008, in press.

173 T. Bohn, Carotenoids, Chronic Disease Prevention and Dietary Recommendations, *Int. J. Vitam. Nutr. Res.*, 2017, **87**, 121–130.

174 P. Molnar, M. Kawase, K. Satoh, Y. Sohara, *et al.*, Biological activity of carotenoids in red paprika, Valencia orange and Golden delicious apple, *Phytother. Res.*, 2005, **19**, 700–707.

175 A. Ranjbar and E. Ranjbar, Brief report Antimicrobial Property of Lycopene Oleoresin on some Food Pathogens Running Head: Lycopene oleoresin antibacterial potent, *Ir. Food Sci. Technol. Res. J.*, 2016, **12**, 382–387.

176 L. R. Natividad and R. R. Rafael, Carotenoid Analyses and Antibacterial Assay of Annato (Bixa orellana L.), Carrot (Daucus carota L.), Corn (Zea mays L.) and Tomato (Solanum lycopersicum L.) Extracts, *Res. J. Recent Sci.*, 2014, **3**, 40–45.

177 T. Nagayama, M. Sugimoto, S. Ikeda and S. Kume, Effects of astaxanthin-enriched yeast on mucosal IgA induction in the jejunum and ileum of weanling mice, *Anim. Sci. J.*, 2014, **85**, 449–453.

178 S. Gattu, Y. J. Bang, M. Pendse, C. Dende, *et al.*, Epithelial retinoic acid receptor beta regulates serum amyloid A expression and vitamin A-dependent intestinal immunity, *Proc. Natl. Acad. Sci. U. S. A.*, 2019, **116**, 10911–10916.

179 A. B. Nair and S. Jacob, A simple practice guide for dose conversion between animals and human, *J. Basic Clin. Pharm.*, 2016, **7**, 27–31.

180 Y. Wang, C. Tang, Y. Tang, H. Yin and X. Liu, Capsaicin has an anti-obesity effect through alterations in gut microbiota populations and short-chain fatty acid concentrations, *Food Nutr. Res.*, 2020, **64**, DOI: 10.29219/fnr.v29264.23525, in press.

181 W. Shen, M. Shen, X. Zhao, H. Zhu, *et al.*, Anti-obesity Effect of Capsaicin in Mice Fed with High-Fat Diet Is Associated with an Increase in Population of the Gut Bacterium Akkermansia muciniphila, *Front. Microbiol.*, 2017, **8**, 272.

182 H. Xia, C. Liu, C. C. Li, M. Fu, *et al.*, Dietary Tomato Powder Inhibits High-Fat Diet-Promoted Hepatocellular Carcinoma with Alteration of Gut Microbiota in Mice Lacking Carotenoid Cleavage Enzymes, *Cancer Prev. Res.*, 2018, **11**, 797–810.

183 B. Guo, B. Yang, X. Pang, T. Chen, *et al.*, Fucoxanthin modulates cecal and fecal microbiota differently based on diet, *Food Funct.*, 2019, **10**, 5644–5655.

184 R. Gonzalez-Prendes, R. N. Pena, E. Sole, A. R. Seradj, *et al.*, Modulatory Effect of Protein and Carotene Dietary Levels on Pig gut Microbiota, *Sci. Rep.*, 2019, **9**, 14582.
185 H. Liu, M. Liu, X. Fu, Z. Zhang, *et al.*, Astaxanthin prevents alcoholic fatty liver disease by modulating mouse gut microbiota, *Nutrients*, 2018, **10**, 1298.
186 L. Li, L. Krause and S. Somerset, Associations between micronutrient intakes and gut microbiota in a group of adults with cystic fibrosis, *Clin. Nutr.*, 2017, **36**, 1097–1104.
187 T. Bohn, Bioactivity of carotenoids – chasms of knowledge, *Int. J. Vitam. Nutr. Res.*, 2017, **10**, 1–5.
188 I. Van Dam, *Nutrition and Rural Development*, Gent University, Gent, 2017.
189 J. Serrano, I. Goni and F. Saura-Calixto, Determination of beta-carotene and lutein available from green leafy vegetables by an in vitro digestion and colonic fermentation method, *J. Agric. Food Chem.*, 2005, **53**, 2936–2940.
190 A. Kaulmann, C. M. Andre, Y. J. Schneider, L. Hoffmann and T. Bohn, Carotenoid and polyphenol bioaccessibility and cellular uptake from plum and cabbage varieties, *Food Chem.*, 2016, **197**, 325–332.
191 F. H. Karlsson, F. Fåk, I. Nookaew, V. Tremaroli, *et al.*, Symptomatic atherosclerosis is associated with an altered gut metagenome, *Nat. Commun.*, 2012, **3**, 1245.
192 B. Gökalsın, B. Aksoydan, B. Erman and N. C. Sesal, Reducing Virulence and Biofilm of Pseudomonas aeruginosa by Potential Quorum Sensing Inhibitor Carotenoid: Zeaxanthin, *Microb. Ecol.*, 2017, **74**, 466–473.
193 I. Demonty, R. T. Ras, H. C. van der Knaap, G. S. Duchateau, *et al.*, Continuous dose-response relationship of the LDL-cholesterol-lowering effect of phytosterol intake, *J. Nutr.*, 2009, **139**, 271–284.
194 N. a. A. N. EFSA Panel on Dietetic Products, Scientific Opinion on the substantiation of a health claim related to 3 g/day plant sterols/stanols and lowering blood LDL-cholesterol and reduced risk of (coronary) heart disease pursuant to Article 19 of Regulation (EC) No 1924/2006, *EFSA J.*, 2012, **10**, 2693.
195 Y. Yoshida and E. Niki, Antioxidant effects of phytosterol and its components, *J. Nutr. Sci. Vitaminol.*, 2003, **49**, 277–280.
196 M. Cuevas Tena, A. Alegría and M. J. Lagarda, Relationship dietary sterols and gut microbiota: A review: Dietary sterols and gut microbiota, *Eur. J. Lipid Sci. Technol.*, 2018, **120**, 1800054.
197 S. Baumgartner, R. P. Mensink, E. Smet, M. Konings, *et al.*, Effects of plant stanol ester consumption on fasting plasma oxy(phyto)sterol concentrations as related to fecal microbiota characteristics, *J. Steroid Biochem. Mol. Biol.*, 2017, **169**, 46–53.
198 L. Song, Y. Li, D. Qu, P. Ouyang, *et al.*, The regulatory effects of phytosterol esters (PSEs) on gut flora and faecal metabolites in rats with NAFLD, *Food Funct.*, 2020, **11**, 977–991.
199 C. Kasai, K. Sugimoto, I. Moritani, J. Tanaka, *et al.*, Comparison of the gut microbiota composition between obese and non-obese individuals in a Japanese population, as analyzed by terminal restriction fragment length polymorphism and next-generation sequencing, *BMC Gastroenterol.*, 2015, **15**, 100.
200 Y. C. Huang, B. H. Wu, Y. L. Chu, W. C. Chang and M. C. Wu, Effects of Tempeh Fermentation with Lactobacillus plantarum and Rhizopus oligosporus on Streptozotocin-Induced Type II Diabetes Mellitus in Rats, *Nutrients*, 2018, **10**, 1143.
201 M. Cuevas-Tena, E. M, G. del Pulgar, A. Benítez-Páez, Y. Sanz, *et al.*, Plant sterols and human gut microbiota relationship: An in vitro colonic fermentation study, *J. Funct. Foods*, 2018, **44**, 322–329.
202 H. Zhang, J. K. DiBaise, A. Zuccolo, D. Kudrna, *et al.*, Human gut microbiota in obesity and after gastric bypass, *Proc. Natl. Acad. Sci. U. S. A.*, 2009, **106**, 2365–2370.
203 H. M. Hamer, D. Jonkers, K. Venema, S. Vanhoutvin, *et al.*, Review article: the role of butyrate on colonic function, *Aliment. Pharmacol. Ther.*, 2008, **27**, 104–119.
204 M. Cuevas-Tena, A. Alegria, M. J. Lagarda and K. Venema, Impact of plant sterols enrichment dose on gut microbiota from lean and obese subjects using TIM-2 in vitro fermentation model, *J. Funct. Foods*, 2019, **54**, 164–174.
205 I. I. Koleva, T. A. van Beek, A. E. Soffers, B. Dusemund and I. M. Rietjens, Alkaloids in the human food chain–natural occurrence and possible adverse effects, *Mol. Nutr. Food Res.*, 2012, **56**, 30–52.
206 J. I. J. Inklebarger J, M. G. Gyer, N. Galanis, M. J. Michael and D. G. Adel, Cinchona Bark For The Treatment Of Covid-19 Pnemonia: A Modern Review Of The Potential Anti-Viral Therapuetic Applications Of An Old Treatment, *Int. J. Med. Sci. Clin. Invent.*, 2020, **7**, 4795–4801.
207 M. Hesse, *Alkaloids: nature's curse or blessing?*, Wiley-VCH, Chichester, UK, 2002.
208 H. Tilg and A. Kaser, Gut microbiome, obesity, and metabolic dysfunction, *J. Clin. Invest.*, 2011, **121**, 2126–2132.
209 K. Nishitsuji, S. Watanabe, J. Xiao, R. Nagatomo, *et al.*, Effect of coffee or coffee components on gut microbiome and short-chain fatty acids in a mouse model of metabolic syndrome, *Sci. Rep.*, 2018, **8**, 16173.
210 S. Gurwara, A. Dai, N. Ajami, H. El-Serag, *et al.*, Caffeine Consumption and the Colonic Mucosa-Associated Gut Microbiota: 196, *Am. J. Gastroenterol.*, 2019, **114**, S119–S120.
211 M. Jaquet, I. Rochat, J. Moulin, C. Cavin and R. Bibiloni, Impact of coffee consumption on the gut microbiota: a human volunteer study, *Int. J. Food Microbiol.*, 2009, **130**, 117–121.
212 X. Jiang, D. Zhang and W. Jiang, Coffee and caffeine intake and incidence of type 2 diabetes mellitus: a meta-analysis of prospective studies, *Eur. J. Nutr.*, 2014, **53**, 25–38.
213 B. Ozçelik, M. Kartal and I. Erdogan Orhan, Cytotoxicity, antiviral and antimicrobial activities of alkaloids, flavonoids, and phenolic acids, *Pharm. Biol.*, 2011, **49**, 396–402.

214 S. H. Tiong, C. Y. Looi, H. Hazni, A. Arya, *et al.*, Antidiabetic and antioxidant properties of alkaloids from Catharanthus roseus (L.) G. Don, *Molecules*, 2013, **18**, 9770–9784.

215 J. Gan, Y. Feng, Z. He, X. Li and H. Zhang, Correlations between Antioxidant Activity and Alkaloids and Phenols of Maca (Lepidium meyenii), *J. Food Qual.*, 2017, **2017**, 3185945.

216 T. K. Beuria, M. K. Santra and D. Panda, Sanguinarine blocks cytokinesis in bacteria by inhibiting FtsZ assembly and bundling, *Biochemistry*, 2005, **44**, 16584–16593.

217 C. Cao and M. Su, Effects of berberine on glucose-lipid metabolism, inflammatory factors and insulin resistance in patients with metabolic syndrome, *Exp. Ther. Med.*, 2019, **17**, 3009–3014.

218 Y. Wang, J. W. Shou, X. Y. Li, Z. X. Zhao, *et al.*, Berberine-induced bioactive metabolites of the gut microbiota improve energy metabolism, *Metabolism*, 2017, **70**, 72–84.

219 J. S. Bang, D. H. Oh, H. M. Choi, B. J. Sur, *et al.*, Anti-inflammatory and antiarthritic effects of piperine in human interleukin 1beta-stimulated fibroblast-like synoviocytes and in rat arthritis models, *Arthritis Res. Ther.*, 2009, **11**, R49.

220 Z. Stojanović-Radić, M. Pejčić, M. Dimitrijević, A. Aleksić, *et al.*, Piperine-A Major Principle of Black Pepper: A Review of Its Bioactivity and Studies, *Appl. Sci.*, 2019, **9**, 4270.

221 Z. Toma, Antimicrobial Activity of Piperine purified from piper nigrum, *J. Basrah Res.*, 2010, **36**, 11.

222 P. Umadevi, K. Deepti and D. V. R. Venugopal, Synthesis, anticancer and antibacterial activities of piperine analogs, *Med. Chem. Res.*, 2013, **22**, 5466–5471.

223 D. Hikal, Antibacterial Activity of Piperine and Black Pepper Oil, *Biosci., Biotechnol. Res. Asia*, 2018, **15**, 877–880.

224 D. H. Dusane, Z. Hosseinidoust, B. Asadishad and N. Tufenkji, Alkaloids modulate motility, biofilm formation and antibiotic susceptibility of uropathogenic Escherichia coli, *PLoS One*, 2014, **9**, e112093.

225 B. Ganesh Bhat and N. Chandrasekhara, Studies on the metabolism of piperine: Absorption, tissue distribution and excretion of urinary conjugates in rats, *Toxicology*, 1986, **40**, 83–92.

226 E. Capuano, M. Dekker, R. Verkerk and T. Oliviero, Food as Pharma? The Case of Glucosinolates, *Curr. Pharm. Des.*, 2017, **23**, 2697–2721.

227 A. Steinbrecher and J. Linseisen, Dietary intake of individual glucosinolates in participants of the EPIC-Heidelberg cohort study, *Ann. Nutr. Metab.*, 2009, **54**, 87–96.

228 B. E. Cavell, S. S. Syed Alwi, A. Donlevy and G. Packham, Anti-angiogenic effects of dietary isothiocyanates: mechanisms of action and implications for human health, *Biochem. Pharmacol.*, 2011, **81**, 327–336.

229 S. I. Vicas, A. C. Teusdea, M. Carbunar, S. A. Socaci and C. Socaciu, Glucosinolates profile and antioxidant capacity of Romanian Brassica vegetables obtained by organic and conventional agricultural practices, *Plant Foods Hum. Nutr.*, 2013, **68**, 313–321.

230 J. W. Fahey, X. Haristoy, P. M. Dolan, T. W. Kensler, *et al.*, Sulforaphane inhibits extracellular, intracellular, and antibiotic-resistant strains of Helicobacter pylori and prevents benzo[a]pyrene-induced stomach tumors, *Proc. Natl. Acad. Sci. U. S. A.*, 2002, **99**, 7610–7615.

231 F. Li, M. A. Hullar, S. A. Beresford and J. W. Lampe, Variation of glucoraphanin metabolism in vivo and ex vivo by human gut bacteria, *Br. J. Nutr.*, 2011, **106**, 408–416.

232 X. Liu, Y. Wang, J. L. Hoeflinger, B. P. Neme, *et al.*, Dietary Broccoli Alters Rat Cecal Microbiota to Improve Glucoraphanin Hydrolysis to Bioactive Isothiocyanates, *Nutrients*, 2017, **9**, 262.

233 F. Li, M. A. Hullar, Y. Schwarz and J. W. Lampe, Human gut bacterial communities are altered by addition of cruciferous vegetables to a controlled fruit- and vegetable-free diet, *J. Nutr.*, 2009, **139**, 1685–1691.

234 J. Borlinghaus, F. Albrecht, M. C. Gruhlke, I. D. Nwachukwu and A. J. Slusarenko, Allicin: chemistry and biological properties, *Molecules*, 2014, **19**, 12591–12618.

235 B. Salehi, P. Zucca, I. Erdogan Orhan, E. Azzini, *et al.*, Allicin and Health: A comprehensive review, *Trends Food Sci. Technol.*, 2019, **86**, 502–516.

236 H.-P. Wang, J. Yang, L.-Q. Qin and X.-J. Yang, Effect of Garlic on Blood Pressure: A Meta-Analysis, *J. Clin. Hypertens.*, 2015, **17**, 223–231.

237 L. Hou, Y. Liu and Y. Zhang, Garlic intake lowers fasting blood glucose: meta-analysis of randomized controlled trials, *Asia Pac. J. Clin. Nutr.*, 2015, **24**, 575–582.

238 S. Panyod, W.-K. Wu, K.-H. Lu, C.-T. Liu, *et al.*, Allicin Modifies the Composition and Function of the Gut Microbiota in Alcoholic Hepatic Steatosis Mice, *J. Agric. Food Chem.*, 2020, **68**, 3088–3098.

239 S. Ankri and D. Mirelman, Antimicrobial properties of allicin from garlic, *Microbes Infect.*, 1999, **1**, 125–129.

240 A. Filocamo, C. Palop, C. Bisignano, G. Mandalari and A. Narbad, Effect of garlic powder on the growth of commensal bacteria from the gastrointestinal tract, *Phytomedicine*, 2012, **19**, 707–711.

241 X. E. Shi, X. Zhou, X. Chu, J. Wang, *et al.*, Allicin Improves Metabolism in High-Fat Diet-Induced Obese Mice by Modulating the Gut Microbiota, *Nutrients*, 2019, **11**, 2909.

242 A. Müller, J. Eller, F. Albrecht, P. Prochnow, *et al.*, Allicin Induces Thiol Stress in Bacteria through S-Allylmercapto Modification of Protein Cysteines, *J. Biol. Chem.*, 2016, **291**, 11477–11490.

243 E. Gonzalez-Burgos and M. P. Gomez-Serranillos, Terpene compounds in nature: a review of their potential antioxidant activity, *Curr. Med. Chem.*, 2012, **19**, 5319–5341.

244 S. Botschuijver, O. Welting, E. Levin, D. Maria-Ferreira, *et al.*, Reversal of visceral hypersensitivity in rat by Menthacarin((R)), a proprietary combination of essential oils from peppermint and caraway, coincides with myco-

biome modulation, *Neurogastroenterol. Motil.*, 2018, **30**, e13299.

245 M. Romo Vaquero, R. Garcia Villalba, M. Larrosa, M. J. Yanez-Gascon, *et al.*, Bioavailability of the major bioactive diterpenoids in a rosemary extract: metabolic profile in the intestine, liver, plasma, and brain of Zucker rats, *Mol. Nutr. Food Res.*, 2013, **57**, 1834–1846.

246 Y. Guo, J. Xie, X. Li, Y. Yuan, *et al.*, Antidepressant Effects of Rosemary Extracts Associate With Anti-inflammatory Effect and Rebalance of Gut Microbiota, *Front. Pharmacol.*, 2018, **9**, 1126.

247 A. L. Lopresti, The Problem of Curcumin and Its Bioavailability: Could Its Gastrointestinal Influence Contribute to Its Overall Health-Enhancing Effects?, *Adv. Nutr.*, 2018, **9**, 41–50.

248 Y. Lou, J. Zheng, H. Hu, J. Lee and S. Zeng, Application of ultra-performance liquid chromatography coupled with quadrupole time-of-flight mass spectrometry to identify curcumin metabolites produced by human intestinal bacteria, *J. Chromatogr. B: Anal. Technol. Biomed. Life Sci.*, 2015, **985**, 38–47.

249 C. T. Peterson, A. R. Vaughn, V. Sharma, D. Chopra, *et al.*, Effects of Turmeric and Curcumin Dietary Supplementation on Human Gut Microbiota: A Double-Blind, Randomized, Placebo-Controlled Pilot Study, *J. Evidence-Based Integr. Med.*, 2018, **23**, 2515690x18790725.

250 A. Shimouchi, K. Nose, M. Takaoka, H. Hayashi and T. Kondo, Effect of dietary turmeric on breath hydrogen, *Dig. Dis. Sci.*, 2009, **54**, 1725–1729.

251 Q. X. Ng, A. Y. S. Soh, W. Loke, N. Venkatanarayanan, *et al.*, A Meta-Analysis of the Clinical Use of Curcumin for Irritable Bowel Syndrome (IBS), *J. Clin. Med.*, 2018, **7**, 298.

252 J. Wang, P. Wang, D. Li, X. Hu and F. Chen, Beneficial effects of ginger on prevention of obesity through modulation of gut microbiota in mice, *Eur. J. Nutr.*, 2020, **59**, 699–718.

253 A. Heintz-Buschart and P. Wilmes, Human gut microbiome: Function matters, *Trends Microbiol.*, 2018, **26**, 563–574.

254 B. Y. L. Peisl, E. L. Schymanski and P. Wilmes, Dark matter in host-microbiome metabolomics: Tackling the unknowns-A review, *Anal. Chim. Acta*, 2018, **1037**, 13–27.

255 J. H. Lee, J. S. Shim, M. S. Chung, S. T. Lim and K. H. Kim, In vitro anti-adhesive activity of green tea extract against pathogen adhesion, *Phytother. Res.*, 2009, **23**, 460–466.

256 Y. Yanagawa, Y. Yamamoto, Y. Hara and T. Shimamura, A combination effect of epigallocatechin gallate, a major compound of green tea catechins, with antibiotics on Helicobacter pylori growth in vitro, *Curr. Microbiol.*, 2003, **47**, 244–249.

257 Y. Yoda, Z. Q. Hu, W. H. Zhao and T. Shimamura, Different susceptibilities of Staphylococcus and Gram-negative rods to epigallocatechin gallate, *J. Infect. Chemother.*, 2004, **10**, 55–58.

258 G. R. Swanson, V. Tieu, M. Shaikh, C. Forsyth and A. Keshavarzian, Is moderate red wine consumption safe in inactive inflammatory bowel disease?, *Digestion*, 2011, **84**, 238–244.

259 N. Augustine, A. K. Goel, K. C. Sivakumar, R. A. Kumar and S. Thomas, Resveratrol–a potential inhibitor of biofilm formation in Vibrio cholerae, *Phytomedicine*, 2014, **21**, 286–289.

260 O. M. Vandeputte, M. Kiendrebeogo, T. Rasamiravaka, C. Stévigny, *et al.*, The flavanone naringenin reduces the production of quorum sensing-controlled virulence factors in Pseudomonas aeruginosa PAO1, *Microbiology*, 2011, **157**, 2120–2132.

261 Y. Sun, S. Chen, R. Wei, X. Xie, *et al.*, Metabolome and gut microbiota variation with long-term intake of Panax ginseng extracts on rats, *Food Funct.*, 2018, **9**, 3547–3556.

262 Y. Ni, C. Mu, X. He, K. Zheng, *et al.*, Characteristics of gut microbiota and its response to a Chinese Herbal Formula in elder patients with metabolic syndrome, *Drug Discov. Ther.*, 2018, **12**, 161–169.

263 S. S. Dhanawade and A. V. Sakhare, Isolation of Lycopene from Tomato and Study of Its Antimicrobial Activity, *Int. J. Sci. Res.*, 2014, **3**, 671–673.

264 T. NengGuo, G. YuMei, L. YueJin and G. Fei, Carotenoids from the peel of Shatian pummelo (Citrus grandis Osbeck) and its antimicrobial activity, *Am.-Eurasian J. Agric. Environ. Sci.*, 2010, **7**, 110–115.

265 A. Dziedzic, R. D. Wojtyczka and R. Kubina, Inhibition of Oral Streptococci Growth Induced by the Complementary Action of Berberine Chloride and Antibacterial Compounds, *Molecules*, 2015, **20**, 13705–13724.

266 S. Kang, Z. Li, Z. Yin, R. Jia, *et al.*, The antibacterial mechanism of berberine against Actinobacillus pleuropneumoniae, *Nat. Prod. Res.*, 2015, **29**, 2203–2206.

267 Q. Liu, H. Niu, W. Zhang, H. Mu, *et al.*, Synergy among thymol, eugenol, berberine, cinnamaldehyde and streptomycin against planktonic and biofilm-associated foodborne pathogens, *Lett. Appl. Microbiol.*, 2015, **60**, 421–430.

268 J. Wang, W. Ke, R. Bao, X. Hu and F. Chen, Beneficial effects of ginger Zingiber officinale Roscoe on obesity and metabolic syndrome: a review, *Ann. N. Y. Acad. Sci.*, 2017, **1398**, 83–98.

269 M. J. Saavedra, A. Borges, C. Dias, A. Aires, *et al.*, Antimicrobial activity of phenolics and glucosinolate hydrolysis products and their synergy with streptomycin against pathogenic bacteria, *Med. Chem.*, 2010, **6**, 174–183.