Host–Microbe Interplay in the Cardiometabolic Benefits of Dietary Polyphenols

F.F. Anhê,[1] B.S.Y. Choi,[2] J.R.B. Dyck,[3] J.D. Schertzer,[1] and A. Marette[2]

[1] Department of Biochemistry and Biomedical Sciences and Farncombe Family Digestive Health Research Institute, McMaster University, Hamilton, ON, Canada
[2] Department of Medicine, Faculty of Medicine, Cardiology Axis of the Québec Heart and Lung Institute and Institute of Nutrition and Functional Foods, Laval University, Québec City, QC, Canada
[3] Cardiovascular Research Centre, Department of Pediatrics, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, AB, Canada

Accepted for publication in *Trends in Endocrinology & Metabolism, 2019*

Highlights

- Human trials using hyperinsulinemic–euglycemic clamps coupled with preclinical studies in animal models have pointed to proanthocyanidins (PACs), ellagitannins, and resveratrol as promising strategies against metabolic syndrome.
- Studies using germ-free models and fecal microbiota transplants (FMTs) are beginning to unveil a causal relationship between gut microbial changes and the cardiometabolic benefits of PACs, ellagitannins, and resveratrol.
- Polyphenols act primarily on the gut lumen; their health benefits possibly derive from reshaping of the interplay between the gut microbes and host im-mune system and/or modification of the set of microbial metabolites bioavailable to the host.
- While recent research has confirmed the prebiotic effect of polyphenols on *Akkermansia muciniphila*, this bacterium is unlikely to be the sole player in the trialog between polyphenols, microbes, and host immunometabolism.

Polyphenols are nonessential phytonutrients abundantly found in fruits and vegetables. A wealth of data from preclinical models and clinical trials consistently supports cardiometabolic benefits associated with dietary polyphenols in murine models and humans. Furthermore, a growing number of studies have shown that specific classes of polyphenols, such as proanthocyanidins (PACs) and ellagitannins, as well as the stilbenoid resveratrol, can alleviate several features of the metabolic syndrome. Moreover, mounting evidence points to the gut microbiota as a key mediator of the health benefits of polyphenols. In this review we summarize recent findings supporting the beneficial potential of polyphenols against cardiometabolic diseases, with a focus on the role of host–microbe interactions.

A New Perspective on the Health Benefits of Polyphenols

Polyphenols were first described by the 1937 Nobel Prize laureate Dr Albert Szent-Györgyi (Box 1 and Figure 1). Since his initial discovery, a wealth of epidemiological studies has documented an inverse correlation between the intake of polyphenol-rich foods and the incidence of **cardiometabolic diseases** (see Glossary) and cancer [1]. While these studies corroborate an aspect of the widespread nutritional recommendation of consumption of five portions of fruits and vegetables per day, preclinical studies in various animal models have been instrumental in deciphering some of the putative mechanisms associated with the health benefits of both isolated polyphenols [2,3] and polyphenol-rich extracts mainly from fruits [4,5]. These mechanistic studies often faced criticism arising from the fact that several polyphenolic compounds are poorly bio-available (Box 2). A potential explanation for this apparent paradox began to emerge when it was realized that the **gut microbiota** was capable of metabolizing polyphenols and that some of their effects on the host could be linked to the interaction between polyphenols and gut micro-organisms. This concept is consistent with the well-demonstrated role of the gut microbiota as a bridge between environmental cues and host metabolism and with dietary factors being a key environmental trigger in changing gut microbial community structures in health or disease [6,7]. Mounting evidence suggests that the health benefits of polyphenols rely on gut microbial alterations and/or microbially derived phenolic metabolites [4,8,9] (Box 2), which allows the definition of polyphenols as **prebiotics** [10]. In line with this beneficial dialog between dietary polyphenols and the gut microbiota, recent studies have demonstrated cardiometabolic benefits (e.g., decreased weight gain and systemic inflammation, increased glucose tolerance) of ingesting polymeric proanthocyanidins (PACs) and ellagitannins in both animal models [4,9,11] and humans [12]. Using a murine model of diet-induced

obesity, our group examined the impact of various extracts of arctic berries on features of **metabolic syndrome**; we found that extracts rich in PACs and/or ellagitannins exerted the most pronounced benefits on fasting and postprandial insulin levels and on insulin resistance [13]. This review is focused on (but not limited to) the cardiometabolic benefits of these two classes of polyphenols. We also review the growing evidence implicating the gut microbiota in the health benefits of resveratrol, which is a new consideration for a nonflavonoid prototypic stilbene that is extensively studied in cardiometabolic health [14,15] (Table 1).

Polymeric Polyphenols and Cardiometabolic Diseases

Polymeric and oligomeric flavan-3-ols are both abundant in cranberries, grapes, apple peel, blueberries, and cocoa. The bioavailability of these compounds is highly dependent on the enzymatic machinery of gut microbes to release monomers of flavan-3-ols and to further oxidize these monomers, yielding valerolactones and other phenolic acids [21]. These compounds are more bioavailable than the parent dietary polyphenols [22] and the concentration of microbially derived phenolics normally surpasses that of the parent compound in the circulation [23]. Several bacterial species have been implicated in the biotransformation of PACs, such as *Flavonifractor plautii*, *Eubacterium* sp. strain SDG2, *Eggerthella lenta*, *Clostridium coccoides*,and *Bifidobacterium infantis* [21,24]. The main products of gut microbial transformation of PACs include 5-(3',4'-dihydroxyphenyl)- -valerolactone, 5-(3'-hydroxyphenyl)- -valerolactone, 3-(3-hydroxyphenyl) propionic acid, 3-hydroxyhippuric acid, and monomers of flava-3-ols, such as catechin and epicatechin. In the case of ellagitannins, both the monomer ellagic acid and the ellagic acid derivative urolithin are generated by Gordonibacter urolithinfaciens [25], although other bacteria are proba-bly involved in this process.

The cardiometabolic relevance of dietary PACs has been demonstrated in humans. Regular consumption or administration of cocoa flavanols was linked to lower blood pressure, reduced low-density lipoprotein (LDL) cholesterol, and lower susceptibility to LDL oxidation by several authors (reviewed in [26]). We are making considerable advances in understanding how PACs improve insulin sensitivity. In a recent study, our group applied hyperinsulinemic–euglycemic clamps and found that the administration of 0.33 g/day of a mixed extract from cranberries and strawberries (rich in PACs and phenolic acids) to obese subjects for 6 weeks increased insulin sensitivity and lowered first-phase insulin secretion without affecting body weight gain, lipid profile, or markers of oxidative stress [12]. Similarly, using hyperinsulinemic–euglycemic clamps, Stull *et al*. showed that the administration of 45 g of blueberries per day to obese volunteers for 6 weeks improved insulin sensitivity and did not alter body weight, lipid profile, or inflammatory biomarkers [27]. Another group studied overweight and obese healthy volunteers challenged with a high-fructose dose. Using hyperinsulinemic–euglycemic clamps the authors found that the administration of 2 g of grape polyphenols per day for 8–9 weeks prevented fructose-induced insulin resistance and muscle oxidative stress [28]. Together, these human studies suggest that: (i) the benefits of PACs on insulin sensitivity are not linked to changes in body weight (and presumably fat mass); and (ii) dietary PACs target postprandial insulin response and possibly fasting insulin.

Recent studies using mouse models support these claims and have begun to reveal underlying mechanisms. Our group showed that mice pre-fed a high-fat diet (HFD) rich in sucrose for 21 weeks and orally treated with a cranberry extract (200 mg/kg/day) for an additional 8 weeks had improved glucose tolerance, lower postprandial and fasting insulin, better insulin sensitivity, and lower hepatic steatosis [16]. In another study, we further showed that concomitant administration of PAC- and ellagitannin-rich extracts of arctic berries to mice fed an obesogenic diet also exerted beneficial effects. Although these extracts had no effect on glucose tolerance (as measured by oral glucose-tolerance tests), they lowered both fasting and postprandial insulin by enhancing hepatic insulin clearance and alleviating hepatic steatosis [13]. Together these data unequivocally point to dietary PACs as a strategy to alleviate metabolic syndrome. As the above extracts contained a mix of polyphenols, and several doses were tested throughout the studies mentioned, research is warranted to narrow down which types of polyphenols are more bioactive (and at what dose) for specific aspects of the metabolic syndrome and **nonalcoholic fatty liver disease (NAFLD)**.

While the benefits of monomers of flava-3-ols, such as (-)-epicatechin, on features of metabolic syndrome have been demonstrated in animal models [29] and humans [30],PAC-derived monomers appear less in the urine than valerolactones after dietary intake of green tea and green coffee extracts [31]. This may suggest higher physiological relevance of valerolactones over monomers released from dietary PACs. A recent *in vitro* study pointed out 5-(3',4'-dihydroxyphenyl)- -valerolactone as bioactive against atherosclerosis [32]; however, *in vivo* validation of these findings is warranted and, overall, more in vivo studies are needed to assess the putative cardiometabolic benefits of valerolactones at **nutritionally relevant doses**. It is noteworthy at this point to mention that several studies using mouse models to evaluate the ef-fects of certain polyphenols on insulin sensitivity and glucose tolerance often do not consider changes in food intake, body weight gain, and fat mass accumulation as key confounding factors in their mechanistic assessments.

Resveratrol and Glucose Homeostasis

Resveratrol (3,5,4'-trihydroxystilbene) is a major bioactive phenol found in red wine, red grapes, and other plant-based food sources. This molecule has been shown to exert beneficial actions in chronic diseases including cancer, neurodegenerative diseases, and obesity [33]. In addition, numerous clinical trials are under way to determine whether resveratrol is beneficial in the setting of type 2 diabetes (T2D) (http://clinicaltrials.gov), which will follow up on a study that showed that a 30-day treatment with resveratrol induces positive metabolic changes in healthy obese patients [34]. That study is in complete agreement with resveratrol improving insulin sensitivity and restoring glucose homeostasis in obese mice [35,36], suggesting that the beneficial metabolic effects of resveratrol are maintained across species. However, despite a recent meta-analysis of 11 randomized controlled trials demonstrating that resveratrol significantly improves glucose homeostasis in people with diabetes [37], there are a number of neutral or negative trials involving resveratrol [38,39]. It is unclear why resveratrol has disparate results on glucose homeostasis, but this is likely to involve differences in dosing and the source of the stilbene used. Supplementation versus dietary source is another key factor to consider, since it has potential implications for the bioavailability of the compound and its interaction with gut microbes. Moreover, whether resveratrol has

direct insulin-sensitizing effects on peripheral tissues [35,36] or whether intra-organ signaling is the primary mechanism of action [40] is still being debated.

Evidence That Polyphenol-Mediated Changes to the Gut Microbiota Are Sufficient (or Necessary) to Improve Cardiometabolic Health

The interaction between dietary polyphenols and gut microbes is a two-way road: while the gut microbiota modifies dietary polyphenols, the latter may also alter the structure of the former, which, could, *per se* impacts host metabolism [4,8]. This implies that the absorption of certain polyphenols is not entirely necessary to generate a metabolic benefit. Recent metagenome-wide association studies, human trials, and preclinical studies using animal models and fecal microbiota transplants (FMTs) have been demonstrating this concept.

Zhernakova *et al*. sequenced the gut **microbiome** of 1135 subjects and calculated how each dietary feature in this population correlated with three metrics of α-diversity (COG richness, gene richness, and Shannon index) and how strongly these dietary habits explained differences in β-diversity (expressed by means of Bray–Curtis distance) [8]. Among the dietary habits positively correlated with gut microbial richness, the frequencies of fruit, coffee, vegetable, red wine, and tea intake – all important sources of polyphenols – stood out as major factors [8].Moreover, the authors showed that the intake of fruits, vegetables, tea, coffee, and red wine were among the variables that more strongly explained differences between the individuals' gut microbial populations [8]. Given that high gut microbial richness is linked to better metabolic fitness [41], this work strongly suggests that dietary polyphenols modify gut microbial community structure in humans to confer cardiometabolic benefits on the host.

PACs, Ellagitannins, and Gut Microbiota

The set of microbial phenolic metabolites produced from dietary polyphenols varies across individuals. The most well-known case is that of daidzein (an isoflavone found in soy). While approximately 30% of the Western population possess microbes in the large intestine capable of producing S-equol from daidzein the rest of the population is unable to produce this metabolite. The existence of two metabotypes driving S-equol synthesis is potentially relevant given the alleged effect of this molecule on glucose and lipid homeostasis [42]. However in a recent study the authors found that individuals from the nonproducing S-equol metabotype did not display cardiometabolic improvements after administration of S-equol [43] calling into question the role of S-equol in the beneficial effects of daidzein or suggesting that other aspects of the gut microbiome of S-equol responders drive the benefits of this soy isoflavone in the host. A similar case was observed in a study using pomegranate (a rich source of ellagitannins). Three metabotypes have been proposed with respect to the microbial conversion of ellagitannins to urolithins: metabotype A produces urolithin A; metabotype B is able to produce urolithin B and isourolithin A; and metabotype 0 is unable to synthesize urolithins [44]. Furthermore preclinical research has identified urolithin A as having great potential to enhance muscle function [45]. The authors administered a pomegranate extract to subjects of metabotype A or B and, while the former showed better lipid profile at baseline than the latter, subjects of metabotype B displayed greater improvements in total cholesterol as well as in high-density lipoprotein (HDL) and LDL cholesterol after treatment [46]. This study challenges the notion of gut microbial urolithin A as the major link between dietary intake of ellagitannins and cardiometabolic health while suggesting that the gut microbiome is importantly involved in promoting cardiometabolic protection after ellagitannin intake.

Our group has examined the impact of the Amazonian fruit camu camu (a rich blend of ellagitannins and PACs) using a murine model of diet-induced obesity. Daily administration of a camu camu extract (200 mg/kg) for 8 weeks prevented fat-mass gain, augmented energy expenditure, and increased markers of brown adipose tissue (BAT) activation [4]. When germ-free mice were colonized with the fecal microbiota of camu camu-treated donor mice, they expended more energy and lost weight compared with germ-free mice colonized with the microbiota of vehicle-treated donor mice [4]. Importantly, the fecal slurry of camu camu-treated donor mice contained trace and negligible amounts of polyphenols, implying that the gut microbiota in these mice is sufficient to transmit the phenotype to germ-free recipient mice.

Liu *et al*. showed that a PAC-rich grape seed extract (300 mg/kg/day) reduced plasma and adipose tissue inflammation in HFD-fed mice, traits that paralleled improved glucose clearance and insulin sensitivity. Antibiotic treatment abolished the benefits of grape seed extract treatment [17], suggesting that gut microbes are necessary for the effect of grape seed polyphenols on glucose homeostasis.

Apigenin, Naringenin, and Gut Microbiota

Two reports on the gut microbial-related metabolic benefits of apigenin and naringenin are note-worthy. The first study, using a mouse model and FMTs, have brought evidence to support gut microbial processing of polyphenols playing a role in host energy balance. Thaiss *et al*. found a microbial signature that persists after weight loss and that favors weight regain in high-fat-fed mice. Among the functional features of such a microbial signature, depleted isoflavonoid biosynthesis and higher flavanone 4-reductase activity stood out [47]. The authors showed that accelerated weight regain is transmissible through the fecal microbiota to germ-free mice and that flavonoid (apigenin and naringenin) replenishment in post-dieting mice prevented the exacerbated weight regain [47]. In the second study, Radulovic *et al*. reported further evidence for the role of gut microbes in the benefits of the flavone apigenin. The authors demonstrated that this molecule protected against dextran sulfate sodium (DSS)-induced colitis and that the effect was transmissible on cohousing and dependent on NOD-like receptor family pyrin domain containing 6 (NLRP6) but independent of inflammasome activation [3]. Studies are warranted to test whether these findings are linked to cardiometabolic benefits, since a damaged gut barrier has been associated with dysglycemia and insulin resistance [48]. Put into perspective, the latter studies suggest that the gut microbiota

mediates the effects of apigenin by complementary mechanisms driven by innate immune responses and by modifying the set of metabolites bioavailable to the host (Box 3).

Resveratrol and Gut Microbiota

Similar to PACs and ellagitannins, resveratrol has low bioavailability when administered orally and accumulates in the intestine [49]; it is not absorbed in any significant amount in that organ and thus reaches the colon unmetabolized, where it can interact with the gut microbiota [50]. Resveratrol can alter the gut microbiome, which is associated with improved glucose homeostasis [14]. Furthermore, transfer of fecal matter from resveratrol-fed mice to conventional C57BL/6 mice fed a HFD was able to significantly improve whole-body glucose clearance and peripheral insulin sensitivity, suggesting that changes in the gut microbiome may be involved in the beneficial effects of resveratrol [15]. However, heat killing of the bacteria in the fecal slurry prior to FMT did not prevent the beneficial effects of the FMT [15], suggesting that metabolites of resveratrol and/or bacterially derived metabolites induced by resveratrol may be responsible for the improved glucose homeostasis in obese mice undergoing FMT from resveratrol-fed donor mice. Alternatively, metabolites from heat-killed bacteria or components of the bacteria (alive or dead) may interact with the intestinal cells to induce metabolic changes in a manner similar to what we observed with the bacterium *A. muciniphila* [51,52]. Thus, identifying how FMT improves glucose homeostasis in obese mice as well as what components of the FMT are responsible for mediating the beneficial effects of resveratrol and other polyphenols could help to identify new strategies for the treatment of T2D.

Although evidence suggests a potential involvement of the gut microbiota in the beneficial effects of resveratrol, in previous work 30–84% of the administered resveratrol was observed in the urine and feces as metabolites of resveratrol, depending on the dose administered (i.e., 50 and 300 mg resveratrol/kg body weight/day for 8 weeks) [53]. This suggests that these metabolites may be important biologically active compounds that could also contribute to the improvements in glucose homeostasis observed with the oral transfer of fecal matter from resveratrol-fed donor mice. In addition, since feces of rats fed resveratrol exhibit b1% to 17% recovery of unmetabolized resveratrol [53], fecal transfer of sufficiently high concentrations of resveratrol to exert a biological effect is unlikely. This is especially true compared with the multifold-higher levels of orally fed resveratrol (for a much longer duration) that are needed to induce effects similar to those observed after an acute FMT protocol [15]. Thus, it is highly possible that one or more metabolites of resveratrol (derived from either liver or intestinal cells [53] or microbes) or some other microbe-derived metabolites/products are also administered to the mice during a FMT protocol [14,15] and that these compounds produce the improvement in glucose homeostasis observed in obese mice. Thus, the elucidation of the mechanisms of action of FMT from resveratrol-fed donor mice and/or the identification of new metabolites of resveratrol that are extremely effective and potent agents that can improve glucose homeostasis in obesity has great potential and could be a significant step forward in the treatment of T2D (Figure 2).

Polyphenols and *A. muciniphila*: What Is Next?

Several lines of evidence from preclinical studies using animal models point to PACs and ellagitannins as having a positive impact on the gut barrier, thereby alleviating metabolic endotoxemia and eliciting favorable cardiometabolic outcomes (Box 3) [4,5,13]. Although more research is warranted, such a mechanism of action seems reproducible in humans and applicable to other types of polyphenols [54]. The gut barrier is in close contact and constantly interacting with both commensals and potential pathogens (Box 3), which implies that the benefits of dietary PACs and ellagitannins to gut barrier homeostasis are, at least in part, dependent on changes in gut microbial communities.

A prototypical example of the polyphenol–gut microbiota–gut barrier trialog is the case of *A. muciniphila*. Lower abundance of *A. muciniphila* has been found in the feces of patients with T2D [55],inflammatory bowel disease (IBD) [56], and appendicitis [57]. Both human and mouse studies have correlated the presence of *A. muciniphila* in the gut microbiota with leanness, higher gut bacterial richness, and better glycemic control [6,58]. Concordantly, studies using animal models have shown a causative role for *A. muciniphila* in protecting the gut barrier, which was associated with increased mucus layer thickness, improved glucose homeostasis, and alleviated metabolic endotoxemia [51]. We demonstrated that oral treatment of obese mice with a PAC-rich cranberry extract had a major prebiotic effect on *A. muciniphila*, which paralleled alleviated endotoxemia and cardiometabolic improvements [5,16]. Similar findings were found by us and by others using extracts from camu [4], pomegranate [59], table grape [18], concord grape [9], rhubarb [60], and lingonberry [13,19] as well as nonabsorbable apple PACs [11].Thesedata not only confirm the prebiotic effect of PACs on *A. muciniphila* but also extend this finding to other classes of polyphenols.

Recent data, however, indicate that not all polyphenols are alike when it comes to changes in *A. muciniphila* population. Resveratrol has been shown to attenuate diet-induced obesity in association with reduced *A. muciniphila* in mice, suggesting that some polyphenols may not mobilize *A. muciniphila* to produce a cardiometabolic benefit for the host [14]. In a recent report, Zhang *et al*. showed that the baseline *A. muciniphila* abundance influences the changes seen in this bacterium after the administration of a PAC-rich grape extract to mice [61], which might explain, in addition to fecal DNA extraction methods and plant source, why some authors did not report changes in *A. muciniphila* population when studying PAC- and ellagitannin-rich extracts [20,46]. The fact that the cardiometabolic benefits of polyphenols are not always dependent on the blooming of *A. muciniphila* in the gut microbiota suggest that this bacterium, despite being influenced by PACs and ellagitannins, is not essential for at least some polyphenols to positively impact health markers [17,18,20,62]. This is in line with the functional redundancy typical of intestinal bacteria, whereby, from an evolutionary view point, it is unlikely that a single species will be the only one accounting for a given function. When studying the impact of various PAC-and ellagitannin-rich extracts in diet-induced obese mice, our group consistently observed a bloom of Barnesiella spp. in mice treated with polyphenolic extracts [4,16]. This genus (possibly *Barnesiella intestinihominis*) has been shown by others to be increased following intake of fruits and vegetables [63] and black tea [62]; moreover, *Barnesiella* spp. were shown to confer resistance to intestinal growth and bloodstream infection with vancomycin-resistant *Enterococcus* [64]. Consistently, administration of *B. intestinihominis* markedly increased the efficacy of the anticancer immunomodulatory agent cyclophosphamide in mice [65]. Together, this identifies *Barnesiella* spp. as a putative prebiotic target of PACs

and ellagitannins and calls for its potential development into a second-generation **probiotic** to aid in the treatment of cardio-metabolic diseases and cancer.

Concluding Remarks an Future Perspectives

Mounting evidence supports the cardiometabolic benefits of polyphenols. Research is now pointing to polymers of polyphenols, such as PACs and ellagitannins, and to resveratrol as promising natural molecules to prevent and/or aid in the treatment of metabolic syndrome's numerous clinical manifestations, such as T2D and NAFLD (see Outstanding Questions). These claims have been supported by human trials using 'gold-standard' techniques such as hyperinsulinemic–euglycemic clamps, which provides a great deal of reliability. Animal studies using germ-free models coupled with FMT have been instrumental in demonstrating causality for the well-known gut microbial changes in response to dietary polyphenols. We are moving from simply knowing the names of bacteria to understanding their causal relevance (see Outstanding Questions).

It seems clear now that polymeric polyphenols and resveratrol (and possibly other polyphenols, such as apigenin and naringenin) act primarily on the gut lumen; their health benefits possibly derive from a reshaping of the interplay between gut microbes and the host immune system and from modification of the set of microbial metabolites bioavailable to the host. These metabolites can stem from or be directly induced by polyphenols, albeit using a nonpolyphenol substrate for its synthesis. Moving forward it will be importanttogobeyondconcepts such as chronic inflammation or systemic insulin resistance and to define the compartmentalized immune and metabolic mechanisms in the gut, immune cells, and key metabolic cells (liver, muscle, and fat) that can modify cardiometabolic disease risk [66].

Research has paved the way for human trials with combinations of PACs, ellagitannins, and resveratrol as an alternative treatment or preventive strategy against the cardiometabolic complications of metabolic syndrome. For human trials, other considerations such as age, sexual dimorphism, and the diversity of the gut microbiome between subjects in populations of interest must be taken into account. Differing baselines may be a confounding factor that influences patient outcomes and thus need to be fully appreciated and/or controlled for prior to the initiation of larger-scale studies. While human FMT studies face obvious ethical hurdles and are extremely difficult to conduct, further studies using animal models remain necessary to better understand the role of gut microbes in the health benefits of polyphenols. While the prebiotic impact of PACs and ellagitannins on *A. muciniphila* was reproducibly reported, this bacterium is hardly the only relevant prebiotic target of polyphenols (see Outstanding Questions). The isolation of new potential bacterial targets of dietary PACs, ellagitannins, and resveratrol and the development of novel probiotic, post-biotic, or symbiotic agents to fight chronic inflammatory disorders such as metabolic syndrome and cancer are important future perspectives.

References

1. Arts, I.C. and Hollman, P.C. (2005) Polyphenols and disease risk in epidemiologic studies. Am. J. Clin. Nutr. 81, 317s–325s
2. Anhê, G.F. et al. (2012) Quercetin decreases inflammatory response and increases insulin action in skeletal muscle of ob/ob mice and in L6 myotubes. Eur. J. Pharmacol. 689, 285–293
3. Radulovic, K. et al. (2018) A dietary flavone confers communicable protection against colitis through NLRP6 signaling independently of inflammasome activation. Mucosal Immunol. 11, 811–819
4. Anhê, F.F. et al. (2019) Treatment with camu (Myrciaria dubia) prevents obesity by altering the gut microbiota and increasing energy expenditure in diet-induced obese mice. Gut 68, 453–464
5. Anhê, F.F. et al. (2015) A polyphenol-rich cranberry extract pro-tects from diet-induced obesity, insulin resistance and intestinal inflammation in association with increased Akkermansia spp. population in the gut microbiota of mice. Gut 64, 872–883
6. Le Chatelier, E. et al. (2013) Richness of human gut microbiome correlates with metabolic markers. Nature 500, 541–546
7. Ridaura, V.K. et al. (2013) Gut microbiota from twins discordant for obesity modulate metabolism in mice. Science 341, 1241214
8. Zhernakova, A. et al. (2016) Population-based metagenomics analysis reveals markers for gut microbiome composition and diversity. Science 352, 565–569
9. Roopchand, D.E. et al. (2015) Dietary polyphenols promote growth of the gut bacterium Akkermansia muciniphila and atten-uate high-fat diet-induced metabolic syndrome. Diabetes 64, 2847–2858
10. Gibson, G.R. et al. (2017) Expert consensus document: the International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. Nat. Rev. Gastroenterol. Hepatol. 14, 491–502
11. Masumoto, S. et al. (2016) Non-absorbable apple procyanidins prevent obesity associated with gut microbial and metabolomic changes. Sci. Rep. 6, 31208
12. Paquette, M. et al. (2017) Strawberry and cranberry polyphenols improve insulin sensitivity in insulin-resistant, non-diabetic adults: a parallel, double-blind, controlled and randomised clinical trial. Br. J. Nutr. 117, 519–531
13. Anhê, F.F. et al. (2018) Arctic berry extracts target the gut–liver axis to alleviate metabolic endotoxaemia, insulin resistance and hepatic steatosis in diet-induced obese mice. Diabetologia 61, 919–931
14. Sung, M.M. et al. (2017) Improved glucose homeostasis in obese mice treated with resveratrol is associated with alterations in the gut microbiome. Diabetes 66, 418–425

15. Kim, T.T. et al. (2018) Fecal transplant from resveratrol-fed do-nors improves glycaemia and cardiovascular features of the met-abolic syndrome in mice. Am.J.Physiol.Endocrinol.Metab. 315, E511–E519

16. Anhê, F.F. et al. (2017) A polyphenol-rich cranberry extract re-verses insulin resistance and hepatic steatosis independently of body weight loss. Mol. Metab. 6, 1563–1573

17. Liu, W. et al. (2017) Grape seed proanthocyanidin extract ame-liorates inflammation and adiposity by modulating gut microbiota in high-fat diet mice. Mol. Nutr. Food Res. 61, 1601082

18. Baldwin, J. et al. (2016) Table grape consumption reduces adiposity and markers of hepatic lipogenesis and alters gut microbiota in butter fat-fed mice. J. Nutr. Biochem. 27, 123–135

19. Heyman-Linden, L. et al. (2016) Lingonberries alter the gut microbiota and prevent low-grade inflammation in high-fat diet fed mice. Food Nutr. Res. 60, 29993

20. Van Hul, M. et al. (2018) Reduced obesity, diabetes, and steatosis upon cinnamon and grape pomace are associated with changes in gut microbiota and markers of gut barrier. Am. J. Physiol. Endocrinol. Metab. 314, E334–E352

21. Ozdal, T. et al. (2016) The reciprocal interactions between polyphenols and gut microbiota and effects on bioaccessibility. Nutrients 8, 78

22. Ottaviani, J.I. et al. (2016) The metabolome of [2-14C](-)-epicate-chin in humans: implications for the assessment of efficacy, safety, and mechanisms of action of polyphenolic bioactives. Sci. Rep. 6, 29034

23. Pimpao, R.C. et al. (2015) Phenolic sulfates as new and highly abundant metabolites in human plasma after ingestion of a mixed berry fruit puree. Br. J. Nutr. 113, 454–463

24. Marin, L. et al. (2015) Bioavailability of dietary polyphenols and gut microbiota metabolism: antimicrobial properties. Biomed. Res. Int. 2015, 905215

25. Selma, M.V. et al. (2014) Gordonibacter urolithinfaciens sp. nov., a urolithin-producing bacterium isolated from the human gut. Int. J. Syst. Evol. Microbiol. 64, 2346–2352

26. Williamson, G. (2017) The role of polyphenols in modern nutri-tion. Nutr. Bull. 42, 226–235

27. Stull, A.J. et al. (2010) Bioactives in blueberries improve insulin sensitivity in obese, insulin-resistant men and women. J. Nutr. 140, 1764–1768

28. Hokayem, M. et al. (2013) Grape polyphenols prevent fructose-induced oxidative stress and insulin resistance in first-degree rel-atives of type 2 diabetic patients. Diabetes Care 36, 1454–1461

29. Cremonini, E. et al. (2016) (-)-Epicatechin improves insulin sensitivity in high fat diet-fed mice. Arch. Biochem. Biophys. 599, 13–21

30. Gutiérrez-Salmeán, G. et al. (2016) A randomized, placebo-controlled, double-blind study on the effects of (-)-epicatechin on the triglyceride/HDLc ratio and cardiometabolic profile of subjects with hypertriglyceridemia: unique in vitro effects. Int. J. Cardiol. 223, 500–506

31. Mena, P. et al. (2018) Inter-individual variability in the production of flavan-3-ol colonic metabolites: preliminary elucidation of urinary metabotypes. Eur. J. Nutr. Published online April 3, 2018. https://doi.org/10.1007/s00394-018-1683-4

32. Lee, C.C. et al. (2017) 5-(3′,4′-Dihydroxyphenyl-γ-valerolactone), a major microbial metabolite of proanthocyanidin, attenuates THP-1 monocyte–endothelial adhesion. Int. J. Mol. Sci. 18, E1363

33. Baur, J.A. and Sinclair, D.A. (2006) Therapeutic potential of res-veratrol: the in vivo evidence. Nat. Rev. Drug Discov. 5, 493–506

34. Timmers, S. et al. (2011) Calorie restriction-like effects of 30 days of resveratrol supplementation on energy metabolism and metabolic profile in obese humans. Cell Metab. 14, 612–622

35. Lagouge, M. et al. (2006) Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1α. Cell 127, 1109–1122

36. Baur, J.A. et al. (2006) Resveratrol improves health and survival of mice on a high-calorie diet. Nature 444, 337–342

37. Liu, K. et al. (2014) Effect of resveratrol on glucose control and insulin sensitivity: a meta-analysis of 11 randomized controlled trials. Am. J. Clin. Nutr. 99, 1510–1519

38. Scribbans, T.D. et al. (2014) Resveratrol supplementation does not augment performance adaptations or fibre-type-specific responses to high-intensity interval training in humans. Appl. Physiol. Nutr. Metab. 39, 1305–1313

39. Poulsen, M.M. et al. (2013) High-dose resveratrol supplementa-tion in obese men: an investigator-initiated, randomized, placebo-controlled clinical trial of substrate metabolism, insulin sensitivity, and body composition. Diabetes 62, 1186–1195

40. Cote, C.D. et al. (2015) Resveratrol activates duodenal Sirt1 to reverse insulin resistance in rats through a neuronal network. Nat. Med. 21, 498–505

41. Cotillard, A. et al. (2013) Dietary intervention impact on gut microbial gene richness. Nature 500, 585–588

42. Usui, T. et al. (2013) Effects of natural S-equol supplements on overweight or obesity and metabolic syndrome in the Japanese, based on sex and equol status. Clin. Endocrinol. 78, 365–372

43. Hazim, S. et al. (2016) Acute benefits of the microbial-derived isoflavone metabolite equol on arterial stiffness in men prospectively recruited according to equol producer phenotype: a double-blind randomized controlled trial. Am. J. Clin. Nutr. 103, 694–702

44. Bolca, S. et al. (2013) Gut metabotypes govern health effects of dietary polyphenols. Curr. Opin. Biotechnol. 24, 220–225

45. Ryu, D. et al. (2016) Urolithin A induces mitophagy and prolongs lifespan in C. elegans and increases muscle function in rodents. Nat. Med. 22, 879–888

46. González-Sarrías, A. et al. (2017) Clustering according to urolithin metabotype explains the interindividual variability in the improvement of cardiovascular risk biomarkers in overweight–obese individuals consuming pomegranate: a randomized clini-cal trial. Mol. Nutr. Food Res. 61, 1600830

47. Thaiss, C.A. et al. (2016) Persistent microbiome alterations mod-ulate the rate of post-dieting weight regain. Nature 540, 544

48. Cani, P.D. et al. (2007) Metabolic endotoxemia initiates obesity and insulin resistance. Diabetes 56, 1761–1772

49. Vitrac, X. et al. (2003) Distribution of [14C]-trans-resveratrol, a cancer chemopreventive polyphenol, in mouse tissues after oral administration. Life Sci. 72, 2219–2233

50. Manach, C. et al. (2004) Polyphenols: food sources and bioavail-ability. Am. J. Clin. Nutr. 79, 727–747

51. Plovier, H. et al. (2017) A purified membrane protein from Akkermansia muciniphila or the pasteurized bacterium improves metabolism in obese and diabetic mice. Nat. Med. 23, 107–113

52. Everard, A. et al. (2013) Cross-talk between Akkermansia muciniphila and intestinal epithelium controls diet-induced obe-sity. Proc. Natl. Acad. Sci. U. S. A. 110, 9066–9071

53. Wenzel, E. et al. (2005) Bioactivity and metabolism of trans-resveratrol orally administered to Wistar rats. Mol. Nutr. Food Res. 49, 482–494

54. Deopurkar, R. et al. (2010) Differential effects of cream, glucose, and orange juice on inflammation, endotoxin, and the expression of toll-like receptor-4 and suppressor of cytokine signaling-3. Di-abetes Care 33, 991–997

55. Yassour, M. et al. (2016) Sub-clinical detection of gut microbial biomarkers of obesity and type 2 diabetes. Genome Med. 8, 17

56. Png, C.W. et al. (2010) Mucolytic bacteria with increased preva-lence in IBD mucosa augment in vitro utilization of mucin by other bacteria. Am. J. Gastroenterol. 105, 2420–2428

57. Swidsinski, A. et al. (2011) Acute appendicitis is characterised by local invasion with Fusobacterium nucleatum/necrophorum. Gut 60, 34–40

58. Dao, M.C. et al. (2016) Akkermansia muciniphila and improved metabolic health during a dietary intervention in obesity: relationship with gut microbiome richness and ecology. Gut 65, 426–436

59. Henning, S.M. et al. (2017) Pomegranate ellagitannins stimulate the growth of Akkermansia muciniphila in vivo. Anaerobe 43, 56–60

60. Neyrinck, A.M. et al. (2017) Rhubarb extract prevents hepatic in-flammation induced by acute alcohol intake, an effect related to the modulation of the gut microbiota. Mol. Nutr. Food Res. 61, 1500899

61. Zhang, L. et al. (2018) Grape proanthocyanidin-induced intesti-nal bloom of Akkermansia muciniphila is dependent on its base-line abundance and precedes activation of host genes related to metabolic health. J. Nutr. Biochem. 56, 142–151

62. Henning, S.M. et al. (2018) Decaffeinated green and black tea polyphenols decrease weight gain and alter microbiome popula-tions and function in diet-induced obese mice. Eur. J. Nutr. 57, 2759–2769

63. Henning, S.M. et al. (2017) Health benefit of vegetable/fruit juice-based diet: role of microbiome. Sci. Rep. 7, 2167

64. Ubeda, C. et al. (2013) Intestinal microbiota containing Barnesiella species cures vancomycin-resistant Enterococcus faecium colonization. Infect. Immun. 81, 965–973

65. Daillere, R. et al. (2016) Enterococcus hirae and Barnesiella intestinihominis facilitate cyclophosphamide-induced therapeu-tic immunomodulatory effects. Immunity 45, 931–943

66. McPhee, J.B. and Schertzer, J.D. (2015) Immunometabolism of obesity and diabetes: microbiota link compartmentalized immu-nity in the gut to metabolic tissue inflammation. Clin. Sci. (Lond.) 129, 1083–1096

67. Grzybowski, A. and Pietrzak, K. (2013) Albert Szent-Györgyi (1893–1986): the scientist who discovered vitamin C. Clin. Dermatol. 31, 327–331

68. Manach, C. et al. (2005) Bioavailability and bioefficacy of poly-phenols in humans. I. Review of 97 bioavailability studies. Am. J. Clin. Nutr. 81, 230s–242s

69. Day, A.J. et al. (2000) Dietary flavonoid and isoflavone glycosides are hydrolysed by the lactase site of lactase phlorizin hydrolase. FEBS Lett. 468, 166–170

70. Nakagawa, K. et al. (1997) Dose-dependent incorporation of tea catechins, (-)-epigallocatechin-3-gallate and (-)-epigallocatechin, into human plasma. Biosci. Biotechnol. Biochem. 61, 1981–1985

71. Moco, S. et al. (2012) Metabolomics view on gut microbiome modulation by polyphenol-rich foods. J. Proteome Res. 11, 4781–4790

72. Selma, M.V. et al. (2014) Description of urolithin production ca-pacity from ellagic acid of two human intestinal Gordonibacter species. Food Funct. 5, 1779–1784

73. Rowland, I. et al. (2018) Gut microbiota functions: metabolism of nutrients and other food components. Eur. J. Nutr. 57, 1–24

74. Amar, J. et al. (2011) Intestinal mucosal adherence and translo-cation of commensal bacteria at the early onset of type 2 diabe-tes: molecular mechanisms and probiotic treatment. EMBO Mol. Med. 3, 559–572

75. Denou, E. et al. (2015) Defective NOD2 peptidoglycan sensing promotes diet-induced inflammation, dysbiosis, and insulin re-sistance. EMBO Mol. Med. 7, 259–274

76. Ghoshal, S. et al. (2009) Chylomicrons promote intestinal ab-sorption of lipopolysaccharides. J. Lipid Res. 50, 90–97

77. Kopp, A. et al. (2010) Toll-like receptor ligands cause proinflam-matory and prodiabetic activation of adipocytes via phosphoryla-tion of extracellular signal-regulated kinase and c-Jun N-terminal kinase but not interferon regulatory factor-3. Endocrinology 151, 1097–1108

78. Jia, L. et al. (2014) Hepatocyte toll-like receptor 4 regulates obesity-induced inflammation and insulin resistance. Nat. Commun. 5, 3878

79. Lelouvier, B. et al. (2016) Changes in blood microbiota profiles associated with liver fibrosis in obese patients: a pilot analysis. Hepatology 64, 2015–2027

80. Schertzer, J.D. et al. (2011) NOD1 activators link innate immunity to insulin resistance. Diabetes 60, 2206–2215

81. Cavallari, J.F. et al. (2017) Muramyl dipeptide-based postbiotics mitigate obesity-induced insulin resistance via IRF4. Cell Metab. 25, 1063–1074.e3

82. Hill, C. et al. (2014) Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nat. Rev. Gastroenterol. Hepatol. 11, 506–514

83. Alberti, K.G. et al. (2006) Metabolic syndrome – anewworld-wide definition. A Consensus Statement from the International Diabetes Federation. Diabet. Med. 23, 469–480

Glossary

Cardiometabolic disease: a global term that includes abdominal obesity, T2D, NAFLD, and cardiovascular disease.

Gut microbiota: previously called gut flora; the ensemble of microbes that colonizes the intestinal lumen and mucosa. It comprises mostly bacteria, but viruses, fungi, and archaea are also integrated in this consortium.

Metabolic syndrome: cluster of cardiometabolic diseases that, when combined, increase the odds of heart disease. According to the most recent consensus from the International Diabetes Federation (IDF), to be defined as having metabolic syndrome a person must have abdominal (or central) obesity plus one of the following conditions: raised triglycerides (≥1.7 mmol/l), low HDL cholesterol (b1.03 mmol/l in men or b1.29 mmol/l in women), raised blood pressure (systolic ≥130 mm Hg, diastolic ≥85 mm Hg), and high fasting blood glucose (≥5.6 mmol/l) [83].

Metabotypes: clusters of individuals according to their metabolic diversity. Such differences can impact nutrient requirements and the individual's response to diet and medication.

Microbiome: set of microbial genes hosted by another living being.

Nonalcoholic fatty liver disease (NAFLD): accumulation of extra fat in the liver resulting from dysregulated lipid and glucose metabolism; it is seen as the hepatic manifestation of metabolic syndrome and comprises a group of common liver maladies whose severity progressively increases as hepatic fat accretion is aggravated. NAFLD ranges from hepatic steatosis and nonalcoholic steatotic hepatitis (NASH) to hepatic fibrosis or cirrhosis and early stages of hepatocellular carcinoma.

Nutritionally relevant dose: dose that mimics the concentration found in the circulation and tissues after a meal.

Prebiotics: substrates selectively utilized by host microorganisms to confer health benefits, according to the most recent consensus from the International Scientific Association for Probiotics and Prebiotics (ISAPP) [10]. This document expands the notion of prebiotics beyond carbohydrate-based substrates [e.g., fructooligosaccharide (FOS), galactooligosaccharide (GOS)], adding noncarbohydrate substrates, like polyunsaturated fatty acids and polyphenols, to the list of prebiotics (providing the health claims are convincingly substantiated by animal or human studies).

Probiotic: live microorganisms that, when administered in adequate amounts, confer a health benefitonthe host [82].

Richness and diversity: key ecological concepts used to describe microbial communities; while the former describes the number of organisms living in a community, the latter considers, in addition to the number of organisms, how evenly distributed they are. In other words, a community is richer when it possesses a wider repertoire of taxa and more diverse when the dominance of a few organisms is lower. There are two types of diversity: α-diversity, which considers communities within the same sample; and β-diversity, which reflects differences in communities between samples. Several indices are applied as ametricofα-diversity, with Chao1, Shannon, and Simpson often used. Chao 1 is a metric of richness, while Shannon and Simpson are indices that measure diversity. Total bacterial gene count (or bacterial gene richness) has also emerged as a robust measure of bacterial richness [6]. Several metrics can be used to express β-diversity, such as UniFrac, Bray–Curtis, and Jaccard distances. Bray–Curtis and Jaccard do not take into account phylogenetic relatedness between taxa whereas UniFrac does. For this reason, UniFrac is often the method of choice to assess β-diversity. Jaccard and unweighted UniFrac are qualitative indices (i.e., they consider only the presence or absence of taxa), whereas Bray–Curtis and weighted UniFrac are both quantitative (i.e., they take relative abundance of taxa into account).

Box 1. Discovery and Classification of Polyphenols

Originally looking for a cure for scurvy [67], Dr Szent-Györgyi prepared an extract from lemons, which effectively alleviated the bleeding gums problem of a friend of his. The effect was then attributed to vitamin C (also discovered by Dr Szent-Györgyi). However, when he gave to his friend a purified version of the extract (enriched in vitamin C), the effect was lost. Dr Szent-Györgyi analyzed the fraction he had removed from the purified extract and found out that it was rich in a molecule he then named vitamin P. The extract enriched in vitamin P alleviated his friend's bleeding gums, which led Dr Szent-Györgyi to conclude that vitamin P was important for vascular health. Further research demonstrated that vitamin P was a nonessential phytonutrient (mostly flavanones), which prompted its withdrawal from the list of vitamins. Nowadays these compounds are broadly classified as polyphenols (or flavonoids) and are known to occur as products of plant secondary metabolism in response to environmental stress. A wide range of polyphenols can be found in nature, from simple phenolic acids (with a single aromatic ring) to flavonoids (with two phenyl rings – A and B – linked by three carbons usually arranged as an oxygenated heterocycle – ring C) (Figure 1A,B). According to the degree of oxidation of ring C, polyphenols are divided into anthocyanins, flavonols, flavones, flavanols (also named flavan-3-ols or catechins), flavanones, and isoflavones; stilbenes and lignans exhibit substantial alterations in the heterocyclic ring C, and together with phenolic acids (which do not harbor the full flavone backbone) are considered nonflavonoid polyphenols (Figure 1A,B). An important feature of flavan-3-ols and phenolic acids is the fact that they naturally occur as oligomers and polymers. Polymeric flavan-3-ols are named condensed tannins (also known as PACs or procyanidins), whereas the term hydrolysable tannin refers to polymeric ellagic acid (also known as ellagitannin) or gallic acid (also known as gallotannin) [68] (Figure 1A,B). The structure of PACs is dependent both on the kind of monomer and the type of linkage between them; hydrolysable tannins, by contrast, comprise a central core formed by a polyol (e.g., flavonoid, sugar) and a phenolic carboxylic acid esterifying the core molecule. Another important aspect is that most flavonoids are present in nature as *O*-glycosides and other conjugates, which increases their lipophobicity while contributing to their complexity and the large number of molecules that have been identified (>5000).

Box 2. Absorption and Metabolism of Polyphenols

The type and position of the sugar naturally linked to polyphenols and the degree of polymerization of PACs importantly impact the bioavailability of dietary polyphenols. They are partially absorbed in the small intestine [68], and hydrolysis of the glycoside moiety is a requisite step for absorption at this level. Multidrug-resistance protein (MRP) and intestinal SGLT1 have both been implicated in flavonoid absorption in the small intestine. Furthermore, endogenous β-glucosidases located at the intestinal brush border, lactase phloridzin hydrolase (LPH) and cytosolic β-glucosidase (CBG), may hydrolyze flavonoids to generate more lipophilic, and thus absorbable, aglycones [69]. Different from most polyphenols, flavan-3-ols, such as (-)-epicatechin, are not glycosylated; these molecules are normally acylated by gallic acid and absorbed through the enterocyte without being deconjugated or hydrolyzed [70]. Dietary polyphenols often escape absorption in the small intestine and accumulate in the colon where they are biotransformed by gut bacteria yielding a complex series of end products whose polarity eases absorption past the lipid bilayer of colonocytes. The enzymatic repertoire of gut microbes encompasses enzymes capable of catalyzing *O*- and *C*-deglycosylation, ester and amide hydrolysis, deglucuronidation of large flavonoids, and fermentation of the flavonoid backbone [71]. The interflavan cleavage of PACs by gut bacteria releases monomers of flavan-3-ols; the latter may be further catabolized to generate valerolactones [32], 4-hydroxybenzoic acid, and vanillic acid (for a thorough description of gut microbial products of flava-3-ols we suggest the review by Ozdal *et al.* [21]). Gut bacteria also mediate ester hydrolysis of ellagitannins, releasing ellagic acid; this molecule can still undergo further biotransformation by gut microbes yielding urolithins [72]. Another relatively well-studied case is that of the soy isoflavone daidzein, whose modification by gut microbes yields the bioactive metabolite S-equol [42]. After absorption, polyphenols undergo extensive biotransformation by enterocytes and hepatocytes, with sulfation, glucuronidation, methylation, and glycine conjugation being the most common reactions [71]. These steps are necessary to increase hydrophilicity and favor urinary excretion. For a more detailed read on gut microbial transformation of dietary polyphenols we recommend the review by Rowland *et al.* [73].

Box 3. Gut Immune System

The intestinal innate immune system is the first line of defense against infection while ensuring tolerance to the normal gut microbiota. This system encompasses the mucus layer (secreted by goblet cells), intestinal epithelial cells (IECs), Paneth cells (secrete antimicrobial peptides), innate lymphoid cells (ILCs), and other fast-responding immune cells, such as macrophages and neutrophils. These components of the enteric innate immune system form the so-called gut barrier. The cohesion of the IEC line depends on tight junctions, which are formed by a network of proteins that seals adjacent epithelial cells in a narrow band and limits the passage of molecules through the intercellular space. The enteric innate immune system is governed by pattern recognition receptors (PRRs) such as toll-like receptors (TLRs) and NOD-like receptors (NLRs), that bind to microbe-associated molecular patterns (MAMPs) from luminal microorganisms to regulate the gut immune response. The inflamed bowel displays a disrupted gut barrier, which facilitates the leakage of bacteria and microbe-related molecules into the circulation [48,74,75]. Translocation of bacterial lipopolysaccharide (LPS), a component of the outer membrane of Gram-negative bacteria, past the damaged gut barrier is one of the most-studied links between intestinal inflammation and systemic insulin resistance; this process was termed metabolic endotoxemia [48]. Alternatively, LPS can also enter the circulation associated with chylomicrons after a fat-rich meal [76]. Metabolic endotoxemia thus impairs insulin sensitivity via the binding of LPS to TLR4 in key metabolic tissues [77,78]. In addition to LPS, evidence supports that translocation of live bacteria may contribute to metabolic syndrome [74] and NAFLD [79]. PRRs other than TLR also participate in MAMP-related control of metabolic inflammation. For instance, NOD1 and NOD2 both recognize bacterial peptidoglycans in adipocytes and hepatocytes, but while NOD1 activation worsens metabolic markers on HFD feeding [75,80], NOD2 activation protects against the detrimental metabolic consequences of HFD [75,81].

Table 1. Evidence Supporting Immunometabolic Benefits of Polyphenols and Their Association with Microbe–Host Interaction

Source of polyphenol	Host organism	Dose	Treatment	Diet (% in kcal)	Principal findings	Refs
Camu camu extract	Mice (C57Bl/6J)	200 mg/kg of BW[b] (daily gavage)	8 weeks	HFD (65% fat, 20% sucrose)	↓ Weight gain; ↓ fat accumulation; ↓ metabolic inflammation; ↓ endotoxemia; ↑ glucose tolerance; ↑ insulin sensitivity; ↓ hepatic steatosis; ↑energy expenditure; ↑ *Ucp1* in BAT; altered plasma BA pool size and composition; drastic changes in GM (e.g., ↑ *A. muciniphila*, ↓ *Lactobacillus*) FMT: ↓ weight gain; ↑ energy expenditure; ↑ *A. muciniphila*, *Barnesiella*, and *Bifidobacterium*; ↓ Lactobacillales	[4]
Cranberry extract	Mice (C57Bl/6J)	200 mg/kg of BW (daily gavage)	8 weeks	HFD (65% fat, 20% sucrose)	↓ Weight gain; ↓ visceral obesity; ↓ liver weight; ↓ liver triglyceride; ↓hepatic oxidative stress and inflammation; ↑ insulin sensitivity; ↓ hyperinsulinemia; ↓intestinal triglyceride content; ↓ intestinal inflammation and oxidative stress; ↑ *A. muciniphila*	[5]
Concord grape polyphenols	Mice (C57Bl/6J)	1% of the diet	13 weeks	HFD (61% fat, 20% sucrose)	↓Weight gain, ↓ adiposity, ↓ serum TNFα, IL-6, and LPS; ↓ glucose intolerance; ↓intestinal expression of *Tnfa*, *Il6*, and *Nos2*; ↓ *Glut2*; ↑ *Ocld* and *Fiaf*; ↑ intestinal *Pcg*; ↑ gut barrier integrity; ↑ *A. muciniphila*; ↓ Firmicutes:Bacteroidetes ratio	[9]
Apple procyanidins	Mice (C57Bl/6J)	0.5% of the diet	20 weeks	HFD	↓ Weight gain, LPS, and gut permeability; ↓ Firmicutes: Bacteroidetes ratio; ↑ *A. muciniphila*	[11]
Cloudberry extract (CLE), alpine bearberry extract (ABE), lingonberry extract (LGE)	Mice (C57Bl/6J)	200 mg/kg of BW (daily gavage)	8 weeks	HFD (65% fat, 20% sucrose)	CLE, ABE, and LGE prevented fasting and postprandial hyperinsulinemia; ↓ liver triacylglycerol deposition; ↓ circulating endotoxins; ↓ hepatic and intestinal inflammation; ↑ *A. muciniphila*, *Oscillobacter*, and *Turicibacter*	[13]
Resveratrol	Mice (C57BL/6N)	0.4% of diet	8 weeks	HFD (45% fat, 17% sucrose)	↑ Glucose tolerance; ↓ fat mass; ↑ *Bacteroides* and *Parabacteroides;* ↓ Turicibacteraceae, *Moryella*, Lachnospiraceae, and *A. muciniphila* FMT: ↑ glucose homeostasis, ↑ *Parabacteroides*; ↓ *Moryella* and *A. muciniphila*	[14]
Cranberry extract	Mice (C57Bl/6J)	200 mg/kg of BW (daily gavage)	8 weeks, after 13 weeks of HFD	HFD (65% fat, 20% sucrose)	↓ Hepatic steatosis; ↑ *Ppara*; ↓ hepatic *Cox2*, *Tnfa*; ↑ glucose tolerance and normalization of insulin sensitivity; ↓ Firmicutes:Bacteroidetes ratio; ↑ *A. muciniphila* and *Barnesiella*	[16]
Grape seed PAC extract	Mice (C57Bl/6J)	300 mg/kg BW (daily gavage)	7 weeks	HFD	↓TNFα, IL-6, and MCP-1, ↓ macrophage infiltration in epididymal fat and liver tissues; ↓ epididymal fat mass; ↑ insulin sensitivity; ↑ *Clostridium* XIVa, *Roseburia*, and *Prevotella*	[17]
Total grape (lyophilized)	Mice (C57Bl/6J)	3% or 5% in the diet	11 weeks	HFD (60% fat, 17% sugars[a])	3% and 5%: ↓Total body and inguinal fat 5%: ↓ Liver weight and triglyceride level; ↓ *Gpat1* 3%: ↓ Hepatic mRNA levels of *Ppara*, *Scd1*, *Fabp4*, and *Gpat1*; ↓ *Desulfobacter*; ↑ *Allobaculum*	[18]
Lingonberries	Mice (C57Bl/6J)	20% in the diet	11 weeks	HFD (45% fat, 17% sugars[a])	↓ Body weight; ↓ plasma levels of markers of inflammation and endotoxemia (SAA and LBP); ↑ *A. muciniphila* and *Faecalibacterium*	[19]
Cinnamon bark (CBE) extract and grape pomace extract (GPE)	Mice (C57Bl/6J)	2 g CBE/kg in the diet or 8.2 g GPE/kg	8 weeks	HFD (60% fat, 20% sucrose)	CBE and GPE: ↓ fat mass gain and adipose tissue inflammation; ↓ liver steatosis and lower plasma NEFA; ↑ glucose homeostasis (↑ glucose tolerance and ↓ insulin resistance); ↑ antimicrobial peptides and tight junction proteins CBE: ↓ *Peptococcus* GPE: ↓ *Desulfovibrio* and *Lactococcus*; ↑ *Allobaculum* and *Roseburia*	[20]
Grape pomace extract	Mice (C57Bl/6J)	1% in the diet	14 days	HFD (62% fat, 20% sugars[a])	↑ Glucose tolerance; ↓ insulin in circulation; ↓ *Glut2* in ileum; ↑ *A. muciniphila*	[60]

Table 1. (continued)

Source of polyphenol	Host organism	Dose	Treatment	Diet (% in kcal)	Principal findings	Refs
Green tea (GT) and black tea (BT) polyphenols	Mice (C57Bl/6J)	0.25% in the diet	4 weeks	HFD	GT and BT: ↓ Firmicutes; ↑Bacteroidetes; *Blautia*, *Bryantella*, *Collinsella*, *Lactobacillus*, *Marvinbryantia*, *Turicibacter*, *Barnesiella*, and *Parabacteroides* were significantly correlated with weight loss BT: ↑ *Pseudobutyrivibrio*; ↑ SCFA production	[62]

[a]Sugars refers to a mix of sucrose, fructose, and glucose.

[b]Abbreviations: BA, bile acid; BW, body weight; GM, gut microbiota; *Cox22*, cyclooxygenase 2; *Glut2*, glucose transporter 2; *Gpat1*, glycerol 3-phosphate acyltransferase; *Il6*, interleukin-6; *Mcp-1*, monocyte chemoattractant protein 1; LBP, LPS-binding protein; NEFA, nonesterified fatty acid; *Nos2*, inducible nitric oxide synthase; OGTT, oral glucose tolerance test; *Ppara*, peroxisome proliferator-activated receptor alpha; SAA, serum amyloid A; Scd1, stearoyl-CoA desaturase; SCFA, short-chain fatty acid; *Tnfa*, tumor necrosis factor alpha;*Ucp1*, uncoupling protein 1.

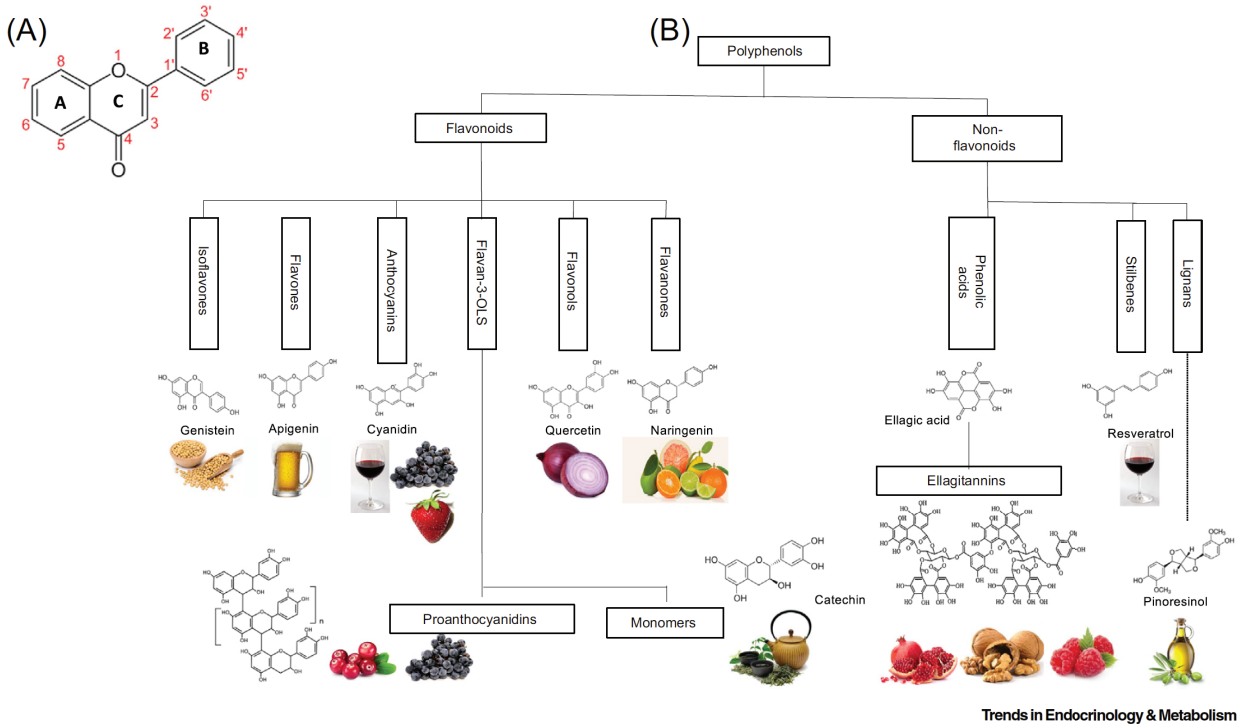

Figure 1. Structure and Diversity of Polyphenols. Common polyphenol backbone (A) and range of polyphenols found in nature (B).

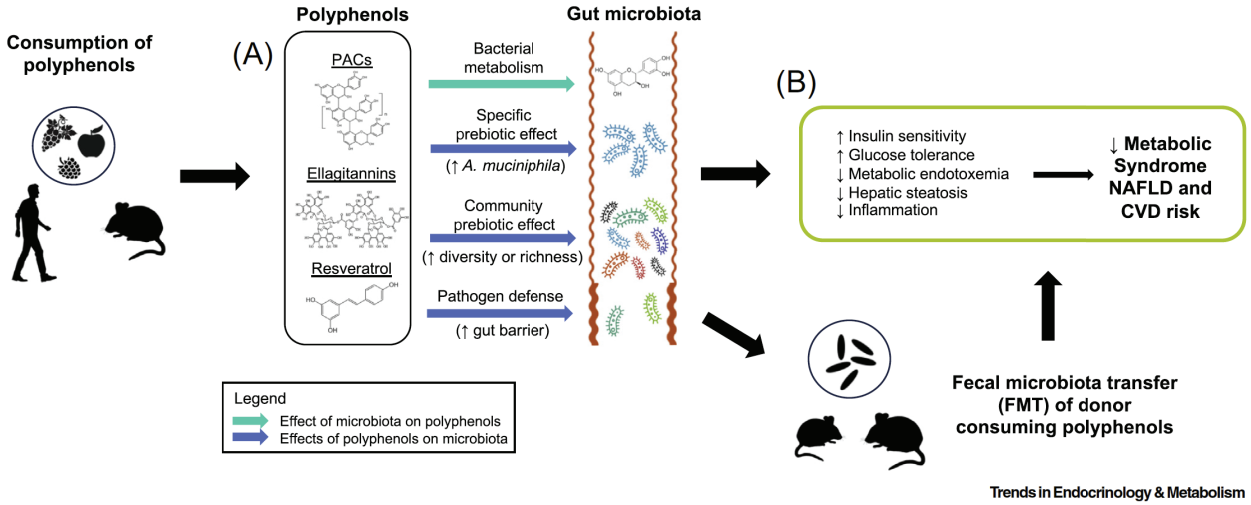

Figure 2. Polyphenol-Mediated Changes to the Gut Microbiota and Metabolism-Associated Benefits. (A) Metabolism of polyphenols by gut bacteria produces smaller and more absorbable phenolic metabolites. Through a prebiotic effect, polyphenols can favor the growth of certain bacteria, such as *Akkermansia muciniphila*, enhance overall bacterial community **richness and diversity**, and improve defense against pathogens by reinforcing gut barrier homeostasis. (B) The cardiometabolic benefits of polyphenol consumption are recapitulated in recipient mice colonized with the fecal microbiota of mice supplemented with polyphenols. Abbreviations: CVD, cardiovascular disease; NAFLD, nonalcoholic fatty liver disease; PACs, proanthocyanidins.