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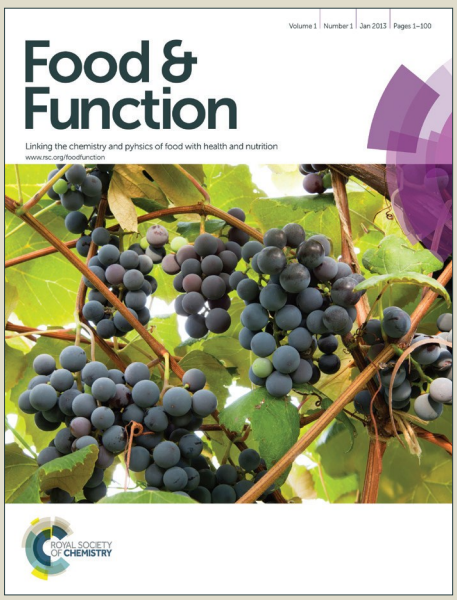

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Relationship between phenolic compounds from diet and microbiota: impact on human health.

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Abstract

The human intestinal tract is home to a complex microbial community called microbiota. This gut microbiota, whilst playing essential roles for the maintenance of the health of host, is exposed to the impact of external factors such as the use of medication or the dietary patterns. Alterations in the composition and/or function of the microbiota have been described in several disease states, underlining the role of the gut microbiota in keeping a health status. Among the different dietary compounds polyphenols constitute a very interesting group as some of them have been found to pose important biological activities, including antioxidant, anticarcinogenic or antimicrobial activities. The term polyphenol comprises thousands of molecules presenting a phenol ring and are widely distributed in plant foods. The bioactivity of these compounds is highly dependent in their intestinal absorption and often they are ingested as non-absorbable precursors that are transformed into bioactive forms by specific microorganisms in the intestine. Some of these microorganisms have been identified and the enzymatic steps involved elucidated. However, little is known about the impact of these ingested polyphenols upon the human gut microbiota. The heterogeneity of the polyphenols compounds and their food sources, as well as their coexistence with other bioactive compounds within a normal diet, together with the complexity of the human gut microbiota difficult the understanding of the interactions between dietary polyphenols and gut microbes. This is, however, an important area of research which promises to expand our knowledge on the food functionality area through understanding the microbiota-food components interaction.

Key-words: Polyphenols, diet, microbiota, microbiome

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Gut microbiota composition along life

The human gut tract harbours a complex microbial community called intestinal microbiota, representing the largest number and concentration of microorganisms found in the human body [1]. The collective genomes of the microbiota are called microbiome and it is estimated to be more than 3 million genes (150 times more than human genes) [2]. The intestine provides a nutrient-rich environment and suitable conditions for intestinal microbiota [3,4], whereas this collection of microorganisms plays important roles carrying out functions essential to the maintenance of the intestinal homeostasis and the human health [5].

The microbial colonization of the gastrointestinal tract starts immediately after birth, resulting essential for the development of the mucosal barrier function, the intestinal homeostasis, the maturation of the immune system and for determining the disease risk in early and later life [6,7]. Perinatal factors, such as feeding type (breastfeeding or formula feeding), delivery mode (vaginally or by caesarean section), gestational age (full-term or pre-term infants) or the use of treatments (antibiotics or probiotics-prebiotics) can also influence the microbial colonization [8,9]. Traditionally, it has been assumed that the intrauterine environment and the new-born infant were sterile until delivery, but recent studies have shown the presence of bacteria in the intrauterine environment, including placenta, amniotic fluid, umbilical-cord blood, and also in meconium [10,11]. The gut microbial colonization of the new-born begins with facultative anaerobes, such as enterobacteria, enterococci and lactobacilli, and continues with strictly anaerobic bacteria, such as *Bifidobacterium*, *Clostridium* or *Bacteroides* [12] (Figure 1). The intestinal microbiota reaches a stable population, similar to that of an adult, around 3 years of age [12-14].

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Advances in metagenomic analysis have revealed that the adult gastrointestinal tract contains eukaryotes (mainly yeasts), bacteria, methanogenic archaea (mainly *Methanobrevibacter smithii*) and viruses (mainly bacteriophages) [15]. The dominant bacteria in the adult healthy state in humans are the *Firmicutes*, and *Bacteroidetes*, with *Actinobacteria*, *Proteobacteria* and *Verrucomicrobia* also present in lower numbers [14]. The adult-like intestinal microbiota is regarded as relatively stable throughout adulthood, until ageing [12]. However, several studies have shown that extrinsic factors, such as diet or antibiotics, induce transient fluctuations in the gut microbiota [16,17]. There have been significant attempts to identify a common core microbiome that is conserved between humans, however, the great variation between individuals, different inclusion criteria and methodological aspects have hindered its clear identification [2,17,18]. It has been proposed that all humans could be divided into one of three gut microbiota clusters called "enterotypes", each one being dominated by a particular bacterial genus: *Bacteroides*, *Prevotella* or *Ruminococcus* [19]. These enterotypes appear independent of nationality, sex, age, or body mass index and have been suggested to be strongly related with long-term diet [20]. However, the classification of human-associated bacteria in enterotypes is a debated concept; some studies, employing short-term intervention, have suggested that these enterotypes appear to be stable [21,22] but, by contrast, other studies have shown that this classification is not clear and that several approaches should be employed, and compared, when testing enterotypes [23,24].

Ageing-related changes in the gastrointestinal tract such as difficulty in swallowing, decreased gastrointestinal motility or increased intestinal transit time, as well as changes in dietary patterns, hospitalization, recurrent infections, frequent use of antibiotics and a reduced functionality of the immune system, often referred as "immunosenescence", will affect the intestinal microbiota [25]. The reported age-related differences in the

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intestinal microbiota composition include a reduction in species diversity, shifts in the dominant species, decline in beneficial microorganisms, increase of facultative anaerobic bacteria and decrease in the availability of total short-chain fatty acids [12]. The gut microbiota of the elderly has been reported to show different microbial composition and greater inter-individual variations compared to younger adults [26]. Furthermore, it seems that the influence of ageing on the abundance of dominant phyla of the intestinal microbiota, *Firmicutes* and *Bacteroidetes*, is controversial, and results are location/geography dependent [27]. At a lower taxonomic level, it has been described differences between the abundances of some genera/species; however, there is no consensus on the key-players in the age-related changes in the intestinal microbial composition between studies, since it seems to be country dependent [12]. Well documented aging effects are the decrease of one of the members of *Clostridium* cluster IV, i.e. *Faecalibacterium prausnitzii* [25], especially in elders that have been hospitalized or have followed an antibiotic treatment [28], and also the highest abundance of the potential pathogen *Clostridium difficile*, causative of the *C. difficile* diarrhoea [29].

Microbiota role in health and disease

Due to the crucial role of the gut microbiota in human health, imbalances in the composition and/or function of gut microbiota (dysbiosis) are possible causes of intestinal, metabolic and autoimmune diseases. High-throughput analytical tools and meta-"omics" technologies have probed the importance of the host-microbiota relationship. These methodologies have provided key information helping to correlate healthy or disease states with a detailed composition of the microbiota [30] or with bacterial richness [31], although the genesis of dysbiosis has not yet been clarified, and in many cases it is not clear if the altered microbiota is the cause or consequence of

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disease. Some examples, however, do exist on specific microbiota alterations that precede the clinical manifestation of disease. These include, among others, early life microbiota alterations preceding the development of atopic disease [32], obesity [33] or the seroconversion to the autoimmune disease Type-I diabetes [34]. Moreover, in preterm infants early microbiota composition has been reported to be a predictor of the later development of necrotizing enterocolitis [35]. Indeed, data from animal studies have demonstrated the importance of the early microbiota for a proper host development and homeostasis in later life. To this regards, alterations in early life microbiota, in spite of later life microbiota restoration, appear to be enough for inducing sustained effects on host metabolism [36] or permanently altering the levels of systemic and tissue specific immune cells [37,38]. Overall, recent data suggest that high microbial diversity is associated with a healthy phenotype, while loss of diversity seems to correlate with disease, although what constitutes a "healthy" gut microbiota remains still incomplete (Figure 1). The list of diseases linked with gut microbiota dysbiosis is increasing and range from intestinal diseases like inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), coeliac disease and colorectal cancer (CRC) to extra-intestinal disorders like metabolic diseases, autoimmune diseases, and other related with the gut-brain axis [39].

IBD [Crohn´s disease (CD) and ulcerative colitis (UC)] is characterized by chronic relapsing inflammation affecting the intestinal mucosa and the key role of the gut microbiota has been well established in these pathologies. Several changes at different taxonomic level, as well as functional changes, have been described and a shift towards a pro-inflammatory state has been reported [40]. In general, patients exhibit a decrease in microbial population and functional diversity with a reduction in specific *Firmicutes* and a concomitant increase in *Bacteroidetes* and facultative anaerobes such as

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Enterobacteriaceae [37]. UC and CD present a lower abundance of the anti-inflammatory microorganism *F. prausnitzii* which is also associated with the prolongation of disease remission [41,42], but significant alterations in the microbiota of CD versus UC patients have also been described [42,43]. A recent study realized with paediatric CD patients has also revealed differences in the gut microbiota composition compared to healthy controls [44]. Regarding IBS, another chronic gastrointestinal disorder, imbalances in microbiota composition have been observed in the different subtypes of disease compared to healthy counterparts, but are not consistent between the different studies [45]. In CRC and coeliac disease several changes in the microbiota composition have also been recognized [46,47]. The *C. difficile-associated disease (CDAI)* is another proven disease in which a dysbiotic microbiota has been observed. The treatment with antibiotics favours the overgrowth of this pathogen and the faecal transplantation has been shown to be an effective treatment against this disorder [48].

There is also growing evidence supporting the role of gut microbiota in obesity and compositional changes in the intestinal microbiota have been observed in obesity with regard to normal weight individuals. The first data reported an increase in the ratio *Firmicutes/ Bacteroidetes* in obese subjects compared to their lean counterparts and a decrease in this ratio following weight loss [49,50], but the relative abundance of these phyla are not consistent between studies and changes at phylum in the context of human obesity remains a matter of debate [51]. It may be possible that defining the bacterial distribution at phylum level is not enough and should be characterized at a more detailed taxonomic level, like genus or species. Indeed, a specific microorganism, called *Akkermansia muciniphila*, has been reported to be reduced in obese animals and the administration of the microorganism was found to reverse metabolic disorder [52]. Moreover, the application of next-generation sequencing techniques and the

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quantification of gut microbial genes have allowed characterizing obese people; they have a low number of gut microbial genes and are characterized by low bacterial gene richness. Besides, this population seem to be quite resistant to dietary intervention, and have a persistent inflammation state [53]. It has also been proposed that obese individuals are more efficient in converting food into energy and in storing this energy in fat than lean individuals, which is related to, and may be a consequence of, the functionality of the intestinal microbiota [54]. Additionally, in patients with type-II diabetes shifts in gut microbiota composition were found, such as a decrease in the abundance of butyrate-producing bacteria, an increase in opportunistic pathogens, and an expansion of the microbial functions conferring sulphate reduction and oxidative stress resistance [30]. Among the several hypothesis made recently, lifestyle seems to have a strong influence in the development of obesity, metabolic syndrome and type-II diabetes. Moreover, it has been demonstrated that diets rich in saturated fats, induces gut microbiota dysbiosis that could contribute to trigger low-grade inflammation and metabolic endotoxemia, most likely caused by impairment of intestinal permeability and barrier function [55,56]. In addition, specific microbial profiles have been associated with obesity-related liver disease suggesting the impact of the gut microbiota on liver pathology [57].

It has also been described that alterations in intestinal microbiota may be involved in extra-intestinal disorders [39], like asthma [58] or systemic lupus erythematosus [59]. Moreover, preclinical studies have shown the potential role of the gut microbiota in several disorders related to the gut-brain axis, including autism spectrum disorders, Parkinson's disease, disorders of mood and chronic pain. Thus, manipulation of gut microbiota could be a promising target for the possible modulation of behaviour and brain functions [60].

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Polyphenols: bioavailability and role in human health

Definition and dietary sources

The term polyphenol comprises several thousand different compounds, found widely in plant foods providing colour, flavour and astringency, and with the common characteristic of presenting at least two phenolic rings in their structure [61]. They are a heterogeneous group of molecules, divided into four main classes according to their chemical structure: flavonoids (including flavonols, flavanols, flavanones, flavones anthocyanidins, chalcones, dihydrochalcones, dihydroflavonols and isoflavones), lignans, stilbenes and tannins. Phenolic acids (hydroxibenzoic, hydroxicinnamic, hydroxyphenylacetic, hydroxyphenylpropanoic and hydroxyphenylactic acids), with only a phenolic ring, are frequently included in this category. At present, there are scarce data about the consumption of the major classes and subclasses of polyphenols in the population and there is certain controversy regarding the accuracy in the method used for the nutritional assessment of dietary polyphenols. Most of these studies use different methodology for dietary assessment and analyse a limited number of compounds by means of different food composition tables, making difficult the comparison between them.

From an analytical point of view, the food content in polyphenols obtained from a food composition database (FCD) is imprecise because the nutritional composition of natural foods is highly variable. However, in nutritional research the value presented in the FCD is representative of the mean analytical values obtained for that particular food and allow us to compare across studies using the same database. Until 2010 most research in this area used the FCD of the United States Department of Agriculture (USDA), which collects data for about 385 flavonoids [62], 128 isoflavones [63] and 205 proanthocyanidins

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[6456], and considering some losses during processing and cooking [65]. Recently, the French National Institute for Agricultural Research published a database with extensive information for more than 500 polyphenols in 400 foods (Phenol-Explorer), allowing a more detailed assessment [66].

The distribution of polyphenols is ubiquitous in plant foods, being identified as the most abundant dietary sources of these compounds: red wine, coffee, cocoa, tea, citrus fruits and berries. Based on information of Phenol-Explorer database, the foods with greater content in each one of the major classes of polyphenols (flavonoids, phenolic acids, lignans and stilbenes) were identified. Cocoa and cocoa products highlighted by its high content in flavonoids, more than three times higher than other food sources such as blackcurrant, berries, beans or soya (Figure 2). Also, examining the content of phenolic acids in foods, chestnuts showed twice as much concentration than the following foodstuff, flaxseed, which, in turn, is a food with a higher content in lignans. Within the group of lignans, significant differences were observed between the listed foods. Although sesame provides much more lignans than other foods, the low quantity and the infrequency in their consumption, lead to not consider it as a major dietary source of these compounds, being sesamin, sesaminol and sesamolin related to endothelial function, inflammation and oxidative stress [67].

Stilbens are consumed by the population at very low amount, being their presence associated with the consumption of red wine and grapes. Red wine is an important constituent of Mediterranean diet, and responsible for a great part of the cardiovascular protective effect attributed to this dietary pattern[68]. This alcoholic beverage is a natural source of antioxidants, among which are phenolic compounds, especially flavonoids, lignans and stilbenes, contained in the skins and seeds of red grapes [69]. Some factors,

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such as grape variety, cultivation, processing and ageing can determine the final polyphenol content of red wines [70]. Apart from the effects that these phenolic compounds exert on the organoleptic properties of this beverage, some authors have proposed their antioxidant capacity as the main reason for the beneficial health effects attributed to the moderate consumption of red wine [71,72]. Specifically, it provides epicatechin, quercetin and trans-resveratrol, compounds that have been considered responsible for a protective effect on diabetes, hypertension and cardiovascular disease [73-76].

Then, it seems expectable that the different dietary patterns among countries impact on quantity and type of polyphenol consumed by their inhabitants. In this sense, the Spanish Mediterranean diet, rich in fruits and vegetables, olive oil, nuts, legumes, whole-wheat bread, fish and red wine, has been associated with a higher intake of total polyphenols in comparison with other European countries [77,78]. Also, Spanish dietary sources of polyphenols differ from other countries such as Poland, where coffee, tea, and chocolate, instead of fruits and vegetables, are the main food sources of these compounds [79] (Table 1).

Bioavailability of polyphenols

The physiological impact of polyphenols depends on their intestinal absorption; however, it is important to bear in mind that the most common polyphenols in diet are not necessarily the most bioavailable, since their structure plays an important role. Most native polyphenols in foods are in glycoside form (flavonols, flavones, flavanones, isoflavones and anthocyanins), together with the less frequent oligomers (proanthocyanidins), which cannot be absorbed in the intestinal mucosa [80]. Only aglycones and some intact glucosides can be absorbed [81]. Therefore, the release of

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native polyphenols from its matrix, conducted by human and microbial enzymes, is a necessary mechanism for them to pass through the intestinal barrier [82,83]. The resulting aglycones and polyphenol monomers can now be transported, via passive diffusion and membrane carriers, into the enterohepatic circulation [80,84]. During their passage into the liver, these compounds will undergo conjugation (mainly glucuronidation and sulphation), and will be returned again to the small intestine with the bile. Polyphenols not absorbed in the small intestinal reach the colon where the presence of microbial glucuronidases and suphatases deconjugates these metabolites allowing the reuptake of aglycones [85]. However, intestinal microbiota can also degrade aglycones releasing more simple aromatic compounds, such as hydroxyphenylacetic acids from flavonols, hydroxyphenylpropionic acids from flavones and flavanones and phenylvalerolactones and hydroxyphenylpropionic acids from flavanols [83]. These compounds can be absorbed and subsequently conjugated, process that has been suggested to reduce their antioxidant potential [86], whereas others propose that it could enhance some of their benefits [87].

Besides these human factors, the bioavailability of polyphenols is also influenced by exogenous factors related to the matrix of polyphenol-rich foods. Polyphenols present in native foods are protected within the cellular structure, but during chewing and food digestion, these compounds can be released and absorbed in the intestinal mucosa [88]. However, while many plant foods are consumed unprocessed, many others are subjected to industrial processing, which may modulate the availability of these phenolic compounds. This occurs, for example, in the manufacture of orange juice, process that can lead to the precipitation of flavanones by combination with pectins and other orange macromolecules [89] resulting in compounds with less bioavailability than the original ones [90]. The same occurs with other foodstuffs, as is the case of almond skin

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when undergoing industrial bleaching, its polyphenols become less bioavailable [91]. Also, polyphenols can interact with some nutrients coming from the same meal resulting in changes in their absorption rate in the mucosa. In line with this, while the surrounding lipids seem to enhance the availability of phenolic compounds [92], dietary fibre can perform the opposite effect [93].

Polyphenols and intestinal microbiota: scientific evidence of the impact on health

The phyto-compounds have received a special attention from the scientific community because of their ability to scavenge the free radicals during some pathological processes such as cancer, cardiovascular diseases, diabetes and neurodegenerative disorders [81,94-97]. However, to date there is scarce literature assessing the regular intake of polyphenols in different populations to suggest an optimal intake level or to propose dietary recommendations [98]. The main difficulty of approaching the study of the effect of polyphenols on health is due to the wide range of different phenolic compounds in foods [99], together with their high variability in both, bioavailability and bioactivity [100], as well as the complex relationship established between these compounds and the intestinal microbiota [101] and other food components such as fibres.

The role that the intestinal microbiota plays in the metabolism of different polyphenols has been extensively studied and nowadays it is know that the microbiota plays a key role determining the functionality of these compounds [102]. Most of the consumed polyphenols are metabolized by intestinal microbiota, in some cases, resulting in metabolites with greater biological activity than their predecessors [103]. The role of the host microbiota in producing molecules with increased bioactivity from food polyphenols has also been repeatedly shown; in some cases the specific microorganisms

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304 involved in this conversion have been identified, such as the production of equol from
305 the soya-isoflavone daidzein [104] or that of urolithin from ellagic acid [105], among others.
306 Thus, there is a bidirectional interaction polyphenols - microbiota in which gut microbes
307 affect the absorption of the polyphenols and, at the same time, the polyphenol
308 metabolites influence the growth of certain bacterial species [96]. At this point, the high
309 inter-individual variability, in terms of gut microbiota composition, may have a direct
310 impact on the functionality for the host of the ingested polyphenols. Therefore, as some
311 groups of bacteria are responsible for metabolism of polyphenols in the colon, the role
312 of these compounds on health could be variable depending on the composition of the
313 individual microbiota [103,106].

314 The study of polyphenols metabolism by the intestinal microbiota constitutes a very
315 active area of research and our knowledge in the field is accumulating rapidly.
316 However, little it is known about the effects that polyphenols intake may have upon the
317 gut microbiota. In addition to their proposed anti-oxidant, estrogenic or anti-
318 carcinogenic activities, some polyphenols are well known because of their antimicrobial
319 activity against pathogenic microorganisms [107]. However, so far, few studies have
320 addressed the effect of polyphenols on the human gut microbiota and, in most cases,
321 they have focused on the administration of polyphenol rich supplements which may
322 show different effects to the dietary polyphenols intake. Although over last decades it
323 has been accumulated evidence, from animal and human studies, showing the modulation
324 of some intestinal bacterial populations after supplementation with polyphenol-rich food,
325 such as red wine [108], tea [109], cocoa [110] or blueberries [111,112], results are inconclusive to
326 date.

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The relationship between ***red wine*** and microbiota has been explored in several studies in the last years. An increase in *Lactobacillus*/*Enterococcus* group has been observed with polyphenol-rich grape seed extract [113]. However, other studies did not found significant effects of red wine polyphenols on the faecal cultures [114]. In a study conducted using an intestinal system simulator both tea and red wine polyphenols were found to increase microorganisms such as *Klebsiella* or *Akkermansia*, but to inhibit others such as bifidobacteria, *Blautia coccoides* or *Bacteroides* [115]. The *in vivo* data on the effect of dietary polyphenols on the gut microbiota do not shown consistent results either. For instance wine phenolic compounds have been indicated to stimulate the growth of bifidobacteria and lactobacilli, inhibiting that of clostridia in experimental animals [116]. However, a recent animal study reports differential effects upon the microbiota of two of the main polyphenols, quercetin and resveratrol, differentially inhibiting certain clostridia, but without detecting any effect upon bifidobacteria [117]. Human intervention studies have reported the ability of red wine to increase the levels of *Enterococcus, Bifidobacterium* or *Eggerthella*, among other microorganisms [108,109], but, on the contrary, regular consumers of red wine have been found to harbour lower levels of different microorganisms including lactobacilli and bifidobacteria [118]. In this context, it has to be considered that the polyphenol amounts consumed under a nutritional intervention or with a polyphenol-enriched supplement may be very different from the intake in the context of a normal diet. In agreement with the reported changes in the phylum *Firmicutes* after red wine administration [108], Cuervo *et al*., have described the association between the regular intake of moderate amounts of red wine and *Faecalibacterium* concentrations [119], supporting the hypothesis about the prebiotic effect of moderate red wine consumption targeted by several authors [116]. Also,

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351 variations in the faecal metabolome upon the administration of red wine have revealed
352 new mechanisms of action of red wine polyphenols in the human body [120].

353 Giving that most ***cocoa-derived foods*** contain saturated fats and sugars, chocolate has
354 been traditionally classified as an unhealthy food with an occasional recommended
355 intake. Nevertheless, in the last years, this aspect has sparked differences since several
356 reports have linked chocolate intake with a better cognitive function [121] and
357 cardiovascular disease protection [122], being some of these positive effects attributed to
358 the antioxidant effect promote by its flavonoid content. Most of the multiple *in vivo* and
359 *in vitro* studies describing the antioxidant effect of cocoa flavanols and their impact on
360 hypertension [123], LDL oxidation [124] or insulin sensitivity [125] are refered to epicatechins
361 and procyanidins, the two groups of cocoa flavanols with highest bioavailability in
362 humans [126,127]. However, as Tzounis *et al*., have suggested the majority of procyanidins
363 in cocoa pass intact to the large intestine, where they are metabolized by the microbiota
364 [128]. Reviewing the literature, differential results are observed between animal and human
365 studies, but it is possible that several factors, including cocoa composition, dose and
366 duration of supplementation and inter-specie or inter-individual variation in microbiota
367 composition [129], make difficult the comparison among them. The decrease of *Bacteroides*,
368 *Clostridium* and *Staphylococcus* showed in animal studies may be due to the represive
369 effect on certain bacterial groups by means of the association of polyphenols with
370 dietary fibers [110]. In humans, an increase in *Lactobacillus* and *Bifidobacterium* has been
371 reported, linked with a lower concentration of C-reactive protein and, subsequently,
372 with cardiovascular protection [128]. Since some gastrointestinal disturbances, as IBS, are
373 characterized by reduced proportions of *Bifidobacteria, Lactobacilli*, and higher
374 numbers of *Clostridia*, the potential effect of chocolate could be remarkable [130].

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Tea consumption has been associated with a reduced risk of cardiovascular disease, being this phenomenon attributed to its content in phenolic compounds [131,132]. Since tea is the second most consumed beverage around the world after water, there is extensive information about its absorption and gut microbiota catabolism. In this line, it has been reported that flavan-3-ols derived in other catabolites, such as phenylvalerolactones and phenylvaleric acids, may have an important role in some of the protective effects linked to tea consumption [133]. Tea phenolic compounds, including epicatechin, catechin or caffeic acid, were reported to inhibit the growth of *Bacteroides* without affecting that of other commensals, such as clostridia, bifidobacteria or lactobacilli [109]. Faecal cultures have also been used and increases on specific microorganisms, including *Bifidobacterium*, have been reported in the presence of polyphenols such as clorogenic acid, caffeic acid, rutin or quercetin [134]. However, there is little evidence about the *in vivo* effect of tea on intestinal microbiota. Jin *et al*., after 10 days of intervention with green tea, found an increase in the proportion of bifidobacteria, but they did not observe a significative change in the composition of *Bifidobacterium* species [135]. Some studies have showed an association between the intake of cathechins from green tea and an adequate body weight regulation, wich may be mediated by the modulation of gut microbiota [136] and saturated fatty acid production [137-139]. At this moment, more studies about the metabolism of catechins are required in order to deep in this association however, evidence from *in vitro* assays has shown a favourable effect of these phenolic compunds on obese microbiota by means of changes in the *Firmucutes/Bacteroidetes* ratio [136]. Also, cathenichins and epigallocatechins from tea have been shown to exert a protective effect against gastrointestinal diseases, such as colitis and colon cancer. Together with the reduction in the concentrations of inflammatory citokines [140] they

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399 promoted the bacterial adhesion of some probiotics like *Lactobacillus rhamnosus* that
400 contributes to the maintenance of mucosal defences [141].

401 In contrast to other food groups, epidemiological evidence has been mounting on the
402 health benefits of ***fruits and vegetables*** consumption [142-144]. Most of these effects have
403 been attributed to their natural content in bioactive compounds. However, some authors
404 have recently reported a possitive association between de frequency of consumption of
405 fruits and vegetables with *Lactobacillus*, *Clostridium coccoides* and *Prevotella* [145]. In
406 this regard, the impact of apple in the maintenance well-being has been widely
407 documented since long time [146-148], but it has been recently when evidence from *in vitro*
408 studies have suggested that some of these benefits could be attributed to the interaction
409 between apple polyphenols and gut microbiota [103,149-151]. Dihydrochalcones from apples
410 have been previously associated with *Bifidobacterium* in animal and humans models
411 [119,152,153] and have also been shown to influence the commensal intestinal microbiota,
412 increasing the levels of some bacteria in the gut, such as *Lactobacillus* species [154]. To
413 this regard, a recent study, carried out in the normal dietary context, only found a
414 significant association (negative) between dietary flavanone intake and *B. coccoides* and
415 *Clostridium leptum*, among the different dietary polyphenols evaluated [155].
416 Interestingly, this study also found concomitant associations with dietary fibres,
417 underlining the fact that in the dietary context a food does not only provide a certain
418 type of nutrient or functional category. Indeed, polyphenols may appear often in fibre
419 rich foods, such as whole grain [156]. Given the well know functional properties of fibre
420 [157], the understanding of the isolated effects of polyphenols within the dietary context
421 may be difficult to achieve. In addition, several other dietary sources of polyphenols are
422 available and may contribute to the total polyphenols intake. Moreover, the total intake
423 of phenolic compounds may be very different in distinct human groups, for instance the

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intake in elderly being less than half that of adults [158]. All these factors difficult the understanding of the interactions between dietary polyphenols and intestinal microbiota but, nevertheless, this is an essential area of research which promises to increase our knowledge on the functionality of dietary polyphenols (Figure 3).

Future perspectives

A single view is enough to realize that the association between polyphenols and microbiota is a hot topic that could generate interesting results in order to improve nutritional strategies or to design new functional foods. Nevertheless, future studies should avoid some limitations regarding this issue.

On one hand, there is limited information about the role of individual polyphenols on microbiota, taking into consideration that results from *in vitro* studies cannot be directly extrapolated to what occurs in the physiological context of the intestinal ecosystem. Besides, intervention works often involves very high doses of individual compounds, or high amounts of polyphenol rich foods (tea, coffee or cocoa being the most frequent), which are not representative of what occurs in the context of a regular diet. In adition, there is high inter-individual variability in polyphenol absorption depending on several factors, such as their microbial transformation in the gut or the nutritional composition of the meal [159]. In relation to inter-individual variability, some authors have proposed that the differences in biotransformation between subjects should be recognized as an essential part of personalized nutrition approaches [103,160,161]. Since foods are mixtures of bioactive compounds that could affect microbiota, there is no doubt about the complexity of analysing the associations for these components. It has been estimated that around 50% of dietary antioxidants, mainly polyphenols, pass through the gastrointestinal tract together with dietary fibre, so it would be interesting in the future

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448 to take into account the dietary source from which polyphenols come, as this could
449 condition its physiological effects [93].

450 On the other hand, whilst there is a trend towards strong polyphenols supplementation
451 with numerous very polyphenol-rich supplements being developed and commercialised,
452 little is known about the potential risks associated with their consumption. An excessive
453 polyphenol intake has been reported to be deleterious for the host [162]. Interactions
454 between these compounds and other bioactive molecules, such as certain drugs, have
455 been described [163]. These issues should be considered and monitored when supplements
456 with high polyphenol content are administered. Moreover, there may be a large
457 variability in the response to polyphenols as a consequence of differences in gut
458 microbiota composition, difficulting the understanding of these interactions. It is
459 possible that the variability in the composition of gut microbiota between population
460 groups involve different diet-microbiota associations [164,165], or that subjects with a well-
461 balanced immune system could be less susceptible to the effect of dietary components
462 than subjects with altered immune responses, therefore in would be interesting for the
463 future to deep in the relationship between polyphenols and microbiota in different
464 groups from the immunological point of view.

465 In addition, in the absence of consensus about a method for polyphenol dietary
466 assessment, nutritional studies use food frequency questionnaire (FFQ) or 24h dietary
467 recall, with the implicit limitations on each one; while FFQ cannot include all potential
468 sources of polyphenols, 24h dietary records are not representative of the regular intake
469 and do not consider seasonal variation, which is of great importance for polyphenol
470 assessment. Also, a food composition databases cannot include analytical information

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about local food variety, losses during processing, storage or cooking of food or changes in polyphenol content with maturation.

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Table 1. Mean intake of total, classes and subclasses of polyphenols in different geographical areas.

Country	Date	n	Dietary intake data-collection method	Food composition tables/database	Group of polyphenols	Mean intake (mg/d)	Food sources
Poland [1]	2014	10,477	FFQ	Phenol-Explorer	Total polyphenols	X = 1756.5 ± 695.8 Me = 1662.5	Coffee, tea and chocolate
Spain [2]	2013	7,200	FFQ	Phenol-Explorer	Total polyphenols	X = 820 ± 323	Fruit
					Flavonoids	X = 443 ± 218	
					Phenolic acids	X = 304 ± 156	
Japan [3]	2013	815	7 day recalls	Phenol-Explorer	Total polyphenols	Me = 1047	
U.S.A. [4]	2012	98,469	FFQ	USDA	Total flavonoids	Men: X = 268; Me = 203 Women: X = 268; Me = 201	

FFQ: food frequency questionnaire; USDA: United States Department of Agriculture. X = mean; Me = median

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Table 1. *Cont.*

Country	Date	n	Dietary intake data-collection method	Food composition tables/database	Group of polyphenols	Mean intake (mg/d)	Food sources
Multicentre [5,6]	2011	36,037	24 h recall	USDA and Phenol-Explorer	Anthocyanidins	Men: X = 29.44 ± 0.53 Women: X = 33.52 ± 0.39	
					Flavonols	Men: X = 29.84 ± 0.48 Women: X = 28.40 ± 0.35	
					Flavanones	Men: X = 32.35 ± 0.72 Woman: X = 37.03 ± 0.52	
					Flavones	Men: X = 4.58 ± 0.08 Woman: X = 4.58 ± 0.06	
France [7]	2011	2,574	24 h recall	Phenol-Explorer	Total polyphenols	Men: X = 1180 ± 512 Women: X = 1120 ± 477	Coffee, fruit, wine and tea
Finland [8]	2007	2,007	24 h recall	Finoli	Total polyphenols	Men: X = 919 ± 458 Women: X = 817 ± 368	Coffee, rye bread, tea and fruits
USA [9]	2007	8,809	24 h recall	USDA	Total flavonoids	190	

USDA: United States Department of Agriculture. X = mean.

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Figure 1. Main key-features of human intestinal microbiota along ageing and in relation to disease.

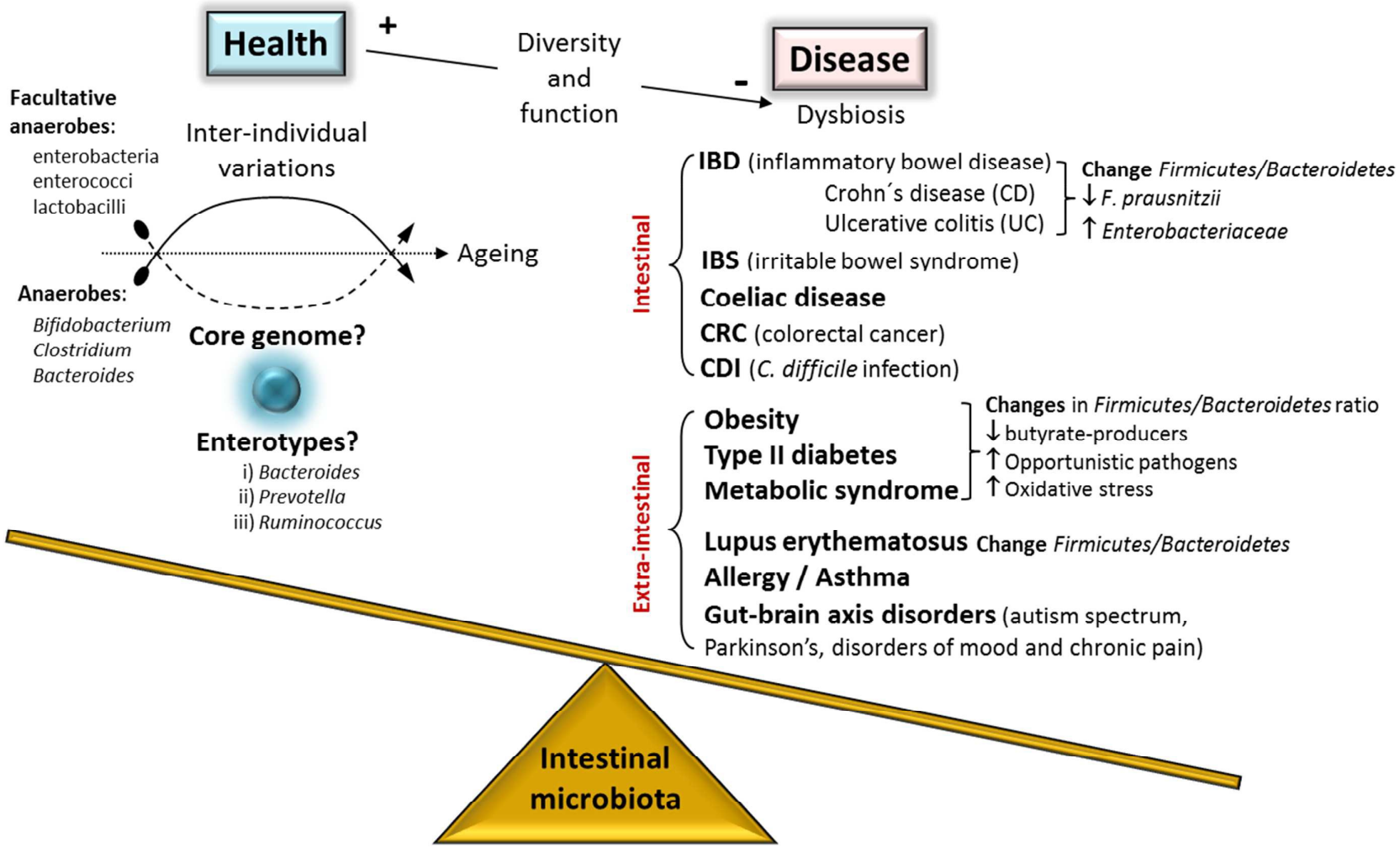

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Figure 2. Mean content (mg/100 g of food) of flavonoids, phenolic acids, lignans and stilbenes in the main food sources of these polyphenol classes, according to data collected in the database Phenol-Explorer.

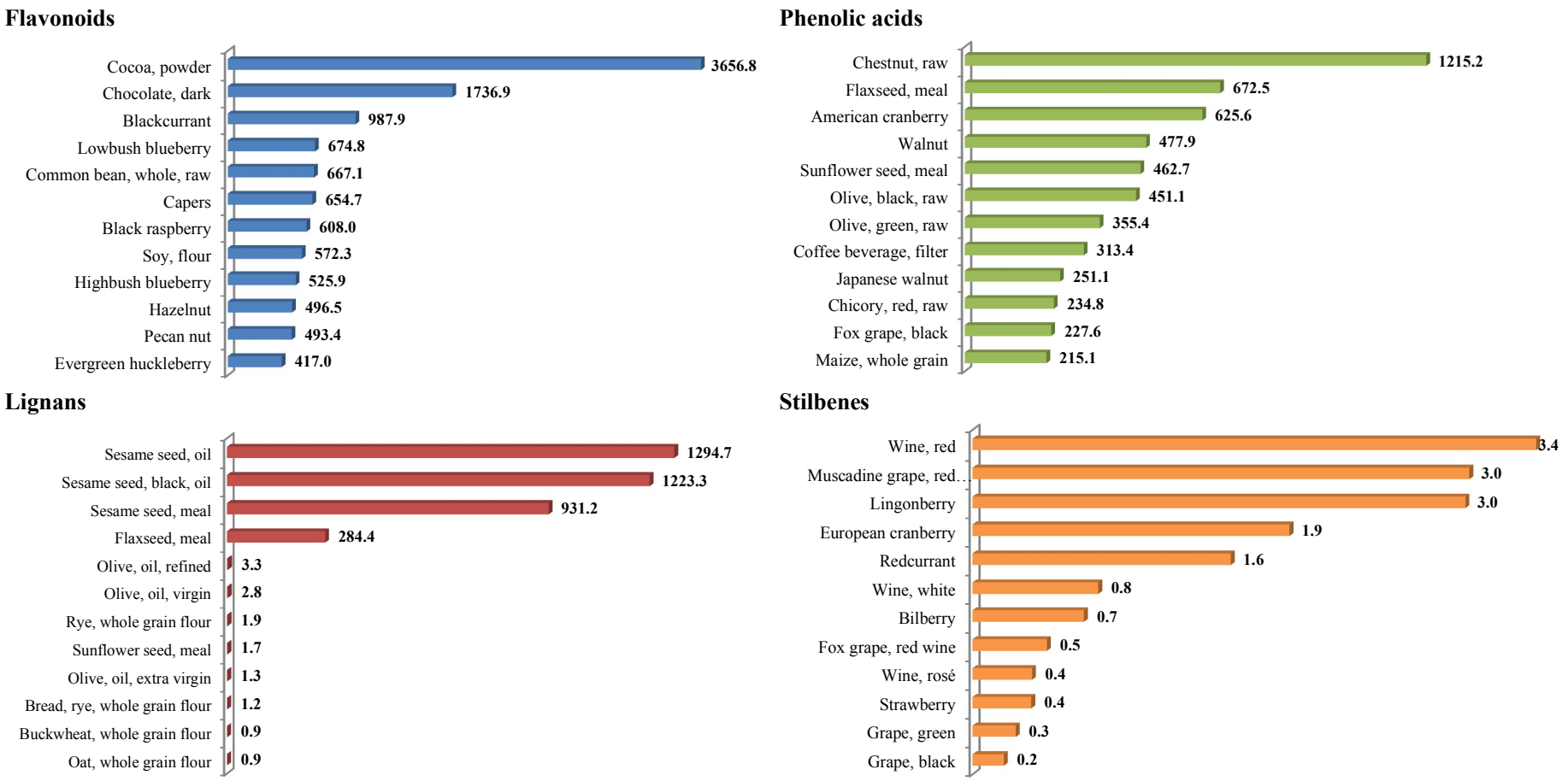

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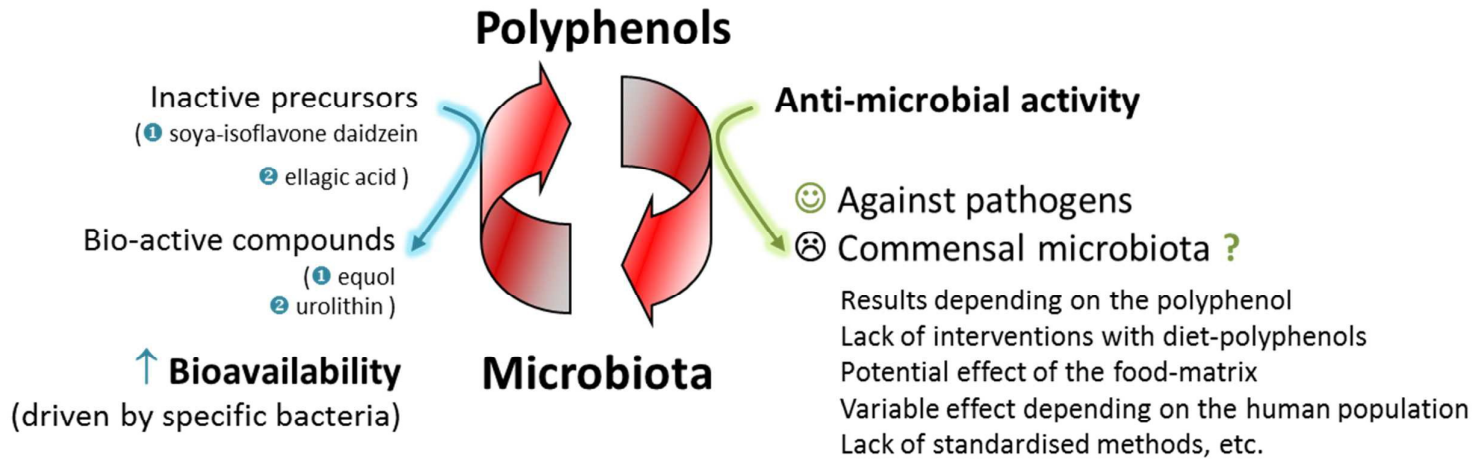
Figure 3. Bidirectional associations between polyphenols and microbiota.



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