

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

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## 13 **Abstract**

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

35 **Key-words:** Polyphenols, diet, microbiota, microbiome

## 36 **Gut microbiota composition along life**

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

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

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

80 Ageing-related changes in the gastrointestinal tract such as difficulty in swallowing,  
81 decreased gastrointestinal motility or increased intestinal transit time, as well as changes  
82 in dietary patterns, hospitalization, recurrent infections, frequent use of antibiotics and a  
83 reduced functionality of the immune system, often referred as “immunosenescence”,  
84 will affect the intestinal microbiota<sup>25</sup>. The reported age-related differences in the

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

## 100 **Microbiota role in health and disease**

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

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

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

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

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

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

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



## 183 **Polyphenols: bioavailability and role in human health**

### 184 *Definition and dietary sources*

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

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

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

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

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

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

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

#### 247 ***Bioavailability of polyphenols***

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

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

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

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

## 285 **Polyphenols and intestinal microbiota: scientific evidence of the impact** 286 **on health**

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

297 The role that the intestinal microbiota plays in the metabolism of different polyphenols  
298 has been extensively studied and nowadays it is known that the microbiota plays a key  
299 role determining the functionality of these compounds <sup>102</sup>. Most of the consumed  
300 polyphenols are metabolized by intestinal microbiota, in some cases, resulting in  
301 metabolites with greater biological activity than their predecessors <sup>103</sup>. The role of the  
302 host microbiota in producing molecules with increased bioactivity from food  
303 polyphenols has also been repeatedly shown; in some cases the specific microorganisms

304 involved in this conversion have been identified, such as the production of equol from  
305 the soya-isoflavone daidzein <sup>104</sup> or that of urolithin from ellagic acid <sup>105</sup>, 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 <sup>96</sup>. 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 <sup>103,106</sup>.

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 <sup>107</sup>. 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 <sup>108</sup>, tea <sup>109</sup>, cocoa <sup>110</sup> or blueberries <sup>111,112</sup>, results are inconclusive to  
326 date.

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

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 <sup>120</sup>.

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 <sup>121</sup> and  
357 cardiovascular disease protection <sup>122</sup>, 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 <sup>123</sup>, LDL oxidation <sup>124</sup> or insulin sensitivity <sup>125</sup> are referred to epicatechins  
361 and procyanidins, the two groups of cocoa flavanols with highest bioavailability in  
362 humans <sup>126,127</sup>. 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 <sup>128</sup>. 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 <sup>129</sup>, make difficult the comparison among them. The decrease of *Bacteroides*,  
368 *Clostridium* and *Staphylococcus* showed in animal studies may be due to the repressive  
369 effect on certain bacterial groups by means of the association of polyphenols with  
370 dietary fibers <sup>110</sup>. 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 <sup>128</sup>. Since some gastrointestinal disturbances, as IBS, are  
373 characterized by reduced proportions of bifidobacteria and lactobacilli and higher  
374 numbers of clostridia, the potential effect of chocolate could be remarkable <sup>130</sup>.



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

399 promoted the bacterial adhesion of some probiotics like *Lactobacillus rhamnosus* that  
400 contributes to the maintenance of mucosal defences <sup>141</sup>.

401 In contrast to other food groups, epidemiological evidence has been mounting on the  
402 health benefits of fruits and vegetables consumption <sup>142-144</sup>. Most of these effects have  
403 been attributed to their natural content in bioactive compounds. However, some authors  
404 have recently reported a positive association between the frequency of consumption of  
405 fruits and vegetables with *Lactobacillus*, *Clostridium coccooides* and *Prevotella* <sup>145</sup>. In  
406 this regard, the impact of apple in the maintenance well-being has been widely  
407 documented since long time <sup>146-148</sup>, 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 <sup>103,149-151</sup>. Dihydrochalcones from apples  
410 have been previously associated with *Bifidobacterium* in animal and humans models  
411 <sup>119,152,153</sup> 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 <sup>154</sup>. 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. coccooides* and  
415 *Clostridium leptum*, among the different dietary polyphenols evaluated <sup>155</sup>.  
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 <sup>156</sup>. Given the well known functional properties of fibre  
420 <sup>157</sup>, 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

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

## 428 **Future perspectives**

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

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

448 to take into account the dietary source from which polyphenols come, as this could  
449 condition its physiological effects <sup>93</sup>.

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 <sup>162</sup>. Interactions  
454 between these compounds and other bioactive molecules, such as certain drugs, have  
455 been described <sup>163</sup>. 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 <sup>164,165</sup>, 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 it 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

471 about local food variety, losses during processing, storage or cooking of food or  
472 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 <sup>1</sup> | 2014 | 10,477 | FFQ                                   | Phenol-Explorer                  | Total polyphenols    | X = 1756.5 ± 695.8<br>Me = 1662.5                  | Coffee, tea and chocolate |
| Spain <sup>2</sup>  | 2013 | 7,200  | FFQ                                   | Phenol-Explorer                  | Total polyphenols    | X = 820 ± 323                                      | Fruit                     |
|                     |      |        |                                       |                                  | Flavonoids           | X = 443 ± 218                                      |                           |
|                     |      |        |                                       |                                  | Phenolic acids       | X = 304 ± 156                                      |                           |
| Japan <sup>3</sup>  | 2013 | 815    | 7 day recalls                         | Phenol-Explorer                  | Total polyphenols    | Me = 1047                                          |                           |
| U.S.A. <sup>4</sup> | 2012 | 98,469 | FFQ                                   | USDA                             | Total flavonoids     | Men: X = 268; Me = 203<br>Women: X = 268; Me = 201 |                           |

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

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<sup>4</sup> McCullough M.L. *et al.* Am J Clin Nutr (2012)95, 454–64

**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 <sup>5,6</sup> | 2011 | 36,037 | 24 h recall                           | USDA and Phenol-Explorer         | Anthocyanidins       | Men: X = 29.44 ± 0.53<br>Women: X = 33.52 ± 0.39 |                                   |
|                            |      |        |                                       |                                  | Flavonols            | Men: X = 29.84 ± 0.48<br>Women: X = 28.40 ± 0.35 |                                   |
|                            |      |        |                                       |                                  | Flavanones           | Men: X = 32.35 ± 0.72<br>Woman: X = 37.03 ± 0.52 |                                   |
|                            |      |        |                                       |                                  | Flavones             | Men: X = 4.58 ± 0.08<br>Woman: X = 4.58 ± 0.06   |                                   |
| France <sup>7</sup>        | 2011 | 2,574  | 24 h recall                           | Phenol-Explorer                  | Total polyphenols    | Men: X = 1180 ± 512<br>Women: X = 1120 ± 477     | Coffee, fruit, wine and tea       |
| Finland <sup>8</sup>       | 2007 | 2,007  | 24 h recall                           | Finoli                           | Total polyphenols    | Men: X = 919 ± 458<br>Women: X = 817 ± 368       | Coffee, rye bread, tea and fruits |
| USA <sup>9</sup>           | 2007 | 8,809  | 24 h recall                           | USDA                             | Total flavonoids     | 190                                              |                                   |

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

<sup>5</sup> Zamora-Ros R. *et al.* Brit J Nutr (2011) 106, 1915–1925

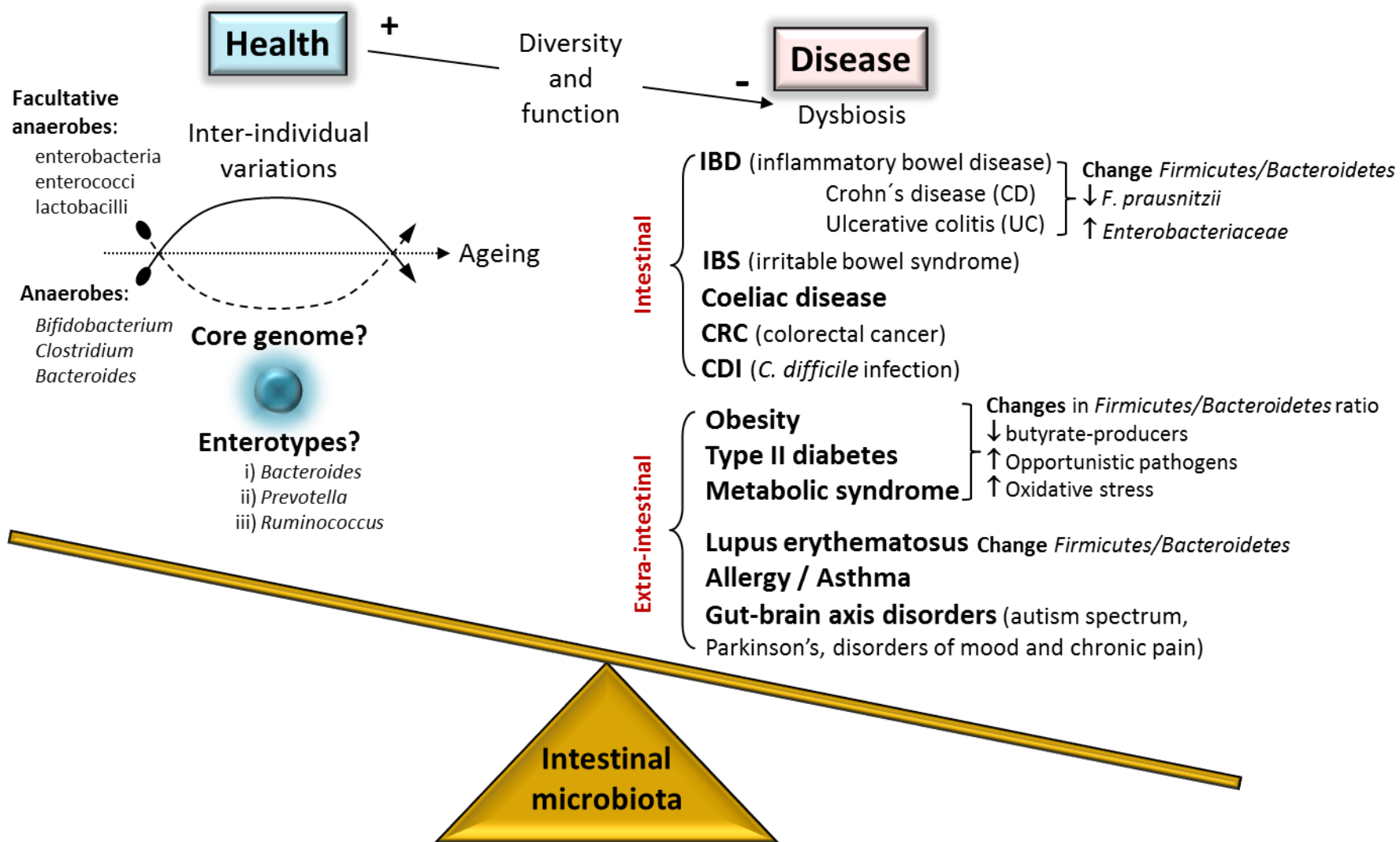
<sup>6</sup> Zamora-Ros R. *et al.* Brit J Nutr (2011) 106, 1090–1099

<sup>7</sup> Kesse-Guyot E. *et al.* J. Nutr (2012) 142, 76–83

<sup>8</sup> Ovaskainen M. *et al.* J. Nutr (2008) 138, 562–566

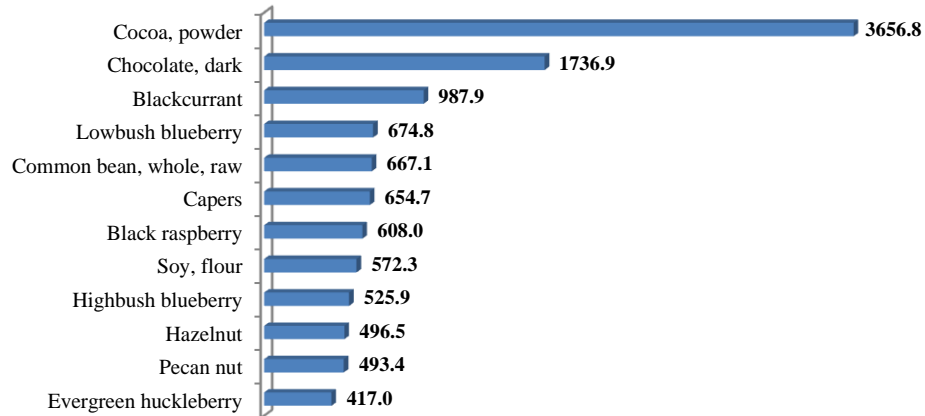
<sup>9</sup> Chun O.K. *et al.* J. Nutr (2007) 137, 1244–1252

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

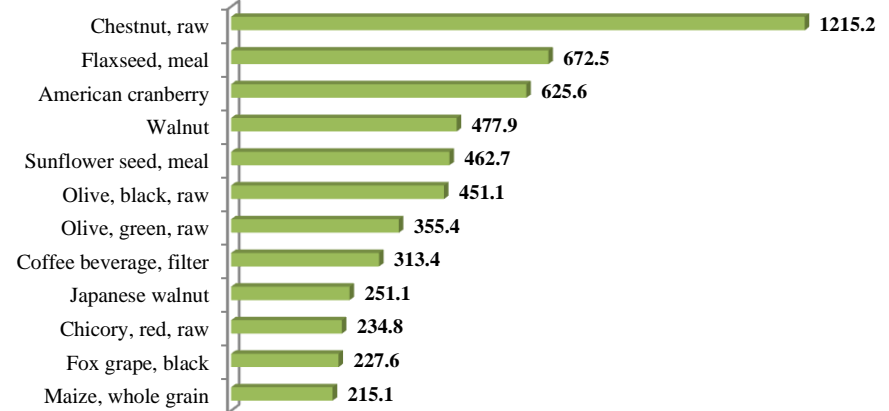


**Figure 2.** Mean content (mg/100 g of food) of flavonoids, phenolic acids, lignans and stilbenes in the main food sources of these polyphenol classes, according to data collected in the database Phenol-Explorer.

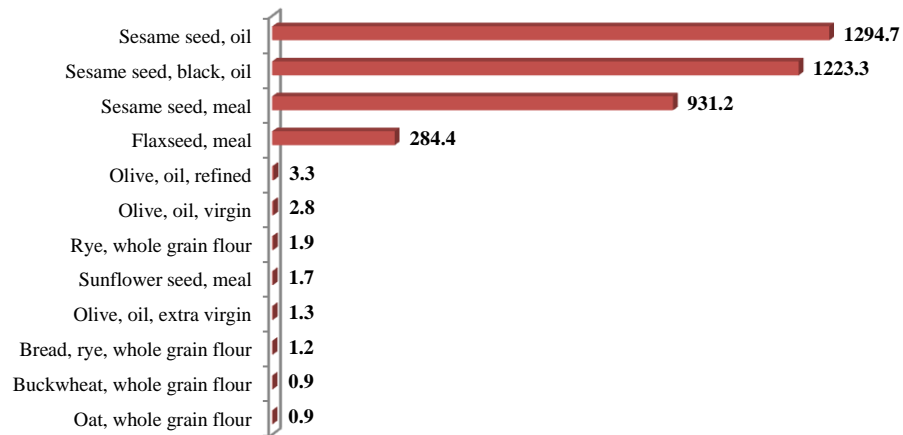
### Flavonoids



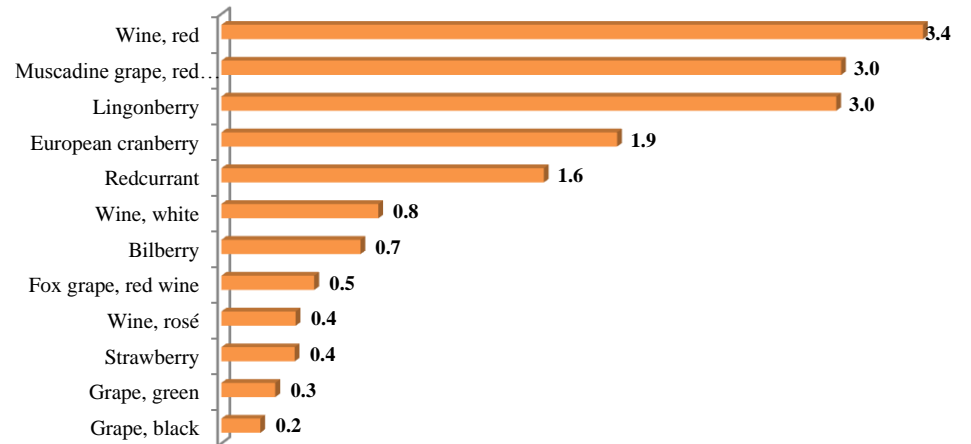
### Phenolic acids



### Lignans



### Stilbenes



**Figure 3.** Bidirectional associations between polyphenols and microbiota.

