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Chapter 2

The Relationship Between Phenolic Compounds from Diet and Microbiota

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Additional information is available at the end of the chapter

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Abstract

All multicellular organisms live in a strong bond with the microorganisms from around the world, and the humans are not the exceptions. Human microbiota (a complex bacterial community) contains about 10^{14} microbial cells, 10 times more than the content of the cells from our body and the microbial genome named microbiome, 1000 more that the human genome. It colonises any surface of the human body, above our skin, in the genitourinary tract, gut and airways. From all this, the gut is the most colonised organ, with an amount of almost 70% of the human microbes. Considering the large size of the gut, compared with a tennis terrain, filled with substances that plays a key, nutritive role for the microbes, polyphenols are micronutrients from our diet, with an emerging role in the modulation of the colonic microbial population composition and activity. Therefore, many studies underline that long-term consumption of diets rich in plants polyphenols offers protection against cancer, cardiovascular diseases, diabetes, osteoporosis and neurodegenerative diseases. This chapter reviews the biological effects of plant polyphenols in the context of relevance to human health, especially considering the food functionality area, together with the complexity of the human microbiota and the bioavailability highly dependent on their intestinal absorption.

Keywords: dietary polyphenols, microbiota, microbial metabolism, human health, interactions

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1. Introduction

Phytochemicals are the richest resources for human consumption because of their various applications. By using phytochemicals, new and novel products for the treatment and prevention of serious diseases could be improved.

Bioactive plant secondary metabolites play a crucial role in plant growth, development and physiology. The effective components of medicinal plants are usually the secondary metabolites, and the synthesis of them is affected by a variety of factors, such as biotic and abiotic effectors. Also, secondary metabolites help plants to survive, defence and compete with others. Thus, the production of the majority of plant phenolic compounds could be induced by the applications of abiotic and biotic elicitors. Due to this knowledge, the usage of elicitors is usually preferred to the optimisation of rare phytochemical sources.

Polyphenols are secondary metabolites from plants, characterised by two aromatic rings, tailored by hydroxylated phenyl moieties, in large amounts in fruits, vegetables, cereals and beverages. The compounds are showing a large diversity, including chlorogenic acids, tannins and flavonoids (flavonols, flavanones, flavan-3-ols, anthocyanins, isoflavones and flavones). Dietary polyphenols are substrates for gut and colonic microbiota. They and their metabolite allow the maintenance of gastrointestinal health, interacting with epithelial cells and modulating the microbial complexity of the gut. Polyphenolic compounds play the role of promoting factors of growth, proliferation or survival for beneficial gut microbiota, exerting beneficial prebiotic activity and inhibiting the proliferation of some pathogenic bacteria (*Salmonella*, *Helicobacter*). Although in the raw material, phenolic compounds occur as glycosylated derivatives, in order to exert their pharmacological effect, these polyphenols undergo various intestinal transformations, allowing the digestive enzymes and also the microbiota metabolism to eliminate the sugar component or other hydroxyl moieties and to release the aglycons that are further absorbed into the blood circulation, and from there, they became relevant for the organs, exhibiting strong biological effect.

2. Polyphenols, gut microbiota and health

The intestinal tract is colonised with a whole bacterial community (microbiota) that has more than 800 different bacterial species [1]. They exert a metabolic effect, due especially to the dietary compounds that provide energy, a supply of nutrients for the organism and transformations of xenobiotics. A normal composition for the gut microbiota implies a good life for the host, while imbalances are tightly associated with metabolic disorders. The factors that influence the gut microbiota are environmental (diet, the intake of antibiotic and xenobiotic) and endogenous (the adult-type microbiota is different from the child-type microbiota).

It develops a large number of functions—protective, immune and metabolic—correlated with the health status of the host. The intestinal microbiota is essential for the postnatal development that is for the content of T cells, intraepithelial T cells and immunoglobulins [2]. It is well known that prebiotics and prebiotic-like phytonutrients may exert a beneficial growth activity of bacteria and inhibit pathogenic bacteria, as a target for the biological compounds orally administered. It is also to mention the genes involved in the utilisation of the carbo-

hydrates and lipids (the microbiome), allowing the enzymes to utilise carbohydrates, host-derived glucuronides (like mucin), deconjugate and dehydroxylate the bile acids, reduce the cholesterol, synthesise some vitamins (K and B groups) and also participate to the amino acids and xenobiotic metabolism.

The gut colonisation starts immediately after birth, being dominated by *Bifidobacterium* population, due to the breast feeding, and stabilises for the first 12 months. Analyses show that adults and weaned children have *Bacteroides* population in their microbiota, followed by *Firmicutes*, like *Eubacterium*, *Ruminococcus*, *Clostridium* and *Bifidobacterium*. In infants, *Escherichia coli*, *Raoultella* and *Klebsiella* form the bacterial complex, dynamic and susceptible to changes, made by dietary factors and other diverse disorders [3].

It is to underline that two categories of enzymes are exerting an important activity of degrading the polysaccharides and xenobiotics: β-glycosidases and β-glucuronidases, which may act a beneficial or harmful role. β-Glycosidases are involved in the nutrient utilisation, which lead to body energy, by fermentation of dietary polysaccharides, thus resulting mainly short-chain fatty acids, with different functions (acetate and propionate access the portal circulation and impact the lipid metabolism, butyrate is used by enterocytes and positively influence the cell growth and differentiation). Unlike the β-glycosidases, β-glucuronidases release the toxins and another endogenous particle that have been glucuronide in the liver and excreted with the bile into the gut. Studies performed on about 40 bacterial strains, dominant in human faeces, showed a low β-glucosidase activity for Gram-positive *Firmicutes*, while the β-glucuronidase activity is noted for some *Firmicutes*, with clostridial cluster [4].

Intestinal enzymes are also related to the cholesterol and bile acid metabolism. Following this pathway, cholesterol is degraded to coprostanol, and bile acids are converted into secondary bile acids through deconjugation and dehydroxylation (deoxycholic acid and lithocholic acid). For the obtaining of this metabolites, incriminated for their carcinogenetic role, are primary mentioned *Bacteroides intestinalis* and secondarily *Bacteroides fragilis* and *Escherichia coli*.

Also, colonic strains are involved actively in the protein synthesis, highlighting the source of amino acids for the human organism. At least 1–20% of circulating lysine and threonine in adults are derived from intestinal microbiota [5].

The colonisation of germ-free mice reduces the levels of circulating fasting-induced adipose factor (Fiaf) and the skeletal muscle and liver levels of phosphorylated AMP-activated protein kinase, contributing to fat storage [6].

There can be described a straight correlation between the polyunsaturated fatty acids and gut microbiota. In vitro studies performed with *Lactobacillus* strains (*L. rhamnosus*, *L. casei*, *L. delbrueckii* subsp. *bulgaricus*) have shown that different concentrations of these acids (10–40 μg/mL) inhibited growth and adhesion to mucus of all tested strains, while low concentration of gamma-linoleic and arachidonic acid (5 μg/mL) exerted a positive effect on the growth and mucus adhesion of *L. casei* [7]. Fatty acids affect the sites for the gastrointestinal microbiota, modifying their composition in the intestinal wall. In clinical trials, atopic eczema children diet supplemented with formulation containing *Bifidobacterium Bb-12* or *Lactobacillus GG* exerted different effects on plasma lipids; the first one increased the level of alpha-linoleic acid, suggesting that interactions between prebiotics and dietary polyunsaturated fatty acids could be established, although further studies in vivo are needed to confirm this hypothesis [8].

Briefly, plant polyphenols have a bioavailability and exert their beneficial effects depending on their transformation by gut microbiota, taking into account the polyphenol type and identifying the responsible microorganism.

It is well known that dietary polyphenols and their metabolites contribute to the health by modulating the gut microbiota, stimulating the beneficial bacteria and inhibiting the pathogens ones, exerting prebiotic-like effects [9].

3. Microbial metabolism of polyphenols

We can distinguish among polyphenols flavonoids and nonflavonoids (**Figure 1**).

Flavonoids are classified into further classes according to their chemical structure: flavanones, flavones, dihydroflavonols, flavonols, flavan-3-ols, anthocyanidins, isoflavones and proanthocyanidins [11].

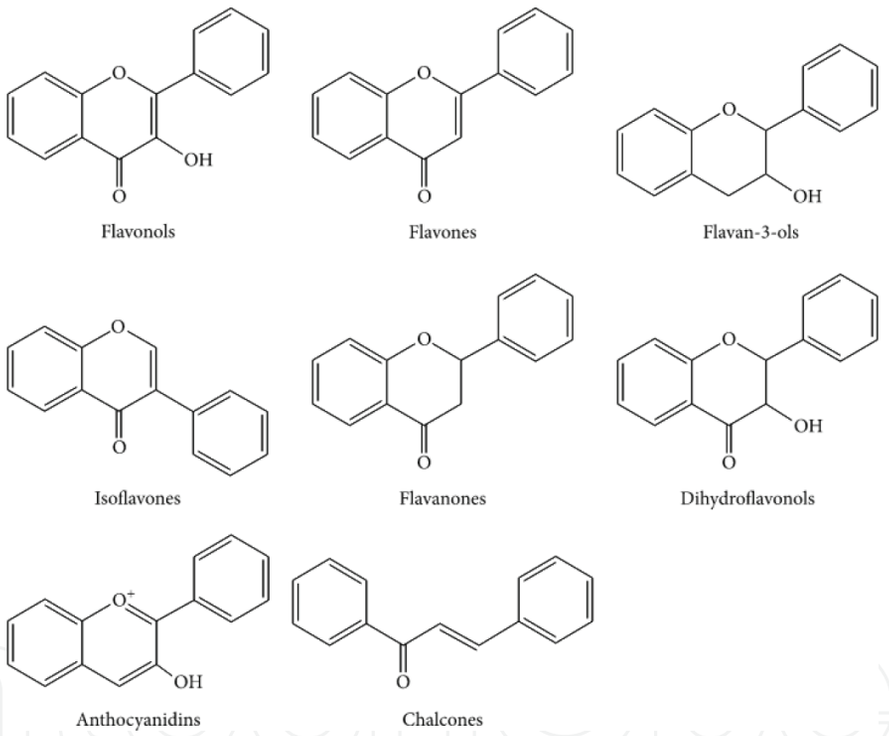


Figure 1. Phenolic compounds encountered in food [10].

Non-flavonoids can be divided into simple phenols, phenolic acids, benzoic aldehydes, hydrolysable tannins, acetophenones and phenyl acetic acids, hydroxycinnamic acids, coumarins, benzophenones, xanthones, stilbenes, lignans and secoiridoids. They can be found in foods and are important to human health. Among these, resveratrol is unique in the grapes and red wine; ellagic acid is found in berry fruits (strawberries and raspberries) and in the skins of different tree nuts. Lignans can be found in flax, sesame and many grains. Curcumin is a strong antioxidant from turmeric. Rosmarinic acid is a dimer of caffeic acid and ellagic acid is a dimer of gallic acid. While gallic acid and ellagic acid are found in the free form, their glucose esters, known as hydrolysable tannins, also exist in plants. The C6-C3 hydroxycinnamate derivatives occur mainly as conjugates with tartaric acid or quinic acid and can be found as

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chlorogenic acids. These last compounds, principally 3-O-, 4-O- and 5-O-caffeoylquinic acids, form 10% of green coffee beans (*Coffea canephora*). Regular consumers of coffee may provide a daily intake in excess of 1 g of chlorogenic acids, and these may conclude the major diet.

Usually, they are metabolic products of chloroplasts, as defence against oxidative damage during photosynthesis [12], but can also be produced by sexual organs as defence against solar UV, at the root level or as defence against virus, bacteria and fungi [13].

After ingestion, depending on their chemical composition, phenolic compounds are absorbed in the small intestine or, in some cases, can be found in the unchanged form in the colon. Only a small percentage (5–10%) of the total polyphenol intake is absorbed in the small intestine. The remaining polyphenols (90–95%) accumulate in the intestinal lumen and, following the bile pathway, represent the target for the gut complex, subject for the enzymatic activity.

Bacteria is well represented in the colon, where around 300–500 different species live. The most common bacteria are *Bacteroides*, in an amount of 30% of all gut, followed by *Clostridium*, *Prevotella*, *Eubacterium*, *Ruminococcus*, *Fusobacterium*, *Peptococcus* and *Bifidobacterium*. The lowest concentrations are described for *E. coli* and *Lactobacillus*. There is a direct established correlation between the levels of *Prevotella* and a children high-fibre diet. Also, there are data that confirm the same higher levels of *Prevotella* in diets' full field with polysaccharide foods, in contrast with a long-term diet rich in saturated fat, in which the microbiota is represented by *Bacteroides* strains [14]. The colonic pH (especially the decrease from 6.5–5.5) plays an important role, with the tendency to suppress *Bacteroides* spp. and promotes butyrate-producing Gram-positive bacteria [15]. After absorption into the small intestine, the phenolic compounds are involved into Phase I reaction (oxidation, reduction and hydrolysis) or, particularly, Phase II biotransformation (conjugation) in the enterocytes and hepatocytes, thus resulting water-soluble metabolites (methyl, glucuronide and sulphate derivatives), released into the blood circulation in order to achieve the organs where the effect is developed or excreted into the urine. But, since all human hosts have their own unique signature of the intestinal complex of bacteria, like the fingerprint, human intestinal microbiota composition can modulate the polyphenol impact on health (**Figure 2**).

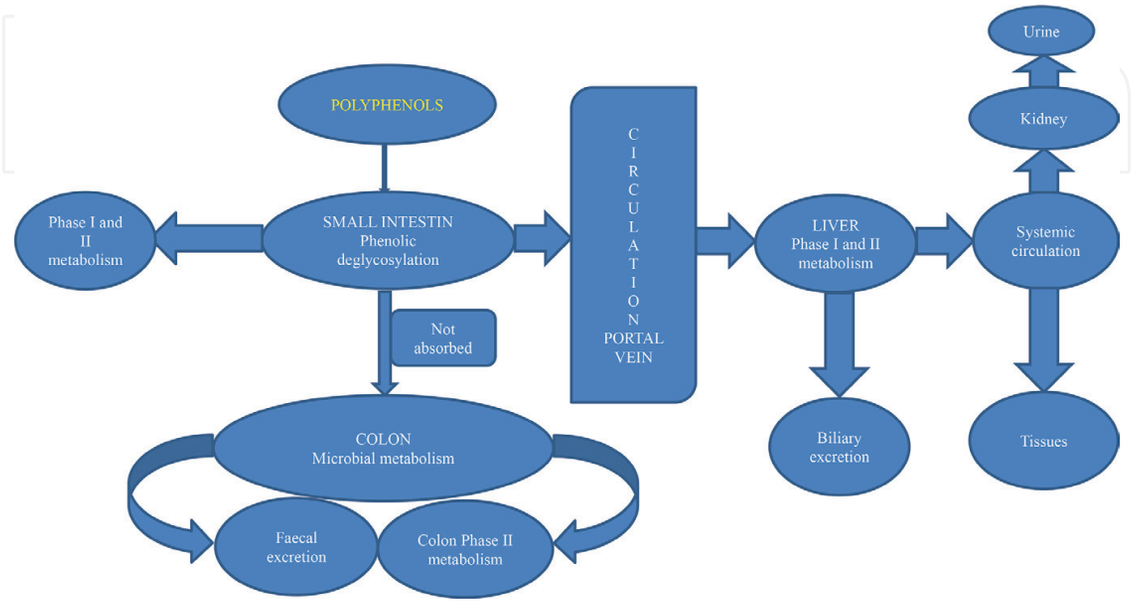


Figure 2. Routes for dietary polyphenols and their metabolites in humans.

4. Influence of phenolic compounds in gut microbiota composition

The level of biotransformation complies with two factors: the chemical structure of the polyphenol, related to the metabolite that can be absorbed and the properties that can generate a beneficial effect, and the composition of gut microbiota, because specific biotransformation requires particular species or strains with special genes for specific enzymes (**Figure 3**).

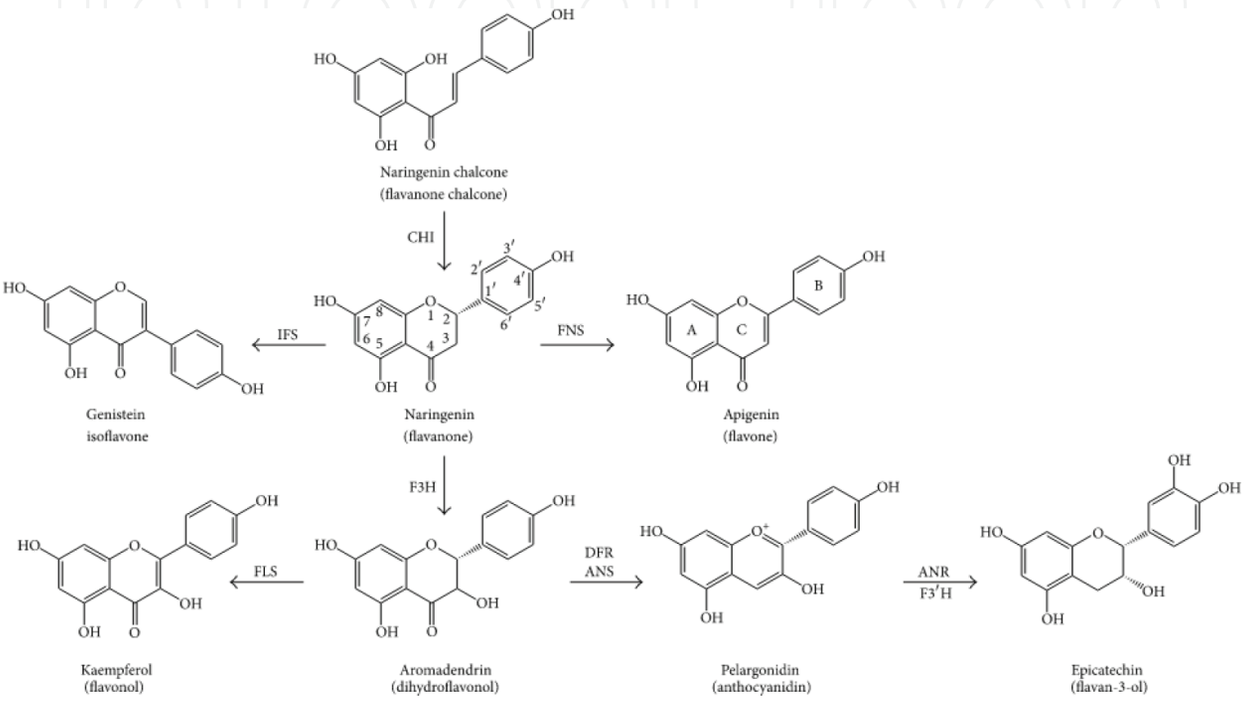


Figure 3. Biosynthesis of the flavonoid families [12].

4.1. Flavonoids

4.1.1. Flavanones and flavonols

The most common flavanones are: hesperitin, naringenin, naringin, hesperidin, abundant in citrus fruits and tomatoes. Well-known flavonols are quercetin and rutin, found as glycosylate derivatives in onions, capers, apples, broccoli, grapefruit and plums. The position of the hydroxyl group may influence the degradation of the compound, related with the glycosidic bond (C- or O-glycoside) and the degradation rates, which seems to be much slower for the C-glycosidic metabolism than for the hydrolysis of the O-glycosidic bond (**Figure 4**). From this point of view, the slow-degrading compound will be more bioavailable, because they can be greater absorbed than the ones that are quicker degraded in the colon.

In different studies involving six bacterial strains (*Bacteroides galacturonicus*, *Lactobacillus* sp., *Enterococcus caccae*, *Bifidobacterium catenulatum*, *Ruminococcus gnavus* and *E. coli*), different concentrations exerted an inhibitory effect on the growth of all analysed bacterial species. For hesperetin, the effect was weaker. This fact was explained by the dependency of the potential of these compounds on the sugar presence/absence in the moiety [16].

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In the presence of different flavonols (galangin, kaempferol, fisetin, quercetin), *Bifidobacterium adolescentis* is conducted to an anti-inflammatory effect, in the presence of nitric oxide, to which fisetin was the first responsive, by decreasing the nitric oxide with 76% [17].

Another study that underlines the viability of four bacterial strains (*E. coli*, *Staphylococcus aureus*, *Salmonella typhimurium* and *L. rhamnosus*) was tested among pure polyphenols, in a range of concentrations between 62.5 and 1000 μg/mL. All tested flavanols decreased the bacterial growth but especially quercetin and naringenin, with the lowest minimum inhibitory concentration (MIC) values. *S. aureus* was the most sensitive, while *L. rhamnosus* required a MIC of 125 μg/mL [18].

Following their bioavailability, flavonols and flavanones are antiviral, in vitro assays performed with quercetin showed an increased bacterial cell membrane, diminishing cell motility, an important factor of the bacterial virulence [12]. From literature data results, quercetol and its heteroside (rutoside) have the greatest therapeutic potential. From this point of view, flavones, especially quercetol, are evaluated for their antioxidant capacity correlated to their use in treatment of different diseases induced by reactive oxygen species (ROS) liberation. These substances act at cellular membrane level (reduce lipid per oxidation and increase membrane resistance) and endoplasmic reticule.

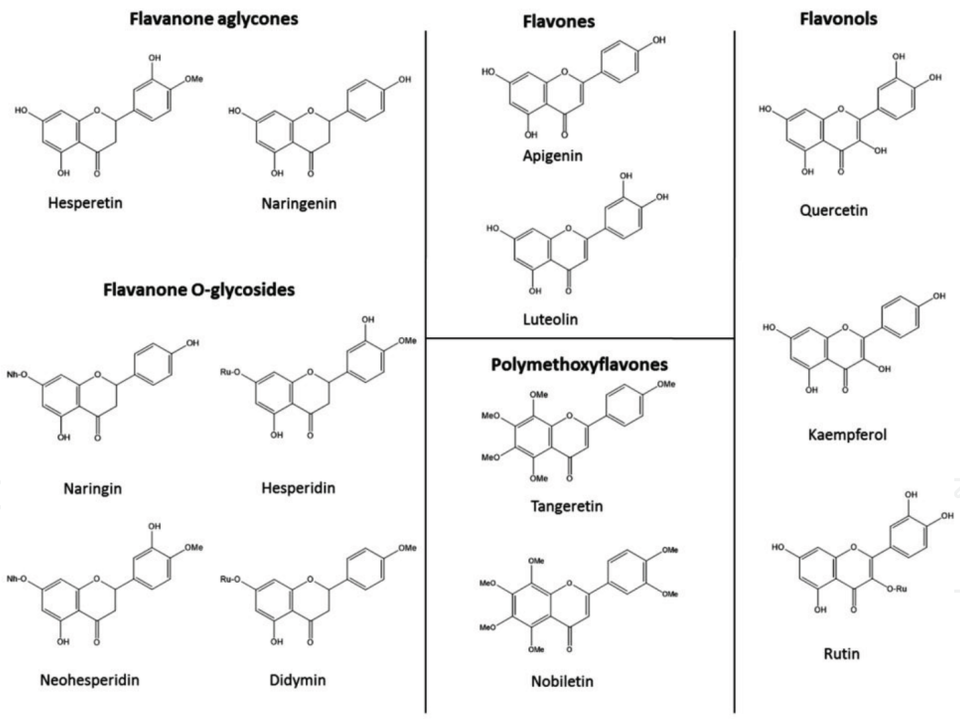


Figure 4. Molecular structure of *Citrus* flavonoids [12].

Antioxidative capacity of flavones from selective dried extracts can be determined in aqueous as well as in different concentrations of alcoholic solutions.

The methods used for antioxidant capacity assessment are based upon antioxidants' possibility to annihilate free radicals action by hydrogen atom transfer (HAT) method or an electron

transfer single electron transfer (SET). Using these methods they can reduce different oxidant substances. HAT methods are solvent type and pH range independent and most rapid than SET methods. The most cited methods for antioxidant capacity determination are ferric reducing antioxidant power (FRAP) (from SET methods) and trolox equivalent antioxidant capacity (TEAC) (from SET and HAT methods).

Previously conducted researches on mice poisoned with lead acetate and treated with quercetol revealed quercetol role in lowering enzymatic activity of superoxide dismutase (SOD), catalase, demonstrating indirect action as possible antidote (ratio of lead acetate bioinactivation/quercetol = 2.18).

4.1.2. Flavanols

(−) Epicatechin and (+) catechin, flavanol monomers, in a range of concentrations of 150–1000 mg/mL promoted the growth of *Eubacterium rectale*, *Clostridium coccoides*, the lowest concentration being registered for *Lactobacillus* spp. and *Bifidobacterium* spp. [19].

The characteristic carbonyl group lacks from the structure of flavan-3-ols aglycones, at C4 (as found in flavonols and flavanones). This may be the reason to understand its transformation by colonic microbiota which modifies other types of flavonoids, as *Eubacterium ramulus*.

Once the initial gallate esters have been metabolised, the aglycones give rise to diphenylpropan-2-diol through a C-ring opening, which is further converted into 5-(3′, 4′-dihydroxyphenyl)-γ-valerolactone. This lactone ring opens and gives rise to 5-(3, 4-dihydroxyphenyl)valeric acid. Further transformations generate OH-phenylpropionic and hydroxy-benzoic acids (**Figure 5**) [2].

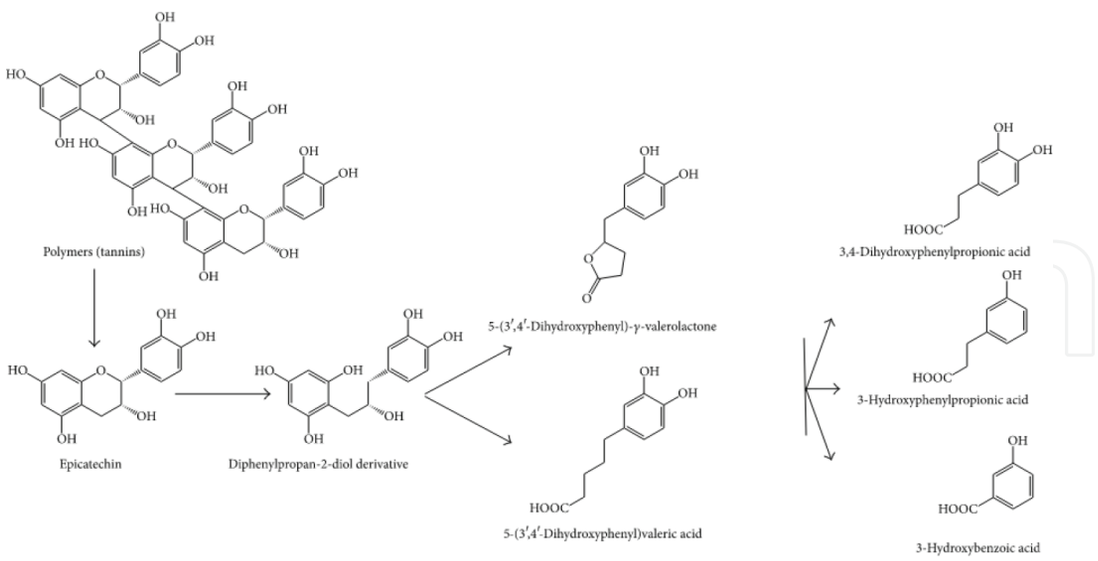


Figure 5. Colonic degradation of epicatechin tannins.

Several studies are focused on the main catechin of green tea leaves, epigallocatechin-3-gallate, that have been reported for the anti-infective properties. The inhibition effects refer to hepatitis

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C virus, HIV-1, influenza virus, adenovirus, Epstein-Barr virus and herpes simplex virus. The mechanism involved is related to the attachment of virions to cells downregulating CD4 cell surface receptor expression; the inhibition of the proviral genome at the time of integrating into the host cell, by binding between the integrase and the viral DNA; also the inhibition of endosomes and lysosomes required for the fusion of viral and cellular membranes; and the inhibition of muraminidase activity responsible for preventing self-aggregation of virus particles [12].

It is to underline that epigallocatechin-3-gallate inhibits epimastigotes' growth of *Trypanosoma cruzi* and the binding of *Plasmodium falciparum* to the ICAM-1 cellular receptor, related to malaria. The lethal mitochondrial damage above *Leishmania donovani* and *Leishmania amazonensis* has been explained by the inhibition of the parasite arginases.

In vitro studies, the main tea phenolic aglycones (3-O-methylgallic acid, gallic acid and caffeic acid), on pathogenic intestinal bacteria inhibited the growth of *Clostridium perfringens*, *Clostridium difficile* and *Bacteroides* subspp. Caffeic acid exerted a strong inhibiting effect above *E. coli*, *Salmonella*, *Pseudomonas*, *Clostridium* and *Bacteroides*.

4.1.3. Isoflavones

Most of the studies performed on isoflavones showed an important effect in the postmenopausal period. Greater concentrations of isoflavones are found in plants from the Fabaceae family (soy, lentils, beans, chickpeas).

All isoflavones (daidzein, genistein, formononetin) are glycosylated and therefore are not absorbed across enterocytes, because they have great polarity and molecular weight. Their bioavailability implies the conversion of glycosides into bioactive aglycones, following the pathway of β-glucosidases from the small intestine (*Lactobacillus*, *Bifidobacterium*). The most important isoflavone, daidzein, is metabolised depending on the gut microbiota. Some individuals produce (s)-equol through dihydrodaidzein and tetrahydrodaidzein, and other produce O-desmethylangolensin, generated by *Clostridium* sp. We can distinguish two types of individuals: (s)-equol producers and non-producers (**Figure 6**). Because of the antioxidant potential performed by the non-polar molecule, due to the penetration more reliable in the cell membrane, (s)-equol binds to the estrogenic receptors, downregulating their activity, with a potential application in breast and prostate cancer therapy.

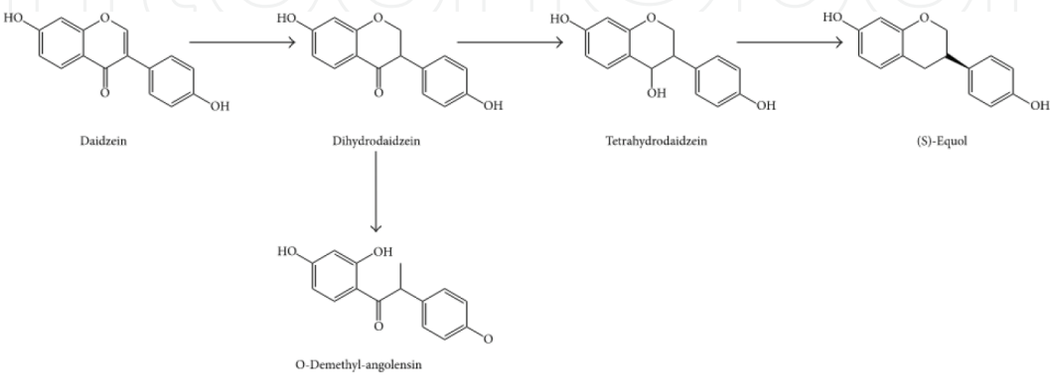


Figure 6. Colonic formation of (s)-equol and O-demethylangolensin from the isoflavone daidzein [12].

4.1.4. Condensed tannins (proanthocyanidins)

The studies performed using tannins introduced in rat diet concluded that animals with gut microbiota enriched with *Enterobacteriaceae*, *Prevotella* and *B. fragilis* had a condensed-tannins diet [20].

Mostly, proanthocyanidins, in their monomeric, oligomeric or polymeric forms, are responsible for the red, blue and purple colour of fruits, of flowers and in a lower manner of leaves, showing an important antioxidant role. Although a lot of these compounds enter the colon and they are depredated by β-glycosidase by the gut microbiota (especially by *Lactobacillus casei*, *Lactobacillus acidophilus* and *Bifidobacterium lactis*), the mechanism that can explain the antimicrobial mechanism is correlated with the disintegration of bacterial membrane, with the presence of amounts of cytoplasmic material and membrane debris outside the cells. Extracts from bilberries and blueberries showed inhibitory effects on the growth of Gram-positive and Gram-negative bacteria but without a biological effect on yeasts.

4.2. Non-flavonoids

4.2.1. Stilbenes

Resveratrol (3, 5, 4′-trihydroxy-trans-stilbene) has antimicrobial effect against pathogenic agents, shown after the administration of this compound to a DSS-induced colitis rat model. An important increase in lactobacilli and bifidobacteria, associated with a decrease of enterobacteria, was observed after a trial of 20 days [21].

4.2.2. Hydrolysable tannins

This class includes gallotannins and ellagitannins, present in raspberries, cranberries, strawberries, grapes and pomegranates. The difference between the two compounds arises at the gut microbial hydrolysis level, glucose and gallic acid for the first one and ellagic acid for the second one (**Figure 7**). This is metabolised in the colon to urolithin A and this monohydrox-

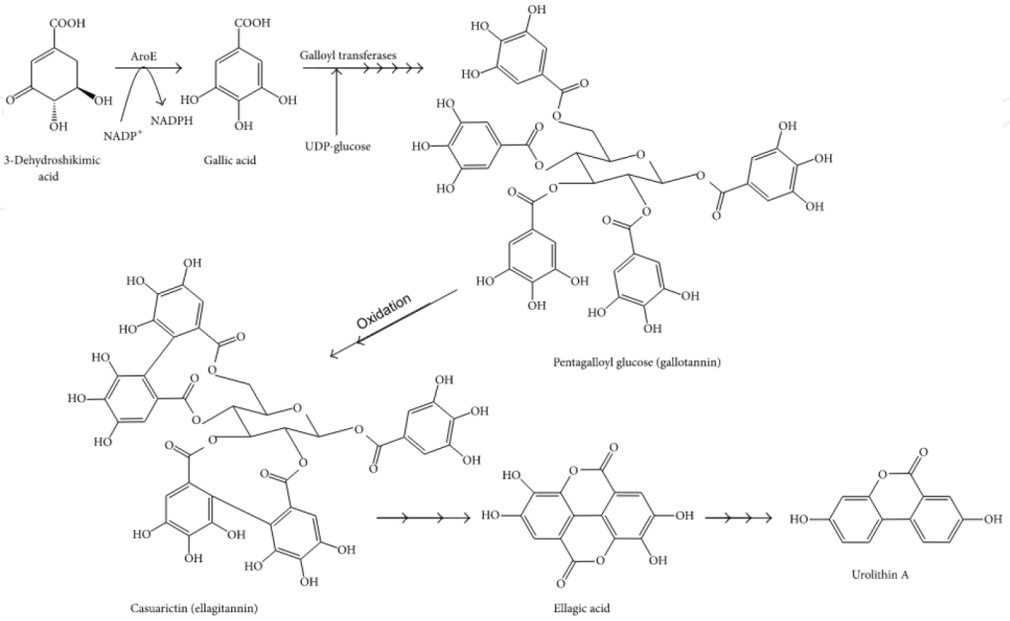


Figure 7. Biosynthetic steps for generation of two hydroxycinnamic acid polymers: ellagitannins and gallotannins [12].

ylated derivate to urolithin B. Of course, the complexity of the microbiota from the colon is responsible for the ellagitannins' metabolisation.

Pomegranate (*Punica granatum*) polyphenols have a suppressive activity against influenza virus A, due to punicalagin, who blocks the replication process of the virus and inhibits the agglutination of red blood cells by the virus. Also, the ellagitannins from this fruit are effective against *S. aureus*, *Salmonella*, *Listeria monocytogenes* and *E. coli* [22], and the ellagic acid inhibits the biofilm of methicillin-resistant *S. aureus* [23].

For ellagic acid, it was described an in vitro antimalarial activity, especially *P. falciparum* strains, regardless the levels of chloroquine and mefloquine resistance, influencing the mature trophozoite and young schizont stages, respectively, the proteins and nucleic acid synthesis. Also, ellagic acid potentiates the activity of current antimalarial drug [24].

4.2.3. Chlorogenic acids

Caffeic acid, ferulic acid and p-coumaric acid are abundant in peaches, plums and coffee seeds.

The main microbial metabolites of caffeic acid are 3-hydroxyphenylpropionic and benzoic acids, under the action of *E. coli*, *B. lactis* and *Lactobacillus gasseri*. The metabolites formed by ferulic acid in the colon are 3-(4-hydroxy-phenyl)-propionic acid and vanillin.

The role played by the gallic acid is underlined against the synthesis of the biofilms by different bacteria (*E. coli*, *Pseudomonas aeruginosa*, *S. aureus* or *Listeria monocytogenes*), the human rhinoviruses, enteroviruses and herpes simplex virus type 2. Gallic acid from *Terminalia nigrovenulosa* bark has shown strong antifungal activity against *Fusarium solani* and *Meloidogyne incognita* [25, 26].

5. Polyphenols-microbiota relationship, at a glance

The interaction between the phenolic compounds as dietary components and gut microbiota has gained a lot of attention in the last years, due to their bioavailability and the interest in human health. Although we acknowledge about this relationship from data literature, studies are lacking, making difficult understanding the exact mechanism of each compound. In vivo studies, focused on the ethical and economic issues, are also difficult to translate into in vitro conditions. It is clear that dietary polyphenols contribute to the maintenance of the human health, especially the gut, by stimulating the growth of beneficial bacteria and the inhibition of the pathogen ones, exerting prebiotic-like effects. A better understanding of the interaction between dietary polyphenols and gut microbiota through the emerging advances would be essential in order to identify genes and micro-organisms involved in polyphenol inactivation and conversion and, thus, to elucidate the implications of diet on the modulation of microbiota for achieving health benefits.

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