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Review

Ginsenosides, catechins, quercetin and gut microbiota: Current evidence of challenging interactions

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ABSTRACT

Recent studies have shown the role of gut microbiota in favoring the absorption of herbal products and the transformation of their active principles into metabolites endowed with biological activity. This review focuses on the evidence supporting the changes occurring, after metabolic reactions by specific bacteria that colonize the human gut, to ginseng-derived ginsenosides, green tea-derived catechins, and quercetin, this latter being a flavonoid aglycon bound to sugars and abundant in some vegetables and roots. Furthermore, the results of several studies demonstrating the potential beneficial effects of the active metabolites generated by these biotransformations on ginsenosides, catechins and quercetin will be reported.

1. Introduction

Over the last decades, several studies have focused on the cytoprotective effects of dietary supplements, thus raising the idea that a daily intake of these products improves the quality of life (Aiello et al., 2016; Corbi et al., 2016). According to the current regulation, herbal products (e.g., crude or commercial preparations of herbs) are considered as dietary supplements (Brown, 2017). The beneficial effects of herbal products depend on the abundance of phytochemicals (e.g. polyphenols and terpenes) with complex mechanisms of cytoprotection, including both the free radical-scavenging activity and enhancement of the cell stress response (Bjørklund and Chirumbolo, 2017; Davinelli et al., 2016; Mancuso, 2015; Hun Lee et al., 2013). However, the variable bioavailability of some phytochemicals, mainly polyphenols, has complicated the ability of randomized clinical trials to evaluate the therapeutic effects of these compounds in many diseases, thus preventing the accumulation of unambiguous evidence on their utility in humans (Mancuso et al., 2015, 2012; Lewandowska et al., 2013).

Quite recently, some papers have appeared in the scientific literature on the role played by the gut microbiota in favoring the beneficial effects of herbal products (Xu et al., 2017; Chen et al., 2016a). According to these studies, intestinal microbiota exerts effects at the pharmacokinetic and/or pharmacodynamic levels. By producing glycosidases and other enzymes catalyzing phase I reactions (e.g., oxygenation or hydrolysis), gut bacteria transform phytochemicals, very often bound to sugar moieties, into smaller molecules easily absorbed or in metabolites endowed with pharmacological effects (Espin et al., 2017; Xu et al., 2017). Although clinical studies unequivocally demonstrate the formation of these metabolites, their activity, in terms of modulation of specific cytoprotective targets, is essentially supported by *in vitro* studies.

Ginseng-derived ginsenosides and green tea-derived catechins have been taken as an example to discuss the multifaceted role of gut microbiota on herb-derived phytochemicals. One of the reasons why we have focused on these herbs, is that they are widely used, not only in the East, but also in the West and their beneficial effects have been extensively advertised. In addition, we have decided to describe the effects of gut microbiota on the flavonoid aglycon quercetin, which exists in nature bound to several sugars (see below) and is very abundant in roots and vegetables (e.g., lettuce, onions, etc.). Another reason that has led us to pick these phytochemicals is the fact that the bacteria involved in their intestinal biotransformation have been clearly identified and fully characterized, as well as the final metabolites formed through these activities. Undoubtedly, in making this choice we had to

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avoid diffusing general information on the chemical and pharmacological properties of ginsenosides, catechins and quercetin, for which we refer to extensive reviews available in the literature (e.g., Mancuso and Santangelo, 2017; Saeed et al., 2017; Anand David et al., 2016). Indeed, the goal of this review is to provide specific information about the changes performed by the gut microbiota on ginsenosides, catechins and quercetin and whether or not these modifications generate metabolites with biological effects.

2. Gut microbiota

In adults, the intestine is colonized by an extremely high number of bacteria, to the point that the intestinal microbiota is considered as a real organ, which performs digestive along with metabolic and endocrine functions (Goulet, 2015). The small intestine (duodenum, jejunum and ileum) contains a number of bacteria ranging from 10^4/ml content to 10^6-10^7/ml at the ileocecal junction, while the large intestine has a number of bacteria ranging between 10^{11} and 10^{12}/g, most of which are non-sporing anaerobes (Westfall et al., 2017; Salminen et al., 1998). Among the latter, *Bacteroidetes*, *Firmicutes* and *Actinobacteria* phyla with the genera *Bacteroides* (Gram-negative rods), *Eubacterium* (Gram-positive rods) and *Bifidobacterium* (Gram-positive rods) prevail, respectively (Westfall et al., 2017; Qin et al., 2010; Salminen et al., 1998). Other bacteria that colonize the human gut are those belonging to the genera *Clostridium* (Gram-positive rods), *Peptostreptococcus* (Gram-positive cocci) and *Ruminococcus* (Gram-positive cocci) (Salminen et al., 1998). Lastly, *Escherichia coli* (Gram-negative rod), the typical bacterium present in the human gut, is also found although in a significantly lower percentage (Salminen et al., 1998). The qualitative composition of the gut microbiota varies according to age: *Proteobacteria* and *Bifidobacteria* prevail in the gut of breast-fed infants, whereas, in babies fed with formula milk, there is a prevalence of *Bacteroides* and *Clostridia* (Fan et al., 2014; Salazar et al., 2014; Arboleya et al., 2012; Bezirtzoglou et al., 2011). During weaning, an increase in *Bacteroidetes* and *Firmicutes* occurs together with a progressive reduction in *Actinobacteria* and *Proteobacteria* (Odamaki et al., 2016; Salazar et al., 2014; Fallani et al., 2011; Koenig et al., 2011). Regarding the elderly, *Bacteroidetes* and *Proteobacteria* tend to increase inversely according to age compared to *Firmicutes* (including the genus *Ruminococcus*) and *Actinobacteria* (mainly, the genus *Bifidobacterium*) (Mancuso and Santangelo, 2018; Westfall et al., 2017; Odamaki et al., 2016).

Gut dysbiosis plays a role in the pathogenesis of several diseases, including Alzheimer's disease and Parkinson's disease (Mancuso and Santangelo, 2018; Sun and Shen, 2018), depression and schizophrenia (Grochowska et al., 2018), gastrointestinal disorders and appetite regulation (Weltens et al., 2018).

3. Ginsenosides

Ginseng is very popular in the Far East, in particular China and Korea, although ginseng-based products, such as some types of tonic beverages, are also highly diffused in the West (Baeg and So, 2013; Yun, 2001). The commercially available preparations of ginseng can be derived from several species of the *Panax* genus. Among these, the most widely used are raw preparations or extracts of *P. ginseng*, the Chinese or Korean species, and *P. quinquefolius*, considered the American species (Baeg and So, 2013; Yun, 2001). *Panax* preparations contain about thirty ginsenosides, which are saponine-type triterpenoid glycosides, endowed with several pharmacological effects (for an extensive overview on this topic, see Mancuso and Santangelo, 2017 and references therein). Ginsenosides are distinguished into two groups, according to their aglycone moieties: 20(S)-protopanaxadiol group (PPD) and 20(S)-protopanaxatriol group (PPT) (Kim et al., 2013b) (see also Table 1). In order to foster their conservation, *P. ginseng* roots may undergo steaming, giving rise to red ginseng, or air-drying and fermentation originating fermented red ginseng (Mancuso and Santangelo, 2017).

Table 1
Ginsenosides belonging to both the 20(S)-protopanaxadiol (PPD) and 20(S)-protopanaxatriol (PPT) groups.

Group	Ginsenosides
20(S)-PPD	Rb1, Rb2, Rg3, Rc, Rd
20(S)-PPT	Re, Rg1, Rg2, Rh1

Interestingly, if, on the one hand, these processes reduce by about half the quantities of ginsenosides compared to the fresh root, on the other hand, they induce the transformation of some ginsenosides into others, such as Rb1 (Koh et al., 2015). Fresh ginseng is often consumed in the form of root, whereas red ginseng is more consumed as a processed product (Baeg and So, 2013).

Several studies have analysed the effectiveness of ginseng supplementation (see below) raising interest towards this herbal product. It has been shown that *P. ginseng* (1–2 g/day for 4 weeks) prevents mental fatigue symptoms in individuals experiencing chronic fatigue for longer than 6 months (Kim et al., 2013a). *P. quinquefolius* (100–400 mg, single dose) has improved short-term working memory in both young and middle-aged healthy adults (Ossoukhova et al., 2015; Scholey et al., 2010). Concerning dementia, Korean red *P. ginseng* (1.5–9.0 g/day for 24 weeks) ameliorated cognitive skills in subjects affected by Alzheimer's disease (AD) (Heo et al., 2012, 2011). In a systematic review, Shishtar et al. (2014) reported that ginseng significantly reduced fasting blood glucose without affecting either fasting plasma insulin or glycated hemoglobin, thus implying a direct effect on glucose metabolism. A poly-furanosyl-pyranosyl-saccharide-rich extract of *P. quinquefolius*, COLD-fX, at the dosage of 200 mg twice a day for 4 months, significantly reduced the incidence of colds, the total symptom score and the total number of days of cold symptoms compared to placebo (Predy et al., 2005). Similar effects were obtained with a standardized *P. ginseng* extract, Ginsana G115 (100 mg/day for 4–12 weeks) (Scaglione et al., 1996). Strikingly, COLD-fX, at the same dosage as above, markedly reduced the incidence of acute respiratory illness (ARI) and ARI-related symptoms in community-dwelling elderly (McElhaney et al., 2006).

However, although these lines of clinical evidence, the European Medicines Agency's Committee on Herbal Medicinal Products (EMA's HMPC) concluded that there is no evidence for a medicinal use of ginseng (EMA, 2014). The same Committee limited the use of *P. ginseng* preparations to counteract symptoms of asthenia, such as fatigue and weakness, for no longer than three months (EMA, 2014).

3.1. Effects of gut microbiota on ginsenosides

Once ingested, ginseng is metabolized by the intestinal microflora through several enzymatic phase I reactions, primarily deglycosylation, oxygenation and hydrolysis (Wang et al., 2011). The ginsenosides Rb1, Rb2, Rb3, Rc and Rd are transformed by deglycosylation into 20-O-β-D-glu-copyranosyl-PPD, also known as compound K, considered the main metabolite with pharmacological activity (Wang et al., 2011; Lee et al., 2009) (Fig. 1). The intestinal bacterial strains - responsible for deglycosylation - belong to the *Bacteroidetes* and *Firmicutes* phyla, in particular *Bacteroides* and *Lactobacillus* genera, whereas oxygenation and hydrolysis are performed by gut bacteria which belong to the *Bacteroides*, *Bifidobacterium*, *Eubacterium*, *Clostridium*, *Lactobacillus*, *Peptostreptococcus*, *Fusobacterium* and *Prevotella* genera (Xu et al., 2017; El Kaoutari et al., 2013). This complex array of enzymatic reactions leads to the biotransformation of the parent ginseng compound into active metabolites with improved bioavailability. This consideration leads to the conclusion that ginseng, similarly to pro-drugs, needs metabolic activation in the gut to give rise to metabolites with beneficial effects.

Clinical studies have shown that compound K, the major metabolite deriving from gut microbiota-induced biotransformation, is absorbed as

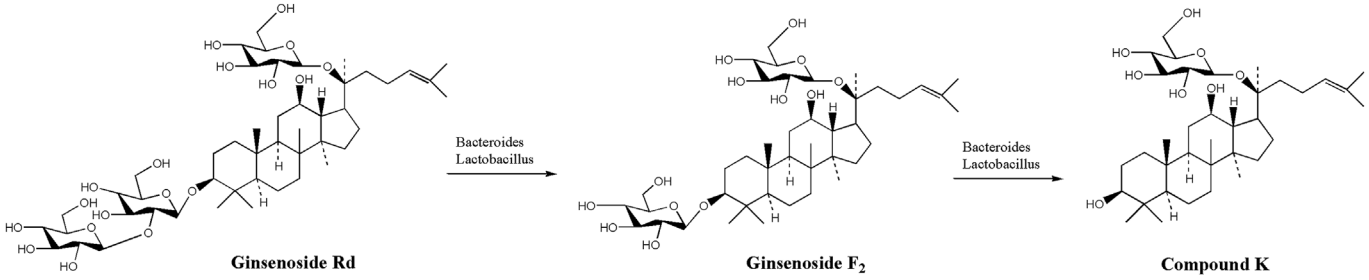

Fig. 1. Chemical structures and representative metabolic biotransformation (i.e., deglycosylation) of ginsenoside Rd into compound K, through the intermediate F_2, by gut bacteria.

early as 4 h and reaches the maximum 9–14 h after ingesting ginseng (Lee et al., 2009). Compound K has a half-life of 10 ± 6 h (Kim et al., 2013a,b). It is worth mentioning that steaming and fermentation speed the absorption of compound K, by reducing the time to reach peak plasma concentration (T_{max}), while the mere fermentation significantly increases the area under the time-concentration curve and, therefore, bioavailability (Mancuso and Santangelo, 2017). Compound K undergoes further metabolism in the liver by both CYP3A4 and CYP2C9 isoforms and is excreted through the feces (Xiao et al., 2016; Qi et al., 2011; Cui et al., 1997).

Preclinical evidence has shown that compound K interacts with several intracellular signal pathways (see also Table 2). Compound K has antitumor properties, greater than parent ginsenosides, by (*i*) up-regulating caspase-3, caspase-8, caspase-9 and cAMP-dependent protein kinase (Lee et al., 2017; Kim et al., 2009), (*ii*) suppressing Bcl-2, nuclear factor kB (NF-kB), janus kinase-1 (JAK-1) and signal transducer and activator of transcription 3 (STAT3) signaling (Chen et al., 2016b; Park et al., 2011; Choo et al., 2008), (*iii*) inhibiting activator protein-1 (AP-1)- and mitogen-activated protein kinase (MAPK)- related matrix metalloproteinase-9 (MMP-9) overexpression (Jung et al., 2006) and (*iv*) blocking basic fibroblast growth factor (bFGF)-induced angiogenesis (Mancuso and Santangelo, 2017; Wang et al., 2011; Jeong et al., 2010). Compound K also has positive effects on both glucose and lipid metabolism secondary to the increase of glucose transporter-2 (GLUT-2) expression and enhancement of peroxisome proliferator-activated receptor-α (PPAR-α) activity, thus modulating endogenous glucose production and lipogenesis in the liver (Gu et al., 2013; Wang et al., 2011; Kim et al., 2009). Lastly, compound K exhibits immunomodulatory effects either by activating NFkB and AP-1 transcription factors in monocytes and macrophages or by regulating the Toll-like receptor 4-associated signaling and inhibiting the expression of interferon-gamma (Yang et al., 2017; Wang et al., 2011).

Overall, the preclinical and clinical evidence summarized above and the role played by intestinal microflora to generate compound K, has suggested that diet enhance the pharmacological effects of ginseng. Wan et al. (2017) reported the influence of Asian or Western diet on the compound K formation and absorption in six healthy male volunteers supplemented with *P. quinquefolius* (2 g/day for 7 days). Subjects eating a Western diet showed a marked increase in compound K plasma levels compared to those consuming an Asian diet (Wan et al., 2017). It is possible that these findings are related to diet pattern differences, the Asian diet being rich in vegetables and rice, and the Western diet containing higher amounts of fats and animal proteins (Wan et al., 2017). These differences might cause changes in the gut microbiota species responsible for ginseng metabolism and absorption (Wan et al., 2017; Genton et al., 2015; Janssen and Kersten, 2015; Simpson and Campbell, 2015; Moco et al., 2012). These findings along with the studies by David et al. (2014) and Wu et al. (2011), who showed how an animal protein-based diet increases the abundance of *Bacteroides*, whereas *Prevotella* is associated with vegetable-based nutrition, have led to hypothesize a major role for *Bacteroides* in the biotransformation of ginseng.

Within the frame of diet-induced modifications of gut microbiota, are the studies by Schmedes et al. (2018) who described how a lean-seafood diet increases *Firmicutes* and *Bacteroidetes*. It is interesting to underlie as to these phyla belong certain bacteria which are considered anti-inflammatory (Mancuso and Santangelo, 2018). Ad hoc designed studies will be necessary to confirm whether gut microflora modification, following specific dietary habits, have clinical relevance to prevent or counteract chronic diseases.

Table 2
Main intracellular targets and pharmacological effects of herbal product-derived active principles. For further details, see text.

Active metabolites	Intracellular targets
Compound K	↑ caspase-8, cAMP kinase ↓ NF-kB, JAK-1, STAT3 ↓ MMP-9 ↓ bFGF ↑ GLUT-2, PPAR-α ↑ NFkB, AP-1
γ-valerolactones	↑ ROS scavenging ↑ CD4(+) T cells, NK cells ↓ ACE ↓ AChE
Hydroxyphenyl valeric acids	↓ ACE
3,4-dihydroxyphenylacetic acid	↑ Nrf2 ↓ mitochondrial complex I, ATP synthesis, O_2 consumption
3-(3-hydroxyphenyl)propionic acid	↑ NO

ACE, angiotensin-converting enzyme; AChE, acetylcholinesterase; AP-1, activator protein-1; bFGF, basic fibroblast growth factor; cAMP kinase, cAMP-dependent protein kinase; GLUT-2, glucose transporter-2; JAK-1, janus kinase-1; MMP-9, matrix metalloproteinase-9; NF-kB, nuclear factor kB; NK, natural killer; NO, nitric oxide; Nrf2, nuclear factor (erythroid-derived 2)-like 2; PPAR-α, peroxisome proliferator-activated receptor-α; ROS, reactive oxygen species; STAT3, signal transducer and activator of transcription 3; ↑ stimulation; ↓ inhibition.

4. Catechins

Tea is one of the most popular drinks in both the Eastern and Western countries. Two are the main types of teas consumed, black tea, which accounts for 60% of the whole product, and green tea accounting for 30% (Clifford et al., 2013). In both cases, the product originates from dried leaves of *Camelia sinensis* in non-fermented (green tea) or fermented (black tea) forms (Schantz et al., 2010). Green tea is rich in polyphenols (about 30% dry weight), among which the (-)-epigallocatechin-3-*O*-gallate (EGCG) is the flavan-3-ol most represented followed, in descending order, by (-)-epicatechin-3-*O*-gallate (ECG), (-)-epigallocatechin, (+)-catechin, (-)-epicatechin and gallic acid (Clifford et al., 2013; Henning et al., 2013; Schantz et al., 2010). Purified green tea is also marketed in the European Union (EU) and US as tablets, capsules and extracts for oral administration. Several clinical studies have investigated the pharmacological properties of green tea and EGCG.

Supplementation with a decaffeinated green tea extract (1315 mg total catechins/day for 12 months) induced a significant decrease in both fasting serum insulin, triglycerides and cholesterol [low-density lipoprotein (LDL) and non-high-density lipoprotein (HDL) fractions] in healthy postmenopausal women. Interestingly, insulin and triglyceride reductions were greater in women with high baseline concentrations (Dostal et al., 2016; Samavat et al., 2016). A marked reduction in total serum cholesterol was also reported in older adults (male/female 20/32) supplemented with 631 mg/day green tea catechins for 14 weeks (Miyazaki et al., 2013). Kobayashi et al. (2016) and Sakata et al. (2013) reported a significant reduction in body fat in obese subjects and patients with non-alcoholic fatty liver disease treated with 25-180-250-1080 mg/day green tea catechins for 12 weeks. The administration of green tea extract (379 mg/day for 3 months) significantly decreased both systolic and diastolic blood pressure with fasting serum glucose, insulin levels and insulin resistance in obese, hypertensive subjects (Bogdanski et al., 2012). Although topical effects cannot be ruled out, EGCG (400–800 mg/day for 56 days) has proven effective in inducing clinically significant remission in subjects with ulcerative colitis compared to those treated with placebo (Dryden et al., 2013).

It is noteworthy to point out that EMA's HMPC suggests the use of green-tea derivatives only for self-medication to counteract symptoms of fatigue and sensation of weakness (EMA, 2013).

4.1. Effects of gut microbiota on catechins

Studies conducted on 10 healthy volunteers supplemented with a bottle of green tea (500 mL, containing 648 μmol of flavan-3-ols), have demonstrated that, in plasma, both unchanged EGCG and ECG were detected together with glucuronide, sulfate, methyl-glucuronide and methyl-sulfate metabolites of (epi)catechin (Clifford et al., 2013; Stalmach et al., 2009). Pharmacokinetic studies have shown T_{max} of 1.9 h e 1.6 h and half-lives di 1.0 h and 1.5 h for EGCG and ECG, respectively (Clifford et al., 2013; Stalmach et al., 2009). Conversely, both the glucuronide and sulfate metabolites of EGCG and ECG exhibited longer T_{max} and half-life values than parent compounds (Clifford et al., 2013; Stalmach et al., 2009). Studies in ileostomists, showed that the plasma profile of catechins and their metabolites overlap with that described for healthy subjects with an intact colon, thus showing undoubtedly as these metabolic reactions occur during absorption in the small intestine (Clifford et al., 2013; Spencer, 2003). However, about two-thirds of the ingested dose of catechins pass through the small intestine and reach the colon, where it is metabolized from the microflora giving rise to both phenylvalerolactones and phenylvaleric acids (Clifford et al., 2013; Henning et al., 2013; Del Rio et al., 2010). Kutschera et al. (2011) have identified two bacterial strains, *Eggerthella lenta* and *Flavonifractor plautii*, responsible for the biotransformation of dietary catechins into valerolactones and hydroxyvaleric acid metabolites (Fig. 2). In particular, *E. lenta* has been shown to transform catechins into 1-(3,4-dihydroxyphenyl)-3-(2,4,6-trihydroxyphenyl)propan-2-ol, whereas *F. plautii* converts the latter into 5-(3,4-dihydroxyphenyl)-γ-valerolactone (diHPVL) and 4-hydroxy-5-(3,4-hydroxyphenyl)valeric acid (4-H-3,4-diHPVA) (Kutschera et al., 2011). These metabolites are subsequently absorbed and undergo glucuronidation: 3'-O-glucuronide conjugate of diHPVL is the most abundant valerolactone species in urine after green tea intake (Clifford et al., 2013; Henning et al., 2013). Additional metabolites, whose urinary excretion resulted increased upon green tea ingestion are 3,4-dihydroxyphenylacetic acid and 4-hydroxyphenylacetic acid (Henning et al., 2013). The diHPVL metabolite exhibited remarkable antioxidant activity *in vitro*, greater than that exerted by ascorbic acid (Sanchez-Patan et al., 2011; Grimm et al., 2004).

Phenylvalerolactones are interesting compounds since they interact with multiple intracellular pathways (Table 2). Phenylvalerolactones (2 μM or 10 μM) exerted cytoprotective effects against 300 μM hydrogen peroxide-induced oxidative stress in brown adipocytes (Mele et al., 2017). Furthermore, 5-(3',5'-dihydroxyphenyl)-γ-valerolactone, a metabolite lacking the 4'-hydroxyl group on the B ring, was shown to be exert both immunostimulatory activity, due to the activation of CD4(+) T cells and enhancement of natural killer (NK) cells cytotoxicity, and neuroprotective effects related to the increase in nerve cell proliferation and neuritogenesis (Unno et al., 2017; Kim et al., 2016). Takagaki and Nanjo (2015) reported the angiotensin-converting enzyme (ACE) inhibitory activities of both hydroxyphenyl valeric acids and valerolactones. In particular, 5-(3,4,5-trihydroxyphenyl)-γ-valerolactone and 5-(3',5'-dihydroxyphenyl)-γ-valerolactone (150–200 mg/kg) showed hypotensive effects in spontaneously hypertensive rats (Takagaki and Nanjo (2015). Lastly, γ-valerolactone inhibited acetylcholinesterase activity *in vitro* (Okello et al., 2012).

5. Quercetin

Although quercetin is not an herbal product *per se*, it is the most common flavonoid present in many consumer foods, such as lettuce, red onion, radish leaves, cranberry and several others, and plants, including lovage, buckwheat, coriander and others more (Guo and Bruno, 2015; Formica and Regelson, 1995). Quercetin is found in nature conjugated to sugar moieties, such as rhamnose or rutinose, giving rise to the corresponding glycosides quercitrin and rutin (Guo and Bruno, 2015). The average consumption of quercetin was calculated between 6 and 18 mg/day in the US, China and Europe (Guo and Bruno, 2015). However, purified quercetin is also available in the EU and US as capsules or aqueous extract administered sublingually. Clinical studies have recently confirmed the pharmacological effects of quercetin on glucose, lipid and protein metabolism. Rezvan et al. (2017) reported that quercetin (1 g/day for 12 weeks *per os*) reduced both testosterone and luteinizing hormone plasma levels as well as insulin resistance in women with polycystic ovary syndrome. Pfeuffer et al. (2013) showed that quercetin (150 mg/day *per os* for 8 weeks) lowered postprandial triacylglycerol levels and increased HDL-cholesterol concentrations in healthy male subjects. Quercetin (500 mg/day *per os* for 4 weeks) lowered plasma uric acid concentrations in healthy males (Shi and Williamson, 2016). Quercetin supplementation has been shown to improve cardiac functions. As reported by Brull et al. (2015), quercetin (150 mg/day or 162 mg/day for 6 weeks) significantly decreased daytime and nighttime systolic blood pressure in hypertensive patients. Egert et al. (2009) reported similar results for quercetin in terms of reduction of systolic blood pressure in overweight-obese volunteers.

5.1. Effects of gut microbiota on quercetin

Once ingested, quercetin glycosides reach the small intestine where undergo deglycosylation by lactate phlorizin hydrolase, a family 1 β-glucosidase, yielding quercetin aglycone; between 65% and 81% of quercetin passes through the small intestine epithelium and reaches the liver, where it is further metabolized thus becoming bioavailable (Bischoff, 2008; Arts et al., 2004; Walle et al., 2000). Indeed, quercetin glucuronide has been detected as the major metabolite in plasma (Moon et al., 2008; Graefe et al., 2001). These complex metabolic reactions, occurring in both the small intestine and liver, account for the variable bioavailability of quercetin, which has been reported to be less than 10% (Goldberg et al., 2003; Gugler et al., 1975; Jin et al., 2010; Moon et al., 2008). As far as gut metabolism is concerned, quercetin is transformed by the microbiota into 3,4-dihydroxyphenylacetic acid, also known as homoprocatechuic acid, 3-(3-hydroxyphenyl)propionic acid, 3,4-dihydroxybenzoic acid and 4-hydroxybenzoic acid (Naimanova et al., 2016; Carrasco-Pozo et al., 2015; Kim et al., 1998) (Fig. 3). *B. fragilis*, *C. perfringens*, *E. ramulus, Streptococcus S-2, Lactobacillus L-2, Bifidobacterium B-9* and *Bacteroides JY-6* have been identified as the bacterial strains responsible for the transformation of quercetin into the metabolites mentioned above (Peng et al., 2014; Zhang et al., 2014; Blaut et al., 2003; Schneider et al., 1999; Kim et al.,

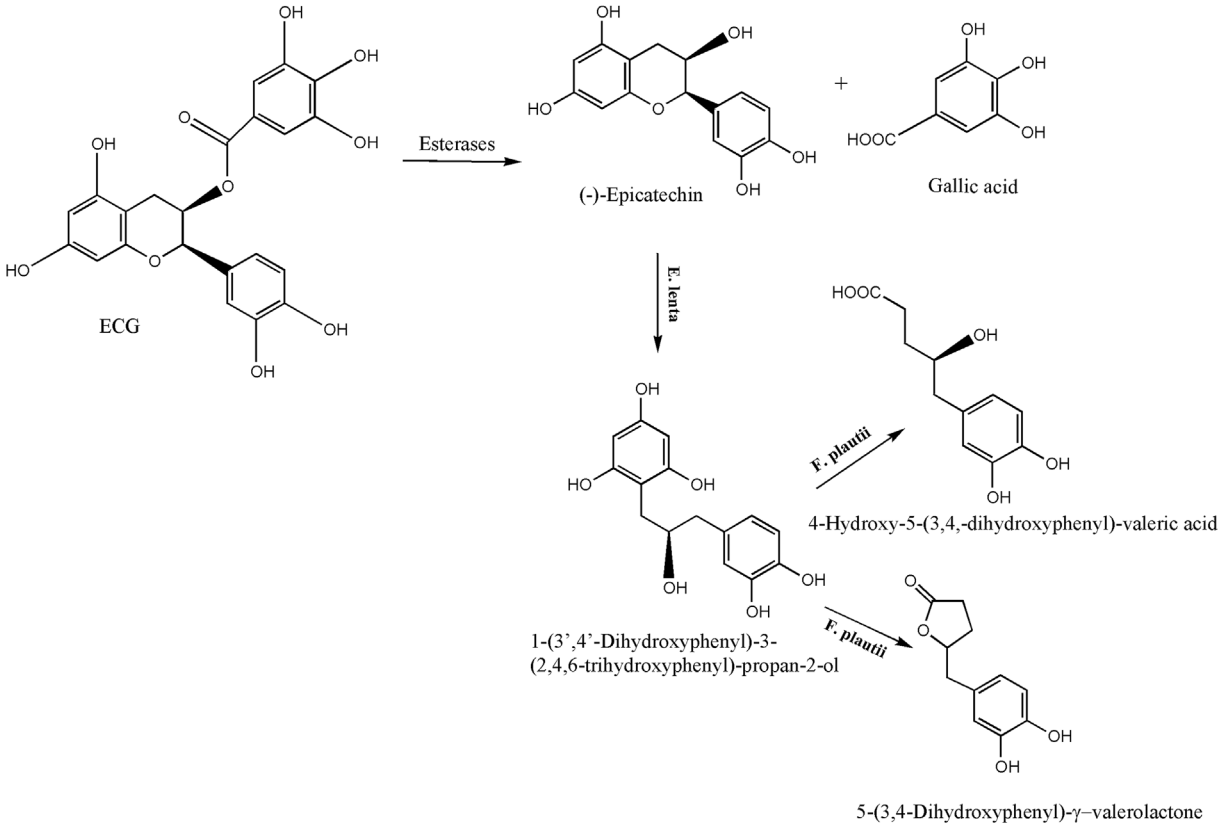

Fig. 2. Catabolism of (-)-epicatechin-3-*O*-gallate (ECG) by gut microbiota.

1998). Interestingly, some of these metabolites have biological activities (Table 2). 3,4-dihydroxyphenylacetic acid has been shown to prevent cholesterol-induced Min6 pancreatic cell dysfunction by counteracting oxidative stress, apoptotic cell death and mitochondrial dysfunction; these changes improved insulin secretion and glucose metabolism (Carrasco-Pozo et al., 2015). Furthermore, 3,4-dihydroxyphenylacetic acid (10–50 mg/kg/day for 3 days) counteracted acetaminophen-induced liver damage through the upregulation of the transcription factor nuclear factor (erythroid-derived 2)-like 2 (Nrf2) in mice (Xue et al., 2016). Lastly, 3,4-dihydroxyphenylacetic acid (0.1–1 mg/kg) exhibited a strong anxiolytic effect in mice (Vissiennon et al., 2012). As for 3-(3-hydroxyphenyl)propionic acid, this metabolite exhibited a significant vasodilatory effect in an *in vitro* system of isolated rat aortic rings pre-contracted with norepinephrine by the modulation of endothelial nitric oxide synthase (eNOS)-derived nitric oxide (NO); interestingly, the quercetin-3-O-glucuronide had no vasodilatory effect (Najmanova et al., 2016). Ultimately, 4-hydroxybenzoic acid showed a strong free radical scavenging activity in an *in vitro* reconstituted system and displayed an inhibitory effect on trypsin activity (Tang et al., 2016; Kim et al., 1998).

6. Conclusions

The first conclusion that can be drawn, by observing the evidence so far provided, is that the gut microflora becomes an important site for metabolic reactions by transforming ginsenosides, catechins and quercetin into active metabolites. This evidence supports the possibility that age-related or antibiotic-induced modifications of gut microflora, can cause important changes in terms of biotransformation of herbal products, thus affecting some of the expected beneficial effects. This is the reason why, considering the differential composition of gut microflora in Western and Eastern populations mainly due to diet habits, the effect of some dietary phytochemicals, (e.g. green tea-derived polyphenols), could change in people of different countries or ethnicities regardless of the quantity ingested. A possible line of intervention to improve the intestinal biotransformation of both ginseng and green tea and quercetin into active metabolites is related to the administration of prebiotics or probiotics. In an *in vitro* model, which resembles gut microbiota and based on the use of a continuous flow anaerobic fermenters, the supply of apple pectin or inulin resulted in the enrichment of *Bacteroides*, whereas pectin strongly promoted *Eubacteria*, in particular *E. eligens* (Chung et al., 2016). These results are not in line with those suggested by Costabile et al. (2010) who showed that the very long chain inulin from globe artichoke (*Cynara scolimus*) - at the dose of 10 g/day for 3 weeks - increased faecal *Bifidobacteria* and *Lactobacilli*, but significantly reduced *Bacteroides* and *Prevotella*. These conflicting results, do not allow to conclude whether prebiotics could improve the intestinal biotransformation of herbal products or not. Further studies are needed to better clarify the therapeutic potential of herb-prebiotic interaction.

Although preclinical studies essentially support the hypothesis regarding the beneficial effects of active metabolites of herbal products produced by gut microbiota, the formation of by-products with deleterious effects must be properly assessed. Indeed, *in vitro* studies have shown that both 3,4-dihydroxybenzoic acid and 4-hydroxybenzoic acid inhibit lactoperoxidase, an enzyme with antioxidant and antimicrobial activities (Koksal et al., 2016) and, therefore, clinicians should be cautious when recommending daily supplementation with quercetin or quercetin-rich foods.

In conclusion, more research must be performed to provide clinical evidence on the risk/benefit balance of these metabolites and their possible involvement in the maintenance or restoration of homeostasis.

Conflicts of interest

The Authors have nothing to disclose.

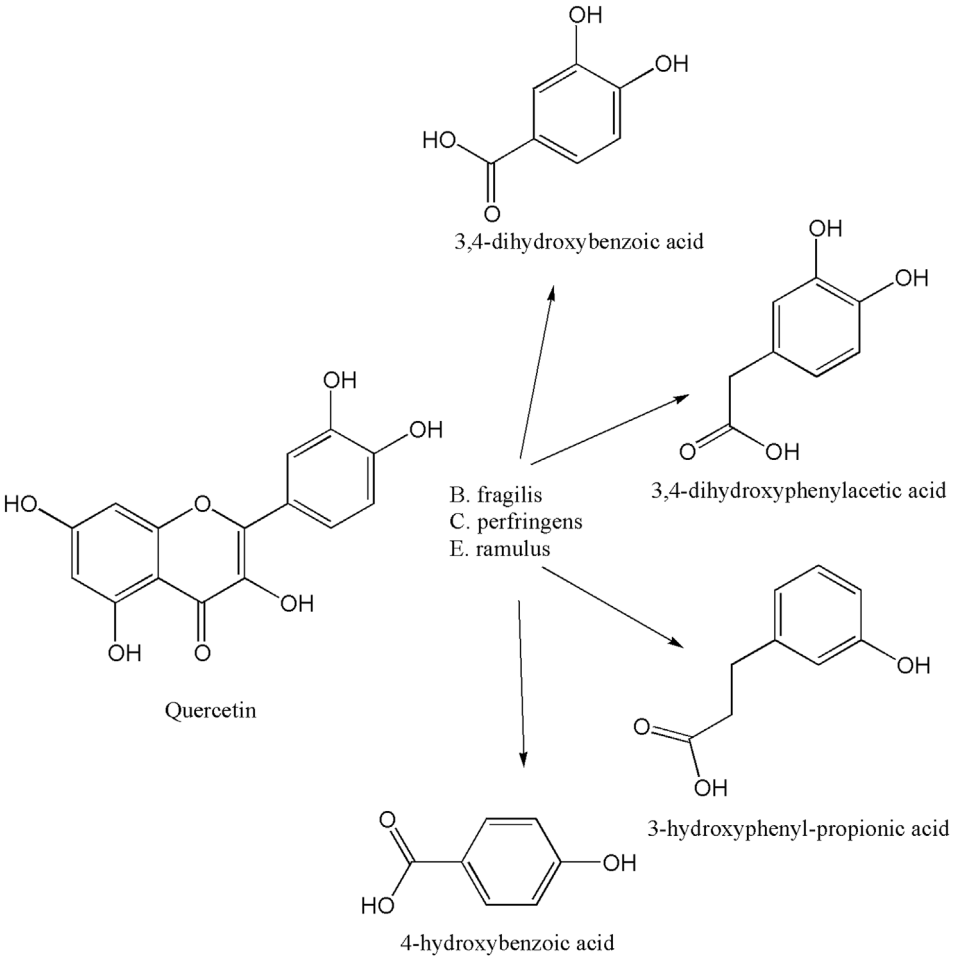

Fig. 3. Chemical structure of quercetin and its biotrasformation by gut microbiota. *B. fragilis, C. perfringens,* and *E. ramulus* are able to convert quercetin into 3,4-dihydroxybenzoic acid, 3,4-dihydroxyphenylacetic acid, 3-hydroxyphenyl-propionic acid and 4-hydroxybenzoic acid.

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