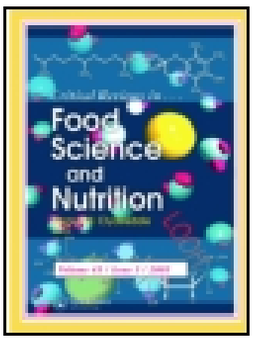

Critical Reviews in Food Science and Nutrition

ISSN: 1040-8398 (Print) 1549-7852 (Online) Journal homepage: https://www.tandfonline.com/loi/bfsn20

Polyphenols and bioavailability: an update

Hui Teng & Lei Chen

To cite this article: Hui Teng & Lei Chen (2018): Polyphenols and bioavailability: an update, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2018.1437023

To link to this article: https://doi.org/10.1080/10408398.2018.1437023

Accepted author version posted online: 06 Feb 2018.
Published online: 07 Jan 2019.

CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
https://doi.org/10.1080/10408398.2018.1437023

Taylor & Francis
Taylor & Francis Group

REVIEW

Polyphenols and bioavailability: an update

Hui Teng and Lei Chen

College of Food Science, Fujian Agriculture and Forestry University, Fuzhou, Fujian, China

ABSTRACT

Based on many cell culture, animal and human studies, it is well known that the most challenge issue for developing polyphenolics as chemoprevention or anti-diabtetic agents is the low oral bioavailability, which may be the major reason relating to its ambiguous therapeutic effects and large inter-individual variations in clinical trials. This review intends to highlight the unscientific evaluation on the basis of the published data regarding in vitro bioactivity of polyphenols, which may sometimes mislead the researchers and to conclude that: first, bio-accessibilities values obtained in the studies for polyphenols should be highly reconsidered in accordance with the abundant newly identified circulating and excreted metabolites, with a particular attention to colonic metabolic products which are obviously contributing much more than expected to their absorptions; second, it is phenolic metabolites, which are formed in the small intestine and hepatic cells,low molecular weight catabolic products of the colonic microflora to travel around the human body in the circulatory system or reach body tissues to elicit bioactive effects. It is concluded that better performed in vivo intervention and in vitro mechanistic studies are needed to fully understand how these molecules interact with human physiological and pathological processes.

KEYWORDS

Polyphenols; bioavailability; colon metabolites; catabolism

Classification of polyphenols

Flavone and flavonols

Flavones are characterized by the presence of a double bond between C2 and C3, and the attachment of the B ring to C2, including aglycones, O- and *C*-glycosylation, O-methylation and hydroxylation, which compose a similar structure with flavonols excepted for a lack of oxygenation at C-3. Flavones, such as chrysin, acacetin, hispidulin, and tricin are detected in celery, parsley, and some other herbs (Figure 1). Most of flavones occur as C-7-*O*-glycosides, although some herbs contain a small amounts of vitexin, isovitexin (C-6-glucoxyl), orientin (glycoxyl at C8 position linked toluteolin aglycone), and isoorientin 6-*C*-glucoside. Comparatively, flavones replaced by polymethoxylation are often found in citrus peel, such as nobiletin and tangeretin.

Flavonols, widely presented in human dietary, are typically determined as conjugated glycosides linking at the C5, 7, 3', 4', and 5'positions. Although the number of aglycones is limited, there are more than 200 sugar conjugates of kaempferol (Strack and Wray 1992). In daily life, the most commonly consumed fruits, vegetables, and beverages such as tea and red wine are especially rich sources of flavonols. However, the content of flavonols can be significantly varied depending on the different cultivars, local growing conditions, climate and the seasonal changes (Aherne and O'Brien 2002). Berry (Mudge et al. 2016), broccoli (Rybarczyk-Plonska et al. 2016), and onion (Smith et al. 2016) are reported to contain especially high contents of quercetin-4'-O-glucoside, quercetin-3, 4'-O-diglucoside, and quercetin-3-O-rutinoside.

Flavanone and flavanonol

The flavanone consists of a wide array of compounds characterized by the absence of C2-C3 double bond and the presence of a chiral center at C-2. In natural plant, it occurs as *O*- or *C*-glycosyl, hydroxy, methoxy, methylenedioxy, C-methyl, C-benzyl, C-hydroxy methyl, C-formyl, and C-isoprenyl derivatives (Figure 2). Flavanones are found at a high concentration in citrus fruits. The most common flavanone glycoside is hesperetin-7-O-rutinoside (hesperidin). In fact, some flavanone glycosides such as 7-rutinosides are tasteless, in contrast to neohesperidin (7-O-neohesperidoside), naringin, and hesperetin (naringenin-7-O-neohesperidoside) which have an intense bitter taste isolated from bitter oranges and grapefruit (Frydman et al. 2013). Following an earlier study reported by Peterson et al. (2006), four major flavanone aglycones including isosakuranetin, hesperetin, naringenin, and eriodictyol, together with their corresponding glycosides such as didymin, eriocitrin, hesperidin, narirutin, naringin, neoeriocitrin, neohesperidin, and poncirin were isolated from oranges, tangerines (mandarins), tangors, and tangelos (Figure 2)

CONTACT Lei Chen chenlei841114@hotmail.com College of Food Science, Fujian Agriculture and Forestry University, Fuzhou, Fujian, China.

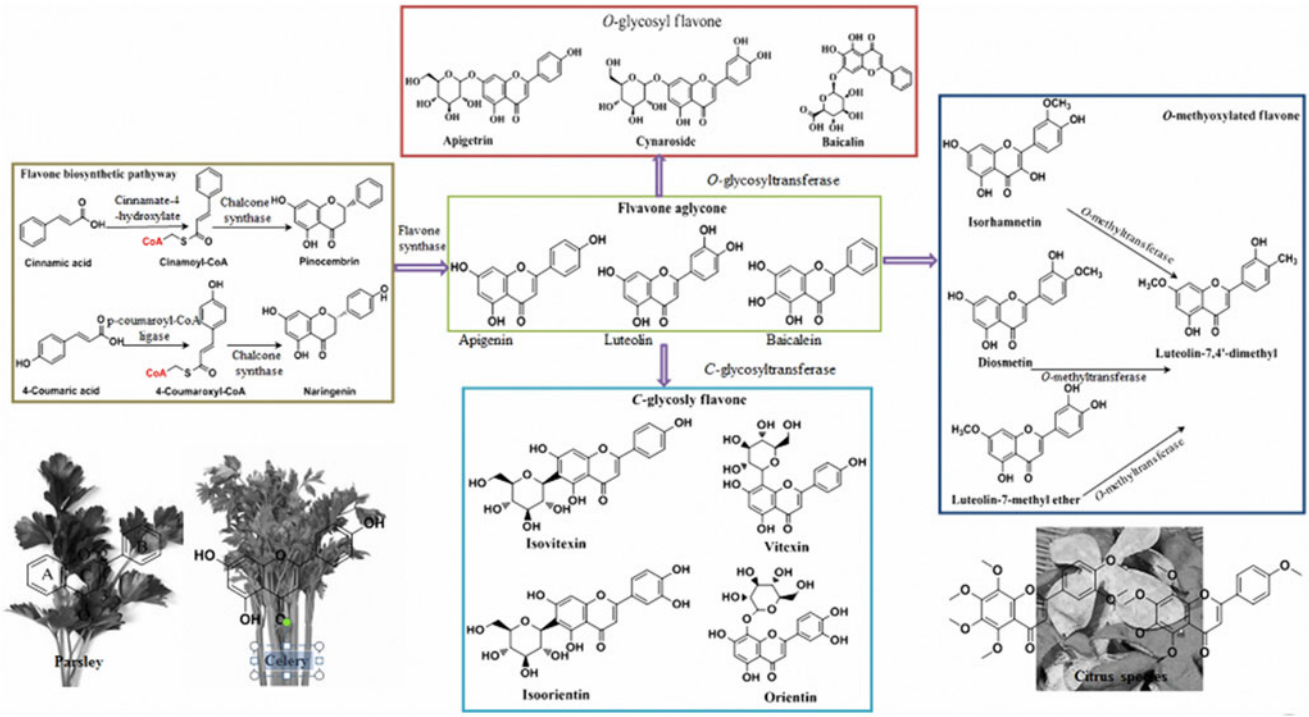

Figure 1. Structures of the flavones and three common flavavone aglycone apigenin, luteolin, and baicalein and their biosynthetic pathway.

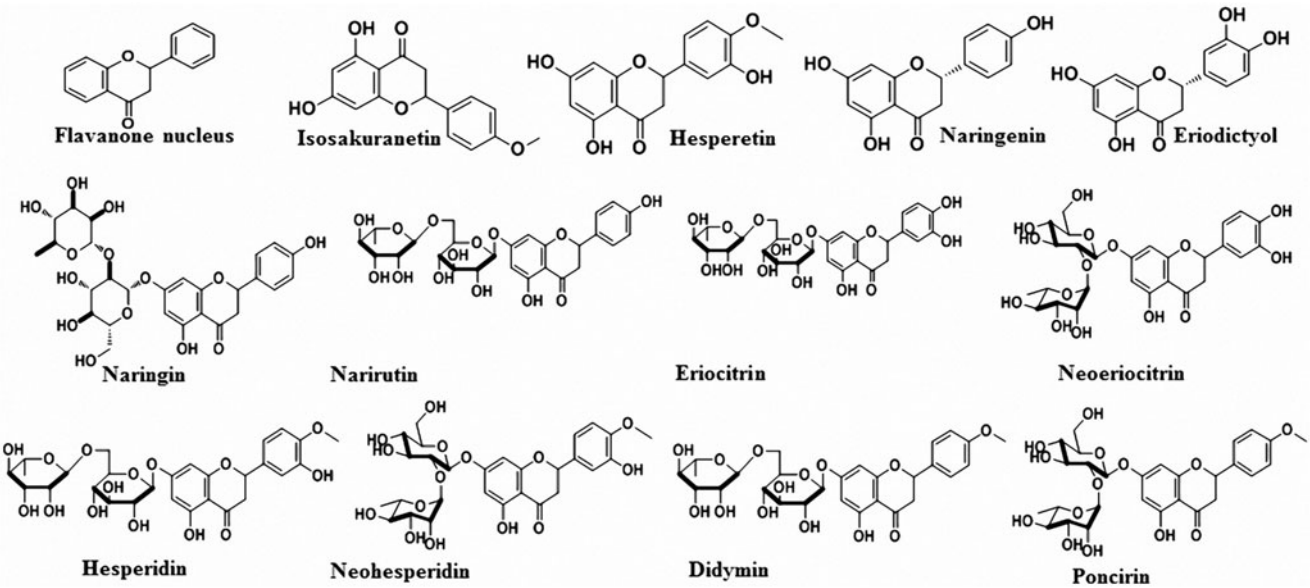

Figure 2. The S-enantiomers of four major flavanone aglycones including isosakuranetin, hesperetin, naringenin, and eriodictyol, together with their naturally occurring glycosidess didymin, eriocitrin, hesperidin, narirutin, naringin, neoeriocitrin, neohesperidin, and poncirin.

Anthocyanidins and flavan-3-ols

Anthocyanins, belong to the polyphenol are water-soluble pigments in plants which contribute to the brilliant colors of blue, red, and mauve in flowers, fruits and leaves. The ionic nature of anthocyanins enables changes of the molecular structure according to the prevailing pH, resulting in different colors and hues at different pH values. It occurs principally when glycosides of their respective aglycone anthocyanidin chromophores generally attached at the 3-position on the C-ring (3-monoglycosides) or the 5-position on the A-ring (3, 5-diglycosides). Anthocyanins are classified according to the number and position of hydroxyl groups on the flavan nucleus which named: cyanidin, delphinidin, petunidin, peonidin, malvidin and pelargonidin (Figure 3). The most common sugar of anthocyanidin glycosides is glucose, nevertheless, rhamnose, xylose, galactose, arabinose, and rutinose (6-O-L-rhamnosyl-D-glucose) can also present. Although very rare, glycosylation at the 3', 4', or 5' positions of the B ring is also possible. The sugar moiety may be acylated by aromatic acids, general hydroxycinnamic acids (caffeic, ferulic, p-coumaric or sinapic acids) and occasionally by aliphatic acids, namely succinic, malic, malonic, oxalic and acetic acids. The acyl moieties are normally linked to

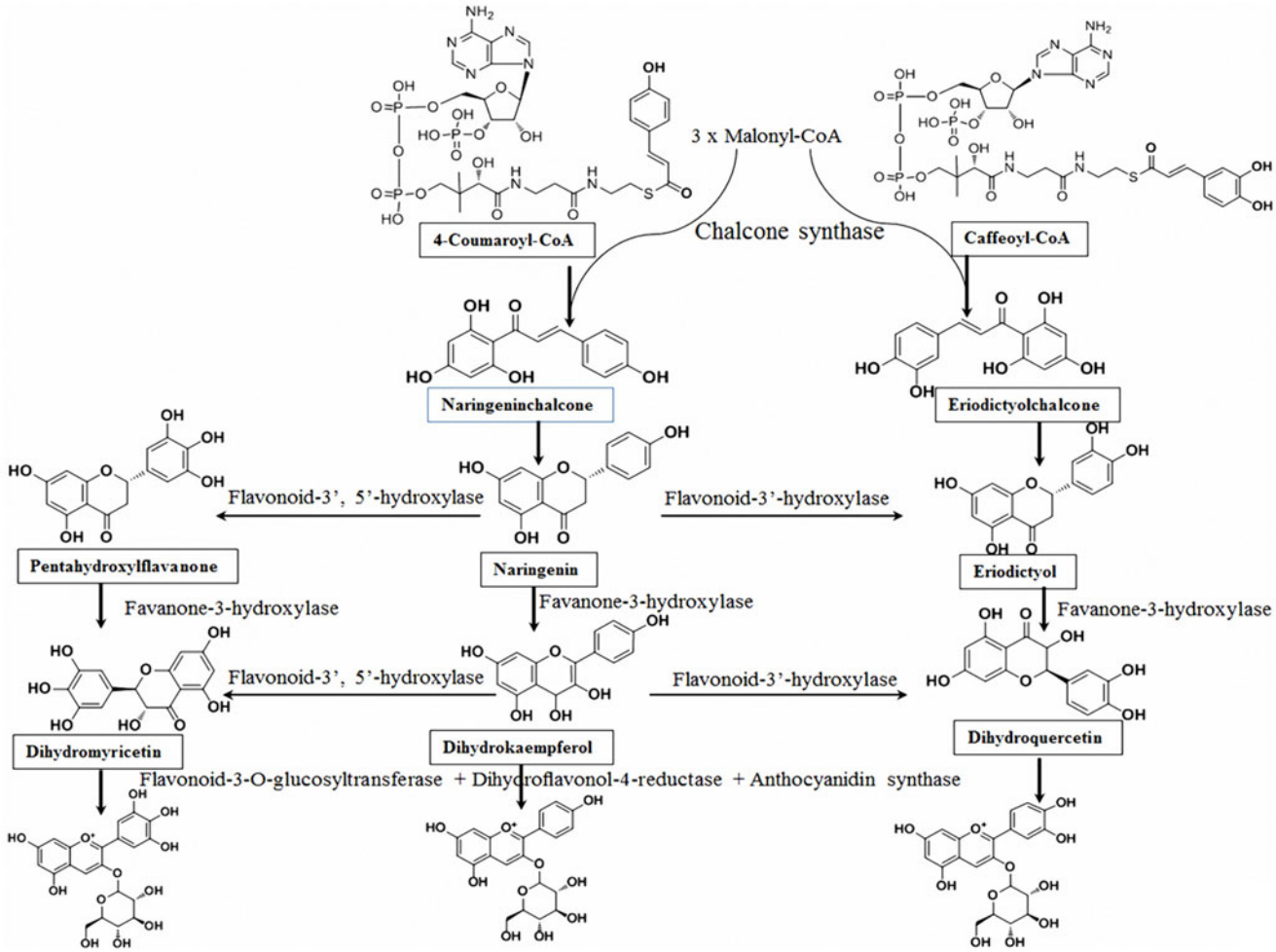

Figure 3. Schematic presentation of the biosynthesis of anthocyanins; first phenylalanine reacts with malonyl CoA to produce 4-hydroxycinnamoyl CoA. Under the catalytic control of chalcone synthase 4-hydroxycinnamoyl CoA condenses with three molecules of malonyl CoA to form a chalcone. Chalcone isomerase closes the heterocyclic ring to form naringenin. The B-ring is moved from the 2-position to the 3-position by isoflavone synthase. Isoflavone dehydratase removes water to generate the C-C3 double bond in the heterocyclic ring.

the sugar at C-3 position. For anthocyanin biosynthesis, some important structural genes and regulatory elements are required. As shown in Figure 3, described that malonyl-COA and p-coumaroyl-COA are necessary for the synthesis of anthocyanins. Three acetate units are catalyzed and condensed step by step from malonyl-COA (with p-coumaroyl-COA) through chalcone synthase to generate naringenin chalcone and eriodictyolchalcone. Then, the stereospecific isornerization of tetrahydroxychalcone (yellow) could be catalyzed to naringenin (colorless) by chalcone isomerase. Naringenin is transformed into dihydrokaempferol by flavanone 3-hydroxylase, and subsequently, dihydrokaempferol could be hydroxylated by flavonoid 3'-hydroxylase to produce dihydroquercetin or to produce dihydromyricetin by flavonoid 3', 5'-hydroxylase. During the process, at least three kinds of enzymes are required for changing the dihydroflavonols (colorless) into anthocyanins. The first of these enzymatic conversions is the reduction of dihydroflavonols to leucoanthocyanidins by dihydroflavonol4-reductase. Further oxidation, dehydration, and glycosylation of the different leuco anthocyanidins produce the corresponding brick-red pelargonidin, red cyanidin, and blue delphinidin pigments. Anthocyanidin-3-glucosides may be further modified by glycosylation, methylation, and acylation.

The glycosides of the three non-methylated anthocyanidins (delphinidin, cyaniding and pelargonidin) are the most abundant found in nature, which represent 80% of leaf pigments, 69% in fruits and 50% in flowers. The most common anthocyanidins found in the edible parts of plants are cyanidin, pelargonidin, peonidin, delphinidin, petunidin, and malvidin. The red color of the raspberry fruit is related to its anthocyanin composition. Profiles of the anthocyanins of red raspberry mainly consist of cyanidin 3-O-sophoroside, cyaniding 3-O- glucorutinoside, and cyanidin 3-O-glucoside. A recent work (Ludwig, et al. 2015) characterized anthocyanins content of commercial red raspberry and found that cyanidin-3-O-sophoroside, cyanidin-3-O-(2"-O-glucosyl) rutinoside, cyanidin-3-O-glucoside, and cyanidin-3-O-rutinoside were 175, 56, 37, and 20 μM/300 g raspberries (Ludwig et al. 2015), respectively. The relative composition was cyanidin-3-sophoroside > cyanidin-3-glucorutinoside > cyanidin-3-glucoside > cyanidin-3-rutinoside > all pelargonidin glucosides combined. All these anthocyanins have also been detected in red raspberries previously, though not in a

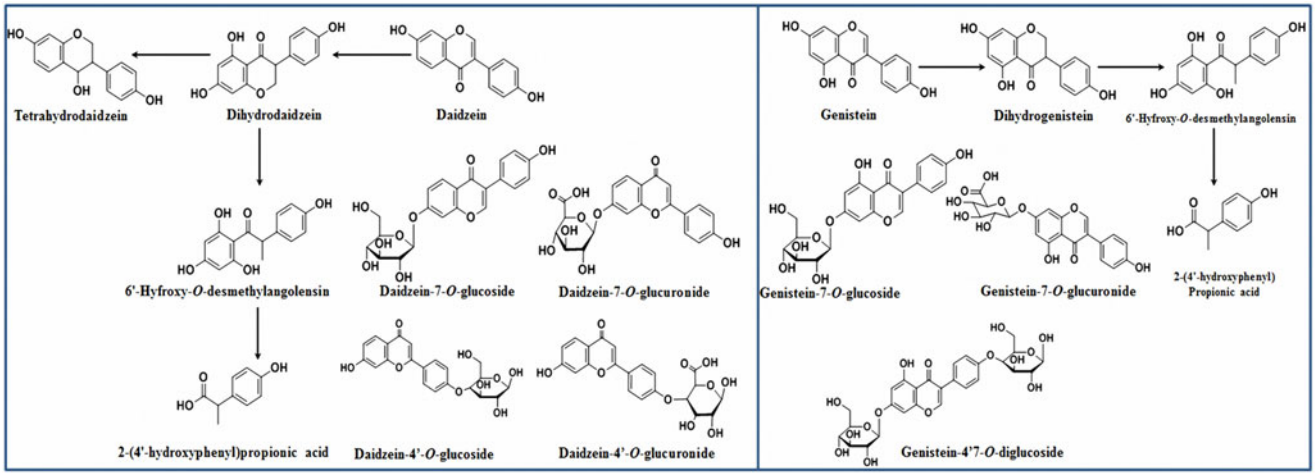

Figure 4. The isoflavone aglycones daidzein and genistein and O-glycosides of daidzein, which along with similar genistein conjugates, are found in soy products.

single cultivar. The different anthocyanin contents found in a single cultivar in different papers may be dedicated to the characterizations of the fruit stages of ripeness, processing, and environmental factors.

Flavan-3-ols, generally, do not exist in natural plant as glycosides but are the most complex subclass of flavonoids, ranging from the simple monomers to the condensed tannins of oligomeric and polymeric proanthocyanidins. Flavan-3-ols have been wildly reported to exhibit many health beneficial effects by acting as antioxidant, chemopreventive, and immunoregulation agents (Yaqub et al. 2016; Asenso et al. 2015). The two chiral carbon atoms of C2 and C3 of monomeric flavan-3-ol have four isomers for each level of hydroxylation linked at B-ring, such as epicatechin and catechin that have a wide distribution in nature, while others such as epiafzelechin is limitedly distributed . Pairs of enantiomers can be resolved by chiral chromatography, but not sensitive to reverse-HPLC, which are consequently ignored easily (Chankvetadze 2012).

Isoflavone and isoflavanone

Isoflavones, of which usually shown as 2 major forms of daidzein and genistein, are obtained primarily from soy products in Asian diets. They have the B-ring attached at C-3 rather than the C-2 position (Figure 4). Daidzein and genistein, with structure named 7-hydroxy-3-(4-hydroxyphenyl)-4H-1-benzopyran-4-one, 4 H and 5,7- dihydroxy-3-(4-hydroxyphenyl)-4H-1-benzopyran-4-one, respectively, are exclusively presented in leguminous plants. In fermented soybean product, isoflavones are always found in their aglycone forms because of the hydrolysis of glycosides (Szeja, Grynkiewicz, and Rusin 2017). Whereas, during the products processing, for example manufactures of soy milk and tofu, the content of isoflavones may be reduced as they mainly formed into isoflavone glucosides, leading to the result of malonyl-ordacetyl-glucosides degradation (Yonemoto-Yano et al. 2014). More specifically, because of their structural similarities to human female hormone, isoflavones are particularly classified as β-estrogen receptor, which can therefore act as estrogen agonists and antagonists that compete for estradiol at the receptor complex (Shimazu et al. 2010). In legumes plant, enzyme 2-hydroxyisoflavanone synthase introduces the isoflavone biosynthetic pathway. This enzyme can convert flavanone to 2-hydroxyisoflavanone by transferring the aromatic B-ring from position C-2 to C-3 and hydroxylation in position C-2. Additionally, microbial metabolism can also transmute isoflavone to isoflavanone. In vitro results by incubations with human fecal and rat cecal microbiota revealed the formation of 2-(4'-hydroxyphenyl) propionic acid from 6'-hydroxy-O-desmethylangolensin, indicating C-ring fission. Genistein is reduced to dihydro genistein, which could further metabolized to 6'-hydroxy-O-desmethylangolensin (Figure 4).

Bioavailability of polyphenols

The absorption, transportation, bioavailability, and bioactivity of polyphenols and related metabolites after food intake have been the research topics of increasing interests in the last decades. After the administration of polyphenolics, some of them first pass in the stomach and get absorbed, but by no means all of them, and compounds such as catechines, flavanols, and flavones into the circulatory system occurs in the small intestine. In general, the absorption of phenolics and their corresponding glycosides, as illustrated in Figure 5, is related to the cleavage and release of the aglycone, partly as a result of microbial metabolism and digestive enzymes activity. Lactase phloridzin hydrolase (LPH), which is specially located in the epithelial cells of small intestine (Danielsen and Danielsen 2016), substrate specificity for flavonoid-O-β-glycosides, and the released aglycone may then enter the epithelial cells by passive diffusion as a result of its increased lipophilicity and proximity to the cellularmembrane (Kay et al. 2017). On the other hand, another digest enzyme named cytosolic β-glucosidase (CBG) existed in the epithelial cells, alternatively hydrolyze some phenolic-glycosides after they have been transported through the epithelium. For CBG-deglycosylation to occur, the glycosides (polar) firstly have to be transported into the epithelial cells,

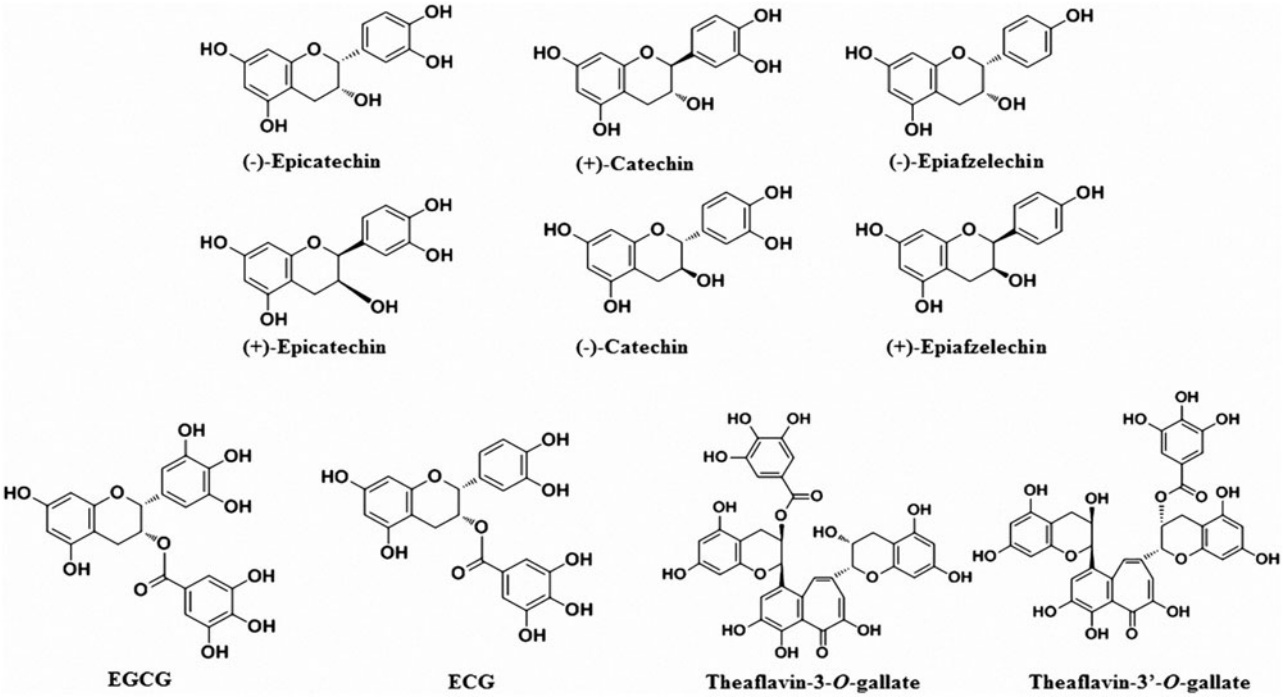

Figure 5. Structures of major tea phenolics and their glycosides.

possibly with the involvement of the active Na^+/glucose cotransporter 1 (SGLT1) (Oliveira et al. 2015). In fact, no matter of which above mentioned routes of the phenolic glycoside conjugates are deglycosylated, the resultant aglycones would appear in the epithelial cells, namely LPH-diffusion and transport-CBG (Kay et al. 2017). However, there is a controversy as to whether intestinal absorption of glycosylated flavonoids, and particularly for the quercetin glycosides involves their uptake in intact form via the human sodium-coupled glucose transporter SGLT1. An investigation by using Xenopuslaevis oocytes as cell model revealed that SGLT1 does not transport flavonoids, such as quercetin, myricetin, and isoquercitrin (Kwon et al. 2007), as well as the glycosylated flavonoids and some aglycones, for example, (+)-catechin, (−)-epicatechin gallate, and (−)-epigallocatechin gallate have the ability to inhibit the glucose transporter (Hossain et al. 2002). In Caco-2 cell model, declared that the aglycones of quercetin and myricetin inhibited GLUT2-dependent glucose uptake of SGLT1, whereas phenolic acids were found with no such effect.

Before passive transport into the hepatic vein and **systemic circulation**, as shown in Figure 6, polyphenolic aglycones are metabolized through their sulfation, glucuronidation, or methylation and undergo some degrees of phase II metabolism through the respective actions of sulfotransferases, uridine-5'-diphosphate glucuronosyltransferases, and catechol-O-methyltransferases (phase-II enzymes responsible for the detoxification and producing glucuronidated, sulfated and methylated conjugates) (Margalef et al. 2017). Otherwise, some of the metabolites efflux back into the lumen of the small intestine, which is supposed to involve the transporters members of the adenosine triphosphate-binding cassette (ABC) family, including multidrug resistance protein (MRP) and P-glycoprotein(Nicholls, Flynn, and Woodhouse 2016). Moreover, it has been proposed that MRP-3 and the glucose transporter 2 (GLUT2) have also been implicated in the efflux of metabolites from the basolateral membrane of the enterocytes (Alvarez-Suarez, Giampieri, and Battino 2013). Using Na+-positive (glucose transporters SGLT1 and GLUT2 both active) and Na+-negative (only GLUT2 active) conditions, Manzano and Williamson showed some polyphenols, phenolic acids, and tannins inhibited glucose transport from the intestinal lumen into cells and also inhibited the GLUT2-facilitated exit on the basolateral side (Manzano and Williamson 2010). Once passive into bloodstream, metabolites rapidly reach the liver, where they can be subjected to further phase II metabolism, and enterohepatic recirculation may result in some recycling back to the small intestine through bile excretion (Figure 6). According to the recent data on the bioavailability of dietary phenolic, there is a growing realization that phenolic-glucuronidation, methylation, and sulfation are treated by the body as xenobiotics, which instead of accumulating in the circulatory system. In another words, compounds with a high degree of polymerization cannot be absorbed at the small intestine, reach the colon to undergo microbial catabolism, leading to the formation of small polyphenols that are able to reach the liver, where they can also be subjected to phase-II conjugation (Cardona et al. 2013; Aragonès et al. 2017; Dudonné et al. 2015). Both phase-II enzymes and microbial metabolites reach the systemic circulation, and are distributed to different organs and tissues, or reach the kidneys to be excreted through the urine. Consequently, although plasma pharmacokinetics of these metabolites provide an useful information, estimates such as of area-under-the curve values do not necessarily yield accurate quantitative data on absorption.

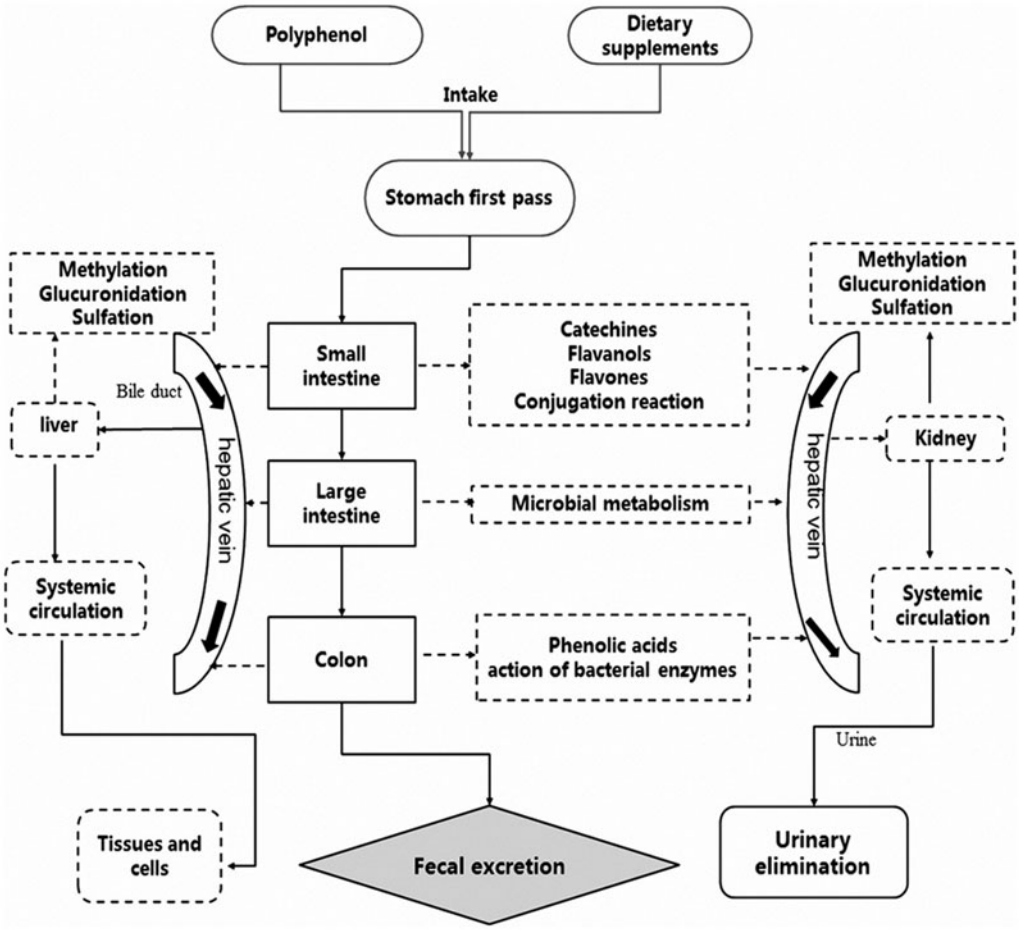

Figure 6. Diagram of metabolic fate of polyphenols.

Flavanones

Following consumption, dietary flavanones were, at least until now, considered to be poorly used by human body with only comparatively small amounts of the ingested dose entering the systemic circulation, not as the parent components but as phase II metabolites. Corresponding glycosides or d sulfate derivatives of phase II metabolites are mainly found, with studies tested plasma after dosing ranging from 63 to 1500 nM (Vallejo et al. 2010) and urinary recoveries <5 –16% of the ingestion. The bioavailability data for flavanones in humans have been developed by theadministration of orange juice with a volume of 250 mL, which contained 168 μmol of hesperidin and 12 μmol of naringenin-glycoside. The hesperidin dose was similar to that of tomato juice containing rutin ingested by healthy volunteers (Jaganath et al. 2006). Hesperetin-7-*O*-rutinoside reduces blood pressure in healthy volunteers and its intestinal absorption and metabolism are fully investigated by Actis-Goretta et al. (2015). Hesperetin-7-*O*-rutinoside and hesperetin-7-*O*-glucoside directly pass into the proximal jejunum of human body, and the glycoside was rapidly hydrolyzed by brush border enzymes, but no hesperetin metabolites were detected in blood and only trace was excreted in urine (Actis-Goretta et al. 2015). The subjects that consumed orange juice containing hesperetin-7-O-glycoside experienced 4-fold higher C_{max} and a much earlier T_{max} for the appearance of hesperetin metabolites than the subjects consuming conventional orange juice (Nielsen et al. 2006). Similarly higher total absorption, C_{max}, and earlier T_{max} values occurred when consuming an α- rhamnosidase-treated orange juice containing naringenin-7-O glucoside rather than the originally presented narirutin (Bredsdorff et al. 2010). In fact, hesperidin cannot be absorbed into the small intestine epithelium and immediate jejunal perfusion in humans. There are two major hesperetin metabolites along with hesperetin-*O*-glucuronide-*O*-sulfates and a hesperetin-*O*-diglucuronide were found in urine after the consumption of orange juice flavanones in humans (Mullen et al. 2008). On the other hand, although no naringenin metabolites were detected in plasma, urine contained naringenin-7-O-glu-curonide, narigenin-4'-O-glucuronide and naringenin-O-diglucuronide in amounts which is equivalent to 17.3% of the ingested naringenin-7-O-rutinoside (Dall'Asta et al. 2013). Many feeding studies have shed light that hesperetin and naringenin metabolites found at different levels and correlated with the amounts of ingestion of flavanones (Ting, Yeh, and Lien 2011; Yoshida et al. 2010). Although both of hesperetin-*O*-glucuronides and quercetin-3-O-rutinoside are absorbed in the large intestine, the C_{max} of former is much higher than that of the latter one despite of the similar ingested concentration (Thilakarathna and Rupasinghe 2013). Nevertheless, supplemented with the higher dose of orange juice to healthy volunteers (Morand et al. 2011), the

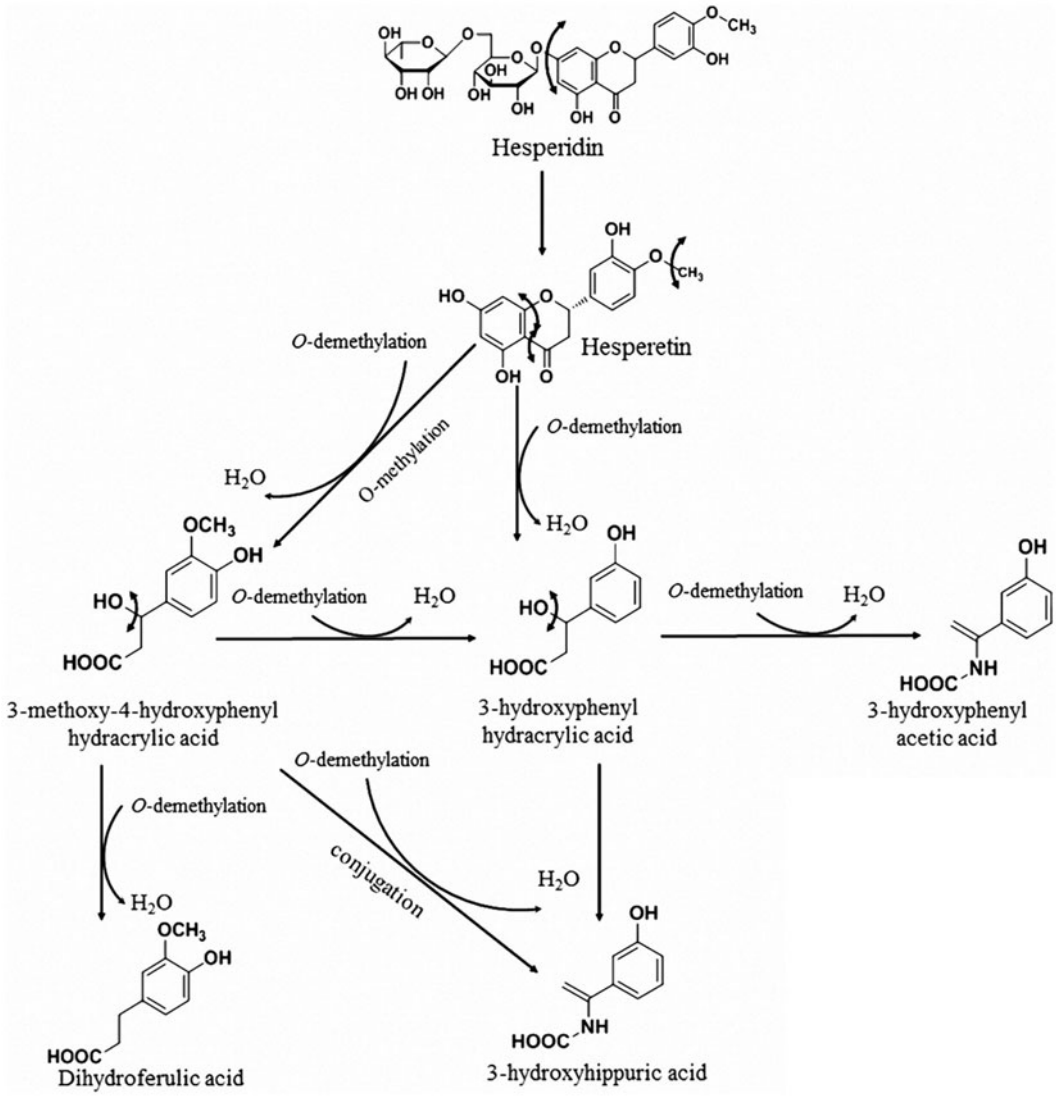

Figure 7. Proposed catabolism of hesperidin in humans.

results revealed that hesperetin-7-*O*-rutinoside after metabolism were absorbed more effectively than those of quercetin-3-*O*-rutinoside. This may explained by that the flavones-rutinoside is converted to its glycoside in the large intestine more effective than quercetin-3-O-rutinoside. Among the flavanones, the metabolism data in intestinal cells is only available for hesperetin, as shown in Figure 7. Demonstrated that hesperetin is absorbed by Caco-2 cells and is subsequently conjugated to produce glucuronide and sulfate metabolites.

Flavonols

Red grapes always contain high contents of flavonols such as quercetin, myricetin, kaempferol, laricitrin, isorhamnetin, and syringetin, which consist of the the proportions of 43.9, 36.8, 6.4, 5.6,3.8, and 3.2%, respectively (Mattivi et al. 2006). In apple peel, the predominant forms of flavonols are quercetin-O-arabinoside, quercetin-3-O-galactoside, quercetin-3-*O*-glucoside, and quercetin-3-*o*rhamnoside, while in the onion powder, quercetin occurred as the quercetin -3, 4′-*O*-glucoside and 4′-O-glucoside (Chen et al. 2014). To date, for all of the flavonoids, only the aglycone form of quercetin is available to manufacturers for the supplementation as food product. Meanwhile, quercetin is most frequently used in human clinical studies. However, de Vries et al. (2001) revealed that the absorption rate for the glycosides was 52%, which was superior to that of the aglycone (24%) in patients (de Vries et al. 2001). Additionally, intake of quercetin glycoside led to a much more rapid and larger rise of quercetin levels in plasma than intake of its rutinoside (Sesink et al. 2005).

After the intake of tomato juice containing flavonols, the metabolites absorption started at 4 h which was characteristic of absorption in the large rather than small intestine, and sorhamnetin-3-glucuronide ($C_{max} = 4.3$ nM) and quercetin-3- glucuronide ($C_{max} = 12$ nM) were detected in plasma of healthy subjects (Jaganath et al. 2006). This result was in a good agreement with the study by Day et al. (2000), who reported that the flavonol disaccharidewas not cleaved by LPH in the epithelial cells of small intestine (Day et al. 2000). Generally, quercetin-rutinoside will pass through the small intestine and reach to colon in vivo, where cleavage of

the sugar moiety by colonic enzymes occurs, and the released aglycone undergoes low-level methylation and glucuronidation before absorption into the portal vein (Mullen et al. 2008). However, intake of quercetin, for example, is easy to subject to its ring fission, resulting in producing 3-hydroxyl-phenylacetic acid, 3-methoxy-4-hydroxy-phenylhydracrylic acid, dihydroferulic acid, and 3-hydroxyhippuric acid catabolites (Del Rio et al. 2010). Interestingly, quercetin released in the small intestine by cleavage of its glycoside can be converted to quercetin-glucuronide, sulfate, and methylated (Biasutto and Zoratti 2014), whereas the production of quercetin in the colon from quercetin- rutinoside is metabolized to methylation derivatives and glucuronide, but not sulfate metabolites (Thilakarathna and Rupasinghe 2013). This suggests that sulfation of flavonols is a procedure of metabolizing enzyme action in the wall of the small intestine rather than the colon or the liver

Anthocyanins

Several reviews have concluded the bioavailability of anthocyanins in recent years (Rein et al. 2013; Carbonell-Capella et al. 2014; Yousuf et al. 2016; Teng et al. 2017). Although the accumulating data have evidenced that the health benefit effects, the plasma concentrations, and the bioavailability of anthocyanins were found to be low. In fact, the intact anthocyanins excreted in urine were found to be less than 0.1% in human subjects (Ludwig et al. 2015). In animal studies, absolute bioavailability of anthocyanins was found to be ranged from 0.26% to 1.8% when intravenous administrations were used for comparisons (Chen et al. 2015; Norberto, et al. 2013). The absorption of anthocyanins is considered to be inefficient, but some of their glycosides could be efficiently absorbed across the gastrointestinal mucosa, for example, 30 and 56% of cyanidin 3-glucoside and pelargonidin 3-glucoside were tested as protocatechuic acid and 4-hydroxybenzoic acid, respectively, in plasma following oral intake in humans (Fang 2014). It seems that low concentrations of anthocyanins were detected in plasma in contrast to the high concentrations of the phenolic acid metabolites.

Isoflavones

Isoflavones are shown specific pharmacokinetic features, for instance, isoflavone-glycosides are considered to be more bioavailable than their aglycones (Gaya et al. 2016; Kay et al. 2017). β-Glucosidases can break down the glycosidic bonds of daidzin, genistin, glycitin and their parent aglycones of daidzein, genistein and glycitein (Krisch et al. 2012). In this regard, bioavailability of soybeans could be significantly increased by using β-glucosidases to convert the isoflavones glycoside and aglycones,improving their promising benefits for food applications. Daidzein was rapidly excreted in urine, whereas genistein enters enterohepatic recycling. It has been reported that the absorption of daidzein in the gastrointestinal tract was very poor, and its absolute absorption was only 6.1% in rats after oral administration (Zhang et al. 2011). It should be noticed that the in vitro IC_{50} values for biological and other health benefit effects of genisitein are much higher than that in its plasma concentration (Sarkar et al. 2006). Genistein also showed very long half-life (with $T1/2 = 46$ h) in vivo (Yang et al. 2010) after oral administration suggesting the recycling of genistein was substantial or an unknown mechanism of elimination in vivo. A few human studies have also identified that intestinal bacteria could catalyze daidzein via dihydrodaidzein to equol (Sánchez-Calvo et al. 2013; Setchell and Clerici 2010; Uehara 2013). As reported by using different doses of genistein at 6.25, 12.5, and 50 mg/kg to rat, the AUC values (area under the curve) for genistein were 23.5, 80.9, and 177.9 mg/min, which indicated non-linear pharmacokinetics in rat. Pharmacokinetic studies indicated that genistein also has $<$15% absorption by humans through oral administration (Xu et al. 1994). Data obtained by compared isoflavones' absorption in human body and showed that the recirculation of genistein induced a delay in urinary elimination, explaining why only 34.4% of genistein was eliminated after 24 h ingestion whereas glycitein elimination ratiowas 66.2%. This may be due, in part, to higher bioavailability of glycitein in humanIt is generally considered that after digestion, the biologically active forms of the naturally occurring isoflavone glycosides such as daidzin and genistin are either aglycone daidzein or genistein or their unconjugated metabolites. In blood, isoflavones are conjugated into glucuronide and sulfate forms by gut, liver and kidney enzymes (Hosoda et al. 2010). In conclusion, isoflavone plasma doses can be affected by the source of variation, food complex, diet difference, frequency of intake, gender difference, and age.

Flavan-3-ols

The bioavailability of flavan-3-ols is always higher than that of other flavonoids, even if it has been already considered to be relatively poor (Tomas-Barberán et al. 2007; Quiñones et al. 2015). More importantly, flavan-3-ols as one class of the chemically active flavonoid occurring in plasma is more diversified than in food (Margalef et al. 2014; Margalef et al. 2015). There is a considerable interest in the bioavailability of flavan-3-ols and cocoa-derived flavonoids such as catechins and procyanidin and their absorptions in vivo. Bioavailability and pharmacokinetic studies on tea extract have proposed significant differences and contentious results, with urinary excretion ranging from unpredictable traces to values around\10% of the ingested amount (Chow et al. 2005; Del Rio et al. 2010). On the other hand, flavan-3-ols are well known to bind macromolecules and nutritional substances such as proteins and polysaccharides, thereby escaping being measured (Wiese et al. 2015). Several works observed similar bioavailability values for green tea flavan-3-ols ranging from 2% to 8.1% (Manach et al. 2005; Stalmach et al. 2009). Study with five healthy subjects after tea ingestion observed that two major flavan-3-ol catabolites, 5-(3', 4', 5'-trihydroxyphenyl)-γ- valerolactone and 5-(3', 4'-dihydroxyphenyl)-γ-valerolactone, accounted for up to 40% of the amount of pure EGC and EC (Li et al. 2000). Ten

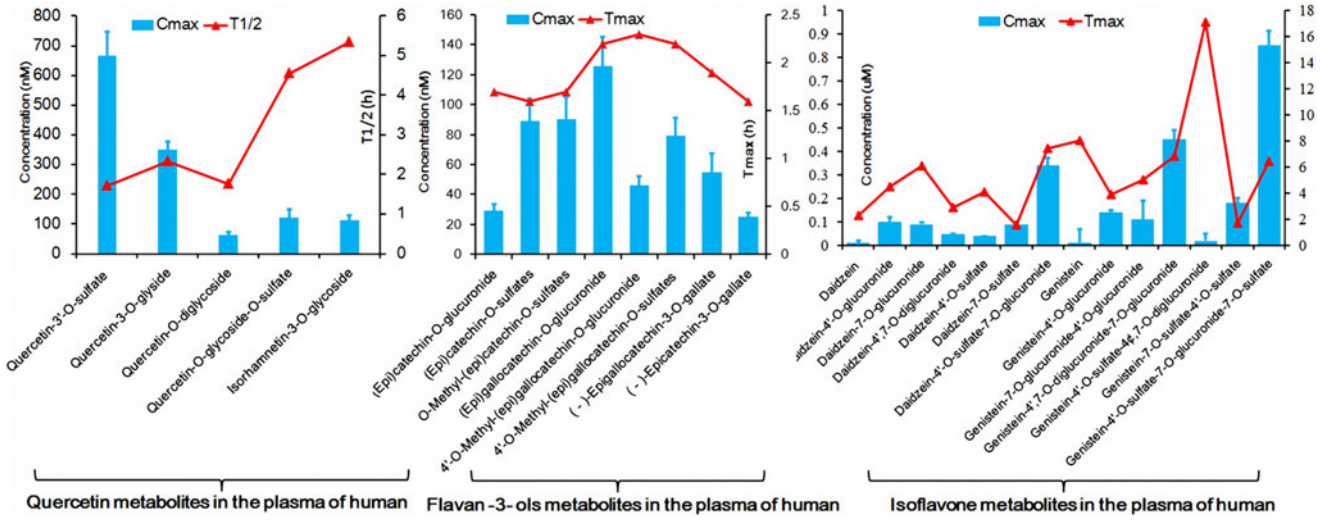

Figure 8. Pharmacokinetic analysis of phenolic metabolites in the plasma of volunteers after the consumption of fried onions, green tea (M), baked soybean (R).

healthy human volunteers consumed green tea(contained 648 μmol of flavan-3-ols), plasma and urine were collected over a 24 h period and analyzed (Stalmach et al. 2009). The results showed that ten metabolites were detected in the plasma, in the forms of *O*-methylated, sulfated and glucuronide conjugates of catechin and gallocatechin, with 29-126 nM peak of C_{max} occurring at 1.6-2.3 h after intake, indicating that these flavan-3-ols were absorped in the small intestine (Stalmach et al. 2009). The fraction of flavan-3-ols not absorbed in the small intestine reaches the large intestine, where it can undergo several microbial processes, consequently hydrolyzed into smaller molecules that can also be absorbed, reaching the liver and, finally getting into the systemic circulation (Clarke et al. 2014). Based on the sites of formation and absorption, the excretion from the human body for these classes of metabolites are remarkably different. Furthermore, differences could be observed when bioavailability evaluations were conducted by using the second source of flavan-3-ols from chocolate (Ostertag et al. 2017), or when single or clusters of molecules, such as EGCG, GC or tea catechin, were introduced as supplements (Smith et al. 2013; Peter, Bosze, and Horvath 2017). Recently, increasing approaches in absorption, metabolism, and bioavailability of flavan-3-ols were carried out, using plasma and urine to examine the changes in the host and microbial metabolism after cocoa consumption in human subjects (Vázquez-Agell et al. 2013; Mastroiacovo et al. 2015; Massot-Cladera et al. 2017).

Cocoa flavan-3-ol

Since flavan-3-ols are more bioavailable as compared to the other polyphenolics, their metabolisms in plasma and urine have been fully investigated extended to their isomeric level, which absolutely clarified by using, for instance, (epi)catechin and (epi)gallocatechin in almost all of the publicationsThe consumption of cocoa flavan-3-ols, and through systemic circulation with β-glucuronidase or sulfatase, and the physiological levels of epicatechin, catechin and epicatechin monomers were determined by HPLC (Rein et al. 2000; Natsume et al. 2000). Actis-Goretta et al. (2012) elucidated that after the consumption of dark chocolate (an (−)-epicatechin-rich food), (−)-Epicatechin-3'-β-D-glucuronide (C_{max} 29 nM), (−)-epicatechin 3'-sulfate (C_{max} 23 nM), and 3'-O-methyl epicatechin sulfates substituted in the 4', 5, and 7 positions were the most relevant metabolites of (−)-epicatechin in the plasma and the total urine excretion of (−)-epicatechin was 20% of the ingested amount (Actis-Goretta et al. 2012). The characteristic of flavan-3-ol absorption is in the gastrointestinal tract rather than in the large intestine. After being absorbed and utilized in the intestine, (−)-epicatechin is rapidly decomposed and metabolized into galloylated epicatechins, epicatechin gallate and epigallocatechin gallate through enterocytes or hepatocytes (Olivé and Casado 2013). The transformations of these metabolites in both cell types were also carried out by UDP-glucuronosyltransferases (UGTs) and catechol-*O*-methyltransferases (COMTs) (Wang et al. 2017). An exact cognition of the influence of the food matrix on the delivery of cocoa flavan-3-ol to the circulation was also conducted by Rodriguez-Mateos et al. (2012). By randomized, double-blind, and three-arm cross-over study design, 15 volunteers were subjected to three groups including a high flavanol (266 mg) chocolate containing maltitol, a high-flavanol (251 mg) chocolate with sucrose, and a low-flavanol (48 mg) chocolate with sucrose. The data showed a positive relationship between intake and (epi)catechin plasma concentrations, and the maximum level of plasma epicatechin metabolites was found between 1 and 2 h after flavanol intake, and by 4 h, plasma epicatechin metabolites were low, suggesting that the plasma flavanol levels post-4 h will greatly contribute to the total plasma flavanol load to the circulation (Rodriguez-Mateos et al. 2012). The general kinetics of bioavailability, metabolism, plasma concentration, and urine excretion of flavan-3-ol reported in cocoa extract are in agreements with previous studies using the similar green tea intervention. Some similar observations for tea flavan-3-ol have already been reported in the literature. For example, at a dose of 22 μmol, the 0–24 h excretion of (epi)gallocatechin metabolites was 5.7–1.9 μmol, and did not increase significantly

with intakes of 55 and 165 μmol. There is, therefore, a strict limit on the extent to which (epi)gallocatechins can be absorbed. After the ingestion of 77 μmol of (epi)catechins, 369 lmol was excreted, and with doses of 192 and 577 μmol, and urinary excretion increased significantly to 107-27 and 262-26 μmol. Thus, unlike (epi)gallocatechins, (epi)catechins is still readily absorbed even at the highest dose,

The addition of a 5'-hydroxyl group to (epi)catechin, therefore, markedly reduces the extent to which the molecule can enter the circulatory system from the small intestine. It is also of note that at the three administration doses, the ratios of the urinary glucuronide, sulfate, and methylated (epi)catechin metabolites changed little (Figure 8), implying that even at the highest intake, the UGT, SULT and COMT enzymes involved in the formation of the (epi)catechin metabolites do not become saturated and limit their conversions. Coffee was used as a rich source of caffeic acid derivatives for human supplementation. The results showed a highly significant increase in the excretion of ferulic, isoferulic, dihydroferulic acid (3-(4-hydroxy-3-methoxyphenyl)-propionic acid), and vanillic acid post supplementation relative to the levels of pre-supple- mentation. Thus, ferulic, isoferulic, and dihydroferulic acids are specific biomarkers for the bioavailability and metabolism of dietary caffeic acid esters. Isoferulic acid is a unique biomarker as it is not a dietary component, however, dihydroferulic acid may well derive from other flavonoids with a structurally related B-ring.

Conclusion

In conclusion, published works endeavored to concentrate on the polyphenols that are found in fruits, vegetables and beverages. However, the design and performance of more researches, especially for human trials, is encouraged to confirm the efficacy of polyphenols at the gut level. The results provided by previous and future studies could be useful for the design of dietary recommendations not only to suppress or reduce symptoms in diseases but also to provide the healthy population with simple tools to promote the maintenance of health.

Acknowledgments

This work is supported by the Natural Science Foundation of China (NSFC, Grant No. 31701520, 31801450)

Funding

Funds for Distinguished Young Scientists (Grant No. kxjq17012) at Fujian agriculture and forestry university of China, National Natural Science Foundation of China.

References

Actis-Goretta, L., T. P. Dew, A. Lévèques, G. Pereira-Caro, M. Rein, A. Teml, C. Schäfer, U. Hofmann, M. Schwab, M. Eichelbaum, et al. 2015. Gastrointestinal absorption and metabolism of hesperetin-7-O-rutinoside and hesperetin-7-O-glucoside in healthy humans. Molecular Nutrition & Food Research *59* (9):1651–62.

Actis-Goretta, L., A. Lévèques, F. Giuffrida, F. Romanov-Michailidis, F. Viton, D. Barron, M. Duenas-Paton, S. Gonzalez-Manzano, C. Santos-Buelga, G. Williamson, and F. Dionisi. 2012. Elucidation of (−)-epicatechin metabolites after ingestion of chocolate by healthy humans. Free Radical Biology and Medicine *53* (4):787–95.

Aherne, S. A., and N. M. O'Brien. 2002. Dietary flavonols: Chemistry, food content, and metabolism. Nutrition (Burbank, Los Angeles County, Calif.) *18* (1):75–81.

Alvarez-Suarez, M., Giampieri, J. F., and M. Battino. 2013. Honey as a source of dietary antioxidants: Structures, bioavailability and evidence of protective effects against human chronic diseases. Current Medicinal Chemistry *20* (5):621–38.

Aragonès, G., F. Danesi, D. Del Rio, and P. Mena. 2017. The importance of studying cell metabolism when testing the bioactivity of phenolic compounds. Trends in Food Science & Technology *69*:230–42 10.1016/j.tifs.2017.02.001

Asenso, J., X. D. Yang, J. Yu, P. Zhou, C. Wang, and W. Wei. 2015. Plant-based anti-inflammatory agents: Progress from Africa and China. Clinical anti-Inflammatory & anti-Allergy Drugs *2* (1):52–66.

Biasutto, L., and M. Zoratti. 2014. Prodrugs of quercetin and resveratrol: A strategy under development. Current Drug Metabolism *15* (1):77–95.

Bredsdorff, L., I. L. F. Nielsen, S. E. Rasmussen, C. Cornett, D. Barron, F. Bouisset, E. Offord, and G. Williamson. 2010. Absorption, conjugation and excretion of the flavanones, naringenin and hesperetin from α-rhamnosidase-treated orange juice in human subjects. British Journal of Nutrition *103* (11):1602–9.

Carbonell-Capella, J. M., M. Buniowska, F. J. Barba, M. J. Esteve, and A. Frígola. 2014. Analytical methods for determining bioavailability and bioaccessibility of bioactive compounds from fruits and vegetables: A review. Comprehensive Reviews in Food Science and Food Safety *13* (2):155–71.

Cardona, F., C. Andrés-Lacueva, S. Tulipani, F. J. Tinahones, and M. I. Queipo-Ortuño. 2013. Benefits of polyphenols on gut microbiota and implications in human health. The Journal of Nutritional Biochemistry *24* (8):1415–22.

Chankvetadze, B. 2012. Recent developments on polysaccharide-based chiral stationary phases for liquid-phase separation of enantiomers. Journal of Chromatography A *1269*:26–51.

Chen, T.-Y., J. Kritchevsky, K. Hargett, K. Feller, R. Klobusnik, B. J. Song, B. Cooper, Z. Jouni, M. G. Ferruzzi, and E. M. Janle. 2015. Plasma bioavailability and regional brain distribution of polyphenols from apple/grape seed and bilberry extracts in a young swine model. Molecular Nutrition & Food Research *59* (12):2432–47.

Chen, Z., S. Zheng, L. Li, and H. Jiang. 2014. Metabolism of flavonoids in human: A comprehensive review. Current Drug Metabolism *15* (1):48–61.

Chow, H. S., I. A. Hakim, D. R. Vining, J. A. Crowell, J. Ranger-Moore, W. M. Chew, and D. S. Alberts. 2005. Effects of dosing condition on the oral bioavailability of green tea catechins after single-dose administration of polyphenon E in healthy individuals. Clinical Cancer Research *11* (12):4627–33.

Clarke, K. A., T. P. Dew, R. E. B. Watson, M. D. Farrar, S. Bennett, A. Nicolaou, L. E. Rhodes, and G. Williamson. 2014. High performance liquid chromatography tandem mass spectrometry dual extraction method for identification of green tea catechin metabolites excreted in human urine. Journal of Chromatography B *972*:29–37.

Dall'Asta, M., E. Derlindati, V. Curella, P. Mena, L. Calani, S. Ray, I. Zavaroni, F. Brighenti, and D. Del Rio. 2013. Effects of naringenin and its phase II metabolites on in vitro human macrophage gene expression. International Journal of Food Sciences and Nutrition *64* (7):843–9.

Danielsen, E. T., and E. M. Danielsen. 2016. Glycol chitosan: A stabilizer of lipid rafts in the intestinal brush border. Biochimica Et Biophysica Acta (BBA)-Biomembranes *1859* (3):360–7.

Day, A. J., F. J. Cañada, J. C. Díaz, P. A. Kroon, R. Mclauchlan, C. B. Faulds, G. W. Plumb, M. R. A. Morgan, and G. Williamson. 2000. Dietary flavonoid and isoflavone glycosides are hydrolysed by the lactase site of lactase phlorizin hydrolase. FEBS Letters *468* (2–3):166–70.

de Vries, J. H., P. C. Hollman, I. van Amersfoort, M. R. Olthof, and M. B. Katan. 2001. Red wine is a poor source of bioavailable flavonols in men. The Journal of Nutrition *131* (3):745–8.

Del Rio, D., L. Calani, C. Cordero, S. Salvatore, N. Pellegrini, and F. Brighenti. 2010. Bioavailability and catabolism of green tea flavan-3-ols in humans. Nutrition (Burbank, Los Angeles County, Calif.) *26* (11-12):1110–6.

Dudonné, S., T. V. Varin, F. Forato Anhê, P. Dubé, D. Roy, G. Pilon, A. Marette, É. Levy, C. Jacquot, M. Urdaci, and Y. Desjardins. 2015. Modulatory effects of a cranberry extract co-supplementation with Bacillus subtilis CU1 probiotic on phenolic compounds bioavailability and gut microbiota composition in high-fat diet-fed mice. Pharma Nutrition *3* (3):89–100.

Fang, J. 2014. Some anthocyanins could be efficiently absorbed across the gastrointestinal mucosa: Extensive presystemic metabolism reduces apparent bioavailability. Journal of Agricultural and Food Chemistry *62* (18):3904–11.

Frydman, A., R. Liberman, D. V. Huhman, M. Carmeli-Weissberg, M. Sapir-Mir, R. Ophir, L. W. Sumner, and Y. Eyal. 2013. The molecular and enzymatic basis of bitter/non-bitter flavor of citrus fruit: evolution of branch-forming rhamnosyltransferases under domestication. The Plant Journal *73* (1):166–78.

Gaya, P., J. L. Arqués, M. Medina, I. Álvarez, and J. M. Landete. 2016. A new HPLC-PAD/HPLC-ESI-MS method for the analysis of phytoestrogens produced by bacterial metabolism. Food Analytical Methods *9* (2):537–47.

Hosoda, K., T. Furuta, A. Yokokawa, and K. Ishii. 2010. Identification and quantification of daidzein-7-glucuronide-4′-sulfate, genistein-7-glucuronide-4′-sulfate and genistein-4′, 7-diglucuronide as major metabolites in human plasma after administration of kinako. Analytical and Bioanalytical Chemistry *397* (4):1563–72.

Hossain, S. J., H. Kato, H. Aoshima, T. Yokoyama, M. Yamada, and Y. Hara. 2002. Polyphenol-induced inhibition of the response of na+/glucose cotransporter expressed in xenopus oocytes. Journal of Agricultural and Food Chemistry *50* (18):5215–9.

Jaganath, I. B., I. B. Jaganath, W. Mullen, C. A. Edwards, and A. Crozier. 2006. The relative contribution of the small and large intestine to the absorption and metabolism of rutin in man. Free Radical Research *40* (10):1035–46.

Kay, C. D., G. Pereira-Caro, I. A. Ludwig, M. N. Clifford, and A. Crozier. 2017. Anthocyanins and flavanones are more bioavailable than previously perceived: a review of recent evidence. Annual Review of Food Science and Technology *8*:155–80.

Krisch, J., O. Bencsik, T. Papp, C. Vágvölgyi, and M. Takó. 2012. Characterization of a β-glucosidase with transgalactosylation capacity from the zygomycete rhizomucor miehei. Bioresource Technology *114*:555–60.

Kwon, O., P. Eck, S. Chen, C. P. Corpe, J. H. Lee, M. Kruhlak, and M. Levine. 2007. Inhibition of the intestinal glucose transporter GLUT2 by flavonoids. Faseb Journal: Official Publication of the Federation of American Societies for Experimental Biology *21* (2):366–77.

Li, C., M.-J. Lee, S. Sheng, X. Meng, S. Prabhu, B. Winnik, B. Huang, J. Y. Chung, S. Yan, C.-T. Ho, and C. S. Yang. 2000. Structural identification of two metabolites of catechins and their kinetics in human urine and blood after tea ingestion. Chemical Research in Toxicology *13* (3):177–84.

Ludwig, I. A., P. Mena, L. Calani, G. Borges, G. Pereira-Caro, L. Bresciani, D. Del Rio, M. E. J. Lean, and A. Crozier. 2015. New insights into the bioavailability of red raspberry anthocyanins and ellagitannins. Free Radical Biology & Medicine *89*:758–69.

Manach, C., G. Williamson, C. Morand, A. Scalbert, and C. Rémésy. 2005. Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. The American Journal of Clinical Nutrition *81* (1):230S–42S.

Manzano, S., and G. Williamson. 2010. Polyphenols and phenolic acids from strawberry and apple decrease glucose uptake and transport by human intestinal caco-2 cells. Molecular Nutrition & Food Research *54* (12):1773–80.

Margalef, M., L. Guerrero, Z. Pons, F. I. Bravo, L. Arola, B. Muguerza, and A. Arola-Arnal. 2014. A dose–response study of the bioavailability of grape seed proanthocyanidin in rat and lipid-lowering effects of generated metabolites in HepG2 cells. Food Research International *64*:500–7.

Margalef, M., Z. Pons, F. I. Bravo, B. Muguerza, and A. Arola-Arnal. 2015. Plasma kinetics and microbial biotransformation of grape seed flavanols in rats. Journal of Functional Foods *12*:478–88.

Margalef, M., Z. Pons, L. Iglesias-Carres, F. I. Bravo, B. Muguerza, and A. Arola-Arnal. 2017. Flavanol plasma bioavailability is affected by metabolic syndrome in rats. Food Chemistry *231*:287–94.

Massot-Cladera, M., J. Mayneris-Perxachs, A. Costabile, J. R. Swann, À. Franch, F. J. Pérez-Cano, and M. Castell. 2017. Association between urinary metabolic profile and the intestinal effects of cocoa in rats. British Journal of Nutrition *117* (05):623–34.

Mastroiacovo, D., C. Kwik-Uribe, D. Grassi, S. Necozione, A. Raffaele, L. Pistacchio, R. Righetti, R. Bocale, M. C. Lechiara, C. Marini, et al. 2015. Cocoa flavanol consumption improves cognitive function, blood pressure control, and metabolic profile in elderly subjects: The cocoa, cognition, and aging (CoCoA) study—a randomized controlled trial. The American Journal of Clinical Nutrition *101* (3):538–48.

Mattivi, F., R. Guzzon, U. Vrhovsek, M. Stefanini, and R. Velasco. 2006. Metabolite profiling of grape: Flavonols and anthocyanins. Journal of Agricultural and Food Chemistry *54* (20):7692–702.

Morand, C., C. Dubray, D. Milenkovic, D. Lioger, J. F. Martin, A. Scalbert, and A. Mazur. 2011. Hesperidin contributes to the vascular protective effects of orange juice: A randomized crossover study in healthy volunteers. The American Journal of Clinical Nutrition *93* (1):73–80.

Mudge, E., W. L. Applequist, J. Finley, P. Lister, A. K. Townesmith, K. M. Walker, and P. N. Brown. 2016. Variation of select flavonols and chlorogenic acid content of elderberry collected throughout the Eastern United States. Journal of Food Composition and Analysis *47*:52–9.

Mullen, W., M. A. Archeveque, C. A. Edwards, H. Matsumoto, and A. Crozier. 2008. Bioavailability and metabolism of orange juice flavanones in humans: Impact of a full-fat yogurt. Journal of Agricultural and Food Chemistry *56* (23):11157–64.

Mullen, W., J.-M. Rouanet, C. Auger, P.-L. Teissèdre, S. T. Caldwell, R. C. Hartley, M. E. J. Lean, C. A. Edwards, and A. Crozier. 2008. Bioavailability of [2-(14)C]quercetin-4'-glucoside in rats. Journal of Agricultural and Food Chemistry *56* (24):12127–37.

Natsume, M., N. Osakabe, M. Yamagishi, T. Takizawa, T. Nakamura, H. Miyatake, T. Hatano, and T. Yoshida. 2000. Analyses of polyphenols in cacao liquor, cocoa, and chocolate by normal-phase and reversed-phase HPLC. Bioscience, Biotechnology, and Biochemistry *64* (12):2581–7.

Nicholls, G., H. Flynn, and N. Woodhouse. 2016. The Role of In vivo Imaging in the Study of Transporter Interactions in Animals and Humans. ed. G. Nicholls, and K. Youdim, 143–94. Drug Transporters: Volume 2: Recent Advances and Emerging Technologies: Royal Society of Chemistry.

Nielsen, I. L. F., W. S. S. Chee, L. Poulsen, E. Offord-Cavin, S. E. Rasmussen, H. Frederiksen, M. Enslen, D. Barron, M.-N. Horcajada, and G. Williamson. 2006. Bioavailability is improved by enzymatic modification of the citrus flavonoid hesperidin in humans: a randomized, double-blind, crossover trial. The Journal of Nutrition *136* (2):404–8.

Norberto, S., S. Silva, M. Meireles, A. Faria, M. Pintado, and C. Calhau. 2013. Blueberry anthocyanins in health promotion: a metabolic overview. Journal of Functional Foods *5* (4):1518–28.

Olivé, N. O., and M. J. M. Casado. 2013. "Polyphenols in cocoa: From in vitro digestion to in vivo bioavailability." chocolate in health and nutrition. New York, NY: Humana Press, 2013, 179–188.

Oliveira, H., I. Fernandes, N. F. Brás, A. Faria, V. De Freitas, C. Calhau, and N. Mateus. 2015. Experimental and theoretical data on the mechanism by which red wine anthocyanins are transported through a human MKN-28 gastric cell model. Journal of Agricultural and Food Chemistry *63* (35):7685–92.

Ostertag, L. M., M. Philo, I. J. Colquhoun, H. S. Tapp, S. Saha, G. G. Duthie, E. K. Kemsley, B. de Roos, P. A. Kroon, and G. Le Gall.

2017. Acute consumption of flavan-3-ol-enriched dark chocolate affects human endogenous metabolism. Journal of Proteome Research *16* (7):2516–26.

Peter, B., S. Bosze, and R. Horvath. 2017. Biophysical characteristics of proteins and living cells exposed to the green tea polyphenol epigallocatechin-3-gallate (EGCg): Review of recent advances from molecular mechanisms to nanomedicine and clinical trials. European Biophysics Journal *46* (1):1–24.

Peterson, J. J., J. T. Dwyer, G. R. Beecher, S. A. Bhagwat, S. E. Gebhardt, D. B. Haytowitz, and J. M. Holden. 2006. Flavanones in oranges, tangerines (mandarins), tangors, and tangelos: A compilation and review of the data from the analytical literature. Journal of Food Composition and Analysis *19*:S66–S73.

Quiñones, M., M. Margalef, A. Arola-Arnal, B. Muguerza, M. Miguel, and A. Aleixandre. 2015. The blood pressure effect and related plasma levels of flavan-3-ols in spontaneously hypertensive rats. Food & Function *6* (11):3479–89.

Rein, D., S. Lotito, R. R. Holt, C. L. Keen, H. H. Schmitz, and C. G. Fraga. 2000. Epicatechin in human plasma: In vivo determination and effect of chocolate consumption on plasma oxidation status. The Journal of Nutrition *130* (8):2109S–14S.

Rein, M. J., M. Renouf, C. Cruz-Hernandez, L. Actis-Goretta, S. K. Thakkar, and M. da Silva Pinto. 2013. Bioavailability of bioactive food compounds: a challenging journey to bioefficacy. British Journal of Clinical Pharmacology *75* (3):588–602.

Rodriguez-Mateos, A., M. J. Oruna-Concha, C. Kwik-Uribe, A. Vidal, and J. P. Spencer. 2012. Influence of sugar type on the bioavailability of cocoa flavanols. The British Journal of Nutrition *108* (12):2243–50.

Rybarczyk-Plonska, A., A. B. Wold, G. B. Bengtsson, G. I. A. Borge, M. K. Hansen, and S. F. Hagen. 2016. Flavonols in broccoli (*Brassica oleracea* L. var. italica) flower buds as affected by postharvest temperature and radiation treatments. Postharvest Biology and Technology *116*:105–14.

Sánchez-Calvo, J. M., M. A. Rodríguez-Iglesias, J. M. Molinillo, and F. A. Macías. 2013. Soy isoflavones and their relationship with microflora: Beneficial effects on human health in equol producers. Phytochemistry Reviews *12* (4):979–1000.

Sarkar, F. H., S. Adsule, S. Padhye, S. Kulkarni, and Y. Li. 2006. The role of genistein and synthetic derivatives of isoflavone in cancer prevention and therapy. Mini Reviews in Medicinal Chemistry *6* (4):401–7.

Sesink, A. L., I. C. Arts, V. C. de Boer, P. Breedveld, J. H. Schellens, P. C. Hollman, and F. G. Russel. 2005. Breast cancer resistance protein (Bcrp1/Abcg2) limits net intestinal uptake of quercetin in rats by facilitating apical efflux of glucuronides. Molecular Pharmacology *67* (6):1999–2006.

Setchell, K. D., and C. Clerici. 2010. Equol: Pharmacokinetics and biological actions. The Journal of Nutrition *140* (7):1363S–8S.

Shimazu, T., M. Inoue, S. Sasazuki, M. Iwasaki, N. Sawada, T. Yamaji, and S. Tsugane. 2010. Isoflavone intake and risk of lung cancer: a prospective cohort study in Japan. The American Journal of Clinical Nutrition *91* (3):722–8.

Smith, A. J., P. Kavuru, K. K. Arora, S. Kesani, J. Tan, M. J. Zaworotko, and R. D. Shytle. 2013. Crystal engineering of green tea epigallocatechin-3-gallate (EGCg) cocrystals and pharmacokinetic modulation in rats. Molecular Pharmaceutics *10* (8):2948–61.

Smith, C., K. A. Lombard, E. B. Peffley, and W. Liu. 2016. Genetic analysis of quercetin in onion (*Allium cepa* L.)'Lady raider. Texas Journal of Agriculture and Natural Resources *16*:24–8.

Stalmach, A., S. Troufflard, M. Serafini, and A. Crozier. 2009. Absorption, metabolism and excretion of choladi green tea flavan-3-ols by humans. Molecular Nutrition & Food Research *53* (S1):S44–S53.

Strack, D., and V. Wray. 1992. Anthocyanins. In The flavonoids: Advances in research since 1986, ed. J. B. Harborne, 1–22. London: Chapman and Hall.

Szeja, W., G. Grynkiewicz, and A. Rusin. 2017. Isoflavones, their glycosides and glycoconjugates. Synthesis and biological activity. Current Organic Chemistry *21* (3):218–35.

Teng, H., T. Fang, Q. Lin, H. Song, B. Liu, and L. Chen. 2017. Red raspberry and its anthocyanins: Bioactivity beyond antioxidant capacity. Trends in Food Science & Technology *66*:153–65

Thilakarathna, S. H., and H. P. Rupasinghe. 2013. Flavonoid bioavailability and attempts for bioavailability enhancement. Nutrients *5* (9):3367–87.

Ting, S., H. S. Yeh, and T. F. Lien. 2011. Effects of supplemental levels of hesperetin and naringenin on egg quality, serum traits and antioxidant activity of laying hens. Animal Feed Science and Technology *163* (1):59–66.

Tomas-Barberán, F. A., E. Cienfuegos-Jovellanos, A. Marín, B. Muguerza, A. Gil-Izquierdo, B. Cerdá, P. Zafrilla, J. Morillas, J. Mulero, A. Ibarra, et al. 2007. A new process to develop a cocoa powder with higher flavonoid monomer content and enhanced bioavailability in healthy humans. Journal of Agricultural and Food Chemistry *55* (10):3926–35.

Uehara, M. 2013. Isoflavone metabolism and bone-sparing effects of daidzein-metabolites. Journal of Clinical Biochemistry and Nutrition *52* (3):193–201.

Vallejo, F., M. Larrosa, E. Escudero, M. P. Zafrilla, B. Cerdá, J. Boza, M. T. García-Conesa, J. C. Espín, and F. A. Tomás-Barberán, 2010. Concentration and solubility of flavanones in orange beverages affect their bioavailability in humans. Journal of Agricultural and Food Chemistry *58* (10):6516–24.

Vázquez-Agell, M., M. Urpi-Sarda, E. Sacanella, S. Camino-López, G. Chiva-Blanch, V. Llorente-Cortés, E. Tobias, E. Roura, C. Andres-Lacueva, R. M. Lamuela-Raventós, et al. 2013. Cocoa consumption reduces NF-κB activation in peripheral blood mononuclear cells in humans. Nutrition, Metabolism and Cardiovascular Diseases *23* (3):257–63.

Wang, L., Q. Chen, L. Zhu, Q. Li, X. Zeng, L. Lu, M. Hu, X. Wang, and Z. Liu. 2017. Metabolic disposition of luteolin is mediated by the interplay of UDP-glucuronosyltransferases and catechol-O-methyltransferases In rats. Drug Metabolism and Disposition: The Biological Fate of Chemicals *45* (3):306–15.

Wiese, S., T. Esatbeyoglu, P. Winterhalter, H. P. Kruse, S. Winkler, A. Bub, and S. E. Kulling. 2015. Comparative biokinetics and metabolism of pure monomeric, dimeric, and polymeric flavan-3-ols: A randomized cross-over study in humans. Molecular Nutrition & Food Research *59* (4):610–21.

Xu, X., H. J. Wang, P. A. Murphy, L. Cook, and S. Hendrich. 1994. Daidzein is a more bioavailable soymilk isoflavone than is genistein in adult women. The Journal of Nutrition *124* (6):825

Yang, Z., W. Zhu, S. Gao, H. Xu, B. Wu, K. Kulkarni, R. Singh, L. Tang, and M. Hu. 2010. Simultaneous determination of genistein and its four phase II metabolites in blood by a sensitive and robust UPLC–MS/MS method: Application to an oral bioavailability study of genistein in mice. Journal of Pharmaceutical and Biomedical Analysis *53* (1):81–9.

Yaqub, S., U. Farooq, A. Shafi, K. Akram, M. A. Murtaza, T. Kausar, and F. Siddique. 2016. Chemistry and functionality of bioactive compounds present in persimmon. Journal of Chemistry *2016*:1.

Yonemoto-Yano, H., M. Maebuchi, K. Fukui, S. Tsuzaki, K. Takamatsu, and M. Uehara. 2014. Malonyl isoflavone glucosides are chiefly hydrolyzed and absorbed in the Colon. Journal of Agricultural and Food Chemistry *62* (10):2264–70.

Yoshida, H., N. Takamura, T. Shuto, K. Ogata, J. Tokunaga, K. Kawai, and H. Kai. 2010. The citrus flavonoids hesperetin and naringenin block the lipolytic actions of TNF-α in mouse adipocytes. Biochemical and Biophysical Research Communications *394* (3):728–32.

Yousuf, B., K. Gul, A. A. Wani, and P. Singh. 2016. Health benefits of anthocyanins and their encapsulation for potential use in food systems: A review. Critical Reviews in Food Science and Nutrition *56* (13):2223–30.

Zhang, Z., Y. Huang, F. Gao, H. Bu, W. Gu, and Y. Li. 2011. Daidzein–phospholipid complex loaded lipid nanocarriers improved oral absorption: in vitro characteristics and in vivo behavior in rats. Nanoscale *3* (4):1780–7.