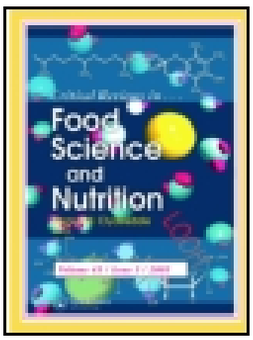

Critical Reviews in Food Science and Nutrition

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/bfsn20

Absorption, metabolism and bioavailability of flavonoids: a review

Lei Chen, Hui Cao, Qun Huang, Jianbo Xiao & Hui Teng

To cite this article: Lei Chen, Hui Cao, Qun Huang, Jianbo Xiao & Hui Teng (2021): Absorption, metabolism and bioavailability of flavonoids: a review, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2021.1917508

To link to this article: https://doi.org/10.1080/10408398.2021.1917508

CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
https://doi.org/10.1080/10408398.2021.1917508

Taylor & Francis
Taylor & Francis Group

REVIEW

Absorption, metabolism and bioavailability of flavonoids: a review

Lei Chen[a], Hui Cao[a], Qun Huang[b,c], Jianbo Xiao[a#], and Hui Teng[a]

[a]College of Food Science and Technology, Guangdong Ocean University, Zhanjiang, China; [b]School of Public Health, The Key Laboratory of Environmental Pollution Monitoring and Disease Control, Ministry of Education, Guizhou Medical University, Guiyang, China; [c]Meat Processing Key Laboratory of Sichuan Province, School of Food and Biological Engineering, Chengdu University, Chengdu, China

ABSTRACT

Flavonoids are stored in various plants and widely presented in different kinds of food in variable amounts. Plant roots, stems, leaves, flowers and fruits are known to have high amounts of flavonoids. However, flavonoid aglycones are found less frequently in natural products, as it requires bioconversion through bacteria, which provide β-glucosidase to convert them. Recently, flavonoids and its metabolites were applied in the prevention and treatment of various diseases such as cancers, obesity, diabetes, hypertension, hyperlipidemia, cardiovascular diseases, neurological disorders and osteoporosis in numerous studies. This review focused on absorption, activity, metabolism, and bioavailability of flavonoids. Also authors organized and collected newly-found reports of flavonoids and their absorption barriers of flavonoids in the gastrointestinal tract, providing the latest findings and evidence from the past decade. Particularly, nanoparticles delivery systems are emphasized regarding fabrication methods and their potential benefits on flavonoids. Moreover, the potential challenges of nanoparticles as delivery system for flavonoids in the gastrointestinal tract are also discussed.

KEYWORDS

Flavonoids; absorption; activity; metabolism; bioavailability

1. Introduction

Flavonoid which mainly refers to two benzene rings (A and B) with phenolic hydroxyl, are connected by three central carbon chains and form a series of compounds with C6-C3-C6 as the basic carbon skeleton. According to the oxidation level of the three carbon bond (C3) and the difference of the B-ring linkage sites, flavonoids can be divided into flavonoids, flavonols, isoflavones, anthocyanins, chalcone, nerone, flavane, etc. (Figure 1). In fact, the C ring is characteristic of each flavonoid subfamily. Among the subfamilies, monomers differ in the type, location and number of substituents (e.g. hydroxyl groups), and some flavonoids can also form oligomers. As a natural pigment, flavonoids possesses many important physiological and benefit on human and animals due to its unique chemical structure. The antioxidant, antibacterial, anti-inflammatory, anti-virus, anti-cancer, anti-aging, liver protection, cardiovascular protection, free radical removal, and improvement immunity and other biological activities could not be underestimated (He et al. 2006; Chen, Lin, Fan, Lv, et al. 2020). In nature, flavonoids usually exist together with other compounds, when dietary food rich in flavonoids, they often take in other compounds, and flavonoids can also interact with other compounds, such as carbohydrate, fat, protein, acid, etc. Food component interaction is closely related to the change of flavonoid's own characteristics and it may change a variety of physiological activities of flavonoids in vivo.

To understand the mechanism of action of dietary flavonoids in the body, it is necessary to determine which chemical forms of the various metabolites are found in systemic circulation, as these would be the physiologically active forms. In the present review, we focused on absorption, activity, metabolism, and bioavailability of flavonoids. Particularly, nanoparticles delivery systems are emphasized regarding fabrication methods and their potential benefits on flavonoids. Moreover, the potential challenges of nanoparticles as delivery system for flavonoids in the gastrointestinal tract are also discussed.

2. Are anthocyanins absorbed?

Anthocyanin is one of the most common flavonoids widely distributed in food product, especially in berries, vegetables and colored grains. In our daily life, we can eat some plants with rich color to access anthocyanin. Wu et al. (2006) analyzed the anthocyanins in more than 100 kinds of fruits and vegetables in the United States, estimated that the appropriate intake of anthocyanins was about 12.5 mg/day with an important role in human health (Wu et al. 2006). Modern pharmacology research shows that anthocyanin has many physiological functions such as antioxidant anticancer, anti-inflammatory, hypoglycemic, and treatment of

CONTACT Qun Huang huangqunlaoshi@126.com; Jianbo Xiao jianboxiao@yahoo.com; Hui Teng tenghui850610@126.com
[#]Present address: Institute of Food Safety and Nutrition, Jinan University, Guangzhou 510632, China; College of Food Science and Technology, Guangdong Ocean University, Guangdong Provincial Key Laboratory of Aquatic Product Processing and Safety, Guangdong Province Engineering Laboratory for Marine Biological Products, Guangdong Provincial Engineering Technology Research Center of Seafood, Key Laboratory of Advanced Processing of Aquatic Product of Guangdong Higher Education Institution, Zhanjiang 524088, China

This article has been corrected with minor changes. These changes do not impact the academic content of the article.

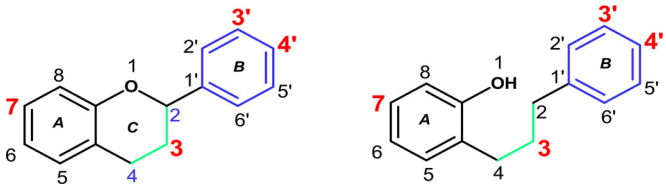

Figure 1. Structure of flavonoids with C6-C3-C6 as the basic carbon skeleton.

cardiovascular diseases, promoting vision, etc., therefore it has attracted extensive attention of the medical community (Bueno et al. 2012; Kaulmann et al. 2014). Meanwhile, anthocyanin, as a natural pigment because of its safety, non-toxic, rich resources, bright colors and good color effect has broad application prospects in food industry.

As shown in Figure 2, anthocyanins are a series of derivatives composed of 2-phenylbenzopyran cationic aglycones and glycosides. Recently, numerous in vivo data confirmed that anthocyanins can be quickly and efficiently absorbed in the form of prototype through the intestinal tract, transferred through the circulatory system and finally excreted through the urine (Yang et al. 2018). The main absorption site of anthocyanin is stomach (Forester et al. 2014). After oral adminstration of anthocyanin, although the retention time of anthocyanin in the stomach is comparatively short, it could be rapidly absorbed in the stomach through in situ fluorescence reaction in the stomach. The overall absorption rate of the administered pelargonidin was 18% after 2 h in stomach (El Mohsen et al. 2006). However, due to the special acid environment and small absorption area of gastric mucosa, the absorption effect of anthocyanins in the stomach is relatively poor. It is well known that anthocyanins are hydrophobic, and their absorption in the small intestine is mainly by passive diffusion (Kay 2006). Additionally, anthocyanins always exist in the form of glycosides and have a relatively large molecular weight, oral anthocyanins c can only be absorbed in the small intestine after being hydrolyzed to aglycones by the bacterial glycosidases in the lower intestine or further degraded into phenolic acids (Kamiloglu et al. 2015; Del Bo' et al. 2012). For example, the absorption of cyanidin-3-glucoside (C3G) was investigated in the gastrointestinal tract of mice and found that the absorption of C3G was mainly in jejunum, less in duodenum, but not in ileum and colon (Marczylo et al. 2009; Guo et al. 2012). Furthermore, He et al. (2006) oral administered different sources of anthocyanin extracts to rats, and found that the glycoside type and quantity of anthocyanin significantly affected the absorption (He et al. 2006). Talavéra et al. (2006) found that the absorption rate of anthocyanins with different structures varied greatly, among which delphinium glycosides had the highest absorption rate (Talavéra et al. 2006). Harada et al. (2004) compared the absorption of acylated and non acylated anthocyanins, and found that acetylated anthocyanins were more easily absorbed (Harada et al. 2004). McGhie et al. (2003) showed that the absorption and excretion of anthocyanin were determined by the properties of glycosyl and anthocyanin (McGhie et al. 2003). Yi et al. (2006) studied the absorption of anthocyanins from blueberry by using Caco-2 cell model. The results showed that anthocyanins with more hydroxyl and less methoxy had lower bioavailability and higher transport efficiency of glucoside than galactoside (Yi et al. 2006). It should be noticed that other components of food composition have different effects on the absorption of anthocyanin. Walton et al. (2006) found that the absorption spectrum of anthocyanins could be prolonged by ingesting food or other flavonoids at the same time (Walton et al. 2006).

As mentioned in the above section, anthocyanin can be absorbed in the stomach, but its absorption mechanism is still unknown at present. Previous studies revealed that organic anion transporter in gastric epithelial cells, might be involved in the absorption of anthocyanin. For instance, Passamonti et al. (2003) studied the effects of D-glucose, phlorizin and quercetin-3-glucoside on the absorption of C3G in jejunum of mice by diffusion cell method in vitro, and confirmed that sodium dependent glucose transporter (SGLT) participated in the trans membrane transport and absorption of anthocyanin (Passamonti et al. 2003). Galvano et al. (2004) established an in vitro organ model to investigate the absorption mechanism of C3G and found that anthocyanin was absorbed by small intestine through biofilm in the form of complete glycoside (Galvano et al. 2004).

3. Are tea flavonoids absorbed?

A special group of flavonoids consist aglycones eg (-)-epicatechin and (+)-catechin, as well as (-)-epicatechin-3-gallate (ECG) and (-)-epigallocatechin-3-gallate (EGCG) are esters of gallic acid. Notably, (+)-catechin was shown decades ago to have quite high absorption and was considered for development as a therapeutic agent (Hirasawa and Takada 2004). However, the other tea flavonoids, although presented more abroad biological activities in cell models, all with very poor bio-accessibility as well as low aborption in the rat (Chow et al., 2005) and humans (Hollman 2004). The absolute bioavailability for ECG recently investigated in vivo to be about 3% (Geven et al. 2019). The limiting factors for the oral bioavailability of the tea flavonoids in humans appear to be a combination of poor transport across the enterocyte and very efficient metabolism of these compounds by conjugation (Kobayashi and Ikeda 2017).

In order to find out the cause of the low bioavailability of tea polyphenols, Cai, Anavy, and Chow (2002) compared tea flavonoids in rat portal vein and peripheral vein, and found that the liver bioavailability of EGCG, EGC and EC were 87.0%, 108.3% and 94.9% respectively, and the pharmacokinetic parameters were basically similar (Cai, Anavy, and Chow 2002), this results indicated that the effect of tea flavonoids on the first pass of liver was very low, suggesting that the elimination of them before oral systemic circulation was not related to the effect of the first pass of liver. It has been shown that transporter mediated intestinal exocytosis may play a critical role in the loss of tea flavonoids before systemic circulation (Zhu, Chen, and Li 2000). The study by using Caco-2 cell model showed that EC cannot be absorbed from the top to the base side, but was discharged from the base side of the top, and the apparent permeability coefficient was considered to be high (Alemdaroglu et al. 2006). This efflux can be inhibited by MK-571, a competitive inhibitor of multidrug resistance associated protein-2

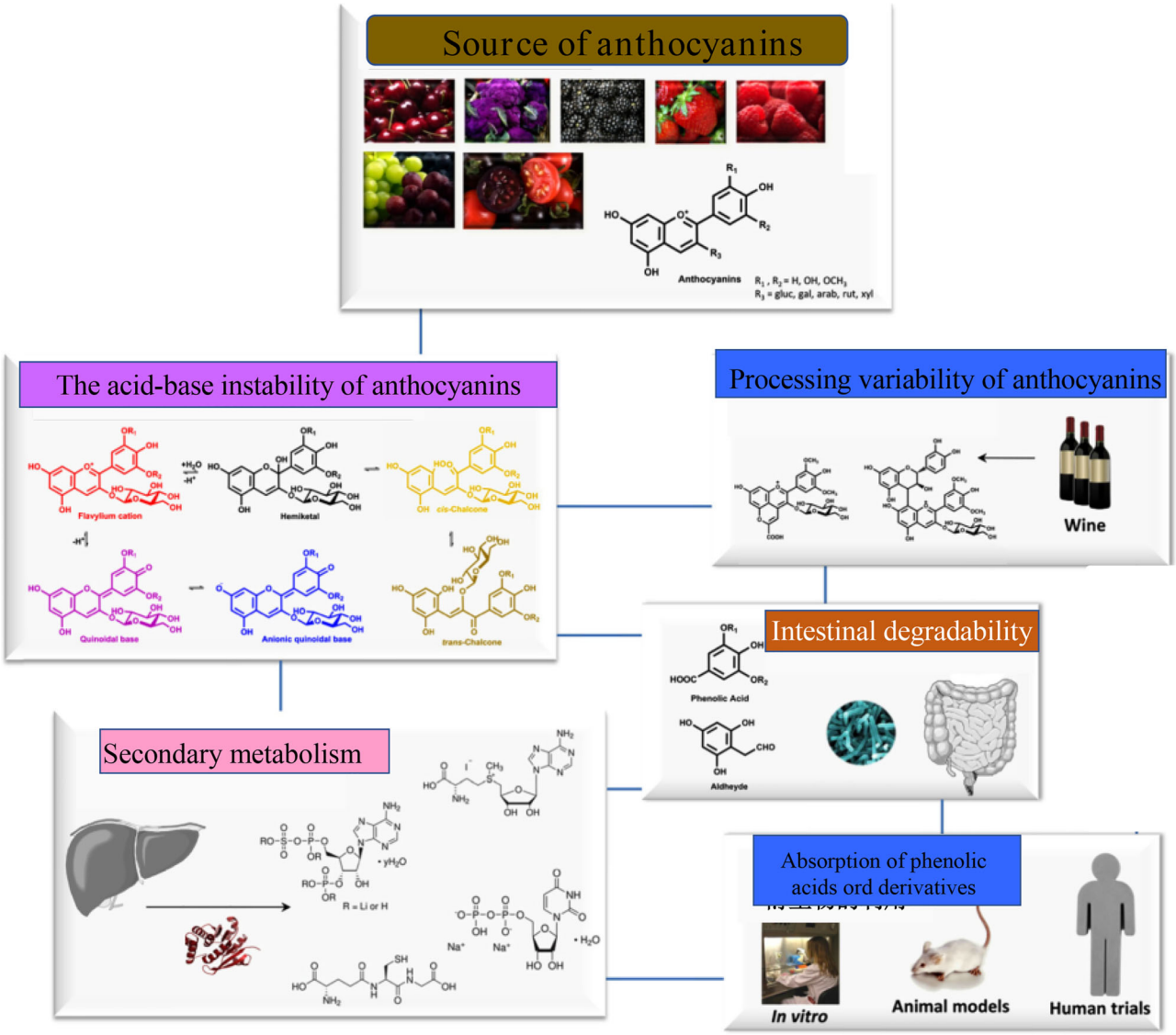

Figure 2. Stability of anthocyanins in absorption and food processing.

(MRP2) transporter, but not by P-gp inhibitor (Becker et al. 2014). Recent studies on EGCG transport in MDCK II cells showed that indomethacin (MRP inhibitor) increased the intracellular accumulation of EGCG and its methylated metabolites (Xiao et al. 2019; Fang et al. 2019). Similarly, MDCK II cells overexpressed with MRP2 increased EGCG and its methylated metabolites by 10–12 times, but MDCK II cells overexpressed with P-gp inhibitor had no significant effect, while HT-29 treated with indomethacin increased EGCG and its methylated conjugates. Taken together, these results suggest that MRPs, rather than P-gp, play a negative role in the bioavailability of EGCG (Lambert et al. 2006). It is also believed that the instability of tea flavonoids in the intestine is one of the reasons for its low bioavailability (Neilson et al. 2010). EGCG and EGC may degrade in the intestinal condition with the pH value of 6–8. As can be seen, 10% EGCG hydrophilic ointment applied to human and mouse skin, resulted in 1%–20% of intradermal uptake (Dvorakova et al. 1999). However, only a small amount of EGCG was absorbed into the systemic circulation in mice, additionally the amount of human skin was also very low (Suppasrivasuseth et al. 2006). In fact, human skin has a more effective barrier function to prevent the application of EGCG from entering the systemic circulation (Suppasrivasuseth et al. 2006).

For distribution of tea flavonoids, Kim et al. (2000) Gave 0.6% green tea flavonoids (EGCG, EGC and EC in solid powder were 590, 76 and 86 mg/g respectively) solution to rats for 8 days, and found the highest content of EGCG, EGC and EC was in large intestine (487.8, 303.2, 925.0 ng/g) and followed by in esophagus (279.9, 185.9, 192.8 ng/g). The absorption site of EGCG was in the following order: large intestine > esophagus > bladder > kidney, prostate > spleen; EGC was bladder > kidney > large intestine > prostate > spleen > esophagus, lung; EC was large intestine > bladder > kidney > prostate, lung > esophagus > spleen. The amount of them in liver, heart and thyroid is low. The amount of catechins in esophagus, large intestine, bladder and kidney was significantly higher than that in liver and

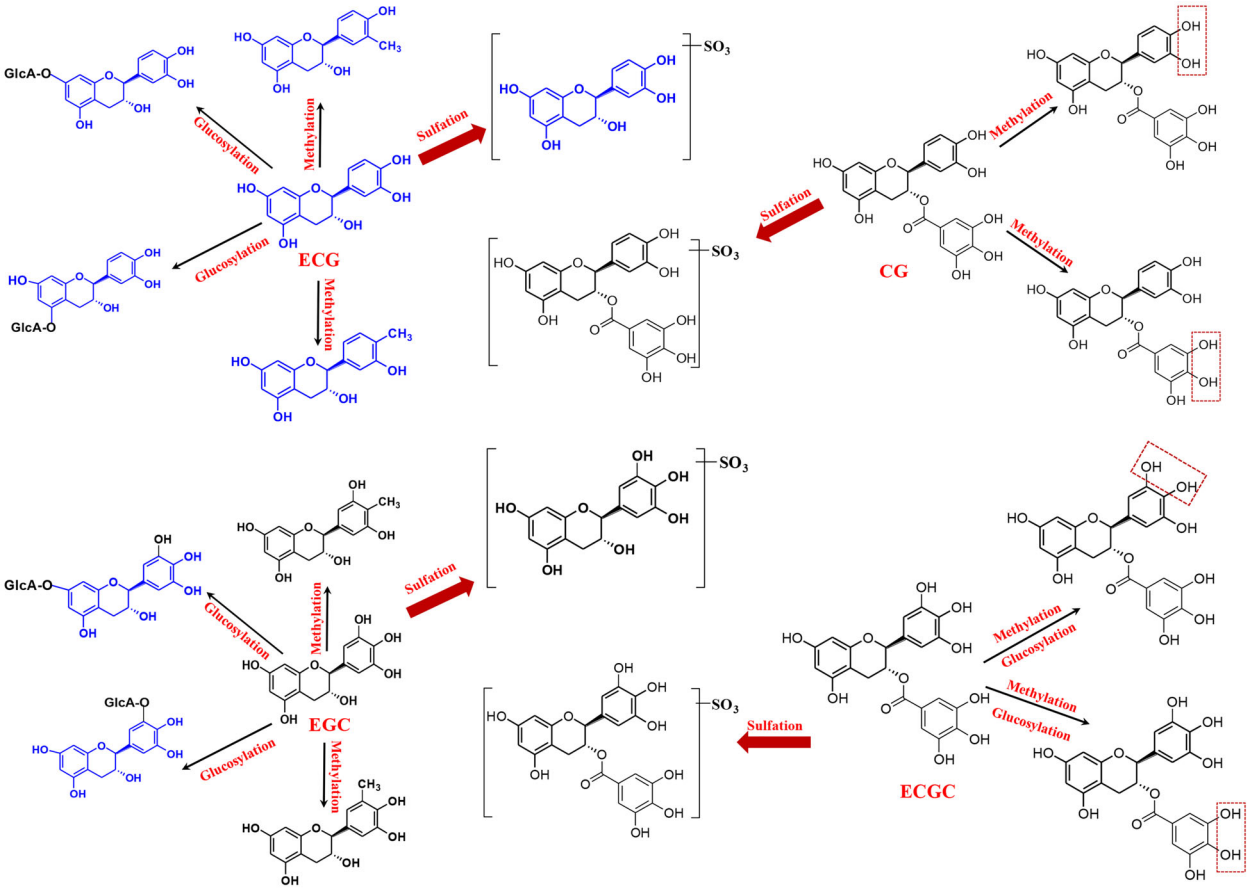

Figure 3. Methylation, glucuronidation and sulfation of major tea catechins.

heart (Kim et al. 2000). Lin et al. (2007) measured the amount of EGCG in brain of rats after administration of 50 mg/kg EGCG for 15 days and found cortex was 6.23 ng/g, brain stem 3.76 ng/g, hippocampus 4.18 ng/g, cerebellum 7.13 ng/g, and striatum was 4.72 ng/g. The low level distribution of EGCG in brain tissue may be due to the presence of bipolar groups in the molecules and the high protein binding rate (> 90%) which makes it difficult to penetrate the blood-brain barrier (Le et al. 2018).

As shown in Figure 2, it has been found that the metabolic transformation of tea flavonoids mainly includes three aspects: firstly is phase II metabolism, because there are many phenolic hydroxyls in the structure which lead to bind with sulfuric acid, glucuronic acidas well as 4′- and 4-hydroxyl groups. Secondly is methylation, which plays an important pathway of tea flavonoids metabolism (Chalet et al. 2018). It has been found that glucuronic acid conjugates on the B or C ring of EGCG can greatly inhibit the methylation of benzene ring, but glucuronic acid conjugates on the a ring will not affect its methylation (Luo et al. 2017). The absorption and metabolism of (+) -C and (-)-EC were studied in the competitive transport of small intestine and jejunum and ileum. the results showed that 45% of glucuronic acid complexes, 30% of 3′- and 4′-O-methyl compounds, and 20% of O-methylated glucuronic acid complexes were produced in the transport process, suggesting that these metabolites may enter the portal vein (Monrad et al. 2018) (Figures 3 and 4).

Furthermore, it has been found that (-)-EC is mainly sulfated in liver cytosol by sulfatase 1A1 (SULT1A1) and SULT1A13 in the small intestine, while other sult isoenzymes have little effect on (-)-EC sulfation (Ambadapadi et al. 2017). The sulfation efficiency of (-) -EC was higher in human than that of rats, without glucuronic acid conjugates were found in human liver, small intestine and jejunum microsomes (Kutsukake et al. 2019). This is suggested that there is no glucuronization of (-)-EC in human liver or small intestine. Lu et al. (2003) have systematically evaluated the glucuronide binding of EGCG and EGC in human, mouse and rat liver microsomes. The results show that 4"-O-glucuronide binding reaction was an important metabolic form for EGCG, and its reaction efficiency order is mouse small intestine > mouse liver > human liver > rat liver; the binding level of EGC and glucuronide is lower than that of EGCG, the order of reaction efficiency of EGC-3′-O-glucuronic acid conjugates was mouse liver > human liver > rat liver (Lu et al. 2003). Generally, for the formation rate of the above two glucuronic acid conjugates, mice were more efficient than rats. However, human glucuronosyltransferase UGT1A1, UGT1A8 and UGT1A9 have high catalytic activity for EGCG: UGT1A1 always expressed in human liver and small intestine; while UGT1A9 expressed in liver and kidney; as a small intestine specific glucuronosyltransferase, UGT1A8 has the highest Vmax/Km value for EGCG, but possesses low catalytic activity for EGC (Yong Feng 2006).

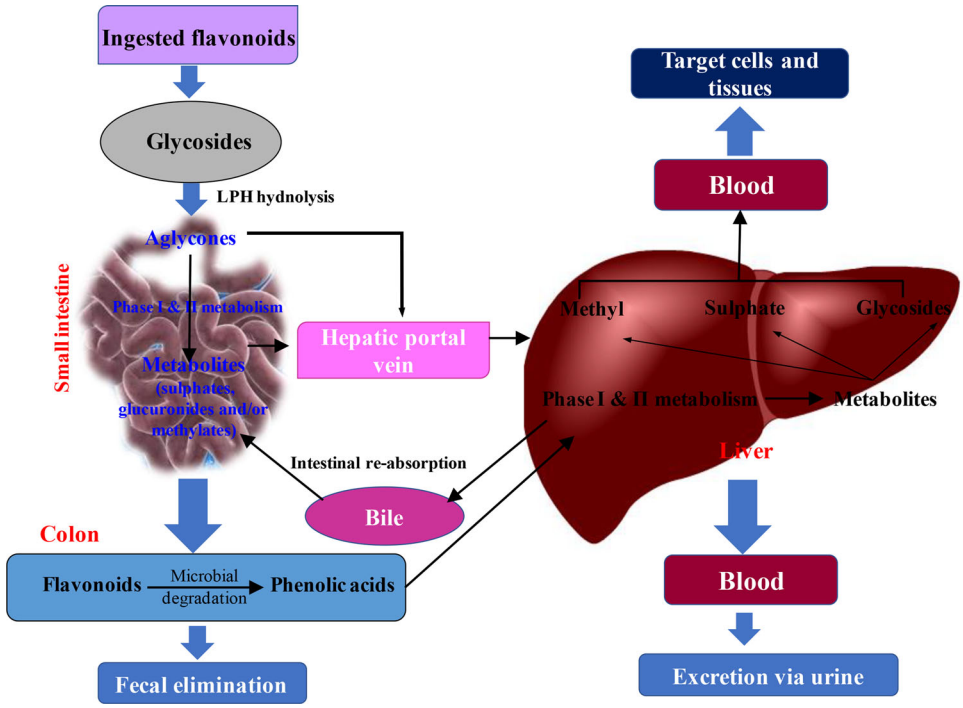

Figure 4. Proposed digestion, absorption, and bioavailibities of diatery flavonoids.

4. Are other flavonoid glycosides absorbed?

Scutellaria baicalensis Georgi, a traditional Chinese medicine, has been recorded in Chinese pharmacopeia with the functions of clearing away heat, drying dampness, purging fire and detoxification (Zhao et al. 2019). Baicalin and baicalein are the main active components of *Scutellaria baicalensis* (Nagashima, Hirotani, and Yoshikawa 2000). As shown in Figure 5, after oral administration, baicalin could be hydrolyzed under the action of β -glucuronidase produced by intestinal flora, and baicalin could be generated and absorbed, thus playing a pharmacological role. Further study has also confirmed that after administration of baicalein in rats; almost no baicalein prototype could be detected in the blood (Wang et al. 2020). Baicalein undergoes metabolic transformation in the absorption process after entering the blood, and produces glucuronization, methoxylation and other metabolites (He et al. 2018). The glucuronization occurs on 5-OH, 6-OH and 7-OH could also generate baicalin 6, 7-di-O-β-glucural acid glycosides, which were accompanied by methylation (Cai et al. 2016). Another example for proposed metabolic pathways of hesperidin and hesperetin in rats was studied by, they identified 52 metabolites including the prototype component of hesperidin and hesperidin from the blood, urine and feces of rats which fed with hesperidin. Hesperidin could hydrolyze glycosyl to produce hesperidin, and could also dehydrated and demethoxylated. The metabolism of hesperidin in rats is mainly glycosylation, demethoxylation, glucuronization and sulfation (Figure 6). In addition, it has been found that hesperidin can be transformed into hesperidin and hesperidin-7-*O*-glucoside by intestinal flora, and then be absorbed by colon through active transport across cell membrane (Teng and Chen 2019).

In natural functional foods, glycosides are generally of low bioavailability, only a few of them are absorbed into the blood, however, they still have definite efficacy, which may be due to their metabolites (secondary glycosides or aglycones) entering the body to play important roles. On the one hand, after oral administration, some of the flavonoids can be directly absorbed, and the others might be metabolized and transformed under the action of intestinal flora and liver metabolizing enzymes to generate active metabolites. Therefore, the flavonoids exist in the body in the form of prototypes and their metabolites (I-phase or II-phase metabolites), which could be also considered as an efficacy form of flavonoids. In addition, flavonoids might be exposed to the gut directly through the regulation of flora to play functional role in vivo (). Up to date, researchers pay enough attention to find the relationship between the therapeutic effect of function food and the change of intestinal flora. As a new potential drug target, intestinal flora has been widely concerned. After the flavonoids enter the intestine, it can regulate the structural composition and abundance of intestinal flora, so as to affect the physiological function of human body or animals and play the role of disease prevention and treatment (Figure 7).

5. Metabolism of flavonoids

5.1. Microorganisms metabolism

It is found that tea flavonoids uptake in the small intestine is relatively low, suggesting the absorption (including absorbed and combined) processing of them will reach the large intestine and contact with the microflora of the colon (Colon and Nerín 2016). Tea flavonoids might be catalyzed

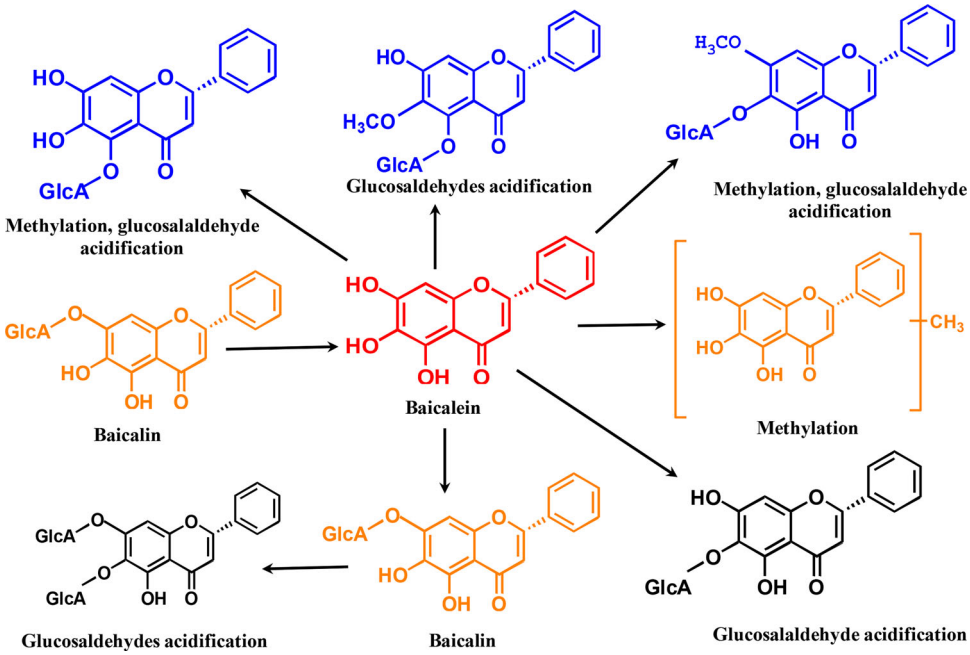

Figure 5. Main metabolic pathways of baicalin and baicalein in rats.

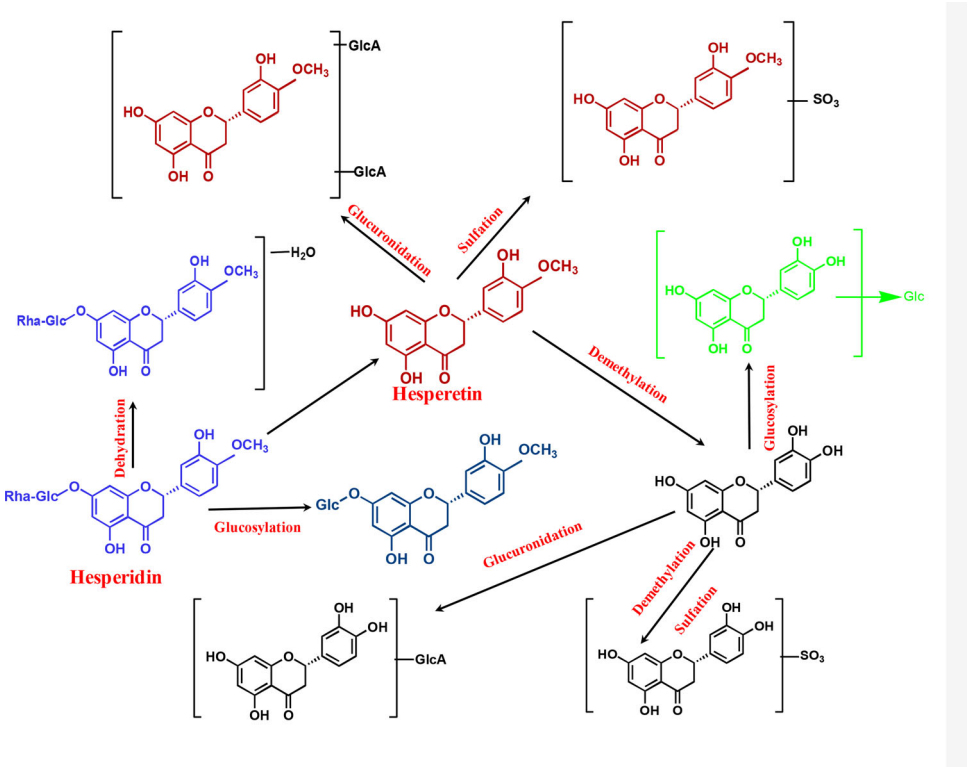

Figure 6. Main metabolic pathways of hesperidin and hesperetin in rats.

to phenolic acid and its glycine conjugates by colonic microorganisms, it has been found that (+)-catechin could be metabolized to phenylpentyl lactone by intestinal flora, and part of them was further converted to phenolic acid (Li et al. 2000), some of which may be methylated, oxidized to benzoic acid derivatives, and bound to glycine (Spencer 2003). The metabolic pathways of (+)-catechin in different species (animals) are basically similar. Several cyclolytic products such as 5-(3′, 4′, 5′-trihydroxyphenyl)-γ-pentyl lactone, 5-(3′, 4′- dihydroxyphenyl) -γ- pentyl lactone and 5-(3′, 5′- dihydroxyphenyl)-γ-pentyl lactone, were detected in human urine and plasma after orally administered 200 mg of EGCG (Cai, Anavy, and Chow 2002). The above three cyclolysis products were also detected by anaerobic culture of EGC, EC and ECG with human flora (Luo et al. 2017).

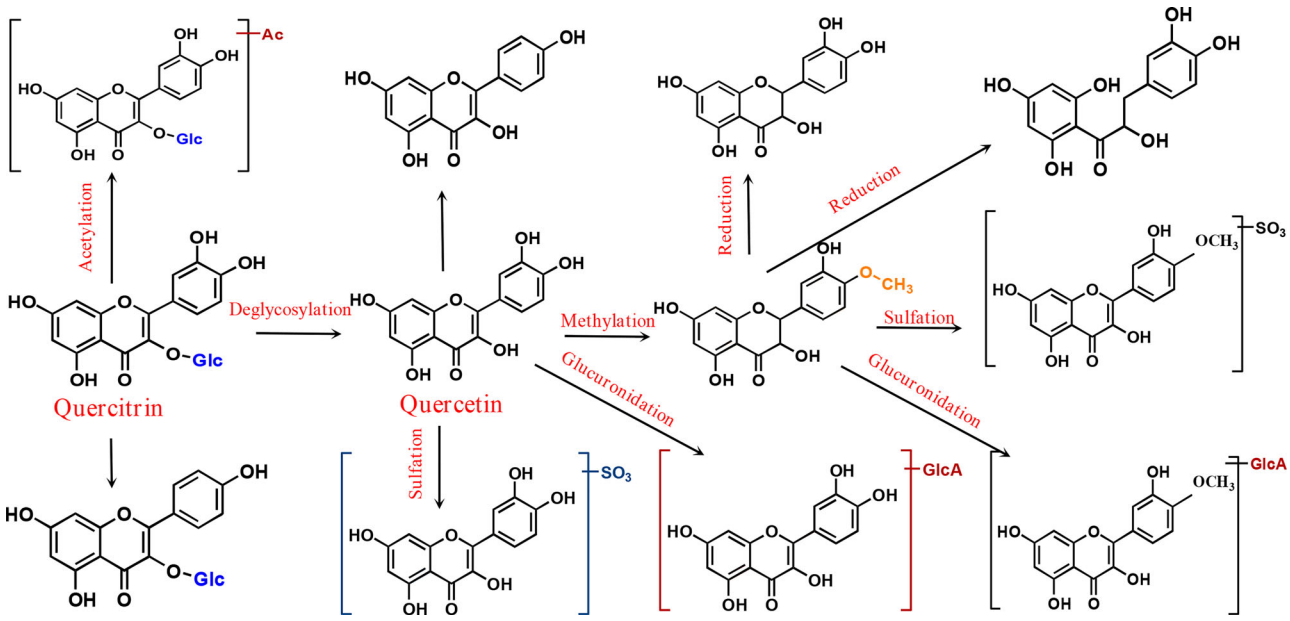

Figure 7. Main metabolic pathways of quercitrin and quercetin in rats and gut flora in vitro.

5.2. Metabolism of flavonoids in small intestine

Most drugs are absorbed into the body through the small intestine. Flavonoid aglycone has a large hydrophobicity and a small molecular structure, which makes it directly absorbed by villous epithelial cells on the wall of small intestine through passive diffusion. Because of the different structure and pH value of flavonoids, their absorption rate is different. It was found that acid medium was favorable for flavonoids to pass through Caco-2 cell model. In the Cacao-2 cell model, the most important factor for quercetin absorption is the pH value, but the change of pH value has little effect on genistein, apigenin and daidzein. Further study showed that the absorption of quercetin (5-hydroxy), luteolin (4-hydroxy), apigenin (3-hydroxy), genistein (3-hydroxy) and daidzein (2-hydroxy) decreased in turn when the pH value changed to be 5.5. It can be concluded that the number of hydroxyl groups located in the structure of flavonoid aglycone and the position of B-ring conjugation significantly effect the absorption of aglycone.

The absorption characteristics of flavonoid glycosides have been attracted many interests for researchers in recent years. Due to the conjugation of glycosyl, flavonoid glycosides possess higher hydrophilicity and molecular weight. It is generally believed that flavonoid glycosides cannot be absorbed directly in the small intestine. They can only be absorbed after being hydrolyzed to aglycone or phenolic acid after oral administration by intestinal flora. Studies have shown that the number and linkage of glycosyl is an important factor that determines the absorption of flavonoid glycosides in human body. Nine volunteers ingested food containing quercetin, quercetin and rutin, their blood samples showed that the maximum blood concentration of quercetin was more than 20 times of quercetin, and Cmax was also 10 times faster than quercetin. Compared with quercetin, the bioavailability of rutin is only 1/5 of quercetin. It can be inferred that quercetin is mainly absorbed in jejunum, while rutin is mainly absorbed in ileum after glycosylation. However, when the absorption of quercetin glucoside in onion was studied in ileostomy volunteers, it was found that the absorption rate was reached to 52% in human body, which was significantly higher than that of quercetin (24%).

At present, there exist two main approaches on the absorption mechanism of flavonoid glycosides in the small intestine. One is that flavonoid glycosides can be hydrolyzed to aglycones by lactase phlorizin hydrolase (LPH), which exists in the margin of small intestine of mammals. LPH, located in the brush border of the mammalian small intestine, could perform this hydrolysis, at least for some flavonoid glycosides. The absorption of flavonoid glycosides may be affected by LPH, for example, quercetin-4′-β-glucoside, quercetin-3-β-glucoside and genistein-7-β-glucoside could be isolated from the intestinal LPH of experimental rat. Another approach is that flavonoid glycosides could be transported through Na^+ depdendent SGLT1 pathway across cell membrane to intestinal epithelial cells. After being hydrolyzed to aglycone by broad-spectrum β-glucosidase, the flavonoid glycosides transported into intestinal epithelial cells via SGLT1 enter the circulation system in the form of aglycone or binding products. However, a drug delivery pump may also affect SGLT1 mediated absorption. Further studies showed that quercetin-4′-β-glucoside could not be absorbed through the Caco-2 monolayer cell model due to the “pump effect” of MRP2. So far, only quercetin-4′-β-glucoside and quercetin-3-β-glucoside can be transported by SGLT1. Taken together, both of the intestinal absorption mechanism revealed that flavonoid glycosides enter the body should be hydrolyzed into aglycones, rather than in the form of its prototype, except for rutin which can be absorbed in the small intestine of rats in the form of its glycosides.

On the other hand, the absorption difference of flavonoids in the small intestine mainly depends on the type, number and position of glycosyl. Firstly, the different types

of glycosyl linked to flavonoid are critical factors affecting the absorption. After taking quercetin-4′-β-glucoside and quercetin-3-β-glucoside in the same dose, the maximum blood concentration of them were similar, while quercetin-3-β-galactoside, 3-β-rhamnoside and 3-α-arabinoside could be absorbed poorly by rat intestine (Morand et al. 2000). Secondly, the different glycosylation may be another important factor influence the absorption of flavonoid glycosides in the small intestine. Flavonoid aglycones are more easily absorbed than flavonoid glycoside. For instance, quercetin-3-O-β-D-glucoside, quercetin-4′-O-β-D-glucoside, quercetin-3, 4′-O-β-D-glucoside and other glucosides could not penetrate the monolayer membrane. The absorption of luteolin glycoside was significantly higher than luteolin, baicalin linked with both monoglycosides was significantly lower than that of luteolin, indicated that the number of linked sugars affected the absorption and the types of linked sugars affected the absorption of flavonoid glycosides.

5.3. Metabolism of flavonoids in intestine

Flavonoid glycoside should be transformed into aglycon and then metabolized into phenolic acid by the action of β-glucosidase, α-rhamnosidase, β-glucuronidase and other enzymes produced by Enterobacter in the intestine. For instance, oral administration of rutin to humans led to the detection of 3-hydroxyphenylacetic acid by rhamnosidase and β-glucosidase (Aura et al. 2002). Glycosidases produced by different genera of bacteria are selective for substrates, including the type of glycosyl group and the position of linkage with flavonoid skeleton. In general, baicalin, daidzein and puerarin can be transformed into aglycones by β-glucuronidase, β-glycosidase and c-glycosidase produced by enterobacteria, respectively (Nemeth and Piskula 2007). Bacteroides SP which isolated from fecal microflora could produce α-rhamnosidase to hydrolyze glycoside of 7-α-rhamnose, but not quercetin glycoside with 3-rhamnose (Aura et al. 2002). In addition, the combined products of flavonoids excreted back to the intestine can also be hydrolyzed into aglycones by the intestinal flora in the large intestine and absorbed into the blood to form the liver intestine circulation. After incubation of quercetin glucuronic acid binding product lmin, the binding product could be hydrolyzed completely. The bacteria in the large intestine are mainly composed of specific anaerobes and can promote the reduction reaction (usually the double bond between C2 and C3 of flavonoid aglycone). Under anaerobic conditions, daidzein and genistein could be hydrolyzed to dihydrodaidzein and dihydrogen genistein, which is separated from human feces (Setchell et al. 2003). In addition, the cleavage in the large intestine could hydrolyze the flavonoid aglycones and further cleave the aglycones to form small phenolic acids. There are four main types of cleft rings in the large intestine: (1) flavones and flavanones to form C6-C3 phenolic acid; (2) flavonols to form C6-C2 phenolic acid; (3) flavanols to form C6-C3 phenol through the intermediate of phenyl-β-sialic acid lactone acids; (4) isoflavones, forming ethyl phenol derivatives (Andrés-Lacueva et al. 2009).

5.4. Metabolism of flavonoids in liver

Liver is a very important metabolic site of flavonoids after absorption into the body. Sulfate, glutathione and 0-methylated forms are considered as one of the most active structural forms. The glutathione and sulfonate conjugates of flavonoids are mainly found in the small intestine and liver, while the *O*-methylated form can only be formed by β-cyclocatechol flavonoids (Figure 4). There are two main metabolic forms of flavonoids in the liver: oxidation reaction and binding reaction. The oxidation reaction is mainly the metabolism of flavonoids by cytochrome P450 enzyme in liver (Hollman 2004). The binding reaction mainly refers to some polar functional groups (such as hydroxyl) contained in the original drug or the I-phase metabolite after oxidation, which are coupled or combined with some endogenous substances to produce various binding products under the action of various catalytic enzymes. The binding reactions of flavonoids in liver mainly include glucuronization, sulfation and methylation (Steed et al. 2017). Ribinsky proposed five basic rules for screening drug molecules (Fang et al. 2019): (1) the molecular weight of the compound is less than 500 daltons; (2) the number of hydrogen bond donors (including hydroxyl, amino, etc.) in the structure of the compound is not more than 5; (3) the number of hydrogen bond receptors in the compound is not more than 10; (4) the logarithm of the fat water partition coefficient of the compound (log P) Between − 2 and 5; (5) no more than 10 rotatable bonds in the compound. At present, it is generally believed that compounds conforming to ribinsky's five rules will have better pharmacokinetic properties and higher bioavailability. However, based on these five rules to measure flavonoids, we found that flavonoids have larger molecular weight, larger dosage form and poor solubility, and their absorption in gastrointestinal tract will be limited, but through dosage form modification And chemical modification can be modified to promote its absorption (Deepika et al. 2019).

5.5. The relationship between bioavailability and microbiota

The commensal bacteria of the intestinal tract could alter the structure of the flavonoids and further effect their absorption and utilization. Bacterial modification of flavonoids is observed in all species of commensal bacteria, with the metabolism primarily hydrolysis, reduction, and deglycosylation of flavonoids (Oteiza et al. 2018). For example, anthocyanins and flavonols can be transformed by C-ring cleavage to protocatechuic acid and the remainder molecules, 2-(2, 4, 6-trihydroxyphenyl) acetic acid in anthocyanins (Becker et al. 2014) and 2-(3, 4-dihydroxy)-phenylacetic acid in flavonols (Wang et al. 2020). Cleavage of the C-ring in catechins as well as the A-ring results in highly water-soluble metabolites excreted in the urine (Zhu, Chen, and Li 2000). Studies have also shown that flavonoids can affect the relative concentration of commensal bacteria in the gut, suggesting that dietary flavonoids may act as prebiotic foodstuffs for gut bacteria.

5.6. Local and systemic effects modulated by microbiota

The interaction of flavonoids and the microbiome offer enormous promise for human health, both locally to the gut and systemically. The ability of flavonoids to shape the microbiome offers the promise of diet based therapies for a wide array of conditions associated with dysbiosis. Orange and apple polyphenols areable to alter the microbiome of patients with systemic lupus erythematosus, with flavanones increasing Lactobacillus and dihydroflavonols increasing Bifidobacterium levels in patients, suggesting it may be possible to correct the dysbiosis associated with systemic lupus erythematosus through flavonoid focused dietary changes (Cuervo et al. 2015). Flavonoid-microbiome interactions may also prove helpful in the treatment of infectious disease. Recent work in mice found that Clostridium orbiscindens is capable of processing flavonoids into desaminotyrosine, which augments type 1 interferon signaling and reduces influenza associated mortality (Steed et al. 2017). The flavone baiclin also appears to inhibit influenza plaque assay, but must be converted into its aglycone baicalein to be absorbed (Xu et al. 2010) which would be dependent on the microbiota.

6. Application of flavonoid nano-particles

It has been observed that benefit of flavonoid is not only dependent on their intake but also their bioavailability. After absorption, flavonoid reaching the blood and tissues are bio transformed and are different from those present in food and evaluation of their biological activity is a big challenge. Only a small amount are available and significant alteration of their redox potential can occurs limiting its bioactivity and reducing its health benefits (Setchell 1998). On the other hand, the absorption, pharmacokinetics and systemic metabolism of flavonoid and their biotransformation by the GI microbiota, as well as interaction with macromolecules such as lipids, polysaccharides and proteins have been extensively studied in the last decade (Awika and Duodu 2017). One of the approaches to improve the bioavailability of flavonoids is by incorporating them into nanoparticles. In recent years, nanotechnology has been rapidly expanding in the food and pharmaceutical industries, especially with the application of nanoencapsulation of bioactive compounds for biological purposes (Chen, Lin, Fan, Qian, et al. 2020b).

Nanoscale approaches to encapsulate phenolic compounds allows protecting them from various factors, which promote their chemical degradation, thereby increasing potential applications. de Dicastillo et al. (2017) extracted Maqui berry flavonoids (consisting mostly of anthocyanins), and encapsulated them using an electrospray methodology and hydroxypropyl-β-cyclodextrin as encapsulating material. Authors report increased thermotolerance under autoclaving (121 °C, 15 min) and baking (180–185 °C, 25 min) conditions, according to minimal losses of phenolics when heated, as compared to non-encapsulated compounds (de Dicastillo et al. 2017). Increased thermotolerance has also been reported in açaí (*Euterpe oleracea* Mart.) anthocyanins encapsulated in electrospray particles, with zein as encapsulating material (De Dicastillo et al. 2016). Treated samples were heated to the same autoclaving and baking conditions mentioned above, where a protective effect was evident; further experiments also showed increased stability under simulated digestion conditions. Others have shown significant increases in half-life of encapsulated flavonoid compounds during storage. For example, Ge et al. (2018) extracted black carrot anthocyanins and incorporated them into nanoscale liposomes, which remained stable during a 21-day storage period. However, authors cautioned that stability was dependent on the percentage of fatty acids present in the system, that is, phenolic oxidation could be induced by oxidized fatty acids under non-ideal ratios. Jeong, Lee, and Lee (2020) evaluated different combinations of fruit (açaí, aronia, blackberry, cranberry, wild berry, raspberry, blueberry and red grape) and vegetable (spinach and cabbage) concentrates, when encapsulated in chitosan/gum arabic or chitosan/carrageenan nanoparticles. Authors determined that, during in vitro digestion, chitosan/gum Arabic particles were not stable, due to their increased polydispersity index. In contrast, the chitosan/carrageenan combination was more stable under conditions evaluated. The protective effects of encapsulation were also evident when antioxidant activity was evaluated, where oxygen radical absorbance capacity (ORAC values) for free compounds decreased almost completely, as compared to retention of 25–50% for encapsulated compounds. Similarly, total phenolic concentration decreased to approximately 25% for free compounds, while encapsulation maintained a higher value of approximately 60%. This evidence suggests that a proper selection encapsulating material is crucial to yield successful results, when treating phenolic compounds. Encapsulated flavonoid compounds of algal origin in nanoliposomes, after optimizing the process. Under ideal conditions, they report that thermo tolerance of the compounds increased, since oxidation of free compounds began at 132.3 °C, while those encapsulated until 157.1 °C, according to differential scanning calorimetry (DSC). Findings also suggest that antioxidant capacity remained acceptable, which led the authors to propose the use of nanoliposome-encapsulated algal flavonoid compounds as antioxidants in lipid-based foods. The increased stability of encapsulated flavonoid compounds can yield other advantages related to their bioactivities. For example, Pereira et al. (2018) extracted phenolic compounds from guabiroba fruit (*Campomanesia xanthocarpa* O. Berg.), and encapsulated them with poly (D,L-lactic-co-glycolic) acid (PLGA) as encapsulating material. Authors evaluated their bioactivity as inhibitors of *Listeria innocua* (as a nonpathogenic surrogate for *L. monocytogenes*). Data showed a significant three-fold lower dose required to inhibit *L. innocua* when the extract was administered encapsulated, as compared to free. This data suggests that encapsulating phenolic compounds increases not only their stability, but potentiates their bioactivity against some microorganisms. Encapsulating phenolics can also serve to protect them when extracted from fruit by-products, for example, Salmazzo et al. (2021) used (poly(lactic-co-glycolic acid) PLGA to encapsulate flavonoid compounds from passion fruit by-products. Controlled release was among results observed, with a kinetic profile similar to that of a bacterial

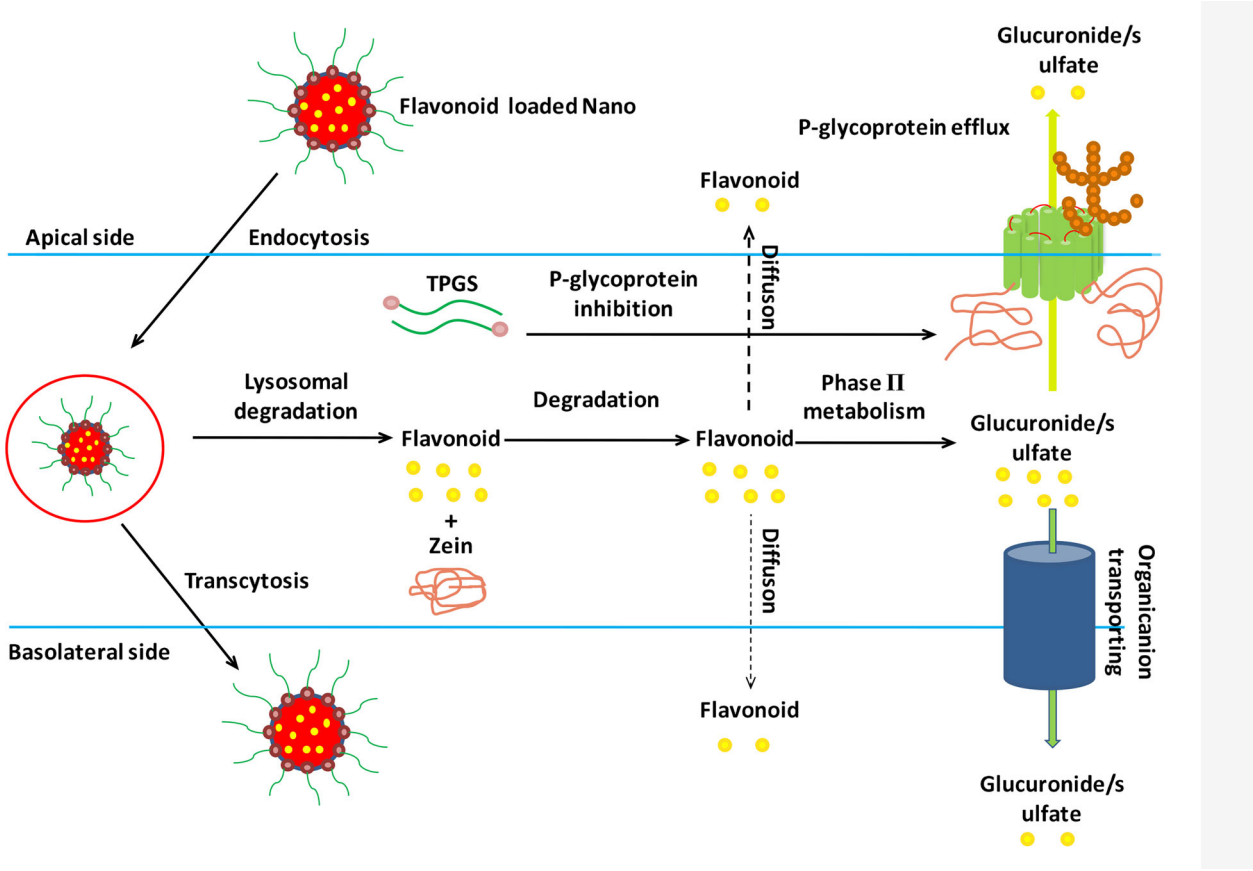

Figure 8. Proposed mechanism of flavonoids-grafted nanoformulation for enhanced stability.

growth curve, which could be mathematically modeled. Stability and bioactivity of the compounds was also obtained when encapsulating them, since this enhanced the antibacterial effects of the extracts, according to an approximately 20-fold lower dose required to inhibit *L. innocua* and *E. coli* growth. Nevertheless, these results varied according to materials used to encapsulate them, as well as their ratios. Practical applications of encapsulated phenolics include masking their bitter flavor, protecting them against processing conditions and changes during storage, among others (Figure 8). Tavakoli et al. (2018) produced an olive leaf extract rich in oleuropein, and encapsulated it within nanoliposomes, which were then added to yogurt in order to improve its functionality. Authors performed numerous analyses and report that enriched yogurt had an increased antioxidant activity, due to oleuropein and other phenolics added. Encapsulating the extracts had the added benefit of avoiding changes to sensorial attributes, which were apparent when yogurt was supplemented with free extract. Stability of the particles varied significantly, requiring an initial optimization process; this prerequisite has been reported by others.

Conclusion

The flavonoids are major compounds that are found in higher quantities in dietary food and have been demonstrated in many studies to present improved bioavailability and bioactivity compared to glucosides in vitro or in vivo. Some researchers have examined different manifestations of the mechanism of flavonoids after digestion in the human body. This review presented an integrated flow chart of flavonoids metabolization, whether through the liver or the intestine, and the diversification of each chemical structure by enzymes. Many studies have discussed the benefits of isoflavone aglycones, though lately more researchers focus on the bioactive effects of isoflavone metabolites in anti-inflammation, anti-cancer, anti-metabolic syndrome and anti-osteoporosis treatment, as well as in gut biota regulation. A collection of reports from the past decade indicating the bioactivities of aglycones and metabolites was presented in this review. These results provide a new perspective on flavonoids metabolites as they apply to daily dietary supplements and potential roles in the prevention of human chronic disease. However, further research on flavonoids aglycones and metabolites in the human body will be needed to strengthen the basic theory of this application in the future.

Based on the research articles published recently, many mechanisms of nano carriers to promote drug absorption are clarified, as shown in Figure 9, including not easy to be limited by traditional absorption mechanisms and drug delivery routes, to avoid the loss and optimize the utilization rate of drugs. However, the role of nano carriers in promoting drug absorption will be affected by their own material properties and many factors during the absorption process. There is still a lot of problems should be improved such as the materials and preparation methods used. Therefore, in the future development of nanodrugs, we should pay attention to the reduction of particle size, the properties of surfactants, and take

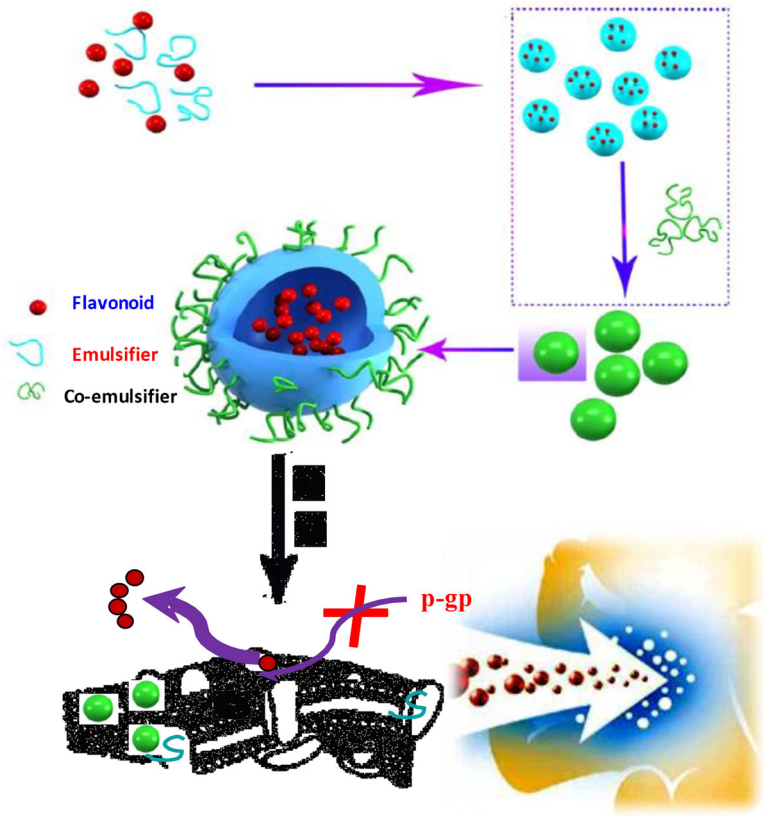

Figure 9. Proposed mechanism of flavonoids-grafted nanoformulation for enhanced absorption. Note: Where green ball is nano-particles of flavonoid and p-gp means P-glycoprotein.

into account the impact of the main absorption environment and the choice of drug delivery mode.

Funding

This work is supported by the National Natural Science Foundation of China (NSFC, Grant No. 31801459; NSFC, Grant No. 32072209), Science and Technology General Projects of Fujian Province (2019J01393), Educational research project for young and middle-aged teachers in Fujian Province (JT180116).

ORCID

Jianbo Xiao http://orcid.org/0000-0003-3311-770X

References

Alemdaroglu, N. C., S. Wolffram, J. P. Boissel, E. Closs, H. Spahn-Langguth, and P. Langguth. 2006. Inhibition of folic acid uptake by catechins and tea extracts in Caco-2 cells. *Planta Medica* 73 (01): 27–32. doi: 10.1055/s-2006-951745.

Ambadapadi, S., P. L. Wang, S. P. Palii, and M. O. James. 2017. Celecoxib affects estrogen sulfonation catalyzed by several human hepatic sulfotransferases, but does not stimulate 17-sulfonation in rat liver. *The Journal of Steroid Biochemistry and Molecular Biology* 172:46–54. doi: 10.1016/j.jsbmb.2017.05.012.

Andrés-Lacueva, C., A. Medina-Remon, R. Llorach, M. Urpi-Sarda, N. Khan, G. Chiva-Blanch, and R. M. Lamuela-Raventos. 2009. Phenolic compounds: Chemistry and occurrence in fruits and vegetables. In *Fruit and Vegetable Phytochemicals: Chemistry, Nutritional Value and Stability*, 53–88. Ames, IA: Blackwell Publishing. doi: 10.1002/9780813809397.

Aura, A.-M., K. A. O'Leary, G. Williamson, M. Ojala, M. Bailey, R. Puupponen-Pimiä, A. M. Nuutila, K.-M. Oksman-Caldentey, and K. Poutanen. 2002. Quercetin derivatives are deconjugated and converted to hydroxyphenylacetic acids but not methylated by human fecal flora in vitro. *Journal of Agricultural and Food Chemistry* 50 (6):1725–30. doi: 10.1021/jf0108056.

Awika, J. M., and K. G. Duodu. 2017. Bioactive polyphenols and peptides in cowpea (Vigna unguiculata) and their health promoting properties: A review. *Journal of Functional Foods* 38:686–97. doi: 10.1016/j.jff.2016.12.002.

Becker, P. M., P. G. van Wikselaar, M. C. Franssen, R. C. de Vos, R. D. Hall, and J. Beekwilder. 2014. Evidence for a hydrogen-sink mechanism of (+) catechin-mediated emission reduction of the ruminant greenhouse gas methane. *Metabolomics* 10 (2):179–89. doi: 10.1007/s11306-013-0554-5.

Bueno, J. M., P. Sáez-Plaza, F. Ramos-Escudero, A. M. Jiménez, R. Fett, and A. G. Asuero. 2012. Analysis and antioxidant capacity of anthocyanin pigments. Part II: Chemical structure, color, and intake of anthocyanins. *Critical Reviews in Analytical Chemistry* 42 (2): 126–51. doi: 10.1080/10408347.2011.632314.

Cai, Y., N. D. Anavy, and H. S. Chow. 2002. Contribution of presystemic hepatic extraction to the low oral bioavailability of green tea catechins in rats. *Drug Metabolism and Disposition: The Biological Fate of Chemicals* 30 (11):1246–9. doi: 10.1124/dmd.30.11.1246.

Cai, Y., S. Li, T. Li, R. Zhou, A. T. S. Wai, and R. Yan. 2016. Oral pharmacokinetics of baicalin, wogonoside, oroxylin A 7-O-β-d-glucuronide and their aglycones from an aqueous extract of Scutellariae radix in the rat. *Journal of Chromatography B* 1026:124–33. doi: 10.1016/j.jchromb.2015.11.049.

Chalet, C., B. Hollebrands, H. G. Janssen, P. Augustijns, and G. Duchateau. 2018. Identification of phase-II metabolites of flavonoids by liquid chromatography-ion-mobility spectrometry-mass spectrometry. *Analytical and Bioanalytical Chemistry* 410 (2):471–82. doi: 10.1007/s00216-017-0737-4.

Chen, L., X. Lin, X. Fan, Q. Lv, H. Fang, Y. Chenchen, and H. Teng. 2020. A self-emulsifying formulation of Sonchus oleraceus Linn for an improved anti-diabetic effect in vivo. *Food & Function* 11 (2): 1225–9. doi: 10.1039/c9fo00772e.

Chen, L., X. Lin, X. Fan, Y. Qian, Q. Lv, and H. Teng. 2020. Sonchus oleraceus Linn extract enhanced glucose homeostasis through the AMPK/Akt/GSK-3β signaling pathway in diabetic liver and HepG2 cell culture. *Food and Chemical Toxicology: An International Journal Published for the British Industrial Biological Research Association* 136:111072. doi: 10.1016/j.fct.2019.111072.

Chow, H.-H. S., I. A. Hakim, D. R. Vining, J. A. Crowell, J. Ranger-Moore, W. M. Chew, C. A. Celaya, S. R. Rodney, Y. Hara, 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: An Official Journal of the American Association for Cancer Research* 11 (12): 4627–33. doi: 10.1158/1078-0432.Ccr-04-2549.

Colon, M., and C. Nerín. 2016. Synergistic, antagonistic and additive interactions of green tea polyphenols. *European Food Research and Technology* 242 (2):211–20. doi: 10.1007/s00217-015-2532-9.

Cuervo, A., A. Hevia, P. López, A. Suárez, B. Sánchez, A. Margolles, and S. González. 2015. Association of polyphenols from oranges and apples with specific intestinal microorganisms in systemic lupus erythematosus patients. *Nutrients* 7 (2):1301–17. doi: 10.3390/nu7021301.

de Dicastillo, C. L., F. Bustos, X. Valenzuela, G. López-Carballo, J. M. Vilariño, and M. J. Galotto. 2017. Chilean berry Ugni molinae Turcz. fruit and leaves extracts with interesting antioxidant, antimicrobial and tyrosinase inhibitory properties. *Food Research International* 102:119–28. doi: 10.1016/j.foodres.2017.09.073.

De Dicastillo, C. L., F. Rodríguez, A. Guarda, and M. J. Galotto. 2016. Antioxidant films based on cross-linked methyl cellulose and native Chilean berry for food packaging applications. *Carbohydrate Polymers* 136:1052–60. doi: 10.1016/j.carbpol.2015.10.013.

Deepika, M. S., R. Thangam, T. S. Sheena, R. Sasirekha, S. Sivasubramanian, M. D. Babu, K. Jeganathan, and R. Thirumurugan. 2019. A novel rutin-fucoidan complex based phytotherapy for cervical cancer through achieving enhanced bioavailability and cancer cell apoptosis. *Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie* 109:1181–95. doi: 10.1016/j.biopha.2018.10.178.

Del Bo', C., P. Riso, A. Brambilla, C. Gardana, A. Rizzolo, P. Simonetti, G. Bertolo, D. Klimis-Zacas, and M. Porrini. 2012. Blanching improves anthocyanin absorption from highbush blueberry (Vaccinium corymbosum L.) purée in healthy human volunteers: A pilot study. *Journal of Agricultural and Food Chemistry* 60 (36):9298–304. doi: 10.1021/jf3021333.

Dvorakova, K., R. T. Dorr, S. Valcic, B. Timmermann, and D. S. Alberts. 1999. Pharmacokinetics of the green tea derivative, EGCG, by the topical route of administration in mouse and human skin. *Cancer Chemotherapy and Pharmacology* 43 (4):331–5. doi: 10.1007/s002800050903.

El Mohsen, M. A., J. Marks, G. Kuhnle, K. Moore, E. Debnam, S. K. Srai, C. Rice-Evans, and J. P. E. Spencer. 2006. Absorption, tissue distribution and excretion of pelargonidin and its metabolites following oral administration to rats. *British Journal of Nutrition* 95 (1):51–8. doi: 10.1079/BJN20051596.

Fang, Y., W. Cao, F. Liang, M. Xia, S. Pan, and X. Xu. 2019. Structure affinity relationship and docking studies of flavonoids as substrates of multidrug-resistant associated protein 2 (MRP2) in MDCK/MRP2 cells. *Food Chemistry* 291:101–9. doi: 10.1016/j.foodchem.2019.03.111.

Forester, S. C., Y. Y. Choy, A. L. Waterhouse, and P. I. Oteiza. 2014. The anthocyanin metabolites gallic acid, 3-O-methylgallic acid, and 2,4,6-trihydroxybenzaldehyde decrease human colon cancer cell viability by regulating pro-oncogenic signals . *Molecular Carcinogenesis* 53 (6):432–9. doi: 10.1002/mc.21974.

Galvano, F., L. La Fauci, G. Lazzarino, V. Fogliano, A. Ritieni, S. Ciappellano, N. C. Battistini, B. Tavazzi, and G. Galvano. 2004. Cyanidins: Metabolism and biological properties. *The Journal of Nutritional Biochemistry* 15 (1):2–11. doi: 10.1016/j.jnutbio.2003.07.004.

Ge, J., P. Yue, J. Chi, J. Liang, and X. Gao. 2018. Formation and stability of anthocyanins-loaded nanocomplexes prepared with chitosan hydrochloride and carboxymethyl chitosan. *Food Hydrocolloids* 74: 23–31. doi: 10.1016/j.foodhyd.2017.07.029.

Geven, C., M. Kox, A. Blet, A. Mebazaa, M. Schroedter, J. Struck, A. Bergmann, and P. Pickkers. 2019. Preclinical safety evaluation of the adrenomedullin-binding antibody Adrecizumab in rodents, dogs and non-human primates. *Toxicology and Applied Pharmacology* 369: 1–16. doi: 10.1016/j.taap.2019.02.014.

Guo, H., M. Xia, T. Zou, W. Ling, R. Zhong, and W. Zhang. 2012. Cyanidin 3-glucoside attenuates obesity-associated insulin resistance and hepatic steatosis in high-fat diet-fed and db/db mice via the transcription factor FoxO1. *The Journal of Nutritional Biochemistry* 23 (4):349–60. doi: 10.1016/j.jnutbio.2010.12.013.

Harada, K., M. Kano, T. Takayanagi, O. Yamakawa, and F. Ishikawa. 2004. Absorption of acylated anthocyanins in rats and humans after ingesting an extract of Ipomoea batatas purple sweet potato tuber. *Bioscience Biotechnology and Biochemistry* 68 (7):1500–7. doi: 10.1271/bbb.68.1500.

He, J., X. Feng, K. Wang, C. Liu, and F. Qiu. 2018. Discovery and identification of quality markers of Chinese medicine based on pharmacokinetic analysis. *Phytomedicine: International Journal of Phytotherapy and Phytopharmacology* 44:182–6. doi: 10.1016/j.phymed.2018.02.008.

He, J., B. A. Magnuson, G. Lala, Q. Tian, S. J. Schwartz, and M. M. Giusti. 2006. Intact anthocyanins and metabolites in rat urine and plasma after 3 months of anthocyanin supplementation. *Nutrition and Cancer* 54 (1):3–12. doi: 10.1207/s15327914nc5401_2.

Hirasawa, M., and K. Takada. 2004. Multiple effects of green tea catechin on the antifungal activity of antimycotics against Candida albicans. *Journal of Antimicrobial Chemotherapy* 53 (2):225–9. doi: 10.1093/jac/dkh046.

Hollman, P. C. H. 2004. Absorption, bioavailability, and metabolism of flavonoids. *Pharmaceutical Biology* 42 (sup1):74–83. doi: 10.3109/13880200490893492.

Jeong, S. J., J. S. Lee, and H. G. Lee. 2020. Nanoencapsulation of synergistic antioxidant fruit and vegetable concentrates and their stability during in vitro digestion. *Journal of the Science of Food and Agriculture* 100 (3):1056–63. doi: 10.1002/jsfa.10110.

Kamiloglu, S., E. Capanoglu, C. Grootaert, and J. Van Camp. 2015. Anthocyanin absorption and metabolism by human intestinal Caco-2 cells-A review. *International Journal of Molecular Sciences* 16 (9): 21555–74. doi: 10.3390/ijms160921555.

Kaulmann, A., M. C. Jonville, Y. J. Schneider, L. Hoffmann, and T. Bohn. 2014. Carotenoids, polyphenols and micronutrient profiles of Brassica oleraceae and plum varieties and their contribution to measures of total antioxidant capacity. *Food Chemistry* 155:240–50. doi: 10.1016/j.foodchem.2014.01.070.

Kay, C. D. 2006. Aspects of anthocyanin absorption, metabolism and pharmacokinetics in humans. *Nutrition Research Reviews* 19 (1): 137–46. doi: 10.1079/NRR2005116.

Kim, S., M. J. Lee, J. Hong, C. Li, T. J. Smith, G. Y. Yang, D. N. Seril, and C. S. Yang. 2000. Plasma and tissue levels of tea catechins in rats and mice during chronic consumption of green tea polyphenols. *Nutrition and Cancer* 37 (1):41–8. doi: 10.1207/s15327914nc3701_5.

Kobayashi, M., and I. Ikeda. 2017. Mechanisms of inhibition of cholesterol absorption by green tea catechins. *Food Science and Technology Research* 23 (5):627–36. doi: 10.3136/fstr.23.627.

Kutsukake, T., Y. Furukawa, K. Ondo, S. Gotoh, T. Fukami, and M. Nakajima. 2019. Quantitative analysis of UDP-glucuronosyltransferase Ugt1a and Ugt2b mRNA expression in the rat liver and small intestine: Sex and strain differences. *Drug Metabolism and Disposition* 47 (1):38–44. doi: 10.1124/dmd.118.083287.

Lambert, J. D., M.-J. Lee, L. Diamond, J. Ju, J. Hong, M. Bose, H. L. Newmark, and C. S. Yang. 2006. Dose-dependent levels of epigallocatechin-3-gallate in human colon cancer cells and mouse plasma and tissues. *Drug Metabolism and Disposition: The Biological Fate of Chemicals* 34 (1):8–11. doi: 10.1124/dmd.104.003434.

Le, C. T., W. P. Leenders, R. J. Molenaar, and C. J. van Noorden. 2018. Effects of the green tea polyphenol epigallocatechin-3-gallate on

glioma: A critical evaluation of the literature. *Nutrition and Cancer* 70 (3):317–33. doi: 10.1080/01635581.2018.1446090.

Li, C., M. J. Lee, S. Sheng, X. Meng, S. Prabhu, B. Winnik, B. Huang, J. Y. Chung, S. Yan, C. T. Ho, et al. 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. doi: 10.1021/tx9901837.

Lin, L. C., M. N. Wang, T. Y. Tseng, J. S. Sung, and T. H. Tsai. 2007. Pharmacokinetics of (-)-epigallocatechin-3-gallate in conscious and freely moving rats and its brain regional distribution. *Journal of Agricultural and Food Chemistry* 55 (4):1517–24. doi: 10.1021/jf062816a.

Lu, H., X. Meng, C. Li, S. Sang, C. Patten, S. Sheng, J. Hong, N. Bai, B. Winnik, C.-T. Ho, et al. 2003. Glucuronides of tea catechins: Enzymology of biosynthesis and biological activities. *Drug Metabolism and Disposition: The Biological Fate of Chemicals* 31 (4): 452–61. doi: 10.1124/dmd.31.4.452.

Luo, K. W., W. F. Fung, W. Y. Lung, X. L. Luo, and W. R. Huang. 2017. Green tea polyphenol, epigallocatechin-3-gallate (EGCG): Mechanisms and application on hepatocellular carcinoma. *SM Liver J* 2 (1):1004.

Marczylo, T. H., D. Cooke, K. Brown, W. P. Steward, and A. J. Gescher. 2009. Pharmacokinetics and metabolism of the putative cancer chemopreventive agent cyanidin-3-glucoside in mice. *Cancer Chemotherapy and Pharmacology* 64 (6):1261–8. doi: 10.1007/s00280-009-0996-7.

McGhie, T. K., G. D. Ainge, L. E. Barnett, J. M. Cooney, and D. J. Jensen. 2003. Anthocyanin glycosides from berry fruit are absorbed and excreted unmetabolized by both humans and rats. *Journal of Agricultural and Food Chemistry* 51 (16):4539–48. doi: 10.1021/jf026206w.

Monrad, R. N., J. Eklöf, K. B. Krogh, and P. Biely. 2018. Glucuronoyl esterases: Diversity, properties and biotechnological potential. A review. *Critical Reviews in Biotechnology* 38 (7):1121–36. doi: 10.1080/07388551.2018.1468316.

Nagashima, S., M. Hirotani, and T. Yoshikawa. 2000. Purification and characterization of UDP-glucuronate: Baicalein 7-O-glucuronosyltransferase from Scutellaria baicalensis Georgi. cell suspension cultures. *Phytochemistry* 53 (5):533–8. doi: 10.1016/S0031-9422(99)00593-2.

Neilson, A. P., B. J. Song, T. N. Sapper, J. A. Bomser, and M. G. Ferruzzi. 2010. Tea catechin auto-oxidation dimers are accumulated and retained by Caco-2 human intestinal cells. *Nutrition Research (New York, N.Y.)* 30 (5):327–40. doi: 10.1016/j.nutres.2010.05.006.

Nemeth, K., and M. K. Piskula. 2007. Food content, processing, absorption and metabolism of onion flavonoids. *Critical Reviews in Food Science and Nutrition* 47 (4):397–409. doi: 10.1080/10408390600846291.

Oteiza, P. I., C. G. Fraga, D. A. Mills, and D. H. Taft. 2018. Flavonoids and the gastrointestinal tract: Local and systemic effects. *Molecular Aspects of Medicine* 61:41–9. doi: 10.1016/j.mam.2018.01.001.

Passamonti, S., U. Vrhovsek, A. Vanzo, and F. Mattivi. 2003. The stomach as a site for anthocyanins absorption from food. *FEBS Letters* 544 (1-3):210–3. doi: 10.1016/s0014-5793(03)00504-0.

Pereira, M. C., D. A. Oliveira, L. E. Hill, R. C. Zambiazi, C. D. Borges, M. Vizzotto, S. Mertens-Talcott, S. Talcott, and C. L. Gomes. 2018. Effect of nanoencapsulation using PLGA on antioxidant and antimicrobial activities of guabiroba fruit phenolic extract. *Food Chemistry* 240:396–404. doi: 10.1016/j.foodchem.2017.07.144.

Salmazzo, G. R., M. H. Verdan, F. Silva, R. M. Cicarelli, J. d. S. Mota, M. J. Salvador, J. E. de Carvalho, and C. A. L. Cardoso. 2021. Chemical composition and antiproliferative, antioxidant and trypanocidal activities of the fruits from Campomanesia xanthocarpa (Mart.) O. Berg (Myrtaceae). *Natural Product Research* 35 (5):853–7. doi: 10.1080/14786419.2019.1607333.

Setchell, K. D. 1998. Phytoestrogens: The biochemistry, physiology, and implications for human health of soy isoflavones. *The American Journal of Clinical Nutrition* 68 (6):1333S–1346. doi: 10.1093/ajcn/68.6.1333S.

Setchell, K. D., M. S. Faughnan, T. Avades, L. Zimmer-Nechemias, N. M. Brown, B. E. Wolfe, W. T. Brashear, P. Desai, M. F. Oldfield, N. P. Botting, et al. 2003. Comparing the pharmacokinetics of daidzein and genistein with the use of 13C-labeled tracers in premenopausal women. *The American Journal of Clinical Nutrition* 77 (2): 411–9. doi: 10.1093/ajcn/77.2.411.

Spencer, J. P. E. 2003. Metabolism of tea flavonoids in the gastrointestinal tract. *The Journal of Nutrition* 133 (10):3255S–3261. doi: 10.1093/jn/133.10.3255S.

Steed, A. L., G. P. Christophi, G. E. Kaiko, L. Sun, V. M. Goodwin, U. Jain, E. Esaulova, M. N. Artyomov, D. J. Morales, M. J. Holtzman, et al. 2017. The microbial metabolite desaminotyrosine protects from influenza through type I interferon. *Science (New York, N.Y.)* 357 (6350):498–502. doi: 10.1126/science.aam5336.

Suppasrivasuseth, J., R. A. Bellantone, F. M. Plakogiannis, and G. Stagni. 2006. Permeability and retention studies of (-) epicatechin gel formulations in human cadaver skin. *Drug Development and Industrial Pharmacy* 32 (9):1007–17. doi: 10.1080/03639040600599889.

Talavéra, S., C. Felgines, O. Texier, C. Besson, A. Mazur, J. L. Lamaison, and C. Rémésy. 2006. Bioavailability of a bilberry anthocyanin extract and its impact on plasma antioxidant capacity in rats. *Journal of the Science of Food and Agriculture* 86 (1):90–7. doi: 10.1002/jsfa.2327.

Tavakoli, H., O. Hosseini, S. M. Jafari, and I. Katouzian. 2018. Evaluation of physicochemical and antioxidant properties of yogurt enriched by olive leaf phenolics within nanoliposomes. *Journal of Agricultural and Food Chemistry* 66 (35):9231–40. doi: 10.1021/acs.jafc.8b02759.

Teng, H., and L. Chen. 2019. Polyphenols and bioavailability: An update. *Critical Reviews in Food Science and Nutrition* 59 (13): 2040–51. doi: 10.1080/10408398.2018.1437023.

Walton, M. C., T. K. McGhie, G. W. Reynolds, and W. H. Hendriks. 2006. The flavonol quercetin-3-glucoside inhibits cyanidin-3-glucoside absorption in vitro. *Journal of Agricultural and Food Chemistry* 54 (13):4913–20. doi: 10.1021/jf0607922.

Wang, Z. Y., Z. M. Jiang, P. T. Xiao, Y. Q. Jiang, W. J. Liu, and E. H. Liu. 2020. The mechanisms of baicalin ameliorate obesity and hyperlipidemia through a network pharmacology approach. *European Journal of Pharmacology* 878:173103. doi: 10.1016/j.ejphar.2020.173103.

Wu, X., G. R. Beecher, J. M. Holden, D. B. Haytowitz, S. E. Gebhardt, and R. L. Prior. 2006. Concentrations of anthocyanins in common foods in the United States and estimation of normal consumption. *Journal of Agricultural and Food Chemistry* 54 (11):4069–75. doi: 10.1021/jf060300l.

Xiao, Y., L. Xin, L. Li, G. Li, X. Shi, G. Ji, J. Mi, and Y. Xie. 2019. Quercetin and kaempferol increase the intestinal absorption of isorhamnetin coexisting in Elaeagnus rhamnoides (L.) A. *Phytomedicine* 53:154–62. doi: 10.1016/j.phymed.2018.09.028.

Xu, G., J. Dou, L. Zhang, Q. Guo, and C. Zhou. 2010. Inhibitory effects of baicalein on the influenza virus in vivo is determined by baicalin in the serum. *Biological & Pharmaceutical Bulletin* 33 (2):238–43. doi: 10.1248/bpb.33.238.

Yang, B., H. Liu, J. Yang, V. K. Gupta, and Y. Jiang. 2018. New insights on bioactivities and biosynthesis of flavonoid glycosides. *Trends in Food Science & Technology* 79:116–24. doi: 10.1016/j.tifs.2018.07.006.

Yi, W., C. C. Akoh, J. Fischer, and G. Krewer. 2006. Absorption of anthocyanins from blueberry extracts by caco-2 human intestinal cell monolayers. *Journal of Agricultural and Food Chemistry* 54 (15): 5651–8. doi: 10.1021/jf0531959.

Yong Feng, W. 2006. Metabolism of green tea catechins: An overview. *Current Drug Metabolism* 7 (7):755–809. doi: 10.2174/138920006778520552.

Zhao, T., H. Tang, L. Xie, Y. Zheng, Z. Ma, Q. Sun, and X. Li. 2019. Scutellaria baicalensis Georgi.(Lamiaceae): A review of its traditional uses, botany, phytochemistry, pharmacology and toxicology. *The Journal of Pharmacy and Pharmacology* 71 (9):1353–69. doi: 10.1111/jphp.13129.

Zhu, M., Y. Chen, and R. C. Li. 2000. Oral absorption and bioavailability of tea catechins. *Planta Medica* 66 (5):444–7. doi: 10.1055/s-2000-8599.