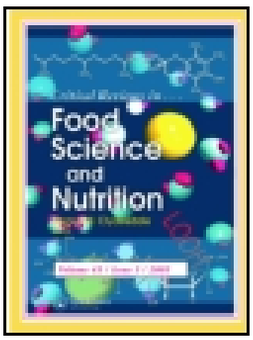

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In-vivo biotransformation of citrus functional components and their effects on health

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REVIEW

In-vivo biotransformation of citrus functional components and their effects on health

Abhisek Karn[a]*, Chengying Zhao[a]*, Feilong Yang[a], Jiefen Cui[a], Zili Gao[b], Minqi Wang[b], Fengzhong Wang[a], Hang Xiao[b], and Jinkai Zheng[a]

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ABSTRACT

Citrus, one of the most popular fruits worldwide, contains various functional components, including flavonoids, dietary fibers (DFs), essential oils (EOs), synephrines, limonoids, and carotenoids. The functional components of citrus attract special attention due to their health-promoting effects. Food components undergo complex biotransformation by host itself and the gut microbiota after oral intake, which alters their bioaccessibility, bioavailability, and bioactivity in the host body. To better understand the health effects of citrus fruits, it is important to understand the *in-vivo* biotransformation of citrus functional components. We reviewed the biotransformation of citrus functional components (flavonoids, DFs, EOs, synephrines, limonoids, and carotenoids) in the body from their intake to excretion. In addition, we described the importance of biotransformation in terms of health effects. This review would facilitate mechanistic understanding of the health-promoting effect of citrus and its functional components, and also provide guidance for the development of health-promoting foods based on citrus and its functional components.

KEYWORDS

Citrus; functional components; structure; biotransformation; health effects

Introduction

Citrus is one of the most popular fruits all over the world, which consists of 150 genera and 1600 species. The most commercially important are orange, tangerine, lime, lemon, and grapefruit (Putnik et al. 2017). Citrus fruits are widely grown in subtropical and tropical regions (Shie and Lay 2013). The annual total global production of citrus fruits is more than 120 million tons, which sustained increases (Patsalou et al. 2017). Citrus fruits are well-known for the attractive colors, special aromas, and delicious tastes, which make them in high consumption. More importantly, citrus has drawn increasing attention due to the nutritive values and health promoting effects, and exploration of citrus functional components, including dietary fibers (DFs), flavonoids, essential oils (EOs), and other components (e.g. synephrines, limonoids and carotenoids) (Figure 1), for human health promoting has been a focal point of scientific investigation (Hung et al. 2018; Qiu et al. 2011; Yang, Wang, et al. 2017). The functional components of citrus are effective against various diseases including cardiovascular, cancer, and inflammatory diseases (Surampudi et al. 2016). Notably, citrus extracts, seeds and especially peels are major sources of citrus flavonoids, which are used as traditional medicines in China, Korea and Japan to treat muscles pain and infections, control blood pressure control, and improve digestion and inflammation (Lv et al. 2015).

Food components undergo complex process in the body after oral intake. In generally, the first step is the release of components from the food matrix by chewing, followed by digestion (e.g. deglycosylation of glucosides) in the gastrointestinal tract to facilitate absorption in the small intestine (Nectoux et al. 2019). All the food components and metabolites are transferred to liver via hepatic portal vein for further extensive phase I reaction (oxidation, reduction, hydroxylation, hydrogenation, dehydrogenation, and methylation) by different enzymes such as cytochrome P450 (CYP) monooxygenase, followed by phase II reactions (e.g. glucuronidation and sulfation) (Braune and Blaut 2016; Zeng et al. 2019; Zheng et al. 2013, 2015). Part of metabolites and their parent compounds enter organs and tissues via systematic circulation to exhibit various physiological functions. They are ultimately excreted in urine. Concurrently, the other parts as bile component reenter the small intestine and colon via enterohepatic recirculation (Selma, Espín, and Tomás-Barberán 2009). Those unabsorbed or undissolved food components in the small intestine immediately enter the colon. Remarkably, human gastrointestinal tract, in particular the colon, is colonized large amount of gut microbiota comprising around 10^{13}–10^{14} bacteria, which is close to the number of human cells in the body (Sender, Fuchs, and Milo 2016). Increasing evidence demonstrates the important role of gut microbiota

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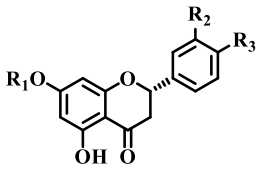
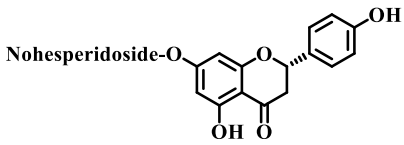
*Both authors have contributed equally to this work.

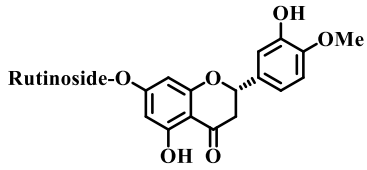
Flavanones



R_1 = H or glycosyl; R_2 and R_3 can be H, OH or OMe

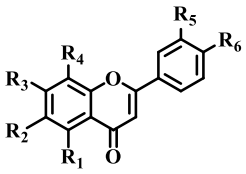


Naringin

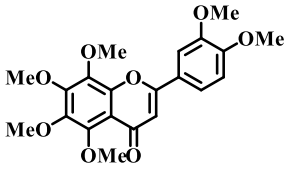


Hesperedin

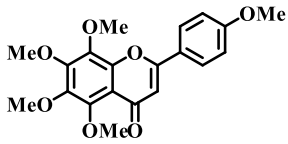
Polymethoxyflavones



R_1~R_6 can be H, OH and OMe, and at least two OMe

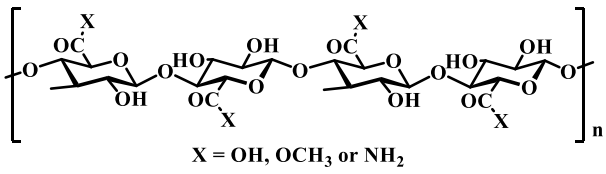


Nobiletin



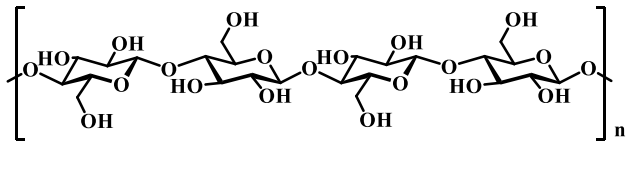
Tangeretin

Dietary fibers



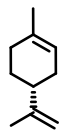
X = OH, OCH_3 or NH_2

Pectin



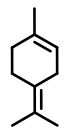
Cellulose

Essential oils

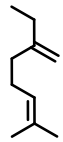


D-Limonene

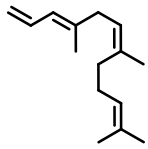
α -Pinene



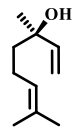
α -Terpinene



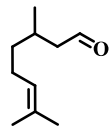
Myrcene



Farnesene

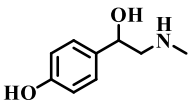


Linalool

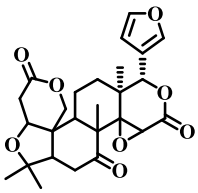


Citronellal

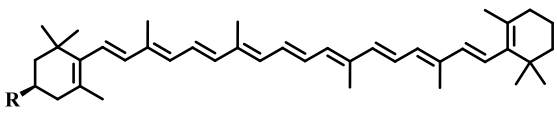
Others



p-Synephrine



Limonin



β -Carotene: R = H
β -Cryptoxanthin: R = OH

Figure 1. Chemical structures of main functional components of citrus fruits.

in the biotransformation of xenobiotics by producing enzymes with much more powerful and distinctive catalysis capacities to those of host, which modify the chemical structures into various metabolites with different bioactivities and toxicities (Koppel, Rekdal, and Balskus 2017), and further impact host health (e.g. energy homeostasis enhancement, colonization resistance, immune system regulation, and synthesis of essential vitamins and nutrients) (Backhed et al. 2004; Buffie et al. 2015; Koppel, Rekdal, and Balskus 2017).

These information demonstrate the complex biotransformation in vivo of food components, which involves extensive chemical structure changes, and results in a

marked change in their bioaccessibility, bioavailability, bioactivity, toxicity and life time in the body (Li et al. 2007). The details of biotransformation vary dramatically among food components, and the biotransformation is affected by food matrix and other components. For citrus flavonoid glycosides, hydrolysis to aglycones by multiple enzymes secreted by the host and the gut microbiota is a prerequisite for absorption; the various metabolites always exhibit distinctive bioactivities. For example, in vivo demethylated metabolites of polymethoxyflavones (PMFs) always show more potent bioactivities than the parent compounds (Li et al. 2007; Song et al. 2016; Wu, Song, Wang, et al. 2015; Wu, Song, et al. 2017; Wu et al. 2018; Zheng et al. 2013). In addition, citrus DFs are resistant to degradation and absorption by the host due to the lack of corresponding enzymes, whereas the gut microbiota ferment citrus DFs into short-chain fatty acids (SCFAs), providing energy to the host and the gut microbiota (Koh et al. 2016). SCFAs affect host physiology and pathology by mediating fortification of epithelial barrier, regulating the immune system, reducing inflammation and tumorigenesis, having beneficial metabolic effects, and affecting liver, brain and adipose tissue (Koh et al. 2016). Therefore, in-depth and systematic studies of biotransformation are needed to reveal the mechanisms underlying the health-promoting effects of citrus and its components.

This review aims to provide systematical profiles about the whole in vivo transformation of various citrus components from taken in to excreted, including the associated organs or tissues, enzymes, pathways, and structure changes. More importantly, special attention is focused on the significance of biotransformation of citrus components in terms of their health-promoting effects. This review delivers more in-depth understanding of the health-promoting effect mechanisms of citrus functional components, and also provides scientific guidance for reasonable design and processing of citrus-based functional foods and diets.

Citrus flavonoids

Flavonoids are the most important functional components in citrus, especially in the peels (Zhao et al. 2020). It has been confirmed that the health promoting effects of citrus mainly depend on the types and contents of flavonoids (Goulas and Manganaris 2012; Yu et al. 2005). Flavonoids exhibit various bioactivities including antioxidant, anti-inflammatory, antitumor, anti-atherosclerosis, hypotension, hypolipidemic and hypoglycemic effects in both in vitro and in vivo models (Gao et al. 2018; Li et al. 2009; Song, Wu, et al. 2017; Wu, Song, Gao, et al. 2017; Wu, Song, Qiu, et al. 2017). Multiple studies have reported that citrus flavonoids undergo complex and extensive biotransformation in intestine and liver to different metabolites with altered biological activities (Figure 2) (Wu, Song, Wang, et al. 2015; Wu et al. 2017; Zheng et al. 2013). Notably, gut microbiota also plays an essential role in the biotransformation and the health promoting function performance of citrus flavonoids (Panche, Diwan, and Chandra 2016). Investigation of the in vivo biotransformation of citrus flavonoids is thus crucial.

Chemical structure and classification of citrus flavonoids

Citrus fruits, especially the peels, are significantly rich in flavonoids. It has reported that the average content of flavonoids is 0.7–2.0% (D.W., dry weight) in citrus peels (M'hiri et al. 2017). More than 250 flavonoids have been identified in citrus, which are constantly discovered with the advancement in techniques (Wang et al. 2019). Although the content and composition vary dramatically among citrus species, flavanones and PMFs are the most important flavonoids in citrus (Di Donna et al. 2013). Flavanones, the most abundant flavonoids in citrus, comprise a 2,3-dihydroflavone skeleton with multiple hydroxyl groups on the basic skeleton. They usually exist as glycosides in citrus. Hesperetin and naringenin along with the corresponding 7-*O*-glucosides (hesperidin and naringin) are the main citrus flavanones (0.02–80.9 mg/g D.W. in citrus peels) (M'hiri et al. 2017; Tripoli et al. 2007). They reportedly have various potent health beneficial effects including antioxidant (Zhao et al. 2020), anti-inflammation (Wu et al. 2016), anti-cancer (Yi, Ma, and Ren 2017), and cardiovascular effects (e.g. anti-atherosclerotic, antihypertensive, and vasoprotective) (Yi, Ma, and Ren 2017). PMFs, special flavones with two or more methoxyl groups on their basic benzene-pyrone skeleton, almost exist exclusively in citrus fruits, especially the peels (0.08–14.5 mg/g D.W.) (Li et al. 2014; M'hiri et al. 2017; Yi, Ma, and Ren 2017). In addition to fully methoxylated PMFs, hydroxylated PMFs are present in aged citrus peels and long-term storage fruits. Over eighty PMFs have been identified from citrus species, among which nobiletin and tangeretin are the most abundant (Gao et al. 2018; Li et al. 2009). Chemopreventive effects of PMFs in in vitro, in vivo and epidemiological studies have been reviewed, which include anti-cancer, anti-inflammation, antioxidant, regulation of metabolic diseases (anti-diabetes, anti-obesity, anti-atherosclerosis and regulating lipid metabolism), neuroprotective effects (Charoensinphon et al. 2013; Gao et al. 2018; Li et al. 2009; Zhao et al. 2020).

Biotransformation of flavanones by the host

Most citrus flavanones are present as glycosides, and hesperidin and naringin are the most abundant (Perez-Jimenez et al. 2010). Due to their high hydrophilicity, glycosides are not readily absorbed directly by the small intestine. The absorption of citrus flavanone glycosides is associated with hydrolysis by multiple enzymes. After orally intake, only a portion of flavanones are rapidly hydrolyzed by brush border enzymes of the small intestine like lactase phloridzin hydrolase (LPH) or directly transported into intestinal epithelial cells through transporter, such as sodium dependent glucose cotransporter (SGLT1), with subsequent hydrolysis by intracellular cytosolic β-glucosidases (CBG) to release aglycones (Nielsen et al. 2006). Remarkably, more than 70% of the corresponding aglycones, hesperidin and naringin,

enter the colon (Braune and Blaut 2016; Nielsen et al. 2006). Only a fraction of hesperetin and naringenin would be absorbed through epithelium by means of passive diffusion and proton coupled active transport or further metabolized. During the absorption and transportation across the small intestine, glucuronidation, sulfation and methylation of aglycones are catalyzed by UDP-glucuronosyltransferases (UGTs), sulphotransferases (SULTs) and catechol-O-methyltransferases (COMT), respectively (Nectoux et al. 2019). All the components absorbed in the intestine are transferred to liver through hepatic portal vein, where extensive metabolism occurs. Flavanones are transformed by phase I enzymes into various metabolites through acetylation, hydrogenation, methylation, dehydrogenation, hydroxylation, and so on (Liu et al. 2012; Zeng et al. 2019). They are subsequently converted into conjugated metabolites by UGTs and SULTs (Nectoux et al. 2019). And glucuronides and sulfates are found to be the main forms of citrus flavanones in plasma and urines (Liu et al. 2012; Zeng et al. 2019). Hesperitin are mainly conjugated at C7 and C3′ position, and hesperitin 3′-*O*-glucuronide and 7-*O*-glucuronide are present as the major metabolites. In a recent study about the biotransformation of naringin, 39 flavonoid metabolites, including naringenin, eriodictyol, apiferol, apigenin, hesperetin, and their corresponding conjugated metabolites (e.g. *O*-glucuronides, *O*-diglucuronides, *O*-sulfates, *O*-disulfates, *O*-glucuronide-*O*-sulfates, *O*-glucoside-*O*-glucuronides and *O*-glucoside-*O*-sulfates), were detected in aged rat, 33 of which were glucuronides or sulfates (Zeng et al. 2019). Flavanones and their metabolites in the liver will be rapidly and widely distributed to different tissues via blood circulation system, with the exception of the brain due to the difficulty of crossing the blood-brain barrier. Taking the total flavanone aglycones into account, pharmacokinetic studies show that T_{max} (time to peak) of hesperidin (6–7 h) is longer than that of naringin (5–6 h), whereas its C_{max} (maximum plasma concentration) is lower than that of naringin following administration of the same dose (Brett et al. 2009), indicating faster and more efficient absorption of naringin than hesperidin. β-Glucuronidase participates in the hydrolysis of conjugated metabolites to enhance their tissue penetration for recirculation. Taking naringin as an example, after oral administration, the top four tissues with the highest content of naringenin are the stomach > small intestine > liver > kidney, while the liver > stomach > small intestine > kidney for total naringenin (free and conjugated forms) (Zeng et al. 2019). Ultimately, about 80% of orally administered citrus flavanones and their metabolites are excreted in urine (Jaeger, Parylak, and Gage 2018). In addition, some bioavailable metabolites might be excreted by bile into feces (Cassidy and Minihane 2017).

Biotransformation of PMFs by the host

The multiple methoxyl groups make the distinct properties of PMFs from those of common flavonoids including their biotransformation progress (Li et al. 2014; Murakami et al. 2001). The low bioavailability for PMFs have been confirmed in multiple studies, which might be contributed to the whole methylation of all the hydroxyl groups and resulting in poor solubility (Gao et al. 2018; Hung et al. 2018). A series of delivery systems, including nanoparticles and emulsion-based delivery systems, have been designed to improve the bioavailability of PMFs (Chen, Fonseca, et al. 2015; McClements and Xiao 2017; Ting et al. 2015; Yang, Zhao, et al. 2017; Yao et al. 2017; Zheng et al. 2014). However, biotransformation studies demonstrated that PMFs undergo various biotransformation to produce metabolites with distinctive bioactivities. Early in vitro and in vivo studies have demonstrated that 3′-demethylnobiletin, 4′-demethylnobiletin and 3′,4′-didemethylnobiletin are the major metabolites of nobiletin (Li, Lo, et al. 2006, Li et al. 2007; Li, Luo, and Ho, 2006; Murakami et al. 2000, 2001, 2002), while 4′-demethyltangeretin and 3′,4′-dihydroxy-5,6,7,8-tetramethoxyflavone are the major metabolites for tangeretin (Breinholt et al. 2003), which indicate that 3′- and 4′-positions of the B ring of PMFs are the major biotransformation sites. CYP enzymes (e.g. CYP 1A1, CYP 1A2, CYP 1B1, CYP 3A4, CYP 3A5 and so on) are found to play important roles in the hepatic demethylation metabolism of PMFs (Koga et al. 2007, 2011; Li et al. 2009, 2014). Our previous studies demonstrated that 5,3′-didemethylnobiletin, 5,4′-didemethylnobiletin and 5,3′,4′-tridemethylnobiletin were the three major metabolites in the urine of male CF-1 mice administrated 5-demethylnobiletin. They were mainly present as conjugated glucuronides and/or sulfates with a free to conjugated form ratio of 1:1.7–1:6.1 (Zheng et al. 2013). Furthermore, to facilitate the identification of demethylated PMFs with beneficial biological effects, we established a method for simultaneous detection of 10 demethylated PMFs using high-performance liquid chromatography (HPLC) coupled with electrochemistry. Seven metabolites (3′-demethylnobiletin, 4′-demethylnobiletin, 3′,4′-demethylnobiletin, 5-demethylnobiletin, 5,3′-didemethylnobiletin, 5,4′-didemethylnobiletin, and 5,3′,4′-tridemethylnobiletin) were identified in the urine of male CF-1 mice administrated nobiletin (Zheng et al. 2015). As for tissue distribution, nobiletin exhibited a notable tendency to localize in mucous membrane and the muscularis layer of the digestive organs of Sprague-Dawley (SD) rats from 1 to 4 h, and accumulates in various tissues and organs, including stomach, intestine (small and large), liver and kidney (Murakami et al. 2002). After 24 h, nobiletin and its metabolites could not be detected in any organ (Murakami et al. 2002). Similarly, tangeretin is also found to widely distribute in different tissues in rats. The tangeretin content in the stomach and small intestine peak at 4 h after oral intake, which is much higher than that of in the cecum and colon (12 h). For vital organs, the highest accumulation is in the kidney, lung and liver (Hung et al. 2018). PMFs and their metabolites are excreted via urine or feces, mainly in conjugated forms in urine (Manthey et al. 2011; Murakami et al. 2002; Zheng et al. 2013, 2015).

Biotransformation of citrus flavonoids by the gut microbiota

The gut microbiota has been found to play an essential role in the overall biotransformation of citrus flavonoids, which

always involves in the enhancement of bioactivities (Cassidy and Minihane 2017; Chen et al. 2014). Large amount of citrus flavanone glycosides (e.g. naringin and hesperidin) reach the colon, and the rhamnose moiety is removed via α-rhamnosidases secreted by the gut microbiota, followed by the remove of glucose by β-glucosidases (Braune and Blaut 2016; Nielsen et al. 2006). The released aglycones are subsequently metabolized by the gut microbiota to various phenolics, which could be absorbed by the host (Stevens et al. 2019). The degradation starts with isomerization of the C ring into the corresponding chalcone phloretin followed by reduction to dihydrochalcone. Phloroglucinol and 3-(4-hydroxyphenyl)-propionic acid (4-HPPA) are produced with a further split at the carbonyl moiety, in which *Clostridium spp.*, *Clostridium scindens*, *Flavonifractor plautii* and *Eubacterium desmolans* are identified to participate (Schoefer et al. 2003). 4-HPPA is further dehydroxylated into 3-phenylpropionic acid (Duynhoven et al. 2011; Olthof et al. 2003; Zou et al. 2015). These metabolites are absorbed in the colon or biotransformed into SCFAs (e.g. acetate, propionate and butyrate) (Duynhoven et al. 2011). In a recent study, 46 microbial-derived phenolic metabolites, including free, glucuronide, sulfate metabolites, were detected (Zeng et al. 2019). Although the metabolite types and content vary depending on the in vivo models, oral intake amount and food matrix, multiple studies indicate that microbe-derived metabolites of flavanones are excreted mainly in urine, then feces (Liu et al. 2012; Zeng et al. 2019). The gut microbiota also catalyzes further transformation of phase I and phase II metabolites, which are returned to the intestine via enterohepatic circulation. The conjugated metabolites are typically hydrolyzed to their corresponding free forms by glucuronidases and sulfatases produced by the gut microbiota (Cassidy and Minihane 2017). In addition, PMFs can be biotransformed to various demethylated metabolites by the gut microbiota, and specific bacterium like *Blautia* sp. MRG-PMF1 has been identified (Burapan, Kim, and Han 2017; Kim, Kim, and Han 2014). The regioselectivity of PMF demethylation generally followed the order of C-7 > C-4′≈C-3′>C-5 > C-3 (Burapan, Kim, and Han 2017). Although the gut microbiota is important in flavonoid metabolism, the mechanism, in particular the participating bacterial taxa, is unclear.

Health effects of the biotransformation of citrus flavonoids

Numerous studies have demonstrated the significant beneficial effects of citrus flavonoids on health. However, the in vivo beneficial effects dramatically depend on the biotransformation of citrus flavonoids, which is associated with extensive changes in chemical structures by the host (phase I and phase II metabolism) and the gut microbiota. In term of deglycosylation effect, because only aglycones can be absorbed by enterocytes, activity of LPH/CBG in the small intestine and of α-rhamnosidases excreted by the gut microbiota is important for improving absorption of flavonoid glycosides (e.g. hesperidin and naringin). The antioxidant effects of citrus flavanone aglycones are potent than their glycosides (Mulvihill, Burke, and Huff 2016). In phase I metabolisms, the functional groups of citrus flavonoids are changed through various reactions, which also lead to the variation of health effects on host. Typically, demethylated metabolites show different, even more potent bioactivities than the parent PMFs (Li et al. 2007; Song et al. 2016; Wu, Song, Wang, et al. 2015; Wu et al. 2017; Wu et al. 2018; Zheng et al. 2013). In our previous study, C3′-, C4′- and C3′,4′- demethylated metabolites of 5-demethylnobiletin showed more potent inhibition toward SW480 and SW620 cells. The IC_{50} values of the three metabolites were 0.12, 5.5, and 4.2 μM to SW620 cells, respectively, while the parent compound 5-demethylnobiletin at 10 μM caused only 37% inhibition after 72 h (Zheng et al. 2013). Oral intake of nobiletin could significantly inhibit AOM/dextran sulfate sodium (DSS) induced colon carcinogenesis in mice, and the total colonic level of the three major metabolites (3′-demethylnobiletin, 4′-demethylnobiletin, and 3′,4′-didemethylnobiletin) was about 20-fold higher than that of nobiletin (Wu, Song, Wang, et al. 2015). The demethylated metabolites of nobiletin show various health promoting effects through attenuating nuclear factor kappa-B (NF-κB) signaling, decreasing the production of reactive oxygen species (ROS), upregulating the expression of GCL, HO-1, NQO1, Nrf2 (Li et al. 2014), downregulating the expression of the proinflammatory cytokines interleukin (IL)−1β, IL-6, prostaglandin E2, inducible nitric oxide synthase, and COX-2 (Guo et al. 2018; Wu, Song, Rakariyatham, et al. 2015), reducing Cu^{2+}-induced low-density lipoprotein (LDL) oxidation (Lo et al. 2010), activating ERK, Akt, JNK signaling (Li et al. 2014), and abrogating uptake of modified LDL by macrophage in THP-1 cells (Lo et al. 2010). As for phase II metabolism, conjugated reactions could significantly improve polarity and water solubility, and accelerate renal excretion, thus, the phase II metabolism is considered as detoxifying reaction. Citrus flavanones metabolites of hesperetin-3′-*O*-sulfate, hesperetin-3′-*O*-glucuronide and naringenin-4′-*O*-glucuronide significantly attenuate monocyte adhesion to on monocyte adhesion to tumor necrosis factor α (TNF-α)-activated human umbilical vein endothelial cells (HUVECs), whereas hesperetin-7-*O*-glucuronide and naringenin-7-*O*-glucuronid show markedly lower potency in this regard (Chanet et al. 2013). As for the hydrolysis of conjugated metabolites by host or gut microbiota, it could significantly increase their lipophilicity and penetrability to cross the cell membrane, and therefor enhance their tissue distribution or reabsorption in the intestinal tract. Gut microbiota-derived metabolites also play an important role in health promoting effects. For example, phloroglucinol exhibits antioxidant and anticancer effects, reduce malondialdehyde (MDA) and intracellular ROS production, and decrease MMP-1 expression at mRNA and protein levels (Mária and Ingrid 2017). 4-HPPA could significantly reduce lipid accumulation in cellular and CD36 mRNA expression in ox-LDL-treated macrophage cells (Zhang et al. 2018). All these studies demonstrated the special significance of the biotransformation for the beneficial effects of citrus flavonoids on health.

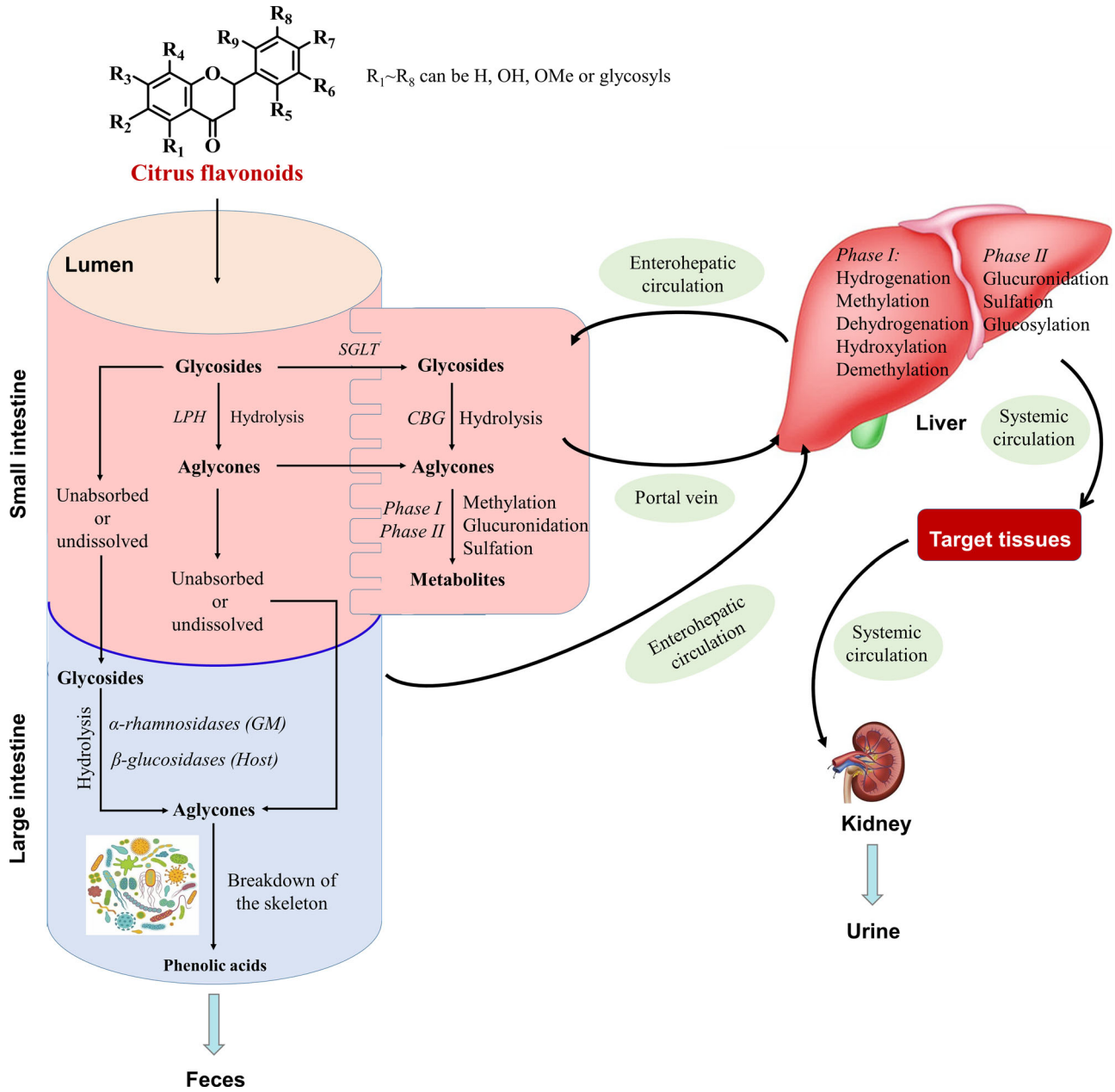


Figure 2. *In-vivo* biotransformation of citrus flavonoids (GM, gut microbiota).

Citrus dietary fibers

As an important by-product, citrus peel is a good source of DFs. Due to their excellent physicochemical properties (e.g. hydration capacity, emulsifying, ion-binding and oil-holding capacity), as well as excellent biocompatibility and safety, citrus DFs are widely used in food, cosmetic, and pharmaceutical industries. It has been suggested that adults should take in 20–35 g of DFs per day (Dhingra et al. 2012). Remarkably, citrus DFs are resistant to digestion and absorption in the human small intestine due to the lack of the required degradative enzymes. Instead, DFs directly enter into the colon, where they are extensively fermented by the gut microbiota into SCFAs to exert various heath beneficial effects, such as providing primary carbon energy source for colon cells, maintaining the gut barrier and microecology, regulating of lipid metabolism, controlling the glycemic level, and inhibiting the proliferation of pathogenic microbes (Figure 3) (Cui et al. 2019; Li, Zhang, and Yang 2018; Sahasrabudhe et al. 2018; Song, Lopez-Pena, et al. 2017).

Chemical structure and classification of citrus DFs

Structurally, citrus DFs are polysaccharides composed of thousands of monosaccharide units connected by glycosidic linkages. According to their solubility, citrus DFs are classified into soluble DFs (SDFs, mainly pectin) and insoluble DFs (IDFs, mainly cellulose and hemicellulose) (Cui et al. 2019; Dhingra et al. 2012). The DF content in citrus peels is about 6.3–78.8% (D.W.), with a greater proportion of IDFs (48.5–50.3%) than SDFs (12.9–14.1%) (Cui et al. 2019; M'hiri et al. 2017). As an important DF in citrus (19%−28% D.W.), pectins are complex heterogeneous polysaccharides

mainly distributed in primary cell walls and the middle lamella (Zhang et al. 2018). Pectins contain three main regions: the homogalacturonan (HG), rhamnogalacturonan I (RG-I), and rhamnogalacturonan II (RG-II). The HG region, known as 'smooth' region, is a linear homo-polymer consisting of α-(1-4) linked D-galacturonic acid (GalA). The RG-I region possesses a backbone composed of diglycosyl repeats of [→2)-α-L-Rha*p*-(1→4)-α-D-Gal*p*A-(1→]. The RG-II region is often considered as a stretch of HG backbone with substitutions of hetero-oligomeric side chain, including rarely detected sugars (Cui et al. 2019). Consumption of pectins from citrus has been widely recommended due to their various health beneficial effects, such as regulating the gut microbiota (Shtriker et al. 2018), alleviating nonalcoholic fatty liver disease (NAFLD) (Li, Zhang, and Yang 2018), and ameliorating intestinal inflammation (Singh et al. 2019). As a type of IDF, cellulose is the major component of citrus cell walls, which consists of an unbranched linear chain of several thousand glucose units with *β*-(1→4) glucosidic linkages. Hemicellulose is also composed of glucose units with *β*-(1→4) glucosidic linkages, along with other types of sugars, and is usually branched. Typically, as a bioactive ingredient, citrus IDFs can be used as effective inhibitors of lipid oxidation in meat products, thereby improving their oxidative stability and prolonging their shelf life (Rafiq et al. 2018).

Fermentation of citrus DFs by the gut microbiota

Human body lack enzymes to degrade polysaccharides. Thus, citrus DFs cannot be directly absorbed and used by the host. Instead, they undergo complete or partial fermentation in the large intestine by enzymes encoded by the gut microbiota (Figure 3). There are two types of enzymes that cleave glycosidic bonds: glycoside hydrolases (GHs)-cleaving bonds through hydrolysis (Koropatkin, Cameron, and Martens 2012), and polysaccharide lyases (PLs)-cleaving bonds through an elimination mechanism (Lombard et al. 2010). A model microbiome of the healthy adult gut was constructed to evaluate the diversity of carbohydrate-active enzymes (CAZymes) in the gut microbiota (Kaoutari et al. 2013). Genes encoding enzymes for GHs and PLs represent

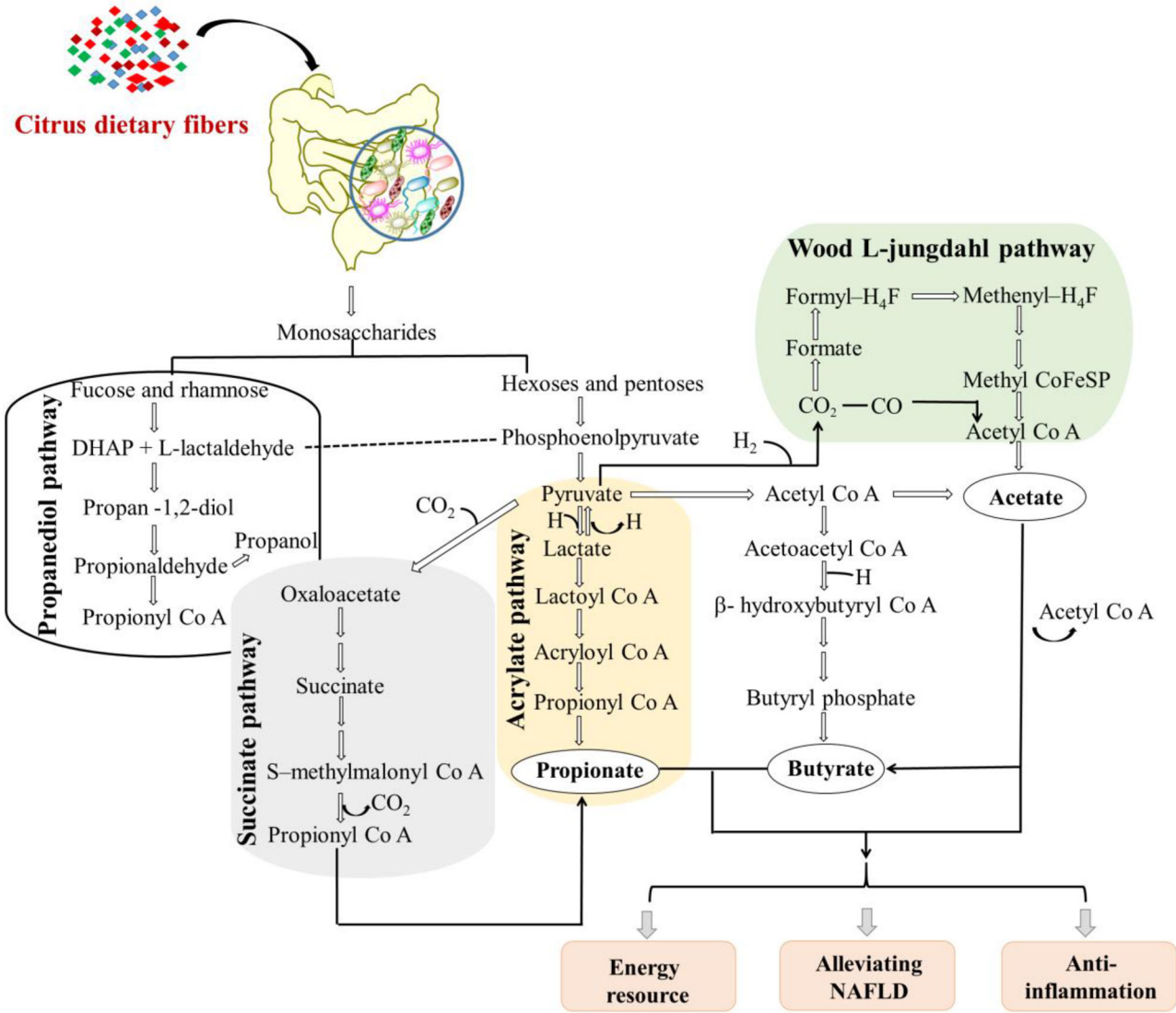


Figure 3. Fermentation of citrus dietary fibers by gut microbiota and its significance for health.

the majority (59%) of CAZyme genes (9120 and 291 candidates for GHs and PLs genes, respectively) (Kaoutari et al. 2013). Gut bacteria of the phylum *Bacteroidetes* encode more CAZymes than those of other phyla in the model mini-microbiome. Remarkably, the fermentation of DFs requires synergistic contribution of multiple enzymes, and their fermentability dramatically depends on their chemical structures (monosaccharide composition, linage between monosaccharide, the backbone and side chains) and phytochemical properties (water-solubility and size). Generally, SDFs like pectin are highly fermentable, while IDFs (e.g. cellulose, hemicellulose) are less fermentable (Cui et al. 2019; Dhingra et al. 2012). For example, cellulose from citrus with low solubility comprising a linear glucose chain is restricted to access digestive enzymes. In comparison, highly branched pectin is well fermented by multiple gut microbiota-derived enzymes to produce SCFAs, especially butyrate (Ndeh et al. 2017). In an investigation of pectin metabolism by the gut microbiota, *Bacteroides thetaiotaomicron* was found to excrete various enzymes to cleave almost all distinct glycosidic linkages (20 of 21 linkages) of RG II. Now, more and more enzymes are identified to be responsible for the metabolism of pectins, such as β-D-glucuronidase, β-L-arabinofuranosidase, β-D-galacturonidase, α-arabinopyranosidase, 2-keto-3-deoxy-D-*lyxo*-heptulosaric acid (DHA)-hydrolase, endo-apiosidase, $\alpha-2$-*O*-methyl-L-fucosidase, and pectin methyl-esterases (Ndeh et al. 2017). The degradation of RG II side chains and backbone are favored to overcome steric constraints (Ndeh et al. 2017). Ultimately, the monosaccharides are further fermented to SCFAs (mainly acetate, propionate, and butyrate) by the gut microbiota (Koh et al. 2016). Acetate is produced from pyruvate via acetyl-CoA or the Wood-Ljungdahl pathway by most gut enteric bacteria like *Bifidobacterium* spp., *Prevotella* spp., *Bacteroides* spp., *Ruminococcus* spp. and *Akkermansia muciniphila* (Koh et al. 2016; Louis, Hold, and Flint 2014). In detail, acetate is synthesized via the reduction of CO_2 to CO from the Western branch (carbon monoxide branch), followed by combination with a methyl group to form acetyl-CoA. Alternatively, the reduction of CO_2 to formate from the Eastern branch (C_1-body branch) also yields acetate (Wood-Ljungdahl pathway) (Koh et al. 2016). In *Bacteroides* spp., *Phascolarctobacterium succinatutens*, *Dialister* spp. and *Veillonella* spp., after the conversion of monosaccharides (hexoses and pentoses) to phosphoenolpyruvate (PEP), oxaloacetate is generated and subsequently reduced to succinate. Succinate is subsequently converted to methylmalonyl-CoA and then to propionyl-CoA to yield propionate (succinate pathway) (Koh et al. 2016). In addition, propionate could also be produced via acrylate pathway, in which PEP is reduced to lactate, acryloyl-CoA and propionyl-CoA in sequence. *Megasphaera elsdenii* and *Coprococcus catus* have been reported to be the associated gut bacteria (Koh et al. 2016). Alternatively, the propanediol pathway with deoxyhexose monosaccharides (e.g. fucose and rhamnose) as substrates is the third reported pathway with the action of *Salmonella* spp., *Roseburia inulinivorans*, *Ruminococcus obeum* (Louis, Hold, and Flint 2014). Start with the conversion of PEP to pyruvate, two molecules of acetyl-CoA are condensed to form acetoacetyl-CoA, which is sequentially reduced to β-hydroxybutyryl-CoA, crotonyl-CoA and butyryl-CoA. Butyrate is produced with the catalysis of phosphotransbutyrylase/butyrate kinase from butyryl-CoA in *Coprococcus* sp., e.g. *Coprococcus comes* and *Coprococcus eutactus* (Louis, Hold, and Flint 2014). Butyrate can also be synthesized by the condensation and reduction of butyryl-CoA and acetyl-CoA via butyryl-CoA: acetate CoA-transferase route (Louis, Hold, and Flint 2014; Duncan et al. 2002).

Biological significances of gut microbiota fermentation of citrus DFs

Citrus DFs exhibit numerous health promoting effects through different mechanisms including physicochemical effects on the intestinal tract, direct interactions between citrus DFs and host cells, and effects of fermentation. DFs can elicit various gut hormones that stimulate insulin release and affect appetite. In the small intestine, SDFs may blunt the postprandial glycemic and insulinemic responses that are thought to determine the rate of return of hunger and subsequent energy intake. IDFs can stimulate gut motility and exert a fecal-bulking effect, thus alleviating constipation. The increased stool volume may dilute hazardous microbial metabolic products and facilitate their removal from the colon. The mechanism of effects originated from fermentation is the most common and important. The digestion and absorption of DFs are through fermentation by the gut microbiota, without which DFs cannot be used by the host, and would be immediately excreted through fecal. Through fermentation by the gut microbiota, chemical energy is converted into energy (ATP) used by colonic cells and the gut microbiota (Grabitske and Slavin 2008). DF fermentation provides about 10% of the daily caloric intake of humans (Kaoutari et al. 2013; Larsbrink et al. 2014). Fermentable carbohydrates are preferred by the gut microbiota as substrates in comparison with energetically less favorable sources of dietary protein and fat (Canfora et al. 2019; Koh et al. 2016). Regarding citrus DFs, pectin can be completely fermented into SCFAs, which exert various physiological effects on the host (Koh et al. 2016). SCFAs contribute to maintaining low pH, which could inhibit pathogens growth, and facilitate to construct healthy gut microbiota. As summarized in our and others' previous reviews, SCFAs could increase IL-18 secretion, and activate G protein coupled receptor (GPR) 109 A and GPR43 to regulate the responses of immune cells such as dendritic cells (DCs), macrophages, and T-regulatory cells (Tregs) (Cui et al. 2019; Kamada et al. 2013; Koh et al. 2016). Specially, acetate and propionate could interact with GPR 43 to regulate anti-inflammatory effect of Tregs (Smith et al. 2013); butyrate regulates the maturation of colonic DCs and macrophages by activating GPR 109 A, and consequently induces Tregs and T-cells (Cui et al. 2019). SCFAs also increase the production of IgA through regulating of B cells, which enhances the ability to block bacterial adherence, and decreases bacterial virulence (Moon et al. 2015). SCFAs have been widely recognized as

anti-cancer agents, especially for colorectal cancer (CRC) (Koh et al. 2016). Butyrate and propionate inhibit histone deacetylase (HDAC) by activating GPR43 and GPR41 (Donohoe et al. 2012; Kaiko et al. 2016). In addition, SCFAs (mainly butyrate and propionate) depress the differentiation of DCs (Singh et al. 2010) and pro-inflammatory effectors in lamina propria macrophages (Chang et al. 2014), and regulate Tregs generation and cytokine expression in T cells by inhibiting HDAC (Shi et al. 2011). Activation effects of SCFAs toward GPRs suppress inflammation, partly by promoting epithelial survival and integrity, but also by inducing the differentiation of Tregs (Singh et al. 2014). Qualitative or quantitative defect in Tregs leads to the development of intestinal inflammation in multiple animal models (Huber et al. 2011). The effects of SCFAs are not limited to the gut, and various in vitro and in vivo studies have demonstrated the causal relationship between SCFAs and metabolism improvement (Cui et al. 2019; Koh et al. 2016). For the glucose homeostasis regulation, it may involve a significant increase in postprandial glucagon-like peptide 1 (GLP-1) and peptide YY (PYY) and a reduced calorie intake (Chambers et al. 2015). It has been reported that butyrate and propionate regulate the level of GLP-1 and PYY, and reduce diet-induced obesity (Chambers et al. 2015; Roshanravan et al. 2017). Acetate promotes metabolic syndrome via modulating GLP-1 (Perry et al. 2016). SCFAs also exhibit significant regulatory effects on vascular function (Cui et al. 2019; Koh et al. 2016). Propionate activates GPR41, leading to relief of hypertension. Olfactory receptor 78 (OLFR78), which can be activated by acetate and propionate, is expressed in vascular smooth muscle cells, including in the renal afferent arteriole. SCFAs (mainly acetate and propionate) activate OLFR78 expression, which stimulates renin secretion mediated by cyclic adenosine monophosphate (cAMP) production, depressing blood pressure (Natarajan et al. 2016). In addition, multiple other distal effects, such as preventing asthma and modulating central nervous system, have been reported (Frost et al. 2014; Thorburn et al. 2015).

Citrus essential oils

Citrus EOs are volatile compounds that can be extracted from citrus peel by cold pressing, steam distillation, solvent extraction, or supercritical CO_2 fluid extraction (González-Mas et al. 2019). Citrus EOs have long been widely used in foods, cosmetics, and pharmaceuticals for their pleasant smell (Sharma et al. 2017) and excellent properties, such as antimicrobial, anti-inflammatory, antitumor, antioxidant and neuroprotective activities (Mannucci et al. 2017), as well as their beneficial effects against generalized anxiety disorder (GAD) and allergic airway inflammation (González-Mas et al. 2019). It has been demonstrated that citrus EOs undergo considerable biotransformation, which alters their effects on health after being absorbed (Figure 4) (Schmidt and Göen 2017; Schmidt, Belov, and Göen 2015).

Chemical structures and classification of citrus EOs

According to the analysis of extractions via steam distillation and cold pressing, citrus EOs roughly account for 0.2–1.7% (F.W.) in citrus peels depending on the species, origin, climate, and harvest time (Sarrou et al. 2013). Most citrus EOs are volatile (93–96%), and the remainder (4–7%) are nonvolatile, including coumarins, diterpenoids, sterols, and fatty acids (González-Mas et al. 2019). Mono- and sesquiterpenes are the two main subgroups of citrus EO volatiles, being polymers of two or three isoprenes. The monoterpenes in citrus EOs, including limonene, α-pinene, β-pinene, α-terpinene, α-terpineol, perillyl alcohol (POH), carvone, cis- and trans-carveol (CAR), are mainly ring-shaped with several bonds unsaturated, and may be oxygen derivatives. In monoterpenes category (nearly 90%), limonene is the most abundant among most of citrus EOs (60–95%), with the exception of *C. bergamia* (30%) and *C. limon* (48%). α-Pinene (2.03%) in *C. junos* and myrcene (2.2%) in C. *aurantium* are usually the following abundant compounds in citrus (Song et al. 2000). Other minor linear monoterpenes are linalool, nerol, and geraniol. The larger molecules in citrus EOs are sesquiterpenes, including bicyclegermacrene, caryophyllene, germacrene B and D (nine-membered ring structure), aromadendrene and spathulenol (3/5/7 ring system), and farnesene (linear carbon skeleton) (González-Mas et al. 2019; Njoroge, Ukeda, and Sawamura 1996). Sesquiterpenes make up around 2.4% of citrus EOs, with the most abundant being biyclogermacrene (0.1–81.0%), followed by farnesene (0.1–0.5%) (Sarrou et al. 2013). Caryophyllene and germacrene D dominate the rest of sesquiterpenes accounting for roughly 0.1% in *C. junos* (Njoroge, Ukeda, and Sawamura 1996). The contents of other volatile components (including α,β-phellandrene, α-terpinene, linalool, geraniol, β-citronellal, octanal, nonanal, and decanal) are typically less than 2.0% (Akdemir 2015). The pleasant aroma of citrus EOs is mediated by their components, although oxygen-free terpinenes contribute little to aroma despite their high abundance. D-limonene influences aroma because of its high concentration in citrus EOs and sweet lemon-like smell. Some oxygen-containing compounds with low content in citrus EOs, such as n-octanol, carvacrol, (+)-p-mentha-1-en-9-ol and octanal, are the main contributors to the aroma of citrus EOs (Njoroge, Ukeda, and Sawamura 1996; Li et al. 2016; Sun et al. 2014). As secondary metabolites of citrus, most citrus EO components have insecticidal and antibacterial effects, which are useful for the plant (Li et al. 2017; Mora et al. 2013). For human, they also show various functional properties. Monoterpenoids, such as d-limonene, carvone, CAR, POH, and geraniol, can alleviate the carcinogenesis of exogenous substance, whereas carvone, geraniol, linalool, and citral exhibit antimicrobial ability (Garzoli et al. 2019; Stević et al. 2014; Togashi et al. 2007). D-limonene, the major citrus EO component, shows antidepressant-like effect probably through influencing neuroendocrine, neurotrophic, and monoaminergic systems (Vieira et al. 2018).

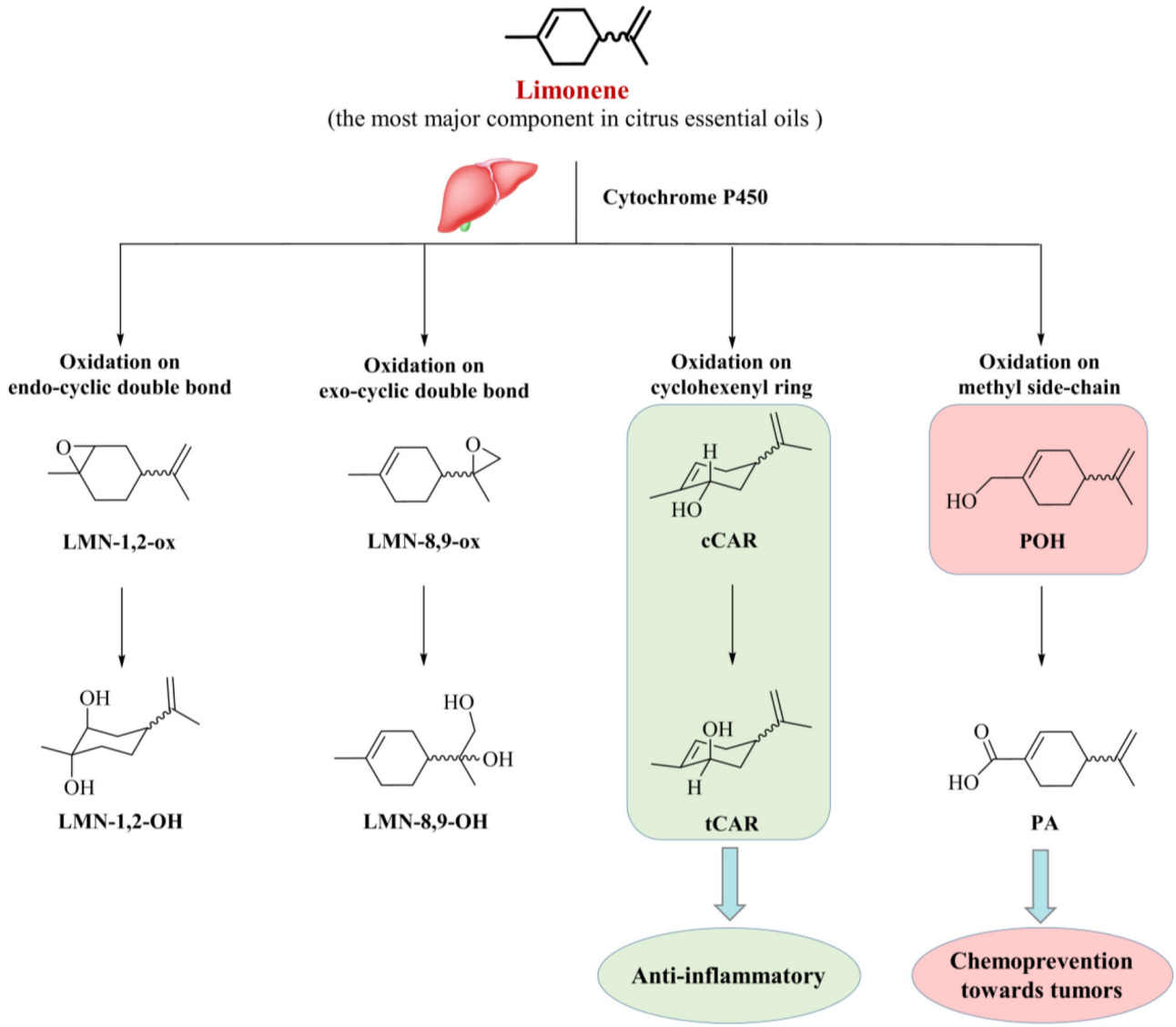


Figure 4. Metabolic pathway of limonene (the most major component in citrus essential oils) in the liver.

Biotransformation of citrus EOs

The bioavailability of citrus EOs is altered by their biotransformation. However, information regarding their bioavailability is still scarce and unclear. Most studies have focused on the metabolic fate of the crucial components of citrus EOs. Limonene makes up a large proportion of most citrus EOs, and the metabolic fate of limonene can reflect that of citrus EOs to some extent (Crowell et al. 1994). Limonene can be absorbed through the skin penetration, inhalation, and oral intake, similar to other terpenoids (Zárybnický et al. 2018). However, moderate amount is recommended due to irritation effect on the mucous membrane and skin (Hamada et al. 2002). The biotransformation of limonene following oral administration has been investigated extensively. Limonene biotransformation in rats is similar to humans in terms of the metabolites and time course (Crowell et al. 1992). A method based on a radioactive substance elucidated the absorption, distribution and excretion of d-limonene in rats (Igimi et al. 1974). After oral administration of labeled d-limonene at a dose of 800 mg/kg, little radioactivity was detected in the large intestine, indicating the absorption before this organ. Blood radioactivity peaked within 2 h, demonstrating rapid absorption of d-limonene. At 1.0 h after oral intake, the d-limonene concentration in the liver peaked at 45.1 dpm (disintegrations per minute)/mg. After a further 1 h, the d-limonene concentration in the adrenal gland and kidney peaked at 77.3 and 21.8 dpm/mg, respectively (Igimi et al. 1974). Liver CYPs play an important role in the bioconversion of limonene by oxidizing it to a variety of products, such as limonene-8,9-diol (LMN-8,9-OH), limonene-1,2-diol (LMN-1,2-OH), perillic acid (PA), perillyl alcohol (POH), and cis- and trans-CAR isomers. POH is an important intermediate for the production of PA, LMN-8,9-OH, and LMN-1,2-OH (Zhang et al. 1999). Limonene enantiomers are catalyzed by CYP2C11 and CYP2B1 to CAR and POH in rats, while oxidized at 6- and 7-positions by CYP2C9 and CYP2C19 in human liver microsome (Miyazawa, Shindo, and Shimada 2002). Limonene biotransformation in humans occurs via four pathways: dihydroxylation of endo- and exo-cyclic double bonds, oxidation of methyl side chain, and allylic oxidation

of C6-cyclus (Schmidt and Göen 2017). Among them, the oxidation of exo-cyclic double bond is prominent, producing LMN-8,9-OH as the main metabolite. In addition, POH, PA, LMN-1,2-OH and CAR isomers are generated by the three other pathways (Schmidt and Göen 2017). Concentrations of the major metabolites of limonene inhaled by children exposed to air in a day care center were as follows: LMN-8,9-OH (0.10 mg/L), LMN-1,2-OH (49 μg/L), PA (2.9 μg/L), POH (5.2 μg/L), and CAR isomers (9.3 μg/L). However, the concentration of limonene in the air was only 2.6 μg/m^3, which suggests that the limonene detected in children originated from other sources (Schmidt, Belov, et al. 2015; Schmidt, Belov, and Göen 2015). Percutaneous absorption of limonene is widely applied and studied with few side effects, and has low cutaneous irritancy and reversible effect on lipids of stratum corneum (Krishnaiah, Satyanarayana, and Bhaskar 2002). Limonene and its metabolites are excreted in urine, feces, and breath after oral intake, and up to 60% are excreted in urine. The biotransformation of limonene is rapid, and both limonene and its metabolites become undetectable within 24 h (Igimi et al. 1974). Other components of citrus EOs also undergo biotransformation. For example, α-pinene, the second most common component in most citrus fruits, is transformed to myrtenol and cis- and trans-verbenol after oral administration (Schmidt and Göen 2017). Carene is bioconverted into caren-10-ol, caren-10-carboxylic acid, and caren-3,4-diol (Schmidt, Belov, and Göen 2015).

Health-promoting effects of citrus EO biotransformation

The health effects of citrus EOs are altered by biotransformation of their components (Crowell et al. 1994; Schmidt and Göen 2017). Herein, we take the main component of citrus EOs, limonene, as an example for further discussion. After the biotransformation, the functional metabolites have taken its role in exerting the health-promoting effects. POH is the most extensively investigated metabolite of limonene since it has been discovered. It significantly reduces the incidence and diversity of colonic invasive adenocarcinoma in rats injected with carcinogen methoxymethane (AOM). Moreover, POH has a greater chemopreventive effect on malignant cancers than limonene (Chen, Fonseca, et al. 2015). Several hypotheses have been proposed to explain the chemopreventive mechanisms of monoterpene, such as G1block, induction of apoptosis, aggravation of endoplasmic reticulum stress and alteration in mevalonate metabolism. Among them, blocking the modification of Ras oncoproteins is thought to be the main mechanism of the chemopreventive effects of POH. POH may inhibit farnesyl-protein transferase (FPTase) and geranylgeranylprotein transferases (GGPTases), interfering modification of Ras oncoproteins, single-unit GTPases of molecular weight. However, more recent researches do not support this hypothesis, leaving a big gap in chemoprevention mechanism of monoterpenes to be bridged (Chen, Fonseca, et al. 2015). Another two metabolites of limonene, cis- and trans-CAR, are reported to have significant anti-inflammatory activity via suppressing superoxide and nitric oxide generation, and the NF-κB signaling pathway (Marques et al. 2019). Metabolites of other components in citrus EOs may also have effects health effects. For example, the transformation of α-pinene to myrtenol and cis- and trans-verbenol after orally administrated could endow citrus EOs with enhanced gastroprotective and anti-ischemic effects (Schmidt and Göen 2017). All these researches demonstrate the great significance of limonene biotransformation for its in vivo health effects.

Others

In addition to flavonoids, DFs and EOs, there are also several other important functional components in citrus, such as synephrines, limonoids and carotenoids, which are protoalkaloids, triterpenoids and isoprenoids, respectively. Although at lower content in citrus compared with flavonoids, DFs and EOs, they also exhibit extensive bioactivities, and are widely used to maintain human health. Various studies have shown that these compounds undergo extensive biotransformation after oral intake, which significantly affects the in vivo health-promoting effects.

Synephrines

Synephrines are widely distributed in immature fruits (peels and pulps) of bitter orange and sweet orange, and the content in peels are usually much higher than that in pulps (Pellati, Benvenuti, and Melegari 2005). The content in bitter orange and sweet orange peels are about 0.1–0.3% and 0.001–0.003% (D.W.), respectively (Mattoli et al. 2005). Chemically, synephrines belongs to protoalkaloids, which possesses a phenethylamine skeleton with an alcoholic hydroxyl group, a phenolic hydroxyl group and an N-methylated amino group. On the basis of their chemical structure, synephrines can be categorized into three different isoforms: *p*-synephrine, *m*-synephrine and *o*-synephrine, for which the hydroxyl (–OH) group is at the para-, meta- and ortho-position of phenyl ethylamine, respectively (Stohs, Preuss, and Shara 2012). *p*-Synephrine is the most common and studied one (Stohs, Preuss, and Shara 2012). It comprises about 90% or more of the total protoalkaloids of bitter orange, which has long been used as traditional medicine for the treatment of heartburn, constipation and indigestion problems (Stohs 2017). Recently, *p*-synephrine has been proved to exhibit various health-promoting effects, such as antioxidant activity (Gutiérrez-Hellín and Del Coso 2018), cardiovascular effects (Penzak et al. 2001; Stohs, Preuss, and Shara 2012), anti-adipogenic activity (Guo et al. 2019), and regulating carbohydrate metabolism and ATP levels in the liver (Maldonado et al. 2018).

Early studies about the pharmacokinetics and metabolism of ^{3}H-synephrine demonstrate the total radioactivity in urine is comparable between oral and intravenous administration, proving complete enteric absorption of synephrines. However, synephrines still exhibit low oral bioavailability, which is contributed to their extensive in vivo biotransformation (Ibrahim et al. 1983). Four metabolites of *m*-synephrine after oral

administration to human were detected in urine, which were 3-hydroxymandelic acid, 3-hydroxyphenylglycol sulfate, phenylephrine 3-*O*-sulfate, and phenylephrine 3-*O*-*β*-D-glucuronide (Ibrahim et al. 1983). Later studies demonstrate the rapid hepatic biotransformation of *p*-synephrine after oral intake, and two hepatic-derived metabolites, *p*-hydroxy-mandelic acid and *p*-hydroxyphenylglycol, were identified (Da Silva-Pereira et al. 2016). Multiple studies have confirmed that intestinal SULT1A3 catalyzes the sulfation of phenylephrine (Bairam et al. 2019). Therefore, orally administrated synephrines are readily absorbed by the small intestine, in which partial phase I and phase II metabolites are produced. Synephrines and their intestinal metabolites are transferred to the liver to be further metabolized. Considering that only limited unchanged synephrines are detected, the wide health-promoting effects of synephrines might be contributed to their metabolites, and further studies are warranted.

Limonoids

Citrus limonoids, a family of highly oxygenated triterpenoid derivatives, mainly in tricyclic or tetracyclic, widely exist in multiple citrus species (Fan et al. 2019). More than 50 limonoid components have been identified from citrus, including aglycones and glucosides derivatives (mainly *β*-D-glucosides). The former, represented by limonin and nomilin, are responsible for the bitter taste, and mostly exist in seeds and peels, while the latter with agreeable taste are produced during maturation of fruits (Sun et al. 2005). The content of limonoid glycosides in citrus fruits and juice are 0.03%, on average, with 56% of limonin glucoside in juice and more than 0.2% (F.W., fresh weight) in citrus byproducts (Arbona, Iglesias, and Gomez-Cadenas 2015). These compounds possess various potent biological activities including antioxidant (Hamdan et al. 2011), anti-inflammatory (Kelley et al. 2015), anti-cancer (Kelley et al. 2015; Jayaprakasha et al. 2010), antibacterial (Vikram et al. 2011), and antiviral activity (Tundis, Loizzo, and Menichini 2014).

Similar to flavonoid glycosides, limonoid glycosides also need to be hydroxylated to aglycone before absorption (Manners et al. 2003). Upon released, aglycones are absorbed through diffusion in the whole intestine segment (Gu et al. 2019). However, the absorption and bioavailability of limonoid aglycones are very low, and only small amount of them enter the blood due to their low permeability as a result of the participation of P-glycoprotein efflux and their poor solubility (Fan et al. 2019; Manners et al. 2003). After absorbed and transported to the liver, various phase I metabolisms other than phase II metabolism take place. The major metabolic pathway is reduction of the carbonyls at C-7 and C-16, hydroxylation, hydrogenation, hydrolysis of lactone, and glycination of reduced limonoids. CYP3A4 and CYP2D6 are found to contribute to the glycination and isomerization of limonoids (Liu et al. 2017, 2018). Notably, the gut microbiota exhibit wider biotransformation of limonin, including carbonyl reduction, hydrolysis, oxidation and decomposition of the epoxy and furan groups (Liu et al. 2017). Limonin is distributed in the duodenum, small intestine, and rectum in rats, among which the concentration in the small intestine is the highest (Fan et al. 2019). It is distributed in the whole gastrointestinal tract in both the digesta and mucosa in mouse, with the concentration in the digesta increasing from the small intestine to the colon. Generally, both digesta and mucosa of the cecum and colon contain higher concentration of limonin, possibly due to the effects of the gut microbiota. In addition, the limonin concentration in other organs including the liver, serum, heart, spleen, lung, kidney and brain are significantly lower than that in the digestive tract. Among them, the concentration in the spleen is the highest (Gu et al. 2019). Limonin is finally excreted in urine and feces in the form of prototype and metabolites (mainly phase I metabolites), and feces is the major excretion way (Fan et al. 2019). Remarkably, the in vivo metabolism of limonoids dramatically varies depending on the animal species, age, gender, lifestyle, and health status. More detail research is urgent to be investigated.

Carotenoids

Citrus carotenoids are a class of C40 isoprenoids, categorized into carotene (hydrocarbonated carotenoids) and xanthophyll containing one or more oxygens (Von Lintig 2010). Approximately 115 carotenoids have been identified in citrus species, including both carotene (α-carotene, *β*-carotene and lycopene) and xanthophyll (*β*-cryptoxanthin, lutein, zeaxanthin and violaxanthin) (Ikoma, Matsumoto, and Kato 2016). They are responsible for the yellow, orange and red color of citrus fruits (Ikoma, Matsumoto, and Kato 2016). During the mutation of citrus fruits, the accumulation of carotenoids are changed from *β*,*ε*-carotenoid (α-carotene and lutein) to *β*,*β*-carotenoid (*β*-carotene, *β*-cryptoxanthin, zeaxanthin, and violaxanthin) in fruit peels of satsuma mandarin, 'Valencia' sweet orange and 'Lisbon' lemon (Kato et al. 2004). Carotenoids are mostly identified in fruit peels and pulps with total amount of 0.0025%—0.03% and 0.001-0.004% (F.W.), respectively (Akyildiz and Ağçam 2014). In addition to the physiological effects in citrus plants, carotenoids have attracted wide attention due to the excellent health-promoting effects, including antioxidant activity (Racchi 2013), cancer chemoprevention (Tanaka et al. 2012), regulation of bone metabolism and osteoporosis (Sugiura et al. 2012), and reducing the risk of liver dysfunction (Sugiura et al. 2005) and metabolic syndrome (Sugiura et al. 2008).

After oral intake, carotenoids are absorbed into intestine via two mechanisms. One is facilitative transport at low oral dose with the assistance of enzymes, such as scavenger receptor class B type 1 (SR-B1), cluster determinant 36, and an epithelia transporter (Borel et al. 2013). The other is passive diffusion at high oral dose (Burri, La Frano, and Zhu 2016; Burri and Clifford 2004). The absorption of carotenoids varies according to the food matrix, the presence of other food components (e.g. fat), animal species and host health status (Maiani et al. 2009; Qian et al. 2012; Roman, Burri, and Singh 2012; Von Lintig 2010; Xia, McClements, and Xiao 2017). Unlike most animals, carotenoids in food matrix are usually fully absorbed by humans (Maiani et al.

Table 1. The composition, biotransformation and corresponding biological significance of citrus functional components (D.W., dry weight; F.W., fresh weight; PMFs, polymethoxyflavones; IDF, insoluble dietary fiber; SDF, soluble dietary fiber).

Components	Content	Classification	Chemical structure	Health effects	Absorption	Biotransformation	Corresponding biological significance
Flavonoids	0.7 – 2.0% (D.W., citrus peels)	Flavanones (glycosides and aglycones)	2,3-Dihydroflavone skeleton with multiple hydroxyl groups	Antioxidant, anti-inflammation, anti-cancer, anti-atherosclerotic, antihypertensive, and vasoprotective effects	1. Less than 30% absorbed in small intestine 2. More than 70% entering into colon	1. Acetylation, hydrogenation, methylation, dehydrogenation, and hydroxylation 2. Glucuronidation and sulfation 3. Hydrolysis and degradation by gut microbiota	1. Altering health effects 2. Improving solubility and facilitating excretion 3. Promoting absorption and exhibit health effects
		PMFs	Benzene-pyrone skeleton with two or more methoxyl groups	Anti-cancer, anti-inflammation, antioxidant, regulating metabolic diseases, and neuroprotective effects	Absorbed in small intestine or entering into colon	1. Demethylation by P450 2. Glucuronidation and sulfation 3. Demethylation and hydrolysis by gut microbiota	1. Improving bioactivities 2. Improving solubility and facilitating excretion 3. Improving bioactivities and re-absorption
Dietary fibers	6.3 – 78.8% (D.W., citrus peels)	SDF (Pectin)	Heterogeneous polysaccharides with HG, RG-I and RG-II regions	Preventing doxorubicin-induced ileitis, regulating lipid metabolism and glycemic level	—	Fermented by gut microbiota	1. Providing energy for gut microbiota and the host body 2. Regulating gut microbiota, alleviating nonalcoholic fatty liver, and ameliorating intestinal inflammation
		IDF (Cellulose hemicellulose)	Unbranched for cellulose or branched for hemicellulose linear chain with β-(1→4) glucosidic linkages	Absorption of bile acid, cholesterol, and metal ions, stimulating intestinal peristalsis	—	—	—
Essential oils	0.2 – 1.7% (F.W., citrus peels)	1. Terpenes: isoprenes 2. Oxygenated terpenes	Monoterpenes, sesquiterpenes, and oxygen-containing derivatives	Insecticidal, antimicrobial, antidepressant, and chemoprevention effects for cancer	Skin penetration, inhalation, and oral intake	Oxidation	1. POH: chemoprevention ability to malignant cancers 2. cis- and trans-CAR: anti-inflammatory activity
Synephrines	0.1 – 0.3% (D.W., bitter orange peels)	*p*-Synephrine, m-synephrine, *o*-synephrine	Phenethylamine skeleton with an alcoholic OH, a phenolic OH and N-methylated amino	Antioxidant, weight loss, cardiovascular effects, anti-adipogenic activity, and regulating carbohydrate metabolism	Complete enteric absorption	1. Hydroxylation and dihydroxylation 2. Glucuronidation and sulfation	—
Limonoids	0.2% (F.W., byproducts)	Aglycones, glucosides	Oxygenated triterpenoids	Antioxidant, anti-inflammatory, anti-cancer, antibacterial, and antiviral activity	Whole intestine segment	Reduction, hydroxylation, hydrogenation, and glycation	—

(*continued*)

Table 1. Continued.

Components	Content	Classification	Chemical structure	Health effects	Absorption	Biotransformation	Corresponding biological significance
Carotenoids	0.0025 – 0.03% (F.W., citrus peels)	Carotene, xanthophyll	C40 isoprenoids	Antioxidant, cancer chemoprevention, regulating bone metabolism and osteoporosis, and reducing the risk of liver dysfunction	Small intestine	Central cleavage, oxidation, and dehydrogenation	1. Vitamin A: precursor for essential bioactive molecules *in vivo* 2. Retinoic acid: multiple health promoting effects

2009). Among the citrus carotenoids, the absorption and bioavailability of β-cryptoxanthin are higher than the others, including α-carotene, β-carotene and lycopene (O'Connell, Ryan, and O'Brien 2007). Taking β-cryptoxanthin as an example, the absorbed carotenoids are biotransferred to retinal in enterocytes or encapsulated into chylomicrons and enter the bloodstream via the lymph (Tyssandier, Lyan, and Borel 2001). The remaining chylomicron is transported to the liver, where some β-cryptoxanthin is subsequently metabolized to retinal, retinol and retinyl esters (Thakkar et al. 2007). Notably, due to the atypical metabolism of carotenoids in humans, few animal species possess carotenoid metabolism similar to that of human (Tanumihardjo 2012). In Mongolian gerbil, most β-cryptoxanthin is stored in the liver followed by adipose tissue and blood (La Frano, Zhu, and Burri 2014), similar to other carotenoids (e.g. β-carotene, lycopene and phytoene) (Conlon et al. 2012; Maiani et al. 2009; Moran, Clinton, and Erdman 2013; Von Lintig 2010). Feces is the main excretion pathway for carotenoids. Notably, the carotenoid metabolite vitamin A (all-*trans*-retinol) is the precursor for some essential bioactive molecules in humans, including 11-*cis*-retinal and all *trans*-retinoic acid (RA). 11-*cis*-Retinal participates in phototransduction by binding to the protein moiety (opsin) of visual pigments (Palczewski 2006). Retinoic acid is crucial for a wide range of biological processes, including embryonic development, reproduction, immunity, cell differentiation, and metabolic control (Petkovich et al. 1987).

Conclusion and prospective

Citrus functional components undergo extensive biotransformation after oral intake, leaving only low quantities of parent compounds in the host body (**Table 1**). Small molecular components in the form of aglycones (flavanones, PMFs, synephrines, limonoids, and carotenoids) are mainly absorbed by small intestine, and metabolized by phase I and phase II enzymes secreted by the small intestine and liver. For glucoside components, only a fraction of them are absorbed by the small intestine after hydrolysis of brush border enzymes. Large amount of them immediately enter the colon, and are metabolized by the gut microbiota to different metabolites like phonics to affect host physiology. Citrus DFs like pectin are fermented by the gut microbiota. In addition, the gut microbiota also participates in the metabolism and re-absorption of those compounds from liver via enterohepatic circulation. In vivo biotransformation is associated with chemical structure changes that lead to altered bioactivities and pharmacokinetics in the body. These results are of special significance for the in vivo health-promoting effect mechanisms of citrus functional components, and scientific reasonable diet for public. However, (1) the detail biotransformation dramatically varies in different components depending on the chemical structures, as well as food matrix, administration dose, animal models, and physiological state of the host. More deep investigation is urgent to reveal the mechanisms of biotransformation, especially the role of gut microbiota; (2) Food is

a complex system with the composition of various components. More complex biotransformation is associated due to the interactions between different components, and synergistic health-promoting effects might be associated after simultaneously taken in; (3) Foodomics, an emerging technology based on multiple omics technologies including genomics, metabonomics and microbiomics, has significant advantages for high-throughput study of food, including compound profiling and biomarker identification for in vivo metabolomics studies of foods. Therefore, foodomics could be an enormous method for in-depth study of biotransformation and health-promoting effects of foods and their components.

Abbreviations

CAR	Carveol
CAZymes	Carbohydrate-active enzymes
CBG	Cytosolic β-glucosidases
CYP	Cytochrome P450
DFs	Dietary fibers
D.W.	Dry weight
F.W.	Fresh weight
EOs	Essential oils
PMFs	Polymethoxyflavones
GHs	Glycoside hydrolases
GPR	G protein coupled receptor
HG	Homogalacturonan
4-HPPA	3-(4-hydroxyphenyl)-propionic acid
IL	Interleukin
LPH	Lactase phloridzin hydrolase
NAFLD	Nonalcoholic fatty liver disease
NF-κB	Nuclear factor kappa-B
PA	Perillic acid
PLs	Polysaccharide lyases
POH	Perillyl alcohol
PYY	Peptide YY
RG-I	Rhamnogalacturonan I
RG-II	Rhamnogalacturonan II
SCFAs	Short-chain fatty acids
SGLT	Sodium dependent glucose cotransporter
SULTs	Sulphotransferases
UGTs	UDP-glucuronosyltransferases

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References

Akdemir, E. G. 2015. Empirical prediction and validation of antibacterial inhibitory effects of various plant essential oils on common pathogenic bacteria. *International Journal of Food Microbiology* 202: 35–41.

Akyildiz, A., and E. Ağçam. 2014. Citrus juices technology. In *Food processing: Strategies for quality assessment*, eds. A. Malik, Z. Erginkay, S. Ahmad, and H. Erten, 37–104. New York Heidelberg Dordrecht London: Springer.

Arbona, V., D. J. Iglesias, and A. Gomez-Cadenas. 2015. Non-targeted metabolite profiling of citrus juices as a tool for variety discrimination and metabolite flow analysis. *BMC Plant Biology* 15 (1):38. doi: 10.1186/s12870-015-0430-8.

Backhed, F., H. Ding, T. Wang, L. V. Hooper, G. Y. Koh, A. Nagy, C. F. Semenkovich, and J. I. Gordon. 2004. The gut microbiota as an environmental factor that regulates fat storage. *Proceedings of the National Academy of Sciences of Sciences* 101 (44):15718–23. doi: 10.1073/pnas.0407076101.

Bairam, A. F., M. I. Rasool, F. A. Alherz, M. S. Abunnaja, A. A. E. Daibani, S. A. Gohal, E. S. Alatwi, K. Kurogi, and M. C. Liu. 2019. Impact of SULT1A3/SULT1A4 genetic polymorphisms on the sulfation of phenylephrine and salbutamol by human SULT1A3 allozymes. *Pharmacogenetics and Genomics* 29:99–105.

Braune, A., and M. Blaut. 2016. Bacterial species involved in the conversion of dietary flavonoids in the human gut. *Gut Microbes* 7 (3): 216–34. doi: 10.1080/19490976.2016.1158395.

Breinholt, V. M., S. E. Rasmussen, K. Brosen, and T. H. Friedberg. 2003. *In vitro* metabolism of genistein and tangeretin by human and murine cytochrome P450s. *Pharmacology and Toxicology* 93 (1): 14–22. doi: 10.1034/j.1600-0773.2003.930102.x.

Brett, G. M., W. Hollands, P. W. Needs, B. Teucher, J. R. Dainty, B. D. Davis, J. S. Brodbelt, and P. A. Kroon. 2009. Absorption, metabolism and excretion of flavanones from single portions of orange fruit and juice and effects of anthropometric variables and contraceptive pill use on flavanone excretion. *British Journal of Nutrition* 101 (5): 664–75. doi: 10.1017/S000711450803081X.

Borel, P., L. Georg, A. Goncalves, F. Szabo de Edelenyi, S. Lecompte, P. Curtis, L. Goumidi, M. J. Caslake, E. A. Miles, C. Packard, et al. 2013. CD36 and SR-B1 are involved in cellular uptake of provitamin A carotenoids by Caco-2 and HEK cells, and some of their genetaic variants are associated with plasma concentrations of these micronutrients in humans. *The Journal of Nutrition* 143 (4):448–56. doi: 10.3945/jn.112.172734.

Buffie, C. G., V. Bucci, R. R. Stein, P. T. McKenney, L. Ling, A. Gobourne, D. No, H. Liu, M. Kinnebrew, A. Viale, et al. 2015. Precision microbiome reconstitution restores bile acid mediated resistance to Clostridium difficile. *Nature* 517 (7533):205–8. doi: 10.1038/nature13828.

Burapan, S., M. Kim, and J. Han. 2017. Demethylation of polymethoxyflavones by human gut bacterium, *Blautia* sp. MRG-PMF1. *Journal of Agricultural and Food Chemistry* 65 (8):1620–9. doi: 10.1021/acs.jafc.7b00408.

Burri, B. J., M. R. La Frano, and C. Zhu. 2016. Absorption, metabolism, and functions of β-cryptoxanthin. *Nutrition Reviews* 74 (2): 69–82. doi: 10.1093/nutrit/nuv064.

Burri, B. J., and A. J. Clifford. 2004. Carotenoid and retinoid metabolism: Insights from isotope studies. *Archives of Biochemistry and Biophysics* 430 (1):110–9. doi: 10.1016/j.abb.2004.04.028.

Canfora, E. E., R. C. R. Meex, K. Venema, and E. E. Blaak. 2019. Gut microbial metabolites in obesity, NAFLD and T2DM. *Nature Reviews Endocrinology* 15 (5):261–73. doi: 10.1038/s41574-019-0156-z.

Cassidy, A., and A. M. Minihane. 2017. The role of metabolism (and the microbiome) in defining the clinical efficacy of dietary flavonoids. *The American Journal of Clinical Nutrition* 105 (1):10–22. doi: 10.3945/ajcn.116.136051.

Chambers, E. S., A. Viardot, A. Psichas, D. J. Morrison, K. G. Murphy, S. E. K. Zac-Varghese, K. MacDougall, T. Preston, C. Tedford, G. S. Finlayson, et al. 2015. Effects of targeted delivery of propionate to the human colon on appetite regulation, body weight maintenance and adiposity in overweight adults. *Gut* 64 (11):1744–54. doi: 10.1136/gutjnl-2014-307913.

Chanet, A., D. Milenkovic, S. Claude, J. A. M. Maier, M. Kamran Khan, N. Rakotomanomana, S. Shinkaruk, A. M. Bérard, C. Bennetau-Pelissero, A. Mazur, et al. 2013. Flavanone metabolites decrease monocyte adhesion to TNF-α-activated endothelial cells by modulating expression of atherosclerosis-related genes. *British*

Journal of Nutrition 110 (4):587–98. doi: 10.1017/S0007114512005454.

Chang, P. V., L. Hao, S. Offermanns, and R. Medzhitov. 2014. The microbial metabolite butyrate regulates intestinal macrophage function via histone deacetylase inhibition. *Proceedings of the National Academy of Sciences* 111 (6):2247–52. doi: 10.1073/pnas.1322269111.

Charoensinphon, N., P. Qiu, P. Dong, J. K. Zheng, Pe Ngauv, Y. Cao, S. M. Li, C. T. Ho, and H. Xiao. 2013. Inhibitory effects of 5-hydroxylnobiletin on human non-small cell lung cancer cells. *Molecular Nutrition & Food Research* 57 (12):2103–11. doi: 10.1002/mnfr.201300136.

Chen, T. C., C. O. D. Fonseca, and A. H. Schönthal. 2015. Preclinical development and clinical use of perillyl alcohol for chemoprevention and cancer therapy. *American Journal of Cancer Research* 5:1580–93.

Chen, J. J., J. K. Zheng, E. A. Decker, D. J. McClements, and H. Xiao. 2015. Improving nutraceutical bioavailability using mixed colloidal delivery systems: Lipid nanoparticles increase tangeretin bioaccessibility and absorption from tangeretin-loaded zein nanoparticles. *RSC Advances* 5 (90):73892–900. doi: 10.1039/C5RA13503F.

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. doi: 10.2174/1389200215011402181250 20.

Conlon, L. E., R. D. King, N. E. Moran, and J. W. Erdman, Jr. 2012. Coconut oil enhances tomato carotenoid tissue accumulation compared to safflower oil in the Mongolian gerbil (*Meriones unguiculatus*). *Journal of Agricultural and Food Chemistry* 60 (34):8386–94. doi: 10.1021/jf301902k.

Crowell, P. L., C. E. Elson, H. H. Bailey, A. Elegbede, J. D. Haag, and M. N. Gould. 1994. Human metabolism of the experimental cancer therapeutic agent d-limonene. *Cancer Chemotherapy and Pharmacology* 35 (1):31–7. doi: 10.1007/BF00686281.

Crowell, P. L., S. Lin, E. Vedejs, and M. N. Gould. 1992. Identification of circulating metabolites of the antitumor agent d-limonene capable of inhibiting protein isoprenylation and cell growth. *Cancer Chemotherapy and Pharmacology* 31 (3):205–12. doi: 10.1007/BF00685549.

Cui, J. F., Y. H. Lian, C. Y. Zhao, H. J. Du, Y. H. Han, W. Gao, H. Xiao, and J. K. Zheng. 2019. Dietary fibers from fruits and vegetables and their health benefits via modulation of gut microbiota. *Comprehensive Reviews in Food Science and Food Safety* 18 (5):1514–32. doi: 10.1111/1541-4337.12489.

Da Silva-Pereira, J. F., G. A. Bubna, G. D. A. Goncalves, F. Bracht, R. M. Peralta, and A. Bracht. 2016. Fast hepatic biotransformation of *p*-synephrine and *p*-octopamine and implications for their oral intake. *Food & Function* 7 (3):1483–91. doi: 10.1039/C6FO00014B.

Dhingra, D.,. M. Michael, H. Rajput, and R. Patil. 2012. Dietary fiber in foods: A review. *Journal of Food Science and Technology* 49 (3):255–66. doi: 10.1007/s13197-011-0365-5.

Di Donna, L., D. Taverna, F. Mazzotti, H. Benabdelkamel, M. Attya, A. Napoli, and G. Sindona. 2013. Comprehensive assay of flavanones in citrus juices and beverages by UHPLC-ESI-MS/MS and derivatization chemistry. *Food Chemistry* 141 (3):2328–33. doi: 10.1016/j.foodchem.2013.05.034.

Donohoe, D. R., L. B. Collins, A. Wali, R. Bigler, W. Sun, and S. J. Bultman. 2012. The Warburg effect dictates the mechanism of butyrate-mediated histone acetylation and cell proliferation. *Molecular Cell* 48 (4):612–26. doi: 10.1016/j.molcel.2012.08.033.

Duncan, S. H., A. Barcenilla, C. S. Stewart, S. E. Pryde, and H. J. Flint. 2002. Acetate utilization and butyryl coenzyme A (CoA): Acetate-CoA transferase in butyrate-producing bacteria from the human large intestine. *Applied and Environmental Microbiology* 68 (10):5186–90. doi: 10.1128/AEM.68.10.5186-5190.2002.

Guo, S. S., X. Wu, J. K. Zheng, N. Charoensinphon, P. Dong, P. J. Qiu, M. Y. Song, Z. H. Tang, and H. Xiao. 2018. Anti-inflammatory effect of xanthomicrol, a major colonic metabolite of 5-demethyltangeretin. *Food & Function* 9 (6):3104–13. doi: 10.1039/C8FO00279G.

Duynhoven, J. V., E. E. Vaughan, D. M. Jacobs, R. A. Kemperman, E. J. J. van Velzen, G. Gross, L. C. Roger, S. Possemiers, A. K. Smilde, J. Doré, et al. 2011. Metabolic fate of polyphenols in the human superorganism. *Proceedings of the National Academy of Sciences of Sciences* 108 (Supplement_1):4531–8. doi: 10.1073/pnas.1000098107.

Fan, S., C. Zhang, T. Luo, J. Wang, Y. Tang, Z. Chen, and L. Yu. 2019. Limonin: A review of its pharmacology, toxicity, and pharmacokinetics. *Molecules* 24:3679.

Faustino, M., M. Veiga, P. Sousa, E. M. Costa, S. Silva, and M. Pintado. 2019. Agro-food byproducts as a new source of natural food additives. *Molecules* 24 (6):1056. doi: 10.3390/molecules24061056.

Frost, G., M. L. Sleeth, M. Sahuri-Arisoylu, B. Lizarbe, S. Cerdan, L. Brody, J. Anastasovska, S. Ghourab, M. Hankir, S. Zhang, et al. 2014. The short chain fatty acid acetate reduces appetite via a central homeostatic mechanism. *Nature Communications* 5 (1):3611. doi: 10.1038/ncomms4611.

Gao, Z., W. Gao, S. L. Zeng, P. Li, and E. H. Liu. 2018. Chemical structures, bioactivities and molecular mechanisms of citrus polymethoxyflavones. *Journal of Functional Foods* 40:498–509. doi: 10.1016/j.jff.2017.11.036.

Garzoli, S., G. Turchetti, P. Giacomello, A. Tiezzi, V. L. Masci, and E. Ovidi. 2019. Liquid and vapour phase of lavandin (*Lavandula* × *intermedia*) essential oil: Chemical composition and antimicrobial activity. *Molecules* 24 (15):2701. doi: 10.3390/molecules24152701.

González-Mas, M. C., J. L. Rambla, M. P. López-Gresa, M. A. Blázquez, and A. Granell. 2019. Volatile compounds in citrus essential oils: A comprehensive review. *Frontiers in Plant Science* 10. Advance online publication. doi: 10.3389/fpls.2019.00012.

Goulas, V., and G. Manganaris. 2012. Exploring the phytochemical content and the antioxidant potential of citrus fruits grown in Cyprus. *Food Chemistry* 131 (1):39–47. doi: 10.1016/j.foodchem.2011.08.007.

Grabitske, H. A., and L. L. Slavin. 2008. Low-digestible carbohydrates in practice. *Journal of the American Dietetic Association* 108 (10):1677–81. doi: 10.1016/j.jada.2008.07.010.

Gu, M., J. Sun, C. Qi, X. K. Cai, T. Goulette, M. Y. Song, X. M. You, D. A. Sela, and H. Xiao. 2019. The gastrointestinal fate of limonin and its effect on gut microbiota in mice. *Food & Function* 10 (9):5521–30. doi: 10.1039/C9FO01274E.

Guo, L. X., G. Chen, Z. Y. Yin, Y. H. Zhang, and X. X. Zheng. 2019. *p*-Synephrine exhibits anti-adipogenic activity by activating the Akt/GSK3*β* signaling pathway in 3T3-L1 adipocytes. *Journal of Food Biochemistry* 43 (11):e13033. doi: 10.1111/jfbc.13033.

Gutiérrez-Hellín, J., and J. Del Coso. 2018. Dose–response effects of *p*-synephrine on fat oxidation rate during exercise of increasing intensity. *Phytotherapy Research* 32 (2):370–4. doi: 10.1002/ptr.5937.

Hamada, M., K. Uezu, J. Matsushita, S. Yamamoto, and Y. Kishino. 2002. Distribution and immune responses resulting from oral administration of D-limonene in rats. *Journal of Nutritional Science and Vitaminology* 48 (2):155–60. doi: 10.3177/jnsv.48.155.

Hamdan, D., M. Z. El-Readi, A. Tahrani, F. Herrmann, D. Kaufmann, N. Farrag, A. El-Shazly, and M. Wink. 2011. Chemical composition and biological activity of *Citrus jambhiri* Lush. *Food Chemistry* 127 (2):394–403. doi: 10.1016/j.foodchem.2010.12.129.

Huber, S., N. Gagliani, E. Esplugues, W. O'Connor, F. J. Huber, A. Chaudhry, M. Kamanaka, Y. Kobayashi, C. J. Booth, A. Y. Rudensky, et al. 2011. Th17 cells express interleukin-10 receptor and are controlled by $Foxp3^{-}$ and $Foxp3^{+}$ regulatory $CD4^{+}$ T cells in an interleukin-10-dependent manner. *Immunity* 34 (4):554–65. doi: 10.1016/j.immuni.2011.01.020.

Hung, W. L., W. S. Chang, W. C. Lu, G. J. Wei, Y. Wang, C. T. Ho, and L. S. Hwang. 2018. Pharmacokinetics, bioavailability, tissue distribution and excretion of tangeretin in rat. *Journal of Food and Drug Analysis* 26 (2):849–57. doi: 10.1016/j.jfda.2017.08.003.

Ibrahim, K. E., J. M. Midgley, J. R. Crowley, and C. M. Williams. 1983. The mammalian metabolism of R-(−)-*m*-synephrine. *The* Journal of Pharmacy and Pharmacology 35 (3):144–7. doi: 10.1111/j.2042-7158.1983.tb04293.x.

Igimi, H., M. Nishimura, R. Kodama, and H. Ide. 1974. Studies on the metabolism of d-limonene (p-mentha-1,8-diene) I. The absorption, distribution and excretion of d -limonene in rats. *Xenobiotica* 4:77–84. doi: 10.3109/00498257409049347.

Ikoma, Y., H. Matsumoto, and M. Kato. 2016. Diversity in the carotenoid profiles and the expression of genes related to carotenoid accumulation among citrus genotypes. *Breeding Science* 66 (1):139–47. doi: 10.1270/jsbbs.66.139.

Jaeger, B. N., S. L. Parylak, and F. H. Gage. 2018. Mechanisms of dietary flavonoid action in neuronal function and neuroinflammation. *Molecular Aspects of Medicine* 61:50–62. doi: 10.1016/j.mam.2017.11.003.

Jayaprakasha, G. K., Y. Jadegoud, G. Nagana, and B. S. Patil. 2010. Bioactive compounds from sour orange inhibit colon cancer cell proliferation and induce cell cycle arrest. *Journal of Agricultural and Food Chemistry* 58 (1):180–6. doi: 10.1021/jf9027816.

Kaiko, G. E., S. H. Ryu, O. I. Koues, P. L. Collins, L. Solnica-Krezel, E. J. Pearce, E. L. Pearce, E. M. Oltz, and T. S. Stappenbeck. 2016. The colonic crypt protects stem cells from microbiota-derived metabolites. *Cell* 165 (7):1708–20. doi: 10.1016/j.cell.2016.05.018.

Kamada, N., S. U. Seo, G. Y. Chen, and G. Núñez. 2013. Role of the gut microbiota in immunity and inflammatory disease. *Nature Reviews Immunology* 13 (5):321–35. doi: 10.1038/nri3430.

Kaoutari, E. A., F. Armougom, J. I. Gordon, D. Raoult, and B. Henrissat. 2013. The abundance and variety of carbohydrate-active enzymes in the human gut microbiota. *Nature Reviews Microbiology* 11 (7):497–504. doi: 10.1038/nrmicro3050.

Kato, M., Y. Ikoma, H. Matsumoto, M. Sugiura, H. Hyodo, and M. Yano. 2004. Accumulation of carotenoids and expression of carotenoid biosynthetic genes during maturation in citrus fruit. *Plant Physiology* 134 (2):824–37. doi: 10.1104/pp.103.031104.

Kelley, D. S., Y. C. Adkins, S. J. Zunino, L. R. Woodhouse, E. L. Bonnel, A. P. Breksa, G. D. Manners, and B. E. Mackey. 2015. Citrus limonin glucoside supplementation decreased biomarkers of liver disease and inflammation in overweight human adults. *Journal of Functional Foods* 12:271–81. doi: 10.1016/j.jff.2014.11.026.

Kim, M., N. Kim, and J. Han. 2014. Metabolism of kaempferia parviflora polymethoxyflavones by human intestinal bacterium *Bautia* sp. MRGPMF1. *Journal of Agricultural and Food Chemistry* 62 (51): 12377–83. – doi: 10.1021/jf504074n.

Koga, N., M. Matsuo, C. Ohta, K. Haraguchi, M. Matsuoka, Y. Kato, T. Ishii, M. Yano, and H. Ohta. 2007. Comparative study on nobiletin metabolism with liver microsomes from rats, Guinea pigs and hamsters and rat cytochrome P450. *Biological & Pharmaceutical Bulletin* 30 (12):2317–23. doi: 10.1248/bpb.30.2317.

Koga, N., C. Ohta, Y. Kato, K. Haraguchi, T. Endo, K. Ogawa, H. Ohta, and M. Yano. 2011. *In vitro* metabolism of nobiletin, a polymethoxy-flavonoid, by human liver microsomes and cytochrome P450. *Xenobiotica* 41 (11):927–33. doi: 10.3109/00498254.2011.593208.

Koh, A., F. De Vadder, P. Kovatcheva-Datchary, and F. Bäckhed. 2016. From dietary fiber to host physiology: Short-chain fatty acids as key bacterial metabolites. *Cell* 165 (6):1332–45. doi: 10.1016/j.cell.2016.05.041.

Koppel, N., V. M. Rekdal, and E. P. Balskus. 2017. Chemical transformation of xenobiotics by the human gut microbiota. *Science* 356 (6344):eaag2770–1257. doi: 10.1126/science.aag2770.

Koropatkin, N. M., E. A. Cameron, and E. C. Martens. 2012. How glycan metabolism shapes the human gut microbiota. *Nature Reviews Microbiology* 10 (5):323–35. doi: 10.1038/nrmicro2746.

Krishnaiah, Y. S. R., V. Satyanarayana, and P. Bhaskar. 2002. Influence of limonene on the bioavailability of nicardipine hydrochloride from membrane-moderated transdermal therapeutic systems in human volunteers. *International Journal of Pharmaceutics* 247 (1-2):91–102. doi: 10.1016/S0378-5173(02)00401-5.

La Frano, M. R., Zhu, C. C., and B. J. Burri. 2014. Assessment of tissue distribution and concentration of β-cryptoxanthin in response to varying amounts of dietary β-cryptoxanthin in the Mongolian gerbil. *British Journal of Nutrition* 111 (6):968–78. doi: 10.1017/S0007114513003371.

Larsbrink, J., T. E. Rogers, G. R. Hemsworth, L. S. McKee, A. S. Tauzin, O. Spadiut, S. Klinter, N. A. Pudlo, K. Urs, N. M. Koropatkin, et al. 2014. A discrete genetic locus confers xyloglucan metabolism in select human gut Bacteroidetes. *Nature* 506 (7489): 498–502. doi: 10.1038/nature12907.

Li, L. J., P. Hong, F. Chen, H. Sun, Y. F. Yang, X. Yu, G. L. Huang, L. M. Wu, and H. Ni. 2016. Characterization of the aldehydes and their transformations induced by UV irradiation and air exposure of white guanxi honey pummelo (*Citrus grandis* (L.) Osbeck) essential oil. *Journal of Agricultural and Food Chemistry* 64 (24):5000–10. doi: 10.1021/acs.jafc.6b01369.

Li, S., C. Y. Lo, and C. T. Ho. 2006. Hydroxylated polymethoxyflavones and methylated flavonoids in sweet orange (*Citrus sinensis*) peel. *Journal of Agricultural and Food Chemistry* 54 (12):4176–85. doi: 10.1021/jf060234n.

Li, S., S. Sang, M. H. Pan, C. S. Lai, C. Y. Lo, C. S. Yang, and C. T. Ho. 2007. Anti-inflammatory property of the urinary metabolites of nobiletin in mouse. *Bioorganic & Medicinal Chemistry Letters* 17 (18):5177–81. doi: 10.1016/j.bmcl.2007.06.096.

Li, S., M.-H. Pan, C.-Y. Lo, D. Tan, Y. Wang, F. Shahidi, and C.-T. Ho. 2009. Chemistry and health effects of polymethoxyflavones and hydroxylated polymethoxyflavones. *Journal of Functional Foods* 1 (1):2–12. doi: 10.1016/j.jff.2008.09.003.

Li, S., H. Wang, L. Guo, H. Zhao, and C. Ho. 2014. Chemistry and bioactivity of nobiletin and its metabolites. *Journal of Functional Foods* 6:2–10. doi: 10.1016/j.jff.2013.12.011.

Li, S., Z. Wang, S. Sang, M. T. Huang, and C. T. Ho. 2006. Identification of nobiletin metabolites in mouse urine. *Molecular Nutrition & Food Research* 50 (3):291–9. doi: 10.1002/mnfr.200500214.

Li, Z. Q., S. Zhang, X. M. Cai, J. Y. Luo, S. L. Dong, J. J. Cui, and Z. M. Chen. 2017. Three odorant binding proteins may regulate the behavioural response of *Chrysopa pallens* to plant volatiles and the aphid alarm pheromone (E)-β-farnesene. *Insect Molecular Biology* 26 (3):255–65. doi: 10.1111/imb.12295.

Li, W., K. Zhang, and H. Yang. 2018. Pectin alleviates high fat (lard) diet-induced nonalcoholic fatty liver disease in mice: Possible role of short-chain fatty acids and gut microbiota regulated by pectin. *Journal of Agricultural and Food Chemistry* 66 (30):8015–25. doi: 10.1021/acs.jafc.8b02979.

Liu, S. J., G. L. Dai, L. N. Sun, B. T. Sun, D. Chen, L. Zhu, Y. Wang, L. Zhang, P. D. Chen, D. Zhou, et al. 2018. Biotransformation and metabolic profile of limonin in rat liver microsomes, bile, and urine by high-performance liquid chromatography coupled with quadrupole time-of-flight mass apectrometry. *Journal of Agricultural and Food Chemistry* 66 (40):10388–93. doi: 10.1021/acs.jafc.8b02057.

Liu, S., D. Chen, N. Zhang, L. Sun, G. Dai, L. Zhu, C. Li, Y. Zhao, L. Zhang, H. Fu, et al. 2017. Comprehensive characterization of the *in vitro* and *in vivo* metabolites of limonin in human samples using LC-Q-TOF/MS. *Journal of Chromatography B* 1068-1069:226–32. doi: 10.1016/j.jchromb.2017.10.035.

Liu, M., W. Zou, C. Yang, W. Peng, and W. Su. 2012. Metabolism and excretion studies of oral administered naringin, a putative antitussive, in rats and dogs. *Biopharmaceutics & Drug Disposition* 33 (3): 123–34. doi: 10.1002/bdd.1775.

Lo, Y. H., M. H. Pan, S. M. Li, J. H. Yen, M. C. Kou, C. T. Ho, and M. J. Wu. 2010. Nobiletin metabolite, 3′,4′-dihydroxy-5,6,7,8-tetramethoxyflvone, inhibits LDL oxidation and down-regulates scavenger receptor expression and activity in THP-1 cells. *Biochimica et Biophysica Acta (Bba) - Molecular and Cell Biology of Lipids* 1801 (2):114–26. doi: 10.1016/j.bbalip.2009.10.002.

Lombard, V., T. Bernard, C. Rancurel, H. Brumer, P. M. Coutinho, and B. Henrissat. 2010. A hierarchical classification of polysaccharide lyases for glycogenomics. *Biochemical Journal* 432 (3):437–44. doi: 10.1042/BJ20101185.

Louis, P., G. L. Hold, and H. J. Flint. 2014. The gut microbiota, bacterial metabolites and colorectal cancer. *Nature Reviews Microbiology* 12 (10):661–72. doi: 10.1038/nrmicro3344.

Lv, X., S. Zhao, Z. Ning, H. Zeng, Y. Shu, O. Tao, C. Xiao, C. Lu, and Y. Liu. 2015. Citrus fruits as a treasure trove of active natural metabolites that potentially provide benefits for human health. *Chemistry Central Journal* 9 (1):1–14. doi: 10.1186/s13065-015-0145-9.

Maldonado, M. R., L. Bracht, A. B. de Sá-Nakanishi, R. Corrêa, J. F. Comar, R. M. Peralta, and A. Bracht. 2018. Actions of *p*-synephrine on hepatic enzyme activities linked to carbohydrate metabolism and ATP levels *in vivo* and in the perfused rat liver. *Cell Biochemistry and Function* 36 (1):4–12. doi: 10.1002/cbf.3311.

Maiani, G., M. J. Periago Castón, G. Catasta, E. Toti, I. G. Cambrodón, A. Bysted, F. Granado-Lorencio, B. Olmedilla-Alonso, P. Knuthsen, M. Valoti, et al. 2009. Carotenoids: actual knowledge on food sources, intakes, stability and bioavailability and their protective role in humans. *Molecular Nutrition & Food Research* 53 (S2):S194–S218. doi: 10.1002/mnfr.200800053.

Manners, G. D., R. A. Jacob, A. P. Breksa, T. K. Schoch, and S. Hasegawa. 2003. Bioavailability of citrus limonoids in humans. *Journal of Agricultural and Food Chemistry* 51:4156−−61. doi: 10.1021/jf0300691.

Mannucci, C., M. Navarra, F. Calapai, R. Squeri, S. Gangemi, and G Calapai. 2017. Clinical Pharmacology of Citrus bergamia: A Systematic Review. *Phytotherapy Research* 31(1):27–39. doi: 10.1002/ptr.5734.

Manthey, J. A., T. B. Cesar, E. Jackson, and S. Mertens-Talcott. 2011. Pharmacokinetic study of nobiletin and tangeretin in rat serum by high-performance liquid chromatography-electrospray ionization-mass. *Journal of Agricultural and Food Chemistry* 59 (1):145–51. doi: 10.1021/jf1033224.

Mária, J., and Ž. Ingrid. 2017. Effects of bioactive compounds on senescence and components of senescence associated secretory phenotypes in vitro. *Food & Function* 8:2394–2418. doi: 10.1039/c7fo00161d.

Marques, F. M., M. M. Figueira, E. F. P. Schmitt, T. P. Kondratyuk, D. C. Endringer, R. Scherer, and M. Fronza. 2019. *In vitro* anti-inflammatory activity of terpenes via suppression of superoxide and nitric oxide generation and the NF-κB signaling pathway. *Inflammopharmacology* 27 (2):281–9. doi: 10.1007/s10787-018-0483-z.

Mattoli, L., F. Cangi, A. Maidecchi, C. Ghiara, M. Tubaro, and P. Traldi. 2005. A rapid liquid chromatography electrospray ionizaton mass spectrometry^{n} method for evaluation of synephrine in *Citrus aurantium* L. samples. *Journal of Agricultural and Food Chemistry* 53 (26):9860–6. doi: 10.1021/jf051270+.

M'hiri, N., I. Ioannou, M. Ghoul, and N. Mihoubi Boudhrioua. 2017. Phytochemical characteristics of citrus peel and effect of conventional and nonconventional processing on phenolic compounds: A review. *Food Reviews International* 33 (6):587–619. doi: 10.1080/87559129.2016.1196489.

McClements, D. J., and H. Xiao. 2017. Designing food structure and composition to enhance nutraceutical bioactivity to support cancer inhibition. *Seminars In Cancer Biology* 46:215–226. doi: 10.1016/j.semcancer.2017.06.003.

Miyazawa, M.,. M. Shindo, and T. Shimada. 2002. Metabolism of (+)- and (−)-limonenes to respective carveols and perillyl alcohols by CYP2C9 and CYP2C19 in human liver microsomes. *Drug Metabolism and Disposition* 30 (5):602–7. doi: 10.1124/dmd.30.5.602.

Moon, C., M. T. Baldridge, M. A. Wallace, C. D. Burnham, H. W. Virgin, and T. S. Stappenbeck. 2015. Vertically transmitted faecal IgA levels determine extra-chromosomal phenotypic variation. *Nature* 521 (7550):90–3. doi: 10.1038/nature14139.

Mora, F. D., L. Alpan, N. D. Tommasi, V. J. McCracken, and M. Nieto. 2013. New antibacterial germacrene from *Verbesina negrensis*. *Planta Medica* 79 (08):707–10. doi: 10.1055/s-0032-1328542.

Moran, N. E., S. K. Clinton, and J. W. Erdman. 2013. Differential bioavailability, clearance, and tissue distribution of the acyclic tomato carotenoids, lycopene and phytoene, in Mongolian gerbils. *The Journal of Nutrition* 143 (12):1920–6. doi: 10.3945/jn.113.181461.

Mulvihill, E. E., A. C. Burke, and M. W. Huff. 2016. Citrus flavonoids as regulators of lipoprotein metabolism and atherosclerosis. *Annual Review of Nutrition* 36 (1):275–99. doi: 10.1146/annurev-nutr-071715-050718.

Murakami, A., Y. Koshiba, K. Koshimizu, S. Kuwahara, Y. Takahashi, K. Ogawa, M. Yano, H. Tokuda, H. Nishino, and Y. Mimaki. 2000. Inhibitory effect of citrus nobiletin on phorbol ester-induced skin inflammation, oxidative stress, and tumor promotion in mice. *Cancer Research* 60:5059–66.

Murakami, A., S. Kuwahara, Y. Takahashi, C. Ito, H. Furukawa, M. Ju-Ichi, K. Koshimizu, and H. Ohigashi. 2001. *In vitro* absorption and metabolism of nobiletin, a chemopreventive polymethoxyflavonoid in citrus fruits. *Bioscience, Biotechnology, and Biochemistry* 65 (1):194–7. doi: 10.1271/bbb.65.194.

Murakami, A., K. Koshimizu, H. Ohigashi, S. Kuwahara, W. Kuki, Y. Takahashi, K. Hosotani, S. Kawahara, and Y. Matsuoka. 2002. Characteristic rat tissue accumulation of nobiletin, a chemopreventative polymethoxyflavonoid, in comparison with luteolin. *Biofactors* 16 (3–4):73–82. doi: 10.1002/biof.5520160303.

Natarajan, N., D. Hori, S. Flavahan, J. Steppan, N. A. Flavahan, D. E. Berkowitz, and J. L. Pluznick. 2016. Microbial short chain fatty acid metabolites lower blood pressure via endothelial G protein-coupled receptor 41. *Physiological Genomics* 48 (11):826–34. doi: 10.1152/physiolgenomics.00089.2016.

Navarra, M., C. Mannucci, M. Delbò, and G. Calapai. 2015. *Citrus bergamia* essential oil: From basic research to clinical application. *Frontiers in Pharmacology* 6:36. doi: 10.3389/fphar.2015.00036.

Ndeh, D., A. Rogowski, A. Cartmell, A. S. Luis, A. Baslé, J. Gray, I. Venditto, J. Briggs, X. Zhang, A. Labourel, et al. 2017. Complex pectin metabolism by gut bacteria reveals novel catalytic functions. *Nature* 544 (7648):65–70. doi: 10.1038/nature21725.

Nectoux, A. M., C. Abe, S. Huang, N. Ohno, J. Tabata, Y. Miyata, K. Tanaka, T. Tanaka, H. Yamamura, and T. Matsui. 2019. Absorption and metabolic behavior of hesperidin (rutinosylated hesperetin) after single oral administration to Sprague-Dawley rats. *Journal of Agricultural and Food Chemistry* 67 (35):9812–9. doi: 10.1021/acs.jafc.9b03594.

Nielsen, I. L. F., W. S. S. Chee, L. Poulsen, E. Offord-Cavin, S. E. Rasmussen, S. E. Rasmussen, H. Frederiksen, M. Enslen, D. Barron, M. N. Horcajada, et al. 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. doi: 10.1093/jn/136.2.404.

Njoroge, S. M., H. Ukeda, and M. Sawamura. 1996. Changes in the volatile composition of yuzu (*Citrus junos* tanaka) cold-pressed oil during storage. *Journal of Agricultural and Food Chemistry* 44 (2):550–6. doi: 10.1021/jf950284k.

O'Connell, O. F., L. Ryan, and N. M. O'Brien. 2007. Xanthophyll carotenoids are more bioaccessible from fruits than dark green vegetables. *Nutrition Research* 27 (5):258–64. doi: 10.1016/j.nutres.2007.04.002.

Olthof, M. R., P. C. H. Hollman, M. N. C. P. Buijsman, J. M. M. van Amelsvoort, and M. B. Katan. 2003. Chlorogenic acid, quercetin-3-rutinoside, and black tea phenols are extensively metabolized in humans. *The Journal of Nutrition* 133 (6):1806–14. doi: 10.1093/jn/133.6.1806.

Palczewski, K. 2006. G protein–coupled receptor rhodopsin. *Annual Review of Biochemistry* 75 (1):743–67. doi: 10.1146/annurev.biochem.75.103004.142743.

Panche, A. N., A. D. Diwan, and S. R. Chandra. 2016. Flavonoids: An overview. *Journal of Nutritional Science* 5:1–15. doi: 10.1017/jns.2016.41.

Patsalou, M., K. K. Menikea, E. Makri, M. I. Vasquez, C. Drouza, and M. Koutinas. 2017. Development of a citrus peel-based biorefinery strategy for the production of succinic acid. *Journal of Cleaner Production* 166:706–16. doi: 10.1016/j.jclepro.2017.08.039.

Pellati, F., S. Benvenuti, and M. Melegari. 2005. Enantioselective LC analysis of synephrine in natural products on a protein-based chiral stationary phase. *Journal of Pharmaceutical and Biomedical Analysis* 37 (5):839–49. doi: 10.1016/j.jpba.2004.09.008.

Penzak, S. R., M. W. Jann, J. A. Cold, Y. Y. Hon, H. D. Desai, and B. J. Gurley. 2001. Seville (sour) orange juice: Synephrine content and cardiovascular effects in normotensive adults. *The Journal of Clinical Pharmacology* 41 (10):1059–63. doi: 10.1177/00912700122012652.

Perez-Jimenez, J., J. Hubert, L. Hooper, A. Cassidy, C. Manach, G. Williamson, and A. Scalbert. 2010. Urinary metabolites as

biomarkers of polyphenol intake in humans: A systematic review. *The American Journal of Clinical Nutrition* 92 (4):801–9. doi: 10.3945/ajcn.2010.29924.

Perry, R. J., L. Peng, N. A. Barry, G. W. Cline, D. Zhang, R. L. Cardone, R. L. Cardone, K. F. Petersen, R. G. Kibbey, A. L. Goodman, et al. 2016. Acetate mediates a microbiome-brain-β-cell axis to promote metabolic syndrome. *Nature* 534 (7606):213–7. doi: 10.1038/nature18309.

Petkovich, M., N. J. Brand, A. Krust, and P. Chambon. 1987. A human retinoic acid receptor which belongs to the family of nuclear receptors. *Nature* 330 (6147):444–50. doi: 10.1038/330444a0.

Putnik, P., F. J. Barba, J. M. Lorenzo, D. Gabrić, A. Shpigelman, G. Cravotto, and D. Bursać Kovačević. 2017. An integrated approach to mandarin processing: Food safety and nutritional quality, consumer preference, and nutrient bioaccessibility. *Comprehensive Reviews in Food Science and Food Safety* 16 (6):1345–58. doi: 10.1111/1541-4337.12310.

Qian, C., E. A. Decker, H. Xiao, and D. J. McClements. 2012. Nanoemulsion delivery systems: Influence of carrier oil on beta-carotene bioaccessibility. *Food Chemistry* 135 (3):1440–7. doi: 10.1016/j.foodchem.2012.06.047.

Qiu, P. J., H. Guan, P. Dong, S. S. Guo, J. K. Zheng, S. M. Li, Y. Chen, C. T. Ho, M. H. Pan, D. J. McClements, et al. 2011. The inhibitory effects of 5-hydroxy-3,6,7,8,3',4'-hexamethoxyflavone on human colon cancer cells. *Molecular Nutrition & Food Research* 55 (10): 1523–32. doi: 10.1002/mnfr.201100070.

Racchi, M. L. 2013. Antioxidant defenses in plants with attention to *Prunus* and *Citrus* spp. *Antioxidants* 2 (4):340–69. doi: 10.3390/antiox2040340.

Rafiq, S., R. Kaul, S. A. Sofi, N. Bashir, F. Nazir, and G. A. Nayik. 2018. Citrus peel as a source of functional ingredient: A review. *Journal of the Saudi Society of Agricultural Sciences* 17 (4):351–8. doi: 10.1016/j.jssas.2016.07.006.

Roman, M. J., B. J. Burri, and R. P. Singh. 2012. Release and bioaccessibility of β-carotene from fortified almond butter during *in vitro* digestion. *Journal of Agricultural and Food Chemistry* 60 (38): 9659–66. doi: 10.1021/jf302843w.

Roshanravan, N., R. Mahdavi, E. Alizadeh, M. A. Jafarabadi, M. Hedayati, A. Ghavami, S. Alipour, N. M. Alamdari, M. Barati, and A. Ostadrahimi. 2017. Effect of butyrate and inulin supplementation on glycemic status, lipid profile and glucagon-like peptide 1 level in patients with type 2 diabetes: A randomized double-blind, placebo-controlled trial. *Hormone and Metabolic Research* 49 (11):886–91. doi: 10.1055/s-0043-119089.

Sahasrabudhe, N. M., M. Beukema, L. Tian, B. Troost, J. Scholte, E. Bruininx, G. Bruggeman, M. van den Berg, A. Scheurink, H. A. Schols, et al. 2018. Dietary fiber pectin directly blocks toll-like receptor 2-1 and prevents doxorubicin-induced ileitis. *Frontiers in Immunology* 9:383. doi: 10.3389/fimmu.2018.00383.

Sarrou, E., P. Chatzopoulou, K. Dimassi-Theriou, and I. Therios. 2013. Volatile constituents and antioxidant activity of peel, flowers and leaf oils of *Citrus aurantium* L. growing in Greece. *Molecules* 18 (9): 10639–47. doi: 10.3390/molecules180910639.

Schmidt, L., V. N. Belov, and T. Göen. 2015. Human metabolism of Δ3-carene and renal elimination of Δ3-caren-10-carboxylic acid (chaminic acid) after oral administration. *Archives of Toxicology* 89 (3):381–92. doi: 10.1007/s00204-014-1251-5.

Schmidt, L., and T. Göen. 2017. Human metabolism of α-pinene and metabolite kinetics after oral administration. *Archives of Toxicology* 91 (2):677–87. doi: 10.1007/s00204-015-1656-9.

Schmidt, L., T. Lahrz, M. Kraft, T. Göen, and H. Fromme. 2015. Monocyclic and bicyclic monoterpenes in air of German daycare centers and human biomonitoring in visiting children, the LUPE 3 study. *Environment International* 83:86–93. doi: 10.1016/j.envint.2015.06.004.

Schoefer, L., R. Mohan, A. Schwiertz, A. Braune, and M. Blaut. 2003. Anaerobic degradation of flavonoids by *Clostridium orbiscindens*. *Applied and Environmental Microbiology* 69 (10):5849–54. doi: 10.1128/AEM.69.10.5849-5854.2003.

Selma, M. V., J. C. Espín, and F. A. Tomás-Barberán. 2009. Interaction between phenolics and gut microbiota: Role in human health. *Journal of Agricultural and Food Chemistry* 57 (15):6485–501. doi: 10.1021/jf902107d.

Sender, R., S. Fuchs, and R. Milo. 2016. Revised estimates for the number of human and bacteriacells in the body. *PLOS Biology* 14 (8): e1002533. doi: 10.1371/journal.pbio.1002533.

Sharma, K., N. Mahato, M. H. Cho, and Y. R. Lee. 2017. Converting citrus wastes into value added products: Economical and environment-friendly approaches. *Nutrition* 34:29–46. doi: 10.1016/j.nut.2016.09.006.

Shi, L. Z., R. Wang, G. Huang, P. Vogel, G. Neale, D. R. Green, and H. Chi. 2011. HIF1α-dependent glycolytic pathway orchestrates a metabolic checkpoint for the differentiation of TH17 and Treg cells. *The Journal of Experimental Medicine* 208 (7):1367–76. doi: 10.1084/jem.20110278.

Shie, P. H., and H. L. Lay. 2013. Component analysis and antioxidant activity of citrus limon. *Academia Journal of Medicinal Plants* 1: 49–58.

Shtriker, M. G., M. Hahn, E. Taieb, A. Nyska, U. Moallem, O. Tirosh, and Z. Madar. 2018. Fenugreek galactomannan and citrus pectin improve several parameters associated with glucose metabolism and modulate gut microbiota in mice. *Nutrition* 46:134–42. doi: 10.1016/j.nut.2017.07.012.

Singh, N., A. Gurav, S. Sivaprakasam, E. Brady, R. Padia, H. Shi, M. Thangaraju, P. D. Prasad, S. Manicassamy, D. H. Munn, et al. 2014. Activation of Gpr109a, receptor for niacin and the commensal metabolite butyrate, suppresses colonic inflammation and carcinogenesis. *Immunity* 40 (1):128–39. doi: 10.1016/j.immuni.2013.12.007.

Singh, N., M. Thangaraju, P. D. Prasad, P. M. Martin, N. A. Lambert, T. Boettger, S. Offermanns, and V. Ganapathy. 2010. Blockade of dendritic cell development by bacterial fermentation products butyrate and propionate through a transporter (Slc5a8)-dependent inhibition of histone deacetylases. *Journal of Biological Chemistry* 285 (36):27601–8. doi: 10.1074/jbc.M110.102947.

Singh, V., B. S. Yeoh, R. E. Walker, X. Xiao, P. Saha, R. M. Golonka, J. Cai, A. C. A. Bretin, X. Cheng, Q. Liu, et al. 2019. Microbiota fermentation-NLRP3 axis shapes the impact of dietary fibers on intestinal inflammation. *Gut* 68 (10):1801–12. doi: 10.1136/gutjnl-2018-316250.

Smith, P. M., M. R. Howitt, N. Panikov, M. Michaud, C. A. Gallini, M. Bohlooly-Y, J. N. Glickman, and W. S. Garrett. 2013. The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. *Science* 341 (6145):569–73. doi: 10.1126/science.1241165.

Song, M., N. Charoensinphon, X. Wu, J. Zheng, Z. Gao, F. Xu, M. Wang, and H. Xiao. 2016. Inhibitory effects of metabolites of 5-demethylnobiletin on human nonsmall cell lung cancer cells. *Journal of Agricultural and Food Chemistry* 64 (24):4943–9. doi: 10.1021/acs.jafc.6b01367.

Song, M., C. L. Lopez-Pena, D. J. McClements, E. A. Decker, and H. Xiao. 2017. Safety evaluation and lipid-lowering effects of food-grade biopolymer complexes (ε-polylysine-pectin) in mice fed a high-fat diet. *Food & Function* 8 (5):1822–9. doi: 10.1039/C7FO00222J.

Song, H. S., M. Sawamura, T. Ito, K. Kawashimo, and H. Ukeda. 2000. Quantitative determination of characteric flavour of *Citrus junos* (yuzu) peel oil. *Flavour and Fragrance Journal* 15 (4):245–50. doi: 10.1002/1099-1026(200007/08)15:4<245::AID-FFJ904>3.0.CO;2-V.

Song, M., X. Wu, N. Charoensinphon, M. Wang, J. Zheng, Z. Gao, F. Xu, Z. Li, F. Li, J. Zhou, et al. 2017. Dietary 5-demethylnobiletin inhibits cigarette carcinogen-induced lung tumorigenesis in mice. *Food & Function* 8 (3):954–63., doi: 10.1039/C6FO01367H.

Stevens, Y., E. V. Rymenant, C. Grootaert, J. V. Camp, S. Possemiers, A. Masclee, and D. Jonkers. 2019. The intestinal fate of citrus flavanones and their effects on gastrointestinal health. *Nutrients* 11 (7): 1464. doi: 10.3390/nu11071464.

Stohs, S. J. 2017. Safety, efficacy, and mechanistic studies regarding *Citrus aurantium* (bitter orange) extract and *p*-synephrine. *Phytotherapy Research* 31 (10):1463–74. doi: 10.1002/ptr.5879.

Stohs, S. J., H. G. Preuss, and M. Shara. 2012. A review of the human clinical studies involving *Citrus aurantium* (bitter orange) extract and its primary protoalkaloid *p*-synephrine. *International Journal of Medical Sciences* 9 (7):527–38. doi: 10.7150/ijms.4446.

Stević, T., T. Berić, K. Šavikin, M. Soković, D. Gođevac, I. Dimkić, and S. Stanković. 2014. Antifungal activity of selected essential oils against fungi isolated from medicinal plant. *Industrial Crops and Products* 55:116–22. doi: 10.1016/j.indcrop.2014.02.011.

Sugiura, M., M. Nakamura, K. Ogawa, Y. Ikoma, and M. Yano. 2012. High serum carotenoids associated with lower risk for bone loss and osteoporosis in post-menopausal Japanese female subjects: Prospective cohort study. *PLoS One.* 7 (12):e52643. doi: 10.1371/journal.pone.0052643.

Sugiura, M., M. Nakamura, K. Ogawa, Y. Ikoma, H. Matsumoto, F. Ando, H. Shimokata, and M. Yano. 2008. Associations of serum carotenoid concentrations with the metabolic syndrome: Interaction with smoking. *British Journal of Nutrition* 100 (6):1297–306. doi: 10.1017/S0007114508978302.

Sugiura, M., M. Nakamura, Y. Ikoma, M. Yano, K. Ogawa, H. Matsumoto, M. Kato, M. Ohshima, and A. Nagao. 2005. High serum carotenoids are inversely associated with serum gammaglutamyltransferase in alcohol drinkers within normal liver function. *Journal of Epidemiology* 15 (5):180–6. doi: 10.2188/jea.15.180.

Su, J. D., J. H. Yen, S. M. Li, C. Y. Weng, M. H. Lin, C. T. Ho, and M. J. Wu. 2012. 3′,4′-Didemethylnobiletin induces phase II detoxification gene expression and modulates PI3K/Akt signaling in PC12 cells. *Free Radical Biology and Medicine* 52 (1):126–41. doi: 10.1016/j.freeradbiomed.2011.10.002.

Sun, C. D., K. S. Chen, Y. Chen, and Q. J. Chen. 2005. Contents and antioxidant capacity of limonin and nomilin in different tissues of citrus fruit of four cultivars during fruit growth and maturation. *Food Chemistry* 93 (4):599–605. doi: 10.1016/j.foodchem.2004.10.037.

Sun, H., H. Ni, Y. Yang, L. Wu, H. N. Cai, A. F. Xiao, and F. Chen. 2014. Investigation of sunlight-induced deterioration of aroma of pummelo (*Citrus maxima*) essential oil. *Journal of Agricultural and Food Chemistry* 62 (49):11818–30. doi: 10.1021/jf504294g.

Surampudi, P., E. Byambaa, A. Erdembileg, and B. Lars. 2016. Lipid lowering with soluble dietary fiber. *Current Atherosclerosis Reports* 18 (12):1–13. doi: 10.1007/s11883-016-0624-z.

Tanaka, T.,. T. Tanaka, M. Tanaka, and T. Kuno. 2012. Cancer chemoprevention by citrus pulp and juices containing high amounts of *β*-cryptoxanthin and hesperidin. *Journal of Biomedicine and Biotechnology* 2012:1–10. doi: 10.1155/2012/516981.

Tanumihardjo, S. A. 2012. Mammalian models for understanding the mechanisms of retinol and retinoid actions. In: *WHO Technical Consultation on Vitamin A in Newborn Health: Mechanistic Studies*, vol. 2012, 93–108. Geneva, Switzerland: World Health Organization.

Thakkar, S. K., B. Maziya-Dixon, A. Dixon, and M. L. Failla. 2007. *β*-Carotene micellarization during *in vitro* digestion and uptake by Caco-2 cells is directly proportional to *β*-carotene content in different genotypes of cassava. *The Journal of Nutrition* 137 (10):2229–33. doi: 10.1093/jn/137.10.2229.

Thorburn, A. N., C. I. McKenzie, S. Shen, D. Stanley, L. Macia, L. J. Mason, L. K. Roberts, C. H. Y. Wong, R. Shim, and R. Robert. 2015. Evidence that asthma is a developmental origin disease influenced by maternal diet and bacterial metabolites. *Nature Communication* 6:7320.

Ting, Y., Y. Chiou, M. Pan, C. Ho, and Q. Huang. 2015. *In vitro* and *in vivo* anti-cancer activity of tangeretin against colorectal cancer was enhanced by emulsion-based delivery system. *Journal of Functional Foods* 15:264–73. doi: 10.1016/j.jff.2015.03.034.

Togashi, N., A. Shiraishi, M. Nishizaka, K. Matsuoka, K. Endo, H. Hamashima, and Y. Inoue. 2007. Antibacterial activity of long-chain fatty alcohols against *Staphylococcus aureus*. *Molecules* 12 (2):139–48. doi: 10.3390/12020139.

Tripoli, E., M. L. Guardia, S. Giammanco, D. D. Majo, and M. Giammanco. 2007. Citrus flavonoids: Molecular structure, biological activity and nutritional properties: A review. *Food Chemistry* 104 (2):466–79. doi: 10.1016/j.foodchem.2006.11.054.

Tyssandier, V., B. Lyan, and P. Borel. 2001. Main factors governing the transfer of carotenoids from emulsion lipid droplets to micelles. *Biochimica et Biophysica Acta (BBA) – Molecular and Cell Biology of Lipids* 1533 (3):285–92. doi: 10.1016/S1388-1981(01)00163-9.

Tundis, R., M. R. Loizzo, and F. Menichini. 2014. An overview on chemical aspects and potential health benefits of limonoids and their derivatives. *Critical Reviews in Food Science and Nutrition* 54 (2):225–50. doi: 10.1080/10408398.2011.581400.

Vieira, A. J., F. P. Beserra, M. C. Souza, B. M. Totti, and A. L. Rozza. 2018. Limonene: Aroma of innovation in health and disease. *Chemico-Biological Interactions* 283:97–106. doi: 10.1016/j.cbi.2018.02.007.

Vikram, A., P. R. Jesudhasan, G. K. Jayaprakasha, S. D. Pillai, and B. S. Patil. 2011. Citrus limonoids interfere with *Vibrio harveyi* cell–cell signaling and biofilm formation by modulating the response regulator LuxO. *Microbiology* 157 (1):99–110. doi: 10.1099/mic.0.041228-0.

Von Lintig, J. 2010. Colors with functions: Elucidating the biochemical and molecular basis of carotenoid metabolism. *Annual Review of Nutrition* 30 (1):35–56. doi: 10.1146/annurev-nutr-080508-141027.

Wang, F., L. Chen, H. P. Chen, S. W. Chen, and Y. P. Liu. 2019. Analysis of flavonoid metabolites in citrus peels (*Citrus reticulata* "Dahongpao") using UPLC-ESI-MS/MS. *Molecules* 24 (15):2680. doi: 10.3390/molecules24152680.

Wu, L. H., C. Lin, H. Y. Lin, Y. H. Liu, C. Wu, C. F. Tsai, P. C. Chang, W. L. Yeh, and D. Y. Lu. 2016. Naringenin suppresses neuroinflammatory responses through inducing suppressor of cytokine signaling 3 expression. *Molecular Neurobiology* 53 (2):1080–91. doi: 10.1007/s12035-014-9042-9.

Wu, X., M. Song, P. Qiu, F. Li, M. Wang, J. Zheng, Q. Wang, F. Xu, and H. Xiao. 2018. A metabolite of nobiletin, 4'-demethylnobiletin and atorvastatin synergistically inhibits human colon cancer cell growth by inducing G0/G1 cell cycle arrest and apoptosis. *Food & Function* 9 (1):87–95. doi: 10.1039/C7FO01155E.

Wu, X., M. Y. Song, Z. L. Gao, Y. Sun, M. F. Wang, F. Li, J. K. Zheng, and H. Xiao. 2017. Nobiletin and its colonic metabolites suppress colitis-associated colon carcinogenesis by down-regulating iNOS, inducing antioxidative enzymes and arresting cell cycle progression. *The* Journal of Nutritional Biochemistry 42:17–25.

Wu, X., M. Song, P. Qiu, K. Rakariyatham, F. Li, Z. Gao, X. Cai, M. Wang, F. Xu, J. Zheng, et al. 2017. Synergistic chemopreventive effects of nobiletin and atorvastatin on colon carcinogenesis. *Carcinogenesis* 38 (4):455–64., doi: 10.1093/carcin/bgx018.

Wu, X., M. Y. Song, M. F. Wang, J. K. Zheng, Z. L. Gao, F. Xu, G. Zhang, and H. Xiao. 2015. Chemopreventive effects of nobiletin and its colonic metabolites on colon carcinogenesis. *Molecular Nutrition & Food Research* 59 (12):2383–94. doi: 10.1002/mnfr.201500378.

Wu, X., M. Y. Song, K. Rakariyatham, J. K. Zheng, S. Guo, Z. Tang, S. Zhou, and H. Xiao. 2015. Anti-inflammatory effects of 4'-demethylnobiletin, a major metabolite of nobiletin. *Journal of Functional Foods* 19:278–87. doi: 10.1016/j.jff.2015.09.035.

Xia, Z., D. J. McClements, and H. Xiao. 2017. Influence of lipid content in a corn oil preparation on the bioaccessibility of *β*-carotene: A comparison of low-fat and high-fat samples. *Journal* of Food Science 82 (2):373–9. doi: 10.1111/1750-3841.13599.

Yang, Y., X. H. Wang, C. Y. Zhao, G. F. Tian, H. Zhang, H. Xiao, L. L. He, and J. K. Zheng. 2017. Chemical mapping of essential oils, flavonoids and carotenoids in citrus peels by Raman microscopy. *Journal of Food Science* 82 (12):2840–6. doi: 10.1111/1750-3841.13952.

Yang, Y., C. Y. Zhao, J. J. Chen, G. F. Tian, D. J. McClements, H. Xiao, and J. K. Zheng. 2017. Encapsulation of polymethoxyflavones in citrus oil emulsion-based delivery systems. *Journal of Agricultural and Food Chemistry* 65 (8):1732–9. doi: 10.1021/acs.jafc.7b00147.

Yao, M., D. J. McClements, F. Zhao, R. Craig, and H. Xiao. 2017. Controlling the gastrointestinal fate of nutraceutical and pharmaceutical-enriched lipid nanoparticles: From mixed micelles to chylomicrons. *NanoImpact* 5:13–21. doi: 10.1016/j.impact.2016.12.001.

Yi, L. Z., S. S. Ma, and D. B. Ren. 2017. Phytochemistry and bioactivity of citrus flavonoids: A focus on antioxidant, anti-inflammatory, anticancer and cardiovascular protection activities; a comprehensive

review on flavanones, the major citrus polyphenols. *Phytochemistry Reviews* 16 (3):479–511. doi: 10.1007/s11101-017-9497-1.

Yu, J., L. Wang, R. L. Walzem, E. G. Miller, L. M. Pike, and B. S. Patil. 2005. Antioxidant activity of citrus limonoids, flavonoids, and coumarins. *Journal of Agricultural and Food Chemistry* 53 (6):2009–14. doi: 10.1021/jf0484632.

Zárybnický, T., I. Boušová, M. Ambrož, and L. Skálová. 2018. Hepatotoxicity of monoterpenes and sesquiterpenes. *Archives of Toxicology* 92 (1):1–13. doi: 10.1007/s00204-017-2062-2.

Zeng, X., W. W. Su, Y. Y. Zheng, Y. D. He, Y. He, H. Y. Rao, W. Peng, and H. L. Yao. 2019. Pharmacokinetics, tissue distribution, metabolism, and excretion of naringin in aged rats. *Frontiers in Pharmacology* 10:34.

Zhang, Z.,. H. Chen, K. K. Chan, T. Budd, and R. Ganapathi. 1999. Gas chromatographic–mass spectrometric analysis of perillyl alcohol and metabolites in plasma. *Journal of Chromatography B: Biomedical Sciences and Applications* 728 (1):85–95. doi: 10.1016/S0378-4347(99)00065-1.

Zhang, Y. Y., X. L. Li, T. Y. Li, M. Y. Li, R. M. Huang, W. Li, and R. L. Yang. 2018. 3-(4-Hydroxyphenyl)propionic acid, a major microbial metabolite of procyanidin A2, shows similar suppression of macrophage foam cell formation as its parent molecule. *RSC Advances* 8 (12):6242–50. doi: 10.1039/C7RA13729J.

Zhao, C., F. Wang, Y. Lian, H. Xiao, and J. Zheng. 2020. Biosynthesis of citrus flavonoids and their health effects. *Critical Reviews in Food Science and Nutrition* 60 (4):566–83. doi: 10.1080/10408398.2018.1544885.

Zheng, J. K., Y. Li, M. Y. Song, X. Xiang, Y. Cao, D. J. McClements, and H. Xiao. 2014. Improving intracellular uptake of 5-demethyltangeretin by food grade nanoemulsions. *Food Research International* 62:98–103. doi: 10.1016/j.foodres.2014.02.013.

Zheng, J. K., M. Y. Song, P. Dong, P. J. Qiu, S. S. Guo, Z. M. Zhong, S. M. Li, C. T. Ho, and H. Xiao. 2013. Identification of novel bioactive metabolites of 5-demethylnobiletin in mice. *Molecular Nutrition & Food Research* 57 (11):1999–2007. doi: 10.1002/mnfr.201300211.

Zheng, J., J. Bi, D. Johnson, Y. Sun, M. Song, P. Qiu, P. Dong, E. Decker, and H. Xiao. 2015. Analysis of 10 metabolites of polymethoxyflavones with high sensitivity by electrochemical detection in high performance liquid chromatography. *Journal of Agricultural and Food Chemistry* 63 (2):509–16. doi: 10.1021/jf505545x.

Zou, W., Y. Luo, M. Liu, S. Chen, S. Wang, Y. Nie, G. Cheng, W. Su, and K. Zhang. 2015. Human intestinal microbial metabolism of naringin. *European Journal of Drug Metabolism and Pharmacokinetics* 40 (3):363–7. doi: 10.1007/s13318-014-0193-x.