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REVIEW

Gut microbiota-mediated metabolism of green tea catechins and the biological consequences: An updated review

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ABSTRACT

Multiple beneficial effects have been attributed to green tea catechins (GTCs). However, the bioavailability of GTCs is generally low, with only a small portion directly absorbed in the small intestine. The majority of ingested GTCs reaches the large intestinal lumen, and are extensively degraded via biotransformation by gut microbiota, forming many low-molecular-weight metabolites such as phenyl-γ-valerolactones, phenolic acids, butyrate, and acetate. This process not only improves the overall bioavailability of GTC-derived metabolites but also enriches the biological activities of GTCs. Therefore, the intra- and inter-individual differences in human gut microbiota as well as the resulting biological contribution of microbial metabolites are crucial for the ultimate health benefits. In this review, the microbial degradation of major GTCs was characterized and an overview of the in vitro models used for GTC metabolism was summarized. The intra- and inter-individual differences of human gut microbiota composition and the resulting divergence in the metabolic patterns of GTCs were highlighted. Moreover, the potential beneficial effects of GTCs and their gut microbial metabolites were also discussed. Overall, the microbial metabolites of GTCs with higher bioavailability and bioactive potency are key factors for the observed beneficial effects of GTCs and green tea consumption.

KEYWORDS

beneficial effects; green tea catechins; gut microbiota; *in vitro* fermentation models; intra- and inter-individual differences; low-molecular-weight metabolites

Introduction

Green tea is mainly manufactured from buds and leaves of *Camellia sinensis* (L.). It originated in China and has been spread worldwide, becoming one of the most accepted beverages that is embraced by both Asian and Western cultures nowadays (Zhou et al. 2020). Typical processing steps during green tea production consist of partial withering, steaming, rolling, drying, and the final firing, in which the steaming step is of importance for maintaining the flavan-3-ols content of green tea (Cabrera, Artacho, and Giménez 2006). The high temperature during steaming inactivates the enzymatic activity of polyphenol oxidase and peroxidase thus preventing the oxidation of monomeric flavan-3-ols (Chacko et al. 2010; Liu et al. 2018).

Besides giving people relaxation and pleasure, regular consumption of green tea has been reported to offer various health beneficial effects to tea consumers, such as reduced cardiovascular disease risk, neuroprotective effects, prebiotic properties, and anti-cancer potential (Cao et al. 2019; Luo et al. 2021; Musial, Kuban-Jankowska, and Gorska-Ponikowska 2020; Xu et al. 2020). These valuable traits of consuming green tea have been attracting continuous attention from researchers all over the world for discovering the underlying mechanisms. Many studies have concluded that green tea polyphenols, especially green tea catechins (GTCs), are the major contributors to these observed health-promoting merits of green tea (Alam et al. 2022; Tang et al. 2019; Zhou et al. 2022). GTCs are typical natural antioxidants, capable of maintaining cellular redox homeostasis (Baranowska et al. 2018; Bernatoniene and Kopustinskiene 2018). With the presence of hydroxyl groups in their benzene rings, GTCs possess antioxidant and radical scavenging potency, which are often listed as the reasons underly the prevention of civilization diseases by green teas (Musial, Kuban-Jankowska, and Gorska-Ponikowska 2020). As GTCs can also exert their beneficial effects via promoting the growth and/or activity of specific beneficial bacterial species and inhibiting the pathogenic ones, they have been recommended as novel prebiotics (Liu, Vincken, et al. 2022).

However, as with other polyphenols, the bioavailability of GTCs is generally low, which often makes it difficult to attribute the observed biological effects to the low blood concentrations detected in the systemic circulation (Zhu, Chen, and Li 2000). A relatively large portion of ingested GTCs reaches the colon and is subjected to extensive microbial degradation, a process that may be essential to improve

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the overall bioavailability of GTCs (or rather their metabolites) and to enrich the biological activities of GTCs via the contributions of their microbial metabolites (Del Rio et al. 2010). Meanwhile, it is widely accepted that inter-individual variability exists in human gut microbiota which can cause a significant difference in the metabolic patterns of GTCs (C. Liu et al. 2020; Mena, Ludwig, et al. 2019). In contrast, the intra-individual differences in the gut microbiome and the resulting difference in the microbial metabolism of GTCs are often considered as not evident or even ignored. However, a recent study conducted by Olsson et al. revealed the intra-individual differences to account for a substantial percentage (23%) of the total compositional variability in human intestinal microbes, suggesting the temporal dynamics of intestinal microbiota is more obvious than we think (Olsson et al. 2022). Therefore, how intra- and inter-individual differences of the host microbiome can result in differences in microbial conversions of GTCs needs further consideration.

In this review, we summarize the microbial metabolism of the major GTCs and the prevalent in vitro models that are used to study their metabolism. The intra- and inter-individual differences in the intestinal microbiome and the resulting differences in the metabolic fate of GTCs are also reviewed. Furthermore, modulatory effects on gut microbiota by GTCs and their colonic metabolites are reviewed and discussed. Additionally, the biological activities of GTCs and their microbial metabolites are also discussed, with emphasis on the potential biological contribution of GTCs' metabolites to the observed beneficial effects of dietary GTCs or green tea consumption.

Main catechins in green tea

The chemical composition of green tea is complicated, consisting of polyphenols, proteins (enzymes), amino acids, carbohydrates, lipids, vitamins, sterols, caffeine, minerals, volatiles, etc (Cabrera, Artacho, and Giménez 2006). Among all these constituents, the polyphenolic compounds are dominant, comprising 30 - 42% of the dry weight of tea leaves, including especially flavan-3-ols (catechins), which are the representative phenolic substances in green teas, contributing up to 30% of the total dry weight (Chacko et al. 2010; Graham 1992; Liu et al. 2018). Generally, it is accepted that, due to the special way of processing after harvesting, green tea possesses more catechins than any other kinds of teas (i.e., oolong tea, white tea, and black tea) (Musial, Kuban-Jankowska, and Gorska-Ponikowska 2020; Unachukwu et al. 2010). The dominant catechins found in green teas are (-)-epigallocatechin gallate (EGCG), (-)-epigallocatechin (EGC), (-)-epicatechin gallate (ECG), and (-)-epicatechin (EC) (Figure 1), especially the EGCG, which represents up to 59% of the total catechins in green teas (Chacko et al. 2010; Musial, Kuban-Jankowska, and Gorska-Ponikowska 2020). These catechins share a similar C_6-C_3-C_6 diphenylpropanoid skeleton, also known as a backbone comprising an A ring and a B ring that are connected by a heterocyclic C ring (Figure 1). EC has an ortho-dihydroxyl moiety at the 3′ and 4′ position of the B-ring, and a hydroxyl moiety at the 3 position on the C-ring. EGC has three vicinal hydroxy groups at the 3′, 4′, and 5′ positions of the B-ring. ECG and EGCG are ester derivatives of EC and EGC, respectively, formed through gallate moiety esterification of the hydroxyl moiety at carbon 3 on the C-ring (Figure 1).

It is worth noting that the content of catechins in tea products can be affected by various factors, such as cultivar, growth condition (e.g., temperature, soil, altitude, humidity), storage conditions, harvesting time, and the brewing condition (Ananingsih, Sharma, and Zhou 2013; Han et al. 2017; Z. Liu, Boeren, and Rietjens 2022; Reygaert 2018). For instance, a study reported that with the increase in cultivation altitude, the content of EGCG and ECG in green tea decreased, but EGC and gallocatechin gallate increased, which might be due to the cultivation altitude/temperature that affects certain enzymes in tea plants, e.g., EC: 1-O-galloyl-β-D-glucose O-galloyltransferase (Han et al. 2017).

Intestinal microbiota and its intra- and inter-individual differences

It is increasingly realized that the intestinal microbiota plays a crucial role in the physiology and biological effects of GTCs (Gan et al. 2018; Li and Van de Wiele 2021; Pérez-Burillo et al. 2021). Therefore, this section discusses the gut microbiota, and the factors that contribute to its variations among different people.

Gut microbiota and its functions

Gut microbiota refers to the collection of eukarya, archaea, and bacteria that colonize the gastrointestinal tract. It has been estimated that there are 3.8×10^{13} microbes in human body, similar to the number of human cells, with most of the microbiota living in the large intestine (Sender, Fuchs, and Milo 2016). With the help of high throughput sequencing techniques, it has been elucidated that *Bacteroidetes*, *Firmicutes*, *Actinobacteria*, *Proteobacteria*, and *Tenericutes* are the predominant bacterial phyla in the human gut, with the first two phyla being dominant. Other bacterial phyla, such as *Fusobacteria*, *Verrucomicrobia*, and *Saccharibacteri*, are generally detected in minor abundance (Almeida et al. 2019; Eckburg et al. 2005; Lozupone et al. 2012). Therefore, the microbiome also has an immense genomic content (more than 100 times the amount of genomic content as the human genome) (Thursby and Juge 2017), and a wide range of catalytic abilities, so that despite its non-human nature, a wide range of physiological effects are at least partially influenced by this "invisible organ" (Li et al. 2020).

A healthy gut microbiota ecosystem benefits the host physiological state via, for example, facilitating nutrient extraction, instructing innate immunity, protecting against pathogens, and regulating intestinal epithelial development (Eckburg et al. 2005). In addition, the highly diverse colonic

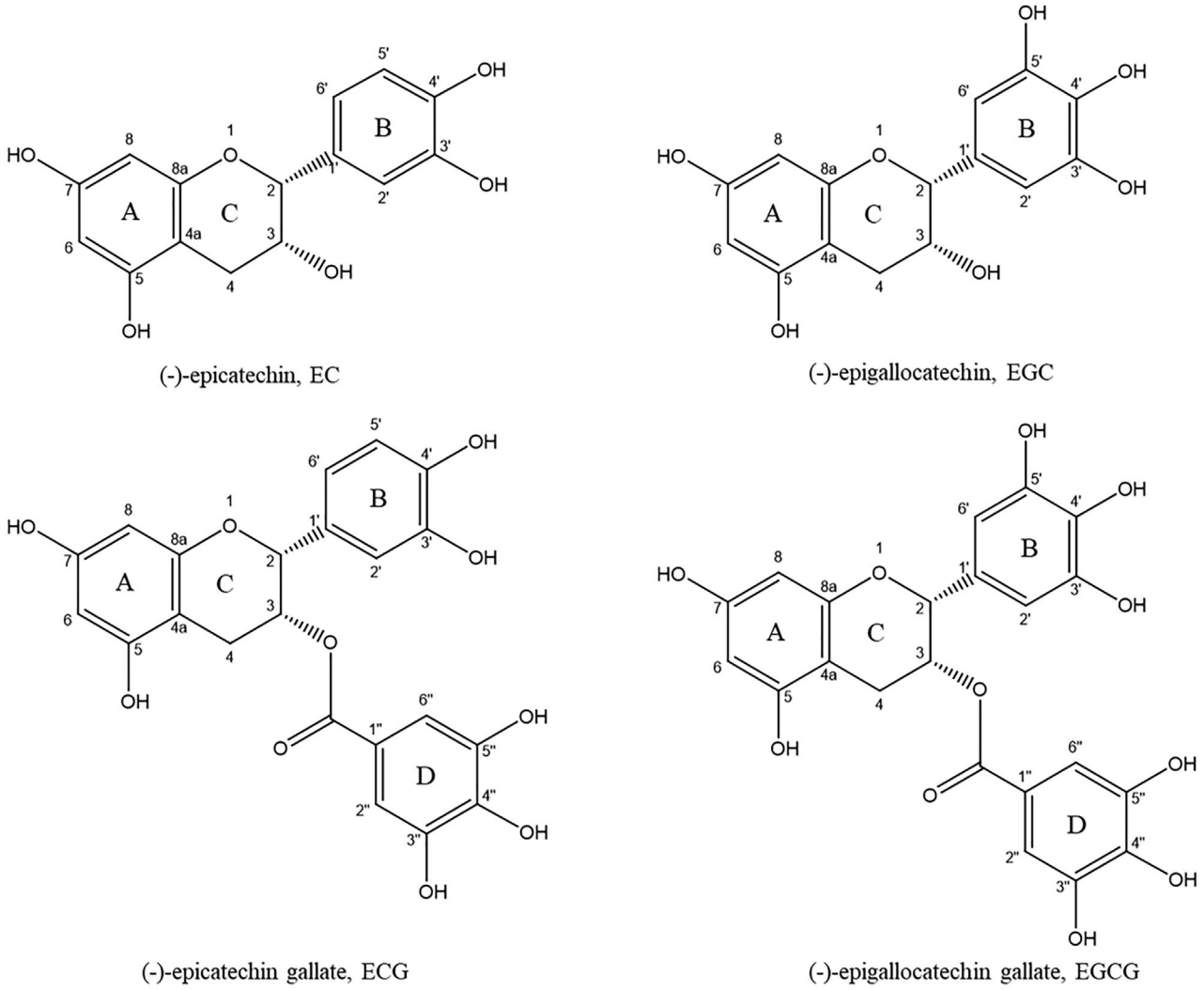

Figure 1. Chemical structures of the principal catechins in green tea (*Camellia sinensis*).

microbial community can contribute to the host's health by metabolizing xenobiotic substances and thereby changing the exposure of the host to those xenobiotics and their metabolites (Eckburg et al. 2005). Some different populations of bacteria may be able to perform similar functions. For instance, the short-chain fatty acid acetate can be produced by most intestinal anaerobes (Louis and Flint 2017). The same holds for the degalloylation of galloylated GTCs, which also seems not to require certain specific phenotypes (Liu et al. 2021) (Table 1). Meanwhile, it is also recognized that biotransformation of certain food ingredients or drugs needs specific microbes. For example, *Adlercreutzia equolifaciens*, *Asaccharobacter celatus*, *Slackia equolifaciens*, *Slackia isoflavoniconvertens Eggerthella lenta*, and *Lactobacillus plantarum* are the bacteria reported to be able to produce the metabolite diphenylpropan-2-ol from C-ring cleavage on epicatechins (or catechins) (Kutschera et al. 2011; Sanchez-Patan et al. 2012; Takagaki and Nanjo 2015; Wang et al. 2001) (Table 1). These bacteria fall into two phyla, namely *Firmicutes* and *Actinobacteria*. Subsequently, *Flavonifractor plautii*, which belongs to the *Firmicutes*, has been reported to be responsible for A ring fission of the diphenylpropan-2-ol to produce 5-(3′,4′-dihydroxyphenyl)-γ-valerolactone (3,4-diHPV) and 4-hydroxy-5-(3′,4′-dihydroxyphenyl)valeric acid (Kutschera et al. 2011; Sanchez-Patan et al. 2012) (Table 1). Table 1 summarizes the gut microbiota species that are capable of bioconversion of tea polyphenols, and respective generated products.

By establishing correlations between relative microbial abundances and formation of GTCs gut microbial metabolites in in vitro anaerobic fecal incubations, a recent study found statistically significant positive correlations between the relative abundance of *Lachnospiraceae* NC2004 and the formation of 1-(3′,4′-dihydroxyphenyl)-3-(2′',4′',6′'-trihydroxyphenyl)-2-propanol (3,4-diHPP-2-ol), of *Phascolarctobacterium* and the formation of 3,4-diHPV and statistically significant inverse correlations were found between the amount of EGCG residuals and the relative compositional proportion of *Bilophila* (Liu et al. 2021). The established correlation between certain microbial phylotypes and specific metabolites provides leading information for future studies on elucidating enzymes or pathways in the respective gut microbes responsible for the GTC conversions.

Table 1. Intestinal bacteria identified in different steps of microbial metabolism of GTCs and respective products formed.

Conversion reactions	Bacteria taxonomy information			Substrates	Products	References
	Species/Strains	Genus	Phylum			
Degalloylation	*Enterobacter aerogenes*	*Klebsiella*	*Proteobacteria*	EGCG	EGC, GA	(Sanchez-Patan et al. 2012; Takagaki and Nanjo 2010)
	Klebsiella pneumoniae subsp. *pneumoniae*	*Klebsiella*	*Proteobacteria*			
	Raoultella planticola	*Raoultella*	*Proteobacteria*			
	Bifidobacterium longum subsp. *infantis*	*Bifidobacterium*	*Actinobacteria*			
	Lactobacillus plantarum IFPL965	*Lactobacillus*	*Firmicutes*			
C-ring cleavage	*Slackia equolifaciens* JCM 16059	*Slackia*	*Actinobacteria*	GC, EGC	1-(3′,4′,5′-trihydroxyphenyl)-3-(2″,4″,6″-trihydroxyphenyl)-2-propanol	(A. Takagaki and Nanjo 2015a; Wang et al. 2001)
	Eggerthella sp. SDG-2	*Eggerthella*	*Actinobacteria*			
	Eggerthella lenta rK3	*Eggerthella*	*Actinobacteria*	(+)-C	1-(3′,4′-dihydroxyphenyl)-3-(2″,4″,6″-trihydroxyphenyl)-2-propanol	(Jin and Hattori 2012; Kutschera et al. 2011; Sanchez-Patan et al. 2012; Takagaki and Nanjo 2015)
	Eggerthella sp. SDG-2	*Eggerthella*	*Actinobacteria*			
	Eggerthella sp. CAT-1	*Eggerthella*	*Actinobacteria*			
	Adlercreutzia equolifaciens	*Adlercreutzia*	*Actinobacteria*			
	Asaccharobacter celatus	*Asaccharobacter*	*Actinobacteria*			
	Slackia equolifaciens	*Slackia*	*Actinobacteria*			
	Slackia isoflavoniconvertens	*Slackia*	*Actinobacteria*			
	Lactobacillus plantarum IFPL935	*Lactobacillus*	*Firmicutes*			
	Eggerthella sp. SDG-2	*Eggerthella*	*Actinobacteria*	C	1-(3′,4′-dihydroxyphenyl)-3-(2″,4″,6″-trihydroxyphenyl)-2-propanol; 1-(3′-hydroxyphenyl)-3-(2″,4″,6″-trihydroxyphenyl)-2-propanol	(Wang et al. 2001)
	Eggerthella sp. SDG-2	*Eggerthella*	*Actinobacteria*	(+)-C, (+)-EC	1-(3′,4′-dihydroxyphenyl)-3-(2″,4″,6″-trihydroxyphenyl)-2-propanol	(Wang et al. 2001)
C-ring cleavage and dehydroxylation	*Adlercreutzia equolifaciens* MT4s-5	*Adlercreutzia*	*Actinobacteria*	EGC	1-(3′,4′,5′-trihydroxyphenyl)-3-(2″,4″,6″-trihydroxyphenyl)-2-propanol; 1-(3′,5′-dihydroxyphenyl)-3-(2″,4″,6″-trihydroxyphenyl)-2-propanol	(Takagaki, Kato, and Nanjo 2014; Wang et al. 2001)
	Eggerthella lenta JCM 9979	*Eggerthella*	*Actinobacteria*			
	Eggerthella sp. SDG-2	*Eggerthella*	*Actinobacteria*			
	Eggerthella lenta rK3	*Eggerthella*	*Actinobacteria*	EC	1-(3′,4′-dihydroxyphenyl)-3-(2″,4″,6″-trihydroxyphenyl)-2-propanol; 1-(3′-hydroxyphenyl)-3-(2″,4″,6″-trihydroxyphenyl)-2-propanol	(Jin and Hattori 2012; Kutschera et al. 2011; Sanchez-Patan et al. 2012; Takagaki and Nanjo 2015; Wang et al. 2001)
	Eggerthella sp. SDG-2	*Eggerthella*	*Actinobacteria*			
	Eggerthella sp. CAT-1	*Eggerthella*	*Actinobacteria*			
	Adlercreutzia equolifaciens	*Adlercreutzia*	*Actinobacteria*			
	Asaccharobacter celatus	*Asaccharobacter*	*Actinobacteria*			
	Lactobacillus plantarum IFPL935	*Lactobacillus*	*Firmicutes*			
	Adlercreutzia equolifaciens JCM 14793	*Adlercreutzia*	*Actinobacteria*	GC	1-(3′,4′,5′-trihydroxyphenyl)-3-(2″,4″,6″-trihydroxyphenyl)-2-propanol; 1-(3′,5′-dihydroxyphenyl)-3-(2″,4″,6″-trihydroxyphenyl)-2-propanol	(Takagaki and Nanjo 2015a)
	Adlercreutzia equolifaciens MT4s-5	*Adlercreutzia*	*Actinobacteria*			
	Asaccharobacter celatus JCM 14811	*Asaccharobacter*	*Actinobacteria*			
	Asaccharobacter celatus JCM 14811	*Asaccharobacter*	*Actinobacteria*	EGC		(Takagaki and Nanjo 2015a)
	Adlercreutzia equolifaciens MT4s-5	*Adlercreutzia*	*Actinobacteria*			
A-ring fission	*Flavonifractor plautii* MT42	*Flavonifractor*	*Firmicutes*	1-(3′,4′,5′-trihydroxyphenyl)-3-(2″,4″,6″-trihydroxyphenyl)-2-propanol	5-(3′,4′,5′-trihydroxyphenyl)-γ-valerolactone	(Takagaki, Kato, and Nanjo 2014)
	Flavonifractor plautii ATCC 29863	*Flavonifractor*	*Firmicutes*			
	Flavonifractor plautii ATCC 49531	*Flavonifractor*	*Firmicutes*			
	Flavonifractor plautii MT42	*Flavonifractor*	*Firmicutes*	1-(3′,5′-dihydroxyphenyl)-3-(2″,4″,6″-trihydroxyphenyl)-2-propanol	5-(3′,5′-dihydroxyphenyl)-γ-valerolactone	(Takagaki, Kato, and Nanjo 2014)
	Flavonifractor plautii ATCC 29863	*Flavonifractor*	*Firmicutes*			
	Flavonifractor plautii ATCC 49531	*Flavonifractor*	*Firmicutes*			
A-ring fission & valerolactone ring opening	*Flavonifractor plautii* aK2	*Flavonifractor*	*Firmicutes*	1-(3′,4′-dihydroxyphenyl)-3-(2″,4″,6″-trihydroxyphenyl)-2-propanol	5-(3′,4′-dihydroxyphenyl)-γ-valerolactone; 4-hydroxy-5-(3′,4′-dihydroxyphenyl)-valeric acid	(Kutschera et al. 2011)
	Flavonifractor plautii DSM 6740	*Flavonifractor*	*Firmicutes*			
Dehydroxylation	*Adlercreutzia equolifaciens* MT4s-5	*Adlercreutzia*	*Actinobacteria*	5-(3′,4′,5′-trihydroxyphenyl)-γ-valerolactone	5-(3′,5′-dihydroxyphenyl)-γ-valerolactone	(Takagaki, Kato, and Nanjo 2014; Takagaki and Nanjo 2015a)
	Adlercreutzia equolifaciens JCM 14793	*Adlercreutzia*	*Actinobacteria*			
	Asaccharobacter celatus JCM 14811	*Asaccharobacter*	*Actinobacteria*			
	Eggerthella lenta JCM 9979	*Eggerthella*	*Actinobacteria*			

Note: GTCs, greent tea catechins; EGCG, (-)-epigallocatechin gallate; EGC, (-)-epigallocatechin; GC, (-)-gallocatechin; EC, (-)-epicatechin; (+)-EC, (+)-epicatechin; (+)-C, (+)-catechin; C, (-)-catechin; GA, gallic acid.

Factors shaping the intra- and inter-individual variations of human gut microbiota

Stable gut microbial composition is one of the most important indicators of a healthy host. However, some internal and external factors can affect this stable status of gut microbiota. For instance, age can be an influential factor driving the changes in host microbiota composition. The microbes of a newborn infant are largely dependent on the mode of birth and the mother's gut microbiome (Odamaki et al. 2016). The gut microbiota of naturally labored infants is initially colonized by organisms from the maternal vagina (Mackie, Sghir, and Gaskins 1999). In contrast, in cesarean-delivered infants, the intestine is mostly colonized by the maternal skin flora (Dominguez-Bello et al. 2010; Mackie, Sghir, and Gaskins 1999). The initial microbiota in the intestine of newborn infants may have a profound impact on an individual's gut microbial composition later in life since the 'priority effects' of microbiota establishment could play a role in the microbial community assembly and succession in time (Debray et al. 2022; Nappi et al. 2022). Over the first 3 to 5 years of life, the child's gut microbiota increases in diversity and stability, and evolves toward an adult-like configuration (Cheng et al. 2016; Odamaki et al. 2016). Odamaki et al. conducted a study using fecal samples from 367 healthy subjects over a large age range (0 to 104 years), and they concluded that the transition from infant to centenarian was accompanied by distinctive bacterial co-abundance group dominance, with a significant abundance of *Megamonas*, *Peptoniphilus*, *Clostridiaceae*, *Bacteroides*, and *Eubacterium* that were relatively enriched in the elderly (Odamaki et al. 2016). Their results also indicate that the nutrients in the intestine might be the reason underlying the compositional changes in gut microbiota with age (Odamaki et al. 2016).

Diet is another important factor that could contributes to microbial diversity and composition. For instance, it is widely accepted that a diet rich in fruits, fibers, and vegetables favors the diversity of the gut microbiome (Laitinen and Mokkala 2019). Compared to infant formula, breast milk contains human milk oligosaccharides which provides a selective growth advantage for *Bifidobacterium* sp (Zivkovic et al. 2011). A higher abundance of *Bacteroides* was associated with a western diet rich in animal protein, sugar, and starch (Wu et al. 2011). Moreover, EGCG treatment has been reported to act as a prebiotic which selectively promoted the abundance of beneficial bacteria, e.g., *Bacteroides*, *Christensenellaceae*, and *Bifidobacterium*, while it reduced the level of pathogenic bacteria, e.g., *Fusobacterium varium*, *Bilophila*, and *Enterobacteriaceae* (Liu et al. 2020b; Z. Liu, Boeren, and Rietjens 2022).

Besides, genetics is another factor driving the differences in human gut microbiota. However, conclusions based on this factor are still unclear since typically different populations not only possess genetic differences but are also under different environmental exposures, such as sanitation levels, frequency of using antibiotics, and differences in diet. A better illustration of the associations between different factors and gut microbiota composition requires expanded studies that sample large populations, and control the confounding factors (Lozupone et al. 2012).

Metabolism of GTCs

Metabolic pathways of catechins

Despite the fact that polyphenols are present in the daily diet at levels ten times higher than vitamin C and 100 times higher than vitamin E (Scalbert, Johnson, and Saltmarsh 2005), the overall bioavailability of polyphenols is considered to be lower than 10% (Clifford 2004), resulting in plasma concentrations of flavan-3-ols to be more than 50 times lower than those of l-ascorbic acid and more than 20 times lower than those of vitamin E (Ottaviani et al. 2016; Schwedhelm et al. 2003). EC is comparatively more bioavailable than other catechins, but still, just about 20 - 30% of the ingested amount is directly absorbed by the small intestine and ends up in systemic circulations (Ottaviani et al. 2016). When EC is ingested, conjugation takes place in the enterocytes, where several structurally-related (-)-epicatechin metabolites (SREMs) are formed, including especially (-)-epicatechin-3′-*O*-sulfate, (-)-epicatechin-3′-*O*-glucuronide, and 3′-*O*-methyl-(-)-epicatechin-5-sulfate (Ottaviani et al. 2016) (Figure 2). These SREMs can be directly passed on to the systemic circulation, indicated by a short T_{max} of 1.0 ± 0.1 h (Ottaviani et al. 2016). Meanwhile, a large amount of unabsorbed EC (~ 70% of intake) reaches the lumen of the large intestine where it is subjected to extensive metabolism by gut microbiota (Borges et al. 2018; Ottaviani et al. 2016; Qu et al. 2021) (Figure 2). Compared to the non-galloylated tea catechin EC, the galloylated ECG and EGCG have very poor bioavailability, amounting to less than 1% of total oral intake (Nakagawa and Miyazawa 1997). Barely no sulfated or glucuronidated ECG and EGCG have been detected in plasma and urine (Kohri, Suzuki, and Nanjo 2003; Monagas et al. 2010). For example, EGCG was detected almost all in free form in plasma in several studies (Chow et al. 2001; Monagas et al. 2010; Narumi et al. 2014).

Thus, the majority of orally ingested GTCs are passed on to the colon (including also catechins excreted back into the intestine upon systemic absorption via bile) and subsequently subjected to extensive microbial degradations. The diversity of microbiota that inhabits the large intestine provides the capability of catalyzing various reactions. These reactions include, for example, hydrolysis of glycosides, sulfates, lactones, and esters, reduction, decarboxylation, and demethylation (Liu et al. 2018) (Figure 2). As a result, the tea catechin conjugates reaching the microbiota can be deconjugated and subsequently, similar to unabsorbed aglycones, degraded by the intestinal microflora. For the galloylated GTCs, namely ECG and EGCG, the microbial conversion starts with the rapid degalloylation by microbial esterases (Figure 3), resulting in the formation of EC and EGC, respectively, and gallic acid which is decarboxylated to give rise to pyrogallol. Pyrogallol can be converted further into molecules including catechol, butyric acid, and acetic acid (Gross et al. 2010; Liu et al. 2021). Meanwhile, in EC

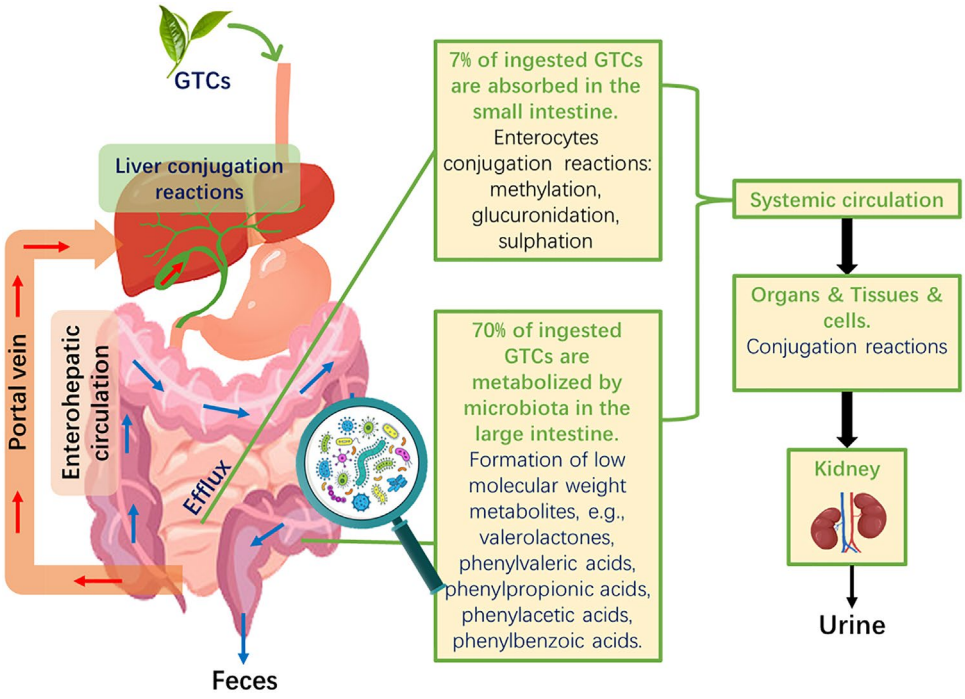

Figure 2. Absorption, distribution, metabolism, and excretion of GTCs in vivo.

and EGC, the 1-2 bond in the heterocyclic C-ring is prone to reductive cleavage, giving rise to diphenylpropan-2-ols, i.e., 3,4-diHPP-2-ol and 1-(3′,4′,5′-trihydroxyphenyl)-3-(2′′,4′′,6′′-trihydroxyphenyl)-2-propanol (Figure 3). Further A-ring fission, lactonization, dehydroxylation, decarboxylation, and beta-oxidation catalyzed by the gut microbiome result in the formation of phenyl-γ-valerolactones and various smaller phenolic compounds (Figure 3), which are more readily absorbed (Kohri et al. 2001; Kohri, Suzuki, and Nanjo 2003; Liu et al. 2018; Monagas et al. 2010).

Previous studies indicate that the dominant microflora-derived metabolite of EC was 3,4-diHPV, while 5-(3′,5′-dihydroxyphenyl)-γ-valerolactone (3,5-diHPV) was one of EGCG's dominant microbial metabolites (Borges et al. 2018; C. Liu et al. 2020; Liu et al. 2021; Meng et al. 2002; Ottaviani et al. 2016). The trihydroxy group in the B ring of EGCG enables the formation of, among others, 5-(3′,4′,5′-trihydroxyphenyl)-γ-valerolactone, 3,4-diHPV, and 3,5-diHPV (Figure 3) upon incubating with fecal samples. It is of interest to note that in anaerobic fecal incubations with EGCG both 5-(3′,4′,5′-trihydroxyphenyl)-γ-valerolactone and 3,4-diHPV were detected at lower levels compared to 3,5-diHPV (Liu et al. 2021). This indicates a preference of the gut microbiota for catalyzing 4′-dehydroxylation over 5′-dehydroxylation in the B-ring of the molecular skeleton. Wang and coworkers observed that the *Eubacterium* sp. strain SDG-2 was able to catalyze 4′-dehydroxylation activity in the B-ring of several catechins including EGC, and they proved that the presence of three vicinal hydroxy groups at 3′, 4′ and 5′ in the B-ring is of importance for this 4′-dehydroxylation activity by *Eubacterium* sp. strain SDG-2 (Wang et al. 2001). This regioselectivity of dehydroxylation is of interest given the role of ortho-hydroxy groups, i.e. a catechol moiety, in the potential beneficial effects of polyphenols, e.g., radical scavenging ability, nuclear factor E2-related factor 2 (Nrf2) signaling inducing potency (see section 4.2) (Lee-Hilz et al. 2006; Muzolf-Panek et al. 2008; Thavasi, Leong, and Bettens 2006). Therefore, it can be expected that 3,4-diHPV may show some superior bioactivities compared to its isomer 3,5-diHPV.

Role of microbial metabolism in the biological activities of GTCs

Techniques for improving the bioavailability of GTCs include emulsion-based systems (e.g., nano-emulsion, double emulsion, Pickering emulsion, and liposome), nano-carrier delivery systems (e.g., protein, carbohydrate, and lipid-based carriers), molecular modification, and co-administration of catechins with other bioactives (Cai et al. 2018; Yin et al. 2022). Meanwhile, the extensive metabolism of GTCs improves both the overall bioavailability of the parental catechins in the form of their metabolites and may at the same time contribute to the bioactivities that are attributed to the parental compounds. For instance, Ottaviani et al. characterized metabolite profiles of 48 h urinary samples from human volunteers upon oral administration of EC. They found that urinary excretion accounted for EC metabolites at a level corresponding to 89% of the ingested EC, with the EC microbial metabolites, including 5-carbon side-chain ring fission metabolites (e.g., phenyl-γ-valerolactones and phenyl-valeric acids) making up the largest portion, amounting to 42% of the total EC ingested (Ottaviani et al. 2016). In another study, 20 healthy volunteers were served 400 mL of green tea infusion and their plasma and

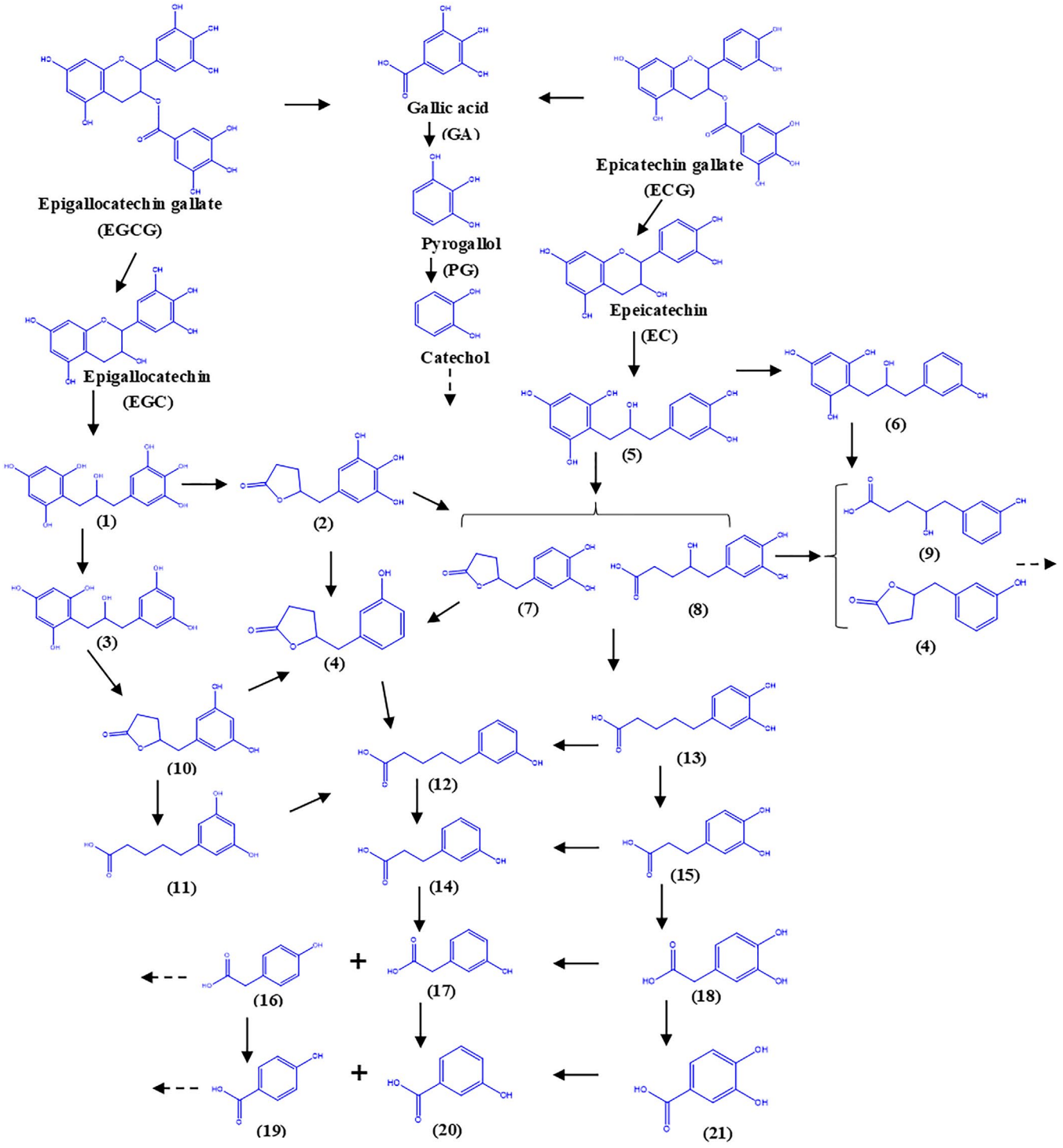

Figure 3. Proposed microbial metabolism pathways of GTCs. Compound 1, 1-(3′,4′,5′-trihydroxyphenyl)-3-(2″,4″,6″-trihydroxyphenyl)-2-propanol; compound 2, 5-(3′,4′,5′-trihydroxyphenyl)-γ-valerolactone; compound 3, 1-(3′,5′-dihydroxyphenyl)-3-(2″,4″,6″-trihydroxyphenyl)-2-propanol; compound 4, 5-(3′-hydroxyphenyl)-γ-valerolactone; compound 5, 1-(3′,4′-dihydroxyphenyl)-3-(2″,4″,6″-trihydroxyphenyl)-2-propanol; compound 6, 1-(3′-hydroxyphenyl)-3-(2″,4″,6″-trihydroxyphenyl)-2-propanol; compound 7, 5-(3′,4′-dihydroxyphenyl)-γ-valerolactone; compound 8, 4-hydroxy-5-(3′,4′-dihydroxyphenyl)-valeric acid; compound 9, 4-hydroxy-5-(3′-hydroxyphenyl)-valeric acid; compound 10, 5-(3′,5′-dihydroxyphenyl)-γ-valerolactone; compound 11, 5-(3′,5′-dihydroxyphenyl)-valeric acid; compound 12, 5-(3′-hydroxyphenyl)-valeric acid; compound 13, 5-(3′,4′-dihydroxyphenyl)-valeric acid; compound 14, 3-(3′-hydroxyphenyl)propionic acid; compound 15, 3-(3′4-dihydroxyphenyl)propionic acid; compound 16, 4′-hydroxyphenylacetic acid; compound 17, 3′-hydroxyphenylacetic acid; compound 18, 3′,4′-dihydroxyphenylacetic acid; compound 19, 4′-hydroxybenzoic acid; compound 20, 3′-hydroxybenzoic acid; compound 21, 3′,4′-dihydroxybenzoic acid.

urine samples were sampled and analyzed for the presence of flavan-3-ols catabolites. The researchers concluded that when colonic ring fission metabolites of GTCs (amounting to 39% of the content of catechins ingested) were taken into account, the bioavailability of these catechins was more promising than previously reported (Del Rio et al. 2010).

Given the systemic bioavailability of the microbial catechin metabolites, the biological activities of these metabolites

are of interest. For instance, one of the major colonic catechin metabolites, 3,4-diHPV, was reported to be capable of inhibiting nitric oxide formation and inducible nitric oxide synthase (iNOS) expression in RAW 264.7 cells, indicating an anti-inflammation potential (Uhlenhut and Högger 2012). Anti-cancer potential of GTCs has especially attracted considerable attention from researchers worldwide aiming to unveil the underlying mechanisms. The mode of action underlying the cancer-preventive effects of GTCs may proceed through the regulation of genes and signaling pathways that are involved in the initiation, promotion, and progression of cancer. Accumulation of reactive oxygen species (ROS) can cause irreversible DNA damage and may lead to cancer pathogenesis (Yang and Wang 2016). Microbial metabolites of GTCs have been reported to be capable of repressing cellular oxidative stress which may contribute to the inhibition of tumorigenesis by GTCs. For instance, Chen et al. found that the C-ring cleavage metabolite, 3,4-diHPP-2-ol, exerted a 2- and 1.8-times higher antioxidant activity than its parental compounds catechin and epicatechin, respectively (Chen et al. 2020). Besides directly acting as antioxidants that scavenge free radicals, including ROS, microbial metabolites of GTCs can exert indirect antioxidative properties, which is via the induction of antioxidant systems. The Nrf2 signaling cascade is an important cellular signaling pathway, whose activation can induce the expression of a wide array of antioxidative and detoxifying enzymes, including glutathione S-transferases (GSTs), glutathione reductases (GRs), superoxide dismutases (SODs), UDP-glucuronosyltransferases (UGTs) and many others (Talebi et al. 2021). For example, a study conducted by Dufour and colleagues revealed that EC was not capable of inducing Nrf2 signaling in HepG2 cells but its gut microbial metabolite 3,4-diHPV possesses this bioactivity with an EC_{50} of 74.55 µg/mL (Dufour et al. 2022). In line with their results, our recent study using a U2OS Nrf2 reporter cell line, also concluded that, in contrast to the inactiveness of EC in triggering the Nrf2 signaling pathway, the metabolite 3,4-diHPV can be a potential Nrf2-activator, though subsequent bioinformatical analysis of proteomics data indicated that the Nrf2-pathway induction may not be among the most dominant bioactivities of 3,4-diHPV (Liu, Boeren, and Rietjens 2022). Table 2 summarizes studies reporting different bioactivities and possible mechanisms of gut microbial metabolites of GTCs. EGCG is often considered to have superior efficacy among the catechins, while our previous studies revealed that some of the catechol-moiety-containing gut microbial metabolites of EGCG, e.g., pyrogallol, have higher potency than EGCG in inducing Nrf2-mediated gene expression (Liu, Boeren, Miro Estruch, et al. 2022; Liu et al. 2021). These findings have provided leading information to explore the potential contribution of microbial metabolites to the beneficial effects of GTCs, especially when considering that some gut microbial metabolites appear in higher concentrations than their parental compounds in the systemic circulation (Carregosa et al. 2022) and/or may have higher intrinsic activities (C. Liu, Boeren, and Rietjens 2022; Liu et al. 2021). For example, pyrogallol conjugates could reach 2.6 µM in plasma after drinking black tea (van Duynhoven et al. 2014).

Due to the rapid microbial conversion of GTCs in the colonic region, the gut microbial metabolites of GTCs may play a more pivotal role than the parental compounds in inhibiting colorectal cancer. Rubert et al. found that the gut microbial metabolites 3,4-diHPV and 4-hydroxy-5-(3′,4′-dihydroxyphenyl)-valeric acid significantly affected spheroid integrity at the early stages of 3D-HTC116 cells (Rubert et al. 2022). Augusti et al. reported that the microbial degradation metabolite dihydroxyphenyl-γ-valerolactone has antiproliferative activity in a 3D-HT29 colorectal cancer cell model (Augusti et al. 2021). Besides, these phenyl-γ-valerolactones have also been reported to exert neuroprotective activity by regulating intracellular proteolysis in SH-SY5Y cells (Cecarini et al. 2021) (Table 2). Other gut microbial metabolites, e.g., phenolic acids, could also contribute to the beneficial effects of GTCs. For instance, 2-(3′-hydroxyphenyl)acetic acid, 2-(3′,4′-dihydroxyphenyl)acetic acid, 3-(3′-hydroxyphenyl)propionic acid, and 3-(4′-hydroxyphenyl)propionic acid have been evaluated as attenuators of neuroinflammation in microglia cells (Carregosa et al. 2020). Gallic acid, one of the microbial metabolites of EGCG and ECG, was reported to be the molecular rival of cancer, by exerting an inhibitory effect on cancer cell growth via, for example, activation of ataxia-telangiectasia mutated kinase, inhibition of ribonucleotide reductase and cyclooxygenase, and depletion of GSH (Verma, Singh, and Mishra 2013).

Therefore, the various physiological effects (Figure 4) that were previously ascribed to GTCs may be at least partially due to the formation of a wide range of metabolites resulting from microbial metabolism in the colon. Especially for in vivo studies on investigating the mechanisms underly the health-promoting properties of GTCs, it is advised to include the potential activities of major intestinal microbial metabolites of GTCs, as they may have a higher potency than their parent compounds (C. Liu, Boeren, and Rietjens 2022; Chen Liu, Boeren, and Rietjens 2022). Moreover, most of the gut microbial metabolites of GTCs were detected in their conjugated forms (i.e., glucuronidated, sulfated, and/or methylated forms) in plasma and urine, suggesting it is of note to unveil how conjugation reactions can alter the bioactivities of these aglycones in vivo (Carregosa et al. 2022; Zhang et al. 2023).

Intra- and inter-individual differences in gut microbial metabolism of GTCs

Owing to the differences in gender, age, ethnic factors, diet, and lifestyle, the human gut microbial profile varies substantially among people, which in turn could result in inter-individual variations in gut microbial degradation of GTCs. Researchers are trying to define certain metabolic phenotypes (aka metabotypes) to characterize subjects that possess distinct microbial-derived metabolic profiles. For example, Mena et al. analyzed the urinary profile of green tea metabolites from 11 subjects who consumed green tea extract daily for eight weeks (Mena, Ludwig, et al. 2019).

Table 2. Beneficial effects and possible mechanisms of unperstream gut microbial metabolites of GTCs.

Microbial metabolites	Concentration(s)	Models	Effects	Mechanisms	References
1-(3′,4′,5′-trihydroxyphenyl)-3-(2′′,4′′,6′′-trihydroxyphenyl)-2-propanol; 5-(3′,4′,5′-trihydroxyphenyl)-γ-valerolactone; 1-(3′,5′-dihydroxyphenyl)-3-(2′′,4′′,6′′-trihydroxyphenyl)-2-propanol; 5-(3′-hydroxyphenyl)-γ-valerolactone; 5-(3′,4′-dihydroxyphenyl)-γ-valerolactone; 5-(3′,5′-dihydroxyphenyl)-γ-valerolactone; 5-(3′,5′-dihydroxyphenyl)-valeric acid; 5-(3′-hydroxyphenyl)-valeric acid	100 to 300 μM	ABTS assay	Antioxidative activity	N/A	(Takagaki, Otani, and Nanjo 2011)
1-(3′,4′,5′-trihydroxyphenyl)-3-(2′′,4′′,6′′-trihydroxyphenyl)-2-propanol; 5-(3′,4′-dihydroxyphenyl)-valeric acid	0.4 to 50 μg/mL	HeLa cells	Anti-proliferation	N/A	(Hara-Terawaki et al. 2017)
1-(3′,4′-dihydroxyphenyl)-3-(2′′,4′′,6′′-trihydroxyphenyl)-2-propanol	0.1 to 1 mg/mL or 0.0156 to 1 mM	ABTS, DPPH, and FRAP assays	Antioxidative activity	N/A	(Chen et al. 2020; Gleńsk et al. 2019)
	10 μM	Male guinea pigs	Antispasmodic potential	Reduction of intestinal smooth muscle contraction	(Gleńsk et al. 2019)
5-(3′,4′,5′-trihydroxyphenyl)-γ-valerolactone; 5-(3′,5′-dihydroxyphenyl)-γ-valerolactone; 5-(3′,5′-dihydroxyphenyl)-valeric acid; 5-(3′-hydroxyphenyl)-valeric acid	25 to 10 mM	In vitro ACE inhibitory assay	ACE inhibitory activity	N/A	(Takagaki and Nanjo 2015b)
5-(3′,4′,5′-trihydroxyphenyl)-γ-valerolactone; 5-(3′,5′-dihydroxyphenyl)-γ-valerolactone; 5-(3′-hydroxyphenyl)-valeric acid	3 μM (1 nM to 10 μM)	L6 skeletal muscle cells	Improve glucose tolerance	GLUT4 translocation; phosphorylation of AMPK;	(Takagaki et al. 2019)
5-(3′,4′,5′-trihydroxyphenyl)-γ-valerolactone; 5-(3′,5′-dihydroxyphenyl)-γ-valerolactone	150 mg/kg and 200 mg/kg	SHR rats	Decrease in systolic blood pressure	N/A	(Takagaki and Nanjo 2015b)
5-(3′,4′,5′-trihydroxyphenyl)-γ-valerolactone	IC_{50}: 15 to 73 μM	KYSE150 cells, HT-29 cells, HCT-116 cells, INT-407 cells, and IEC-6 cells	Inhibit cell growth	N/A	(Lambert et al. 2005)
	IC_{50} = 20 μM	Lipopolysaccharide-stimulated RAW264.7	Inhibit the NO production	N/A	(Lambert et al. 2005)
	10 to 100 μM	LNCaP cells	Chemoprevention of prostate cancer	Antiproliferative activity; inhibition of PSA secretion and enhanced retention of AR in the cytoplasm	(Stanisławska et al. 2019)
5-(3′,4′-dihydroxyphenyl)-γ-valerolactone	10 to 100 μM	T24 bladder epithelial cells	Potentially prevent urinary tract infections	Inhibition of the adherence of *Escherichia coli* to bladder epithelial cells	(Mena et al. 2017)
	15 to 150 μM	U2OS Nrf2 CALUX cells	Cytoprotective potential	Activation of Nrf2-mediated gene expression	(Chen Liu, Boeren, and Rietjens 2022)
	EC_{50} = 74.55 μg/mL	HepG2 cells	Cytoprotective potential	Activation of Nrf2-mediated gene expression	(Dufour et al. 2022)
	30 to 100 μM	3D-HTC116 cells	Decrease spheroid size at early stages of spheroid aggregation	Downregulation of matrix metalloproteinase-7	(Rubert et al. 2022)
	10,000 μg/mL	3D-HT29 colorectal cancer cell model	Antiproliferative activity	N/A	(Augusti et al. 2021)
	50 μM	KYSE150 cells	Inhibit cell growth	N/A	(Lambert et al. 2005)
	IC_{50} = 32.07 μM	HepG2 cells	Anti-inflammation	Inhibition of NF-κB signaling	(Sun et al. 2016)
	N/A	ABTS assay	Antioxidative activity	N/A	(Unno et al. 2003)
	1, 2 and 4 μM	Primary human dermal fibroblasts	Antiwrinkle effects	Inhibition of UVB-induced matrix metalloproteinases-1 expression	(J. E. Kim, Song, et al. 2016)
	2 to 10 μM	C57 BAT cells	Reverse H_2O_2 induced ROS accumulation	N/A	(Mele et al. 2017)
	0.1 to 50 mg/mL	RAW264.7 cells	Inhibit NO production	Downregulation of iNOS expression	(Uhlenhut and Högger 2012)
	IC_{50} = 0.5 μg/mL	Human monocytes	Anti-inflammation	Inhibition of metalloproteinase-9 release; superoxide scavenging ability	(Grimm, Schäfer, and Högger 2004)
	7.5 to 30 μM	HUVECs	Prevent atherosclerosis	Inhibition of monocyte-endothelial adhesion via the suppression of vascular cell adhesion molecule; attenuation of the TNF-α-stimulated upregulation of MCP-1 protein secretion and mRNA expression; inhibition of NF-κB signaling	(Lee et al. 2017)
	1 and 5 μM	SH-SY5Y cells	Neuroprotective activity	Regulation of intracellular proteolysis	(Cecarini et al. 2021)
	Intraperitoneal injection of 2 mg/kg/day, for 7 days	Male Wistar rats	Potential neuroprotective effects	Cross the blood-brain barrier	(Angelino et al. 2019)

Table 2. (Continued)

Microbial metabolites	Concentration(s)	Models	Effects	Mechanisms	References
5-(3′,5′-dihydroxyphenyl)-γ-valerolactone	0.05 μM	SH-SY5Y cells	Neuritogenic activity	N/A	(Unno et al. 2017)
	0.32 to 64 mg/kg/BW	Male ICR mice	Improve glucose tolerance	GLUT4 translocation; phosphorylation of AMPK	(Takagaki et al. 2019)
	10 mg/kg/BW	Male BALB/c mice	Immunostimulatory activity	Enhancement of CD4+ T cell activity and natural killer cell cytotoxic activity	(Y. H. Kim, Song, et al. 2016)
5-(4′-hydroxyphenyl)-γ-valerolactone	Low (nM) concentrations	Human brain microvascular endothelial cells	Preserve brain vascular endothelial cell integrity	Modulation of cellular pathways including cell adhesion, cytoskeleton organization, focal adhesion signaling pathways, pathways regulating endothelial permeability, and interaction with immune cells.	(Corral-Jara et al. 2021)
	10 pM to 50 nM	Yeast cells	Prevent of β23-induced growth inhibition and reduce the accumulation of A11-reactive amyloid oligomers	N/A	(Ruotolo et al. 2020)
	EC_{50} = 0.1 pM	HEK239 cells	Anti-proteotoxic activity	N/A	(Ruotolo et al. 2020)
	1, 3, 10 μM	AβO-treated C57BL/6 mice	Reduce memory impairment and neuroinflammation	Reduction of glial activation	(Ruotolo et al. 2020)

Note: GLUT4, Glucose transporter 4; AMPK, AMP-activated protein kinase; ACE, Angiotensin I-converting enzyme; SHR, Spontaneously hypertensive rats; NO, nitric xoide; iNOS, inducible NO synthase; PSA, Prostate-specific antigen; AR, Androgen receptor; MCP, Monocyte chemoattractant protein; *β*23, *β*-oligomer-forming polypeptide; AβO, Amyloid-*β* oligomers; N/A, not available.

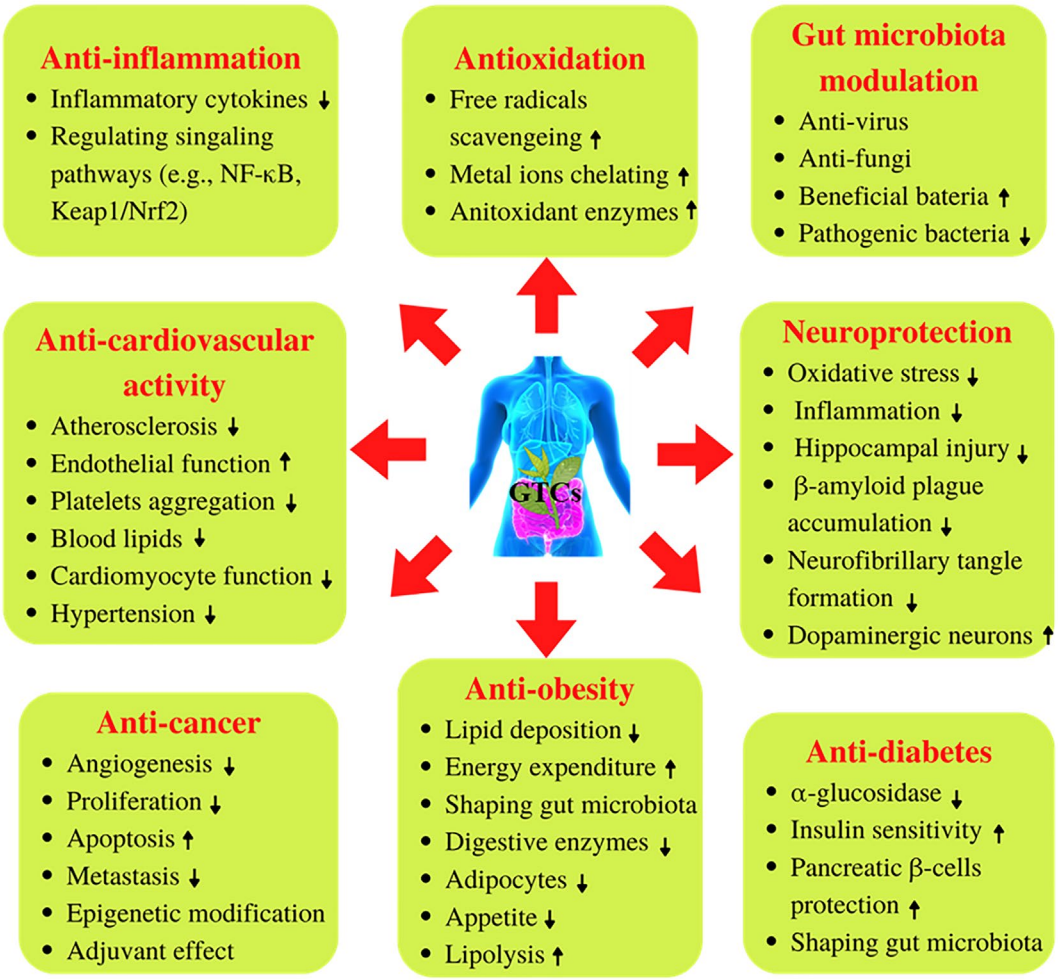

Figure 4. Claimed beneficial effects of GTCs and underlying mechanisms. NF-κB, nuclear factor-κB; Keap/Nrf2, Kelch-like ECH-associated protein 1/nuclear factor E2-related factor 2.

They putatively proposed three metabotypes which were characterized by the different proportions of four important microbial metabolites of GTCs, namely mono-hydroxypheny l-γ-valerolactones, dihydroxyphenyl-γ-valerolactones, trihydroxyphenyl-γ-valerolactones, and hydroxyphenyl propionic acids, quantified in urine samples from different volunteers (Mena, Bresciani, et al. 2019; Mena, Ludwig, et al. 2019). Ottaviani and colleagues conducted another human intervention study with eight participants consuming an EC-containing drink. They also found striking inter-individual differences in both urinary and plasma metabolic profiles of EC microbial metabolites. For example, 3.6- and 3.2-fold differences in colon-derived 5-carbon side-chain ring fission metabolites were detected in the plasma and urine of volunteers. Moreover, the lower molecular weight microbial 3/1-carbon-side chain ring fission metabolites (e.g., phenylbenzoic acids, phenylacetic acids, and phenylpropanoic acids) presented a much more substantial variation (9-fold) (Borges et al. 2018; Ottaviani et al. 2016). This was likely due to the higher number of conversion steps required for producing the lower molecular-weight metabolites, which probably requires the involvement of more types of bacteria to increase the chances of inter-individual differences.

In addition to these in vivo studies, it can be anticipated that in vitro studies using fecal anaerobic incubation models can provide useful alternative models to study colonic metabolism and potential inter-individual variabilities in gut microbial metabolism. For instance, Liu et al. performed anaerobic fecal incubations using fecal samples from 24 individuals to investigate inter-individual variations in human colonic degradation of EC. The results revealed substantial inter-individual differences both in the rate of EC conversion and its metabolite pattern. Specifically, two slow EC metabolizers among 24 volunteers were defined (C. Liu et al. 2020). Similarly, Li and colleagues discovered significant inter-individual variability in metabolic efficiency of (+)-catechin microbial metabolism among 12 tested donor microbiota by using the in vitro anaerobic fecal incubation model (Li et al. 2021).

In contrast to the well-accepted existence of inter-individual differences in human microbiota composition and metabotypes, the intra-individual differences in human gut microbial metabolism are often ignored or considered not evident. This may be the case because the microbial composition is considered to be steady within healthy humans (Bäckhed et al. 2012; Fassarella et al. 2021). To what extent the

intra-individual differences of microbiota composition would cause differences in the metabolic pattern of GTC degradation still awaits to be elucidated. Our recent study compared the intra- and inter-individual differences in the gut microbial metabolism of EC and the concomitant production of the main metabolite 3,4-diHPV showing that intra-individual variations existed in human gut microbial degradation of EC and formation of 3,4-diHPV, though inter-individual differences was more distinct than intra-individual differences (Chen Liu, Boeren, and Rietjens 2022). Another study conducted by Olsson and colleagues elucidated the intra- and inter-individual differences of intestinal microbial profiles in 75 volunteers, and concluded that the intra-individual difference of the intestinal microbial composition and its diagnostic and clinical relevance remain underestimated (Olsson et al. 2022). For instance, some of the functions, such as catabolism of sugars, fermentative processes, and the tricarboxylic acid cycle were predicted to have higher variance within individuals than between individuals (Olsson et al. 2022). The results of these studies indicate the intra-individual difference in the human gut microbiota and the resulting GTC metabolic patterns might be more distinct than generally assumed. Therefore, future studies are encouraged to address which microbes are responsible for the differences in the metabolic patterns of GTCs.

In vitro models to study gut microbial metabolism

As briefly mentioned in the preceding section, in vitro fermentation models using feces as the primary material are considered adequate tools to study the microbial conversion of a wide array of substances, including dietary ingredients, e.g., polysaccharides, polyphenols, dietary fibers, proteins, pathogens, pharmaceuticals, and toxins, without ethical constraints (Aura et al. 2002; Rowland et al. 2018; Titgemeyer et al. 1991). These models can also be used to study microbial modulation effects by food components, toxins, and xenobiotics (Chen et al. 2020; Fehlbaum et al. 2018; Liu et al. 2018; Liu et al. 2020a). Fecal samples have shown to be representative of the luminal microbiota in the distal large intestine in terms of diversity and abundance (Couch et al. 2013; Thomas, Clark, and Doré 2015; van den Bogert et al. 2011). Lagkouvardos et al. performed a comprehensive review on the cultivation of microbiota from the mammalian intestine and concluded that up to 65% of the molecular species detected by sequencing in pig intestinal samples have corresponding strains in the bacterial cultivation (Lagkouvardos, Overmann, and Clavel 2017). Another study compared microbial-related in vivo metabolic changes in feces, cecum content, and gut tissue of rats treated with antibiotics and concluded that feces provides a suitable matrix for studying gut microbial metabolism without the need for invasive sampling methods (Behr et al. 2018). Therefore, fecal anaerobic fermentation models appear to provide a useful approach to characterizing intestinal microbial metabolism. These in vitro fecal fermentation models are mainly divided into two categories: (1) one-compartment fermentation models and (2) dynamic fermentation models (Verhoeckx et al. 2015). Based on different research purposes, researchers could select the appropriate fermentation model based on the advantages and limitations of the two types of models.

One compartment fermentation models are also known as batch (static) fermentation models which are comparatively simple as compared to dynamic fermentation models and normally consist of closed bottles/tubes or controlled reactors inoculated with fecal samples from the selected host (Aura et al. 1999; Ouyang et al. 2020). These models are often used to conduct anaerobic incubations over short-term periods (less than 72 h) as in longer simulations the accumulation of the microbial metabolites may alter the conditions and the microbial composition compared to the conditions and the microbial composition at the initial stage. On the other hand, one-compartment fermentation models are both financially sustainable and allow high-throughput studies. They provide an appropriate approach to studying inter-individual variabilities in intestinal microbial metabolism of food-borne ingredients and xenobiotics (Ouyang et al. 2020). Moreover, these models require small quantities of chemicals of interest and are easy to operate. In addition, the use of the batch (static) fermentation model to define kinetic constants for so-called physiologically based kinetic (PBK) models, like V_{max} and K_m for intestinal microbial metabolism, was previously validated for daidzein metabolism in rats, for which PBK model-based predictions were in agreement with experimental data on C_{max} levels for both daidzein and its gut microbial metabolite S-equol (Mendez-Catala, Wang, and Rietjens 2021; Wang et al. 2020). A similar study for the mycotoxin zearalenone and its gut microsomal metabolite α-zearalenol further supported the use of the anaerobic fecal incubations to define PBK model kinetic parameters (Mendez-Catala, Wang, and Rietjens 2021). Besides these advantages, certain limitations of one-compartment fermentation models are worth mentioning. For example, these models are not able to provide a constant refreshment of nutrients and removal of microbial metabolites. Also, they cannot mimic the dialysis and peristalsis of the intestines (Verhoeckx et al. 2015).

It is also of interest to note that using static anaerobic fecal incubations to characterize gut microbial metabolism, substantial differences were found in the level of deoxynivalenol conversion by the microbiota isolated from the different intestinal segments in chicken. Differences were likely due to the different compositions of the microbiota in different intestinal segments (Jin et al. 2021). Thus, it may be interesting to investigate the metabolic patterns of GTCs converted in anaerobic incubations with samples from different regions of the intestines.

In contrast to static fermentation models, a dynamic fermentation model enables the mimicking of the entire human gastrointestinal tract. One example of such a dynamic fermentation model is the human intestinal microbial ecosystem (SHIME) which consists of multi-compartment reactors to simulate the different conditions of the large intestinal lumen, namely ascending

colon, transverse colon, and descending colon (Koper et al. 2019; Li et al. 2021; Wu et al. 2018). Besides SHIME, other representative dynamic fermentation models are the TNO computer-controlled, dynamic in vitro gastro-Intestinal Model of the colon (TIM-2) and SIMulator Gastro-Intestinal (SIMGI) (Barroso et al. 2015; Minekus et al. 1999). Generally, these dynamic fermentation models are considered to be able to maintain gut microbiota stability for longer timeframes and to simulate peristalsis and dialysis of the gut. The limitations of these dynamic models are also obvious, e.g., requiring large amounts of model compounds, requiring experienced personnel, relatively expensive, and time-consuming (Verhoeckx et al. 2015).

Modulatory effects of GTCs and their microbial metabolites on human gut microbiota

As elaborated in the aforementioned sections, gut microbiota plays a crucial role in the degradation of GTCs and the production of microbial metabolites. Meanwhile, recent studies have shown that the GTCs can, on the other hand, modulate the human intestinal microbial composition, which may also contribute to the effects on hosts' health (Chen et al. 2020; Gowd et al. 2019; Guo et al. 2019; Z. Liu et al. 2020b; Z. Liu, Boeren, and Rietjens 2022). For instance, GTCs and tea infusions have been reported to prevent the decrease in the α-diversity of the gut microbiota induced by the high-fat diet (HFD), ultraviolet B radiation, as well as by selected xenobiotics (Chen and Yang 2020; Jung et al. 2017; Liu et al. 2016; Wang et al. 2018). Moreover, catechins are also able to modulate the relative microbial composition in the gut (Chen and Yang 2020). It has been reported that tea polyphenols can inhibit the growth of pathogenic bacteria including *Bilophila*, *Enterobacteriaceae*, *Escherichia coli* O157:H7, *Fusobacterium varium*, *Helicobacter pylori*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Salmonella typhimurium* DT104 (Chen et al. 2020; Zhang et al. 2018). Beneficial bacteria, such as *Bifidobacterium*, *Akkermansia muciniphila*, and *Lactobacillus*, that could enhance intestinal barrier integrity, and counteract various pathogens were stimulated by tea polyphenols (Chen et al. 2020; Jin et al. 2012; Liao et al. 2016; Ouyang et al. 2020). The selective effects may be due to different interactions of GTCs with cell membranes of the gut microbiota (Bouarab-Chibane et al. 2019). Zhang et al. observed selective prebiotic effects and anti-microbial activities of a catechin metabolite, namely (-)-epigallocatechin 3-*O*-(3-*O*-methyl) gallate (EGCG3"Me), showing preventive effects on weight-gaining in HFD-induced obesity in mice, which may be due to its ameliorating effect on the HFD-induced gut dysbiosis resulting in a decrease of the ratio of *Firmicutes*/*Bacteroidetes* (Zhang et al. 2018). The mechanisms underlying the microbial modulatory effects of tea phenolics could be the result of a series of events, e.g., different sensitivity of bacteria toward polyphenols, a more anaerobic gut environment created by polyphenols, or a tea polyphenol-altered nutrient environment in the gut (Chen and Yang 2020). However, as mentioned previously, GTCs are prone to extensive microbial degradation in the colon, thus producing many metabolites which in turn may also have effects on the microbiota, gut environment and/or nutrient availability. For instance, Lee and colleagues investigated the influence of tea phenolics and their colonic metabolites on gut microbiota and discovered the growth of some pathogenic bacteria, e.g., *Bacteroides* spp., *Clostridium perfringens*, and *Clostridium difficile* was significantly inhibited by GTCs and their metabolites (i.e., gallic acid, 4-hydroxyphenylpropionic acid, phenylpropionic acid, and 4-hydroxyphenylacetic acid), while commensal anaerobes such as *Clostridium* spp. and probiotics such as *Bifidobacterium* spp. and *Lactobacillus* sp. were less severely repressed (Lee et al. 2006). Interestingly, *Clostridium* and *Bacteroides* genera which comprise the majority of the human gut microbiota were more severely inhibited by GTCs' metabolites, e.g., gallic acid, 3-O-methyl gallic acid, and several phenylphenolic acids than by the parent GTCs (Lee et al. 2006). Nevertheless, research focusing on how different microbial metabolites of GTCs can contribute to the gut microbiota modulatory effect of parental catechins remains scarce. With the growing recognition of the importance of integrating the microbiome into nutrition research (Armet et al. 2022), the mechanisms of GTCs and their intestinal microbial metabolites in modulating gut microbiota may become fundamentally meritorious for host health promotion.

Conclusions and perspectives

Regular consumption of green tea has been linked with various health-promoting effects and the bioactive ingredients, catechins, are often reported to be responsible. However, though scientists put many endeavors into figuring out the causality behind it, the low bioavailability of GTCs makes it difficult to make solid conclusions. In this review, the gut microbial metabolic fates of major GTCs were characterized along with a summary of in vitro models that are often used to reveal the microbial metabolism of GTCs. The intra- and inter-individual variations of the driving factor, human gut microbiota, were also introduced, and subsequently, the resulting divergences in the metabolic patterns of GTCs were reviewed. In addition, the role of microbial metabolism in the biological activity of GTCs was discussed with emphasis on the biological contribution of the gut microbial GTC metabolites to the effects of GTCs. Lastly, the modulatory effects of GTCs and their gut microbial metabolites on human gut microbiota were highlighted as another mode of action by which GTCs may affect human health. Due to the existence of intra- and inter-individual differences in host gut microbiota profile, further investigations on the determination of the functional core microbiome, instead of merely determination of the microbiota composition at the microbial organism level, could be more effective and would allow to predict the metabolic patterns and eventually establish 'enterotypes' or 'metabotypes' for GTC metabolism. Moreover, future studies investigating the molecular mechanisms of GTCs are advised to take into consideration the

potential contributions of main intestinal microbial metabolites of GTCs, as they may even have a higher potency than their parent compounds. Besides carrying on studies using verified in vitro models, which are useful to identify functions and mechanisms of GTCs and their metabolites at tissue and molecular level, well-designed essential in vivo animal studies and human interventions are encouraged.

Disclosure statement

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