Chapter 2

Pharmacokinetics and Disposition of Green Tea Catechins

Kai On Chu and Calvin C.P. Pang

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.74190

Abstract

Green tea reportedly possesses many health beneficial effects as a beverage. Its usage has even been elevated to therapeutic level for treatment of diseases, including cancer, after increasing the catechin constituents in green tea extract or through purified catechins compounds. However, the therapeutic effectiveness of green tea extract or catechin formulae on different diseases is still questionable and inconsistent in reported studies. One reason is the low and variable bioavailability of catechins or unknown constituents in green tea extract. The plasma levels of total catechins are usually at submicromolar level which is well below the effective dose in many *in vitro* studies. Besides their variable chemical structures that cause heterogeneity of absorption, green tea catechins are subject to extensive metabolism by phase II process and catabolism by colonic microbes that result in complicated pharmacokinetics. It is essential to understand the factors affecting the pharmacokinetics and metabolic profiles in plasma and tissues based on animal and human studies before green tea catechins can be applied for therapeutic use.

Keywords: green tea extract, catechins, pharmacokinetics, bioavailability, absorption, metabolism

1. Introduction

Tea is the most commonly consumed beverage in most populations across the world. Leaves of the tea plant *Camellia sinensis* were processed by careful steaming and roasting to produce green tea for drinks. The major biologically active constituent of green tea is polyphenols, mainly catechins and their gallate derivatives: (+)-catechin (C), (−)-epicatechin (EC), (−)-gallocatechin (GC), (−)-epigallocatechin (EGC), (−)-catechin-3-gallate (CG), (−)-epicatechin-3-gallate (ECG), gallocatechin-3-gallate (GCG) and (−)-epigallocatechin-3-gallate (EGCG) (**Figure 1**).

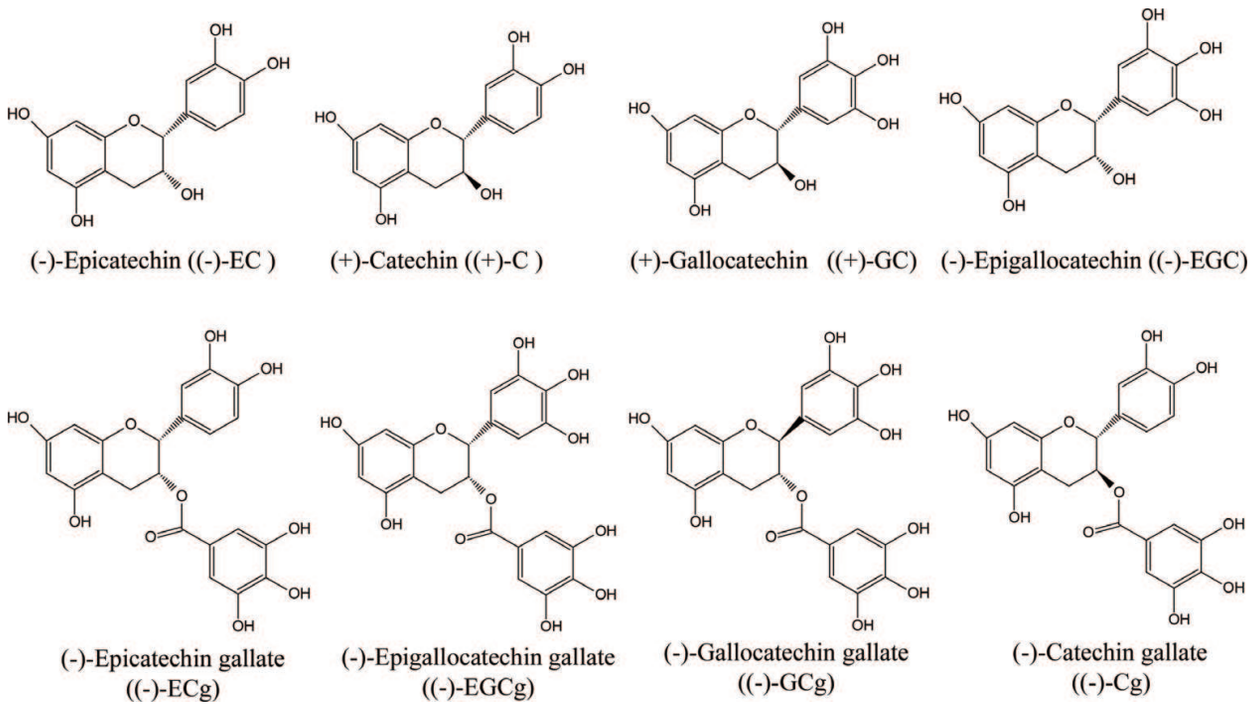

Figure 1. Structures of catechins.

Minor constituents include caffeine, theobromine, and theophylline. Among green tea catechins, EGCG is the most abundant and biologically active based on animal and human studies [1, 2]. The biological activity is attributed to its structure moiety and hydroxyl groups [3].

Health benefits are evident for green tea catechins including anticancer [4] and antimicrobial activities [5]. Cancer prevention has been found in the colon, duodenum, esophagus, stomach, large intestine, liver, lung, mammary glands, and skin [6, 7]. There were *in vitro* anticancer effects on adult T-cell leukemia (ATL) caused by a latent infection of human retrovirus HTLV-1 [8]. Drinking green tea could reduce HTLV-1 provirus load in asymptomatic HTLV-1 carriers [9]. Although the underlying mechanisms for cancer-prevention is not well understood, their antioxidation, free radical scavenger activities [10], and NF-κB inhibitory effect [11] have been attributed as the major factors.

Although biological and intervention studies have indicated various beneficial effects, results of clinical studies are not conclusive [12, 13]. Inconsistent findings may be attributed to variations of methodologies and study conditions such as differences in infusion techniques, consumption behavior, production methods, compositions of green tea constituents, and absorption profiles, among different study cohorts. Pharmacokinetics of green tea catechins have been studied using defined green tea catechin extract (GTE), Polyphenon E, and EGCG with variable doses of administration [14, 15]. Oral bioavailability of tea catechins in human plasma was found having 5 to 50 times lower than the level needed to exert biological activities in *in vitro* systems [16, 17]. Other studies showed very high free EGCG peak plasma concentrations, 300, 1970, and 2020 ng/mL, after ingestion of 3, 5, or 7 capsules of Sunphenon DCF-1 (containing 225, 375, and 525 mg EGCG), which is a green tea extract obtained by a defined protocol [18, 19]. Dosage affects the bioavailability of catechins. Many studies showed large

variations of bioavailability of catechins which is related to their beneficial effects. Understanding the pharmacokinetics of catechins is important.

2. Pharmacokinetics of catechins

It is essential to know the effective concentrations and forms of catechins present in plasma and tissues after ingestion. Pharmacokinetics is a study of the absorption, distribution, metabolism, elimination, and bioavailability of catechins following administration. In brief, after oral administration of green tea or extract, catechins are absorbed from the small intestine and remaining excess catechins pass to the colon. In the small intestine, catechins are conjugated with glucuronic acid, sulfate or by O-methylation. Some catechins with secreted bile in an enterohepatic recirculation process pass into the colon and are degraded into different flavonoid rings by resident microorganisms. The catabolized phenolic acids can be reabsorbed into the circulation and excreted into urine. Catechins, their conjugated metabolites, and a large amount of catabolized small phenolic acids can be distributed to various organs and tissues, absorbed by tissue cells, further metabolized, and perform various biological actions (**Figure 2**).

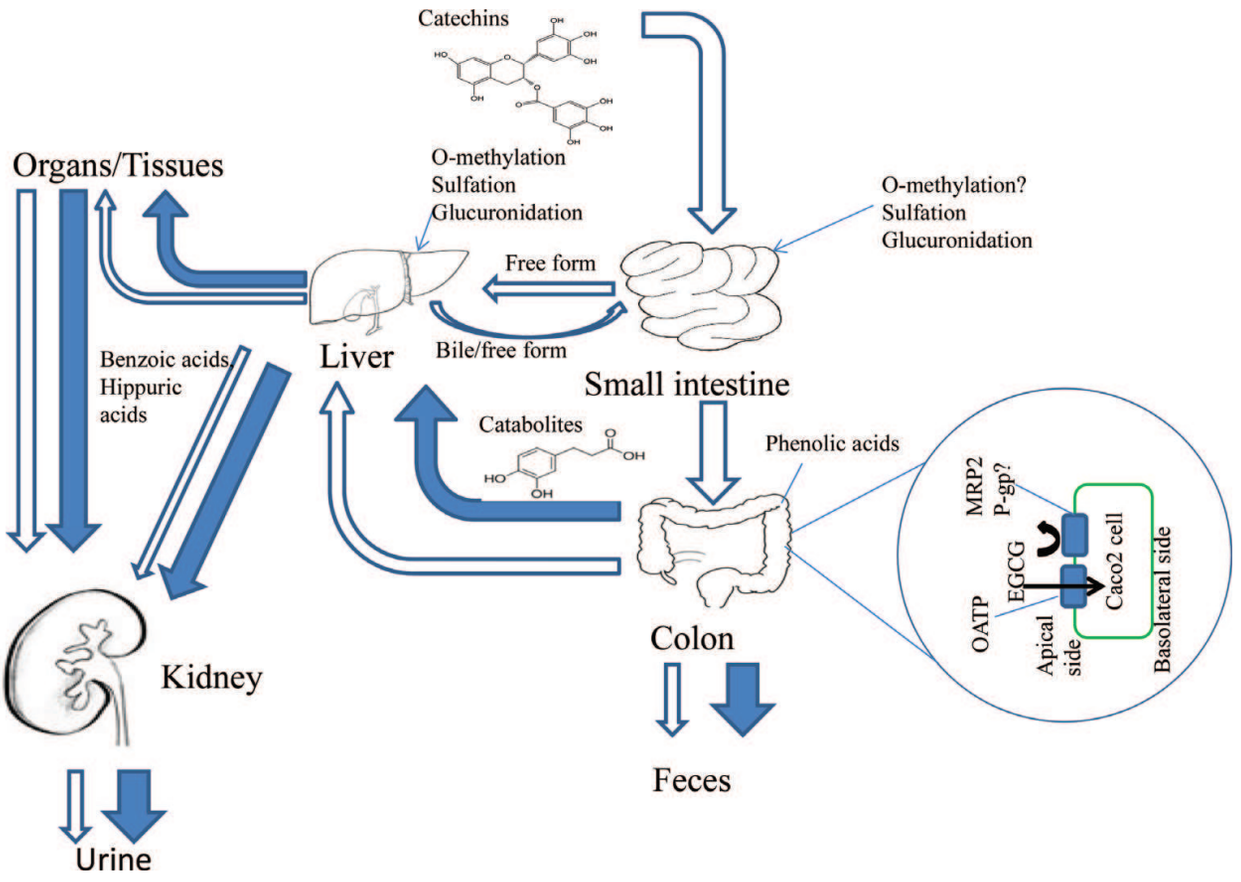

Figure 2. Schematic diagram showing the absorption, distribution, metabolism, elimination of catechins in the body. Thick and fill arrows indicate the flow of large amount of colon metabolites. Thin and hollow arrows depict low amount of present catechins flowing in the body.

3. Absorption

3.1. Conditions affecting absorption

Unlike other flavonoids, catechins exist as aglycone form. Their absorption is not influenced by glucosidase digestion in the small intestine [20]. They can be absorbed directly across the intestinal surface. The absorption depends on the physicochemical properties such as molecular size, steric configuration, solubility, hydrophilicity, pKa, and the presence of galloylated derivatives [21]. The presence of food matrix and drugs in the intestinal cavity also influences the absorption.

The oral bioavailability or catechins absorption is usually relatively low [22, 23]. The plasma concentration is usually 5–50 times less than the effective biological active concentrations in many *in vitro* studies [23]. In one study, green tea extract tablets containing 16.7 mg of EC, 44.9 mg of EGC, 11.1 mg of ECG, and 42.9 mg of EGCG were given to eight human subjects. Their mean maximum plasma levels (Cmax) were 34.7, 60.6, 20.9, and 42.8 ng/mL, respectively [24]. The absorption process of catechins and their metabolites may involve efflux transporters, like multidrug resistance-associated protein 2 (MRP2), in the small intestine resulting in low bioavailability [25]. It has been reported that ungallated catechins were effluxed by MRPs expressed in a Caco-2 monolayer cells model [26]. In human, a non-proportional surge of area under curve (AUC), Cmax, and total and free plasma level of EGCG appeared following increase of oral dosage of a green tea extract (GTE) preparation, Polyphenon E, from 800 to 1200 mg [27]. It was possible that the efflux mechanism was saturated at higher dose causing surge of catechins absorption at high dose.

P-glycoprotein (P-gp) is a transporter or efflux transporter for many molecules including catechins [28, 29]. EGCG can interact with P-gp and affect the absorption of other drugs. On the contrary, co-administration of some drugs can affect the absorption of green tea catechins [30]. Polymorphisms of P-gp in human and *in vitro* studies were associated with variations of Cmax and AUC of catechins after ingestion of green tea extract [31]. Competitive catechin-drug interaction of transporters also reduced plasma concentration of β-blocker nadolol mediated by organic anion-transporter OATP1A2 [32]. Oral catechins absorption can also be affected by food intake. The average maximum free EGCG and EGC plasma concentrations in human, following administration of the GTE Polyphenon E, increased 3.5-fold from the fasting condition. While the total plasma levels of free and conjugated epigallocatechin (EGC) were not affected, the plasma level of total epicatechins was lowered [33]. In addition, the bioavailability of EGCG taken in capsule form was 2.7 and 3.5 times higher from fasting condition than when taken with light breakfast or strawberry sorbet [34].

EGCG is stable in acidic condition as in the stomach but unstable in higher pH in the intestine. After passing through the stomach, the EGCG present in the gastric juice is neutralized by bicarbonate ions secreted by the pancreas in the duodenum where EGCG is degraded rapidly [29, 33]. Only about 1% EGCG can be measured in the small intestines after 1-h incubation [35]. Although the acidic condition in a strawberry sorbet or fruit juice could protect EGCG, the subsequently bicarbonate neutralization still leads to EGCG degradation. In addition, food can

delay gastric emptying rate. The delay would subsequently reduce the Cmax (824.2 ± 75.1 ng/mL for EGCG without food; 231.8 ± 134.3 ng/mL and 218.0 ± 160.0 ng/mL with breakfast and strawberry sorbet) due to prolonging the time to Cmax (Tmax) (60 ± 34.6 min for EGCG without food; 120 ± 34.6 and 120 ± 34.6 min with breakfast and strawberry sorbet).

3.2. Absorption in the presence of food

On the other hand, lower bioavailability is not due to the elimination difference in the presence of food because the half-life of elimination was not significantly different between empty stomach and with food [36]. Moreover, food components could irreversibly and reversibly interact with catechins to affect their absorption in the proximal region of small intestine [37]. It also increased the viscosity of digestive fluid to reduce the dissolution of catechins [38], and induced bile acid secretion to promote elimination of the absorbed catechins. These are factors causing low oral and variable bioavailability of catechins. Despite catechins being stable in the stomach, the oligomer form of catechins, proanthocyanidins, are hydrolyzed to monomer or dimer in the acidic condition [39]. However, an *in vivo* study has not shown hydrolyzed product present in the gastric juice [36].

Milk has been reported to reduce catechin absorption [11] due to interaction with protein molecules [40]. Alcohol increased the solubility of catechins but did not increase plasma levels of catechins [41]. Co-administration of butter with tea, on the other hand, could decrease the Cmax of EGCG, EGC, EC, GCG, GC, and ECG by more than 40%. It also prolonged the mean residence times (MRT) of free EGCG, EGC, EC, GC and ECG by more than 40%. However, the levels of total (free and conjugated) catechins were not affected. Butter could modify catechins metabolism by increasing the conjugation in the intestine possibly through increasing the expression of UGT1A1 [42, 43]. Both forms of catechins excreted into feces increased from 124 to 232%. It suggests biliary secretion of EGCG, EGC, EC, GCG, and GC increased in response to lipid absorption. Similarly, obese SD rats with hyperlipidemia also increased fecal excretion of catechins from 0.52–1.3 to 1.2–3.4% when compared to normal rats. Lipids may alter the metabolism and the relative proportions of the microflora in the colon [44] and, subsequently, affect catechin catabolism. Since catechin catabolites have been attributed to many biological activities [45], the consequence of suppressing catechins metabolism remains to be elucidated. Furthermore, lipids can delay the gastric emptying causing Tmax increase [46]. Chocolate supplement caused the Tmax delay from 1–2 to 3.2–3.8 h [47].

In contrast to a lipid meal, carbohydrate rich meals, could increase the oral bioavailability (AUC) of flavanol by 140% [48]. The bioavailability of EGC and EGCG was significantly enhanced when administered with mixture of GTE (50 mg), sucrose and ascorbic acid (3237.0 and 181.8 pmol*h/L respectively) comparing to green tea (1304.1 and 61.0 pmol*h/L plasma respectively) in Sprague Dawley (SD) rats [49]. In addition, green tea mixed with vitamin C and xylitol also improved flavanols absorption in human. The Cmax, Tmax, and AUC of flavanols in plasma were 5980.58 μg/mL, 2.14 h, and 18,915.56 h.μg/mL, respectively comparing to the AUC of green tea control, 13,855.43 h.μg/mL. Sugar also delays gastric emptying, that in turns delays the Tmax [50]. Ascorbic acid and sucrose can improve catechin absorption through suppressing intestinal effluxing the absorbed catechins and stabilizing catechins in the

lumen. Consistently, there was 6–11 times increase in intestinal uptake of total catechins comparing to green tea control following administered green tea with xylitol/citric acid and xylitol/vitamin C [51].

Besides the effect of food and drug interaction, we found catechins absorption steric and structural dependent [52]. In one study, we fed 550 mg/kg GTE to SD rats. After normalization with the input oral doses, the relative $AUC_{0\text{-}20\ h}$ of epi-isomers in the plasma was higher than its enantiomers, with the level of EGC > GC, EC > C, and EGCG>GCG. Also, the plasma levels of ungallated catechins (EGC, GC, and EC) were higher than gallated catechins (EGCG, GCG,

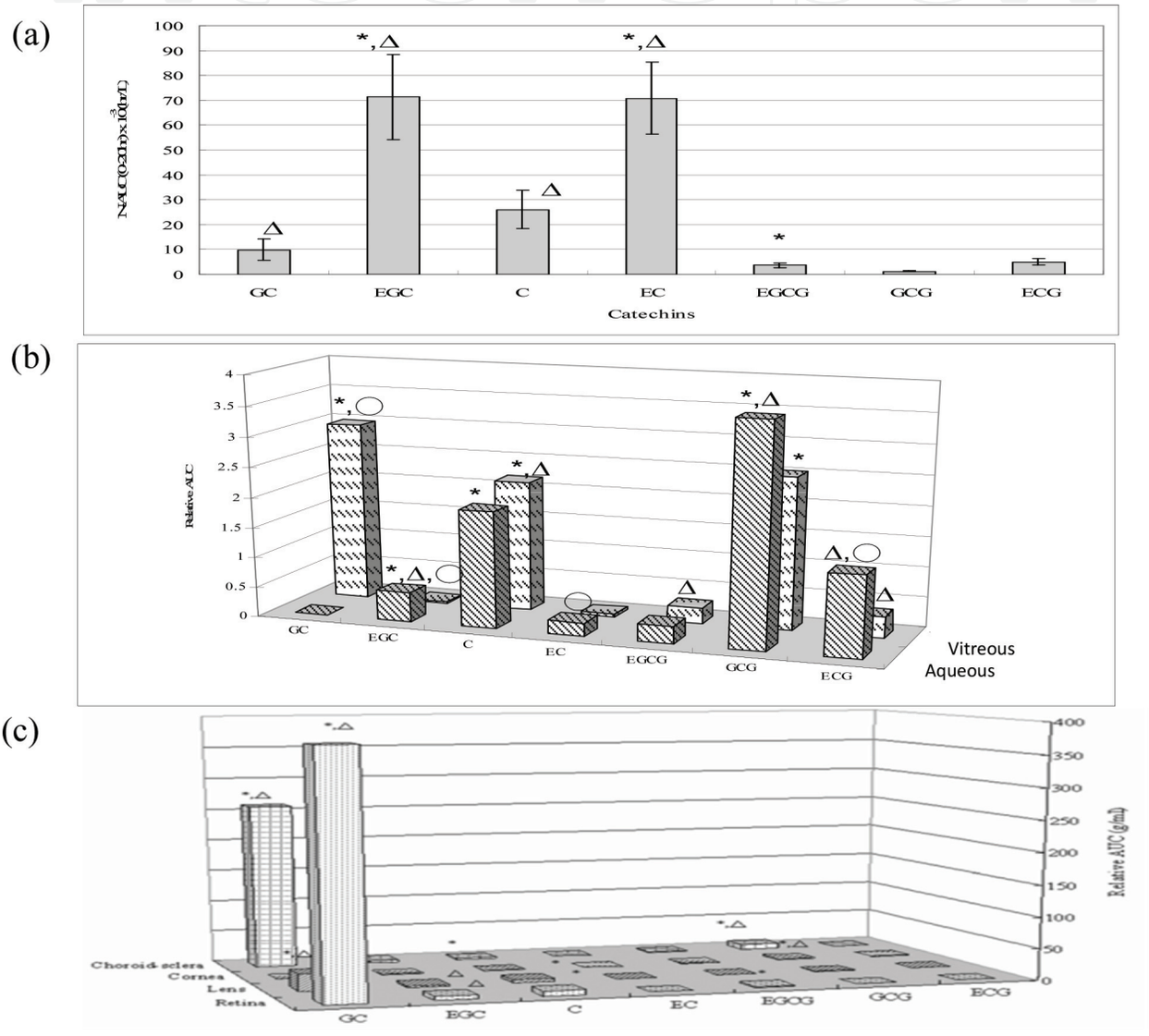

Figure 3. Diagrams showing the normalized relative AUC levels of total catechins (conjugated and free form) in ocular fluid and tissues. (a) Relative AUC levels of different catechins in the plasma after normalization by the corresponding input catechin dose in the GTE. Ungallate levels showed higher than gallate derivatives while epimers were higher than non-epimers. (b) Relative AUC levels of catechins in vitreous and aqueous humor. Vitreous humor showed selective to non-epimer but no selectivity on gallated and ungallated catechins. No particular trends of catechins selectivity appeared in aqueous humor. (c) Relative AUC levels of catechins in retina, lens, cornea and choroids-sclera. Adapted from Chu et al. [52].

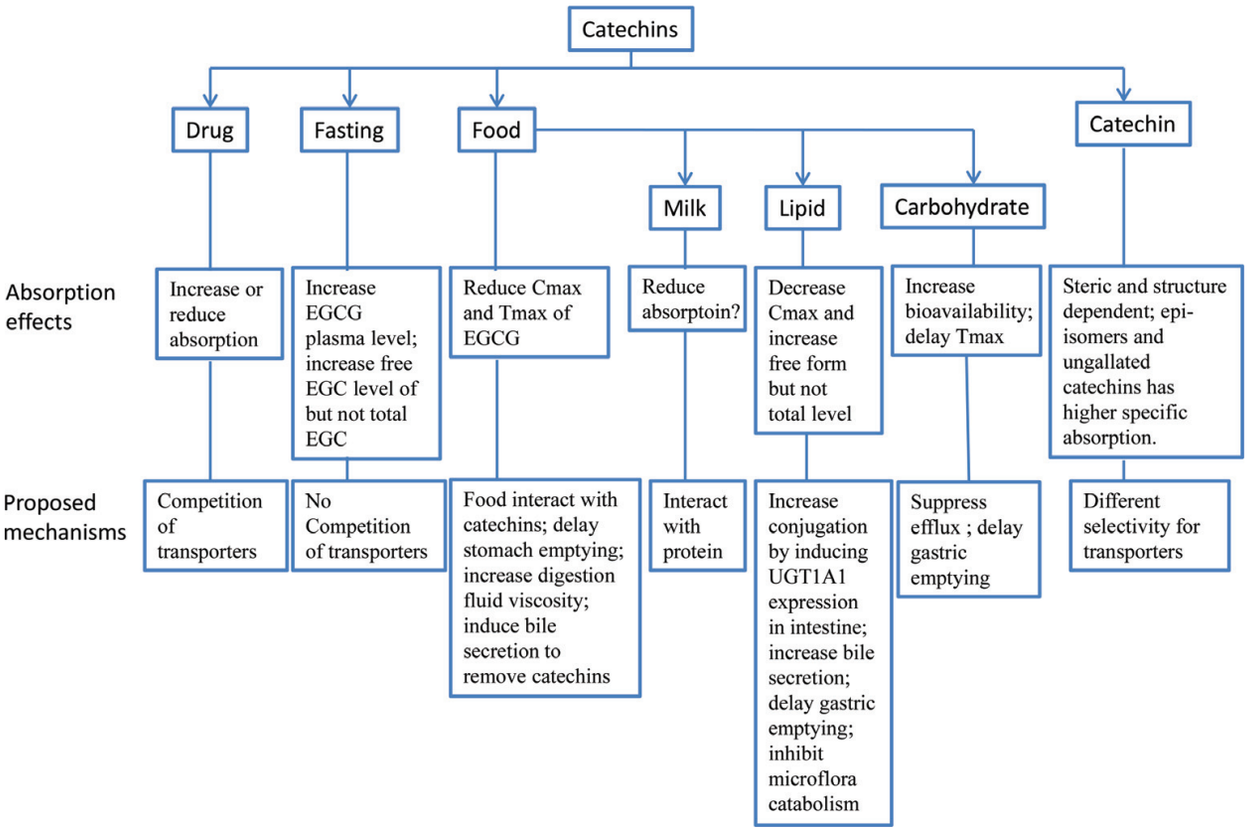

Figure 4. Summary of factors influencing the bioavailability and absorption.

and ECG) (**Figure 3**). Catechins absorption should involve selective mechanisms and different transporters. Moreover, when administrated with another GTE with higher proportion of EGCG orally, the relative AUC of GC is higher than EC while other patterns of the AUC levels remained the same [53]. It indicated that unknown interaction of absorptions between catechins and EGCG promotes catechin absorption. In addition, although EGCG is dominantly present in the GTE, its relative AUC level is very low, suggesting EGCG was not favorably absorbed in the intestine (**Figure 4**).

4. Metabolism

4.1. Effects of conjugations

Catechins are mainly metabolized by phase 2 conjugation processes through methylation, sulfation, and glucuronidation in the intestine and liver after oral administration. Glucuronidation and sulfation mainly occur in the intestine, whereas glucuronidation, sulfation, and methylation occur in the liver. Some conjugates are further methylated. Glucuronidation and sulfation can increase the polarity of catechins to enhance solubility and facilitate their eliminations through urine. EGCG, EGC and EC glucuronide and sulfate were commonly found in plasma [20, 27]. O-methyl-EGC-O-glucuronides and O-methyl-EC-O-sulfates were found in human urine [54] and

methylated EGC conjugates were detected in human plasma after oral GTE administration [55], but the metabolites were not found in plasma in the other study [56].

A large amount of catechins were further catabolized by microflora in the colon, reabsorbed into plasma, and eliminated through urine. Major catechins catabolites were phenylvaleric acid and phenylvalerolactones, such as 5-(3′, 4′, 5′-trihydroxyphenyl)-γ-valerolactone (M4) and 5-(3′, 4′-dihydroxyphenyl)-γ-valerolactone (M6) [57]. They can be further metabolized and shortened to C6-C1 phenolic and aromatic acids, and then reabsorbed to enter the circulation and excreted into urine. These small phenolic acids can be conjugated to valerolactone-3′-O-sulfate, pyrogallol-2-O-sulfate, Pyrogallol-2-O-glucuronide, and vanilloylglycine for excretion in urine [58]. EGC and EC were metabolized into M4 and M6 and excreted likewise. EGCG was metabolized to EGC and 5-(3′,5′-dihydroxyphenyl)-γ-valerolactone in the rat. The amount of metabolites was about 6–39% of the ingested EGC and EC [59]. Elevated hippuric acid (N-benzoylglycine) in excretion after green tea consumption by healthy volunteers comparing to ileostomist also indicated extensive catabolism of catechins in the colon [60].

Owing to extensive metabolism, a wide variety of metabolites of catechins were found in the plasma and urine after green tea consumption [61]. Ten metabolites, in the form of O-methylated, sulfated, and glucuronide conjugates of EC and EGC, were identified in human plasma, where only low levels, 55 and 25 nM, of intact EGCG and ECG were present. The phase II catechin metabolites in urine were about 8% of the total catechin intake. Ileal fluid from ileostomist fed with catechins contained about 33% parent compounds and 37% of 23 catechins conjugates, similar to healthy subjects [62]. About 70% of the ingested catechins that were found as naïve catechins and conjugated metabolites, indicated that catechins were mainly metabolized after glucuronidation, sulfation and methylation, and were effluxed back into the lumen without extensive catabolism in the intestine. These compounds entered into the colon and were subsequently hydrolyzed by resident microflora to remove the conjugated moieties, releasing the aglycones and further catabolized into low molecular weight phenolic acids by ring fission. Consequently, substantial amount of the gallated catechins (47% of input dose) were detected in ileal fluid, and small amount of phenolic acids, pyrocatechol and pyrogallol derived from the gallic acid moiety, were detected in human urine after green tea consumption [63]. Other catabolites, 4-hydroxybenzoic acid, 5-(3,4,5-trihydroxyphenyl)-γ-valeric acid, 3-(3-hydroxyphenyl)-3-hydroxypropionic acid, hippuric acid, 3-methoxy-4-hydroxyphenylacetic acid, and 4-hydroxyphenylacetic acid, were also found in urine. These phenolic acid catabolites account to about 40% of the intake, and would account for the major biological activity of catechins instead of the low bioavailability of the parent compounds.

4.2. Microbial metabolism

The efficiency of microbial metabolism on catechins was well reported in a GTE study on cows [64]. Different doses of GTE was applied intraruminally (10 and 50 mg/kg) and duodenally (10, 20 and 30 mg/kg BW) to dairy cows. No catechin could be found in the plasma for both doses after intraruminal administration. However, plasma concentrations of EC, EGC, and EGCG were increased on increasing dosage after intraduodenal administration. It demonstrated the high metabolism efficiency of ruminal microorganisms under intraruminal administration.

4.3. Effects of metabolism on pharmacokinetics

Catechins are suffered from extensive and different types of metabolisms. Also, some conjugates formation, like sulfates, are resistant to enzymatic hydrolysis during the sample preparation of chemical analysis [65]. These are reasons contributing to the large variation of pharmacokinetics data in reported studies.

Catechins contain many epimers with different steric structures, the enantiomers are absorbed and metabolized differently. For example, absorption of (−)-C was lower than (+)-C [66]. A study on metabolism of flavan-3-ols in human males ingested with equal quantities of (−)-EC, (−)-C, (+)-EC, and (+)-C reported different bioavailability. The plasma and urine showed different levels of stereoisomers with (−)-EC > (+)-EC > (+)-C > (−)-C. Also, different levels of non-methylated conjugations, and 3′- and 4″-O-methylation of epimers were found, indicating stereoisomers can affect the metabolism of each other in the phase II metabolism [67]. Unlike ungallated catechin, the conjugation of gallate derivatives, such as ECG and EGCG, were not found in plasma and urine [68]. The galloyl moiety might inhibit phase II metabolism. In another study, about 50% of ingested EGCG was found from ileal fluid in ileostomists indicating EGCG was hardly absorbed. Only 1% of phase II conjugate of EGCG was detected in ileal fluid, showing excretion of EGCG directly from the enterocytes rather than being metabolized in the liver and entering into the enterohepatic recirculation [69].

5. Distribution

Most distribution studies were conducted in rodents. In one study, green tea polyphenols (0.6%) were given to rats for 8 days. Total (conjugated and free) EGC and EC levels were found in the bladder, large intestine, kidney, lung, and esophagus at 2–3, 1–3, 1–2, 0.5–1, 0.5–0.7 micromole levels, respectively. However, they were almost undetectable in spleen, liver, thyroid, and heart [70]. The total EGCG levels in large intestine, esophagus, and bladder were 1.1, 0.61, and 0.44 micromoles while kidney, prostate, spleen, liver, and lung were undetected. In a 12-day study in mice, Tmax of tea catechins in the lung and liver occurred on Day 4, but the level was decreased from then on. Catechin concentrations in the lung were always higher than that in the liver [67]. In an EGCG study on rats at 500 mg/kg orally, the Cmax of EGCG in the small intestine mucosa, colon mucosa, liver, plasma, and brain were 565, 69, 48, 12, and 0.5 μmol/L, respectively [68]. It appears the level of distribution is related to the extent of catechins contact to the tissues.

Furthermore, we found that catechins can be distributed into various ocular tissues including aqueous humor, vitreous humor, choroid-sclera, retina, lens, and cornea. After feeding 550 mg/kg GTE to SD rats, the Cmax of GC and ECG can reach to more than 10 and 1 μmol/kg, respectively, in the choroid-sclera and retina and 1 μmol/kg in the lens [52] (**Table 1**). Levels of catechins disposed in the ocular tissue could reach the effective dose. In our studies, green tea extract can exert anti-oxidation, anti-inflammation and anti-apoptotic effects on the ocular tissues especially for retina [52, 53, 69]. However, doubled the dose of EGCG in another GTE resulted surge of EGCG deposing in the ocular tissues and caused the retina turning to

	GC	EGC	C	EC	EGCG	GCG	ECG
Cmax (nM)							
Plasma	91.5 ± 57.4	754.9 ± 235.8	139.0 ± 57.0	1258.4 ± 294.0*	310.4 ± 59.9	50.8 ± 10.4	159.1 ± 33.9
Aqueous humor	–	602.9 ± 116.7*	127.4 ± 62.8	138.9 ± 58.5	13.2 ± 5.1	33.5 ± 20.4	47.8 ± 8.1
Vitreous humor	110.6 ± 22.1*	15.9 ± 7.0	96.5 ± 23.3*	20.5 ± 10.6	15.4 ± 2.7	20.9 ± 9.9	14.0 ± 5.1
Cmax (pmol/g)							
Choroid-sclera	11461.8 ± 5168.7*	1506.3 ± 941.1	477.6 ± 346.9	283.5 ± 66.5	184.4 ± 39.0	220.5 ± 69.7	10.7 ± 4.3
Retina	22729.4 ± 4229.4*	8020.8 ± 1658.49*	492.7 ± 235.2	608.0 ± 112.0	259.1 ± 67.2	3.2 ± 1.9	–
Lens	1558.1 ± 318.4*	1172.3 ± 207.8*	300.0 ± 151.5	72.3 ± 19.1	149.1 ± 26.5	18.0 ± 6.6	90.3 ± 45.8
Cornea	–	359.4 ± 66.8*	58.5 ± 15.4	30.6 ± 5.7	25.2 ± 15.5	10.7 ± 3.9	91.1 ± 18.7

Adapted from Chu et.al. [52].
* Indicates that the catechin(s) has significant higher ($p < 0.05$, $n = 6$) level of the parameter in the corresponding biological fluid or tissue than the others as analyzed by compared by nonparametric Kruskal-Wallis H method.

Table 1. Maximum concentration of catechins in plasma, humors, eye tissues after a single dose of 550 mg/kg of Sunphenon DCF-1 green tea extract administrated orally to rats.

pro-oxidative status and reducing the anti-apoptotic effect. Catechins disposition into ocular compartments also exhibited steric selectivity. Vitreous humor was selective to non-epimer catechins but without any structural preference to ungallated catechins as shown in the plasma. Ocular tissues, on the contrary, did not show any specific disposition except GC was dominated in retina, choroid-sclera, and the lens. Of note, it is our study on rat fetus. We also found catechins can penetrate into various fetal tissues, including brain, eye, lung, heart, liver, and kidney, following feeding to pregnant SD rat [71]. However, the Cmax levels of catechins were below micromolar level. The effective biological activity on the fetus is still questionable. Nevertheless, the Cmax of EGCG in the fetal eye could reach to 0.83 μM that may affect the ocular development in this critical stage.

We have found GTE, Theaphenon® E, containing 70% EGCG, exerted biological effects on various ocular diseases models. High oral dose of GTE, 550 mg/kg, suppressed various inflammation responses in the iris and ciliary body, and aqueous humor following LPS-induced ocular inflammation [69]. Our latest unpublished data also showed that it inhibited retina inflammation through reduction of microglial cells and suppression of astroglial reactions. In another sodium iodate-induced retina degeneration model, oral administration of 550 mg/kg Theaphenon® E or catechins mixtures containing 438 mg/kg EGCG could protect retina from disruptive folding caused by sodium iodate [72]. Such effects were possibly exerted through their anti-oxidative effects as demonstrated by the reduction of 8-iso-PGF2α, superoxide dismutase, and glutathione peroxidase levels in the retina. The anti-oxidative properties also contributed to cataract inhibition, through cataracto-static ability as convincingly revealed by Thiagarajan et al. [73]. The antioxidation protection was also supported by our previous study [53]. Theaphenon® E increased the GSH/GSSG ratio and reduced 8-iso-PGF2α level in the lens, although the catechins levels inside the lens was relative low comparing to other ocular tissues.

In a human study, green tea and black tea were given to patients 5 days prior to undergoing prostatectomy surgery. Four main catechins were found in the prostate tissue ranging from 21 to 107 pmol/g [74]. Similar amount of EGCG and 4″-O-methyl EGCG were found in the prostate tissue in a following study [75]. Since only trace amounts of 4″-O-methyl EGCG were present in human plasma after green tea consumption, it suggested that catechol O-methyltransferase was present in prostate to methylate EGCG [76].

6. Elimination

Catechins are mainly cleared through urinary and biliary excretion. Non-galloylated catechins are mainly excreted in urine in the form of parent and conjugated compounds. Galloylate catechins are mainly excreted through biliary excretion to the colon. In one study, minor epi- or gallocatechin-O-sulfates were detected in urine, while aglycones, ECG and EGCG, were absent after green tea consumption [68]. No conjugates of ECG and EGCG were detected in urine suggesting the gallate derivatives did not undergo phase II metabolism. The flavan-3-ol metabolites excreted were equivalent to 8.1% of ingested green tea flavan-3-ols [68]. Other studies found catechin metabolites accounted for 28.5% of intake, whereas gallocatechin metabolites accounted for 11.4% of the ingested (−)-epigallocatechin and (+)-gallocatechin [77]. EGCG cannot be detected in urine showing its elimination is not renal. On the other hand, EGCG may be degalloylated to other catechins in the liver after absorption through small intestine, subsequently metabolized and eliminated into urine resulting EGCG absent in there. However, EGCG and its metabolites could not be found in ileostomists urine suggested EGCG was not eliminated through the internal degalloylation process [78] because EGCG could be absorbed through colon and eliminated directly into urine. In addition, the half-lives of non-gallated catechins, EGC and EC, were shorter than gallated catechins, EGCG and ECg [31]. It may be because the more hydrophobic gallated catechins bind stronger to serum proteins and exist in non-conjugated free form that is not favorable for renal excretion [79, 80]. On the other hand, oral administration of catechins in rats found relative amounts of EC, EGCG, and ECG, respectively, at 4.72, 0.17, and 0.25% in urine and 11.0, 7.89, and 5.80% in feces [81]. In an isotope tracing study in rats, about 77% of the total radioactivity was present in bile but only 2.0% in the urine after intravenous administration of [4-^{3}H]-EGCG [82]. These evidences suggested that the galloyl catechin are excreted through the bile and eliminated through the feces.

In our study on GTE, Sunphenon, the elimination rates of catechins in retina and choroid-sclera were in general higher than the humors and plasma. The elimination rate was from 0.19 h^{-1} for GC to 2.4 h^{-1} in the retina, while the rate was from 0.04 for EGC to 0.24 for ECG in vitreous humor in SD rats [52]. However, when the dose of EGCG was doubled in another GTE, Theaphenon® E, we found the elimination rates of all catechins in the ocular tissues, particularly the retina, lower than the plasma [53] (**Table 2**). It appeared that some active elimination or metabolic mechanisms in ocular tissues facilitated the elimination. The elimination mechanism actively removed the catechins in the ocular tissues, but the mechanism was suppressed by the increased EGCG concentration. On the other hand, in our rat fetus study,

	GC	EGC	C	EC	EGCG	GCG	ECG
λz (h^{-1})							
(a)							
Plasma	0.107 ± 0.010	0.213 ± 0.015	0.104 ± 0.038	0.371 ± 0.000*	0.236 ± 0.007	0.171 ± 0.013	0.211 ± 0.010
Aqueous humor	–	0.045 ± 0.001	0.209 ± 0.012	0.093 ± 0.062	0.304 ± 0.012*	0.111 ± 0.033	0.124 ± 0.043
Vitreous humor	0.166 ± 0.010	0.041 ± 0.001	0.106 ± 0.030	0.067 ± 0.004	0.058 ± 0.012	0.042 ± 0.006	0.224 ± 0.035*
Choroid-sclera	0.057 ± 0.001	0.461 ± 0.015	0.220 ± 0.014	0.488 ± 0.007	0.267 ± 0.019	0.929 ± 0.049*	–
Retina	0.188 ± 0.045	0.203 ± 0.050	0.245 ± 0.010	2.432 ± 0.154*	0.413 ± 0.040	–	–
Lens	0.302 ± 0.049*	0.084 ± 0.020	0.234 ± 0.032	0.049 ± 0.004	0.269 ± 0.011	3.16 ± 0.13	–
Cornea	–	0.170 ± 0.031	0.116 ± 0.007	0.043 ± 0.012	0.125 ± 0.001	0.372 ± 0.006	0.477 ± 0.021*
(b)							
Plasma	0.27 ± 0.03	0.39 ± 0.04	0.37 ± 0.08	0.40 ± 0.05	0.23 ± 0.02	1.25 ± 0.38	0.21 ± 0.04
Aqueous humor	0.11 ± 0.02	0.24 ± 0.02	0.13 ± 0.03	0.21 ± 0.04	0.09 ± 0.02	–	0.13 ± 0.12
Vitreous humor	0.02 ± 0.01*	0.11 ± 0.09	0.11 ± 0.06	0.10 ± 0.03	0.08 ± 0.02	–	–
Choroid-sclera	–	0.25 ± 0.09	0.22 ± 0.09	0.37 ± 0.06	0.08 ± 0.04*	–	0.15 ± 0.07
Retina	–	0.04 ± 0.03	0.04 ± 0.01	0.06 ± 0.02	0.04 ± 0.02	–	0.09 ± 0.03
Lens	–	–	–	–	0.13 ± 0.06	–	–
Cornea	–	–	0.22 ± 0.10	0.22 ± 0.10	0.09 ± 0.02*	–	0.10 ± 0.09

Adapted from (a) Chu et al. [52] and (b) Chu et al. [53].
* Indicates that the catechin(s) has significant higher ($p < 0.05$, $n = 6$) level of the parameter in the corresponding biological fluid or tissue than the others as analyzed by compared by nonparametric Kruskal-Wallis H method.

Table 2. Elimination of catechins in plasma, humors, eye tissues after a single dose of 550 mg/kg of (a) Sunphenon DCF-1 green tea extract, and (b) Theaphenon® E administrated orally to rats.

the elimination rates of catechins in the maternal plasma, in general, were faster than the fetal tissues. The elimination rate of GC and EC were 0.26 and 0.3 h^{-1} for maternal plasma, whereas 0.08 and 0.1 h^{-1} for fetal kidney [71].

7. Conclusions

Many pharmacokinetics studies of green tea catechins were conducted on rodents and less studies in rabbits, dogs, or human. Most of them are oral administration studies. Although the plasma levels of total catechins are at submicromolar level, which is below the effective dose in many *in vitro* studies, tissue dispositions could be much higher. Ungallated catechins are mainly metabolized by phase II process in the small intestine and liver to form glucuronide/sulfate conjugates in the plasma and urine while gallated catechins mostly remain intact in the plasma and are excreted through bile and metabolized by microflora in the colon. High levels of small metabolized phenolic acids can be reabsorbed into blood stream that may contribute to the *in vivo* biological effects.

Catechins can be widely distributed into various tissues including lung, eye, brain, gastrointestinal tract, kidney, bladder, and even passing through the placenta to the fetal organs. The disposition can be stereo-specific, and affected by food, drug, and catechins themselves indicating the absorption and distribution may involve some sort of transporters mechanisms. Before applying green tea catechins for therapeutic purpose, it is essential to understand their pharmacokinetics behavior and metabolites profiles not only in the plasma but also in various tissues in animals and in humans.

Author details

Kai On Chu and Calvin C.P. Pang*

*Address all correspondence to: cppang@cuhk.edu.hk

Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Hong Kong

References

[1] Pastore RL, Fratellone P. Potential health benefits of green tea (Camellia sinensis): A narrative review. Explore (New York, NY). 2006;**2**:531-539. DOI: 10.1016/j.explore.2006.08.008

[2] Yang CS, Lambert JD, Ju J, Lu G, Sang S. Tea and cancer prevention: Molecular mechanisms and human relevance. Toxicology and Applied Pharmacology. 2007;**224**:265-273. DOI: 10.1016/j.taap.2006.11.024

[3] Du GJ, Zhang Z, Wen XD, Yu C, Calway T, Yuan CS, Wang CZ. Epigallocatechin Gallate (EGCG) is the most effective cancer chemopreventive polyphenol in green tea. Nutrients. 2012;**4**:1679-1691

[4] Butt MS, Ahmad RS, Sultan MT, Qayyum MM, Naz A. Green tea and anticancer perspectives: Updates from last decade. Critical Reviews in Food Science and Nutrition. 2015;**55**: 792-805. DOI: 10.1080/10408398.2012.680205

[5] Friedman M, Henika PR, Levin CE, Mandrell RE, Kozukue N. Antimicrobial activities of tea catechins and theaflavins and tea extracts against *Bacillus cereus*. Journal of Food Protection. 2006;**69**:354-361

[6] Serafini M, Ghiselli A, Ferro-Luzzi A. In vivo antioxidant effect of green and black tea in man. European Journal of Clinical Nutrition. 1996;**50**:28-32

[7] Dreosti IE, Wargovich MJ, Yang CS. Inhibition of carcinogenesis by tea: The evidence from experimental studies. Critical Reviews in Food Science and Nutrition. 1997;**37**:761-770. DOI: 10.1080/10408399709527801

[8] Li HC, Yashiki S, Sonoda J, Lou H, Ghosh SK, Byrnes JJ, Lema C, Fujiyoshi T, Karasuyama M, Sonoda S. Green tea polyphenols induce apoptosis in vitro in peripheral blood T lymphocytes of adult T-cell leukemia patients. Japanese Journal of Cancer Research. 2000;**91**:34-40

[9] Sonoda J, Koriyama C, Yamamoto S, Kozako T, Li HC, Lema C, Yashiki S, Fujiyoshi T, Yoshinaga M, Nagata Y, Akiba S, Takezaki T, Yamada K, Sonoda S. HTLV-1 provirus load in peripheral blood lymphocytes of HTLV-1 carriers is diminished by green tea drinking. Cancer Science. 2004;**95**:596-601

[10] Leung LK, Su Y, Chen R, Zhang Z, Huang Y, Chen ZY. Theaflavins in black tea and catechins in green tea are equally effective antioxidants. The Journal of Nutrition. 2001; **131**:2248-2251

[11] Gu JW, Makey KL, Tucker KB, Chinchar E, Mao X, Pei I, Thomas EY, Miele L. EGCG, a major green tea catechin suppresses breast tumor angiogenesis and growth via inhibiting the activation of HIF-1α and NFκB, and VEGF expression. Vascular Cell. 2013;**5**:9. DOI: 10.1186/2045-824X-5-9

[12] Zhong L, Goldberg MS, Gao YT, Hanley JA, Parent ME, Jin F. A population-based case-control study of lung cancer and green tea consumption among women living in Shanghai, China. Epidemiology. 2001;**12**:695-700

[13] Nagano J, Kono S, Preston DL, Mabuchi K. A prospective study of green tea consumption and cancer incidence, Hiroshima and Nagasaki (Japan). Cancer Causes & Control. 2001; **12**:501-508

[14] Chow HH, Cai Y, Alberts DS, Hakim I, Dorr R, Shahi F, Crowell JA, Yang CS, Hara Y. Phase I pharmacokinetic study of tea polyphenols following single-dose administration of epigallocatechin gallate and polyphenon E. Cancer Epidemiology, Biomarkers & Prevention. 2001;**10**:53-58

[15] Chow HH, Cai Y, Hakim IA, Crowell JA, Shahi F, Brooks CA, Dorr RT, Hara Y, Alberts DS. Pharmacokinetics and safety of green tea polyphenols after multiple-dose administration of epigallocatechin gallate and polyphenon E in healthy individuals. Clinical Cancer Research. 2003;**9**:3312-3319

[16] Hong J, Smith TJ, Ho CT, August DA, Yang CS. Effects of purified green and black tea polyphenols on cyclooxygenase- and lipoxygenase-dependent metabolism of arachidonic acid in human colon mucosa and colon tumor tissues. Biochemical Pharmacology. 2001; **62**:1175-1183

[17] Jung YD, Kim MS, Shin BA, Chay KO, Ahn BW, Liu W, Bucana CD, Gallick GE, Ellis LM. EGCG, a major component of green tea, inhibits tumour growth by inhibiting VEGF induction in human colon carcinoma cells. British Journal of Cancer. 2001;**84**:844-850. DOI: 10.1054/bjoc.2000.1691

[18] Nakagawa K, Okuda S, Miyazawa T. Dose-dependent incorporation of tea catechins, (−)-epigallocatechin-3-gallate and (−)-epigallocatechin, into human plasma. Bioscience, Biotechnology, and Biochemistry. 1997;**61**:1981-1985

[19] Yang CS, Chen L, Lee MJ, Balentine D, Kuo MC, Schantz SP. Blood and urine levels of tea catechins after ingestion of different amounts of green tea by human volunteers. Cancer Epidemiology, Biomarkers & Prevention. 1998;**7**:351-354

[20] Sesink AL, Arts IC, Faassen-Peters M, Hollman PC. Intestinal uptake of quercetin-3-glucoside in rats involves hydrolysis by lactase phlorizin hydrolase. The Journal of Nutrition. 2003;**133**:773-776

[21] Lee MJ, Wang ZY, Li H, Chen L, Sun Y, Gobbo S, Balentine DA, Yang CS. Analysis of plasma and urinary tea polyphenols in human subjects. Cancer Epidemiology, Biomarkers & Prevention. 1995;**4**:393-399

[22] Chen L, Lee MJ, Li H, Yang CS. Absorption, distribution, elimination of tea polyphenols in rats. Drug Metabolism and Disposition. 1997;**25**:1045-1050

[23] Lambert JD, Lee MJ, Lu H, Meng X, Hong JJ, Seril DN, Sturgill MG, Yang CS. Epigallocatechin-3-gallate is absorbed but extensively glucuronidated following oral administration to mice. The Journal of Nutrition. 2003;**133**:4172-4177

[24] Narumi K, Sonoda J, Shiotani K, Shigeru M, Shibata M, Kawachi A, Tomishige E, Sato K, Motoya T. Simultaneous detection of green tea catechins and gallic acid in human serum after ingestion of green tea tablets using ion-pair high-performance liquid chromatography with electrochemical detection. Journal of Chromatography. B, Analytical Technologies in the Biomedical and Life Sciences 2014;945–946:147-153. DOI: 10.1016/j.jchromb.2013.11.007

[25] Hong J, Lambert JD, Lee SH, Sinko PJ, Yang CS. Involvement of multidrug resistance-associated proteins in regulating cellular levels of (−)-epigallocatechin-3-gallate and its methyl metabolites. Biochemical and Biophysical Research Communications. 2003;**310**:222-227

[26] Zhang L, Zheng Y, Chow MS, Zuo Z. Investigation of intestinal absorption and disposition of green tea catechins by Caco-2 monolayer model. International Journal of Pharmaceutics. 2004;**287**:1-12. DOI: 10.1016/j.ijpharm.2004.08.020

[27] Chow HH, Hakim IA, Vining DR, Crowell JA, Ranger-Moore J, Chew WM, Celaya CA, Rodney SR, Hara Y, Alberts DS. Effects of dosing condition on the oral bioavailability of green tea catechins after single-dose administration of Polyphenon E in healthy individuals. Clinical Cancer Research. 2005;**11**:4627-4633. DOI: 10.1158/1078-0432.CCR-04-2549

[28] Song Q, Li D, Zhou Y, Yang J, Yang W, Zhou G, Wen J. Enhanced uptake and transport of (+)-catechin and (−)-epigallocatechin gallate in niosomal formulation by human intestinal Caco-2 cells. International Journal of Nanomedicine. 2014;**9**:2157-2165. DOI: 10.2147/IJN.S59331

[29] Spencer JP. Metabolism of tea flavonoids in the gastrointestinal tract. The Journal of Nutrition. 2003;**133**:3255S-3261S

[30] Jodoin J, Demeule M, Beliveau R. Inhibition of the multidrug resistance P-glycoprotein activity by green tea polyphenols. Biochimica et Biophysica Acta. 2002;**1542**:149-159

[31] Hung CC, Chiou MH, Teng YN, Hsieh YW, Huang CL, Lane HY. Functional impact of ABCB1 variants on interactions between P-glycoprotein and methadone. PLoS One. 2013; **8**:e59419. DOI: 10.1371/journal.pone.0059419

[32] Misaka S, Yatabe J, Müller F, Takano K, Kawabe K, Glaeser H, Yatabe MS, Onoue S, Werba JP, Watanabe H, Yamada S, Fromm MF, Kimura J. Green tea ingestion greatly reduces plasma concentrations of nadolol in healthy subjects. Clinical Pharmacology and Therapeutics. 2014;**95**:432-438. DOI: 10.1038/clpt.2013.241

[33] Spencer JP, Schroeter H, Rechner AR, Rice-Evans C. Bioavailability of flavan-3-ols and procyanidins: Gastrointestinal tract influences and their relevance to bioactive forms in vivo. Antioxidants & Redox Signaling. 2001;**3**:1023-1039. DOI: 10.1089/152308601317203558

[34] Naumovski N, Blades BL, Roach PD. Food inhibits the oral bioavailability of the major green tea antioxidant epigallocatechin gallate in humans. Antioxidants (Basel). 2015;**4**:373-393. DOI: 10.3390/antiox4020373

[35] Tenore GC, Campiglia P, Giannetti D, Novellino E. Simulated gastrointestinal digestion, intestinal permeation and plasma protein interaction of white, green, and black tea polyphenols. Food Chemistry. 2015;**169**:320-326. DOI: 10.1016/j.foodchem.2014.08.006

[36] Rios LY, Bennett RN, Lazarus SA, Rémésy C, Scalbert A, Williamson G. Cocoa procyanidins are stable during gastric transit in humans. The American Journal of Clinical Nutrition. 2002;**76**:1106-1110

[37] Welling PG. Effects of food on drug absorption. Annual Review of Nutrition. 1996;**16**:383-415. DOI: 10.1146/annurev.nu.16.070196.002123

[38] Reppas C, Eleftheriou G, Macheras P, Symillides M, Dressman JB. Effect of elevated viscosity in the upper gastrointestinal tract on drug absorption in dogs. European Journal of Pharmaceutical Sciences. 1998;**6**:131-139

[39] Spencer JP, Chaudry F, Pannala AS, Srai SK, Debnam E, Rice-Evans C. Decomposition of cocoa procyanidins in the gastric milieu. Biochemical and Biophysical Research Communications. 2000;**272**:236-241. DOI: 10.1006/bbrc.2000.2749

[40] Hollman PC, Van Het Hof KH, Tijburg LB, Katan MB. Addition of milk does not affect the absorption of flavonols from tea in man. Free Radical Research. 2001;**34**:297-300

[41] Donovan JL, Bell JR, Kasim-Karakas S, German JB, Walzem RL, Hansen RJ, Waterhouse AL. Catechin is present as metabolites in human plasma after consumption of red wine. The Journal of Nutrition. 1999;**129**:1662-1668

[42] Zhang L, Han Y, Xu L, Liang Y, Chen X, Li J, Wan X. The effects of co-administration of butter on the absorption, metabolism and excretion of catechins in rats after oral administration of tea polyphenols. Food & Function. 2015;**6**:2249-2256. DOI: 10.1039/c5fo00114e

[43] Osabe M, Sugatani J, Fukuyama T, Ikushiro S, Ikari A, Miwa M. Expression of hepatic UDP-glucuronosyltransferase 1A1 and 1A6 correlated with increased expression of the

nuclear constitutive androstane receptor and peroxisome proliferator-activated receptor alpha in male rats fed a high-fat and high-sucrose diet. Drug Metabolism and Disposition. 2008;**36**:294-302. DOI: 10.1124/dmd.107.017731

[44] Xu LW, Liang YH, Chen X, Chen B, Han YH, Zhang L. Hyperlipidemia affects the absorption, distribution and excretion of seven catechins in rats following oral administration of tea polyphenols. RSC Advances. 2015;**5**:97988-97994. DOI: 10.1039/C5RA19699J

[45] Chow HH, Hakim IA. Pharmacokinetic and chemoprevention studies on tea in humans. Pharmacological Research. 2011;**64**:105-112. DOI: 10.1016/j.phrs.2011.05.007

[46] Gentilcore D, Chaikomin R, Jones KL, Russo A, Feinle-Bisset C, Wishart JM, Rayner CK, Horowitz M. Effects of fat on gastric emptying of and the glycemic, insulin, and incretin responses to a carbohydrate meal in type 2 diabetes. The Journal of Clinical Endocrinology and Metabolism. 2006;**91**:2062-2067. DOI: 10.1210/jc.2005-2644

[47] Mullen W, Borges G, Donovan JL, Edwards CA, Serafini M, Lean MEJ, Crozier A. Milk decreases urinary excretion but not plasma pharmacokinetics of cocoa flavan-3-ol metabolites in humans. The American Journal of Clinical Nutrition. 2009;**89**:1784-1791. DOI: 10.3945/ajcn.2008.27339

[48] Schramm DD, Karim M, Schrader HR, Holt RR, Kirkpatrick NJ, Polagruto JA, Ensunsa JL, Schmitz HH, Keen CL. Food effects on the absorption and pharmacokinetics of cocoa flavanols. Life Sciences. 2003;**73**:857-869

[49] Peters CM, Green RJ, Janle EM, Ferruzzi MG. Formulation with ascorbic acid and sucrose modulates catechin bioavailability from green tea. Food Research International. 2010;**43**: 95-102. DOI: 10.1016/j.foodres.2009.08.016

[50] Phillips WT, Schwartz JG, Blumhardt R, McMahan CA. Linear gastric-emptying of hyperosmolar glucose solutions. Journal of Nuclear Medicine. 1991;**32**:377-381

[51] Shim SM, Yoo SH, Ra CS, Kim YK, Chung JO, Lee SJ. Digestive stability and absorption of green tea polyphenols: Influence of acid and xylitol addition. Food Research International. 2012;**45**:204-210. DOI: 10.1016/j.foodres.2011.10.016

[52] Chu KO, Chan KP, Wang CC, Chu CY, Li WY, Choy KW, Rogers MS, Pang CP. Green tea catechins and their oxidative protection in the rat eye. Journal of Agricultural and Food Chemistry. Feb 10, 2010;**58**:1523-1534. DOI: 10.1021/jf9032602

[53] Chu KO, Chan KP, Y2 Y, Qin YJ, Li WY, Chan SO, Wang CC, Pang CP. Effects of EGCG content in green tea extract on pharmacokinetics, oxidative status and expression of inflammatory and apoptotic genes in the rat ocular tissues. The Journal of Nutritional Biochemistry. 2015;**26**:1357-1367. DOI: 10.1016/j.jnutbio.2015.07.001

[54] Li C, Meng X, Winnik B, Lee MJ, Lu H, Sheng S, Buckley B, Yang CS. Analysis of urinary metabolites of tea catechins by liquid chromatography/electrospray ionization mass spectrometry. Chemical Research in Toxicology. 2001;**14**:702-707

[55] Meng X, Lee MJ, Li C, Sheng S, Zhu N, Sang S, Ho CT, Yang CS. Formation and identification of 4'-O-methyl-(−)-epigallocatechin in humans. Drug Metabolism and Disposition. 2001;**29**:789-793

[56] Wang JS, Luo H, Wang P, Tang L, Yu J, Huang T, Cox S, Gao W. Validation of green tea polyphenol biomarkers in a phase II human intervention trial. Food and Chemical Toxicology. 2008;**46**:232-240. DOI: 10.1016/j.fct.2007.08.007

[57] Li C, Lee MJ, Sheng S, Meng X, Prabhu S, Winnik B, Huang B, Chung JY, Yan S, Ho CT, et al. Structural identification of two metabolites of catechins and their kinetics in human urine and blood after tea ingestion. Chemical Research in Toxicology. 2000;**13**:177-184

[58] van der Hooft JJJ, de Vos RCH, Mihaleva V, Bino RJ, Ridder L, de Roos N, Jacobs DM, van Duynhoven J, Vervoort J. Structural elucidation and quantification of phenolic conjugates present in human urine after tea intake. Analytical Chemistry. 2012;**84**:7263-7271. DOI: 10.1021/ac3017339

[59] Kohri T, Matsumoto N, Yamakawa M, Suzuki M, Nanjo F, Hara Y, Oku N. Metabolic fate of (−)-[4-(3)H]epigallocatechin gallate in rats after oral administration. Journal of Agricultural & Food Chemistry. 2001;**49**:4102-4112. DOI: 10.1021/jf001491+

[60] Mulder TP, Rietveld AG, van Amelsvoort JM. Consumption of both black tea and green tea results in an increase in the excretion of hippuric acid into urine. The American Journal of Clinical Nutrition. 2005;**81**(Suppl):256S-260S

[61] Stalmach A, Troufflard S, Serafini M, Crozier A. Absorption, metabolism and excretion of Choladi green tea flavan-3-ols by humans. Molecular Nutrition & Food Research. 2009;**53** (Suppl 1):S44-S53. DOI: 10.1002/mnfr.200800169

[62] Stalmach A, Mullen W, Steiling H, Williamson G, Lean ME, Crozier A. Absorption, metabolism, and excretion of green tea flavan-3-ols in humans with an ileostomy. Molecular Nutrition & Food Research. 2010;**54**:323-334. DOI: 10.1002/mnfr.200900194

[63] Roowi S, Stalmach A, Mullen W, Lean ME, Edwards CA, Crozier A. Green tea flavan-3-ols: Colonic degradation and urinary excretion of catabolites by humans. Journal of Agricultural and Food Chemistry. 2010;**58**:1296-1304. DOI: 10.1021/jf9032975

[64] Wein S, Beyer B, Gohlke A, Blank R, Metges CC, Wolffram S. Systemic absorption of catechins after intraruminal or intraduodenal application of a green tea extract in cows. PLoS One. 2016;**11**:e0159428. DOI: 10.1371/journal.pone.0159428

[65] Saha S, Hollands W, Needs PW, Ostertag LM, de Roos B, Duthie GG, Kroon PA. Human O-sulfated metabolites of (2)-epicatechin and methyl-(2)-epicatechin are poor substrates for commercial aryl-sulfatases: Implications for studies concerned with quantifying epicatechin bioavailability. Pharmacological Research. 2012;**65**:592-602. DOI: 10.1016/j.phrs.2012.02.005

[66] Donovan JL, Crespy V, Oliveira M, Cooper KA, Gibson BB, Williamson G. (+)-Catechin is more bioavailable then (−)-catechin: Relevance to the bioavailability of catechin from cocoa. Free Radical Research. 2006;**40**:1029-1034. DOI: 10.1080/10715760600868545

[67] Ottaviani JI, Momma TY, Heiss C, Kwik-Uribe C, Schroeter H, Keen CL. The sterochemical configuration of flavanols influences the level and metabolism of flavanols in humans and their biological activity in vivo. Free Radical Biology & Medicine. 2011;**50**: 237-244. DOI: 10.1016/j.freeradbiomed.2010.11.005

[68] Nakagawa K, Miyazawa T. Absorption and distribution of tea catechin, (−)-epigallocatechin-3- gallate, in the rat. Journal of Nutritional Science & Vitaminology. 1997;**43**:679-684

[69] Qin YJ, Chu KO, Yip YW, Li WY, Yang YP, Chan KP, Ren JL, Chan SO, Pang CP. Green tea extract treatment alleviates ocular inflammation in a rat model of endotoxin-induced uveitis. PLoS One. 2014;**9**:e103995. DOI: 10.1371/journal.pone.0103995

[70] Kim S, Lee MJ, Hong J, Li C, Smith TJ, Yang GY, Seril DN, Yang CS. Plasma and tissue levels of tea catechins in rats and mice during chronic consumption of green tea polyphenols. Nutrition & Cancer. 2000;**37**:41-48. DOI: 10.1207/S15327914NC3701_5

[71] Chu KO, Wang CC, Chu CY, Choy KW, Pang CP, Rogers MS. Uptake and distribution of catechins in fetal organs following in utero exposure in rats. Human Reproduction. 2007; **22**:280-287. DOI: 10.1093/humrep/del353

[72] Yang YP, Qin YJ, Yolanda Yip WY, Chan KP, Chu KO, Chu WK, Ng TK, Pang CP, Chan SO. Green tea catechins are potent anti-oxidants that ameliorate sodium iodate-induced retinal degeneration in rats. Scientific Reports. 2016;**6**:29546. DOI: 10.1038/srep29546

[73] Thiagarajan G, Chandani S, Sundari CS, Rao SH, Kulkarni AV, Balasubramanian D. Antioxidant properties of green and black tea, and their potential ability to retard the progression of eye lens cataract. Experimental Eye Research. 2001 Sep;**73**(3):393-401. DOI: 10.1006/exer.2001.1049

[74] Henning SM, Aronson W, Niu Y, Conde F, Lee NH, Seeram NP, Lee RP, Lu J, Harris DM, Moro A, et al. Tea polyphenols and theaflavins are present in prostate tissue of humans and mice after green and black tea consumption. The Journal of Nutrition. 2006;**136**:1839-1843

[75] Wang P, Aronson WJ, Huang M, Zhang Y, Lee RP, Heber D, Henning SM. Green tea polyphenols and metabolites in prostatectomy tissue: Implications for cancer prevention. Cancer Prevention Research (Philadelphia, PA). 2010;**3**:985-993. DOI: 10.1158/1940-6207. CAPR-09-0210

[76] Meng X, Sang S, Zhu N, Lu H, Sheng S, Lee MJ, Ho CT, Yang CS. Identification and characterization of methylated and ring-fission metabolites of tea catechins formed in humans, mice, and rats. Chemical Research in Toxicology. 2002;**15**:1042-1050

[77] Manach C, Williamson G, Morand C, Scalbert A. Re'me'sy C. Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. The American Journal of Clinical Nutrition. 2005;**81**:230S-242S

[78] Auger C, Hara Y, Crozier A. Bioavailability of polyphenon E flavan-3-ols in humans with an ileostomy. The Journal of Nutrition. 2008;**138**(Suppl):1535S-1542S

[79] Ishii T, Ichikawa T, Minoda K, Kusaka K, Ito S, Suzuki Y, Akagawa M, Mochizuki K, Goda T, Nakayama T. Human serum albumin as an antioxidant in the oxidation of (−)-epigallocatechin gallate: Participation of reversible covalent binding for interaction and stabilization. Bioscience, Biotechnology, and Biochemistry. 2011;**75**:100-106. DOI: 10.1271/bbb.100600

[80] Ishii T, Minoda K, Bae MJ, Mori T, Uekusa Y, Ichikawa T, Aihara Y, Furuta T, Wakimoto T, Kan T, Nakayama T. Binding affinity of tea catechins for HSA: Characterization by high-performance affinity chromatography with immobilized albumin column. Molecular Nutrition & Food Research. 2010;**54**:816-822. DOI: 10.1002/mnfr.200900071

[81] Zhu M, Chen Y, Li RC. Oral absorption and bioavailability of tea catechins. Planta Medica. 2000;**66**:444. DOI: 10.1055/s-2000-8599

[82] Kohri T et al. Synthesis of (−)-[4-3H]epigallocatechin gallate and its metabolic fate in rats after intravenous administration. Journal of Agricultural and Food Chemistry. 2001;**49**: 1042. DOI: 10.1021/jf0011236