Pharmacokinetics and Biotransformation of Tea Polyphenols

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Abstract: Tea is an infusion of the leaves of the Camellia sinensis plant and is the most widely consumed beverage in the world after water. The main chemical components in teas are phenolic compounds (tea polyphenols, mainly tea catechins). A large number of in vitro and in vivo scientific studies have supported that the tea polyphenols can provide a number of health benefits such as, reducing the incidence of coronary heart disease, diabetes and cancer. Recently, tea polyphenols have proven highly attractive as lead compounds for drug discovery programs. A clear understanding of chemistry, stability, pharmacokinetics and metabolic fate of tea will be significant to elucidate many medicinal effects by biochemical theory and pharmaceutical development. This article reviews the current literature on the pharmacokinetics and biotransformation of tea catechins. The half-lives of tea polyphenols are 2-4h and their absorption and elimination are rapid in humans. The peak times (tmax) are 1 and 3 h after oral administration and the peak plasma concentrations are low μM range. It has been reported that catechins are easily metabolized by enzyme and microbe, and the main metabolic pathways are methylation, glucuronidation, sulfation, ring-fission metabolism, and so on. The information is important to discuss some of the challenges and benefits of pursuing this family of compounds for drug discovery.

Keywords: Biotransformation, metabolite, pharmacokinetics, tea polyphenols.

1. INTRODUCTION

Tea (Camellia sinensis L.) is the 2nd most consumed beverage in the world next to water. The tea plant has been widely used for centuries by ancient cultures for its medicinal properties. Tea is popularly consumed in unfermented (green tea), semi-fermented (oolong tea), and fermented (black and pu-erh or red) forms [1]. Green and black tea account for about 20% and 78% of worldwide tea consumption respectively, whereas approximately 2% is consumed as oolong tea. In regional preferences, green and oolong tea are dominant in China and Japan, and black tea occupies the majority of the market in western countries [2]. As described in literature, tea consumption has been associated with anti-inflammatory, anti-oxidative, anti-mutagenic, and anti-carcinogenic effects [3-9]. Most of the beneficial effects are attributed to the flavonoids [10-12]. Green tea is rich in catechins, of which (−)-epigallocatechin-3-gallate (EGCG) is the most abundant. Theaflavins and thearubigins are the major polyphenols in black tea, which are produced by the oxidation and polymerization of catechins during the process of fermentation [13,14]. Over the last decade, tea polyphenols had an increasing impact on answering key questions and understanding vital functions of biological systems. They are highly attractive as lead compounds for drug discovery programs. However, they are relatively unstable, poorly bioavailable, and readily undergo a number of metabolic transformations by intestinal microbiota and human enzymes. Further, these compounds target a wide array of biological systems. Therefore, they are far from optimum to become drugs [15]. In order to better understand the biological effects of tea constituents and modify the structures of polyphenols, more and more attentions have been attracted to the pharmacokinetics and biotransformation of tea polyphenols [16-18]. The current review article focuses on the pharmacokinetics and the major biotransformation pathways of tea polyphenols. Care has been taken to cover the most relevant and recent references. We hope that this review will expose areas for further study and encourage research on important public health issue, and provide information for pursuing the family of polyphenolic compounds for drug discovery.

2. THE CHEMICAL COMPONENTS OF TEA

The chemical components of tea chiefly include polyphenols, caffeine, and amino acids. Tea polyphenols are thought to be active in protecting against carcinogen-induced DNA damage as well as in promoting apoptosis of tumor cells and inhibiting angiogenesis. Catechins and their dimers (theaflavins) and polymers (thearubigins) are the main polyphenolic constituents in tea.

2.1. Catechins, Flavonols and Flavones

Catechins are a family of flavonoids and the flavan-3-ols, and the structures are characterized by di- or tri-hydroxyl group substitution of the B ring and the meta-5,7-dihydroxy substitution of the A ring (See Fig. 1). (−)-epigallocatechin gallate (EGCG), (−)-epigallocatechin (EGC), (−)-epicatechin gallate (ECG), and (−)-epicatechin (EC) are four major catechins. EGCG accounts for 50–80% of the total catechins in tea. Galloallocatechin gallate (GCG), galloallocatechin (GC), catechin gallate (CG), catechin (C), epigallocatechin digallates, epicatechin digallate, 3-O-methyl EC, 3-O-methyl EGC, and azelechin are in small amount. 3’-O-methyl-EGCG and 4’-O-methyl-EGCG are present in different tea samples. Flavonols account about 0.5–2.5% (w/w) extract as aglycone in tea infusions, including quercetin, kaempferol, myricetin, their glycosides (mono-, di-, and tri-) and so on. Flavonols make up a very small proportion of the tea polyphenols [15,16,19-21].

2.2. Theaflavins, and Thearubigins

Theaflavins, and thearubigins are major tea polyphenols in black tea, which are formed by the oxidation and polymerization of catechins during fermentation. The basic skeleton of theaflavins is a benzotropolone, which is a bicyclic ring containing the tropolone structure (Fig. 1). The color of benzotropolone compounds ranges from dark orange to dark brown, whereas, theaflavins are orange or orange-red and they are the major pigments in black tea. Under the catalysis of polyphenol oxidase (PPO) and peroxidase (POD), the four major epicatechins, namely EC, ECG, EGC and ECG, are
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oxidized and consequently dimerized to theaflavins. Theaflavin (TF1), theaflavin 3'-O-gallate (TF2a), theaflavin 3'-O-gallate (TF2b) and theaflavin 3,3'-O,O-di-gallate (TF3) are four main theaflavins in black tea. The theaflavins are formed from an epicatechin and epigallocatechin. For example, TF1 is formed from EC and EGC; TF2a from ECG and EGC. Thearubigins are the complexes of the multi-molecular reaction system and multiple reaction sites. Relaying on LC/MS/MS, many thearubigin structures and valuable chemical information have been provided, but more information about thearubigins, such as structure confirmation and formation, isolation of individual compounds and their characterization, evaluation of contribution to taste, and more importantly, knowledge of biological properties etc., is currently unavailable and needs to be studied. Several identified thearubigins to date are dibenzotropolones, theadibenzo[tropolones A, B, and C, tribenzotropolones, theatribenzotropolone etc. [22-26].

3. PHARMACOKINETICS OF TEA POLYPHENOLS

A number of papers reported the pharmacokinetics of tea polyphenols. The half-lives of tea polyphenols are 2-4h and their absorption and elimination are rapid in humans. The peak times (tmax) are 1 and 3 h after oral administration and the peak plasma concentrations are low μM range. There are some controversial issues in pharmacokinetics of tea polyphenols, such as the competitive absorption effect and variable oral bioavailability. The saturation absorption and competition absorption would occur in the gastrointestinal tract at high doses of tea catechin extracts. Further tea polyphenols undergo extensive biotransformation in vivo, which may interfere with the observation of the pharmacokinetic properties of tea polyphenols [28-31].

3.1. Pharmacokinetics of (-)-epicatechin

Some literature reported the plasma pharmacokinetics of EC in rats, rabbit, dogs, and humans. When a mixture of catechins was administrated, because of competing for binding to plasma protein or inhibiting the glucuronidation and sulfation, the pharmacokinetic behavior of each catechin could be influenced by the other catechin. Pure EC at lower dose was administrated to rabbits by intravenous, intraperitoneal, and oral route. EC showed dose-independent pharmacokinetics after intravenous administration. The area under the concentration-time curve (AUC) was proportional to the dose over the range 5-25 mg/kg. After intraperitoneal administration of 25 myricetin. In addition to the compounds mentioned above, more tea polyphenol related substances have been identified, such as theacitrins [13, 27].
mg/kg, a high percentage of EC escaped from first-pass hepatic elimination. After oral administration of 50 mg/kg, there was a great variation in the pharmacokinetics, and the mean oral bioavailability of EC was 4%. Renouf et al. [31] detected significant amounts of EC, epigallocatechin, and epigallocatechin gallate in human plasma after feeding 400 mL of green tea, and 1.25% infusion to nine healthy subjects. EC was absorbed very quickly with a Cmax of 202.6 ± 21.1 nM around 1–2 h after ingestion, and clearance from plasma was also rapid and back to baseline 6–8 h after ingestion with a monophasic response. EC was present predominantly in plasma as conjugates, and the conjugated forms of EC were two-thirds as sulfate and one-third as glucuronide. El-Hady et al. [32] also determined the levels of EC in human plasma after administration of green tea, and the concentration was 11.0 nM/mL, being about 1.8% of the administered dose in the 2 h plasma collection. The human volunteers were given different amounts decaffeinated green tea extract (DGT) and the blood and urine concentrations of tea catechins were detected. There was 25 mg EC in one gram of the DGT. After consumption of 1.5 g DGT, the average peak plasma concentration (Cmax) of EC was 0.65 μM. The Cmax increased with dosage, and Cmax values did not increase, when the doses were more than 4.5 g. The half-lives of EC were 3.2-5.7 h after oral administration of 1.5-4.5 g of DGT. In addition, pharmacokinetics of EC in rat brain and blood were also studied by microdialysis sampling coupled to high-performance liquid chromatography with chemiluminescence detection. The t1/2 values of EC were 13.67 ± 4.33 min for blood and 41.67 ± 9.14 min for brain. The maximum brain concentrations of EC were observed after about 20 min of administration. EC have relatively short t1/2 in blood and long t1/2 in brain, indicating that EC suffer more intense biotransformation in blood than in brain. The brain distribution ratio (AUCbrain/AUCblood) of EC was 0.1065 ± 0.0531 [33].

3.2. Pharmacokinetics of (−)-epigallocatechin Gallate
Pharmacokinetics experiments showed that EGCG is absorbed rapidly in the gut following oral administration, and membrane permeability of EGCG was low [34]. Ullmann et al. [35] examined the safety, tolerability, and pharmacokinetic properties of EGCG in human. Peak concentrations were reached between 1.3 and 2.2 h. When oral doses of EGCG were more than 1000 mg, the maximal plasma EGCG concentrations were greater than 1 μM. Single-dose of EGCG and polyphenon E capsule (containing 200 mg EGCG) were administrated to human. The results showed that if the EGCG doses were same, the pharmacokinetics of EGCG were similar in both formulations. The Cmax of EGCG were 0.16, 0.24, 0.37, 0.96 μM after 200, 400, 600, and 800 mg dose of EGCG, respectively. The average Cmax of EGCG was 0.16, 0.27, 0.36, 0.82 μM after giving Polyphenon E containing 200, 400, 600, and 800 mg EGCG, respectively. EGCG was present in human plasma mostly as unchanged form, which was proved by deconjugating enzymes (β-glucuronidase/sulfatase) experiment [36]. While EG and EC were present in human plasma as phase II metabolites. The pharmacokinetics and oral bioavailability studies of green tea catechins were performed in laboratory animals. The oral bioavailability of EGCG in rats was 1.6% when 10 mg/kg EGCG was given by intravenous and 75 mg/kg was administrated by oral route. The oral bioavailabilities of EGCG, EGC, and EC were 0.1%, 13.7%, and 31.2%, respectively, where DGT was also administered to rats via intravenous (25 mg/kg) and oral (200 mg/kg) routes. The bioavailability of EGCG were different after pure EGCG and DGT administration, which may come from the effect of other components in DGT on the oral absorption of EGCG and form conjugated metabolites during the pre-systemic first-pass metabolism. The oral bioavailability of unchanged EGCG in mice was about 15.8% and higher than bioavailability in rats. Recent clinical studies have examined tea catechin absorption in the small intestine in individuals with an ileostomy. When 200 mg of Polyphenon E was administrated to patients, the average recovery was 27% for the nongallated catechins, EC and EGC, and was 59% for the gallated catechins, EGCG and ECG, in the ileal fluid [18]. The results were similar after green tea consumption. Therefore, the nongallated catechins are absorbed from the small intestine more efficiently than their gallated analogs [19]. Recently, the pharmacokinetics of crystal EGCG was reported. EGCG cocrystals exhibit far lower aqueous solubilities, increased variability and the Cmax, unchanged Tmax and improved bioavailability [37].

3.3. Pharmacokinetics of (−)-epigallocatechin and (−)-epicatechin Gallate
The pharmacokinetics parameters of tea catechins, such as AUC and Cmax, increased with the increasing dose of Polyphenon E. The plasma levels of unchanged EGCG and ECG were higher than that of unchanged EGC and EC. Gallated catechins, EGCG and ECG, were present in plasma mostly as the unchanged form, whereas nongallated catechins, EGC and EC, were mostly present as the glucuronide and sulfate conjugates. Additionally, Food can also affect the bioavailability of tea catechins. There was a 3- to 5-fold increase in plasma levels of EGCG and ECG when Polyphenon E was taken on an empty stomach after an overnight fast than when taken with food, and the plasma levels of total (unchanged plus glucuronide and sulfate conjugates) EGCG did not significantly change, but resulted in lower plasma levels of total EC. Polyphephon E capsules (containing 37 mg EGCG) were administrated to human; the levels of EGCG were low or undetectable. EGC levels increased substantially after the plasma samples were treated with deconjugating enzymes, so the main metabolites of EGCG in plasma were the glucuronide and sulfate conjugates. Green tea and decaffeinated green tea were administrated to rats. Secondary peaks were observed in the pharmacokinetic profiles of each catechin at around 90 min, suggesting the presence of enterohepatic recirculation. Each catechin reached the maximum plasma concentration at 0.6–0.8 h. The variation of time at secondary peak among catechins may be ascribed to the pharmacokinetic differences between gallated catechins and nongallated catechins. The terminal elimination rate of ECG and EGC were 0.009/min and 0.010/min, respectively. The clearance rate of EGCG was higher than that of ECG. The bioavailability of catechins with a galloyl moiety was extremely low, whereas EGCG had greater bioavailability than ECG. The opposite result in terminal half-life between intravenous and intragastric administration of green tea was attributed to the difference in the dose administrated and the degree of pharmacokinetic interaction among catechins [38].

3.4. Pharmacokinetics of Metabolites of Tea Polyphenols
The pharmacokinetics of other tea polyphenols and their metabolites were also reported [39–47]. For example, a methylated form of EGC (4′-O-Me-EGC) was present in plasma at higher concentration than EGC. The amount of 4′-O-Me-EGC represented 8–31% of the ingested EGC and its T max was measured at 1.7 ± 0.5 h [47]. In contrast, Renouf et al. [31] found that AUC and Cmax of 4′-O-Me-EGC were consistently lower than that of EGC. In another study, a methylated form of EGCG, namely 4′,4″-DiMe-EGCG, was identified in plasma. Its Cmax reached 20.5 ± 7.7 nmol/L at 2 h after ingestion [48].

Little information is available on the pharmacokinetics of black tea polyphenols. The plasma peak concentration of theaflavins in human was only 2–7 nM after consuming 700 mg mixed theaflavins (equivalent to about 30 cups of black tea). The very low systemic bioavailability of theaflavins after oral ingestion may be attributed to their large molecular structures. The pharmacokinetics of thearubigins has not been reported.

4. BIOTRANSFORMATION OF TEA POLYPHENOLS
Tea polyphenols are easily metabolized by enzymes or microbes, and the main biotransformation pathways are methylation,
4.1. Methylation of Tea Polyphenols

The enzyme of catechol-O-methyltransferase (COMT) can catalyze the metabolic O-methylation of various catecholic compounds including the major tea polyphenols, which are ubiquitously present in humans and rodents [49-51]. The COMT can eliminate the potentially active or toxic catechol structures of endogenous and exogenous compounds. 4″-O-methyl EGCG, and then 4″, 4″-di-O-methyl-EGCG are the major the methylated metabolites of EGCG. Methylation on the B-ring or the D-ring of EGCG greatly inhibited the glucuronidation on the same ring, however, it did not affect glucuronidation on the A-ring of EGCG or EGC. EC and EGC were methylated to produce 3″- and 4″-O-methyl-EC, 4″-O-methyl EGC, and 4″-O-methyl ECG, respectively. EGC and EGCG were methylated to 4″-O-methyl EGC and 4″, 4″-di-O-methyl-EGCG in human [52-55].

4.2. Glucuronidation and Glucosidation of Tea Polyphenols

Glucuronidation and glucosidation of tea polyphenols are the major Phase II metabolites of tea polyphenols. Studies using microsomal, cellular, and animal models consistently indicate that rapid conjugation, especially glucuronidation in the intestine and liver, is primarily responsible for the poor bioavailability of phenolics, although other factors such as stability and solubility might also be involved sometimes. Glucuronidation is mediated by UDP-glucuronosyltransferases (UGTs) (EC 2.4.1.17), and together with cytochrome P450 (CYP) enzymes, they represented more than 80% of the metabolic pathways. UDP-glucuronosyltransferases (UGTs) are a multigenic family of membrane-bond enzymes, which catalyze the binding of glucuronic acid from UDP-glucuronic acid with a hydroxyl, carboxyl, amine, or thiol group [56-59]. Glucuronidation of phenolics often occurs at the nucleophilic -OH group attached to the aromatic ring (also refers to O-glucuronidation). For molecules with more than one hydroxyl group, multiple glucuronide isomers are often generated. EC was not glucuronidated in the human liver and small intestinal microsomes; however, it can be glucuronidated and formed glucuronides in rat liver microsomes [60-62]. EGCG-4″-O-glucuronide was the major EGCG glucuronide in human, mouse, and rat microsomes. EGCG is more easily glucuronidated than EGC, and the major EGC glucuronide is EGC-3″-O-glucuronide [63]. EGCG can react with sucrose to form three EGCG glycosides by Leuconostoc mesenteroides B-1299CB [64]. The 7 of the A-ring and 4″ of the B-ring are the active positions of EGCG for glucosidation. EGCG-4″-O-β-D-glucopyranoside and 7-
4.3. Sulfation of Tea Polyphenols

Sulfotransferases (SULT) can transfer a sulfate group from a donor molecule to an acceptor alcohol or amine, and 3'-phosphoadenosine-5'-phosphosulfate (PAPS) is the most common sulfate donor [68].

The sulfate conjugations of EC, EGC, and EGCG occurred both in the rat liver and in human liver cytosol [69], however, the chemical structures of those sulfate metabolites are still unknown. EGCG is time- and concentration-dependently sulfated by human, mouse, and rat liver cytosol. The rat cytosol has the greatest activity to sulfate EGCG, followed by the mouse and the human liver cytosol [70,71].

4.4. Glutathione and Cysteine Conjugation of Tea Polyphenols

Tyrosinase metabolized (+)-catechin to form a cytotoxic o-quinone, which further reacts with glutathione to form mono-, bi-, and triglutathione conjugates of (+)-catechin and mono- and biglutathione conjugates of a (+)-catechin dimmer. Only monoglutathione conjugates of (+)-catechin were formed by peroxidase and hydrogen peroxide. (+)-catechin also oxidized to produce glutathione conjugate in rat liver microsomes [72,73]. It was reported that oral or intraperitoneal administration of EGCG to mice resulted in the formation of two cysteine metabolites: 2'-cysteinyl-EGCG and 2'-cysteinyl-EGCG. It is hypothesized that these metabolites form after the oxidation of EGCG to a quinone, which results in the activation of the 2'- or 2'-carbons of the B- and D-rings, respectively [74]. Subsequently, a Michael-type reaction occurs between these activated carbons and the thiol group of cysteine. Chemical synthesis of cysteine and other thiococjugates of EGCG, and studies in cell culture, seem to support this proposed mechanism. A small amount of thiol conjugates of EGCG is detected only after rather high doses of EGCG are given to the mice. Normally, methylation, glucuronidation, and sulfation of EGCG are the major metabolic pathways. At toxic doses of EGCG, these pathways may be saturated, and the excessive amount of EGCG is oxidized to form EGCG quinone and then form thiol conjugates [75].

4.5. Ring-fission Metabolism of Tea Polyphenols

The human colon contains 1000 bacterial species, amounting to over 100 trillion bacteria. Colonic microflora catalyzes the breakdown of polyphenols into simple compounds, such as phenolic acids and their glycine conjugates, such as derivatives of hippuric acid [76]. The tea polyphenols are metabolized to produce the ring fission metabolites 5-(3',4',5'-trihydroxyphenyl)-γ-valerolactone, 5-(3',4'-dihydroxyphenyl)-γ-valerolactone and 5-(3',5'-dihydroxyphenyl)-γ-valerolactone by human intestine, which further degrade to form lower molecular weight phenolic acids. 4-Hydroxybenzoic acid, 3,4-dihydroxybenzoic acid, 3-methoxy-4-hydroxy-hippuric acid, and 3-methoxy-4-hydroxybenzoic acid. The ring fission products are also found in human urine and plasma approximately 13 h after drinking green tea. Vanillic acid was detected as the major tea metabolite in the human urine sample [77-79]. EGCG underwent ring fission by rat intestinal microbiota to produce 4-hydroxy-5-(3,5-dihydroxyphenyl) valeric acid as main metabolite in the gut tract. Akiko et al. [80] reported the catabolism of EC in rat intestinal microbiota. They found 4 new metabolites including 4-hydroxy-5-(3-hydroxyphenyl) valeric acid, 4-oxo-5-(3,4-dihydroxyphenyl) valeric acid, 4-oxo-5-(3-hydroxyphenyl) valeric acid and 1-(4-hydroxyphenyl)-3-(2,4,6-trihydroxyphenyl) propan-2-ol.

4.6. Biotransformation of Theaflavins and Thearubigins

Biotransformation of theaflavins and thearubigins, theaflavin 3-gallate, theaflavin 3'-gallate, methylated theaflavin 3,3'-digallate, and gallic acid were the major metabolites of theaflavin 3,3'-digallate in mouse fecal sample. Neither glucuronidated nor sulfated metabolites were detectable. Theaflavin 3,3'-digallate can be degraded by gut micro flora or COMT, and form gallic acid, theaflavin and theaflavin mono-gallate. Because of their large molecular weight, it is impossible for thearubigins to be absorbed in the small intestine [81]. The higher molecular weight polyphenols can be metabolized by the microbiota, however, the bacterial metabolites of thearubigins are still unknown.

CONCLUSIONS

The article reviews the current literature on the pharmacoknetics and biotransformation of tea catechins. A number of papers reported the pharmacokinetic studies of tea polyphenols, however, some controversial issues have not been resolved. Tea polyphenols undergo considerable biotransformation, including methylation, glucuronidation, sulfation, and ring-fission metabolism. Information of pharmacokinetics and metabolism on black tea polyphenols is still lacking. The biochemistry and biological activity of thearubigins are almost totally unknown. The large molecular weight black tea polyphenols are difficult to be absorbed, and they can exert effects by their microbial metabolites. It is significant to understand the chemistry, stability, bioavailability and biotransformation of tea polyphenols for illuminating the pharmacology of tea and pharmaceutical development.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>AUC</td>
<td>Area under the plasma concentration</td>
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<td>Cmax</td>
<td>Maximum concentration</td>
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<td>CL</td>
<td>Clearance</td>
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<tr>
<td>Cmax</td>
<td>Maximum concentration</td>
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<td>Tmax</td>
<td>Time to maximum concentration</td>
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<td>DGT</td>
<td>Decaffeinated green tea</td>
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<td>EC</td>
<td>(+)-catechin</td>
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<td>EGC</td>
<td>(−)-epigallocatechin</td>
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<td>EGCG</td>
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<td>EC</td>
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<td>UGTs</td>
<td>UDP-glucuronosyltransferases</td>
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<td>BBB</td>
<td>Blood–brain barrier</td>
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<tr>
<td>C = (+)-catechin</td>
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<td>DGT = Decaffeinated green tea</td>
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<td>i.v. = Intravenous(ly)</td>
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<td>CL = Clearance</td>
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<td>Tmax = Time to maximum concentration</td>
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<td>Cmax = Maximum concentration</td>
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<td>AUC = Area under the plasma concentration vs. time curve</td>
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<td>UGTs = UDP-glucuronosyltransferases</td>
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<td>CYPs = Cytochrome P450s</td>
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<td>HPLC = High-performance liquid chromatography</td>
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<td>BBB = Blood–brain barrier</td>
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