Journal of Pharmaceutical Care
jpc.tums.ac.ir

Drug Interactions of Green Tea

Mahsa Meyboodi[1], Amir Hooshang Mohammadpour[2,3*], Seyed Ahmad Emami[4], Hedyieh Karbasforooshan[2]

[1]School of pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran.
[2]Department of Clinical Pharmacy, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran.
[3]Pharmaceutical Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran.
[4]Department of Pharmacognosy, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran.

Received: 2020-04-18, Revised: 2020-06-08, Accepted: 2020-06-09, Published: 2020-12-30

ARTICLE INFO

Article type:
Review article

Keywords:
Camellia sinensis;
Green Tea Extract;
Epigallocatechin-3-gallate;
Drug Interactions;
Pharmacokinetics

ABSTRACT

Green tea (GT) is among the most common drinks in the world. There are some reports on interactions between GT and some drugs. This paper attempts to provide a comprehensive review of this subject. The data are collected by searching PubMed, Scopus, Web of science, and Embase. The keywords used as search terms are "camellia sinensis", "pharmacodynamics", "pharmacokinetic", "EGCG", and "drug interaction". We have found 24 eligible articles. Finally, the related papers are given in our review. GT is containing polyphenols that interfere with many drugs. The most important of these polyphenol compounds is epigallocatechin-3-gallate (EGCG), which most of the reported interactions are due to the presence of EGCG. Interaction of GT with different drugs occurs in the context of both pharmacodynamics and pharmacokinetics that includes drug absorption, metabolism, and renal excretion. The mechanisms of these interactions consist of increase in the concentration included several medications such as melatonin, midazolam, and amlodipine consuming after GT; these interactions can be toxic. Additionally, it has been reported that serum levels of several drugs such as nadolol, digoxin, amoxicillin, and clozapine are decreased and their efficacy are reduced when they simultaneously administer with GT. The serum concentration of rhodamin 123, quinidine, and doxorubicin have increased when these drugs were co-administered with GT. GT has pharmacodynamics interactions with a few drugs such as a hydrochlorothiazide. As proposed and discussed here, GT has the potential for interactions with numerous other drugs and thus clinicians should be aware of reported and potential interaction of GT with various medications in order to avoid adverse reactions and achieve expected clinical response.

J Pharm Care 2020; 8(4): 196-203.

► Please cite this paper as:
Meyboodi M, Mohammadpour AH, Emami SA, Karbasforooshan H. Drug Interactions of Green Tea. J Pharm Care 2020; 8(4): 196-203.

Introduction

Green tea (Camellia sinensis) is very common among beverages in Asia and it has gained a lot of popularity around the world (1). Green tea (GT) has also attracted attention because of its healthy benefit ranging from improvement of metabolic syndrome to cancer prevention (2). GT contains a large number of catechin polyphenolic compounds. Types of catechins in GT include: epigallocatechin, epigallocatechin-3-gallate (EGCG) and epicatechin-3-gallate. The richest and most biologically active in GTE is EGCG (3).

Different epidemiologic studies, evaluating food and beverage patterns of different population have considered the use of GT and their potential for interaction with various drugs as important parameters for evaluation. This wide use of GT is important in light of the fact that in known such drink can interact with different drugs, especially concomitantly (4). Thus this review discusses the primary

*Corresponding Author: Dr Amir Hooshang Mohammadpour
Address: Department of Clinical Pharmacy, School of Pharmacy, Mashhad University of Medical Sciences, P.O. Box 91775-1365, Mashhad, Iran. Tel:+985131801592, Fax: +985138823251.
Email: mohamadpoorah@mums.ac.ir

properties of GT, which can lead to pharmacodynamics or pharmacokinetics drug interaction. Then, report and study evaluating and/or indicating drug interaction with GT is reviewed.

Methods

The data are collected by searching PubMed, Scopus, Web of science, and Embase. The keywords used as search terms are "camellia sinensis", "green tea extract", "EGCG", "pharmacodynamics", "pharmacokinetic", "absorption", "elimination", "distribution", "metabolism", and "drug interaction".

Results

By searching these databases, 891 articles are found. 867 of them are including review articles and unrelated articles. Finally, a total of 24 relevant articles up to the date of publication are studied for review. They are summarized in Table 1. 1case report, 1cross-sectional study base on questionnaires, 8 in-vitro studies and 18 in-vivo studies on pharmacodynamics and pharmacokinetic drug interaction with green tea between 1961 and 2019 are in this review. Most of papers relating to GT interactions are about pharmacokinetic interactions in the level of absorption by inhibited intestinal P-gp and creating insoluble complexes with the drug. In the articles the number of interactions with all the mentioned drugs are the same except for nadolol, which is examined in two separate articles.

3.1. Green tea and types of drug interaction

GT has main properties that can lead to drug interaction at different levels whose main chemical components are tea polyphenols (30% dry weight). Polyphenol compounds in GT have lots of catechins and catechins including EGCG, epicatechin-3-gallate (ECG), epicatechin (EC), and epigallocatechin (EGC). EGCG has the highest frequency among green tea polyphenols. The ECGC content of GT can be a source of different interactions with drugs discussed below. Methyl xanthine's and purine alkaloids found in plants are found in beverages (coffee, tea, cocoa) consumed worldwide. Methyl xanthine's can be cause of different interactions, too. There are different types of drug interactions with GT. These GT-drug interactions can be classified as resulting from either a change in the drugs pharmacokinetic and pharmacodynamics parameter.

3.1.1. Green tea extract and change in a drug's pharmacodynamics properties

Pharmacodynamics interactions are the interface between chemical medicines and herb, which affect similar physiological pathways and directly influence each other's effect (5). Below are 3 studies in this field.

Chakraborty et al. have investigated the interaction of GT and hydrochlorothiazide by designing an in-vivo test in mice. Their results show that co-administration of GT extract (GTE) with hydrochlorothiazide can reduce the QRS and PR-interval and its related side-effects and illustrate myocardial protection due to pharmacodynamics interaction of GTE whit hydrochlorothiazide (6).

Ali et al. have investigated the interaction between GT and acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) by designing an in-vitro test. AChE and BChE are two groups of cholinesterases (ChEs), both of them are within the nervous system. Their study suggests that polyphenol compounds in GT increases the cholinergic neurotransmission by prolonging the time with inhibiting AChE as well as BChE (7).

Shehab et al. have investigated the interaction between dabigatran and GT by designing an animal study on rats. Dabigatran is a direct thrombin inhibitor that restrain free and clot bound thrombin and thrombin platelet aggregation. Their results show that 500 mg/kg of GT orally for 1hr after administration of dabigatran (1.83 mg/kg) causes on significant increase in the bleeding time, International Normalized Ratio (INR) and Prothrombin Time (PT). Their results show that synergistic interaction happens between dabigatran etexilate with GTE (8).

3.1.2. Green tea extracts change in the pharmacokinetic parameters of a drug

Pharmacokinetic interaction include the interface at the level of absorption, distribution, metabolism, and elimination of drugs, which all can affect the effective concentration of drugs at its site(s) of action (5). Below are 21 studies in this field.

3.1.2.1. GTE and pharmacokinetic interaction at the level of drug absorption

At the drug absorption level, there are two important steps: the dissolution of the drug in gastrointestinal fluids and the diffusion of the drug from gastrointestinal (GI) membranes into the blood (9). Many drugs are weak acids or weak base and can exist in either the ionized or unionized from depending upon the PH of their environment. The most important factor affecting this proportion is the PKa of these

drugs and the PH of fluids in the GI tract (10). Polyphenols are binding to amine-containing molecules, and that made insoluble complex. This interaction may lead to reduce the bioavailability (11). Several drug molecules contain amine functionalities, and the most common drink with a remarkably high polyphenol content is tea, especially GT. As a result, polyphenol compounds can lead to change in the extent of dissolution when co-administration with drugs has amine functionalities (11). Tea catechins are called to be restrains of receptor tyrosine kinases, and by this mechanism, when co-administration GT with tyrosine kinase inhibitors (e.g. erlotinib and lapatinib) can reduce its overall absorption (12). Below are 14 studies in this field.

Kiss et al. have investigated co-administration of GT and amoxicillin by designing an animal study on rats. The amoxicillin molecule has amine functionalities; thus it might have ingredients to the interaction with polyphenols. The results of their studies show that AUC is not significantly decreased but Cmax is significantly decreased. This interaction is probably due to the reaction between the polyphenols presented in the GT and the amines presented in the amoxicillin, which results in the formation of an insoluble compound (11).

Misaka et al. have investigated that the interaction EGCG with nadolol by designing an animal study on rats. Nadolol is a non-selective-adrenoreceptor antagonist used for the treatment of angina and hypertension. The results of their studies show that EGCG causes significantly decreased AUC and Cmax of nadolol. The exact mechanism of this interaction is unknown maybe because of the inhibited of p-gp or OATP on the surface of intestinal cells (13, 14).

Shan et al. have investigated the interaction between EGCG and atenolol by designing an animal study on rats. Atenolol is a cardio-selective beta blacker. The results of their studies show that EGCG can bind to atenolol and AUC, Cmax and Tmax decreased significantly (15).

Helen et al. have investigated the interaction between chlorpromazine and green tea by designing an animal study on rats. The results of their studies show that administration of 15 mg/kg chlorpromazine with a standard tea solution (1ml) can significantly reduce the cataleptic activity of chlorpromazine by forms an insoluble compound of chlorpromazine (16).

Ikeda et al. have investigated the interaction between GT and Propericiazine (PCZ) by designing an in-vitro study. PCZ is a typical antipsychotic agent for the treatment of schizophrenia. It should not be administered as an undiluted solution in order to avoid inadvertent use. GT consumption with PCZ decreases its absorption because of the insoluble composition of PCZ (17).

Ohata et al. have investigated the interaction between GT and piperazine derivatives(PD) by designing an in-vitro study. PD used in their study are Cetirizine dihydrochloride, lomerizine dihydrochloride, and hydroxyzine dihydrochloride. Their results show that PD with EGCG forms an insoluble compound of PD and reduces PD absorption (18).

Oda et al. have investigated the interaction of GT with rhodamine 123 by designing an in-vitro study. Their result show that GT increases the intestinal uptake of rhodamine 123 by suppressed P-gp function (19).

Keisuke Oda and Teruo Murakami has investigated interaction GT with quinidine by designing an in-vitro study. Quinidine is occasionally used as a class I antiarrhythmic agent to prevent ventricular arrhythmias and its substrates for P-gp. Their results show that GT enhanced quinidine absorption in the ileum of rats by suppressed P-gp function (19).

Tae-Eun Kim et al. has investigated the interaction between GT and digoxin on 16 subjects with a mean age of 25 years for 29 days. Digoxin is one of the substrates of P-gp. Therefore, its absorption and excretion are affected by P-gp. Their studies show that AUC and Cmax are decreased by the consumption of 0.5 mg of digoxin and 650 mg of GT capsules but Tmax is not significantly changed. This interference is probably due to P-gp inhibition by GT (20). Also Keisuke Oda and Teruo Murakami has investigated the interaction of GT with digoxin by designing an animal study on rats and their results show that Cmax of digoxin is increased by the co-administration of GT with digoxin due to enhanced digoxin solubility (19).

Hadir et al. have investigated the interaction between GTE and erlotinib (ERL) or lapatinib (LAP) by designing an animal study on rats. LAP and ERL are TKIs and they substrate of P-gp. Their results indicate that the administration of GTE with erlotinib or lapatinib result in a significant decrease in the AUC and Cmax of both ERL and LAP (12). This interaction is probably due to P-gp inhibited by EGCG (21).

Dan-Dan et al. have investigated the interaction between GTE and raloxifene by designing an animal study on rats and an in-vitro study. EGCG can inhibit UDP-sglucuronosyl transferases (UGTs). Their results indicate that the administration of GTE with raloxifene result in a reduction bioavailability of raloxifene and this interaction is due to the inhibition of UGTs intestinal by ECG (22).

Jang et al. have investigated the interaction between clozapine and GT by designing an animal study on rats. Their results show that co-administration 175mg/kg of GT with 20mg/kg of clozapine causes a significant reduction on AUC and Cmax and increase Tmax. The reduced intestinal absorption of clozapine may be due to the delayed gastric emptying by GT (23).

Takashi Mizuma and Shoji Avazu has investigated the interaction between EC and phenolic drugs, α-naphthol(α-NA) by designing an animal study on isolated rat small intestine. Their results show that co-administration EC and α-NA causes the inhibition of glucuronidation and promotion of intestinal drug absorption. An increase in the intestinal absorption of phenolic drugs caused by the inhibition of glucuronidation can be expected based on unknown parameters (24).

3.1.2.2. GTE and pharmacokinetic interaction at the level of drug distribution

Drug distribution can be defined as the post absorptive transfer of drug from one location in the body to another. In lots of cases, the distribution process of drugs is reversible symmetry and does not need to input of energy. However, these is enhancing know that receptor-mediated endocytosis and carrier-mediated active transport also play essential roles in either enhancing or limiting the extent of drug distribution (25). The compounds in GTcan alter the distribution of some drugs. Below are 2 studies in this field.

Fleisher et al. conclude the interaction between GT and dasatinib by designing an in-vitro study. Dasatinib is a tyrosine kinase inhibitors (TKIs). Many TKIs are CYP3A substrates and many of them substitute for two important transporter effluxes called P-gp and Breast Cancer Resistance Protein (BCRP). P-gp and BCRP are expressed in many normal tissues and play important roles in medicine absorption, distribution, and excretion. Results of this experiment show that 50 μM of each of the 6 compounds in GT with dasatinib have no significant positive effects on intracellular concentrations of the dasatinib (21).

Yuan et al. have investigated the effect of ECG and EGCG on the binding of tegafur(TF) to human serum albumin(HAS) by designing an in-vitro study. The affinity to binds HAS are ranged in the order of EGCG> ECG> TF, and the interaction are spontaneous and exothermic. Finally, their results point out that the existence of ECG and EGCG influences the binding of TF to HSA and can increases the free concentration of TF (26).

3.1.2.3. GTE and pharmacokinetic interaction at the level of drug metabolism

The results of Satoh et al. paper is to evaluate the inhibitory effects in human liver microsomes on drug metabolizing enzymes, namely, cytochrome P450 (CYP) 1A2, CYP2C9, CYP2D6, and CYP3A4 by eight catechins in green tea drinks (27). These are isoenzyme is the most essential metabolic pathway of some medicines. This interaction is more important for medications with a narrow therapeutic index. This competitive inhibition by EGCG of medications that are metabolizing by CYP450 may result to increased serum levels of this medication, which could give rise to toxic effect. Thus, all drugs that are substrates of CYP450 could potentially be affected when they are ingested with GT. Amlodipine, carbamazepine, melatonin, midazolam, and palbociclib are all examples of drugs that are substrates for CYP3A4 and CYP1A2. The field of research that evaluates drug-drug interaction deserves more attention as it pertains to GT extract-drug interaction and their potential adverse side effects. Below are 5 studies in this field.

Xue et al. have performed in-vitro study and animal study on mices to examine the interaction between GT and doxorubicin. It is needful to develop the co-administration with the corresponding molecular mechanisms to decrease the side effects and improve the sensitivity of doxorubicin. According to the existing studies, EGCG can inhibit metabolism of doxorubicin in the in-vitro medium as well as in-vivo. Their results show that preincubation by catechin for 48h significantly increases the doxorubicin concentrations in the cancer cells (28).

Jana et al. have performed in-vitro and in-vivo studies on rats to investigate the interaction of melatonin with quercetin or caffeic acid, which are highly metabolized in GT. The another study found that CYP1A1 and CYP1A2 contribute to the metabolism of melatonin in human. Their study shows that the quercetin inhibits the metabolism of melatonin by CYP1A2 and in-vivo studies also show that the concomitant administration of caffeic acid and quercetin with melatonin enhance the AUC of melatonin (29).

Nishikawa et al. have performed an animal study on rats to investigate that the interaction between 400 mg / 10ml / kg EGCG and (10mg / kg) iv or (20mg / kg (orally) of midazolam. Midazolam is a substrate for the CYP3A enzyme in human beings. Their results point out that the oral administration of midazolam with EGCG increase significantly AUC and Cmax. Their results show that this interaction is due to the inhibition of CYP3A by EGCG which leads to reduced

metabolism of midazolam (30).

Han et al. have performed an animal study on rats to investigate the interaction between GT and amlodipine. Amlodipine is a substrate of CYP enzymes. Their in-vivo studies show that the parameters Cmax and AUC for amlodipine are significantly increased and Tmax is decreased with the pretreatment of EGCG. In-vitro studies indicate that both EGCG and GTE could inhibit the metabolism of amlodipine in rat liver microsomes through inhibiting the activity of CYP3A enzymes (3).

Paul et al. have performed an in-vitro study and animal study on rats to investigate the interaction between palbociclib (PAL) and GT. PAL is reported to be primarily metabolized by CYP3A4 enzyme. GTE is already reported to be inhibitors of CYP3A4 and it may or may not effect on PAL pharmacokinetic outcomes. Their results point out that the administration of GTE with PAL result in a reduction of bioavailability of PAL with a reduction in Cmax and AUC for short and long term respectively (31).

3.1.2.4. GTE and pharmacokinetic interactions at the level of drug excretion:

The kidney plays an important role in maintaining the total body homeostasis and the eliminating toxic xenobiotics and metabolites. Various medicines and their metabolites are finally eliminated in the urine. The reabsorption and secretion functions of the nephron are mediated by a variety of transporters located in the basolateral and luminal membranes of the tubular cells (32). There are few studies designed to evaluate the interaction between GTE with drugs at this level. Below are 4 studies in this field.

Han et al. have performed an animal study on rats to investigate the interaction between GT and amlodipine. Their in-vivo studies show that the parameter T1/2 for amlodipine is significantly increase by the pretreatment of EGCG (3).

Nishikawa et al. have performed an animal study on rats to investigate the interaction between 400 mg / 10ml / kg EGCG with (10mg / kg) iv or (20mg / kg (orally) midazolam to mice. Their results show that co-administration EGCG with midazolam causes t1/2 of midazolam to be decreased significantly as compared with the control group and clearance decreases significantly. Their study show that this interaction is due to the inhibition of CYP3A by EGCG that leads to decrease the metabolism and excretion of midazolam (30).

Paul et al. have performed an animal study on rats to investigate the interaction between PAL and GT. Their results point out that the administration of GTE with PAL has no significant change in the Tmax and t1/2 and does not effect on the elimination of the PAL (31).

Jang et al. have performed an animal study on rats to investigate the interaction between clozapine and GT. Their Results show that the co-administration 175mg/kg of GT with 20mg/kg of clozapine causes no significant differences in the elimination half-life of clozapine (23).

3.1.3. unknown mechanism:

There are 4 studies on the interaction of GT with drugs, the mechanism of them is unclear. These studies are as follows.

Al-Arifi et al. have performed a cross–sectional study based on the questionnaires to investigate the interaction between the warfarin and GT. Their results show that the administration of GT with warfarin has the interaction (33).

Koren et al. have performed a cross–sectional study based on the questionnaires to investigate the interaction between GT and anti-platelet aggregates. Their study shows that the co-administration of GT with anti-platelet aggregates increases the rate of bleeding risk (34).

Alemdaroglu et al. have performed an animal study on rats to investigate the interaction between GT and folic acid (0.4 mg-5mg). Folic acid is a stable and synthetic form of the folates that is appropriate to the group of water soluble vitamins and needs to be provided through nutrition. Their study shows that the co-administration of GT with low and high dose of folic acid decrease the bioavailability and does not effect on the elimination process of the folate from the blood (35).

Lu et al. have performed an animal study on rats to investigate the interaction of acetaminophen (APAP) with 1000 mg/kg of GTE for 3h before APAP treatment alone. An overdose of APAP can stimulate the acute liver injury associated with the hepatic centrilobular necrosis in animals and human beings. Their observations suggest that GTE could have the protective effects against the APAP-induced hepatotoxicity (36).

Misaka et al. have experimented on rats to analyze the interaction of compounds in GT with nadolol. Their results show that the urinary benefit of nadolol is also significantly reduced in concomitant administration with GT but its mechanism is not clear (13, 14).

Table 1. Reports and studies indications between green tea extract(GTE) and drugs.

	Drug	Green tea amount	PK or PD outcome	Study design/reference
1	Tegafur	ECGC & ECG from 0-32 µM	Increasing the free concentration	Spectroscopic methods, TIC, and molecular docking (26)
2	Amoxicillin	0.5 g powdered green tea extract	Not significantly decreasing AUC but Cmax decreasing significantly	Animal study on rats (11)
3	Nadolol	GTE 400mg/kg & EGCG 150mg/kg	Decreasing AUC and Cmax & decreasing urinary excertion	Animal study on rats (13, 14)
4	Atenolol	Oxidative tea polyphenol 500 mg/kg	Decreasing AUC, Cmax and Tmax	Animal study on rats (15)
5	Chlorpromazine	Standard tea solution(1ml)	Decreasing cataleptic activity	Animal study on rats (16)
6	Propericiazine	16.5 ml of tea-based drink	Decreasing absorption	In-vitro study (17)
7	Piperazine derivatives	NA	Decreasing absorption	Isothermal titration micro calorimetry and molecular modeling study (18)
8	Rhodamine123	NA	Increasing intestinal uptake	In-vitro study (19)
9	Quinidine	1ml of Isotonic solution of quinidine (2µM) containing 50% GT	Increasing absorption	In-vitro study (19)
10	Digoxin	2m/kg	Increasing Cmax	Animal study on rats (19)
11	Digoxin	650mg	Decreasing AUC	Case report (20)
12	Dasatinib	NA	No significant effecting	In-vitro study(LC/MS/MS) (21)
13	Erlotinib	400 mg GTE	Decreasing AUC and Cmax	Animal study on rats (12)
14	Lapatinib	400 mg GTE	Decreasing AUC and Cmax	Animal study on rats (12)
15	Melatonin	15mg/kg of caffeic acid and quercetin	Increasing AUC & decrease plasma clearance	In-vitro study and animal study on rats (29)
16	Midazolam	400mg/10ml/kg	Decreasing metabolism, excertion and t1/2	Animal study on rats (30)
17	Palbociclib	200mg/kg of decaffeinated GTE	Decreasing Cmax & AUC and no effect on t1/2 & Tmax	In-vitro study(UHPLC-QTOF/MS) & animal study on rats (31)
18	Raloxifen	200mg of dried leaves	Decreasing AUC	In-vitro to in-vivo extrapolation (22)
19	Amlodipine	30mg/kg/day for 10 days	Increasing AUC, Cmax, and t1/2 and decreasing Tmax	Animal study on rats (3)
20	Acetaminophen	1000mg/kg GTE 3h before acetaminophen	Protective effects against APAP-inducing hepatotoxicity	Animal study in mice (36)
21	Hydrochlorothiazide	100mg/kg (GTE-100) and 500 mg/kg(GTE-500) for 10 days	Reducing the PR-interval and QRS and associated side-effects and exhibiting myocardial protection	Animal study on rats (6)
22	Doxorubicin	25mg/kg	Increasing doxorubicin concentration in the cancer cell	In-vitro study and animal study on mices (28)
23	Dabigatran	500mg/kg after administration dabigatran	Increasing the bleeding time, INR & PT	Animal study on rats (8)
24	Warfarin	NA	Probably increasing the bleeding time	Cross –sectional study based on questionnaires (33)
25	Anti- platelet aggregates	NA	Increasing the rate of bleeding	Cross-sectional study based on questionnaires (34)
26	Clozapine	175mg/kg of GTE for 4 days	Decreasing AUC and Cmax and increasing Tmax	Animal study on rats (23)
27	Folic acid	0.3 g extract/250 ml	Decreasing AUC and Cmax	Animal study on rats (35)
28	α-naphtol	NA	Inhibiting of glucoronidation and promoting of intestinal drug absorption	Animal study on isolated rat small intestine (24)

GT: green tea, ECGC: epigallocatechin gallate, EGC: epigallocatechin, GTE: green tea extract, NA: not available, AUC: area under the curve, Cmax: peak plasma concentration, Tmax: time to rich Cmax, PK: pharmacokinetics, PD: pharmacodynamics

Conclusion

GT is a common beverage worldwide. We discussed how GTE potentiate the interaction between GT and various drugs about pharmacodynamics and pharmacokinetics, which included the processes of drug absorption, drug metabolism, and renal excretion. It is important to altering the metabolism of various drugs that are taken with GT, it should be emphasized that EGCG-related interactions are usually important only in the case of excessive consumption of GT. It has been also discussed in this review and reported elsewhere that serum concentration of melatonin, midazolam, anti-platelet aggregates, amlodipine, and α-naphtol were increased following simultaneous consumption of GT, which suggests the potential for drug-related adverse effects. Additionally, it has been reported that serum levels of PCZ, nadolol, atenolol, digoxin, raloxifene, clozapine, folic acid, chlorpromazine, PD, TKIs, amoxicillin, and PAL were observed to decrease when administered with GT, which ultimately causes a reduction in their efficacy. Moreover, the serum concentration of erlotinib, quinidine and rhodamine123 had increased when these drugs were co-administrated with GT. Importantly, these interactions could be favorable with regard to the therapeutic efficacy of the erlotinib, quinidine and rhodamine 123. As discussed in this review, GT has the potential for interactions with many other classes of drugs. Clinicians must be made aware of the reported and potential interactions of medications with consumption of GT, especially if those medications have a narrow therapeutic index.

References

1. P Werba J, Misaka S, G Giroli M, et al. Overview of green tea interaction with cardiovascular drugs. Curr Pharm Des 2015;21(9):1213-9.
2. Kim T-e, Ha N, Kim Y, et al. Effect of epigallocatechin-3-gallate, major ingredient of green tea, on the pharmacokinetics of rosuvastatin in healthy volunteers. Drug Des Devel Ther 2017;11:1409-16.
3. Han X, Zhang H, Hao H, Li H, Guo X, Zhang D. Effect Of epigallocatechin-3-gallate on the pharmacokinetics of amlodipine in rats. Xenobiotica 2019;49(8):970-4.
4. Asher GN, Corbett AH, Hawke RL. Common herbal dietary supplement—drug interactions. Am Fam Physician 2017;96(2):101-7.
5. Cascorbi I. Drug interactions—principles, examples and clinical consequences. Dtsch Arztebl Int 2012;109(33-34):546-55.
6. Chakraborty M, Kamath JV. Pharmacodynamic interaction of green tea extract with hydrochlorothiazide against ischemia-reperfusion injury-induced myocardial infarction. J Adv Pharm Technol Res 2014;5(3):134-9.
7. Ali B, MS Jamal Q, Shams S, et al. In silico analysis of green tea polyphenols as inhibitors of AChE and BChE enzymes in Alzheimer's disease treatment. CNS Neurol Disord Drug Targets 2016;15(5):624-8.
8. Shehab NG, Khan RKG, Elgailani ESE, Shawish KYA. Possible intrusive food interaction with oral dabigatran's anticoagulant activity in a rat models. Tropical Journal of Pharmaceutical Research 2018;17(10):2031-2036.
9. Zhao YH, Abraham MH, Le J, et al. Rate-limited steps of human oral absorption and QSAR studies. Pharm Res 2002;19(10):1446-57.
10. Schanker L. Mechanisms of drug absorption and distribution. Annual Review of Pharmacology 1961;1(1):29-45.
11. Kiss T, Timár Z, Szabó A, et al. Effect of green tea on the gastrointestinal absorption of amoxicillin in rats. BMC Pharmacol Toxicol 2019;20(1):54.
12. Maher HM, Alzoman NZ, Shehata SM, Abahussain AO. UPLC–ESI–MS/MS study of the effect of green tea extract on the oral bioavailability of erlotinib and lapatinib in rats: Potential risk of pharmacokinetic interaction. J Chromatogr B Analyt Technol Biomed Life Sci 2017;1049-1050:30-40.
13. Misaka S, Miyazaki N, Fukushima T, Yamada S, Kimura J. Effects of green tea extract and (−)-epigallocatechin-3-gallate on pharmacokinetics of nadolol in rats. Phytomedicine 2013;20(14):1247-50.
14. Abe O, Ono T, Sato H, et al. Role of (−)-epigallocatechin gallate in the pharmacokinetic interaction between nadolol and green tea in healthy volunteers. Eur J Clin Pharmacol 2018;74(6):775-83.
15. Shan Y, Zhang M, Wang T, et al. Oxidative tea polyphenols greatly inhibit the absorption of atenolol. Front Pharmacol 2016;7:192.
16. Cheeseman HJ, Neal M. Interaction of chlorpromazine with tea and coffee. Br J Clin Pharmacol 1981;12(2):165-9.
17. Ikeda H, Tsuji E, Matsubara T, et al. Incompatibility between propericiazine oral solution and tea-based drink. Chem Pharm Bull (Tokyo) 2012;60(9):1207-11.
18. Ohata T, Ikeda H, Inenaga M, et al. Drug-tea polyphenol interaction (II) complexation of piperazine derivatives with green tea polyphenol. Thermochimica Acta 2017;653:1-7.
19. Oda K, Murakami T. Pharmacokinetic interaction of green tea beverage containing cyclodextrins and high concentration catechins with P□glycoprotein substrates in LLC□GA 5□COL 150 cells in vitro and in the small intestine of rats in vivo. J Pharm Pharmacol 2017;69(12):1736-44.
20. Kim T-E, Shin K-H, Park J-E, et al. Effect of green tea catechins on the pharmacokinetics of digoxin in humans. Drug Des Devel Ther 2018;12:2139-47.
21. Fleisher B, Unum J, Shao J, An G. Ingredients in fruit juices interact with dasatinib through inhibition of BCRP: a new mechanism of beverage-drug interaction. J Pharm Sci 2015;104(1):266-75.
22. Tian D-D, Kellogg JJ, Okut N, et al. Identification of intestinal UDP-glucuronosyltransferase inhibitors in green tea (Camellia sinensis) using a biochemometric approach: application to raloxifene as a test drug via in

vitro to in vivo extrapolation. Drug Metab Dispos 2018;46(5):552-60.

23. Jang E, Choi J, Park C, Lee SK, Kim C, Park H, et al. Effects of green tea extract administration on the pharmacokinetics of clozapine in rats. J Pharm Pharmacol 2005;57(3):311-6.

24. Mizuma T, Awazu S. Dietary polyphenols (−)-epicatechin and chrysin inhibit intestinal glucuronidation metabolism to increase drug absorption. J Pharm Sci 2004;93(9):2407-10.

25. Huang S-M, Lertora JJ, Markey SP, Atkinson AJ, editors. Principles of clinical pharmacology. Third ed. Academic Press; 2012.

26. Yuan L, Liu M, Shi Y, Yan H, Han J, Liu L. Effect of (–)-epicatechin-3-gallate and (–)-epigallocatechin-3-gallate on the binding of tegafur to human serum albumin as determined by spectroscopy, isothermal titration calorimetry, and molecular docking. J Biomol Struct Dyn 2019;37(11):2776-88.

27. Satoh T, Fujisawa H, Nakamura A, Takahashi N, Watanabe K. Inhibitory effects of eight green tea catechins on cytochrome P450 1A2, 2C9, 2D6, and 3A4 activities. J Pharm Pharm Sci 2016;19(2):188-97.

28. Jiang X, Sun Y, Shang L, Yang C, Kong L, Zhang Z. Green tea extract-assembled nanoclusters for combinational photothermal and chemotherapy. J Mater Chem B 2019;7(39):5972-82.

29. Jana S, Rastogi H. Effects of caffeic acid and quercetin on in vitro permeability, metabolism and in vivo pharmacokinetics of melatonin in rats: potential for herb-drug interaction. Eur J Drug Metab Pharmacokinet 2017;42(5):781-91.

30. Nishikawa M, Ariyoshi N, Kotani A, et al. Effects of continuous ingestion of green tea or grape seed extracts on the pharmacokinetics of midazolam. Drug Metab Pharmacokinet 2004;19(4):280-9.

31. Paul D, Surendran S, Chandrakala P, Satheeshkumar N. An assessment of the impact of green tea extract on palbociclib pharmacokinetics using a validated UHPLC–QTOF–MS method. Biomed Chromatogr 2019;33(4):e4469.

32. Bajaj P, Chowdhury SK, Yucha R, Kelly EJ, Xiao G. Emerging Kidney Models to Investigate Metabolism, Transport, and Toxicity of Drugs and Xenobiotics. Drug Metab Dispos. 2018 Nov;46(11):1692-1702.

33. Al-Arifi MN, Wajid S, Al-Manie NK, et al. Evaluation of knowledge of Health care professionals on warfarin interactions with drug and herb medicinal in Central Saudi Arabia. Pak J Med Sci 2016;32(1):229-33.

34. Koren R, Lerner A, Tirosh A, et al. The use of complementary and alternative medicine in hospitalized patients with type 2 diabetes mellitus in Israel. J Altern Complement Med 2015;21(7):395-400.

35. Alemdaroglu NC, Dietz U, Wolffram S, Spahn□Langguth H, Langguth P. Influence of green and black tea on folic acid pharmacokinetics in healthy volunteers: potential risk of diminished folic acid bioavailability. Biopharm Drug Dispos 2008;29(6):335-48.

36. Lu Y, Sun J, Petrova K, et al. Metabolomics evaluation of the effects of green tea extract on acetaminophen-induced hepatotoxicity in mice. Food Chem Toxicol 2013;62:707-21.