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Review Article

Update of green tea interactions with cardiovascular drugs and putative mechanisms

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ABSTRACT

Many patients treated with cardiovascular (CV) drugs drink green tea (GT), either as a cultural tradition or persuaded of its putative beneficial effects for health. Yet, GT may affect the pharmacokinetics and pharmacodynamics of CV compounds. Novel GT-CV drug interactions were reported for rosuvastatin, sildenafil and tacrolimus. Putative mechanisms involve inhibitory effects of GT catechins at the intestinal level on influx transporters OATP1A2 or OATP2B1 for rosuvastatin, on CYP3A for sildenafil and on both CYP3A and the efflux transporter p-glycoprotein for tacrolimus. These interactions, which add to those previously described with simvastatin, nadolol and warfarin, might lead, in some cases, to reduced drug efficacy or risk of drug toxicity. Oddly, available data on GT interaction with CV compounds with a narrow therapeutic index, such as warfarin and tacrolimus, derive from single case reports. Conversely, GT interactions with simvastatin, rosuvastatin, nadolol and sildenafil were documented through pharmacokinetic studies. In these, the effect of GT or GT derivatives on drug exposure was mild to moderate, but a high inter-individual variability was observed. Further investigations, including studies on the effect of the dose and the time of GT intake are necessary to understand more in depth the clinical relevance of GT-CV drug interactions.

1. Introduction

The proposal in supermarkets, herbalist's shops, drugstores and pharmacies of herbs and herb-derived industrialized derivatives with allegedly preventive and therapeutic actions has increased dramatically. Among these, green tea (GT) and GT byproducts gained enormous popularity due to their apparent beneficial effects, through multiple mechanisms, on a range of pathologic disorders including cardiovascular (CV)

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diseases [1,2]. At the same time, the utilization of CV medications raised steadily [3,4]. The potential consequence of these trends is an increased chance of GT-CV drug interactions. Although a variety of components in GT may account for GT-CV drug interactions, the main active principles implicated are the so-called "catechins", which include epigallocatechin gallate (EGCG), epicatechin gallate (ECG), epigallate catechin (EGC), and epicatechin (EC). EGCG represents 50–65% of the total GT catechins. Inasmuch as catechins are also supposed to provide most of the beneficial effects of GT for health, many people may choose to consume high volumes of GT, more concentrated infusions or even "high-strength catechins" byproducts, with increased likelihood of herb–drug interactions. It is worth to note that GT also contains vitamin K, beyond many antioxidants and several nutrients.

This paper is a narrative review aimed to disseminate updated information on reported interactions between GT or GT derivatives and CV drugs prescribed for prevention and therapy. For each interaction, the putative underlying pharmacological mechanisms is described.

2. Search strategy

The present work updates a previous review on this topic published by our group in 2015 [5]. We herein replicated the data search strategy used in that work, extending the time span. Briefly, we searched in PubMed from January 1995 to August 2017 using the following terms: herb, green tea, catechin, epigallocatechin gallate or EGCG, drug interaction, and cardiovascular drug, with their plurals and combinations. Furthermore, references in retrieved articles as well as papers that cited our previous studies on GT-CV drug interactions were hand searched for relevant original information. This review is focused on observational or experimental clinical studies. Yet, studies in vitro or in animals were revised to address putative mechanisms of interaction.

3. Green tea – cardiovascular drug interactions

CV diseases are still the major cause of death worldwide, which account for the high rate of prescription of CV drugs. Studies on new interactions between GT and CV drugs published in the last years involve rosuvastatin, sildenafil and tacrolimus, which add to the already reported interactions with simvastatin, nadolol and warfarin.

3.1. *Green tea and statins*

Statins are the first-choice drugs in patients with hypercholesterolemia or combined hyperlipidemia in either primary or secondary CV prevention [6]. Atorvastatin, simvastatin and rosuvastatin are among the first 30 drugs consumed in terms of volume and cost in Italy [7], an example of the extent of statin use in a developed country.

In 2008, we published the first case report of an interaction between GT and simvastatin in a 61-year-old Italian man with a history of primary hypercholesterolemia and previous early muscle intolerance to simvastatin, atorvastatin and rosuvastatin [8]. Subsequently, two extended pharmacokinetic studies were carried out in healthy male volunteers, one in Italians and the other in Japanese. These studies, described in detail elsewhere [5], demonstrate an evident pharmacokinetic interaction between GT and simvastatin of substantial size in some subjects, probably depending on the dose of GT assumed and/or individual predisposition. The mean effect and the putative mechanisms are briefly summarized in Table 1.

More recently, a study was conducted by a Korean group to assess the effect of EGCG on the pharmacokinetics of rosuvastatin [9]. In this study, thirteen healthy volunteers (2 male and 11 female, age 20–55 years) were enrolled. Capsules of pure crystalline EGCG (Teavigo®, 300 mg) were used as source of catechins and tablets of rosuvastatin 20 mg were assumed in kinetic studies. Four days after a first kinetic study with rosuvastatin alone, a second kinetic study was carried out to assess the effect of a single dose of EGCG on rosuvastatin exposure. Subsequently, to evaluate the effect of a chronic pretreatment plus acute intake of EGCG on rosuvastatin exposure, the participants assumed 300 mg/day of EGCG for 12 days and then repeated the procedure carried out in the second kinetic study. The analysis was stratified according to genetic polymorphisms in some genes (organic anion transporting polypeptide OATP1B1, OATP2B1 and breast cancer resistance protein (BCRP)) known to affect the metabolism of rosuvastatin. Compared with the rosuvastatin-only regimen, the single-dose concomitant administration of rosuvastatin and EGCG significantly reduced rosuvastatin exposure by 19% (90% C.I. 3–33%) whereas, curiously, the EGCG pre-treatment abolished the effect of the acute co-administration of EGCG with rosuvastatin. Some individual variability was observed in these experiments, though the overall size of the effect of EGCG on rosuvastatin kinetics was small. The authors found that the polymorphism 935G > A in the OATP2B1 gene influences the exposure to rosuvastatin but did not patently affect the interaction of EGCG with the statin.

Rosuvastatin is a hydrophilic statin, which undergo minor metabolism through CYP enzymes such as CYP2C9 and CYP2C19 and is excreted mainly unchanged with a bioavailability of 20% [10]. This compound has been shown to be a substrate of many drug transporters such as OATP1A2, OATP1B1, OATP1B3, OATP2B1, P-glycoprotein, and BCRP [11]. Among them, OATP1B1 (hepatic uptake) and BCRP (intestinal efflux and biliary excretion) have been proved to be clinically important transporters of rosuvastatin [11,12]. In addition, OATP1A2 and OATP2B1 localize in the apical membrane of enterocytes and may play a role in absorptive transport of rosuvastatin from the gastrointestinal tract [13].

In vitro experiments showed that GT catechins non-competitively inhibit CYP3A with inhibition constant (Ki) of approximately 20 μM (13–31 μM) in human intestinal and liver microsomes or recombinant CYP3A-expressing system [14,15]. CYP2C8 activity is also inhibited by GT extract (GTE) and EGCG in human liver microsomes [14]. With respect to drug transporters, Wang et al. found that EGCG inhibited OATP1B1-mediated uptake of dehydroepiandrosterone sulfate with half-maximal inhibitory concentrations (IC50) of 14 μM in vitro [16]. In line with this, EGCG and ECG potently

Table 1 – Interactions of green tea or epigallocatechin-3-gallate* with cardiovascular drugs.

Compound	References	Type of study	Main reported effects	Putative mechanism
Simvastatin	Werba et al., 2014 [5]	Pk	Italian study: $AUC_{0\text{-}6}$ SL and SA, NS increase	Inhibition of intestinal CYP3A4-mediated first pass metabolism and p-glycoprotein mediated efflux
			Japanese study: $AUC_{0\text{-}6}$ SL, NS increase; SA +22% ($p < 0.01$)	
*Rosuvastatin	Kim et al., 2017 [9]	Pk	AUC_{last} −19% (90% CI 3–33%)	Inhibition of intestinal OATP1A2 or OATP2B1-mediated uptake
Nadolol	Misaka et al., 2014 [24]	Pk/Pd	$AUC_{0\text{–}48}$ −85% ($p < 0.001$)	Inhibition of intestinal OATP1A2-mediated uptake
			Significant suppression of SBP-lowering effect	
Sildenafil	Hegazy et al., 2014 [27]	Pk	AUC_{∞} +50% ($p < 0.05$)	Inhibition of intestinal CYP3A-mediated first pass metabolism
Tacrolimus	Vischini et al., 2011 [32]	SCR	two-fold increase vs previous level	Inhibition of intestinal CYP3A4-mediated first pass metabolism and p-glycoprotein mediated efflux
Warfarin	Taylor et al., 1999 [35]	SCR	clinically significant reduction of INR (from 3.79 to 1.37)	Supply of vitamin K. Data on the effect of GT on warfarin pharmacokinetic is not available

Pk: pharmacokinetic studies in healthy volunteers; Pd: pharmacodynamic study; SCR: single case report; AUC: area under the curve; SA: Simvastatin acid; SL: simvastatin lactone; SBP: systolic blood pressure; INR: international normalized ratio; NS: not statistically significant.

inhibited OATP1B1-mediated estrone-3-sulfate uptake with IC50s of 8 and 59 μM, respectively [17]. There are many reports of the inhibition of P-glycoprotein by GT and especially gallated catechins such as EGCG and ECG at relatively high concentrations around 50–100 μM [18–20]. In contrast, GT catechins have no inhibitory effects on BCRP-mediated efflux transport of substrates such as mitoxantrone [21]. Considering the low bioavailability of GT catechins [22], pharmacokinetic interactions of orally administered drugs with GT may occur primarily in the gastrointestinal tract, as in the case of grapefruit juice [23]. Thus, the putative mechanism underlying rosuvastatin-GT interaction may be the inhibition of intestinal OATP1A2 or OATP2B1 [9] (Table 1).

3.2. *Green tea and nadolol*

Nadolol is a non-metabolized beta-adrenoceptor blocker utilized for the therapy of arterial hypertension, angina pectoris and some forms of cardiac arrhythmias. The effect of GT on the pharmacokinetics and pharmacodynamics of nadolol was assessed in healthy Japanese volunteers. The study demonstrated that GT noticeably reduce the exposure to nadolol and significantly suppress the systolic blood pressure-lowering effect of nadolol throughout the 48 h after drug administration. The mean effect and putative mechanisms, discussed elsewhere [24], are briefly summarized in Table 1.

3.3. *Green tea and sildenafil*

Sildenafil is a potent and selective inhibitor of phosphodiesterase type 5 (PDE5) prescribed in the CV field for the treatment of pulmonary hypertension [25], beyond its well known use for the management of erectile dysfunction which is, incidentally, a very prevalent condition in patients with silent or overt CV disease [26]. The effect of a single dose of GT on the pharmacokinetics of sildenafil was investigated in healthy Egyptian volunteers (n = 10; age 18–40 years, all males) [27]. A commercial GT extract in powder form (Mepaco®, Anshas El-Raml, Sharqia, Egypt) and 50 mg sildenafil tablets were used in these studies. Sildenafil was coadministered with midazolam as a probe drug. Using a random crossover study design, two kinetic studies were performed, with a 7-day washout period in-between. The declared content of total catechins in the GT preparation used in this study was 60 mg. Single-dose GT concurrently assumed with sildenafil increased sildenafil exposure by about 50% and this change was rather uniform among volunteers.

Sildenafil is metabolized mainly by CYP3A and to a lesser extent by CYP2C9 [28,29], and undergoes extensive first-pass metabolism after oral administration with oral bioavailability of 38% [30]. It is unknown whether sildenafil is a substrate of drug transporters. GT catechins have inhibitory effect not only on CYP3A and CYP2C8, as described above, but also on CYP2C9 in vitro [14,15]. Previous studies demonstrated that grapefruit juice slightly increased sildenafil exposure possibly by inhibiting intestinal CYP3A [31]. Therefore, GT-sildenafil interaction might be explained by an inhibition of CYP3A-mediated sildenafil metabolism (Table 1). It should be noted, however, that because sildenafil was coadministered with midazolam, a prototypical CYP3A substrate, along with GT in

the study [27], it cannot be excluded that coadministered midazolam could have offset in part the change observed in sildenafil exposure after GT intake.

3.4. *Green tea and tacrolimus*

Tacrolimus is a macrolide immunosuppressant indicated for the prophylaxis of rejection in patients with allogeneic organ transplants, including heart transplant. A description of an interaction between GT and tacrolimus was reported in a 58-year-old male kidney transplant recipient [32].

In this patient, during routine clinical monitoring of immunosuppression, tacrolimus levels were found two-fold vs previous levels, a couple of days after assuming GT. Tacrolimus levels progressively returned to baseline within e few weeks after GT interruption. This case report describes an observation from usual care and not pharmacokinetic studies. Moreover, the authors did not inform the type or the amount of GT consumed by the patient.

Tacrolimus is extensively metabolized by intestinal and hepatic CYP3A subfamily with a bioavailability of 5–70% [33]. Tacrolimus is also a substrate of P-glycoprotein [34]. As described above, GT catechins could increase tacrolimus exposure by inhibiting both CYP3A and P-glycoprotein in the intestine [14,15,18–20] (Table 1).

3.5. *Green tea and warfarin*

Warfarin is an anticoagulant indicated for the prevention and treatment of thromboembolism in patients with atrial fibrillation, prosthetic heart valves and deep-vein thrombosis. This drug is a vitamin K antagonist that inhibits the coagulation cascade and reduces the risk of thrombus formation. The literature describes a single case report of GT interaction with Warfarin [35]. Curiously, even though this case has been repeatedly cited [36–38], no further studies were reported in the literature to support this observation. The pharmacodynamics effect of GT and its putative mechanisms, discussed elsewhere [5], are briefly summarized in Table 1.

4. Discussion

GT is the most popular beverage consumed in Asian countries. Moreover, this typically oriental infusion has gained wide use in western countries not only as teas but also as industrialized drinks and extracts. One reason for the popularity of GT is the diffuse message of its claimed generic benefits for overall health and in specific diseases, including some risk factors for CVD [1]. This may encourage patients with overt CVD treated with CV drugs to consume these products. However, as reviewed in this paper, GT or GT derivatives may interact with several CV drugs, potentially leading to reduced drug efficacy or increased risk of drug toxicity. The number of GT-CV drug interactions reported in humans increased in the last years and now include simvastatin, rosuvastatin, nadolol, sildenafil, tacrolimus and warfarin. However, the list might be actually longer, as suggested by the results of animal experiments with diltiazem, verapamil and nicardipine [39]. The mean magnitude of the effect of GT on CV drugs exposure was in each case mild to moderate (at most a two-fold change), and much smaller than those observed, for example, between grapefruit juice and simvastatin [40] (13.5-fold increase) or between clarithromycin and simvastatin [41] (about 10-fold increase).

However, a large interindividual variability of the GT effect was observed in pharmacokinetic studies, and in some particularly susceptible subjects, the interaction might be clinically relevant. Except for the interaction with warfarin, which might be mediated at least in part by the vitamin K content of GT, catechins are the components of GT more probably responsible for the interactions with CV drugs. When specified in the papers reviewed herein, the daily intake of total catechins shown to interact with the different CV drugs widely varied among studies, from 60 mg for the GT-sildenafil interaction to more than 600 mg for the GT-simvastatin and GT-nadolol interactions.

The risk of interaction might be higher in patients who consume high volumes of GT, GT plant varieties and infusions with high catechin content or "high-strength" GT derivatives. Although this is a reasonable hypothesis, dose-effect studies of GT or pure catechins on CV drug exposure have not been performed so far. Such studies might also help to gain knowledge on issues of practical importance such as: Is there a lower threshold of GT intake below which no interaction is observed with each specific CV compound? Is there an upper threshold of GT intake above which each interaction reaches a plateau?

As previously reported with grapefruit juice [40], the time span between GT intake and CV drug intake may also determine the chance of interaction, mainly if a GT effect on drug metabolism in intestinal cells is mechanistically involved. However, data about the influence of the timing of GT and CV drugs intake on the chance of interaction is also lacking.

Besides, the effect of a chronic or sub-chronic consumption of GT may differ between GT-drug interactions. In fact, a sub-chronic pretreatment with EGCG abolished the acute effect of EGCG on rosuvastatin levels whereas a sub-chronic pretreatment with GT increased simvastatin levels and decreased nadolol levels. Further studies are required to know whether these differences are related to an effect of GT compounds not present in pure EGCG or to actual dissimilar effects of GT pretreatment on the interaction of GT with the different CV drugs.

GT increased the exposure to some CV drugs (simvastatin, sildenafil and tacrolimus) and reduced the expose to others (rosuvastatin and nadolol). In vitro studies suggested that an effect of GT on P450 CYP isoforms mediate the former whereas an effect on transporters of the OATP family mediate the later.

Pharmacodynamic effects are described only for two of the interactions herein reviewed: a reduction of INR for GT-warfarin and a suppression of the blood pressure-lowering for GT-nadolol. Further data on the pharmacodynamic changes associated with other GT-CV drug interactions might help to gain knowledge on their clinical relevance.

Moreover, it is worth noting that the information regarding the interactions between GT and both tacrolimus and warfarin derives from single case reports. Given the narrow therapeutic index of these two drugs, full studies are warranted to substantiate these observations.

Altogether, data available up to now suggest that a low-to-moderate consumption of traditional GT infusion may barely

lead to severe problems of interaction with CV drugs, probably with the exception of a subset of susceptible individuals, which warrants a certain clinical suspicion of GT intake in cases of reduced drug response or intolerance.

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