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REVIEW

Adverse effects of concentrated green tea extracts

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A myriad of health claims are being made in favor of the consumption of green tea. However, mostly due to the easy availability and greater than ever popularity of highly concentrated green tea extracts, sometimes combined with an attitude of more-is-better, certain health risks of green tea consumption have begun to emerge. Among such risks are the possibility of liver damage, the potential to interact with prescription drugs to alter their therapeutic efficacy, and the chance to cause harm when combined with other highly popular herbal remedies. This review will summarize documented examples of adverse effects of green tea in humans, and will discuss risks of copious consumption of highly concentrated green tea extracts as indicated by studies in animals. While there is no intention to minimize any of the scientifically established benefits of the use of green tea, the purpose of this review is to focus primarily on the potential for adverse effects and raise awareness of the rare, yet underappreciated risks.

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1 Introduction

Herbal supplements are commonly perceived by the public as ''innocent'' or ''holistic'' and have become hugely popular as unrestrictedly available, supposedly ''cure-all'' remedies. Green tea in particular, besides being the most widely consumed beverage second only to water and having been part of Eastern medicine for millennia, has become increasingly popular in the West as well. In addition to conventional green tea infusion, concentrated green tea extract (GTE) in liquid or capsule formulations have become the consumption of choice for healthy individuals seeking to increase their overall health. Purported health effects of green tea and its concentrated derivatives are plentiful, although many claims are not supported by scientific evidence (see, for example, reviews [1–4] and references therein).

Among the well-characterized effects of GTE is its ability to induce thermogenesis and stimulate fat oxidation [5], which can lead to modest, but statistically significant reduction in body mass index (BMI) and body weight [6–10]. Within the background of the spreading obesity pandemic, the message of weight loss-supportive effects of GTE has been welcomed by the overweight public, and has triggered a huge demand for highly concentrated GTE liquids and capsules. Other health claims for green tea, such as its purported cardiovascular protection and anti-cancer effects (see critical reviews [1, 2]), have further contributed to the increasingly widespread consumption of large dosages of GTE. Cancer patients in particular may be tempted to self-medicate with such supplements in hopes to delay the progression of their disease and/or reduce the side effects associated with conventional chemotherapy [11–13]. Such liberal use, often unbeknownst to the patients' healthcare providers [12–14], is encouraged by a myriad of Internet websites and the over-the-counter availability of a large variety of green tea products on the Internet and at local grocery, pharmacy, and health food stores. However, while there is evidence of beneficial outcomes from the consumption of green tea and GTE, there are also indications that copious use of green tea infusions and

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Abbreviations: CYP3A4, cytochrome P450 3A4; **DSI EC,** Dietary Supplement Information Expert Committee; **EC,** epicatechin; **ECG,** epicatechin gallate; **EGC,** epigallocatechin; **EGCG,** epigallocatechin gallate; **GTE,** green tea extract; **Pgp,** P-glycoprotein; **Poly E,** Polyphenon E; **UGT1A1,** uridine diphosphate glucuronosyltransferase 1A1; **USP,** United States Pharmacopeia

concentrated GTE is able to generate adverse events, which in rare and extreme cases can be life threatening.

2 Components of green tea and GTE

Green tea (*Camellia sinensis*) is a heterogeneous product that contains a great variety of components. The predominant contents are the four polyphenolic catechins epigallocatechin gallate (EGCG), epicatechin gallate (ECG), epigallate catechin (EGC), and epicatechin (EC), which are presumed to provide the majority of the surmised health benefits of this herb [15–17]. EGCG comprises about 50–60% of green tea catechins, and there are minor amounts of other catechin monomers, gallocatechin gallate (GCG), gallocatechin (GC), catechin gallate (CG), and catechin (C) as well. Other components include the flavonoids kaempferol, quercetin, and myricetin, the amino acid derivative theanine, the xanthine alkaloid caffeine, theophylline, theobromine, saponins, tannins, as well as 300 additional substances. Morever, green tea might contain trace levels of pesticides, such as organochlorines, organophosphates, and pyrethrins [18, 19].

The quantitative proportions of most active green tea ingredients vary according to clonal variation, cultivation (climatic region, altitude), and the growth state of the leaves. For example, while younger leaves contain the highest amount of caffeine, older leaves have larger amounts of total catechins [20]. For considerations of potentially beneficial or detrimental effects of these green tea components, it is also noteworthy that their absorption after oral ingestion varies greatly, resulting in disparate bioavailability.

Besides conventional tea leaves for infusion, a large selection of commercially available GTE products in liquid or capsule form offer highly concentrated versions of green tea that are enriched for catechin content. To name only a few representatives of the very many available products: 250 mg Teavigo® EGCG+capsicum capsules (DSM Nutritional Products) are caffeine-free and contain natural EGCG with a purity of a minimum of 94% (i.e. $\geq$235 mg EGCG per capsule); NOW Foods' EGCG Green Tea Extract® comes as 400 mg capsules containing 200 mg EGCG; ProHealth's Green Tea Mega EGCG 725 mg capsules contain 95% polyphenols and provide 290 mg EGCG plus 109 mg other catechins. Liquid versions of GTE, which are also sold by a number of companies, may contain anywhere from 10 to 50% EGCG as per label claim. For example, the recommended dose for liquid GreenTeaPure® (WellnessPartners.com) contains 480 mg GTE with 98% polyphenols (plus Acai and Goji berry extract); Platinum Green Tea® (Nature's Answer) is decaffeinated liquid GTE (+extracts from a variety of fruits) with a label claim of 95% polyphenols and 50% EGCG (i.e. 50 mg EGCG per serving size). For comparison purposes, one cup (8 oz in the US) of infused green tea supplies an average of 50–300 mg polyphenols (20–150 mg EGCG), although there is considerable variability both in total phenol and catechin content (as well as caffeine content), depending on the brand of product, the region the tea was grown, the age of the leaves, the manufacturing process conditions, infusion time, etc. [21–24].

Polyphenon® is the trademark applied to a series of high-grade, highly standardized GTEs, which are manufactured by Mitsui Norin of Japan. The most widely used of these GTEs is Polyphenon E®(Poly E), which has been manufactured by the Mutsui subsidiary Polyphenon Pharma [http://www.polyphenon-pharma.com] in the US for oral and topical [25–27] applications. The defined catechin composition of Poly E, a decaffeinated GTE with a total catechin fraction of 89% (65% EGCG, 9% EC, 6.6% ECG, 3.8% EGC, 3.5% CCG, 1.0% C, 0.2% GC, and 0.2% CG [28]), has supported its use in the clinic, and there are more than a dozen studies ongoing throughout North America, in which the therapeutic potential of this GTE is being tested against a broad range of diseases.

3 Pharmacokinetic and safety studies

Catechins, representing the most abundant components of green tea, have been measured in the plasma of healthy volunteers as well as patients and have provided significant information about the pharmacokinetics of green tea constituents. Among the first reports [29–31] to investigate pharmacokinetic properties of such catechins in humans was a study by Yang et al. [32], where healthy volunteers ingested a decaffeinated beverage formulation containing 1.5, 3.0, and 4.5 g of GTE, corresponding to 282, 564, and 846 mg of catechins (EGCG+EGC+ECG+EC), respectively. These single dosages were equivalent to approximately 3, 6, and 9 cups (8 oz) of green tea, respectively. The plasma levels of these catechins reached peak levels between 1.5 and 2.5 h in almost all subjects and declined to undetectable levels after 24 h. C_{max} for EGCG, EGC, and EC at the highest dosage was 321, 550, and 190 ng/mL, respectively. The $t_{1/2}$ value for EGCG was approximately 5 h, and the $t_{1/2}$ value for EGC was about 2.7 h. Altogether, no apparent adverse effects in the 18 volunteers of this study were reported (Table 1).

A subsequent phase I trial with 49 adult cancer patients sought to determine the maximally tolerated dose (MTD) of oral GTE on a once daily and three times daily schedule [33]. The subjects were given GTE capsules containing 27% total catechins and 7% caffeine, at increasing dosages up to a total dose of 8–10 g GTE once daily, or 10–13 g distributed over three daily dosages, for 4 wk to a maximum of 6 months. Mild to moderate toxicities (National Cancer Institute grade 1–3) were seen at most dose levels and promptly reversed on discontinuation of GTE. The dose-limiting toxicities were caffeine related and included gastrointestinal (GI) (flatulence, nausea, and abdominal bloating), neurological (insomnia, restlessness, tremor, headache, pain, and paresthesias) and cardiovascular

Table 1. Major pharmacokinetic and safety studies of GTE

Subjects	Dosage	Schedule	Reported effects	Ref.
Healthy volunteers ($n = 18$)	Up to 846 mg catechins (incl. caffeine)	Single dosage	No apparent adverse effects	[32]
Adult cancer patients ($n = 49$)	Up to 3500 mg catechins (incl. caffeine)	Distributed over 3 daily dosages up to 6 months	GI, neurological and cardiovascular (''caffeine related'')	[33]
Healthy volunteers ($n = 40$)	Up to 800 mg EGCG or Poly E	Daily for up to 4 wk	Mild adverse events (''well tolerated'')	[37]
Healthy volunteers ($n = 36$)	Up to 800 mg EGCG (crystalline)	Daily for 10 days	''Safe and very well tolerated''	[39]
Healthy volunteers ($n = 30$)	Up to 1200 mg EGCG (as Poly E)	Single dose	Mild and transient nausea (''generally well tolerated'')	[40]
Healthy volunteers ($n = 60$)	Up to 1600 mg EGCG (crystalline)	Single dose	No adverse events (''safe and very well tolerated'')	[41]
Cancer patients ($n = 33$)	Up to 1800 mg catechins (as Poly E)	Daily for 1 month	Mostly well tolerated; 2 patients with grade 2 toxicities	[43]
Healthy volunteers ($n = 17$)	714 mg GTE (incl. caffeine)	Daily for 3 wk	No effects on risk biomarkers for liver, kidney or CVD	[65]

(palpitations) effects. The measurements of t_{max} and C_{max} were comparable to those reported by the prior study by Yang et al. mentioned above [32]. Based on these results, it was concluded that 2 g GTE, taken three times per day (equivalent to three to four 8 oz cups three times a day), would be well tolerated and likely could be administered on a long-term basis, as would be required in a chemopreventive setting, for example.

The major dose-limiting ingredient in GTE, as suggested in the report by Pisters et al. [33], appears to be caffeine, which can range in content from 10 to 50 mg per cup (8 oz) and up to 10% in GTE [24], [http://www.polyphenon.jp]. Although this would suggest the preferential use of decaffeinated GTE products, there are indications in the literature that caffeine perhaps might contribute to at least some of the beneficial effects of green tea. For example, in two studies [34, 35] investigating the anticancer effects of tea on tumor growth in laboratory mice and rats, it was found that (i) complete tea was more potent than decaffeinated tea in inhibiting tumor growth, (ii) adding caffeine back to decaffeinated tea restored biologic activity, and (iii) caffeine alone in the drinking water inhibited tumor formation. Moreover, many epidemiological studies (for example, ref. [36]) are based on the consumption of regular (as opposed to decaffeinated) green tea, and therefore are not able to differentiate between the contribution of catechins versus caffeine.

More recently, several clinical studies have analyzed pharmacokinetics and safety of purified EGCG and Poly E, the highly standardized, decaffeinated GTE. With healthy volunteers as subjects, it was demonstrated that both of these catechin formulations exhibited similar pharmacokinetic profiles and were well tolerated at the dosages used (up to 800 mg/day for up to 4 wk) [37–39]. Subsequent studies increased these dosages even further, and also determined the effects of catechin administration after fasting or with food. A single dose of 1200 mg EGCG (as Poly E) or 1600 mg crystalline EGCG was given to healthy volunteers [40, 41]. Although considered safe and well tolerated, it was found that plasma C_{max} of EGCG was several-fold higher when given after an overnight fast, as compared to the same dose given with food. This was also confirmed in a follow-up study were crystalline EGCG was administered to healthy subjects for 10 days after overnight fasting [39]. Combined, these studies consistently demonstrated that plasma concentrations of EGCG are significantly increased when GTE is consumed under fasting conditions.

The observation that plasma EGCG concentrations in humans are substantially higher when catechins are given in the fasted state, were also confirmed in dogs, where 500 mg/kg/day of an EGCG preparation (80% EGCG+5% other catechins) revealed no adverse effects when given to pre-fed animals, but caused morbidity when given to fasted dogs as a single bolus dose [42]. Although the dog model was considered an unrealistic comparison to the human condition (translating to about 25 g of catechins for a 60 kg human), in February 2006 the U.S. Food and Drug Administration (FDA) temporarily suspended all human trials with GTE in order to allow additional review of toxicity data (see below). As a result of this appraisal, the Food and Drug Administration mandated that all future US clinical trials administer catechins with food. Consequently, several ongoing clinical trials had to be modified and had to switch to the administration of Poly E together with food. One such phase I study was published very recently by Shanafelt et al. [43]. Here, 33 patients with chronic lymphocytic leukemia (CLL) were given 400–2000 mg oral Poly E twice a day, and plasma EGCG was measured after one month. The results show that this regimen was well tolerated by these patients, although two of them experienced dose-limiting grade 2 dysphagia and intestinal problems, respectively [43] (Table 1).

Altogether, all studies with human subjects showed that purified EGCG, GTE, or Poly E, equivalent to the EGCG content of 8–16 cups of green tea, were safe and well tolerated. However, a major limitation of all of these clinical trials was their open-label, small-scale design, which does not possess the statistical power to detect any adverse effects other than those that are very common.

4 Liver toxicity of green tea extract

Contrasting the encouragingly positive results presented above are an increasing number of case studies reporting detrimental effects after the ingestion of large amounts of green tea or GTE (Fig. 1). For example, individual cases of acute hepatotoxicity from copious green tea consumption are described in the literature and may range from acute hepatitis to acute liver failure. In many cases, resolution followed withdrawal, and recurrence followed re-challenge, suggesting a cause-and-effect relationship (see detailed references in [44–48]). Frequently, however, the green tea products were not fully characterized and oftentimes contained other herbal components in addition to *C. sinensis*; this multiplicity of ingredients and co-ingestants can make it difficult to establish a definitively causal relationship between extracts of green tea and reported cases of hepatotoxicity.

A comprehensive and very thorough analysis of the safety of GTE was recently published by the US Pharmacopeia

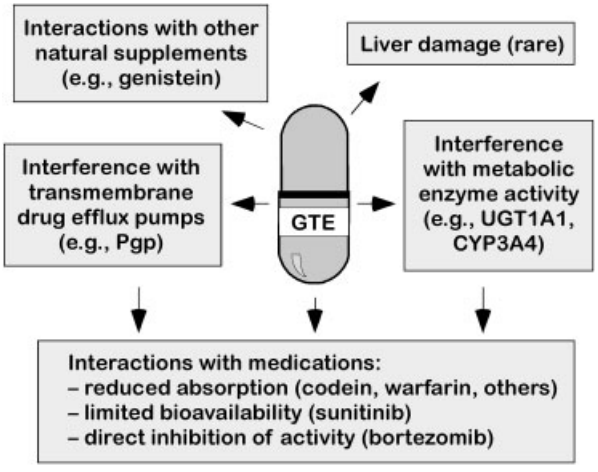

Figure 1. Potentially detrimental effects of concentrated GTE. Note that GTE is not synonymous with catechins. For example, reduced absorption of iron supplements or of codeine, warfarin and some other drugs is primarily caused by the tannin content of GTE. The noted mild to moderate toxicities (flatulence, insomnia, and palpitations) of large dosages of GTE have been ascribed to caffeine (see text). On the other hand, studies with individual components of GTE, such as crystalline EGCG, have unequivocally established that certain effects are caused by catechins (see text). In the case of liver damage, however, the causative GTE components have remained unidentified.

(USP), an independent, science-based public health organization that sets the standards for food ingredients and dietary supplements [www.usp.org]. Its reference materials and documentary standards are recognized not only in the US, but also in about 130 nations worldwide. Established verification programs of the USP assist manufacturers in assuring the public that they are making good-quality dietary supplements [49]. In 2008, the USP Dietary Supplement Information Expert Committee (DSI EC) systematically reviewed the safety information for green tea products [48]. This review had been arranged in response to the suspension of GTE-containing weight-loss products by regulatory agencies in France and Spain due to hepatotoxicity concerns, and by the publication of adverse event case reports involving green tea products. Among other types of information, the committee analyzed a total of 216 case reports, including 34 on liver damage [48].

Of the 34 case reports indicating hepatotoxicity of GTE, the DSI EC categorized 27 as ''possible causality'' and 7 as ''probable causality'' (based on the Naranjo causality algorithm scale [48], assessing the likelihood that exposure to green tea products caused hepatotoxicity). For example, in the case of Exolise® (Arkopharma Laboratories), a weight loss product containing a hydroalcoholic extract of green tea named AR25 (standardized to 25% catechins), 13 patients in Spain and France taking this supplement demonstrated elevated liver enzymes (alanine aminotransferase (ALT) and aspartate aminotransferase (AST)) with an onset that ranged from 9 days to 5 months. The frequency of these reported adverse effects was very rare and was estimated at 1 case per 100 000 boxes of Exolise sold from 1999 to 2003. In 12 of these patients, hepatitis was resolved after discontinuation of Exolise consumption; in the one remaining patient the problem did not resolve but progressed to liver failure (possibly due to other confounding factors, such as alcohol and drug use) (see detailed references and discussion in Ref. [48]). In 2003, health authorities in Spain and France suspended the sale of Exolise, and Arkopharma voluntarily withdrew the product from other countries where it had been available.

Besides Exolise, other specific GTE-based products also were found to be reason for concern. For example, Tealine®, a product containing an aqueous extract of green, white, and red tea (40–50% catechins), was also linked to liver damage in four known cases in France [50], which were classified as either probable or possible causality on the Naranjo scale [48]. Other case reports evaluated by the DSI EC [48] involved several additional GTE-containing products from different countries, and some of these constituted multi-herb products, such as Hydroxycut® [51], a formulation that also contains *Garcinia cambogia*, *Gymnema sylvestre*, guarana extract, calcium, chromium polynicotinate, potassium, glycomannan, α-lipoic acid, willow bark extract, L-carnitine, and caffeine – in addition to 91 mg EGCG. Naturally, in the case of multi-component products, the presence of these confounding variables makes it difficult to ascribe

potentially adverse reactions to a single ingredient. For example, in the case of Hydroxycut, chromium piccolinate may have been the likely ingredient responsible for the observed hepatotoxicity [52].

A link between liver damage and the consumption of green tea has also been investigated in numerous in vitro and animal studies. Interestingly, several studies reported hepatoprotective effects of green tea preparations [53–60], whereas others demonstrated hepatotoxic effects (usually at higher concentrations) of GTE [61–64]. These conflicting data are echoed in observations in humans. For instance, the numerous case studies discussed above, which suggest hepatotoxic effects of GTE in human subjects, are contrasted by reports that failed to demonstrate liver damage in response to the consumption of GTE. For example, in a recent trial with healthy men consuming 714 mg catechins per day for 3 wk, the authors did not detect impaired liver function [65], although, as pointed out elsewhere [48], the small-scale design of this study ($n = 17$) does not possess the statistical power to detect any adverse effects other than those that are very common. A recently published systematic review of interventional and observational studies on green tea consumption and liver disease concluded that green tea may reduce the risk of liver disease [66], in particular liver cancer [67]; however, several confounding variables, including caffeine content of green tea [68], make it difficult to establish the precise contribution of catechins.

5 Drug interactions of green tea

Several studies have identified situations where green tea or GTE may interfere with the absorption, bioavailability, or activity of prescription drugs and other compounds (Fig. 1). A well-known example is interference with the absorption of iron supplements, where the tannin content in green tea reduces the bioavailability of iron. For this reason, iron supplements should not be ingested together with green tea components, and subjects deficient in iron or susceptible to iron deficiency should use GTE sparingly. Similarly, green tea tannins may reduce the absorption of codeine, atropine, ephedrine, pseudoephedrine, theophylline, aminophylline, warfarin, Cardec DM®, Lomotil®, Lonox®, and green tea caffeine may increase the pharmacological effects of ephedrine, pseudoephedrine, theophylline, and aminophylline, while inhibiting the hemodynamic effects of adenosine [69–74].

5.1 Interactions with P-glycoprotein (Pgp)

Green tea catechins have been found to modulate the activity of P-glycoprotein (also called ABCB1 and MDR1), a member of the superfamily of ATP-binding cassette (ABC) transporters, which transport various molecules, including specific drugs, across cellular membranes. Pgp in particular is an efflux pump for xenobiotic compounds and has broad substrate specificity [75]. Therefore, the discovery that catechins are able to inhibit Pgp activity has broad implications for the treatment of patients with medications that are substrates for Pgp [76, 77]. Intriguingly, while some catechins were found to be inhibitors of Pgp, others appeared to increase Pgp-mediated drug transport by heterotropic allosteric mechanism [77]. Several studies in rats or mice have established that oral EGCG indeed is able alter the pharmacokinetics and efficacy of co-administered prescription drugs, such as nicardipine, tamoxifen, doxorubicin, diltiazem, or verapamil [78–82].

While a desirable and beneficial consequence of Pgp inhibition by EGCG may increase chemosensitivity of multidrug-resistant cancer cells [81, 83–86], there are potentially detrimental consequences as well. For instance, as Pgp is involved in biliary excretion of some drugs [87, 88], its inhibition by catechins may interfere with drug excretion into the biliary tract, and thus may result in elevated plasma levels of drug and increased risk of systemic toxicity. A specific example of reduced bile efflux after administration of EGCG has recently been described for the cancer drug irinotecan (CPT-11) and its active metabolite SN-38, a topoisomerase I inhibitor, in studies with rats [89]. Animals that were pretreated with EGCG displayed reduced biliary elimination of these drugs, and as a result plasma half-life and area under the curve (AUC) of CPT-11 and SN-38 were significantly increased.

5.2 Interactions with uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1)

An additional mechanism of EGCG and SN-38 interaction was suggested [89] in relation to the known glucuronidation of EGCG by UGT1A1 in the liver [90, 91]. Because UGT1A1 is also the enzyme that inactivates SN-38 by forming glucuronidated, inactive SN-38G, it is likely that reduced SN-38G formation in the presence of catechins may be due to a mechanism of competitive inhibition [89, 92–94]. In view of the well-recognized side effects of CPT-11 therapy (severe diarrhea and extreme suppression of the immune system) and the unpredictable occurrence of these adverse reactions [95], it is essential that the dosage of this chemotherapy is carefully chosen and kept within its narrow therapeutic range. For this reason, potential interactions with herbal supplements should be avoided and green tea products should not be consumed during this type of therapy [89].

5.3 Interactions with cytochrome P450 system

Yet another key metabolic enzyme that may be affected by green tea catechins is cytochrome P450 3A4 (CYP3A4),

which has broad substrate specificity and is responsible for the metabolism of more than 50% of clinical pharmaceuticals. As well, CYP3A4 appears to be a key enzyme in food–drug interactions [96, 97]. A few recent studies investigated several commonly used herbal compounds for their ability to inhibit CYP3A4 activity in vitro [98–101]. Among ginseng, garlic, black cohosh, mistletoe, grape seed extract and GTE, the latter was found to produce the most pronounced inhibition of CYP3A4, which ranged from 6 to 90%, depending on the particular commercially available GTE product tested [98]. Similarly, individual catechins (EGCG, EGC, ECG, and EC) were found to inhibit CYP3A4, as well as CYP1A1 and CYP1A2, when these enzymes were expressed in genetically engineered *Salmonella typhimurium* [102]. Combined, these in vitro studies indicated that GTE might have the potential to significantly impede the pharmacokinetics of many clinical pharmaceuticals.

Interestingly, several studies have shown that inhibition of P450 cytochromes by green tea catechins reduced metabolic activation of procarcinogens, which was consistent with a number of reports indicating chemopreventive effects of green tea polyphenols toward chemical carcinogenesis (see detailed references in [102–104]). Thus, the potentially beneficial effects resulting from the inhibition of P450 cytochromes by green tea catechins (i.e. reduced metabolic activation of dietary carcinogens) may be curbed by the potentially detrimental outcome in case of altered pharmacokinetic profiles of prescription drugs.

Altogether, the precise effects of GTE on P450 cytochrome activity in vivo have not convincingly been established. On one hand, several studies in rats have documented altered activity of some of these enzymes after the administration of GTE (for selected examples, see Refs. [104–107]). In addition, altered bioavailability and pharmacokinetics of several drugs, such as tamoxifen, clozapine, or midazolam, have been reported for rats treated with GTE or EGCG [79, 82, 100, 108]. On the other hand, studies in humans so far have failed to establish major effects. For example, CYP3A4 activity was measured in 42 healthy volunteers after daily ingestion of Poly E (800 mg EGCG) for 4 wk and the use of buspirone as a CYP3A4 substrate [109]. The obtained results were consistent with a reduction in CYP3A4 activity, but the effect was small and the authors concluded that it was ''not likely to result in clinically significant effects on the disposition of drugs metabolized by CYP enzymes'' [109]. In another study with 11 healthy volunteers [110], catechins (844 mg/day) were given for 2 wk, and this dosing was continued while the CYP3A4 substrate (in this case, alprazolam) was administered. However, no significant differences in alprazolam pharmacokinetics were observed, which led the authors to conclude that GTE ''is unlikely to alter the disposition of medications primarily dependent on the CYP2D6 or CYP3A4 pathways of metabolism'' [110].

5.4 Direct molecular interactions with bortezomib and sunitinib

Besides herbal–drug interactions that are mediated via the altered activities of metabolic enzymes or transmembrane drug transport proteins, there are also clinically relevant examples of direct molecular interactions between green tea catechins and therapeutic pharmacological agents. Two such examples will be presented here. A study by Golden et al. [111] reported that green tea catechins were able to effectively and completely block the therapeutic efficacy of bortezomib (Velcade®), a proteasome inhibitor that is being used for the treatment of multiple myeloma and mantle cell lymphoma [112], in vitro and in an animal tumor model in vivo. Another study, by Ge et al. [113], demonstrated interactions between EGCG and sunitinib (Sutent®), an oral multi-kinase inhibitor that is approved for the treatment of unresectable GI stromal tumors and advanced renal cell carcinoma [114] (see details below).

For the evaluation of the clinical relevance of in vitro studies using green tea catechins, it is important to consider the concentrations required to achieve a biological effect. In this context, it is noteworthy that the vast majority of published reports employ concentrations of EGCG in the range of 10–100 μM, and it is not unusual to find studies using even higher concentrations (for representative examples, see Refs. [62, 115, 116]). Indeed, many biological effects of EGCG in vitro, in particular the induction of tumor cell death, generally are not observed at concentrations below 10 μM. In comparison, pharmacokinetic studies of EGCG in healthy subjects (see details in Section 3) have established an upper limit of approximately 8 μM as the achievable peak plasma catechin concentration in humans, although most often this value may be substantially lower due to wide variations between individuals. Thus, with regards to in vitro studies, it is difficult to assign potential physiological relevance to results that can be produced only at EGCG concentrations above 10 μM.

Within the context of physiologically relevant catechin concentrations, the study by Golden et al. [111] is quite pertinent, because liquid GTE with EGCG content in the submicromolar range sufficed to generate biological effects in vitro, i.e. reduction of the efficacy of tumor cell killing by bortezomib, and 5 μM crystalline EGCG completely blocked the tumoricidal effects of bortezomib by 100%. This extremely effective antagonism could also be verified in the in vivo setting, where EGCG potently neutralized the antitumor effects of bortezomib in a mouse tumor model [111]. Further detailed studies by this group established that this pronounced antagonistic function of EGCG (and other catechins) was evident only with boronic acid-based proteasome inhibitors, such as bortezomib, MG-262, or PS-IX, but not with non-boronic acid proteasome inhibitors, such as MG-132, PS-I, or nelfinavir (Viracept®). The molecular basis for EGCG-bortezomib interaction resided in their chemical structures. In the chemical sciences, it had been

known for a long time that molecules with 1,2-diol groups (as is the case with EGCG, EGC, ECG, and EC) are able to form covalent cyclic boronate moieties with boronic acid in a tight manner, resulting in one of the strongest single-pair reversible functional group interactions in an aqueous environment [117–119]. Indeed, as established by NMR spectroscopy, the EGCG molecule directly interacted with the bortezomib molecule, thereby eliminating its biological activity [111, 120].

A study by Ge et al. [113] was triggered by the observation that tea drinking disturbed the symptom control of sunitinib in a clinical case of metastatic renal cell carcinoma. Subsequent in vitro and in vivo animal studies established that EGCG directly interacted with sunitinib to form a precipitate, which caused sticky semisolid contents in the stomachs of mice co-administered with both substances. In parallel, plasma concentrations of sunitinib were markedly lower in these animals, with C_{max} and area under the curve reduced by 50% [113]. The authors concluded that intragastric formation of sticky complexes between EGCG and sunitinib impaired the absorption of sunitinib, and thus led to significant reduction of its bioavailability. The structural requirements for EGCG-sunitinib interaction were not resolved in this study, and therefore it is unclear whether this type of interaction should also be expected for other small-molecule kinase inhibitors, such as sorafenib (Nexavar®), dasatinib (Sprycel®), and several others.

The above examples of cancer drug inactivation by green tea catechins, if taking place in patients, could lead to potentially life-threatening consequences. It is well known that many cancer patients consume copious amounts of GTE (and/or other herbal compounds) [11–14]. If cancer drug inactivation indeed were to take place in these patients, one would expect that most of the dreaded side effects of cancer drug treatment would subside, leading to increased well-being of the patient. As a consequence of improved well-being, these patients may feel encouraged to further increase consumption of green tea products, which might lead to even further improvements – while at the same time, and unknowingly, the therapeutic efficacy of their drug treatment may be severely blunted, if not entirely obliterated [11, 89, 111, 113, 120].

5.5 Interactions with other natural supplements

Healthy persons seeking to remain in good health, as well as patients seeking to self-medicate, oftentimes consume a variety of herbal and other type of dietary supplements in addition to green tea or GTE [121]. Because of the ''natural'' character of these products, it is generally expected that no harm can be done. In this regard, a large number of combinations are possible, but there are few studies that have begun to investigate the potential benefits – or dangers – of this very complex field.

A recent study by Lambert et al. [122] may serve as an instructive example to illustrate that the combination of dietary supplements harbors the potential to generate adverse outcomes. The authors investigated the effects of a combination of EGCG and the flavonoid genistein (a phytoestrogen present in soy, which is also available in highly concentrated capsule formulation) in vitro and in tumor-prone adenomatous polyposis coli ($APC^{min/+}$) mice in vivo. They found that genistein caused increased concentrations of EGCG in the cytosol of cultured tumor cells, which resulted in greater inhibition of tumor cell growth. Similarly, the presence of genistein led to elevated levels of EGCG in the plasma of mice. However, contrary to their expectations, the group discovered that co-treatment of adenomatous polyposis coli mice enhanced intestinal tumorigenesis, i.e. the combination of these two herbal compounds dramatically increased the multiplicity of tumors in the intestine. Thus, despite genistein's ability to enhance EGCG bioavailability and in vitro growth-inhibitory activity, the combination displayed cancer-promoting effects in vivo [122]. Importantly, this adverse outcome was achieved at herbal dosages that are possible to attain with the respective dietary supplements in humans.

In yet another twist in green tea's proposed cancer preventive activity, several studies from You's laboratory [29, 123, 124] provided examples where EGCG displayed in vivo anticancer activity only when administered as Poly E, but not when given by itself without other green tea constituents. In these studies, three catechin preparations were compared: pure EGCG, Poly E, and Poly E without EGCG (Poly E-EGCG), which were administered with the diet or via aerosol delivery to carcinogen-treated mice. Lung tumorigenesis of these mice was investigated, and it was found that Poly E, but not EGCG or Poly E without EGCG, significantly decreased tumor multiplicity and tumor load. Thus, at least under the conditions of this experimental design, EGCG required the presence of other green tea catechins in order to exert its chemopreventive efficacy. The authors proposed that the presence of other catechins may slow the degradation of EGCG, thereby increasing its residence time in plasma and providing greater potency [28]. However, other mechanisms may be involved as well. For example, in vitro experiments have shown that low concentrations of EC are able to synergistically enhance the ability of EGCG to induce apoptosis of cultured tumor cells [125, 126]. Altogether, these studies suggest that complex GTE, such as Poly E, might be more suitable for cancer preventive applications than individual green tea components, such as highly concentrated EGCG-only capsules, because other catechins may possibly amplify the beneficial effects of EGCG.

6 Concluding remarks

A myriad of health claims are being made in favor of the consumption (and marketing) of concentrated green tea products. At the same time, suspected or documented

adverse effects, though seemingly rare, receive very little attention or may be ignored. However, in some authors' opinions, ''it is a matter of public health to refrain from providing people with confusing information about the unproven therapeutic potential of tea derivatives without consistent information on their toxicity'' [127], and ''there no longer can be a reasonable doubt that ingestion of concentrated extracts of Chinese green tea … poses a real and growing risk to liver health'' [47].

As detailed above, in 2007 a systematic safety review of green tea was performed by the USP, which focused primarily on reported cases of liver damage related to GTE consumption. In their conclusions [48], the DSI EC members noted that ''multiple aspects of available information point to the possibility of liver damage associated with concentrated GTEs, especially when taken under fasting conditions. Clearly, liver failure is a serious problem.'' However, they also emphasized ''the wide usage of green tea as a beverage and the low incidence of a causal relationship to hepatotoxicity'' [48]. Considering this information, the committee proposed to assign a Class 2 safety to GTE (exempting traditional green tea infusions), which would require that safety information is transmitted through a warning statement in the monograph labeling section. The intention of this proposal was to alert consumers and healthcare professionals of the need to be vigilant when using concentrated GTE, so as to minimize potential risks. However, after reviewing additional information and several stakeholders' comments, in June 2008, the DSI EC decided to defer approval of this cautionary labeling requirement [128].

There is a possibility that adverse events caused by GTE may be underreported, and thus more vigilance may be appropriate. As suggested by Lambert et al. [129], more in-depth studies on the potential detrimental effects of dietary phytochemicals are required in order to assess their potential toxicities, as well as to determine their potential usefulness as disease preventive and treatment agents. Towards this goal, ongoing human intervention studies should be large-scale and include protocols to assess potential adverse effects, including hepatotoxicity.

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