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FOCUS ON THE USE OF GREEN TEA IN CANCER SETTING: BETWEEN LIGHTS AND SHADOWS

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Abstract – *Green tea (GT) is a beverage derived from the unfermented leaves of* Camellia sinensis*, a plant native to Asia. Green tea extract is marketed as an antioxidant and dietary supplement to support cardiovascular, metabolic, cognitive, and cellular health. Data on the use of GT in oncology are controversial, mainly because of the risk of interference with anticancer drugs. To date, the use of GT is recommended as supportive treatment in most oncological diseases.*

KEYWORDS: *Green Tea, Cancer, Drugs, Interactions, Antioxidants.*

INTRODUCTION

Green tea (GT) is a beverage obtained from the *Camellia sinensis* plant. Fresh leaves of the plant are steamed to make tea. It can be taken orally as a beverage or in pills/tablets as a dietary supplement.

In the latter case, green tea extract is marketed for its antioxidant properties that support cardiovascular, metabolic, cognitive, and cellular health[1]. Active constituents include polyphenols, among which epigallocatechin-3-gallate (EGCG) is the most abundant, caffeine and theanine. Green tea polyphenols have various biological effects, such as the aforementioned antioxidant and cardiovascular prevention effects and anti-cancer effects[2-4].

Studies have shown that regular consumption of GT can reduce the risk of dementia, hypertension, cardiovascular disease, and all-cause mortality, except for cancer[5]. Currently, there are conflicting data on the ability of GT to reduce the risk of gastric and esophageal cancer. Other data suggest a preventive benefit of GT and its active ingredients against precancerous oral cavity lesions and for people at high risk for liver or colorectal cancer. An association between the consumption of GT and the risk of developing blood cancer has not yet been established[6-9].

There are limited data on the effect of oral intake of EGCG and the biological response in patients with chronic lymphocytic leukemia or the reduction of radiation-induced esophagitis in patients with lung cancer. However, EGCG intake does not appear to have an effect on reducing recurrence in advanced ovarian cancer. Preliminary data suggest that topical EGCG may help alleviate radiation-induced dermatitis in patients with breast cancer.

In general, it can be argued that studies on GT and cancer in humans have produced controversial results. In fact, the National Cancer Institute does not recommend the use of GT to reduce the risk of any type of cancer[10]. Although the Cochrane Review[11,12] concluded that there is insufficient data to make recommendations on the use of GT extract and cancer incidence or mortality, patients frequently consume it. The use of GT in cancer therapy is often considered a complementary and integrative approach.

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GREEN TEA AND PRECLINICAL STUDIES

Chemo-preventive properties are attributed to polyphenols, particularly EGCG, which is able to inhibit enzymes involved in cell replication and DNA synthesis[13]. *In vitro* data suggest that concentrations of 30 mcg/ml EGCG and epigallocatechin (EGC) are able to inhibit arachidonic acid metabolism by 30-75%, reducing the risk of colon cancer[14]. Other studies in human colon cancer cell lines suggest that EGCG selectively inhibits the enzyme topoisomerase I, which is involved in DNA replication[15]. EGCG also inhibited both DNA replication and vascular endothelial growth factor (VEGF) in leukemia cell lines by promoting their apoptosis[16,17]. A study in animal models suggests that caffeine in GT is able to inhibit UVB light-induced carcinogenesis[18].

GREEN TEA AND CLINICAL STUDIES

It has been shown that in patients with prostate cancer (PC), supplementation with a mixture of GT, pomegranate, broccoli, and curcumin had a protective effect after radical treatment[19]. In addition, GT consumption lowered PSA levels in patients prior to prostatectomy[20]. However, some studies have shown that combined high-dose but nontoxic supplementation of GT-derived catechins, selenium, and lycopene was associated with a high incidence of CP in patients considered to be high-risk, whereas long-term intake of an EGCG-containing product did not reduce the risk of PC[21,22]. Regular consumption of GT has been shown to increase breast cancer risk in some postmenopausal women[23]. Therefore, large and well-designed studies are needed to clarify the potential effect of green tea extract in oncology[12]. Table 1 summarizes the evidence reported in the literature on the effect of green tea in different settings in relation to tumor types.

GREEN TEA AND CANCER DRUG INTERACTIONS

The risk of interactions between natural products and drugs is an important issue, especially in oncology, representing a possible risk factor for both the development of toxicity and loss of drug efficacy[24]. EGCG, the major green tea polyphenol, undergoes extensive metabolism (Figure 1), resulting in poor oral bioavailability (less than 2% of EGCG reaches the systemic circulation after ingestion)[25].

Despite limited bioavailability, EGCG potentially interferes with anticancer drugs by affecting the activity of their metabolizing enzymes[26]. Catechins in GT affect the activity of cytochromes, enzymes involved in the metabolism of many drugs, and some membrane transporters. In particular, GT extract and EGCG were found to be strong competitive inhibitors of CYP2B6 and CYP2C8 in hepatic microsomes, suggesting that drugs metabolized by the latter are more sensitive to GT catechins intake. EGCG was also found to be a moderate noncompetitive inhibitor of CYP3A and CYP2C19 and a weak *in vitro* inhibitor of CYP2D6 in an uncompetitive manner (liver and intestinal microsomes)[27]. The low oral bioavailability of GT catechins makes this herbal product essentially safe. However, the drug-herbal product interaction must also be evaluated considering particular phenotypes, as cytochromes are encoded by highly polymorphic genes affect-

TABLE 1. Evidences of green tea activities in different cancers and settings.

Tumor site	*Pre-clinical studies*	*Clinical studies*	*Prevention*	*Treatment*	*Support Treatment*	*Recommendation*
Breast	✓✓✓	×	×	✓	✓✓	ST
Bladder	✓✓	×	×	×	✓	ST
Colon	-	-	-	-	-	-
Esophageal	✓✓	×	×	×	✓	ST
Gastric	×	✓✓	✓	✓✓✓	✓✓	ST
Haematological	-	-	-	-	-	-
Lung	-	-	-	-	-	-
Ovarian	✓	×	×	×	×	×
Prostate	×	✓	×	✓	✓	ST

Scoring: ✓✓✓ Probably efficacious (data from RCTs); ✓✓ Might be efficacious (data from RCTs with smaller samples; ✓ Could be effective (single-arm studies); × No sufficient data; - data not available; ST support treatment.

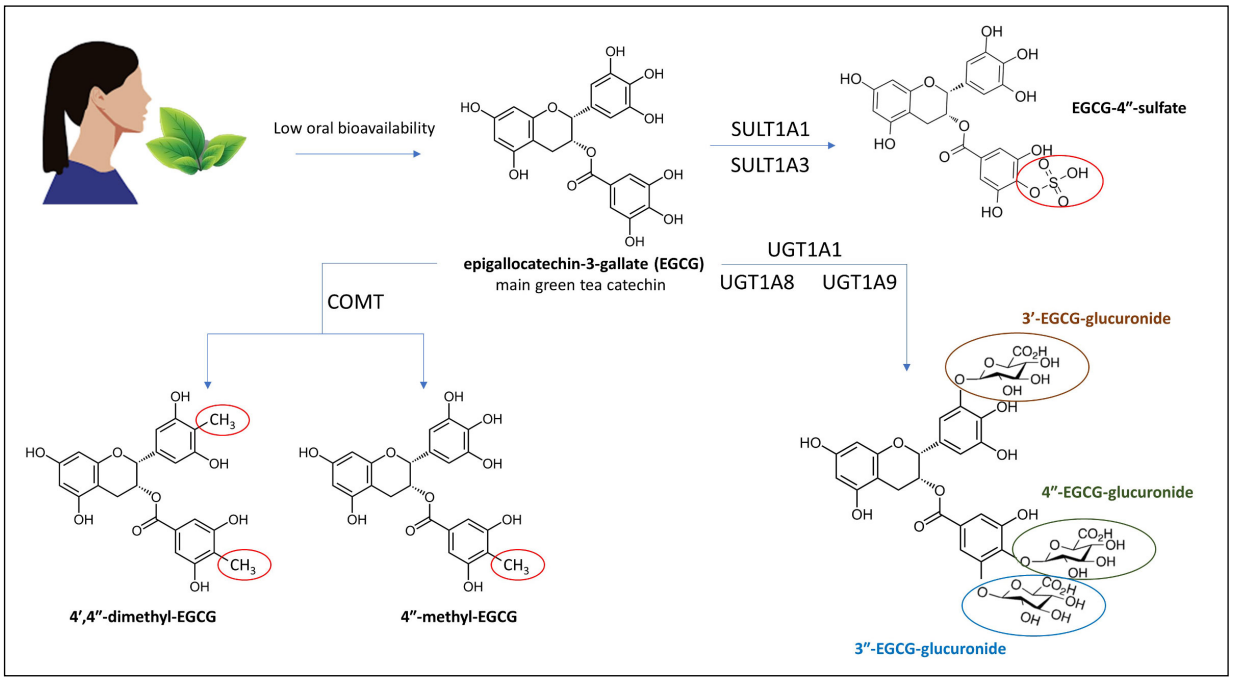

Fig. 1. Green tea catechins are absorbed through passive diffusion mainly in the small intestine. EGCG undergoes extensive phase II metabolism in enterocytes and hepatocytes following oral intake. The main phase II conjugation reactions involve sulfation, methylation and glucuronidation. Abbreviations: EGCG epigallocatechin-3-gallate; SULT sulfotransferase isoenzymes 1A1 and 1A3; UGT UDP-glucuronosyltransferase isoenzymes 1A1, 1A8 and 1A9; COMT catechol-o-methyltransferase.

ing their enzymatic activity[28]. Currently, some evidence has been reported in the literature on the interactions between GT extract and some anticancer drugs widely used in the treatment of solid and non-solid tumors (Table 2).

CONCLUSIONS

The use of GT in cancer patients requires well-designed clinical trials to demonstrate its role in this setting, especially with regard to the risk of interactions with anticancer therapies (ACTs). It is well known that dietary supplements based on GT are considered natural products in the collective imagination and, therefore, free of toxicity, and that cancer patients tend to take them without consulting their physician[33,34]. This practice sometimes carries the risk of unexpected toxicities and failure of ACTs[35].

Although GT usually refers to the totality of "natural or organic" products/methods that are considered less toxic overall, there are concerns that GT may have interactions with drugs, especially in patients participating in clinical trials with experimental agents and, therefore, still poorly known[36,37]. Green tea may be responsible for serious adverse events (AE), as shown in Table 2. In our opinion the use of GT in cancer setting should be used as a supportive treatment (e.g., to treat cancer-related fatigue) as already highlighted for vitamins C and D, mycotherapy extracts,

TABLE 2. Main interactions of GT extract with anticancer drugs.

Drug-GT interaction	*Metabolic pathway involved*	*Result*	*Reference*
Imatinib	CYP3A4 inhibition	↑ imatinib plasma level	[26]
Irinotecan/SN38	P-gp inhibition	↑ irinotecan/SN38 plasma level	[29]
Tamoxifen	P-gp and CYP3A4 inhibition	↑ tamoxifen and 4-hydroxytamoxifen oral bioavailability	[30]
Palbociclib	CYP3A4 inhibition	↓ oral bioavailability of PAL	[31]
Bortezimib	Direct EGCG-BZM interaction	↓ anticancer effect	[32]

Abbreviations: GT: green tea; P-gp: permeability glycoprotein; PAL: palbociclib; BZM: bortezimib; EGCG: epigallocatechin gallate. ↑: increase; ↓: decrease.

and acupuncture[38-43], within a complementary and integrative approach and previous evaluation of the risk of interactions with ACTs.

Moreover, thanks to Drug-Drug-Interactions checker programs and excellent educational materials from reputable sources, we have the opportunity to recommend the right integrative approach to cancer patients, especially those being treated with anticancer drugs and polypharmacy use[44,45]. In the near future, we would like to see a robust integrative oncology program as a cancer treatment in hospitals, available to physicians and patients.

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