

Review

Current View on Green Tea Catechins Formulations, Their Interactions with Selected Drugs, and Prospective Applications for Various Health Conditions

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Abstract: Green tea extract (GTE) is one of the most popular beverages globally, traditionally prepared from *Camelia sinensis* leaves. Therefore, it is beneficial to define the impact of GTE and its ingredients on the human organism. Epigallocatechin-3-O-gallate (EGCG) is the most abundant catechin in green tea leaves, belonging to the group of tannins and flavonoids, demonstrating pharmacological activity, but so far, it has not been applied as a drug. This is because EGCG does not present sufficient stability and quickly decomposes through epimerization or autooxidation mechanisms under the influence of light, temperature, changes in pH, or the presence of oxygen. Another limiting factor is EGCG's low bioavailability after oral administration. Nevertheless, the growing market of dietary supplements together with increasing growing consumption of green tea extracts should prompt us to pay more attention to the safety of both EGCG itself, as well as its influence on other simultaneously used drugs. Previously published data confirm the relationship between healthcare professionals' access to professional knowledge and their willingness to engage in patient education. For this reason, in this review article, we report the formulations of EGCG and GTE, discuss the data on the safety of EGCG and its possible interactions with drugs, as well as gather various recommendations from medical specialists. Particular attention should be paid to the consumption of green tea during pregnancy and breastfeeding, as well as in the elderly. Patients taking clozapine, digoxin, and warfarin should avoid consuming GTE extracts and dietary supplements containing EGCG. Professional consultation seems especially important for patients treated with statins, calcium channel blockers, or sildenafil.

Keywords: (-)-epigallocatechin-3-O-gallate (EGCG); green tea extract (GTE); drug delivery systems; pharmacokinetics; green tea catechins (GTC)

1. Introduction

Tea is one of the most consumed beverages in the world. The leaf extract is rich in both flavanols and their derivatives, as well as in several other natural components such as terpenes, oxygenated terpenes, sesquiterpenes, and organic acids [1]. Among diverse catechins present in the green tea extract, the most abundant is (-)-epigallocatechin 3-O-gallate (EGCG). It is a polyphenolic compound that belongs to tannins and flavonoids. Chemically, it is an ester of gallic acid and epigallocatechin [2,3]. EGCG exhibits a broad

spectrum of biological and pharmacological effects, including antioxidant, anti-inflammatory, antifibrotic, antibacterial, antiviral, pro-osteogenetic, and is protective against an excess of ultra-violet (UV) radiation. It was also found that EGCG supports the treatment of obesity, as well as metabolic, and neurodegenerative diseases [2,4]. In the preclinical studies, it was demonstrated that polyphenols obtained from green tea and EGCG could inhibit cell proliferation and induce cell death in certain types of cancers, including epithelial colon adenocarcinoma, acute lymphocytic leukemia [5], lung cancer [6,7], breast cancer [8,9], and bladder cancer [10]. The antitumor activity of EGCG was found to be multimodal and consists of anti-proliferative, pro-apoptotic effects, inhibition of angiogenesis, and limitation of the invasiveness of tumor cells. Several studies indicate that the antitumor activity of EGCG is responsible for the activation or inhibition of specific signaling pathways, usually by direct binding of EGCG to a given protein [8,10].

In view of such a broad spectrum of potential therapeutic possibilities, a growing consumption of both green tea extracts and dietary supplements containing EGCG has been noted. According to forecasts, their global production will annually grow by about 7.5%. In parallel, the value of the global green tea market will increase from nearly USD 13 billion in 2019 to over USD 23 billion in 2027 [11]. The growing demand for products rich in antioxidants leads to the increased interest in functional beverages among consumers worldwide.

Poland is one of the three largest tea consumers among European countries. Green tea segment accounts for only about 8% in Poland, even though Poles consume a lot of tea. It is worth noting that 15 thousand tons of tea were consumed in Poland in 2015. The dynamically developing market of dietary supplements deserves attention. According to the PMR report, the share of dietary supplements on the Over-The-Counter (OTC) market in Poland has exceeded for many years the level of 40% [12].

It is also worth noting that the analysis carried out by Karwowska and Smiechowska [13] showed that not all dietary supplements available on the market and containing tea were correctly labeled, and the information on the labels was not easily accessible and illegible for the consumer.

Considering the above, and at the same time taking into account the intensive media campaigns promoting the use of dietary supplements, the role of community pharmacists and other healthcare professionals in rationalizing dietary supplement consumption and health education of patients is gaining importance. However, recently published data indicate that despite the willingness of pharmacists in public pharmacies to the provision of health education, one of the factors limiting their intention to undertake these activities is the lack of well-established knowledge in this area and not clearly defined expectations regarding the scope of provided services [14].

Thus, this review aims to organize and discuss the essential data concerning tea in the medical and pharmaceutical context. Numerous pro-health effects of EGCG and the widespread global consumption of green tea extract prompted us to study the impact of tea products on healthy and sick people, as well as the effects appearing during the combined consumption of EGCG and medications.

2. Background of Tea Preparation's Technological Aspects

The domestication of tea plants dates back at least to 207 BCE when the Han dynasty ruled in China [15]. The first known technique of tea processing was to immediately steam the freshly harvested tea leaves and dry them for preservation. In recent times over 20,000 different teas in the world have been recognized [16]. Two of the most important species of tea plant are *Camellia sinensis* var. *sinensis* (China type tea) and *Camellia sinensis* var. *assamica* (Masters) [17]. The most important types of teas are white, green, yellow, oolong, black (red), and pu'erh (fermented). The criterion for dividing teas into the above groups is the method of processing and thus the degree of oxidation of the tea leaves. In the case of white and green teas, the oxidation process is stopped quickly after harvesting, resulting in an oxidation level lower than 10%. Yellow and oolong teas are mid-oxidized

with the degree of oxidation in the range of 10–85%. Black tea is almost completely oxidized (>85%). Chemical composition and hence the flavor of tea changes depending on the oxidation level and processing. Less oxidized tea leaves contain more catechins (e.g., epigallocatechin gallate-EGCG), whereas more oxidized ones contain more enzymatic polymerization products, namely theaflavins and thearubigins [16,18]. As a result, black tea has a richer, fuller, and more robust taste. The final taste of a cup of tea and its chemical composition, depend on many factors such as variety, terroir, production, processing, and brewing. Therefore, plant extracts used for research must be accurately characterized in terms of chemical content.

3. Formulations of Green Tea Extracts and EGCG in Food Industry

Three types of tea products are manufactured from *Camellia sinensis* in the food industry: black tea (78%), green tea (20%), and oolong (2%) [19]. Green tea can be obtained in the traditional manufacturing process, where the leaves are harvested, withered, rolled, and then quickly treated with high temperature (steamed or heated) to hamper enzymatic degradation of polyphenols and other bioactive components [20]. The infusion of green tea is known as one of the most popular beverages in the world due to its pleasant aroma and taste. In addition, its regular drinking can provide many health benefits, which are mostly due to a high concentration of catechins, primarily EGCG, known for its antioxidant properties [21].

Green tea extract containing EGCG can also be found in many food products due to the growing interest in its use as a dietary supplement and food preservative. The purchase of diverse groceries containing a green tea extract is becoming more popular among consumers worldwide. This can especially be seen in ready-to-eat meals (also containing meat), cereals, bakery products, salad dressings, mayonnaise, margarine, oils (vegetable, marine, frying), and various beverages (soft drinks, energy drinks, juices). In many studies performed on food products containing green tea extract or isolated EGCG, poor stability during storage and oral bioavailability of catechins were highlighted [22]. The main limitation of the widespread use of EGCG is its low stability. EGCG quickly decomposes under the influence of light, temperature, changes in pH, or in the presence of oxygen. The main reactions of EGCG breakdown are epimerization and autooxidation [2,3]. It was also found that EGCG is unstable when it is sterilized at high temperatures. For this reason, uncommon novel methods should be employed instead of high-temperature sterilization. This would include ionizing radiation or the filtration method followed by freeze-drying [22].

Green tea extracts and isolated EGCG have been combined with food additives such as vitamin C, xylitol, sucrose, citric acid, butylated hydroxytoluene (dibutylhydroxytoluene, BHT), and EDTA. They were also dispersed in milk, as well as drinks from soy and rice, and citrus juices, such as orange, grapefruit, lemon, and lime. In all these studies, the stability and bioavailability of obtained formulations were assessed. In detail, formulations of green tea extract with ascorbic acid and xylitol or sucrose increased intestinal transport of EGCG [23,24]. Additionally, the digestive recovery of green tea catechins was either increased or decreased by various common food additives, one such being citrus juices which causes a significant increase [25]. Incorporating powdered green tea extract into food components can also affect the stability of EGCG, making it critical to consider any additional component in a final product due to this potential interaction and influence [26]. Following this issue, Lavelli et al. obtained a dry apple food product enriched with green tea extract (green tea extract-fortified product), which presented good stability over one month [27].

4. Formulations of Green Tea Extracts and EGCG in Pharmaceutical and Cosmetic Applications

Due to antioxidant and antiaging activities, green tea extracts, including catechins such as EGCG, have been used for the preparation of many advanced drug and cosmetic

formulations for topical and other applications (Figure 1). Results of many studies on the topical application of catechins revealed significant advantages of this method of administration, which was found superior to oral or intravenous ones [28]. Model creams (oil-in-water emulsions), ointments, hydrogels, and some microsphere suspensions, e.g., niosomes and ethosomes containing EGCG, were assessed for their photostability, skin penetration and retention (bioavailability), stratum corneum, and transepidermal water content and loss, skin elasticity. However, hydrogel formulations of EGCG were studied not only for topical but also for oral delivery systems. For example, Garcia et al. prepared ionic hydrogel consisting of gelatin- γ -polyglutamic acid [29]. The obtained biopolymer showed significant protection of EGCG at different pH values present in the gastrointestinal tract environment.

Several studies reported on the increase of the transdermal and intradermal concentration of EGCG. For example, the permeation abilities study performed by dal Belo et al. using various cosmetic formulations revealed that the highest amounts of delivered catechin were found in the stratum corneum [30]. In contrast, significant loss of EGCG concentration was noted in deeper tissues. Following that observation, Dvorakova et al. examined 10% of EGCG in hydrophilic ointment USP and noted high concentrations of EGCG in the skin accompanied by low systemic influence [31]. However, in studies performed by Scalia et al., 1% of EGCG oil-in-water emulsion revealed permeation potential into the deep region of the human stratum corneum when compared to gel formulation [32]. This finding emphasizes the importance of topical vehicles being used in formulation studies. It could also be concluded that when systemic activity of EGCG is unattainable, its topical formulations could reveal an excellent potential for moisturizing skin [33].

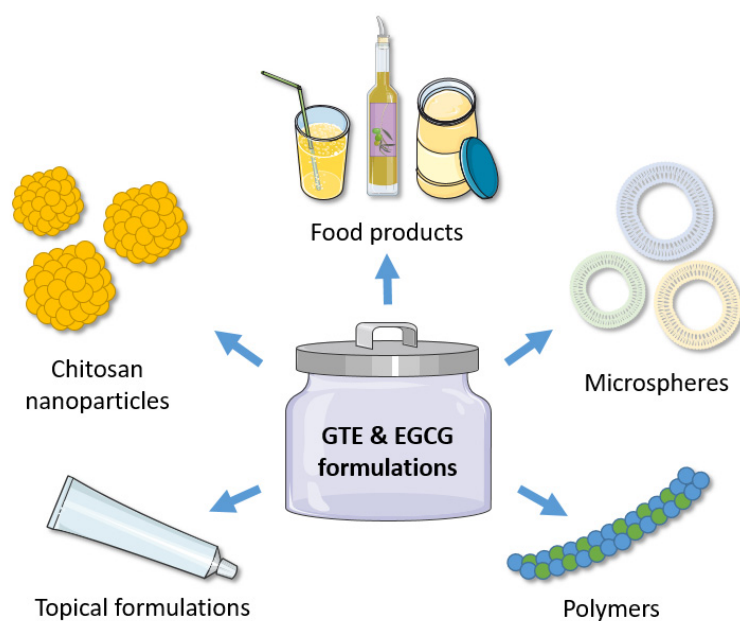


Figure 1. Various formulations of green tea extracts (GTE) and (–)-epigallocatechin-3-O-gallate (EGCG) in pharmaceutical and cosmetic applications.

Many efforts have been made to increase the systemic bioavailability of EGCG through topical applications. Lambert et al. noticed that transdermal delivery of EGCG allows the achievement of higher plasma levels of this compound than drinking tea [34]. It was found that the bioavailability of EGCG can be increased through the application of some nanoparticles. Specifically, microspheres containing EGCG were studied in terms of their stability and skin permeation properties, among which were niosomes, wherein

catechins were incorporated with surfactant and cholesterol to form niosomal gels presenting prolonged stability [35]. Other interesting particles used in EGCG formulations were ethosomes and transethosomes. These modern lipid nanovesicles prepared from phospholipids, and containing high concentrations of alcohol, water, and penetration enhancers, revealed better drug penetration properties than classic liposomes and were more elastic. Ethosomal and transethosomal formulations of EGCG were found to improve its stability and increased its intake through the skin [36,37].

(-)-Epigallocatechin-3-gallate is known for its photo protecting ability due to strong UVB absorption, which subsequently leads to its photodegradation. In this way, all catechins reveal potential antiphotocarcinogenic activity. Thus, they can hamper DNA damage and prevent neoplastic skin changes [38]. Therefore, it is necessary to improve EGCG stability upon light irradiation to maintain its antioxidant features when applied to the skin. Many studies have focused on the photostability of EGCG in topical formulations. Due to the significant photodegradation of catechins in creams, ointments, and hydrogels, diverse preservatives have been considered in these compositions to protect the active EGCG ingredient from the UV irradiation. It concerns especially such EGCG protectors as benzophenone-4, glutathione, vitamin C and E, butylated hydroxytoluene, and α -lipoic acid, which were used as experimental co-oxidant agents preventing its photodegradation [39–41]. An increase in the stability of green tea extracts in topical formulations was achieved by the preparation of 5% tannase-converted green tea extract, which revealed good physicochemical properties and activity even after 16 weeks of storage [42].

Despite the above-mentioned topical formulations, (-)-epigallocatechin-3-gallate for oral administration purposes was also encapsulated in diverse natural and synthetic particles, such as proteins, lipids, and sugars to obtain its improved stability, precise delivery, controlled release, increased mucoadhesion, and intestinal permeation. Many techniques aiming to obtain such formulations have been developed for EGCG. For example, this catechin was encapsulated in proteins by emulsification, ionic gelation, freeze-drying, electrospraying, self-assembly, layer-by-layer assembly, vacuum evaporation, precipitation, and covalent grafting. Carbohydrate forms were obtained by homogenization and spray drying, gas saturated solution drying, self-assembly, and ionic gelation. Lipids, such as solid lipid nanoparticles, were obtained by homogenization, organic solvent evaporation, and dynamic high-pressure microfluidization [2].

EGCG was also successfully incorporated into chitosan nanoparticles (sometimes zein-coated) to prepare both topical and oral drug delivery systems. All studies confirmed the advantages of such an approach, which was accompanied by additional benefits such as enhanced antioxidant and antibacterial activities, increased bioavailability, and, consequently, high plasma levels of catechin [43–45]. In addition, coating the nanoparticles with zein has also provided the controlled release feature and allowed for prolonged protective actions of some ingredients, such as fatty acids, from oxidative stress [45].

Various studies have been performed on (-)-epigallocatechin-3-gallate incorporated in liposomes and liposome-like particles, such as phytosomes and niosomes. Anionic liposomal formulation of EGCG and $MgCl_2$, prepared by Laudadio et al., was quickly and efficiently synthesized and considered a good delivery system for catechin [46]. Liposomes containing EGCG were also combined with other active pharmaceutical ingredients (API) such as paclitaxel (PTX)—a well-known antitumor agent, to prepare a co-delivery system. Biological studies showed that such a combination reveals better bioavailability than in liposomes loaded with PTX separately [47]. In another study, by Rashidinejad et al., some natural products such as soy-lecithin were used to prepare EGCG-containing liposomes which were incorporated in low-fat hard cheese therefore belonging to the group of food products with a high concentration of antioxidants [48]. Despite classic liposomes, advanced microspheres such as niosomes (liposomes with some other compounds present in lipid bilayers such as cholesterol) were prepared to

encapsulate EGCG. These formulations were used in biological study on human cell lines, such as Caco-2 and HepG2, and demonstrated potent antioxidant and antiproliferative ability [49,50]. In addition, very interesting nanovesicles–phytosomes, consisting of green tea leaf extract and phospholipids containing 30% phosphatidylcholine, were prepared by Anwar et al. and assessed in terms of protective features towards EGCG [51].

EGCG or green tea extract along with zein were also encapsulated by coating with sodium caseinate, as a colloidal stabilizer or with the use of gelatin by electrospraying [52,53]. Both formulations improved EGCG delivery. However, further study on the formulation with gelatin showed that a real food processing condition during biscuit preparations could be harmful to catechin molecules. Thus, this issue needs to be more deeply analyzed in future. Gelatin was also used to obtain a stable catechin formulation using the layer-by-layer (LbL) assembly method performed by Shutava et al. [54]. Some other natural EGCG formulations with starch, soybean lecithin, and β -glucan were prepared by a unique method called ‘particles from gas saturated solutions drying’ (PGSS-drying). This technique allows the obtaining of stable products with preserved bioactive properties for further development [55]. Lecithin formulations of green tea extract named “Greenselect Phytosome” (GSP) were developed by Lazzeroni et al. and allowed the increase of the bioavailability of EGCG in breast cancer treatment [56]. Improved absorption of EGCG was also achieved by Hu et al. [57,58], who created self-double-emulsifying drug delivery systems (SDEDDS) for oral and transdermal administration of catechin. These formulations when suspended in water can easily form emulsions, thus demonstrating an increased cellular uptake of EGCG.

(–)-Epigallocatechin-3-gallate has also been used as an adjuvant in drug formulations. EGCG when combined with tannic acid, was applied as a solubilizing agent for the preparation of better soluble drug formulations of previously mentioned APIs, such as paclitaxel, docetaxel, amphotericin B, curcumin, and rapamycin, significantly improving the solubility of these drugs in aqueous solutions [59]. Lamarié et al. studied EGCG encapsulated in transferrin-bearing vesicles for intravenous administration [60], which revealed significant tumor suppression.

A separate group of catechin formulations for pharmaceutical purposes are polymers. EGCG-loaded microspheres with Eudragit® S100, non-ionic block copolymer Pluronic F127 or PLGA were prepared and investigated towards intestinal diseases, antihyperlipidemic and anti-obesity activity [61–63]. The main formulations of EGCG were summarized in Figure 2.

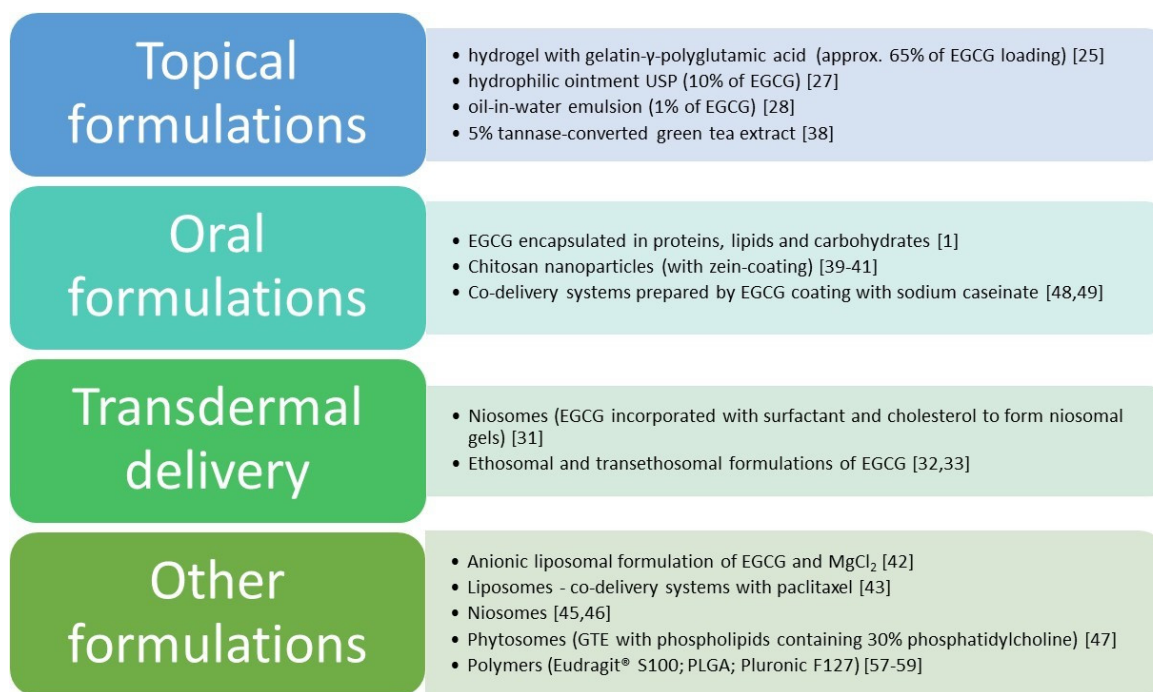
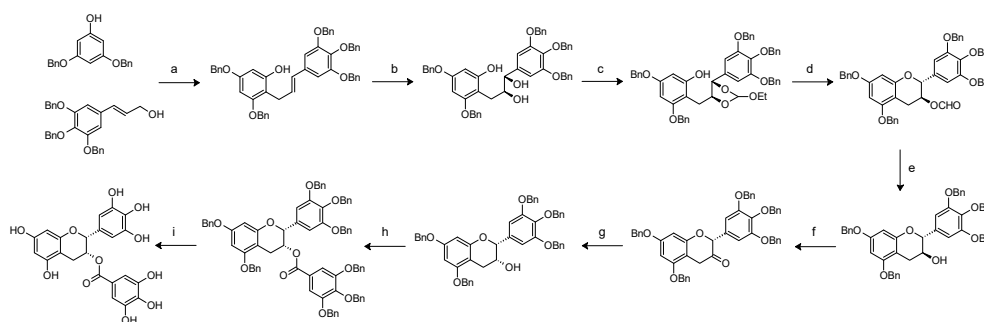


Figure 2. The main formulations of EGCG mentioned in this review.

5. De Novo Synthesis of EGCG and Methods of Isolation

Total and enantioselective synthesis of epigallocatechin 3-O-gallate was carried out in 2000 by Li and Chan with an overall 19% yield [64]. The key step in this synthesis route was a stereospecific cyclization of the Sharpless asymmetric dihydroxylation intermediate. Substrates were simple aromatic compounds with hydroxyl groups protected with benzyl moieties (Scheme 1). The synthetic pathway consists of 8–9 steps and at some points involves low-temperature conditions (−78 °C). To sum up, the synthetic procedure is complex and lengthy. Therefore, many methods of EGCG extraction from raw plant materials have been applied and become more popular than chemical synthesis approaches.

Isolation of EGCG is also not an easy process due to the presence of many structurally related compounds in the extract [65]. Methods used to isolate biomolecules from tea extract, which have been presented in the literature concern the following approaches: conventional solvent extraction technique, ultrasound-assisted extraction (UAE), microwave-assisted extraction (MAE), high-pressure processing (HPP), supercritical fluid extraction (SFE), and subcritical water extraction (SWE) [66]. When performing isolation of catechins from tea, one should remember to plan the decaffeination step during the process. Separation of tea polyphenols is performed by membrane separation (ultrafiltration), supercritical fluid extraction (SFE) with carbon dioxide, precipitation, as well as adsorption on polymers (resins) [18]. These methods differ in many aspects. Some of them are better in terms of cost-effectiveness, some others are recognized as green chemistry. The analysis provided by Monsanto shows that the most promising method for isolation of polyphenols from green tea is precipitation, whereas for black tea, adsorption methods are recommended [18].



Scheme 1. The representative synthetic route of EGCG [64]. Reagents and conditions: (a) $\text{H}_2\text{SO}_4(\text{SiO}_2)/\text{CH}_2\text{Cl}_2/\text{CS}_2$, rt; (b) $\text{OsO}_4(\text{cat})/\text{NMO}/\text{acetone}/\text{H}_2\text{O}$; (c) $\text{CH}(\text{OEt})_3/\text{PPTS}/\text{CH}_2\text{Cl}_2$, rt; (d) $\text{CH}(\text{OEt})_3/\text{PPTS}/\text{CH}_2\text{Cl}_2$, 60 °C; (e) $\text{K}_2\text{CO}_3/\text{MeOH}$, rt; (f) Dess–Martin periodinane/ CH_2Cl_2 , rt; (g) L-Selectride/THF, (−78) °C; (h) 3,4,5-tris(benzyloxy)benzoyl chloride/DMAP/ CH_2Cl_2 , rt; (i) $\text{H}_2/\text{Pd}(\text{OH})_2/\text{MeOH}/\text{THF}$, rt. Bn–benzyl group, PPTS–pyridinium p-toluenesulfonate, DMAP–dimethylaminopyridine, NMO–N-methylmorpholine-N-oxide, THF–tetrahydrofuran.

6. Interactions of Green Tea Extracts and EGCG with Selected Active Pharmaceutical Ingredients

Interactions of green tea extracts and EGCG with various active pharmaceutical ingredients were noted in various areas, namely at biopharmaceutical level, as well as pharmacokinetics and pharmacodynamics.

Taking into account biopharmaceutical level, very interesting interactions of green tea extracts, EGCG and components of their formulations were observed with selected APIs. An interesting preliminary study on this subject was performed by Oda et al. with the use of beverages containing green tea extract and cyclodextrins [67]. They observed interactions of various P-glycoprotein substrates such as digoxin with cyclodextrins that can significantly increase the solubility of this API leading to its overdose and to subsequent toxic effects. Therefore, the authors concluded that cyclodextrin-containing foods and beverages, which also contain green tea extracts (GTSs) should be avoided when a patient uses some other low-soluble drugs.

Many other interesting interactions of green tea extracts and EGCG and components of their formulations were observed with selected APIs on the pharmacokinetics and pharmacodynamics levels. Many published studies describe the synergistic and additive effect of EGCG and anticancer agents as well as their influence on the inhibition of neoplastic processes both in vitro and in vivo. A significant analysis on the subject was presented by Lecumberri et al. [68]. They offered various possibilities of EGCG leading to an increase in the effectiveness and safety of anticancer treatment. First, it was found that when EGCG is used as a chemosensitizer, doses of many anticancer drugs, including 5-fluorouracil, cisplatin, or tamoxifen, can be decreased, thus simultaneously reducing the risk of their side effects. Secondly, both EGCG and its metabolites are thought to modulate tumor cells' response to ionizing radiation. Finally, the EGCG antioxidant and anti-inflammatory activity could reduce the risk of various side effects caused by chemo- and radiotherapy, including intestinal mucosa damage, changes in hematological parameters or nephro- and cardiotoxicity. Noteworthy is also the publication of recent studies confirming the legitimacy of continuous efforts for the development of treatments combining EGCG and doxorubicin [69], sunitinib [70], or 5-fluorouracil [71]. Other research demonstrated the ability of polyphenols and clofarabine combinations in the promotion of cancer cell death. Not only that but the reactivation of DNA methylation-silenced tumor suppressor genes in breast cancer cells with different invasive potential was also observed [72]. What is essential is that EGCG inhibited telomerase expression significantly and enhanced the effect of cisplatin and tamoxifen in both 1321N1 and U87-MG cells. In addition, EGCG may sensitize glioma cells to cisplatin and tamoxifen [73].

Meanwhile, data from several animal and clinical studies brought new light to the explanation of interactions between EGCG and commonly used drugs (Table 2). Putative pharmacokinetic mechanisms concern the inhibiting effect of EGCG on the organic anion transporting polypeptides (OATPs) [74,75], CYP3A4-mediated metabolism and P-glycoprotein mediated efflux [23,76–80]. Despite presented reports describing numerous EGCG interactions that could lead to increased bioavailability of some APIs e.g., statins or calcium channel blockers, additional studies have indicated that the concomitant use of EGCG does not necessarily cause therapeutic benefits for the patient. For example, Kim et al. [81] studied the effect of concomitant administration of green tea extracts (GTE) and digoxin. Although the mechanism of observed effects was not identified, the authors concluded that GTE might significantly reduce the systemic exposure of digoxin. Taking into account the narrow therapeutic index of digoxin, possible fluctuations in its concentration in blood should be avoided. Noteworthy, Alemdaroglu et al. [82] found that EGCG can also reduce the bioavailability of orally administered folic acid, although AUC and C_{max} differences did not reach statistical significance. In another study, the absorption of epi-isomers of EGCG in plasma was found to be more favorable than their non-epi-isomer counterparts. EGCG had the highest level of exposure (AUC) and the highest C_{max} in the fetus, implying it may have potential for in utero antioxidant protection [83]. In a case study of a 44-year-old man who was receiving warfarin because of a mechanical valve replacement, regularly drinking between a half and one gallon (1.9–3.9 L) of green tea per day, caused a significant decrease in the international normalized ratio (INR) values. Changes in other factors, such as diet, medications, or diseases, which could potentially affect INR values were excluded. As only green tea drinking was stopped, the INR values mostly returned to the therapeutic level [84]. Plasma ECG and EGCG concentrations are reliable biomarkers for green tea consumption at the population level [85]. EGCG alone or combined with rosiglitazone was found to increase the phosphorylation of AktS473, leading to the increase of glucose uptake into C2C12 cells. The authors concluded that EGCG alone or in combination with rosiglitazone could exhibit some therapeutic effects for the prevention or treatment of type 2 diabetes due to its substantial effect on the increase of phosphorylation of AktS473 and the subsequent glucose uptake into the cells [86].

Table 1. Processing conditions of main types of teas.

Fresh tea leaves			Fixation (Panning or steaming)	Shaping (rolling)	Drying	Green tea
	Wilting	Bruising and partial oxidation	Fixation (Panning or baking)	Shaping (rolling)	Drying	Oolong tea
	Wilting	Bruising and full oxidation		Shaping (rolling)	Drying	Black tea

Various interesting observations considering pharmacodynamics interactions of EGCG with APIs were presented in the literature, but researchers' attention has also been focused on evaluating the effect of GTE on enzymes and transporters activities. In vitro studies have confirmed such interaction for, among others, atorvastatin [87], raloxifene [88], cysteamine [89], and azoles [90]. A natural progression of these studies was to analyze those interactions in the in vivo model. This seems especially important in the light of data provided by Choi & Burm [77], who identified that the type of changes observed could depend on the route of administration. Noteworthy, as presented in Table 2, there are a few cases (nadolol, rosuvastatin) in which results of studies conducted on rats differ from those obtained in clinical studies.

Table 2. Changes in pharmacokinetic parameters of selected drugs after their co-administration with epigallocatechin-3-gallate [EGCG] or green tea extract [GTE].

Therapeutic Group		
Drug Name Route of Administration	Animal Studies	Clinical Studies
statins		
fluvastatin <i>iv</i>		[GTE] no significant change in plasma concentrations [91]
rosuvastatin <i>po</i>	[GTE] ↑AUC, [EGCG] ↑AUC [92]	[EGCG] ↓AUC, ↓C _{max} , ↑CL [74]
simvastatin <i>igas</i>	[EGCG] ↑AUC, ↑t _{1/2} , ↓CL [93]	
simvastatin <i>po</i>	[GTE] ↑AUC, ↓t _{1/2} [94]	[GTE] ↑AUC, ↑C _{max} [95] [GTE] ↑AUC, ↑C _{max} [80]
calcium channel blockers		
amlodipine <i>po</i>	[EGCG] ↑AUC, ↑C _{max} , ↑t _{1/2} , ↓CL, ↓T _{max} [76]	
diltiazem <i>po</i>	[EGCG] ↑AUC, ↑C _{max} , ↓CL [78]	
nicardipine <i>iv</i>	[EGCG] no significant change in plasma concentrations [77]	
nicardipine <i>po</i>	[EGCG] ↑AUC, ↑C _{max} [77]	
verapamil <i>po</i>	[EGCG] ↑AUC, ↑C _{max} [23]	
β-blockers		
atenolol <i>po</i>	[EGCG] no significant change in serum level and tissues distribution [96]	
nadolol <i>igas</i>	[GTE] ↑AUC, [EGCG] ↑AUC [97]	
nadolol <i>po</i>		[GTE] ↓AUC, ↓C _{max} [98] [GTE] ↓AUC, ↓C _{max} [99] [GTE] ↓AUC, ↓C _{max} [75]
psycholeptics		
alprazolam <i>po</i>		[GTE] no significant change in alprazolam pharmacokinetics [100]
bupirone <i>po</i>		[GTE] ↑AUC [101]
clozapine <i>po</i>	[GTE] ↓AUC, ↓C _{max} [102]	
midazolam <i>iv</i>	[GTE] ↓t _{1/2} , ↑ke [103]	
midazolam <i>po</i>	[GTE] ↑AUC, ↑C _{max} , ↓CL [103]	
quetiapine <i>po</i>	[GTE] ↓AUC, ↓C _{max} [104]	
other		
caffeine <i>po</i>		[GTE] no significant change in caffeine plasma concentration [101]

cyclosporine A <i>iv & po</i>	[EGCG] ↑C _{max} , ↑AUC (smaller dose 3~30 mg·kg ⁻¹) [EGCG] ↓C _{max} , ↓AUC, ↑CL (higher dose 100 mg·kg ⁻¹) [105]	
dextromethorphan <i>po</i>		[GTE] no significant change in urine dextromethorphan levels [101] [GTE] no significant change in dextromethorphan metabolic ratio [100]
digoxin <i>po</i>		[GTE] ↓AUC, ↓C _{max} [81]
lisinopril <i>po</i>		[GTE] ↓AUC, ↓C _{max} , no significant change in t _{max} or CL, the amount of lisinopril excreted into urine over 24 h in the GTE phase was significantly reduced [106]
losartan <i>po</i>		[GTE] no significant change in urine losartan levels [101]
metformin <i>po</i>	[EGCG] ↑serum level, higher tissues distribution [96]	
oxcarbazepine <i>ip</i>	[EGCG] ↓AUC, ↓C _{max} [107]	
ticagrelor <i>iv</i>	[GTE] no significant differences in the pharmacokinetic parameters [108]	
ticagrelor <i>po</i>	[GTE] ↓AUC, ↓C _{max} , ↑CL, no difference in t _{1/2} [108]	
sildenafil <i>po</i>		[GTE] ↑AUC, ↑C _{max} , ↑t _{1/2} , ↓k _e [79]
tacrolimus <i>iv</i>	[EGCG] ↓C _{max} , ↓AUC, ↑CL [105]	
tacrolimus <i>po</i>	[EGCG] ↓C _{max} , (regardless of the dose) ↓AUC, ↑CL (higher dose 100 mg·kg ⁻¹) [105]	
tamoxifen <i>po</i>		[GTE] no significant differences in the pharmacokinetic parameters [109]

↓—decrease; ↑—increase; AUC—area under the curve; t_{1/2}—terminal half-life, C_{max}—maximum plasma concentration; CL—clearance; k_e—elimination rate constant; *po*—oral administration; *igas*—intra gastric administration; *iv*—intravenous administration; *ip*—intrapertitoneal administration.

Some studies also indicate that the intensity of observed changes may be related to the dose administered [77,98]. The exact time between taking the drug and drinking green tea that could be considered safe is also unknown. In some studies, the wash-out period was established at 3-days [74], while in others at 7-days [100,103,110]. Changes in pharmacokinetic parameters of intravenously administered midazolam were observed even after a week [103]. However, the above-listed potential interactions may occur between EGCG and drugs, which should be taken on a daily basis. Kim et al. [74] suggested that both regular and occasional intake of GTE may affect other drug pharmacokinetics. In addition, Misaka et al. [99] stated that observed changes might persist even 1 h after drinking a cup of green tea.

These findings cannot be extrapolated to all patients for the following reasons. First, clinical trials conducted so far are usually carried out in small groups of healthy volunteers. Secondly, the high inter-individual variability of CYP450 and diverse consumption of green tea depends on the country [80] and seems to form an additional uncontrolled factor. What is interesting, and was indicated by Abe et al. [98], is that interethnic differences cannot be excluded either. Supporting the aforementioned

limitations, the most prominent finding to emerge from this study is that due to insufficient data, the complete safety of concomitant use of drugs and green tea cannot be confirmed. Unfortunately, some of the substances, whose bioavailability could be affected by EGCG, are available as OTC products or have a narrow therapeutic index.

7. Human Safety Data with an Indication of the Role of Health Care Providers

Many scientific studies proved that GTE have the potential to be used for different diseases [111] (Figure 3). These concern antimicrobial and neuroprotective activities, anti-inflammatory, photoprotective action, and possibilities for hyperlipidemia, hyperuricemia, diabetes, overweight, heart, and cerebrovascular diseases, genital warts treatment, and anticancer potential.

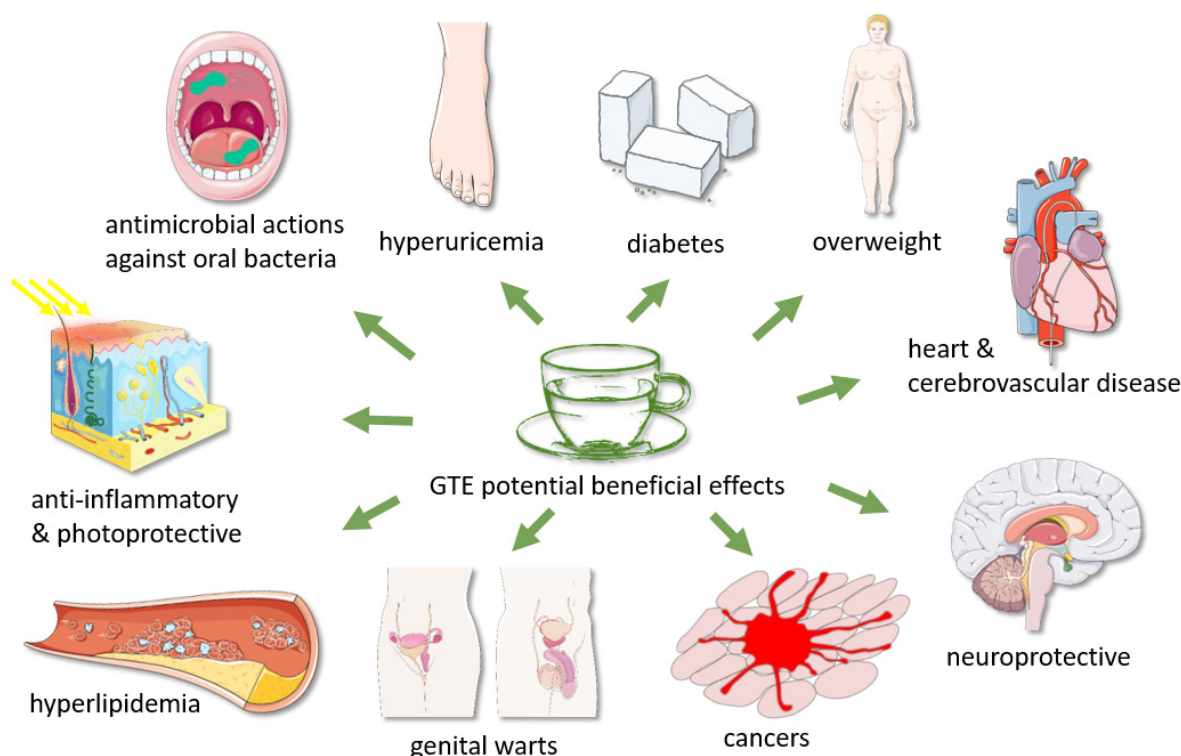


Figure 3. Beneficial effects of green tea extracts (GTE).

Lately Cheng et al. reviewed GTE applications and indicated that patients with various types of cancers could benefit from its usage [112]. Furthermore, it was noted that overweight women taking GTE, capsaicin, and ginger co-supplements, could observe beneficial effects connected with weight, body mass index, markers of insulin metabolism and plasma glutathione levels [113]. Green tea supplements have many indications, but there is not enough scientific evidence to support these uses. Taken orally, it may have a positive effect on hyperlipidemia [114]. GTE also reveals neuroprotective properties and can be used against depression [111]. For diabetes, many studies confirmed a positive influence on glycosylated hemoglobin (HbA1c). However, several articles reported lack of GTE effect on insulin sensitivity, fasting blood glucose, and glucose tolerance [115,116]. Interestingly, it was found that drinking 3–4 cups of GTE per day could decrease total cancer and respiratory disease mortality in women. More than 5 cups a day may lower the risk of all-cause mortality, especially for heart and cerebrovascular disease [117]. Taking 3 or more cups daily (720 mL) could reduce the incidence of stroke [118]. Capsules containing GTE can reveal hypouricemic effects [119]. Furthermore, consuming GTE at least twice each day could be associated with the reduced odds of chronic obstructive lung

disease in middle-aged and older adults [120]. GTE, when topically applied, reveals an anti-inflammatory effect on skin and reduces its redness [121]. It can also be used as a topical photoprotective agent [122]. Moreover, a foot bath with green tea polyphenols can improve the treatment of interdigital tinea pedis, such as interdigital erythema, desquamation, maceration [123]. Green tea mouthwash may reduce pain, exhibits antimicrobial actions against oral bacteria, and inhibits amylase activity in human saliva. Green tea can also be used in an ointment for genital warts [124–126].

In general, there is no evident confirmation of EGCG effectiveness in treating medical conditions according to FDA opinion. Studies on obesity/weight loss and diabetes have shown minimal treatment effects and no overall therapeutic benefit. What is essential, oral bioavailability of GTE is minimal and may be a factor in limiting clinical results [127]. Certainly, GTE should not be used instead of the medication prescribed by a physician and without pharmacist consultation. Unfortunately, there are no recommendations for many herbal compounds which could be contaminated with toxic metals or other drugs [128]. The increasing consumption and popularity among patients led to the development of recommendations for GTE use, primarily due to potential side effects (Table 3). It is worth mentioning that there are many different GTE products in community pharmacy e.g., ready-to-drink green tea beverages, food supplement products in capsule and tablet forms.

Table 3. What health care providers would suggest remembering about supplements?

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- ✓ Health care providers, including pharmacists in community pharmacies, need to draw the attention of patients to the fact that “natural” is not always “safe” [111].
 - ✓ It is worth paying attention to the disturbing fact that in the United States, patients spent a total of USD 8.842 billion on herbal supplements across all market channels in 2018. Compared to 2017, it is an increase of approx. USD 757 million in sales [129]. According to the FDA opinion, it encompasses a nearly USD 40 billion the market. Three out of four American consumers take a dietary supplement on a regular basis and among older Americans it constitutes 4 out of 5 people [130].
 - ✓ Furthermore, in the USA, 23,000 emergency department visits per year are related to supplement use [131]. In Poland, the value of the dietary supplements market is 4.4 billion PLN (USD 1.11 billion). Three quarters of Poles use supplements every day [132].
 - ✓ It is confirmed that there is a need for greater attention to improve regulation and protect consumers in optimal conditions [133]. Laboratory tests of dietary supplements commissioned by the Supreme Audit Office in Poland have shown that many supplements do not have the features stated by the manufacturers. This can be harmful to health [122].
 - ✓ Next to reliable preparations, dietary supplements can be adulterated by e.g., pathogenic bacteria, substances banned from the psychoactive list, or structurally similar amphetamine stimulants [134].
 - ✓ Herbal supplements should be purchased from a community pharmacy only after pharmacist counseling. There is a strong need for proper communication between caregivers, medical providers, and scientists about potential benefits and risks for GTE adverse effects [135].
 - ✓ Some recommendations state that most complementary therapies cannot be either encouraged or discouraged because of the lack of sufficient safety and efficacy data [136]. It is also essential to familiarize health care professionals with popular supplements to educate patients in a proper way to maximize benefits and minimize risks [137].
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A review of Hu et al. on toxicological evidence from laboratory studies confirmed the GTE hepatotoxicity in the liver. It was strongly associated with doses and positively correlated with total catechin and EGCG content [138]. Several 159 human intervention studies confirmed toxicological evidence. Catechin-rich green tea preparations resulted in hepatic AEs (adverse event) in a dose-dependent manner when ingested in large bolus doses, but not when consumed as brewed tea or extracts in beverages or even as part of food. The internal dose of catechins is vital for the occurrence and severity of hepatotoxicity. It is worth mentioning that the safe intake level is 338 mg EGCG/day (fed or fasted) in solid dosage form for adults. An Observed Safe Level (OSL) of 704 mg EGCG/day (fed or fasted) might be for tea preparations in beverage form [138]. According to United States Pharmacopeia adverse event case reports, hepatotoxicity with EGCG intake is from 140 mg to ~1000 mg/day and substantial inter-individual variability in susceptibility, possibly due to genetic factors [139]. Intake of EGCG with green tea infusions and GTE-based beverages is up to about 450 mg EGCG/person/day in Europe and even higher in Asia [140]. It is essential to point out that in clinical intervention studies, liver effects were not observed after intakes below 600 mg EGCG/person/day, so a tolerable upper intake level of 300 mg EGCG/person/day is proposed for food supplements [140]. GTE may have hepatotoxic solvent or pesticide residues, pyrrolizidine alkaloids, and elemental impurities. The monograph of Powdered Decaffeinated Green Tea Extract contains information about not taking on an empty stomach and in the case of a liver problem. Patients should have a medical consultation when liver problems occur, such as abdominal pain, dark urine, or jaundice (yellowing of the skin or eyes) [139]. The dietary supplements are suspected of inducing liver damage, e.g., SLIMQUICK® as a weight loss product can lead to severe acute hepatocellular liver injury, which may result in transplantation. GTE should be studied further as a possible cause for liver injury [141]. In the review from 2018, there were 65 studies from 104 that indicated that green tea or GTE was generally well tolerated without side effects. AEs were mostly related to gastrointestinal disturbance, such as primary nausea (22 studies), abdominal pain or discomfort (17 studies), diarrhea (14 studies), dyspepsia/indigestion (12 studies) and/or elevated liver enzymes (11 studies). Green tea preparations consumed in beverage forms are better tolerated than in solid bolus dose exposure. Treatment-related early death and severe toxicity in the liver, kidney, thymus, spleen and pancreas were reported in the studies involving highly concentrated green tea catechins or purified EGCG administered via bolus dose (gavage or capsules) as low as 150 mg EGCG/kg/day [138]. It is worth mentioning that the application of nanosized vitamin E can increase the absorption rate to a greater extent than in the case of normal food-related material. These results were obtained in safety analyses performed on food-related nanoscale materials for human consumption. The discussed combination for sure does not lead to signs of acute toxicity in rats, treated as a research model [142].

8. Techno Economic Challenges and Future Research Directions

Tea is the most widely consumed beverage in the world after water. Moreover, it is inexpensive and exhibits many beneficial health effects [143]. In 2020, global consumption of tea reached 6.3 billion kilograms and it is estimated to reach 7.4 billion kilograms by 2025 [144]. The tea market will probably grow over time if the world population continues to increase. No breakthrough in tea-making technology is expected in the near future. Possible discoveries and inventions related to tea will the most likely be associated with the post-processing of its beverages or preparation of original flavor combinations that may convince more customers. An interesting area of research covers the design and development of novel nano-emulsified vitamin E and micro-sized green tea formulations that can improve their efficacy, overcome the problem of their bioavailability while still maintaining the essential therapeutic activity [142]. Future study could also focus on preparing mixtures with other ingredients that demonstrate unique impact on the human body. Such activities can also be oriented to specific ailments and set further directions of

development. It is worth paying attention to the research of new forms of green tea tailored to consumers, mainly intended for selected age groups and maybe even ethnic ones.

The consumption of green tea has been increasing over the past 10 years. As a result, a rapid development of technology and techniques of green tea production, accompanied by an increase in world tea production, has been noted. In addition, waste management from tea production and consumption has become an equally important issue as well as the ecological approach, which turned to be now highly appreciated [145,146].

9. Discussion and Conclusions

Drinking tea is basically safe and does not have many contraindications. It is important to use it wisely while pregnant or for the elderly. In complicated cases such as multidrug use, it is always better to consult one's physician (GP) or pharmacist. A particular recommendation concerns patients taking clozapine and digoxin. They should not drink GTE nor take supplements containing EGCG as there is a risk of a significant reduction in AUC and C_{max} of these drugs resulting in no therapeutic effect or even life-threatening conditions. It is worth noting that digoxin has a very narrow therapeutic index. Patients taking warfarin should avoid drinking green tea extract or monitor their INR level more frequently. Patients taking statins, calcium channel blockers, or sildenafil should refrain from drinking GTE or otherwise remain cautious because side effects may occur.

Green tea as a whole may have many benefits, but all too often, it is used without supervision by a healthcare provider. It is essential to remember the importance of monitoring patient use of all dietary supplements and herbal products [147]. Overall, the results from human intervention studies of green tea preparations suggest that consumption in beverage forms is better tolerated than in solid bolus dose exposure. Herbal and dietary supplements may have many additional ingredients. Thus, there is an essential role of health care providers to discourage the patient from using herbal or dietary supplements containing complex mixtures in self-treatment. It is good to remember that while the mechanism of GTE hepatotoxicity remains unclear, factors related to the patient often become evident [141]. It is worth pointing out that GTE does not manifest a major teratogen, mutagen, or carcinogen effect. However, there are limited data on using them during pregnancy. Therefore, it is incumbent on pharmacists in community pharmacies to reliably inform patients about the use of tea products, including supplements containing GTE/EGCG, paying attention to the careful use of them in pregnancy or during breastfeeding [111]. Therefore, questions asked by health care professionals regarding health condition, currently taken medications or potential allergies are very important. Precise patient counseling and observations carried out with the patient can guarantee the proper drugs use. Paying attention to patients' self-medication can ensure pharmacotherapy correctness and improve the quality of one's life.

To sum up, in view of the increasing number of reports on the impact of green tea ingredients on the human body, it is necessary to pay attention to the rational consumption of GTE and dietary supplements containing EGCG by patients. Take-home messages for the reader are presented in Figure 4 while particular attention was paid to supporting healthcare professionals in their everyday practice (Figure 5).

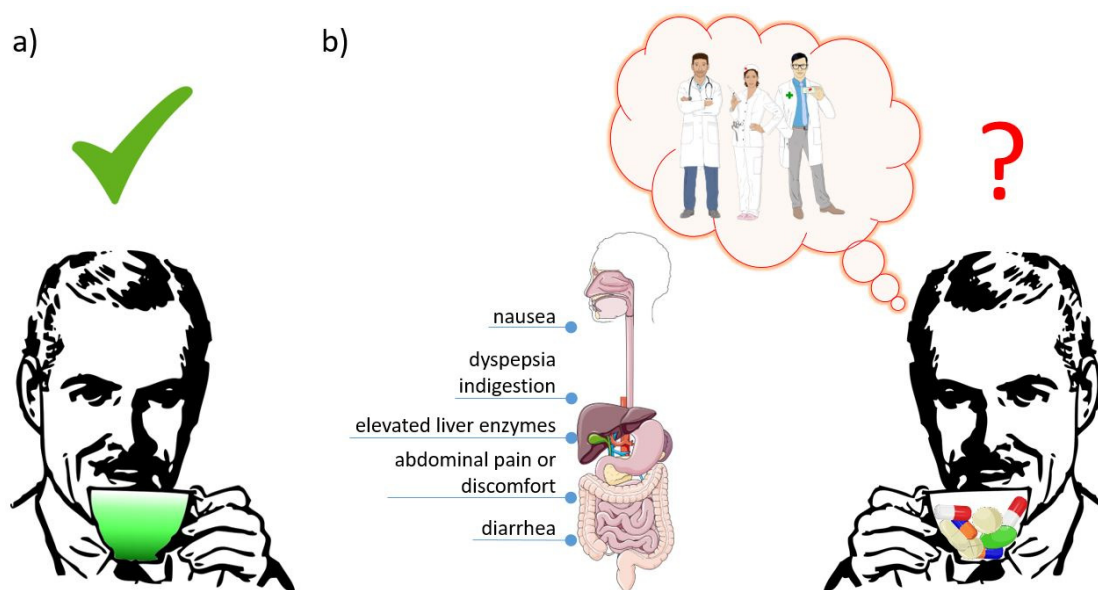


Figure 4. Take-home messages: (a) Drinking tea is basically safe and does not have many contraindications; (b) Green tea extracts (GTE) should not be used instead of the medication prescribed by a physician and without consultation by health care providers, including pharmacists. The increasing consumption and popularity among the patients of GTE products in community pharmacy e.g., ready-to-drink green tea beverages, food supplement products in capsule and tablet forms led to the development of recommendations for their use, primarily due to potential side effects, mainly concerning gastrointestinal disturbances.

- Patients taking clozapine and digoxin should not drink GTE nor take supplements containing EGCG due to the risk of reduced effectiveness of pharmacological treatment.
- Patients taking warfarin should avoid drinking GTE or monitor their INR level more frequently.
- Patients taking statins, calcium channel blockers, or sildenafil should quit drinking GTE to avoid side effects of these medications.
- Pregnant women and elderly patients should be advised to avoid using dietary supplements containing EGCG without prior consultation with healthcare professional.
- GTE intake and dietary supplements consumption should be considered as a part of a routine medical and pharmaceutical interview.

Figure 5. Guidelines for healthcare professionals: The scope of patient education resulting from the review.

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