

Block Copolymer Based Composition of Epigallocatechin-3-gallate with Improved Oral Bioavailability as a Way to Increase its Therapeutic Activity

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Abstract

At the present, a high potential of epigallocatechin-3-gallate (EGCG) as a new preventive and therapeutic agent in oncology and several other indications is well established. EGCG exerts its antitumor activity through induction of cell cycle arrest and apoptosis, inhibition of tumor angiogenesis, migration, and metastasis due to its ability to interact with multiple targets in cancer cell. Unfortunately, very low oral bioavailability of EGCG prevents its efficient development as novel medicine. In this work, we have developed a polymer based nano-formulation of EGCG that significantly improved its oral bioavailability by increasing systemic exposure of the compound by about 8-fold. This formulation comprises a well-known inactive ingredient non-ionic block copolymer Pluronic F127 that has recently been successfully used to increase bioavailability of another promising phytonutrient, 3,3'-diindolylmethane. The pharmacokinetic parameters established in the present study revealed that AUC and C_{max} of the new formulation dosed at 500 mg/kg were $578.5 \pm 73.8 \mu\text{g}\cdot\text{h/mL}$ and $49.3 \pm 2.9 \mu\text{g/mL}$, while in the case of control EGCG administered in the equivalent dose AUC and C_{max} were $72.9 \pm 14.7 \mu\text{g}\cdot\text{h/mL}$, and $10.7 \pm 1.1 \mu\text{g/mL}$.

Keywords: Epigallocatechin-3-gallate; EGCG; Pluronic F127; Bioavailability

Introduction

Over the last two decades a number of epidemiological studies have suggested that green tea consumption correlated with a reduced risk of various malignancies [1,2]. Green tea is very rich in polyphenols, plant compounds that demonstrate health-promoting properties and may act to prevent a number of chronic diseases and cancers. A major class of tea polyphenols is represented by catechins and the most abundant and active catechin is epigallocatechin-3-gallate (EGCG) that accounts for 50-80% of the total amount of catechins in green tea. Large amount of encouraging data from *in vitro* and animal models indicated that pure EGCG or Polyphenon E, a standardized pharmaceutical grade preparation of tea polyphenols containing EGCG as a major component, inhibited carcinogenesis in various cells and tissues including breast, prostate, lung, skin, esophagus, stomach, liver, blood, and etc. [1,3]. Moreover, cancer-preventive effects of EGCG were demonstrated in several clinical studies, especially in prostate cancer [1].

EGCG is thought to exert its antitumor activity through induction of cell cycle arrest and apoptosis, inhibition of proliferation, tumor angiogenesis, migration, and metastasis, the basic biological processes underlying the carcinogenesis. The proposed mechanisms of EGCG multi-targeted action in cancer cells comprise inhibition of NF- κ B, EGFR, IGF-I, RAS/MAPK, and PI3K/Akt signalling, suppression of ubiquitin-proteasome pathway, as well as inhibition of matrix metalloproteinases, urokinase-plasminogen activator, androgen receptor, telomerase activity and stabilization of p53 [2,4,5]. Other important targets of EGCG in cancer cells are VEGF and hypoxia inducible factor HIF-1 α [6]. Accumulating evidence has demonstrated that all or part of these anticancer mechanisms can be responsible for the activity of EGCG against cancer stem cells (also known as tumor-initiating cells) [7], and also for epigenetic activity. EGCG was shown to inhibit DNA methyltransferase and histone deacetylase, as well as to modulate expression of microRNAs [8].

EGCG also possesses strong anti-inflammatory and antioxidant activity, and is able to reduce the level of cholesterol, normalize glucose metabolism and T-cell immunity. That is why in addition to its cancer preventive properties, EGCG also may have therapeutic potential in other indications, such as arthritis [9], neurodegenerative [10-12] and cardiovascular [13] diseases, obesity [14,15], diabetes [15,16], and autoimmune diseases [17].

Despite of a high solubility in water, EGCG possesses inefficient systemic delivery and very low bioavailability, which is major obstacle in its therapeutic use. Due to unfavourable pharmacokinetic of this substance, epidemiological inferences with EGCG are sometimes conflicting and *in vitro* and *in vivo* studies may seem discrepant. The absolute bioavailability of EGCG after oral administration of decaffeinated green tea to rats is found to be only 0.1% [18]. The bioavailability of EGCG in mice following oral administration of EGCG was higher but still comprising just several percent [19]. In several pharmacokinetics studies in healthy volunteers, the highest concentration of EGCG in plasma after administration of 800 mg EGCG (maximum dose that is used in most of clinical studies) was in the range of 0.6-3.3 μM [20-22]. These concentrations are more than

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order of magnitude lower than effective concentrations that are used in cell culture experiments to demonstrate EGCG activity, typically 10-50 μM . Low bioavailability of EGCG seems to be related to its extensive gastrointestinal degradation, poor membrane permeability, and transporter-mediated intestinal efflux [2].

Nevertheless, despite its poor oral bioavailability, EGCG has been included in many dietary supplement formulations. Conventional pre-formulation methods have been previously employed to improve the bioavailability of EGCG. They include, for example, production of crystalline or co-crystalline forms of EGCG [23]. However, these methods produced increase in oral bioavailability of only 37%, which is far from being sufficient to achieve therapeutically meaningful levels of the compound in circulation. Nanolipidic particles of EGCG were slightly more efficient in enhancement of oral bioavailability, but this approach requires the use of ethanol suspension, which significantly limit the use of such product in humans [24]. Another nanoparticle-mediated approach recently used for the improvement of EGCG delivery to the target tissues, prostate cancer in particular, included its encapsulation in polylactic acid-polyethylene glycol nanoparticles [25]. However, no means for oral administration of such compositions are feasible [26]. Thus, practical solutions that would offer a considerable increase in oral bioavailability of EGCG have not been suggested yet and novel technology approaches that would be able to considerably improve oral bioavailability of EGCG, are highly needed to fully explore therapeutic potential of this compound. Furthermore, to assure a rapid and successful introduction of EGCG as preventive and/or therapeutic agent in practice, it is very important that such technologies were compatible with industrial development settings and used well established pharmaceutical ingredients.

Recently, we have reported that by using a non-ionic block copolymer Pluronic F127 it is possible to substantially (over 10-fold) increase oral bioavailability of 3,3'-diindolylmethane (DIM) [27], another important phytonutrient that shows a high potential in oncology and some other indications [28]. In this work we have used a similar nanotechnology approach to improve oral bioavailability of EGCG. The results described here suggest that a much greater concentrations of EGCG in circulation could be achieved upon its formulation with Pluronic F127.

Materials and Methods

Reagents and materials

Green tea derived EGCG (90% purity by HPLC) was purchased from QianShengKang Pharmaceutical Co., Ltd (China). Pluronic F127 was kind gift from BASF Corporation (USA). All solvents were HPLC grade purity from JT Baker (USA).

Formulation preparation

Various amounts of 200 mg/ml EGCG stock solution in anhydrous ethanol were added to 20% w/v Pluronic F127 solution in aqueous 85% ethanol. Depending on the dose the EGCG to Pluronic ratios were ranging from 1.6 (for the dose of 50 mg/kg) to 3.2 (for the dose of 500 mg/kg respectively). The mixture was stirred for 30 min at room temperature, and then organic phase was evaporated using rotary evaporator. Then the resulted waxy mixture was dried under a high vacuum until a solid powder was formed. The dried EGCG formulation was stored under vacuum in darkness and was dissolved in distilled water before use. The control EGCG dosing solution was prepared by dissolving EGCG in distilled water.

Animals

Female Sprague-Dawley rats (250-350 g) were purchased from Charles River Canada Inc. (St. Constant, Canada). The animals were kept three per cage with an air filter cover under light (12 h light/dark cycle, light on at 06:00) and temperature ($22^\circ \pm 1^\circ\text{C}$)-controlled environment. All manipulations with the animals were performed under a sterilized laminar hood. The animals had ad libitum access to Purina mouse chow (Pro Lab PMH 4018, Trademark of Agway, USA) and water. The animal studies were conducted according to the "Guidelines for Care and Use of Experimental Animals". The animals were fasted overnight and anesthetized before the start of perfusion.

Dosing and sampling

EGCG formulations and controls were administered orally to rats by gavage at the dose levels of 50, 100, 500 and 2500 mg/kg. Four rats were used for each group. After various time intervals (10, 30 min, 1, 1.5, 2, 3, 8, and 24 hrs) post-administration, the blood samples were collected. The rats were anaesthetised by general inhalation of Isoflurane (Bimeta-MTC, Animal Health Inc. Canada). The blood samples were collected from the jugular vein and kept on ice for 5 to 10 min. Blood was centrifuged at 10000 RPM for 5 minutes, and plasma was collected. The plasma samples were immediately frozen in dry ice and stored at -80°C until further use.

Sample extraction and analysis

The plasma samples were defrosted and 100 μL aliquots were transferred to plastic tubes. The samples were extracted with 2 mL of ethyl acetate by 5 min shaking on 180° rotator. Then, the samples were centrifuged at 10000 RPM for 10 minutes. The supernatant was separated and transferred to glass tubes. After phase separation the extraction procedure was repeated twice. The residual organic phase was evaporated in the stream of nitrogen at $+40^\circ\text{C}$ until dryness. The dried samples were kept at -80°C before HPLC analysis. The samples were dissolved in 50 μL of mobile phase and the 20 μL aliquots were injected into HPLC for analysis.

For HPLC analysis C18 reversed phase column 250 \times 4.6 mm, 5 μm C18(2) Phenomenex®Luna® was used. The column temperature was maintained at $+30^\circ\text{C}$, flow rate was 1 mL/min. The mobile phase was linear gradient of buffer B from 13 to 28% (buffer A: 5% acetonitrile 0.1% TFA, buffer B: 90% acetonitrile 0.1% TFA) and run time was 15 minutes. EGCG was detected by UV absorption at 278 nm.

Quantification of EGCG in rat plasma

The 1 mg/mL EGCG stock solution was prepared in 2% ascorbic acid buffer containing 0.4M NaH_2PO_4 and 0.1% EDTA, pH 3.5. The standard spiking solutions were prepared by diluting the stock solution to 25, 50, 125, 250, 500, and 1000 $\mu\text{g}/\text{mL}$ with the same buffer. All standard solutions were protected from light and stored at -20°C .

Calibration curve preparation

For this analysis the calibration curve was prepared comprising 2.25 to 100 $\mu\text{g}/\text{mL}$ range of the standard concentrations. The calibration curve was prepared by spiking blank rat plasma (Gene Tex Inc., USA) containing sodium heparin as preservative with the standard solutions. The calibration curve performance was within acceptable range for bioanalytical methods acceptance ($R^2 > 0.99$). Limit of quantification (LOQ) was 0.52 $\mu\text{g}/\text{mL}$.

The EGCG concentrations in rat plasma were calculated from area

under the peak (AUP) using calibration curve. Areas under the curves (AUC) were calculated by trapezoidal method.

Results and Discussion

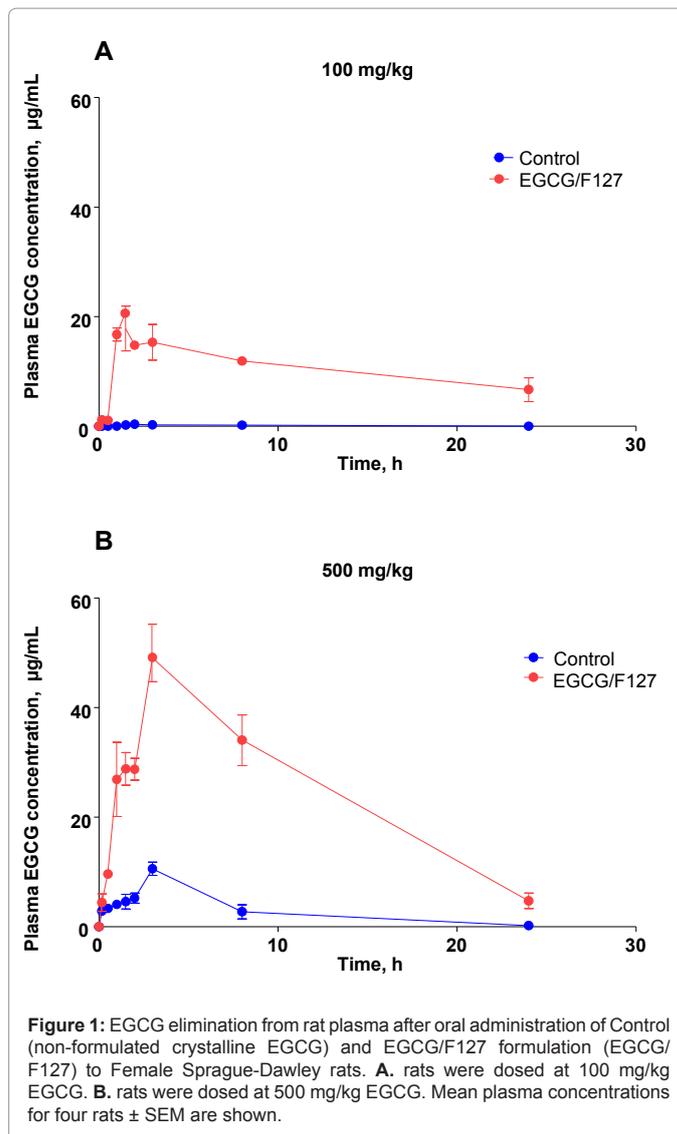
Poor oral bioavailability of EGCG is the major problem for its use as therapeutic agent. To overcome this problem we have used a proprietary formulation based on non-ionic block copolymer Pluronic F127. Pluronic F127 belongs to a family of symmetric three-block copolymers of poly-oxiethylene and poly-oxipropylene that broadly used as pharmaceutical excipients and food additives in variety of applications. By using these nonionic block copolymers an improved pharmaceutical performance of a drug is achieved by incorporating it into self-assembled micelles - colloid nanoparticles formed spontaneously by the excipients. Depending on the composition, the size of these particles ranges from 10 to 100 nm, which is suitable for intravenous and for oral administration routes. According to our preliminary results, the particle size of micellar complexes formed by EGCG and Pluronic F127 is about 50 nm as demonstrated by dynamic light-scattering. A detailed review of the properties, size, size distribution and the mechanism of action of block copolymer-drug complexes can be found in Kabanov et al. and Alakhov et al. [29,30].

The results of pharmacokinetics studies presented here indicate that this formulation provides a substantial increase in EGCG oral bioavailability in rats. Neither control, no formulation dosed at 50 mg/kg delivered EGCG plasma levels that would be detectable by the analytical method used in this study. Figure 1 demonstrates plasma elimination curves for the formulation and control EGCG dosed at 100 and 500 mg/kg. The results demonstrate that C_{max} and AUC were substantially higher in case of the formulation compared to the control. The control EGCG dosed at 100 mg/kg was poorly absorbed and still could not be detected. On the other hand, the same dose of the formulation was easily detectable in plasma with C_{max} of ~22 $\mu\text{g/mL}$ and AUC of ~254 $\mu\text{g}\cdot\text{h/mL}$. The estimated values for C_{max} and AUC for various EGCG dose levels are shown in Table 1. The formulation given at the dose of 500 mg/kg provides EGCG with 7.9-fold higher exposure and 4.6-fold higher C_{max} as compared to the non-formulated compound administered at the equivalent dose. On molar scale maximum plasma concentrations achievable at 100 and 500 mg/kg doses of the formulation were 47 and 107 μM of EGCG, respectively. These concentrations are just those typical concentrations of EGCG required to achieve its maximum biological activities in cell culture [31,32]. Thus, the results suggest that using EGCG formulation it is possible to translate the *in vitro* activities of EGCG to the *in vivo* conditions. It is important to note that the highest dose of non-formulated EGCG (2500 mg/kg) used in this study was highly toxic, and three out of four rats died within 24 hours after the dosing. Still, this dose provided a 2-fold lower exposure to the compound compared to that of the formulation given at the dose of 100 mg/kg. Except for 2500 mg/kg, all other doses of non-formulated and formulated EGCG did not induce any obvious

Treatment, dose	C_{max} [$\mu\text{g/mL}$]	AUC _{0-24h} [$\mu\text{g}\cdot\text{h/mL}$]
Control, 2500 mg/kg	58.6 \pm 22.4	128.1 \pm 78.8
EGCG/F127, 500 mg/kg	49.3 \pm 2.9	578.5 \pm 73.8
Control, 500 mg/kg	10.7 \pm 1.1	72.9 \pm 14.7
EGCG/F127, 100 mg/kg	21.7 \pm 2.5	254.1 \pm 18.2
Control, 100 mg/kg	Below LOQ*	---
EGCG/F127, 50 mg/kg	Below LOQ*	---

*LOQ – Limit of Quantification, 0.52 $\mu\text{g/mL}$

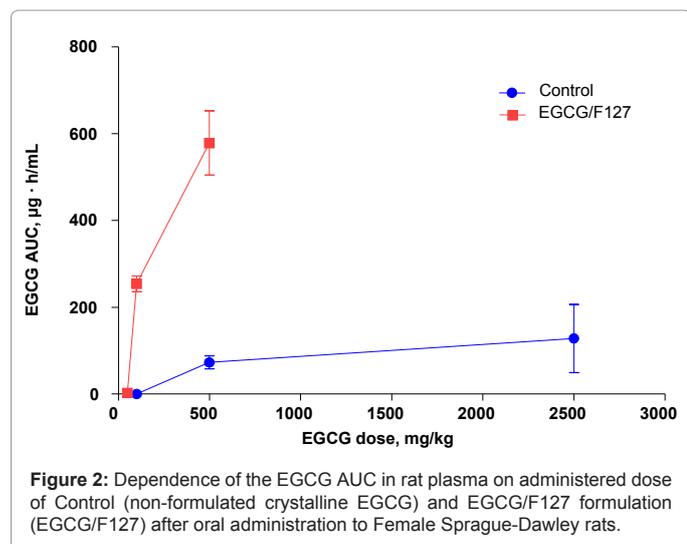
Table 1: C_{max} and AUC_{0-24h} values calculated for the animals treated with Control (non-formulated EGCG) and EGCG/F127 formulation (EGCG/F127).



toxic reactions. It corroborates with the previously reported data [33] that NOAEL (no observable adverse effect level) of EGCG was 500 mg/kg, when administered to rats for 13 consecutive weeks.

Our results indicate that the dose dependence in the case of non-formulated EGCG is not linear and the exposure to the compound reaches a plateau at the dose of about 500 mg/kg (Figure 2). According to *t*-test, the difference in AUC between 500 and 2500 mg/kg doses was not significant, $p=0.36$. Thus, it is impossible to achieve a higher exposure to EGCG by increasing the dose of the non-formulated compound. At the same time, formulated EGCG provides much greater exposure at all doses in dose-dependent manner, although establishing dose proportionally requires a more detailed study. These results are in support to our recent preliminary finding that a better therapeutic index could be achieved in clinical settings by using the formulated EGCG with Pluronic F127 (EGCG/F127) compared to the non-formulated compound [34].

Although the ability of Pluronic F127 to enhance oral bioavailability of EGCG reported herein is significant, and seems to be translatable into human setting, at least in some proliferative pathologies, the



mechanistic side of this phenomenon remains to be understood, mainly due to very complex and largely unknown metabolic fate of EGCG. Incorporation of EGCG into the micelles formed by Pluronic may affect multiple transformations of this molecule and its interactions with epithelial transporters that occur upon its oral administration (reviewed in [35] and should be further investigated). Nevertheless, therapeutically meaningful plasma concentrations observed upon oral dosing of this composition seem to be highly promising for its further clinical investigations.

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