

EXPERIMENTAL PAPER

Effect of *Camellia sinensis* extract on the expression level of transcription factors and cytochrome P450 genes coding phase I drug-metabolizing enzymes

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S u m m a r y

Green tea (*Camellia sinensis*) is widely used as a popular beverage and dietary supplement that can significantly reduce the risk of many diseases. Despite the widespread use of green tea, the data regarding the safety as well as herb-drug interactions are limited. Therefore, the aim of our study was to assess the influence of standardized green tea extract (GTE) containing 61% catechins and 0.1% caffeine on the expression level of rat CYP genes and the corresponding transcription factors expression by real-time PCR. The findings showed that GTE resulted in a significant decrease of CYP2C6 expression level by 68% ($p < 0.001$). In case of CYP3A1 and CYP3A2, the mRNA levels were also reduced by extract but in a lesser degree compared to CYP2C6. Simultaneously the significant increase in the mRNA level of CAR, RXR and GR factors was observed by 54% ($p < 0.05$), 79% ($p < 0.001$) and 23% ($p < 0.05$), respectively after 10 days of green tea extract administration. In addition, there was noted a small increase of CYP1A1 expression level by 21% ($p > 0.05$) was noted. No statistically significant differences were observed for CYP1A2 and CYP2D1/2. In the same study we observed an increase in amount of ARNT gene transcript by 27% ($p < 0.05$) in the long-term use. However, green tea extract showed the ability to stimulate HNF-1 α both after 3 and 10 days of treatment by 30% ($p < 0.05$) and 80% ($p < 0.001$), respectively. In contrast, no change was observed in the concentration of HNF-4 α cDNA. These results suggest that GTE may change the expression of CYP enzymes, especially CYP2C6 (homologue to human CYP2C9) and may participate in clinically significant interactions with drugs metabolized by these enzymes.

Key words: CYP enzymes, *Camellia sinensis*, induction, inhibition, expression level

INTRODUCTION

Green tea (*Camellia sinensis*) is one of the most popular beverages in the world. It is highly consumed as a dietary supplement for the prevention and treatment of cardiovascular disease and other degenerative diseases [1-3]. Epidemiological studies have reported that consumption of green tea is also associated with a lowered risk of cancer [4]. It results from activity of polyphenolic compounds that possess chemopreventive properties. Green tea and its extracts are rich sources of flavonoids, commonly known catechins. Epigallocatechin gallate (EGCG) is the major catechin in green tea comprising about 50–80% of the total catechins that has beneficial effects related to its antioxidative activity. It is suggested that EGCG as a chemopreventive agent may not only inhibit the growth of cancer cells but also can induce the process of apoptosis in some of existing cancer cells [5, 6].

Based on recent studies, it is postulated that the protective effects of green tea polyphenols are attributed to the inhibition of CYP enzymes, which are involved in bioactivation of carcinogens [7]. Furthermore, green tea polyphenols can activate the mitogen-activated protein kinase (MAPK) through a potential signaling pathway involved in the regulation of phase II metabolic enzymes gene expression by ARE (antioxidant-responsive element) and may result in a significant activation of *c-Jun* N-terminal kinase 1 (JNK1) as well as extracellular, signal-regulated kinase 2 (ERK2) [5, 7]. However, despite the widespread use of green tea, data regarding its effect on CYP enzymes activities mainly involved in the drugs metabolism and procarcinogens activation are limited. Hence, further studies are needed to provide important information about possible herb-drug interactions as well as development of chemical carcinogenesis by induction of CYP enzymes. The CYP2C, CYP2D and CYP3A subfamilies are the most active CYPs responsible for drug biotransformation, especially the CYP3A4 isoform that is involved in the metabolism of more than 50% of clinically used drugs [8]. The CYP1A and CYP2E subfamilies metabolize some drugs but also many protoxins and procarcinogens to their ultimate reactive metabolites [9]. However, the metabolism of foreign compounds by these enzymes does not always lead to their detoxification and in some cases, reaction products of CYP enzymes can initiate chemical carcinogenesis [10]. The regulation of cytochrome P450 gene expression depends on the interaction of the xenobiotics with the receptors. It was shown that the CYP1 subfamily can be induced by the AhR/ARNT pathway in response to xenobiotics such as PAHs. Similarly, the constitutive androstane receptor (CAR) and pregnane X receptor (PXR) form a heterodimer with the retinoid X receptor (RXR) and transcriptionally activate the promoters of CYP2C9 and CYP3A gene expression [11]. One of the studies shows that HNF1 and HNF4 are a general regulators supporting the constitutive expression of major CYPs (CYP2D6, CYP3A4, CYP2C9, CYP1A) in hepatocytes [12]. Studies on the expression and activity of enzymes catalyzing the biotransformation of xenobiotics are important from the perspective of herb-drug interaction and their physiological functions.

The aim of our study was to assess whether green tea extract (GTE) may influence the gene expression of CYP using animal model. In present paper, we also examined

the effect of green tea on the transcription factors regulating the expression of major CYP enzymes. It is necessary to underline that the human CYP1A1/2 and CYP2E1 are known as highly conserved through the species represented in rats by their counterparts CYP1A1/2 and CYP2E1, whereas the human CYP3A4/5 and CYP2C9 correspond to rat CYP3A1/2 and CYP2C6, respectively. In case of human CYP2D6, it is represented in rats by an orthologous CYP2D1 enzyme, but also by rat CYP2D2 that metabolizes one of the marker substrates of CYP2D6, dextrometorphan.

MATERIALS AND METHODS

Green tea extract

Standardized green tea extract (GTE) containing 61% catechins expressed as EGCG was obtained from TTD International, Australia. The alcoholic GTE contained small quantities of caffeine (0.1%) and could be considered as a decaffeinated extract. This powdered GTE was kept in a dark and dry place at a room temperature until used.

Animals

The experiment with male Wistar rats (200–250 g) was performed in accordance with Polish governmental regulations (Decree on Animal Protection 21.01.2005, Dz. U. No 33; 289). The study has been approved by Local Ethic Committee of the Use of Laboratory Animals in Poznan (No 43/2005). The animals were housed in plastic cages in the Department of Pharmacology, Poznan University of Medical Sciences which possesses animal quarters. Rats were maintained in a climate-controlled room with 12 h light/dark cycle with access to a commercial rat chow and tap water *ad libitum*. The animals were randomly divided into four groups from A to D (n = 10). Group A was treated with the standardized extract of green tea 300 mg/kg p.o., once daily, for 3 days and group B was fed with standard diet as controls. Group C was treated the same extract like group A (300 mg/kg p.o., once daily) but for 10 days, whereas group D used as controls for group C. The rats were decapitated sixteen hours after the last administration. The samples of liver were immediately frozen in liquid nitrogen and stored at –80°C until used.

RNA extraction and cDNA synthesis

Total cellular RNA was isolated from the rat livers using TriPure Isolation Reagent (Roche, Germany) according to the manufacturer's protocol. The concentrations and the purity of RNA were determined by measuring the absorbance at 260 and 280 nm in a spectrophotometer (BioPhotometer Eppendorf, USA). RNA samples were stored at –80 °C. Complementary DNA was synthesized from 2 µg

of total RNA in a total volume of 20 μ l using the SuperScriptTM III First-Strand Synthesis System (Invitrogen, USA) and oligo(dT)₂₀ primer. The obtained transcripts were stored at -20°C or used directly for the real-time quantitative PCR (RT-PCR).

Real-time PCR

The level of mRNA expression in the rat liver tissues was analyzed by using RT-PCR. The primers and RT-PCR conditions used for CYP1A1/2, CYP2D1/2, CYP3A1/2, CYP2E1, CYP2C6 and GAPDH amplifications were described by Mrozikiewicz et al. [13]. The primers and RT-PCR conditions used for CAR, PXR, RXR, GR, AHR, ARNT, HNF-1 and HNF-4 amplifications are described in table 1. All oligonucleotide sequences were synthesized by TIB Molbiol (Poland). Amplicon size and reaction specificity were confirmed by agarose gel electrophoresis and melting curve analysis (fig. 1). RT-PCR was carried out using a LightCyclerTM Instrument (Roche, Germany) and a LightCycler DNA Master SYBR Green I kit (Roche, Germany) according to the manufacturer's protocol. GAPDH was used as a housekeeping gene for normalization. The PCR program was initiated with an activation at 95°C for 10 min. Each PCR cycle comprised a denaturation step at 95°C , an annealing step at a specific temperature and an extension step at 72°C . The last PCR cycle included a final extension at 95°C for 1 min. The quantitative PCR was monitored by measuring the increase in fluorescence by the binding of SYBR Green I dye to the generated double-stranded cDNA. The data were evaluated with the Roche LightCycler Run 5.32 software.

Table 1.

Sequences of primers used for the RT-PCR analysis and PCR conditions

Gene	Primer sequence (5' → 3')	Product size (bp)	PCR conditions			
			Cycle	Denaturation	Annealing	Extension
CAR F CAR R	GGA GGA CCA GAT CTC CCT T GAC CGC ATC TTC CAT CTT GT	130	35	95°C , 8s	58°C , 8s	72°C , 8s
PXR F PXR R	TCC ACT GCA TGC TGA AGA AG AAC CTG TGT GCA GGA TAGGG	187	35	95°C , 8s	55°C , 8s	72°C , 8s
RXR F RXR R	CCT GAG TTC TCC CAT CAA TG GAC GCC ATT GAG GCC TAG A	190	35	95°C , 8s	57°C , 7s	72°C , 8s
GR F GR R	CTG GAA TAG GTG CCA AGG CT CCG TAA TGA CAT CCT GAA GCT	210	40	95°C , 10s	58°C , 8s	72°C , 8s
AHR F AHR R	ATAGTACTCCACTTCAGCC TCATGCCACTTTCTCCAGTC	244	35	95°C , 8s	52°C , 8s	72°C , 8s
ARNT F ARNT R	CAG AAC TGT CAG ACA TGG TAC AGT CAG AGA CAT ACA CCA CTC	246	40	95°C , 8s	57°C , 7s	72°C , 8s
HNF-1 α F HNF-1 α R	GCT CGG AAG ATG ACA CGG AT CTT GTT GAG GTG CTG GGA CA	245	35	95°C , 8s	60°C , 7s	72°C , 8s
HNF-4 α F HNF-4 α R	CTG GAG GAT TAC ATC AAC GAC GTG TTC TTG CAT CAG GTG AG	164	40	95°C , 8s	57°C , 7s	72°C , 8s

F – Forward, R – Reverse

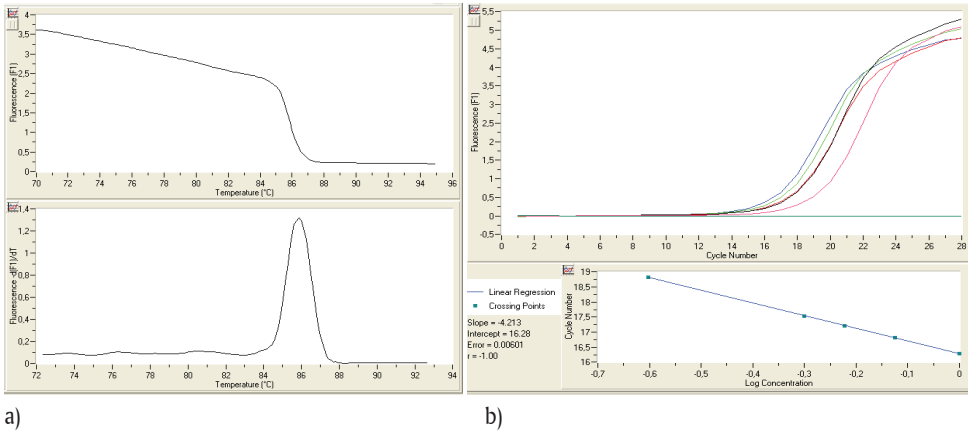


Figure 1.

Real-time PCR reaction for analyzed gene. a) melting curve analysis – T_m=85.90°C, b) standard curve

Statistical analysis

The mRNA content for studied genes was expressed as mean ±SEM. The experimental data were analyzed using the SPSS 17.0 for Windows software. Mean values were compared by one-way ANOVA test. The value of $p < 0.05$ was considered as statistically significant.

RESULTS

In this study, we investigated the influence of standardized green tea extract on mRNA abundance of CYP isozymes involved in detoxification of xenobiotics. The level of mRNA expression in liver tissues was analyzed by using RT-PCR method. As shown in fig. 2, a standardized green tea extract resulted in a small decrease of rat hepatic CYP2C6 expression level by 11% ($p > 0.05$) after 3 days of treatment, whereas statistically significant difference was observed for this gene after long application of GTE. The level of CYP2C6 mRNA was reduced by 67% ($p < 0.001$) in comparison with the control group. Similar effect to rat CYP2C6, it was observed for CYP3A1 relating to the decrease of expression level by 13% ($p > 0.05$) and 38% ($p < 0.001$), respectively. In case of CYP3A2, the mRNA transcription of this gene was also inhibited by GTE, but in a lesser degree compared to CYP2C6. However, statistically significant difference was observed only for CYP3A2 after 10 days of treatment because GTE decreased the CYP3A2 gene expression by 50% ($p < 0.001$). In addition, a small increase of CYP1A1 mRNA level by 21% ($p > 0.05$) after long application was noted. No statistically significant differences were observed for CYP1A2, CYP2D1 and CYP2D2 and CYP2E1 after both 3 and 10 days.

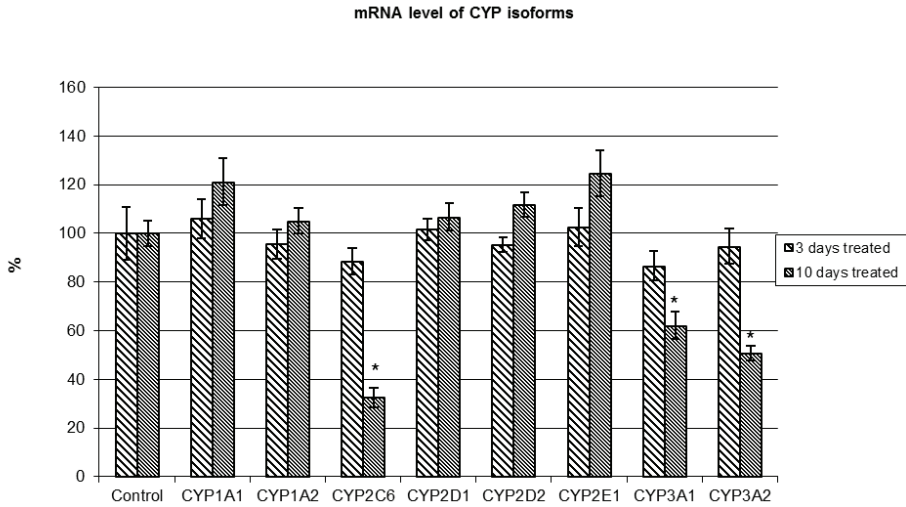


Figure 2.

The influence of *Camellia sinensis* (300 mg/kg) on expression level of CYP genes in the rat liver after 3 and 10 days of treatment. The control group was defined as 100%. Data were presented as mean \pm SEM of 10 rats in each group. * $p < 0.05$ as compared with the control group.

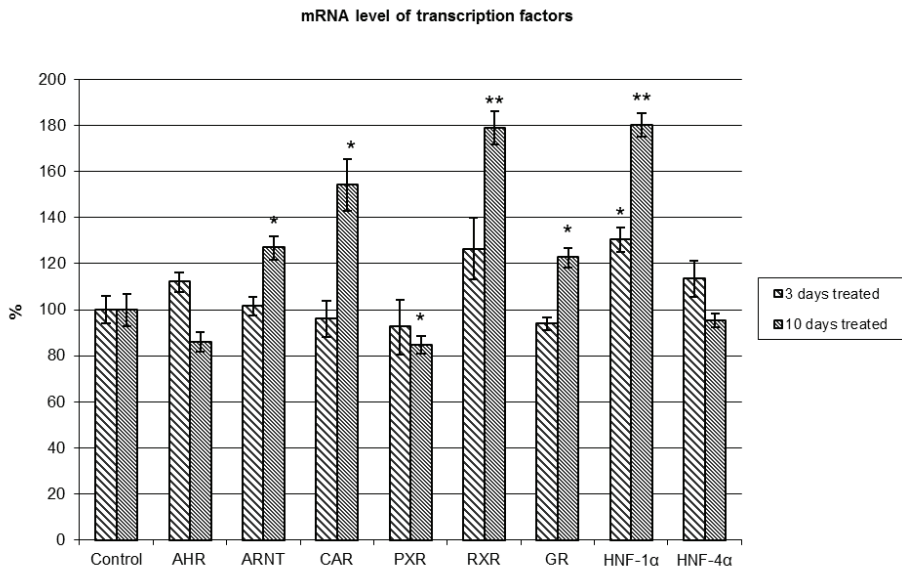


Figure 3.

The effect of *Camellia sinensis* (300 mg/kg) on expression level of CYP transcription factors in the rat liver after 3 and 10 days of treatment. The control group were defined as 100%. Data were presented as mean \pm SEM of 10 rats in each group. * $p < 0.05$; ** $p < 0.001$ as compared with control group.

The significant increase in the mRNA level of CAR, RXR and GR factors was observed by 54% ($p < 0.05$), 79% ($p < 0.001$) and 23% ($p < 0.05$), respectively after 10 days of the extract administration (fig. 3). In addition, an enhanced expression of RXR we observed in a shorter period of GTE administration by more than 26%, as compared to the control group. On the other hand, described result was not statistically significant. At the same time there was a slight decrease in the amount of cDNA PXR by 15% ($p < 0.05$) only in the long-term administration. In this study we observed an increase in amount of ARNT gene transcript by 27% ($p < 0.05$) in the long-term use. However, green tea extract showed the ability to stimulate HNF-1 α both after 3 and 10 days of treatment by 30% ($p < 0.05$) and 80% ($p < 0.001$), respectively. In contrast, no change was observed in the concentration of HNF-4 α cDNA.

DISCUSSION

Many *in vitro* studies have reported that catechins are attributed to protective effects against degenerative diseases [14-16]. However, it is difficult to extrapolate these findings to *in vivo* situations. Since the concentrations of catechins used in *in vitro* studies are often higher than these found in animal or human plasma [17-18]. Green tea is a rich source of catechins and may participate in clinically significant interactions with drugs by modulation of CYP activity. Hence, in pharmacological studies there is an urgent need to understand the molecular mechanism of interactions between herbal medicines and synthetic drugs. Furthermore, several studies have reported that one of the biochemical mechanism responsible for cancer prevention is the modulation of CYP enzyme activities in the detoxification of carcinogens and other xenobiotics by green tea catechins [19-20], because the potent chemopreventive effects may partially explain the presence of enzymes inhibition, such as CYP1A1, CYP1A2 and CYP3A4 involved in carcinogens activation.

In the present study, the influence of a standardized green tea extract containing 61% catechins and small quantities of caffeine on the mRNA transcription level of the major CYP enzymes and their several transcription factors were demonstrated. Our results indicated that GTE caused significant decrease of rat CYP2C6 (homologue to human CYP2C9) expression level after long application. Similar effect was observed for CYP3A1 (human CYP3A4) and CYP3A2 (human CYP3A5) since this extract resulted in the decrease of their mRNA expression but in a lesser degree compared to CYP2C6 transcription level. Hence, the inhibition of the above enzymes can result in a decreased metabolism of used drugs and may lead to clinical consequences, especially in case of synthetic drugs with a low therapeutic index. Hence, decrease of CYP activities may result in a rise in plasma drug levels leading to an undesirable pharmacological effect and the appearance of toxic symptoms of overdose. Similarly, the analysis of Mikasa et al. [21] demonstrated that EGCG moderately inhibits CYP3A in a noncompetitive manner. These results and our observations may suggest that green tea catechins can cause

clinical interactions with substrates of CYP3A. Our observations support the suggestions received by Misaka et al. [22] concerning the inhibitory effect of GTE on CYP3A enzyme activity and metabolism of simvastatin in rat. On the other hand, the molecular mechanism of GTE action is not fully understood. In this study, it was observed an increase in quantities of selected transcription factors described CYPs in the longer term of use including CAR, RXR and GR.

According to Nishikawa et al. [23], it was observed that administration of GTE may inhibit of the CYP2C9, CYP2D6 and CYP3A4 activities in human liver microsomes. Similar effect to CYP3A4 was also shown in *in vivo* study in case of applications of catechins derived from green tea [24]. The available data suggest that catechins, such as EGCG and ECG may be responsible for the inhibitory effect of GTE on CYP activities *in vitro* [25]. Another research by Donovan et al. [26] reported that decaffeinated green tea extract (DGT-844mg/d of catechins, 14 days) do not alter CYP2D6 or CYP3A4 activities in healthy individuals. These findings indicated that GTE does not influence on the metabolism of clinically used drugs dependent on the CYP2D6 or CYP3A4 enzymes. A clinical study conducted on 42 healthy volunteers also showed that green tea catechin (800 mg/d of EGCG, 4 weeks) administration had no effects on CYP1A, CYP2D6 and CYP2C9 activities, whereas the CYP3A4 activity was insignificantly reduced [27]. Therefore, it is postulated that the isolated substance may act in a different manner than whole extract. In view of the fact that EGCG as an active compound, might interact synergistically or additively with the other catechins present in green tea.

In contrast to our findings, another *in vivo* investigation demonstrated that subchronic ingestion of GTE (400 mg/kg, 7 days) caused the induction of CYP3A in rat liver as well as a reduction of CYP3A activity to 70% in intestinal microsomes. However, no significant change in CYP3A activity was observed by a single administration of GTE (400 mg/kg) [28]. Therefore, based on the presented studies, it may be claimed that the data regarding the CYP enzyme activities are discordant and it can result from other phytochemical profile of these extracts as well as period of their long-term administration.

In our study, there was also noted insignificant increase of rat CYP1A1 (homologue to human CYP1A1) expression after long application of GTE extract. This change occurred with increased expression of ARNT factor involved in the induction pathway of CYP1A enzymes. Furthermore, lack of green tea extract effect was observed for rat CYP1A2 and CYP2D1/2 that correspond to the human CYP1A2 and CYP2D6, respectively. In addition, this study suggests that GTE does not make big effect on CYP2E1 expression. According to Maliakal and Wanwimolruk [29], *in vivo* study demonstrated that green tea extract (0.1%; 4 weeks) administration caused no alterations of CYP2D and CYP3A activities in rat liver microsomes. The conclusions derived from *in vitro* studies often provide incomplete and contradictory information about the effect of GTE on CYP1A and CYP2E1. The results of this study indicate that the modulation of the expression of CYP1A is not a result of action of individual catechins present in the GTE but is the effect of

complex action of all the components. It can be concluded that green tea extract contains low levels of AhR agonists or agonists with low affinity [30]. Preclinical studies suggest that green tea catechins and polyphenols can modulate the activity of CYP450 enzymes as observed in the case of its long-term consumption, which caused an increase of CYP1A1 and CYP1A2 activities but not CYP2B1 and CYP2E1 [31]. Maliakal et al. [20] also demonstrated a significant increase of CYP1A1 and CYP1A2 activities in rats after green tea (2%, 4 weeks) administration. Therefore, it was claimed that it is difficult to explain a beneficial effect of green tea against carcinogens involving modulation of this metabolic pathway. Clinically, the use of epigallocatechin gallate EGCG for 4 weeks did not alter the activity of CYP1A2 [27]. Generally, the induction of CYP1A1 and CYP1A2 activities in preclinical studies could be attributed to caffeine contained in the green tea that is a potent inducer of CYP1A2 [32, 33]. However, it is debatable due to the few literature data. Thus, the lack of effect on CYP1A expression level observed in our study may be explained by GTE administration containing the vestigial amount of caffeine. Moreover, several studies postulate that protection against cancers may be due to the inhibition of CYP1A activity by green tea catechins. Because the inhibition of CYP1A1 and CYP1A2 enzymes may decrease a risk of carcinogenicity by deactivation of some compounds to their carcinogenic metabolites. In addition, it is important to mention that the effect of green tea extracts on the level of human CYP1A expression can also result from the action of a complex mixture than individual tea catechins [30]. As suggested Nikaidou et al. [34], the green tea extract contains both agonists and antagonists AhR factor, wherein the epigallocatechin gallate is considered as a potential inhibitor of the receptor. There is a theory according to which EGCG does not bind to the active site but AhR interact directly with the Hsp90 chaperone protein, which causes conformational change of AhR migrating to the nucleus but lacking the ability to bind DNA [35]. It was demonstrated that the chronic administration of a 2.5% solution (4 weeks) of green tea ad libitum increases the activity of CYP1A1 in rat liver microsomes after incubation with a specific substrate. Simultaneously there was no change in the activity of CYP1A2 which would be consistent with the result obtained in our study at the mRNA level [28]. Furthermore, in the fully differentiated hepatocytes the constitutive activity of P450 proteins may also be regulated by transcription factors such as C/EBP, HNF4, HNF-1 α , HNF3 and HNF6 [36]. The effect of transcriptional activation of CYP1A2 may be the result of HNF1 action, although HNF4 stimulates the expression of CYP2C9 [37, 38]. Moreover, it was also showed that the factor HNF1 α activates the CYP2E1 gene expression in rat hepatocytes [39]. The effect of GTE on the expression of these factors remained unknown so far. We describe the first results indicating the inductive action of green tea extract on the HNF-1 and no change in HNF-4. Due to the wide participation of hepatocyte nuclear factors in a number of physiological functions their transcription changes are very important.

In summary, observations from individual clinical trials show no effect of green tea extract administered in capsules containing a daily dose $4 \times 211 \pm 25$ mg of

catechins and less than 1 mg of caffeine for 14 days on CYP2D6 and CYP3A4 (Donovan et al., 2004). There were no changes on CYP1A2 activity under the influence of GTE containing 80% - 98% of catechins, mainly epigallocatechin gallate (EGCG) 50% -75% after 4 weeks at a dose of 800 mg EGCG [26]. Consequently, it can be considered that the repeated use of the green tea catechins, mainly to support the weight loss, at the doses described in the studies does not usually lead to significant changes in the metabolism of substrates for tested isoforms. But it should be noted that there is little research on the safety of GTE use in the context of a herb-drug interactions. Further research on the GTE are aimed to determine the safe daily dose this beverage for human in the context of potential interactions at the stage of biotransformation reactions.

CONCLUSIONS

We showed that standardized GTE with a small amount of caffeine may decrease statistically significant mRNA level of rat hepatic CYP3A1, CYP3A2 and CYP2C6. In this regard, the results suggest that green tea extracts may cause *in vivo* the inhibition of CYP3A4, CYP3A5 and CYP2C9 in human liver and may participate in clinically significant interactions with drugs metabolized by these enzymes leading to their toxicity or lack of efficacy. Moreover, the lack of GTE effect on CYP1A transcription level may be explained by the presence of small quantities of caffeine that is a potent inducer of CYP1A2. However, it is necessary to underline that data regarding the effect of green tea and its compounds on CYP activity are not as well characterized. Hence, further *in vivo* studies are needed to evaluate the potential influence of green tea on CYP450 because the changes of the enzyme activity could be helpful in determining the risk of interactions with synthetic drugs and the development of chemical carcinogenesis.

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WPŁYW EKSTRAKTU Z *CAMELLIA SINENSIS* NA POZIOM EKSPRESJI CZYNNIKÓW TRANSKRYPCYJNYCH I GENÓW CYTOCHROMU P450 KODUJĄCYCH ENZYMY I FAZY METABOLIZMU LEKÓW

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Streszczenie

Zielona herbata (*Camellia sinensis*) jest powszechnie stosowana jako napój i suplement diety i może istotnie zmniejszać ryzyko wystąpienia wielu chorób. Pomimo powszechnego

zastosowania zielonej herbaty, dane dotyczące bezpieczeństwa jak i interakcji preparatu roślinnego i leku syntetycznego są bardzo ograniczone. Celem badania była ocena wpływu standaryzowanego ekstraktu z zielonej herbaty (GTE) zawierającego 61% katechin i 0,1% kofeiny na poziom ekspresji szczyrczych genów CYP i czynników transkrypcyjnych stosując technikę real-time PCR. Wyniki wykazały, że GTE znacznie obniża poziom ekspresji CYP2C6 o 68% ($p < 0,001$). W przypadku CYP3A1 i CYP3A2 poziom mRNA tych genów był również zredukowany przez ekstrakt, ale w mniejszym stopniu w porównaniu do CYP2C6. Istotny wzrost w poziomie mRNA obserwowano dla czynników CAR, RXR i GR odpowiednio o 54% ($p < 0,05$), 79% ($p < 0,001$) i 23% ($p < 0,05$) po 10 dniach stosowania ekstraktu. Dodatkowo, zanotowano niewielki wzrost poziomu ekspresji CYP1A1 o 21% ($p > 0,05$). Brak istotnych różnic zaobserwowano dla CYP1A2 i CYP2D1/2. W badaniu wykazano również wzrost ilości transkryptu genu ARNT o 27% ($p < 0,05$) podczas dłuższego stosowania. Ponadto, ekstrakt z zielonej herbaty wykazał zdolność do stymulacji HNF-1 α zarówno po 3, jak i 10 dniach trwania eksperymentu odpowiednio o 30% ($p < 0,05$) i 80% ($p < 0,001$). Brak zmian obserwowano w przypadku stężenia cDNA dla HNF-4 α . Wyniki te sugerują, że GTE może zmieniać ekspresję enzymów CYP, szczególnie w przypadku CYP2C6 (homolog ludzki CYP2C9) i może uczestniczyć w klinicznie istotnych reakcjach z lekami metabolizowanymi przez te enzymy.

Słowa kluczowe: *enzymy CYP, Camellia sinensis, indukcja, inhibicja, poziom ekspresji*