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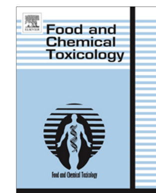

Effect of commercially available green and black tea beverages on drug-metabolizing enzymes and oxidative stress in Wistar rats

Hsien-Tsung Yao [a,*], Ya-Ru Hsu [a], Chong-Kuei Lii [a,b], Ai-shen Lin [a], Keng-Hao Chang [a], Hui-Ting Yang [a,*]

[a] Department of Nutrition, China Medical University, 91, Hsueh-shih Road, Taichung 404, Taiwan
[b] Department of Health and Nutrition Biotechnology, Asia University, 500, Lioufeng Road, Wufeng, Taichung 413, Taiwan

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ABSTRACT

The effect of commercially available green tea (GT) and black tea (BT) drinks on drugmetabolizing enzymes (DME) and oxidative stress in rats was investigated. Male Wistar rats were fed a laboratory chow diet and GT or BT drink for 5 weeks. Control rats received de-ionized water instead of the tea drinks. Rats received the GT and BT drinks treatment for 5 weeks showed a significant increase in hepatic microsomal cytochrome P450 (CYP) 1A1 and CYP1A2, and a significant decrease in CYP2C, CYP2E1 and CYP3A enzyme activities. Results of immunoblot analyses of enzyme protein contents showed the same trend with enzyme activity. Significant increase in UDP-glucuronosyltransferase activity and reduced glutathione content in liver and lungs were observed in rats treated with both tea drinks. A lower lipid peroxide level in lungs was observed in rats treated with GT drink. Electrophoretic mobility shift assay revealed that both tea drinks decreased pregnane X receptor binding to DNA and increased nuclear factor-erythroid 2 p45-related factor 2 binding to DNA. These results suggest that feeding of both tea drinks to rats modulated DME activities and reduced oxidative stress in liver and lungs. GT drink is more effective on reducing oxidative stress than BT drink.

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1. Introduction

Cytochrome P450 (CYP) enzymes are the most important Phase I drug-metabolizing enzymes (DMEs) and are responsible for catalyzing the oxidative biotransformation of many drugs, xenobiotics, and endogenous compounds. Phase II enzymes catalyze the conjugation of glucuronate, glutathione, sulfate, or glycine to foreign molecules (Rendic, 2002) to facilitate the elimination of electrophiles and reactive oxygen species (ROS) generated by Phase I enzyme reactions, thereby protecting organisms against chemical insult (Krajka-Kuz' niak, 2007; Kondraganti et al., 2008). Induction of Phase II enzymes, such as glutathione S-transferase (GST), UDP-glucuronosyltransferase (UGT), and NADPH:quinone oxidoreductase 1 (NQO1), and reduction of ROS is most pronounced in the prevention of chemical-induced tissue injuries and carcinogenesis (Krajka-Kuz' niak, 2007). CYP and Phase II enzymes have been shown to be modulated by complex mixtures of phytochemicals in fruits and vegetables (Rodríguez-Fragoso et al., 2011). Induction or inhibition of DMEs may change the pharmacological activities and toxicities of drugs and carcinogens and may also cause drug interactions (Rodríguez-Fragoso et al., 2011).

A number of nuclear receptors, including pregnane X receptor (PXR), constitutive androstane receptor, peroxisome proliferator-activated receptor, retinoid X receptor, and aryl hydrocarbon receptor (AhR), and transcription factors, including nuclear factor-erythroid 2 p45-related factor 2 (Nrf2), have been demonstrated to play important roles in the transcription of Phase I and II enzymes and Phase III transporter genes (Xu et al., 2005). For example, AhR transcriptionally induces the expression of human CYP1A1, CYP1A2, and CYP1B1 (Beischlag et al., 2008). AhR can be induced by chemicals such as 2′,3′,7′,8′-tetrachlorodibenzo-p-dioxin (TCDD) (Budinsky et al., 2010). Studies have also indicated

Abbreviations: AhR, aryl hydrocarbon receptor; ARE, antioxidant response element; BT, black tea; CYP, cytochrome P450; DME, drug-metabolizing enzymes; DR4, direct repeat with 4 bp spacer; DRE, dioxin response elements; GT, green tea beverage; EC, epicatechin; EGC, epigallocatechin; EGCG, epigallocatechin gallate; GCG, gallocatechin gallate; GA, gallic acid; GT, green tea; GST, glutathione-S-transferase; NQO1, NADPH:quinone oxidoreductase 1; Nrf2, nuclear factor erythroid 2-related factor 2; PXR, pregnane X receptor; UGT, UDP-glucuronosyltransferase; GCLc/m, glutamate cysteine ligase catalytic and modifier subunits; GSH, reduced glutathione; GSSG, oxidized glutathione; MRP2, multidrug resistance-associated protein 2; OATP1a1, organic anion transporting protein 1a1; ROS, reactive oxygen species; SDS, 1-chloro-2,4-dinitrobenzene, sodium dodecylsulfate.

* Corresponding authors. Tel.: +886 4 22053366x7526; fax: +886 4 22062891 (H.-T. Yao). Tel.: +886 4 22053366x7525; fax: +886 4 22062891 (H.-T. Yang).

E-mail addresses: htyao@mail.cmu.edu.tw (H.-T. Yao), lulu0319@mail.cmu.edu.tw (H.-T. Yang).

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that CYP3A as well as CYP2C are regulated by PXR (Pascussi et al., 2000; Rana et al., 2010). Nrf2 is a transcription factor that is activated in response to electrophiles and oxidative stress that is involved in the transcription of some Phase II enzymes, such as GST and UGT (Aleksunes and Manautou, 2007; Saracino and Lampe, 2007) and glutamate cysteine ligase (GCL), the rate-limiting step in the formation of the cellular antioxidant glutathione (GSH) (Huang et al., 2013).

Green tea (GT) and black tea (BT) have been reported to act as chemoprevention agents by modulating both Phase I CYP and Phase II conjugating enzymes (Yang and Pan, 2012; Murugan et al., 2008). Previous studies have indicated that the polyphenols in GT and BT induce the activation of Nrf2 (Mann et al., 2007; Patel and Maru, 2008; Han et al., 2012) and inhibit AhR-regulated genes (e.g., CYP1A1) and the binding of toxic chemicals to the AhR (Fukuda et al., 2004, 2005; Han et al., 2012). Rats treated with GT or BT extracts have been reported to have increased hepatic CYP1A2 and UGT activities (Bu-Abbas et al., 1997; Nikaidou et al., 2005). However, GT was also reported to have no effect on hepatic CYP1A2 and CYP3A activities in rats (Niwattisaiwong et al., 2004). Inhibition of CYP3A and 2E1 in liver by GT catechins has also been reported in mice (Chen et al., 2009). Furthermore, an increase of GST and NQO1 activities in both liver and lungs was observed in mice treated with BT polyphenols (Patel and Maru, 2008). On the other hand, mice that were treated with decaffeinated GT and BT extracts were found to have lower CYP enzyme activities in the lungs than control mice (Shi et al., 1994). These results indicate that the effects of tea or tea extracts on DMEs in tissues differ depending on the experimental conditions. Although the effects of various tea components on the regulation of DMEs are not consistent, these results do indicate that GT and BT consumption may play an important role in modulating DMEs and redox status.

Recently, commercially available tea beverages have become more popular worldwide. Sugar is supplemented to various tea beverages to reduce the bitterness of taste and to provide an energy source. To date, little or no data on the effects of sugar-containing tea beverages on DMEs and oxidative stress have been reported. In this study, therefore, the effects of consumption of commercially available GT and BT on DMEs and oxidative stress in rats were investigated. The possible regulation of PXR, AhR, and Nrf2 in liver by the GT and BT was also evaluated.

2. Materials and methods

2.1. Tea beverages

GT and BT (Manufactured by Uni-President Enterprises Corp, Taiwan) were obtained commercially. The concentrations of ascorbate, caffeine, gallic acid, and catechins in the tea beverages were determined by a high-performance liquid chromatography (HPLC) method reported previously (Wu et al., 2011). The sucrose concentration in the tea beverages was determined with a commercial assay kit (Megazyme, Bray, Ireland). Two consecutive batches of beverages were used for this experiment. The concentrations of the major constituents in the tea beverages are shown in Table 1.

2.2. Chemicals

Epicatechin (EC), epigallocatechin (EGC), epigallocatechin-gallate (EGCG), epicatechin-gallate (ECG), gallocatechin gallate (GCG), gallic acid (GA), caffeine, formic acid, ammonium acetate, testosterone, ethoxyresorufin, methoxyresorufin, pentoxyresorufin, resorufin, *p*-nitrophenol, 4-nitrocatechol, NADPH, glutathione, glutathione reductase, 1-chloro-2,4-dinitrobenzene, sodium dodecylsulfate (SDS), cytochrome c, heparin, Ponceau S, phenacetin, diclofenac (sodium salt), chlorzoxazone, 1,1,3,3-tetraethoxypropan, thiobarbituric acid, and pyrogallol were obtained from Sigma (St. Louis, MO, USA). 4-Hydroxydiclofenac, 6-hydroxychlorzoxazone, midazolam, 6-β-hydroxytestosterone, and 1-hydroxymidazolam were purchased from Ultrafine Chemicals (Manchester, UK). All other chemicals and reagents were of analytical grade and were obtained commercially.

Table 1
Constituents of green tea (GT) and black tea (BT) beverages.[a]

	Amount (μg/ml)	
	GT	BT
Gallic acid (GA)	3.2	24.6
Epigallocatechin (EGC)	201.9	25.0
Epigallocatechin gallate (EGCG)	271.5	59.1
Epicatechin (EC)	29.2	2.6
Epicatechin gallate (ECG)	32.6	3.7
Gallocatechin gallate (GCG)	49	1.8
Total catechins[b]	587.4	116.8
Caffeine	179.7	208.3
Ascorbic acid	21.1	6.0
Total phenolics[c] (gallic acid Eq/mL)	576.6	323.2
Sucrose (g/L)	65.5	70.2

[a] Two bottles of tea from the same batch were pooled and the constituents were then determined in triplicate. Values are expressed as the mean of two batches of tea beverages.
[b] Total catechins = EGC + EGC + ECG + EGCG + GCG.
[c] The total phenol content of the tea beverages is expressed as μg of gallic acid equiv/mL of tea.

2.3. Animals and treatments

Eighteen male Wistar rats, weighing approximately 150 g (4 weeks old) each, were obtained from BioLASCO, Taiwan (Ilan, Taiwan). During the adaptation period, the rats were fed a pelleted diet for 1 week. Then the animals were randomly divided into three groups with six rats in each group. The animals in the control group were given a standard pelleted diet with tap water. The animals in the other two groups were given the same diet with GT or BT. The tea beverages were the sole source of drinking fluid in the tea groups. All drinking fluid was given to rats in plastic bottles, which were replaced daily with fresh water or tea.

Rats were housed in individual plastic cages in a room kept at 23 ± 1 °C and 60 ± 5% relative humidity with a 12-h light and dark cycle. Food and drinking fluid were available *ad libitum* for 5 weeks. Body weight and food intake were determined every week. This study was approved by the Animal Center Management Committee of China Medical University. The animals were maintained in accordance with the guidelines for the care and use of laboratory animals as issued by the Animal Center of the National Science Council, Taiwan.

2.4. Collection of blood and tissue samples

At the end of the 5-week feeding period, animals were fasted overnight (12 h) before being killed by exsanguination via the abdominal aorta while under carbon dioxide (70%/30%, CO_2/O_2) anesthesia. Heparin was used as the anticoagulant. Plasma was separated from the blood by centrifugation (1750*g*) at 4 °C for 20 min and stored at −20 °C. Plasma alanine aminotransferase was determined by using a commercial kit (Randox Laboratories, Antrum, UK) within 2 weeks. The liver and lungs from each animal were excised, weighed, and stored at −80 °C.

2.5. Determination of DME activities

The frozen livers and lungs were thawed and the same portion of each liver or lung sample was used to prepare microsomes. Each gram of liver or lung was then homogenized with 4 mL of ice-cold 0.1 M phosphate buffer (pH 7.4) containing 1 mM EDTA. The homogenates were centrifuged at 10,000*g* for 15 min at 4 °C. The supernatant was then re-centrifuged at 105,000*g* for 1 h at 4 °C. The resulting microsomal pellet was suspended in 0.25 M sucrose solution containing 1 mM EDTA and was stored at −80 °C until use.

The microsomal protein concentration was determined by using a BCA protein assay kit (Pierce, Rockford, IL). The contents of total CYP and cytochrome b5 in the microsomes were quantified according to the method of Omura and Sato (1964). NADPH-CYP reductase activity was measured according to the procedure of Phillips and Langdon (1962) by using cytochrome c as the substrate. A number of substrates were used to determine the activity of each specific CYP enzyme as reported previously (Yao et al., 2011). Ethoxyresorufin (2 μM), methoxyresorufin (5 μM), and pentoxyresorufin (5 μM) were respectively used as the probe substrates for ethoxyresorufin *O*-deethylation (CYP1A1), methoxyresorufin *O*-demethylation (CYP1A2), and pentoxyresorufin *O*-depentylation (CYP2B). Diclofenac (4 μM), dextromethorphen (5 μM), *p*-nitrophenol (50 μM), testosterone (60 μM), midazolam (2.5 μM), and lauric acid (100 μM) were respectively used as the probe substrates for diclofenac 4-hydroxylation (CYP2C), dextromethorphen *O*-demethylation (CYP2D), *p*-nitrophenol 6-hydroxylation (CYP2E1), testosterone 6β-hydroxylation (CYP3A), midazolam 1-hydroxylation (CYP3A), and lauric acid 12-hydroxylation (CYP4A). Microsomal proteins (0.2 mg/mL) and the incubation time (15 min) were the same for all metabolic reactions except for the midazolam 1-hydroxylation (CYP3A) reaction, which was incubated for 5 min. The metabolites

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