

Carbonated soft drinks alter hepatic cytochrome P450 isoform expression in Wistar rats

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Abstract. The aim of the current study was to examine the effects of chronic consumption of soft drinks (SDs) on hepatic oxidative stress and cytochrome P450 enzymes (CYPs) expression in the livers of Wistar rats. For 3 consecutive months, the rats had free access to three different soft drinks, Coca-Cola, Pepsi-Cola and 7-UP. The rats were subsequently compared with control group rats that had consumed water. Blood and hepatic tissue samples were assayed for the changes in antioxidants, liver function biomarkers and hepatic gene expression for different isoforms of hepatic CYP. The results indicated that SD consumption (SDC) decreased serum antioxidant levels and increased malondialdehyde secretion, and increased liver biomarkers (glutamate pyruvate transaminase and glutamate oxaloacetate). SD induced alterations in mRNA expression of hepatic antioxidants and cytochrome isoforms. The expression of peroxidase, catalase, CYP1A2, CYP3A2 and CYP2C11 in the liver were upregulated following SDC. By contrast, CYP2B1 was downregulated after 3 months of SDC in liver tissue samples. Thus, the present findings indicate that SDs induced oxidative stress in the liver of Wistar rats and for the first time, to the best of our knowledge, indicate that SDC disrupts hepatic CYP enzymes that may affect drug metabolism. Therefore, drug-dosing programs should be carefully designed to take these novel findings into consideration for the treatment of diseases.

Introduction

During the last 30 years, consumption of soft drinks (SDs) has increased worldwide (1). SDs predominantly contain

water, phosphoric acid, caffeine, sugar as a sweetener and other preservatives, colorings, as well as flavors (2). The increase in consumption of SDs is not good for health and is concerning (2-4), as SDs contain high levels of caffeine, which cause addiction as it is rapidly absorbed from the intestine (5). A correlation between SDs and incidence of certain diseases, such as obesity, diabetes mellitus and cardiovascular disease has been confirmed (6-8). In addition, it has been shown that Coca-Cola consumption delayed elimination of methotrexate and, therefore, is a predisposing factor for acute renal failure (9).

Cytochrome P450 enzymes (CYPs) are capable of catalyzing the oxidative biotransformation of the majority of therapeutic agents and other lipophilic xenobiotics, therefore, they are particularly relevant for clinical pharmacology (10). Drug and metabolite clearance depends on CYP enzyme activities; their inhibition leads to drug-drug interaction and toxicity (11), while their induction increases drug and elimination (12). A large number of factors, such as components of food cause CYP modulation in rats (13). Therefore, SD consumption (SDC) may affect CYP profiles, and induce oxidative and hepatic stress.

A positive association between caffeine and coffee consumption and ovarian cancer was suggested to be modified by the CYP1A2 genotype and associated with consumption of certain foods (14). In Saudi Arabia and the Middle East, consumption of SDC (three times per day) with meals (15) is common. Therefore, the current study was conducted to examine the effect of chronic SDC on serum oxidative stress biomarkers and alteration in hepatic enzyme activity. Furthermore, mRNA expression of hepatic antioxidants [catalase and glutathione peroxidase (GSH-Px)] and hepatic CYP isoforms (CYP1A2, CYP3A2, CYP2B1 and CYP2C11) were examined.

Materials and methods

Chemicals, materials and kits. Ethidium bromide for agarose preparation and Tris-Borate-EDTA buffer were purchased from Sigma-Aldrich (St. Louis, MO, USA) and agarose was purchased from Bio Basic Int. (Markham, ON, Canada). The

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Table I. PCR conditions for examined genes in the liver.

Name	Sense 5'-3'	Anti-sense 5'-3'	Annealing temperature	Product size (bp)
β-actin	ATGTACGTAGCCATCCAGGC	TCCACACAGAGTACTTGCGC	56°C	628
CYP1A2	GCAGGTCAACCATGATGAGAA	CGGCCGATGTCTCGGCCATCT	56°C	334
CYP2C11	TGCCCTTTTACGAGGCT	GGAACAGATGACTCTGAATTCT	55°C	368
CYP3A2	TTGATCCGTTGTTCTTGTC	GGCCAGGAAATACAAGCAA	52°C	342
CYP2B1	TCTCACTCAACACTACGTTT	CTGGGAAAGGATCCAAGCCTGGG	58°C	450
Catalase	ACGAGATGGCACACTTTGACAG	TGGGTTTCTCTTCTGGCTATGG	55°C	341
Glutathione peroxidase	AAGGTGCTGCTCATTGAG AATG	CGTCTGGACCTACCAGGAAGTT	57°C	406

CYP, cytochrome P450; PCR, polymerase chain reaction.

Table II. Serum changes in MDA, and tissue levels of GSH-Px and catalase levels in the liver of rats after chronic consumption of soft drinks.

Group	MDA (nmol/g protein)	GSH-Px (U/g protein)	Catalase (U/g protein)
Control	32.7±2.7	52.1±4.8	31.7±1.9
Coca-Cola	63.7±7.6 ^a	41.9±4.2 ^a	18.6±1.1 ^a
Pepsi-Cola	96.7±9.8 ^a	38.3±4.8 ^a	22.3±2.1 ^a
7-UP	59.1±3.7 ^a	36.3±2.9 ^a	17.5±1.9 ^a

Values are presented as means ± standard error of the mean for three independent experiments per treatment. ^aP<0.05 vs. control. MDA, malondialdehyde; GSH-Px, glutathione peroxidase.

Wistar rats (n=40) were purchased from King Abdel-Aziz University, King Fahd Center for Scientific Research (Jeddah, Saudi Arabia). The malondialdehyde (MDA), glutathione peroxidase (GSH-Px) and catalase kits were purchased from Bio-Diagnostic Co., (Giza, Egypt). Coca-Cola (The World of Coca-Cola, Atlanta, GA, USA), Pepsi-Cola (Pepsi Co, Purchase, NY, USA) and 7-UP (Dr Pepper Snapple Group, Inc., Plano, TX, USA) were used and were purchased from Ta'if markets in Saudi Arabia. The DNA 100-bp ladder was purchased from MBI Fermentas (Thermo Fisher Scientific, Inc., Waltham, MA, USA). Oligo dT primer and dNTPs were obtained from SibEnzyme Ltd. (Novosibirsk, Russia). Qiazol reagent (for RNA extraction) was bought from Qiagen, Inc. (Valencia, CA, USA).

Experimental animals, design and sampling. The current study was approved by the Ethics Committee of the College of Applied Medical Sciences, Ta'if University (Turabah, Saudi Arabia; project no. 3792/34/1). Forty male Wistar rats (age, 12 weeks), weighing 200–280 g were allocated into four groups. The rats were handled every day at 9:00 a.m., and kept under observation for 1 week for complete acclimatization. Rats were housed at 20±50°C under a 12-h light/dark cycle and received free access to food and water for the first week. Next, the rats were divided into four groups as follows: Control group, no treatment; Coca-Cola group (group 2); Pepsi-Cola (group 3) and 7-UP group (group 4). Rats in

groups 2–4 received SD *ad libitum* for 3 consecutive months. After 3 months of SDC, all rats were anesthetized by inhalation of diethyl ether. Blood (~5 ml) and small samples (50 mg) of liver tissues were collected from the anesthetized rats into sterilized vacutainer tubes. Serum was extracted following centrifugation of the clotted blood for 15 min at 3,000 x g at 40°C, and maintained at -20°C until biochemical measurements were obtained. For mRNA expression of hepatic genes, liver samples were maintained at -80°C in QIAzol reagent for RNA extraction.

Serum biochemical assays. MDA, GSH-Px, and catalase were assayed spectrophotometrically using the available commercial ELISA kits, and glutamate pyruvate transaminase (GPT) and glutamate oxaloacetate (GOT) were assayed spectrophotometrically using commercial kits (all kits were purchased from Bio-Diagnostic, Co.). Methods were performed according to the manufacturer's instructions.

cDNA preparation, synthesis and gene expression analysis. Total RNA was extracted from tissue samples as previously described (16). The integrity of RNA was visualized and confirmed after running in denaturated agarose gel (1.5%), then stained with ethidium bromide. Oligo dT primer (0.5 ng) was added to 2 µg total RNA to induce denaturation and was then used for cDNA synthesis (16). For semi-quantitative gene expression analysis, specific primers were designed for genes

(Table I) using the Oligo-4 computer program by (Macrogen Co., Seoul, South Korea). Semi-quantitative polymerase chain reaction (PCR) was conducted in a total volume of 25 μ l as previously described (15). Using a Bio-Rad T100™ Thermal Cycle machine, PCR was performed with the following cycling conditions: 95°C for 4 min (1 cycle), followed by 27 cycles (to achieve optimal gene expression), each consisting of denaturation at 95°C for 60 sec, annealing as presented in Table I for 60 sec and extension at 72°C for 60 sec, with an additional final extension at 72°C for 10 min. Glyceraldehyde-3-phosphate dehydrogenase expression served as an internal standard and as a reference. The PCR products were electrophoresed at 100 V for 30 min after running in 1.5% agarose gel and stained with ethidium bromide in Tris-Borate-EDTA buffer. The PCR products were visualized using the InGenius 3.0 gel documentation system (Syngene, Frederick, MD, USA) and under ultraviolet light. The densitometric analysis for PCR bands was performed using ImageJ software version 1.47 (<http://imagej.en.softonic.com/>).

Statistical analysis. Data are presented as the mean \pm standard error of the mean. One-way analysis of variance (ANOVA) was used to analyze data together with post hoc descriptive tests using SPSS software version 11.5 (SPSS, Inc., Chicago, IL, USA). $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Carbonated soft drinks alter serum levels of MDA, GSH-Px, catalase and hepatic biomarkers in Wistar rats. SDC for 3 consecutive months disrupted liver activity, as demonstrated by the significant increase in serum levels of MDA ($P < 0.05$; Table II) when compared with control rats. By contrast, antioxidants activity of GSH-Px and catalase were significantly decreased ($P < 0.05$) in the serum of rats in the Coca-Cola, Pepsi-Cola and 7-UP groups when compared with the control rats (Table II). As shown in Table III, Coca-Cola and Pepsi-Cola consumption significantly increased the serum levels GPT and GOT ($P < 0.05$; Table III).

Carbonated SDs downregulate catalase and peroxidase mRNA expression in Wistar rats. SDC for 3 months in Wistar rats caused downregulation in mRNA expression of hepatic catalase. The downregulation was more apparent in the Coca-Cola and 7-UP groups compared with the Pepsi-Cola group (Fig. 1A). In addition, mRNA expression of hepatic peroxidase was downregulated in all SDC treated groups. The magnitude was greater in Coca-Cola, followed by Pepsi-Cola then 7-UP (Fig. 1B).

Carbonated SDs affect mRNA expression of hepatic CYP1A2 in Wistar rats. Hepatic CYP1A2 mRNA expression in the liver tissue samples was upregulated significantly ($P < 0.05$) following SDC for 3 months. The upregulation of CYP1A2 mRNA expression was 0.5-, 1- and 1.3-fold in the Coca-Cola, Pepsi-Cola and 7-UP groups, respectively (Fig. 2).

Carbonated SDs alter mRNA expression of hepatic CYP3A2 and CYP2B1 in Wistar rats. SDC for 3 months in Wistar rats

Table III. Serum changes in GPT and GOT levels following chronic consumption of soft drinks.

Group	GPT (U/l)	GOT (U/l)
Control	55.4 \pm 2.8	130.6 \pm 2.6
Coca-Cola	68.6 \pm 3.0 ^a	158.1 \pm 9.5 ^a
Pepsi-Cola	84.9 \pm 3.5 ^b	212.7 \pm 31.4 ^b
7-UP	60.4 \pm 3.7	145.9 \pm 12.1

Values are presented as means \pm standard error of the mean for three independent experiments per treatment. ^a $P < 0.05$ vs. control and ^b $P < 0.05$ vs. Coca-Cola and 7-UP. GPT, glutamate pyruvate transaminase; GOT, glutamate oxaloacetate.

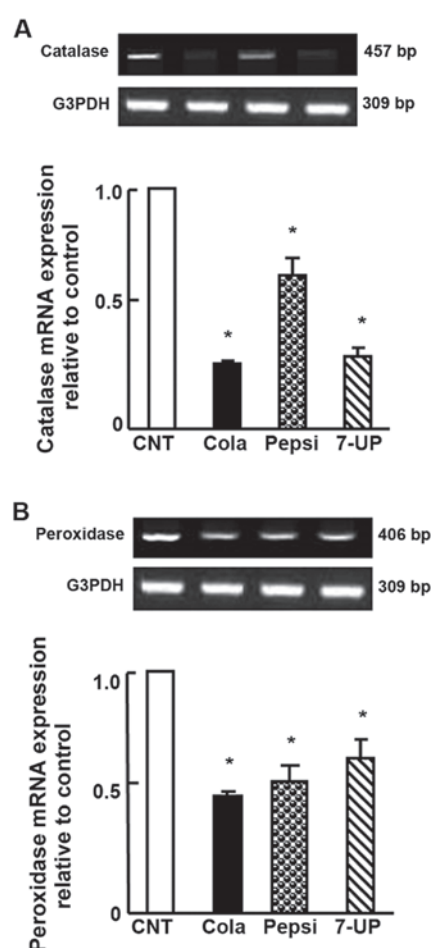


Figure 1. Semi-quantitative reverse transcription-polymerase chain reaction analysis of (A) catalase and (B) glutathione peroxidase in liver tissue samples from Wistar rats following chronic administration of three soft drinks for 3 months. Densitometric analysis was performed for five different rats per group. Values are presented as means \pm standard error of the mean ($n = 5$ rats per group). * $P < 0.05$ vs. CNT. CNT, control; GAPDH, glyceraldehyde-3-phosphate dehydrogenase.

caused upregulation of hepatic CYP3A2 mRNA expression by 1.7-, 3.2- and 2.7-fold in the Coca-Cola, Pepsi-Cola and 7-UP groups, respectively (Fig. 3A). By contrast, SDC for 3 months downregulated hepatic CYP2B1 mRNA expression ($P < 0.05$) when compared with the control. The pattern

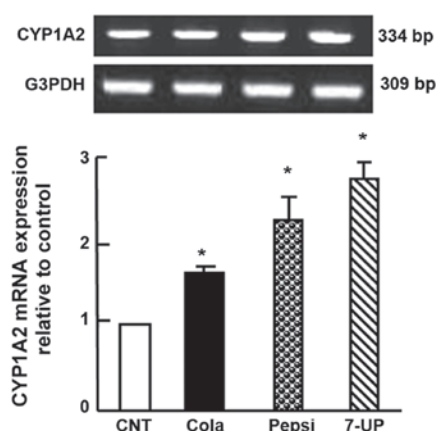


Figure 2. Semi-quantitative reverse transcription-polymerase chain reaction analysis of CYP1A2 in liver tissues after chronic administration of soft drinks for 3 months in Wistar rats. Densitometric analysis was performed for five different rats per group. Values are presented as means \pm standard error of the mean (n=5 rats per group). *P<0.05 vs. CNT group. CYP, cytochrome P450; CNT, control; GAPDH, glyceraldehyde-3-phosphate dehydrogenase.

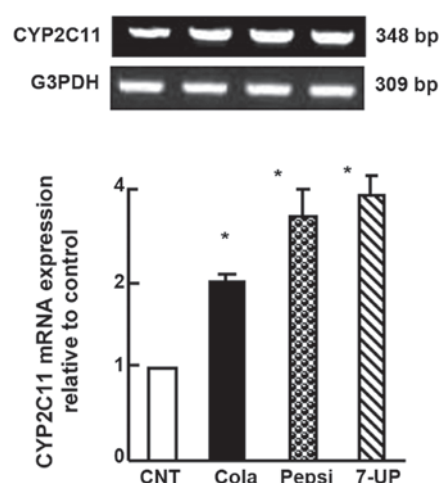


Figure 4. Semi-quantitative reverse transcription-polymerase chain reaction analysis of CYP2C11 in liver tissue samples after chronic administration of soft drinks for 3 months in Wistar rats. Densitometric analysis was performed for five different rats per group. Values are presented as means \pm standard error of the mean (n=5 rats per group). *P<0.05 vs. CNT group. CYP, cytochrome P450; CNT, control; GAPDH, glyceraldehyde-3-phosphate dehydrogenase.

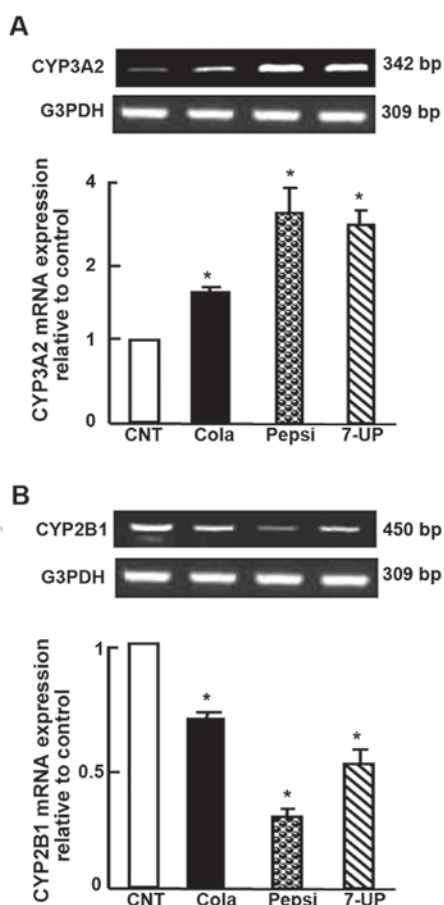


Figure 3. Semi-quantitative reverse transcription-polymerase chain reaction analysis of (A) CYP3A2 and (B) CYP2B1 after chronic administration of soft drinks for 3 months in Wistar rats. Densitometric analysis was performed for five different rats per group. Values are presented as means \pm standard error of the mean (n=5 rats per group). *P<0.05 vs. CNT group. CYP, cytochrome P450; CNT, control; GAPDH, glyceraldehyde-3-phosphate dehydrogenase.

of downregulation was 0.3-, 0.8- and 0.5-fold when compared with the control group for the Coca-Cola, Pepsi-Cola and 7-UP groups, respectively (Fig. 3).

Carbonated SDs affected mRNA expression of hepatic CYP2C11 in Wistar rats. SDC for 3 months in Wistar rats caused upregulation in hepatic CYP2C11 mRNA expression (P<0.05) when compared with control rats. The increase in mRNA expression was 1-, 2- and 2.2-fold for the Coca-Cola, Pepsi-Cola and 7-UP groups, respectively (Fig. 4).

Discussion

In the current study, oxidative stress and alterations in cytochromes expression were demonstrated to be induced in hepatic tissue samples following SDC. The inability of antioxidant defense mechanisms to scavenge excessive levels of reactive oxygen species (ROS) and/or reduction in the basal antioxidant defense mechanisms are the primary causes for oxidative stress in tissues (17). Therefore, degenerative diseases, including hepatopathies are caused by this oxidative stress (17,18). Lipid peroxidation is demonstrated to induce disturbance of membrane function and integrity (19). It is monitored by the increase of serum MDA levels, one of the most commonly used biomarkers for lipid peroxidation (20). Thus, the increased levels of MDA due to consumption of SDs indicate increased lipid peroxidation. Furthermore, it may indicate the potential carcinogenic effect of SDC, as MDA is believed to originate under stress conditions and is highly capable of reacting with multiple biomolecules, such as proteins or DNA that lead to the formation of adducts (21,22). This assumed potential carcinogenic effect of SDC is augmented by the reduction of levels of antioxidant enzymes, GSH-Px and catalase, following SDC. In malignant cells (23) and in primary cancer tissues (24) the level of ROS-scavenging enzymes, such as GSH-Px was significantly decreased.

Furthermore, SDC upregulated CYP1A2 mRNA expression levels and this may indicate the potential carcinogenic effect of SD. The activity of CYP1A2 is a possible risk factor that determines the carcinogenicity of heterocyclic amines in

humans (25). In addition, hepatic CYP1A2 is a key enzyme, which exerts an important role in the metabolic clearance of 5% of currently marketed therapeutic agents (26). The induction of CYP1A2 by SDs may also indicate its accelerating effect on the metabolism of certain therapeutic agents that act as substrates for CYP1A2, such as theophylline, caffeine, phenacetin and propranolol (27). As is known, caffeine is a significant component of SDs.

Rat CYP3A2 exhibits a 73% homology to the amino acid sequences of human CYP3A4 (28). The induction of CYP3A2 by carbonated SDs may indicate its potential ability to induce human CYP3A4 due to their close homology (29). A significant correlation was reported between enzyme activity and mRNA expression for CYP3A4 in human liver samples (30). Rat CYP3A2 and human CYP3A4 are involved in the metabolism of erythromycin, nifedipine, lidocaine, testosterone, aflatoxin B1 and benzo[a]pyrene (28,30). Furthermore, CYP3A4 is highly expressed in the adult liver and small intestine (30), and metabolizes xenobiotics and carcinogens (32,33), as well as numerous endogenous compounds, such as bile acids, cholesterol, prostaglandins, fatty acids, retinoids, leukotrienes and biogenic amines (32,34). The induction of CYP3A2 by SDC may be attributed to the presence of taurine, as it was demonstrated that taurine enhanced the induction of CYP3A4 by rifampicin in HepG2 cells (35). SDs contain caffeine as a main ingredient and caffeine was shown to stimulate 5'-AMP-activated protein kinase (AMPK) in the extensor digitorum longus muscle (36). Furthermore, metformin was recently demonstrated to enhance constitutive active/androstane receptor (CAR) phosphorylation in human hepatocytes in part via an AMPK-dependent signaling pathway and suppression of CYP2B6 (37). Thus, the suppressive effect of SDs on CYP2B1 mRNA expression, which was revealed in the current study, may be mediated through caffeine stimulation of AMPK-dependent enhancement of CAR phosphorylation (38).

The upregulation of CYP2C11 by SDC in the current study may be mediated by caffeine. Caffeine is a non-selective adenosine receptor antagonist, which binds with very similar (relatively high) affinity to adenosine A1 and A2A receptors (39). Caffeine was reported to significantly inhibit cyclic adenosine monophosphate (cAMP) in hepatic stellate cells (40). Furthermore, epinephrine, which elevates cAMP via the β_2 - and the α_1 -adrenergic receptors in hepatocytes (41) downregulated CYP2C11. In addition, exposure of hepatocytes to increasing concentrations of cAMP for 24 h caused a concentration-dependent suppression of CYP2C11 expression to ~20% of control levels (39). Diclofenac is predominantly metabolized by CYP2C11 in male rats and CYP2C9 in humans (42). CYP2C9 is a major human CYP isoform involved in metabolizing therapeutic agents, such as phenytoin and S-warfarin (42). Therefore the upregulation of CYP2C11 by SDs may increase the elimination of such therapeutic agents that are substrates of CYP2C11 and, thus, decrease the efficacy of those therapeutic agents. Therefore, SDC must be considered during medication prescription and dosing.

In conclusion, the present findings demonstrate the disruption of hepatic CYP enzymes as a result of carbonated SDC, as well as induction of oxidative stress, which may affect drug metabolism. Special care must be taken for patients who consume SDs whilst taking medications for certain diseases.

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