Journal of
Food Biochemistry

Journal of Food Biochemistry ISSN 1745–4514

POTENTIAL PROTECTIVE EFFECT OF COLD-PRESSED *CORIANDRUM SATIVUM* OIL AGAINST CARBON TETRACHLORIDE-INDUCED HEPATOTOXICITY IN RATS

ABDALLA E. EL-HADARY[1] and MOHAMED FAWZY RAMADAN[2,3,4]

[1]Biochemistry Department, Faculty of Agriculture, Banha University, Banha, Egypt
[2]Agricultural Biochemistry Department, Faculty of Agriculture, Zagazig University, Zagazig 44519, Egypt
[3]Scientific Research Deanship, Umm Al-Qura University, Makkah, Kingdom of Saudi Arabia

[4]Corresponding author.
TEL: +2-055-2320282 or +2-012-9782424;
FAX: +2-055-2287567 or +2-055-2345452;
EMAIL: hassanienmohamed@yahoo.com

Received for Publication December 14, 2014
Accepted for Publication September 15, 2015

doi:10.1111/jfbc.12211

ABSTRACT

The protective effect of cold-pressed coriander (*Coriandrum sativum*) oil (CO) against the toxicity caused by carbon tetrachloride (CCl_4) in rats was studied. CO is characterized by its high levels of monounsaturated fatty acids and polyunsaturated fatty acids, tocopherols and phenolic compounds. Male Wistar rats were orally treated with two doses of CO (100 and 200 mg/kg) with administration of CCl_4 (1 mL/kg, CCl_4 in olive oil) for 8 weeks. Liver biochemical parameters were determined in animals treated with CO. The results clearly demonstrated that CO augments the antioxidants' defense mechanism against CCl_4-induced toxicity and provides evidence that CO may have a therapeutic role in free radical–mediated diseases. Treatment with CO significantly reduced the impact of CCl_4 toxicity on aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase, kidney function indicators, protein profile, lipid profile and antioxidant markers of CCl_4-induced liver injury rats. The overall potential of the antioxidant system was significantly enhanced by the CO supplements as the hepatic malondialdehyde levels were lowered, whereas reduced glutathione levels were elevated. The hepatoprotective impact of CO was also supported by histopathological studies of liver tissue. Histopathological examination showed that CO reduced fatty degeneration, cytoplasmic vacuolization and necrosis in CCl_4-treated rats. The results indicate the potentiality of CO to act as natural antioxidant by preventing the peroxidative damage caused by CCl_4.

PRACTICAL APPLICATIONS

Biologically active natural compounds are of interest for pharmaceutical industry in the prevention of different diseases caused by lipid peroxidative damage (i.e., ischemia, coronary atherosclerosis, Alzheimer's disease and carcinogenesis). In the present study, the capability of cold-pressed *Coriandrum sativum* oil (CO) to protect against CCl_4-induced hepatotoxicity was investigated. The study suggested that CO has potent hepatoprotective activity in CCl_4-induced liver injury in rats. CO possesses antioxidant potential and inhibits the deleterious effect of free radicals generated by CCl_4. CO is rich in tocols, phenolic compounds and other bioactive constituents, which might be responsible for the protective effects. These observations provide biochemical data supporting the potential clinical use of CO in the treatment of some hepatic disorders. The results suggest that the ability of CO to ameliorate CCl_4-induced liver injury is associated with its antioxidant and radical-scavenging characteristics.

INTRODUCTION

The liver plays an important role in metabolisms of endogenous and exogenous substances, wherein the hepatic injury is associated with distortion of these functions. Liver, therefore, is susceptible to diseases including hepatitis, cirrhosis, alcohol-related disorders and liver cancer. A major cause of these disorders is due to exposure to different environmental xenobiotics and pollutants (e.g., CCl_4, thioacetamide, paracetamol and alcohol). These toxicants mainly damage the liver by producing reactive oxygen species (ROS) (Liu *et al.* 2011). ROS have been known to produce tissue injury through covalent binding and lipid oxidation and have been shown to augment fibrosis as seen from increased collagen synthesis (Blomhoff 2005; Adesanoye and Farombi 2010). Scavenging of free radicals by defense systems could reduce the fibrosis process in the tissues (Qian *et al.* 2008; Shim *et al.* 2010). Cooperative defense systems that protect body from free radical damage include antioxidants and enzymes [superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx)]. The role of protective enzymes is well known and has been studied deeply with *in vivo* models.

Carbon tetrachloride (CCl_4), an industrial solvent, is extensively used xenobiotic to induce chemical liver injury. CCl_4 is metabolized by hepatic microsomal cytochrome P_{450} to free radical such as trichloromethyl radical ($\cdot CCl_3$) and proxy trichloromethyl radical ($\cdot OOCCl_3$) (Lee *et al.* 2004; Akram *et al.* 2011). Trichloromethyl, hepatotoxic metabolite of CCl_4, can react with sulfhydryl groups (e.g., glutathione and protein thiols) and enzymes such as CAT and SOD. Overproduction of trichloromethyl-free radicals initiates membrane lipid oxidation, eventually leading to various liver pathological processes, such as steatosis and fibrosis or cirrhosis.

Nowadays, many people are suffering from hepatic damage induced by alcohol, chemicals and infections. Therefore, liver diseases continue to be a serious health problem worldwide. Interest in the role of naturally originated agents for the treatment of liver diseases was considered. Some natural compounds are demonstrated to have a protective role against liver diseases (Pramyothin *et al.* 2007; Wan *et al.* 2009; Shaker *et al.* 2010). Studies revealed that natural antioxidants protect the liver against lipid oxidation and impairment in antioxidant status induced by CCl_4 (Noyan *et al.* 2006; Sanmugapriya and Venkataraman 2006; Shaker *et al.* 2010, 2011). ROS production is linked with oxidative stress, which is defined as an imbalance in the generation of oxidants and the antioxidant defense. With regard to the central role of ROS in liver disease, antioxidants might prevent hepatic damage through scavenging activity and increase the activity of intracellular antioxidant enzymes including SOD, GPx and CAT (Upur *et al.* 2009). In addition, studies reported that natural antioxidants are efficacious in preventing oxidative stress-related liver pathologies due to particular interactions and synergisms (Vitaglione *et al.* 2004; Yeh *et al.* 2013).

There is much evidence indicating that natural bioactive compounds from vegetable, fruits, oilseeds and medicinal plants exhibit strong antioxidant potential that could act against hepatic toxicity. One such candidate is coriander (*Coriandrum sativum*), which was chosen in the present study. *C. sativum* is a medicinal plant from the Umbelliferae family (Samojlik *et al.* 2010). The dried fruits are extensively employed as a condiment, especially for flavoring of sauces, meat products, bakery and confectionery items. The seeds contain an essential oil rich in linalool (a monoterpenoid), whereas the leaves contain good amount of phenolic acids such as caffeic, ferulic, gallic and chlorogenic acid (Bajpai *et al.* 2005; Sreelatha *et al.* 2009). *C. sativum* solvent-extracted fixed oil contain high levels of petroselinic acid (Δ^6-*cis*-octadecenoic acid, 18:1*n*-12) as part of triacylglycerols (Ramadan and Moersel 2002a; Ramadan *et al.* 2008). Solvent-extracted *C. sativum* seed oil had been intensively studied, wherein the results indicated that the crude seed oil is a highly promising oil with high levels of bioactive lipids (Ramadan and Moersel 2002b, 2003, 2004, 2006; Ramadan *et al.* 2003).

Studies documented the beneficial effects on health, particularly against coronary heart diseases, of ingestion of dietary fats having high levels of the monounsaturated fatty acid (MUFA), e.g., oleic acid (18:1*n*-9) (Mensink *et al.* 1989; Wahrburg *et al.* 1992). Few studies reported on the effects of dietary lipids with high levels of positional isomers of oleic acid, such as petroselinic acid (Weber *et al.* 1995, 1997). As far as we know, there have been no previous investigations on the protective effect of *C. sativum* oil against CCl_4-induced hepatotoxicity in rats.

Over the past years, interest in cold-pressed oils has been increased because cold pressing involves no heat or chemical treatments. Cold pressing also involves no refining process and may contain a high level of lipophilic bioactive phytochemicals (Ramadan *et al.* 2012). Recently, it was reported that cold-pressed *C. sativum* seed oil (CO) is a rich source of essential fatty acids and bioactive compounds including tocols and phenolic compounds. CO was also characterized by its high antiradical potential against free radicals including 1,1-diphenyl-2-picrylhydrazyl radical (DPPH)$\cdot$ and galvinoxyl radicals (Ramadan 2013).

It is hard to find data in the literature on the protective impact of CO on CCl_4-induced oxidative damage in rats. In the present study, we investigated the protective impacts of CO against CCl_4-induced oxidative stress and hepatotoxicity in rats. The extent of CCl_4-induced liver injury was monitored by measuring the biochemical and histopathological parameters.

MATERIALS AND METHODS

Chemicals

Cold-pressed CO was purchased from a local market (Zagazig City, Egypt). CCl_4 and standards used for tocols were purchased from Merck (Darmstadt, Germany). Assay kits and other chemicals were of the highest purity available and purchased from Sigma Chemical Co. (St. Louis, MO).

Methods

Gas Chromatography Analysis of Fatty Acid Methyl Esters (FAMEs) in CO. Fatty acids of CO were transesterified into methyl esters (FAMEs) by N-trimethylsulfoniumhydroxide (Macherey-Nagel, Düren, Germany) according to Arens *et al.* (1994). FAMEs were detected on a Shimadzu GC-14A equipped with flame ionization detector (FID) and C-R4AX chromatopac integrator (Kyoto, Japan). The flow rate of the carrier gas helium was 0.6 mL/min and the split value with a ratio of 1:40. A sample of 1 µL was injected on a 30 m × 0.25 mm× 0.2 µm film thickness Supelco SPTM-2380 (Bellefonte, PA) capillary column. The injector and FID temperature was set at 250C. The initial column temperature was 100C programmed by 5C/min until 175C and kept 10 min at 175C, then 8C/min until 220C and kept 10 min at 220C. A comparison between the retention times of the samples with those of an authentic standard mixture (Sigma, St. Louis, MO; 99% purity specific for gas–liquid chromatography), run on the same column under the same conditions, was made to facilitate identification.

High-Performance Liquid Chromatography (HPLC) Analysis of Tocopherols in CO. A solution of 250 mg of CO in 25 mL of *n*-heptane was directly used for the HPLC (Ramadan 2013). The HPLC analysis was conducted using a Merck-Hitachi low-pressure gradient system, fitted with an L-6000 pump, a Merck-Hitachi F-1000 fluorescence spectrophotometer (the detector wavelength was set at 295 nm for excitation and at 330 nm for emission) and a D-2500 integration system; 20 µL of the samples was injected by a Merck 655-A40 autosampler onto a Diol phase HPLC column 25 cm × 94.6 mm I.D. (Merck) using a flow rate of 1.3 mL/min. The mobile phase used was *n*-heptane/*tert*-butyl methyl ether (99:1, v/v).

Extraction and Quantification of Phenolic Compounds in CO. One gram of CO was dissolved in *n*-hexane (5 mL) and mixed with 10 mL of methanol–water (80:20, v/v) in a glass tube for 2 min in a vortex (Ramadan *et al.* 2010). After centrifugation at 1077 g for 10 min, the hydroalcoholic extracts were separated from the lipid phase by using a Pasteur pipette, then combined and concentrated *in vacuo* at 30C until a syrup consistency was reached. The lipidic residue was redissolved in 10 mL of methanol–water (80:20, v/v) and the extraction was repeated twice. Hydroalcoholic extracts were redissolved in acetonitrile (15 mL) and the mixture was washed three times with *n*-hexane (15 mL each). Purified phenols in acetonitrile were concentrated *in vacuo* at 30C and then dissolved in methanol for further analysis. Aliquots of phenolic extracts were evaporated to dryness under nitrogen. The residue was redissolved in 0.2 mL of water and diluted (1:30), and Folin–Ciocalteu phenol reagent (1 mL) was added. After 3 min, 7.5% sodium carbonate (0.8 mL) was added. After 30 min, the absorbance was measured at 765 nm using a UV-260 visible recording spectrophotometer (Shimadzu). Gallic acid was used for the calibration and the results of triplicate analyses are expressed as parts per million (ppm) of gallic acid.

Experimental Animal

Experimental procedures involving the animals and their care were conducted in conformity with the institutional guidelines and the Guidelines for Care and Use of Laboratory Animals in Biomedical Research as adopted and promulgated by the World Health Organization. Healthy adult male albino rats (Wister Strain) of approximately same age, weighing approximately 120–140 g were purchased from Organization of Biological Products and Vaccines (Helwan Farm, Helwan, Egypt). Animals were housed under ambient temperature (25 ± 2C) with 50 ± 5% relative humidity and a 12 h light–dark cycle. Rats received standard pellet diet composed of 20% crude protein, 5% fat, 4.5% crude fiber, 8% ash, 2% calcium, 0.6% phosphorus, 3.4% glucose, 2% vitamins and water *ad libitum*.

Experimental Protocol

Twenty-four rats were used to study the protective role of CO on the CCl_4-induced hepatotoxicity in rats. CCl_4 was mixed with olive oil in the ratio 1:1 (w/w) and subjected for hepatoprotective potential against CCl_4-induced liver damage. Animals were divided randomly into equal four groups (six rats each) as follows:

Group 1 (Negative control group): Rats were fed standard synthetic diet and received olive oil orally (three times a week) by gastric gavage at a dose of 1 mL/kg (body weight [b.w.]) for 8 weeks.

Group 2 (Positive control group): Rats were fed standard diet (including 1 mL/kg olive oil three times a week) and

received equal mixture of CCl_4 and olive oil orally (three times a week) by gastric gavage at a dose of 1 mL/kg (b.w.) for 8 weeks.
Group 3: Rats were fed standard diet (including 1 mL/kg olive oil three times a week) and received CO orally (three times a week) by gastric gavage at a dose of 100 mg/kg, simultaneously with equal mixture of CCl_4 and olive oil by gastric gavages at dose of 1 mL/kg during the last 4 weeks.
Group 4: Rats were fed standard diet (including 1 mL/kg olive oil three times a week) and received CO orally (three times a week) by gastric gavage at a dose of 200 mg/kg, simultaneously with equal mixture of CCl_4 and olive oil by gastric gavage at dose of 1 mL/kg during the last 4 weeks.

Blood Sampling and Biochemical Evaluation

Blood samples were collected at the end of experiment and obtained from the retro-orbital plexus veins from the individual rat by means of fine capillary heparinized tubes. Blood samples were collected and allowed to clot; serum was separated by centrifugation at 3,000 rpm for 15 min. Serum was used to investigate the biochemical parameters, including liver function tests, kidney function tests and serum lipid profile.

Activities of liver enzymes including alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP) as well as the serum total bilirubin (TB), direct bilirubin (DB), total protein and serum albumin were determined according to the methods of Reitman and Frankel (1957), Tietz *et al.* (1983), Doumas *et al.* (1973) and Doumas *et al.* (1971), respectively. The globulin was calculated by subtracting the albumin from serum total protein. Kidney function parameters, including urea, uric acid and creatinine, were measured by using the method of Amer *et al.* (2007). Lipid profile, including total lipids (TL), triglycerides (TAG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and very-low-density lipoprotein cholesterol (VLDL-C), was determined according to the methods of Ramadan *et al.* (2008).

Antioxidant Markers

Liver samples were washed immediately with ice-cold saline to remove excess blood. Liver tissue was homogenized in cold 0.1 M potassium phosphate saline (pH = 7.4) at a concentration of 10% (w/v). The homogenate was then centrifuged at 2991 g for 10 min at 4C to obtain the supernatant, which was used to investigate antioxidant markers. Lipid peroxides (malondialdehyde [MDA]) were measured according to Mihara and Uchiyama (1978). Reduced glutathione (GSH) content in the liver was measured spectrophotometrically using Ellman's reagent (DTNB) following the method described by Moron *et al.* (1979). The absorbance was read at 412 nm and the standard graph was drawn using different concentrations of a standard GSH solution and GSH contents were calculated as nM/mg of the tissue protein.

Histopathological Examination

Small tissue specimens were collected from fresh liver tissue of the rats and rapidly fixed in 10% neutral buffered formalin. After proper fixation, thin paraffin sections were routinely prepared and stained with hematoxylin and eosin stain (H&E) for the histopathological lesions in hepatic and renal tissues. The liver sections were graded numerically to assess the degree of histopathological features of acute hepatic injury. Hepatocyte necrosis, fatty change, hyaline degeneration, ballooning degeneration and infiltration of Kupffer cells and lymphocytes were prominent in the histological findings.

Statistical Analysis

All data were analyzed by one-way analysis of variance (ANOVA). Duncan's new multiple range test was used to resolve the difference among treatment means. All statistical analyses were performed using the statistical software SPSS 11.0 (SPSS, Ltd., Surrey, U.K.). A P value <0.05 was considered statistically significant. Ratio values were not arcsin transformed before statistical analysis.

RESULTS

Fatty Acids and Bioactive Lipids in CO

Petroselinic acid (C18:1*n*-12) as the main fatty acid in CO accounted for 47.9%, followed by linoleic acid (36.6%). Levels of other fatty acids including C14:0, C16:0, C18:0, C18:3 and C21:1 were 0.09, 7.82, 4.97, 1.66 and 0.27%, respectively. The amount of petroselinic acid detected is similar to that formerly reported by Ramadan and Moersel (2002a). A striking feature of CO was the relatively high level of MUFA, especially petroselinic acid. CO is characterized by high levels of unsaponifiables and γ-tocopherol was the main component (3,944 mg/kg), wherein the amounts of α, β and δ-tocopherols were 54.9, 38.7 and 110 mg/kg, respectively. Tocopherols are the most efficient antioxidants, while β-tocopherol has 25–50% of the antioxidative activity of α-tocopherol, and γ-isomer 10–35% (Ramadan 2013). In addition, CO was also characterized by high level of phenolics (4.3 mg GAE/g).

TABLE 1. CHANGES IN LIVER ENZYMES IN CCL_4-INDUCED OXIDATIVE DAMAGE IN RAT LIVER

Group	Treatment	ALT (U/mL)	AST (U/mL)	ALP (U/L)	TB (mg/dL)	DB (mg/dL)
1	Negative control (Normal)	28.33 ± 3.50^{b}	29.00 ± 4.67^{b}	95.11 ± 1.22^{b}	0.75 ± 0.022^{c}	0.123 ± 0.011^{b}
2	Positive control (CCl_4)	138.3 ± 3.11^{a}	171.6 ± 6.11^{a}	293.3 ± 1.21^{a}	1.65 ± 0.028^{a}	0.623 ± 0.014^{a}
3	Coriander oil (100 mg/kg) + CCl_4	31.66 ± 2.53^{b}	37.33 ± 4.55^{b}	99.02 ± 1.55^{b}	0.90 ± 0.024^{b}	0.140 ± 0.016^{b}
4	Coriander oil (200 mg/kg) + CCl_4	32.33 ± 2.63^{b}	30.00 ± 4.32^{b}	93.90 ± 1.67^{b}	0.78 ± 0.020^{c}	0.153 ± 0.013^{b}

There is no significant difference ($P > 0.05$) between any two means with the same superscript letter in each column.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DB, direct bilirubin; TB, total bilirubin.

Effect of CO on Liver Enzymes, Kidney Function Indicators, Protein Profile, Lipid Profile and Antioxidant Markers in CCl_4-Induced Liver Injury Rats

The effect of two doses of CO on the serum liver enzymes in CCl_4-intoxicated rats was studied and the results are given in Table 1. After injection of CCl_4, activities of AST, ALT and ALP enzymes in the CCl_4-treated group (group 2) were significantly increased ($P < 0.05$) as compared to the negative control (group 1). Administration of CO attenuated the increased levels of AST, ALT and ALP enzymes induced by CCl_4 and caused a subsequent recovery toward normalization, comparable to the negative control (group1). Treatment of animals with both doses of CO significantly reduced the activities of serum AST, ALT and ALP enzymes as compared to the positive group of CCl_4-treated alone. In addition, levels of TB and DB were also reduced significantly upon treatment with CO (groups 3 and 4).

Table 2 presents the impact of CO on kidney function indicators and protein profile of CCl_4-intoxicated rats. Levels of creatinine, urea and uric acid in negative control (group 1) after 8 weeks of experiments were 0.716, 25.3 and 3.63, respectively. The treatment with CCl_4 (group 2) resulted in an increase in the levels of creatinine, urea and uric acid levels (1.85, 56.3 and 7.93, respectively). On the contrary, treatment with CO resulted in a decrease of creatinine, urea and uric acid levels. Concerning the protein profile (total protein, albumin, globulin and A/G ratio), the results revealed that treatment with CCl_4 (group 2) did reduce protein parameters in general (Table 2), while treatment with both doses of CO increased protein profile to levels that resemble the negative control (group 1).

The impact of CO on the lipid profile of CCl_4-induced liver injury rats is presented in Fig. 1. Generally, treatment with CCl_4 resulted in a significant increase in all lipid parameters (TL, TC, TAG, LDL-C and VLDL-C), except HDL-C. After 8 weeks of experiment, levels of TL, TC, TAG, LDL-C and VLDL-C in positive control (group 2) were 213.5, 292.6, 691.6, 119.5 and 58.5, respectively. After the same period (8 weeks) with 200 mg/kg CO treatment, levels of TL, TC, TAG, LDL-C and VLDL-C were decreased to 167, 195.3, 584.5, 74.6 and 39.0, respectively. Concerning HDL-C, treatment with CCl_4 resulted in decreased level (35.5) after 8 weeks of experiment, while treatment with both doses of CO did increase HDL-C levels.

As shown in Table 3, the MDA (nmol/mg) level was markedly higher in CCl_4-intoxicated rats (group 2) after 8 weeks. Expected increases in lipid oxidative indices in the CCl_4-treated model confirmed that oxidative damage has been induced. Negative control (group 1) and groups (3 and 4) that were treated with CO were characterized by lower levels of MDA. It could be concluded that CO inhibited the elevation of MDA levels upon CCl_4 administration. On the contrary, GSH level was markedly lower in CCl_4-intoxicated rats (group 2). However, the GSH level was significantly increased by CO treatment (groups 3 and 4) when compared with the positive control group. Administration of CO (groups 3 and 4) did significantly increase ($P > 0.05$) the activity of GSH as compared to the CCl_4-treated group.

Histopathology of the Liver

The results of hepatic histopathological examination are shown in Fig. 2A–D. The histological observations supported the obtained results. Liver sections from negative

TABLE 2. IMPACT OF CORIANDER OIL ON KIDNEY FUNCTION INDICATORS AND PROTEIN PROFILE IN CCL_4-INDUCED INJURY IN RAT

Group	Treatment	Creatinine	Urea	Uric acid	T-protein	Albumin	Globulin	A/G ratio
1	Negative control (Normal)	0.71 ± 0.016^{c}	25.33 ± 1.01^{c}	3.63 ± 0.13^{b}	6.50 ± 0.23^{b}	3.78 ± 0.055^{b}	2.72 ± 0.15^{b}	1.40 ± 0.11^{ab}
2	Positive control (CCl_4)	1.85 ± 0.012^{a}	56.33 ± 1.02^{a}	7.93 ± 0.15^{a}	5.40 ± 0.25^{c}	3.01 ± 0.036^{c}	2.38 ± 0.29^{b}	1.312 ± 0.09^{b}
3	Coriander oil (100 mg/kg) + CCl_4	0.59 ± 0.013^{d}	33.00 ± 1.05^{b}	3.58 ± 0.12^{b}	6.16 ± 0.19^{bc}	4.06 ± 0.041^{a}	2.10 ± 0.28^{b}	1.98 ± 0.19^{a}
4	Coriander oil (200 mg/kg) + CCl_4	0.89 ± 0.015^{b}	32.66 ± 1.07^{b}	3.08 ± 0.18^{b}	7.93 ± 0.21^{a}	3.70 ± 0.011^{b}	4.22 ± 0.24^{a}	0.89 ± 0.17^{b}

There is no significant difference ($P > 0.05$) between any two means with the same superscript letter in each column.

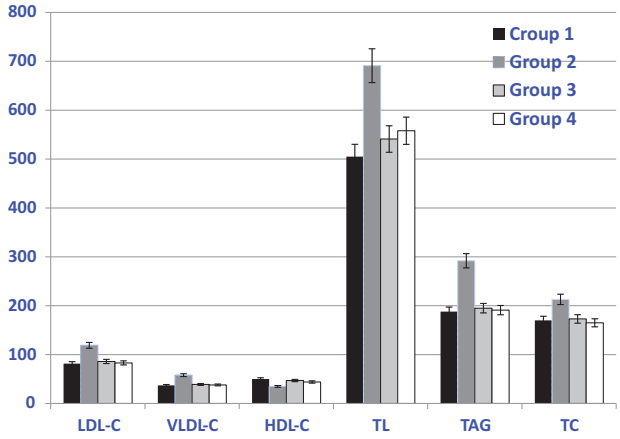

FIG. 1. CHANGES IN LIPID PROFILE IN CCl_4-INDUCED INJURY IN RAT
Error bars show the variations of three determinations in terms of standard deviation.
HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TAG, triglycerides; TC, total cholesterol; TL, total lipid; VLDL-C, very-low-density lipoprotein cholesterol.

control rats showed normal lobular architecture, hepatic cells with a well-preserved cytoplasm, and well-defined nucleus and nucleoli (Fig. 2A). When compared with the normal liver tissues of controls, liver tissue in the rats treated with CCl_4 revealed extensive liver injuries characterized by moderate to severe hepatocellular hydropic degeneration and necrosis around the central vein, lipidosis, hepatic fibrosis and cholangiocyte hyperplasia (Fig. 2B). The liver of rats that received CCl_4 showed severe fatty changes in the hepatocytes; the cytoplasm of hepatocytes showed clear vacuoles which upon squeezing their nuclei in one side give a signet ring shape (Fig. 2B). The histopathological hepatic lesions induced by administration of CCl_4 were only remarkably ameliorated in the central lobular necrosis, hepatic lipidosis and hepatic fibrosis by treatment with CO (Fig. 2C and D). In group 3, which received CO (100 mg/kg), only mild degenerative changes in the hepatocytes in the form of vacuolar degeneration and activation of von Kupffer cells, together with focal mononuclear aggregations in the portal areas, were shown (Fig. 2C). The liver of group 4, which received a 200 mg/kg dose of CO, showed congestion of the central vein and mild congestion of the hepatic sinusoids (Fig. 2D).

DISCUSSION

The liver, a key organ of metabolism and excretion, is constantly endowed with the task of detoxification. Hepatotoxicants, including viruses, fungal products, bacterial metabolites, environmental pollutants and chemotherapeutic agents, can induce various disorders of the liver (Ha *et al.* 2005). Hepatotoxins, such as ethanol, acetaminophen and CCl_4, sparked liver injury, which is characterized by varying degrees of hepatocyte degeneration and cell death (Yeh *et al.* 2013). CCl_4 is a well-known hepatotoxic agent and the preventive action of liver damage by CCl_4 has been widely used as an indicator of liver protective activity of drugs. The changes associated with CCl_4-induced liver damage are similar to that of acute viral hepatitis. It is metabolized in the liver to excretable glucuronide and sulfide conjugates. Vitaglione *et al.* (2004) suggested that ROS, including superoxide and hydroxyl radicals, were proved to be associated with the intoxication by CCl_4. Evidence suggested that CCl_4 has been used as a hepatotoxin in experimental hepatopathy (Hsu *et al.* 2008). Covalent binding of the metabolites of CCl_4, trichloromethyl-free radicals, to cell proteins is considered to be the initial step in a chain of events that eventually lead to membrane lipid oxidation and finally to cell death.

An obvious sign of hepatic injury is the leaking of cellular enzymes into the plasma due to the disturbance caused in the transport function of hepatocytes. When liver cell plasma is damaged, a variety of enzymes located in the cytosol is released into the blood, causing increased enzyme level in the serum. The estimation of enzymes in the serum is a useful marker of the extent and types of hepatocellular damage (Jadon *et al.* 2007; Sreelatha *et al.* 2009).

There has been a substantial increase in the use of phenolics and alternative therapies to treat patients with liver disease. Epidemiological studies suggested an inverse relationship between the consumption of phenolic-rich foods and the risk of cancers and cardiovascular diseases (Arts

TABLE 3. CHANGES IN ANTIOXIDANT MARKERS IN CCl_4-INDUCED INJURY IN RAT

Group	Treatment	MDA (nmol/mg)	GSH (mmol/g)
1	Negative control (Normal)	3.35 ± 0.122^{c}	1.48 ± 0.0185^{b}
2	Positive control (CCl_4)	9.25 ± 0.141^{a}	0.83 ± 0.0146^{c}
3	Coriander oil (100 mg/kg) + CCl_4	4.25 ± 0.130^{b}	1.54 ± 0.0193^{b}
4	Coriander oil (200 mg/kg) + CCl_4	4.06 ± 0.147^{b}	1.67 ± 0.0191^{a}

There is no significant difference ($P > 0.05$) between any two means with the same superscript letter in each column.
GSH, glutathione; MDA, malondialdehyde.

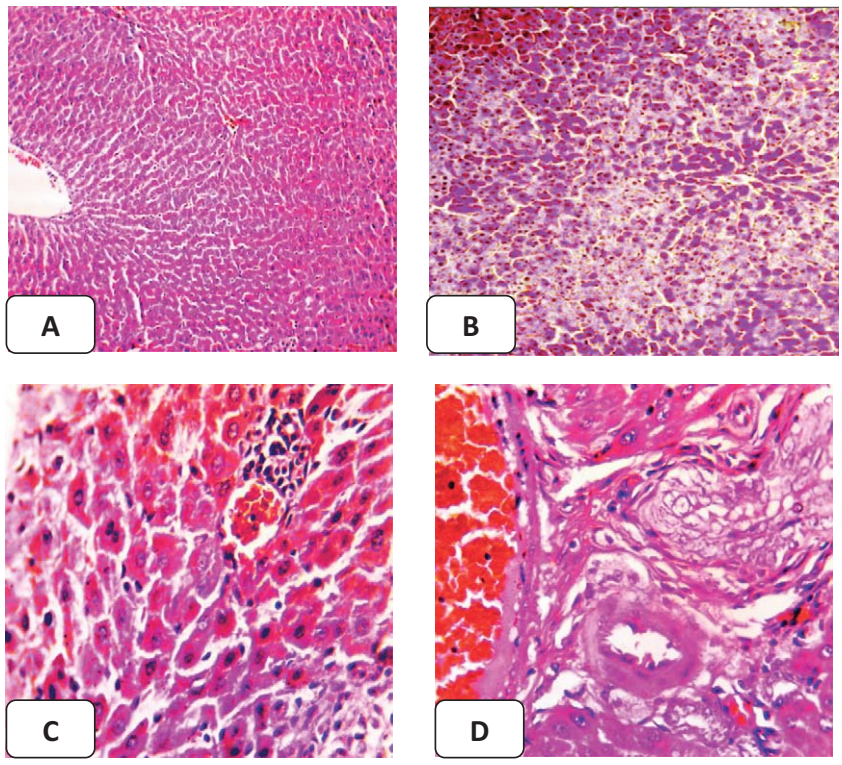

FIG. 2. PHOTOMICROGRAPHS OF LIVER FROM (A) CONTROL RATS SHOWING NORMAL HISTOPATHOLOGICAL STRUCTURE (H&E ×300), (B) RATS RECEIVED CCL_4 (100 MG/KG) SHOWING SEVERE FATTY CHANGE IN THE HEPATOCYTES (H&E ×300), (C) RATS RECEIVED CCL_4 (100 MG/KG) AND CORIANDER (*CORIANDRUM SATIVUM*) OIL (CO) (100 MG/KG) SHOWING DEGENERATIVE CHANGES IN HEPATOCYTES IN THE FORM OF VACUOLATION WITH FOCAL MONONUCLEAR AGGREGATION (H&E ×300), (D) RATS RECEIVED CCL_4 (100 MG/KG) AND CO (200 MG/KG) SHOWING CONGESTION OF THE CENTRAL VEIN AND HEPATIC SINUSOIDS (H&E ×300)

and Hollman 2005). In this regard, there has been a great deal of interest in the screening and characterization of novel potentially therapeutic of phenolics, phenolic-rich foods and medicinal plants (Murcia *et al.* 2001; Seeram *et al.* 2005). The antioxidant properties of phenolic compounds and their ability to modulate the activity of enzymes have been demonstrated in *in vitro* studies and are believed to be a primary mechanism for their biological impacts. However, the question remains whether these properties demonstrated in *in vitro* studies are relevant to protect against oxidative damage *in vivo*, where phenolic compounds are found at a very low concentrations depending on bioavailability and metabolism.

The present study reports the potential hepatoprotective activity of CO against hepatic injury induced by CCl_4 in rats. In the present investigation, the dose of CCl_4 used caused liver injury in rats, whereas the rats treated with CCl_4 developed significant hepatic damage. CCl_4 increased lipid oxidation and affects different blood biochemical parameters, including liver enzymes, kidney function indicators, protein profile, lipid profile and antioxidant markers.

CO appears to be effective in reducing the injurious effect of CCl_4, as observed in the study. Total protein is performed to evaluate the toxicological nature of various chemicals (Nevin and Vijayammal 2005; Sreelatha *et al.* 2009). The decreased total protein in the CCl_4-treated groups is due to the damage to the liver caused by CCl_4. The ability of CO to maintain the total protein may be due to the antioxidant constituents found in the oil.

The protective role of CO was accompanied by a partial prevention of GSH depletion in the liver tissue. It is considered that hepatic GSH represents an enzyme reserve of the liver, which is responsible for reducing the hepatotoxicity induced by the active metabolites of CCl_4. As GSH is also a crucial determinant of tissue susceptibility to oxidative damage, the partial protection of CO on GSH reserves provides an additional action not only to remove the active metabolites of CCl_4 but also to scavenge free radicals, which are involved in lipid oxidation.

Hepatic cells participate in a variety of metabolic activities and contain a host of enzymes. In tissues, AST and ALT are found in higher levels in the cytoplasm, and AST in particular also exists in the mitochondria. In liver injury, the transport function of the hepatocytes is disturbed, resulting in the leakage of plasma membrane, thereby causing an increased enzyme level in the serum, and soluble enzymes such as AST will also be similarly released. The elevated activities of AST and ALT in the serum are indicative of cellular leakage and loss of functional integrity of cell membranes in the liver (Rajesh and Latha 2004). Administration of CCl_4 significantly raised the levels of the serum enzymes such as AST and ALT in rats. Oral administration of CO

caused a decrease in the activity of the above enzymes, which may be a consequence of the stabilization of plasma membrane as well as repair of hepatic tissue damaged by CCl_4.

Some flavonoids exert a stimulatory action on transcription and gene expression of certain antioxidant enzymes (Rohrdanz *et al.* 2002). The antioxidant enzyme system plays an important role in the defense of cells against oxidative insults. The study examined the ameliorating effect of CO on oxidative stress induced by CCl_4. The levels of glutathione approached the normal control in CO-treated animals exposed to CCl_4. MDA is a major reactive aldehyde that appears during the peroxidation of the biological membrane of PUFA (Vaca *et al.* 1988). Therefore, the hepatic content of MDA is used as an indicator of liver tissue damage involving a series of chain reactions. Lipid peroxidation of hepatocyte membranes is one of the principal causes of CCl_4-induced hepatotoxicity and is mediated by the production of free radical derivatives of CCl_4 (Basu 2003; Weber *et al.* 2003). In the present study, treatment with CCl_4 resulted in a significant increase in the hepatic MDA concentration, indicating increased lipid peroxidation caused by CCl_4.

It has been hypothesized that one of the principal causes of CCl_4-induced liver injury is formation of lipid peroxides by free radical derivatives of CCl_4. Thus, the antioxidant potential or the inhibition of the generation of free radicals is important in protection against CCl_4-induced hepatopathy. The body has an effective defense mechanism to prevent and neutralize the free radical–induced damage by a set of endogenous antioxidant enzymes such as SOD and CAT. These enzymes constitute a mutually supportive defense team against ROS. Lipid peroxidation, an ROS-mediated mechanism, has been implicated in the pathogenesis of various liver injuries and subsequent liver fibrogenesis in experimental animals. The significant non-dose-dependent decrease in the hepatic lipid hydroperoxide confirmed that treatment with CO could effectively protect against the hepatic lipid oxidation induced by CCl_4. Hence, it is possible that the mechanism of hepatoprotection of CO may be due to its antioxidant activity.

The effect of CO was further confirmed by histopathological examinations. CO offers a hepatoprotection impact in central lobular necrosis, hepatic lipidosis and cholangiocyte hyperplasia in rats. The histological observations basically supported the results obtained from serum enzyme assays. The liver of CCl_4-intoxicated rats showed massive fatty changes gross necrosis, broad infiltration of lymphocyte and Kupffer cells around the central vein and loss of cellular boundaries. The histopathological observations of the liver of rats pretreated with CO and subsequently given CCl_4 showed a more or less normal architecture of the liver having reversed to a large extent, the hepatic lesions produced by the toxins, almost comparable to the normal control. The stimulation of hepatic regeneration makes the liver more resistant to damage by the toxin (Sadasivan *et al.* 2006). CO inhibited liver lipid peroxidation and resultant tissue degeneration, thus acting as an effective antioxidant.

Spices are believed to play an important role in human health. CO contains high levels of petroselinic acid. Several epidemiological and clinical studies demonstrated that oleic acid can be as effective as PUFA for the prevention of diseases. Very few investigations to demonstrate the beneficial effects of petroselinic acid on lipid metabolism have been carried out. *In vitro* study showed that triacylglycerols containing petroselinoyl moieties are hydrolyzed by pancreatic lipase at much lower rates than those containing oleoyl and other C-18 acyl moieties (Weber *et al.* 1995). Petroselinic acid from triacylglycerols of *C. sativum* is incorporated extensively into the lipids of heart and liver of rats and, concomitantly, the level of arachidonic acid in these tissues was reduced (Weber *et al.* 1997). The decrease in the level of arachidonic acid is envisaged to be caused by the presence of petroselinic acid having a Δ^6-double bond that inhibits the Δ^6-desaturase as a pseudo-product by mimicking the structure of 18:3*n*-6, a precursor of arachidonic acid (Weber *et al.* 1999). CO might be useful for modulating the amounts of arachidonate in the cerebral membranes in specific conditions of health and disease. Moreover, petroselinic acid is metabolized in the rat liver via β-oxidation and chain elongation to shorter and higher homologs, respectively; however, petroselinic acid is a dead-end metabolite of the desaturation–chain elongation reaction cycle (Weber *et al.* 1997).

From the health point of view, MUFAs have been shown to lower "bad" LDL-C and retain "good" HDL-C. This is the major benefit of olive oil over the highly polyunsaturated oils (Ramadan *et al.* 2010). It has been reported that antioxidant potential of vegetable oils *in vitro* is directly connected to their bioactive sterols, tocopherols, polar lipids and phenolic content (Ramadan and Moersel 2006). Maybe this is the answer to the question as to why oils rich in MUFA do not have the same positive effect. CO contains also high levels unsaponifiables, tocopherols and phenolic compounds. Oils rich in phenolics may play a role in reducing the risk of many diseases. The antioxidant potential of phenolics is mainly due to their redox properties and is the result of various mechanisms: antiradical activity, transition-metal-chelating activity and/or singlet-oxygen-quenching capacity (Bettaieb *et al.* 2010). Phenolics exhibit favorable hepatoprotective effects and could prevent chemical-induced dyslipidemia, inflammatory response and mitochondrial oxidative damage of rat hepatocytes. Therefore, bioactive compounds with remarkably high antioxidant activity, superior free radical-scavenging ability and

inhibition of lipid oxidation are contributed to the hepatoprotective effect in rats against liver damage induced by CCl_4 (Hu *et al.* 2012; Tang *et al.* 2012). Because the phytochemical analysis of CO showed the presence of tocopherols and phenolic compounds, and hepatoprotective activities of such constituents are well known, there has been speculation that these constituents might be responsible for the observed hepatoprotective roles.

CONCLUSION

It could be concluded that CO, in tested doses, exhibits *in vivo* antioxidant activity, which could have a beneficial effect against oxidative liver damage induced by CCl_4. Bioactive constituents in CO protected plasma membrane and increased the regenerative and reparative capacity of the liver. Beneficial impact of CO may be due to the presence of phenolics that have membrane-stabilizing effects. The results suggest that the active compound in CO efficiently works on the liver to keep normal function and minimize cell membrane disturbances. CO rich in bioactive compounds appear to be promising for safe use in folk medicine, pharmaceutical and novel food industries.

REFERENCES

ADESANOYE, O.A. and FAROMBI, E.O. 2010. Hepatoprotective effects of *Vernonia amygdalina* (Asteraceae) in rats treated with carbon tetrachloride. Exp. Toxicol. Pathol. *62*, 197–206.

AKRAM, E., MARYAM, E., AL-EBRAHIMC, M., ROHANI, A.H. and MORTAZAVI, P. 2011. Protective effects of sodium molybdate on carbon tetrachloride-induced hepatotoxicity in rats. J. Trace Elem. Med. Biol. *25*, 67–71.

AMER, M.M.A., RAMADAN, M.F. and ABD EL-GLEEL, W. 2007. Impact of *Pulicaria incisa*, *Diplotaxis harra a*nd *Avicennia marina* as hypocholesterolemic agent. Dtsch. Leben. Rund. *103*, 320–327.

ARENS, M., SCHULTE, E. and WEBER, K. 1994. Fettsäuremethylester, Umesterung mit Trimethylsulfoniumhydroxid (Schnellverfahren). Fat Sci. Technol. *96*, 67–68.

ARTS, I.C. and HOLLMAN, P.C. 2005. Polyphenols and disease risk in epidemiologic studies. Amer. J. Clini. Nutr. *81*, 317S–325S.

BAJPAI, M., MISHRA, A. and PRAKASH, D. 2005. Antioxidant and free radical scavenging activities of some leafy vegetables. Inter. J. Food Sci. Nutr. *56*, 73–81.

BASU, S. 2003. Carbon tetrachloride-induced lipid peroxidation: Eicosanoid formation and their regulation by antioxidant nutrients. Toxicology *189*, 113–127.

BETTAIEB, I., BOURGOU, S., WANNES, W.A., HAMROUNI, I., LIMAM, F. and MARZOUK, B. 2010. Essential oils, phenolics, and antioxidant activities of different parts of cumin (*Cuminum cyminum* L.). J. Agric. Food Chem. *58*, 10410–10418.

BLOMHOFF, R. 2005. Dietary antioxidants and cardiovascular disease. Curr. Opin. Lipidol. *16*, 47–54.

DOUMAS, B.T., WATSON, W.A. and BIGGS, H.G. 1971. Albumin standards and the measurement of serum albumin with bromcresol green. Clin. Chem. Acta. *31*, 87–96.

DOUMAS, B.T., PERRY, B.W., SASSE, E.A. and STRAUMFJORD, J.V. 1973. Standardization in bilirubin assays: Evaluation of selected methods and stability of bilirubin solutions. Clin. Chem. *19*, 984–993.

HA, K.T., YOON, S.J. and CHOI, D.Y. 2005. Protective effect of *Lycium chinense* fruit on carbon tetrachloride-induced hepatotoxicity. J. Ethnopharmacol. *96*, 529–535.

HSU, Y.W., TSAI, C.F., CHANG, W.H., HO, Y.C., CHEN, W.K. and LU, F.J. 2008. Protective effects of *Dunaliella salina*, a carotenoids-rich alga, against carbon tetrachloride-induced hepatotoxicity in mice. Food Chem. Toxicol. *46*, 3311–3317.

HU, Q.H., ZHANG, X., PAN, Y., LI, Y.C. and KONG, L.D. 2012. Allopurinol, quercetin and rutin ameliorate renal NLRP3 inflammasome activation and lipid accumulation in fructose-fed rats. Biochem. Pharmacol. *84*, 113–125.

JADON, A., BHADAURIA, M. and SHUKLA, S. 2007. Protective effect of *Terminalia belerica* Roxb. and gallic acid against carbon tetrachloride induced damage in albino rats. J. Ethnopharm. *109*, 214–218.

LEE, K.J., WOO, E.R., CHOI, C.Y., SHIN, D.W., LEE, D.G., YOU, H.J. and JEONG, H.G. 2004. Protective effect of acteoside on carbon tetrachloride-induced hepatotoxicity. Life Sci. *74*, 1051–1064.

LIU, Q., BAOHUA, K., LI, G., NING, L. and XIUFANG, X. 2011. Hepatoprotective and antioxidant effects of porcine plasma protein hydrolysates on carbon tetrachloride-induced liver damage in rats. Food Chem. Toxicol. *49*, 1316–1321.

MENSINK, R.P., DE-GROOT, M.J.M., VAN DEN BROEKE, L.T., SEVERIJNEN-NOBELS, A.P., DEMACKER, P.N.M. and KATAN, M.B. 1989. Effects of monounsaturated fatty acids vs complex carbohydrates on serum liproteins and apoproteins in healthy men and women. Metabolism *38*, 172–178.

MIHARA, M. and UCHIYAMA, M. 1978. Determination of malonaldehyde precursor in tissues by thiobarbituric acid test. Anal. Biochem. *86*, 271–278.

MORON, M.S., DEPIERRE, J.W. and MANNERVIK, B. 1979. Levels of GSH, GR and GST activities in rat lung and liver. Biochim. Biophys. Acta *582*, 67–78.

MURCIA, M.A., JIMENEZ, A.M. and MARTINEZ-TOME, M. 2001. Evaluation of the antioxidant properties of Mediterranean and tropical fruits compared with common food additives. J. Food Prot. *64*, 2037–2046.

NEVIN, K.G. and VIJAYAMMAL, P.L. 2005. Effect of *Aerva lanata* on solid tumor induced by DLA cells in mice. Fitoterapia *74*, 578–580.

NOYAN, T., KÖMÜROGLU, U., BAYRAM, I. and SEKEROGLU, M.R. 2006. Comparison of the effects of melatonin and

pentoxifylline on carbon tetrachloride-induced liver toxicity in mice. Cell Biol. Toxicol. *22*, 381–391.

PRAMYOTHIN, P., NGAMTIN, C., POUNGSHOMPOO, S. and CHAICHANTIPYUTH, C. 2007. Hepatoprotective activity of *Phyllanthus amarus* Schum. Et. Thonn. extract in ethanol treated rats: *In vitro* and *in vivo* studies. J. Ethnopharmacol. *114*, 169–173.

QIAN, Z.J., JUNG, W.K. and KIM, S.K. 2008. Free radical scavenging activity of a novel antioxidative peptide purified from hydrolysate of bullfrog skin, *Rana catesbeiana* Shaw. Bioresour. Technol. *99*, 1690–1698.

RAJESH, M.G. and LATHA, M.S. 2004. Protective effect of *Glycyrrhiza glabra* Linn. on carbon tetrachloride-induced peroxidative damage. Ind. J. Pharmacol. *36*, 284–286.

RAMADAN, M.F. 2013. Healthy blends of high linoleic sunflower oil with selected cold pressed oils: Functionality, stability and antioxidative characteristics. Ind. Crops Prod. *43*, 65–72.

RAMADAN, M.F. and MOERSEL, J.-T. 2002a. Oil composition of coriander (*Coriandrum sativum* L.) fruit-seeds. Eur. Food Res. Technol. *215*, 204–209.

RAMADAN, M.F. and MOERSEL, J.-T. 2002b. Direct isocratic normal phase assay of fat-soluble vitamins and β-carotene in oilseeds. Eur. Food Res. Technol. *214*, 521–527.

RAMADAN, M.F. and MOERSEL, J.-T. 2003. Analysis of glycolipids from black cumin (*Nigella sative* L.), coriander (*Coriandrum sativum* L.) and niger (*Guizotia abyssinica* Cass.) oilseeds. Food Chem. *80*, 197–204.

RAMADAN, M.F. and MOERSEL, J.-T. 2004. Oxidative stability of black cumin (*Nigella sativa* L.), coriander (*Coriandrum sativum* L.) and niger (*Guizotia abyssinica* Cass.) upon stripping. Euro. J. Lipid Sci. Technol. *106*, 35–43.

RAMADAN, M.F. and MOERSEL, J.-T. 2006. Screening of the antiradical action of vegetable oils. J. Food Comp. Anal. *19*, 838–842.

RAMADAN, M.F., KROH, L.W. and MOERSEL, J.-T. 2003. Radical scavenging activity of black cumin (*Nigella sativa* L.), coriander (*Coriandrum sativum* L.) and niger (*Guizotia abyssinica* Cass.) crude seed oils and oil fractions. J. Agric. Food Chem. *51*, 6961–6969.

RAMADAN, M.F., AMER, M.M.A. and AWAD, A. 2008. Coriander (*Coriandrum sativum* L.) seed oil improves plasma lipid profile in rats fed diet containing cholesterol. Eur. Food Res. Technol. *227*, 1173–1182.

RAMADAN, M.F., KINNI, S.G., SESHAGIRI, M. and MÖRSEL, J.-T. 2010. Fat-soluble bioactives, fatty acid profile and radical scavenging activity of *Semecarpus anacardium* seed oil. J. Amer. Oil Chem. Soc. *87*, 885–894.

RAMADAN, M.F., ASKER, M.M.S. and TADROS, M. 2012. Antiradical and antimicrobial properties of cold-pressed black cumin and cumin oils. Eur. Food Res. Technol. *234*, 833–844.

REITMAN, S. and FRANKEL, S. 1957. Colorimetric GOT and GPT determination. Amer. J. Clin. Pathol. *28*, 56–63.

ROHRDANZ, E., OHLER, S., TRAN-THI, Q.H. and KAHL, R. 2002. The phytoestrogen daidzein affects the antioxidant enzyme system of rat hepatoma H4IIE cells. J. Nutr. *132*, 370–375.

SADASIVAN, S., LATHA, P.G., SASIKUMAR, J.M., RAJASHEKARAN, S., SHYMAL, S. and SHINE, V.J. 2006. Hepatoprotective studies on *Hedyotis corymbosa* (L.) Lam. J. Ethnopharm. *106*, 25–249.

SAMOJLIK, I., LAKIĆ, N., MIMICA-DUKIĆ, N., DAKOVIĆ-SVAJCER, K. and BOZIN, B. 2010. Antioxidant and hepatoprotective potential of essential oils of coriander (*Coriandrum sativum* L.) and caraway (*Carum carvi* L.) (Apiaceae). J. Agric. Food Chem. *58*, 8848–8853.

SANMUGAPRIYA, E. and VENKATARAMAN, S. 2006. Studies on hepatoprotective and antioxidant actions of *Strychnos potatorum* Linn. seeds on CCl_4-induced acute hepatic injury in experimental rats. J. Ethnopharmacol. *105*, 154–160.

SEERAM, N.P., ADAMS, L.S., HENNING, S.M. and HEBER, D. 2005. *In vitro* antiproliferative, apoptotic and antioxidant activities of punicalagin, ellagic acid and a total pomegranate tannin extract are enhanced in combination with other polyphenols as found in pomegranate juice. J. Nutr. Biochem. *16*, 360–367.

SHAKER, E., MAHMOUD, H. and MNAA, S. 2010. Silymarin, the antioxidant component and *Silybum marianum* extracts prevent liver damage. Food Chem. Toxicol. *48*, 803–806.

SHAKER, E., KHALED, R.Z., WAJAHAT, Z.M., GAMAL, E.S. and TAREK, M.I. 2011. Comparison of imatinib, nilotinib and silymarin in the treatment of carbon tetrachloride-induced hepatic oxidative stress, injury and fibrosis. Toxicol. Appl. Pharma. *252*, 165–175.

SHIM, J.Y., KIM, M.H., KIM, H.D., AHN, J.Y. and SONG, J.Y. 2010. Protective action of the immunomodulator ginsan against carbon tetrachloride-induced liver injury via control of oxidative stress and the inflammatory response. Toxicol. Appl. Pharma. *242*, 318–325.

SREELATHA, S., PADMA, P.R. and UMADEVI, M. 2009. Protective effects of *Coriandrum sativum* extracts on carbon tetrachloride-induced hepatotoxicity in rats. Food Chem. Toxicol. *47*, 702–708.

TANG, Y., GAO, C., XING, M., LI, Y., ZHU, L., WANG, D., YANG, X., LIU, L. and YAO, P. 2012. Quercetin prevents ethanol-induced dyslipidemia and mitochondrial oxidative damage. Food Chem. Toxicol. *50*, 1194–1200.

TIETZ, N.W., RINKER, A.D. and SHAW, L.M. 1983. International Federation of Clinical Chemistry. IFCC methods for the measurement of catalytic concentration of enzymes. Part 5. IFCC method for alkaline phosphatase (orthophosphoric-monoester phosphohydrolase, alkaline optimum, EC 3.1.3.1). J. Clin. Chem. Clin. Biochem. *21*, 731–748.

UPUR, H., AMAT, N., BLAZEKOVIC, B. and TALIP, A. 2009. Protective effect of *Cichorium glandulosum* root extract on carbon tetrachloride-induced and galactosamine-induced hepatotoxicity in mice. Food Chem. Toxicol. *47*, 2022–2030.

VACA, C.E., WILHELM, J.M. and HARMS-RIHSDAHL, M. 1988. Interaction of lipid peroxidation product with DNA. Mutat. Res. Rev. Gen. Toxicol. *195*, 137–149.

VITAGLIONE, P., MORISCO, F., CAPORASO, N. and FOGLIANO, V. 2004. Dietary antioxidant compounds and liver health. Crit. Rev. Food Sci. Nutr. *44*, 575–586.

WAHRBURG, U., MARTIN, H., SANDKAMP, M., SCHULTE, H. and ASSMANN, G. 1992. Comparative effects of a recommended lipid-lowering diet vs a diet rich in monounsaturated fatty acids on serum lipid profiles in healthy young adults. Am. J. Clin. Nutr. *56*, 678–683.

WAN, X.Y., LUO, M., LI, X.D. and HE, P. 2009. Hepatoprotective and antihepatocarcinogenic effects of glycyrrhizin and matrine. Chem. Biol. Interact. *181*, 15–19.

WEBER, L.W.D., BULL, M. and STAMPFL, A. 2003. Hepatotoxicity and mechanism of action of haloalkanes: Carbon tetrachloride as a toxicological model. Crit. Rev. Toxicol. *33*, 105–136.

WEBER, N., RICHTER, K.-D., SCHULTE, E. and MUKHERJEE, K.D. 1995. Petroselinic acid from dietary triacylglycerols reduces the concentration of arachidonic acid in tissue lipids of rats. J. Nutr. *125*, 1563–1568.

WEBER, N., VOSMANN, K., BRÜHL, L. and MUKHERJEE, K.D. 1997. Metabolism of dietary petroselinic acid: A dead-end metabolite of desaturation/chain elongation reactions. Nutr. Res. *17*, 89–98.

WEBER, N., KIEWITTI, I. and MUKHEJEE, K.D. 1999. Modulation of brain lipids of rats by various dietary oils: Sunflower, high-oleic sunflower, olive, rapeseed or coriander oil. Nutr. Res. *19*, 997–1007.

YEH, Y.-H., HSIEH, Y.-L. and LEE, Y.-T. 2013. Effects of yam peel extract against carbon tetrachloride-induced hepatotoxicity in rats. J. Agric. Food Chem. *61*, 7387–7396.