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Modulatory Effects of Aerial Parts of *Coriandrum sativum L.* On Carbon-Tetrachlorid Induced Hepatorenal Toxicity

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Abstract: Carbon tetrachloride (CCL_4) is a potent hepato and nephro toxin. Its toxicity resides from its reactive metabolites. *Coriandrum sativum* (CS) possesses multiple pharmacological properties including antioxidant, antidiabetic and antihyperlipidemic effects. The present study investigated the hepatorenal protectant activity of CS against CCL_4 induced toxicity in rats. Also, CS phenolics were evaluated. Our data revealed that CS aerial parts (stem and leaves) total phenolics were 4.08 mg/g tannic acid equivalent and isoflavones were 12.29 mg/g catechin equivalent. HPLC analysis showed that genstin (3%w/w), rutin (0.56%), dadzin (0.17%), vanillin (0.14%) and quercetin (0.1%) were the major phenolics in CS aerial parts. Concerning CCL_4 intoxication, CCL_4 significantly increased liver enzymes; alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) as compared to the normal control. Also, CCL_4-induced kidney damage as evidenced by a marked increase in plasma creatinine, urea and uric acid levels as compared to normal rats. Furthermore, oxidative stress in CCL_4 group was manifested by an extreme reduction of both erythrocyte superoxide dismutase (SOD) and plasma catalase (CAT) activities. Feeding CS stem and leaves showed a marked decrease, in a dose dependent manner, in liver and kidney biomarkers as compared to CCL_4 group, indicating a significant protection of CS against CCL_4 intoxication. In addition, the ameliorating effects of CS on the antioxidant enzymes SOD and CAT, in a dose dependent manner were noticed as compared to CCL_4 treated rats suggesting that the antioxidant effects of CS phenolics could be implicated as a mechanism against CCL_4 deleterious effects. Our results demonstrated the protective role of CS against CCL_4- induced hepatotoxicity and nephrotoxicity. Increasing CS consumption is recommended, especially in cases of heavy contaminants.

Key words: Carbon Tetrachloride · *Coriandrum Sativum* · Liver · Kidney · Antioxidants

INTRODUCTION

The liver is a master metabolic gland. It plays a pivotal role in regulating various physiological processes in the body such as metabolism, secretion and storage. It also has a great capacity to detoxificate toxic substances and synthesize useful ones. Therefore, damage on the liver inflicted by hepatotoxic agents is of grave consequences. Hepatic injury is a fundamental pathological process in most chronic disease. Hepatic diseases represent the major cause of human mortality in the world. They are characterized by a progressive evolution from steatosis to chronic hepatitis, fibrosis, cirrhosis and hepatocellular carcinoma [1]. A major cause of these disorders is due to exposure to different environmental pollutants and xenobiotics such as, alcohol, paracetamol, carbon tetrachloride and thioacetamide [2-5].

Also, the kidneys possess the common xenobiotic metabolizing enzymes, mainly localized in proximal tubular cells [6]. A number of environmental contaminants, chemicals and drugs dramatically alter the structure and function of the kidneys [7].

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Carbon tetrachloride (CCl_4), an industrial solvent, cleaner and degreaser. It was demonstrated that liver is not the only target organ for CCl_4 toxicity, but also the kidney [8, 9]. The initial step in biotransformation of CCl_4 is reductive dehalogenation [10] with a production of various free radicals. As electrophils, these free radicals initiate the lipid peroxidation process and induce damages and dysfunctions of DNA and proteins. Moreover, CCl_4 was demonstrated to induce tissue apoptotic changes and apoptosis [11, 12]. Also, CCl_4 upregulates the gene expression of many inflammatory markers [13, 14], mean- while down regulates the gene expression of many antioxidant enzymes triggering an oxidative stress [15]. Chronic injury by Ccl_4 induced significant over- expression of profibrogenic cytokines and activating nuclear factor kapp B (NF-KB) [16, 17]. CCl_4 challenge potentiates the immune reactions [18]. Overall, the pathogenesis of kidney and liver by CCl_4 is multifactorial ranging from gene expression, oxidation, inflammation, immune reactions, apoptosis and necrosis.

Accordingly, the administration of compounds with antioxidant activity has been successfully used to prevent or ameliorate CCl_4 induced nephrotoxicity and hepatic damage such as vitamin C [19] and melatonin [20].

In recent years, the concept of chemoprevention by naturally occurring dietary substances has been strengthened. Various phytochemical components, especially polyphenols such as flavonoids, phyenyl propanoids, phenolic acids, tannins and others. Coriander contains about 1% volatile oil mainly linalool, 20% oleic, petroselinic and linolenic fatty acids, monoterpene hydrocarbons, up to 26% flavonoid glycosides [21] demonstrated that CS has considerable levels of carotenoids. These compounds are known to be responsible for the antioxidant activities and to be inversely associated with cytotoxicity [22]. Besides, they have shown biological activities as anti-tumor, chemopreventive and anti-inflammatory agents and may play a role in regulating the activity and/ or expression of certain enzymatic systems that are included in apoptosis, tumor promotion , intracellular signal transduction or xenobiotic metabolizing enzymes [23]. *Coriandeum sativum* (Coriander) of family Umbelliferae is a well known plant derived from the traditional system of medicine in India and a native of Mediterranean region. CS is considered as a rich source of biologically active compounds mainly polyphenolic compounds. It has been reported to possess diuretic, carminative, digestive, anthelmintic, antioxidant [24] and antibacterial and antifungal activities [25]. Moreover, coriander has been shown to possess cardioprotective effects [26], anti rheumatic activity [27], cognitive- enhancing power [28] and improving memory in Alzheimer's disease [39]. In addition, the seed has a significant hypolipidemic action [30] and hypoglycemic effects [31].

However, scientific studies on the hepatorenal protective potential of CS leaves and stem are lacking. Therefore, this study was planned to investigate the ability of coriander's leaves and stem to overcome or modulate the toxic effects of CCL_4 in rat liver and the kidneys and to postulate the possible mechanistic way for such protection.

MATERIALS AND METHODS

Plant Material: The fresh leaves and stem of coriander were collected from the local market at Cairo, Egypt and authenticated by a taxonomist in phytochemistry and plant systematic Department, National Research Center (NRC), Egypt. A voucher specimen has been deposited at the Herbarium unit of NRC. The plant samples were air-dried for 10 days and powdered. The powdered samples were placed in air tight container for future use.

Phenolics Estimation

Determination of Total Phenolic Content: Total phenols content in CS powder were estimated by a colorimetric analysis based on procedures described in AOAC [32]. Briefly, known weights of dried sample 100 mg was used, 10 ml hydrochloric acid (0.1N) were added and strongly sharked. The mixture was heated at 100°C for 1 hour, cooled and filtered. One ml of the filtrate was mixed with 0.5 ml folin (Diluted 1:1 with distilled water) and 1ml sodium carbonate and the volume were completed to 10 ml with distilled water. After 30 minutes the intensity of the blue color was measured at 760 nm. A calibration curve was constructed using tannic acid standard solution. Sample concentration of total phenolics was expressed as tannic acid equivalent.

***Determination of Flavonoids*:** Flavonoids were estimated according to Price *et al.* [33] procedure. Briefly, 0.2 gm dried CS powder was extracted for 1 hour at room temperature with 10 ml methanol. Hcl.(1%). After filtration, an aliquot (0.5 ml) was thoroughly mixed with vanillin reagent (2.5 ml) and incubated in water bath at 30 °C for 20 minutes. The absorbance was measured at 500 nm. Catechin was used as standard for the construction of a calibration curve and the concentration was expressed as catechin equivalent.

Identification of Individual Phenolic Compounds: High performance liquid chromatography (HPLC) was used to identify individual phenolics. Phenolic compounds were extracted according to the method of Duck *et al.* [34]. Phenolics were identified by comparing their relative retention times with those of standard chromatogram.

Animals: Adult male Sprague-Dawely rats weighing 120-150 gm were purchased from Animal House of the National Research Center (NRC), Dokki, Giza, Egypt. They were kept individually in stainless steel wire bottomed cages at room temperature (25±2 °C) under 12 hr dark light cycle. Animals were fed balanced diets. Rats had free access to food and water. They were used after acclimatization period of one week. Animal experiments were conducted according to the guidelines of Animal Care and Ethics Committee of the NRC.

Experimental Design: Animals were randomly assigned to four groups each of six rats. Group one was the control that fed balanced diet. Second group, was CCL_4 group that fed balanced diet and administered CCL_4 (1ml/kg body weight) intraperitoneally [35] twice per week for two weeks. Third group was fed 20% coriander diet (Table 1) and injected with CCL_4 as group 2. The fourth group was fed 40% coriander powder and administered CCL_4. The experiment was lasted after four weeks after which all animals were starved over night and then blood samples were collected on heparin under light ether anesthesia from retro orbital vein. One part of blood was left for SOD analysis and other part was centrifuged at 4000 rpm for 20 min under cooling and plasma was separated and stored at -80°C for subsequent determinations.

Biochemical Assays: Plasma aspartate and alanine aminotransferases activities were determined according to Reitman and Frankel [37]. Alkaline phosphatase activity in plasma was determined according to the principle of Belfield and Golbderg [38]. Lactate dehydrogenase activity was evaluated by kinetic procedure according to Young's method using kit provided from Biosystems. s.A. Plasma urea, uric acid and creatinine levels were estimated according to Fawcett and Scatt [39], Watts [40] and Hauot [41], methods respectively using Bio Diagnostics kits. Plasma catalase was evaluated by reacting a known quantity of hydrogenperoxide (H_2O_2) in the presence of peroxidase. The remaining H_2O_2 formed a chromophore with a color intensity inversely proportional to the amount of catalase in the sample [42]. Finally, SOD was estimated by the method of Nishikimi *et al.* [43]. This assay relied on the ability of SOD to inhibit the phenazine- methosulphate mediated reduction of nitroblue tetrazolium dye.

Table 1: The composition of the tested diets (g / kg).

		Coriander	
Ingredients	Control[a]	20%	40%
Casein	120	120	120
Sucrose	100	100	100
Hydrogenated fat	100	100	100
Oil	50	50	50
Salt mix.	35	35	35
Vitamin mix.	10	10	10
L-Cystin	1.8	1.8	1.8
Cholin chloride	2.5	2.5	2.5
Coriander powder	-	200	400
Starch	580.7	380.7	180.7

[a.] The control diet contents [36].

Statistical Analysis: Data were expressed as mean ± standard error. Student's T-test (2- tailed) was applied to compare between groups. Differences were considered to be significant at $p< 0.05$.

RESULTS

Total phenolics in aerial parts of CS were determined as tannic acid equivalents. The level of total phenolics was 4.08mg/g tannic acid equivalents. Meanwhile, total isoflavones were evaluated as catechin equivalent. Leaves and stem of CS had 12.29mg/g catechin equivalent. Also, individual phenolics were analysed using HPLC. The major phenolics in the methanolic extract of CS were genstin (3%w/w), rutin (0.56%), dadzin (o.17%), vanillin (0.14%) and quercetin (0.1%) as shown in Table (2).

Table 2: HPLC analysis of polyphenols in the methanolic extract of coriander.

Ingredients	mg/100g powder
Gallic acid	10
Phenol	10240
Catechin	10
Caffic acid	180
Vanillin	140
Salicylic acid	80
Dadzin	170
Ferulic	130
Genstin	3040
Rutin	560
Cinnamic	30
Dadazien	36
Quercetin	100
Genstein	11
Phenol phethalin	3300
Gulangin	30
Aca catachin	10
3,5 di(OH) isoflavin	30

Table 3: Effects of coriander diets on hepatic enzymes activities in CCL4 intoxicated rats.

	Groups			
Parameters	Control	CCL_4	CCL_4 +20% coriander	CCL_4 +40% coriander
AST (U/ml)	51.8±0.448	67±1.49 a**	65.8±3.82	52.2±2.40 b**
ALT (U/ml)	16.3±0.514	36.4±1.85a**	19.2±0.27 b**	17.4±0.284b**
ALP (U/L)	105±0.547	266±10.6 a**	180±0.85 b**	130±2.57 b**
LDH (U/L)	116±0.968	173±5.23 a**	134±1.28 b**	123±3.36 b**

Values are expressed as mean ± S.E.

[a]: values significantly differ from normal control.

[b]: values significantly differ from CCL4 group

*: P< 0.01 **: P< 0.001

Table 4: Effects of coriander diets on renal biomarkers in CCL4 intoxicated rats.

	Groups			
Parameters	Control	CCL_4	CCL_4 +20%coriander	CCL_4 +40%coriander
Urea (mg/dl)	35.2±o.702	45.9±o.411 a**	33.7±0.715 b**	26.9 ±1.30 b**
Uric acid (mg/dl)	2.51±0.154	4.35 ±0.15 a**	2.73±0.193 b**	2.38 ±0.121b**
Creatinine (mg/dl)	0.77±0.056	1.16 ±0.012 a**	0.79 ±0.033 b**	0.71 44±0.022 b**

Values are expressed as mean ± S.E.

[a]: values significantly differ from normal control.

[b]: values significantly differ from CCL4 group

*: P< 0.01 **: P< 0.001

Table 5. Changes of superoxide dismutase and catalase activities in intoxicated rats.

	Groups			
Parameters	Control	CCL_4	CCL_4 +20%coriander	CCL_4 +40%coriander
SOD (U/ml)	399±o.86	204±2.50 a**	245±1.75 b**	291±3.12 b**
Catalase (U/ml)	600±18.50	105±9.17 a**	208±15.80 b**	336±22.10 b**

Values are expressed as mean ± S.E.

[a]: values significantly differ from normal control.

[b]: values significantly differ from CCL4 group

*: P< 0.01 **: P< 0.001

DISCUSSION

Ccl_4 intoxication in animals is an experimental model that mimics oxidative stress in many physiological situations. Moreover, CCl_4 induced hepatotoxicity is similar to that of viral hepatitis. Cumulative data suggest a role of ROS as one of the postulated mechanisms for CCl_4. Also, in recent years, there has been considerable interest in free radical- mediated damage in biological systems due to environmental pollution and pesticide exposure [45]. An interest has increased in naturally-occurring antioxidants that can be used to protect from oxidative stress damage induced by CCl_4 [46-49]. This is largely due to the afford ability of these products along with no or fewer side effects they produced as compared to conventional drugs. CS is commonly used as a food ingredient, is claimed to be useful for various ailments via its antioxidant activity [30, 50]. The present study was designed to reveal the hepato-renal protective effects of CS against CCl_4 intoxication in this study [51].

CS leaves and stem, in our work, were found to contain180 mg caffeic acid/ 100 g of dry weight [52]. Meanwhile, they had 100 mg/ 100g quercetin as shown in our result. Hashim *et al.* [53] reported the presence of 49.8-397mg/ 100g quercetin as a major antioxidant in CS.

Our emerged data revealed that CCl_4 treatment causes severe hepatic damage through a substantial increment in the blood levels of hepatic biochemical markers like ALT, AST and ALP [9, 54-56]. The most important function of the liver is detoxification of toxicants and different medications such substances impose excess stress on the liver filtering function. If accumulation of toxins is faster than the liver metabolizing ability, hepatic damage may occur [57]. In liver, CCl_4 is biotransformed by cytochrome P_{450} to produce its active metabolite trichloromethyl free radical (CCl^{-}_{3}) [58] which bind to the macromolecules and induces peroxidative degradation of membrane lipids which are rich in polyunsaturated fatty acids. This leads to the formation of lipid peroxide, which in turn produces toxic aldehyde that causes damage to liver [59]. When the

liver cell membrane is damaged, a variety of enzymes normally located in the cytosol are released in to blood stream like, AST, ALT and ALP. AST and ALT are found in higher concentrations in the cytoplasm and AST in particular also exists in mitochondria. AST is found in the liver, cardiac muscle, skeletal muscles, pancreas, kidney and others, meanwhile, ALT level is highest in the liver and therefore, it appears to be more sensitive test for hepatocellular damage than AST [60]. However, the elevated activities of AST and ALT are indicative of cellular leakage and loss of functional integrity of cell membranes in liver [61]. On the other hand, ALP is excreted normally via bile by the liver. CCl_4 impairs the integrity, structure and function of the hepatocytes via its ROS, leading to defective secretion of the bile which is reflected by increasing ALP levels in the blood [4]. Our results also demonstrated that lactate dehydrogenase activity was elevated by CCl_4 [62, 63] LDH is an oxidoreductase enzyme in glycolytic pathway whose activity is necessary for the reversible reaction in which pyruvate and lactate are interconvert. Classically, five LDH isoenzymes are present; LDH_4 and LDH_5 are predominantly in liver. LDH is used as a marker for liver injury [62]. Tissue LDH concentration is much higher than in serum or plasma. So, the increased enzyme activity in plasma is indicative to extreme necrosis of the liver tissue during intoxication [64, 64]. The leakage of LDH from hepatic cells is used as a signs of cytotoxicity [65].

It is well known that the kidneys play a pivotal role in the regulation of various chemicals. They participate in the maintenance of constant extracellular environment that is required for adequate functioning of the cells. This is achieved by excretion of the waste products of metabolism such as urea, uric acid and creatinine. Administration of CCl_4 causes nephrotoxicity as indicated by significant increase of plasma creatinine, urea and uric acid levels [9, 51, 66, 67]. The elevated concentrations of the above renal markers could be attributed to the damaged structural integrity of nephron by CCl_4. Makni *et al*.[67] reported that CCl_4 caused a significant damage to renal structure, manifested as marked glomeruli and tubular damages probably due to the generation of ROS. So, hydroperoxides accumulated in kidney could cause cytotoxicity associated with membrane phospholipids peroxidation, the basis for renal damage and necrotic renal cells. In addition, the vasoconstriction that induced by CCl_4produced a local ischemic environment Aggravates cellular damages [47]. However, CCl_4 intoxication also altered the proximal tubular epithelial cells, mitochondria and lysosomes. The later released their contents into the tubular lumen with concomitant tubular damage [68]. Also, CCl_4- treatment resulted in massive DNA fragmentations, a hallmark feature of renal necrosis [51].

Reactive oxygen species are produced during normal aerobic metabolism. The intracellular concentration of ROS is a consequence of both their production and their removal by various antioxidants. A major antioxidant system in mammalian cells consists of SOD, catalase and glutathione peroxidase (GPx). These enzymes work in concert to detoxify superoxide anion (O_2^-) and H_2o_2 in cells. In fact, SOD catalyzes the dismutation of superoxide radical to hydrogen peroxide which is consequently reduced by catalase or GPx to H_2O [69]. CCl_4 intoxication extremely reduced both SOD and catalase. It is conceivable, that the overproduction of ROS by CCl_4 consumed the antioxidant enzymes [9, 62, 70]. CCl_4 induced a condition of oxidative stress due to the increased ROS production that consumed the antioxidant enzymes leading to their depletion. Besides, the decrease of these enzymatic activities could be explained by the crosslinking of their molecules caused by the formation of malodialdehyde- protein adducts which affects their conformation and biological activity. The exposure of CCl_4 increased the level of malondialdehyde (MAD). Where, MAD reacts with protein amino, sulfhydryl and imidazole groups [71]. Moreover, CCl_4 down regulates the expression of SOD and catalase genes with concomitant reduction of their activities.

Pretreatment with CS before introduction of CCl_4 had significantly reduced the elevated plasma enzyme levels of ALT, AST, ALP and LDH indicating a hepato- protectant activity of CS. Our results confirm those written earlier [4, 54, 71]. Feeding CS also profoundly modulated renal function as demonstrated by a significant reduction of creatinine, urea and uric acid levels. Aga *et al.* reported that CS decreased severe lead induced injury in the kidneys. Moreover, CS consumption restored the antioxidant enzymes (SOD and catalase). The antioxidant potential of CS was reported previously [25, 74]. The effects of CS were dose dependent as 40% CS in diet produced more pronounced effects than 20% level.

The hepatorenal protection of CS against CCl_4 as manifested from our data is attributed to various mechanisms; primarily, its antioxidant activity which results from the polyphenolic constituents in CS. Polyphenols of CS act as antiperoxidative agents for the prevention of oxidative damage in living systems [52]. CS via its antioxidant activity quenches ROS produced by CCl_4, reserves antioxidant enzymes and restores their

levels and protects cellular organelles from CCl_4 damage such as cell membrane, lysosomes, mitochondria and microsomes. Generally, some flavonoids exert a stimulatory action on transcription and gene expression of certain antioxidant enzymes [72] that play an important role against oxidative insults. Vanillin, a polyphenolic compound, in CS was found to be effective in preventing DNA fragmentation caused by CCl_4 [51]. Additionally, the aqueous extract of CS was reported to mitigate DNA damage induced by toxins [73]. Moreover, CS has an anti-apoptotic effect. It protected the mitochondria and restored mitochondrial function. Where, mitochondrial dysfunction is considered from CCl_4 pro-apoptosis signals [11].Besides, CS exhibited an anti inflammatory and cytoprotective effects [74, 75]. Both CS flavonoids [15] and carotenoids [76] are potent anti- inflammatory compounds. Finally, xenobiotics are detoxified from the body by metabolizing enzymes which is affected by certain nutrients [77]. CS induced glutathione S transferase, a detoxifying enzyme in phase II [9].

The results of the present study showed that CCl_4 intoxication considerably damaged both the liver and kidneys as manifested by the increase of their plasma markers. It also depleted the antioxidant enzymes. CS treatment conspicuously protected the liver and kidneys from CCl_4 deleterious effects by conserving the endogenous antioxidant mechanism and scavenging free radicals. As a result, consumption of CS enriched in phenolic compounds can protect humans against nephrotoxicity and hepatotoxicity induced by various xenobiotics and help maintain healthy liver and kidneys.

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