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Protective Effect of Cinnamon and/or Parsley Oils Against Carbon Tetrachloride (CCl4) Induced Hepatotoxicity in Rats

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Abstract

In the present study the hepatoprotective potential cinnamon and/or parsley oils was assessed on CCl4 induced toxicity in rat. In the present study 49 male albino rats were randomly assigned into 7 equal groups (7 rats each). Group 1: rats which served as the control was administered saline (the vehicle) orally once daily for 30 consecutive days. Group 2: rats in this group were served as cinnamon treated group and were orally administered (400 mg/kg b.wt.), once daily for 30 days. Group 3: rats in this group were served as parsley treated group and were orally administered (200 mg/kg b.wt.), once daily for 30 days. Group 4: Rats in this group were served as CCl4 treated group and was only injected with 1 ml/kg body weight of CCl4 intraperitoneally (CCl4: olive oil; 2:8 v/v), 3 times/week/ 4 weeks. Group 5: rats in this group were administered cinnamon and CCl4. Group 6: rats in this group were administered parsley and CCl4. Group 7: rats in this group were administered both cinnamon and parsley and CCl4. Concentration of alanine transaminase (ALT), alkaline phosphatase (ALP) and aspartate transaminase (AST) increased whereas level of total protein and albumin decreased in serum of CCl4 treated rats. Moreover, lipid profile was estimated. In hepatic sample of rat, CCl4 administration declined the antioxidant enzymes; superoxide dismutase (SOD), catalase (CAT) and in reduced glutathione (GSH). Also, histopathological alterations were induced with administration of CCl4 to rats. The altered levels of various parameters provoked by CCl4 toxicity restored towards the control level by cinnamon and/or parsley oils administration. These results suggested the presence of antioxidant phyto-constituents in these oils.

Keywords: CCl_4; Cinnamon; Parsley; Liver; Rats

Introduction

Liver disorders are among the major health problems and are the 5th common cause of death worldwide [1,2]. Liver is the largest internal organ of human body plays a crucial role in detoxification of detrimental substances and is accountable for maintaining body homeostasis by regulating many vital metabolic functions [3]. Carbon tetrachloride (CCl_4) as a standout amongst the hepatotoxins, is generally utilized to induce experimental models [4]. It is accepted that CCl_4 hepatotoxicity occurs due to its reductive dehalogenation reaction which is catalyzed by cytochrome P-$_{450}$ in hepatocytes [5]. This response actuates the generation of a few sorts of Reactive Oxygen Species (ROS) [6]. These ROS can bind to lipids or proteins resulting in creation of distinctive radicals and initiation of lipid peroxidation which end up in membrane injury and consequently damage the liver [7,8].

Cinnamon (*Cinnamomum zeylanicum*) is well-known as a potential supplement of natural antioxidants due to its high content of polyphenolic compounds. Cinnamon is a widely used herbal plant in the folk medicine with a diverse of pharmacological actions such as antioxidant, anti-inflammatory, anti-diabetic, and anti-microbial effects [9,10]. Cinnamaldehyde, cinnamic acid, and eugenol are the major components identified in the cinnamon extract with a powerful free radical scavenging activity which in turn suppress the oxidative damage through restoring the redox hemostasis and normal cell function [11]. Parsley, *Petroselinum crispum* (Mill.), is used as a flavoring agent in food products or fragrance in perfumery and cosmetics, as stated in many patents. Antimicrobial, diuretic and weak antioxidant activities of parsley essential oil have been reported [12]. Myristicin from parsley oil is a potential cancer chemoprotective agent [13]. Antioxidants act as radical scavengers, inhibiting lipid peroxidation and oxidation processes and protect the human body from several diseases attributed to the reactions of radicals [14]. Therefore; the goal of the present

research work was to study if the hepatic toxicity induced by CCl_4 can be ameliorated by the use of cinnamon and/or parsley oils in rats.

Materials and Methods

Drugs

Carbon tetrachloride (CCl4), were purchased from Sigma-Aldrich (St. Louis, MO, USA). Cinnamon and parsley were obtained from El-Captain Company for extracting natural oils, herbs, and cosmetics, El-Obour City, Cairo, Egypt.

Experimental animals

The present study was carried out on 49 Wister albino male rats weighing 190-220 gm. Rats were obtained from Laboratory Animal center, Faculty of Veterinary Medicine, Benha University, Egypt. Rats received standard commercial diet and water ad libitum. Ethics Committee of the Faculty of Veterinary Medicine, Benha University approved the use of rats and the study protocol.

Experimental Design

Rats were randomly assigned into 7 equal groups (7 rats each). Group 1: rats which served as the control was administered saline (the vehicle) orally once daily for 30 consecutive days. Group 2: rats in this group were served as cinnamon treated group and were orally administered (400 mg/kg b.wt.), once daily for 30 days [15]. Group 3: rats in this group were served as parsley treated group and were orally administered (200 mg/kg b.wt.), once daily for 30 days [16]. Group 4: Rats in this group were served as CCl_4 treated group and was only injected with 1 ml/kg body weight of CCl_4 intraperitoneally (CCl_4: olive oil; 2:8 v/v), 3 times/week/ 4 weeks [17]. Group 5: rats in this group were administered cinnamon and CCl_4. Group 6: rats in this group were administered parsley and CCl_4. Group 7: rats in this group were administered both cinnamon and parsley and CCl_4.

Sampling

After the end of experiment, blood samples were collected directly from the caudal vena cava and kept at room temperature without anticoagulant for serum separation intended for the biochemical studies. Liver tissues were also collected for oxidative cascade determination and histopathological examinations.

Serum Biochemical Studies

Sera were used for spectrophotometric estimation of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) enzyme activities and total protein, albumin, cholesterol, triglycerides, HDL cholesterol concentrations using commercial assay kits (Biodiagnostic, Chemical Co., Egypt).

Preparation of liver homogenates and determination of oxidative cascade

Oxidative status was done by determination of malondialdehyde (MDA) level [18], catalase (CAT) activity [19], superoxide dismutase (SOD) activity [20], and GSH concentration [21], using special diagnostic kits obtained from Bio diagnostic Co, Egypt.

Histopathological examinations

Tissue samples were collected from liver were prepared and stained with H&E [22].

Statistical Analysis

Statistical analysis was performed using SPSS (Version 20.0; SPSS Inc., Chicago, IL, USA). The significant differences between groups were evaluated by one-way ANOVA using Duncan test as a post hoc. Results are expressed as mean ± SE. All values at $P \leq 0.05$ were considered significant.

Results

Table 1: Biochemical changes of cinnamon and/or parsley oils on CCl_4 induced hepatic toxicity in rats.

Groups	AST (U/L)	ALT (U/L)	ALP (U/L)	T. Protein (g/dl)	Albumin (g/dl)
Control	77.51±3.21^{d}	37.65±1.06^{d}	121.42±6.45^{d}	7.84±0.23^{a}	4.80±0.03^{a}
CN	74.18±2.25^{d}	36.86±1.45^{d}	124.53±2.02^{d}	7.42±0.08^{b}	4.80±0.03^{a}
PR	76.74±1.74^{d}	37.51±0.45^{d}	125.78±3.09^{d}	7.78±0.05^{a}	4.72±0.08^{a}
CCl_4	193.64±6.81^{a}	104.04±5.1^{a}	266.69±19.60^{a}	5.43±0.02^{e}	3.29±0.05^{d}
CCL_4+CN	158.29±2.92^{b}	83.64±3.25^{b}	222.27±7.01^{b}	6.16±0.03^{d}	4.01±0.01^{c}
CCL_4+PR	152.47±3.50^{b}	85.58±1.15^{b}	208.38±6.59^{b}	6.14±0.03^{d}	4.02±0.01^{c}
CCL_4+CN+PR	117.23±2.76^{c}	71.78±2.41^{c}	178.59±4.92^{c}	6.76±0.07^{c}	4.36±0.03^{b}

Values are represented as Mean ± SE (n = 7). Means within the same column carrying different superscript are significant at ($p<0.05$).
CN; cinnamon, PR; parsley, CCl4; carbon tetrachloride.

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Table 2: Lipid profile parameters after cinnamon and/or parsley oils on CCl4 induced hepatic toxicity in rats.

Groups	Cholesterol (mg/dl)	Triglycerides (mg/dl)	HDL-cholesterol (mg/dl)	LDL-cholesterol (mg/dl)
Control	81.89±1.81^{d}	148.8±3.20^{d}	45.12±1.22^{ab}	6.99±2.54^{d}
CN	82.60±1.70^{d}	146.69±5.08^{d}	46.35±0.36^{a}	6.90±1.05^{d}
PR	81.84±1.01^{d}	155.20±2.39^{d}	44.08±0.31^{b}	6.72±0.94^{d}
CCl_4	184.26±4.12^{a}	262.71±3.44^{b}	21.98±0.46^{e}	110.33±4.8^{a}
CCl_{4+}CN	152.30±3.27^{b}	231.79±2.81^{b}	28.68±0.42^{d}	77.25±3.25^{b}
CCl_{4+}PR	145.15±3.64^{b}	224.17±3.67^{b}	28.77±0.21^{d}	71.53±4.14^{b}
CCl_{4+}CN+PR	121.64±3.21^{c}	189.28±2.88^{c}	36.12±0.45^{e}	47.65±3.28^{c}

Values are represented as Mean ± SE (n = 7). Means within the same column carrying different superscripts are significant at (p<0.05).
CN; cinnamon, PR; parsley, CCl4; carbon tetrachloride.

Table 3: Oxidative stress biomarkers after cinnamon and/or parsley oils on CCl4 induced hepatic toxicity in rats.

Groups	MDA (nmol/g)	CAT (U/g)	SOD (U/g)	GSH (mg/g)
Control	58.81±0.99^{de}	3.55±0.06^{a}	25.57±0.63^{a}	60.86±0.76^{a}
CN	59.92±2.25^{de}	3.62±0.04^{a}	25.16±0.30^{a}	59.19±1.10^{a}
PR	55.05±2.74^{e}	3.59±0.04^{a}	23.98±0.51^{b}	58.42±1.93^{a}
CCl_4	122.78±3.67^{a}	1.75±0.04^{d}	11.67±0.31^{e}	31.16±0.17^{d}
CCL_4+CN	98.73±3.14^{b}	2.40±0.02^{c}	15.06±0.29^{d}	40.75±0.44^{c}
CCL_4+PR	89.24±1.53^{c}	2.36±0.03^{c}	14.84±0.35^{d}	39.51±0.68^{c}
CCL_4+CN+PR	65.11±0.89^{d}	2.98±0.02^{b}	20.30±0.28^{c}	49.83±0.58^{b}

Values are represented as Mean ± SE (n = 7). Means within the same column carrying different superscripts are significant at (p<0.05).
CN; cinnamon, PR; parsley, CCl4; carbon tetrachloride.

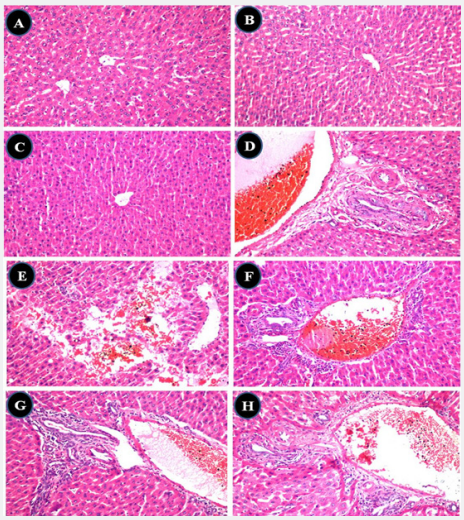

Figure 1: Histopathological changes after cinnamon and/or parsley oils on CCl4 induced hepatic toxicity in rats.

Liver of control group, cinnamon oil and parsley oil treated groups showed no histopathological alteration and the normal histological structure of the central vein and surrounding hepatocytes in the parenchyma was recorded in Figure 1 (A & B & C), respectively. Liver of carbon tetrachloride (CCL4) treated group showed congestion in the portal vein with periductal fibrosis surrounding the bile ducts (Figure 1D) and focal hemorrhage in the hepatic parenchyma (Figure 1E). Liver of carbon tetrachloride (CCL4) and cinnamon oil treated group showed dilatation and congestion in both central and portal veins associated with inflammatory cells infiltration as well as aggregation in the portal area with fatty change in the surrounding hepatocytes (Figure 1F). Liver of carbon tetrachloride (CCL4) and parsley oil treated group showed dilatation was observed in the central and portal vein associated with inflammatory cells infiltration in the portal area (Figure 1G). Liver of carbon tetrachloride (CCL4), cinnamon oil and parsley oil treated group showed dilatation in the central and portal veins associated with periductal inflammatory cells infiltration surrounding the bile ducts at the portal area (Figure 1H).

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Concerning to biochemical parameters results, rats administrated CCl_4 showed significant elevation of AST, ALT, ALP, cholesterol, triglycerides and LDL-cholesterol and significant decrease in total protein, albumin and HDL-cholesterol concentrations when compared to control groups. Considerable improvement in these parameters was observed following cinnamon and/or parsley administration and these results were recorded in Tables 1 & 2. Regarding to the results of oxidative stress (Table 3), the rats administrated CCl_4 showed marked increase in MDA and significant decrease in CAT, GSH and SOD in hepatic tissues when compared to control groups. Considerable improvement in these parameters was observed following cinnamon and/or parsley administration. Our results of histopathological examination of hepatic tissues in different treated groups showed alterations in their histological architecture. An improvement in histopathology was observed following cinnamon and/or parsley administration (Figure 1).

Discussion

Elevation in serum ALT, AST and ALP activity induced by CCl_4 have been ascribed to hepatic structural damage because these enzymes are generally localized in the cytosol and released into the blood circulation after cellular damage [23]. In the present study, the levels of all these enzymes increased in CCl_4 group (CCl_4-treated group) indicating liver damage induced by CCl_4. Restoration of serum enzyme activities to normal amounts in rats after treatment with cinnamon oil and/or parsley oil showed prohibition of the leakage of intracellular enzymes by maintaining the integrity of liver cells membrane. In this experiment, CCl_4 also decreased serum total protein and albumin while cinnamon oil and/or parsley oil significantly restored the protein synthesis and similar results were recorded [24]. The hepatoprotective effect of cinnamon oil and/or parsley oil was further investigated by the histopathological examinations.

Treatment of rats with CCl_4 increased the concentration of total cholesterol, triglycerides and LDL while the concentration of HDL decreased in the serum as compared to control group of rats. These results suggested the overwhelming production of ROS caused by CCl_4 administration which impaired the metabolic function of liver and consequently the altered level of total cholesterol, triglycerides, LDL and HDL was recorded in this study. In previous investigations similar effects of CCl_4 on the above parameters have been reported [25]. The altered level of total cholesterol, triglycerides, LDL and HDL in serum of rat induced with CCl_4 was reverted towards the control group by the co-administration of cinnamon oil and/or parsley oil to rats. These results suggest that antioxidant phyto-constituents may be responsible for the lipid homeostasis obtained with co-administration of cinnamon oil and/or parsley oil to rat. Significant increase of lipid profile indicated a severe lipid peroxidation and regarding the studied groups, of the present study, an increase of the parameters of the lipid profile was observed in the animals with CCl_4-induced hepatopathy, concerning total cholesterol, triglycerides, LDL and also lowering HDL; administering cinnamon oil and/or parsley oil determined a regulation of these parameters. Furthermore, antioxidant activity and/or inhibition of free radicals production was important with regards to the protection of liver against CCl_4-induced damage [26]. It had been proven that cinnamon oil and/or parsley oil had strong protective effects against liver damage.

Oxidative stress also plays an important role in the etiology of hepatic fibrosis [27,28]. Free radicals that are released in cells when toxic substances are not fully metabolized can cause liver damage. Treatment with carbon tetrachloride (CCl_4) is widely used to create a hepatotoxicity model for experimental studies [29,30]. When metabolized by hepatic microsomal enzymes, CCl_4 forms free radicals that cause liver damage by triggering multiple harmful reactions including lipid oxidation [31].

Lipid peroxidation is a major index of oxidative stress. Elevated levels of liver MDA induced by CCl_4 imply enhanced lipid peroxidation which leads to hepatocellular damage and failure of natural antioxidant defense system to prevent overproduction of free radicals [32]. It has been presumed that one of the main underlying mechanisms of CCl_4-induced liver damage is formation of lipid peroxides by free radicals produced by CCl_4. Hence, the antioxidant activity or the prohibition of the production of free radicals is important in the defense against CCl_4-induced hepatotoxicity [33]. The body has an impressive defense system to hinder and nullify the free radicals-induced harm. This system possesses a collection of endogenous antioxidant enzymes like SOD and CAT. These enzymes establish a supportive group of defense system against ROS [34]. In hepatotoxicity induced by CCl_4, the balance between ROS formation and these antioxidant defenses may be vanished and oxidative stress occurs; oxidative stress during a series of events, disturbs the cellular functions leading to hepatic damage. Diminished activities of SOD, CAT and GST indicate the hepatic injury in the rats administered with CCl_4 [24], but treatment with cinnamon oil and/or parsley oil showed significant elevation in the level of these enzymes, which reflects its antioxidant activities. Concerning non-enzymatic antioxidants, GSH is a crucial determinant of tissue proneness to oxidative damage and the depletion of hepatic GSH has been shown to be related with an enhanced toxicity to chemicals, including CCl_4 [35]. In this study, a decrease in liver tissue GSH level was observed in CCl_4-treated groups. The increase in hepatic GSH level in the animals treated with cinnamon oil and/or parsley oil may be due to GSH synthesis or GSH regeneration.

In a histological study of male Sprague-Dawley rats that were exposed to CCl_4, [36] reported hepatocellular degeneration, necrosis, inflammatory cell infiltration, sinusoidal dilation and congestion. We also found focal necrotic areas with degenerated hepatocytes, sinusoidal dilation and hyperemia in rats treated with CCl_4. These pathological findings were nearly eliminated by cinnamon oil and/or parsley oil administration.

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Antioxidants present in cinnamon oil may help trap ROS and peroxidation products and protect enzymes. This hypothesis is supported by the recent finding of *in vitro* antiradical and antioxidant activities of cinnamon oil [37,38]. Cinnamaldehyde was the main compound responsible for the antioxidant activity of cinnamon oil [39]. These compounds could interact with the ROS induced by CCl_4, which induce aggressive oxidants [37]. Therefore, our results show that cinnamon oil exhibits a strong protective effect and may be a useful source of cellular defense agents in liver tissues against CCl_4. Our findings are supported by previous data reported the antioxidant and organ-protective effects of parsley oil. Parsley has many pharmacological effects, including antioxidant and hepatoprotective effects [40-42].

Conclusion

Overall, our findings provide clear biochemical, histopathological evidence that administration of cinnamon oil and/or parsley oil protects rat liver tissue from the toxic effects of CCl_4. Cinnamon oil and/or parsley oil reduces lipid oxidation and exerts a clear hepato-protective effect. The anti-hepatotoxic effects of cinnamon oil and/or parsley oil likely are due to two mechanisms: they act as antioxidants by scavenging active oxygen and free radicals, and by preventing lipid oxidation.

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