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Ameliorative Effect of Cinnamon Extract Against Induced Hepatotoxicity in Male Rats

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Abstract

Background Carbon tetrachloride (CCl4) causes oxidative stress in a variety of pathophysiological circumstances that can induce liver damage. Finding an effective antioxidant that can repair liver damage brought about by CCl4 is crucial. Aim This study investigated whether cinnamon ethanolic extract (CE) could reduce liver damage brought on by CCl4. Methods Twenty male rats were divided into four identical groups of five rats each; group I, the normal control: rats were fed on basal diet, group II: rats were administered CE at a dose of 0.1mg/kg b.wt daily for four weeks , Group III: rats were subjected to IP injection of CCl4 at a dose of 0.5ml/kg b.wt twice weekly for four weeks, Groups IV: rats were co-administered oral dose of CE (0.1 mg/kg daily) and IP injection of CCl4 (0.5 ml/kg twice weekly) for four weeks . Results CCl4 dramatically increased MDA, TNF-α and TNO levels and decreased SOD activity, and GSH level compared to normal group while CE considerably decreased MDA, TNF-α, and TNO levels and improved SOD activity as well as GSH level comparative to the CCl4. Additionally, CCl4 caused a considerable rise in liver enzymes levels related to the control group, CCl4 also increased TC, TG and LDL-C along with a significant decrease in HDL-C levels . Histopathological analyses of the livers revealed that CE considerably decreased the toxicity of CCl4 and preserved the histoarchitecture of the liver tissue. Conclusions Constructed on its strong antioxidant activity and its phenolic and flavonoid contents, CE expressively reduced oxidative damage compared to CCl4 treated group.

1. INTRODUCTION

The primary organ in the body accountable for the breakdown of both endogenous and foreign substances is the liver. Hepatotoxicity may be caused by any harm that decreased liver function as a toxic non-infectious agent [1]. Hepatotoxic substances can interact with the fundamental elements of cells to cause virtually every type of liver damage. Among the primary etiopathogenetic causes of acute liver failure are toxins and medications [2]. Nevertheless, chemical poisons are frequently served as a model for experimental damage to hepatocytes both in vivo and in vitro (e.g., carbon tetrachloride, acetaminophen, galactosamine, and thioacetamide) [3], [4].

CCl_4 has been utilized extensively as a potent hepatotoxic, prooxidant, and nephrotoxic substance to develop hepatocellular carcinoma, cirrhosis, liver damage, chemical hepatitis, renal failure, and nephrotoxicity models in experimental animals. The primary mechanism of CCl_4 detrimental effect occurs by inducing oxidative damage, which begins after CCl_4 is converted by the cytochrome P450 enzyme to the highly toxic trichloromethyl ($CCl_3^{\bullet}$) and trichloromethyl peroxyl ($CCl_3O_2^{\bullet}$) radicals. Oxidative damage is characterized by total lipid disruption (i.e., lipid peroxidation). Free radicals and antioxidants need

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to coexist in equilibrium for normal physiological function [5].

By suppressing peroxidation of lipids and enhancing the antioxidant enzyme activity, multiple studies have demonstrated that botanical extracts with antioxidant performance guard against CCl_4 hepatotoxicity [5]**;** [6]. Plant extracts offer anti-inflammatory, anti-allergic, antithrombotic, antiviral, additionally to their capacity as anti-carcinogenic properties, neutralize free radicals. Cinnamomum zeylanicum is one of the most important and available herbal medication. The main chemical components of cinnamon are cinnamonaldehyde and cinnamic acid [7] **.** Cinnamon and its extracts have various health benefits as reducing total cholesterol, low-density lipoprotein, and triglycerides [8], anti-inflammatory and antibacterial properties [9], lowering level of glucose in blood [10] , antiangiogenetic [11] , anti- yeast effect [12], and immunizing against influenza [13].

In this investigation, oxidative stress, lipid profile, liver function tests, inflammatory indicators, and histopathology analyses were all employed to investigate whether Cinnamomum zeylanicum ethanolic extract (CE) is effective in reducing the hepatotoxicity brought on by CCl_4.

2. MATERIAL AND METHODS

2.1. Chemicals

The supplier of CCl_4 from Merck, Germany. Kamiya Company, USA provided the assay kits for the following: malondialdehyde (MDA), glutathione reduced (GSH), total nitric oxide (TNO), tumor necrosis factor alfa (TNF-α) and superoxide dismutase (SOD). Alanine aminotransferase (ALT), Aspartate aminotransferase (AST) and Alkaline phosphatase (ALP) were purchased from Spectrum company, Cairo, Egypt. All the chemicals used in the experiment were only analytical grade. Total cholesterol (TC), Triglycerides (TG), High density lipo-protein -Cholesterol (HDL-C) kits were purchased from Biomed company, Cairo, Egypt.

2.2. Preparation and extraction of the plant powder

The extraction was done According to Eidi, A et al., [14] at the Faculty of Science, Chemistry Department, Suez Canal University, Ismailia, Egypt. The plant was identified by Dr. Yasmin M. Hassan in the Suez Canal University Herbarium (SCUI), Botany and Microbiology Department, Faculty of Science, Suez Canal University, Egypt. In a nutshell, Cinnamomum zeylanicum barks were purchased from a local market, dried, ground, and extracted for 4 hours using 80% ethanol. Three duplicates of the extraction procedure were completed. After rotational evaporation and freeze drying, the finished dry powder was stored at -20 °C in the dark until it was needed in this study.

2.3. Identification of main polyphenols in CE by High Performance Liquid Chromatography (HPLC) Analysis of CE:

Agilent Technologies 1100 series HPLC equipped with an auto sampler and a diode-array detector was used in accordance with Kim KH et al., [15] to quantitatively analyze the polyphenols content in CE content of CE.· The analytical column was an Eclipse XDB-C18 (150 X 4.6 μm; 5 μm) with a C18 guard column (Phenomenex, Torrance, CA). Acetonitrile (solvent A) and 2% acetic acid in water (v/v) (solvent B) make up the mobile phase, the flow rate was kept at 0.8 ml/min for a total run time of 60 min. Peaks were identified by congruent retention times and UV spectra and compared with twenty various polyphenols standards

2.4. Experimental animals

Twenty adult male Albino rats, weighing between 180 and 200 g, were obtained from animal house, faculty of pharmacy, Suez Canal University . The animals were kept in stainless steel cages that had a 12 h:12 h light/dark cycle, a humidity level of 50–60%, and an ambient temperature 25 °C all the time. A standard diet of pellets was feed to rats and water adlibitum. Rats were kept a week for acclimatization before the onset of the experiment. Faculty of Veterinary Medicine's ethical committee approved the experiment (Approval # 2022010).

2.5. Experimental design

According to Ogeturk, M et al., [16], CCl_4 was injected intraperitoneally twice weekly for four weeks at a concentration of 0.5 mL/kg. CE was crushed and suspended in olive oil and given to rats orally

in a dose of 0.1 g/kg b.wt. /day [14]. twenty rats were divided into four equal groups (five rats each). Group I served as the baseline control group, receiving orally pure olive oil and a basal diet; Group II served as cinnamon extract; Group III served as the CCl_4; and Group IV received CCl_4 + CE. The body weights of rats were estimated continuously during the experimental period to adjust the doses.

2.6. Biochemical evaluation

At the end of the experiment, rats were fasted for 12 hours, weighed then blood samples were collected from retro orbital capillary plexus in the medial canthus of eye using micro-hematocrit tubes, which centrifuged at 3000 rpm for 10 minutes to get clear sera. Sera used to determine lipid profile (TC, TG, HDL and LDL), serum ALT, AST, and ALP activities. Rats were decapitated then liver specimen of each rat were collected and split into two parts: part for histological analysis, and the other was frozen at -20 ^{o}C. Frozen Liver specimens homogenized in the saline buffer (10%, w/v) (NaCl, pH 7.4). The homogenate aliquots were kept at -20 °C to be used for estimation of SOD activity, GSH, MDA, TNF-α, and TNO levels. Biochemical analysis was done by using commercially test kits according to manufacture instructions.

2.7. Histopathological techniques

Freshly removed liver specimen was fixed immediately in 10% neutral formalin. The paraffin-embedded fixed hepatic tissues, cut into 5 mm slices using a rotary microtome, and stained with hematoxylin and eosin (H&E). The liver slices were histologically examined with a camera attached to a light microscope (Nikon E400) [17].

2.8. Statistical analysis

The latest version of GraphPad Prism for Windows (9.4.1) was used to evaluate the results. Mean ± SD (n = 5) was used to express the results. One-way ANOVA followed by Tukey's test was performed to recognize any significant variations between groups. lower P values than 0.05 were considered significant [18].

3. Results

3.1. High Performance Liquid Chromatography (HPLC) analysis of CE

Cinnamic acid, p-coumaric acid, and rutin were present in CE at quantities of 4.73 mg/g, 3.099 mg/g, and 0.028 mg/g, correspondingly, according to HPLC analysis (fig. 1).

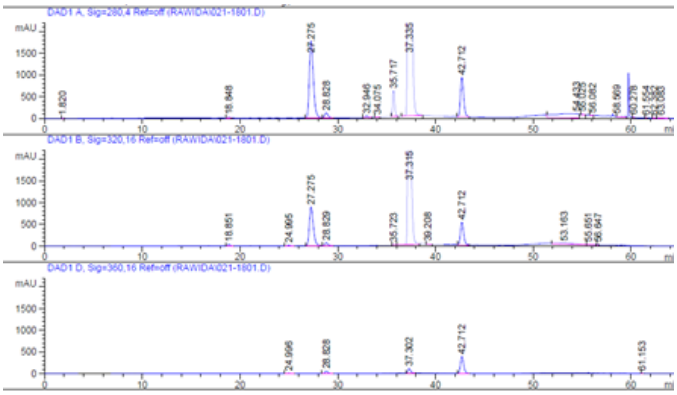

Figure 1: HPLC chromatogram for CE

3.2. Body weight and weight of liver

Rats' body weight was significantly reduced after receiving CCl_4 treatment compared to control rats (Table 1). The rats co-treated with CCl_4 and cinnamon extract (0.1 g/kg b.wt.) had a significant increase in body weight gain comparing to CCl_4 alonetreated group. In comparison to control rats, CCl_4-treated animals had larger liver weights and liver indices (the ratio of liver weight to body weight). In comparison to rats treated with CCl_4, co-treatment with cinnamon extract (0.1 g/kg b.wt) dramatically decreased liver weights and liver indices.

3.3. Biochemical analysis

Regarding to lipid profile our results showed that CCl_4 significantly ($P< 0.05$) increased TC, TG and LDL-C along with a significant decrease in HDL-C levels when compared to control rats (Table 2).

Serum ALT, AST and ALP levels significantly increased after CCl_4 injection in comparison to the healthy control group (Table 3). These serum biochemical indicators' levels were significantly reduced in CCl_4 + CE group comparing to CCl_4 alone

Table 1: Body weight and liverweight of acute CCl_4 (CCl_4)-treated rats with or withoutcinnamon ethanolic extract

Parameters	Control	Cinnamon extract	CCl_4	CCl_4 + Cinnamon extract (g/kg b.w.)
Initial weight (g)	182.6 ^{a} ± 7.65	186.4 ^{a}± 6.95	180.6 ^{a}± 5.32	182.5 ^{a}± 8.34
b.wt 1st week (g)	190.0 ^{a}± 7.74	194.2 ^{a}± 7.15	186.1 ^{a}± 5.94	190.1 ^{a}± 9.34
b.wt 2nd week (g)	197.6 ^{a}± 8.12	201.3 ^{a}± 7.33	191.4 ^{a} ± 6.42	197.3 ^{a}± 9.95
b.wt 3rd week (g)	206.5 ^{a}± 7.94	210.4 ^{a}± 6.88	196.2 ^{b} ± 5.72	204.6 ^{a}± 8.12
b.wt 4th week (g)	215.6 ^{a}± 7.82	220.4 ^{a} ± 7.01	203.6 ^{b}± 6.12	211.5 ^{a}± 8.74
Liver weight (g)	6.3 ^{a}±0.25	6.04^a± 0.20	8.99 ^{b}±0.17	7.6 ^{c} ±0.30
Liver index (g)	2.16 ^{a}±0.04	2.07 ^{a}± 0.02	3.64 ^{b} ±0.06	2.34 ^{c}±0.03

Each value represents the mean ± SD (n = 5);means carrying different superscripts (a, b, c) within the same row wereconsidered significant at P<0.05

group. Hepatic TNF- α, MDA, and TNO activity were substantially more in the CCl_4 treatment group than in the healthy control group. SOD activity and GSH level were both considerably lower in the group treated with CCl_4 than in the control group. However, compared to the CCl_4 treatment group, co-administration with CE (0.1 g/kg b.wt.) boosted both SOD and GSH activity. The control rats which received only cinnamon extract showed no appreciable difference.

3.4. Histopathological results:

Normal hepatic lobules with centrally situated core veins and radiating cords of liver cells were visible in the normal case of liver and cinnamon control groups. Each liver cell contains a sizable nucleus and a lot of cytoplasm that is eosinophilic. The CCl_4 livers exhibited discrete or limited hepatocyte necrosis, perivascular edema, and minor vacuolar degeneration of hepatocytes. Along with focal moderate vacuolation of hepatic cells, there was focal proliferation of the hepatic tissue with few lymphocytic aggregations. Hepatic sinusoids have a little broadening. The hepatic tissue significantly improved in the cinnamon-treated group (fig. 2).

4. Discussion

In the current investigation, cinnamon ethanolic extract (CE) was demonstrated to evaluate if it has hepatoprotective and antioxidant effects against CCl_4-induced liver damage in male rats. The liver is in charge of detoxifying harmful substances like medications and poisonous chemicals. Various studies demonstrated that CCl4 is widely used to induce liver damage because it is metabolized in hepatocytes by cytochrome P450 [14]. According to the current findings, CE contained a number of bioactive chemicals that were in charge of its antioxidant activity which concurred with the conclusions of Qureshi, A et., al [19]. Cinnamic acid, the primary polyphenol in CE, is thought to have anti-inflammatory, antioxidant, and hepatoprotective properties [20]. P-coumaric acid, one of the main polyphenols in CE, was suggested to exhibit hepatoprotective effects by inhibiting intracellular ROS generation, lipid peroxidation, and upregulation of detoxifying enzymes [21]. Also, rutin, the main flavonoid in CE, was suggested to prevent oxidative stress by scavenging free radicals and inhibiting lipid peroxidation. The polyphenolic chemicals in CE were primarily responsible for the its potent antioxidant capabilities. The chain oxidation reaction is stopped by the phenolic group's ability to take an electron and create relatively stable phenoxy radical **[22]**.the HPLC analysis showed that the cinnamon extract contained rutin, p-coumaric acid and cinnamic acid, 4.731 of cinnamic mg/g, 3.099 mg/g of p-coumaric and 0.028 mg/g of rutin. These results were parallel to finding of Mehrinoosh et al., [23]. The lower weight growth caused by CCl_4 intoxication was consistent with [24], who

Table 2: Effects of cinnamon ethanolic extract on lipid profile indices in CCl_4-inducedhepatotoxicity in rats

Parameters	Control	Cinnamon extract (0. 1 g/kg b.w.)	CCl_4	CCl_4 + Cinnamon extract (g/kg b.w.)
TC (mg/dl)	82.5^{a}± 1.76	91.2^{b} ± 2.77	107.2^{c}± 4.55	93.9^{b} ± 3.01
TG (mg/dl)	87.6^{a}± 5.51	96.6^{b} ± 5.0	112.8^{c} ± 2.28	100.2^{b}± 3.14
HDL (mg/dl)	32.36^{a}± 3.76	32.40^{a}± 1.29	35.10^{a} ± 3.10	32.90^{a} ± 1.67
LDL (mg/dl)	32.70^{a}± 3.11	39.60^{b}± 3.74	49.80^{c}± 4.35	41.00^{b}± 1.77

Each value represents the mean ± SD (n = 5); means carrying different superscripts (a, b, c) within the same row were considered significant at P<0.05

Table 3: Effects of cinnamonethanolic extract on serum and liver biochemical indices in CCl_4-inducedhepatotoxicity in rats

Parameters	Control	Cinnamon extract (0. 1 g/kg b.w.)	CCl_4	CCl4 + Cinnamon extract (g/kg b.w.)
ALT (IU/L)	29.88^{a}±3.22	23.73^{a}±2.07	96.18^{b}±10.44	48.48^{c}±3.78
AST (IU/L)	31.04^{a}±2.06	27.24^{a}±6.60	96.95^{b}±7.06	49.13^{c}±4.00
ALP (IU/L)	71.88^{a}±5.21	71.10^{a}±5.50	209.1^{b}±15.33	102.7^{c} ±6.44
SOD (U/mg. Tissue)	11.30^{a}±0.26	11.20^{a}±0.11	7.08^{b}±0.44	9.32^{c}±0.11
GSH (μg/mg. Tissue)	19.09^{a}±0.24	19.40^{a}±0.44	13.32^{b}±0.25	16.04^{c}±0.18
MDA (μmol/mg.tissue) Tissue)	0.81^{a}±0.01	0.82^{a}±0.02	2.80^{b}±0.08	1.23^{c}±0.04
TNF–α (pg./mg. Tissue)	15.99^{a}±0.19	16.11^{a} ±0.17	34.91^{b}±0.54	26.21^{c}±0.25
TNO (pg./mg. Tissue)	21.51^{a}±0.56	22.03^{a}±0.0.69	34.27^{b}±0.12	25.27^{c}±0.14

Each value represents the mean ± SD (n = 5); means carrying different superscripts (a, b, c) within the same row were considered significant at P<0.05

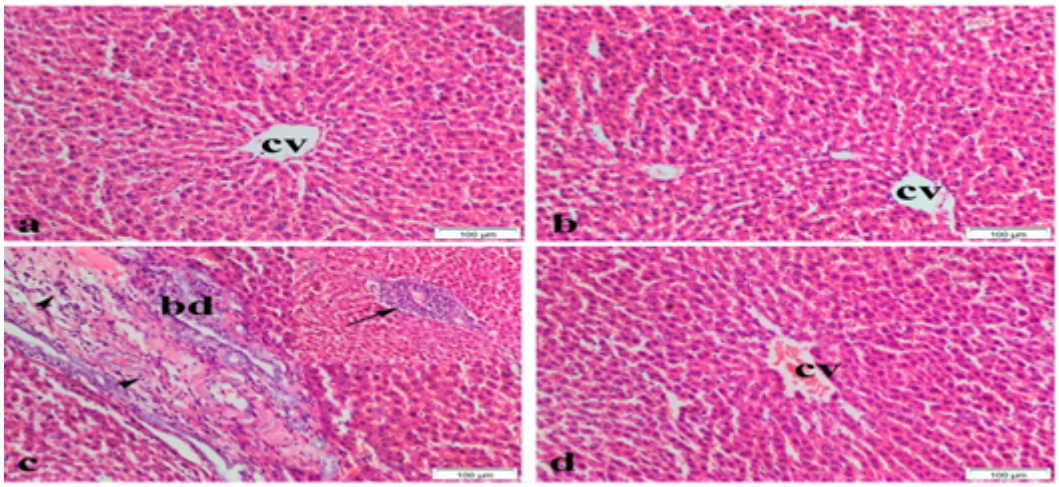

Figure 2: Liver demonstrating normal hepatic tissue with centrally placed central veins in (a) the control non-treated group and (b) the control cinnamon group (cv). (c) Hepatic regions with significant CCl4 fibrosis (arrow heads), proliferating bile ducts (bd), and lymphocytic infiltrations (arrows). (d) displaying a slight sinusoidal and central vein congestion. Bar H&E 100 m.

demonstrated that CCl_4 intoxication caused a substantial decrease in the brain-to-body weight ratio ($p < 0.0001$) in the CCl_4 treatment group. The decline in weight growth caused by CCl_4 was ameliorated by co-administration of CE. These outcomes might be explained by CE's antioxidant activity, which was demonstrated by HPLC analysis. Additionally, CCl_4 toxicity markedly raised the relative liver weights that were consistent with [25] . This might be linked to the CCl_4-induced hepatic retrogressive alterations seen in the histopathology section. The elevated relative liver weights caused by CCl_4 were reduced by the administration of CE. Cinnamic acid, p-coumaric acid, and rutin, three of the active phenolic components in CE, were responsible for these actions [7] **.**

CCl_4 administration increased cholesterol and triglycerides significantly compared to the control rats. These results agreed with [26] who attributed the significant increase in liver weight in CCl_4 treated mice to increase accumulation of fat vacuoles, increased hepatic cholesterol and triglyceride levels. Lipid profile alterations caused by CCl_4 could be a causal factor for excessive lipid peroxidation [27]. ALT, AST, and ALP concentrations were higher in the rats treated with CCl_4's which evidenced the liver damage because these enzymes leak out of the liver into the blood at the moment of tissue injury, which is typically accompanied by hepatic injury [28]. The co-administration of CE significantly decreased a measure of these marker enzyme levels in comparison to the CCl_4 group. Hepatocyte activity is correlated with activity of ALP. The reduction of increased ALP activity following chronic CCl_4 hepatic injury in rats indicates stabilization of biliary dysfunction in the liver.

Because CCl_4 is metabolized by cytochrome P450 in hepatocytes and creates a highly reactive carbon-based trichloromethyl radical that starts a chain reaction ended by lipid peroxidation and causes hepatic fibrosis, it is frequently used as a model of liver damage [29]**;** [30]. Hepatic oxidative stress caused by CCl_4 was shown by decreased hepatic GSH content and SOD activity and elevated MDA levels. Reduced GSH and SOD, which may be caused by protein oxidative modification [31], are signs of the depletion of antioxidant defense caused by the overproduction of ROS that carbon tetrachloride primed [32]. Oxidative stress often happens when the pro-oxidant/antioxidant equilibrium is shifted in favour of the pro-oxidants. Lipid perioxidation is a helpful measure for examining the oxidative damage caused by polyunsaturated fatty acid content in cellular membranes. The protein's sulfhydryl groups can be bound by MDA, a lipid perioxidation end product which is capable of crosslinking the protein and reduce or eliminate it [32] . A decrease in membrane fluidity and an inability of the antioxidant defense systems to scavenge free radicals are both associated with elevated MDA levels. Damage to tissue is influenced by each of these factors [33]. Reactive oxygen species (ROS) and environmental harm are prevented by antioxidant defense elements like SOD and GSH. The first line of defense against ROS is glutathione. Additionally, enzymes reliant on GSH by detoxifying the damaging ROS by products, serve as a vital line of defense. Lower GSH levels in the liver could be explained by increased GSH utilization against peroxides. Numerous studies have demonstrated that GSH is essential for the removal of CCl4's harmful metabolites and that organ damage starts when levels of GSH are significantly depleted [34] . These results were in line with those of [35] ; who showed that administering essential oil of cinnamon to rats had a significant anti-free radical effect and mitigated the hepato-renal damage caused by CCl_4.

As shown in our investigation, oxidative stress was reduced by CE in CCl_4-intoxicated groups by drastically reducing MDA levels while significantly raising GSH content and SOD activity.

These findings confirmed CE's putative hepatoprotective properties, which were a result of its phenolic and flavonoid contents. They contain antioxidant activity that scavenges free radicals, protecting the cell membrane of hepatocytes and preventing the seepage of enzymes as previously hypothesized [36]. Additionally, CCl_4-induced histopathological alterations were lessened by the phytoconstituent of CE, which has a tissue-protective action against different toxic metabolites [37].

The progression of inflammation is significantly

influenced by oxidative stress, which also adds to the pathophysiology seen in the hepatic tissue [39].

A proinflammatory cytokine called TNF-α, which is produced when there is sudden inflammation, participates in a number of cell signaling system that cause necrosis or apoptosis [13]. TNF-α levels were considerably greater in the hepatic tissues homogenate of CCl_4-treated rats compared to the normal control rats. A key step in limiting the harm caused by CCl_4 is to inhibit inflammation. The current findings demonstrated that CE could reduce CCl_4-induced hepatotoxicity as demonstrated by a notable drop in TNF-α content in rat liver homogenate. Our results are in line with [38] who found that the injection of polyphenolic substances dramatically decreased TNF-α expression level due to their anti-inflammatory effect.

5. Conclusion

The results of this study demonstrated that CE succeed to ameliorate the hepatic intoxication and it's advised to be used to modulate the side effects. The hepatoprotective effects of CE could be attributed mainly to its strong antioxidant activity, due to the presence of cinnamic acid, p-coumaric acid and rutin, and increasing the antioxidant-defense system via increasing GSH content and SOD activity.

6. Recommendations

Cinnamon extract has an excellent antioxidant effect against CCl_4 hepatoxicity so, it's recommended for oral use to counteract hepatoxicity.

7. Conflicts of interest:

There are no conflicts to declare.

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