Original Communication

Hepatoprotective Activity of Linalool in Rats Against Liver Injury Induced by Carbon Tetrachloride

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Abstract: This study aimed to investigate and compare hepatoprotective activity of *Coriandrum sativum* (Cs) and it is major component linalool (Ln) against experimentally induced hepatotoxicity in rats. Essential oil of Cs was isolated by hydrodistillation method and chemical composition was determined by GS-MS analysis. 42 male Wistar Albino rats were divited into 7 groups each containing 6. The experimental groups were designed as: Normal control group, 1 ml/kg CCl_4 administirated group, 25 mg/kg Silymarin and CCl_4 administirated group, 100 and 200 mg/kg Cs and CCl_4 administirated groups, 100 and 200 mg/kg Ln and CCl_4 administered groups. The protective activities were determined according to the results of liver biomarkers (AST, ALT, ALP), antioxidant parameters (GSH, GPx, CAT), lipid peroxidation (MDA) and histopathological examination. Linalool percentage of Cs was 81.6%. The groups treated with linalool (100 and 200 mg/kg) ($p < 0.01$) and coriander (200 mg/kg) ($p < 0.05$) had significantly reduced AST (262–375) and ALT (101–290) levels (U/L) compared to the CCl_4 (600–622) group. The levels (nmol/g protein) of MDA (11–12) were significantly lower ($p < 0.01$), the levels of GSH (11–12) and the activities of CAT (23–24) were significantly higher ($p < 0.01$) in linalool groups (100 and 200 mg/kg) compared to the CCl_4 (18-5-10 respectively) group. These results were also supported by histopathological findings and indicate that Cs and Ln shows hepatoprotective activity against liver damage. In this regard, evaluation of activities of major components are needed to compare to medicinal plants in experimental diseases models.

Keywords: Carbon tetrachloride, *Coriandrum sativum*, hepatoprotective, linalool

Introduction

As the largest and most complex organ in the body, the liver is responsible for secretion, metabolism, and detoxification [1, 2]. If the liver is unable to detoxify harmful substances, significant pathologically acute health problems, such as chronic liver disease, can develop [3, 4].

Carbon tetrachloride (CCl_4) is a chemical commonly used to induce liver damage in experimental animal models to increase lipid peroxidation. During lipid peroxidation, free radicals damage biological molecules by breaking down their structure and interfering with their functioning and protein or DNA injuries occur during aerobic metabolism [1, 3, 4]. This is a common situation among organisms that have contracted diseases [5]. Antioxidant enzymes and substances play important roles in compensating for the toxic effects of free radicals [6].

With the adverse effects, low efficacies and high costs of conventional medicinal therapies, the popularity of herbal medicine in veterinary and human medicinal treatments has been steadily increasing [7–9]. In addition, using plants to treat liver diseases has become more common [7, 10]. The essential oil of *Coriandrum sativum* (Cs), obtained from dried seed, contains many active components, such as monoterpenes that have antioxidant, anthelmintic, antiprotozoal, antidiabetic, antiulcer, antitumoral, anticonvulsant, and hepatoprotective effects [11]. Linalool (Ln), a major component of some medicinal plants like Cs, also has antioxidant, antitumor and anti-inflammatory effects. Protective effects of Ln were demonstrated in experiments involving mice with acute lung and hepatic injuries that were induced by lipopolysaccharide/galactosamine [1].

The aim of this study was to investigate and compare hepatoprotective activities of Cs and its major component Ln against hepatic injury in rats.

Materials and Methods

Plants

Dried Cs grains were obtained from a local (Hatay, Turkey) herbal market in May 2016. Identification, extraction and chemical composition analysis of Cs essential oils were performed in the Department of Medicinal Aromatic Plants of Agricultural Faculty of Hatay Mustafa Kemal University.

Chemicals

The essential oil was obtained by hydrodistillation after three hours. The oil was kept in closed glass vials at 4 °C until analysis. The other chemicals were purchased from Sigma-Aldrich (Seelze, Germany). CCl_4 was obtained from Merck (Darmstadt, Germany) and dissolved in olive oil (1:1 v/v). Silymarin was suspended in 2% carboxymethyl cellulose.

Preparation of essential oil and gas chromatography/mass spectrometry (GC-MS) analysis

Essential oils extraction of Cs was performed by classical hydrodistillation method using neo-clevenger apparatus and chemical composition was determined by GC-MS analysis according to previously described method [13].

Animals

Forty-two healthy adult male Wistar Albino rats (250 ± 10 g) were involved in this study. The experimental applications were carried out according to laboratory animal care procedures in standard laboratory conditions (12 h light-12 h dark and 21 ± 1 °C). Fresh drinking water and standard commercial pellet diets were provided *ad libitum* to the rats during the experiment. The experimental procedures were conducted in accordance with local guidelines and approval by the local Animal Ethical Committee (No: 2015/7-7).

Experiment protocol

Rats were randomly divided into seven groups each containing 6 animals. The normal control and CCl_4 groups received only saline by oral gavage for seven days. Silymarin + CCl_4 group received Silymarin (25 mg/kg) orally by gavage for seven days. Cs-100 + CCl_4 and Cs-200 + CCl_4 groups intragastrically received Cs (100 and 200 mg/kg) for seven days. Ln-100 + CCl_4 and Ln-200 + CCl_4 groups intragastrically received linalool (100 and 200 mg/kg) for seven days. Twenty-four hours after the final treatment, a single dose of CCl_4 (1 ml/kg) was administered orally by gavage to each group except for normal control group. The doses of silymarin [13], Cs [14], linalool [15] and CCl_4 [13] were determined based on previously studies.

Blood and liver sample collection

Twenty-four hours after the final administration, blood samples were collected by intracardiac route under a xylasine-ketamine anesthesia. Serums were separated and stored at −80 °C for biochemical analysis. After weighed, one lobe of the livers were fixed in 10% formalin and other parts were stored at −80 °C.

Determination of the biochemical parameters

The levels of Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), and Alkaline phosphatase (ALP) in the serum were determined using an automatic biochemistry analyzer (Olympus AU 600).

Determination of antioxidant parameters and lipid peroxides

The liver tissues were homogenized in a 1.15% KCl solution (1:10 w/v), and the tissue lipid peroxide (MDA) was determined using the spectrophotometric method [16]. The remaining parts were centrifuged at 2376 rcf for one hour at 4 °C and the supernatants were separated. The levels of glutathione (GSH), activity of catalase (CAT), and glutathione peroxidase (GPx) in the tissue samples were measured spectrophotometrically (2R/Ultraviolet-visible; Shimadzu, Tokyo, Japan). GSH levels, GPx and CAT activities and the protein concentrations in the tissue were determined according to previously described methods [17–20]. MDA and GSH enzyme levels were expressed in nmol/g protein, GPx activity in IU/g protein and CAT protein concentrations in k/g protein.

Histopathological examination

At the end of the experimental protocol, the liver tissue samples were placed in 10% buffered formalin solution for the histopathological examination. The materials were passed through an alcohol and xylene series for dehydration and fixation, following standard protocol. Five μm-thick paraffin block sections were stained with hematoxylin-eosin (H&E) [21] and then examined under a light microscope (Olympus CX31). Microphotographs were obtained.

Histopathological findings were evaluated according to the following criteria:

Grade 0: Histopathologic changes in less than 5% of the whole area;

Grade 1: Mild histopathologic changes in 5–33% of the whole area;

Grade 2: Moderate histopathological changes in 33–66% of the whole area;

Grade 3: Severe histopathological changes in more than 66% of the whole area [22].

Statistical analysis

Results were evaluated statistically using a SPSS 23.0.0 package program, according to ANOVA and Tukey HSD tests. Statistical significance was considered at $p < 0.05$. The distribution equality and equality of variance of data were assessed by the Kolmogorov–Smirnov test and Levene's test respectively.

Results

Content of essential oil

The chemical composition of the coriander essential oil was expressed in percentages. Linalool was the major compound (81.6%), and the others (>0.2%) ranked as follows: α-Pinene (3.62%), β-Pinene (0.31%), γ-Terpinene (3.94%), Camphor (1.49%), Geranyl acetate (2.10%), o-Cymene (0.82%), Limonene (0.68%), Camphene (0.24%), and Myrcene (0.24%).

Biochemical findings

The levels of the markers commonly used to evaluating liver damage were collected and shown in Figure 1. The levels of AST, ALT, and ALP had increased in the CCl_4 control group as compared to the normal control group ($p < 0.01$). The Silymarin and other treatment groups (Cs-100, Cs-200, Ln-100, and Ln-200) had significantly reduced AST and ALT levels as compared to the CCl_4 control group, except AST levels in the Cs-100 group ($p < 0.05$). Although the differences in the ALP levels did not reach statistical significance, ALP tended to be lower in the Ln-100, Ln-200, Cs-100, and Cs-200 groups as compared to the CCl_4 control group. Additionally, though the differences in relative liver weight in the Ln-100, Cs-100, and Cs-200 groups did not reach statistical significance, the liver weights in these groups tended to be lower than the liver weights in the CCl_4 control group.

Histopathological findings

Grades of histopathologic findings in liver tissues of groups were given in Table 1. Normal histological structure was observed in the liver tissues of the normal control group (Figure 2A). In the CCl_4 control group, it was observed that the vena centralis have expanded with the accumulation of erythrocytes and hyalinous material. Similarly, local enlargement due to erythrocyte accumulation in the inter-hepatocyte sinusoidal region was noted (passive congestion). Parenchymal degeneration and fatty vacuoles were observed in the hepatocytes. Additionally, a few of the hepatocytes had experienced balloon degeneration (Figure 2B). In the Silymarin group, parenchymal and hydropic degeneration were present in a few of the hepatocytes, but ballooning degeneration was not observed. In addition, the fatty vacuoles observed in the small diameter were more limited, and they were usually located around the central vein (Figure 2C). Degenerative changes, including inflamed cells, fatty vacuoles, and balloon degeneration, were seen with smaller numbers in the Cs-100 (Figure 2D) and Cs-200 (Figure 2E) groups than in the CCl_4 control group. Degenerative changes and fatty vacuoles were seen in a few hepatocytes. Hepatic cellular damage was at its lowest level in the Ln-100 (Figure 2F) and Ln-200 (Figure 2G) groups as compared to all groups.

Antioxidant enzymes and lipid peroxidation findings

As shown in Figure 3, the liver MDA levels were significantly higher in the CCl_4 control group as compared to the normal control group ($p < 0.01$). However, the MDA levels in the Silymarin, Cs-200, Ln-100, and Ln-200 groups were significantly lower than in the CCl_4 control group ($p < 0.01$).

The GSH levels in the Silymarin, Ln-100, and Ln-200 groups were significantly higher than GSH levels in the CCl_4 control group ($p < 0.01$). Although not statistically significant, the GSH levels were higher in the Cs-100 and Cs-200 groups.

While GPx levels were higher in all treatment groups than in the CCl_4 control group, only the increase in the Ln-200 group was statistically significant ($p < 0.01$).

There were significant increase in CAT activity in Silymarin and Cs-200, Ln-100, Ln-200 groups compared to the CCl_4 control group ($p < 0.05$). Only the increase in Cs-100 group was not statistically significant ($p < 0.05$).

Discussion

The liver plays a key role in protein, carbohydrate, and fat metabolism and in detoxification and excretion of drugs

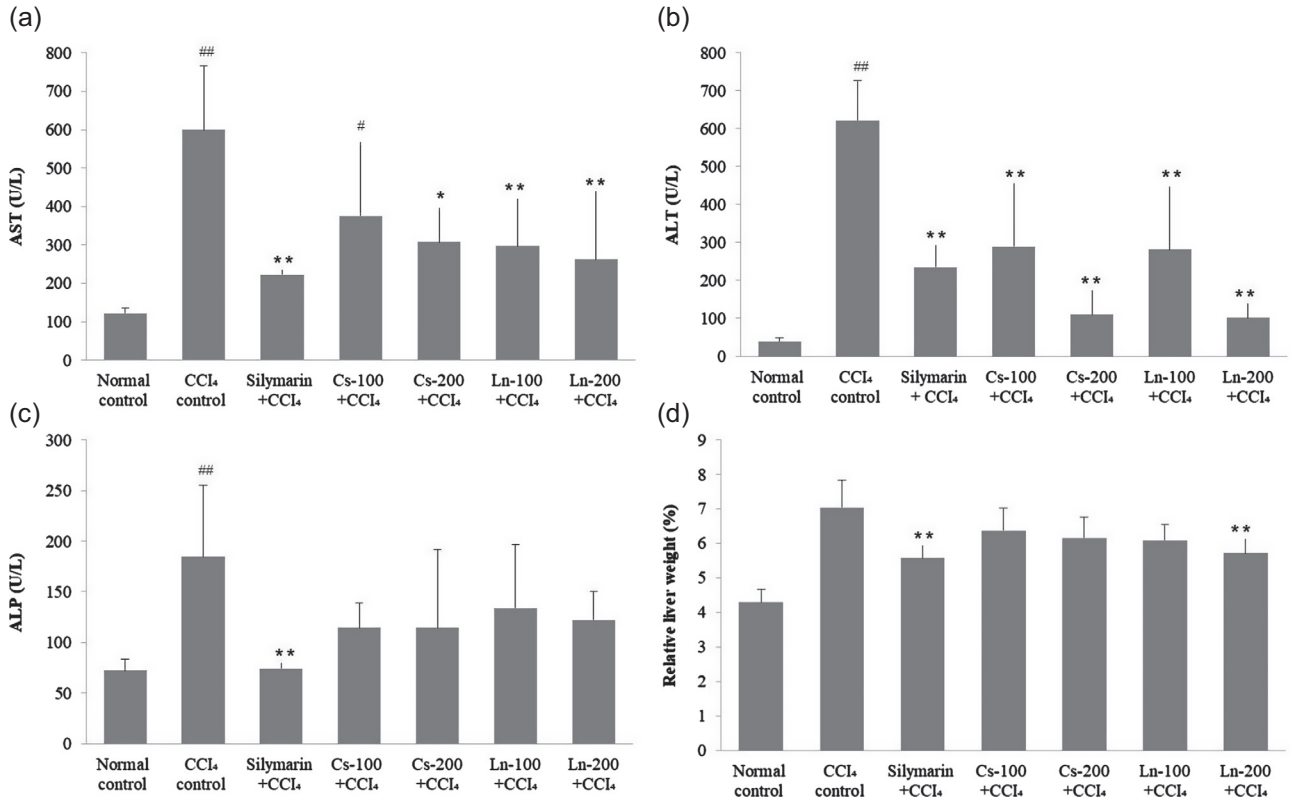

Figure 1. Effects of Silymarin, *Coriandrum sativum* (Cs), Linalool (Ln) on serum Aspartate aminotransferase (AST) (A), Alanine aminotransferase (ALT) (B) and Alkaline phosphatase (ALP) (C) and and relative liver weight (%) (liver weight / body weight × 100) (D) in Carbon tetrachloride (CCl_4)-treated rats. Normal control group; CCl_4 control group (1 ml/kg); Silymarin (100 mg/kg) + CCl_4 (1 ml/kg) group; Cs-100 (100 mg/kg) + CCl_4 (1 ml/kg) group; Cs-200 (200 mg/kg) + CCl_4 (1 ml/kg) group; Ln-100 (100 mg/kg) + CCl_4 (1 ml/kg) group; Ln-200 (200 mg/kg) + CCl_4 (1 ml/kg) group. Values are given as mean ± sd (n = 6). *p < 0.05, **p < 0.01 vs. CCl_4 control group; # p < 0.05, ## p < 0.01 vs. normal control group.

Table 1. Grades of histopathologic findings in liver tissues of normal control, Carbon tetrachloride (CCl_4) control (1 ml/kg), Silymarin (100 mg/kg) + CCl_4 (1 ml/kg), *Coriandrum sativum* (Cs) 100 and 200 mg/kg + CCl_4 (1 ml/kg), Linalool (Ln) 100 and 200 mg/kg + CCl_4 (1 ml/kg) groups.

	Inflammation	Lipoidosis	P. hyperemia	Degenerative changes			Necrotic changes	
				Parenchyma	Hydropic	Balloon	Increase in cytoplasmic eosinophilia	Hyperkromosis in the nucleus
Normal control group	0	0	0	0	0	0	0	0
CCl_4 control group	3	3	3	3	3	3	3	3
Silymarin + CCl_4	1	1	2	2	2	0	1	1
Cs-100 + CCl_4	2	2	2	2	2	2	2	2
Cs-200 + CCl_4	1	1	2	2	1	1	1	1
Ln-100 + CCl_4	1	1	1	1	1	0	1	1
Ln-200 + CCl_4	1	1	1	1	1	0	1	1

and toxins. Hepatotoxins, infectious, or parasitic pathogens, and systemic or metabolic disorders can cause acute hepatic injury. Liver diseases are a major health problem for humans and animals worldwide. Synthetic drugs, like analgesics, anticonvulsants and antimicrobials, have hepatotoxicity potential in addition to their therapeutic effects [10]. With this potential, alternative medicinal treatments, such as herbal preparations, have become more popular [23]. While the hepatoprotective effect of Cs was reported in the experimental model [14], the protective potential of linalool was not investigated and compared with Cs. The present study showed the hepatoprotective effect of the Cs essential oil and its major component, linalool.

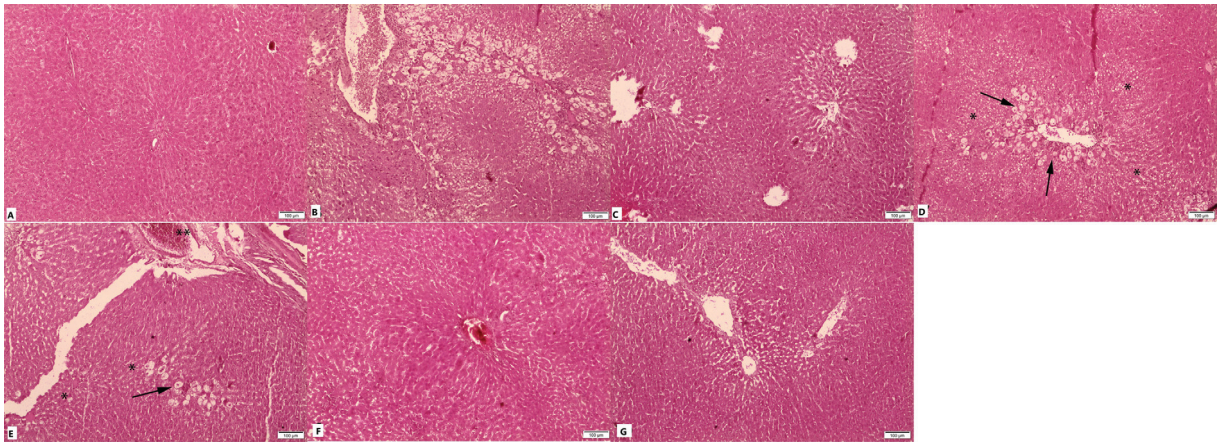

Figure 2. Effects of Silymarin, *Coriandrum sativum* (Cs), Linalool (Ln) on histopathological changes in Carbon tetrachloride (CCl_4)-treated rats. (100X H&E). A - Normal control group; B - CCl_4 control group (1 ml/kg); C - Silymarin (100 mg/kg) + CCl_4 (1 ml/kg) group; D - Cs-100 (100 mg/kg) + CCl_4 (1 ml/kg) group; E - Cs-200 (200 mg/kg) + CCl_4 (1 ml/kg) group; F - Ln-100 (100 mg/kg) + CCl_4 (1 ml/kg) group; G - Ln-200 (200 mg/kg) + CCl_4 (1 ml/kg) group. (→ inflammatory infiltration; * ballooning degeneration)

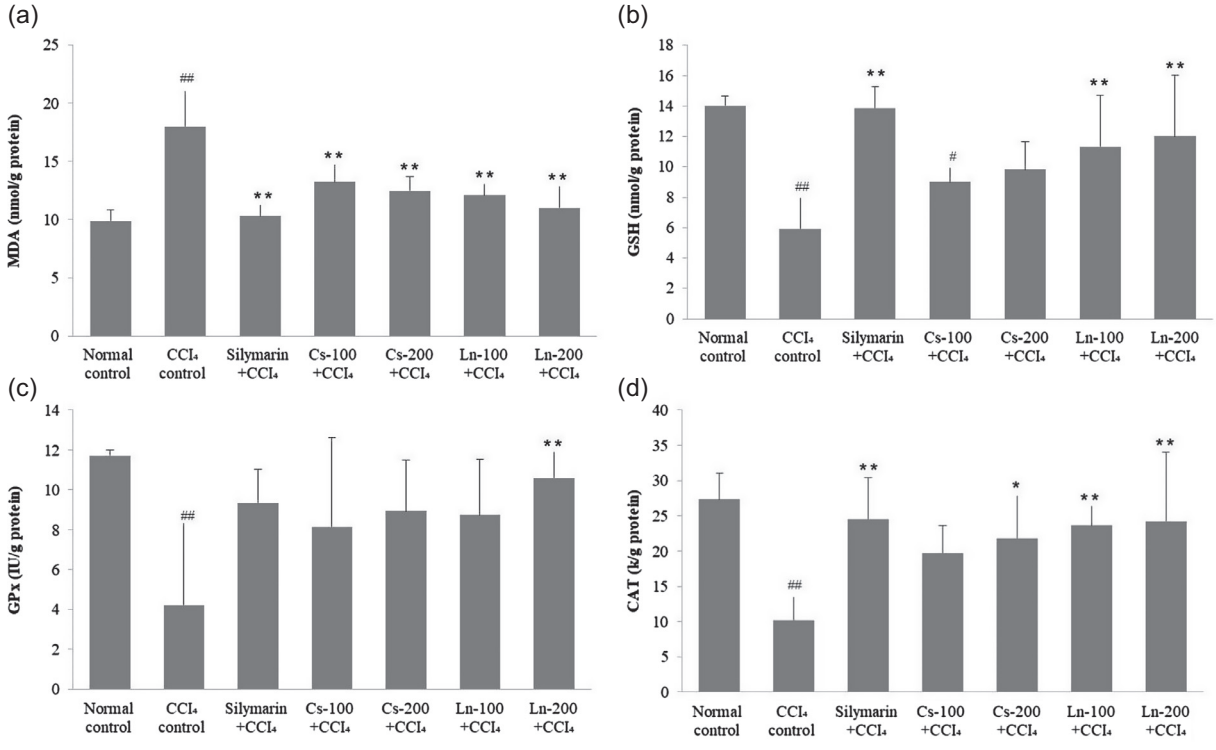

Figure 3. Effects of Silymarin, *Coriandrum sativum* (Cs), Linalool (Ln) on lipid peroxidation MDA (A) and antioxidant parameters glutathione (GSH) (B), glutathione peroxidase (GPx) (C), catalase (CAT) (D) on Carbon tetrachloride (CCl_4)-treated rats. Normal control group; CCl_4 control group (1 ml/kg); Silymarin (100 mg/kg) + CCl_4 (1 ml/kg) group; Cs-100 (100 mg/kg) + CCl_4 (1 ml/kg) group; Cs-200 (200 mg/kg) + CCl_4 (1 ml/kg) group; Ln-100 (100 mg/kg) + CCl_4 (1 ml/kg) group; Ln-200 (200 mg/kg) + CCl_4 (1 ml/kg) group. Values are given as mean ± sd (n = 6). *p < 0.05, **p < 0.01 vs. CCl_4 control group; # p < 0.05, ## p < 0.01 vs. normal control group.

Using CCl_4 to induce liver damage is one of the most common models in experimental animal studies because it causes cellular damage by producing free radicals. These free radicals cause the peroxidation of fatty acids in the phospholipids in cell membranes, leading to cellular damage. Thus, they play prominent roles in the pathogenesis of liver diseases [1, 7].

In our study, histopathological evidence of the acute hepatotoxicity of CCl_4 administration (observed as inflammatory infiltration, ballooning degeneration, and

hepatocellular necrosis) dilated sinusoidal spaces (Figure 2). This result is accordance with the results of previous studies [9, 14]. In addition, the decrease of degenerative and fatty changes in the Silymarin and Cs groups similar to the previous report [21].

MDA is the final product of lipid peroxidation and is used as a marker of oxidative stress [19]. CCl_4 administration is known to cause oxidative damage by significantly elevating the MDA level and significantly lowering GPx levels, GSH, and CAT activities, as case in our study [9, 24]. As an antioxidant, Cs restrains lipid peroxidation and tissue degeneration in the liver [14, 25]. The results of our study indicated that Cs was able to protect against hepatic lipid peroxidation by decreasing MDA Levels.

Previous studies have reported that extract of Cs has been antioxidant activity by depending on the components [25–30]. In addition, these studies showed that the various fruit and leaf extracts of coriander significantly increased antioxidant enzyme levels (GSH, GPx, and CAT) [27, 31]. Our results support the antioxidant efficiency of Cs.

Enzymes like ALT and AST are directly related to liver membrane damage and release into the bloodstream in membrane damage [29]. These enzymes are specific markers that indicate the presence of hepatocellular damage. Previous studies have shown that AST, ALT and ALP enzyme activities become elevated in proportion to the degree of damage induced by CCl_4 [6, 9, 29, 32]. Our study, as expected, showed the significant elevation in AST, ALT, and ALP levels and histopathological changes in single oral dose (1 ml/kg) of CCl_4 administered rats. However, pretreatment with the essential oil of Cs before CCl_4 administration significantly lowered the elevated serum levels of AST, ALT, and ALP. A similar study [14] showed that the enzyme activity of Cs (200 mg/kg) was comparable to that of the reference drug Silymarin. In addition, linalool reduced the toxic effect of CCl_4 more than Cs. These results were supported by histopathological examination.

The Cs essential oil contains a monoterpenoid linalool as a major bioactive component [33, 34]. In the present study, the percentage of linalool was 81.6%, as determined by GC-MS analyses and similarly reported by another study [35]. Linalool is reported to play a principal role in antioxidant, antimicrobial, hypoglycemic, hypolipidemic, anxiolytic, analgesic and anti-inflammatory effects [34, 36, 37]. In the present study, biochemical and histopathological results suggested that linalool has a potential protective effect in the Cs essential oil. The results indicate that the medicinal potentials of plants may originate from their major components. Their major component may provide the same efficacy in a lower dose, avoiding the unnecessary effects of other bioactive compounds.

The study showed that protective effect of Cs against the possibility of liver injury. This effect may due to linalool and can provide the same efficacy in a single compound.

However, it has not been determined whether the medicinal effects of the essential oil are caused by the substance or by the composition of the substance. The composition of the compounds in the essential oils of medicinal plants may show synergistic effects but may also cause antagonistic effects, thus reducing their potent activity. On the other hand, using medicinal plants or essential oils totally may lead to adverse effects on non-target organs and systems in the body because they contain many other bioactive compounds. In conclusion, *C. sativium* and its major component, linalool, have preventative potentials against hepatic injury and result in increased antioxidant activity. However, the evaluation of the individual activities of the major components is needed to compare the essential oils of medicinal plants in experimental disease models.

This study indicated that Cs has a significant role in hepatoprotective effect and it may be thought that this effect originated from its major component linalool. The results also pointed that linalool at 200 mg/kg dose that may be recommended against liver injury instead of Cs essential oil. Further studies involving in vitro, dose response, toxicity and other parameters (expression levels of proinflammatory cytokines and tissue proteins etc.) is needed to examine the effects of linalool.

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Conflict of interest

The authors declare that there are no conflicts of interest

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