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Hepatoprotective Properties of *Cuminum cyminum* Seeds Powder as Post-Treatment for Acetaminophen-Induced Injury

Afsaneh Mozaffarinia, Ali Gol*, Aghileh Mohammadzadeh

Dept. of Biology, Faculty of Science, Shahid Bahonar University of Kerman, Kerman, Iran

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Corresponding Information:
Ali Gol,
Dept. of Biology, Faculty of Sciences, Shahid Bahonar University, Kerman, Iran

E-Mail: agol@uk.ac.ir

ABSTRACT

Background & Objective: Acetaminophen overdose can result in hepatic injury, mainly through oxidative stress. We investigated the protective effect of *Cuminum cyminum* (*C. cyminum*) seeds powder after acetaminophen administration.

Materials & Methods: In this study, 30 male rats were allocated into five groups of six in number as follows: control, acetaminophen (A), and acetaminophen + *C. cyminum* 200, 400, and 800 mg/kg (A+C). After 24 hours of fasting, the control group received distilled water, and groups A and A+C received acetaminophen 1,000 mg/kg orally through gavage. Six hours later, the control group and group A were given distilled water, and groups A+C received *C. cyminum* 200, 400, and 800 mg/kg by gavage. Twelve hours after the second gavage, hepatic markers of oxidative stress and serum ALT and AST were assessed.

Results: In group A, the activities of serum ALT and AST, the concentration of hepatic malondialdehyde and H_2O_2 increased, and peroxidase & catalase activities decreased substantially compared to the control group. *C. cyminum* administration in groups A+Cs resulted in the return of these changes toward group control.

Conclusion: These results suggest that *C. cyminum*, due to its flavonoid and polyphenol contents, could diminish hepatic injury induced by acetaminophen.

Keywords: Acetaminophen, Hepatotoxicity, *Cuminum cyminum*, Oxidative stress, Hepatic function

Introduction

Drug-induced liver injury (DILI) can cause all types of acute and chronic hepatic diseases (1). Acetaminophen (N-acetyl-Para-Aminophenol) is used widely as a pain and fever reliever medicine. As it is available over-the-counter and is easy to purchase, some people intentionally take a large single dose in an attempt to commit suicide, and or become overdose unintentionally by taking multiple large doses to relieve pain. As a result, acetaminophen overuse has been among the most common causes of DILI and even death (2). For this reason, the mechanisms of acetaminophen-induced hepatotoxicity have been investigated in animal models and humans for years (3, 4). Production of N-acetyl-p-benzoquinone imine (NAPQI), an acetaminophen reactive metabolite from its metabolic activation by the cytochrome P-450 family (mainly CYP2E1), is the most important event in the development of hepatic injury (4). NAPQI can be detoxified by glutathione (GSH); however, GSH is depleted in acetaminophen overdose. Hence, NAPQI covalently binds with cellular proteins, leading to mitochondrial dysfunction and oxidative stress (5). Oxidative stress is the most frequent mechanism by which most toxicities occur and is important in acetaminophen toxicity (6). NAPQI leads to increased production of superoxide anion, hydrogen peroxide, and peroxynitrite. Oxidative stress, possibly associated with the commencement of signal transduction and the following mitochondrial permeability transition, leads to the loss of mitochondrial membrane potential and depletion of ATP resulting in necrosis (7). In addition, the covalent binding in hepatic cells inactivates some crucial functional proteins resulting in cell death that causes aminotransferases, namely ALT and AST, to elevate in the plasma (8). Contrary to the remarkable progress in modern medicine, the traditional form of medicine (especially the herbal one) has always found its position. As fundamentals of traditional medicine, plants have led to some important drugs that are still used (9). Seeds of *Cuminum cyminum L.* (*C. cyminum*) belonging to the family Apiaceae have been used for culinary and flavoring purposes and also for the treatment of some diseases (e.g., diabetes (10) and liver steatosis (11)) since

antiquity in various countries including Iran (12). The effects of several compounds of cumin seeds powder and their extracts on liver damage caused by hepatotoxins have been investigated (13, 14). Essential oil of cumin consists of a large amount of phenolic compounds, in particular cumin aldehyde (4 - isopropyl benzaldehyde). This compound is an aromatic monoterpenoid component that has been used to protect against oxidative stress-induced liver injury. Ebada reported two-week preventive effects of chamomile (250 mg/kg) and cumin oil (400 mg/kg) administration on hepatotoxicity induced by acetaminophen (15). Flavonoids belong to a class of plant secondary metabolites having several subgroups, which include chalcones, flavones, flavonols, and isoflavones. Almost all groups of flavonoids have the capacity to act as antioxidants (16). Elhabib et al. reported that hepatotoxicity induced by acetaminophen at 500 mg/kg has been alleviated by 6% *C. cyminum* fruit or 6% N. sativa seeds. The recovery of paracetamol hepatotoxicity was proven by a substanitial improvement in serobiochemical and hematological variables (13).

Materials and Methods

Chemicals

Trichloroacetic acid (TCA) was purchased from Sigma Aldrich Chemical Co. Ltd. (USA), thiobarbituric acid (TBA) from Merck Co (Germany), and assay kits for assessment of enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT) from Pars Azma (Iran).

Animals and groups

Thirty male Wistar rats (250±20 g) were obtained from the Animal House Unit of the Faculty of Sciences, Shahid Bahonar University of Kerman, Kerman, Iran. They were adapted to the environment for 7 days before starting the experiment. They were given human care based on the criteria in the "Guide for the Care and Use of Laboratory Animals" by the National Academy of Science and published by The National Institutes of Health.

Experimental design

Animals were allocated into five groups of 6 rats:

a) Control: After 24 hours of fasting, rats received distilled water orally and 6 hours later were given distilled water

b) Acetaminophen (A): After 24 hours of fasting (17), they were gavaged acetaminophen 1,000 mg/kg, and 6 hours later were given distilled water.

c) Acetaminophen+ *C. cyminum* (A+C200): After 24 hours of fasting, they were gavaged acetaminophen 1,000 mg/kg and 6 hours later were given 200 mg/kg *C. cyminum*.

d) Acetaminophen+ *C. cyminum* (A+C400): After 24 hours of fasting, they were gavaged acetaminophen 1,000 mg/kg and 6 hours later were given 400 mg/kg *C. cyminum.*

e) Acetaminophen+ *C. cyminum* (A+C800): After 24 hours of fasting, they were gavaged acetaminophen 1,000 mg/kg and 6 hours later were given 800 mg/kg *C. cyminum.*

Induction of hepatotoxicity

Acetaminophen was purchased from Darou Pakhsh Holding. Hepatotoxicity was induced with a single dose of 1,000 mg/kg of acetaminophen dissolved in distilled water, immediately before use.

Preparation of *C. cyminum* powder

C. cyminum seeds were bought from the local market in Kerman, Iran. The seeds were identified by the botanist and ground to a fine powder. Finally, 200, 400, and 800 mg/kg of the powder were dissolved in distilled water and fed by gavage.

Serum preparation

Twelve hours after the second gavage, the animals were killed and blood samples for serum collection were obtained to analyze enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST).

Assessment of aminotransferases (ALT and AST) in serum

ALT enzyme catalyzes the transfer of amine group from alanine to α-ketoglutarate and AST enzyme catalyzes the transfer of amine group from aspartate to α-ketoglutarate. Pyruvate and oxaloacetate are produced respectively, which are converted into lactate and malate by lactate dehydrogenase and malate dehydrogenase enzymes. At the same time, the change in NADH concentration is created and measured by spectrophotometric method, which is proportional to the activity of ALT and AST.

Liver preparation

The liver was removed, washed, and then kept frozen in nitrogen until oxidant and antioxidant factors were assayed.

The indicators of oxidative stress

Determination of Malondialdehyde (MDA) concentration

Hepatic malondialdehyde (as an indicator of lipid peroxidation) was assessed by the method of Uchiyama and Mihara (1978). To test tubes, containing 4 ml of TCA 20% with TBA 0.5%, 1 ml of hepatic tissue supernatant was added, and the reaction mixture was heated for 30 min at 95℃. After cooling, it was centrifuged for 10 min and the MDA-TBA complex was measured spectrophotometrically at 532 nm (18).

Determination of H_2O_2 concentration

H_2O_2, as an index of oxidants, was measured in the liver by the method proposed by Velikova et al. In 1 ml TCA (0.1%), 0.1 g of the liver was homogenized, and the resulting homogenate was centrifuged at 4℃ for 10 min. H_2O_2 concentration was measured in a cuvette containing 0.5 ml of tissue supernatant, 0.5 phosphate buffer 10 mM

(pH=7), and 1 ml of potassium iodide 1 mM. Eventually, it was measured spectrophotometrically at 390 nm (19).

Determination of catalase (CAT) activity

After homogenizing the liver in 50 Mm phosphate buffer (pH=7.5), the resulting homogenate was centrifuged at 4°C for 10 min. The enzyme activity was measured by the method proposed by Aebi. To a cuvette containing 1.5 ml of catalase mixture (PBS 50 Mm (pH=7) + H_2O_2 15 Mm), 100 µl liver supernatant was added. Next, the reaction was begun by the decomposition of H_2O_2, and CAT activity was measured at 240 nm (20).

Determination of peroxidase (POD) activity

POD activity of liver tissues was measured by the method by Cakmak and Marshner. About 20 µl of liver supernatant was added to a cuvette containing 2.5 ml of POD mixture (H_2O_2 0.3% + PBS 50mM (pH=7) + guaiacol) and the reaction was initiated by the guaiacol oxidation. Finally, the POD activity was measured at 470 nm (21).

Statistical Analysis

Statistical analysis was performed using the "Statistical Package for the Social Sciences" (SPSS) version 19.0. First normality and homogeneity of variances were checked, and then one-way analysis of variance (ANOVA) and TUKEY as the post-test were done. Data are expressed as mean ± standard deviation (SD). The study was accomplished with ethical approvement with the code number IR.UK.VETMED.REC.1399.19.

Results

Figure 1 presents serum alanine transferase in experimental groups. The acetaminophen group showed a significant increase compared to the control group ($p<0.001$). Groups A+C_{200} and A+C_{800} ($p<0.05$) and A+C_{400} ($p<0.01$) had a significant decrease compared to the acetaminophen group.

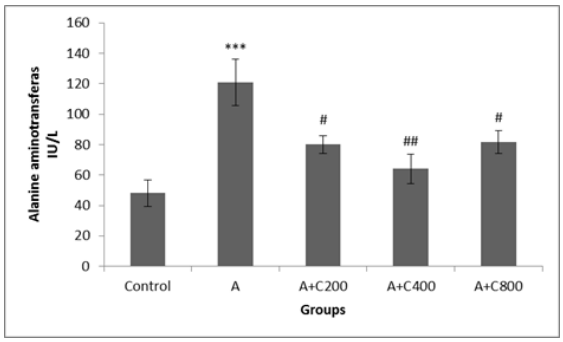

Figure 1. Effect of oral *C. cyminum* consumption on serum ALT in experimental groups. Each bar indicates mean ± S.E.M. * Significant difference ($p<0.001$) with the control group. #, ## Significant difference ($p<0.05$) and ($p<0.01$) with acetaminophen group, respectively (A=acetaminophen, A+C200= acetaminophen+*C. cyminum* 200 mg/kg, A+C400= acetaminophen+*C. cyminum* 400 mg/kg, A+C800= acetaminophen+*C. cyminum* 800 mg/kg).**

Figure 2 illustrates that serum aspartate transferase in the acetaminophen group increased significantly compared to the control group ($p < 0.001$). Also, A+C_{200} ($p<0.05$) and A+C_{400} ($p<0.001$), and A+C_{800} ($p<0.01$) groups illustrated a significant reduction compared to the acetaminophen group.

Figure 3 shows the concentration of MDA in experimental groups. As can be seen, the acetaminophen group had a significant increase ($p < 0.001$) compared to the control group. Groups A+C_{200} ($p<0.01$) and A+C_{400} and A+C_{800} ($p<0.001$) had a significant decrease compared to the acetaminophen group.

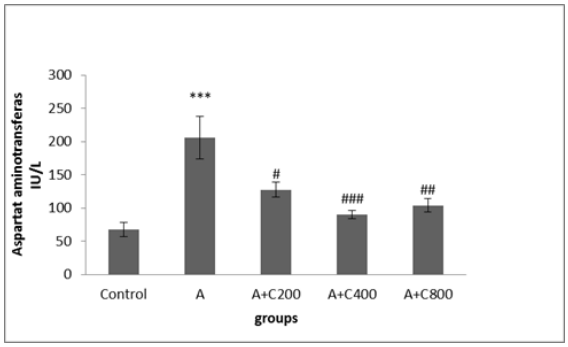

Figure 2. Effect of oral *C. cyminum* consumption on serum AST in experimental groups. Each bar indicates mean ± S.E.M. * Significant difference ($p<0.001$) with the control group. #, ##, ### Significant difference ($p< 0.05$) and ($p<0.01$) and ($p<0.001$) with acetaminophen group**

(A = acetaminophen, A+C200= acetaminophen+*C. cyminum* 200 mg/kg, A+C400= acetaminophen+*C. cyminum* 400 mg/kg, A+C800= acetaminophen+*C. cyminum* 800 mg/kg).

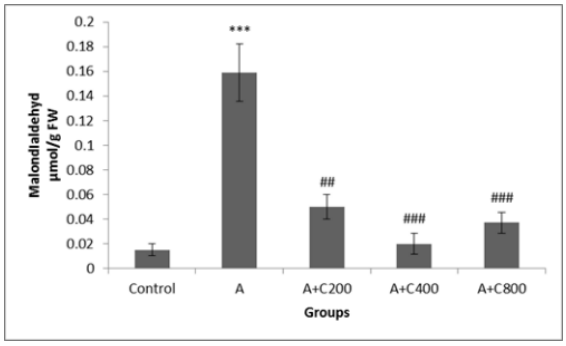

Figure 3. Effect of *C. cyminum* consumption on malondialdehyde (MDA) in experimental groups. Each bar indicates mean ± S.E.M. * Significant difference ($p<0.001$) with the control group. ##, ### Significant difference ($p<0.01$) and ($p<0.001$) with acetaminophen group, respectively (A= acetaminophen, A+C200= acetaminophen+*C. cyminum* 200 mg/kg, A+C400= acetaminophen+*C. cyminum* 400 mg/kg, A+C800= acetaminophen+*C. cyminum* 800 mg/kg).**

Figure 4 depicts hydrogen peroxide levels in experimental groups. The acetaminophen group had a significant increase compared to the control group ($p<0.01$). Groups A+C_{400} and A+C_{800} showed a significant decrease ($p<0.01$ and $p<0.05$ respectively) compared to the acetaminophen group.

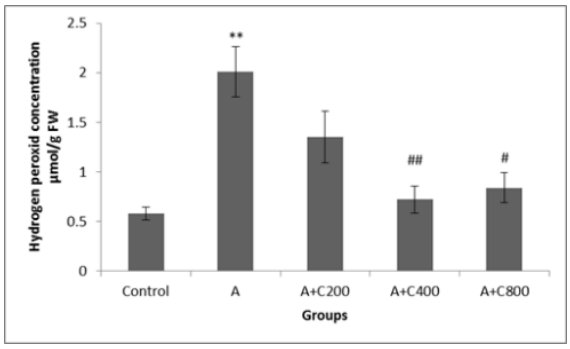

Figure 4. Effect of *C. cyminum* consumption on Hydrogen peroxide (H_2O_2) in experimental groups. Each bar indicates mean ± S.E.M. ** Significant difference (p<0.01) with the control group. #, ## Significant difference (p<0.05) and (p<0.01) with acetaminophen group, respectively (A=acetaminophen, A+C200= acetaminophen+*C. cyminum* 200 mg/kg, A+C400= acetaminophen+*C. cyminum* 400 mg/kg, A+C800= acetaminophen+*C. cyminum* 800 mg/kg).

Figure 5 represents catalase activity in experimental groups. As can be seen, the acetaminophen (p<0.01) and A+C_{200} (p<0.05) groups had a significant reduction compared to the control group.

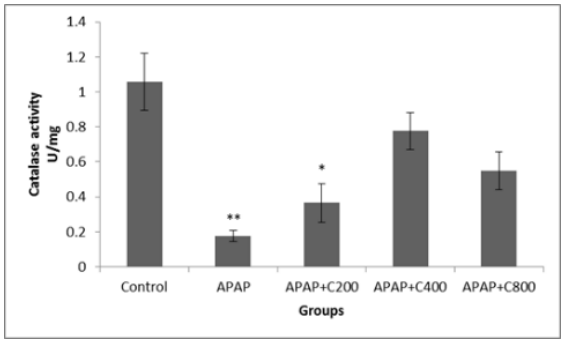

Figure 5. Effect of oral administration of *C. cyminum* on catalase (CAT) activity in experimental groups. Each bar indicates mean ± S.E.M. *, ** Significant difference (p<0.05) and (p<0.01) with the control group, respectively (A = acetaminophen, A+C200= acetaminophen+*C. cyminum* 200 mg/kg, A+C400= acetaminophen+*C. cyminum* 400 mg/kg, A+C800 = acetaminophen+*C. cyminum* 800 mg/kg).

Figure 6 shows peroxidase activity in experimental groups. According to this figure, the acetaminophen group (p<0.001) and A+C_{200} and A+C_{800} groups (p<0.01) had a significant decrease compared to the control group. Also, group A+C_{400} (P<0.001) and groups A+C_{200} and A+C_{800} (P<0.01) showed a significant increase compared to the acetaminophen group.

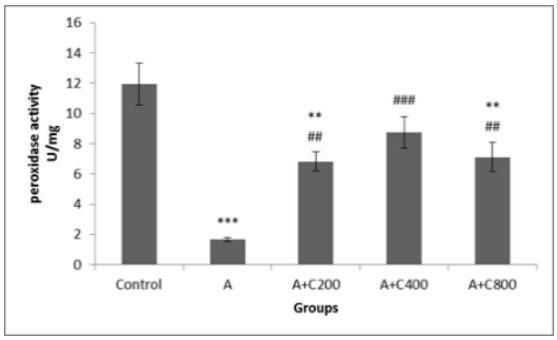

Figure 6. Effect of *C. cyminum* consumption on peroxidase (POD) activity in experimental groups. Each bar indicates mean ± S.E.M. **, * Significant difference (p<0.01) and (p<0.001) with the control group. ##, ### Significant difference (p<0.01) and (p<0.001) with acetaminophen group, respectively (A= acetaminophen, A+C200= acetaminophen+*C. cyminum* 200 mg/kg, A+C400= acetaminophen+*C. cyminum* 400 mg/kg, A+C800 = acetaminophen+*C. cyminum* 800 mg/kg).**

Discussion

In this study, we observed that acetaminophen increased serum ALT & AST activities. Also, it increased levels of H_2O_2 and MDA and decreased activities of CAT and POD in hepatic tissue, showing its effect in inducing hepatic injury. Moreover, treatment of rats with *C. cyminum* powder reduced the injury induced by acetaminophen with the most effective dose at 400mg/kg.

Using natural antioxidants is a suitable method for preventing and treatment of liver diseases caused by oxidative stress (22). Acetaminophen is generally used as an analgesic and antipyretic medicine and it is safe in therapeutic doses. However, in overdose or long-term usage, it leads to free radical generation, defeating the antioxidant defense system and consequently hepatic injury results (2). In this study, acetaminophen with the dose of 1,000 mg/kg increased the activities of serum ALT & AST enzymes. During hepatic injury, hepatocyte function is disturbed, and as a result of plasma membrane disintegration, serum aminotransferases increase. Treatment with *C. cyminum* powder with doses of 200, 400, and 800 mg/kg decreased ALT and AST, which can be a result of plasma membrane stability (13). Of the three doses, 400 mg/kg was the most effective one having protective properties. Ebada reported that Cumin oil reduced the elevated ALT and AST in serum and preserved the liver structure in acetaminophen-intoxicated rats (15). Also, Elhabib et al. reported a decrease in serum level of aminotransferases by Cumin in acetaminophen toxicity (13), which are consistent with the results of our study. Membrane lipids are rich in polyunsaturated fatty acids, which are very sensitive in oxidative reactions and their peroxidation indicates oxidant stress such that their high level indicates an antioxidant potential decrease (22). Donmez et al. showed that oral administration of acetaminophen increased lipid peroxidation, which is consistent with

our results (23). Treatment with *C. cyminum* seeds powder caused MDA reduction. It has been reported that phenols by giving hydrogen atoms from hydroxyl groups attached to the benzene ring prevent lipid peroxidation showing their antioxidant activity (24). Singh et al. reported that many phenolic compounds have been detected in *C. cyminum* seeds, including phenolic acids and flavonoids. These compounds have shown antioxidant activities and play key roles in the inhibition of lipid peroxidation and different kinds of oxidizing agents (25). Mushtaq et al. investigated the effects of the hydroalcoholic extract of *C. cyminum* seeds on hepatotoxicity induced by Nimesulide. They showed that 100, 200, and 300 mg/kg doses of this extract decreased MDA significantly compared to a group receiving Nimesulide, showing antioxidant properties of *C. cyminum* (14). Hepatic necrosis occurs when produced NAPQI is much more than the hepatic reserve of GSH binding capacity. NAPQI results in oxidant production such as superoxide anion and H_2O_2 (26). In this research, an H_2O_2 increase was observed in the acetaminophen group, which is consistent with the work of Chang et al. They injected acetaminophen intraperitoneally by 200 and 400 mg/kg in rats and observed an H_2O_2 increase in the liver. H_2O_2 reduction in the treated group with *C. cyminum* seeds powder may be due to the phenol and other constituents such as flavonoids. These compounds convent H_2O_2 to water by donating oxygen to it (27).

Antioxidant enzymes scavenge free radicals. Acetaminophen overdose leads to an impressive reduction of antioxidant enzyme activity. Catalase and peroxidase are two ROS-removing enzymes. A reduction in these enzymes' activity increases superoxide and hydrogen peroxide levels (28). In this study, we observed a reduction in catalase and peroxidase activity in the hepatic tissue of rats receiving acetaminophen, which was also reported by Gupta et al. (29). In our study, treatment of rats with *C. cyminum* seeds powder reversed the reduction induced by acetaminophen. This antioxidant property of *C. cyminum* seeds could be due to the scavenging activity of flavonoids, polyphenols, tannin, and terpins that it contains. Kaur and Sharma showed that *C. cyminum* seeds are rich in polyphenolic flavonoids, thereby contributing to their antioxidant capacity (30). In this process, they form complexes with iron, copper, and zinc polyphenols to reduce their absorption (31). *C. cyminum* seeds also contain flavonoids such as luteolin and apigenin having reducing power. In a preventive study, Tia et al. showed that luteolin administration orally (100,200 mg/kg) protected hepatic injury by acetaminophen injection (i.p.) (32). Moreover, Yang et al. reported that apigenin administration (100, 300 mg/kg) for seven days declined serum aminotransferase and as a result reduced hepatic injury. In addition, reduced oxidative stress parameters, such as MDA and reactive oxygen species (ROS), showed a protective effect on acetaminophen-induced liver injury (33). The results of our study also demonstrated that consumption of *C. cyminum* seeds powder lowered serum levels of alanine & aspartate aminotransferases (ALT/AST) and increased the activity of enzymes antioxidant (CAT and POX) compared to the acetaminophen group. The activity of the antioxidant enzymes in the A+C400 group compared to the A+C200 and A+C800 groups showed that they are the best dose of the protective effect of C. cyminum seeds powder. There are several reports about the hepatoprotective and antioxidant properties of spices (34, 35). El-Ghorab et al. suggested that cumin and ginger can be potential sources of natural antioxidants (34). Also, Barakat et al. have compared the hepatoprotective effects of the five-week pretreatment of cumin, ginger, and mustard against acetaminophen-induced hepatic injury (35). Our study shows the post-treatment protective effect of C. cyminum even after acetaminophen overdose.

Conclusion

Our study illustrated that C. cyminum seeds could result in oxidative stress reduction and improvement of liver function even after acetaminophen overdose.

Acknowledgments

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Conflict of Interest

The authors declare that they have no conflict of interests.

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