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Full Length Research Paper

Assessment of *Foeniculum vulgare* in ameliorating acute carbon tetrachloride-induced hepato-renal toxicity *in vivo*

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Carbon tetrachloride (CCl_4) toxicity is a well-established model for studying liver and kidney injury. *Foeniculum vulgare*, a medicinal herb, has shown hepatoprotective effects in various liver injury models, but its efficacy in acute CCl_4-induced toxicity remains underexplored. To evaluate the hepatoprotective potential of *F. vulgare* in an acute CCl_4 toxicity rat model through biochemical and histopathological assessments. Male Sprague Dawley rats were divided into three groups: Control, CCl_4-exposed, and *F. vulgare*-treated. Liver and kidney function markers, including urea, creatinine, albumin, cholesterol, and liver enzymes (alanine aminotransferase (ALT) and aspartate aminotransferase (AST)), were analyzed. Liver and kidney tissues underwent histopathological examination. CCl_4 exposure significantly reduced urea and creatinine levels, indicating kidney impairment, and decreased albumin levels, suggesting compromised liver function. *F. vulgare* treatment restored urea levels and attenuated creatinine decline but did not fully normalize albumin levels. Cholesterol levels increased following CCl_4 exposure, with partial mitigation by *F. vulgare*. Histopathological findings showed severe hepatotoxicity and nephrotoxicity in CCl_4-exposed rats, while *F. vulgare* treatment ameliorated these changes. *F. vulgare* exhibited hepatoprotective effects against acute CCl_4-induced liver and kidney injury, as evidenced by biochemical and histopathological findings. These results support its potential therapeutic role in mitigating hepatotoxin-induced organ damage.

Key words: *Foeniculum vulgare*, carbon tetrachloride, hepatoprotective, liver injury, kidney injury.

INTRODUCTION

Liver injury induced by hepatotoxic agents remains a significant global health concern, with carbon tetrachloride (CCl_4) being one of the most extensively studied hepatotoxins in experimental models (Recknagel et al., 1989). CCl_4-induced hepatotoxicity serves as a paradigm for investigating mechanisms of liver injury, with relevance to understanding human liver diseases such as drug-induced liver injury, alcoholic liver disease, and viral hepatitis (McGill and Jaeschke, 2014). Upon administration, CCl_4 undergoes metabolic activation primarily in the liver, leading to the generation of highly reactive free radicals, including the trichloromethyl radical (•CCl3) and the peroxy trichloromethyl radical (•OOCCl3). These radicals initiate lipid peroxidation, protein oxidation, and DNA damage, culminating in hepatocyte necrosis, inflammation, and fibrosis (Sahu et al., 2013).

In recent years, there has been growing interest in exploring natural compounds and plant extracts for their potential hepatoprotective effects against CCl_4-induced liver injury. *Foeniculum vulgare*, commonly known as fennel, is an aromatic herb that has been used in traditional medicine for centuries. *F. vulgare* possesses a wide range of pharmacological properties, including antioxidant, anti-inflammatory, antimicrobial, and hepatoprotective activities, attributed to its rich phytochemical content, including phenolic compounds, flavonoids, and volatile oils (Özbek et al., 2003). The hepatoprotective effects of *F. vulgare* have been demonstrated in various experimental models of liver injury, including those induced by chemicals, drugs, and alcohol (Yemitan and Izegbu, 2006; Amin and Mahmoud-Ghoneim, 2009). Herbal extracts has been previously reported to combat oxidative stress (Noh et al., 2018), and protect against liver (Zhu et al., 2013) and kidney (Soussi et al., 2009) toxicity. Indeed, natural products have been reported to provide protection against a range of toxicities (Pu et al., 2024; Aljohani et al., 2025; Służały et al., 2024).

Carbon tetrachloride is known for its nephrotoxic effects, which can cause significant damage to the kidneys, leading to renal failure and impaired kidney function (Unsal et al., 2021). When CCl_4 is metabolized in the body, it produces free radicals that can initiate lipid peroxidation and oxidative stress, leading to cellular damage (Sahu et al., 2013). This can result in necrosis of renal tubular cells, inflammation, and ultimately, impaired kidney functions. Prolonged exposure to CCl_4 can cause chronic kidney injury, characterized by fibrosis and reduced glomerular filtration rate, potentially leading to renal failure. The nephrotoxic effects of CCl_4 underscore the importance of minimizing exposure to this chemical to protect renal health.

Despite the promising pharmacological properties of *F. vulgare*, limited studies have investigated its efficacy in acute CCl_4-induced liver injury models. Therefore, this study aims to elucidate the hepatoprotective effects of *F. vulgare* in an acute CCl_4 toxicity rat model. By evaluating histopathological changes, serum biochemical markers of liver function (such as alanine transaminase, aspartate transaminase, and bilirubin levels), we seek to provide comprehensive insights into the mechanisms underlying the protective effects of *F. vulgare* against CCl_4-induced hepatotoxicity. The renoprotective properties of *F. vulgare* may be largely attributed to its potent anti-inflammatory activities (Namoune et al., 2018). These beneficial effects have been demonstrated in several experimental models.

Fennel contains a variety of bioactive compounds, such as flavonoids, phenolic acids, and essential oils. These compounds help in scavenging free radicals and reducing oxidative stress, a major factor in kidney damage. By neutralizing these free radicals, *F. vulgare* helps to protect renal cells from oxidative damage and supports the maintenance of cellular integrity and function (Tognolini et al., 2007).

In addition to its antioxidant capabilities, *F. vulgare* exhibits significant anti-inflammatory effects. Inflammation is a key pathological process in many kidney diseases, and by reducing inflammatory responses, *F. vulgare* helps to protect the kidneys from injury and promotes healing. The anti-inflammatory action of *F. vulgare* is mediated through the downregulation of pro-inflammatory cytokines and inhibition of inflammatory pathways, which reduces the overall inflammatory burden on renal tissues (Al-Snafi, 2018).

Studies using various experimental models have shown that *F. vulgare* can attenuate markers of kidney damage and improve renal function. For instance, in models of chemically induced nephrotoxicity, *F. vulgare* administration has been observed to reduce levels of serum creatinine and urea, indicating better kidney function. Additionally, *F. vulgare* ability to lower oxidative stress and inflammation has been linked to decreased renal fibrosis and improved histological architecture of the kidneys (Al Hunduwan et al., 2025; Al-Snafi, 2018; Tognolini et al., 2007).

This article aims to review the pathophysiology of CCl_4-induced hepatotoxicity, discuss the pharmacological properties of *F. vulgare*, and present the rationale for investigating its hepatoprotective effects in CCl_4-induced

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liver injury models. Furthermore, this study contributes to the growing body of evidence supporting the potential therapeutic utility of *F. vulgare* in liver diseases, with implications for the development of novel hepatoprotective agents and herbal remedies.

MATERIALS AND METHODS

Animals and *in vivo* work

This study was conducted using male Sprague Dawley rats, weighing between 200 and 250 g. Animals were housed under standard laboratory conditions, with a 12 h light/dark cycle, at a temperature of 22±2°C, and 55±10% relative humidity. They had free access to standard pellet food and water *ad libitum*. The experimental protocols were approved by the Institutional Animal Care and Use Committee of the college of pharmacy, Taibah University (No. COPTU-REC-20210113-2 ElSayed), in compliance with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health.

Preparation of *F. vulgare* extract

F. vulgare seeds were authenticated by a botanist and were ground into a fine powder. The powder was subjected to extraction with 70% ethanol using a Soxhlet extractor for 72 h. The extract was then filtered, and the solvent was evaporated under reduced pressure using a rotary evaporator. The resultant extract was stored at -20°C until further use.

Experimental design

Rats were randomly divided into three groups, each consisting of five animals. The control group received only vehicle (olive oil). The second group (CCl_4) Group received CCl_4 at a dose of 1 mL/kg (Foaud et al., 2018), mixed with olive oil at a 1:1 ratio, and administered intraperitoneally (i.p.). The third group were treated as second group but with a pretreatment with *F. vulgare* extract orally at a dose of 200 mg/kg body weight for 7 days (Bhatti et al., 2018), followed by a single dose of CCl_4 (1 mL/kg) on the 8th day. On the final day, animals were euthanized under anesthesia using ketamine, and blood, kidneys, and liver were collected. Tissues were preserved in paraformaldehyde before staining with hematoxylin and eosin. Outcome assessment and data analysis were conducted blinded to group allocation. The reporting of this study conforms to ARRIVE 2.0 guidelines (Percie du Sert et al., 2020).

Histopathological examination

Liver and kidney tissues were collected for histopathological examination. Tissues were fixed in 10% formalin, embedded in paraffin, sectioned at 5 µm thickness, and stained with Hematoxylin and Eosin (H&E) for examination under a light microscope.

Biochemical analysis

Blood samples were collected from the rats' 24 h post-CCl_4 administration through cardiac puncture while under deep anesthesia to ensure minimal stress and pain. The collected blood was allowed to clot at room temperature for 30 min and then centrifuged at 3000 rpm for 15 min to separate the serum. The obtained serum was carefully pipetted out and stored at -20°C until the time of analysis to prevent degradation of biomarkers.

The biochemical parameters including urea, creatinine, albumin, and cholesterol levels were quantitatively measured using commercial diagnostic kits supplied by Randox Laboratories Ltd (UK). The assays were performed according to the manufacturer's protocols provided with each kit. Urea was assessed using the urease method, creatinine by the Jaffe method, albumin using the bromocresol green method, and cholesterol levels were determined through an enzymatic colorimetric method using spectrophotometer (Hawash, China).

Liver function was evaluated by measuring the activities of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), utilizing commercial kits from BioSystems S.A. The determination of ALT and AST activities was based on the kinetic method described by the manufacturer, which involves measuring the rate of NADH oxidation as it correlates with the enzymatic activity present in the serum. This method provides a reliable measure of liver health, as both enzymes are released into the bloodstream in greater amounts when there is liver damage Randox Laboratories Ltd (UK).

All assays were performed using a spectrophotometer or an automated biochemical analyzer as appropriate, under conditions specified by the kit manufacturers. The results were calculated based on the calibration curves established using standards provided with the kits. Care was taken to ensure that all measurements were within the linear range of the assay to maintain accuracy and reliability.

Data from the biochemical analyses were recorded meticulously and processed statistically to determine the effects of CCl_4 and the protective role of *F. vulgare* extract on the hepatic and renal functions of the rats.

Statistical analysis

Data were expressed as mean ± standard deviation (SD). Differences between groups were evaluated using one-way ANOVA followed by Tukey's post hoc test. A value of $p<0.05$ was considered statistically significant.

Ethical approval

The experimental protocols were approved by the Institutional Animal Care and Use Committee of the College of Pharmacy, Taibah University (No. COPTU-REC-20210113-2ElSayed), in compliance with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health.

RESULTS

Histopathological changes in liver and kidney

Effect of F. vulgare on hepatic histopathology

In the healthy control group, the hepatic tissue exhibited a standard histological structure with hepatic lobules properly oriented, highlighted by a distinct portal area (P) and central vein (C). The arrangement of hepatic plates in rows of hepatocytes, indicated by arrows, separated by blood sinusoids, marked by arrowheads, showcased the intact liver architecture. Conversely, the hepatic tissue

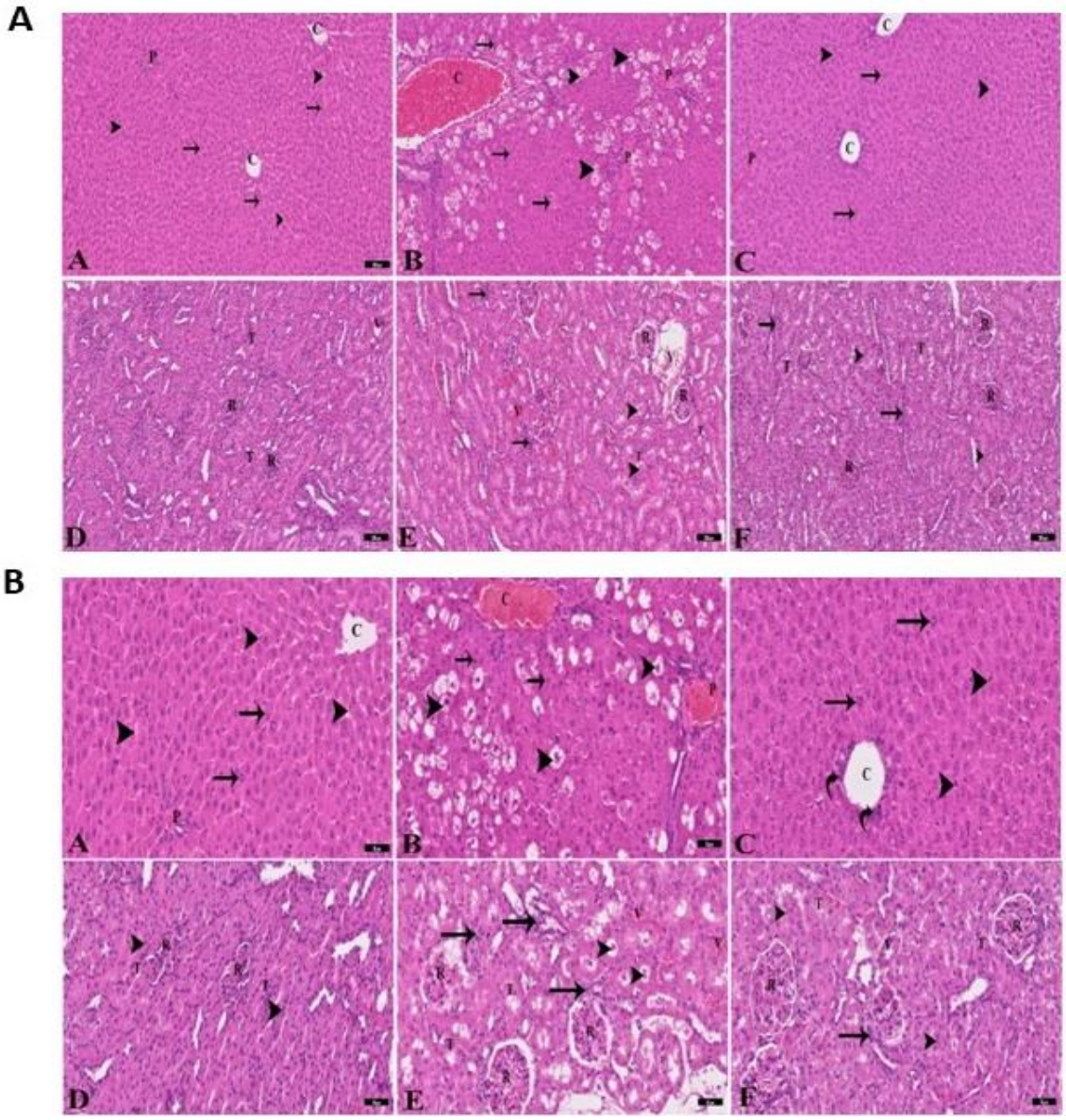

Figure 1. Histopathological changes in liver and kidney tissues. Sections of liver are shown in the upper panel of figure A and B. Sections of kidneys are shown in the lower panel of figure A and B. Figure B shows a higher magnification of the liver and kidney in adult albino rats. For both figures, A and D represent tissues extracted from health rat. B and E denotes tissues from rats treated with CCl_4. C and F are tissues from animals pretreated with *F. vulgare* extract for a week before exposure to CCl_4. Each figure is a representative of 5 replicates (n=5). Arrows indicate histopathological findings.

from the CCl_4-treated group revealed signs of hepatotoxicity, including disorientation of the hepatic lobule structure and significant congestion in the central vein (C) and portal vessels (P). Hepatocytes near the portal area, shown by arrowheads in Figure 1A, underwent severe degenerative changes, whereas those around the central vein, denoted by arrows, appeared relatively unaffected, indicating localized impacts of the toxic exposure (Figure 1). The group treated with *F. vulgare* showed hepatic tissues rebounding towards a normal histological appearance. The portal area (P) and the central vein (C) looked normal, with hepatic plates forming regular rows of large hepatocytes, pointed out by arrows, and blood sinusoids that housed Van Kupfer cells, identified by arrowheads, suggesting the protective drug mitigated the hepatotoxic effects of CCl_4 (Figure 1).

Looking into more details using higher magnification, additional findings were noted. In the examination of hepatic tissue from the healthy control group, the architecture showcased well-defined hepatic lobules, highlighted by the presence of the portal area and the central vein. Hepatic plates were neatly organized into rows of large, active hepatocytes characterized by granular cytoplasm and prominent spherical nuclei. These hepatocytic cords were interspersed with blood sinusoids, which housed the conspicuously large Van Kupfer cells, demonstrating the liver's optimal functioning and structural integrity (Figure 1). Contrastingly, hepatic tissue from the CCl_4-treated group illustrated pronounced hepatotoxicity, evident from the significant congestion within the central vein and portal vessels. Around the portal areas, hepatocytes displayed severe degenerative changes including ballooned cytoplasm and pyknotic nuclei, while those around the central vein exhibited mild hydropic degeneration. Notably, the Van Kupfer cells in the sinusoids were extremely proliferated, indicating an inflammatory response and liver damage. In the *F. vulgare* group, hepatic tissue appeared considerably normal with a clear central vein. Hepatic plates formed regular rows of large hepatocytes, mirroring the healthy control in terms of granular cytoplasm and spherical nuclei, albeit with marked lymphocytic infiltration around the central vein. This suggested a protective effect of *F. vulgare*, albeit with signs of immune response (Figure 1).

Effect of F. vulgare on renal histopathology

Regarding renal tissue, the healthy control group presented with a normal histology, where the renal cortex featured renal corpuscles (R), renal tubules (T), and renal blood vessels (V), reflecting a healthy kidney structure. In stark contrast, renal tissue from the CCl_4-treated group showed evidence of damage, including atrophied renal corpuscles (R) and degenerated renal tubules (T) filled with acidophilic materials, indicated by arrowheads, alongside highly congested renal blood vessels (V). There was also lymphocytic infiltration, marked by arrows, in the renal interstitial tissue, highlighting the adverse effects of CCl_4 on renal health (Figure 1). The renal tissue from the *F. vulgare* group, however, appeared largely normal with renal corpuscles (R), renal tubules (T), and renal blood vessels (V) displaying no significant pathological changes, indicating the *F. vulgare* effectiveness in protecting against CCl_4-induced renal damage. These findings elucidate the differential impact of CCl_4 exposure and the protective actions of *F. vulgare* on hepatic and renal tissues, with *F. vulgare* showing a capability to alleviate the histopathological alterations induced by CCl_4 in both liver and kidney tissues.

Upon closer examination using higher magnification, additional findings were observed. The healthy control group showed a normal renal cortex with renal corpuscles having very narrow Bowman's spaces, and renal tubules lined by normal epithelium, reflecting healthy kidney structure and function. However, the renal tissue from the CCl_4-treated group depicted a stark contrast with atrophied renal corpuscles, expanded Bowman's spaces, and tubules undergoing severe degeneration and sloughing, filled with acidophilic materials. The renal blood vessels were notably congested, and lymphocytic infiltration was present in the interstitial tissue, signaling significant renal distress and inflammation. The renal tissue from the group treated with *F. vulgare*, however, demonstrated a restoration towards normalcy, with renal corpuscles maintaining normal Bowman's spaces and minor lymphocytic infiltration around the corpuscles. The renal tubules, lined with normal epithelium, and the renal blood vessels remained unchanged in size, indicating some efficacy of *F. vulgare* in mitigating CCl_4-induced renal damage (Figure 1).

Effect on urea, creatinine, albumin and cholesterol levels

Urea levels serve as critical biomarkers for kidney and hydration status. The control group represents the baseline measurements or healthy controls. The CCl_4-treated group showed a significant decrease in urea levels as compared to controls. *F. vulgare* treatment restored urea levels to near normal values. The increase in urea levels in *F. vulgare* treated group as compared to CCl_4 group was significant (Figure 2). Creatinine levels were measured as an indicator of kideny functions. Treatment with CCl_4 resulted in a significant decrease in creatinine levels. Notably, the reduction is statistically significant compared to the Control group. In rats treated with the natural extract (*F. vulgare*), creatinine levels increased again but remained below those of the Control group. The treatment with *F. vulgare* appears to mitigate the decline induced by CCl_4 exposure, yet it does not fully restore creatinine levels to the baseline (Figure 2A and B).

Albumin is primarily produced by the liver. It serves as a vital indicator of liver function, where lower levels can signify liver damage or impaired liver function. Albumin levels can affect overall fluid distribution and organ function, including the liver and kidneys. CCl_4 exposure significantly decreases albumin levels compared to the Control group. A significant decrease was observed in the levels of albumin in CCL_4 treated group when compared to negative controls. The decrease was still decreased in the *F. vulgare* treated group as no significant increase was noted (Figure 3). Cholesterol levels are an important marker of liver health and function. Figure 3 also demonstrates the comparative cholesterol levels among the Control, CCl_4-exposed, and *F. vulgare*-treated groups. In the CCl_4 group, there is a notable increase in cholesterol

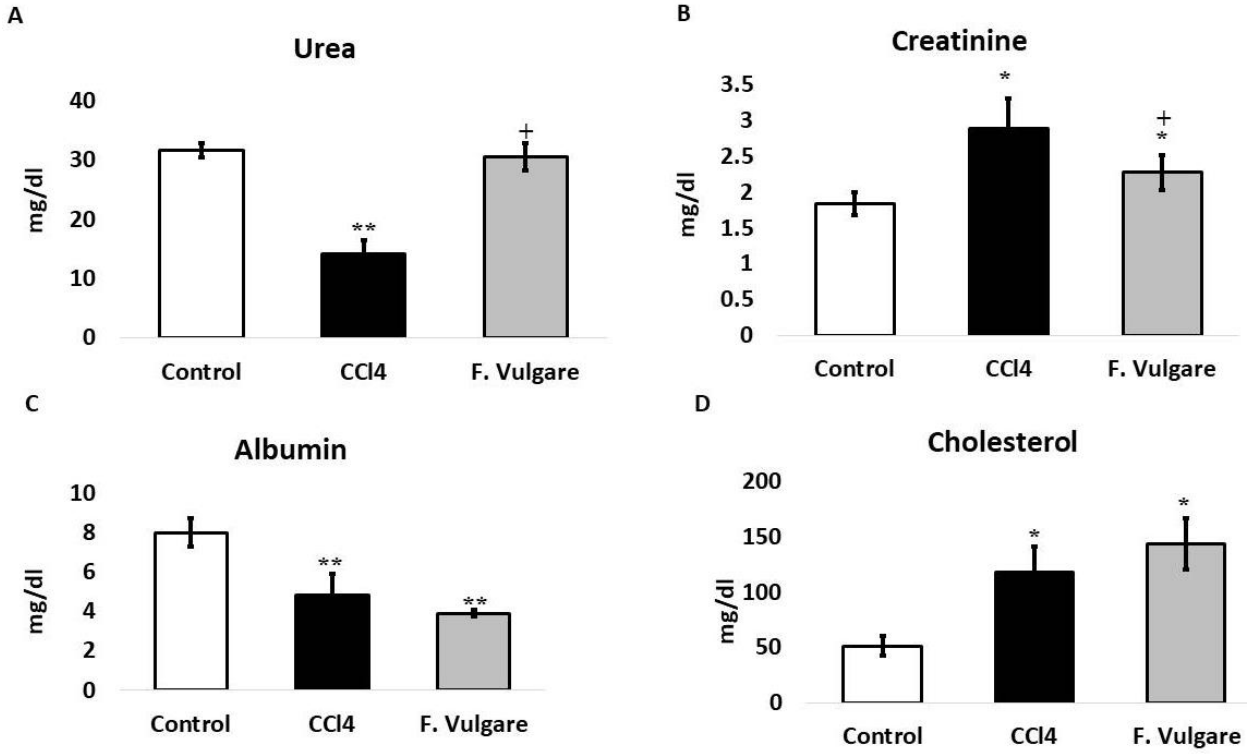

Figure 2. Indicators of liver and kidney functions. Columns represent the average from 5 measurements of urea (A), creatinine (B), albumin (C) and cholesterol (D) levels. Controls are represented with white columns, CCl_4 treated rats are represented with black columns, while rats pretreated with *F. vulgare* are represented in grey columns. Standard deviation is represented by error bars. P values ≤ 0.05% were considered significant. * Indicate significance differences between controls and a given group, while + indicates significant differences between CCL_4 group and *F. vulgare* group.

levels, reaching approximately 150 mg/dl, indicative of the hepatotoxic impact of CCl_4 that disrupts normal liver function and cholesterol metabolism. Conversely, the *F. vulgare* treatment group, while still displaying elevated cholesterol levels relative to the Control, shows a reduction in cholesterol elevation compared to the CCl_4 group (Figure 2C and D).

Liver function markers

Measuring ALT and AST levels plays a critical role in studies investigating the hepatoprotective effects of *F. vulgare* against CCl_4. AST levels across the Control, CCl_4-exposed, and *F. vulgare*-treated groups. The CCl_4 group shows a significant elevation in AST levels, with values approaching 175 U/l, signaling liver damage as a consequence of CCl_4 exposure, which promotes the release of AST into the bloodstream. In contrast, the *F. vulgare* treatment group presents with increased AST levels relative to the Control group but demonstrates a reduction in AST elevation when compared to the CCl_4 group. This pattern indicates a potential protective effect of *F. vulgare* against CCl_4-induced liver damage, as evidenced by lower AST levels (Figure 3A).

In the group exposed to CCl_4, there's a pronounced increase in ALT levels, nearly reaching 175 U/l. This significant rise is indicative of liver damage due to CCl_4 toxicity, which causes ALT, an enzyme located primarily in the liver, to leak into the bloodstream. Meanwhile, the group treated with *F. vulgare* shows elevated ALT levels compared to the Control group, yet these levels are notably lower than those in the CCl_4 group. This observation implies that *F. vulgare* treatment could mitigate the adverse effects on liver function as indicated by elevated ALT levels, following CCl_4 exposure (Figure 3B).

DISCUSSION

This study investigated the hepatoprotective effects of *F. vulgare* in an acute carbon tetrachloride (CCl_4) toxicity rat model. Our findings demonstrate that *F. vulgare* treatment mitigated the adverse effects of CCl_4-induced liver and kidney injury, as evidenced by biochemical and

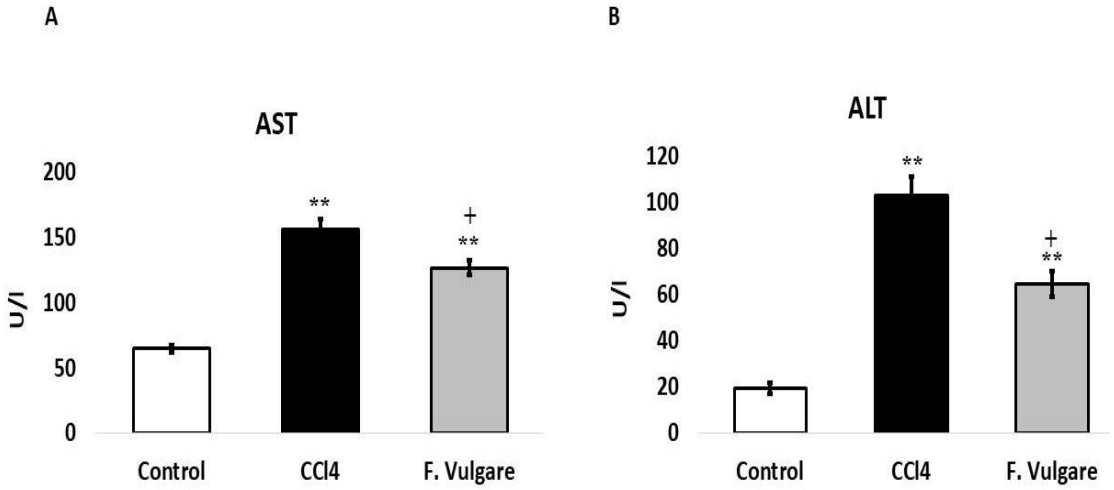

Figure 3. Liver function tests. Columns represent the average from 5 measurements of AST (A) and ALT (B) levels. Controls are represented with white columns, CCl_4 treated rats are represented with black columns, while rats pretreated with *F. vulgare* are represented in grey columns. Standard deviation is represented by error bars. P values ≤ 0.05% were considered significant. * Indicate significant differences between controls and a given group, while + indicates significant differences between CCL_4 group and *F. vulgare* group.

histopathological assessments.

The observed decrease in urea levels in the CCl_4-exposed group suggests impaired kidney function, which is consistent with previous studies demonstrating the nephrotoxic effects of CCl_4 (Özbek et al., 2003). However, *F. vulgare* treatment restored urea levels to near-normal values, indicating its potential renoprotective effects. The renoprotective properties of *F. vulgare* may be attributed to its antioxidant and anti-inflammatory activities, as evidenced by its ability to attenuate oxidative stress and inflammation in various experimental models (Al-Snafi, 2018; Tognolini et al., 2007).

Similarly, CCl_4 exposure resulted in a significant decrease in creatinine levels, indicative of impaired kidney function. Notably, *F. vulgare* treatment attenuated the decline in creatinine levels induced by CCl_4 exposure, although levels remained below those of the control group. Creatinine is a reliable marker of glomerular filtration rate and renal function (Levey et al., 2015). The protective effects of *F. vulgare* on renal function can be via the modulation of oxidative stress, inflammation, and apoptosis pathways, as suggested by previous studies (Rather et al., 2016; Boudjadi et al., 2016).

Albumin, a major plasma protein synthesized by the liver, plays a crucial role in maintaining oncotic pressure and transporting various substances in the blood. Our results revealed a significant decrease in albumin levels following CCl_4 exposure, indicating impaired liver function. While *F. vulgare* treatment attenuated the decrease in albumin levels induced by CCl_4 exposure, no significant increase was observed compared to the CCl_4 group. The hepatoprotective effects of *F. vulgare* may involve modulation of hepatic inflammation, fibrosis, and regeneration pathways (Sahreen et al., 2011; Khoso et al., 2022).

Cholesterol levels were significantly elevated in the CCl_4-exposed group, reflecting hepatotoxicity-induced disruption of cholesterol metabolism. Interestingly, *F. vulgare* treatment partially mitigated the increase in cholesterol levels induced by CCl_4 exposure, suggesting its potential hepatoprotective effects. The hepatoprotective properties of *F. vulgare* may be attributed to its ability to regulate lipid metabolism, inhibit cholesterol synthesis, and enhance bile acid excretion (Raghunatha, 2010; Gurunath, 2006).

Liver function enzymes, such as AST and ALT, are sensitive markers of hepatocellular injury. Consistent with previous reports, our study demonstrated a significant elevation in AST and ALT levels following CCl_4 exposure, indicative of liver damage (Mohamed et al., 2021; Elkhamesy et al., 2022). However, *F. vulgare* treatment attenuated the increase in AST and ALT levels induced by CCl_4 exposure, suggesting its hepatoprotective effects. The hepatoprotective mechanisms of *F. vulgare* may involve suppression of oxidative stress, inflammation, and apoptosis pathways, as demonstrated in various experimental models (Mazani et al., 2018; Mahmoud et al., 2022).

Histopathological analysis further supported the biochemical findings, revealing marked hepatotoxicity and nephrotoxicity in the CCl_4-exposed group, which were ameliorated by *F. vulgare* treatment. The histological

improvements observed in the *F. vulgare*-treated group are consistent with previous studies demonstrating the hepatoprotective and renoprotective effects of *F. vulgare* in various experimental models (Elham et al., 2021; Rajasekaran et al., 2006).

Conclusions

This study provides evidence for the hepatoprotective and reno-protective effects of *F. vulgare* in an acute CCl_4 toxicity rat model. These findings highlight the therapeutic potential of *F. vulgare* in mitigating liver and kidney injury induced by hepatotoxins like CCl_4. Further studies are warranted to elucidate the underlying mechanisms and optimize the therapeutic use of *F. vulgare* in liver and kidney diseases.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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