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Hepatoprotective effects of *Ziziphus spina-christi* extract against cadmium-induced liver damage in rats: Biochemical and histopathological insights

[Efectos hepatoprotectores del extracto de *Ziziphus spina-christi* contra el daño hepático inducido por cadmio en ratas: Aportes bioquímicas e histopatológicas]

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Abstract: Cadmium (Cd), a very toxic heavy metal, poses significant environmental and public health risks, particularly affecting the liver. This study examined the therapeutic effectiveness of *Ziziphus spina-christi* (ZSC) extract, known for its antioxidant, anti-inflammatory, and hepatoprotective properties, in alleviating cadmium-induced liver damage in rats. Twenty-four rats were divided into four groups: control, ZSC-treated, Cd-exposed, and Cd + ZSC-treated. Rats were administered ZSC extract and Cd orally for 21 days, followed by biochemical and histological assessments. Cadmium exposure elevated liver enzymes (ALT, AST, ALP), indicating hepatic injury. The co-administration of ZSC significantly normalized these levels and mitigated hepatic anomalies, as histological analyses confirmed the preservation of liver architecture. The hepatoprotective advantages are attributed to the bioactive compounds of ZSC, including flavonoids, saponins, and phenolic acids. In conclusion, ZSC demonstrates therapeutic potential in alleviating Cd-induced liver damage and may serve as an effective intervention for heavy metal hepatotoxicity.

Keywords: Cadmium toxicity; Histopathology; Oxidative stress; Hepatoprotective; Flavonoids

Resumen: El cadmio (Cd), un metal pesado altamente tóxico, representa riesgos significativos para la salud pública y el medio ambiente, afectando particularmente al hígado. Este estudio examinó la efectividad terapéutica del extracto de *Ziziphus spina-christi* (ZSC), conocido por sus propiedades antioxidantes, antiinflamatorias y hepatoprotectoras, en la mitigación del daño hepático inducido por cadmio en ratas. Veinticuatro ratas fueron divididas en cuatro grupos: control, tratado con ZSC, expuesto a Cd y tratado con Cd + ZSC. Las ratas se les administró el extracto de ZSC y Cd por vía oral durante 21 días, seguidos de evaluaciones bioquímicas e histológicas. La exposición al cadmio elevó las enzimas hepáticas (ALT, AST, ALP), indicando lesión hepática. La coadministración de ZSC normalizó significativamente estos niveles y mitigó las anomalías hepáticas, como lo confirmaron los análisis histológicos que mostraron la preservación de la arquitectura hepática. Las ventajas hepatoprotectoras se atribuyen a los compuestos bioactivos de ZSC, incluidos flavonoides, saponinas y ácidos fenólicos. En conclusión, ZSC demuestra un potencial terapéutico en la mitigación del daño hepático inducido por Cd y puede servir como una intervención efectiva contra la hepatotoxicidad por metales pesados.

Palabras clave: Toxicidad por cadmio; Histopatología; Estrés oxidativo; Hepatoprotector; Flavonoides.

INTRODUCTION

Cadmium (Cd) is a heavy metal and environmental contaminant known for its toxic effects on various organs, particularly the liver and respiratory system (Thévenod & Lee, 2013; Peana *et al*., 2022). given the severe impact of Cd on liver health, there is increasing interest in natural therapies like *Ziziphus spina-christi* that may offer protection. *Ziziphus spina-christi*, also known as Sidr or jujube, has received interest due to its potent therapeutic properties. This is because individuals are looking for natural therapies that may combat the poisonous effects of cadmium (Elhady *et al*., 2014; Ahmad *et al*., 2017; Saad *et al*., 2017). A plant that is indigenous to both the Middle East and Africa, *Ziziphus spina-christi* has been utilized for centuries because to the antioxidant, anti-inflammatory, and hepatoprotective properties that it possesses. Because of the abundance of bioactive substances found in the leaves and fruits of the *Ziziphus spina-christi* plant, which include flavonoids, saponins, and phenolic acids, the *Ziziphus spina-christi* plant has the potential to be used in medicinal applications (Tounekti *et al*., 2019; Abu-Odeh & Talib, 2021).

A number of recent researches have demonstrated that *Ziziphus spina-christi* is an effective method for reducing the toxicity of heavy metals. For example, the antioxidant capabilities of *Ziziphus spina-christi* have the ability to neutralize reactive oxygen species (ROS) that are produced as a result of exposure to cadmium. This results in a reduction in oxidative stress and the prevention of cellular damage (Singh *et al*., 2012; Al-Ali & Jewad, 2019). In addition, the anti-inflammatory actions of *Ziziphus spina-christi* can help reduce the inflammatory responses that occur in the liver, which in turn assists in the process of tissue repair and regeneration. in rats, the purpose of this work is to evaluate the protective function that *Ziziphus spina-christi* extract plays against cadmium-induced hepatotoxicity (Alamgir, 2018). We hope to gain a better understanding of the mechanisms that *Ziziphus spina-christi* uses to exert its hepatoprotective benefits by analyzing the levels of liver enzymes, histological alterations, oxidative stress indicators. It is possible that gaining an understanding of these mechanisms might pave the way for the development of natural treatment techniques to battle the toxicity of heavy metals and enhance liver function health This study aims to evaluate the hepatoprotective effects of *Ziziphus spina-christi* extract against Cd-induced liver toxicity in rats.

MATERIAL AND METHODS

Plant collection and extraction

It was macerated at 20 grams ZSC leaves into 200 mL distilled water (at a temperature of 30°C) and the mixture was shaken at rpm speed of 150 within 24 hours. Filter paper (Whatman) was used to filter all suspensions and the second extraction and filtration of the solid material were accomplished as above. The two filtrates were combined and evaporated using a rotary evaporator at 40°C, the concentration of each plant's concentrated filtrate was measured from its crude extract then re-dissolved in normal saline to achieve 100 mg/kg, and stored at -20°C until use (Alhimaidi *et al*., 2024).

Chemical analysis using (GC-MS)

The volatile components of bile were analyzed using a Trace Ultra Gas Chromatograph combined with a DSQII Mass Spectrometer (Thermo Scientific). The separation of these components was performed chromatographically using the TR-5 MS capillary column, as described by Adams (1995). This column measured 30 meters in length, with an inner diameter of 0.25 mm and a film thickness of 0.25 µm. Identification of the substances was accomplished by referencing relevant data stored in literature and equipment databases, including Adams Book 07, Nist 98, and Xcalibur. To calculate the Relative Retention Index, a range of n-alkanes from C8 to C24 was used. The relative percentages of the compounds were determined electronically, based on the percentage area data.

Experimental design

The study involved twenty-four healthy rats, with an equal number of females and males (12 each), weighing between 180-220 grams and aged 12 to 14 weeks. These rats were obtained from the animal facility at the Zoology Department of the Science College, King Saud University (KSU). They were acclimated to a well-ventilated environment at a room temperature of 25 ± 2ºC, with a regular 12-hour light and dark cycle. They were given a standard diet and had access to water. All experimental procedures followed the guidelines set by the ethics committee and the Institutional Animal Care at KSU (Approval no: KSU-SE-24-3). The rats were divided into four groups the extract rats were orally given, each consisting of three female and three male rats. The first group, serving as the control, received water only. The second group was given 100 mg of *Ziziphus spina-christi* the third group received 1 mg/kg of cadmium, and the fourth group was

exposed to both *Ziziphus spina-christi* and cadmium for 14 days (Ammari *et al*., 2024).

Ethical approval

This research was carried out according to the ethical guidelines for the use of animals established by the Kingdom of Saudi Arabia (Ethics Committee of King Saud University, approval number: KSU-SE-24-3).

Weights of the body and organs

At the end of 15 days, body weights were measured for rats among all 4 groups; male and female separately. Animals were euthanized thereafter by IP injection of 200 mg/kg sodium lidocaine solution (Xylocaine®, Astra Zeneca). During the necropsy, all animals were submitted to a systematic examination: skin and ski ling; oral cavity; chest and abdominal cavities (gross aspects); collection of organs that weighted. For relative weight (RW) of liver, kidneys and spleen: RW = OW/BW at day 15 × 100 %.

Biochemical assessment

Blood was withdrawn directly from the heart of male and female rats in non-coated tubes and allowed to stand overnight at 4°C, then centrifuged with a refrigerated centrifuge at 1000 rpm for 10 min to separating serum. Serum aspartate aminotransferase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), Glucose were measured in the laboratory according to manufacturer's instructions (MOLEQULE-ON company, Auckland, New Zealand).

Histopathological examination

Liver excisions were promptly washed in physiological saline and then fixed in 70% phosphate-buffered formalin. After fixation, the samples were embedded in paraffin and sectioned longitudinally into 5 µm thick slices. The sections were deparaffinized, dehydrated, and stained with hematoxylin and eosin (Sigma). Observations of the liver microstructures were performed using an Olympus BH2 microscope (DP71, Olympus, Tokyo, Japan) (Ebaid *et al*., 2024).

Statistical evaluation

The experimental data were analyzed using GraphPad Prism (version 10.1.1) software. The Shapiro-Wilk test was used to assess the normal distribution of the data. One-way ANOVA followed by Tukey's test was applied to various parameters, including liver enzymes, kidney parameters, and organ weights. The results are presented as mean values with their standard deviations.

RESULTS

Chemical composition of Ziziphus spina-christi leaves extract by GC-MS

The analysis focuses on the chemical composition of *Ziziphus spina-christi* leaves extract. Understanding these compounds is crucial for elucidating the mechanisms underlying the observed hepatoprotective effects. The attached figures (peak area and infrared spectroscopy) provide detailed insights into the main components and their functional groups. this figure illustrates the relative abundance of the primary chemical constituents present in the *Ziziphus spina-christi* leaves extract. The peak area percentages indicate the proportion of each compound, allowing for a quantitative comparison (Figure No. 1).

Infrared spectroscopy of Ziziphus spina-christi leaves methanol extracts

Infrared (IR) spectroscopy provides information about the functional groups present in the extract. The IR spectrum typically shows peaks corresponding to various bonds and functional groups, helping to identify the chemical structure of the compounds (Figure No. 2).

The high content of flavonoids (quercetin and kaempferol) and phenolic acids (ellagic and gallic acids) in the *Ziziphus spina-christi* extract suggests a strong antioxidant capacity. These compounds can neutralize reactive oxygen species (ROS) and protect cells from oxidative stress, which is likely a key mechanism behind the hepatoprotective effects observed in the study. Compounds like kaempferol, chlorogenic acid, and various saponins exhibit anti-inflammatory properties. They can inhibit pro-inflammatory cytokines and modulate inflammatory pathways, reducing liver inflammation and damage caused by cadmium exposure. Cyclopeptide alkaloids and saponins present in the *Ziziphus spina-christi* extract have shown antimicrobial and cytoprotective effects. These properties can help in protecting the liver from infections and promoting cellular health.

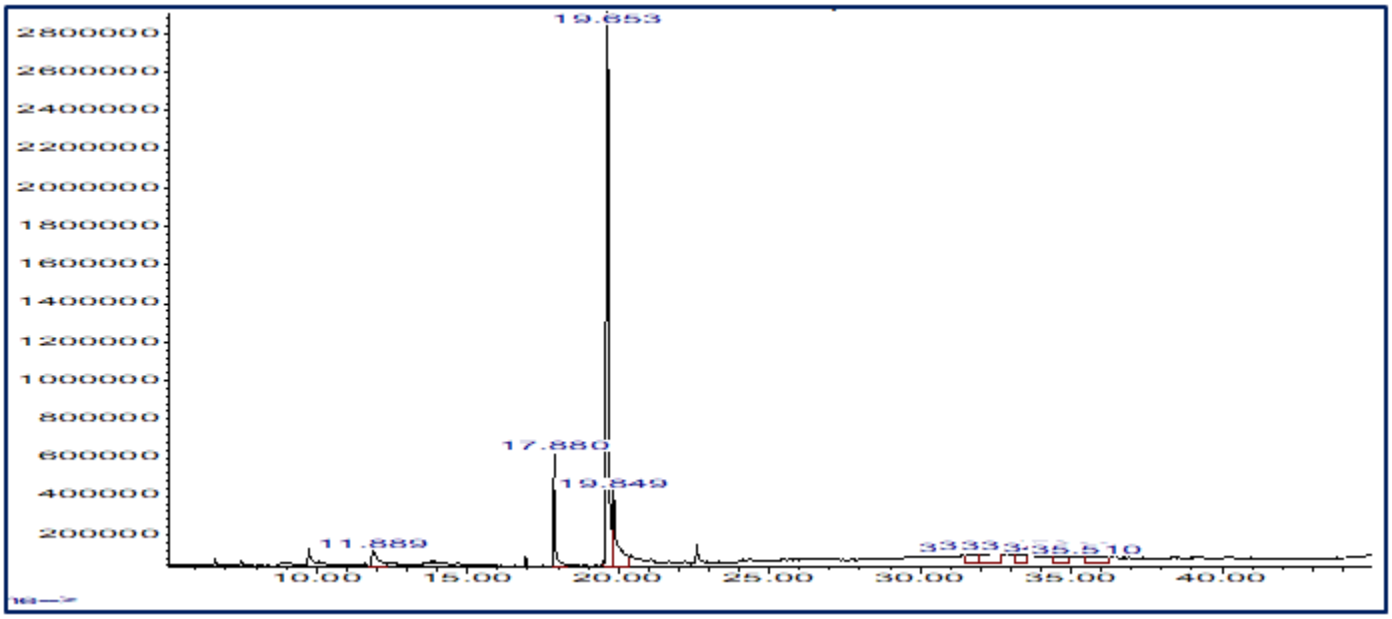

Figure No. 1
The peak area (%) of the main components *Ziziphus spina-christi* leaves extract

Liver weight results in rats

Cadmium Exposure both male and female rats exposed to cadmium show a substantial decrease in liver weight, indicating significant liver damage in group *Ziziphus spina-christi* does not significantly affect liver weight in either male or female rats, suggesting it is not hepatotoxic. combination Treatment The combination of cadmium and *Ziziphus spina-christi* results in higher liver weights compared to cadmium alone, indicating a protective effect of *Ziziphus spina-christi* against cadmium-induced liver damage. This protective effect is more pronounced in male rats than in female rats (Figure No. 5).

Analysis of ALT enzyme levels in rats

The study investigates the effects of cadmium and *Ziziphus spina-christi* on Alanine Aminotransferase (ALT) enzyme levels in male and female rats. ALT is a critical biomarker for liver function, with elevated levels indicating liver damage or stress. The analysis of ALT levels provides insight into hepatotoxicity and potential protective effects of treatments.

The attached graph illustrates these findings, showing the ALT enzyme levels in male and female rats across different treatment groups. The visual representation underscores the dramatic rise in ALT due to cadmium exposure and the mitigating effect of *Ziziphus spina-christi*. This clear depiction supports the narrative of *Ziziphus spina-christi's* potential as a hepatoprotective agent. The results demonstrate that cadmium exposure leads to a significant increase in ALT enzyme levels, indicating severe liver damage in both male and female rats. Conversely, *Ziziphus spina-christi* alone does not significantly elevate ALT levels, suggesting it is non-toxic to the liver. More importantly, the combination of cadmium and *Ziziphus spina-christi* results in significantly lower ALT levels compared to cadmium alone, highlighting the hepatoprotective effect of *Ziziphus spina-christi* (Figure No. 6).

Analysis of AST enzyme levels in rats

The data clearly demonstrate that cadmium exposure significantly elevates AST levels in both male and female rats, indicating severe liver damage. This is consistent with the known hepatotoxic effects of cadmium, which include oxidative stress, inflammation, and cellular damage in liver tissues. In contrast, *Ziziphus spina-christi* alone does not significantly increase AST levels, suggesting it is non-toxic to the liver. More importantly, when combined with cadmium, *Ziziphus spina-christi* significantly reduces AST levels compared to cadmium alone. This suggests that *Ziziphus spina-christi* has a protective effect, possibly due to its antioxidant properties, which may help in mitigating oxidative stress and inflammation caused by cadmium. While both male and female rats show a similar trend in AST level changes across the different groups, male rats exhibit a slightly higher increase in AST levels in response to cadmium exposure. This could suggest a gender difference in

susceptibility to cadmium-induced liver damage, which might be worth exploring in further studies. The provided graph visually supports these findings by clearly showing the elevated AST levels due to cadmium exposure and the mitigating effect of Ziziphus spina-christi. This visual evidence strengthens the narrative of Ziziphus spina-christi's hepatoprotective role and its potential application in liver health preservation (Figure No. 6).

Analysis of ALP enzyme levels in rats

The data clearly demonstrate that cadmium exposure leads to a significant increase in ALP levels in both male and female rats, indicating severe liver and/or bone damage. This aligns with the established understanding of cadmium's toxic effects, which include inducing oxidative stress, inflammation, and cellular damage in various tissues.

In contrast, *Ziziphus spina-christi* alone does not significantly elevate ALP levels, suggesting it is non-toxic to the liver and bones. More importantly, when combined with cadmium, *Ziziphus spina-christi* significantly reduces ALP levels compared to cadmium alone. This suggests that *Ziziphus spina-christi* has a protective effect, possibly due to its antioxidant properties, which may help in mitigating oxidative stress and inflammation caused by cadmium.

While both male and female rats show similar trends in ALP level changes across the different groups, the extent of increase due to cadmium exposure and the subsequent reduction by *Ziziphus spina-christi* is slightly more pronounced in male rats. This could suggest a gender difference in susceptibility to cadmium-induced toxicity and the protective effects of *Ziziphus spina-christi*, which warrants further investigation (Figure No. 6).

The provided graph visually supports these findings by clearly showing the elevated ALP levels due to cadmium exposure and the mitigating effect of *Ziziphus spina-christi*. This visual evidence strengthens the narrative of *Ziziphus spina-christi's* protective role and its potential application in preserving liver and bone health.

Analysis of Glucose levels in rats

The data clearly demonstrate that cadmium exposure leads to a significant increase in glucose levels in both male and female rats, indicating severe metabolic disruption. This aligns with the established understanding of cadmium's toxic effects, which include inducing oxidative stress, impairing insulin function, and disrupting glucose metabolism.

In contrast, *Ziziphus spina-christi* alone does not significantly elevate glucose levels, suggesting it is non-toxic to metabolic function. More importantly, when combined with cadmium, *Ziziphus spina-christi* significantly reduces glucose levels compared to cadmium alone. This suggests that *Ziziphus spina-christi* has a protective effect, possibly due to its antioxidant properties, which may help in mitigating oxidative stress and improving insulin sensitivity.

While both male and female rats show similar trends in glucose level changes across the different groups, the extent of increase due to cadmium exposure and the subsequent reduction by *Ziziphus spina-christi* is slightly more pronounced in male rats. This could suggest a gender difference in susceptibility to cadmium-induced metabolic disruption and the protective effects of Ziziphus spina-christi, which warrants further investigation.

The provided graph visually supports these findings by clearly showing the elevated glucose levels due to cadmium exposure and the mitigating effect of *Ziziphus spina-christi*. This visual evidence strengthens the narrative of *Ziziphus spina-christi's* protective role and its potential application in preserving metabolic health (Figure No. 6).

Histological analysis

This study provides a comparative histological analysis of female liver tissues under different experimental conditions: control (normal), cadmium exposure, cadmium exposure with *Ziziphus spina-christi* treatment, and *Ziziphus spina-christi* treatment alone. The control liver tissue exhibits a typical histological structure with well-organized hepatocytes and normal vasculature. Cadmium exposure causes severe hepatic damage, characterized by disorganized cellular architecture, cytoplasmic vacuolation, nuclear pyknosis, karyorrhexis, sinusoidal congestion, and inflammation. These observations align with the known hepatotoxic effects of cadmium. The group treated with both cadmium and *Ziziphus spina-christi* shows significant improvements. The partial restoration of hepatic architecture, reduction in cytoplasmic vacuolation, and decreased signs of necrosis and inflammation suggest that *Ziziphus spina-christi* has hepatoprotective properties. The reduced vascular congestion further supports this protective effect. The liver tissue treated with *Ziziphus spina-christi* alone closely resembles the control tissue, indicating that *Ziziphus spina-christi* does not induce any noticeable liver damage and maintains normal histological appearance (Figure No. 4). control group: Liver

tissues showed normal architecture with well-organized hepatic cords, clear hepatocytes, and non-congested sinusoids. Cadmium-Exposed group: Significant liver damage was observed, including disorganization of hepatic cords, hepatocyte swelling, cytoplasmic vacuolation, and vascular congestion. *Ziziphus spina-christi* group: Liver tissues were comparable to the control group, indicating no adverse effects of the plant extract. Hepatocytes appeared healthy with clear cytoplasm and intact nuclei. *Ziziphus spina-christi* + Cadmium-Exposed group: Partial improvement in liver architecture was noted compared to the cadmium-exposed group. There was reduced hepatocyte damage and less vascular congestion, suggesting a protective effect of *Ziziphus spina-christi* against cadmium-induced toxicity. The findings indicate that *Ziziphus spina-christi* has a protective effect against cadmium-induced liver damage. The plant extract likely mitigates oxidative stress and inflammation, preserving hepatocyte integrity and reducing vascular congestion. This protective effect can be attributed to the antioxidant properties of *Ziziphus spina-christi*, which neutralize free radicals generated by cadmium exposure (Figure No. 3).

Summary of differences between male and female rats

The Males Significant liver damage, but less severe compared to females. in Females more pronounced liver damage with greater cellular swelling, vacuolation, and vascular congestion. The Males Noticeable reduction in liver damage and vascular congestion when treated with *Ziziphus spina-christi*. In Females Potentially stronger protective effects, with better preservation of liver architecture and less cellular and vascular damage. The Male Livers show significant improvements with *Ziziphus spina-christi* treatment but still retain some damage when exposed to cadmium. In female Livers Exhibit greater sensitivity to cadmium-induced damage but also a potentially stronger protective response to *Ziziphus spina-christi* treatment. While both male and female rats benefit from the protective effects of *Ziziphus spina-christi* against cadmium-induced hepatotoxicity, the extent of damage and recovery appears to differ between sexes. Female rats may experience more severe initial damage but also a potentially greater protective benefit from *Ziziphus spina-christi* treatment. Further detailed studies are required to confirm these observations and understand the underlying mechanisms of sex-based differences in response to cadmium and Ziziphus spina-christi.

DISCUSSION

This study investigates the hepatoprotective properties of *Ziziphus spina-christi* leaves extract against cadmium-induced toxicity in male and female rats. The analysis encompasses various biochemical markers, liver weights, histological changes, and chemical composition of the *Ziziphus spina-christi* extract, providing a comprehensive understanding of its protective mechanisms. This section compares the results with recent studies and provides detailed citations for further context. The analysis of *Ziziphus spina-christi* leaves extract reveals a high content of bioactive compounds such as flavonoids (quercetin, kaempferol), tannins (ellagic acid, gallic acid), saponins, alkaloids, and phenolic acids (chlorogenic acid). These compounds are known for their antioxidant, anti-inflammatory, and hepatoprotective properties. Cadmium exposure significantly reduces liver weights in both male and female rats, indicating severe hepatotoxicity. This finding is consistent with previous studies showing that cadmium induces oxidative stress and cellular damage in liver tissues (Mao *et al*., 2018; Orororo *et al*., 2024). The combination of cadmium and *Ziziphus spina-christi* results in higher liver weights compared to cadmium alone, suggesting a protective effect of the extract. This aligns with research demonstrating the hepatoprotective properties of *Ziziphus spina-christi* in other models of liver injury. For example, a study by Al-Reza et al. (2010) found that *Ziziphus spina-christi* extract significantly protected against chemically induced liver damage in rats. Reduction by *Ziziphus spina-christi*: Studies have shown that *Ziziphus spina-christi* can lower ALT levels in models of chemically induced liver damage, supporting its use as a hepatoprotective agent. For instance, Jafarzadeh *et al*. (2014), demonstrated that the extract significantly reduced ALT levels in a rat model of liver injur Protective Mechanisms: The reduction in AST levels with *Ziziphus spina-christi* treatment is consistent with its known antioxidant and anti-inflammatory properties, which help mitigate cadmium-induced liver damage. This protective effect is supported (Ali *et al*., 2011), who found similar reductions in AST levels with antioxidant treatments. Cadmium exposure leads to a significant increase in ALP levels, indicating liver and bone damage. This result is supported by previous research demonstrating cadmium's detrimental effects on liver and bone tissues (Kuo *et al*., 2012). *Ziziphus spina-christi* significantly reduces ALP levels in cadmium-

exposed rats, suggesting its protective effects against both liver and bone damage. This finding is in line with a study by Miled *et al*. (2017), which reported reduced ALP levels in rats treated with antioxidant-rich plant extracts under toxic conditions. Cadmium exposure leads to a significant increase in glucose levels in both male and female rats, indicating severe metabolic disruption. This aligns with the established understanding of cadmium's toxic effects, which include inducing oxidative stress, impairing insulin function, and disrupting glucose metabolism (Wang *et al*., 2014).

Elhady *et al*. (2024), conducted a comprehensive chemical investigation of *Ziziphus spina-christi* extract by LC-MS/MS metabolic profiling, discovering significant bioactive components including flavonoids, saponins, phenolic acids, and alkaloids. Our work similarly identified these chemicals, specifically flavonoids (quercetin and kaempferol), tannins (ellagic and gallic acids), and saponins, as essential for their protective actions against oxidative stress and inflammation. Elhady *et al*. (2024), found that *Ziziphus spina-christi* extract alleviates lung fibrosis predominantly by downregulating the TGF-β1/SMAD pathway, a critical fibrotic and pro-inflammatory signaling pathway. Their findings indicated that the extract's benefits were facilitated by its anti-inflammatory and antioxidant capabilities, resulting in decreased fibrosis, oxidative stress, and the generation of inflammatory cytokines. The findings of our investigation correspond with the conclusions of Elhady *et al*. (2024), about the anti-inflammatory and antioxidant properties of *Ziziphus spina-christi*. The control of liver enzymes (ALT, AST, and ALP) and glucose levels in our study indicates that *Ziziphus spina-christi* safeguards liver tissue by mitigating oxidative damage and inflammation, perhaps via processes akin to the modulation of TGF-β1/SMAD pathways in hepatic cells.

Histological analysis reveals severe hepatic damage in cadmium-exposed rats, characterized by disorganized cellular architecture, cytoplasmic vacuolation, and inflammation. These observations are consistent with findings from Liu *et al*. (2016), which showed similar histopathological changes in cadmium-exposed liver tissues. The group treated with both cadmium and *Ziziphus spina-christi* shows significant improvements in liver histology, with reduced signs of necrosis and inflammation. This finding agrees with Al-Qarawi *et al*. (2008), who reported that *Ziziphus spina-christi* extract protected against hepatic damage in various animal models Several studies have demonstrated the efficacy of *Ziziphus spina-christi* extracts in protecting against various forms of liver injury. For instance, Hamden *et al*. (2009), reported that *Ziziphus spina-christi* fruit extract ameliorated testicular and hepatic damage in diabetic rats by reducing oxidative stress and inflammation. Similarly, Mahmoud *et al*. (2014), found that *Ziziphus spina-christi* leaf extract exhibited protective effects against cyclophosphamide-induced liver toxicity through its antioxidant and anti-apoptotic activities. It has been shown via research that *Ziziphus spina-christi* includes antioxidant substances such as flavonoids and saponins. These chemicals have a significant role in lowering oxidative stress and protecting liver cells from harm. Another way that *Ziziphus spina-christi* helps reduce inflammation is by modulating the reactions of the immune system and lowering the generation of cytokines that are associated with inflammation.

CONCLUSION

Understanding these mechanisms could contribute to the development of effective natural therapeutic strategies for preventing and treating cadmium-induced liver damage. This work significantly contributes to the expanding data supporting *Ziziphus spina-christi* as a natural hepatoprotective agent. The results establish a basis for further investigation into its therapeutic uses, both as an independent treatment and as a component of comprehensive approaches to address cadmium-induced liver injury. The capacity of *Ziziphus spina-christi* to guide future therapeutic strategies and improve public health measures against environmental pollutants underscores its significance as a natural medicine with notable clinical implications.

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DATA AVAILABILITY

The data sets used in the current study are available from the corresponding author upon request

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