Original Research

**Journal of Advanced Veterinary Research**
(2024) Volume 14, Issue 5, 813-818

# *Ziziphus spina-christi* extract alleviate Cisplatin induced hepatorenal toxicity in rat via oxidative stress and apoptosis modulation

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**ARTICLE INFO**

Recieved: 08 December 2023

Accepted: 09 February 2024

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Keywords:

Cisplatin
*Ziziphus spina-christi* oil extract
Gas-chromatography
TNF alpha
Anticancer

**ABSTRACT**

Cisplatin is famous, effective anti-cancer drug but has some adverse effects such as nephrotoxicity and hepatotoxicity. This work was planned to assess the protective effect of *Ziziphus spina-christi* oil extract against Cisplatin induced hepatorenal toxicity. A total of 24 male albino rats divided into equal four groups for 14 consecutive days. G1(control), G2(*Ziziphus spina-christi*), G3(cisplatin), G4(cisplatin+ *Ziziphus spina-christi*). Cisplatin treated rats showed increased serum AST, ALP, ALT, triglyceride, cholesterol, LDL- cholesterol, urea, creatinine concentrations and decreased total protein and albumin concentration. Furthermore, cisplatin treated rats significantly increased the MDA level and decreased both of CAT and SOD levels in hepatic and renal tissue compared to control. Administration of *Ziziphus spina-christi* oil extract orally at dose of with once intraperitoneal IP at 10th day of experiment renormalized cisplatin hepatorenal damaged group by exerting antioxidant, anti-inflammatory and anticancer effects. Both of histopathological and immunohistochemical (TNF alpha) changes showed good changes, recovered after using of *Ziziphus spina-christi* oil extract orally.

## Introduction

Cisplatin is a chemotherapeutic pharmaceutical medication that causes multi-organ toxicity by inducing inflammation, apoptosis, and disrupting intracellular antioxidant mechanisms. Cisplatin is considered a potent anticancer drug that is used to treat solid tumors, with associated side effects including acute liver damage (Eisa *et al*., 2021) and nephrotoxicity (Ali *et al*., 2020). This might be due to Cisplatin's cytotoxic effects on cancer cells, which are assumed to be due to its interaction with DNA, resulting in the formation of covalent adducts between DNA bases and the platinum molecule.. It may inhibit cellular division and induce apoptosis, resulting in DNA damage and apoptosis (El-Hak *et al*., (2022).

Cisplatin-induced oxidative stress is another side effect. Cisplatin cause loss of mitochondrial protein, inhibits calcium absorption and lowers the potential of the mitochondrial membrane, which is thought to promote lipid peroxidation and apoptosis (El-Hak *et al*., (2022).

*Ziziphus spina-christi* plant (cider plant) oil extract has a traditional herbal medicinal feature, it has good flavor, great medicinal feature like anti-inflammatory, antidiabetic, analgesic, sedative, and hypoglycemic (Khaleel *et al*., 2021; Atwaa *et al*., 2022). *Ziziphus spina-christi* leaf oil extract demonstrated hepatoprotection against drug-induced liver damage by activating the antioxidant response element pathway. Cider also reduced the synthesis and expression of pro-inflammatory cytokines and pro-apoptotic proteins while increasing the production and expression of anti-apoptotic proteins (Ramadan *et al*., 2021). Moreover, it cures kidney tissue from toxicities (Sindi, 2020).

Based on the available literature, no data were recorded about studying the protective role of *Ziziphus spina-christi* oil extract (cider) against cisplatin. So, the present work was planned to evaluate the protective effect of *Ziziphus spina-christi* against Cisplatin by investigating oxidative stress, serum biochemical, histopathological and immune-histochemical changes in liver and kidney.

## Materials and methods

### *Chemicals*

Cisplatin pharmaceutical product available commercially as Cisplatin (MYLAN®) [1 mg/ml] was purchase from El Ezaby Pharmaceuticals, Egypt. *Ziziphus spina-christi* oil extract was purchased from Imtenan Company (Cairo, Egypt). All analytical kits were obtained from Bio diagnostic Company, Cairo, Egypt.

### *Gas chromatography–mass spectrometry (GC-MS) analysis*

The chemical composition of *Ziziphus spina-christi* was determined using a Thermo- Scientific GC-TSQ mass spectrometer with a direct capillary column TG-5MS (30 m x 0.25 mm x 0.25 m film thickness). The column oven temperature was kept at 60°C for 2 minutes before being increased by 5°C/min to 250°C for 2 minutes before being increased to 300 with 30°C/min. The temperature of the injector was kept constant at 270°C. Helium was employed as a carrier gas out at a constant flow rate of one milliliter per minute. The solvent delay was 4 minutes, and diluted samples of 1 l were automatically injected using an Auto-sampler AS3000 linked with a GC in split mode. In full scan mode, EI mass spectra were acquired at 70 eV ionization voltages spanning the m/z 50-650 range. The temperatures of the ion source and transfer line were set to 200°C and 280°C, respectively. The components were identified by comparing their mass spectra to the mass spectral databases WILEY 09 and NIST14.


ISSN: 2090-6277/2090-6269/ 

International journal of analytical mass spectrometry and chromatography, 2016, 4, 14-25.

*Animals*

A total of 24 male albino rats were procured from the Veterinary Serum and Vaccine Research Institute in Cairo, Egypt. They were originally weighed between 200 and 240 g and fed a regular powder meal with 0.85% phosphorus, 1.12% calcium, 0.35% magnesium, 25.3% crude protein, and 2.5 IU g1 vitamin D3.

All methods utilized in this experiment were authorized by the Ethical Committee of the Faculty of Veterinary Medicine at Benha University in Egypt (Ethical No BUFVTM 21-02-23).

*Experimental design*

Twenty-four rats and divided randomly into 4 equal groups. For 14 Consecutive days, Group1: rats which served as the control administered corn oil once daily. Group 2: rats were administered 400mg oil extract of *Ziziphus spina-christi* plant /kg.b.wt., orally. Group 3: rats were administered 7.5 mg cisplatin /kg.b.wt. once IP on the 10th day of experiment. Group 4: rats were administered 400mg oil extract of *Ziziphus spina-christi* plant /kg.b.wt., orally daily + 7.5mg cisplatine/kg b.wt. once intraperitoneal on the 10$^{th}$ day. The experiment continued for 14 consecutive days, during this time all rats in all groups was observed daily.

*Serum collection and tissue sampling*

Rats were anaesthetized with isoflurane one day following the final treatment at the end of the experiment. Blood was drawn direct piercing of the heart hole of rats. The blood was put in plain tubes, allowed to coagulate, and then centrifuged at 3000 rpm for at least 15 minutes. All biochemical analyses were carried out using the acquired clear sera. Following blood collection, the rats were slaughtered, and their liver and kidneys were promptly removed. The isolated liver and kidney tissues were split in two. The first component was kept at 80°C to prepare tissue homogenates for determining the activities of malondialdehyde (MDA), catalase (CAT), and superoxide dismutase (SOD). The second half was kept in 10% neutral-buffered formalin for histopathological and immunohistochemical analyses.

*Serum biochemical analysis*

Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) (Babson *et al*., 1966), total protein and albumin levels (Doumas *et al*., 1971; Koller and Kaplan, 1984), lactate dehydrogenase (LDH) (Zimmerman and Henery, 1979), serum urea (Coulombe and Favreau, 1963), creatinine (Bartels *et al*., 1972), cholesterol, triglycerides, HDL-cholesterol concentrations (Friedewald, 1972), and LDL-cholesterol were measured by using commercial kits (Bio Diagnostics Company, Egypt) and strictly following to the instructions provided by the manufacturers.

*Determination of antioxidant parameters*

One gram of liver and kidney tissue was homogenized in 5 ml of phosphate buffer pH 7.4 using an electrical homogenizer. Tissue homogenates were centrifuged at 105,000 g for 60 minutes at 4°C. The resultant supernatants were split into (aliquots) and kept at 80°C to assess oxidative stress and antioxidant status. The level of MDA (Ohkawa *et al*., 1979), catalase (CAT) activity (Aebi, 1984) and SOD activity was determined in the hepatic and renal tissues (Nishikimi *et al*., 1972).

*Histopathological analysis*

Tissues from the kidney and liver were cut to a thickness of 3-4 mm, fixed in 10% formalin. Tissue paraffin sections were routinely prepared and stained with H&E (Bancroft and Stevens, 2016). These stained sections were examined using a Leica microscope (CH9435 Hee56rbrugg)

*Immunohistochemistry examination*

Immunohistochemistry was performed on (paraffin tissue) slices that were fixed on positively charged slides using the ABC technique. Mouse Anti-TNF alpha Monoclonal Antibody (Cat# E-AB-22159, Dil: 1:50) was tested. Sections from each group were treated with the previously mentioned antibodies before incorporating the chemicals used in the ABC technique. Peroxidase was used to detect marker expression, and diaminobenzidine (DAB) was used to discriminate an antigen-antibody complex. Negative controls were included by using non-immune serum in place of the main or secondary (antibodies Immuno-stained sections) were examined and photographed using a (Leica microscope) at various magnification powers.

*Statistical analysis*

Using the SPSS software program, ver. 20.0 (SPSS Inc., Chicago, IL), all data were statistically analyzed using one-way (ANOVA) with Duncan's multiple comparison test. P value of 0.05 or less was considered as statistically significant.

## Results

*Gas chromatography–mass spectrometry (GC-MS) analysis of Ziziphus spina-christi plant oil extracts*

The GC-MS analysis of *Ziziphus spina-christi* plant (Table 1, Figure 1) revealed the detailed presence of 24 different phytochemical constituents. The most abundant constituents were octadecene, eicosene and erucic acid, also volatile oils, which are a mixture of triglyceride- cholesterol- phospholipids and saturated fatty acids such as stearic acid- palmitic acid and unsaturated (oleic acid and linoleic acid) acids.

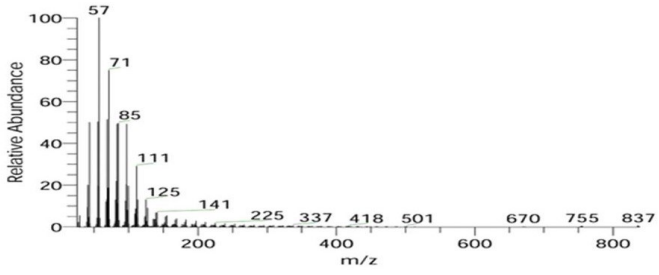


Fig. 1. GC-MS analysis of (*Ziziphus spina-christi*) oil extract.

*Effect of Ziziphus spina-christi oil extract and/or Cisplatin on serum biochemical parameters*

Cisplatin (7.5 mg/kg.b.wt.) injection on the 10th day of the experiment caused significant increases in serum activities of ALT, ALP, AST, and creatinine, and urea levels, and decreases in albumin and serum total protein levels compared with those in control group. Supplementation of 400mg oil extract of *Ziziphus spina-christi* plant /kg.b.wt., together with cisplatin (7.5 mg cisplatine/kg.b.wt.) for 14 consecutive day showed ameliorative corrected results on liver and renal bio markers ($P \leq 0.05$; Figs. 2, 3).

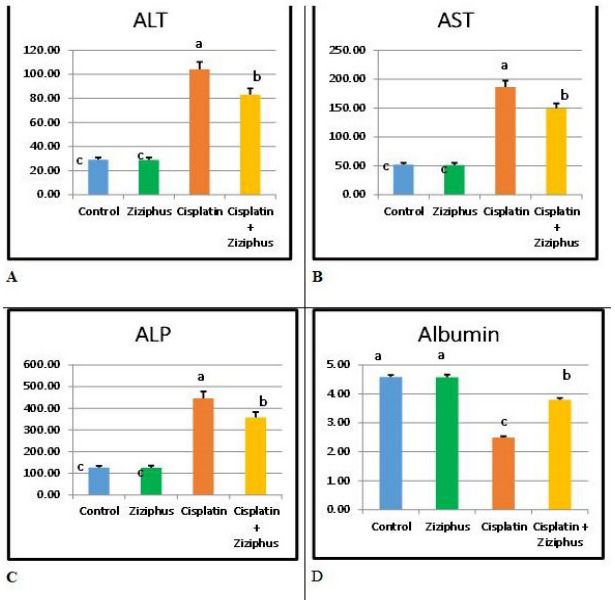


Fig. 2. Effect of *Ziziphus spina-christi* oil extract and/or Cisplatin on ALT (A) , AST (B), ALP (C) and Albumin (D) n serum of male albino rats.

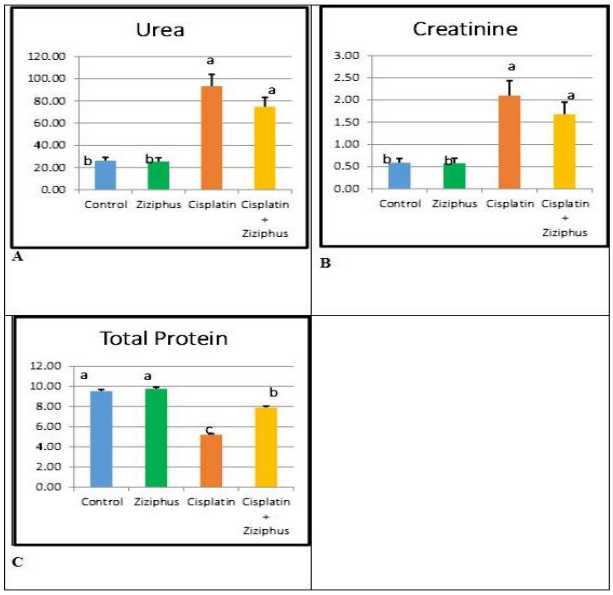


Fig. 3. showed the effect of *Ziziphus spina-christi* oil extract and/or Cisplatin on urea (A), creatnine (B) and Total protein (C) on serum of male albino rats.

*Effect of Ziziphus spina-christi oil extract and/or Cisplatin on lipid profile*

IP injection of Cisplatin (7.5 mg/kg.b.wt.) on the 10th day of the experiment significantly elevated the lipid profile parameters (LDL, cholesterol, triglycerides levels) and decreased the HDL level compared to the control group. Administration of 400mg ethanolic leaf extract of *Ziziphus spina-christi* plant /kg.b.wt.) for 14 consecutive days resulted in significant decline in LDL, cholesterol, triglycerides levels and increased HDL level compared with cisplatin group. ($P \leq 0.05$; Fig 4).

*Effect of Ziziphus spina-christi oil extract and/or Cisplatin on oxidative stress markers*

Injection of Cisplatin at 7.5 mg/kg.b.wt. on the 10th day of the experiment dramatically increased hepatorenal MDA and decreased CAT and SOD compared with the control group. On the other hand, administration of 400mg ethanolic leaf extract of *Ziziphus spina-christi* plant /kg.b.wt., co-treated with cisplatin significantly attenuated the lipid peroxidation and renal oxidative stress when compared with cisplatin group ($P \leq 0.05$; Fig 5). The histopathological and immunohistochemical findings were displayed in Figs. 6-9.

Table 1. Chemical composition of *Ziziphus spina-christi* oil extract as identified by GC.MS.

| NO | Compound Name | Area % | RT | Molecular Formula |
|---|---|---|---|---|
| 1 | Hexadecanoic acid, methyl ester | 3.21 | 25.73 | $C_{17}H_{34}O_2$ |
| 2 | Palmitic Acid methyl ester | 3.21 | 25.73 | $C_{17}H_{34}O_2$ |
| 3 | 9,12-Octadecadienoic acid (Z,Z)-,methyl ester | 24.9 | 28.76 | $C_{19}H_{34}O_2$ |
| 4 | Linoleic Acid methyl ester | 24.9 | 28.76 | $C_{19}H_{34}O_2$ |
| 5 | cis-13-Octadecenoic acid, methyl ester | 34.92 | 28.94 | $C_{19}H_{36}O_2$ |
| 6 | trans-13-Octadecenoic acid, methyl ester | 34.92 | 28.94 | $C_{19}H_{36}O_2$ |
| 7 | Octadecanoic Acid, Methylester | 5.01 | 29.49 | $C_{19}H_{38}O_2$ |
| 8 | Heptadecanoic acid, 16-methyl-,methyl ester | 5.01 | 29.49 | $C_{19}H_{38}O_2$ |
| 9 | Heptadecanoic acid, 10-methyl-,methyl ester | 5.01 | 29.49 | $C_{19}H_{38}O_2$ |
| 10 | 17-Pentatriacontene | 1.81 | 31.24 | $C_{35}H_{70}$ |
| 11 | Pentatriacontane | 1.81 | 31.24 | $C_{35}H_{72}$ |
| 12 | Ethanol, 2-(octadecyloxy)- | 1.81 | 31.24 | $C_{20}H_{42}O_2$ |
| 13 | Heptacosane | 1.81 | 31.24 | $C_{27}H_{56}$ |
| 14 | Tetrapentacontane, 1,54-dibromo- | 2.42 | 32.52 | $C_{54}H_{108}Br_2$ |
| 15 | 1,54-Dibromotetrapentacon Tane | 2.42 | 32.52 | $C_{54}H_{108}Br_2$ |
| 16 | Dotriacontane | 2.42 | 32.52 | $C_{32}H_{66}$ |
| 17 | 14-á-H-PREGNA | 2.42 | 32.52 | $C_{21}H_{36}$ |
| 18 | Octatriacontyl pentafluoropropionate | 2.2 | 34.54 | $C_{41}H_{77}F_5O_2$ |
| 19 | cis-13-Eicosenoic acid | 6.13 | 37.56 | $C_{20}H_{38}O_2$ |
| 20 | 2,2-Dideutero Octadecanal | 6.13 | 37.56 | $C_{18}H_{34}D_2O$ |
| 21 | cis-11-Eicosenoic acid | 6.13 | 37.56 | $C_{20}H_{38}O_2$ |
| 22 | Erucic acid | 6.13 | 37.56 | $C_{22}H_{42}O_2$ |
| 23 | Z-(13,14-Epoxy)tetradec-11-en-1-ol Acetate | 8.01 | 39.59 | $C_{16}H_{28}O_3$ |
| 24 | (E)-13-Docosenoic acid | 4.23 | 39.84 | $C_{22}H_{42}O_2$ |

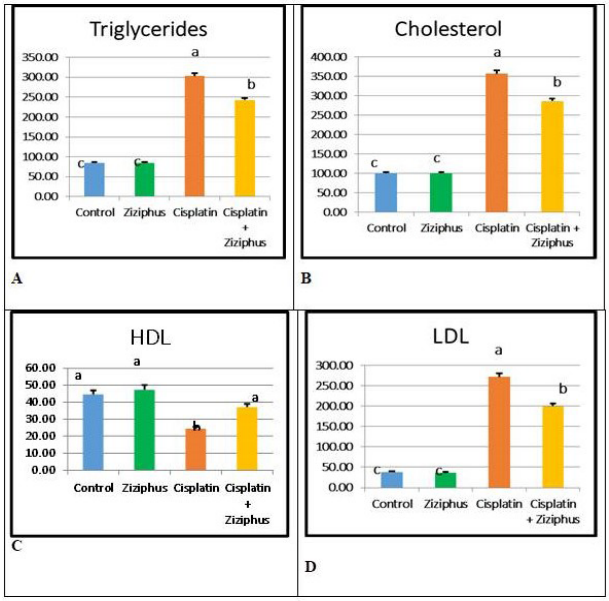


Fig. 4. Effect of *Ziziphus spina-christi* oil extract and/or Cisplatin on lipid profile Triglyceride (A), cholesterol (B), HDL (C), and LDL (D) n serum of male albino rats.

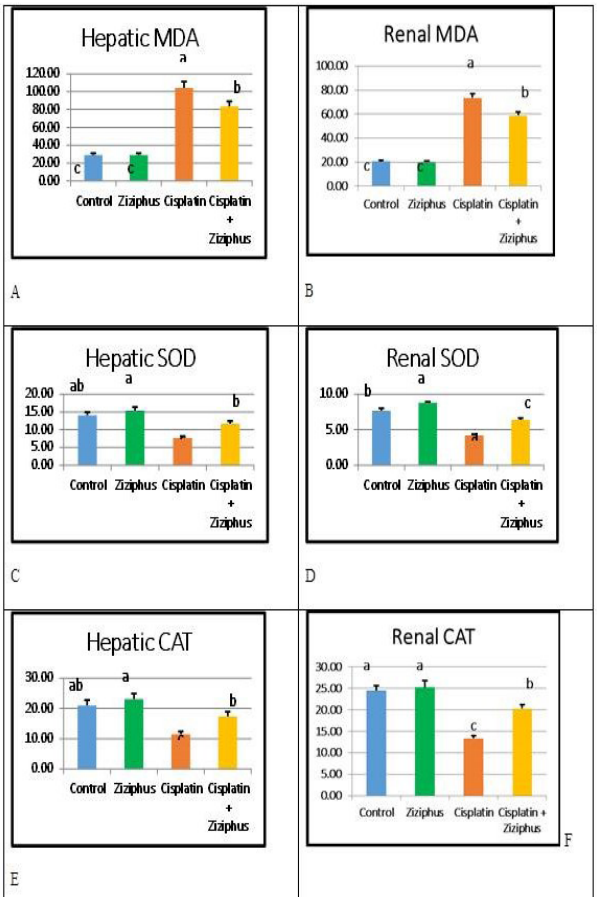


Fig. 5. Effect of *Ziziphus spina-christi* oil extract and/or Cisplatin on hepatic and renal antioxidant Hepatic MDA (A) , renal MDA (B), hepatic SOD (C), renal SOD (D), hepatic CAT (E) and renal CAT (F) on serum of male albino rats.

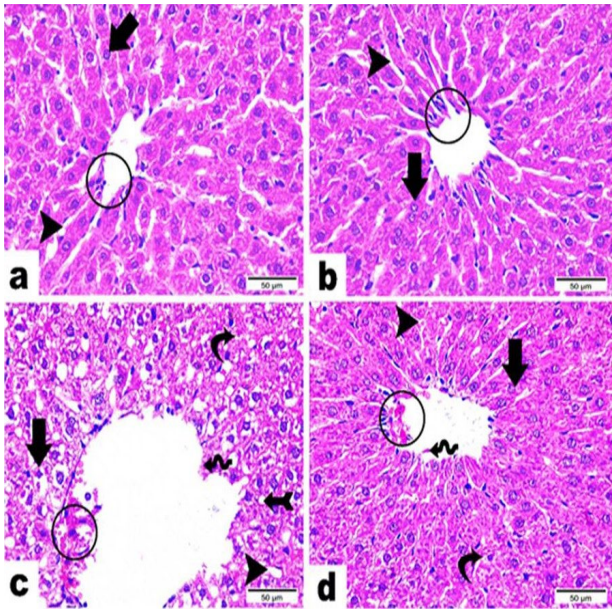


Fig. 6. Photomicrographs displaying the outcome of ziziphus on hepatic tissue (central vein area) in the examined groups (H& E stain, x400 & scale bar= 50 µm) as follow: Section from control group (a) & ziziphus group (b) exhibiting the normal structure of hepatic tissue as central vein appear normal with intact endothelial lining (circle), hepatic cords also seen normal with light & vesicular hepatocytes (arrows), along with hepatic sinusoids seen with its normal structure (arrowheads). Section from cisplatin group (c) marking sever degenerative changes along hepatic tissue with loss of hepatic cords organization & necrotic area (curvy arrow), most hepatocytes existed with hydropic degeneration (arrow), sever degeneration & congestion of central vein (circle) with degeneration of its endothelial lining (wave arrow). Also notice the microvascular steatosis (arrow with tail). Hepatic sinusoids emerged either atrophied except few ones spotted in normal look (arrowhead). Section from cisplatin & ziziphus group (d) displaying obvious development along hepatic tissue as central vein appear with few degenerations (circle), also appeared with moderate dilatation & endothelial desquamation (wave arrow). Most hepatocytes appeared normal with light & vesicular nuclei (arrow), while some appeared with hydropic degeneration & deep basophilic apoptotic nuclei (curvy arrow). Notice hepatic sinusoid marked with some congestion (arrowhead).

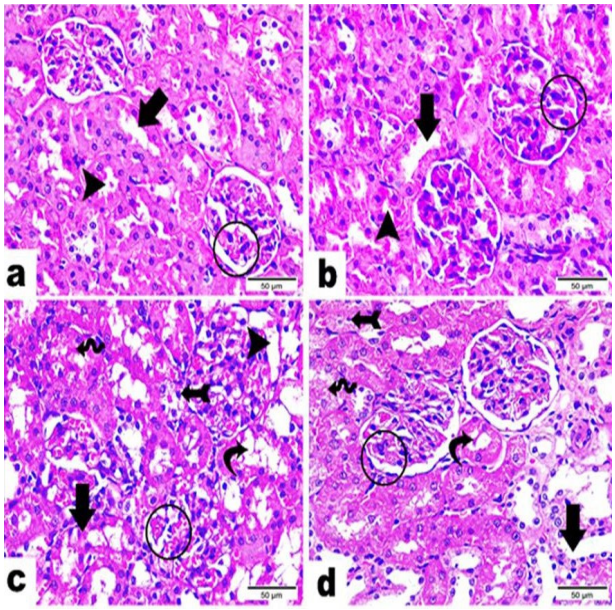


Fig. 7. Photomicrographs presenting the effect of ziziphus on the kidney in the examined groups (H& E stain, x400 & scale bar= 50 µm) as follow: Section from control group (a) & ziziphus group (b) revealing the typical structure of renal cortex area with intact glomerulus & renal corpuscle (circles), regular proximal convoluted tubules (arrowheads), & distal convoluted tubules (arrows). Section from cisplatin group (c) highlighting sever injury along renal cortex presented in atrophy of glomerulus with large number of red blood cells & deep basophilic apoptotic lining cells (circle), with increasing of glomerular space (arrowhead). Some renal tubules appear degenerated (arrow), with epithelial desquamation (wave arrow), others lined with deep basophilic apoptotic nuclei (arrow with tail), also notice the vacuolation along renal tubules (curvy arrow). Section from cisplatin & ziziphus group (d) highlighting noticeable improvement along renal cortex area as most renal corpuscle appear with its regular shape (circle), most renal tubules appeared normal with light & vesicular lining cells (arrow), while few ones still appeared with epithelial desquamation (curvy arrow), others emerged with hydropic degeneration (wave arrow), & others assembled with deep basophilic apoptotic nuclei (arrow with tail).

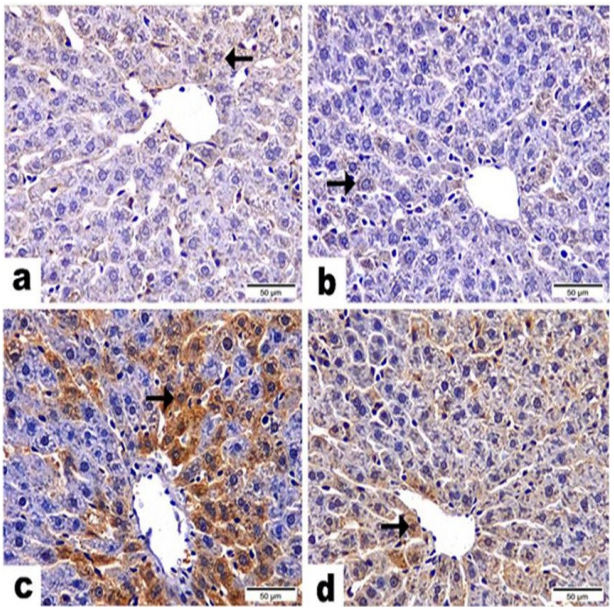


Fig. 8. Photomicrographs display the expression of tumor necrosis factor alpha (TNF-α) along hepatic tissue (central vein area) between inspected groups (TNF-α, x400, scale bar= 50µm) as follow: Sections from control group (a) & ziziphus treated group (b) exhibiting scarce positive cytoplasmic reactivity with TNF-α along hepatocytes (arrows). Section from cisplatin group (c) demonstrated the intense positive cytoplasmic reactivity with TNF-α along hepatocytes (arrow). Section cisplatin & ziziphus group (d) revealed moderate positive cytoplasmic reactivity with TNF-α along hepatocytes (arrow).

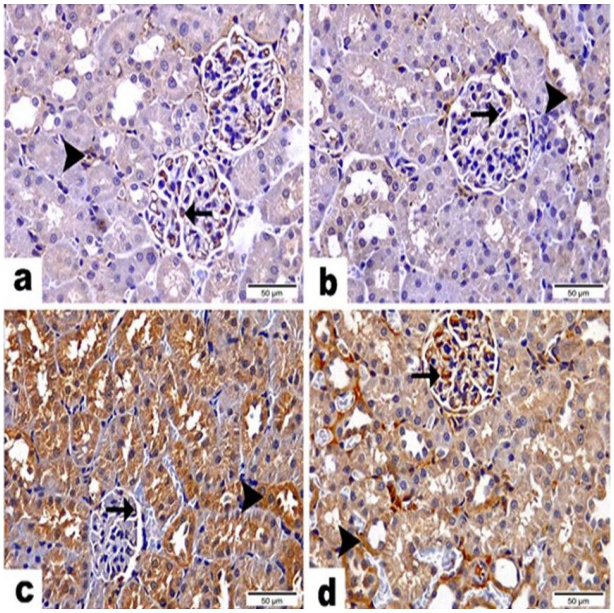


Fig. 9. Photomicrographs representing the expression of tumor necrosis factor alpha (TNF) along kidney tissue (renal cortex area) between inspected groups (x400, scale bar= 50µm) as follow: Sections from control group (a) & ziziphus group (b) exhibiting very few positive cytoplasmic reactivity with TNF-α along renal corpuscle (arrows), & renal tubules (arrowheads). Section from cisplatin group (c) demonstrating the intense positive cytoplasmic reactivity with TNF-α along renal corpuscle (arrow), likewise renal tubules (arrowhead). Section cisplatin & ziziphus group) (d) revealing moderate positive cytoplasmic reactivity with TNF-α along renal corpuscle (arrow), & renal tubules (arrowhead).

## Discussion

Cisplatin is a super chemotherapeutic agent used to treat several cancer types. However, its use is restricted due to its hazardous effects on several organs. The primary issues were nephrotoxicity and hepatotoxicity. The aim of this investigation was to assess the antioxidant effect of *Ziziphus spina-christi* oils (cider) against the cisplatin pharmacological group in male rats suffering from severe liver and kidney damage. In spite of dysfunction coming from use,

Ziziphus (cider) samples were evaluated for GC-MS which performed to identify the main volatile substances and molecules that found inside ziziphus (oil extract). More than 24 of most relative molecules were detectedin cider oil extract through GC-MS analysis.. After GC MS, we found that zizi contain these bioactive components (fatty acids): Hexadecanoic acid, methyl ester which is an active compound with the highest antimicrobial effect against the clinical pathogenic bacteria according to research discussion of Shaaban *et al*. (2021). Palmitic Acid methyl ester work as a chemical composition of ziziphus has physico-chemical characteristics, work as DNA protective, cytotoxic and has antitumor activities (Andonova *et al*., 2023). Methyl 9-cis, 11-trans-octadecadienoate is a form of phytochemical compound according to Singh *et al*. (2020). Phytochemicals have high antioxidant medical properties according to Nwozo *et al*. (2023). 9, 12-Octadecadienoic acid (Z, Z)-, methyl ester which reported that it has anticancer, antioxidant, antimicrobial, anti-androgenic, anti-inflammatory and hepatoprotective properties according to Momodu *et al*. (2022). 1, 54-Dibromotetrapentacon Tane) is also a bioactive compound that is considered a new source of therapy. Octatriacontyl pentafluoropropionate), (Tetrapentacontane, 1,54-dibromo-), (1,54-Dibromotetrapentacon Tane, (Dotriacontane), (17-Pentatriacontene) is herbal alternative for various diseases and has biological activities like antioxidant, antimicrobial, sedative, anxiolytic, anti-cancer, anti-inflammatory, anti-microbial according to result of Fathi *et al*. (2022). Erucic acid plays as a drug carrier and has neuroprotective effect according to research of Galanty *et al*. (2023), also (Erucic acid) classified as an (omega 9 fatty acid) according to Kumar and Sharma (2022). Omega-9 fatty acids are derived from the primary mono-unsaturated fatty acids present in plants and animals. They are semi-essential fatty acids. According to the discussion of Farag and Gad (2022), it is a healthier option to saturated animal fats and has various health advantages such as anti-inflammatory and anti-cancer properties.

The obtained results revealed that injection of Cisplatin caused significant increases in serum enzymes (ALT, AST), urea and creatinine, cholesterol, triglycerides and LDL levels, and significant decreases in serum levels of total proteins, albumin and HDL. Furthermore, it resulted in significant decreases in hepatic activities of SOD and CAT, with a decrease in hepatic MDA level. These findings agreed with Aladaileh *et al*. (2021); Li and Jamdade *et al*. (2021); Bademci *et al*. (2021); Pınar *et al*. (2022) and Elgendey *et al*. (2021). The significant decrease in hepatic SOD activity agreed with Mesbahzadeh *et al*. (2021).

Our investigation revealed that administration of a single dose of cisplatin induced hepato-renal injury through hepatocytes degeneration with nuclear condensation, sinusoidal dilatation in the liver, infiltration of cells, and tubular congestion, glomerular deterioration in the kidney, these findings agreed with Un *et al*. (2020) and Prasad *et al*. (2021). Confirmed by histopathological result in both hepatic and renal tissues (Figs. 6, 7).

Cisplatin leads to downregulating TNF-α (Altindağ *et al*., 2022) along hepatic and renal tissue Section from cisplatin group demonstrating the intense positive cytoplasmic reactivity with TNF-α along hepatic and renal tissue. Also lead to accumulation of platinum in the kidney and alter its function, induced nephropathy , apoptotic and necrotic cell.. Because the kidney is the primary excretory pathway for cisplatin, renal parenchyma accumulates more than other tissues; moreover, suppression of carnitine synthesis causes kidney harm. Copper induces nuclear DNA damage and the creation of ROS, which finally leads to cell death. After infusion, cisplatin diffuses quickly into multiple organs, reaching larger amounts in the liver as well. Cisplatin is biotransformed by CYP450 enzyme complex. One of these enzymes, CYP2E1, is the most important enzyme implicated in hepatotoxicity, particularly in medicines metabolized by (CYP2E1) (Abd Rashid *et al*., 2021). This was confirmed by the immunohistochemically result in hepatic and renal tissue for tumor necrosis factor alpha Photomicrographs display the expression of tumor necrosis factor alpha (TNF -α) (Figs. 8, 9).

Groups treated with combination between cisplatin and *Ziziphus spina-christi* showed renormalized ALT, AST, ALP, creatinine, urea levels also corrected TP, albumin and LDL, triglycerides, HDL, SOD, CAT and MDA which agreed with El-Araby (2021).

*Ziziphus spina-christi* leaf extract also reduced the production and expression of pro-inflammatory cytokines and pro-apoptotic proteins while increasing the production and expression of anti-apoptotic proteins (Ramadan *et al*., 2021). Zizyphus is considered prebiotics because it contains bioactive compounds that can effectively protect the liver from oxidative stress and DNA damage according to work of Badr *et al*. (2022).

## Conclusion

These findings indicate that *Ziziphus spina-christi* oil extract cures cisplatin-induced hepatorenal damage via antioxidant, anti-inflammatory, and anticancer properties. So, cider oil extract (*Ziziphus spina-christi* oil extract Cisplatin) is considered a source of a new therapy, we recommend upgrade its usage in the medical field, specifically with cases suffer from cancers.

## Conflict of interest

The authors declare that they have no conflict of interest.

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