

# Ameliorative Effect of Parsley and Pumpkin Seeds Oils against Cisplatin Induced Hepatorenal Injury in Male Albino Rats (Physiological and Histological Study)

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## ABSTRACT

**Background:** Cisplatin is a widely used chemotherapeutic agent with significant hepatotoxic and nephrotoxic side effects.

**Objective:** This study aimed to investigate the protective effects of parsley oil (PO) and pumpkin seed oil (PSO) against cisplatin-induced organ toxicity in male albino rats.

**Methods:** A batch of male albino rats weighing between 160 and 200 grams was divided into four groups. Group 1 functioned as the control group. Group 2 was administered a solitary dose of cisplatin at a dosage of 7.5 mg per kilogram of body weight, intraperitoneally. Groups 3 and 4 were pre-treated with PO or PSO (0.1 ml/kg BW, orally) for ten days and then received cisplatin on the sixth day. On day 11, blood samples were obtained for biochemical examination. Histopathological examination of kidney samples was also conducted.

**Results:** Cisplatin administration significantly elevated ALT, AST, urea, and creatinine levels, indicating liver and kidney damage. Pre-treatment with PO and PSO significantly mitigated these effects, normalizing the biochemical markers. Histopathological analysis supported these findings, showing reduced tissue damage in PO and PSO groups.

**Conclusion:** Parsley oil and pumpkin seed oil provided defense against liver and kidney damage caused by cisplatin in rats, suggesting their potential as adjuncts in chemotherapy.

**Keywords:** Cisplatin, Hepatotoxicity, Nephrotoxicity, Parsley oil, Pumpkin seed oil, Antioxidants, Chemotherapy.

## INTRODUCTION

The high incidence due to cancer and the detrimental side effects of frequently employed chemotherapy treatments pose substantial challenges for researchers striving to develop new interventions to reduce these toxicities<sup>(1)</sup>.

Cisplatin, a highly effective chemotherapeutic agent, is widely recognized for its efficacy in cancer treatment. However, it is also associated with significant Organ toxicity, particularly renal, hepatic, gastrointestinal tract, and nervous system damages. Cisplatin induces nephrotoxicity and hepatotoxicity by inhibiting critical antioxidant enzymes and proteins<sup>2</sup>. Numerous ongoing studies aim to mitigate the harmful effects of cisplatin during chemotherapy. Recent research suggests that the combination of cisplatin with plant extracts can improve antitumor efficacy while reducing its adverse side effects<sup>3</sup>.

Parsley (*Petroselinum crispum*) exhibits a diverse array of pharmacological effects, such as antioxidant, hepatoprotective, and cardioprotective capabilities. It also possesses nephroprotective, neuroprotective, anti-diabetic, analgesic, spasmolytic, anti-platelet, laxative, diuretic, antibacterial, and antifungal effects<sup>4</sup>.

Pumpkin (*Cucurbita maxima*) seeds, often considered agro-industrial byproducts, are nutrient-dense and have significant nutritional values. Historical and contemporary studies have demonstrated that pumpkin seeds are used in traditional medicine to treat various conditions,

including infections, diabetes, hypertension, and kidney and urinary disorders<sup>5</sup>.

## MATERIALS AND METHODS

The vial of cisplatin (50 mg/50 ml) was obtained from Al-Hikma pharmaceutical company located in Giza, Egypt. All other compounds utilized were of an analytical grade. Parsley oil and Pumpkin seed oil were purchased from EL-Hawag for Natural Oils Company.

**Experimental animals:** Male albino rats weighing between 160 and 200 grams were obtained from the animal house of NODCAR in Egypt. The animals were kept in a room maintained at a consistent temperature of  $22 \pm 1^\circ\text{C}$ , with alternating 12-hour periods of light and darkness. They were provided with unrestricted access to both food and tap water.

### Experimental designs:

The rats were partitioned into four groups, each including 6 rats as follows:

- **Group 1:** (Control group) comprised of normal rats.
- **Group 2:** Rats received a single dose (7.5 mg/kg b. w., i.p) of cisplatin on the sixth day of experiment.
- **Group 3:** Rats received the parsley oil (0.1 ml/kg b.w.) by oral administration for ten days and in the

sixth day of treatment rats were injected with cisplatin (6 mg/kg BW, i. p.).

- **Group 4:** Rats received pumpkin seed oil (0.1ml/1kg b.w.) by oral administration for ten days and in the sixth days of treatment Rats were administered Cisplatin by injection (6 mg/kg BW, i. p.).

Blood was collected on day 11, all fasting animals were euthanized and their heads were removed in order to collect blood for the purpose of determining ALT, AST, urea, creatinine TP, albumin, and globulin levels and albumin/globulin ratio in serum. Blood samples were withdrawn from rats' retro-orbital sinuses. Serum was frozen after separation until analysis.

### 1- Determination of liver function:

a) Determination of Alanine aminotransferase (ALAT) and aspartate aminotransferase (ASAT). ALAT and ASAT were measurement by using Bio Merieux SA kits.

### 2- Determination of kidney function:

a) **Determination of urea and creatinine**  
Enzymatic determination of urea and creatinine levels were assessed using Bio Merieux SA kits.

### 3- Determination of serum protein profile:

a) **Determination of Total protein and Albumin**  
were measurement by utilizing Bio Merieux SA Kits.

b) **Determination of Globulin levels and the Albumin/globulin (A/G) ratio** were then calculated as follows:

- Globulin (g/dl) = Total protein (g/dl) – albumin (g/dl).

- Albumin/globulin ratio (A/GR) = albumin/globulin.

### Histopathological examination:

Autopsy samples were collected from the kidneys of rats belonging to various groups and immersed in a 10% formal saline solution for a duration of twenty-four hours. The washing process involved using tap water, followed by the use of alcohol (specifically methyl, ethyl, and absolute ethyl) in serial dilutions for dehydration. The specimens underwent xylene clearance and were then embedded in paraffin beeswax to create tissue blocks. These blocks were prepared for sectioning at a thickness of 4 microns using a rotary LEITZ microtome. The tissue sections were collected

on glass slides, treated to remove paraffin, and stained with hematoxylin and eosin stain for examination using a light microscope.

### Statistical analysis

The statistical analysis was conducted using the SPSS version 16.0 program for Windows software (SPSS). Anova & t-test were employed to assess the data. The results were reported as the mean ± standard error (SE). A significance level of  $P \leq 0.05$  was regarded significant, while a significance level of  $P \leq 0.01$  was considered extremely significant.

**Ethical consideration: The Ethics Committee of Al-Azhar University's Faculty of Science gave its approval to the experiment. The work was carried out in compliance with ethical protocols and standards that were authorized by the Animal Care and Use Committee of the Faculty of Science, Al-Azhar University, Cairo, Egypt.**

### RESULTS

Table (1) illustrated the comparison of ALT and AST levels among the four experimental groups: Control (Group 1), Cisplatin alone (Group 2), Cisplatin + Parsley oil (Group 3), and Cisplatin + Pumpkin seed oil (Group 4).

The administration of cisplatin alone resulted in a notable rise in both ALT and AST levels when compared to the control group ( $p < 0.001$ ). This indicated a considerable liver damage. Group 3, which received parsley oil showed a reduction in ALT levels by 47.94%.

In comparison with the control group, there was a 28.65% decrease observed in the cisplatin alone group. The AST levels in group 3 exhibited a reduction of 48.33% compared to the control group and a reduction of 28.14% compared to the cisplatin alone group.

In Group 4, which received pumpkin seed oil, ALT levels decreased by 224.39% compared to the control group and 31.05% in comparison with the Cisplatin alone group. AST levels exhibited a drop of 115.4% when compared to the control group, and a decrease of 29.65% when compared to the Cisplatin alone group. Overall, pumpkin seed oil demonstrated a more substantial hepatoprotective effect than parsley oil in mitigating the elevated liver enzymes induced by cisplatin.

**Table (1):** Comparison between the studied four groups regarding ALT levels and AST levels of the studied cases

	Group 1 (Control)	Group 2 (Cisplatin alone)	Group 3 (Cisplatin + Parsley oil )	Group 4 (Cisplatin + Pumpkin Seeds oil)	Test value	P- value	Sig.
	No. = 6	No. = 6	No. = 6	No. = 6			
<b>ALT (mg/dl)</b>							
Mean ± SD	16.17 ± 1.60	73.50 ± 7.66 <sup>a</sup>	37.83 ± 5.78 <sup>a, A</sup>	52.17 ± 4.62 <sup>a, A</sup>	77.033•	<0.001	HS
% of change Vs Control group	–	357.84	135.23	224.39			
% of change vs Cisplatin alone	–	–	-47.94	-28.65			
<b>AST (mg/dl)</b>							
Mean ± SD	24.00 ± 3.46	61.83 ± 4.88 <sup>a</sup>	31.33 ± 3.88 <sup>a, A</sup>	52.33 ± 5.01 <sup>a, A</sup>	40.389	<0.001	HS
% of change Vs Control group	–	164.19	34.6	123.92			
% of change vs Cisplatin alone	–	–	-49.35	-15.14			

P-value > 0.05: Non-significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant

•: One Way ANOVA test, a: difference from negative control; A: difference from Cisplatin group.

Table (2) compared the urea and creatinine levels among the four groups. Cisplatin alone significantly increased both urea and creatinine levels compared to the control group (p < 0.001), reflecting renal impairment. Group 3, treated with parsley oil, exhibited a decrease in urea levels by 45.44% when compared to the control group, the experimental group showed a 39.45% decrease in comparison with the group treated with cisplatin alone. Group 3 experienced a 66.11% decrease in creatinine levels compared to the control group and 41.4% compared to the cisplatin alone group. Group 4, treated with pumpkin seed oil, showed a reduction in urea levels by 42.33% compared to the control group and 41.66% when compared to the group that received only cisplatin. Group 4 experienced a decrease in creatinine levels of 71.25% when compared to the control group and there was a decrease of 45.06% in comparison with the group treated with Cisplatin alone. Parsley oil had a slightly more pronounced nephroprotective effect compared to pumpkin seed oil, particularly in reducing urea levels.

**Table (2):** Comparison between the studied four groups regarding Urea levels and Creatinine levels of the studied cases

	Group 1 (Control)	Group 2 (Cisplatin alone)	Group 3 (Cisplatin + Parsley oil)	Group 4 (Cisplatin + Pumpkin Seeds oil)	Test value	P- value	Sig.
	No. = 6	No. = 6	No. = 6	No. = 6			
<b>Urea (mg/dl)</b>							
Mean ± SD	44.88 ± 8.91	109.23 ± 7.46 <sup>a</sup>	65.80 ± 10.02 <sup>a, A</sup>	63.47 ± 9.23 <sup>a, A</sup>	27.342	<0.001	HS
% of change Vs Control group	–	151.02	53.25	45.46			
% of change vs Cisplatin alone	–	–	-39.45	-41.6			
<b>Creatinine (mg/dl)</b>							
Mean ± SD	0.18 ± 0.07	1.62 ± 0.39 <sup>a</sup>	0.66 ± 0.11 <sup>a, A</sup>	0.30 ± 0.09 <sup>A</sup>	42.960•	<0.001	HS
% of change Vs Control group	–	927.6	331.32	86.69			
% of change vs Cisplatin alone	–	–	-58.02	-80.14			

P-value > 0.05: Non-significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant, •: One Way ANOVA test

a: difference from negative control; A: difference from Cisplatin group

Table (3) presented the comparison of the amounts of total protein, albumin, globulin, and the albumin/globulin ratio where cisplatin alone significantly decreased total protein and albumin levels compared to the control group ( $p < 0.001$ ), indicating substantial liver damage.

In Group 3, treated with parsley oil, total protein levels increased by 30.43% compared to the control group and by 40.68% when compared to the group that received only cisplatin. Group 3 had an elevation in albumin levels by 50.47% compared to the control group and by 27.9% compared to the cisplatin alone

group. In group 4, treated with pumpkin seed oil, total protein levels increased by 46.68% compared to the control group and by 58.33% compared to the cisplatin alone group.

Albumin levels in group 4 increased by 56.95% compared to the cisplatin alone group and by 35.97% compared to the control group. Both parsley oil and pumpkin seed oil improved protein parameters and the albumin/globulin ratio, with pumpkin seed oil showing a slightly higher efficacy in enhancing these liver function markers.

**Table (3):** Comparison between the studied four groups regarding total protein and albumin and globulin and albumin /globulin ratio (g/dl) of the studied cases

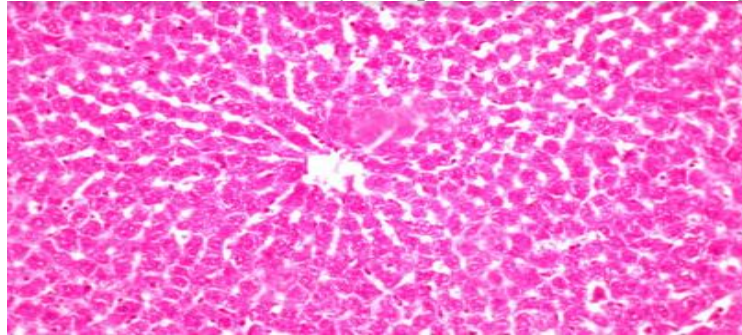
Groups	Group 1 (Control)	Group 2 (Cisplatin alone)	Group 3 (Cisplatin + Parsley oil)	Group 4 (Cisplatin + Pumpkins Seeds oil)	Test value	P-value	Sig.
	No. = 6	No. = 6	No. = 6	No. = 6			
<b>T protein (gm/ml)</b>	8.27 ± 0.41	3.03 ± 0.37 <sup>a</sup>	4.97 ± 0.28 <sup>a, A</sup>	4.74 ± 0.85 <sup>a, A</sup>	20.578•	<0.001	HS
% of change Vs Control group	–	-63.27	-39.87	-42.59			
% of change vs Cisplatin alone	–	–	66.03	59.04			
<b>Albumin (gm/ml)</b>	5.15 ± 0.29 <sup>a, A</sup>	1.80 ± 0.40 <sup>a, A</sup>	3.17 ± 0.53 <sup>a, A</sup>	2.63 ± 0.40 <sup>a, A</sup>	14.882•	<0.001	HS
% of change Vs Control group	–	-64.98	-38.36	-49.19			
% of change vs Cisplatin alone	–	–	85.11	52.8			
<b>Globulin (g/dl)</b>	3.12 ± 0.38	1.23 ± 0.26 <sup>a</sup>	1.80 ± 0.63 <sup>a</sup>	2.12 ± 0.66	3.329•	0.007	HS
% of change Vs Control group		-59.64	-40.28	-30.50			
% of change vs Cisplatin alone			50.84	75.65			
<b>Albumin globulin ratio (g/dl)</b>	1.65 ± 0.23	1.46 ± 0.45	1.76 ± 0.41	1.24 ± 0.44	3.475•	0.003	HS
% of change Vs Control group	–	-11.34	6.69	-24.84			
% of change vs Cisplatin alone	–	–	20.62	-15.03			

P-value > 0.05: Non-significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant  
 •: One Way ANOVA test; ≠: Kruska-Wallis test, a: difference from negative control; A: difference from Cisplatin group.

## **HISTOPATHOLOGICAL FINDINGS**

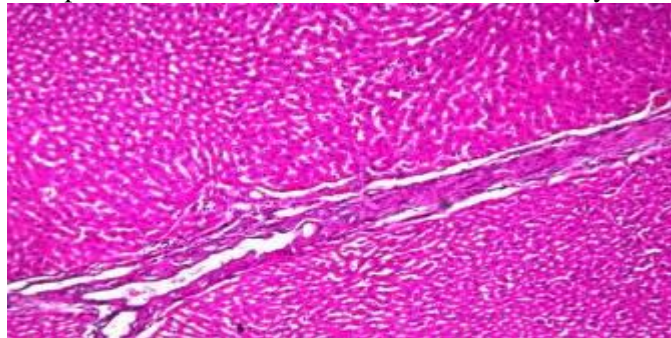
### **A. LIVER**

- 1- **Group 1 (Control):** The normal histological structure of the central vein and the surrounding hepatocytes in the parenchyma were noted in the absence of any histopathological alterations (Figure 1).



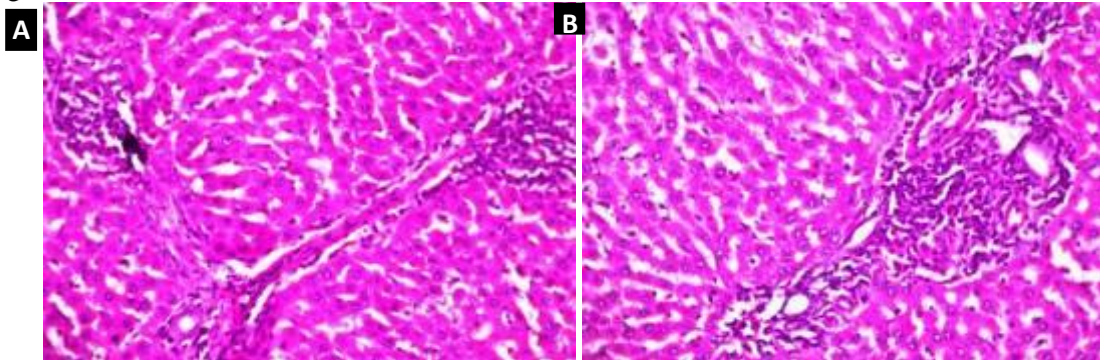
**Figure (1):** The central vein with normal histological structure and the hepatocytes that surround it in the parenchyma. H & E, X40.

- 2- **Group 2 (Cisplatin):** The portal area showed fibrosis with inflammatory cells infiltration (Figure 2).



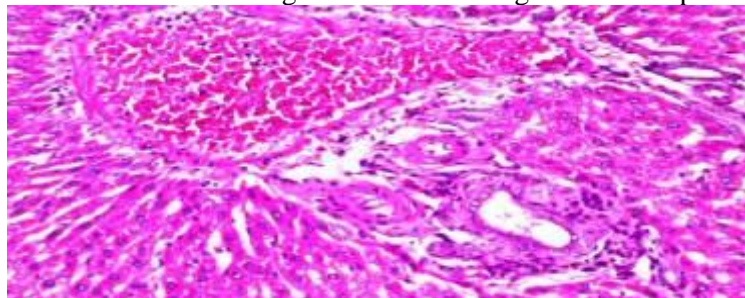
**Figure (2):** Fibrosis with inflammatory cells infiltration in the portal area, H & E, X40.

- 3- **Group 3 (Parsley Oil (PO) + Cisplatin):** Inflammatory cells aggregation was detected in the portal area (Figure 3, A & B).



**Figure (3):** A) Inflammatory cells aggregation in the portal area, B) The magnification of (figure A) to identify the inflammatory cells aggregation in the portal area (H & E, X40).

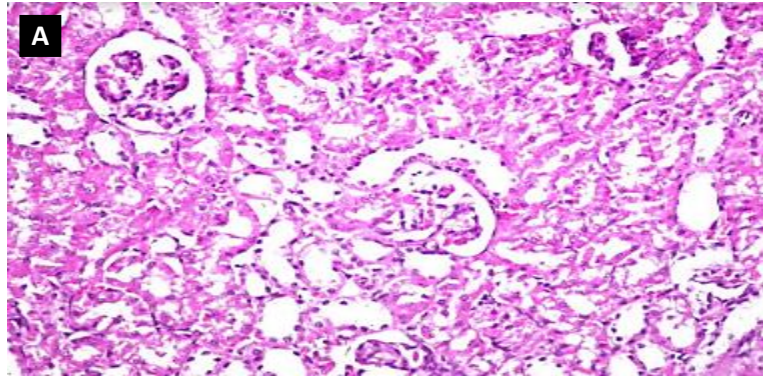
- 4- **Group 4 (Pumpkin seeds oil (PSO) + Cisplatin):** Few inflammatory cells were infiltrated into the portal region, encircling the bile ducts and causing dilatation and congestion in the portal vein (Figure 4).



**Figure (4):** Dilatation and congestion in the portal vein with few inflammatory cells infiltration surrounding the bile duct at the portal area, H & E, X40.

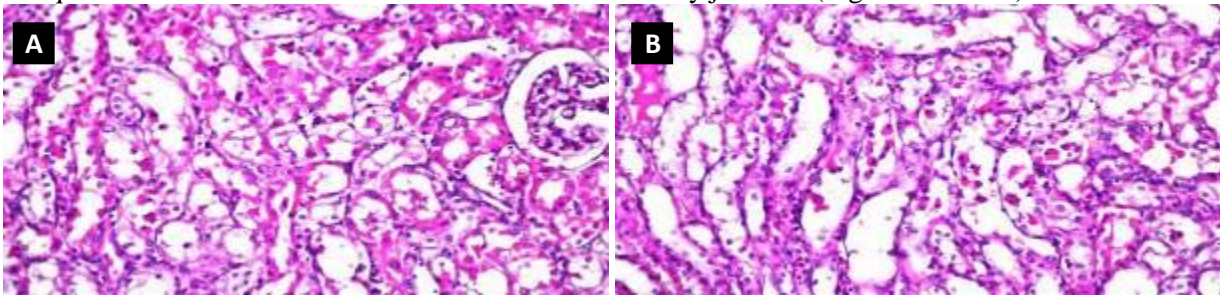
**B. KIDNEY**

- 1. Group 1 (Control):** The glomeruli and tubules at the cortex had their usual histological structure and there was no histopathological modification (Figure 5).



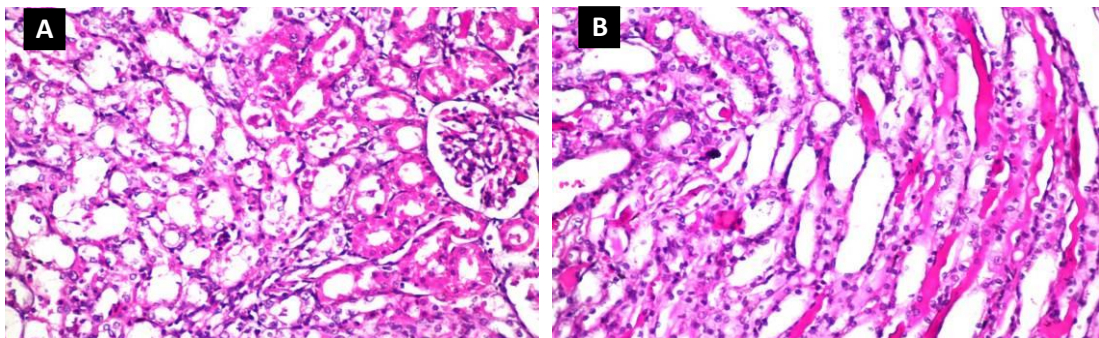
**Figure (5):** The glomeruli and tubules' typical histological structure at the cortex (H&E, x40).

- 2. Group 2 (Cisplatin):** Degenerative changes, necrosis and in the lining tubular epithelium near the cortex, desquamation was found as well as in the corticomedullary junction (Figure 6 .A & B).



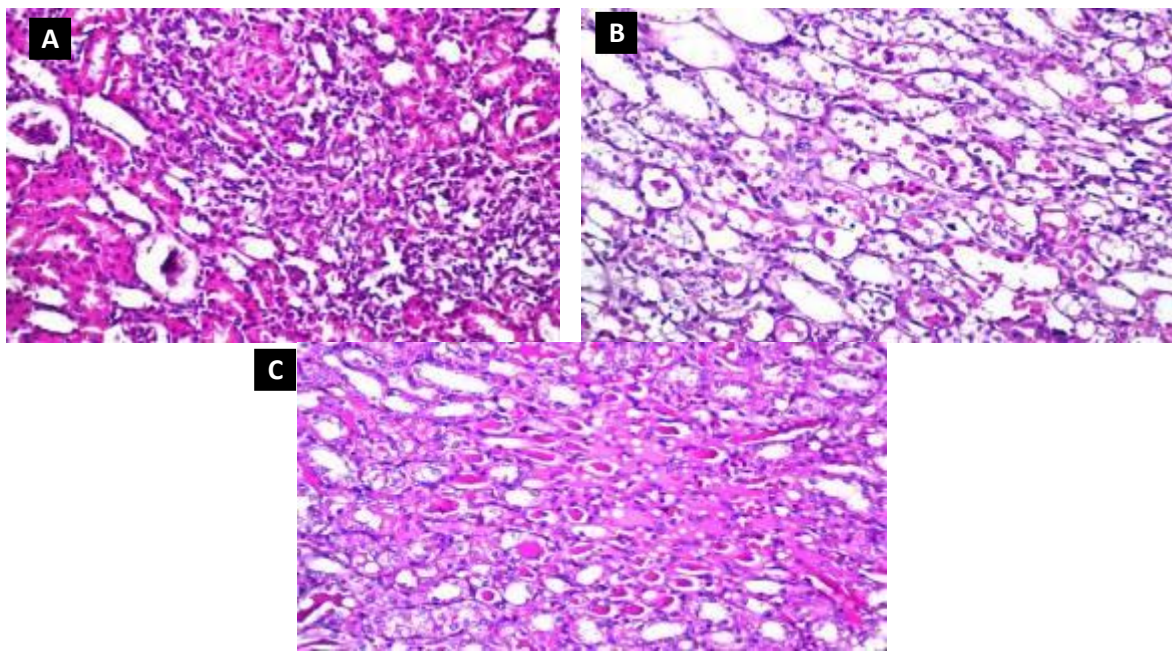
**Figure (6):** A) tubular lining epithelial degradation, necrosis, and desquamation at the cortex, B) Tubular lining epithelium deterioration and necrosis, and desquamation at the corticomedullary portion (H & E, x 40).

- 3. Group 3 (Parsley oil (PO) + cisplatin):** Mild degeneration was observed in epithelial cells that line the tubules at the cortex (Figure 7-A) whereas the corticomedullary portion's tubules displayed cystic dilatation with few eosinophilic cast formation in the lumen (Figure 7-B).



**Figure (7):** A) Mild degeneration in the tubular lining epithelium at the Cortex, B) Cystic dilatation with few eosinophilic casts formation in tubules at the corticomedullary portion (H & E, x 40).

- 4. Group 4 (Pumpkin Seeds Oil (PSO)+ Cisplatin):** Infiltration of focal inflammatory cells was seen between the tubules at the cortex (Figure 8-A). Corticomedullary section displayed tubule desquamation, necrosis, and degeneration of the epithelial cells (Figure 8-B), while there were eosinophilic casts in the medullary portion formation of some tubular lumen (Figure 8-C).



**Figure (8):** A) Focal inflammatory cells infiltration in between the tubules at the Cortex, B) Degeneration, necrosis and desquamation of tubular lining epithelial at the corticomedullary part, C) The production of eosinophilic casts in some tubules' lumen at the medulla (H & E, x40).

## DISCUSSION

Cisplatin is a very powerful chemotherapy drug that is widely used to treat various malignancies. However, its clinical application is often constrained by significant side effects, including nephrotoxicity and hepatotoxicity. These toxicities are primarily mediated through the inhibition of crucial antioxidant enzymes and proteins leading to oxidative stress and subsequent damage to the kidneys, liver, gastrointestinal tract, and nervous system<sup>7</sup>. Efforts to mitigate these adverse effects have led researchers to explore the co-administration of natural antioxidants such as plant extracts to be with cisplatin to enhance its therapeutic efficacy while minimizing toxicity.

In this investigation, we assessed the defense capabilities of pumpkin seed oil and parsley oil against cisplatin-induced organ damage. Both oils significantly reduced liver and kidney damage markers compared to the cisplatin only group indicating a substantial decrease in hepatotoxicity and nephrotoxicity. Specifically, groups treated with parsley oil or pumpkin seed oil, which exhibited marked lowering in histology studies, levels of urea, creatinine, ALT, and AST. These findings underscore the potential of these natural oils to attenuate cisplatin-induced organ damage.

The active ingredients in parsley oil, such as apiol, myristicin, and flavonoids like apigenin and luteolin, possess potent antioxidant properties<sup>8</sup>. These compounds can scavenge free radicals and enhance the activity of endogenous antioxidant enzymes, thereby reducing oxidative stress. The hepatoprotective and nephroprotective effects of parsley oil are likely due to these antioxidant activities, which help maintain

cellular homeostasis and prevent tissue damage. Additionally, the anti-inflammatory properties of these compounds further contribute to their protective role by mitigating inflammation-induced organ damage<sup>9</sup>. **Yılmaz *et al.***<sup>(8)</sup> reported similar findings, highlighting the broad pharmacological benefits of parsley oil, including its antioxidant and protective effects against various toxic insults.

Pumpkin seed oil is rich in bioactive compounds such as tocopherols, carotenoids, and phytosterols<sup>10</sup>. These constituents have been shown to exhibit strong antioxidant and anti-inflammatory activities. Tocopherols, for example, are known for their ability to neutralize free radicals and protect cellular membranes from oxidative damage. Carotenoids and phytosterols also contribute to the overall antioxidant capacity of pumpkin seed oil, enhancing its protective effects on the liver and kidneys. **Abdel-Raheem *et al.***<sup>(10)</sup> demonstrated the efficacy of pumpkin seed oil in mitigating oxidative damage, further supporting its role in protecting against cisplatin-induced toxicity.

Comparing the effects across the four groups, it was evident that the combination of cisplatin with either parsley oil or pumpkin seed oil provided substantial protection against organ damage. The groups treated with natural oils showed significant reductions in toxicity, demonstrating the efficacy of these interventions. **Mansour *et al.***<sup>(11)</sup> and **Gurer-Orhan *et al.***<sup>(12)</sup> have similarly documented the protective effects of natural antioxidants in reducing chemotherapy-induced toxicity, corroborating our findings. These results align with earlier research that have highlighted the role of natural antioxidants in

reducing the adverse effects of chemotherapeutic agents<sup>(13-15)</sup>.

These results suggest that incorporating parsley oil and pumpkin seed oil into chemotherapy regimens could enhance patient outcomes by reducing the side effects of cisplatin without compromising its anticancer efficacy. This is supported by a growing body of evidence indicating that plant-derived antioxidants can improve the therapeutic index of conventional chemotherapeutic agents while reducing their toxicity<sup>(13)</sup>. Such findings open new avenues for enhancing cancer treatment protocols through the use of natural antioxidants. Further research is warranted to elucidate the precise mechanisms of action and to validate these findings in clinical settings.

## CONCLUSION

In conclusion, the co-administration of parsley and pumpkin with cisplatin significantly reduced hepatic and renal toxicity, as evidenced by the normalized liver enzymes, urea and creatinine levels. The antioxidant properties of parsley and pumpkin play a crucial role in mitigating cisplatin-induced oxidative stress and cellular damage. These findings support the potential use of natural antioxidants as adjuvants in chemotherapy to enhance patient outcomes and reduce side effects.

- **Conflict of Interest:** None.
- **Acknowledgment:** None.
- **Funding Source:** None.

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