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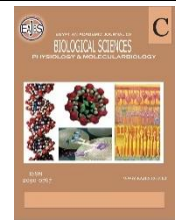
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**Amelioration of Cisplatin-Induced Kidney and Liver Damage in Rabbits by Fresh Carrot (*Daucus carota* L) Juice.**

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**ABSTRACT**

The present study was carried out to investigate the protective effects of fresh carrot juice on Hepato renal injuries induced by a single intraperitoneal injection of cisplatin (CP) (5 mg/kg). The AST, ALT activities, and the levels of creatinine, urea were significantly ( $P < 0.05$ ) increased in the serum of CP-treated rabbits (positive control) as compared to the normal rabbits (negative control). In contrast, Triglycerides and cholesterol concentrations were significantly decreased in the serum of CP-treated rabbits as compared to the normal rabbits. A dose of 5ml /kg body weight of fresh carrot juice was orally administered for 4 consecutive days before (CP) injection and 3 consecutive days after the (CP) injection reduced activities of AST, ALT and serum urea, serum creatinine levels which were altered by (CP), and succeeded in restoring of Triglycerides, cholesterol concentrations significantly to the normal range. On the other hand, histopathological Hepato renal tissue damage mediated by (CP) was greatly ameliorated by fresh carrot juice treatment. It was concluded that fresh carrot juice represents a potential therapeutic option to protect against (CP) Hepatorenal injuries commonly encountered in clinical practice.

**INTRODUCTION**

There are a number of pharmaceutical agents including many antibiotics and anti-cancer chemotherapeutics that have a severe side effect of nephrotoxicity. Cisplatin [cis-diamminedichloridoplatinum(II)] Pabla and Dong,2008; Siddik, 2003 (CP) is the most commonly used and potent chemotherapeutic agent against different solid organ cancers, including head, neck, lung, breast, bladder, and ovary. Besides its multiple advantages, (CP) also induces several side effects, including ototoxicity, gastrotoxicity, myelosuppression, and allergic reactions (Casanova *et al.*,2020). Its use is mainly limited by two factors: acquired resistance to (CP) and severe side effects in normal tissues, especially renal tissues. (CP) -induced nephrotoxicity is a major complication in cancer therapy and had dose-limiting toxicity (Saleh,2014). (CP) is a simple, small, inorganic platinum-based drug (Pabla and Dong,2008; Siddik, 2003). The (CP) molecule binds to the guanine DNA base and inhibits DNA, RNA, and protein synthesis. When (CP) binds to DNA, it forms an interface and intrastrand, resulting in a faulty genetic code model and a halt in its formation and duplication (Fang,2021).

It induces cell death by binding DNA, leading to the formation of intra- and inter-strand crosslinks Cohen and Lippard, 2001; Siddik, 2003; this can result in the formation of faulty DNA templates, leading to cell cycle arrest and ultimately cell death. Cancer cells are particularly susceptible to the cytotoxic mechanism of action of (CP) largely because they are rapidly dividing, which increases the likelihood of (CP) binding to DNA and eliciting its cytotoxic action. (CP) is eliminated through renal excretion, where it is metabolized to a nephrotoxic metabolite and consequently has a dose-limiting side effect of nephrotoxicity Pabla and Dong, 2008; Townsend *et al.*, 2003 observed in over 30% of patients administered (CP) (Miller *et al.*, 2010). Nephrotoxicity leads to a reduction in glomerular filtration rate and an increase in creatinine and blood urea nitrogen in the serum, ultimately increasing blood pressure and fluid retention in the body (overhydration) (Saylor *et al.*, 2021). Many side effects are known, Von Hoff 1979 but the dose-limiting side effect is its nephrotoxicity, expressed as an increase in the serum creatinine concentration or a decrease in creatinine clearance (Madias *et al.*, 1978; Krakoff, 1979). However, its clinical use is limited due to its toxic side effects including nephrotoxicity, neurotoxicity, ototoxicity and hepatotoxicity (Mansour *et al.*, 2006). (CP) hepatotoxicity is observed during aggressive treatment protocols in which higher doses than required for effective tumour suppression were used but the liver injury is also encountered during low-dose repeated (CP) therapy (Lee *et al.*, 2008; Pratibha, 2006). Hepatotoxicity is the less well-known aspect of (CP) treatment, and there is little information about the underlying mechanism. The major alterations reported in cisplatin toxicity Yzhang and Lindup 1993 are the occurrence of oxidative stress linked to the accumulation of reactive oxygen species (ROS) Chirino and Pedraza-Chaverri 2009 and decreased efficiency of some antioxidant defence

systems including antioxidant enzymes (Sadzuka *et al.*, 1992). Prevention of (CP) side effects is one of the major clinical issues, and in this respect, the use of free radical scavengers has been recently explored (Davis *et al.*, 2001). Plants have widely been used in foods to engender good odor, flavor, color and preservative, it is clear fact that they possess antioxidant activity and the reason for decreasing oxidation potential of lipids in foodstuffs, ten of them have been used as a natural defense against diseases and infections Namvaran *et al.*, 2011, *Daucus carota* L commonly known as “ carrot “ is one of the most important vegetables belonging to family Apiacea is an annual or biannual herb mostly confined to the temperate regions of Europe, Asia and Africa, it’s active ingredients including, volatile oils, steroids, tannins, flavonoids and carotene have been isolated (Mahran *et al.*, 1991; Jasicka-Misiak *et al.*, 2005; Vasudevan *et al.*, 2006). Carrot seeds are rich in antioxidants Yu *et al.*, 2005, on the other hand, carrot contains carotenoids which are natural pigments with lipophilic properties and antioxidant characteristics. The major carotenoids in human plasma are B-carotene and lycopene. They are transported in blood complexes to plasma lipoproteins, mainly to the LDL particle which is supplemented with B-carotene or with lycopene and renders and increases resistance to oxidation (Fuhrman *et al.*, 2000; Sesso, 2006).

The present study aimed to investigate the protective effect of fresh carrot juice on kidney, liver functions and some hematological parameters, in rabbits treated with cisplatin (CP).

## MATERIALS AND METHODS

### Chemicals:

Cisplatin solution (50 mg/50 ml) was obtained from (pfizer Australia Pty «The date of manufacture of the drug 08/2019»).

### Plant Material and Preparation:

Fresh carrot roots are used to make a carrot extract (juice). Carrot roots were cleaned by water, chopped and put into the

apparatus (Robert Bosch Hausgerate GmbH/Type CNCJ02/Slovenia) to make a juice without adding water, fresh juice was prepared daily till the end of the experiment. All other chemicals used in this study were of known functions and structure.

#### **Experimental Animals:**

A total of 15 rabbits (10.97 – 2249 g) were used in the present study. The animals were grouped and housed in cages (70 x 44 x 103 cm) at the laboratories of the zoology department, Sirt University. the photoperiod was regulated at 12 hours light / 12 hours dark cycle and temperature was adjusted at  $25\pm 1^{\circ}\text{C}$ . The rabbits were fed on commercial standard pellets and offered drink water ad libitum. after acclimatizing to laboratory conditions for one week before the commencement of the experiment.

#### **Experimental Design:**

The rabbits were randomly divided into 3 equal groups; the first group served as (negative control) and received a single intraperitoneal dose of 0.9% saline. Rabbits from the second group (positive control) were intraperitoneally injected with a single 5 mg/kg body weight (CP)dose (Okoko and Oruambo, 2008; Yasuyuki *et al.*,1991). The third group of rabbits was treated with fresh carrot juice by oral gavage at the dose of 5ml /kg body weight for 4 consecutive days before (CP) injection and 3 consecutive days after the (CP)injection.

At the end of the experimental period, overnight fasting rabbits (deprived of food but allowed free access to drinking water) were sacrificed by decapitation. The shed blood was collected in two cleaned vials, one (with EDTA) for hematological parameters, where, the erythrocyte count (RBCs/ $\mu\text{l}$ ), hematocrit (HCT %), platelets (PLTs/ $\mu\text{l}$ ), leukocyte count (WBCs/ $\mu\text{l}$ ), Heamoglobine (g/dl), were determined using an electronic blood counting machine (system R800), the second vail without anticoagulant for serum separation. These vials were centrifuged at 3000 rpm for 20 minutes. The serum was analyzed to determine the triglycerides, total cholesterol,

activities of aspartate transaminase (AST), alanine transaminase (ALT), urea and creatinine.

#### **Histological Examination:**

The liver and right kidney tissue samples from all animals were dissected out, washed with normal physiological saline solution, dried with filter paper and fixed in 10% formalin solution and then dehydrated in ascending grades of alcohol and embedded in paraffin. Sections at 5 $\mu\text{m}$ -thickness were taken, stained with hematoxylin and eosin (H&E) and examined under a light microscope by a pathologist unaware of the treatment conditions.

#### **Statistical Analysis:**

The results were analyzed using SPSS. All values were recorded as Mean+ standards error of the mean, whereas, the statistical differences between the means were determined by ANOVA, and the  $P < 0.05$  was accepted as a significant level (Steel, and Torrie,1980).

## **RESULTS**

#### **Liver Biomarkers of Rabbits:**

As shown in Table 1 and figures 1&2, the (CP) administration (5 mg/ kg I.P.) resulted in a significant increase ( $P < 0.05$ ) in serum AST, ALT, activities were observed in positive control rabbits, the percentage elevated were 74.70%, 73.88 respectively as compared to the negative control group ( $P < 0.05$ ). By contrast, when animals received the oral fresh carrot juice treatment, the AST enzyme activity remained similar to the control values and the ALT enzyme activity was restored to the normal range.

Serum triglycerides and total cholesterol levels were decreased in CP-treated rabbits and the percentage of decrease was 41.87% and 72.38% respectively when compared with the normal control rabbits. Daily administration of fresh carrot juice for 7 days succeeded in restoring their concentrations significantly ( $P < 0.05$ ) to the normal range (Table1 and Figs. 3 & 4).

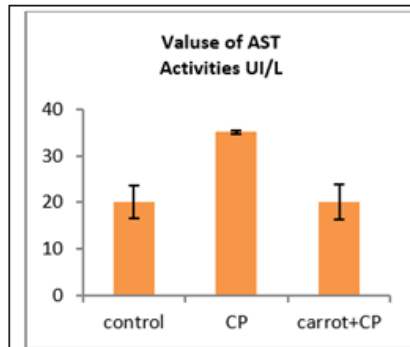
**Table1:** Values of AST, ALT, Triglycerides, and Cholesterol (Means±SE) for control and treated groups of rabbits.

Parameters	Control G1	Cisplatin G2	Cislatin+carrot G3
AST(UI/L)	20.08±3.45	35.08±0.45 <sup>a</sup>	20.100±3.74 <sup>b</sup>
% of change from G1		74.70	0.11
% of change from G2			42.70
ALT(UI/L)	20.99±0.58	36.34±1.10 <sup>a</sup>	31.66±2.20 <sup>ab</sup>
% of change from G1		73.88	51.48
% of change from G2			12.88
Triglycerides (mg/ dl)	100.80 ± 4.25	58.60± 13.30 <sup>a</sup>	89.80±7.51 <sup>b</sup>
% of change from G1		41.87	10.91
% of change from G2			53.24
Cholesterol (mg/dl)	36.200±2.71	10.00± 1.48 <sup>a</sup>	53.40 ± 6.65 <sup>ab</sup>
% of change fromG1		72.38	47.51
% of change fromG2			434

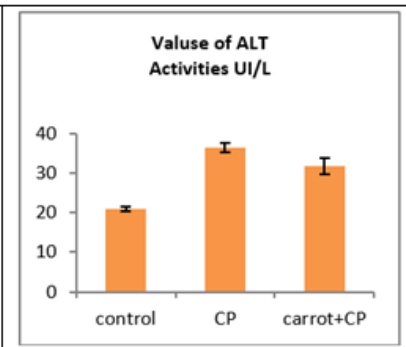
Values are given as mean ± SE for 5 rabbits in each group.

<sup>a</sup> significant (p<0.05) as compared with (G1)

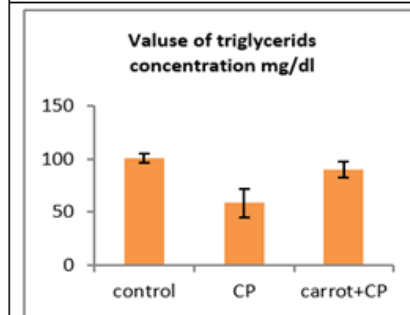
<sup>b</sup> significant (p<0.05) as compared with the (G2).



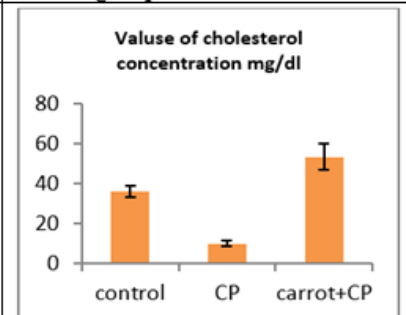
**Fig. 1:** Values of AST activities (Means ± SE) for control and treated groups of rabbits.



**Fig.2:** Values of ALT activities (Means ± SE) for control and treated groups of rabbits.



**Fig. 3:** Values of triglycerides levels (Means ± SE) for control and treated groups of rabbits.



**Fig. 4:** Values of cholesterol levels (Means ± SE) for control and treated groups of rabbits.

### Kidney Biomarkers of Rabbits:

A significant ( $P < 0.05$ ) elevation in serum urea and creatinine levels was observed in CP-treated rabbits, the percentage elevated were 237.9% and 144% respectively as compared to the negative control group. However, the serum levels of

these biomarkers revealed a significant ( $P < 0.05$ ) decrease in fresh carrot juice + CP-treated rabbits the percentage decreased were 56.1% and 112.8% respectively as compared to the CP-treated group (positive control) Table 2 and figures 5 & 6.

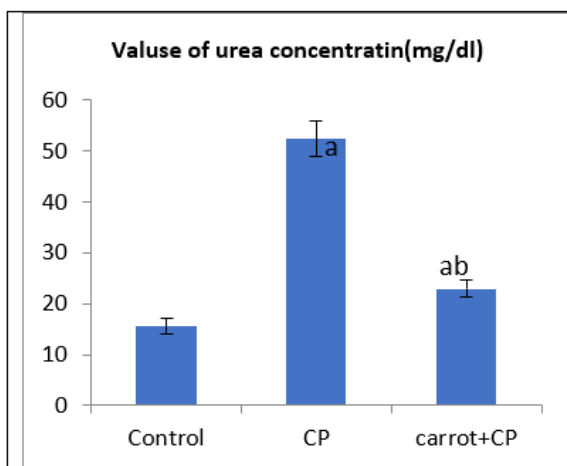
**Table2:** Values of Urea and Creatinine (Means±SE) for control and treated groups rabbits

Parameters	Control	Cisplatin	Cislatin+carrot
Urea(mg/ dl)	15.52 ± 1.58	52.44± 3.52 <sup>a</sup>	23.00±1.61 <sup>ab</sup>
% of change from G1		237.9	48.20
% of change from G2			56.1
Creatinine (mg/dl)	0.75±0.08	1.83± 0.08 <sup>a</sup>	0.86 ± 0.06 <sup>b</sup>
% of change fromG1		144	14.7
% of change fromG2			112.8

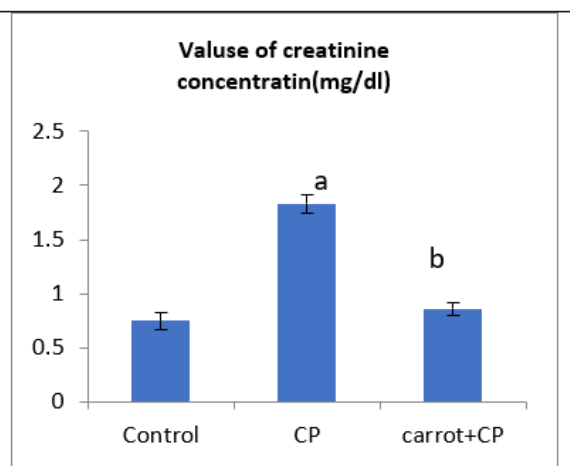
Values are given as mean ± SE for 5 rabbits in each group.

<sup>a</sup> significant (p<0.05) as compared with (G1)

<sup>b</sup> significant (p<0.05) as compared with the (G2).



**Fig. 5:** Values of urea levels (Means ± SE) for control and treated groups of rabbits.



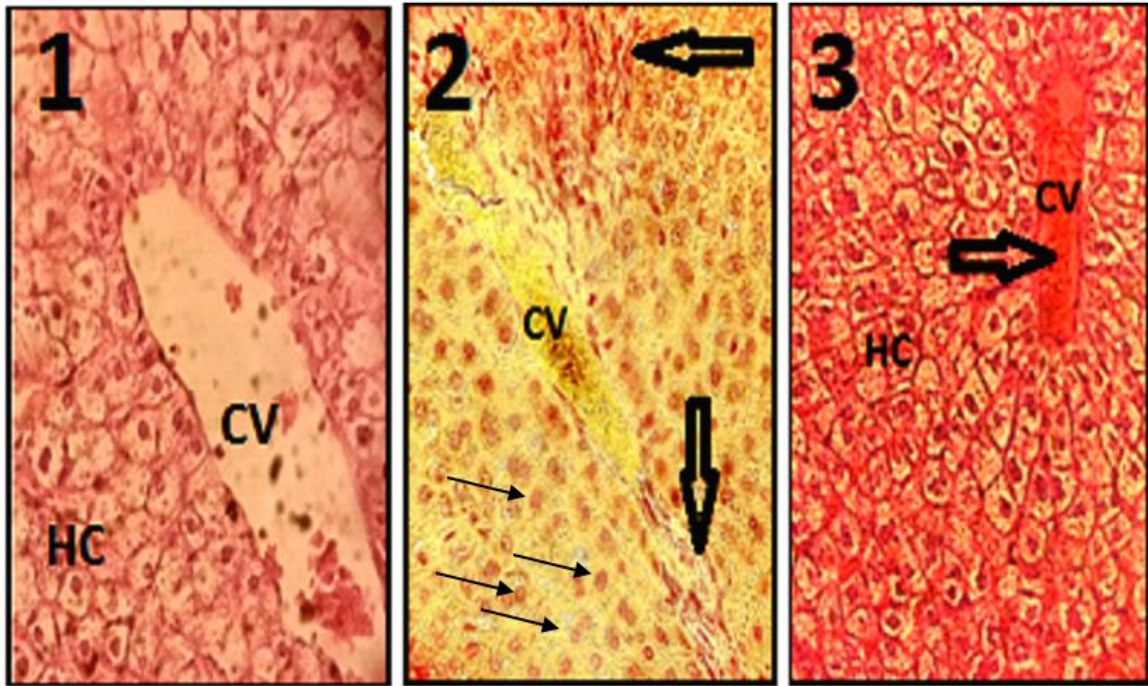
**Fig. 6:** Values of creatinine levels (Means ± SE) for control and treated groups of rabbits.

#### Effects of CP and fresh carrot juice treatment on liver histopathology:

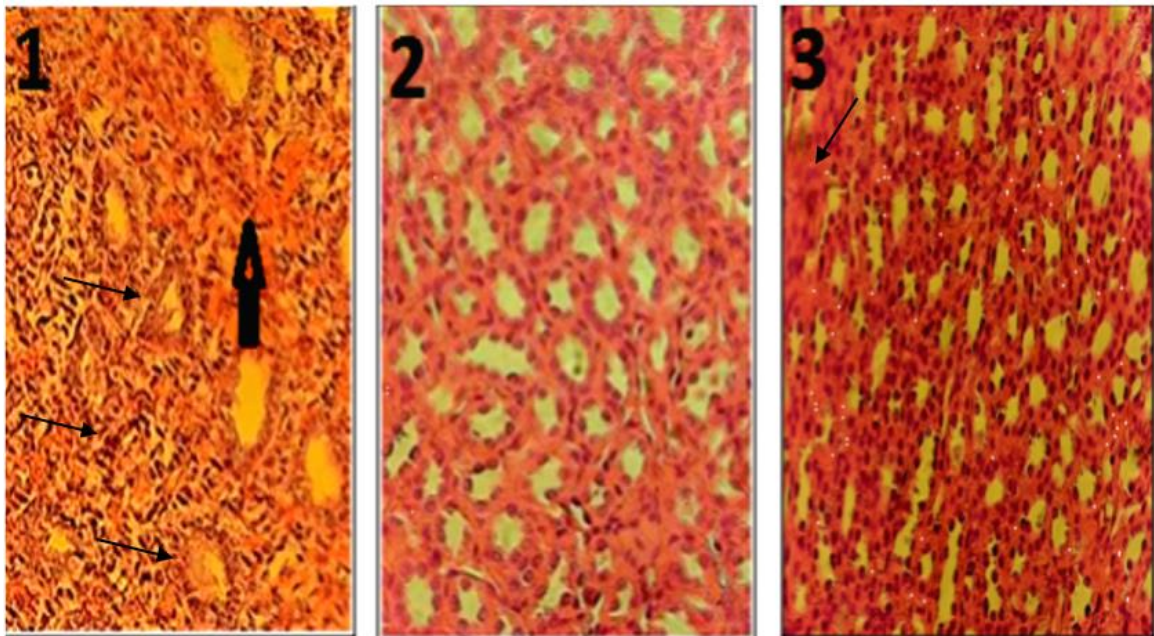
The normal architecture of radiating cords of hepatocytes from the central vein with blood sinusoids lined by flat endothelial and large kupffer cells in-between was observed in the centrilobular zone of the hepatic lobule in control rabbits (Fig. 7, plate 1), while hepatitis with inflammation around the central vein and massive ballooning degeneration of hepatocytes was seen in CP-treated rabbits (Fig. 7, plate 2). However, in rabbits treated with CP and fresh carrot juice, mild congestion of the central vein was seen and the liver histological alterations were less intense (Fig. 7, plate 3) compared to CP-treated rabbits.

#### Effects of cisplatin and fresh carrot juice treatment on kidney histopathology:

Kidney sections of the positive control (CP-treated rabbits) group showed mild parenchymal congestion and mild chronic pyelonephritis and renal damage mostly in form of glomerular and tubular injury (Fig. 8 plate 1) compared to the negative control group (Fig 8, plate2). While, kidney sections of the fresh carrot juice treated group showed a nearly normal histological picture with minimal pathological changes (Fig. 8, plate 3) compared to cisplatin-treated rabbits. fresh carrot juice had reduced the renal damage in this study compared to the positive control group.



**Fig. 7:** liver Sections for rabbits of study groups: plate(1) control group, Normal architecture of radiating cords \of hepatocytes(HC) from the central vein(CV). plate(2) CP group, hepatitis with inflammation around the central vein (thick arrow), massive ballooning degeneration of hepatocytes (HC thin arrow). plate(3) CP + fresh carrot juice group, mild congestion of central vein (arrow), and liver histological alterations were less intense.



**Fig. 8:** Right kidney Sections for rabbits of study groups: **plate (1):** CP group, shows mild parenchymal congestion and mild chronic pyelonephritis (thin arrow) and renal damage mostly in form of glomerular and tubular injury (thick arrow). **plate (2)** Control group showing normal tissue. **plate (3)** CP + fresh carrot juice group, shows a nearly normal histological picture with minimal pathological changes (arrow).

#### DISCUSSION

A number of studies have demonstrated some side effects of

chemotherapeutic drugs cisplatin is one of the most cytotoxic agents that is widely used to treat a variety of cancers but it is

associated with toxic side effects on different body organs. The oxidative stress through the formation of free radicals is one of the mechanisms of CP-induced toxicity (Kart *et al.*,2010). Different natural products and dietary compounds have been recently investigated and evaluated as potential protective antioxidant agents against CP-induced hepatotoxicity (Kart *et al.*, 2010; Mansour *et al.*, 2006; Abdelmeguid *et al.*,2010). *Daucus carota* L. commonly known as carrot, a very widely consumed vegetable in South Asia, has been shown to provide protection against hepatotoxicity, It was documented that this plant had the potential of hypotension, Gilani *et al.*,2000, hepatoprotective, Bishayee *et al.*,1995, antispasmodic, Gambhir *et al.*,1979, antibacterial, Kumarasamy *et al.*, 2002, monoamine oxidase inhibition, Gupta *et al.*,1973, and cyclooxygenase enzyme inhibition. Momin *et al.*,2003. However, traditionally, it was used in the treatment of nephrosis as a nephroprotective agent (Duke *et al.*,2002).

In the present study, using an experimental model of cisplatin-induced kidney and liver injuries in rabbits (single dose of 5 mg/ kg I.P.). The current data demonstrated the occurrence of serum hypotriglyceridemia and hypocholesterolemia in CP-treated rabbits. Under normal physiological conditions, cells control reactive oxygen species levels by balancing the generation of reactive oxygen species with their elimination by scavenging system (reduced glutathione-GSH, superoxide dismutase-SOD, and catalase-CAT). But under oxidative stress conditions, excessive reactive oxygen species can damage cellular proteins, lipids and DNA. Oxidative stress is one of the most important mechanisms involved in cisplatin toxicity. The mitochondrion is the primary target for cisplatin-induced oxidative stress, resulting in loss of mitochondrial protein sulfhydryl group, calcium uptake inhibition and reduction of mitochondrial membrane potential (Saad *et al.*,2004). In the present study extracted juice of *Daucus carota* L. has

been used for its protective action against induced by Cisplatin. Animals that received the oral fresh carrot juice treatment at the dose of 5ml /kg bodyweight for 4 consecutive days before cisplatin injection and 3 consecutive days after the cisplatin injection caused a significant increase in cholesterol and triglycerides levels leading to the restoring their concentrations significantly to the normal range. These findings agree with Nicolle *et al.*,2003, who indicated that Carrot consumption improved the antioxidant status.

AST and ALT are the most sensitive biomarker enzymes used in the evaluation of the function and integrity of liver cells. Both enzymes are present mainly in the cytoplasm of hepatocytes (Adaramoye *et al.*,2008). Cisplatin-induced liver toxicity is characterized by a mild or moderate rise in transaminases (Iseri *et al.*,2007). Transaminases are the most sensitive biomarkers that reflect cellular damage and toxicity because they are localized mainly in the cytoplasm and are released after cellular damages (Saad *et al.*, 2009; Stockham and Scott 2002). The present study illustrated a significant increase in serum AST and ALT activities in CP-treated rabbits as compared with the negative control group. These results agree with the findings recorded by Kandemir *et al.*,2012 and Kart *et al.*,2010 reported that there was an increase in the levels of liver biomarkers in CP-treated rabbits. Mansour *et al.*,2006, Abdelmeguid *et al.*, 2010, Adaramoye *et al.*, 2008 and Nasr 2014 determined in a similar study conducted on rats that reported that cisplatin treatment in rats caused significant changes in circulating AST and ALT activities due to hepatocyte damage. The elevation in the serum activity of ALT, a liver cytoplasmic enzyme, indicates necrotic lesions in the liver cells (El-Sharaky *et al.*,2009). Oral administration of fresh carrot juice prior to and after CP significantly reduced its toxic effect on serum activities of AST and ALT enzymes compared to untreated rabbits this can be attributed to the hepatoprotective activity of the carrot juice. In agreement with



the results of the present study, administration of fresh carrot juice caused a significant reduction in the serum activities of AST and ALT in rabbits treated with Carbon tetrachloride (Fahima 2014).

In agreement with our results, the biochemical findings in CP-treated rabbits were confirmed by the histopathological changes in the liver, where hepatitis with inflammation around the central vein and massive ballooning degeneration of hepatocytes was seen, and many histopathological and ultrastructural abnormalities in the liver including inflammatory infiltration, hyperplasia, periportal fibrosis, marked disruption of hepatic cords, centrilobular necrotic changes, apoptotic nuclear changes and dilated blood sinusoids, were observed. These results agree with the findings recorded by Taghizadeh *et al.*, 2021 reported that CP can significantly induce hepatotoxicity in mice confirmed by elevations in serum liver enzyme activities and histopathological changes. Congestion of veins and blood sinusoids within the hepatic parenchyma might be in part due to the direct irritant effect of cisplatin on the wall of blood vessels or secondary to the fibrotic changes in periportal areas affecting the intra-biliary system with subsequent obstruction of the Hering duct and dual blood supply of the liver (Shona *et al.*, 2012). CP is thought to kill cells primarily by forming DNA adducts, causing G2 arrest in the cell cycle, triggering apoptosis (Kishimoto *et al.*, 2000).

The kidney accumulates CP to a greater degree than other organs and is the major route for its excretion. CP concentration in proximal tubular epithelial cells is about 5 times the serum concentration (Kuhlmann *et al.*, 1997). The disproportionate accumulation of cisplatin in kidney tissue contributes to CP-induced nephrotoxicity (Arany and Safirstein 2003). The nephrotoxicity of CP limits the usefulness of this important chemotherapeutic agent (Rosenberg 1985). Although several studies have been performed to elucidate the molecular

mechanisms that cause cisplatin nephrotoxicity, the factors responsible are not fully understood, although recently, free radicals have been proposed to participate in this process (Baldeu *et al.*, 1990). Creatinine and urea levels are used as biochemical markers of kidney injuries, thus elevated levels of these markers may indicate kidney dysfunction, though the test for creatinine is a better indicator than urea (Rajakrishnan *et al.*, 2017). The findings of our study show alterations in renal function as a significant increase in serum creatinine and urea of CP-induced rabbits (single dose of 5 mg/ kg I.P.) compared to the negative group and these results are compatible with those observed by many other studies (Gamal el-Din *et al.*, 2006; Kim *et al.*, 2010; Saleh *et al.*, 2014). It has been reported that cisplatin-induced nephrotoxicity is closely associated with an increase in lipid peroxidation in the kidney manifested by increased MDA as well as a decrease in anti-oxidant activity with depletion of GSH. Administering fresh carrot juice to CP-induced rabbits caused a significant decrease in the levels of urea and creatinine. These findings agree with Sodimbaku *et al.*, 2016, who indicated supplementation of *Daucus carota* L., ameliorated the gentamicin-induced elevated serum levels of urea, blood urea nitrogen (BUN), uric acid, and creatinine in rats. Similar results were observed by Iqbal *et al.*, 2021 that the co-administration of CP + *Daucus carota* L extract significantly improved renal function by reducing urinary creatinine. These results notified the improved renal function by the effective clearance of urea, BUN, creatinine, and uric acid.

Acute kidney injury (AKI) is commonly caused by nephrotoxic injury to kidney tissue, resulting in acute tubular necrosis Hanif *et al.*, 2020. Inflammatory pathways have been linked to major pathophysiological mechanisms resulting in CIAKI (CP-induced Acute Kidney Injury) (Zhang *et al.*, 2020; Tan *et al.*, 2020; Liu *et al.*, 2020). Damaged renal tubular epithelial cells recruit many immune cells, such as

macrophages, dendritic cells, and T cells, which release a variety of inflammatory factors (Salei *et al.*,2020).

Histopathological results of this study showed that cisplatin had induced severe kidney damage characterized by severe necrosis of tubular cells, inflammatory cell infiltration, mild parenchymal congestion, mild chronic pyelonephritis, renal damage mostly in form of glomerular and tubular injury. These results are in agreement with the results in other studies (Saleh *et al.*, 2014; Gamal el-Din *et al.*, 2006; Kim *et al.*,2010). Arda-Pirincci and Bolkent 2009 mentioned that lipid peroxidation mediated by oxygen free radicals causes destruction and damage to cell membranes resulting in necrosis. Cisplatin-induced acute kidney injury effects on the renin-angiotensin system. A large focus has been on inhibition or genetic deletion of angiotensin II type 1 receptor (AT1 receptors) and angiotensin II type 2 receptor (AT2 receptors), both of which show amelioration in CIAKI (Hosoda *et al.*,2020).

Many high-efficacy and low-toxicity drugs from natural products have been developed to protect against cisplatin-induced AKI. For example, ginseng, curcumin, and pomegranate can act as antioxidants and anti-inflammatory agents and possibly protect against oxidative stress by restoring the levels of antioxidant enzymes (Ridzuan *et al.*,2019). Results of the present study that the Histopathological examination of liver and kidney tissues showed that fresh carrot juice has marked beneficial of alleviating inflammation effectively. fresh carrot juice greatly ameliorated the histopathological changes; examination of kidney tissue showed a nearly normal histological picture with minimal pathological changes, very mild inflammatory cells infiltration, no atrophy, minimal necrosis, and tubules almost back to normal compared to cisplatin-treated rabbits. The present study is in agreement with Sodimbaku *et al.*,2016 who indicated The increased wet kidney weight of gentamicin-

treated rats due to edema induced by acute tubular necrosis was even normalized by the *Daucus carota* extract treatment. Thus, the results notified that *Daucus carota* L. may act by antagonizing the gentamicin-implicated acute renal tubular necrosis and acidosis to attenuate the nephrotoxicity (Sodimbaku *et al.*,2016). Christensen and Brandt 2006 indicated that histopathology results demonstrated the ablated inflammatory events by the cellular anti-inflammatory properties of polyacetylenes present in carrots. Polyphenolic compounds are reported to possess a nephroprotective property by promoting an antioxidant enzyme system, thereby attenuating ROS generation and lipid peroxidation (Wongmekiat *et al.*,2008). In evidence of this, the polyphenolic compounds of *Daucus carota* L. can contribute to nephroprotection by their antioxidant activity. Natural antioxidants such as  $\beta$ -carotene, a terpenoid constituent of the crude extract can ameliorate nephrotoxicity by its free radical scavenging activity (Sharma *et al.*,2012).

Rabbit co-treatment with fresh carrot juice has significantly alleviated hepatotoxicity in the present study since histopathological changes were markedly less pronounced, mild congestion of the central vein was seen and the liver histological alterations were less intense compared to animals treated with CP alone. The histopathological observations also revealed the protective role of *Daucus carota* L. in parallel to the results of biochemical analysis. These results were also observed by Muriel *et al.*,2001 and Althnaian *et al.*,2013 who stated that carrot contains volatile oils, and other materials such as flavonoids, carotene and vitamin C which may contribute to explain its protective effect on oranges. The most abundant phytonutrients present in carrots are phenolics, polyacetylenes, carotenoids, ascorbic acid, and tocopherol Liu *et al.*,2020. *Daucus carota* L. commonly known as carrot is folklorically used as ethnomedicine to treat nephrosis and other urinary disorders (Iqbal *et al.*,2021).

**CONCLUSION**

Hepato renal injuries were found to be major factors induced by (CP). fresh carrot juice (5ml/ kg/ orally) had protective effects against CP-induced Hepato renal injuries in rabbits. The treatment was found to induce significant effects in maintaining normal liver and kidney functions and preventing histopathological changes.

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