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Protective Effects of Quercetin against Cisplatin Induced Hepatotoxicity and Nephrotoxicity in Rats

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ABSTRACT

Cisplatin (CDDP) is one of the cytotoxic agents used to the treatment of cancers and has adverse effects with some organs. The present study was designed to determine the effects of cisplatin on liver and kidney with the protective role of quercetin to reduce these injuries. Rats were divided into six groups. group one (control) received 2ml distal water orally , group two (cisplatin) injected of single dose I.P with cisplatin 4 mg/ kgbody weight , group three(cisplatin) injected of single dose I.P.with cisplatin 8 mg/kg body weight , group four (quercetin 50 mg/kg) treated for 7 consecutive days by gavage needle with , groupfive (quercetin + cisplatin) was given quercetin (50mg/kg)orally once daily for 7 days before and 7 days after a single dose of cisplatin (4 mg/kg) I.P, group six (quercetin + cisplatin) was given quercetin (50mg/kg) orally once daily for 7 days before and 7 days after a single dose of cisplatin (8mg/kg) I.P. We found that cisplatin induced toxic effects of liver and kidney which are characterized by varies degree of degeneration, necrosis of effected cells, congestion, dilatation of blood vessels and infiltration of mononuclear inflammatory cells, these changes were clearly observed with high dose of cisplatin compared to low dose. However the uses quercetin was reduced the changes which vary with groups. In conclusion, the oxidative stress was playing an important role of damage tissues induced by cisplatin. On the other hand, the uses of quercetin as antioxidant in order to ameliorate toxic effect of cisplatin.

Key Words: cisplatin, toxicity, quercetin, histopathology, liver, kidney

HOW TO CITE THIS ARTICLE

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INTRODUCTION

Chemotherapy its one of the important ways which is involves the use of chemical agents for treatment of different types of neoplasm. However, the problem of its effect to the normal healthy cells in the body including different system of bodies [1].Cisplatin (Cis DichloroDiammine Platinum (CDDP) is regarded as a one potent anticancer drug that contains a heavy metal of group VIII transition metals and one of the most important cytostatic agents administered to treat a variety of cancers such as testicular, ovarian, bladder, cervical, lung, and neck cancers [1, 2, 3]. The main cytotoxic effect of cisplatin is due to its interaction with DNA, via the formation of covalent adducts between certain DNA bases and the platinum compound [4]. The important side effects of cisplatin showed its causes nephrotoxicity and hepatotoxicity [5]. In several studies, it had been founded that administrated of cisplatin produced several alterations in the kidney and liver functions which are closely associated with an increase of lipid peroxidation and formation of Reactive Oxygen Species (ROS) in the tissues [6,7, 8].

In the liver cisplatin interact with some mechanisms which lead to injury, structural mitochondrial damage, apoptosis, and disturbance in Ca2+ homeostasis [9, 10]. Which is histological revealed as degenerative changes, especially cells near to central vein, cytopalsmic vacuolization and sinusoidal dilatations of liver cells [11]. While in the renal effect it has been founded that the major site of renal injury is the S3 segment of the proximal tubule in the outer medulla of the kidney. The effect in epithelial cells is histologically characterized by tubular necrosis, several degree of degenerating

and loss of microvilli these structural alterations are accompanied by functional disturbance of various cell organelles [12, 13].Quercetin is natural flavonoidpresent in high concentration in fruits and vegetableslike apples, onion, potatoes, broccoli, tea, soybeans, and redwine. It has been shown to have very potent antioxidant and cytoprotective effects in preventing endothelialapoptosis caused by oxidants [14,15] .The aim of the our present study was to investigate the possible protective effect of quercetin as antioxidant on the hepatic and renal changes before and after the administration of cisplatin in adult male rats.

MATERIAL ANDMETHODS

Experimental animals

A total numbers of 36 Male Albino ratsweighting 250-300gm were obtained from the animal house of college veterinary Medicine, Duhok University. The rats were housed in a standard condition at a room temperature of about 24C^{o} and all rats were allowed for free access to laboratory pellet foods and tap water until end of experiment. The study was approved by the Animal Ethics Committee of the College of Veterinary Medicine, University of Duhok.

Experimental design

The rats were randomly divided into 6 groups (six animals for each group):

Group one: was treated with equivalent volume of distilled water 2ml orally.
Group two: was given a single dose of 4 mg/kg (I.P) intraperitoneally.
Group three: was given a single dose of 8 mg/kg I.P
Group four: was given quercetin at a dose of 50 mg/kg orally at first day of experiments and once daily for 7 days.
Group five: was given quercetin 50mg/kg orally once daily for 7 days before and 7 days after a single dose of cisplatin 4 mg/kg I.P.
Group six: was given quercetin 50mg/kg orally once for 7 days before and 7 days after a single dose of cisplatin 8 mg/kg I.P.
The doses of cisplatin and quercetin were determined according to previous researches published[16, 17].

Histopathological study

The rats were scarified at 8th day after the end of treatment (all of groups) and specimens from kidney, heart and liver were obtained and fixed in neutral buffer formalin 10 %. All the animals were euthanized al the same time. Small pieces 2-3 mm in size in each organ were dehydrated with gradual grades of ethanol (70%, 90%, and 100%),then by using of xylene for clearing and finally embedded in pure paraffin wax at a melting point (56-68 c). Serial section of 4-5 microns in thickness were prepared using Rotatory Microtome (Leica, Germany) and stained with Harris Haematoxylin and Eosin (H&E). The slides were analyzed using an optic microscope with Digital camera Leica, Germany [18, 19].

RESULTS

Results of histological examination of tissue sections of the liver rats treated with cisplatin 8mg/kg showed sever degeneration and necrosis of hepatic cells with a focal mononuclear cellular infiltration speciallyaround ofportal area as well as sever dilatation, hemorrhage, congestion of sinusoidsand blood vessels were observed.The degenerative changes(fatty changes)mainly characterized by sever vacuolar degenerationaround the central vein which appears as small clear vacuoles inside of cytoplasm of the hepatocytes which is varies in size and shape and some timedisplace of the nuclei to the periphery of the cells. The nucleus of hepatocytes appears some of nuclear changes, such as pyknosis and larryohexis, nuclei were seen compared to group control (Fig 1,a and b)

In other hand, the histopathological abnormalities observed in rats treated with cisplatin8 mg/kgand Querecetin involved moderate degradation of hepatic cords, which appeared as empty vacuoles aligned by strands of necrotic hepatocytes compared to group cisplatin alone(Fig1,c). Whilemild degeneration ofhepatic cords associateda less incidence of vacuolar degeneration,proliferation of apoptotic cell death and increase number of kupffer cells were absorbed in group of Querecetin alone as well as no any evidence of congestion, dilatation and hemorrhage of portal vein, sinusoids and portal artery compared with groups of cispaltin alone and cisplatin with Quercetin (Fig1,d). Section from rats treated cisplatin 4 mg/kg revealed moderate to severe congestion of the central vein, disorganization of hepatic cords, necrosis, degeneration of hepatocyes and moderate to severe dilatation, congestion and hemorrhage of sinusoids (Fig1,e). While sections from cisplatin treated group 4 mg/kgand Quercetinexhibited mild to moderate congestion of the heapatic artery, sinusoids and portalvein, with dilatation of the portal vein and mild disorganization of hepatic cords and moderate fatty changes of hepatocytes compared to rats received cisplatin 4 mg/kg alone. (Fig1,f). The general structure of hepatocytes nearly return to normal structurewith rats received Quercetin alone (Fig1,d).

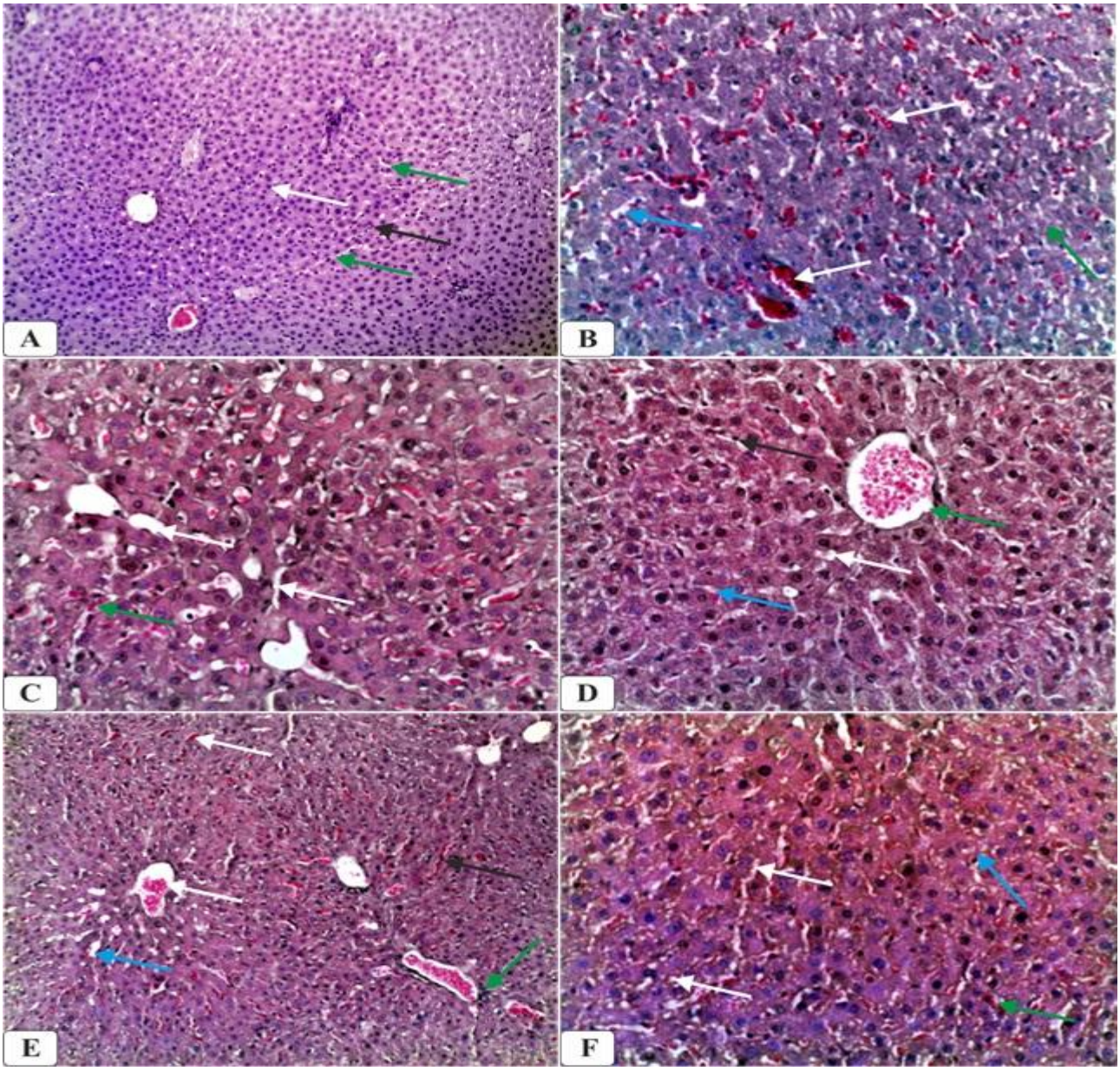

Fig 1**: (a) Microscopical observation of control liver rats showed normal large polygonal cells with prominent nuclei and eosinophilic cytoplasm (red arrow) with few spaced hepatic arranged in between the hepatic cords (green arrow) with fine arrangement of kupffer cells (black arrow) H&E 10x. (b) liver rats with Cisplatin 8mg showed sever congestion and hemorrhage of hepatic tissues (red arrow) dilatation of sinusoids (blue arrow) and sever vacuoles degeneration ,necrosis and distortion of hepatocytes (green arrow) H&E 10x. (c) liver rats wit Cisplatin 8mg and Qurecetin showed sever vacuolar cytoplasmic degeneration and dilatation of sinusoids (red arrow) , moderate congestion and hemorrhage of hepatic vein and sinuosoides (green arrow) and slight proliferation of kuffer cells as will as no infiltration of mononuclear inflammatory cells H&E 20x. (d) liver rats wit Qurecetin showed slightly normal architecture of hepatic tissue, with slight vacuoles (red arrow) and slight congestion of portal vein (Green arrow) and sinusoids(blue arrow) with fine arrangement of kupffer cells (black arrow) H&E 10x. (e) liver rats wit Cisplatin 4mg showed sever congestion and hemorrhage of hepatic tissues and sinusoids (red arrow) , sever vacuoles cytoplasmic degeneration (blue arrow) , and infiltration of mononuclear cells near to the central vein (green arrow) and proliferation of kuffer cells (black arrow) H&E 10x. (f) liver rats wit Cisplatin 4mg and Quercectin showed moderate vacuolar cytoplasmic degeneration and dilatation of sinusoids (red arrow) , slight congestion and hemorrhage of hepatic vein and sinuosoides (green arrow) , slight degenerative and necrosis of hepatocytes (blue arrow) . H&E 20x.**

Histopathological section of kidney from rats received cisplatin 4 mg/kg showed a homogenous casts material inside the lumen,sloughing of tubular epithelial cells from its basement membrane, moderatethrombosis, congestion and hemorrhage (Fig2a b). While the section of kidney from rats treated with cisplatin4 mg/kg and quercetin showed mild to moderate tubular necrosis and degeneration, especially inthe proximal convoluted tubule, mild infiltration of inflammatory cells in the interstium of kidney as well as slight hemorrhage andcongestion of blood vessels (Fig2, c). Sections from rats received quercetin alone, showed the general structure of tubular cells was similar to that of the control group (Fig2, d).

The histopathological evaluation of kidney rats treated with cispaltin 8 mg/kg showed sever changes compared to groups of rats treated with cisplatin 4mg/kg which is characterized by atrophy of glomeruli, sever tubular degenerations, dilation, congestion and hemorrhage of its blood vessels. Sloughing of epithelial cells lining of the proximal convolutedrenal tubules and losses of its brush border. As well as infiltration of inflammatory cells in tinterstitial tissue of kidney in comparison with other groups of rats treated with cisplatin and quercetin and quercetine alone as show in (Fig2,e). the study showed that rats which were received quercetin and cisplatininduced renal damage was moderately reduced with presence of acidophilic cytoplasmic with rounded nuclei of some of renal tubules, necrosis and degenerative changes appears as a pale vacuolated cytoplasm rounded nuclei (Fig2, f). While the group of rats which is received quercetin alone showed slight normal structure of renal tissues(Fig2, d).

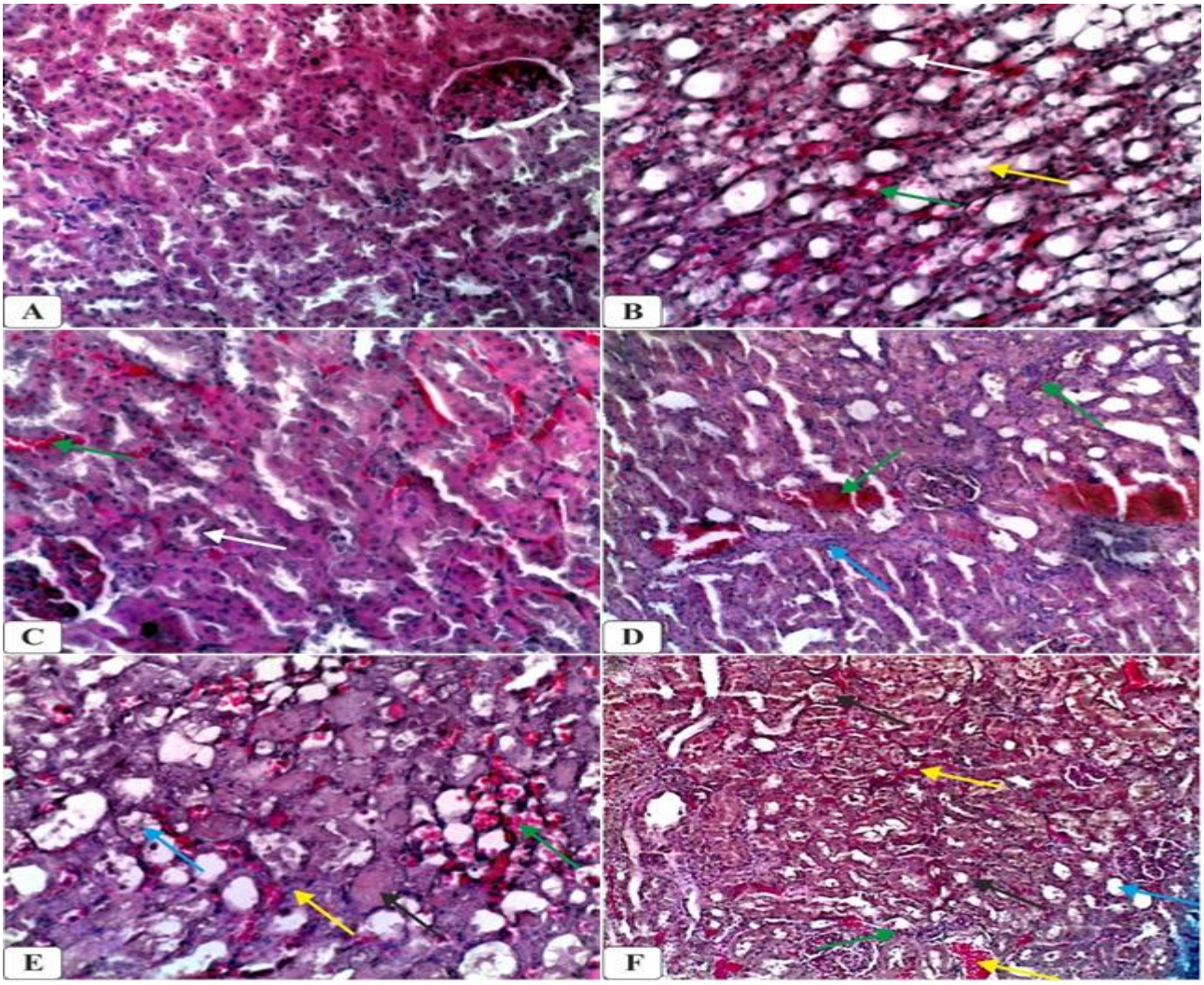

Fig 2: (a) Microscopical observation of control kidney rats showed normal histological architecture of kidney rat, characterized by the presence of proximal and distal convoluted tubules and renal corpuscles. The proximal tubules are lined by large cubodal cells with acidophilic cytoplasm and large rounded nuclei, the luminal border of the cells has brush border. The distal tubules 'have wider lumen and shorter cells with less acidophilic cytoplasm and less brush border than the proximal tubules .H&E 20x. (b) kidney rats withcispaltin 4mg showed marked dilatation of proximal convoluted tubules with slogging of almost entire epithelium (black arrow). The most of proximal convoluted tubular cells were exfoliated in the lumen of tubules and some other cells exhibited dense cytoplasm with dark irregular nuclei (yellow arrow), sever congestion, and hemorrhage of some of renal veins (red arrow). H&E 10x. (c) kidney rats withcispaltin 4mg and Quercetin showed slight normal of architecture of the renal tubules (black arrow). slight congestion, and hemorrhage of some of renal veins (red arrow), and no infiltration of mononuclear inflammatory cells n the interstitium of kidney . H&E 20x. (d) kidney rats with Quercetin showed slight normal histological architecture of tubules and Glomerular of kidney , slight congestion and thrombosis of some of veins (red arrow) and mild infiltration of inflammatory cells in the interstistium (blue arrow). H&E 10x. (e) kidney rats withcispaltin 8mg showed marked loss of architecture of the tubules (black arrow). The most of proximal convoluted tubular cells were exfoliated in the lumen of tubules (blue arrow), some cells exhibited dense cytoplasm and dark irregular nuclei (yellow arrow), sever congestion, thrombosis and hemorrhage of some of veins (red arrow). H&E 20x. (f) kidney rats withcispaltin 8mg and Quercetin showed moderate loss of architecture of the tubules (black arrow). Some of tubular cells exhibited acidophilic cytoplasm, dilatation of its lumen and rounded nuclei (blue arrow), moderate congestion, thrombosis and hemorrhage of some of renal veins (red arrow), and mild infiltration of mononuclear inflammatory cells n the interstitium of kidney (green arrow). H&E 10x.

DISCUSSION

Many of chemo-protective agents particularly those are a widely used as chemotherapeutic agent, it has a great efficacy in a variety of human malignancies whichis counteract the damage induced by free radicals generated by these drugs [21]. Cisplatin is one of these important drugs which is used in the treatment many types of cancers [1, 2, 3]furthermore, many research showed the cytotoxic effect of Cisplatin is enhanced by the elevation of the dose, It has been suggested that oxidative stress is an important mechanism of cisplatin-induced toxicity due to depletion of many of antioxidative enzymes from the liver, and kidney [8, 21, 22].Ingenerallycisplatin acts on cancer cells by forming free radicals such as superoxide radicals, hydroxy radicals, peroxyl radicals, and singlet oxygen, which at the same time cause damage a cell. Free radicals are known to attack the cell membrane to induce lipid peroxidation, which is considered a key process in many pathological events and is one of the reactions induced by oxidative stress[3]thisdamage were confirmed by current study after cisplatin administration with two doses 4 and8 mg/kg B.W. Which is might be occurring during cell injury that related to oxidative stress of cisplatin [23].The liver is known to accumulate significant amounts of cispaltin then to the kidney [24],thus hepatic toxicity and nephrotoxicity could happen when cisplatin is administered at high doses which is similar to our results[25, 26].

Fatty changes was one of the important histopathological alteration recorded in this study with all groups which are received cispaltinalone with liver and kidney, and this changes was reduced with groups which are received Quercitin and cisplatin, and this finding supported with the previously reported by the others [11,27, 28] where they describedand suggested that the cytoplasm which is filled with numerous vacuoles and lipid droplets is mainly a consequence to considerable disturbance in lipid and fat metabolism and this reduced with using of Quercitin and cisplatin . The congestion of blood capillaries with mononuclear cellular infiltration was observed in hepaticsinusoids and renal tissues,and these changes could be due to endothelial injuries of blood vessel after cisplatin administration that may be caused by free radicalinduced lipid peroxidation of the membrane system and this was accordance with this opinion reported that cisplatin causes severe endothelial injury [29].

While in the group which are received Quercetin with both doses of cisplatin8mg/kg and 4mg/kg B.W showed less histopathological abnormalities in liver and kidney, and this might be due to a protective role of quercetin to prevent the damge of tissues caused by oxidative stress which induced by using of cispaltin [17, 18]or might be due to the ability of liposomes to modify the bio-distribution of the entrapped drugs[30]. In addition,Quercetin prevents depletion of some hepatic enzymes which acted as intracellular free radical scavengers and protected cellsdamage[31].

The histological changes of kidney rats after cisplatin treatment showed varies degree of degeneration and necrosis according to doses used, in 8mg/kg the changes was more sever compared to 4mg/kg. These changes included acute tubular necrosis which confirmsirreversible injury to kidney, severe atrophy of glomerulus which was occurring due to the reduction in its size and sever destruction of renal tubules due to desquamation of tubular epithelium.These results obtained in the study is run parallel with the other previous studies,where the demonstrated that cisplatininduced acute renal necrosis, congestion, hemorrhage and dilatation of blood vessels as well as glomerular atrophy[32].Furthermore, the cisplatin causes total absence of microvilli of the epithelium in some areas,andthese changes is agreement with the prior observations made by [33], they showed the cisplatin treatment in rabbits caused nephrotoxicity, which is evidenced by significant loss of brush border microvilli and supposed to be responsible for reducing the area for active glucose reabsorption.[34].

In addition, acute focal necrosis of renal tubule is the important microscopical changes which is occur due to complications of cisplatin administration in cancer patients and the severity of necrosis of patient outcome are doseand time dependent which is completely agreement as we found in the present study [35]. Also itthought that inflammatory cells and inflammatory cytokines are a part of the pathogenesis of cisplatininduced acute renal failure [36]. As well as[21] showed that the disability of renal cells to metabolize cisplatin due to toxic effect, interact with apoptotic pathways and reactive oxygen metabolites as major mechanisms underlying cisplatininduced renal cell injury. Our result found that the Quercetin play an important role to reduce the renal damage caused by cispaltin treated when two groups of cisplatin were received quercetin 50mg/kg which are revealed by less histopathological abnormalities of renal tissues.

CONCLUSION

Oxidative stress was playing an important role in thepathogenesis of tissue injury induced by cisplatin**.** Cisplatin causes liver and kidney damage depending on the doses concentration; our results provide histopathological evidence of cisplatin toxicity, on the other hand, the possibility of recovery by using of querecetin as antioxidant in order to ameliorate its toxic effects.Therefore, this study identified pathological features in tissues which could be used as the basis for determining the appropriate dose of these drugs andquercetin to reduce the toxicity of chemotherapeutic agents.

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