



A Histopathological Study of Cisplatin-induced Acute Vascular Injuries in Vital Organs and Protective Effect of *Achillea millefolium*

Zahra Eslamifar¹ and Susan Sabbagh^{2*}

¹Department of Biochemistry, School of Paramedical Sciences, Dezful University of Medical Sciences, Dezful, Iran.

²Department of Anatomy, Faculty of Medicine, Dezful University of Medical Sciences, Dezful, Iran.

Authors' contributions

This work was carried out in collaboration between both authors. Author ZE designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors SS and ZE managed the analyses of the study. Author SS managed the literature searches. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2020/v32i1030492

Editor(s):

(1) Dr. Syed A. A. Rizvi, Nova Southeastern University, USA.

Reviewers:

(1) Mohamed Hamzawy, Fayoum University, Egypt.

(2) Veronica L. Martinez Marignac, Argentina.

Complete Peer review History: <http://www.sdiarticle4.com/review-history/58433>

Original Research Article

Received 20 April 2020
Accepted 25 June 2020
Published 29 June 2020

ABSTRACT

The aim was to study the protective effect of ethanolic extract of *Achillea millefolium* on acute vascular injuries induced by cisplatin in liver, heart and renal tissues 24 hour after administration and using histopathological surveys in wistar rats. 24 adult male wistar rats were randomly divided into four groups. Group I (control group) received physiological saline for 10 days. Animals of group II had single dose of injection of CP (cisplatin) (6 mg/kg, IP) on the ninth day. Group III received *Achillea millefolium* extract (250 mg/kg, gavage) for 10 consecutive days. Group IV had both *Achillea millefolium* extract (250 mg/kg, gavage) for 10 consecutive days and a single dose of injection of CP (6 mg/kg, IP) on the ninth day. Kidney, liver and heart organs were collected on 10th day from sacrificed rats and subjected to histopathological analysis. Then the possible histopathological vascular effects of cisplatin on liver, heart, kidney tissues and the protective effect of *Achillea millefolium* extract was analysed. Obtained data showed the vascular injuries in CP

*Corresponding author: E-mail: sabbaghsusan@yahoo.com;

group as congestion of cardiac capillaries ($p=0.00$) and interstitial edema ($p=0.03$). In the kidney, shrinkage of glomeruli ($p=0.04$), widening of Bowman's space ($p=0.04$), dilatation of cortical capillaries ($p=0.01$) were significantly altered. The findings of liver organ were increased sinusoidal space ($p=0.00$) and infiltration of neutrophils in portal space ($p=0.01$). Pretreatment with ethanolic extract of *Achillea millefolium* could attenuate these vascular injuries. Briefly, 24 hour after single injection of cisplatin the inflammatory process was seen in vital organs and administration of *Achillea millefolium* could mitigate these side effects.

Keywords: Cisplatin; vascular injuries; rat; *Achillea millefolium*.

1. INTRODUCTION

Cis-diamminedichloroplatinum or cisplatin is one of the most effective anti-tumor chemotherapeutic agent and commonly recommended drug that improve survival in patients with solid tumors such as head, neck, lung, breast, ovarian and testicular [1]. Also cisplatin has an important and effective therapy in patients with other cancers such as bladder, esophageal, prostate, melanoma, Hodgkin's and non-Hodgkin's lymphomas and so on [2].

There are three platinum based drugs that are used for chemotherapeutic purpose including cisplatin, carboplatin, and oxaliplatin [3].

Platinum-based drugs bind to peptides and proteins that contain sulfur residues especially to glutathione as antioxidant, but the main target of these drugs is nuclear DNA that finally prevents replication and transcription of DNA and initiates apoptosis [4].

Despite the common use of cisplatin and related platinum-based therapeutics, this drugs exert serious side effects include nausea and vomiting, neurotoxicity, hepatotoxicity, apoptosis, inflammation and oxidative stress. Kidneys are one of the target organs against toxic effects of chemical drugs and especially cisplatin [5]. Various studies have tried to mitigate the cisplatin side effects such as rapid decrease in glomerular filtration rate and damage to kidney blood vessels, acute tubular necrosis and nephrotoxicity [6].

Prevalence of nephrotoxicity has been reported in about one-third of patients treated with cisplatin [7,8]. In the early days after injection, approximately one-third of patients exhibited reduced filtration rate [9].

Cisplatin on tubular cells of kidney could activate a signaling pathway that causes the damage and death of tubular cells. Then an inflammatory reaction and more severe damage to the kidney

tissue would be triggered. In addition, renal damage caused by cisplatin is a complex process which involving several factors [1].

Besides different concentrations of cisplatin has shown varying degrees of pathological alterations in liver [10-12]. The pathogenicity of the liver damage has not been fully elucidated. Histological investigation of liver has showed the changes of cytoplasmic and around cells of the central vein, sinusoidal dilatations and hepatocellular vacuolization [9,13].

Liver toxicity after high doses of cisplatin administration, can occur, which has been an obstacle for the further usage of cisplatin [14]. Some researchers reported that cisplatin at high doses, could produce abnormal liver tests, especially alanine transaminase (ALT) and aspartate transaminase (AST). The authors suggested that cisplatin-induced acute hepatic injury is dose-related [15].

Cardiac toxicity is not considered as a typical side effect of cisplatin, but there is evidence for cardiac toxicity after cisplatin treatment such as cardiovascular damage, and severe injuries including arrhythmia, cardiac failure, myocarditis and pericarditis [16,17].

About the mechanisms of action of cisplatin, some researchers stated this mechanism was not completely understood, but there is a widely held view that cisplatin binds to purine bases in DNA and leading to the formation of cross-links and cisplatin-DNA inter- and intra-strand [1,18].

If DNA mildly damaged, it can be repaired but extensive damage leads to irreversible changes and finally cell death [1].

Some studies reported that when this chemotherapy agent is introduced into the cell, water molecules replace the chloride atoms of cisplatin, which produces active electrophilic products [8,19,20].

The experimental study proved that the most important mechanisms involved in cisplatin cardiac injury is the production of reactive oxygen radicals and reduction of antioxidant enzymes such as glutathione, catalase and so on. It leads to peroxidation of the lipids and resulting damage of DNA, proteins and cell membrane [21]. Therefore, antioxidants may be effective for improving side effects of cisplatin [22,23].

Natural antioxidants may reduce the toxicity of cisplatin-induced ROS, without affecting its anticancer activity. Even though antioxidant effective ingredient is unknown, if their protective effects are confirmed in humans, they can be used as an appropriate treatment agent [1].

Achillea millefolium(yarrow) is one of the plants belong to Asteraceae family and an extensively distributed medicinal herbal one. This plant has been used for over 3000 years [24]. *Achillea millefolium* is rich in phenolic acid and flavonoid compounds [25]. The therapeutic use of this plant contains numerous items including inflammation, spasmodic diseases, pain, hemorrhages, wounds, headaches [26], diabetes, external bleeding, influenza, eczema and etc. [27,28].

Nowadays drugs made from *Achillea millefolium* have been shown to have liver protective activities [29], anti-inflammatory, antimicrobial, antioxidant and antitumor properties [30-32].

Application of dietary antioxidants has a broad range of approaches worldwide to protect against the drug side effects [33]. Ojha et.al reported that *Achillea millefolium* can decrease the lipid peroxidation and finally the cisplatin nephrotoxicity [34].

The purpose of the current study was histopathological investigation of the acute vascular effect and inflammatory response of single injection of cisplatin after 24h administration on different vital organs of adult male wistar rats and possible anti-inflammatory effect of pretreatment with *achillea millefolium* ethanolic extract (AMEE).

2. MATERIALS AND METHODS

2.1 Plant Collection

Achillea millefolium was collected in khoramabad Iran from Sep., 2018 till Oc., 2018. The plant

Research Center of the Faculty of pharmacy, jentashapier, Iran (Herbarium number A190100701AP), performed the identification of herbarium.

2.2 Preparation of Ethanolic Extract

The flowers of plant was dried in shadow, room temperature and then powdered. As the solvent, the powder was dripped in 70% alcohol and for three consecutive days in a tightly closed container was shaken continuously. After that, by using rotary evaporator, the mixture was meshed to separate the solute and finally extract dried in oven at 40°C. Before gavage to make ready qualified concentrations, the dried extract was dissolved in distilled water every day.

2.3 Chemicals

Cisplatin was obtained from Mylan Company.

2.4 Experimental Design of Animals

24 male wistar rats weighing 180–220 gr and aged 6 weeks were obtained from the Animal House Division, Faculty of Medicine of Dezful Medical University, Iran, and randomly divided into four groups of 6 animals each.

Group I control (con): Was intra peritoneally (IP) injected with a single dose of 1mg/Kg normal saline for ten days.

Group II cisplatin (CP): Received single IP injected dose of cisplatin at concentrations of 6 mg/kg body weight at ninth day 24hrs before sacrificed. The choice of dose was according to Zhang et al [35].

Group III *achillea millefolium* ethanolic extract (AMEE) and Group IV cisplatin + *achillea millefolium* ethanolic extract (CP+AMEE) were gavaged with 250 mg/Kg AMEE for 10 consecutive days, while group IV received single IP injection of cisplatin one day (24 h) before sacrificed.

The dose of AMEE was determined according to Karwasra, et al. and Mustafa, et al. [36,37].

Rats were hosted in stainless-steel cages under constant conditions of relative humidity (50–60%), temperature (23 ± 2°C), and lighting (12 h light/dark cycles). They were adapted for one week before experiment. Animals fed with a standard commercial rat diet and distilled water.

At 10th day, animals were sacrificed with an overdose of thiopental sodium (100 mg/kg BW). The abdominal cavities of the rats opened, and immediately fresh small specimens of left ventricle of heart, liver and left kidneys separated and washed in cold normal saline.

2.5 Histopathological Study

Tissue samples fixed by 10% formaldehyde for 24 hours and undergo routine histological processing for paraffin block, then blocks were sectioned using a rotary ultramicrotome at thickness of 4-5 μm , distributed onto glass slides, stained with hematoxylin and eosin (H&E) dyes. For each organ, two slide prepared.

All sections were examined under a light microscope (Olympus BX 52, Tokyo, Japan).

Twenty fields of each slides in randomly chosen areas observed under x40, x100 objective magnification for following parameters:

Heart: Edema, congestion of capillaries and infiltration of inflammatory cells.

Liver: Congestion of central vein, dilatation of sinusoid and infiltration of inflammatory cells in portal space.

Kidney: Congestion of cortical capillaries and infiltration of leukocytes.

Qualitative evaluation was performed for all sections.

2.6 Histo-morphometric Study

In the kidney's slides, glomeruli diameter (from one side basal lamina to the basal lamina of other side) and Bowman's space (from parietal layer of Bowman's capsule to glomerular tuft) in 30 fields were determined using Motic software at x10 objective magnification for each specimen. In order to measure the glomeruli parameters approximately from center of the structure, only glomeruli that had urinary or vascular poles were analyzed. The areas of these glomerular regions stated in μm . Mean values calculated and recorded.

2.7 Statistical Study

The mean values and standard deviation of the histological data obtained ($\pm\text{SD}$).

Then the significance level of the intergroup difference was identified using one-way ANOVA followed by the Tukey's test. All statistical analyses were performed using "IBM SPSS Statistics Version 20" program and a p value of <0.05 was considered significant.

3. RESULTS

3.1 Histopathological and Histo-morphometrical Results

3.1.1 Group I (Control group)

1a: Examination of H&E stained sections of the heart tissue of control animals showed the normal histological pattern of cardiac muscle fibers with elongated, branched fibers and central nuclei with oval shape. The delicate connective tissue of intercellular space comprise fibroblast and small blood capillaries. There were not polymorphonuclear cells between cardiac myocytes (Fig. 1A).

1b: Observation of liver slides of control animals stained with H&E revealed normal architect with large polygonal hepatocytes arranged as hepatic cords and between cords fine space; hepatic sinusoids. Hepatic cord surround central vein and between hepatic lobules portal space was arranged (Fig. 1B).

1c: Assessment of haematoxylin and eosin stained sections of kidney tissue of control animals showed normal pattern of cortex and medulla. Cortical area contains transverse sections of proximal and distal convoluted tubules, renal corpuscle that consisted of a glomerular capillary tuft encircled by Bowman's capsule with a narrow urinary space in-between. Urinary space was arranged with regular delicate space between outer layers of glomerulus. Also as many as small capillaries was seen (Fig. 1C).

3.1.2 Group II (CP)

IIa: Observation of cardiac muscle fibers showed almost normal pattern. Striated and acidophilic sarcoplasm of cardiac muscle fibers was apparent. Congestion of blood capillaries and infiltration of neutrophil cells between cardiac muscle fibers and increased intercellular space (edema) were observed (Fig. 2A,2B).

IIb: sections of liver organ of this animal group showed normal arrangement of hepatic cords, sinusoidal space among hepatocytes were

markedly broad also dilation of some central veins with as many as blood cells, infiltration of neutrophil cells into portal space was obvious (Fig. 2C,2D,2E).

IIC: Haematoxylin and eosin stained sections of cortical areas of this animal kidney group were evaluated. Proximal and distal convoluted tubules had normal appearance. congestion of cortical capillaries and infiltration of neutrophils in interstitial space of cortical area were seen. In addition, many of glomeruli had become shrinkage, enlarged urinary space and irregular feature (Fig. 2F,2G,2H).

3.1.3 Group III (AMEE)

The histopathological findings of slides from different organs of this group, showed almost normal characteristic feature (Fig. 3A,3B,3C).

3.1.4 Group IV (CP+ AMEE)

IVa: Cardiac myocytes had normal feature with striated sarcoplasm and central oval nuclei. Inter cellular space had almost normal feature and very few dilated capillaries was observed (Fig. 4A).

IVb: evaluation of specimens of liver organ of this group showed that arrangement of hepatic cords was normal. Hepatocytes had acidophilic cytoplasm with one or two central nuclei. Sinusoids had normal size and central veins had not enlarged lumen. Triad of Portal space with bile duct, hepatic artery and vein had nearly normal feature, congestion of vein in portal space was not seen. There was not infiltration of acute inflammatory cells in portal space (Fig. 4B).

IVc: Evaluation of cortical part of kidney slides from this group animal was done. Both proximal and distal convoluted tubules had normal epithelium. Most of the glomeruli had equal size and the urinary space was narrow and almost regular shape. No congestion of cortical capillaries was seen (Fig. 4C).

Histopathological findings of rat heart organ showed statistically significant differences in parameters of capillary congestion and interstitial edema between control and CP groups. Pretreatment with AMEE could reduce both congestion of capillaries and edema significantly.

Assessment of microscopic features in liver specimens' of control and CP groups showed considerably enlargement of sinusoids. Administration of AMEE could ameliorate this parameter after injection of CP significantly.

Data analysis was carried out and results showed statistically significant relationship for neutrophil cell infiltration into portal space of liver slides, between control and CP groups; meanwhile after use of AMEE the infiltration of inflammatory cell was significantly reduced.

Microscopic findings from kidney slides of control and CP groups showed that diameters of glomeruli and Bowman's space of these groups had statistically significant correlation and finally administration of AMEE could ameliorate these parameters significantly.

Table 1 represents the obtained data.

4. DISCUSSION

Cisplatin is used as one of the most effective chemotherapy drugs to treat several different human cancers [38]. Today, in combination with other drugs, cisplatin is used in more than half of oncological treatments [39].

The side effects of platinum-based drugs are grouped into seven groups: ototoxicity, nephrotoxicity, hepatotoxicity, neurotoxicity, hematological toxicity, gastrointestinal toxicity and cardiotoxicity [40].

Many studies have shown that the toxic effects of cisplatin appear about 3- 5 days after administration [41,42].

For the first time, the present study showed that 24 hours after a single injection of cisplatin, vascular damage occurs in various vital organs, including the kidneys, liver and heart. Subsequently, against of cisplatin side effects, the protective effect of *Achillea millefolium* extract was investigated as an anti-inflammatory agent in these organs.

We found that, administration of 6mg/kg body weight of cisplatin for rats is a common choice in other studies [35,43-45], because of different side effects in vital organs.

Table 1. The mean ± SD and significance values of different vascular parameters of kidney, heart and liver organs among the experimental groups

Group	Kidney						Heart				Liver			
	Glomeruli diameter		Bowman's space		Congestion		Edema		Congestion		Dilatation of sinusoid		Infiltration of inflammatory cells	
	Mean ± SD	P value	Mean ± SD	P value	Mean ± SD	P value	Mean ± SD	P value	Mean ± SD	P value	Mean ± SD	P value	Mean ± SD	P value
control	98.04±1.27	0.002	14.51±1.47	0.00	0.4±0.55	0.04	1.05±0.20	0.01	1.20±0.45	0.01	0.00±0.00	0.00	0.25±0.50	0.04
CP	88.67±16.43	0.04	25.46±3.97	0.04	1.8±0.45	0.01	3.65±0.35	0.03	3.00±0.00	0.00	2.00±0.00	0.00	2.00±0.00	0.01
AMEE	129.56±9.51	0.00	19.27±3.94	0.04	1.50±0.58	0.02	0.96±0.40	0.04	0.75±0.50	0.04	0.25±0.50	0.00	0.00±0.00	0.00
CP+ AMEE	124.15±6.72	0.001	20.69±2.25	0.03	0.75±0.96	0.01	1.21±0.31	0.01	1.25±0.50	0.02	0.50±0.58	0.00	0.00±0.00	0.02

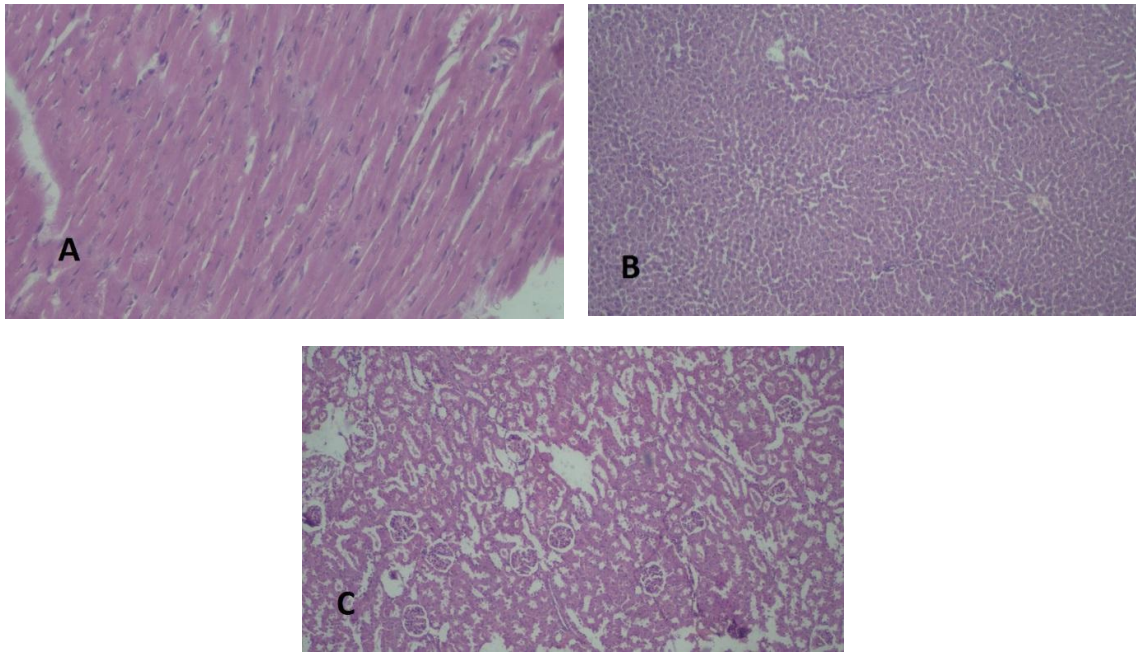
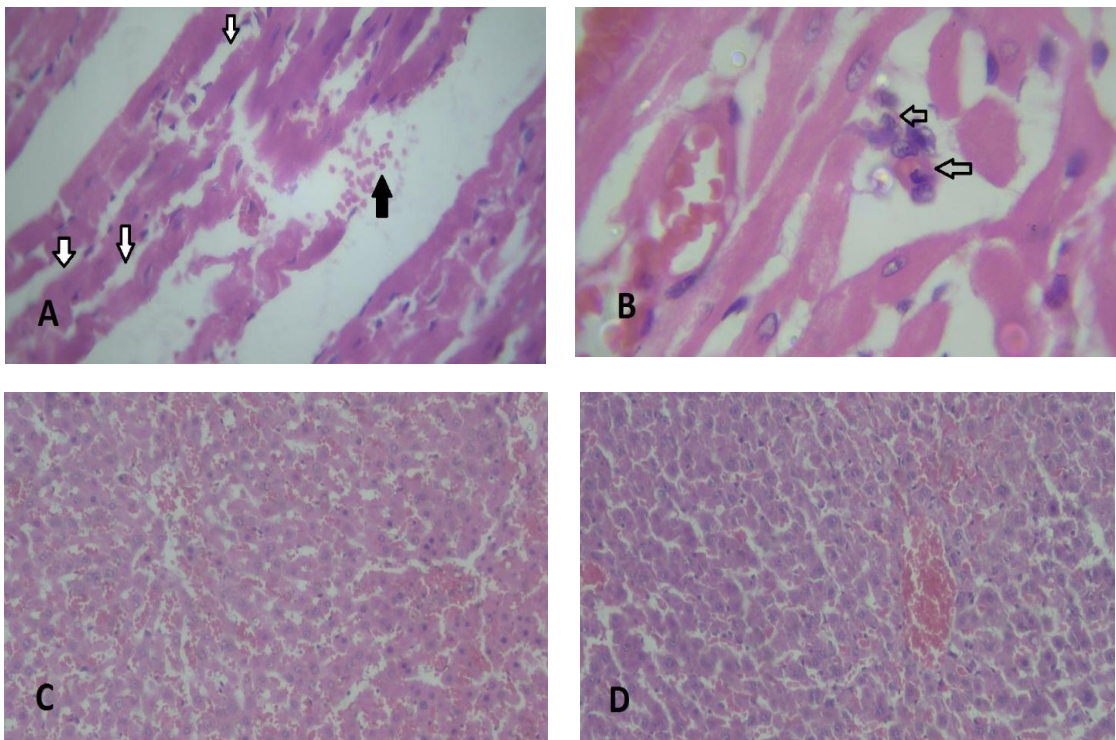


Fig. 1. Photomicrographs of different tissues of normal study group, stained with H&E (×100). **A:** cardiac tissue; indicate longitudinal sections of cardiac myocytes, narrow interstitial space between cells contain many small capillaries. **B:** liver; note the normal structure of hepatic lobules contain central vein, cords of hepatocytes, narrow sinusoidal space between cords and portal spaces between lobules. **C:** Renal cortex with normal feature of proximal, distal convoluted tubules, glomerulus and narrow urinary space surround glomerulus



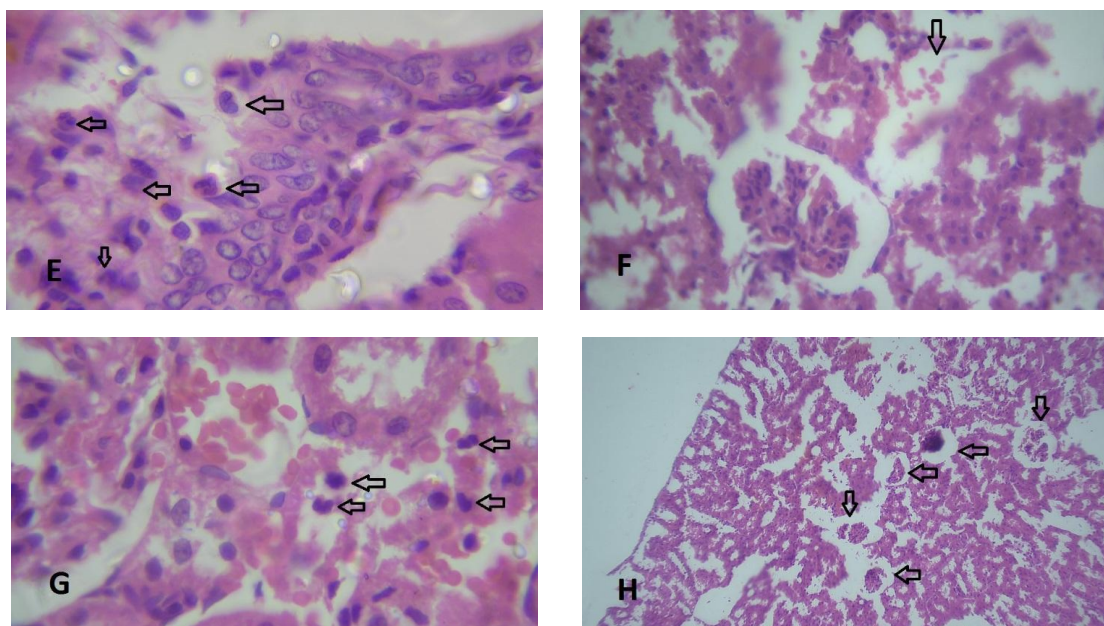


Fig. 2. Quantification of renal, cardiac and hepatic tissue, vascular damage due to cisplatin administration. A: cardiac tissue; white arrowhead indicate interstitial eadema between cardiac myosites and black arrowhead shows congestion of capillary ×400. B: same group, infiltration of neutrophils between cardiac myocytes ×1000. C: shows dilatation of hepatic sinusoids×100, D: congestion of portal vein ×100, E: infiltration of neutrophils in portal space ×1000. F: congestion of cortical capillary of kidney×400. G: arrowheads indicate presence of neutrophills between renal tubules ×1000. H: arrowheads shows shrinkage of renal glumeruli ×100

Investigations had shown that *Achillea millefolium* extract has active compounds such as polyphenolic compounds [46], flavonoids [47] which considered as potent antioxidant compounds [47,48]. Also the study of Tozy et al has proved the anti-inflammatory effect of this extract [49].

According to research by Benedek et al in 2007, *Achillea millefolium* due to having flavonoid and poly phenolic compounds, inhibit matrix metalloproteinases (MMP-2 and -9) and human neutrophil elastase (HNE) associated with the inflammatory process. Therefor they introduce this medicinal herbal plant insights into the pharmacological activity of *Achillea* and confirm the its application as antiphlogistic drug [50].

Nephrotoxicity is one of the most common side effects of Cisplatin [51-55]. Investigations has shown that in rodents, after injecting a single dose of cisplatin at a low dose of 4-10 mg/kg, about 50% of the drug is secreted in the first 24

hours in the urine during the first 24 hours [56]. According to studies by Moreno-Gordaliza et al. Cisplatin accumulation in the renal cortex and its damage begins in the renal cortex [57]. According to the present study, 24 hours after injection of cisplatin, congestion of cortical capillaries was detected. This result is similar to the study of Amin et al. They have reported that the changes occur five days after a single cisplatin injection. [58]. Akcay et al found that interleukin 33(IL-33) as a novel bio-marker in vascular injury of kidney, was elevated one day after injection of cisplatin. They stated that this probably due to diffuse endothelial injury. [59]. In the current study, Shrinkage of glumeri and enlargement of periglomerular space were other findings of injury of kidney due to the injection of cisplatin after 24h, so that dilatation of urinary space could cause loss of normal morphological feature of glomeruli. These findings were in accordance with Cure et al, five days after single injection of cisplatin [60] and Kanter et al. [61] that have announced similar results three months after injection of cisplatin.

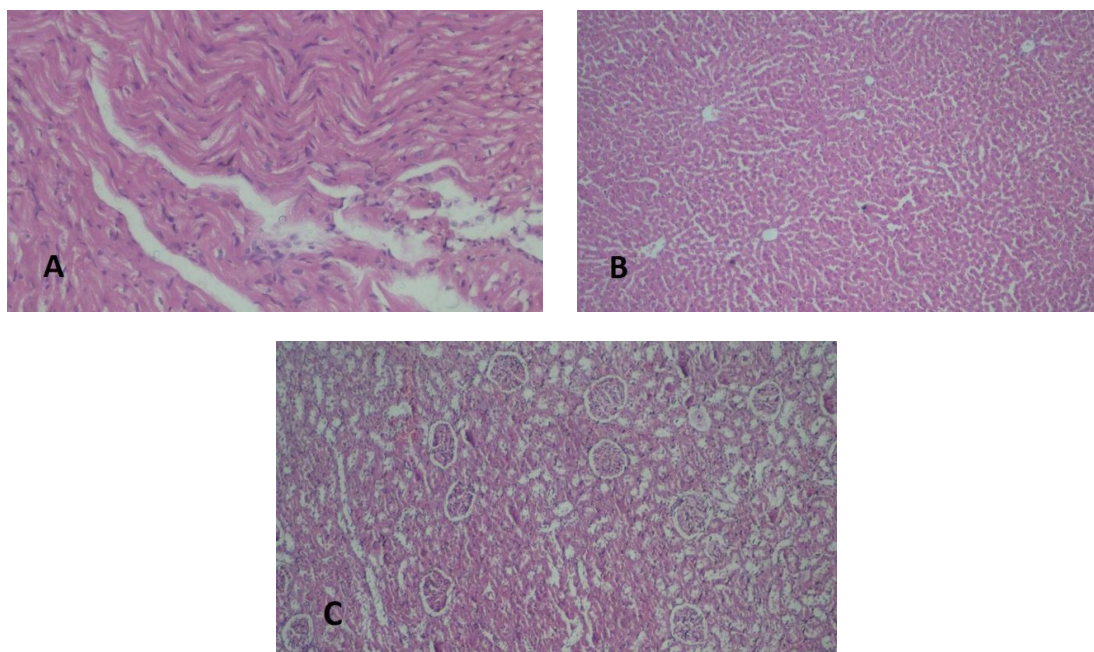


Fig. 3. Light micrographs of different organs of AMEE group ×100. A: cardiac, B: liver and C: kidney tissue: note the normal histological appearance ×100

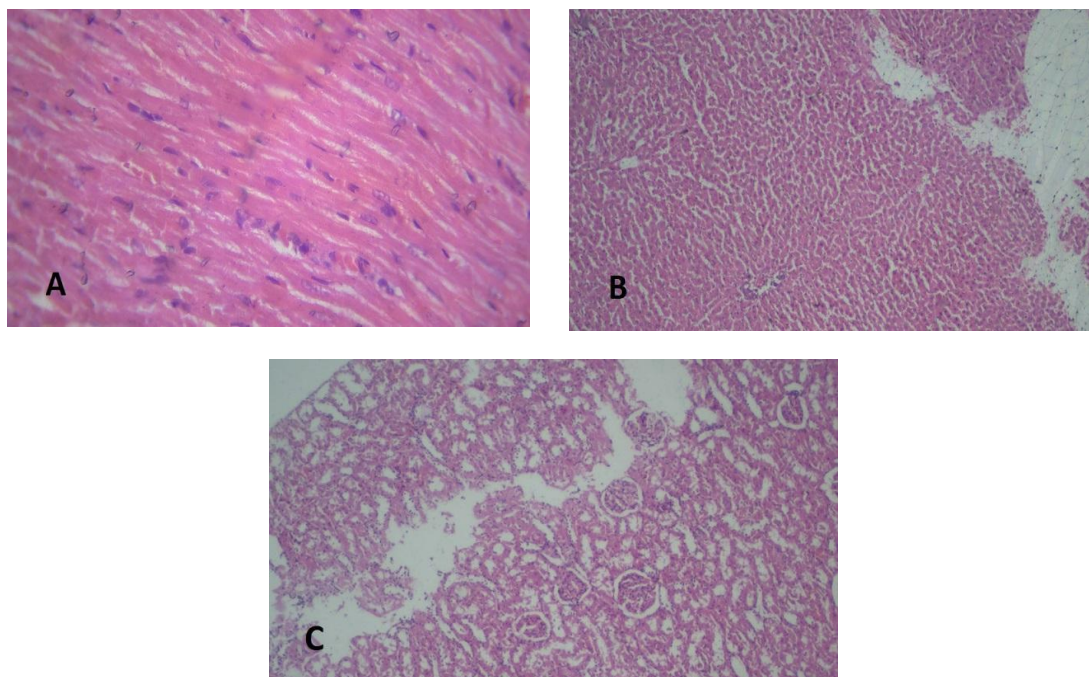


Fig. 4. Histopathological slides of same tissues of CP + AMEE group shows Treatment with AMEE significantly improved cisplatin-induced acute vascular injuries. ×100. A: cardiac tissue; note the normal interstitial space between cardiac myocytes. Also capillaries have normal feature. B: liver; AMEE could attenuate inflammatory condition induced by cisplatin. C: kidney: glomeruli have almost normal architecture

According to current study, administration of *Achillea millefolium* extract prior to injection of cisplatin could able to compensate the inflammatory effect of drug in rat's kidney. This investigation have showed both capillary congestion and alteration in morphology of glomeruli in the presence of extract that were statistically reduced.

Different studies shows protective effect of *Achillea millefolium* on kidney diseases. Zangeneh et al previously stated the protective effect of *Achillea millefolium* on nephrotoxicity in diabetic mice model [62]. Bafrani et al performed an experimental study to investigate the protective effect of *Achillea millefolium* extract on Nephropathy. Authors reported that this extract had curative and ameliorative effect on ethylene glycol induced "renal stone" in wistar rats [63]. A preliminary study by Vahid et al conducted to evaluate plasma nitric oxide concentration of patients with chronic kidney disease and that is there an effect of administration of the *Achillea millefolium* extract? The authors concluded that plasma nitric oxide metabolites were marginally decreased after "*Achillea millefolium*" administration in chronic kidney disease patients [64].

Another finding of the present study was the inflammatory process of the heart muscle, which occurred 24 hours after the single dose of cisplatin injection, which was detected by congestion of blood capillaries and increased intercellular edema in the rat's heart muscle. Some other studies had been reported same results, but these studies investigated different time of exposure to cisplatin [38,65,66]. Additionally Bano et al concluded that in the children, Cisplatin could cause cardiotoxicity because children are more sensitive to cardiotoxicity than adults [67]. The mechanism of cardiotoxicity caused by cisplatin is unknown. researchers have supposed to that either cardiotoxicity is as a secondary toxic effect of nephrotoxicity due to magnesium weak reabsorption [40] or due to direct attack of ROS to heart [68].

Due to the effect of "*Achillea millefolium*" extract on increasing levels of antioxidant enzymes in the heart muscle, Mahmoudabadi et al. have reported a positive effect of this extract on antioxidant enzymes level in rat model of heart ischemia-reperfusion [69]. The results of our experiments also have showed the beneficial

effect of this plant against the side effects of cisplatin.

Finally, we investigated the acute effect of cisplatin on vascular state of liver organ. Obtained data have showed significantly dilatation of sinusoids and so infiltration of inflammatory cells into portal space. These findings are similar to the results of Palipoch et al [9].

Platinum based drugs are known to have the capability to damage liver sinusoids, (the vessels that bring oxygen to the hepatocytes) [70]. Damage of these narrow vessels could lead to sinusoidal dilatation and finally results in dysfunction of hepatocytes [71]. Also injury of sinusoids may result in nodular hyperplasia which is the increase of benign tumors in the Liver tissue [72].

Present study showed the protective effect of "*Achillea millefolium*" extract on acute vascular injuries of hepatic organ that is similar to Dadkhah et al [73].

Liver is a unique organ because of rich blood circulation, this organ receives a dual blood supply from the hepatic portal vein and the hepatic arteries that enter to liver to deliver oxygen and nutrition [74]. It seems that high blood circulation appears to cause an early response to inflammatory conditions and to absorb immune cells much earlier than other organs [75]. Present study demonstrated infiltration of inflammatory cells into the portal space that take place 24 hour after injection of cisplatin. We observed anti-inflammatory property of AMEE so that there was not infiltration of neutrophils in portal space and other vascular sites of liver.

5. CONCLUSION

Current studies have demonstrated acute vascular injuries of vital organs 24h after administration of single injection of cisplatin (6mg/kg body weight) for the first time. This dose is very common in other studies of rat models of toxicity of different vital organs. *Achillea millefolium* administration along with cisplatin could attenuate these side effects due to anti-inflammatory and anti-oxidant property.

CONSENT

It is not applicable.

ETHICAL APPROVAL

Prior to experiment, Ethics committee approval was obtained from University Animal Experiments Local Ethics Committee (IR.DUMS.REC1396.17), based on the Helsinki Protocol (Helsinki, Finland, 1975).

ACKNOWLEDGEMENT

The authors would like to thank Mr. Mohammad Reza Esmail Chegeni, the head of Imam Hassan Mojtaba center of chemotherapy and radiotherapy in dezfoul, Iran, for help in gift cisplatin drug.

Research Affairs of Dezful University of Medical Science financially supported this work

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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