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Evaluation vital role of silymarin in reducing histological effects of nephrons induced by cisplatin

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Abstract :

Medicinal herbs have a vital role in improving kidney function and repairing damage caused by medications. The present study aimed to evaluate the role of silymarin in the repair of tissue damage caused by the use of cisplatin. Thirty female rat divided into six groups and treated following, control group administrated orally with 1ml/kg. B.W physiological solution (0.9%). Second group injected Cisplatin single dose beginning of the experiment (5mg/kg i.p).third group treated Silymarin (150mg/kg) orally daily and Cisplatin. Fourth group treated just Silymarin. Fifth group injected Cisplatin end of experiment. Sixth group treated Silymarin daily and Cisplatin end of experiment. The results of the microscopic examination showed damage to the nephrons of the kidneys in the cisplatin-treated groups, including necrosis, hemorrhage, and swelling in the glomerulus. The same damages appeared in the therapeutic and preventive groups treated with cisplatin and silymarin, while Silymarin did not show any damage to the kidneys, which indicates the presence of drug interaction. We conclude from the foregoing that cisplatin caused severe damage to the kidney tissue after 24 hours its injection, and treatment with silymarin caused more damage to the kidney tissue, while no damage appeared in the silymarin group alone. This indicates that there was a drug interaction when silymarin was used with cisplatin, which resulted in tissue damage.

Keywords: Cisplatin, Silymarin, damage renal tissue, drug interaction.

تقييم الدور الحيوي للسليمارين في تقليل التأثيرات النسجية للنفرونات التي يسببها عقار سيسبلاتين

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مستخلص:

للأعشاب الطبية دور حيوي في تحسين وظائف الكلى وإصلاح الاضرار التي تسببها الادوية. هدفت الدراسة الحالية الى تقييم دور السليمارين في اصلاح تلف نسيج الكلى الناجم عن استخدام سيسبلاتين .ثلاثون من اناث الجرذان البيض قسمت الى ست مجموعات وتمت معاملتها كالاتي: مجموعة السيطرة تم معاملتها فمويا بالمحلول الملحي الفسلجي(0.9٪) ، مجموعة سيسبلاتين بداية التجربة حقنت عقار سيسبلاتين بتركيز (5mg/kg) تحت البريتون، المجموعة العلاجية المعاملة بالسليمارين (150mg/kg)) مع سيسبلاتين (5mg/kg) بداية التجربة، المجموعة المعاملة بالسليمارين فقط يوميا (150mg/kg) فمويا، مجموعة سيسبلاتين نهاية التجربة(5mg/kg) تحت البريتون والمجموعة الوقائية المعاملة بالسليمارين يوميا (150mg/kg)) وحقنت سيسبلاتين نهاية التجربة (5mg/kg) تحت البريتون. أظهرت نتائج الفحص المجهري حدوث تلف في نفرونات الكلية في المجموعتين المعاملتين بالسيسبلاتين وحده بداية ونهاية التجربة اذ تبين وجود نزف ، تورم الكبيبات ، ارتشاح للخلايا الالتهابية ونخر. وظهرت الاضرار نفسها في المجموعتين العلاجية والوقائية المعاملة بعقار سيسبلاتين والسليمارين ، بينما لم يسبب سليمارين لوحده أي ضرر. نستنتج مما سبق ان عقار سيسبلاتين تسبب بحدوث اضرار نسجية في الكلى بعد 24 ساعة من الحقن، كما ان المعالجة بالسليمارين تسببت بضرر اكبر مما يشير الى وجود تداخل دوائي سلبي بين عقار سيسبلاتين وسليمارين أدى الى ظهور تلف في نفرونات الكلى.

كلمات مفتاحية: سيسبلاتين ، سليمارين ، تداخل دوائي ، تلف نسيج الكلى .

Introduction

Cisplatin (CP) also is known as cisplatinum or cis-diamminedichloroplatinum (II) is major and potent platinum-based antineoplastic agent that it used in the treatment of a wide range of cancers such as breast, neck cancer, ovarian and esophagus cancer It causes apoptosis by crosslink of purine bases in the DNA followed by DNA damage(1,2). The major limitation of this drug is the side effect such as nephrotoxicity (3). The kidney is highly sensitive to chemical poisoning, compared to other organs, partly due to its unequally high blood flow, and because of its complexity both functionally and anatomically, Kidney is a vital organ to achieve homeostasis and has important biological function in regulation of extracellular fluid volume, acid-base balance, electrolytes and excretion of metabolic wastes. Cisplatin is mainly removed from the body by kidneys and cisplatin is specifically accumulated due to basolateral organic cation system(4). Although most studies in cell lines and animal model lead to the hypotheses that cisplatin-induced nephrotoxicity is mediated by the interplay of oxidative stress, cell death, and inflammation (5). There was a need to find natural compounds that reduce the toxicity of cisplatin.

Silymarin, a flavonoid compound, is derivated from Silybum marianum seeds. It is a combination of silydianine, silychristine, isosilybinin and silibinin. Silymarin creates a protective role in liver because of its radical scavenger effects(6). Silymarin and one of its component silybin are available now as capsules and tablets under trade names such as legalon forte, and silipide(7). Silymarin has antioxidant properties and stabilizes cell membranes and also regulates the intracellular GSH (reduced glutathione) and chelates metal (copper and iron) ions(8,9).Silymarin is a safe herbal compound soon it used according to the physiological recommended doses(10) This study aimed to detect the biological vitality of silymarin against nephrotoxicity induced by Cisplatin.

Materials and methods

Experimental design

Thirty animals of white female rats were enrolled in this study weighed between 195 - 210 g and ages between

10-12 weeks. The animals were placed in plastic cages in the animal house at the Faculty of Veterinary Medicine / University of Tikrit and underwent the necessary laboratory conditions during the 21days. divided into six groups treated as the following: the first group control treated orally with physiological solution (0.9%), the second group injected single dose of Cisplatin beginning of the experiment intraperitoneal (5mg/kg)(11), the third group (therapeutic group) injected single dose Cisplatin (5mg/kg) with Silymarin (150mg/kg)(12) orally daily, the fourth group treated Silymarin 150mg/kg) orally daily, the fifth group injected single dose Cisplatin end of the experiment intraperitoneal (5mg/kg), the sixth group (preventive group) treated Silymarin (150mg/kg) orally daily.

Histological study

Kidney tissue were obtained to evaluate whether Cisplatin and silymarin elicit alteration in the kidney tissue. Tissue immediately fixed in 10% formalin for 24 hours then washed via water and dehydrated by gradient series concentration of alcohol, embedded in paraffin and slices of 5 µm thickness by microtome, sections stained with Hematoxylin and Eosin (HE) (13) Slides were observed using light microscopy for diagnosis the kidney histology and morphology.

Results

The results of microscopic examination of kidney tissue indicated that there was no change in the control group, and the glomeruli appear normal in the silymarin group, While the kidney tissue damage appeared in the group injected with cisplatin alone at the beginning and end of the experiment compared to control group. Kidney tissue damage was also shown in the preventive and therapeutic groups treated with cisplatin and silymarin, such as glomeruli swelling, inflammatory cell infiltration, hemorrhage, cell degeneration, and necrosis, compared to Silymarin group.

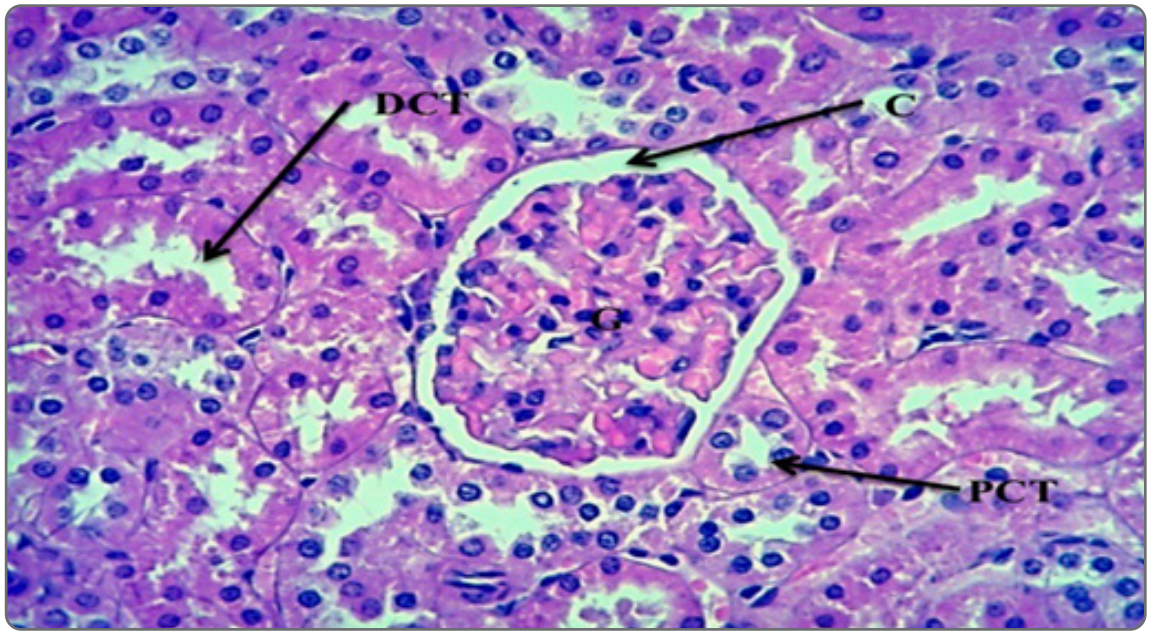

Figure1: Control group showing normal kidney tissue. glomeruli (G), distal convoluted tubules(DCT), capsule glomeruli (C), proximal convoluted tubules (PCT).H & E 400X.

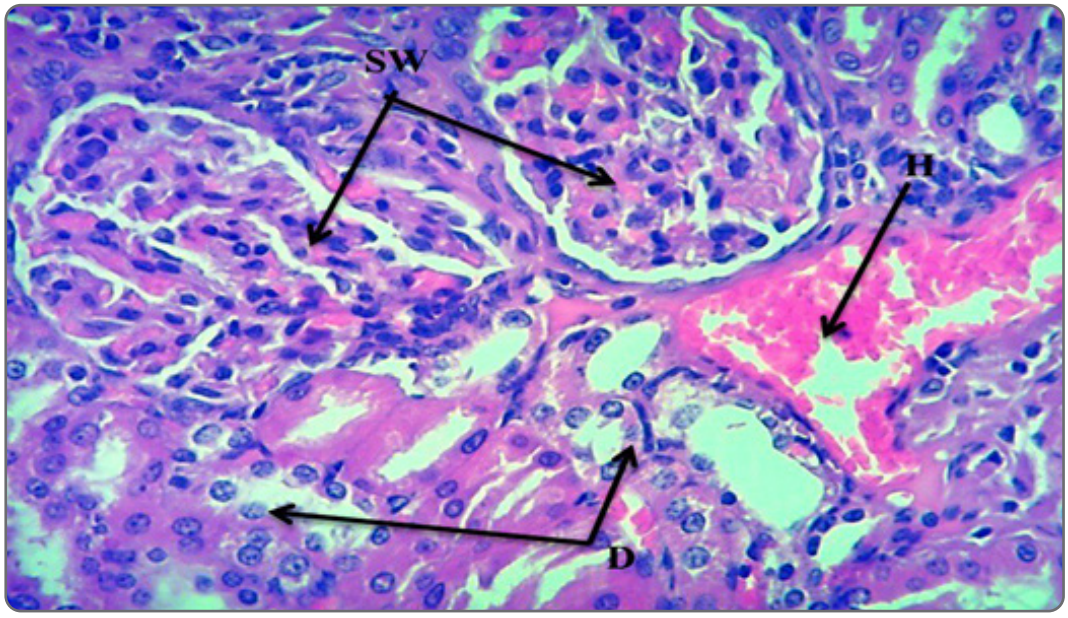

Figure2: Cisplatin group injected beginning experiment, Shows renal damage: swollen glomerulus (SW), Hemorrhage(H), Degeneration(D). H & E 400X.

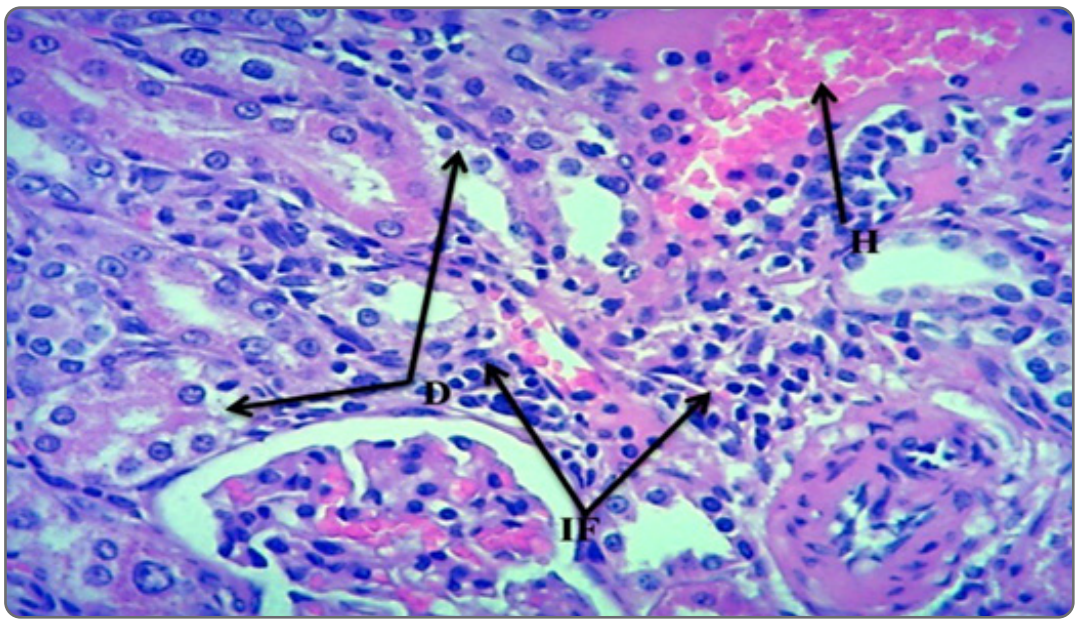

Figure3-A: therapeutic group treated Cisplatin beginning experiment with Silymarin. Shows renal damage: Hemorrhage(H), Degeneration(D), severe infiltration of inflammatory cells (IF). H & E 400X.

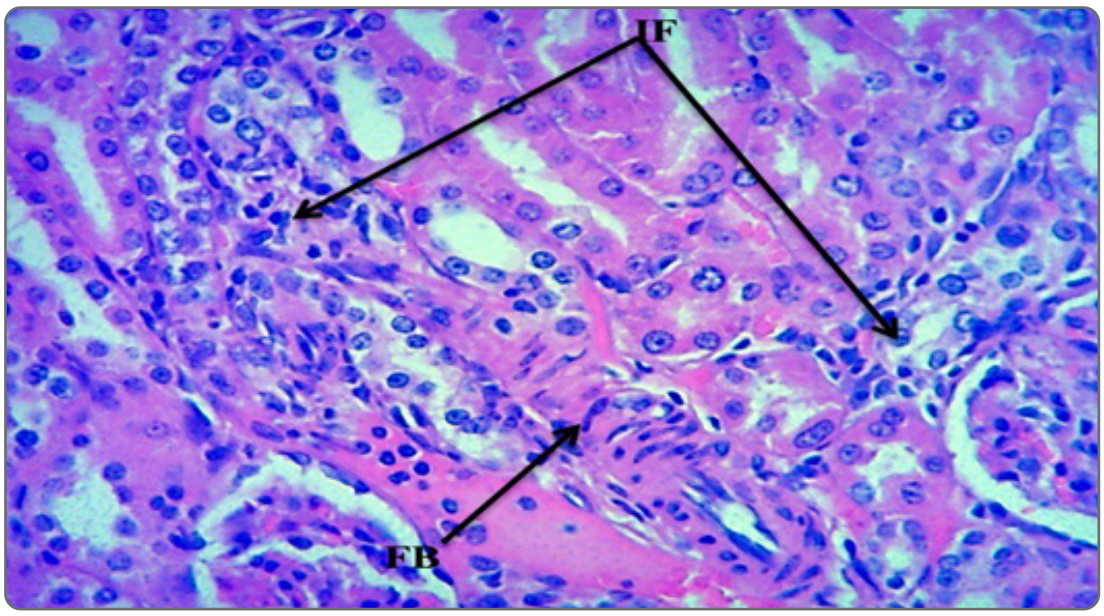

Figure3-B therapeutic group treated Cisplatin beginning experiment with Silymarin. Shows renal damage: infiltration of inflammatory cells (IF),Fibrosis(FB). H & E 400X.

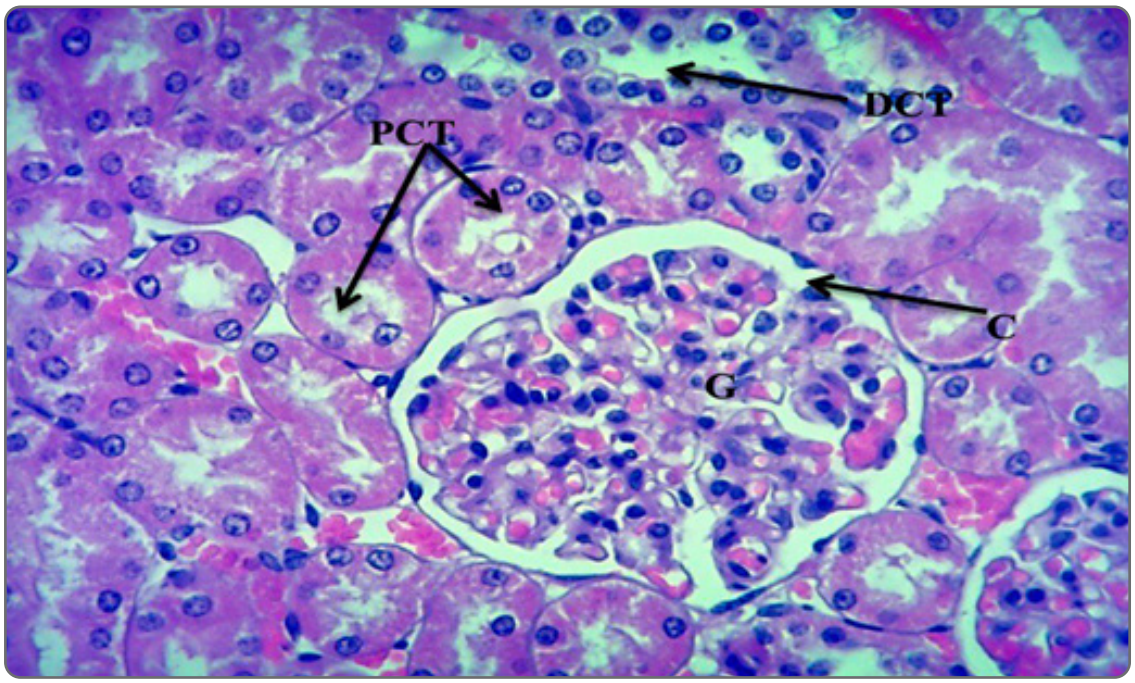

Figure 4: Silymarin group showing normal kidney tissue. glomeruli (G), distal convoluted tubules(DCT), capsule glomeruli (C), proximal convoluted tubules (PCT).H & E 400X.

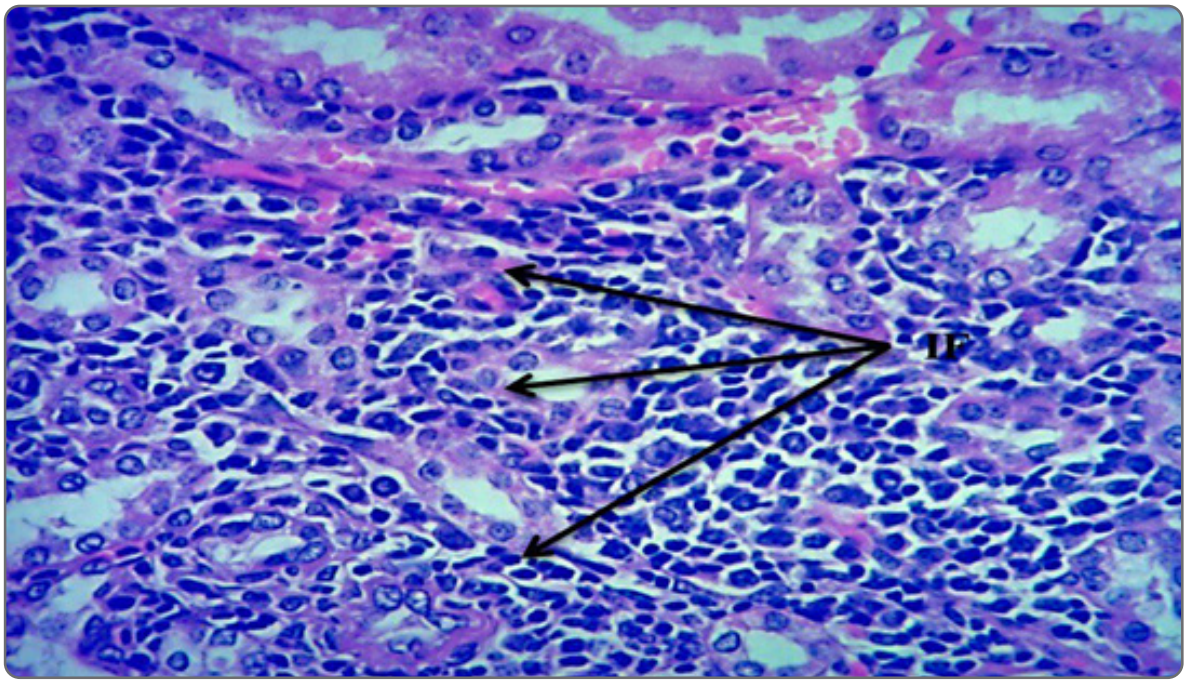

Figure 5: Cisplatin group injected end of the experiment Shows a severe infiltration of inflammatory cells (IF). H & E 400X.

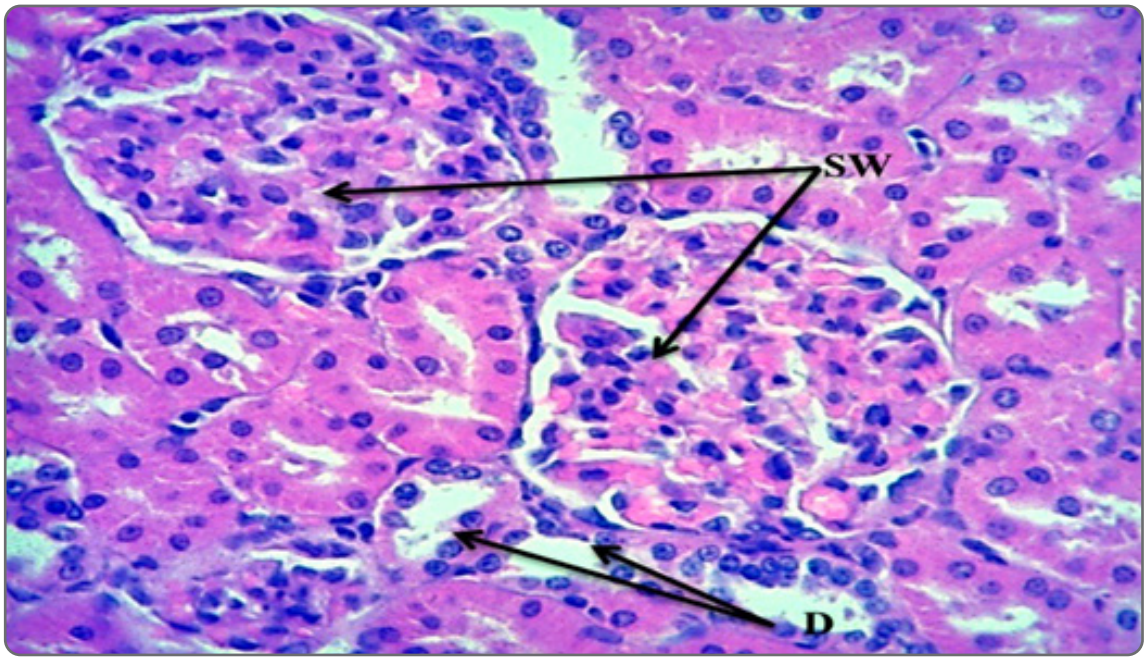

Figure6-A: Preventive group injected Cisplatin end of the experiment with Silymarin Shows renal damage: Degeneration(D), swollen glomerulus (SW). H & E 400X.

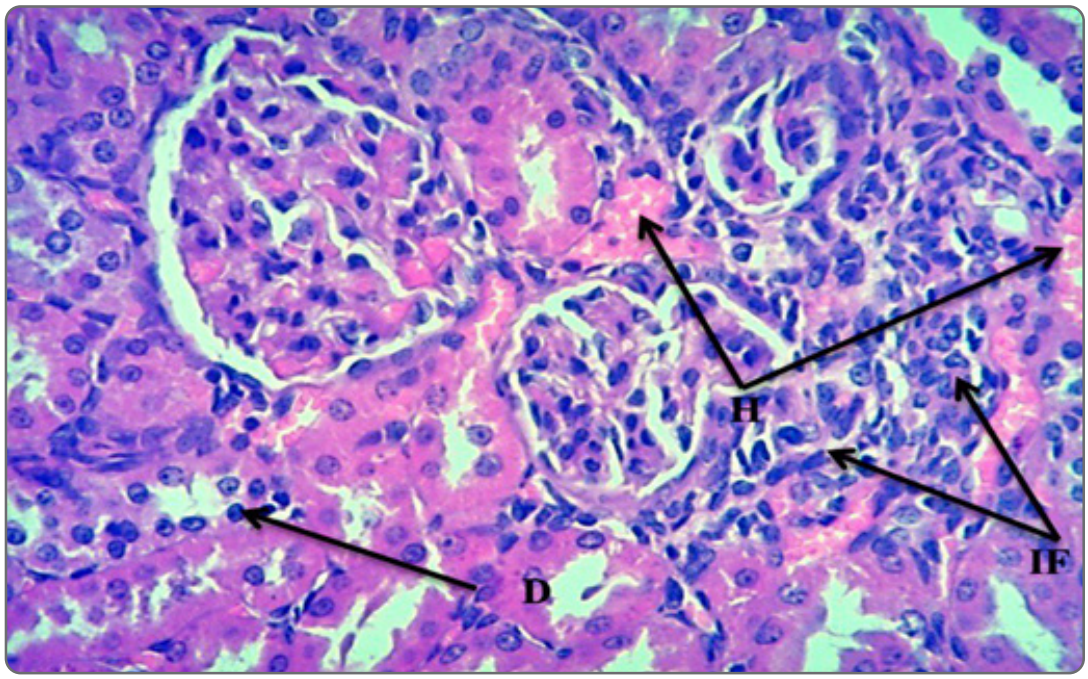

Figure6-B: Preventive group injected Cisplatin end of the experiment with Silymarin Shows renal damage: Degeneration(D),Hemorrhage(H), infiltration of inflammatory cells (IF) H & E 400X.

Discussion

Extensive use of cisplatin for the management of oncology is usually associated with long-term non-hematological toxicity such as nephrotoxicity (14). You mentioned several lines of evidence so far Reactive oxygen species play a detrimental role in It causes nephrotoxicity Which stimulate apoptosis signals such as caspase 3,9 and thus damage renal tubule cells (15). The results of the microscopic examination of the kidney tissue showed pathological changes in the tissues, as it was found that there was degeneration of the endothelium of the renal tubules, hemorrhage, infiltration of inflammatory cells, and swelling of the glomeruli (Figure2,5). The appearance of these damages is due to the toxicity of cisplatin to the organs responsible for detoxification and medication(16). Cisplatin induces inflammation and cellular damage by increasing the secretion of pro-inflammatory cytokines such as interleukins ,TNF-alpha that cause inflammatory cells to aggregate at the site of damage(17). Microscopic examination of kidney tissue in the therapeutic and preventive groups treated with silymarin and cisplatin showed significant damage to the kidney nephrons such as hemorrhage, necrosis, fibrosis and infiltration of inflammatory cells(Figure3,6), which indicates the existence of a negative drug interaction that led to damage to the kidney nephrons. What confirms this is that there was no change in the nephrons of the group treated with silymarin alone (Figure4). Several studies indicated(18) that the use of medicinal herbs with chemical drugs caused exacerbation of the disease due to drug interaction, mentioned(19) that the use of a drug temozolomide to treat tumors with some Chinese herbs led to toxicity in the liver.

Conclusion

We conclude from the current study that cisplatin caused damage to the kidney tissue, such as swelling of the glomerulus, necrosis, hemorrhage, and severe infiltration of inflammatory cells. Use of silymarin to reduce the toxicity of cisplatin also caused damage to the kidney tissue, which indicates the existence of a drug interaction between cisplatin and silymarin.

Recommendations

- Studying the effect of silymarin on the immune level, such as interleukins
- Conducting a study on liver tissue and its enzymes to find out the effect of using cisplatin and silymarin on liver tissue.

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