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Evaluation the Protective Effect of *Capparis spinosa* Fruits Hydroalcoholic Extract Against Nephrotoxicity Induced by Cisplatin in Rats

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Abstract

The present study was carried out to evaluate the kidney abnormality changes, and nephrotoxicity after using the cisplatine and investigate the protective effect of capparis spinosa fruit extract against these effects and evaluate the kidney function test urea, cratenine, total protein tests and histopathological changes of kidney . Twenty one (21) male rats were randomly divided into three groups (7 rats/ each). First group was received distilled water orally for 10 days and served as control group. Second group was received cisplatin only (10 mg/kg, i.p.) as a single dose at day 8 and served as a cisplatin treated group. Third group, was received *capparis spinosa* fruit extract (100 mg/kg B.W) for 10 days and 10 mg/kg cisplatin as a single dose at day 8 . The results showed that the animals that treated with cisplatine alone were severed from histopathological changes and significantly increasing in the level of (Urea, Cr and Total protein). While the third group (that treated with hydroalcoholic extract of capparis spiosa fruit ethanol 70%) showed decreasing in the histopathplogical changes in kidney , also significantly decrease in the level of (Urea, Cr and Total protein). In this study csplatine induced histopathplogical changes, alteration and increasing in the level of (Urea, Cr and Total protein), while the (hydroalcoholic extract of *capparis spiosa* fruit ethanol 70%) was have ability to maintain kidney function test .

Key words: Nephrotoxicity, Capparis spinosa, Cisplatin, Rats,

I. INTRODUCTION

Nephrotoxicity is described as renal impairment brought on by exposure to substances like medications or toxins found in the environment **(1).** One of the most well-known kidney issues is nephrotoxicity, which develops when the body is exposed to poisonous substances or dangerous treatments, as well as in people with diabetes or high blood pressure **(2).** Examples of medications associated risk factors include cisplatin, diuretics, non-steroidal anti-inflammatory drugs, cephalosporin, amphotericin B, iodide-containing contrast medium, vancomycin, and cyclosporine **(3).** Nephrotoxicity is distinguished by

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reduced urine concentration capacity, lysosomal enzyme uria, tubular proteinuria, moderate glucosuria, ammonium excretion decreased, lowered glomerular filtration rate, increased serum creatinine, and more (Blood Urea Nitrogen) **(4), (5).**

Cisplatin, also known as (SP-4-2)-diamminedichloridoplatinum, is one of the most common and successful drugs for the treatment of numerous solid malignancies (II) **(6).** The main side effect of cisplatine that contributes to increased morbidity and death is acute renal damage **(7).** Numerous factors, such as an increased oxidative state, an inflammatory response, and apoptosis, contribute to the nephrotoxicity caused by cisplatine **(8).** Another explanation for cisplatin-induced nephrotoxicity is DNA structure alteration. **(9) , (10) .**

The caper, Capparis spinosa L., belongs to the family Capparidaceae and is widely cultivated around the world **(11).** Capparis spinosa Extract shows a noteworthy protective effect contra oxidative stress and breaks the ROS signal loop in systemic sclerosis **(12).** due to it is content of phytochemical and nine compounds , including luteolin, catechin, coumarin, rutin, kaempferol, vanillic acid, epicatechin, resveratrol and gallic acid, the fruit of Capparis spinosa has been used for kidney disease treatment for centuries **(13).** The molybdate assay's determination of the total capacity of antioxidant in Capparis spinosa pollen ranged from 99.54 mg to 0.9 mg of AAE (Ascorbic Acid Equivalent) per g **(14).**

Caper fruits were distinguished by having a green exocarp throughout all phases of growth, a decline in protein content as the fruit grew, and high levels of flavonoids, total phenols, and flavanols **(15).** Previous studies using ethanol extracts of the Capparis spinosa fruit shown nephroprotective properties, and histological research revealed that the extracts may prevent tissue fibrosis **(16).** All biochemical indicators were brought back to normal with a regular intake of Capparis spinosa leaf or buds corrected kidney damage, and offered varied percent of organ protection because of the herb's antidiabetic and antihyperlipidemic properties **(17).** Hence, this study aimed to evaluating the protective effect of capparis spniosa fruits extract by reduce nephrotoxicity induced by cisplatin in rats.

II. MATERIALS AND METHODS

Plant Materials and Extraction

From an Iraqi local market, Capparis spinosa fruits were collected . The plant was recognized and authorized in the Ministry of Agriculture /State Board for Seed Certification and Testing in (Abu Graib- Baghdad) at the certification number (2859) in 11/11/2021 . Fruits were washed thoroughly in water, dried in shade at 25°C cut into small pieces and grind until it becomes a powder. 90 grams of the capers fruit powder was then poured into a one-liter flask using a Soxhlet extractor, and hydro alcoholic extract (ethanol 70 percent) was added to keep the powder level covered. The solution was filtered after 72 hours, and the ethanolic extract was then concentrated using a rotary evaporator apparatus at 50 ° C with a turn speed of 70 rpm to **(18).**

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Animals:

Twenty one (21) male rats that were 200–250 g in weight and were around three months old . Were employed to carry out the study's experiment. Rats were kept in plastic cages and kept in the College of Veterinary Medicine's special housing area for two weeks so they could become acclimated to it. Tap water and common rodent food (commercial feed pellets) were also freely available. Housing conditions were kept at 20-25 Co in air-conditioned rooms, where the air was regularly changed using ventilation vacuums and the light/dark cycle was 14/10. The cages' litter was replaced once a week.

Experimental Design:

Twenty one (21) male rats were divided equally into three groups as following.

1- First group was received distilled water orally for 10 days and served as negative control group.

2-Second group (positive control) was received cisplatin only (10 mg/kg, i.p.) as a single dosage at day 8 **(19)** and worked as a cisplatin treated group.

3-Third group, was received *capparis spinosa* fruit extract (100 mg/kg B.W) for 10 days **(20)** and 10 mg/kg cisplatin as a single dosage at day 8 .

In every group 7 of animals were sacrificed in day 11 and the sample of blood was collected directly from the heart while the kidney served for histopathology.

The following parameters have been studied

1. Blood Urea Nitrogen (BUN)

Urea, sometimes referred to as BUN, is a nitrogen-containing molecule that is created in the liver as a byproduct of protein metabolism in the urea cycle. Around 85% of the urea is excreted via the kidneys, with the remaining urea being passed through the GI tract. Serum urea levels increase when renal clearance decreases (as in acute and chronic renal failure/impairment). A spike in urea can also be caused by other conditions such upper GI bleeding, dehydration, catabolic states, and high-protein meals that are unrelated to renal diseases. Urea generation may be decreased in hunger, low-protein diets, and serious liver diseases. While serum creatinine is a more accurate indicator of renal function than urea, which is raised sooner in renal illness, **(21)**.

2. Creatinine

The endogenous marker known as creatinine is the one that is most frequently used to evaluate glomerular function. A GFR indicator is produced using the computed creatinine clearance. To do this, urine must be collected continuously over a 24-hour

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period, preferably within a carefully timed window of 5 to 8 hours as 24-hour samples are notoriously unreliable. After that, the equation is used to determine creatinine clearance:

C = (U x V) / P C

C = clearance, U = urinary concentration, V = urinary flow rate (volume/time i.e. ml/min), and P = plasma concentration

3. Total protein

The test looks for protein in either urine or the serum, as the liquid portion of the blood is known to medical personnel. Using a serum total protein test, you may determine how much albumin and globulin are in your blood's serum **(22).** Half of the total protein in blood plasma is made up of albumin protein. reliable source to stop water from seeping out of the blood vessels, it controls the plasma's oncotic pressure **(23).**

4. Histopathology

Rat kidneys from all groups were utilized as samples for a histopathological analysis at 11 days of the experiment. After the animal was given a chloroform anesthesia (by inhalation), the kidneys were removed and placed in plastic containers with formalin solution (10%) and tissue produced in accordance with **(24).**

III. RESULTS AND DISCUSSION

The Effects of Cisplatine and Hydro Alcoholic Extract of *Capparis Spinosa* Fruit on Urea, Creatinine and Total protein.

Rats treat with cisplatine (10 mg/kg b.w orally) alone showed greatly increasing (P≤0.05) in the level of (T. bilirubin, Urea, Cr and Total protein) as compared with negative control group, were not significantly changed as in (table .1). These results were in agreement with those obtained by (Zhu et al ., 2017). In addition, According to earlier investigations, cisplatine increased levels of urea and creatinine (Elkomy et al., 2020). Reduced glomerular filtration rate is the cause of increased creatinine and urea levels (Salman et al., 2019). According to this theory, the toxicity effect of the cisplatine on the kidneys is occur due to free radicals that form in these organs' cells and cause lipid peroxidation, which in turn causes oxidative stress and cell destruction. Cisplatine intoxication lowers protein synthesis after liver injury and changes the kidney's functional integrity, causing proteinuria and, eventually, lower levels of circulating protein. (Sen *et al* ., 2013).

In other hand the rats that treated with *capparis spinosa* fruit ethanol extract (100 mg/kg b.w orally) showed significantly decreasing (P≤0.05) in the level of (Urea, Cr and Total protein) as compared with positive control group and became nearly to negative control group. These result agreed with those obtained by **(25).**

Table (1): The Effects of Cisplatine, and Ethanolic Extract of Capparis Spinosa Fruits on Urea, Cr and Total protein

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Group	Mean ± SE (mg/dl)		
	Urea	Creatinine	Total protein
Negative control	9.84 ±1.04 B	0.089 ±0.04 B	1.781 ±0.29 B
Cisplatine 10 mg/k ip	21.14 ±1.92 A	0.640 ±0.0 A	4.124 ±0.46 A
Capparis spinosa fruit extract 100 mg /k orally	7.21 ±0.27 B	0.015 ±0.01 C	1.430 ±0.12 B
LSD value	4.42	0.15	1.7
Means having the different letters in same column differed significantly. (P≤0.05).			

The Effects of Cisplatine, and Hydro Alcoholic Extract of *Capparis Spinosa* Fruit on Histopathology of kidney Tissue.

Histopathological sections of kidney in the negative control group showed normal kidney tissue consists of nephrous (glomeruli (G) and tubules (T) with interstitium .(figure 1)

While in the second group (cisplatine only), kidney findings renal tubules showed marked tubular cystic dilation with flat epithelial lining accompanied with glomerular tuft atrophy as adjacent glomerular (figure2) , while other findings revealed moderate swelling of epithelial lining of major tubules with little changes of adjacent glomeruli (figure 3), these results agreed with those results obtained by **(26).** The primary side effect of cisplatine that poses a risk of death and is dose-limiting is nephrotoxicity **(27).** Maladaptive tubular cells release a number of substances in response to injury that draw inflammatory cells into the tubulointerstitial region. The invading cells release cytokines that further induce tubular cells to adopt a mesenchymal phenotype and change the tubulointerstitial milieu where the myofibroblasts are activated **(28).**

Histopathological sections of the kidney in third group showed congestion and thickened wall of renal blood vessels accompanied with mild intestinal MNCS infiltration and few fibroblast proliferation (Figure 4), these results agreed with those obtained by **(29).** Capparis spinosa extrect's intriguing antioxidant activity, nephroprotective, and its phenolic components could be substantially responsible for its nephroprotective qualities **(30).** This scavenging ability of phenolic compounds is

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probably due to their antiradical scavenging action **(31).**In other hand the kidney findings showed the majority of blood vessels in renal tissue were congestion with thickened wall accompanied with mild tubular epithelial swelling as well as interstitial infiltration of MNCS and mix with few young fibroblast proliferation and the result also showed diffuse hemorrhage with minimal tubular cystic dilation accompanied with hypertrophied muscular media of some dilated renal vessel (Figure 5), In fact, when the O __H bond is homolyzed, When phenolics release a proton, they can change into the incredibly stable phenoxy radical. Additionally, it has been suggested that the C2 C3 double link, which has been recognized as the reason for electron delocalization from ring B and enhances the antioxidant potential, is formed with a 4-keto configuration, is responsible for the radical-scavenging ability of flavonoids **(32).**

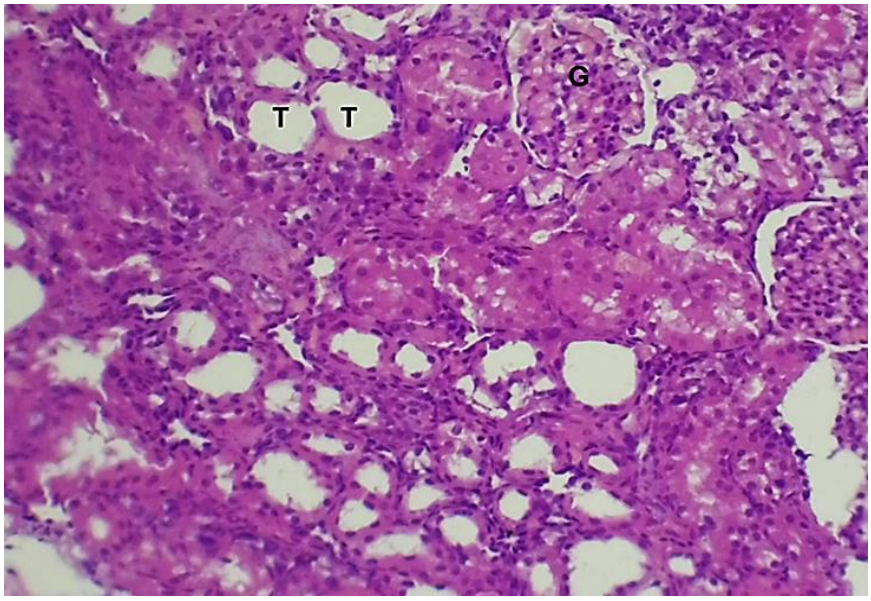

Figure 1: Histological section in the kidney of rats (negative control group) with normal limit structure (H&E stain, X10).

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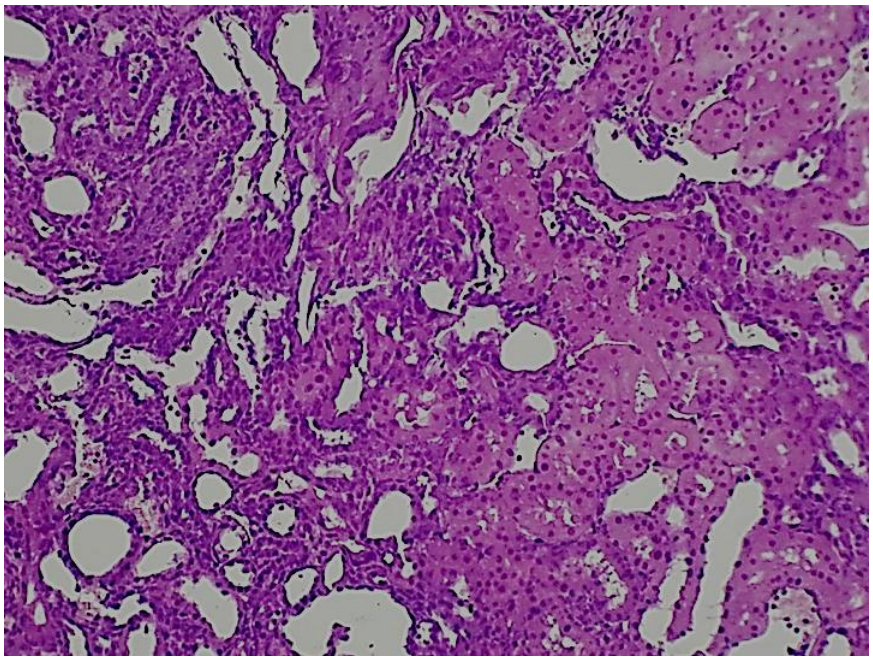

Figure 2: Histological section in the kidney of rats (positive control group), show marked tubular cystic dilation with slightly MNCS infiltration (H&E stain, X10).

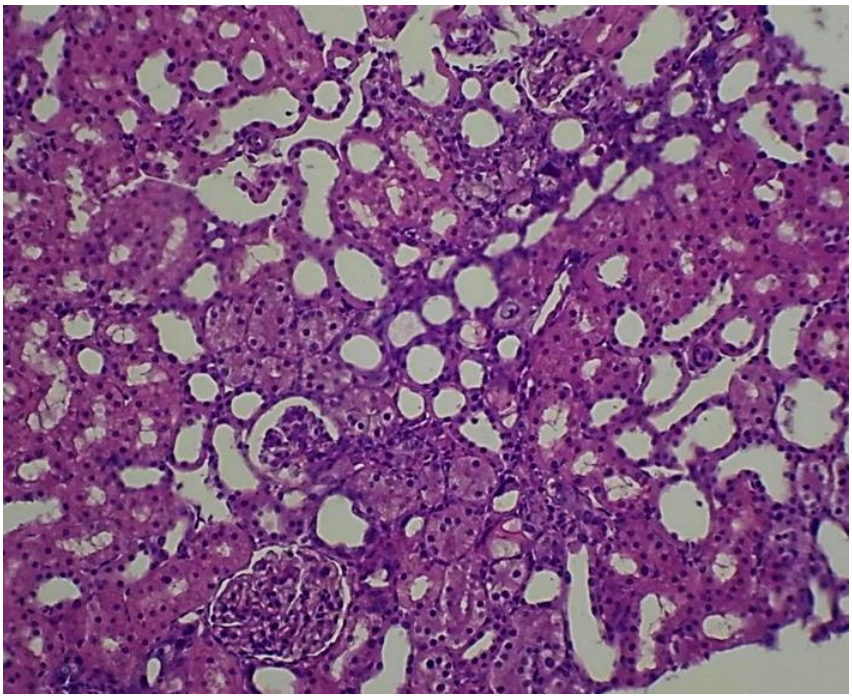

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Figure 3: Histological section in the kidney of rats (positive control) show moderate swelling of epithelial lining of some tubules with cystic dilation and atrophic tuft findings of few glomeruli (H&E stain, X10).

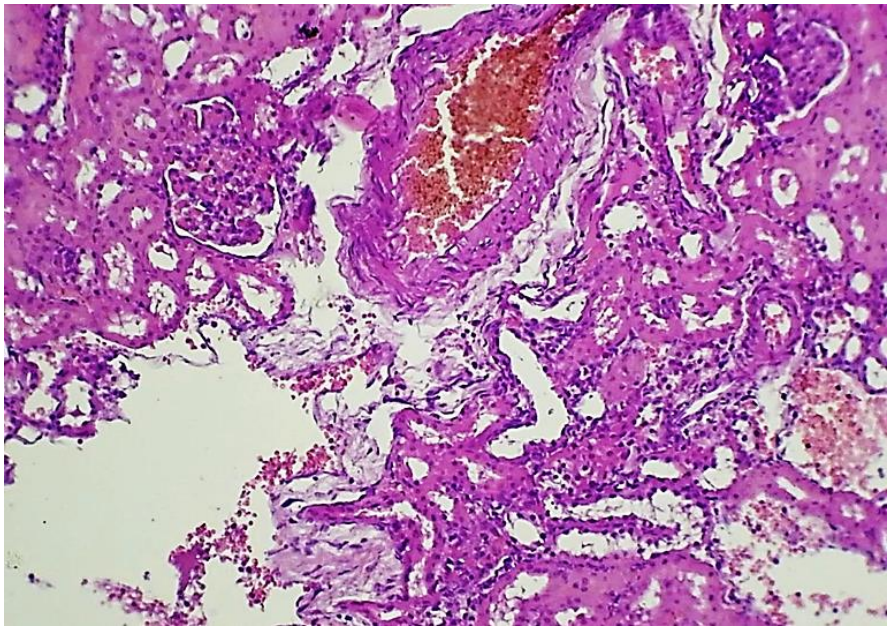

Figure 4: Histological section in the kidney of rats (ethanol extract of capparis spinosa fruit) obvious renal blood vessel congestion with mild MNCS infiltration with few fibroblast proliferation (H&E stain, X10).

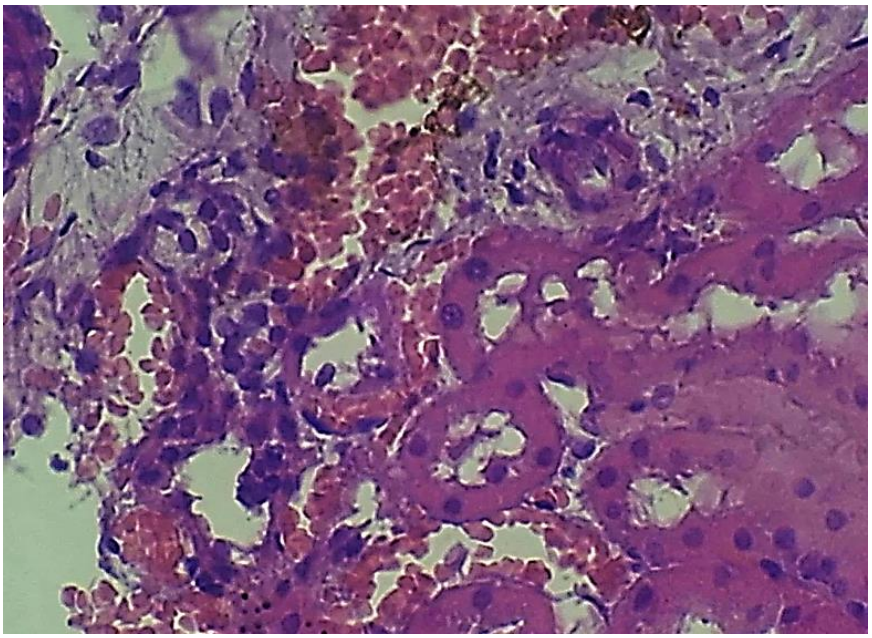

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Figure 5: Histological section in the kidney of rats (ethanol extract of capparis spinosa fruit) show renal blood vessel congestion with mild MNCS infiltration (H&E stain, X40).

IV. REFERENCES

1. **Varghese, H. S., & Raj, G. G. (2021).** Protective role of Benincasa hispida (Thunb.) Cogn. fruit extract against gentamicin induced nephrotoxicity in rats. Indian Journal of Experimental Biology (IJEB), 59(9), 633-639.
2. **Kiliś-Pstrusińska, K., & Wiela-Hojeńska, A. (2021).** Nephrotoxicity of Herbal Products in Europe—A Review of an Underestimated Problem. International Journal of Molecular Sciences, 22(8), 4132.
3. **Wargo, K. A., & Edwards, J. D. (2014).** Aminoglycoside-induced nephrotoxicity. Journal of pharmacy practice, 27(6), 573-577.
4. **Swati, P. and Rajashekhar, I. (2015).** Role of plants as nephroprotective agents. A Review. International Journal of Therapeutic Applications, 26 : 6 – 14.
5. **Muhammad Assumaidaee, A. A., Ali, N. M., & Fadhil, A. A. (2022).** Effect of Vitamin E as α-Tocopherol Acetate on Mercuric Chloride-Induced Chronic Oxidoreductive Stress and Nephrotoxicity in Rats:The Iraqi Journal of Veterinary Medicine, 43(2), 98–108
6. **Ghosh, S. (2019). Cisplatin: The first metal based anticancer drug. Bioorganic chemistry, 88, 102925.**
7. **Abd El-Kader, M., & Taha, R. I. (2020).** Comparative nephroprotective effects of curcumin and etoricoxib against cisplatin-induced acute kidney injury in rats.
8. **Li, W., Yan, M. H., Liu, Y., Liu, Z., Wang, Z., Chen, C., ... & Sun, Y. S. (2016).** Ginsenoside Rg5 ameliorates cisplatin-induced nephrotoxicity in mice through inhibition of inflammation, oxidative stress, and apoptosis. Nutrients, 8(9), 566.
9. **Geyikoglu, F., Emir, M., Colak, S., Koc, K., Turkez, H., Bakir, M., ... & Ozek, N. S. (2017)**. Effect of oleuropein against chemotherapy drug-induced histological changes, oxidative stress, and DNA damages in rat kidney injury. Journal of food and drug analysis, 25(2), 447-459.
10. **Salman, A. D. (2014).** The Protective role of Pomegranate seed oil (Pometon) on kidney (functional and structural) damage induced by Methionine overload in adult female Rabbits. *The Iraqi Journal of Veterinary Medicine*, *38*(2), 66–73
11. **Rakhimova, T., Vaisova, G. B., Rakhimova, N. K., & Matkarimova, A. (2021).** Phytocoenotic Distribution of Capparis Spinosa L.(Capparaceae) Under Different Ecological Conditions in Uzbekistan. Annals of the Romanian Society for Cell Biology, 25(6), 7882-7895.

12. **Mirzakhani, N., Farshid, A. A., Tamaddonfard, E., Tehrani, A., & Imani, M. (2020).** Comparison of the effects of hydroalcoholic extract of Capparis spinosa fruit, quercetin and vitamin E on monosodium glutamate-induced toxicity in rats. Veterinary research forum : an international quarterly journal, 11(2), 127–134.
13. **Shahrajabian, M. H., Sun, W., & Cheng, Q. (2021).** Plant of the Millennium, Caper (Capparis spinosa L.), chemical composition and medicinal uses. Bulletin of the National Research Centre, 45(1), 1-9.
14. **Bakour, M., Campos, M. D. G., Imtara, H., & Lyoussi, B. (2020).** Antioxidant content and identification of phenolic/flavonoid compounds in the pollen of fourteen plants using HPLC-DAD. Journal of Apicultural Research, 59(1), 35-41.
15. **Grimalt, M., Hernández, F., Legua, P., Almansa, M. S., & Amorós, A. (2018).** Physicochemical composition and antioxidant activity of three Spanish caper (Capparis spinosa L.) fruit cultivars in three stages of development. Scientia horticulturae, 240, 509-515.
16. **Zhu, P., Wang, Y., & Zhang, X. (2022).** Preparation and characterization of electrospun nanofibre membranes incorporated with an ethanol extract of Capparis spinosa L. as a potential packaging material. Food Packaging and Shelf Life, 32, 100851.
17. **Mollica, A., Zengin, G., Locatelli, M., Stefanucci, A., Mocan, A., Macedonio, G., ... & Novellino, E. (2017).** Anti-diabetic and anti-hyperlipidemic properties of Capparis spinosa L.: in vivo and in vitro evaluation of its nutraceutical potential. Journal of functional foods, 35, 32-42.
18. **Al-Birawee, A. R., & Nasser, A. K. (2019).** Gel extraction from caper fruits (Capparies spinosa L.) and assess its effectiveness as antioxidants. Basrah Journal of Agricultural Sciences, 32(2), 74-84.
19. **Gaona-Gaona, L., Molina-Jijón, E., Tapia, E., Zazueta, C., Hernández-Pando, R., Calderón-Oliver, M., ... & Pedraza-Chaverri, J. (2011).** Protective effect of sulforaphane pretreatment against cisplatin-induced liver and mitochondrial oxidant damage in rats. Toxicology, 286(1-3), 20-27.
20. **Mirzakhani, N., Farshid, A. A., Tamaddonfard, E., Tehrani, A., & Imani, M. (2020).** Comparison of the effects of hydroalcoholic extract of Capparis spinosa fruit, quercetin and vitamin E on monosodium glutamate-induced toxicity in rats. In Veterinary Research Forum (Vol. 11, No. 2, p. 127). Faculty of Veterinary Medicine, Urmia University, Urmia, Iran
21. **Fehrman-Ekholm, I., & Skeppholm, L. (2004).** Renal function in the elderly (> 70 years old) measured by means of iohexol clearance, serum creatinine, serum urea and estimated clearance. *Scandinavian journal of urology and nephrology*, *38*(1), 73-77.
22. **Lockyer, W. J. (2014).** *Essentials of ABO-Rh Grouping and Compatibility Testing: Theoretical Aspects and Practical Application*. Elsevier.

ISSN Onlin:2708-9347, ISSN Print: 2708-9339 Volume 11, Issue 2 (2022) PP 25-35
https://jam.utq.edu.iq/index.php/main *https://doi.org/10.54174/UTJagr.Vo11.N2/03*

23. **Gianazza, E., Miller, I., Palazzolo, L., Parravicini, C., & Eberini, I. (2016).** With or without you—Proteomics with or without major plasma/serum proteins. *Journal of proteomics*, *140*, 62-80.
24. **Luna, A.G. (1968).** Manual of histological staining methods of the armed force institute of pathology. (3rd Ed.). london: Mc Graw Hill Book Co.pp.24-25
25. **Assadi, S., Shafiee, S. M., Erfani, M., & Akmali, M. (2021).** Antioxidative and antidiabetic effects of Capparis spinosa fruit extract on high-fat diet and low-dose streptozotocin-induced type 2 diabetic rats. Biomedicine & Pharmacotherapy, 138, 111391.
26. **Abd El-Kader, M., & Taha, R. I. (2020).** Comparative nephroprotective effects of curcumin and etoricoxib against cisplatin-induced acute kidney injury in rats. Acta Histochemica, 122(4), 151534.
27. **Kim, Y. J., Lee, M. Y., Son, H. Y., Park, B. K., Ryu, S. Y., & Jung, J. Y. (2014).** Red ginseng ameliorates acute cisplatin-induced nephropathy. Planta medica, 80(08/09), 645-654.
28. **Qi, R., & Yang, C. (2018).** Renal tubular epithelial cells: the neglected mediator of tubulointerstitial fibrosis after injury. Cell death & disease, 9(11), 1-11.
29. **Tlili, N., Feriani, A., Saadoui, E., Nasri, N., & Khaldi, A. (2017**). Capparis spinosa leaves extract: source of bioantioxidants with nephroprotective and hepatoprotective effects. Biomedicine & Pharmacotherapy, 87, 171-179.
30. **Pires, T. C., Barros, L., Santos-Buelga, C., & Ferreira, I. C. (2019).** Edible flowers: Emerging components in the diet. Trends in Food Science & Technology, 93, 244-258.
31. **Gismondi, A., Di Marco, G., Canuti, L., & Canini, A. (2017).** Antiradical activity of phenolic metabolites extracted from grapes of white and red Vitis vinifera L. cultivars. VITIS-Journal of Grapevine Research, 56(1), 19-26.
32. **Pan, P. H., Lin, S. Y., Wang, Y. Y., Chen, W. Y., Chuang, Y. H., Wu, C. C., & Chen, C. J. (2014).** Protective effects of rutin on liver injury induced by biliary obstruction in rats. Free Radical Biology and Medicine, 73, 106-116.