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Time-Dependent Protective Effects of Ginger on Paracetamol-Induced Nephrotoxicity in Rabbits

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التأثيرات الوقائية للزنجبيل المعتمدة على الزمن ضد السمية الكلوية المستحثة بالباراسيتامول في الأرانب

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Abstract:
This study was conducted to identify the physiological and histological changes in the rabbit kidney resulting from administering a single dose of paracetamol (750mg/kg) and to determine the protective role of ginger according to the time period. This study used 48 rabbits divided into 8 groups: negative control group, positive control group (paracetamol 750mg) and the remaining groups were given an aqueous extract of ginger at different concentrations (100,200,400) mg/kg and different periods (15days, 30days). The results showed that paracetamol caused kidney tissue damage, increase urea, creatinine and uric acid levels. Pre-dose of aqueous ginger extract (100,200,400) mg for 15 days improved the physiological and histological changes. While prior dosing with ginger (100,200,400) mg/kg for 30days caused a severe decrease in uric acid levels compared with the positive control group.

Keywords: Ginger, Paracetamol, Kidney, rabbit.

الملخص
اجريت هذه الدراسة لتحديد التغيرات الفسيولوجية والنسيجية في كلى الارانب الناتجة عن اعطاء جرعة واحدة من الباراسيتامول(750ملغ/كغ)، ولتحديد الدور الوقائي للزنجبيل تبعا للفترة الزمنية. حيث استخدم في هذه الدراسة 48 أرنباً قسمت إلى 8 مجموعات: المجموعة الضابطة السلبية، والمجموعة الضابطة الايجابية (750ملغ من الباراسيتامول) بينما اعطيت المجموعات المتبقية مستخلص الزنجبيل المائي بتراكيز مختلفة (100,200,400) ملغ/كغ ولفترات زمنية مختلفة (15يوم, 30يوم). واظهرت النتائج أن الباراسيتامول تسبب في حدوث ضرر بأنسجة الكلى، وزيادة مستويات اليوريا والكرياتينين وحمض اليوريك. وقد حسن التجريع المسبق بالمستخلص المائي للزنجبيل (100,200,400) ملغ/كغ لمدة 15 يوم من التغيرات الفسيولوجية والنسيجية، في حين أن التجريع المسبق لمستخلص الزنجبيل المائي

(100,200,400) ملغ/كغ لمدة 30 يوم تسبب في حدوث انخفاض حاد في مستوى حمض اليوريك مقارنة بالمجموعة الضابطة السلبية والايجابية.

الكلمات المفتاحية: الزنجبيل، الباراسيتامول، الكلى، الارانب.

1. Introduction

The kidney is one of the most important organs that body needs in a basic way. its maintain the body's balance and regulate the environment outside the cell, as its works to remove toxins and excrete toxic metabolites and drugs. (Ferguson *et al.*, 2008) the kidney is made up of a large number of cells organized into nephrons, and any stimuli that lead to cell loss can cause kidney damage and failure. (Barnett & Cummings, 2018) There are many substances and compounds that cause kidney toxicity, including antibiotics, heavy metals, anti-cancer drugs, pesticides of all kinds, long-term drug use, and high doses of painkillers.

Drugs often cause inflammation in the glomeruli, proximal tubules, and surrounding cellular area of the kidney. The proximal convoluted tubules are highly susceptible to toxicity due to the concentration and reabsorption processes in the glomerulus. (Perazella, 2005) Cytotoxicity is caused by increased oxidative stress through the generation of free radicals and damage to mitochondria in the tubules. (Markowitz & Perazella, 2005) And at high doses of paracetamol it causes a great depletion of glutathione (GSH) from the kidney cells, which results in the generation of free radicals, so it causes kidney toxicity. (هاجر, 2011) At the van's attention, he turned to the use of medicinal plants in the prevention and treatment of diseases as an alternative to chemical drugs. Among these plants is ginger *Zingiber officinale*, belonging to the Zingiberaceae family, where it has been used in Chinese and Indian medicine for more than 25 centuries. (Castleman, 2001) and the widespread use of ginger in medicine is attributed to the presence of some antioxidant phenolic compounds. (Schmid *et al.*, 1994) Therefore, the aim of this study was the effects of different doses of aqueous ginger extract (100,200,400) mg administered for 15 and 30 days on paracetamol-induced nephrotoxicity.

2. Materials and Methods

2.1 Experimental animals:

This study used 48 male local rabbits, weighing between 800 and 2000 grams approximately, which were obtained from the markets and were housed in cages and provided with all laboratory conditions.

2.2 Plant sample collection:

Ginger roots were obtained from local markets, where they were cleaned, dried and ground with an electric mixer to obtain a fine powder.

2.3 Preparation of the aqueous extract of ginger:

The aqueous extract of ginger was prepared by following the (Shalaby & Saifan, 2014) method, where one liter of distilled water was added to 200 grams of plant powder and left to boil for 10 minutes, then the solution was left to cool, and then the solution was filtered using a filter paper (Wattman No 1). The extract concentration of 200mg/ml, half of which is (100mg) and double that amount (400mg) and the extract was kept in the refrigerator until it was used to dose rabbits through the gastric tube.

2.4 Chemicals:

Paracetamol tablets 500 mg were used from the company BRISTOL LABORATORIES LTD Which were purchased from local pharmacies and then one and a half tablets were dissolved in 5 ml of distilled water.

2.5 Experimental design:

The Experimental rabbits, which numbered 48, were randomly divided into 8 groups, which were treated as follows:

Group1: negative control group was treated with a normal saline for 30 days.
Group2: positive control group was given a single dose of Paracetamol (750 mg /kg). based on previous searches that used paracetamol at the same dose and duration (هاجر, 2011; Mejbel *et al.*, 2024)
Group 3,4,5: Daily dose of ginger extract dose 100,200,400 mg / kg respectively, for 15 days and after 30 minutes of the last dose, a dose of paracetamol 750 mg / kg.
Group 6,7,8: Daily dose of ginger extract dose 100,200,400 mg /kg respectively, for 30 days and after 30 minutes of the last dose, a dose of paracetamol 750 mg /kg.

2.6 Biochemical analyses:

Serum uric acid was measured according to (Thomas, 1998) and urea was measured using the enzyme-linked UV assay (Thomas, 1998), serum creatinine was measured according to (Dominiczak, 1999).

2.7 Histopathological study:

Samples of kidney tissue were embedded in paraffin blocks, dehydrated in increasing alcohol grades, and fixed in a 10% buffered formalin solution. After cutting 4-5 µm slices from the prepared blocks and staining them with haematoxylin and eosin (H&E). the pathologist used a ligth microscope (Optika microscope) made in italy to see the preparations. (الانصاري & سلامة, 1999)

2.8 Statistical analysis:

The results were analyzed statistically using the (SPSS-25) statistical program. And were expressed as mean ± the (SEM) standard error. One-way analysis of variance (ANOVA) was used to examine the data for comparisons between various variables. Comparisons between groups were performed using the Dunnett test, and the predictive value of (P-value) was used, which indicates the statistical significance if it is less than 5%.

3. Results:

The results indicated in (Table 1) that when local male rabbits were exposed to a single dose of paracetamol (750 mg/kg), it caused an increase in the levels of urea, creatinine and uric acid in the blood by 60.97%, 75.75%, 27% respectively, compared to the negative group. Meanwhile, the groups pre-dose with an aqueous extract of ginger (200,400) for 15days showed a significant improvement in urea, creatinine and uric acid levels by (55.55%, 39.65%, 73.4%) (50%, 39.65%, 73.4%) respectively, compared to the positive control group. On the other hand, the group pre-dosed with ginger extract (100mg) for 15 days showed no significant difference in urea and creatinine levels, while uric acid levels decreased by 72.34% compared to the positive control group. Similarly, urea levels improved in the group's pre-dose with ginger (100,200,400) mg for 30 days by 54.54%, 56.56%, 33.33% respectively, and creatinine levels by 43.96%, 48.27%, 39.65% respectively, compared to the positive control group. While prior dosing with ginger (100,200,400) mg/kg for 30days caused a severe decrease in uric acid levels by 97.44%, 98.7%, 98.29% respectively, compared to the positive control group (Figure 3).

Table (1) changes in Urea, Creatinine and Uric acid are shown in the experimental groups

Groups	Urea	Creatinine	Uric acid
Negative control	30.75±4.26	0.66±0.14	3.7±0.25
Positive control (APAP)	49.5±3.5*	1.16±0.16*	4.7±0.1*
100mg ginger +APAP(15D)	41.5±1.5	0.75±0.05	1.3±0.02*#
200mg ginger +APAP(15D)	22±1#	0.7±0.05#	1.25±0.11*#

400mg ginger +APAP(15D)	24.6±2.3#	0.7±0.05#	1.25±0.02*#
100mg ginger +APAP(30D)	22.5±4.5#	0.65±0.06#	0.12±0.1*#
200mg ginger +APAP(30D)	21.5±0.5#	0.6±0.08#	0.06±0.14*#
400mg ginger +APAP(30D)	33±2#	0.7±0.05#	0.08±0.3*#

Samples were taken based on the mean ± standard error (SE) (*) significant change (p-value <0.05) compared to the negative control, (#) significant change (p-value <0.05) compared to the Positive control (APAP)

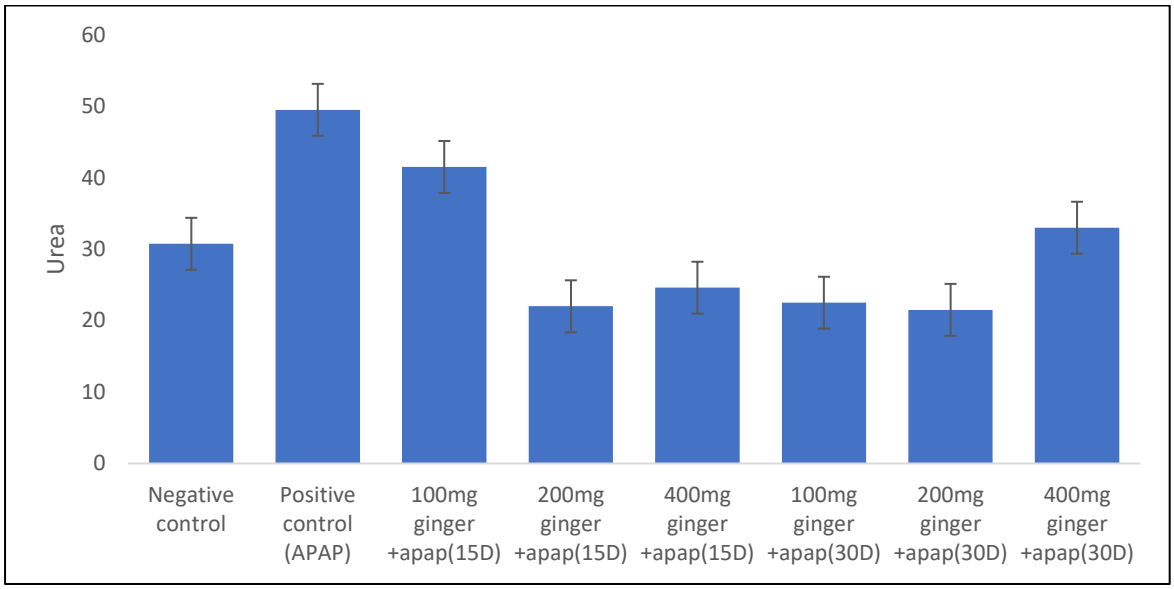

Figure (1) shows the effect of paracetamol and aqueous extract of ginger on the average concentration of the Urea (Ur) in the blood serum of rabbits.

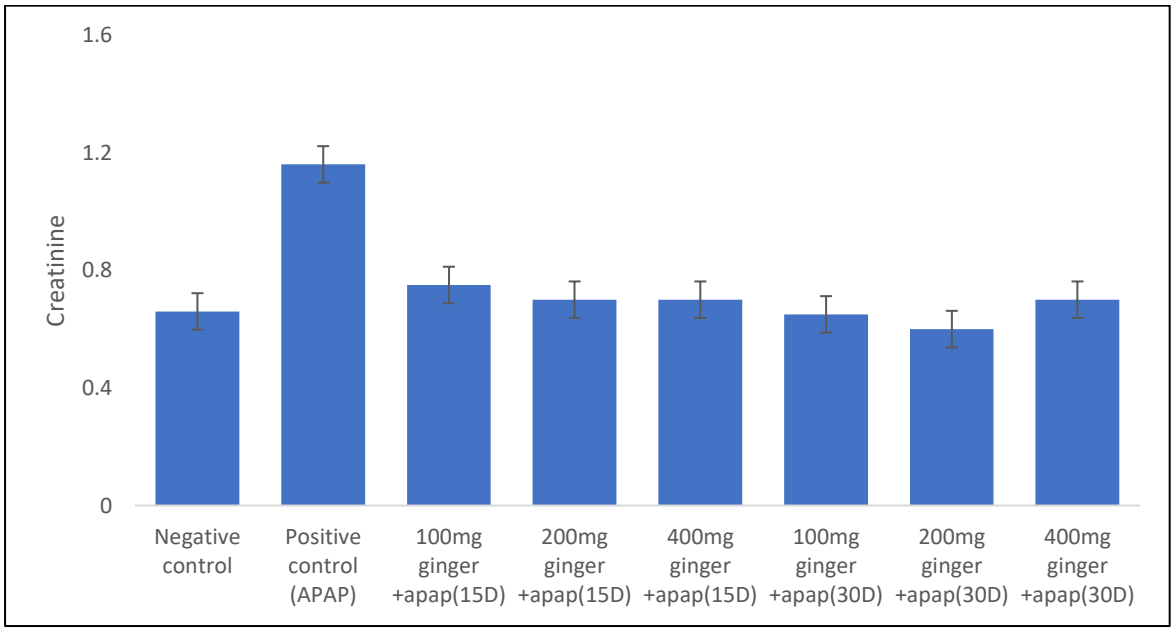

Figure (2) shows the effect of paracetamol and aqueous extract of ginger on the average concentration of the creatinine (Cr) in the blood serum of rabbits.

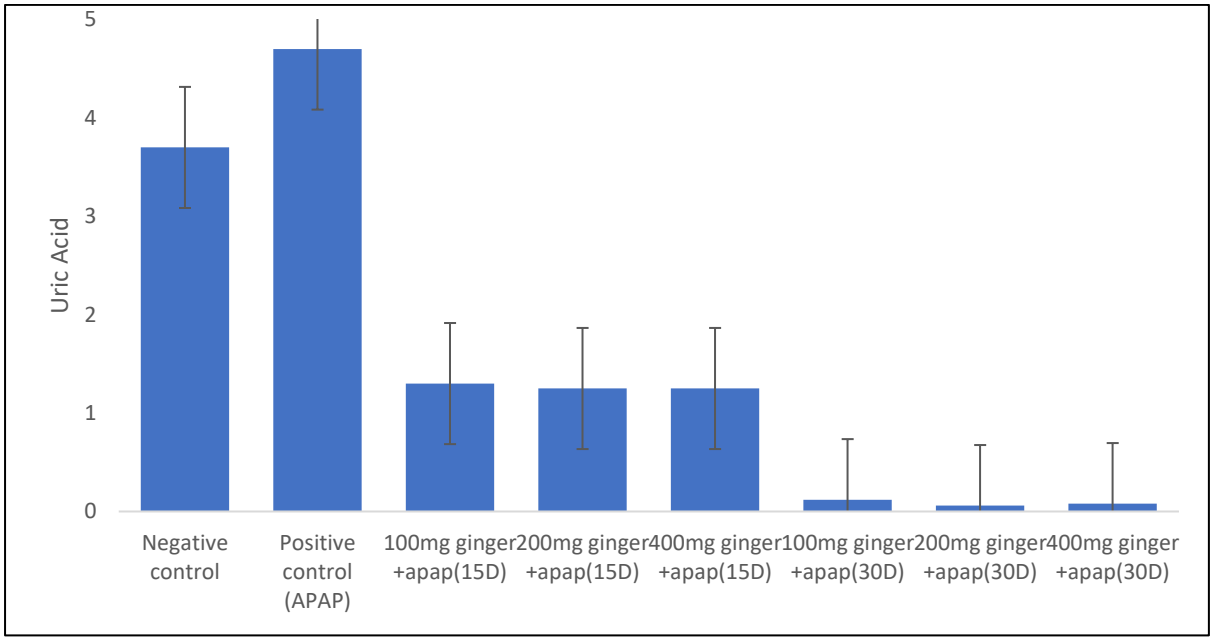

Figure (3) shows the effect of paracetamol and aqueous extract of ginger on the average concentration of the Uric acid (UA) in the blood serum of rabbits.

3.2 Histological changes

The microscopic examination of the kidney tissue showed the negative control group, interstitial tissue and renal tubes in their normal form. In contrast, the results of the microscopic examination in the positive control group showed severe disintegration and deterioration of the renal glomerulus, severe dilation of the renal tubules with severe congestion and dilation of blood vessels and small focal hemorrhages.

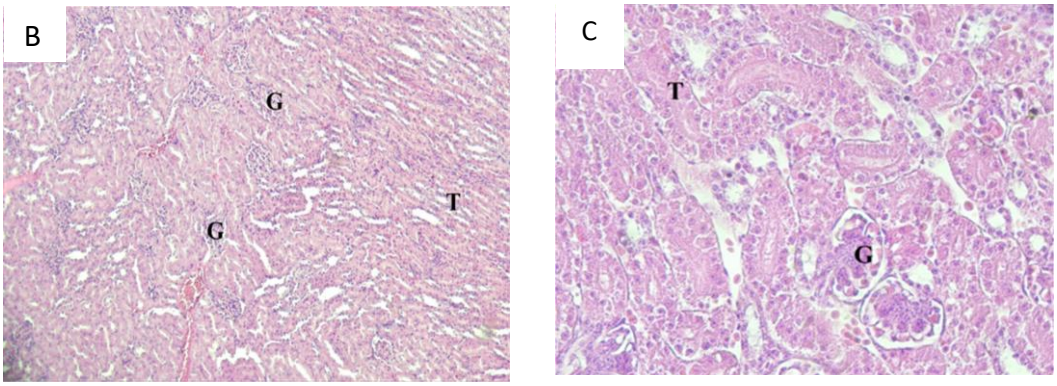

Figure (4) shows microscopic images of kidney tissue sections in the negative control group: A,B: renal glomeruli (G), renal tubules(T) (H&E; 40x), C: renal glomeruli (G), renal tubules(T) (H&E; 100x)

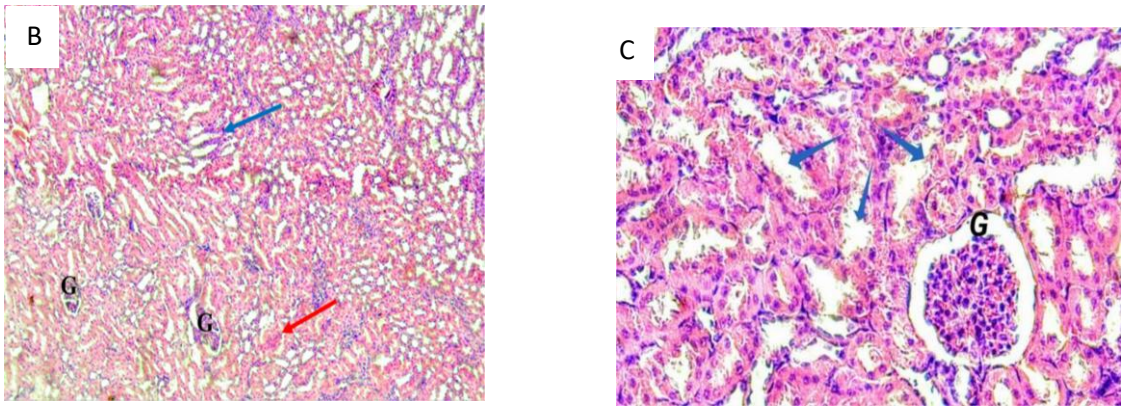

Figure (5) shows microscopic images of kidney tissue sections in the group treated with a single dose of 750mg of paracetamol: renal glomeruli (G), renal tubules(blue arrow) focal hemorrhages (red arrow) (A,B: H&E; 40x) (C: H&E; 100x)

The results of the kidney histological study in the groups pre-dosed with an aqueous extract of ginger (100,200,400) mg/kg for 15 days showed a significant improvement in the renal glomerulus along with a decrease in the diameter of the dilated renal tubules compared to the positive control group. In contrast, the groups pre-dose with (100,200,400) mg/kg of ginger extract for 30days reduced the harmful effects on kidney tissue, showing only slight degeneration of the renal glomerulus and slight dilation and congestion of the renal tubules and blood vessels compared to the positive control group.

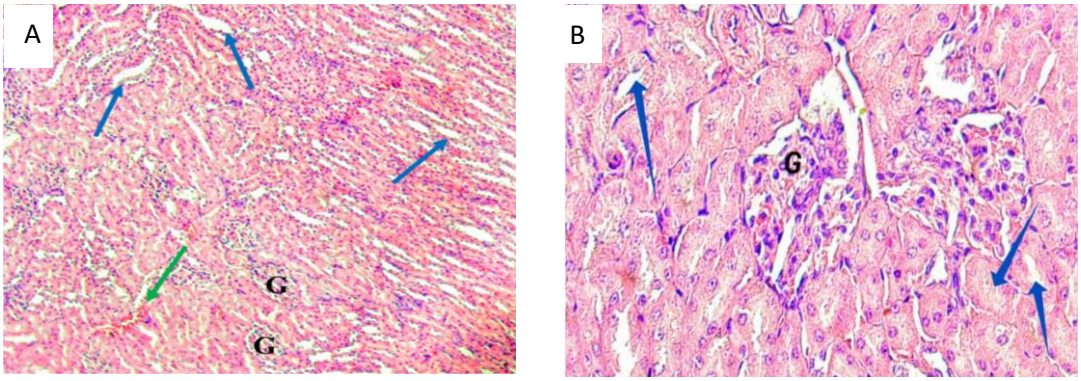

Figure (6) shows microscopic images of kidney tissue sections in the group dosed with 100mg of ginger extract for 15 days + single dose of paracetamol (750mg): A,B: renal glomeruli (G), renal tubules(blue arrow) blood vessels (green arrow) (H&E; 40x) (H&E; 100x).

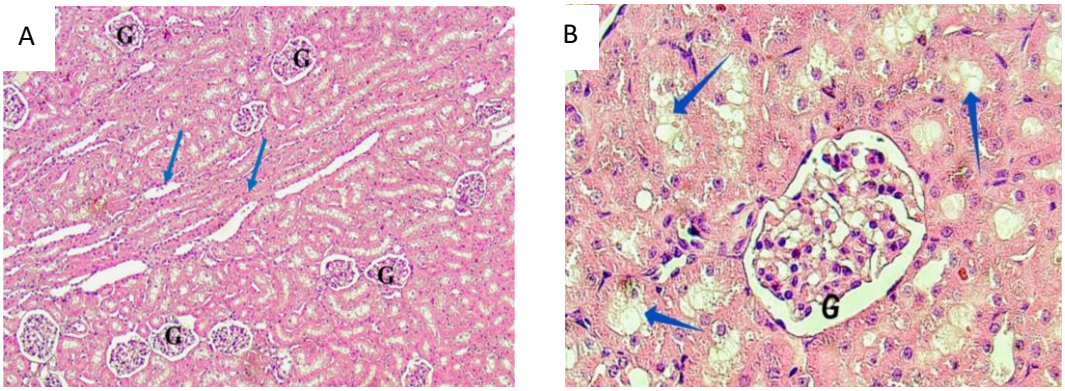

Figure (7) shows microscopic images of kidney tissue sections in the group dosed with 200mg of ginger extract for 15 days + single dose of paracetamol (750mg): A,B: renal glomeruli (G), renal tubules(blue arrow) (H&E; 40x) (H&E; 100x)

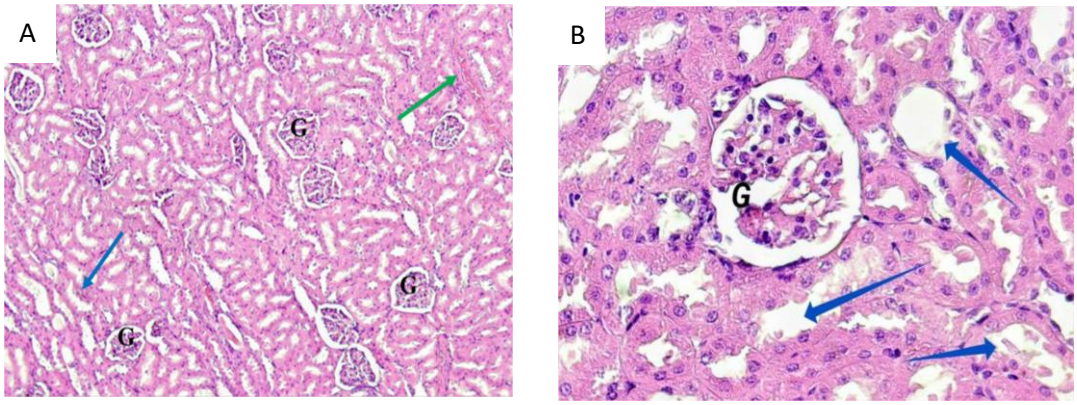

Figure (8) shows microscopic images of kidney tissue sections in the group dosed with 400mg of ginger extract for 15 days + single dose of paracetamol (750mg): A,B: renal glomeruli (G), renal tubules(blue arrow) blood vessels (green arrow) (H&E; 40x) (H&E; 100x)

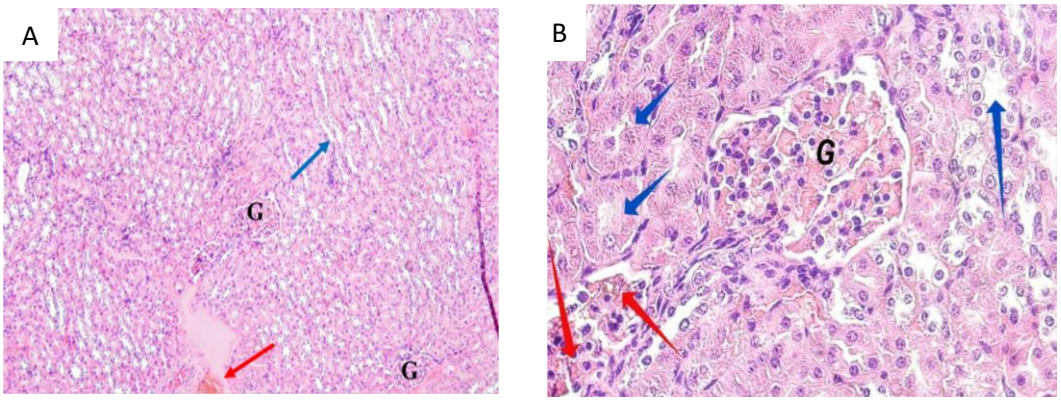

Figure (9) shows microscopic images of kidney tissue sections in the group dosed with 100mg of ginger extract for 30 days + single dose of paracetamol (750mg): A,B: renal glomeruli (G), renal tubules(blue arrow) congestion (red arrow) (H&E; 40x) (H&E; 100x)

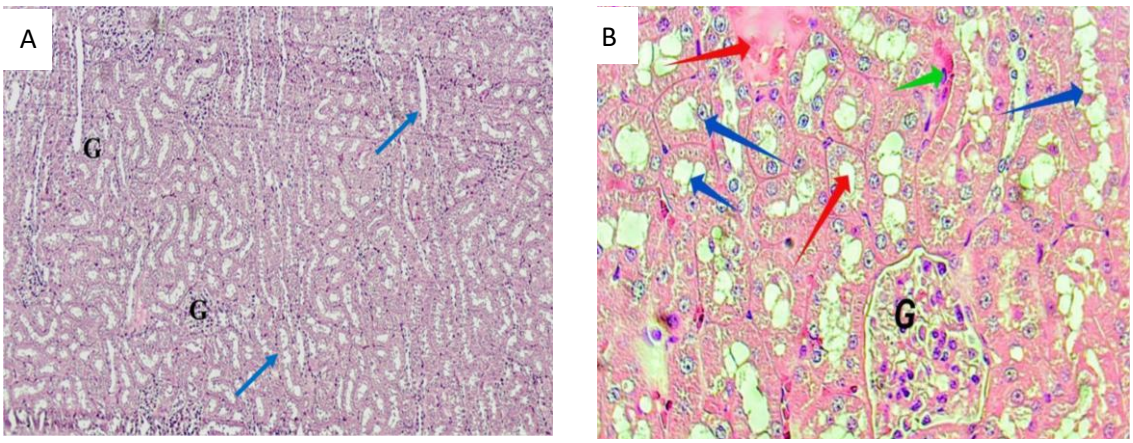

Figure (10) shows microscopic images of kidney tissue sections in the group dosed with 200mg of ginger extract for 30 days + single dose of paracetamol (750mg): A,B: renal glomeruli (G), renal tubules(blue arrow) congestion (red arrow) blood vessels (green arrow) (H&E; 40x) (H&E; 100x)

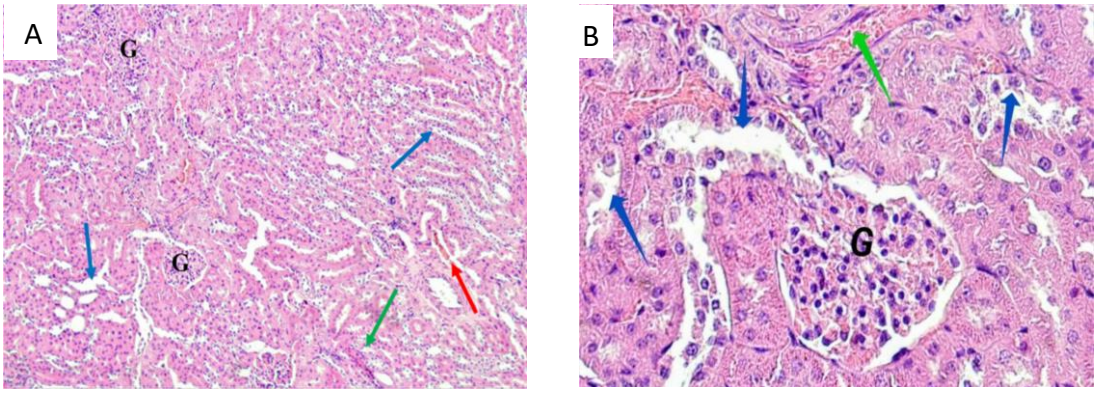

Figure (11) shows microscopic images of kidney tissue sections in the group dosed with 400mg of ginger extract for 30 days + single dose of paracetamol (750mg): A,B: renal glomeruli (G), renal tubules(blue arrow) congestion (red arrow) blood vessels (green arrow) (H&E; 40x) (H&E; 100x)

4. Discussion

The kidney performs essential homeostatic functions, primarily the excretion of nitrogenous metabolic wastes such as creatinine, urea, and uric acid, which are critical markers of renal integrity. Renal dysfunction is clinically characterized by the accumulation of these metabolites in the blood, indicating a failure in glomerular filtration capacity. In the current study, the administration of a single toxic dose of paracetamol (750 mg/kg b.w) induced significant hypercreatinemia, uremia, and hyperuricemia compared to the control group. These biochemical alterations are hallmark indicators of drug-induced nephrotoxicity, where paracetamol's reactive metabolite, N-acetyl-p-benzoquinone imine (NAPQI), overwhelms cellular detoxification mechanisms, leading to oxidative damage.

Regarding the therapeutic intervention, ginger (aqueous extract) displayed a dose-dependent nephroprotective effect. The superior biochemical recovery observed in the 200 and 400 mg/kg groups administered for 15 days suggests that ginger may effectively neutralize oxidative stress during the acute phase of toxicity. Interestingly, while 30-day administration also yielded improvements, the 15-day regimen appeared more robust in restoring homeostatic levels of urea and creatinine. This may imply that the prolonged systemic exposure to certain

phytochemicals could trigger adaptive pathways or feedback loops that slightly modulate their short-term antioxidant efficacy.

The protective efficacy of *Zingiber officinale* is fundamentally rooted in its rich profile of bioactive polyphenols and flavonoids. These compounds exert their effect by scavenging free radicals and inhibiting lipid peroxidation, thereby preventing the inflammatory cascade within renal tissues. This therapeutic potential is corroborated by a broader scientific framework of phytochemical characterization. Specifically, Salem (2026) emphasized that the specific phytochemical composition of aerial plant parts is the primary driver of their pharmacological potency. This principle is further supported by Alshawish et al. (2025), who validated that multi-target biological screening is essential for verifying how medicinal extracts protect against cellular degradation. Furthermore, the findings are consistent with Salem et al. (2023), who linked specific biochemical interactions to therapeutic outcomes, and Salem and Lakwani (2020), whose work established that detailed chemical profiling is a non-negotiable prerequisite for determining the protective and antioxidant properties of natural extracts in physiological models.

Histological evaluation provided structural evidence for these biochemical improvements. The positive control group displayed severe glomerular disintegration, tubular dilation, vascular congestion, and hemorrhage, reflecting the acute nephrotoxic assault of paracetamol. These structural alterations are clinically significant as they often precede measurable increases in nitrogenous waste markers. Given that proximal convoluted tubules are highly rich in mitochondria—the main sites of oxidative free radical production—the paracetamol-induced oxidative stress likely disrupted the glomerular basement membrane and triggered tubular cell dysfunction.

Treatment with ginger extract significantly attenuated these histological lesions. The mitigation of glomerular degeneration and tubular congestion suggests that ginger-derived antioxidants effectively maintain mitochondrial structural integrity and minimize the permeability of the glomerular filtration barrier. While both 15-day and 30-day treatments provided protection, the enhanced structural preservation observed in the 15-day group suggests that the early administration of ginger may be more effective in preventing the initial cascade of oxidative necrosis before irreversible tissue damage occurs.

5. Conclusion

The results of this study showed that the pre-dosed of ginger's aqueous extract reduced the harmful effects of paracetamol. The 15day dosage was better than 30 day. As the 30 day stripes caused a sever decrease in the level of uric acid. Further experimental studies are needed to understand this decline.

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