



Physiological and Histological Ameliorative Effects of Walnuts-pulp Extract on Kidney Function of Rats Treated with Citalopram

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ABSTRACT

Background: Citalopram is a class of antidepressant drugs that works by increasing the amount of serotonin to maintain mental balance. However, the risk of kidney damage associated with Citalopram use remains an area of ongoing research, with several potential mechanisms implicated in its pathogenesis. This experimental study aims to evaluation of physiological and histological renal damages due to low and high doses of Citalopram and the ameliorative role of walnuts-pulp extract in reducing nephrotoxic damages.

Methods: An overall 28 mature albino male rats were purchased, acclimated and divided equally and randomly into four groups; NG given distilled-water only, EG1 given Citalopram (0.6 mg/kg.BW) and walnut-pulp extract (10 mg/kg.BW), EG2 given Citalopram (20 mg/kg.BW) and walnut-pulp extract (10 mg/kg.BW) and PG given Citalopram only (0.6 mg/kg.BW). Blood was sampled from all animals in the day-1 and day-60 of experiment; while, renal tissues were collected after the ending of experiment (60 days).

Result: Our findings showed that the concentrations of blood urea and creatinine at day-1 were differed insignificantly ($p>0.05$) among study groups; however at day-60, significant elevation in concentration of urea was seen in EG2 and PG; while, increases in concentration of creatinine was found in EG2 when compared to other study groups. In comparison between the values of study groups at day-1 and day-60, significant increases were identified in concentration of urea of EG2 and PG; as well as creatinine of EG2 at day-60. In tissue sections of NG, EG1 and EG2; the results of light microscopy at 100X and 200X revealed the presence of normal structures in tubules and glomeruli without any significant occupied lesions. In tissue sections of PG, the results of light microscopy at 100X and 200X showed clearly the presence of renal vein congestion with excessive perivascular leukocyte cuffing and infiltration of homogenous and pinkish materials. Also, there was a narrowing in the renal artery diameter and glomeruli, with presence of atrophy characteristics in the glomerular tuft.

Key words: Antidepressant, Creatinine, *Juglans regia*, Nephrotoxicity, Urea.

INTRODUCTION

Kidneys perform several vital functions that including the excretion of waste products, maintenance of water, electrolyte and acid-base balance, hematopoietic and endocrine functions, regulation of blood pressure and blood calcium levels (Ofori, 2022; Kerber *et al.*, 2021). Normally, both kidneys receive about 25% of the heart output and the glomeruli filtered about 180 liters daily. However, excessive damage could be developed in kidneys (nephrotoxicity) due to various factors including acute infections, chronic diseases and frequent exposure to toxic metabolites for long periods leading to rapid decline in kidney function (Kwiatkowska *et al.*, 2021).

Citalopram is a selective serotonin re-uptake inhibitor (antidepressant), which prescribed usually to treating the major depressive, obsessive-compulsive, panic and social-anxiety disorders (Laux, 2021; Edinoff *et al.*, 2021). Although, it is well tolerated, Citalopram has a wide range of side effects that can markedly impact the patient compliance and overall therapy outcomes (Chiarotti *et al.*, 2017). These effects have been detected in gastrointestinal (nausea, diarrhea and constipation), central nervous (headache, dizziness and somnolence), cardiovascular (hypotension, bradycardia, QT-interval prolongation and

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ventricular arrhythmia) and urogenital (hyponatremia, elevation in blood urea and creatinine, decreased libido,

erectile dysfunction and anorgasmia) systems; in addition to many other disturbances such as weight loss, exacerbating hyperglycemia, sweating, drowsiness and insomnia (Wang *et al.*, 2022; Oliva *et al.*, 2021; Worofin *et al.*, 2019).

In last decades, the integration of herbal medicine with conventional pharmaceutical treatments represents a burgeoning field of study, particularly concerning the mitigation of adverse drug reactions (Raj and Rani, 2024; Ahmed *et al.*, 2024). The rise in popularity of herbal remedies is propelled by several factors including the undesirable side effects often associated with synthetic drugs, the absence of curative treatments in modern medicine for certain chronic conditions and the increasing prevalence of microbial resistance (Mabel *et al.*, 2025; Terde *et al.*, 2022; Mensah *et al.*, 2019). Walnuts (*Juglans regia*) are an exceptional rich plant-based source of α -linolenic acid, antioxidants (melatonin, γ -tocopherol and carotenoids) and phytosterols especially polyphenols (Ros and Sala-Vila, 2020). The intricate matrix present in walnuts underlies their capacity to interact with molecular targets involved in drug metabolism, inflammation and cellular stress responses (Shabbir *et al.*, 2024).

Taken together, there is reason to hypothesize that walnuts might be beneficial against kidney damage as demonstrated by several studies (Meraati *et al.*, 2025; Askin *et al.*, 2022). Therefore, this experimental study aims to evaluation of physiological and histological renal damages due to low and high doses of Citalopram and the ameliorative role of walnut-pulp extract in reducing these damages.

MATERIALS AND METHODS

Preparation of walnuts-pulp extract

An overall 1000 gm of walnuts-pulp were purchased from the local supermarket, grounded, extracted by Soxhlet, solved in ethanol (70%) for 72 hours, filtered and the mixture was kept at -20°C (Askin *et al.*, 2022; Jiheel and Arrak, 2015).

Study animals

Totally, 28 male rats of 118-159 grams of weight were purchased from the private animal house in Baghdad province (Iraq) and transported to the Animal House in the College of Science in University of Wasit during May to August (2024). Initially, the study animals were subjected to a preparation period of 1 week, during which they were fed a pellet, presented to tap water and exposed to 12/12 hours of light/dark.

Study design

Randomly, the study rats were divided equally into 4 groups as following:

- 1. Negative control group (NG):** In which, rats were given distilled-water only by the oral gavage for 60 days.
- 2. Experimental group 1 (EG1):** In which, rats were given Citalopram at a low dose (0.6 mg/kg.BW) and then, walnut-

pulp extract at a dose of 10 mg/kg.BW orally by the gavage for 60 days.

- 3. Experimental group 2 (EG2):** In which, rats were given Citalopram at a high dose (20 mg/kg.BW) and then, walnut-pulp extract at a dose of 10 mg/kg. BW orally by the gavage for 60 days.

- 4. Positive control group (PG):** In which, rats were given Citalopram only (0.6 mg/kg.BW) orally by the gavage for 60 days.

Blood sampling

At day-1, 1 ml of blood was collected from the tail of each animal into labeled free-anticoagulant glass-gel tube, centrifuged and the obtained sera were transferred into labeled Eppendorf tube to be saved frozen until be used. At day-60, all study animals were anesthetized to direct collection of blood from heart and the obtained sera were saved frozen until be used.

Collection of kidney tissues

After blood sampling, kidneys of each animal were collected into labeled plastic containers and fixed in neutral buffered formalin (10%).

Biochemical measurement of blood urea and creatinine

According to manufacturer instructions of quantitative ELISA kits (SunLong Biotech, China), the serum samples as well as the contents of each kit were prepared, processed and the optical density (OD) was read at 450 nm by the Microplate ELISA Reader. Then, the concentrations of urea and creatinine in the tested samples were quantified based on the ODs and concentrations of Standards as well as the ODs of samples (Al-Eodawee *et al.*, 2024; Gharban and Yousif, 2020).

Histology

According to previously described protocol, the fresh tissue sections were dehydrated, cleared, infiltrated, paraffin-embedded, sectioned by the micrtome, mounted on glass slides, stained with Hematoxylin and Eosin and visualized by light microscope (Alyasiri *et al.*, 2025; Hussien *et al.*, 2024).

Statistical analysis

One- and Two-Way ANOVA in Graph Pad Prism Software were used to identify significant differences between values (mean $\pm$ standard error) of study groups at $p < 0.05$ (Al-Khatawi *et al.*, 2025).

RESULTS AND DISCUSSION

Blood urea and creatinine

This study showed that the results of blood urea at day-1 were differed insignificantly ($p > 0.05$) among various groups; NG (27 ± 3.5 mg/dl), EG1 (28 ± 3.14 mg/dl), EG2 (26.14 ± 3.16 mg/dl) and PG (26.28 ± 2.18 mg/dl); whereas at day-60, significant elevation ($p < 0.05$) was seen in values of EG2 (61 ± 2.94 mg/dl) and PG (59.85 ± 6.19 mg/dl) when

compared to NG (27.42 ± 3.17 mg/dl) and EG1 (27.85 ± 4.18 mg/dl) (Fig 1, 2). In comparison between the values of day-1 and day-60 among various study groups, the findings of NG (27 ± 3.5 mg/dl and 27.42 ± 3.17 mg/dl, respectively) and EG1 (28 ± 3.14 mg/dl and 27.85 ± 4.18 mg/dl, respectively) were differed insignificantly ($p > 0.05$); however, values of EG2 (61 ± 2.94 mg/dl) and PG (59.85 ± 6.19 mg/dl) were elevated significantly ($p < 0.05$) at day-60 when compared to those at day-1 (26.14 ± 3.16 mg/dl and 26.28 ± 2.18 mg/dl, respectively) (Fig 3).

Concerning the blood creatinine, the findings of day-1 reported that no significant variation ($p > 0.05$) between values of NG (0.83 ± 0.72 mg/dl), EG1 (0.82 ± 0.12 mg/dl), EG2 (0.83 ± 0.1 mg/dl) and PG (0.82 ± 0.12 mg/dl); While at day-60, significant higher value ($p < 0.05$) was detected in EG2 (1.52 ± 0.08 mg/dl) than those of other study groups; NG (0.8 ± 0.1 mg/dl), EG1 (0.81 ± 0.12 mg/dl) and PG (0.82 ± 0.45 mg/dl), (Fig 4, 5). In comparison between the values of study groups at day-1 and day-60, there were no significant differences ($p > 0.05$) between values of NG (0.83 ± 0.72 mg/dl and 0.8 ± 0.1 mg/dl, respectively), EG1

(0.82 ± 0.12 mg/dl and 0.81 ± 0.12 mg/dl, respectively) and PG (0.82 ± 0.12 mg/dl and 0.82 ± 0.45 mg/dl, respectively); however, the findings of EG2 at day-60 (1.52 ± 0.08 mg/dl) were elevated significantly ($p < 0.05$) when compared to those at day-1 (0.83 ± 0.1 mg/dl), (Fig 6).

Numerous researches have been reported the great benefits of herbal compounds in treatment of various kidney disease by preventing or controlling the deleterious pathways like inflammation, oxidative stress, necrosis, apoptosis and deprivation in nitric oxide which caused injuries to blood vessels (Basilicata *et al.*, 2022; Uddin *et al.*, 2021; Kang *et al.*, 2021). In traditional medicine, herbs have been used to treat kidney disorders caused by various drugs or toxins and many medicinal plants have also been tested in order to protect the kidneys (Yang *et al.*, 2018; Liwa and Jaka, 2016). Guasch-Ferré *et al.* (2018) concluded that daily consumption of 30-100 g of walnuts could lower the risk factors of cardiovascular disease in individuals did not undergo from hyperlipidemia. Quantitative determination of walnut extract showed the highest level of total phenol, fatty acids, stigmasterol,

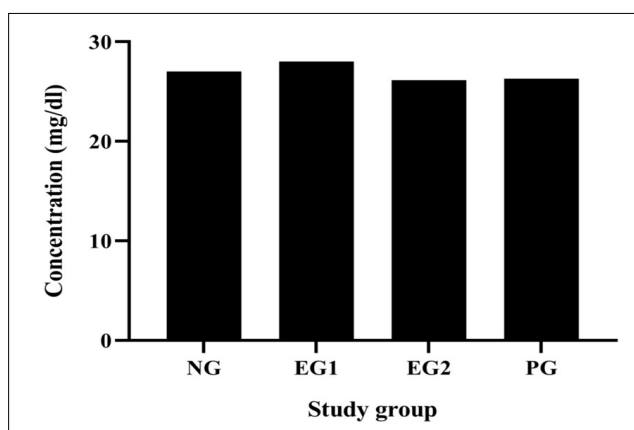


Fig 1: Concentration of urea (mg/dl) among rats of various study groups at the day-1 of experiment.

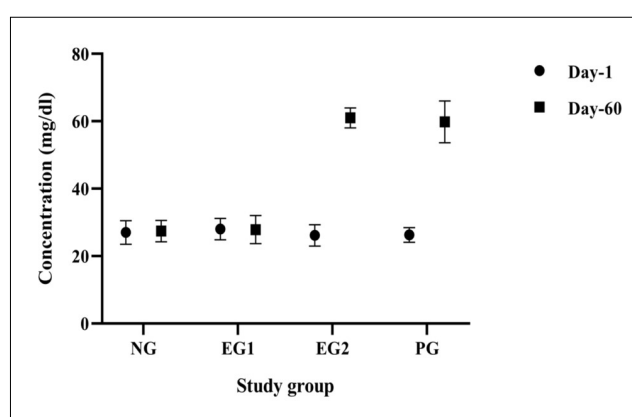


Fig 3: Comparison between the concentration of urea (mg/dl) among the rats of various study groups at the day-1 and day-60 of experiment.

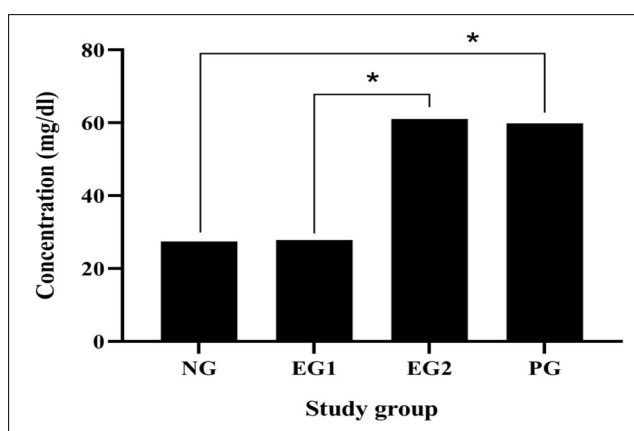


Fig 2: Concentration of urea (mg/dl) among rats of various study groups at the day-60 of experiment.

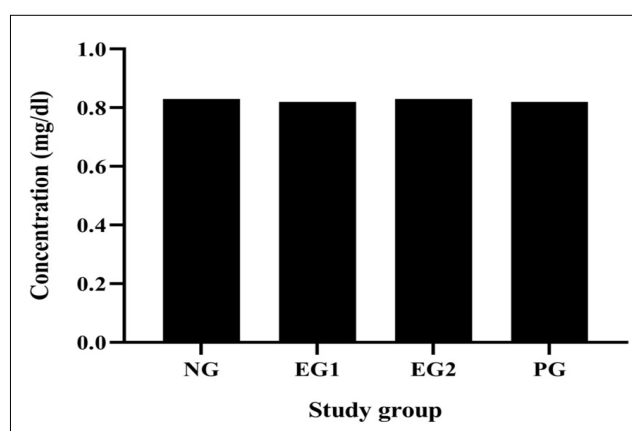


Fig 4: Concentration of creatinine (mg/dl) among rats of various study groups at the day-1 of experiment.

campestral and β -sitosterol (Ortiz and Martirosyan, 2024). Other studies have been demonstrated the role of administration of walnut extracts in improving of histopathological, biochemical and parameters of cytogeneticists (Roque *et al.*, 2024; Sindete *et al.*, 2021). Olas (2024) recorded that dietary supplementation of walnuts pulp, 15 g/day for reduction risk factor of cardiovascular diseases. Other studies have focused for role of walnut in reduction of risk factors associated with diabetes, coronary heart disease and cardio-vascular disease and neurological disorders (Tepavčević *et al.*, 2024; Rahbardar and Hosseinzadeh, 2024). The investigations of strong relationship between consumption of walnut kernel and prevention as well as treatment of some cancers have been reported by many studies (Fan *et al.*, 2023; Ni *et al.*, 2022).

Histopathological finding

In tissue sections of NG, EG1 and EG2; the results of light microscopy at 100X and 200X revealed the presence of normal structures in tubules and glomeruli without any

significant occupied lesions (Fig 7-13). In tissue sections of PG, the results of light microscopy at 100X and 200X showed clearly the presence of renal vein congestion with excessive perivascular leukocyte cuffing and infiltration of homogenous and pinkish materials. Also, there was a narrowing in the renal artery diameter and glomeruli, with presence of atrophy characteristics in the glomerular tuft (Fig 14-18). These effects may be related to oxidative stress or cytotoxicity of antidepressants as recorded by several researchers (Nabekura *et al.*, 2022; Then *et al.*, 2017). In addition, other studies explained the role of antidepressants in causing of inflammation, increasing the cytotoxicity in different tissue and increasing the risk incidence of tumors, diabetes millets, cardiovascular diseases and obesity (Anand *et al.*, 2025; Bonilla-Jaime *et al.*, 2022; Szałach *et al.*, 2019).

Atrophy of renal glomeruli or vasoconstrictions in kidneys may be related to effects of serotonin which increased when treated by antidepressant, in kidney serotonin considers as a vasoconstrictor material mainly by activation of 5-HT₂ receptor (González-Hernández *et al.*, 2023;

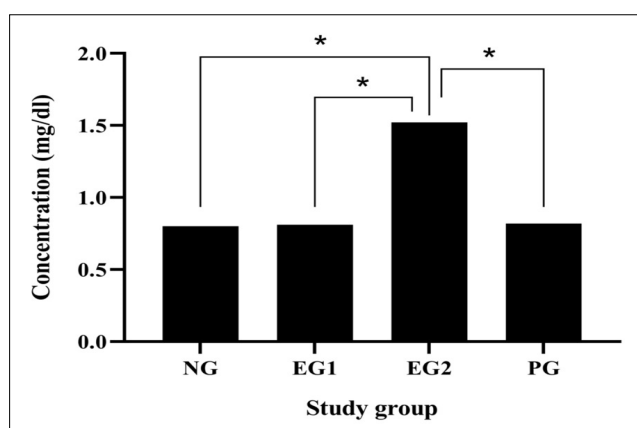


Fig 5: Concentration of creatinine (mg/dl) among rats of various study groups at the day-60 of experiment.

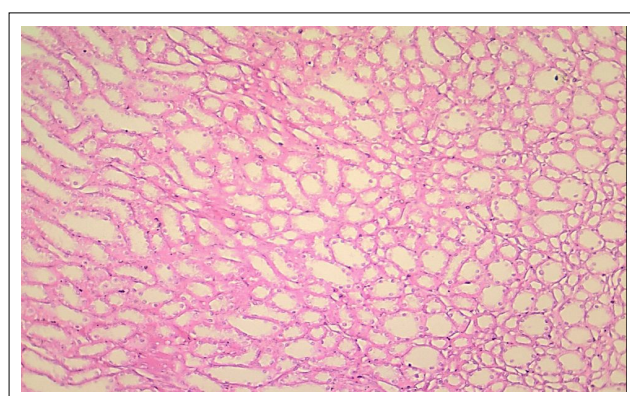


Fig 7: Histological section of kidney tissues in rats of NG; in which, normal histological structure of renal tubules without any significant occupied lesions were shown (H and E stain, 100X).

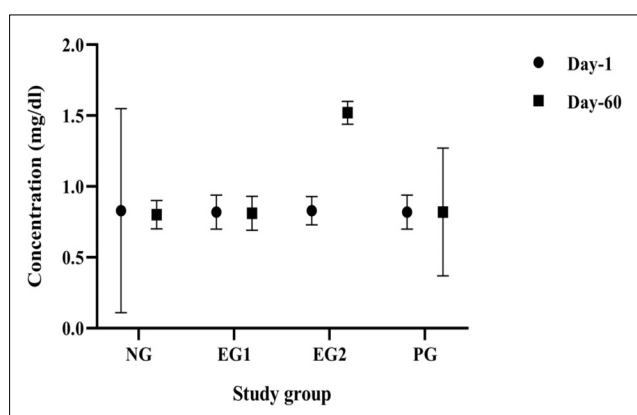


Fig 6: Comparison between the concentration of creatinine (mg/dl) among the rats of various study groups at the day-1 and day-60 of experiment.

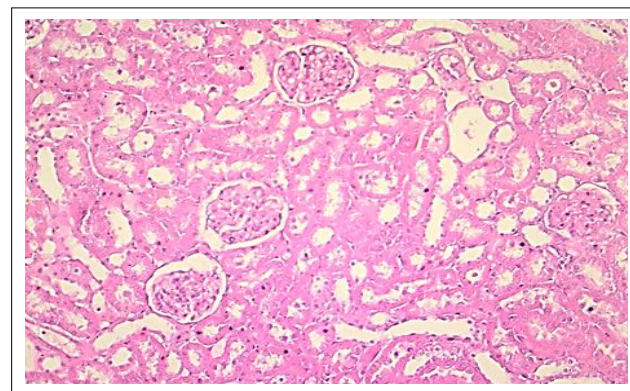


Fig 8: Histological section of kidney tissues in rats of NG; in which, normal histological structure of renal glomeruli without any significant occupied lesions were shown (H and E stain, 200X).

Lee *et al.*, 2021). Also, antidepressants cause an increasing in the risk of gastrointestinal hemorrhage especially in individuals has kidney dysfunctions (Worof *et al.*, 2019; Bixby *et al.*, 2019). This may be another reason

for the congestion that occurred in vessels of kidneys of experimental animals. Many studies have been reported the complications that threatening the life such as intracranial bleeding, cataract, arrhythmia and increasing of blood

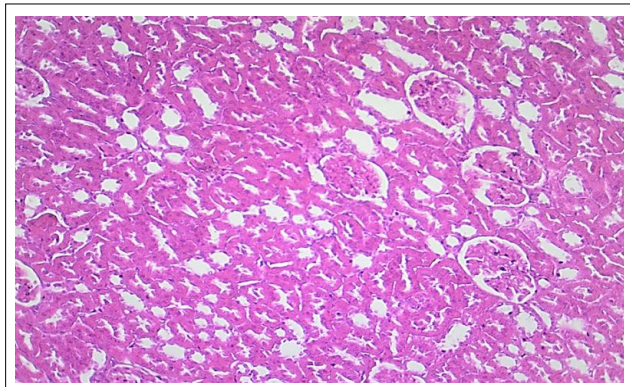


Fig 9: Histological section of kidney tissues in rats of EG1; in which, normal histological structure of renal glomeruli without any significant occupied lesions were shown (H and E stain, 100X).

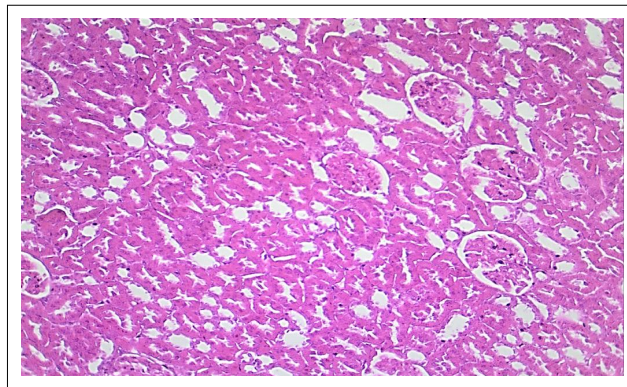


Fig 12: Histological section of kidney tissues in rats of EG2; in which, normal histological structure of renal glomeruli without any significant occupied lesions were shown (H and E stain, 200X).

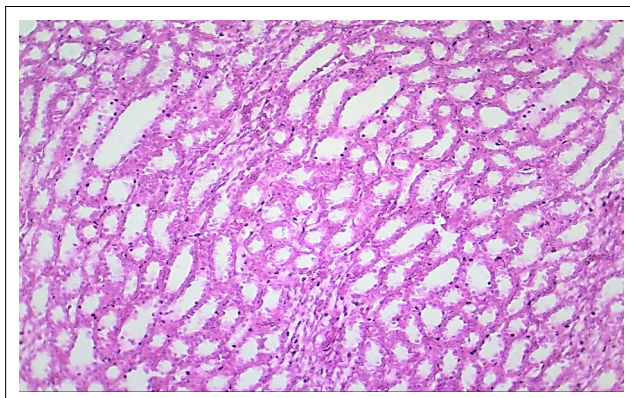


Fig 10: Histological section of kidney tissues in rats of EG1; in which, normal histological structure of renal tubules without any significant occupied lesions were shown (H and E stain, 200X).

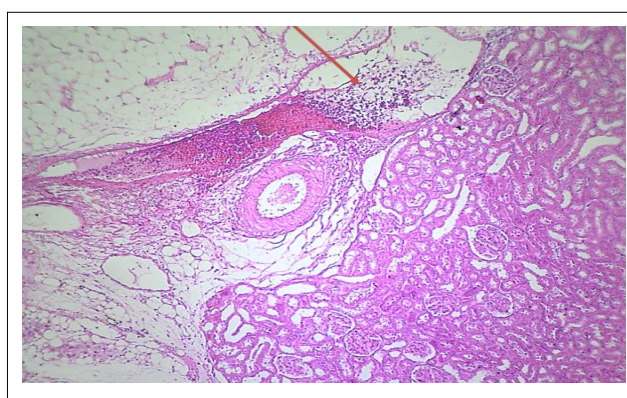


Fig 13: Histological section of kidney tissues in rats of PG; in which, clear renal vein congestion with excessive perivascular leukocyte cuffing (red arrow) were shown (H and E stain, 100X).

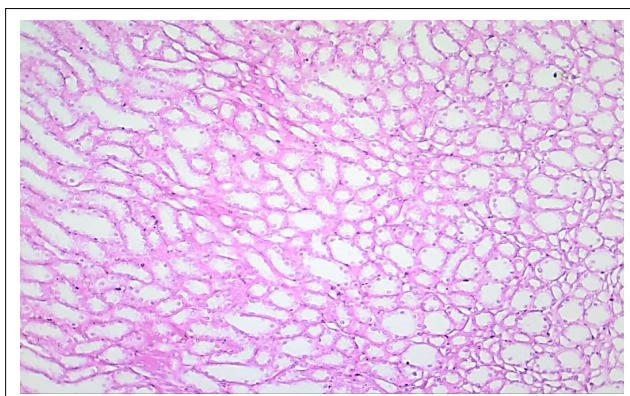


Fig 11: Histological section of kidney tissues in rats of EG2; in which, normal histological structure of renal tubules without any significant occupied lesions were shown (H and E stain, 100X).

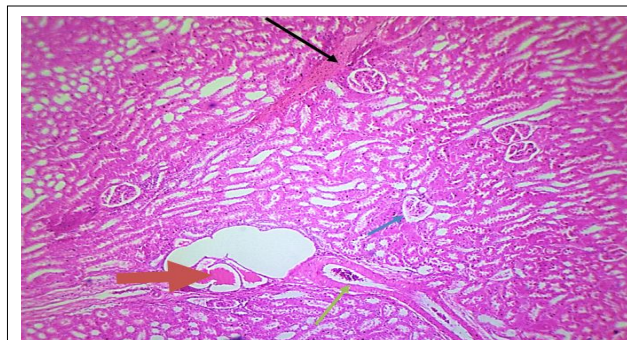


Fig 14: Histological section of kidney tissues in rats of PG; in which, renal blood vessels congestion (Black arrow) with infiltration of homogenous and pinkish material (Amyloidosis, Red arrow) and narrowing of renal artery diameter (Green arrow) were shown. The renal glomeruli shows atrophy characteristics in glomerular tuft (Yellow arrow), (H and E stain, 200X).

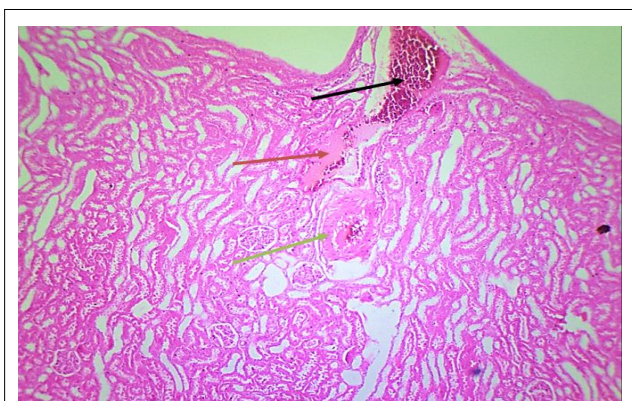


Fig 15: Histological section of kidney tissues in rats of PG; in which, renal blood vessels congestion (Black arrow) with infiltration of homogenous and pinkish material (Amyloidosis, Red arrow) and narrowing of the renal artery diameter (Green arrow) were shown (H and E stain, 100X).

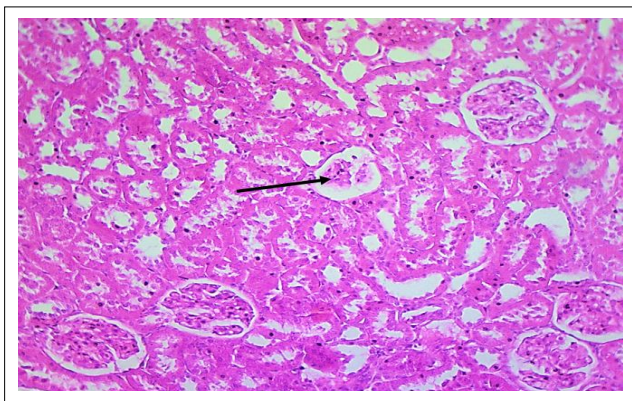


Fig 16: Histological section of kidney tissues in rats of PG; in which, clear glomerular tuft atrophy (Black arrow) was shown (H and E stain, 200X).

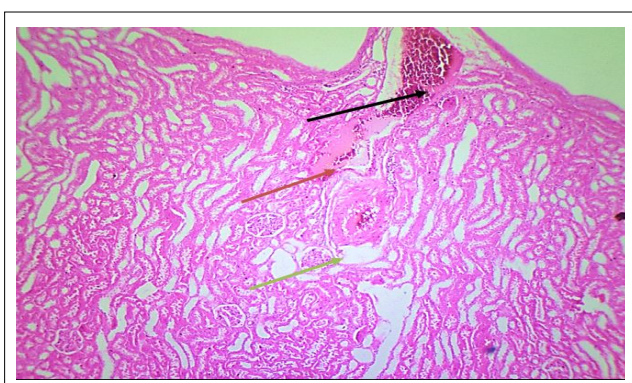
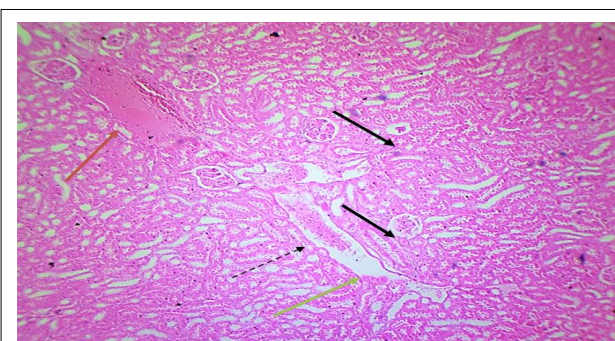


Fig 17: Histological section of kidney tissues in rats of PG; in which, renal blood vessels congestion (Black arrow) with infiltration of homogenous and pinkish material (Amyloidosis, Red arrow) and narrowing of the renal artery diameter (Green arrow) were shown (H and E stain, 100X).



The section shows lesions of atrophy in glomerular tufts (Black arrows), (H and E stain, 200X).

Fig 18: Histological section of kidney tissues in rats of PG; in which, renal blood vessels congestion (interrupted black arrow) with infiltration of homogenous and pinkish material (amyloidosis, Red arrow) and narrowing of the renal artery diameter (Green arrow) were shown.

pressure (Calvi *et al.*, 2021; Carvalho *et al.*, 2016). The pathological mechanisms of adverse effects of antidepressants relate to homeostatic imbalance, oxidative stress, inflammation and immunomodulation (Dos Santos *et al.*, 2022).

CONCLUSION

The results of the experiment showed the following facts; antidepressants have a detrimental effect on renal tissue. The alcoholic extract of walnuts-pulp has a protective effect against the side effects of antidepressants. The study also showed that light doses of the extract have the same protective effect as higher doses. Use of high doses of alcoholic extract of walnuts-pulp has a negative effect on kidney functions.

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Disclaimers

The views and conclusions expressed in this article are solely those of the authors and do not necessarily represent the views of their affiliated institutions. The authors are responsible for the accuracy and completeness of the information provided, but do not accept any liability for any direct or indirect losses resulting from the use of this content.

Informed consent

All animal procedures for experiments were approved by the Committee of Experimental Animal care and handling techniques were approved by the University of Animal Care Committee.

Conflict of interest

The authors declare that there are no conflicts of interest regarding the publication of this article. No funding or sponsorship influenced the design of the study, data collection, analysis, decision to publish or preparation of the manuscript.

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