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# Protective effect of vitamin E against methamphetamine-induced renal damage in male rats

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## Abstract

The present study was designed to study the toxicity effects of methamphetamine on renal histological architecture of male rats and its possible protective effect by Vitamin E and was carried out at the Animal house and the laboratories of the College of veterinary medicine, Tikrit University, from 1st October 2025 till 1st November 2025. The study included a total of 32 adult male Sprague–Dawley rats randomly divided into four experimental groups comprised of eight rats per group. Each group was then split into four subgroups for 15- and 30-days treatment periods. The first group was used as a control group which was fed with a regular diet and water during the experimental period. The second group received methamphetamine for 15 and 30 days at the dose of 0.1 mg/kg (1 mL/day). The third group was treated with Vitamin E 0.1 mL/day for the same durations. The 4th group received methamphetamine (0.1 mg/kg, 1 mL/day) and Vitamin E (0.1 mL/day) for 15 and 30 days. In the experimental period, the methamphetamine-treated animals showed significant differences in their behavior, such as hyperactivity, increased locomotor activity within the cages, heightened irritability and aggression. There was also a significant drop in the consumption of food and water. After completion of each experimental period, animals were killed by anesthetic injection and blood was drawn directly from the heart using a 4 mL sterile syringe. The samples were placed in serum separator tubes (SST) for biochemical analysis of kidney function evaluation. The animals were then killed and kidney tissue samples were collected for histopathological analysis. Histopathological evaluation revealed multiple renal lesions in methamphetamine-treated animals, including glomerular atrophy, widening of Bowman's space, degeneration and desquamation of tubular epithelial cells, inflammatory cell infiltration, hemorrhage, vascular congestion, and hemolyzed blood exudation. Biochemical results also showed marked changes in renal function parameters, which suggest that the methamphetamine exposure caused poor renal function.

They found that methamphetamine use caused progressive renal damage, worsening with the length of time the drug was administered. Renal lesions began to develop from early changes following 15 days of treatment, up to extensive tissue necrosis and the formation of thrombi after 30 days. In addition, Vitamin E showed a significant protection effect in short-term exposure by enhancing functional and histopathological renal parameters. But its protective effects decreased with chronic exposure to methamphetamine.

**Keywords:** Methamphetamine; Vitamin E; Nephrotoxicity; Methamphetamine renal histopathology; Methamphetamine-induced nephrotoxicity; Renal Function.

## 1. Introduction

Methamphetamine is a very potent psychostimulant with a high capacity to penetrate the blood-brain barrier and release large amounts of neurotransmitters, especially dopamine and norepinephrine, causing extensive action in the central nervous system and other body systems. These properties have led it to become one of the most widely used and addicted drugs in the world and consequently there has been growing interest in the study of the toxic effects on important organs. Recent studies have suggested that methamphetamine is a multi-organ toxicant, and the kidney is

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one of the most vulnerable organs, with renal excretion being important for elimination of methamphetamine and its metabolites and with the capacity of inducing functional and structural disturbances in renal tissue (Zhang et al., 2023). The kidneys are essential for maintaining the internal homeostasis of the body, as they filter blood, excrete metabolic wastes, regulate water balance and electrolytes and maintain acid-base stability. Therefore, any damage to renal tissue may impair the efficiency of these vital functions, leading to elevated serum urea and creatinine levels and increased protein excretion in the urine, and may progress to acute kidney failure or chronic kidney disease. Although there is clinical evidence linking methamphetamine use to an increased risk of kidney disease, experimental studies examining its direct histological effects on the kidney remain relatively limited, particularly regarding the characterization of pathological changes associated with dose and duration of exposure, as well as the molecular mechanisms responsible for renal damage.Several studies have indicated that oxidative stress is one of the most important pathological mechanisms responsible for the nephrotoxicity caused by methamphetamine, as this drug increases the production of reactive oxygen (ROS) and enhances the processes of lipid pyroxia, causing damage to the cell membranes. Mitochondrial dysfunction and activation of inflammation and apoptosis pathways, which are reflected in the integrity and function of renal tissue (Ding *et al*., 2022). Proceeding from the pivotal role of oxidative stress in the development of these pathological changes, antioxidants have received increased attention as potential preventive factors to reduce damage from methamphetamine. E (α-Tocopherol) is one of the most important fat-soluble antioxidants, as it effectively inhibits lipid peroxidation reactions and protects cell membranes from oxidative damage, in addition to its role in reducing the inflammatory response and maintaining the integrity of cells and tissues. Numerous experimental studies have shown that vitamin E administration contributes to reducing markers of oxidative stress and improving histological changes in various models of drug-induced and renal toxicity, suggesting its potential as a protective agent against methamphetamine-induced renal damage (Choung *et al*., 2024). Therefore, the present study aimed to evaluate the protective effect of vitamin E against methamphetamine-induced renal histological changes in male white rats, and to investigate its ability to reduce tissue damage associated with oxidative stress, thereby contributing to a better scientific understanding of the pathophysiological mechanisms associated with this toxicity and supporting the development of future preventive and therapeutic strategies (Dong *et al*., 2023).

## 2. Materials and methods

### 2.1. Laboratory animals

A total of 32 healthy female Sprague-Dawley rats of (150–200) g and (2–4) months old were used in this study. The animals were kept in controlled environmental conditions, with a constant temperature of 25°C, and were fed and watered.

### 2.2. Experimental design

Randomly, rats were divided into 4 groups, 3 experimental and 1 control groups with 4 rats in each group, the weights of each group were considered as much as possible before the study was started and then the rats in each group were subdivided into 2 groups, one with 4 rats each treated for 30 days and the other treated for 15 days. The animals were randomly divided into four groups (8 animals in each group) and exposed to the following:

- Group 1 (G1, control): rats were given nutrients and water for 30 days without any treatment.
- Group 2 (G2): Rats were fed 0.1 mg/kg of body weight of Methamphetamine dissolved in 1 ml of distilled water for 15 days or 30 days in the first subgroup (rats n = 4) and the second subgroup (rats n = 4) respectively.
- Group 3 (G3): This group was also divided into two subgroups. The first subgroup included rats (n = 4) treated with Vitamin E at a dose of 0.1 ml for 15 days, while the second subgroup included rats (n = 4) treated for 30 days.
- Group 4 (G4): This group was divided into two subgroups. The first subgroup included rats (n = 4) co-administered methamphetamine at a dose of 0.1 mg/kg together with Vitamin E at a dose of 0.1 ml for 15 days, while the second subgroup received the same treatment regimen for 30 days.

The food and water were available to all experimental groups during the period of their respective study.

### 2.3. Preparation of Histological Sections

The tissue sections were made in the histology laboratory. Tikrit University – College of Science. Microscopical sections were processed according to the method described by Al-Hajj (2015) which involved the following steps:

Segments of kidney were removed and preserved for 24 hrs in 10% NBF. The tissues were then dehydrated in a series of ethanol (70, 80, 90 and 100%) and cleared in xylene before being embedded in paraffin wax at 60°C and then cut into 6µm sections on a rotary microtome. These were then cut and stained with hematoxylin and eosin (H&E) and mounted on slides using D.P.X. and covered with a slip of glass. Finally, the ready-made slides were viewed under a light microscope and photographed with a digital camera whose lens was modified for microscopic photography.

## 3. Results and Discussion

### 3.1. Biochemical examination

The study results confirmed that methamphetamine administration led to a statistically significant increase in creatinine and urea levels compared to the control group ($P<0.05$), indicating impaired renal function; the effect was more pronounced after 15 days for urea. Administration of vitamin E alone also resulted in a statistically significant increase in creatinine levels during both study periods, while it did not produce any clear statistically significant changes in urea levels after 30 days. Conversely, combined treatment with methamphetamine and vitamin E was associated with a statistically significant increase in both creatinine and urea levels compared to the control group, indicating that vitamin E was unable to completely prevent the methamphetamine-induced changes in renal function, although a relative decrease in urea levels was observed after 30 days compared to the 15-day period as shown in tables (1), (2), and (3).

**Table 1** Serum creatinine and urea levels in the methamphetamine-treated (G2) and control groups at 15 and 30 days (mean ± standard deviation)

| **Variable** | **Tested Mean ± SD** | | **Control Mean ± SD** |
|---|---|---|---|
| | 15 Days | 30 Days | |
| Creatinine | 0.41 ± 0.02* | 0.4 ± 0.02* | 0.33 ± 0.02 |
| Urea | 42.4 ± 2.07* | 32.2 ± 1.92* | 35.8 ± 1.64 |

**Table 2** Serum creatinine and urea levels in the vitamin E treatment (G3) and control groups at 15 and 30 days (mean ± standard deviation)

| **Variable** | **Tested Mean ± SD** | | **Control Mean ± SD** |
|---|---|---|---|
| | 15 Days | 30 Days | |
| Creatinine | 0.45 ± 0.03* | 0.44 ± 0.02* | 0.33 ± 0.02 |
| Urea | 46.8 ± 1.92* | 35.0 ± 1.58 | 35.8 ± 1.64 |

**Table 3** Serum creatinine and urea levels in the vitamin E-treated, methamphetamine-treated (G4), and control groups at 15 and 30 days (mean ± standard deviation).

| **Variable** | **Tested Mean ± SD** | | **Control Mean ± SD** |
|---|---|---|---|
| | 15 Days | 30 Days | |
| Creatinine | 0.44 ± 0.02* | 0.460±0.025* | 0.33 ± 0.02 |
| Urea | 52.8 ± 2.39* | 43.8±2.5* | 35.8 ± 1.64 |

This results showed that there is a statistically significant rise in urea and creatinine levels, suggesting renal dysfunction and lower GFR after methamphetamine administration. This is attributed to oxidative stress resulting from increased production of reactive oxygen species (ROS), in addition to renal vasoconstriction and impaired blood perfusion, leading

to damage to glomerular and tubular cells (Kaye *et al*., 2007; Yamamoto *et al*., 2010). Higher creatinine levels were seen in the vitamin E group and higher urea levels in the same group after 30 days were found to be similar to control group, which showed that the administration of vitamin E alone was not protective on renal function. Vitamin E has been shown to be effective as an antioxidant, inhibiting lipid peroxidation and maintaining cell membrane integrity, but its effects may be dose and condition dependent and may not be apparent in healthy animals (Niki, 2014). The levels of urea and creatinine in the group treated with both methamphetamine and vitamin E did not fall to the control group level, suggesting that vitamin E did not fully protect against methamphetamine induced renal toxicity. The findings of this study indicate that oxidative stress is likely one of the critical mechanisms involved with the development of methamphetamine-induced renal damage, and the administration of vitamin E at the recommended dosage and duration of exposure was not adequate to normalize renal function. The findings of the present study are similar to those of many recent reports, which indicate that methamphetamine use is associated with functional and structural alterations in the kidney, due to increased oxidative stress, inflammatory response of cells and cellular dysfunction, as seen in the elevated levels of serum urea and creatinine. Recent studies have shown that the nephrotoxicity of methamphetamine is associated with increased production of reactive oxygen species (ROS) and activation of inflammatory pathways leading to damage to tubular and glomerular cells (Wang et al., 2023). The results are in line with the observation of Ramli et al. (2025), which reported that the chronic toxic effects of methamphetamine are not limited to the nervous system but it has a significant effect on multiple organs such as the kidneys, which is due to methamphetamine causing persistent oxidative stress, inflammation, and cellular damage. As for vitamin E, some studies have observed that its protective effect is dose-dependent, lasting over time, and influenced by the severity of the oxidative damage; and that vitamin E alone might be ineffective to reverse functional changes in severe cases of toxicity (Jomova et al., 2023), as seen in the current study, which showed a limited protection effect of vitamin E against methamphetamine-induced nephrotoxicity.

### 3.2. Histological examination

Histological examination of the kidney sections of the control group (G1) showed that the kidney had a normal architecture both in the cortex and medulla, when examined under the microscope. The renal corpuscles, including Bowman's capsule and capsular space, appeared normal, while the medullary region showed normal urinary tubules and Henle's loops without any pathological alterations Figs. (1 and 2).

In the methamphetamine-treated group (G2), marked histopathological lesions were observed after 15 days of treatment. These changes were characterized by inflammatory cell infiltration within the renal interstitium, widening of the capsular space, glomerular atrophy, degeneration of tubular epithelial cells, and focal interstitial hemorrhage Figs. (3–5). The severity of these lesions increased after 30 days of treatment, with more pronounced glomerular atrophy, extensive tubular epithelial degeneration and desquamation, intertubular hemorrhage, and persistent inflammatory cell infiltration in both cortical and medullary regions Figs. (6–8). Kidney sections from the Vitamin E-treated group (G3) exhibited relatively mild histopathological alterations after 15 days, including slight inflammatory cell infiltration and limited tubular epithelial desquamation, while the overall renal architecture remained largely preserved Figs. (9 and 10). However, after 30 days, moderate pathological changes were observed, including cortical hemorrhage, glomerular atrophy, congestion of blood capillaries, tubular epithelial desquamation, and inflammatory cell infiltration within the interstitial tissue Figs. (11 and 12). The combined methamphetamine and Vitamin E-treated group (G4) showed less severe renal lesions compared with the methamphetamine-only group. After 15 days, only mild glomerular atrophy, moderate widening of the urinary space, focal tubular epithelial degeneration, mild inflammatory cell infiltration, and vascular congestion were detected Figs. (13 and 14). Following 30 days of treatment, the renal tissue continued to exhibit relatively mild pathological alterations represented by limited glomerular atrophy, mild tubular epithelial degeneration and desquamation, and slight inflammatory cell infiltration within the interstitial tissue Figs. (15 and 16). Overall, the concurrent administration of Vitamin E appeared to attenuate the severity of methamphetamine-induced renal damage, as evidenced by the reduced extent of histopathological lesions compared with those observed in the methamphetamine-treated group.

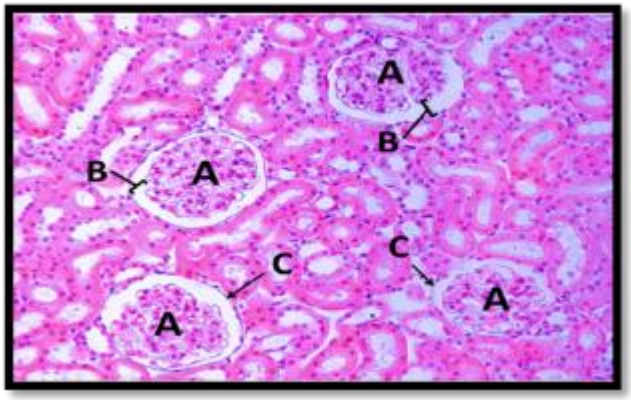


**Figure 1** Photomicrograph of a G1 control rat kidney cortex showing a normal renal glomerulus (A), capsular space (B), and Bowman's capsule (C). H&E stain, ×40. (H&E, 40X).

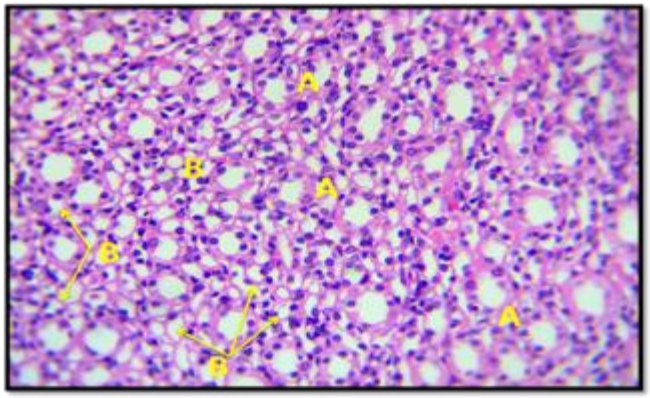


**Figure 2** Photomicrograph of a G1 control rat kidney medulla showing normal urinary tubules (A) and Henle's loops (B). (H&E, 40X).

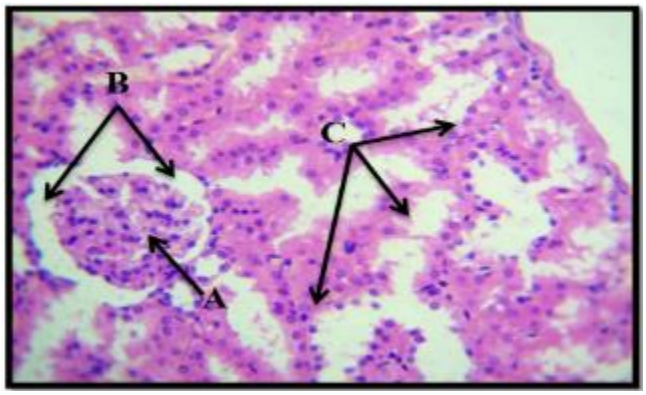


**Figure 3** Photomicrograph of the kidney cortex of a rat group that were treated with Methamphetamine (G2) for 15 days, showing a renal glomerulus with surrounding lymphocytes and macrophages (A), wide capsular space (B), and epithelial degeneration of the convoluted tubules (C). (H&E, 40X).

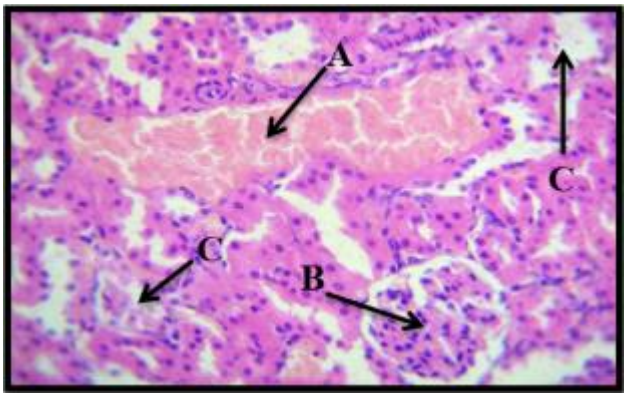


**Figure 4** Interstitial hemorrhage (A), glomerular atrophy (B), degenerated and desquamated epithelial cells within the lumen of convoluted tubules (C) are shown in the photomicrograph of rat kidney cortex treated with methamphetamine (0.1 mg/kg/day) for 15 days. . (H&E, 40X).

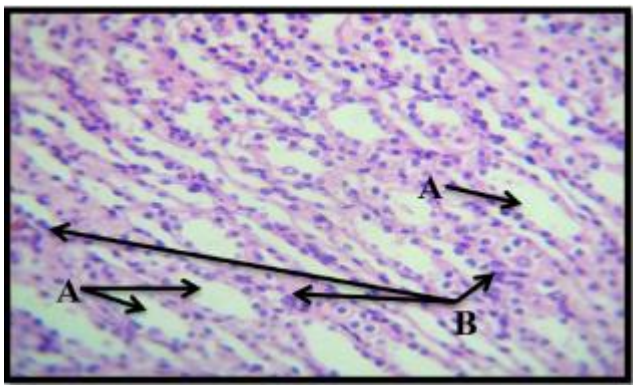


**Figure 5** Renal tubules lined by simple cuboidal epithelium (A) and infiltrated with inflammatory cells in the interstitium (B) in a rat kidney medulla treated with Methamphetamine (G2: 0.1 mg/kg/day for 15 days). (H&E, 40X).

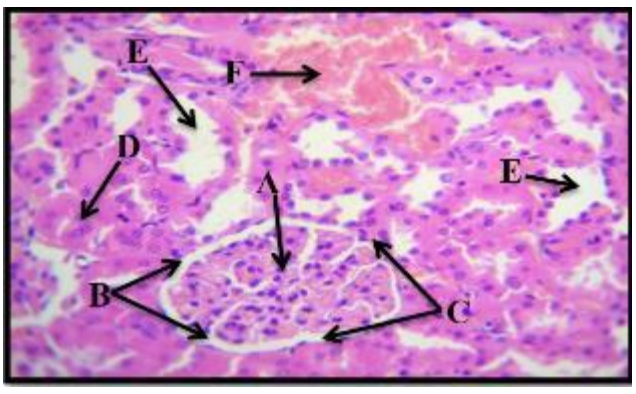


**Figure 6** Photomicrograph of the kidney cortex of a rat that received methamphetamine for 30 days (G2 (0.1 mg/kg, 1 mL/day)), which demonstrated glomerular atrophy (A), urinary space (B), Bowman's capsule (C), proximal convoluted tubules (D), distal convoluted tubules (E), and intertubular hemorrhage (F). (H&E, 40X).

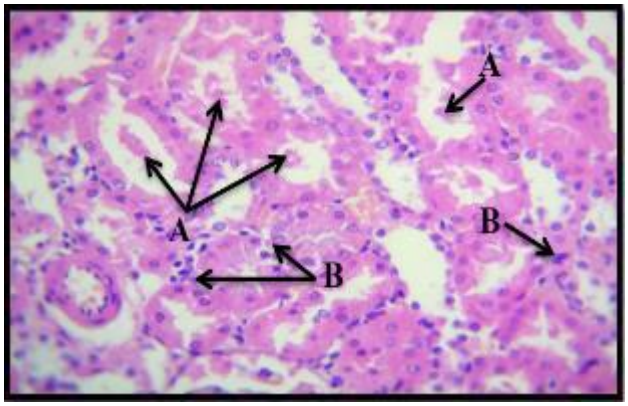


**Figure 7** Photomicrograph of rat kidney medulla following treatment with Methamphetamine (G2(0.1 mg/kg, 1 mL/day) for 30 days) depicts the degeneration, desquamation and sloughing of epithelial cells into the tubular lumen (A) and inflammatory cell infiltrate in interstitial tissue (B) (H&E, 40X).

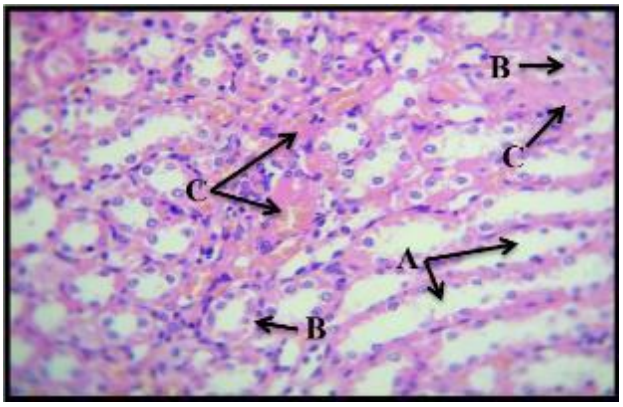


**Figure 8** Desquamation and shedding of epithelial cells into the tubular lumens (A) and blood exudate with hemolysed blood in association with inflammatory cell infiltration in the interstitial tissue (B) in a rat kidney medulla after 30 days of treatment with G2 (0.1 mg/kg, 1mL/day) Methamphetamine. (H&E, 40X).

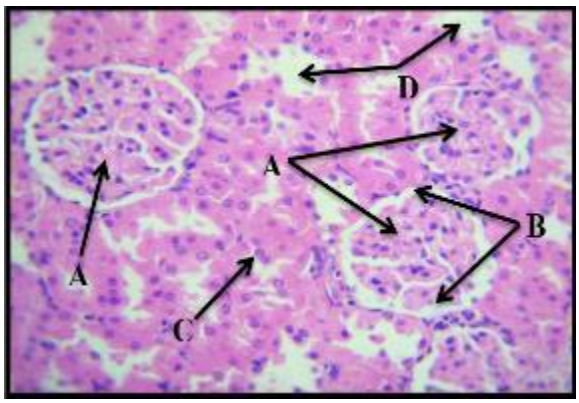


**Figure 9** Photomicrograph of kidney cortex from G3 (0.1 mL/day of Vitamin E for 15 days) with relatively normal renal glomeruli (A) with presence of inflammatory cells on the surface, widening of capsular space (B), Proximal convoluted tubules (C) and Distal convoluted tubules (D) (H&E, 40X).

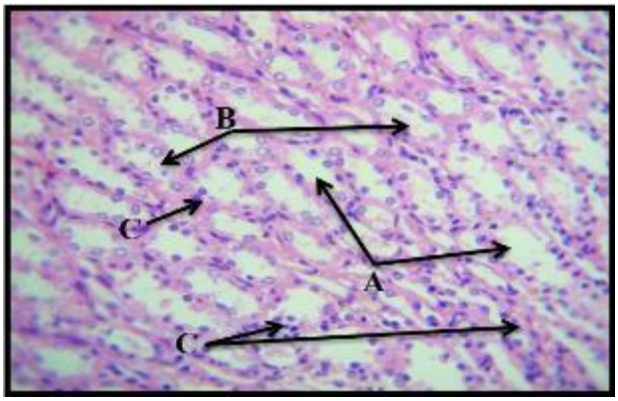


**Figure 10** Photomicrograph of the medulla of a rat kidney from G3 (0.1 mL/day of Vitamin E for 15 days) demonstrating: (A) renal tubules lined with simple cuboidal epithelium, (B) desquamation of the renal tubule epithelium in the tubular lumen, and (C) infiltration of inflammatory cells in the interstitial tissue. (H&E, 40X).

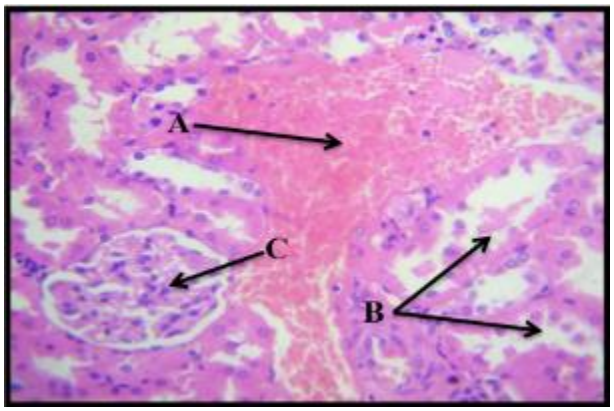


**Figure 11** Photomicrograph of a rat kidney cortex from G3 (0.1 mL/day of Vitamin E for 30 days), showing extensive cortical hemorrhage (A), desquamation of

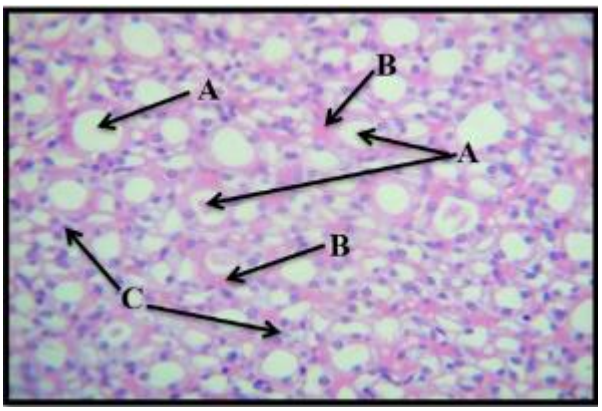


**Figure 12** Photomicrograph of a rat kidney medulla from G3 (0.1 mL/day of Vitamin E for 30 days), showing renal tubules lined by simple cuboidal epithelium (A),

epithelial cells into the tubular lumen (B), and glomerular atrophy (C).(H&E, 40X).

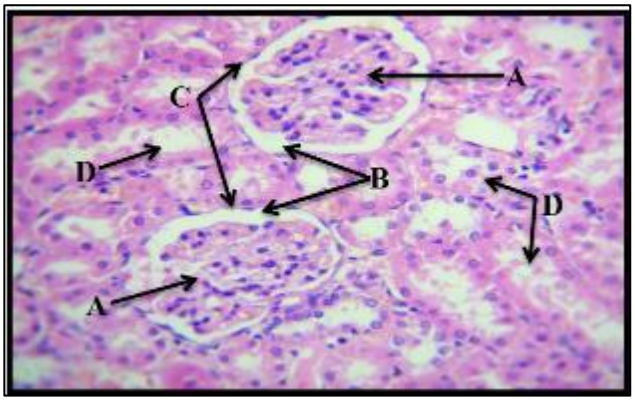


**Figure 13** Photomicrograph of kidneys of rat from G4 (methamphetamine (0.1 mg/kg, 1 mL/day) and Vitamin E (0.1 mL/day) for 15 days): Mild glomerular atrophy (A), widening of the urinary space (B), Bowman's capsule (C), and desquamated degenerative epithelial cells in the lumen of some convoluted tubules (D). (H&E, 40X).

congested blood capillaries (B), and inflammatory cell infiltration within the interstitial tissue (C). (H&E, 40X).

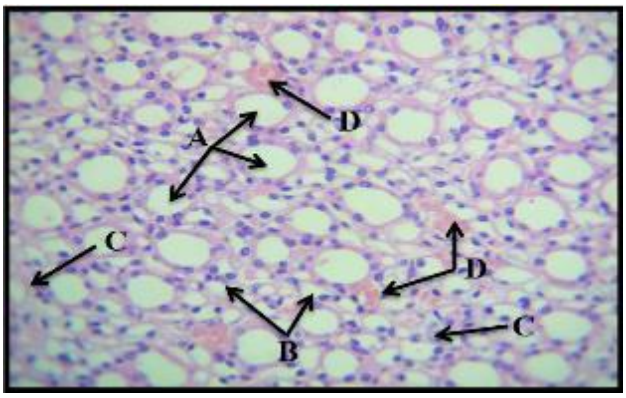


**Figure 14** A photomicrograph of the medulla of the kidney in the rat of the G4 group (methamphetamine (0.1 mg/kg, 1 mL/day) and Vitamin E (0.1 mL/day) for 15 days) shows renal tubules with low cuboidal epithelium (A), Henle's loops with simple squamous epithelium (B), inflammatory cell infiltration (C), and congestion of blood capillaries (D). (H&E, 40X).

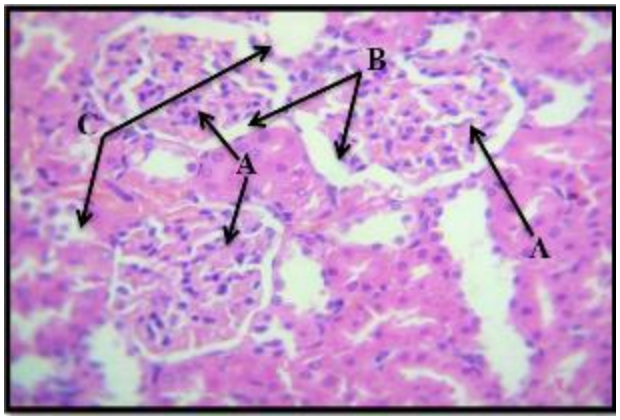


**Figure 15** Photomicrograph of a rat kidney cortex from G4 (methamphetamine (0.1 mg/kg) and Vitamin E (0.1 mL/day) for 30 days), showing degenerated and desquamated epithelial cells in the lumen of some renal tubules (C), widening of the capsular space (B) and glomerular atrophy (A). (H&E, 40X).

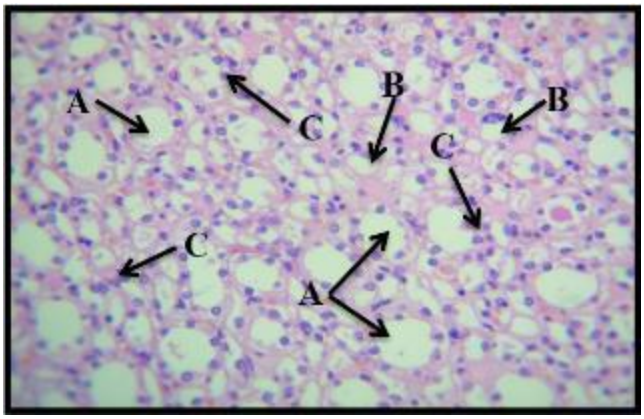


**Figure 16** Photomicrograph of rat kidney medulla of G4 (methamphetamine (0.1 mg/kg, 1 mL/day) and Vitamin E (0.1 mL/day) for 30 days) stained with haematoxylin and eosin showing the thin limbs of Henle's loops (A) and inflammatory cell infiltration within the interstitial tissue (B). (H&E, 40X).

The present results demonstrated that the control group (G1) exhibited a normal histological architecture of the kidney in both the cortical and medullary regions, indicating intact renal structural integrity under physiological conditions Figs. (1, 2). In contrast, the methamphetamine-treated group (G2) showed marked histopathological alterations that increased in severity with the duration of exposure. These changes included interstitial inflammatory cell infiltration, glomerular atrophy, widening of Bowman's capsule space, degeneration and desquamation of tubular epithelial cells, and interstitial hemorrhage. These findings suggest a direct and indirect toxic effect of methamphetamine on renal tissue, mainly mediated through oxidative stress and impaired renal microcirculation. Recent studies have reported that methamphetamine induces excessive production of reactive oxygen species (ROS) and mitochondrial dysfunction, leading to damage of renal tubular epithelial cells, cellular degeneration, and apoptosis, as well as activation of inflammatory responses within renal tissue (Wang *et al*., 2023). Furthermore, methamphetamine-induced renal microcirculatory disruption can cause vascular changes including congestion and interstitial hemorrhage, which can cause local hypoxia and further aggravate tissue damage ( Zhang et al., 2021).The present study has confirmed the above changes in the histopathological changes of gills in stress condition, which confirms the findings of above. (3–8), where renal injury increased in severity after 30 days, suggested that the nephrotoxicity caused by the use of

methamphetamine is dose-, time- and duration-dependent. The vitamin E treated group (G3) exhibited relatively mild histopathological alterations, such as less inflammatory cell infiltration and mild tubular epithelial desquamation with the overall renal architecture preserved. This could be due to the strong antioxidant effect of vitamin E, which neutralizes free radicals and prevents lipid peroxidation, thus preserving the integrity of cell membranes (Kumar et al., 2021). The slight changes observed after 30 days however, Figs. According to (11, 12), vitamin E cannot totally prevent damage, but it is able to lessen the severity of the damage.A definite improvement in renal histology was seen in the methamphetamine plus vitamin E group (G4) when compared with the methamphetamine alone group. Slight glomerular atrophy, widening of the urinary spaces and a limited degree of tubular epithelial degeneration were still noted, as was a mild inflammatory infiltration. The results are suggestive of a possible protective role for vitamin E against the renal toxicity associated with methamphetamine use, which may be mediated by its antioxidant properties and inhibition of inflammatory pathways (Baltušnikienė, et al., 2023). Protection, however, was not complete as normal histology was not restored, and appeared to be related to the intensity and duration of exposure. Overall, it is concluded that methamphetamine is clearly nephrotoxic, with a time dependency that vitamin E has a protective effect but does not prevent all methamphetamine-induced histopathological changes.

## 4. Conclusion

Methamphetamine is toxic to the kidneys, resulting in chronic histological changes that range from tubular degeneration to glomerular atrophy, inflammation and interstitial hemorrhage, depending on the length of exposure. There are simultaneous and significant abnormalities in biochemical markers of renal function, including increases in creatinine and urea levels, which indicate renal tissue functional and structural deterioration. Vitamin E had a significant protective action, which resulted in a decrease in the severity of histological changes and enhanced biochemical markers by inhibiting oxidative stress, but did not completely prevent the occurrence of damage. Overall, there is a strong relationship between the toxicity of the tissues and kidney function impairment resulting from methamphetamine use, in which vitamin E appears to play a role.

## Compliance with ethical standards

### *Disclosure of conflict of interest*

No conflict of interest to be disclosed.

### *Statement of ethical approval*

The ethical standards and guidelines for the care and use of laboratory animals have been followed strictly in this study. Ethics Committee of Medical Biotechnology Department, College of Science, Tikrit University, Iraq reviewed and approved the experimental procedures.

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