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Original Paper

Therapeutic effects of meropenem on renal histological changes of laboratory rats induced by *Proteus mirabilis*

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ABSTRACT

Antibiotics are essential agents for controlling bacterial infections and play a central role in reducing infection-related mortality. This study aimed to investigate the effect of *Proteus mirabilis* infection on kidney tissue in rats and to evaluate the biochemical and histological effects of different doses of meropenem. Twenty laboratory rats were used and divided into four groups: a control group that received PBS only (group 1), an infected untreated group that received a *P. mirabilis* inoculum without treatment (group 2), and two infected groups treated with meropenem at 10 mg/kg (group 3) and 30 mg/kg (group 4). The results showed that the infected untreated group had a clear increase in renal injury markers, including urea and creatinine, as well as the oxidative stress marker malondialdehyde (MDA), accompanied by a decrease in glutathione (GSH), compared with the control group. Treatment with 10 mg/kg meropenem produced only partial improvement in these changes. In contrast, the 30 mg/kg dose produced broader improvement and restored most measured biochemical markers closer to normal levels.

The histological findings were consistent with the biochemical results. Kidney sections from the infected untreated group showed obvious structural damage, whereas the treated groups showed recovery of renal architecture. The improvement was most pronounced in the 30 mg/kg meropenem group, in which renal tissue appeared close to normal. These findings indicate that meropenem limited the harmful effects of *P. mirabilis* infection and helped preserve kidney structure and function, with greater renal protection observed at the higher dose.

Keywords: *Meropenem, Kidney, Laboratory rats., Proteus mirabilis*

1 INTRODUCTION

Urinary tract infections (UTIs) are among the most common diseases globally. *Proteus mirabilis* is frequently associated with UTIs and is a major cause of different infections, including wound infections, burn infections, central nervous system infections, including meningitis, and middle ear infections [1, 2]. It is also associated with autoimmune complications in individuals genetically predisposed to rheumatoid arthritis (RA) [3]. Swarming motility is a key identifying feature of *P. mirabilis* when cultured on solid media. This motility acts as a virulence factor that enables the organism to invade the urinary tract by ascending to the upper urinary tract, including the kidneys. *P. mirabilis* is considered one of the common causes of UTIs in patients with urinary catheters [4]. Catheterization provides a surface that supports colonization and makes persistent infection more likely.

The bacterium induces urinary stone formation and is responsible for many apatite and struvite stones in the bladder and kidney, making treatment of UTIs more challenging [5]. The organism adapts efficiently to stressful conditions by producing enzymes such as urease and protease and by forming biofilms. These traits increase its survival, resistance to treatment, and ability

to maintain long-lasting infection [6].

P. mirabilis infections have been linked to tissue injury and acute pyelonephritis, and several studies have indicated that this damage occurs more frequently in males than in females [7]. The resulting damage to urinary tract tissues is caused not only by the direct presence of bacteria but also by the contribution of the host inflammatory response to structural damage and loss of function in the affected tissue.

Antibiotics remain essential for controlling bacterial infections and have played a central role in reducing mortality [8]. At the same time, selective pressure from heavy and repeated antibiotic use has accelerated the development of resistance, which is now considered a major global health concern [9]. Meropenem is a broad-spectrum carbapenem antibiotic that is often used against multidrug-resistant Gram-negative bacteria, including *P. mirabilis*. It acts by disrupting bacterial cell wall synthesis, leading to cell lysis and loss of viability. Meropenem is already used clinically, especially in severe infections where renal involvement is a concern. However, despite its wide use, relatively few studies have described how meropenem affects biochemical indicators of kidney injury and the microscopic histopathological appearance of renal tissue during active infection [10, 11].

In this study, we focused on the kidney because it is a direct target in ascending urinary infection. The aim was twofold: first, to evaluate how *P. mirabilis* infection alters renal tissue and renal function in a controlled rat model; and second, to test whether meropenem at defined doses can limit this damage. By comparing infected untreated rats with infected rats treated with meropenem at different doses, using non-infected rats as a control reference, we assessed both biochemical markers and histological changes. The goal was to determine the extent to which meropenem can protect renal tissue from infection-related injury and to generate evidence that may be useful for future applications in human and veterinary settings.

2 MATERIALS AND METHODS

2.1 Preparation of bacterial inoculum

The *P. mirabilis* inoculum was prepared by culturing the bacteria in a 250 mL glass flask containing 100 mL of sterile nutrient broth. The medium was inoculated with isolated and purified bacteria and incubated for 24 h. The appearance of turbidity in the medium indicated bacterial growth, and this culture was used as the bacterial inoculum. A tenfold serial dilution series was then prepared. From the seventh dilution, 0.5 mL was plated on nutrient agar to determine bacterial density by counting the colonies that grew on the surface of the medium. This dilution was then used for intraperitoneal (IP) injection in laboratory rats to induce infection.

2.2 Preparation of the treatment

Meropenem powder was used to treat rats infected with *P. mirabilis*. Two dosing preparations were prepared. For the lower dose, 12.5 mg of antibiotic powder was dissolved in 2.5 mL of sterile normal saline. This preparation corresponded to a working dose of 10 mg/kg. For the higher dose, 37.5 mg of powder was dissolved in 2.5 mL of sterile normal saline to obtain a dose of 30 mg/kg.

2.3 Laboratory animals used in the study

The experiment was carried out in the animal house of the Department of Life Sciences, College of Education for Pure Sciences, University of Anbar, which was equipped with the required materials for the study. A total of 20 male Sprague Dawley rats were used. The animals weighed 180–220 g and were 6–8 weeks old. They were kept in plastic cages with metal lids prepared for this work and maintained under controlled conditions. The light cycle was set to 11 h of light and 13 h of darkness, and the room temperature was maintained at 22 ± 2 °C. The cages were cleaned and sterilized, and the sawdust bedding was replaced twice per week. A commercial diet and water were supplied to the rats throughout the study period. The animals were acclimatized for 2 weeks before the experiments to ensure that they were free from disease and in normal health condition.

2.4 Experimental design

Twenty laboratory rats were divided into four groups, with five rats in each group and approximately similar body weights. Group 1 served as the control group and received a single intraperitoneal injection of 0.5 mL phosphate-buffered saline (PBS). Group 2 rats were infected with 0.5 mL of *P. mirabilis* inoculum taken from the seventh bacterial dilution by IP injection four times over 7 days. Group 3 rats were infected with the same bacterial inoculum and treated with a low dose of meropenem at 10 mg/kg 3 h after inoculum injection. The animals were injected twice over 14 days, and the antibiotic was administered five times over the same

period. Group 4 was treated in the same manner as group 3, but with a higher meropenem dose of 30 mg/kg.

2.5 Collection of blood samples

After anesthesia in accordance with institutional animal care guidance, whole blood samples of 5 mL were collected directly by cardiac puncture. The samples were collected in anticoagulant-free test tubes and kept at room temperature for 15–20 min to allow clot formation. The tubes were then centrifuged at 3000 rpm for 15 min, and the serum was separated for biochemical analysis.

2.6 Biochemical tests

Biochemical tests were performed according to each kit manufacturer's instructions, including urea [12], creatinine concentration [13], oxidative stress assessment by measuring malondialdehyde (MDA) [14], and antioxidant assessment by measuring glutathione (GSH) levels [15].

2.7 Tissue sampling

Fresh rat kidney tissue was excised and fixed in 10% formalin. The samples were then dehydrated in a graded ethanol series of 70%, 80%, 90%, and 100% and prepared for embedding in paraffin wax. Tissue sections were cut using a rotary microtome at a thickness of 5–7 µm and stained with standard hematoxylin and eosin (H&E). The stained sections were examined under a light microscope equipped with a digital camera.

2.8 CFU determination from infected kidney tissues

After each kidney was excised and before fixation in formalin for histological examination, 1 g of kidney tissue was placed in a tube containing 2 mL of normal saline. The tissue was homogenized and then subjected to a series of decimal dilutions in sterile saline. Then, 0.5 mL of the seventh dilution was transferred into a sterile Petri dish, and nutrient agar was poured into the dishes. The plates were incubated at 37 °C for 24 h. Colonies were counted as colony-forming units (CFU) per gram of tissue to quantify bacterial load.

2.9 Statistical analysis

GraphPad Prism 8.0 software was used to statistically analyze differences among treatment groups. One-way analysis of variance (ANOVA) was used, and significance was assessed at $p < 0.05$. Group comparisons were interpreted using Duncan's multiple range test [16]. Mean values were calculated for each group.

3 RESULTS AND DISCUSSION

Figures 1 and 2 show a significant increase in both urea and creatinine levels in group 2, which received the *P. mirabilis* bacterial inoculum, compared with the control group. In group 3, which was injected with the bacterial inoculum and then treated with meropenem at 10 mg/kg, urea levels showed a significant decrease, whereas creatinine levels did not show a significant reduction compared with group 2. In group 4, which received the bacterial inoculum followed by meropenem at 30 mg/kg, both urea and creatinine levels showed a clear and significant decrease compared with group 2. The results indicated a significant increase in serum urea concentration in group 2, which was infected with *P. mirabilis*. This increase indicates renal dysfunction caused by the spread of the bacteria and the resulting renal tissue damage.

P. mirabilis is known to cause pyelonephritis and can directly damage the renal tubules. This damage may weaken the ability of the tubules to eliminate waste products such as urea. The nephrons may also be affected, leading to a reduction in glomerular filtration rate (GFR), which results in the accumulation of urea in the blood [17]. Urease produced by *P. mirabilis* cleaves urea into ammonia and carbon dioxide. The produced ammonia increases urinary alkalinity and promotes salt precipitation and deposition, leading to the formation of struvite stones. These stones may obstruct urine flow, increase pressure on the kidneys, interfere with normal renal function, and contribute to renal failure and urea accumulation in the blood [18]. Systemic inflammation and activation of the immune response may also impair renal perfusion through systemic and renal vascular changes. Reduced renal perfusion decreases blood delivery to the kidneys and limits the clearance of metabolic products such as urea. In contrast, the third and fourth groups, which received treatment, showed a reduction in serum urea concentration. This reduction was most evident in group 4, which received meropenem at 30 mg/kg. In this group, urea levels decreased significantly and approached the values of the control group. This pattern suggests that treatment improved kidney function by limiting the harmful effects of the bacteria, restricting the spread of infection into renal tissue, and helping to preserve the structure of the renal tubules.

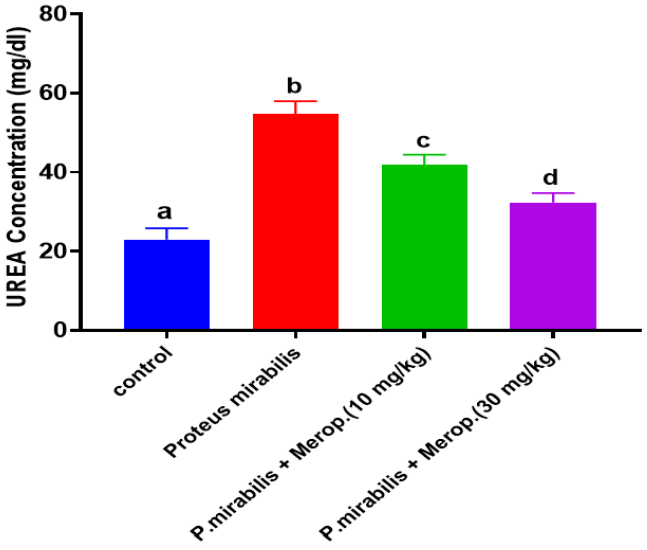

Fig. 1 The effect of Meropenem treatment on Urea levels in the renal tissue of rats (5 for each group) infected with *P. mirabilis* bacteria. Different English letters indicate significant differences at the probability level ($P \leq 0.05$).

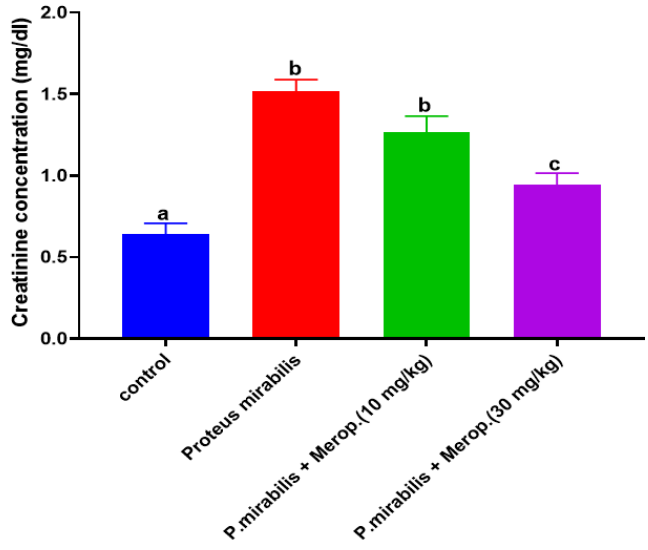

Fig. 2 The effect of Meropenem treatment on Creatinine levels in the renal tissue of rats (5 rats for each group) infected with *P. mirabilis* bacteria. Letters indicate significant differences at the probability level of $p \leq 0.05$.

Creatinine is a product of creatine breakdown in muscle and is normally excreted by the kidneys. Therefore, it is widely used as an indicator of renal function. Group 2 animals showed an increase in creatinine levels. This increase may have resulted from direct damage to the renal tubules and glomerular cells, systemic inflammatory activation, reduced renal perfusion, urease activity, and stone formation [19]. Compared with group 2, group 3 did not show a significant reduction in creatinine levels. This may be due to the lower meropenem dose, which may not have been sufficient to overcome the bacterial effects or achieve complete functional recovery in the kidney. A significant decrease in creatinine level was observed in group 4 compared with the other infected groups. This finding suggests that the higher meropenem dose was more effective in limiting renal damage, restoring part of the filtration capacity, and improving renal function. This effect is consistent with reduced bacterial load in renal tissue and reduced systemic inflammatory response.

Figures 3 and 4 indicate an increase in MDA concentration and a decrease in GSH concentration in group 2, which was infected with *P. mirabilis*, compared with the control group. In group 3, MDA levels decreased and GSH levels increased compared with group 2. Group 4 showed a similar pattern, with decreased MDA levels and increased GSH levels compared with group 2. The results indicated a marked increase in MDA levels. MDA is a byproduct of lipid peroxidation and is commonly used as a marker of oxidative stress and cell membrane injury. Group 2 showed severe oxidative stress, as indicated by the high MDA level, which was likely driven by the inflammatory response resulting from bacterial infection,

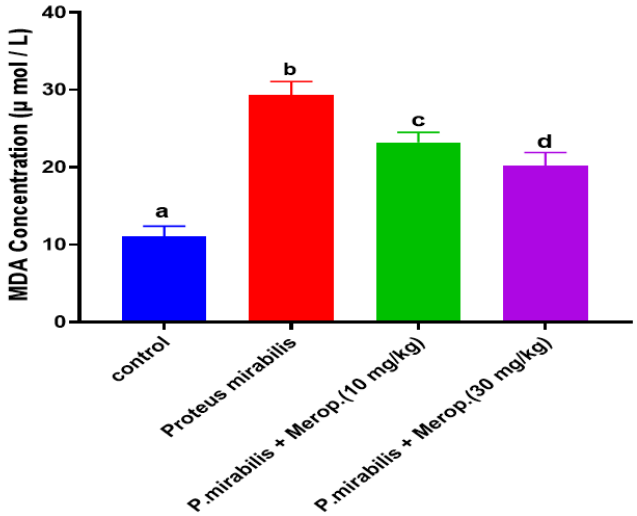

Fig. 3 Effect of Meropenem treatment on MDA levels in the renal tissue of rats (5 for each group) infected with *P. mirabilis* bacteria. Different English letters indicate significant differences at the probability level ($P \leq 0.05$).

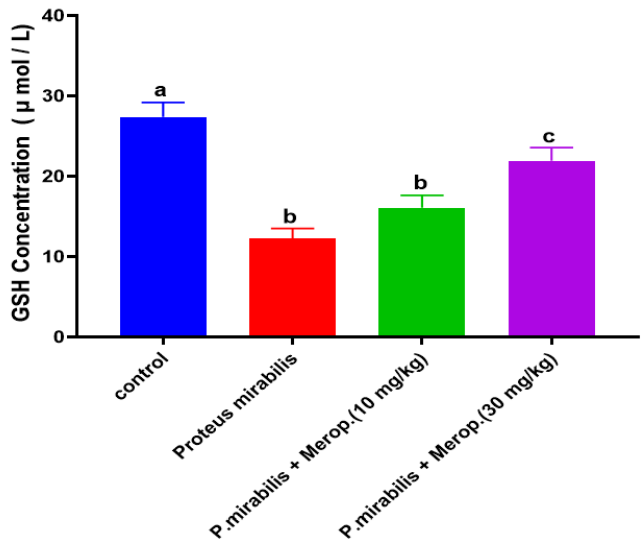

Fig. 4 Effect of Meropenem treatment on GSH levels in the renal tissue of rats (5 for each group) infected with *P. mirabilis* bacteria. Different English letters indicate significant differences at the probability level ($P \leq 0.05$).

possibly due to lipopolysaccharide (LPS) in the bacterial cell wall. LPS can stimulate innate immune receptors, such as Toll-like receptor 4 (TLR-4), leading to macrophage and neutrophil activation and increased generation of reactive oxygen species (ROS).

ROS attack unsaturated fatty acids in cell membranes, leading to extensive lipid peroxidation and disruption of membrane integrity [20]. The lower MDA levels observed in groups 3 and 4 may indicate partial improvement in oxidative status, especially in group 4. These results suggest that meropenem treatment helped protect cells and tissues during bacterial infection. This effect may be related to the ability of meropenem to reduce bacterial burden, thereby decreasing LPS-mediated TLR-4 stimulation, excessive immune activation, inflammatory cytokine release, and ROS generation [21].

Glutathione (GSH) is one of the main endogenous antioxidant molecules in the body. It neutralizes free radicals and limits oxidative damage. GSH levels were markedly decreased in group 2, reflecting severe oxidative stress induced by innate immune responses to bacterial LPS. Under these conditions, neutrophils and macrophages produce large amounts of ROS, while GSH is rapidly consumed in an attempt to neutralize these reactive species [22]. ROS may also increase because of enhanced pro-oxidant enzyme activity, which accelerates GSH depletion. Similarly, inflammatory cytokines may stimulate ROS-generating pathways and interfere with normal GSH regeneration. These effects disrupt the redox balance [23]. GSH levels showed mild recovery in group 3, whereas a higher level was observed in group 4 compared with the infected untreated group. These findings may indicate partial restoration of the antioxidant defense system in the treated groups. The higher dose of meropenem may have reduced the bacterial load, thereby decreasing ROS production, lowering oxidative pressure on cells, and allowing GSH levels to recover. This pattern supports cell membrane stabilization and partial restoration of redox balance.

Figure 5 shows the histological examination of kidney tissue from the control group. The renal cortex contained renal corpuscles with glomeruli (G) surrounded by the capsular space and Bowman's capsule (BC), which was lined by simple squamous epithelium. Bowman's space (BS) was visible, and the cortex showed a dense field of convoluted tubules (CT). Both the glomeruli and tubules showed normal morphology.

In group 2, which was injected with the *P. mirabilis* bacterial inoculum, the renal tissue showed clear pathological changes (Figures 6 and 7). The observed changes included glomerular damage (GD), complete glomerular lysis (GL), cellular degeneration (D), inflammatory infiltration (IL), deposition of necrotic material (NM), dilation of convoluted tubules (CT), congestion (CON), and segmental lesions (SL). In group 3, which received the bacterial inoculum followed by meropenem at 10 mg/kg, the histological sections showed glomeruli (G), Bowman's capsule (BC), dilated convoluted tubules (CT), congestion (CON), endothelial cell degeneration (D), and inflammatory infiltration (IL) (Figures 8 and 9). These findings indicate partial improvement, although inflammatory and degenerative changes were still present. In group 4, which received the bacterial inoculum followed by meropenem at 30 mg/kg, renal tissue showed glomeruli with a near-normal appearance (G), along with convoluted tubules (CT) and Bowman's capsule (BC) (Figures 10 and 11). However, hemorrhage (H) and inflammatory infiltration (IL) were still observed. These features suggest that meropenem improved renal architecture at the higher dose, although complete histological recovery was not achieved.

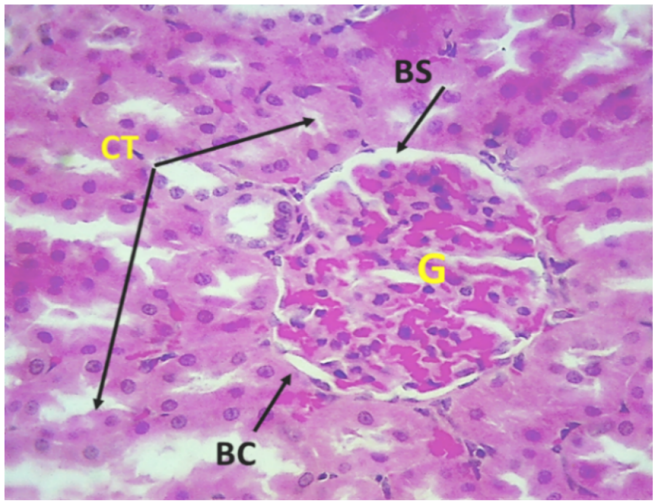

Fig. 5 A cross section of control group kidney showing Glomerulus (G), Convoluted Tubules (CT), Bowman's capsule (BC), and Bowman's space (BS). (H & E stain. 400X).

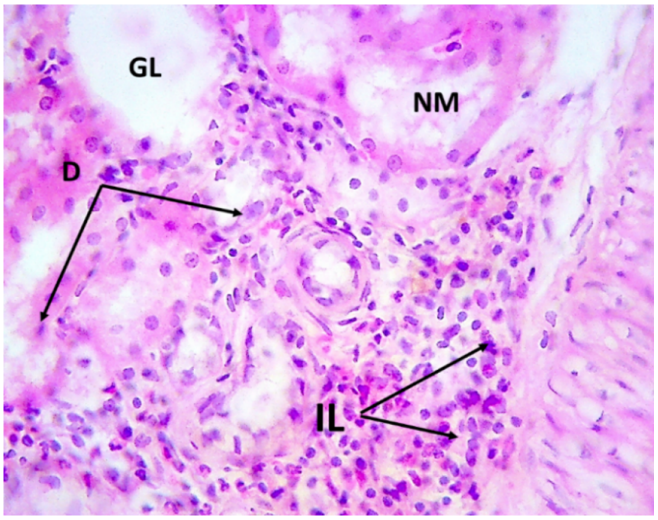

Fig. 7 A cross section of kidney of the second group showing complete Glomerular Degeneration (GL), deposition of Necrotic Material (NM), Degeneration of cells (D), and Inflammatory Infiltration (IL). (H & E stain. 400X).

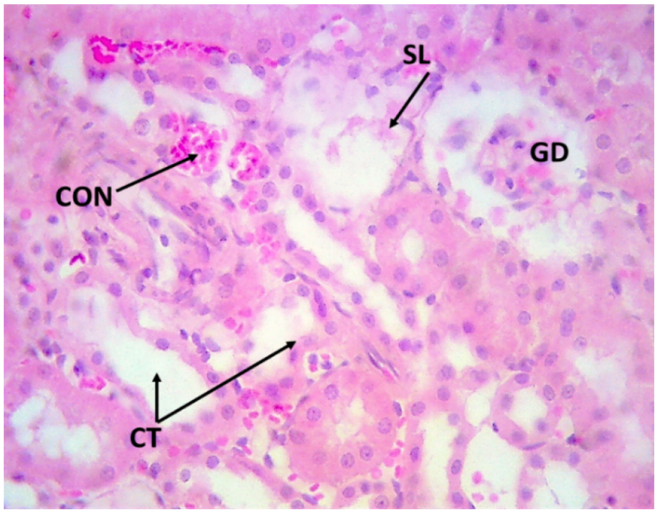

Fig. 6 A cross section of kidney of group II showing Glomerular Degeneration (GD), dilatation of Convoluted Tubules (CT), Congestion (CON), and Sloughing of tubule Lining (SL). (H & E stain. 400X).

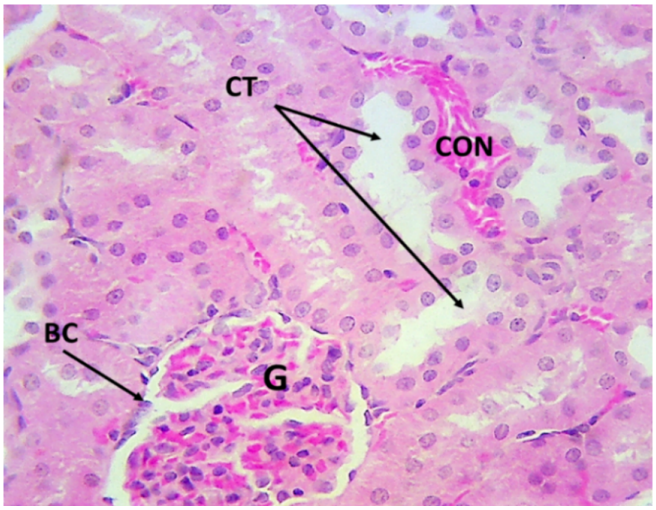

Fig. 8 A cross section of kidney of group III showing Glomerulus (G), Bowman's capsule (BC), Convoluted Tubule dilatation (CT), and Congestion (CON). (H & E stain. 400X).

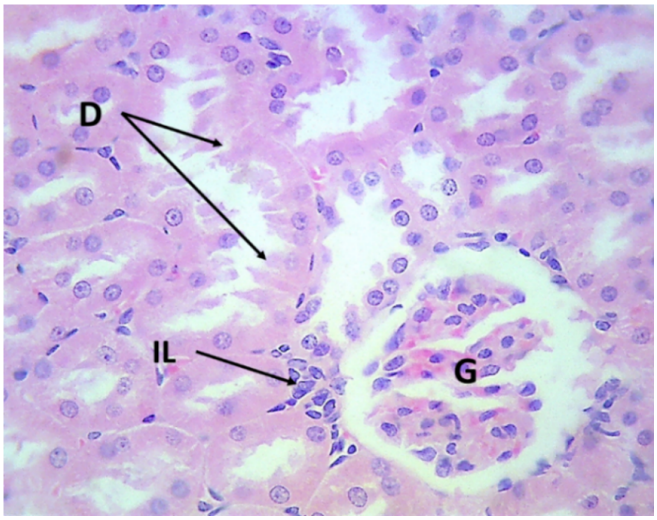

Fig. 9 A cross section of kidney of group III showing Glomerulus (G), endothelial cell Degeneration (D), and Inflammatory Infiltrate (IL). (H & E stain. 400X).

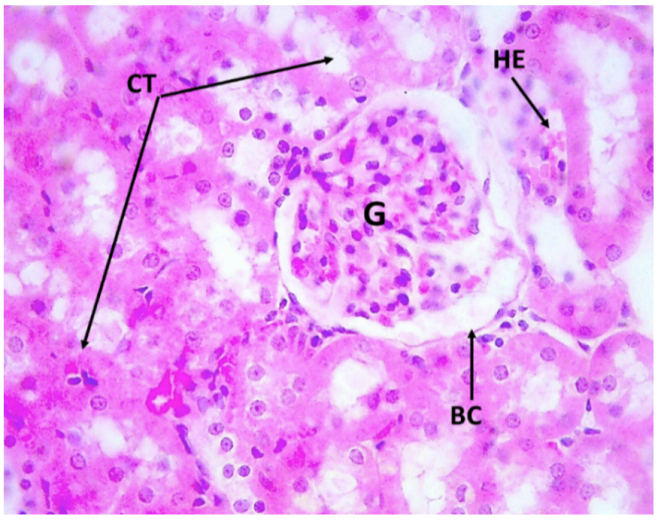

Fig. 10 A cross section of kidney of group IV showing Glomerulus (G), Convoluted Tubules (CT), Bowman's capsule (BC), and Hemorrhage (HE). (H & E stain. 400X).

Histological examination of renal tissue from the control group showed normal architecture. The glomerulus (G) appeared partially lobulated and was enclosed within Bowman's capsule (BC), with an intact Bowman's space (BS) lined by simple squamous cells. Numerous convoluted tubules (CTs) were present, with clear lumens and preserved cellular structure.

These findings indicate that the procedure alone, represented by PBS injection, did not affect renal architecture. The normal serum urea and creatinine values in this group further support its use as the baseline comparator for the other groups.

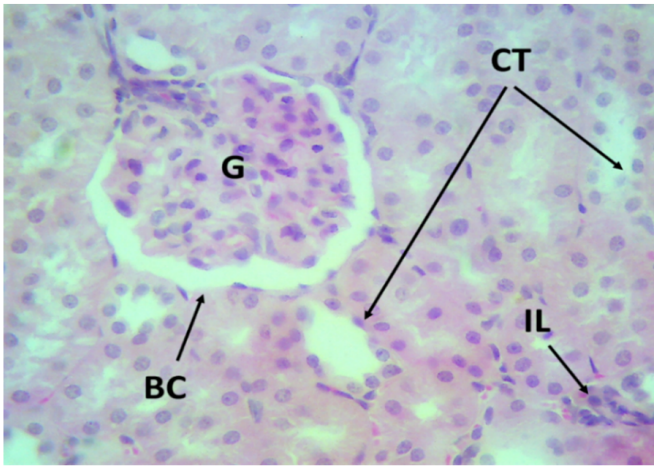

Fig. 11 A cross section of kidney of group IV showing Glomerulus (G), Convoluted Tubules (CT), Bowman's capsule (BC), and Inflammatory Infiltrate (IL). (H & E stain. 400X).

By contrast, kidneys from the *Proteus mirabilis*-infected group showed pronounced histopathological changes. Tissue sections revealed glomerular damage (GD) and, in some areas, complete glomerular lysis (GL), indicating injury to the primary filtration unit. Segmental lesions (SL), tubular dilatation, inflammatory infiltrates (IL), congestion (CON), and necrotic material (NM) were also evident. These lesions are consistent with the known virulence mechanisms of *P. mirabilis*. Urease alkalinizes urine and promotes crystal deposition, which can mechanically injure renal tubules and the urothelium, while endotoxin lipopolysaccharide (LPS) induces inflammation, recruits leukocytes, and contributes to tissue injury and scarring. Hemolysin HpmA and proteases may further injure tubular cells and degrade cellular components [24, 25]. Functionally, these changes are consistent with elevated serum urea and creatinine levels, reflecting reduced filtration and nitrogenous waste retention. In addition, ZapA can degrade immune proteins, including IgA and IgG, facilitate mucosal translocation in the urinary tract, and contribute to glomerular basement membrane (GBM) disruption [26], allowing plasma leakage and worsening glomerular injury.

In group 3, renal tissue showed partial improvement compared with the untreated infected group. However, some abnormalities persisted, including dilatation of

convoluted tubules, inflammatory infiltrates, and other residual lesions. These findings suggest that the lower meropenem dose reduced renal injury and limited infection-related damage but did not fully restore normal histology. Continued bacterial toxin activity may have sustained the inflammatory response. The modest reduction in serum urea and creatinine levels compared with group 2 is consistent with this partial recovery.

In group 4, histological examination indicated clearer recovery of renal microanatomy. The glomeruli (G) and convoluted tubules (CTs) appeared closer to normal, and Bowman's capsule (BC) and Bowman's space (BS) showed a more regular outline [27]. Minor hemorrhage (H) and residual inflammatory infiltrates were still present, consistent with ongoing repair and residual infection-related effects. This histological improvement paralleled the marked decline in serum urea and creatinine levels, supporting the greater efficacy of the higher meropenem dose in controlling infection, attenuating inflammation, and improving both structural and functional renal integrity.

3.1 Bacterial count from infected renal tissues

After preparation of the bacterial inoculum, the bacterial count was determined using the colony-forming unit (CFU) method. In this assay, 0.5 mL of the inoculum at the seventh dilution contained 95×10^7 CFU. The bacterial count measured at the seventh dilution (10^7) from renal tissue infected with *P. mirabilis* showed clear differences among the groups. The infected untreated group had the highest bacterial load, at 6×10^7 CFU/g, indicating extensive bacterial proliferation without treatment. In the group that received the low meropenem dose of 10 mg/kg, the count decreased to 2×10^7 CFU/g, showing a moderate reduction in bacterial load. In the group treated with the higher meropenem dose of 30 mg/kg, the count decreased further to 1×10^7 CFU/g, indicating that the higher dose was more effective in reducing the bacterial burden in kidney tissue.

4 CONCLUSION

In this rat model, infection with *P. mirabilis* disrupted kidney function and structure. The infected untreated group showed increased renal function markers, including urea and creatinine, together with clear evidence of oxidative stress and renal tissue injury. Treatment with meropenem reduced these harmful biochemical changes and improved the histological appearance of kidney tissue, especially at the higher dose. Overall, these findings indicate that meropenem helped limit renal damage caused by *P. mirabilis* infection and supported both structural recovery and functional improvement of the kidney.

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Author contributions

All authors contributed to the conception, design, data collection, analysis, interpretation, and drafting of the manuscript. All authors read and approved the final version.

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Data availability

N/A

DECLARATIONS

Conflict of interest

The authors declare no conflict of interest.

Consent to publish

N/A

Ethical approval

The study was approved by the Research Ethics Committee at Anbar University on December 26, 2024, under reference 267.

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