

The Alteration of Blood Picture and Histopathological Changes by *Proteus Mirabilis* in Albino Male Rats

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Abstract:

Thirty (30) male rats used in the study and were divided equally into three groups: 1st group (GI): given (1CC /animal) an oral dose of phosphate buffer saline (PBS) by a stomach tube as a control group for 60 days, 2nd group (GII): One dose weekly were given 1CC viable *Proteus Mirabilis* (1×10^9 CFU/ml) orally by stomach tube for 60 days, 3rd group (GIII): twice dose weekly were given 1CC viable *Proteus Mirabilis* (1×10^9 CFU/ml) orally by stomach tube for 60 days. After 60 days of experiment collected the blood from heart for hematological analysis and collected tissue sample from kidney and urinary bladder were taken for pathological examination.

The results of hematological analysis showed significant decrease in RBC, Hb, HCT, platelets, while significant increase in WBC, neutrophils, lymphocytes & monocytes in 2^{ed} group and 3^{ed} group compare with control group.

The histopathological changes of Kidney in 2nd group include: all the cell lining of the proximal convoluted tubules are swollen due to acute cellular swelling and mild infiltration of inflammatory cells, other section showed bands of interstitial fibrosis with dense infiltration of mononuclear cells, Dense protein cast in the tubules, In 3rd group showed all tubules hydropic (acute cellular swelling), heavy infiltration around glomeruli and in the interstitial with chronic inflammatory cells, most of one lobule is necrotic and disrupted with many nuclear fragment and adherent to epithelial of Bowman capsule.

The histopathological changes of urinary bladder in 2nd group showed thickened connective tissue of stroma, ulcer of transitional layer, edema with mononuclear cells infiltration, also congested of blood vessels inside the gland, congested blood vessels in the muscular layer with monocytes, In 3rd group showed chronic inflammatory cells infiltration mostly macrophage in the lumen and stroma of bladder, congested of blood vessels in submucosal layer, homogenous to hyalinized like mucosa, squamous cells of transitional layer.

The aim and position of this study to clarify the belongings of *Proteus Mirabilis* on blood profile and kidney with urinary bladder tissue after exposure orally.

Keywords: *Proteus Mirabilis*, kidney and urinary bladder, blood profile, pathological changes, Albino male rats.



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Introduction:

Proteus mirabilis, a pathogenic bacterium belonging to the Enterobacteriaceae family, is ubiquitously distributed across a myriad of natural environments (Lian *et al.*, 2025). Recognized as one of the predominant pathogens responsible for urinary tract infections (UTIs), *P. mirabilis* can instigate both acute pyelonephritis and cystitis (Mirzaei *et al.*, 2019). This type of bacterium can be found in a wide variety of ecological niches, including water, sewage, soil, and is even described as a commensal organism in the intestines of humans and other animals (Vaez *et al.*, 2022). Factors of *Proteus* virulence that are considered. *mirabilis*-induced UTIs encompass adhesions, motility, biofilm formation, immuneavoidance mechanisms, toxins, and the acquisition of nutrients (Fox-Moon & Shirtliff, 2024).

Proteus, commonly found as normal flora in the intestinal tract, exhibits saprophytic behavior. However, certain strains of his bacteria may assume parasitic status and pose opportunistic pathogens, capable of causing diverse infections when they leave their natural habitats (Brooks *et al.*, 2007). Inside the intestines of humans and domesticated and wild animals, as well as in the natural habitat, *Proteus* bacilli, under favorable conditions, can induce pathological lesions in various organs, including the

respiratory tract, skin, ear, eye, nose, throat, burns, and wounds; and additionally, they can cause gastroenteritis (Manos and Belas, 2006).

The harshness of every contagion produced by the memberships of the genus *Proteus* be contingent on the suitability of virulence issues, Virulence factors that drive inflammatory processes are possessed by *Proteus mirabilis* such as the production hemolysin and urease, movement in waves (swarming), the capacity of attaching to epithelial cell, and production of endotoxin (Jacobsen and Shirtliff, 2011).

Materials and methods:

The isolation of urine samples from Al Khalis Hospital and Al Khalis station, From Diyala which were collected in sterile tube, transport to the laboratory, Department of Medicine College of Veterinary Medicine University of Diyala. The sample was centrifuged at (3000 rpm for three minutes); floating was neglected and apart of sediment was taken by loop and cultured on media (MacConkey and blood agar) for 24 hours at 3 °C in the incubator, and *Proteus Mirabilis* was identified by VITEK-2system.

A standardized suspension of *Proteus mirabilis* was meticulously prepared to attain a final concentration of approximately 1×10^9 CFU/ml. A solitary, well isolated a colony was transferred aseptically from a recently developed nutrient agar plate into a sterile test tube containing 10 ml of tryptic soy broth (TSB). The inoculated broth was incubated aerobically at 37°C for a duration of 18 hours to facilitate adequate bacterial proliferation. Subsequent to incubation, the bacterial suspension was calibrated to align with the turbidity of McFarland standard No. 3.0, which corresponds to an approximate concentration of (1×10^9 CFU/mL). Turbidity was quantified spectrophotometrically at 600 nm (OD600) or visually compared with the standard utilizing a McFarland (McFarland, 1907).

Ethics approval: The College of Veterinary Medicine, University of Diyala, Iraq, approved this research project under its scientific research with the necessary rules and regulations governing the ethics of scientific research (approval No.: VM 202; February 2025, A and A).

This study was carried out at the animal house of the Department of Internal Medicine and Preventive Medicine, College of Veterinary Medicine, University of Diyala after the adaptation period of 30 albino male rats for two weeks. Thirty male rats were divided into three groups, as follows: 1st group (GI): a stomach tube dose of phosphate buffer saline (PBS) orally, at 1CC/animal, as a control for 60 days, 2nd group (GII): 1CC viable *P. Mirabilis* (1×10^9 CFU/ml) by stomach tube once a week for 60 days, 3rd group

(GIII): 1CC viable *P. Mirabilis* (1×10^9 CFU/ml) by stomach tube twice a week for 60 days(Zhang *et al.*, 2021).

Collection of blood samples:

After 60 day of experiment, the whole blood samples were collected from the heart to use of hematological analysis, the blood isolated from each rat in EDTA tube, the analysis was carried out at the College of Veterinary Medicine, University of Baghdad and the complete blood count (CBC) was collected from blood samples by using an auto-hematology analyzer, including RBC, Hb, HCT, platelets, WBC, neutrophils, lymphocytes & monocytes.

Histopathological changes examination:

After 60 days of the research, one-centimeter examples were obtained from the kidney and urinary bladder, fixed in 10% formaldehyde for 72 hours. Immediately after removal, the kidney and urinary bladder tissues were washed with tap water for additional dispensation. This comprised 70% alcohol to two changes of 100% alcohol, two hours each. The last step was to clear in xylol and embed in paraffin wax. The tissues were then treated with xylol for clearing and embedded in paraffin wax; lastly, the tissues were impregnated with semi-liquid paraffin wax at 58 °C; this was done in two changes. The specimens are then sectioned with a rotary microtome at 5 mm for all kinds of tissue. All tissues are to be stained with hematoxylin and eosin (H & E) for staining (Suvarna *et al.*, 2018).

Results:

Hematological analysis:

The below table (Table 1) showed significantly decrease of RBCs, Hb, HCT and platelets in 2nd and 3rd group compared with control group, while showed significantly increase of WBCs, neutrophils, lymphocytes and monocytes in 2nd and 3rd group compared with control group.

Table 1: Effect of *P. Mirabilis* on complete blood counts in albino rats different groups.

Parameter	group 1	group 2	group 3
RBCs (100000 per/ul)	8.60±0.19a	6.80±0.15b	5.95±0.45b
Hb (g/dl)	15.10±0.76a	13.85±0.45b	13.25±0.22b
HCT	41.65±1.25a	38.60±2.25b	37.90±2.80b
Platelets (10 ³ per/ ul)	750±70.89a	710±0.1b	625±1.2c
WBCs (10 ³ cells/ mm ³)	12.40±0.25b	13.10±2.10b	15.20±1.75a
Neutrophiles	23.78±2.80b	24.95±2.25b	26.15±1.35a
Lymphocytes	55.70±5.10b	57.30±4.10b	60.25±4.75a
Monocytes	13.5±0.75c	14.9±0.22b	16.5±0.85a

Key: results are represented as mean±standard error (SE). Different letters indicate significant changes ($P \leq 0.05$) in blood parameters.

Histopathological changes:

There were no histopathological changes lesions observed in the control group, kidney tissue revealed normal tubules, glomeruli and kidney parenchyma (Figure 1) and the urinary bladder tissue was normal and showed gland-like invagination of epithelium, the transitional epithelial layer and typical stellate lumen with connective tissue (Figure 2).

2nd group of kidneys showed swollen cells (all the cell lining of the proximal convoluted tubules) due to acute cellular swelling and mild infiltration of inflammatory cells (Figure 3). Also, it showed heavy infiltration of mononuclear cells in the muscular layer (Figure 4). Another section showed bands of interstitial fibrosis with dense infiltration of mononuclear cells (Figure 5), in urinary bladder showed thickened connective stromal tissue, ulceration of transitional layer, and edema with mononuclear cells infiltration (Figure 6). Also, it revealed congested blood vessels inside glands, congested blood vessels in the muscular layer, and thickened stroma (Figure 7).

3rd group of kidneys showed Glomeruli were enlarged and proliferative changes were diffused in the kidney's parenchyma, and the numbers and size of the endothelial and mesangial cells were increased. Also, edema mixed with mononuclear cells was present in interlobular septa. Furthermore, renal tubules showed acute cellular swelling and focal chronic inflammation (Figure 8). Heavy fibrotic band in the interstitial layer

with heavy chronic inflammatory cells mostly macrophage also appeared in the renal tissue. In addition, Eosinophilic fluid, tubular swelling (hydropic degeneration) and vacuoles within cells were evident (Figure 9), other sections showed hyperchromatic nuclei, congested blood vessels, and acute cellular swelling of tubular epithelial cells (Figure 10). In urinary bladder showed chronic inflammatory cells infiltration mostly macrophages in the lumen and stroma of the bladder, congested of blood vessels in the submucosal layer, homogenous to hyalinized like mucosa, squamous cells of transitional layer (Figure 11), also, it showed a well differentiated transitional epithelium, thin-walled blood vessels in connective tissue, and vascular stroma with eosinophilic fluid (Figure 12).

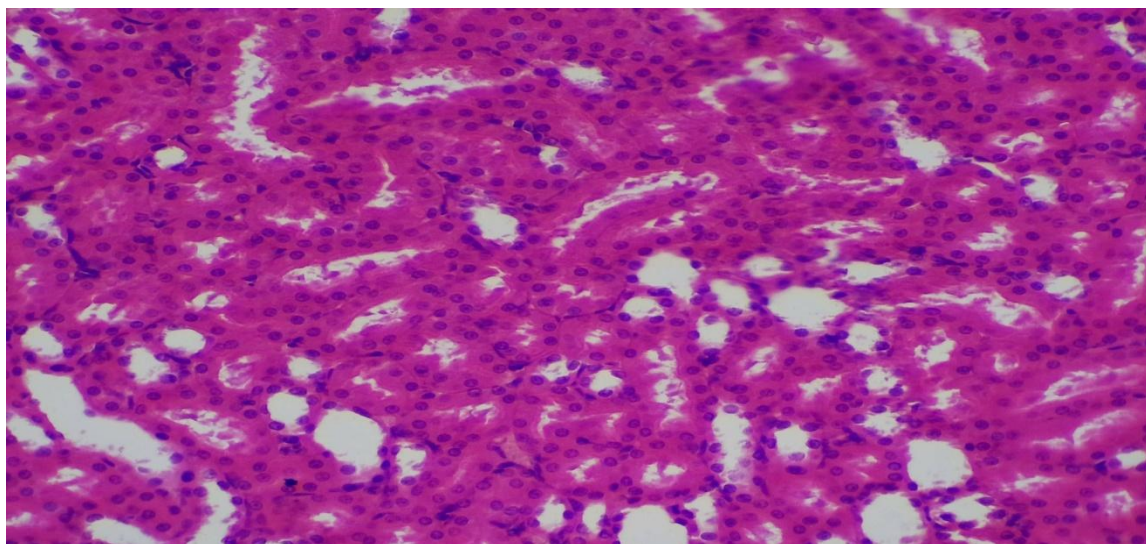


Figure 1: Histological section of kidney in the first group (controls) showed normal renal tissue (H and E stain; X20).

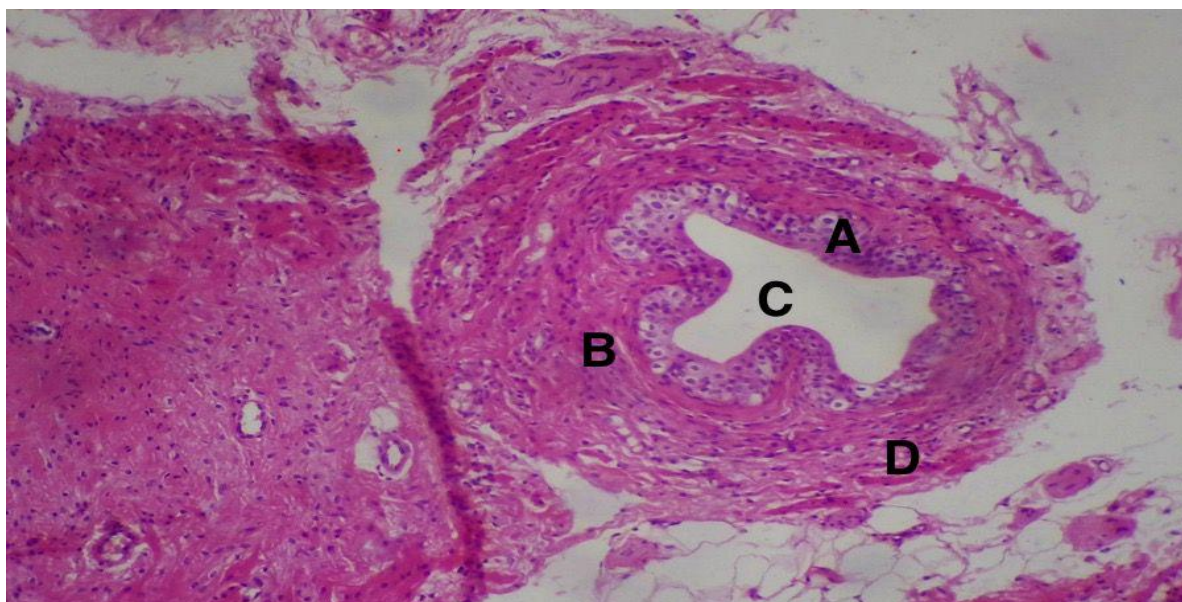


Figure 2: Histological sections of urinary bladder from the first group (control) demonstrated A) normal gland, B) epithelium layer, C) stellate lumen, and D) connective tissue. (H and E stain; X20).

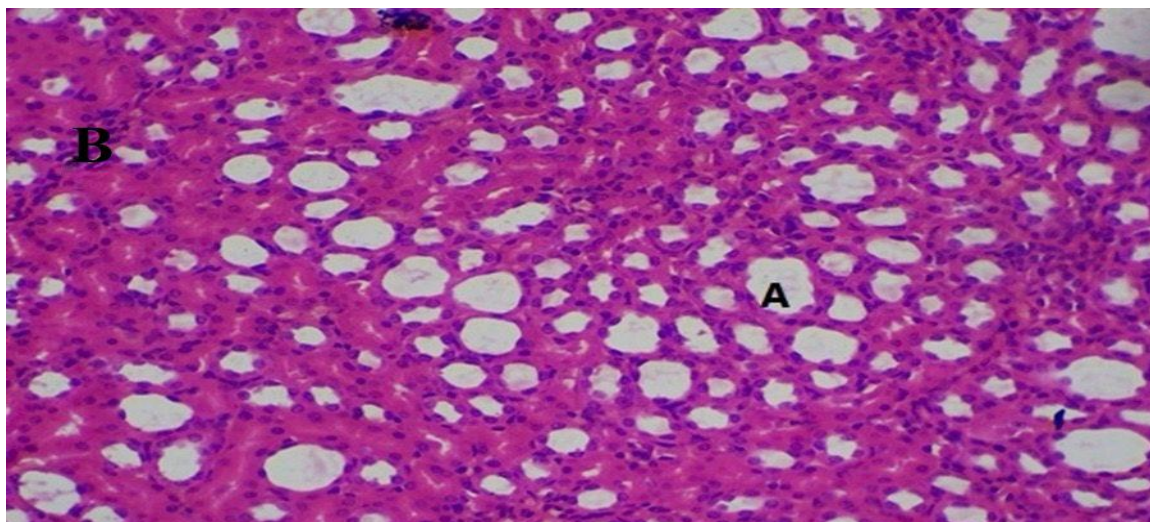


Figure 3: Micrograph of kidney in the second group showed A) Acute cellular swelling, and B) Mild infiltration of inflammatory cells. (H and E stain; X10).

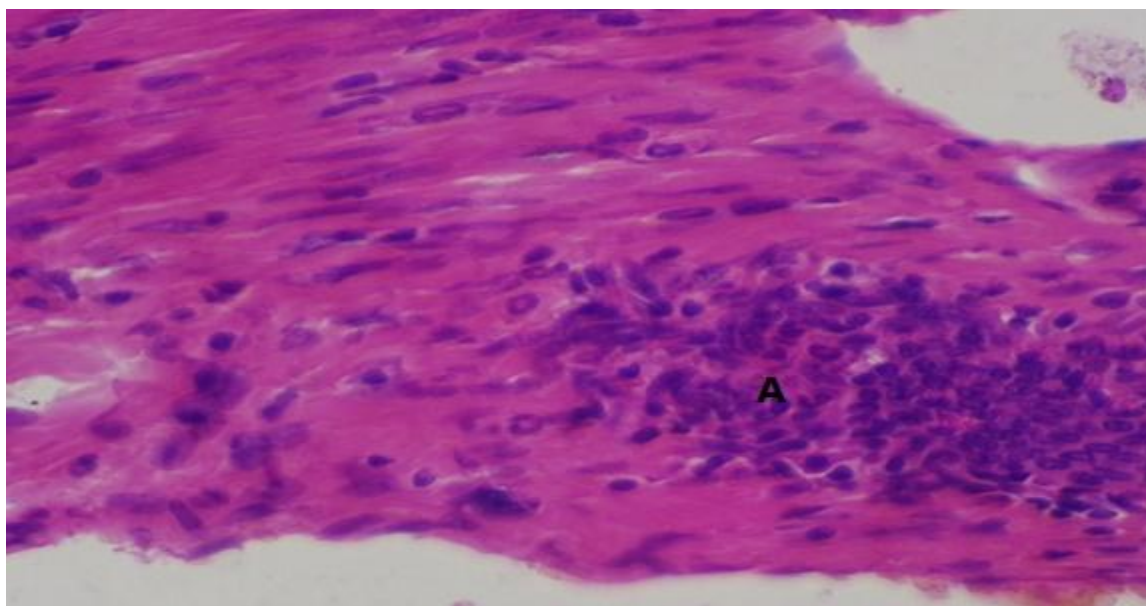


Figure 4: Micrograph of kidney in the second group showed heavy infiltration of mononuclear cells (A). (H and E stain; X40).

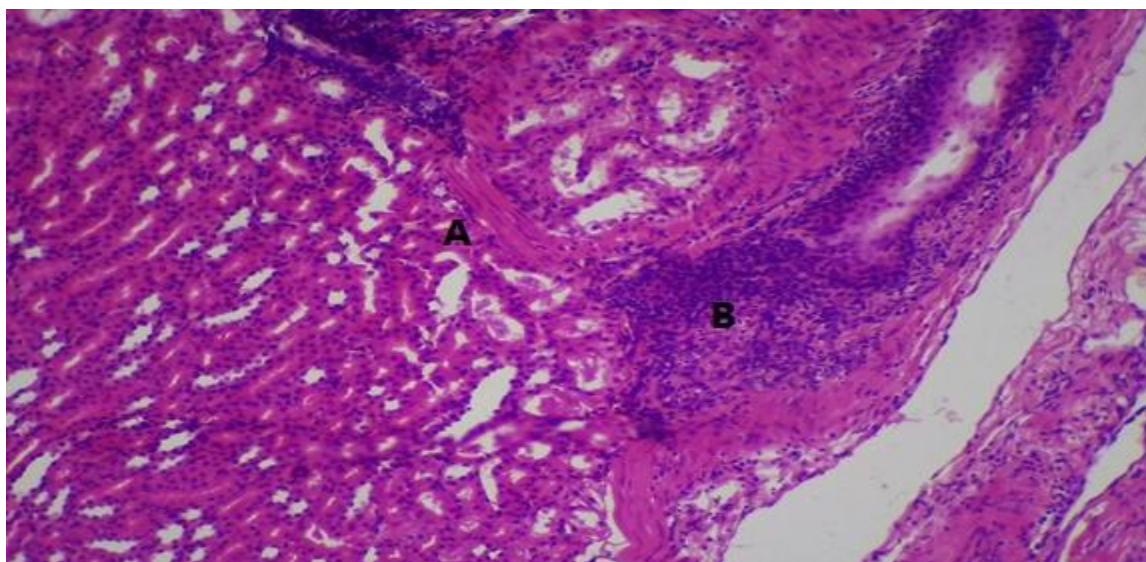


Figure 5: Micrograph of kidney in the second group showed A) bands of interstitial fibrosis, and B) dense infiltration of mononuclear cells. (H and E stain; X10).

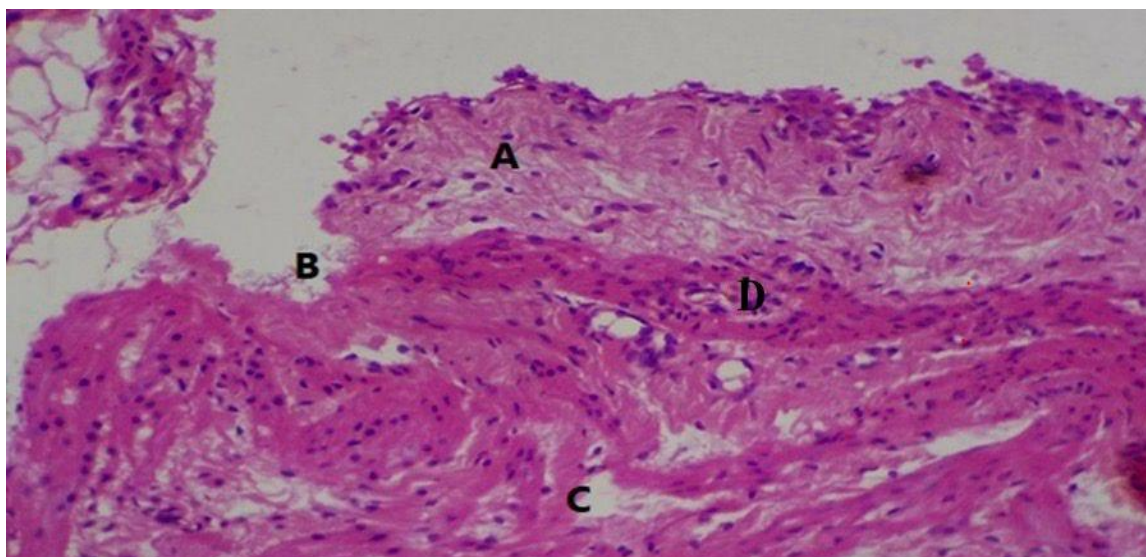


Figure 6: Micrograph of urinary bladder in the second group showed A) thickened connective tissue in stroma, B) ulcer of transitional layer, C) edema, and D) mononuclear cells infiltration. (H and E stain; X20).

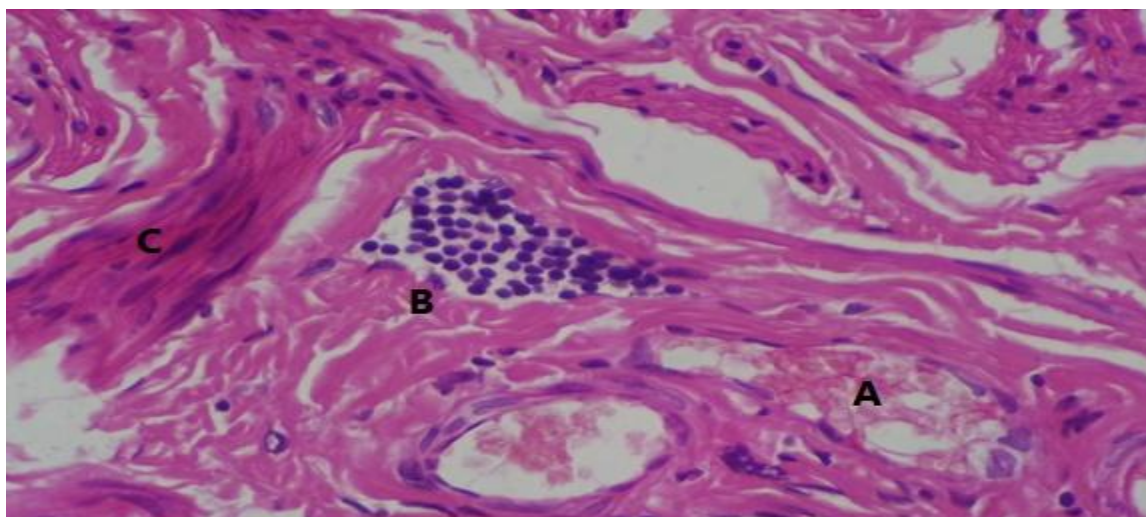


Figure 7: Micrograph of urinary bladder in the second group showed A) congested of blood vessels, B) congested of blood vessels in muscular layer with monocytes, and C) thickened stromal connective tissue. (H and E stain; X40).

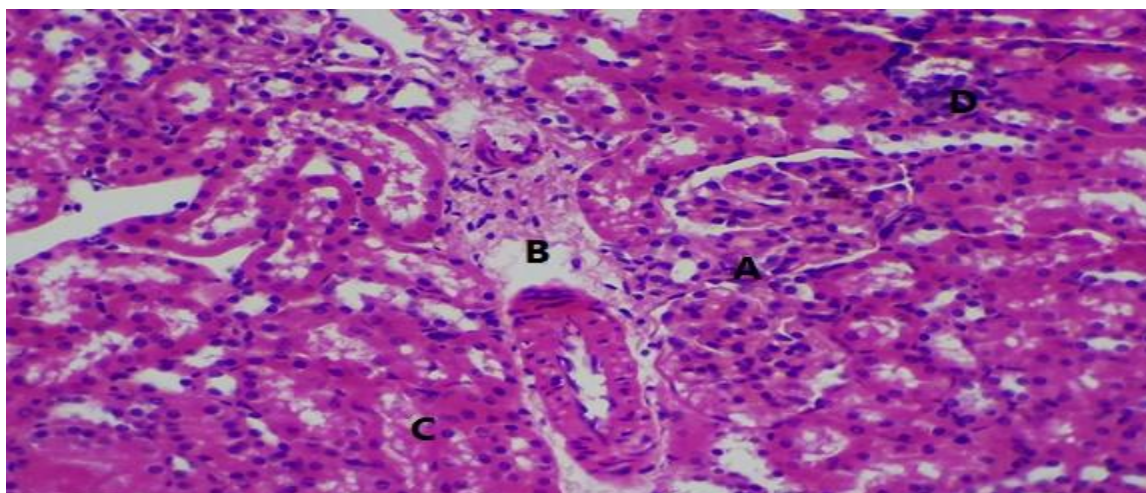


Figure 8: Micrograph of kidney tissue represent the third group reveled A) the glomeruli enlarged with diffuse proliferative change, B) edema in the interlobular septa, C) acute cellular swelling of tubules, and D) foci of chronic inflammatory cells. (H and E stain; X20).

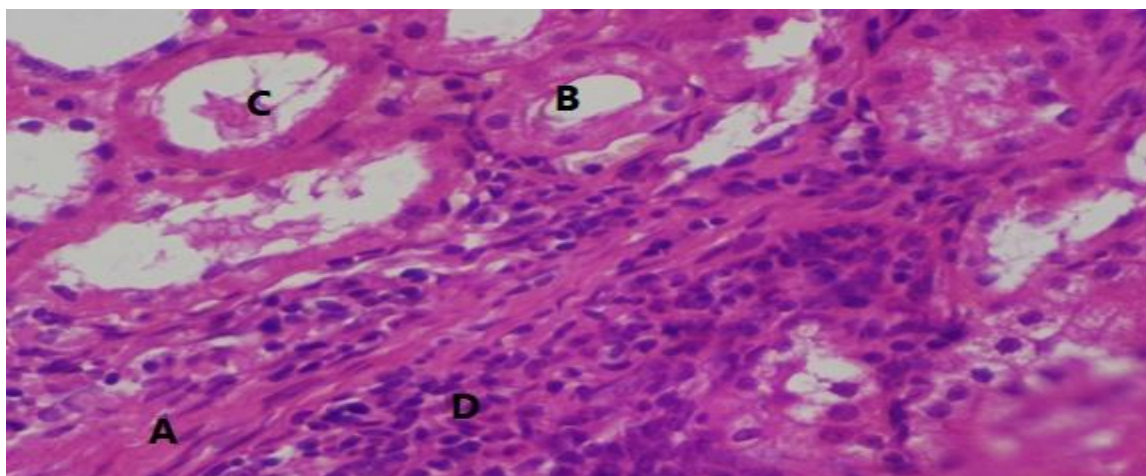


Figure 9: Representative image of kidney tissue from the third group showed A) heavy fibrotic band in the interstitial layer, B) hydropic degeneration of tubules with vacuoles in the cells, C) eosinophilic fluid, and D) heavy infiltration of inflammatory cells mostly macrophage. (H and E stain; X40).

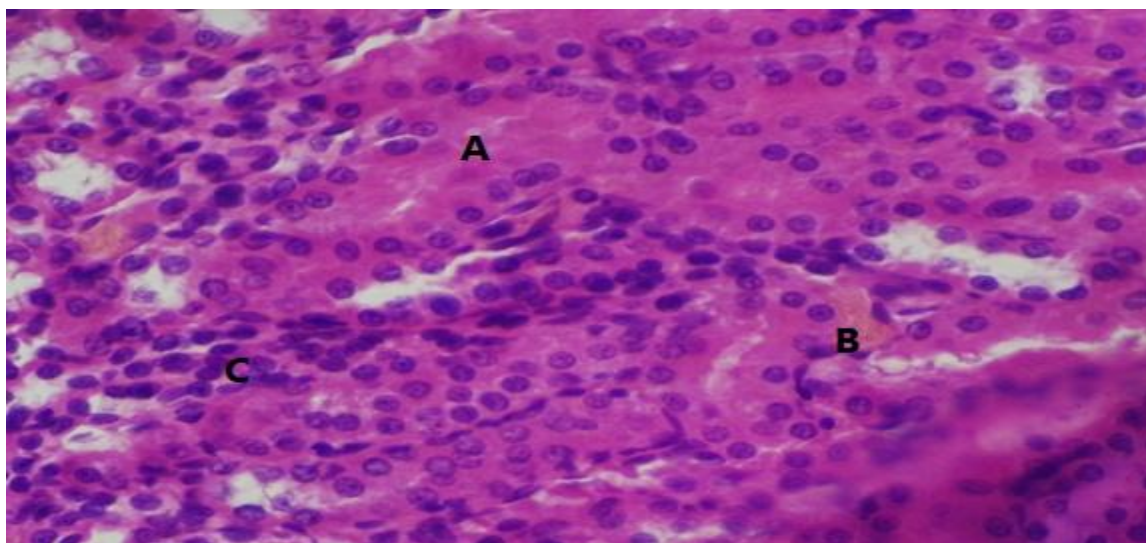


Figure 10: Micrograph of kidney tissue from the third group showed A) acute cellular swelling of tubular epithelium, B) congested of blood vessels, and C) hyperchromatic nuclei. (H and E stain; X40).

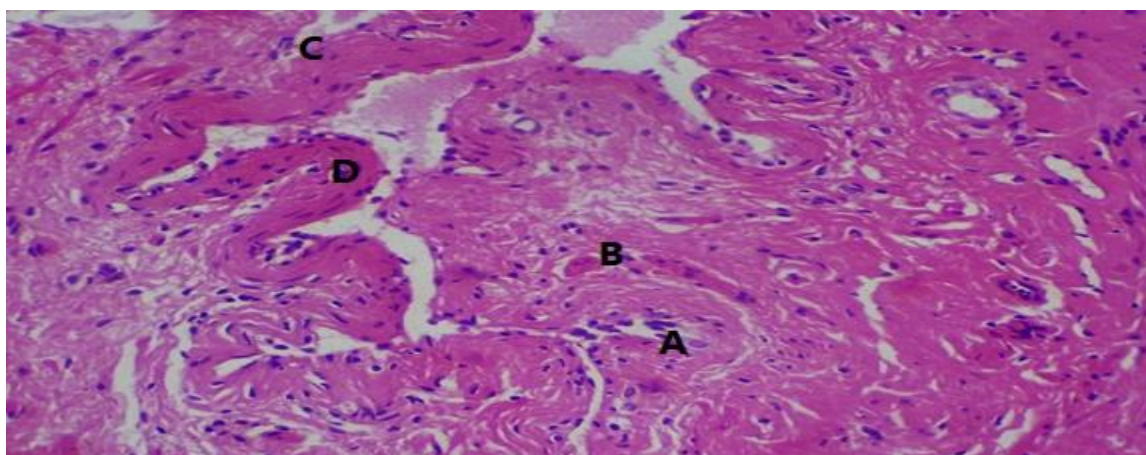


Figure 11: Micrograph of urinary bladder tissue from the third group showed A) infiltration of chronic inflammatory cells in lumen and stroma of bladder, B) congested of blood vessels in submucosa layer, C) homogenous to hyalinized like mucosa, and D) squamous cells of transitional layer. (H and E stain; X20).

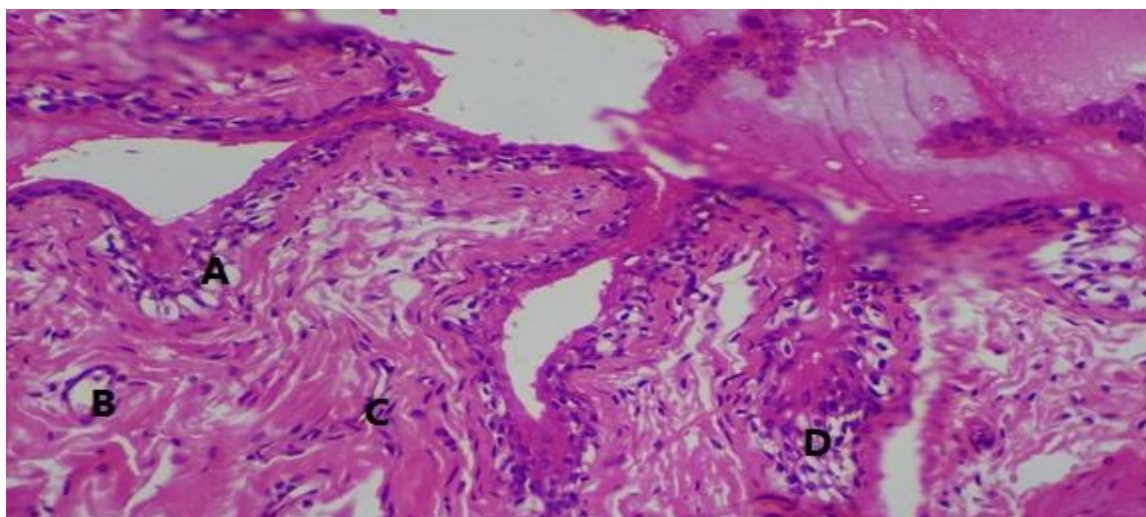


Figure 12: Micrograph of urinary bladder tissue from the third group showed A) a well differentiated transitional epithelium, B) thin-walled blood vessels in connective tissue, C) vascular stroma, and D) hyperplasia of transitional layer with glycogen vacuolation. (H and E stain; X20).

Discussion:

UTI is a condition that arises due to injury to one or more part of the urinary system when a type of microorganism can cross strong natural lines of defense. UTI is a common condition that can strike at any age. It is caused due to the entry of bacteria through the opening of the urethra and its subsequent spread to the bladder in 95% of cases. In a minority of instances, bacteria gain access to the kidney by traveling through the bloodstream (Chevins, 2001). UTI cause is attributed to multiple types of bacteria among these *E. coli* and *Proteus* spp. are the most considerable causative agents (Heimer & Mobley, 2001).

Bacterial lipopolysaccharide (LPS) is one of the pathogen-associated molecular patterns that can induce host responses through interaction with the pattern recognition receptor, including toll-like receptor 4. Therefore, direct interactions of LPS with platelets may be facilitated in this way (Vallance et al., 2017). However, the effect of LPS on platelet function has been controversial, as reported previously (Kappelmayer et al., 2013; Martyanov et al., 2020; Galgano et al., 2022). Some of these discrepancies may arise from differences in the sources of LPS used, bacterial strains, serotypes, purity, or forms of lipopolysaccharide.

The current study showed that *Proteus mirabilis* can inhibit platelet aggregation, and this result agreed with Lidia et al. (2024). Reports of other researchers show that the

effect of LPS (obtained from *Proteus mirabilis*) on platelet activation involves both stimulatory and inhibitory mechanisms, which depend on its concentration in the induction of nitric oxide and reactive oxygen species (Saluk-Juszczak et al., 2007). The activation of platelets by oxidative and nitrative stress can lead to pathological penalties, such as coagulation or outflow (Freedman, 2008). However, no direct measurements of the effects of lipopolysaccharide (obtained from *Proteus mirabilis*) on combination and other platelet purposes have been reported.

These results are somewhat in agreement with Tadatsugu et al. (2017) who noted cellular foci, necrotizing tissue with less dense cellular infiltration, and moderate fibrosis in renal tissue. They also noted very mild atrophy in glomeruli and that necrosis extended to the outer edge of the outer medulla as well as inflammatory cells infiltration in the tubules (mostly neutrophils). They further showed multiple hemorrhage and moderate edema. A recent paper described renal histopathology due to *Proteus mirabilis* in mice. Thus, histologic changes were observed in the kidneys of mice (Alamuri et al., 2009).

The results of the current study are agreed with Wurood et al. (2024) who showed acute cellular swelling with necrosis in the epithelial cells lining the tubules and glomeruli. Furthermore, they demonstrated the presence of congestion, inflammatory cells infiltration near the blood vessels and narrowing of the lumen of tubule.

Here in this study, necrosis and tubular cells death due to tissue hypoxia have been attributed to the toxic effect of bacteria on the urinary tubules. Off note, the cellular metabolic processes depend on the oxygen supplied by blood vessels, and any damage to the blood vessels can lead to poor blood flow through these vessels and thus lack of oxygen supply to the cells.

The bacterial toxin usually causes breakdown of tubular epithelial cells wall and mitochondria especially in the distal convoluted tubules. This may alter the level of ions and oxygen concentrations in the blood and result cellular oxygen deprivation thus the occurrence of focal thrombotic necrosis. This might stimulate the production of tumor necrosis factors to stimulate the secretion of special chemical mediators. These mediators may attract inflammatory cells (lymphocytes and phagocytes) and induce inflammation in the kidney. This might be indicated by the presence of certain pathological changes such as hemorrhage. Presence of hemorrhage is an indication of vascular and cellular changes in the tissue occurred through increased permeability (Roelofs et al., 2006). In this study, the presence of macrophage, necrosis, congestion, fibrosis, and infiltration of mononuclear inflammatory cells in the renal tissue attributed to the fact that these cells

move towards the higher concentration of some toxic substances which appear in the form of inflammation.

The histopathological changes observed in the kidney and urinary bladder were attributed to endotoxin, which might have led to acute tubular necrosis through changes observed in the cytoplasm and cell nucleus. These pathological changes may be initiated as simple alterations and then progressed to changes in the physical position of proteins within the more specialized cells of the renal tubules (Yang et al., 2002).

Proteus mirabilis is considered a major pathogen of UTI, and the intestinal tract is known to be a significant reservoir of this bacterium (Drzewiecka, 2016; Armbruster et al., 2018). There is an increased concern over potential transmission of pathogenic bacteria between humans and their companion animals (Damborg et al., 2016; Pomba et al., 2017). These worries were evoked by findings of studies claiming that strains of *E. coli* and *Klebsiella pneumonia* could be shared between companion animals and humans from the same household (Naziri et al., 2016; Marques et al., 2019). *P. mirabilis* was confirmed by Drzewiecka (2016) as a common uropathogen among cats, dogs, and humans. However, no studies have been undertaken on the colonization of epidemiologically related companion animals and humans.

Proteus mirabilis is a major pathogen of complicated urinary tract infections (UTIs) in both humans and animals. Typically, it infects patients with chronic indwelling urinary catheters or those with structural abnormalities in the urinary tract (Pearson & Mobley, 2007). UTI patients with *P. mirabilis* often develop bacteriuria, cystitis, acute pyelonephritis, and kidney and bladder stones (Burall et al., 2004; Wang et al., 2006). In rats inoculated with *Proteus mirabilis*, renal failure, urinary calculi, bladder dysfunction, and pyelonephritis were observed (Barros et al., 2008). Most experimental models applied mechanical manipulations to ensure a high frequency of pyelonephritic infection, such as bladder or kidney massage, while the current ascending UTI infection with *Proteus mirabilis* does not involve mechanical manipulation and causes minimal trauma or injury to the urinary tract. It has been reported that *Proteus mirabilis* can induce chronic renal infection in rats after a single reflux challenge. The infection was accompanied by varying degrees of renal failure increased blood urea nitrogen and serum creatinine (Al-Murayati et al., 1997).

In their study, Imad et al. (2011) It was noted that pyelonephritis presented hyperemia and edema of the medullary areas, with associated infiltration of inflammatory cells. These changes initiated interstitial inflammation involving both cortex and medulla.

In the interstitium, mononuclear cells were detected. The observed inflammation was more severe in the medulla than in the cortex while an increasing proportion of kidneys displayed cortical damage. The cortical area showed severe interstitial fibrosis and mononuclear cell infiltration with marked destruction of tubules and glomeruli.

Host defense evasion is an integral part of the survival strategy for mucosal pathogens. It has been reported that strains of *Proteus mirabilis* exhibit IgA degrading protease activity. This activity was detected in the urine of infected patients (Loomes et al., 1992). The infection by *Proteus mirabilis* can provide these bacteria with several advantages: protection from the host immune system; that of the immune system to the ureters; ammonia toxicity to host cells and direct tissue damage, all of which may lead to the formation of a protective and nutrient-rich environmental niche for these microorganisms (Baldo & Rocha, 2014).

Proteus mirabilis species are thought to enhance or induce formation of calculi (Torzewska et al., 2003; Torzewska and Rozalski, 2015). Purulent inflammation has been noted in association with renal calculi infected experimentally with *Proteus mirabilis* (Li et al., 2002). The presence of bacteria in the host will prevent the innate and adaptive immune reaction (Norsworthy and Pearson, 2017). The pathogenesis of *Proteus mirabilis* is typical of uropathogenicity associated with renal stone formation. This is facilitated by retaining urine as a bacterial reservoir to evade from the host immune system (Belas et al., 2004; Habibi et al., 2015; Fusco et al., 2017). Fimbriae have been clearly identified as critical virulence factors contributing to UTI associated with *Proteus mirabilis*. Many reports have shown fimbriae to be critical virulence factors in establishing colonization of the urinary tract by *Proteus mirabilis* (Zunino et al., 2001).

Conclusions:

Oral administration of *Proteus Mirabilis* led to changes in hematological parameters, it showed a considerable decrease in RBCs, Hb, HCT and platelets in 3rd group compared with control group, also the total leukocyte count, neutrophils, lymphocytes and monocytes have increased significantly in 3rd group in comparison to the control group, in addition the oral administration of *Proteus Mirabilis* has caused histopathological changes in kidney and urinary bladder.

Recommendations:

Investigating immunotoxin effects of *Proteus Mirabilis* on animals immunized with different vaccines or other treatments is also recommended.

Conflict of interest:

The authors declare no conflict of interest.

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Authors contributions:

All of authors contributed equally to the conception, design, data, collection, analysis and writing of the manuscript.

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