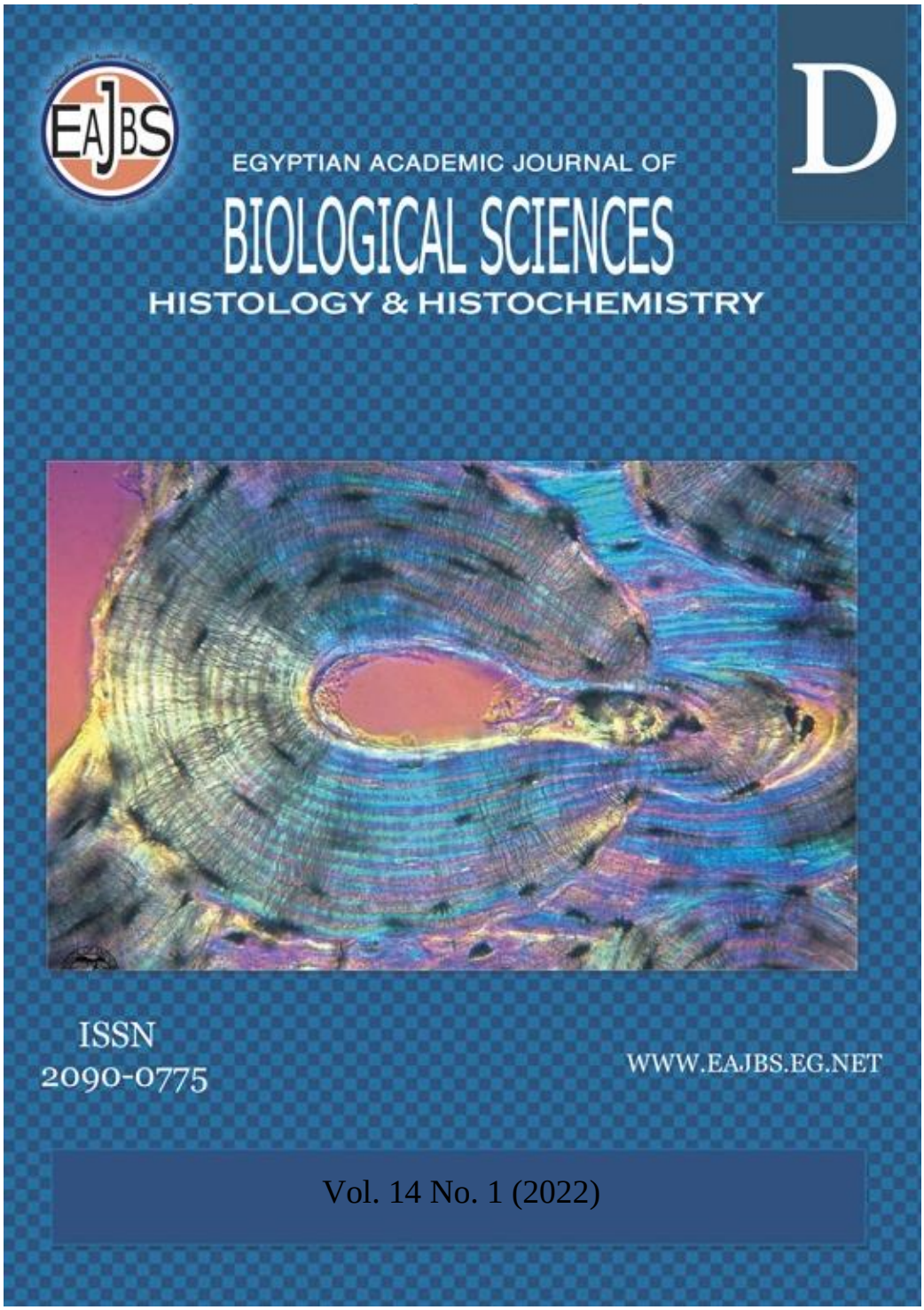

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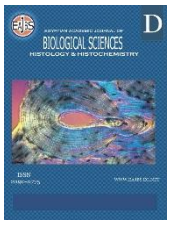

Pathological and Biochemical Performance on the Therapeutic Effect of Misoprostol and Omeprazole on Gentamicin-Induced Kidney Failure in Albino Rats

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ABSTRACT

Background: The drug interactions between anti-peptic ulcer drugs misoprostol and omeprazole in gentamicin induced renal impairment rats. ***Materials and methods:*** Thirty-six animals were randomly allocate into 6 equal groups (n=6). The rats in gp1 were given an orally equivale volume of the solvent (distilled water) once daily for 16 consecutive da and will serve as a negative control group. Rats received gentamycin wi a dose of 80 mg/kg intraperitoneal (i.p.) once daily for eight consecuti days in gps (2, 3), followed with misoprostol with a dose of 100 µg /k omeprazole with a dose of 20 mg/kg orally daily for other 8 consecuti days either alone or combined together in gps (4,5,6), respectively. A animals were examined and sacrificed at 16th dpa, while the second grou was sacrificed at 8th dpa. The blood samples were collected and sera we separated and kept for biochemical examination. Kidneys samples we collected for histopathological examination. ***Results:*** The impair kidney rats (gp 2) showed a highly significant increase in serum ure creatinine and uric acid when compared to treated groups, while n significant difference in sodium and potassium in all groups. Moreove the total antioxidant capacity showed a highly significant decrease in g (2, 3), meanwhile, highly significant increase in treated groups. Seve tubulo-interstitial nephritis was shown in gps (2, 3), while moderat lesions were shown in the treated groups (gps 3, 4, 5). ***Conclusion:*** could be concluded that some beneficial drug interactions betwe misoprostol and omeprazole in gentamicin induced renal impairment.

INTRODUCTION

The kidneys are key organs with important vital functions in regulating the hydro-electrolyte equilibrium, in the elimination of the waste products from the blood, and in maintaining the organism's acid-base balance (Teslariu *et al.,* 2016). In acute kidney injury, the kidney filtration capacity is altered, which results in an accumulation of excessive amounts of wastes and also in a marked deterioration of renal structure with cell necrosis and apoptosis (Bihorac *et al.,* 2009).

Gentamicin is an aminoglycoside broad-spectrum antibiotic-induced nephrotoxicity due to the accumulation of gentamicin in the renal cortex (Alftfian *et al.,* 1973 and Luft and Kleits 1974). Gentamicin nephrotoxicity is one of the most common causes of acute renal failure (ARF). Acute kidney injury (AKI) due to acute tubular necrosis is a complication of aminoglycoside therapy, with a rise in serum creatinine. The syndrome of it occurs due to accumulating waste products and unable to maintain electrolyte, acid-base and water balance (Tögel and Westenfelder, 2014). Chronic kidney failure (CKD) is characterized by progressive deterioration of kidney function, associated with decreased urinary excretion leads to retention of metabolites in the organism as creatinine, urea, electrolytes, water (Cibulka *et al.,* 2005 and Cibulka, 2007).

Drug-drug interactions (DDIs) are means that some drug affects the activity of other drugs when both are administered together. This action can be synergistic or antagonistic when the effect of the drug increases or decreases, respectively or may induce a new effect that neither produces on its own (Pegram *et al.,* 1999).

Misoprostol [15-deoxy-16-hydroxy-16methyl-PGE1 methyl ester], was the first synthetic prostaglandin analogue to be made available for the treatment of peptic ulcer, it was promoting healing of these ulcers smoke (Clark *et al.,* 2000 and Donald *et al.,* 1987). Prostaglandins (PGs) regulate vascular tone and salt and water homeostasis in the mammalian kidney and are involved in the mediation and/or modulation of hormonal action (Smith *et al.,* 1992). In addition, PGE2 is involved in the regulation of sodium and water reabsorption and PGI2 increases potassium secretion mainly by stimulating the secretion of rennin (Villa *et al.,* 1997). Prostaglandin E2 and prostaglandin I2 are widely synthesized in the kidney where they regulate hemodynamics and tubular transport (Navar *et al.,* 1996). PGs also buffer the renal vasoconstrictor and antidiuretic actions of angiotensin II (Arima *et al.,* 1994).

Omeprazole is 5-Methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl] sulfinyl] -1H-benzimidazole, magnesium salt. Omoprazol is one of the "proton pump inhibitors" (PPIS), used for the treatment of duodenal ulcer, gastric ulcers, reflux esophagitis, and Zollinger-Ellison syndrome (Ferron *et al.,* 2001). Omeprazole is a type of PPIS that is associated with the development of kidney disease as acute tubule-interstitial nephritis, leads to chronic kidney disease. proton pump inhibitors (PPI), treat gastroesophageal reflux and peptic ulcers through inhibition of gastric acid synthesis, have shown to be closely associated with acute interstitial nephritis (AIN), reduction of glomerular filtration rate (GFR) and the development of CKD (Moledina *et al.,* 2016, Schoenfeld *et al.,* 2016, Xie *et al.,* 2017 & João Victor Marques Guedes *et al.,* 2020). In the glow of the previous, therefore the aim of work is to evaluate the biochemical and histopathological effects of misoprostol and omeprazole alone or together on gentamycin-induced renal failure kidneys.

MATERIALS AND METHODS

Experimental Animals:

Thirty-six apparently healthy adult male Wistar albino rats (200-250 g b. wt), at age, 60-90 days were purchased from animal house, Faculty of Veterinary Medicine, Assuit University. The animals were housed in stainless-steel cages in a clean ventilated room at 40-60% relative humidity, a temperature of 25±2°C and 1k2 hours light/dark cycle. They were fed on standard commercial pellets, and water was provided *ad libitium* throughout the experiment period. They were left for two weeks to adapt to the place of the experiment and examined for free from bacteria, viruses and parasites. The experimental protocol was approved by

the research ethics committee of the Faculty of Veterinary Medicine, South Valley University, Qena, Egypt.

Chemicals:

All chemicals were purchased from El Naser Company for the pharmaceutical and chemical industries (Gesr El-Suez, Cairo, Egypt). The chemicals and dose preparation for experimental rats were used for induction renal failure with the expected substances for treated effects.

a- Garamycin 20 mg ampoules (used for induction renal impairment), each mL contains gentamicin sulfate equivalent to 10 mg gentamicin. Dose: rats injected with gentamicin 80 mg/kg i.p , each rat which weighs about 250 mg is injected with 2 ml of the solution intraperitoneal.

b- Cytotec tablets (used as a treated substance), each contain 200 micrograms of misoprostol. Dose: rats given misoprostol orally by gastric tube and administered in a dose of 100 µg /kg each tablet crushed and suspended in 10ml distilled water, each rat which weighs about 250 mg given orally about 1.25 ml of the suspension.

c- Pepzol-mr 20 mg capsule (used as a treated substance), each gastro-resistant capsule contains 10 mg, 20 mg, or 40 mg of omeprazole. Dose: rats given orally by gastric tube in a dose of 20 mg/kg, each capsule suspended in 6 ml distilled water, each rat which weighs about 250 mg given orally about 1.5ml of the suspension.

Experimental Design:

Animals were randomly divided into six groups (n=6).

Group 1: (Negative group), the rats were given an orally equivalent volume of the solvent (distilled water) once daily for 16 consecutive days and will serve as a negative control group.

Group 2: (Induction group), the rats were injected intraperitoneal (i.p.) with gentamicin 80 mg/kg once daily for eight consecutive days and the animals were sacrificed on the 8th day of the experimental period (Abdelsameea *et al,* 2016).

Group 3: (Positive group), the rats were injected with gentamicin 80 mg/kg (i.p.) once daily for eight consecutive days and the animals were left for another eight consecutive days without treatment, until the end of the experiment.

Group 4: The rats were injected with gentamicin 80 mg/kg (i.p.) once daily for eight consecutive days followed with misoprostol orally given by gastric tube in a dose of 100 µg /kg suspended in 10ml distilled water, for 8 consecutive days until the end of the experiment (Ahmed *et al.,* 2011).

Group 5: The rats were injected with gentamicin 80 mg/kg (i.p.) once daily for eight consecutive days followed with omeprazole orally administrated by gastric tube in a dose of 20 mg/kg suspended in 6 ml distilled water for other 8 consecutive days until the end of the experiment (Watanabe *et al.,* 1994).

Group 6: The rats were injected with gentamicin 80 mg/kg (i.p.) once daily for eight consecutive days followed with a combination of omeprazole in a dose of 20 mg/kg and misoprostol in a dose of 100 µg /kg orally administration for 8 consecutive days (Welage and Berardi, 2000).

The experimental animals were examined daily during the experiment. Blood samples were collected at the end of the experiment, after overnight fasting, from retro-orbital plexus of rats using a non-heparinized capillary tube (Van Herck *et al.,* 1998). In each collection, about 2 ml of blood was taken into a non-heparinized tube and centrifuged at 1000 RPM/min for 10 min. Serum was then collected carefully, stored at -20 ºC and used for biochemical examination (Al-Majed *et al.,* 2002).

All animals were euthanized by xylazine (40mg/kg) and ketamine (400mg/kg) (Leary et al., 2013) and then group (2) was sacrificed on the 8th day at the end of gentamycin injection but the other groups (1, 3- 6) were sacrificed at 16th day at the end of treated substance

administration. Tissue samples were collected from the right and left kidneys of all experimented animals, for histopathology examinations. Other samples were taken from the kidneys and kept frozen at -80°C for antioxidant measurement.

A-Biochemical Analysis:

a- Kidney function tests:

Determination of Serum Urea, Uric Acid and Creatinine Levels:

They were determined by the enzymatic calorimetric method using spectrophotometer Spinreact kits produced from El-Nasr Company, Egypt (Fossati *et al.,* 1980, Kaplan *et al.,* 1984 and Kaplan *et al.,*1984).

b- Serum Electrolytes:

Determination of Sodium (Na) and Potassium (K) Analysis:

They were determined by calorimetric method using spectrophotometer Spinreact kids purchased from El-Nasr Company, Egypt according to (Trinder *et al.,* 1951 and Henry *et al.,* 1974).

c- Antioxidant Activities:

Determination of Total Antioxidant Capacity:

It was determined by calorimetric method using spectrophotometer bio-diagnostic kits produced by bio-diagnostic laboratories, Dokki, Giza, Egypt, according to (Henry *et al.,* 1974).

B- Histopathology Examination:

Kidney samples were collected from all groups and fixed in buffered formalin, and then embedded into paraffin wax. Paraffin blocks were sectioned into 5 μm sections in thickness, and hematoxylin-eosin stained and then used for histopathological examination

C- Statistical Analysis*:*

All statistical analyses were performed using SPSS software v20.0 (SPSS, Chicago, IL, USA). The mean and standard error (SE) were used to describe the distribution of variables and compare cases and controls. The Mann–Whitney U test was used to compare values between groups. The difference was regarded as significant when $P< 0.05$, and highly significant when $P < 0.01$.

RESULTS

A- Biochemical Results:

a- Kidney function Test Findings:

Table (1), Figure (1) showed a highly significant increase in serum urea, creatinine and uric acid in the impaired kidney rats (gp 2) when compared to negative control rats (gp 1) but the injured kidney rats which left untreated until the sacrificed day (16 d p.i) (gp 3) showed no significant increase in creatinine, uric acid compared to control group (gp 1) but significant increase in urea when compared to (gp 1) but significant decrease in all parameters in compared with (gp 2). Meanwhile, treated the animal with misoprostol or omeprazole alone (gps 4, 5) showed a significant decrease in serum urea and uric acid level but no significant decrease in serum creatinine but in the combination group (gp 6) there was no significant decrease in serum urea and creatinine but significant decrease in uric acid level in compared to (gp 3).

Table 1: Effect of gentamicin followed with single and combined administration of misoprostol and omeprazole on kidney function tests.

Measured parameter	Urea (mg/dl)	Creatinine (mg/dl)	Uric acid(mg/dl)
Negative Control (Distilled water)	38.5 ± 2.54	0.95± 0.08	1.63± 0.15
Gentamicin	278.4± 26.34***	8.38 ± 0. 73***	3.18± 0.26**
Positive control (Gentamicin treated)	55.0 ± 5.2*	1.02 ± 0.7	2.0± 0.17
Misoprostol	42.4 ± 3.47*	0.988± 0.075	1.16± 0.108*
Omeprazole	40.68 ± 2.04*	0.995± 0.08	0.85± 0.07*
Omeprazole+Misoprostol	50 ± 4.42	1.03± 0.093	1.39± 0.097*

Data represents mean ± SE of 6 observations.
* Significant difference ($p<0.05$) from control values.
*** Very Highly significant difference ($p<0.0001$) from control values.
** Highly significant difference ($p<0.001$) from n control values.

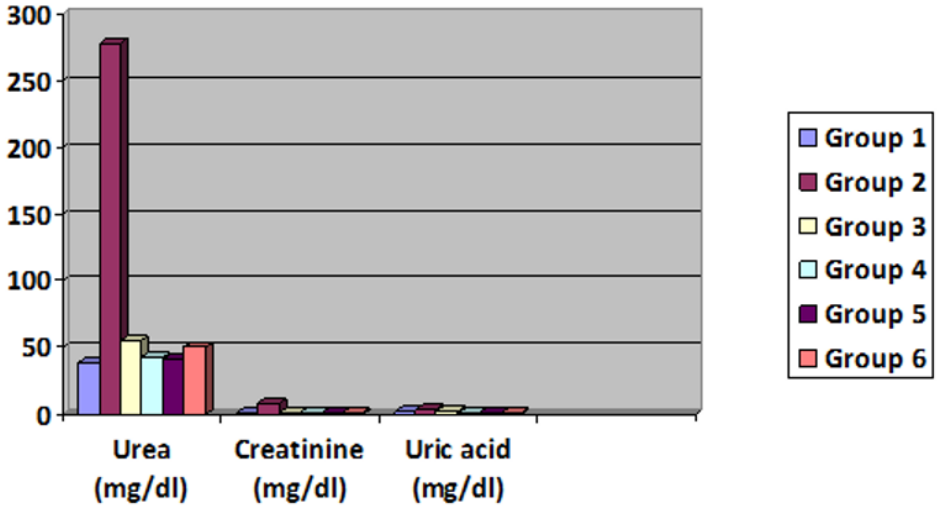


Fig. 1. Effect of gentamicin followed with single and combined administration of misoprostol and omeprazole on kidney function tests.

b- Serum electrolytes level (Serum sodium and Potassium) findings:

Table (2), Figure (2) showed no significant differences in the level of serum sodium and potassium among the inducted (gps 2,3) and treated groups (gps 4-6) compared to control group.

Table 2: Effect of gentamicin followed with single and combined administration of misoprostol and omeprazole on serum sodium and potassium levels.

Measured parameter	Sodium	Potassium
Negative Control (Distilled water)	138.3 ± 3.06	5.1 ± 0.456
Gentamicin	136.6 ± 6.76	5.74 ± 0.48
Positive control (Gentamicin treated)	128.7 ± 5.8	4.84 ± 0.39
Misoprostol	136.4 ± 6.47	3.7 ± 0.22
Omeprazole	137.5 ± 5.07	5.3 ± 0.52
Omeprazole+Misoprostol	138.8 ± 2.63	5.0 ± 0.38

Data represents mean ± SE of 6 observations.
No significant difference ($p<0.05$) from control values.

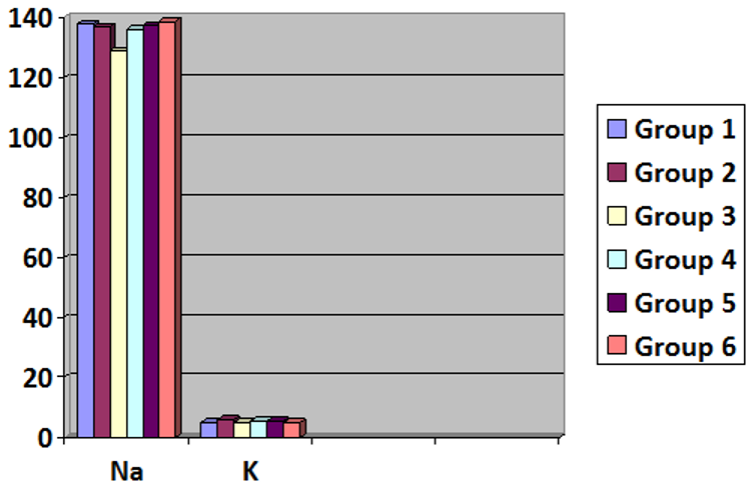


Fig. 2. Effect of gentamicin followed with single and combined administration of misoprostol and omeprazole on serum sodium and potassium levels.

c- Antioxidants finding (total antioxidant capacity) (TAC):

Table (3), Figure (3) revealed a highly significant decrease in TAC in the rats in (gps 2, 3) compared to (gp 1). Meanwhile, the rats in (gps 4- 6) showed a highly significant increase in TAC compared to (gp 3).

Table 3: Effect of gentamicin followed with single and combined administration of misoprostol and omeprazole on TAC.

Measured parameter	TAC (mmol/ml)
Negative Control (Distilled water)	0.947 ± 0.08
Gentamicin	0.48 ± 0.03**
Positive control (Gentamicin treated)	0.53 ± 0.05**
Misoprostol	1.14 ± 0.07**
Omeprazole	1.08 ± 0.09**
Omeprazole+ Misoprostol	1.173 ± 0.093**

Data represents mean ± SE of 6 observations.
** Highly significant difference ($p<0.01$) from control values.

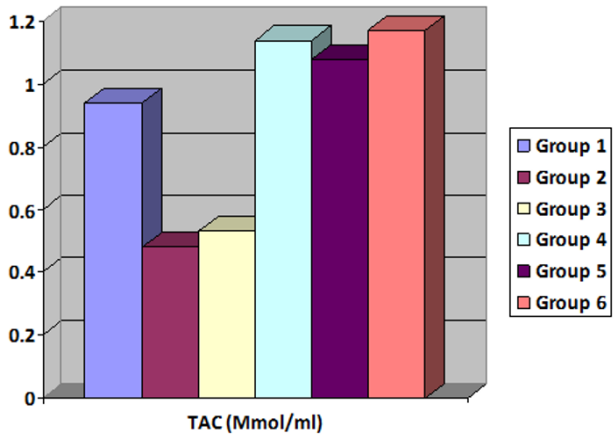


Fig.3. Effect of gentamicin followed with single and combined administration of misoprostol and omeprazole on TAC.

B- Histopathological Findings:

Clinical Signs:

The rats appeared apparently normal with no signs obvious in all groups except that treated omeprazole in toxicity kidney induced by gentamycin in group (5) which noticed emaciation with a decrease in food intake in most rats.

Macroscopic Appearance:

The Kidneys in the rats in both groups (2, 3) appeared slightly enlarged in size with normal consistency and slightly dark in color, progressed into severe enlarged in size with soft in consistency and pale in color in group (5) but reached normal in size, color, shape and consistency in groups (4, 6).

Microscopic Appearance:

The kidneys in most rats in groups (2, 3) which were inducted with gentamycin and sacrificed at 8, 16 days showed degenerative and necrotic changes in renal tubules with compensatory dilation in other lined with flattening epithelium, besides renal casts inside the lumen. Tubulo-interstitial nephritis manifested by thickening in the wall of blood vessels with inflammatory edema mainly neutrophils and fibroblasts surrounded it in (gp 2), besides recent thrombus. In addition, the necrotic change occurred in epithelial cells of tubular and glomerular tufts with dilation in bowman's capsules with cloudy swelling in tubular epithelium besides fibrosis surrounding the collecting tubules in (gp 3) (Fig. 4). However, the rats that were treated with misoprostol and omeprazole alone or combined in gps (4, 5, 6) respectively, showed a necrotic change in renal tubules, with detached from the basement membrane and aggregation of mononuclear mainly macrophages, giant cells and fibroblast cells in (gps 4, 5). Regeneration of necrotic cells noticed manifested by increased mitosis with crowded nucleus along the affected tubules, fibrous tissue proliferation and congestion in renal blood vessels were detected in gps (4-6), besides angiogenesis characterized by the network from the newborn blood vessels around collecting tubules with compensatory dilation in some. Hypercellularity in the glomerular tufts with dilation in glomerular capillaries and narrowing in Bowman's space, besides aggregation of leukocytic cells, replaced the adherent tubules with hypertrophied tubular epithelium in omeprazole treated group. Meanwhile, the combination of both drugs in (gp 6) treated the impairment of kidneys resulting in a decreased ratio of necrotic changes in renal tubules (Fig. 5).

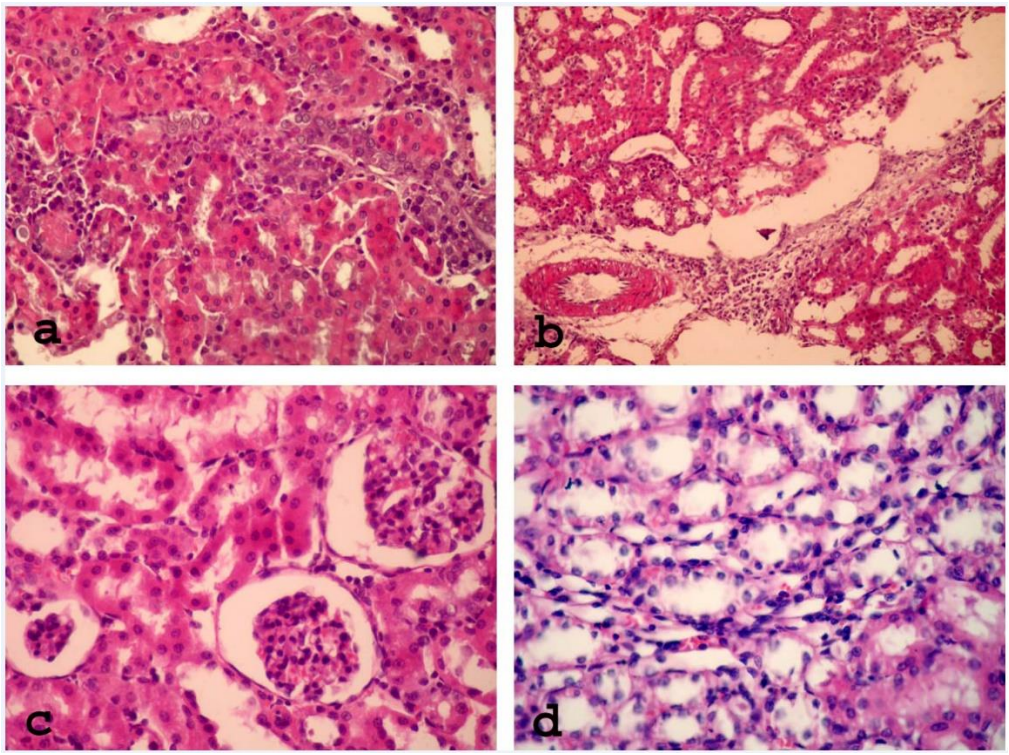
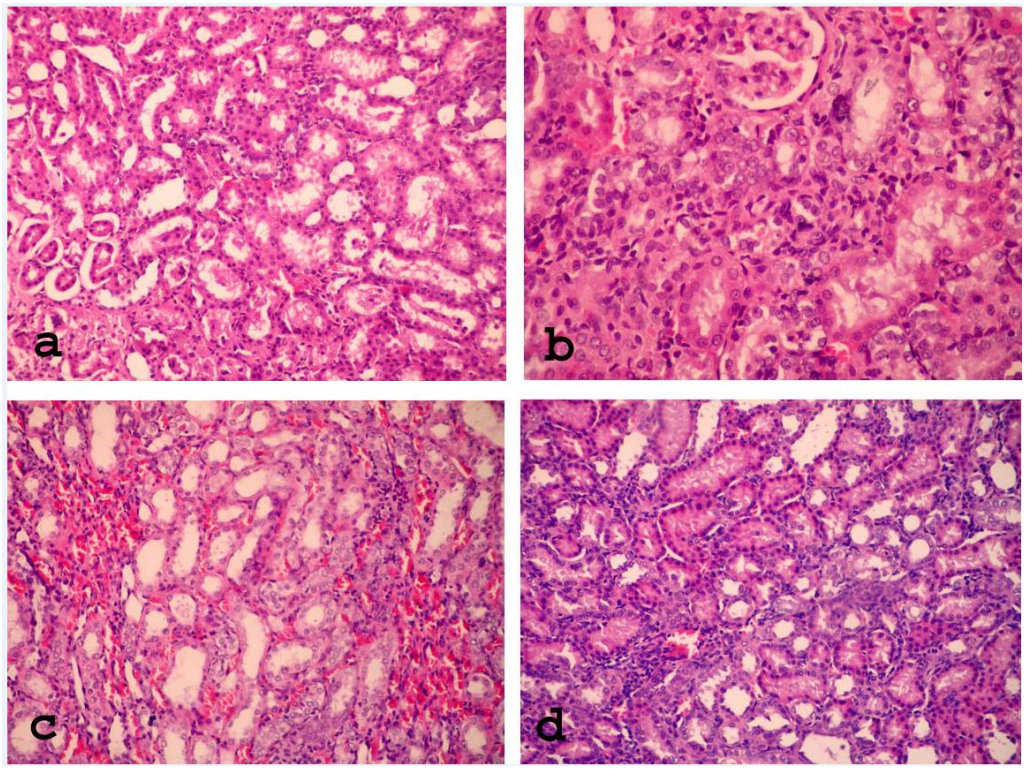


Fig. 4. The kidneys of rats injected with gentamycin alone for 8th d (a,b), 16th d (c,d) showing degenerative and necrotic changes in renal tubules with compensatory dilation with flattening epithelium in other, besides renal casts inside the lumen and inflammatory edema around renal blood vessels (a, b). Necrosis in glomerular tufts with dilation in bowman's capsules, besides cloudy swelling in tubular epithelium (c,d). (H&E., x 200, 120, 60)



Fi g. 5. The kidneys of rats injected with gentamycin and treated with misoprazol (a), omoprazol (b,c) and combination of both (d) for 16 d showing necrotic changes in renal tubules with detached from basement membrane (a),regeneration of necrotic cells noticed declared of mitosis in the epithelial lining induced new cells, besides angiogenesis characterized by network from the newborn blood vessels around collecting tubules with compensatory dilation in some (b, c), few areas of necrotic changes in renal tubules (d). (H&E., x 60, 200, 120)

DISCUSSION

The kidneys are key organs with important vital functions. The high prevalence of kidney injury and its relation to peptic ulcer allow the patient to use multi anti-peptic ulcer drugs. Accordingly, our study was designed to explore the possible drug interaction between classic anti-peptic ulcer agents "misoprostol" and "omeprazole" in gentamicin-induced kidney injury in rats.

Gentamicin is known to generate ROS associated with an increase in lipid peroxidation and decrease in antioxidant enzyme activity in the kidney (Banday *et al.,* 2008).. The mechanism is that gentamicin throughout the endocytic pathway is taken up into the epithelial cells of the renal proximal tubules and stays there for a long time, which leads to nephrotoxicity. Hydroxyl radicals play a role in the pathogenesis of gentamicin nephrotoxicity, gentamicin can induce suppression of Na (+)- K (+)- ATPase activity and DNA synthesis in rats proximal tubules leading to renal injury (Padmini and Kumar, 2012).

In the present study, the experimental rats in gentamycin group (gps 2, 3) revealed a highly significant increase in the blood levels of urea, uric acid and creatinine that attributed to nephrotoxicity disease (Zeeni *et al.,* 2007, Chaware *et al.,* 2011 & Babu *et al.,* 2011). The serum levels of uric acid, Na, K, in the present study showed no change similar to that reported by (Sener *et al.,* 2002, Ali *et al.,* 2005 and Eslami *et al.,* 2011). There was a highly significant decrease in the level of total antioxidants capacity in our work confirmed the nephrotoxic effect of gentamicin that led to acute kidney injury and the renal dysfunction model seemed compatible too (Parlakpinar *et al.,* 2003, Ali et al., 2005 & Kadkhodaee *et al.,* 2005) Our work displayed necrobiotic changes of the renal tubules, it confirmed the significant structural changes of the kidney (*Smith et al.,* 1988). The findings of the present investigation showed that exposure to gentamicin resulted in progressive tubular, glomerular and interstitial histological alterations. The tubular necrosis and degenerative changes seen in the present work agreed with the previous investigations (Saleemi *et al.,* 2009, Ali *et al.,* 2011 and Dehghani *et al.,* 2011). Our results showed obvious reversibility in kidney function tests and total antioxidants (TAC), although the solvent couldn't return the parameters to control values. However, our result unlike the other previous study, which found that reversibility of gentamicin nephrotoxicity in rats progressed from acute tubular necrosis on day 10 to near normal morphology on and after day 21 (Gilbert *et al.,* 1978).

The administration of both misoprostol orally in a dose of 100 µg /kg for 8 days (gp 4) and omeprazole treated rats in gp (5), orally in a dose of 20 mg/kg for 8days alone, after gentamicin nephrotoxicity showed markedly restored levels of urea, creatinine and uric acid. It is attributed to the improvement of kidney functions with an increase in total antioxidants capacity. We guessed that the reversibility that happened may be due to the discontinuation of gentamicin or a protective effect of misoprostol. Renal histopathology showed some improvement manifested by less necrosis and tubular dilatation than groups (2, 3), angiogenesis obviously appeared which may reveal regeneration. All these results strongly may be due to some nephroprotective effects of misoprostol and omoprazol alone and its potent antioxidant role (Gao *et al.,* 2019). In the previous study, that reported the effect of misoprostol on ibuprofen-induced renal dysfunction showed that Ibuprofen causes renal dysfunction, whereas misoprostol may have some protective renal effects (Ackerman *et al.,* 2002). Another study was done by Gurkowski *et al.,* 1995 discussed the effects of misoprostol on

contrast-induced renal dysfunction reported that the short-term administration of misoprostol is a useful adjunct for contrast procedures. Also, another study revealed that misoprostol administration after cisplatin application protects renal tissue, as misoprostol has antioxidant, cytoprotective and antiapoptotic or other beneficial (Mehmet *et al.*, 2011). Our results disagreed with previous studies that reported kidney injury induced due to administration of Misoprostol to Celecoxib-Induced kidney Injury in rats. These findings suggested that misoprostol does not exhibit renal protection in the presence of celecoxib (Dustin *et al.*, 2014). Same to (Yu-JieTanChun-Ling ZhuHua-Xiong, 2016) who reported that misoprostol was not observed to have any protective effect against diclofenac in obstructed kidneys. While, another study (Voorhorst *et al.*, 2000) reported that effects of omeprazole on kidney functions showed renal failure due to acute interstitial nephritis after use of omeprazole for 4 months. The same results were displayed in gp (6) that received the concomitant administration of omeprazole and misoprostol for 8 days after nephrotoxicity produced by gentamicin injection for 8 days. It is attributed to obvious reversibility in kidney function and total antioxidants. The kidney parameter results were confirmed by the histopathological results were, there was mild necrosis and degeneration, cellular inflammation, and hyperplasia or cast formation.

CONCLUSION:

Our result was concluded that the effects of combined administration showed the maximal positive effect compared to the single administered drugs and the single administered drugs give a positive effect compared to the positive control. These results suggest some beneficial drug interactions between misoprostol and omeprazole in gentamicin-induced renal impairment.

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