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EFFECT OF ROYAL JELLY ON GENTAMICIN-INDUCED NEPHROTOXICITY IN RATS

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ABSTRACT : In this study, the effect of royal jelly on the nephrotoxicity of Gentamicin in the kidneys of female rats was investigated by evaluation of serum indices and histopathological analyses. Thirty female Wistar albino rats were randomly divided into five groups; Group (1) negative control (NC) inoculated intraperitoneally IP with NS for 10 days; Group (2) Royal Jelly (RJ) 50 mg/kg body weight was given orally for 10 days; Group (3) Gentamicin (Gen) 100 mg/ kg inoculated IP for 10 days served as positive control; Group (4) RJ + Gen was given royal jelly orally at a dose of 50 mg/ kg body weight for 10 days and thereafter, 100 mg/ kg Gen was administered IP for 10 days; and Group (5) Gen + RJ was inoculated IP with Gen for 10 days as a dosage of 100 mg/ kg and thereafter, was given RJ orally as a dose of 50 mg/ kg body weight. Gentamicin has a significant effect on serum urea and creatinine where urea in positive control (Gen) group found to be significantly higher (242±53.5) in comparison to negative control (NC) group (58±4.0). The effect of gentamicin on serum urea was almost nullified when royal jelly was given after gentamycin (43±4.0) while royal jelly given before gentamicin slightly lowers urea but the effect is not statistically significant (209±41.7). Royal jelly alone has no significant effect on serum urea (35±4.4). Almost the same was observed regarding the creatinine in positive control (Gen) group was found to be significantly higher (2.41±0.455) in comparison to negative control (NC) group (0.47±0.005). The effect of gentamicin on serum creatinine was almost nullified when royal jelly was given after gentamicin (0.61±0.053) while royal jelly given before gentamicin slightly lowers creatinine but the effect is not statistically significant (1.67±0.238). Royal jelly alone has no significant effect on serum creatinine (0.47±0.005).

Histopathological sections revealed gentamicin group 3 to exert massive degeneration of the tubular epithelium with presence of eosinophilic hyaline cast in the lumen plus dilatation of the renal tubules. In addition there was thickening of the basement membrane of the glomeruli and congestion of the glomerular tuft with sometimes detachment and disappearance of the tubular epithelium of the glomerular membrane. Regarding the groups of royal jelly given before or after gentamicin; there was dilatation of the renal tubules showed some of the tubules to be filled with eosinophilic hyaline material plus thickening of the basement membrane of the glomeruli, vacuolation of the glomerular epithelium, capillary congestion, degeneration of the tubular epithelium when gentamicin was given after royal jelly, this is nearly similar to NC group. The picture was seemed to be better when royal jelly has been given after gentamicin where it was showed no significant pathological changes in glomeruli and tubular epithelium compared to NC group. Royal jelly alone showed wide spread of dilation of renal tubules without significant c pathological changes of tubules.

No significant effect in the serum indices for uric acid, total protein and albumin in all groups.

Key words : Gentamicin nephrotoxicity, Royal Jelly, Urea, Creatinine, Rat.

INTRODUCTION

Gentamicin is an aminoglycoside antibiotic. It is well known to treat many types of infections caused by Gram-negative organisms. However, serious complications resulting from its nephrotoxicity are a major limiting factor for its clinical usage (Mondorf *et al*, 1978; Luft & Patel, 1978; and Humes, 1998). Therefore, several studies have been carried out to find substances, which can ameliorate the nephrotoxicity induced by gentamicin. An angiotensin II receptor blocker (ARB), losartan (Angiotensin II inhibitor), has been shown to reduce the effect of the gentamicin induced kidney damage in rats (Heeba ,2011). In addition, an ACE inhibitor captopril also has shown a renal-protective effect against gentamicin-induced nephrotoxicity in rats (Rahman, 2009). Also previous studies showed that many antioxidant agents reduce the nephrotoxicity of gentamycin (Göksel Sener1 *et al*, 2002; Ihab Talat *et al*, 2009). On the other hand, the Aliskiren,

a new renin inhibitor, ameliorated organ damage, lowered BP and albuminuria, and normalized serum creatinine (Pilz *et al*, 2005) and provides similar renoprotection as compared with an ARB in a rat model of hypertensive nephropathy (Muller and Luft, 2006; Ching *et al*, 2012). It also showed a renoprotective effect in diabetic rats with nephropathy (Hans-Henrik, 2008; Ching *et al*, 2012). Aliskiren, unlike ACEi and ARBs, lowers plasma renin activity, angiotensin I and angiotensin II levels, may thereby provide greater benefit compared to ACEi or ARB alone (Kelly, 2007).

Royal jelly contains many important compounds with biological activity such as free amino acids, proteins, sugars, fatty acids, minerals, and vitamins (Karaali *et al*, 1988). It has been demonstrated to possess several pharmacological activities including vasodilative and hypotensive activities, disinfectant action, antitumour activity, antihypercholesterolemic activity, anti-inûammatory, and immunomodulatory activities (Shinoda *et al*, 1978; Sver *et al*, 1996).

Previous studies found gentamicin to induce increased renal inflammatory cytokines. They have reported the renal damage as a result of gentamicin-induced tubular necrosis stimulates inflammatory events at the site of injury leading to enhance the migration of monocytes and macrophages to the site of tissue damage (Ali *et al*, 2014). The prolonged gentamicin treatment may lead to acute renal failure with acute tubular necrosis (Juan *et al*, 2007). The kidney sections showed normal histological structure in mice treated at a dosage of 50 and 100 mg/kg, while royal jelly at dose of 200 mg/kg the kidney showed mild inûammatory cells inûltration and hyperemic (Morales *et al*, 2010). It is stated that royal jelly had been proved to have oxygen radical scavenging and antioxidant (Karaali *et al* 1988; El-Nekeety *et al*, 2007).

Royal jelly, a natural antioxidant product produced by the honeybee (Kültiðin *et al* , 2009), has recently received particular attention as a highly efficient antioxidant and has free radical scavenging capacity (Jamnik *et al*, 2007; El-Nekeety *et al*, 2007). However, royal Jelly has not yet been investigated against the nephrotoxicity induced by gentamicin although its antibacterial (Abdalla *et al*, 1995; Fontana *et al*, 2004), and anti-inflammatory activity (KOHNO *et al*, 2004) may enhance the bacterial effect of gentamicin. There are some reports in the literature that indicated royal jelly due to its an anti-inflammatory properties might augment the antibacterial efficacy of gentamicin. Royal jelly has been shown to reduce the nephrotoxicity induced by other agents such as cisplatin (Ali Karadeniz *et al*, 2011) and cadmium (Kültiðin *et al*, 2009).

The objectives of the current study is to examine the possible protective effect of royal jelly on gentamicin-induced nephrotoxicity. The investigations were carried out using rats as experimental animal model.

MATERIALS AND METHODS

Experimental design

Thirty female Wistar albino rats weighing (150-200 gm) (10-12 weeks old) were used during this study. The rats were divided randomly into five groups; Group (1) NC "Negative Control" inoculated "IP" with NS for 10 days; Group (2) RJ "Royal Jelly" given orally for 10 days as a dosage of 50 mg/kg body weight; Group (3) Gen "Gentamicin" "Positive Control" inoculated for 10 days as a dosage of 100 mg/ kg administered IP; Group (4) RJ

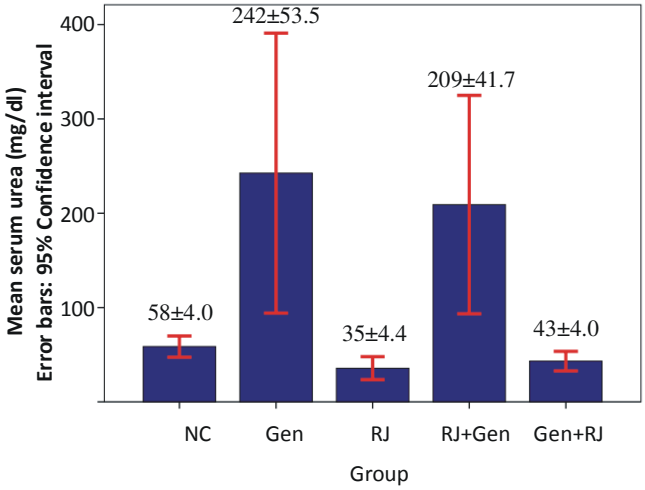


Fig. 1 : Bar graph shows serum urea in rats inoculated with normal saline (NC), gentamicin (Gen), royal jelly (RJ), gentamicin after royal jelly (RJ + Gen); and royal jelly after gentamicin (Gen + RJ); mean ± standard error of mean; * P < 0.05.

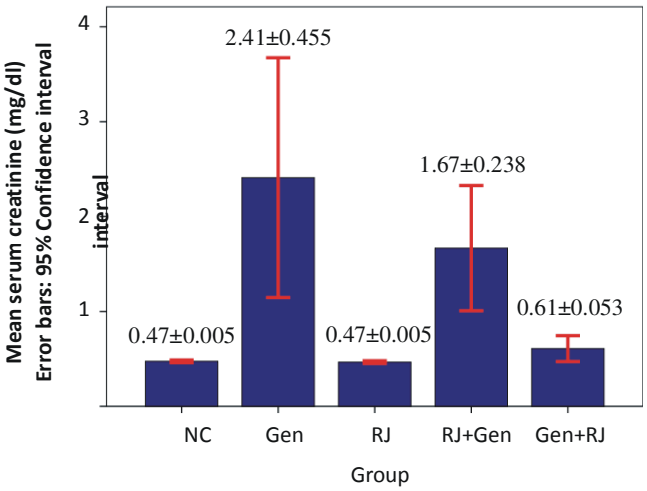
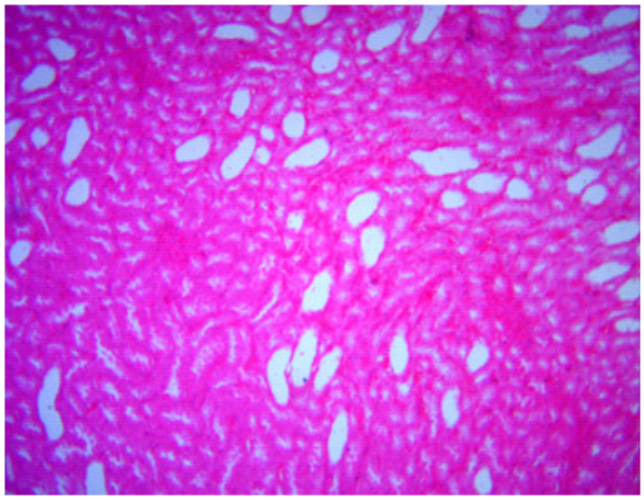
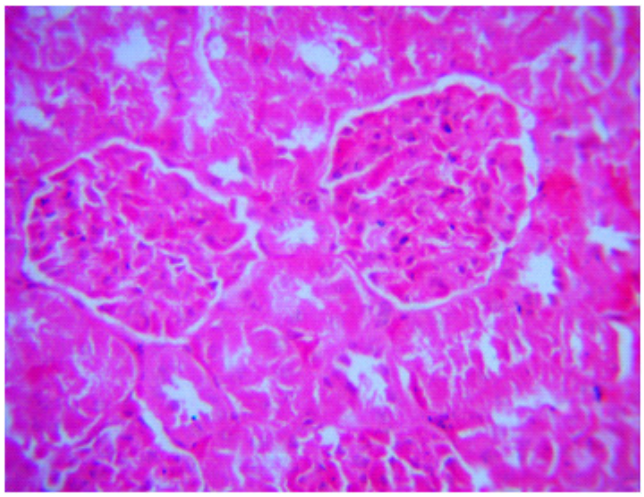


Fig. 2 : Bar graph shows serum creatinine in rats ingesting normal saline (NC), gentamicin (Gen), royal jelly (RJ), gentamicin after royal jelly (RJ + Gen); and royal jelly after gentamicin (Gen + RJ); mean ± standard error of mean; * P < 0.05.



a- Wide spread of dilation, no significant pathological changes of tubules (X100)



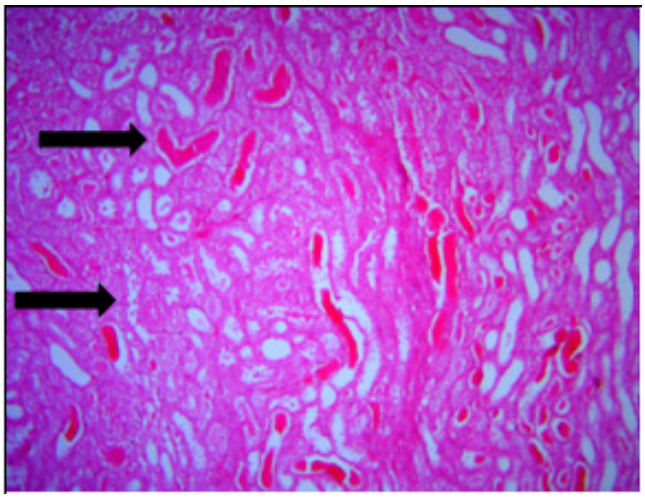
b-Wide spread of dilation, no significant pathological changes of tubules (X400)

Fig. 3 : Royal Jelly given orally (a-X100 & b-X400).

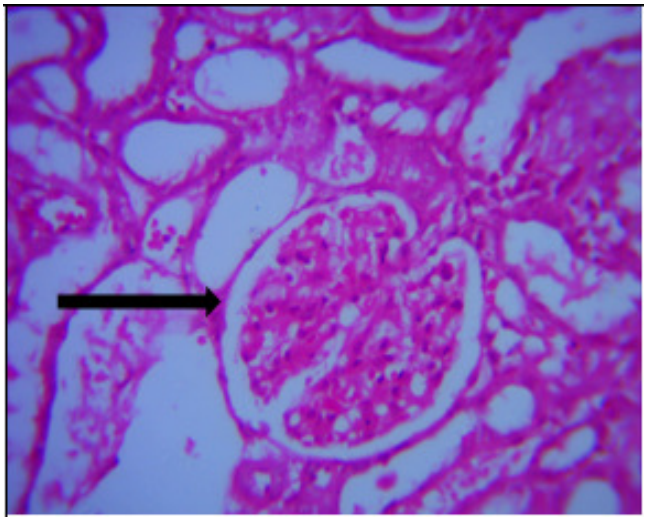
+ Gen given orally royal jelly dose 50 mg/ kg body weight for 10 days and thereafter, inoculated IP with G for 10 days as a dosage of 100 mg/ kg; and Group (5) Gen + RJ were inoculated IP with gentamicin for 10 days as a dosage of 100 mg/kg and thereafter were given orally royal jelly as a dose of 50 mg/ kg body weight. At the end of the experiment we had 27 rats out of the thirty where three rats were missed (died) one from each of the groups RJ (2); Gen (3) & RG (4).

Scarification of animals and laboratory work

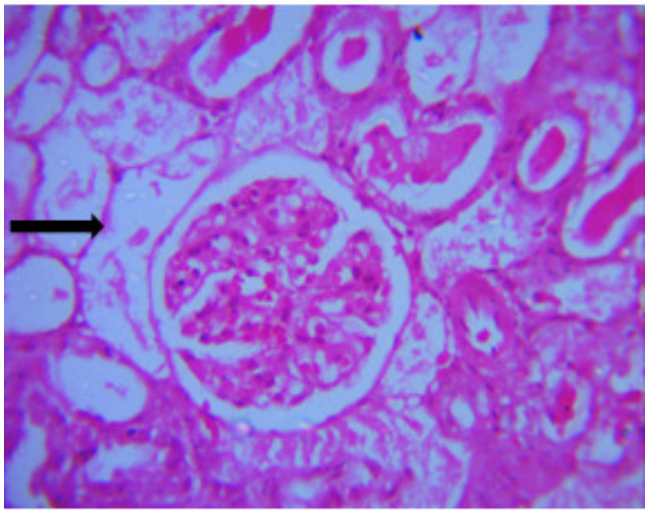
All rats were scarified after 24 hours from last dose. Blood samples were collected directly from the heart and sera samples were separated to test biochemical indices. Kidneys were harvested from the rats and fixed in 10% buffer formosaline. Paraffin sections of thickness 3-4 µm were prepared and stained with haematoxylin and eosin (H & E) for histopathological examination under



a- Massive degeneration of the tubular epithelium with presence of eosinophilic hyaline cast in the lumen. There is dilation of the renal tubules.



b- Thickening of the basement membrane of the glomeruli & congestion of the glomerular tuft.



b- Detachment and disappearance of the tubular epithelium of the glomerular membrane.

Fig. 4 : Gentamicin inoculated IP (PC group) (a-X100 & b-X400).

light microscopy (Drury and Wallington, 1980, Bancroft *et al*, 1996). All procedures were in accordance with the University of Hail (UOH, KSA) Health's Guide for the care as the guidelines of the Animal Committee Unit.

Renal function

Assessment of renal function was carried out using the following indices: Blood Urea Nitrogen (BUN) level, serum creatinine (SCr) level, total protein, uric acid and albumin.

Drugs and chemicals

Drugs and Chemicals : Gentamicin sulfate were purchased from the Saudi Pharmaceutical Industries & Medical Appliances Corporation "SPIMACO". All other chemicals were of analytical grade.

Statistical analysis

The results were analyzed using SPSS version 20. ANOVA was used to compare the means of the different groups. Results are expressed as means ± Standard Error of the Mean (SE) (Levesque, 2007). A p value less than 0.05 was considered to be significant.

RESULTS

Renal indices: (Serum urea and creatinine)

In this study, gentamicin has a significant effect on serum urea and creatinine.

The mean urea in positive control group 3 was found to be significantly higher (242±53.5) than in negative control NC (58±4.0). Royal jelly, given after gentamycin, significantly reduced serum urea to its normal level (43±4.0). Royal jelly given before gentamicin slightly lowers urea but the effect is not statistically significant (209±41.7). Royal jelly alone has no significant effect on serum urea (35±4.4) (Fig. 1).

The mean creatinine in positive control group 3) group (2.41±0.455) was found to be significantly higher in comparison to negative control (1) NC (0.47±0.005). Royal jelly, given after gentamycin, significantly reduced serum urea to its normal level (43±4.0). Royal jelly given before gentamicin slightly lowers creatinine but the effect is not statistically significant (1.67±0.238). Royal jelly alone has no significant effect on serum creatinine (0.47±0.005) (Fig. 2).

Renal indices: (Serum uric acid, total protein, and albumin)

No significant changes were found in serum uric acid, total protein and albumin between groups.

Histopathological sections

In gentamicin treated group positive control the kidneys histopathological sections revealed gentamicin (Fig. 4) to exert massive degeneration of the tubular epithelium with presence of eosinophilic hyaline cast in the lumen with dilatation of the renal tubules. In addition there was thickening of the basement membrane of the glomeruli and congestion of the glomerular tuft with sometimes detachment and disappearance of the tubular epithelium of the glomerular membrane. Regarding the groups of royal jelly given before or after gentamicin as seen in Figs. 5 & 6.

There was dilatation of the renal tubules showed some of the tubules to be filled with eosinophilic hyaline material plus thickening of the basement membrane of the glomeruli, vacuolation of the glomerular epithelium, capillary congestion, degeneration of the tubular epithelium when gentamicin was given after royal jelly (Fig. 5).

The picture was seemed to be better when royal jelly has been given after gentamicin where it was showed no significant pathological changes in glomeruli and tubular epithelium compared to NC group (Fig. 6).

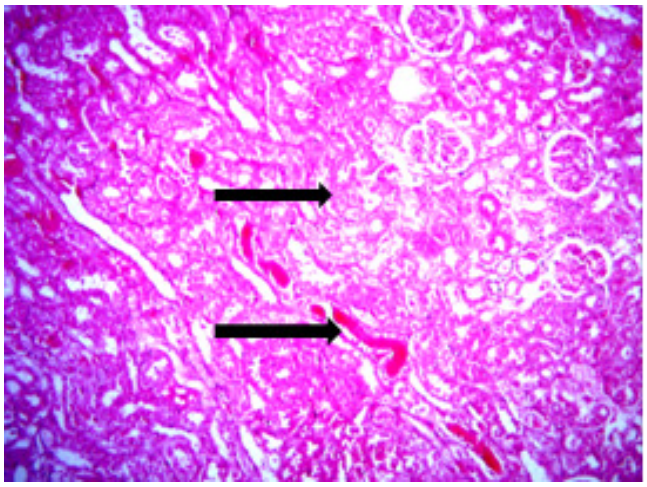
Royal jelly alone showed wide spread of dilation of renal tubules without significant pathological changes in the renal tubules (Fig. 3).

Photomicrograph of rat kidney section (H & E).

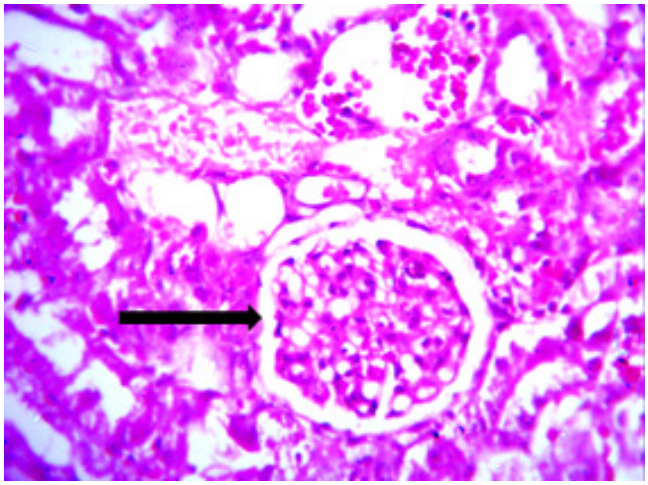
DISCUSSION

In this study, we tried to investigate the effect of royal jelly on gentamicin-induced nephrotoxicity. Gentamicin caused a marked reduction in renal functions characterized by changes in renal indices for serum urea and creatinine. The mean urea was found to be statistically higher "242±53.5" when compared to negative control "58±4.0" this is almost similar to the findings of Naif Al-Harbi *et al* (2014), when he used Aliskerin to reduce gentamicin nephrotoxicity. The effect of gentamicin on serum urea was almost nullified when royal jelly was given after gentamycin "43±4.0". The are studies showed royal jelly to reduce the nephrotoxicity induced by other agents such as cisplatin (Ali Karadeniz *et al*, 2011) and cadmium (Kültiðin *et al*, 2009). Royal jelly given before gentamicin slightly lowers urea but the effect is not statistically significant "209±41.7". Royal jelly alone has no significant effect on serum urea (35±4.4).

While the mean creatinine "2.41±0.455" was found to be significantly higher compared to negative control "0.47± 0.005" (Naif Al-Harbi *et al*, 2014). The effect of gentamicin on serum creatinine was almost nullified when royal jelly was given after gentamicin (0.61±0.053). Royal jelly given before gentamicin slightly lowers creatinine but the effect is not statistically significant "1.67±0.238". Royal jelly alone has no significant effect on serum

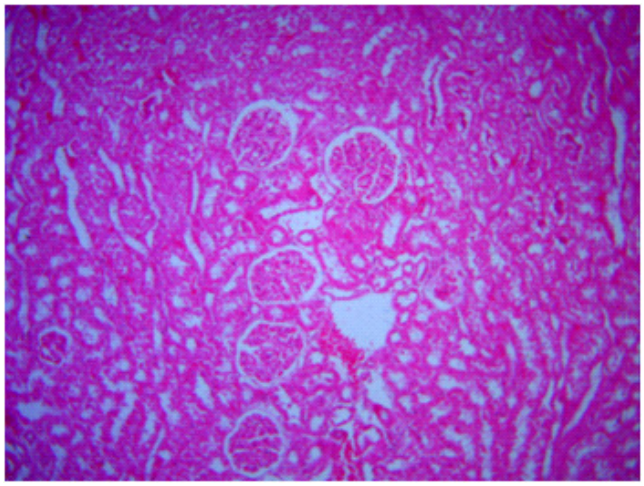


a- Dilatation of the renal tubules. Some of the tubules were filled with eosinophilic hyaline material.

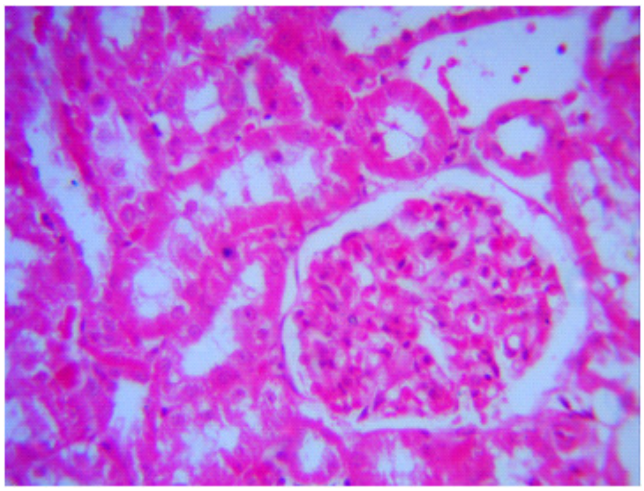


b- Thickening of the basement membrane of the glomeruli. Vacuolation of the glomerular epithelium, capillary congestion, degeneration of the tubular epithelium.

Fig. 5 : Royal jelly given orally before gentamicin inoculated IP (a-X100 & b-X400).



a- No significant pathological changes in glomeruli and tubular epithelium (X100).



b- No significant pathological changes in glomeruli and tubular epithelium (X400).

Fig. 6 : Royal jelly given orally after gentamicin inoculated IP (a-X100 & b-X400).

creatinine "0.47±0.005". These findings were corroborated by many researchers (Morales *et al*, 2010; El-Nekeety *et al*, 2007; Karaali *et al*, 1988). With regard to the royal jelly given after gentamicin interestingly enough, the effect of royal jelly is very good where it improved or lowered serum urea and creatinine.

Histopathological sections revealed gentamicin to exert a massive degeneration on the tubular epithelium with presence of eosinophilic hyaline cast in the lumen with dilatation of the renal tubules. In addition, there was thickening of the basement membrane of the glomeruli and congestion of the glomerular tuft with sometimes detachment and disappearance of the tubular epithelium of the glomerular membrane. These may to some extent agreed with the findings of Ali *et al* (2014), Juan *et al* (2007), Sahu *et al* (2014), Servais *et al* (2005) and Naif Al-Harbi *et al* (2014). It worth mentioning that the effect of gentamicin on histology of the kidney that in previous studies gentamicin induced tubular necrosis where here we found degeneration, this might be due to the factor of the gender where the previous studies were carried out in male rats.

The group of royal jelly given before gentamicin inoculation; there was changes shown as dilatation of the renal tubules where some of the tubules were filled with eosinophilic hyaline material plus thickening of the basement membrane of the glomeruli, vacuolation of the glomerular epithelium, capillary congestion, degeneration of the tubular epithelium and this is to an extent nearly similar to picture showed in positive control group.

The picture was seemed to be better when royal

jelly given after gentamicin where it showed no significant pathological changes in glomeruli and tubular epithelium in comparison to negative control group.

Royal jelly alone showed wide spread dilation of renal tubules without significant pathological changes of tubules.

Royal jelly has decreased the nephrotoxicity induced by gentamicin as was observed in histopathological sections. These finding might be agreed with previous studies carried by (Morales *et al*, 2010; El-Nekeety *et al*, 2007; Karaali *et al*, 1988; Shinoda *et al*, 1978). Royal jelly ameliorated gentamicin-induced nephrotoxicity, also the extent of histologic injury and reduced inflammatory infiltration in renal tubules; these findings suggest that royal jelly given after gentamicin attenuates renal dysfunction and structural damage through the reduction of oxidative stress, inflammation, and apoptosis in the kidney and this is may be agreed with the study by Ali *et al* (2014), Juan *et al* (2007).

In royal jelly given after gentamicin the morphology revealed a nearly regular appearance of glomeruli and tubules (El-Neekety *et al*, 2007), same authors have reported co-treatment with royal jelly resulted in a signiûcant improvement in tested parameters such as creatinine level towards normal values. In this study, it is observed that inoculated gentamicin followed by oral royal jelly caused a signiûcant reduction in the extent of tissue lesions resulted from gentamicin. This protection may be attributed to antioxidant and radical scavenging activity of royal jelly. It could be concluded that royal might have protective effect against gentamicin-induced nephrotoxicity and oxidative stress.

CONCLUSION

1. There is a significant effect of gentamicin on rats' kidneys causing severe nephrotoxicity exemplified by effect on serum urea and creatinine levels and alteration of normal kidney sections.

2. Reducing effect of royal jelly on both gentamicin given before and after but better effect especially when given after where it normalized serum urea and creatinine in addition to kidney histology.

3. No significant effect on total protein, albumin, and uric acid.

Conflict of interests

The authors declare that they have no conflict of interests.

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