Nephroprotective potential of artichoke leaves extract against gentamicin in rats: Antioxidant mechanisms

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Abstract: Nephrotoxicity represents a major health problem. This study aims to determine nephroprotective of artichoke leaves extract (ALE) against gentamicin (GM) injection in male rats. Rats (n=30) were divided into; negative control, nephrotoxic (GM) injected intraperitoneally (i.p.) with GM (100 mg/kg b.wt/d for 10 days), and groups administered orally with ALE (200, 400 or 600 mg/kg b.wt/d) and injected with GM. The results revealed that, GM injection induced marked nephrotoxicity as evidenced by significant increase in kidney functions, albumin and potassium (K^+), with significant decrease in serum levels of total protein and sodium (Na^+) as compared with negative control group. There was significant increase in malondialdehyde (MDA) level in GM group compared with negative control group. Renal examined tissues showed severe changes manifested by atrophy of glomerular tuft, necrosis of epithelial lining renal tubules with apoptosis of tubular epithelium and renal hemorrhage. Simultaneous administration of ALE during GM therapy protected kidney tissues as evidenced by normalization of kidney biochemical parameters and minimized the histopathological changes. Therefore, ALE has nephroprotective and antioxidant effects, thus could be beneficial for kidney patients.

Keywords: Artichoke leaves extract, gentamicin, kidney functions, antioxidant.

INTRODUCTION

Aminoglycosides are antibiotics with a heterocyclic structure. The most widely used drug in this category is GM. Gentamicin is a nephrotoxic antibiotic, which causes acute tubular necrosis, and its toxicity remains a major problem in clinical use (Boroushaki *et al*., 2014). Heibashy *et al*. (2010) showed that prooxidants have a pivotal role in GM-mediated nephrotoxicity, it induced impairment of renal functions. Flavonoids have aroused considerable interest due to their broad pharmacological activity (Galvez *et al*., 2001).

A growing interest in the artichoke (*Cynara scolymus* L.) is a focus on new uses as a functional food has been observed (Lattanzio *et al*., 2009). It is a rich source of dietary antioxidants mainly polyphenols and flavonoids. Artichoke leaves extract reduce the intracellular reactive oxygen species (ROS) (Zapolska-Downar *et al*., 2002), and used as choleretic and diuretic (Speroni *et al*., 2003). It decreases serum lipids, hepatic and cardiac oxidative in rats (Kucukgergin *et al*., 2010). Therefore, this study aims to determine the antioxidant effect of ALE against nephrotoxicity in young male rats.

MATERIAL AND METHODS

Chemicals and kits

Gentamicin (Gentam-80) as gentamicin sulphate (each 1 ml of gentam-80 contains gentamicin sulphate equivalent to 40 mg gentamicin base) was obtained from King Abdulaziz University (KAU) Hospital, Jeddah, KSA. All chemical and kits with high grade obtained from Sigma-Aldrich (St. Louis, MO) Chemical Co.

Extraction of plant material

Artichoke (*Cynara scolymus* L., Family Asteraceae) plant obtained from Al Taif, Saudi Arabia. The plant material was authenticated by Prof. Dr. Alaa Eldin M.S. Khedr, Department of Pharmaceutical and Phytochemistry, Faculty of Pharmacy, KAU, Jeddah, Saudi Arabia. Fresh leaves were separated and cleaned (weighed 2000 gm), it mechanically blended with 2000 ml distilled water then filtered through two-layer of cheese cloth, and the resultant residue was re-dissolved in 1000 ml distilled water by using magnetic stirrer for 1h. The later aqueous extract was added to the first one. The combined aqueous extract was condensed in rotary evaporator under vacuum then lyophilized and stored at 4°C until further use. Lyophilization was conducted by using Freeze-Dryer Lyophilizer, Virtis, USA in KFCMR. The method of extraction was carried out according to (Jimenez-Escrig *et al*., 2003). 100 gm of ALE yielded (4.73 ± 0.361, as mean ± SE) gm.

Ethical approval

This study was approved by Biomedical ethics Research Committee, Faculty of Medicine, King Abdulaziz University, reference no (HA-02-J-008). The experiment was conducted at King Fahd Center for Medical Research (KFCMR), KAU accordance with international guidelines for care and use of laboratory animals.

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Experimental protocol

Male Wister albino rats (n=30) (90-110 gm) were obtained from animal experimental unit of KFCMR, KAU. Rats were allowed one week for acclimatization in standard laboratory conditions before being used for the study. All animals fed standard diet and drinking water *ad libitum*. After adaptation period, rats divided into to five groups (6 each) as follows: Control (-ve) group; rats administered orally by gavage dist. water and injected i.p. with saline for ten consecutive days. Control positive (nephrotoxic group); rats injected i.p. with GM (100 mg/kg b.wt.) for ten consecutive days according to (Morales *et al*., 2002). Nephrotoxic groups pre-treated with ALE; rats received orally ALE at three doses (200, 400 or 600 mg/kg b.wt.) one hour before i.p. injected with GM as in (nephrotoxic group). During experimental period feed intake (FI) and animal's weight were recorded. The 24 hrs urine collections were obtained from individual rats by using metabolic cages. Twenty four hours after the last dose of the GM drug, blood samples withdrawn from each rat under anesthesia for separate serum.

Biochemical analysis

Determination of serum level of kidney functions (creatinine, urea nitrogen and uric acid according to (Henry, 1974, Patton and Grouch, 1977 and Fosssati *et al*., 1980, respectively), protein metabolism parameters (total protein (TP) and albumin according to Henry, 1964 and Doumas *et al*., 1971, respectively), malondialdehyde (MDA) (Yoshioka *et al*., 1979) and ionic metals (Niels *et al*., 1984).

Histopathological examination

Kidney sections were fixed immediately in 10% formalin and prepared for examined microscopically.

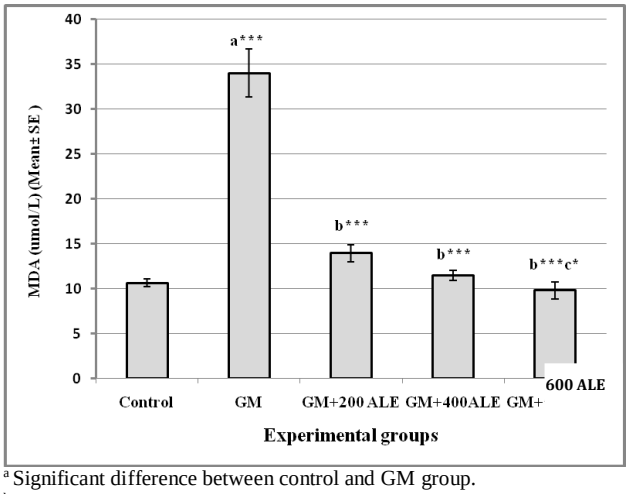
Statistical analysis

Data analyzed statistically by SPSS using L.S.D. test, one way ANOVA, post hoc multiple comparisons.

RESULTS

Biological evaluation

Table (1) showed the effect of ALE with three doses on biological evaluation parameters. Nephrotoxic group (+ve) revealed significant reduction ($p<0.01$) in final b.wt and BWG% as compared with control (-ve). Oral administration of ALE induced improvement in final b.wt and BWG %. There were no significant change when compared the three doses of ALE (200, 400 or 600 mg/kg b.wt) with control (-ve). Pretreatment with ALE showed significant difference as compared with GM (+ve), at all the three used doses ($p<0.05$ for low dose and $p<0.001$ for medium and high doses) as comparing with GM (+ve) group. Comparing between pretreated effect of different doses of ALE, there was significant ($p<0.05$) difference between low (200 mg) compared with both medium (400 mg) and high (600 mg) doses in final b.wt and BWG%, while non-significant difference between medium and high dose was recorded. Concerning FI, there was significant difference between GM (+ve) and control (-ve) groups in FI. Regarding the effect of different doses of ALE pretreatment groups, there was significant difference when compare between low (200 mg) to both medium (400 mg) and high (600 mg) doses, while no significant difference between medium dose and high dose was reported.



[a] Significant difference between control and GM group.
[b] Significant difference between GM (+ve) and GM+ALE groups.
[c] Significant difference between GM + 200 ALE and the other two doses (400 & 600) ALE.
[d] Significant difference between GM + 400 ALE and GM + 600 ALE.
($^{*}p<0.05$, $^{**}p<0.01$ and $^{***}p<0.001$).

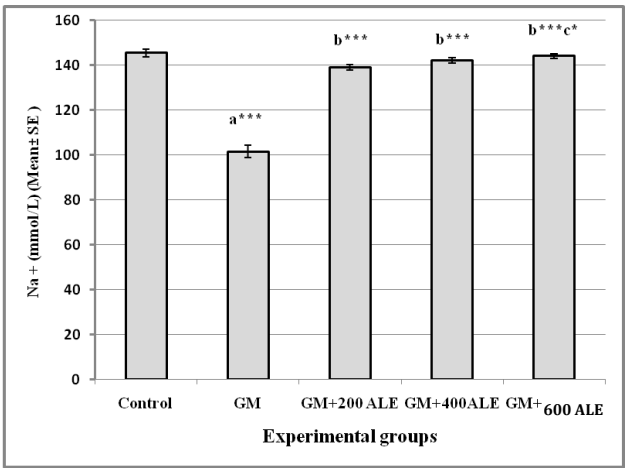
Fig. 1: Effect of ALE on malondialdehyde (MDA) level in nephrotoxic rats

Organ index weight and urine volume

Kidney index weight significant increase in GM (+ve) group as compared with control (-ve) group. Pretreatment of GM groups with ALE at low dose revealed significant difference as compared with control (-ve) group, while medium and high doses showed non-significant changes as compared with control (-ve) group. Low dose of ALE (200 mg) showed significant difference compared with both medium and high doses (table 2).

Results revealed that, GM injection induced significant increase in urine volume with percentage (72.78%) as percent change from control (-ve) group. While comparison between control (-ve) group with the three doses (200, 400 or 600 mg/kg b.wt) of ALE pre-treated GM groups, there was normalize in the urine volume with no significant changes between medium and high doses pretreated groups, expect low dose of ALE revealed significant elevate in urine volume compared with control (-ve) group. ALE pretreatment to GM-injected groups, showed significant improvement in urine volume compared with GM (+ve) group. A dose response trend

was observed with various levels of ALE, where low dose revealed significant difference compared with both medium and high doses, while medium and high doses recorded non-significant difference between them in urine volume. Examination of urine specimens for color and turbidity in different groups revealed that, normal clear urine color range from colorless to pale yellow with no turbidity was observed in control (-ve) group. Injection of GM induced change in urine appearance, where dark, cloudy and turbidity was observed in GM (+ve) compared with control rats. Pretreatment of GM groups with ALE induced change in urine color and turbidity. A dose response trend were observed with various levels of ALE, where yellow-brown hazy and slightly cloudy was observed in low dose, while the urine apparent normal in both medium and high doses of ALE.

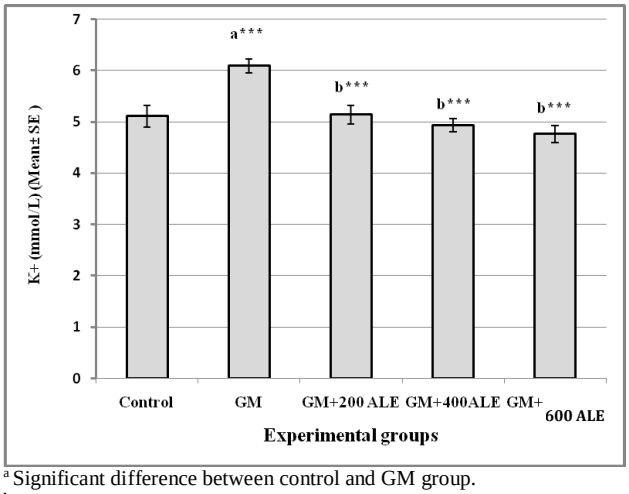


[a] Significant difference between control and GM group.
[b] Significant difference between GM (+ve) and GM+ ALE groups.
[c] Significant difference between GM + 200 ALE and the other two doses (400 & 600) ALE.
[d] Significant difference between GM + 400 ALE and GM + 600 ALE. ($^{*}p$<0.05, $^{**}p$<0.01 and $^{***}p$<0.001).

Fig. 2: Effect of ALE on sodium (Na^+) in nephrotoxic rats

Kidney functions and protein metabolism

The results revealed that, acute intoxication of rats by GM induced significant elevation in creatinine, urea nitrogen and uric acid concentrations in GM (+ve) group when compared with control (-ve) group. In both medium and high doses of ALE pretreated groups, there were no significant difference compared with control (-ve) group. Oral administration of ALE to GM injected rats, showed significant amelioration in all tested kidney function parameters. The ALE lowers the elevated serum level of creatinine, urea nitrogen and uric acid. There were significant (p<0.001) difference between pretreated groups at all the three dose levels (200, 400 or 600 mg/kg b.wt) and GM (+ve) group at (p<0.001). There was significant difference in creatinine, urea nitrogen and uric acid in GM rats received low dose compared with high dose, as well as in urea nitrogen compared with medium dose (table 3).



[a] Significant difference between control and GM group.
[b] Significant difference between GM (+ve) and GM+ ALE groups.
[c] Significant difference between GM + 200 ALE and the other two doses (400 & 600) ALE.
[d] Significant difference between GM + 400 ALE and GM + 600 ALE. ($^{*}p$<0.05, $^{**}p$<0.01 and $^{***}p$<0.001).

Fig. 3: Effect of ALE on potassium (K^+) in nephrotoxic rats

The effect of ALE on serum levels of protein metabolism parameters against GM-induced nephrotoxicity in young male rats is shown in table (4). Serum level of TP and globulin exhibited significant decrease (p<0.01 and p<0.001, respectively), while albumin level and A/G ratio showed significant increase (p<0.01 and p<0.001, respectively) in GM (+ve) group when compared with the corresponding values of control (-ve) group. As seen in table (4), oral pretreatment with ALE to GM-injected rats showed significant improvement in all tested protein metabolism parameters, their values revealed no significant change compared with the corresponding values in control (-ve) group for all doses used. The improvement in low dose of ALE was non-significant difference in TP, while in serum levels of albumin and globulin recorded significant (p<0.05) difference as compared with GM (+ve) group. On the other hand, there was a significant difference in all tested protein metabolism parameters when compared both medium and high doses of ALE with the corresponding values in GM (+ve) untreated group. In A/G ratio there was significant (p<0.001) decrease in the three doses used when compared with GM (+ve) group. Low dose showed significant (p<0.05) change as compared with high dose in globulin and A/G ratio. There were no significant changes between both medium and high doses in all tested protein metabolism parameters.

Lipid peroxidation (malondialdehyde)

Nephrotoxic GM (+ve) group recorded significant elevation in MDA compared with control rats. Receiving ALE pre-GM injection caused a marked protection evidenced by significant reduction (p<0.001) in MDA level, there was a non-significant change in all pre-treated

Table 1: Effect of ALE on biological evaluation in nephrotoxic rats

Experimental groups	Initial body weight (g)	Final body weight (g)	BWG %	FI (g/rat/day)
Control (-ve)	112.67±1.58	142.19±3.47	26.20±2.16	13.97±0.82
GM (+ ve)	110.44±1.86	127.74±2.26$^{a\ **}$	15.67±1.80 $^{a\ **}$	8.72±0.55$^{a\ ***}$
GM + 200 ALE	111.17±1.47	137.66±1.93$^{b\ *}$	23.83±1.96 $^{b\ *}$	12.60±0.60 $^{b\ ***}$
GM + 400 ALE	114.01±1.08	149.49±4.45 $^{b\ ***c*}$	31.13±3.09 $^{b\ ***\ c*}$	14.77±0. 49 $^{b\ ***\ c*}$
GM + 600 ALE	113.40±1.10	150.01±4.00 $^{b\ ***c*}$	32.28±2.97 $^{b\ ***\ c*}$	14.94±0.54$^{b\ ***\ c*}$

Table 2: Effect of ALE on kidney index weight and urine volume in nephrotoxic rats

Experimental groups	Kidney IW (g/100g b.wt)	Urine volume (ml/24 hrs)
Control (-ve)	0.847±0.054	19.58±1.55
GM (+ve)	1.003±0.053 ^{a*}	33.83±1.84 $^{a\ ***}$
GM + 200 ALE	0.999±0.032 ^{a*}	24.58±1.49$^{a*\ b\ ***}$
GM + 400 ALE	0.851±0.04 $^{b*\ c*}$	20.25±1.03$^{b\ ***c*}$
GM + 600 ALE	0.825±0.032 $^{b**\ c**}$	16.77±0.96$^{b\ ***c**}$

Table 3: Effect of ALE on kidney functions in nephrotoxic rats

Experimental groups	Creatinine (µmol/L)	Urea nitrogen (mmol/L)	Uric acid (umol/L)
Control (-ve)	26.00±1.29	8.01±0.47	63.83±3.28
GM (+ve)	50.79±3.51^{a***}	18.82±1.23$^{a\ ***}$	127.50±4.84$^{a\ ***}$
GM + 200 ALE	33.59±1.61$^{a*\ b\ ***}$	10.51±0.73$^{a*\ b\ ***}$	80.67±5.62$^{a*\ b\ ***}$
GM + 400 ALE	29.02±1.92$^{b\ ***}$	8.27 ±0.32$^{b\ ***c*}$	74.58±4.07$^{b\ ***}$
GM + 600 ALE	27.24±1.71$^{b\ ***\ c*}$	7.78±0.41$^{b\ ***c*}$	66.33 ±3.18$^{b\ ***c*}$

Table 4: Effect of ALE on protein metabolism parameters in nephrotoxic rats

Experimental groups	Total protein (g/dl)	Albumin (g/dl)	Globulin (g/dl)	A/G ratio
Control (-ve)	7.29±0.28	4.09±0.20	3.20±0.24	1.28±0.11
GM (+ ve)	6.21±0.23 $^{a\ **}$	5.19±0.25 $^{a\ **}$	1.01±0.19 $^{a\ ***}$	5.14±0.30 $^{a\ ***}$
GM + 200 ALE	6.82±0.13	4.48±0.10 $^{b\ *}$	2.34±0.14$^{b\ *}$	1.92±0.28 $^{b\ ***}$
GM + 400 ALE	7.37±0.30 $^{b\ **}$	4.38±0.31 $^{b\ *}$	2.98±0.53 $^{b\ **}$	1.47±0. 25 $^{b\ ***}$
GM + 600 ALE	7.55±0.39 $^{b\ **}$	4.14±0.29 $^{b\ **}$	3.41±0.50 $^{b\ ***\ c*}$	1.22±0.23 $^{b\ ***\ c*}$

Results represents mean of 6 rats ± SE.
[a] Significant difference between control and GM group.
[b] Significant difference between GM (+ve) and GM+ ALE groups.
[c] Significant difference between GM + 200 ALE and the other two doses (400 & 600) ALE.
[d] Significant difference between GM + 400 ALE and GM + 600 ALE. ($^{*}p<0.05$, $^{**}p<0.01$ and $^{***}p<0.001$).

groups (three doses) compare with control (-ve) group. At the same time, there was significant ($p<0.001$) difference when compared pre-treated groups at the three doses level with GM (+ve) group. A dose response trend was observed with various levels of ALE, where significant ($p<0.05$) changes in MDA was found between low (200 mg/kg b.wt of ALE) and high doses (600 mg kg b.wt of ALE), while medium and high doses showed no significant change between them (fig. 1).

Ionic sodium and potassium

Regarding serum level of ionic sodium (Na^+) and potassium (K^+) in different groups (figs. 2&3). Injection with GM revealed significant difference comparing with control group, there were significant decrease in Na^+ concomitant with significant increase in K^+ in GM injected group as compared with control (-ve) group. All pre-treated groups showed non-significant difference compared with control (-ve) group, expect low dose of ALE in Na^+ level ($p<0.05$) as compared with control (-ve) group. On the other hand, oral administration of ALE prior to GM-injection markedly preserved the changes in ionic Na^+ and K^+ levels, there were significant difference ($p<0.001$) between GM (+ve) group and all groups pre-treated with ALE at the three doses used (200, 400 and 600 mg/kg b.wt). A dose response improvement was observed with various levels of ALE, where a significant difference ($p<0.05$) in Na^+ level between low (200 mg ALE) and high doses (600 mg ALE), while medium and high doses revealed non-significant difference between them.

Histopathological investigation

In our experiment, sections of kidney from control (-ve) group revealed no histopathological changes fig (4(1)). Sections from GM (+ve) group showed severe changes as

evidence by atrophy of glomerular tuft, interstitial nephritis with basement membrane thickening fig (4(2.a)), necrosis of epithelial lining renal tubules with apoptosis and karyomegaly of nuclei of tubular epithelium fig (4(2.b)), atrophy of glomerular tufts, marked interstitial nephritis, coagulative necrosis of renal tubular epithelium and local renal haemorrhage figs (4(2.c&d)). Concerning GM group received (200 mg/kg b.wt) ALE showed moderate to mild changes; it revealed small local interstitial inflammatory cells infiltration fig (4(3.a)), while other sections showed congestion of glomerular tuft fig (4(3.b)). Kidney sections of GM group received (400 mg/kg b.wt) ALE showed mild to no changes; it revealed congestion of glomerular tuft fig (4(4.a)), while other sections showed apparent normal renal parenchyma fig (4(4.b)). In GM group treated with (600 mg/kg b.wt) ALE no histopathological changes was observed fig (4(5.a)), except slight congestion of glomerular tuft in some sections fig (4(5.b)).

DISCUSSION

Nephrotoxicity accounts for high incidence among population all over the world (Jain *et al*., 2013). Therapeutic doses of GM and other aminoglycoside antibiotics when given for more than seven days course therapy produce nephrotoxicity in humans and animals (Awodele *et al*., 2014). Of interest it was reported that, GM nephrotoxicity in rats was positively correlated with its outcome in humans. Therefore, the nephrotoxic effect of GM has limited the extent of its clinical use nowadays.

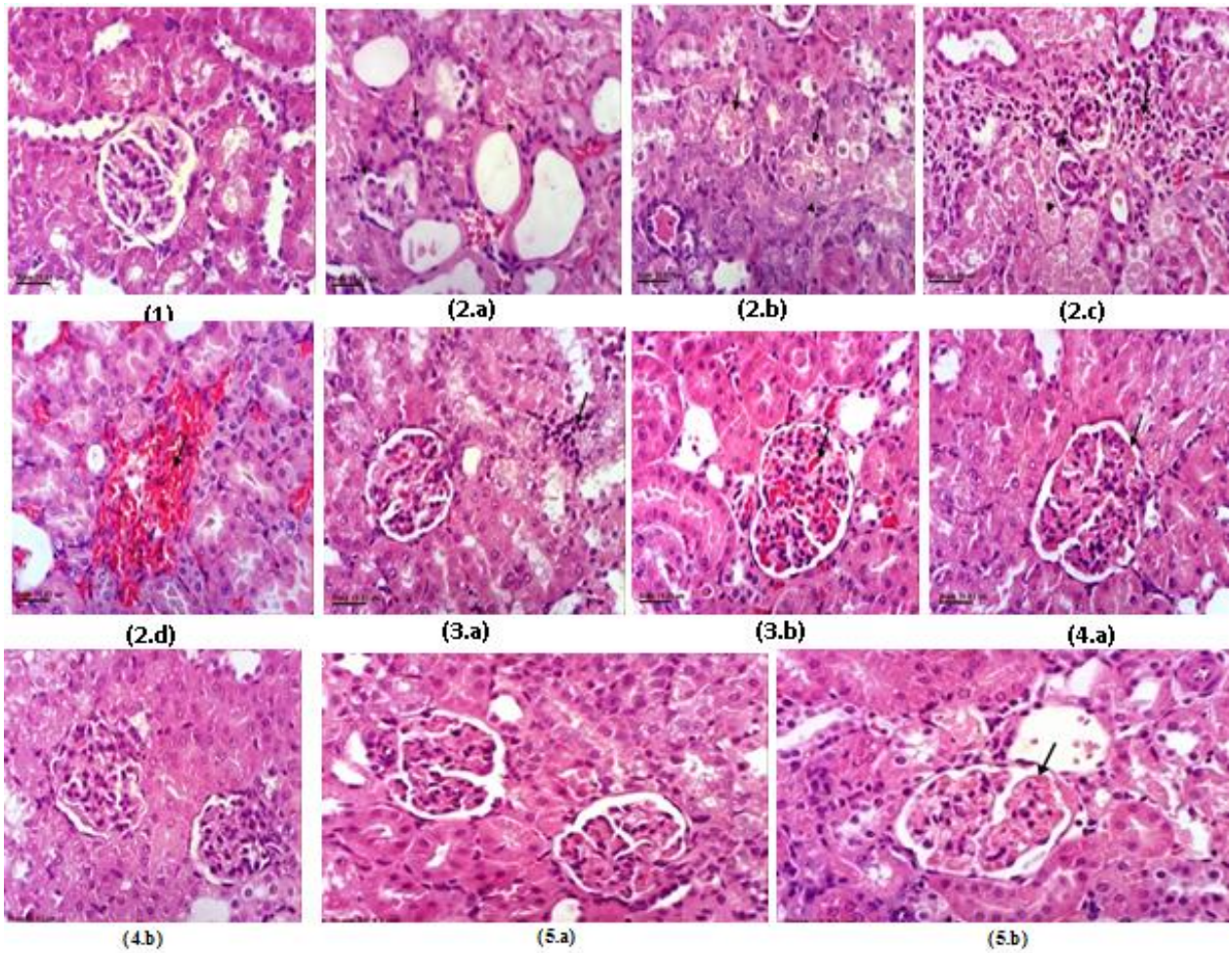


Fig. 4: Kidney of control (-ve) group (1) showing no histopathological changes. Sections of rat from GM group showing atrophy of glomeruler tuft (small arrow), interstitial nephritis (large arrow) with thickening of basement membrane (arrow head) (2.a.), necrosis of epithelial lining renal tubules (small arrow), apoptosis (large arrow) and karyomegaly of nuclei of tubular epithelium (arrow head) (2.b.) ,atrophy of glomerular tufts (small arrow), marked interstitial nephritis (large arrow) and coagulative necrosis of renal tubular epithelium (arrow head) (2.c.) and local renal haemorrhage (arrow) (2.d.). Sections from GM+200 ALE group showing small local interstitial inflammatory cells infiltration (arrow) (3.a) and congestion of glomerular tuft (arrow) (3.b). Sections from GM+400 ALE group showing congestion of glomerular tuft (arrow) (4.a) and normal renal parenchyma (4.b). Sections from GM+600 ALE group showing no histopathological changes (5.a.), expect some sections showing slight congestion of glomerular tuft (arrow) (5.b). (H&E stain x400)

Reactive oxygen species are potential mediators involved in GM-induced renal injury (Avdagić *et al*., 2007; Reddy *et al*., 2011). Artichoke leaves extract have high antioxidant activity (Speroni *et al*., 2003).

Body weight is the most sensitive indicator of adverse effects of chemical toxicants and xenobiotics. Gentamicin induced statistical significant loss of body weight in GM compared with control. This result was agree with Ezejiofor *et al*. (2014). This may be attributed to GM-produced renal failure that resulted in acidosis associated with anorexia caused by the drug, which lead to a decrease in body weight as reported by (Houghton *et al*., 1975). The increase catabolism accompanied by anorexia and the decrease of feed intake may be the causes of body weight loss seen in GM injection. On the other hand, ALE administrated to GM-injected rats induced marked amelioration on body weight at the three used doses, in dose dependent manner as comparing with GM (+ve) group. These results agree with Ezejiofor *et al*. (2014). Our finding could be explained by the antioxidant effect of ALE due to its high content of flavonoids, which might be able to alternate nutrients absorption and metabolic utilization and act as growth promoter in animals (El Saeed *et al*., 2012).

In the present work, it was found that there was a significant increase in kidney index weight in GM compared with control. Finding similar to the results of Ezejiofor *et al*. (2014). This could be explained by tissues damage, function alteration and edema due to GM drug induced tubular necrosis (Rana *et al*., 2014). Pre-treatment with ALE in GM-injected groups resulted in an improvement of kidney index weight, which was found to be a dose dependent. Our results confirming by Shimeda *et al*. (2005).

In the current study the results revealed that, the 24-hrs urine volume in the GM injected rats was significant increase with changes in urine appearance, from clear amber yellow with no turbidity in the control (-ve) group to dark, cloudy and turbid urine in GM (+ve) group. The obtained results agreed with Khan *et al*. (2011). These results may be attributed to GM- induced polyuria and nonoliguric due to it induced acute renal failure (Rana *et al*., 2014). Pretreatment with ALE to GM injected rats showed significant improvement in urine volume and normalized in the urine color and turbidity as compared to GM (+ve) group. A dose response trend was observed with various doses of ALE in urine volume and appearance. These findings may be attributed to antioxidant effect of ALE as a rich source of potent antioxidants, as found in the present study.

The present results indicated that, there were significant elevation in creatinine, urea nitrogen and uric acid in GM (+ve) group as compared with control (-ve) group. Our results in the same line with El-Tantawy *et al*. (2013) and Ezejiofor *et al*. (2014). These findings may be attributed to GM toxic effect that may influence the various metabolic kidney pathways. Gentamicin induced oxidative kidney injury causing tubular damage and renal impairment (Khan *et al*., 2011). Moreover, free radicals generated by GM-treatment induced cells contraction and modified the ultra-filtration coefficient which reflected the severity of renal insufficiency (Swan, 1997).

Administration of ALE to GM injected rats, showed significant amelioration in all tested kidney function parameters as compared with the GM (+ve) group. The present findings were in the same line with those reported by Abdel-Kader *et al*. (2014). These may be explained by the cynarin content of artichoke accelerates the metabolism of urea and improves dieresis, which may trigger the excretion of urea and creatinine (Stoev *et al*., 2002). Moreover, the prevalent antioxidant activity in ALE due to its phenolic compounds content, this property may contribute in enhancing renal functions *via* suppressing oxidative stress which induced tubular injury.

The present results revealed that, serum level of TP and globulin exhibited significant decrease accompanied by significant increase in albumin and A/G ratio in GM (+ve) group as compared with the corresponding values of the control (-ve) group. The reduction in TP level may be explained by Wolf and Ziyadeh (2007) who found that, GM-induced proteinuria, which is associated with glomerular sclerosis and tubule interstitial fibrosis. In addition, GM injection to rats induced destruction of protein synthesizing subcellular structures (Heibashy *et al*., 2010). Gentamicin treatment causes depletion in albumin, which might be depressed as a result of defective protein synthesis (Khan *et al*., 2011). In addition, decreased albumin/ globulin ratio (A/G) is an important predictor of progression of kidney diseases. Pretreatment with ALE showed significant improvement in all tested protein metabolism parameters. This finding could be explained by artichoke leaves extract had efficient protective properties against oxidative stress imposed on renal endothelial cells (Zapolska-Downar *et al*., 2002).

Gentamicin group revealed significant elevation in MDA compared with the control (-ve) group. The present results were similar to the previous findings reported by and El-Tantawy *et al*. (2013). Aminoglycoside antibiotics can stimulate the formation of ROS (Reddy *et al*., 2011). Receiving ALE pre-GM injection caused a marked protection evidenced by significant reduction in MDA levels. The protective effect of ALE might be due its high content of bioactive phytochemicals which may regulate and repair injured tissues (Khan *et al*., 2011). Nephrotoxicity is associated with increase MDA, which damages cell membranes, the inhibition of this process is mainly attributed to the ability of ALE to scavenger free radicals (Shanmugasundaram and Venkataraman, 2006).

Ionic metals disturbed significantly in the GM injected rats compared with control (-ve) rats. This agrees with El-Tantawy *et al*. (2013). Lower sodium level indicates kidney inability to conserve sodium. In turn, elevate potassium level may due to renal tubular epithelium lesions (Padmini and Kumar, 2012). A dose response improvement was observed with various levels of ALE, where pretreatment of rats with ALE markedly preserved the change in ionic Na^+ and K^+. There were significant difference between GM (+ve) group and all groups pre-treated with ALE at the three doses levels. The antioxidant property of ALE could be attributed to its phenolic components, which may be responsible for reducing the oxidative stress and hence improving renal tubular functions (Shanmugasundaram and Venkataraman, 2006).

In this study, the biochemical data were concordant with pathological findings. Examination of kidney sections of GM (+ve) group showed severe histological changes as evidence by atrophy of glomerular tuft, interstitial nephritis, necrosis of epithelial lining renal tubules with apoptosis and karyomegaly of nuclei of tubular epithelium. This may be due to gentamicin accumulation in renal cortex causing degeneration and necrosis of the epithelial cells (Shirwaikar *et al*., 2003). Administration of ALE remarkably minimized the structural changes in kidney, which was observed in high dose used, thus may be explained by antioxidative activity of ALE that may be attributed to its antioxidant constituents (Baker *et al*., 1998).

CONCLUSION

In conclusion, the present study demonstrates that artichoke leaves extract possesses significant nephroprotective and antioxidant effects. It has an ability to prevent and ameliorate the degeneration and tubular necrosis induced by GM in the kidney of rats. Therefore, the extract should be further investigated as a supplement for the management of kidney diseases with minimal side effects.

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