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Protective Effect of Ginseng against the Gentamicin-Induced Renal Toxicity

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Abstract

A frequent adverse effect of medicines is nephrotoxicity. One of the most popular alternative therapies is ginseng, and each of its components improves renal function. Due of gentamicin's harmful effects, particularly on the kidneys, use is now restricted. The aim of the current research was to assess how ginseng affected gentamicin-induced nephrotoxicity. Twenty-one male albino rats aged 6 to 8 weeks had been divided into three groups. Group-A acted as the control group and received a typical rat diet. Gentamicin, dissolved in one milliliter of distilled water, was administered intraperitoneally to Group-B for fifteen days at a dose of 80 mg-Kg-day. For 15 days, Group-C received 100 mg-Kg-day of ginseng orally dissolved in 1 ml water in addition to 80 mg/Kg per day of gentamicin. Each animal had blood taken from them by heart puncture at the conclusion of the experiment in order to examine their kidney function. Then, kidneys from each animal were killed and collected for standard histopathological investigations. When compared to group A, group B's animals and kidneys were lighter, and mean serum urea, creatinine, and the intraluminal diameter of the proximal convoluted tubules all increased significantly. In this group, there were mild to severe necrotic and degenerative alterations in the proximal convoluted tubules. When ginseng and gentamicin were administered simultaneously, improvements in renal function tests, tubular diameter, and the mean body and kidney weights were all statistically significant. Ginseng seems to have some protective effects against nephrotoxicity brought on by gentamicin.

Key words: *Kidney, Nephrotoxicity, Gentamicin, Oxidative stress, Ginseng.*

Introduction

One of the aminoglycoside antibiotics, gentamicin is used to treat gram-negative bacterial infections. However, according to reports, nephrotoxicity will occur in 10% to 30% of gentamicin-treated patients. [1] It is commonly accepted that oxidative stress, which manifests as an increase in lipid peroxidation level and a decrease in antioxidant enzyme activities, occurred in the gentamicin-induced nephrotoxicity.[2] Treatment with gentamicin causes nephrotoxic consequences because it builds up in renal cortical tubular epithelial cells. Lysosomes, mitochondria, and microsomes are among the membrane-bound organelles that gentamicin might harm. Critical intracellular functions, such as mitochondrial respiration, microsomal protein synthesis and the electron transport chain may be disrupted by the release

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of acid hydrolases during the lysis of lysosomes containing gentamicin.[3]

Ginseng is one herbal substance that has been reported to have anti-nephrotoxic properties against drug-induced nephrotoxicity in test animals. [4] Ginseng probably works through the hypothalamus-pituitary-adrenal axis to exert its effects. Ginseng may help to maintain cell membranes, lessen the cell damage brought on by toxins, and guard tissues from harm by preventing lipid peroxidation. These results are a result of ginseng's antioxidant properties. [5] Nephrotoxi city caused by gentamicin results in markedly elevated blood levels of urea and creatinine. Ginseng therapy has been shown to normalize elevated blood urea and creatinine readings.

Due to the latter's impact on cell wall formation, gentamicin and -lactam antibiotics work together to increase the diffusion of the former into the bacterium. Bacterial resistance to gentamicin may be caused by the medication's inability to cross the cell membrane, abnormal ribosome binding, or drug degradation by bacterial enzymes. The aminoglycosides can result in three distinct adverse effects in addition to various typical types of toxicity (such as hypersensitivity reactions and drug-induced fever): ototoxicity, neuromuscular inhibition, and nephrotoxicity. [6] Acute renal failure caused by gentamicin nephrotoxicity accounts for 10% to 15% of all cases. Gentamicin can be concentrated by the cells of the proximal renal tubules several times more than it can in the plasma. [7]. In order to assess the possible cytoprotective impact of ginseng in a model of gentamicin-induced nephrotoxicity and to investigate the precise mechanisms associated with the role of oxidative stress, mitochondria, and apoptosis in this event, this study was created.

Materials and Methods

Our work was conducted in accordance with the PSA University's Al-Kharj Ethical Committee's guidelines for the use and care of animals in research. (SCBR-083-2023).

The study, which lasted from April 2022 to March 2023, was experimental.

Ginseng" syrup 120 ml was obtained from "Pharco Pharmaceuticals - Alexandria - Egypt". Each 100 ml of syrup contains ginseng extract 933 mg (9.33 mg/ml). The dose was calculated according to body weight of each rat as 100 mg/kg/day [8]. Garamycin" ampoules 40 mg/ ml was obtained from "Memphis Company for Pharmaceutical and Chemical Industries - Cairo - A.R.E.". A toxic dose of 100 mg/kg/day was calculated according to the body weight of each rat [9].

21 healthy, 10-week-old albino rats (weighing between 250 and 310 g) were used in the study. They were taken in from a PSA University animal care facility. They were housed in animal housing and fed a conventional food at the animal care facility. Before the trial began, rats were monitored for roughly 14 days to allow for acclimatization. The animals were split into three groups, each of which had seven rats. Healthy rats in the control group got methyl cellulose orally for 10 days in a row along with an intraperitoneal injection of saline. Group-A acted as the control group and received a typical rat diet. Gentamicin, dissolved in 1 ml of water (distilled), was administered intraperitoneally to Group-B for fifteen days at a dose of 80 mg/Kg/day. For 15 days, Group-C received 100 mg/Kg per day of ginseng orally dissolved in one ml of distilled water in addition to 80 mg/Kg per day of gentamicin intraperitoneally dissolved in one ml of distilled water. By making a median abdominal incision on the specified dates, the kidneys were removed from the rats, preserved in 10% buffered formalin, and then processed for paraffin slices. Then, ether inhalation anesthesia was administered to the rats. To get ready for paraffin sectioning, all specimens were kept in 10% formol saline solution for

three days. The kidney was removed right away and left to cure for three days in 10% formal saline solution. The specimens were completely dehydrated before being treated with ethyl alcohol at ascending concentrations for a total of three hours after a day in which they were treated with 70%, 90%, and finally, absolute alcohol. The samples were benzene-cleared for 24 hours. The cleaned samples were immersed three times for an hour each in paraffin wax. After that, the samples were firmly embedded in paraffin wax. Hematoxylin and eosin (H&E) stain were alternately applied to the successive slides made from each specimen. Using Masson's trichrome dye, collagen fibers were made visible. For the goal of detecting neutral mucopolysaccharides, use Periodic Acid Schiff. Each animal had blood taken from them by heart puncture at the conclusion of the experiment in order to examine their kidney function. Then, kidneys from each animal were killed and collected for standard histopathological investigations. In the present study, blood samples and specimens of kidneys belonged to the experimental rats of all groups were subjected to serological and histological studies respectively. In addition to that, recording of body weight of each animal twice weekly were done. Using SPSS software Version 16, statistical analysis of measurements of the mean diameters of the glomeruli, distal and proximal convoluted tubules was performed. The mean and SD (standard deviation) were used to represent the variables. Finally, the significance was evaluated in accordance with the p-value.($p<0.05$ significant)

Results

After gentamicin injection, group B's body weights considerably fell, continuing to decline through the eleventh day. However, when gentamicin and ginseng were administered simultaneously, group C showed improvement. Table (1) contains a summary of these facts. At the conclusion of their trial period, all of the rats in-group A had blood samples drawn, and the sera of those samples exhibited normal levels of urea and creatinine. While they shifted toward the control group in group C when ginseng was administered along with gentamicin, serum urea and creatinine levels were considerably higher in rats who received gentamicin injections alone (group B) (Table2). Light microscopic analysis of renal cortex slices from control rats stained with haematoxylin and eosin revealed the cortex's normal histological structure. The inner medulla demonstrated the renal papilla forming the apex of the medullary pyramid where the renal papilla was surrounded by Cup-shaped minor calyx. (Figure 1) Rats in the gentamicin group's renal cortex showed obvious changes to the glomeruli, tubules, and interstitium. The majority of glomeruli showed mesangial hypercellularity as an alteration. A mixture of active endothelial and mesangial cells obscured and partially blocked the capillary loops. The proximal and distal convoluted tubules were affected by tubular changes brought on by gentamicin therapy. Clearly dilated tubular lumina were present. Additionally, it was seen that certain tubules' lining epithelium had desquamated and lost their brush border. Rats given gentamicin demonstrated cortical interstitial edema in the kidneys, along with dilated and congested peritubular capillaries. The buildup of edematous fluid caused the intertubular gaps to widely split from one another. (Figure 2) Ginseng and gentamicin-treated rats' renal cortex showed less glomerular, tubular, and interstitial changes. The vast majority of glomeruli were mildly hypercellular. Compared to group B, this group's kidneys displayed fewer tubular abnormalities. Compared to group B, the peritubular capillaries were less crowded and less dilated. Compared to group B, the kidneys from group C displayed reduced nephrotoxicity. (Figure 3) Comparing the effects of group C with those of group B revealed a statistically significant difference in tubular necrosis and inflammatory cellular infiltration. Percentages of tubular necrosis were shown to be significantly correlated with various groups . Proximal

tubular necrosis in group B was mild (++) in two animals and severe (+++) in the remaining animals, with respective percentages of 15.43 and 79.99%. Proximal tubular necrosis was mild (+) in two animals in group C, moderate (+++) in three, and severe (+++) in the other two animals, with percentages of 17.55 and 15.44%, respectively, indicating a considerable improvement in kidney parenchyma condition.

Table 1: The Recorded Body Weight Averages for Each Group.

Days (d)	**Averages of body weight (g)**		
	Group A	Group B	Group C
Day 1	244	243.6	228.2
Day 4	251.4	239.5	231.4
Day 7	256.4	227	235.2
Day 11	261.8	221.2	238.8

Table 2: Shows the Estimated Average Serum Urea and Creatinine Values for Each Group at the Conclusion of the Experiment.

Groups	**Serological Parameters**	
	Serum urea (mg/dl)	Serum creatinine (mg/dl)
Group A	22.6	0.60
Group B	66.7	2.23
Group C	46.4	1.26

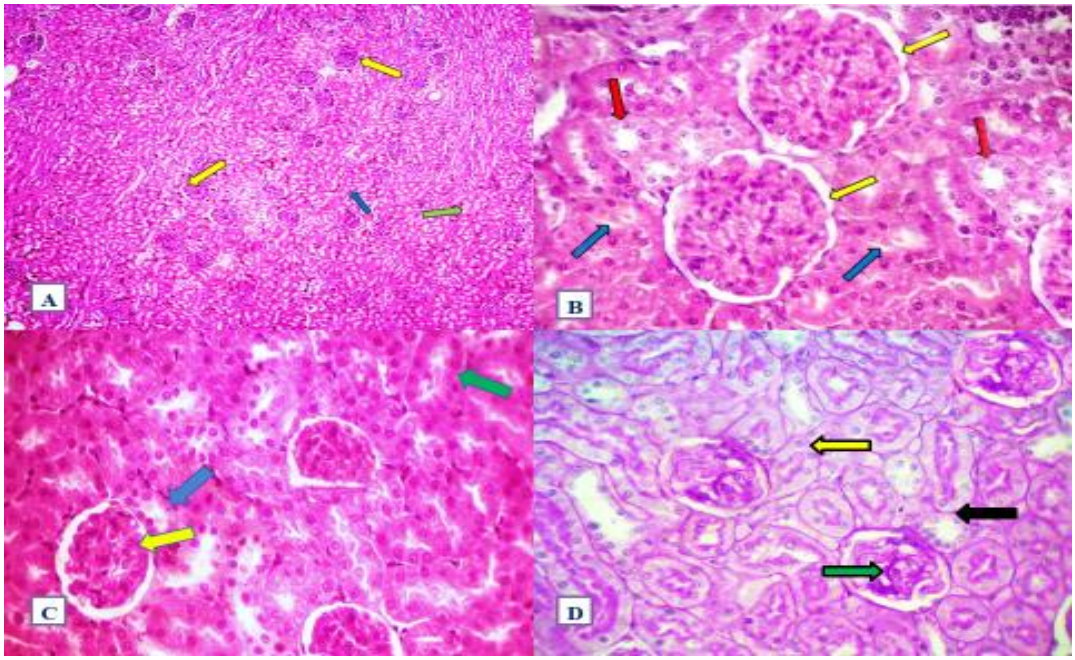

Figure 1: Different Sections in Kidney from Control Group. A) Renal Corpuscles Made of Glomeruli Are Visible in the H&e Stain and Are Encased in Bowman's Capsule (Yellow Arrow). The Proximal (Green Arrow) and Distal (Blue Arrow) Renal Tubules Are Shown. (X100). B) the Pct Has a Narrow Lumen and is Lined by Cuboidal Epithelium and Vesicular Central Rounded Nuclei (Red Arrow), Whereas the Dct Has a Wider Lumen and is Lined by Cubical Cells (Blue Arrow). These Findings Are Shown in H&e Staining. (×400) C) the Pct has a Narrow Lumen and is Lined by Cuboidal Epithelium and Vesicular Central Rounded Nuclei (Green Arrow), While the Dct Has a Wider Lumen and is Lined by Cubical Cells (Blue Arrow). (×200) D) Pas-positive Components Were Found in the

Renal Tissue, the Bowman's Membrane, the Brush Boundary, the Renal Tubules, and the Glomeruli (Black Arrow, Yellow Arrow, and Green Arrow). (Pas Stain 400x).

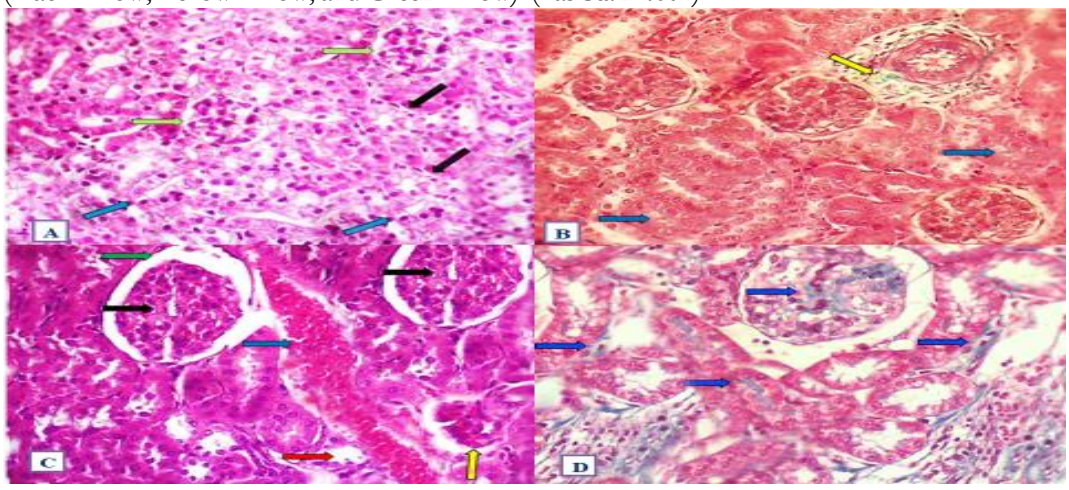

Figure 2: Different Sections in Kidney From Gentamicin Group. A) Tubular Vaculation may be Seen in the H&e Image (Blue and Black Arrows). The Bowman's Space is Getting Wider (Yellow Arrow). (× 200). B) the Afferent Arteriole is Surrounded by a Little Quantity of Collagen, as Indicated by the Blue and Yellow Arrows in the Masson T. Stain, Respectively. (X400). C) H&e Stain Demonstrating Hemorrhagic Vacuolated Glomerulus (Black Arrow), Interstitial Hemorrhage (Blue Arrows), Enlargement of the Bowman's Space in the Glomeruli (Green Arrow), and Additional Atrophied and Vacuolated Glomeruli (Yellow Arrow) (×400). D) Increased Collagen Fibers Are Visible in the Glomeruli, Interstium, and Surrounding and Within the Renal Tubules (Blue Arrows) After Masson T Staining. (X400).

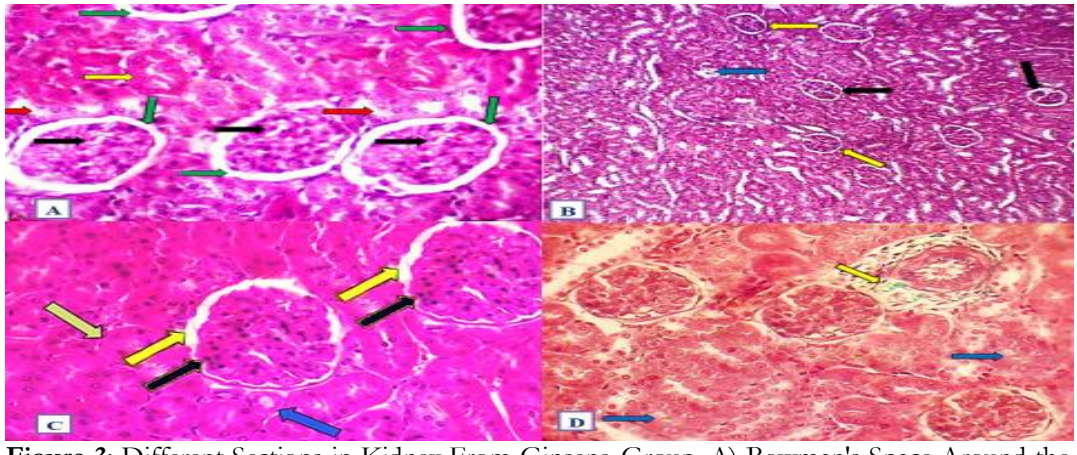

Figure 3: Different Sections in Kidney From Ginseng Group. A) Bowman's Space Around the Marginally Vacuolated Glomerulus (Green Arrows), Restoration of the Brush Border of the Majority of the Proximal Tubules (Yellow Arrow), and Mild Vacuolations in Some Tubules Are All Depicted in the H&e Stain. (X200). B) H&e Stain Demonstrating Minor Tubular Vacuolization at Certain Proximal Cells (Blue Arrow), Slight Lobular Affection of Some Glomeruli with Dilated Urinary Space (Black Arrows), and Other Glomeruli That Are Normal (Yellow Arrows). (× 100). C) Bowman's Space Around the Marginally Vacuolated Glomerulus (Black Arrow), Restoration of the Brush Border Around the Majority of the Proximal Tubules (Yellow Arrow), and Mild Vacuolations in Certain Tubules Are All Depicted in the H&e Stain. (X400). D) Afferent Arteriole

is Surrounded by a Small Quantity of Collagen (Blue Arrow), and the Capillary Tuft of the Glomerulus is Normal (Yellow Arrow) in Masson T Staining. (X400).

Discussion

According to our research, gentamicin alone caused a statistically significant drop in body and kidney weight in-group B. However, the body and kidney weights of the group C animals improved when gentamicin was administered together with the ginseng. According to the findings, when given alone, gentamicin raised the serum levels of urea and creatinine. However, group C animals also demonstrated improvement in these measures, as well as in body and organ weights. Histological tests confirmed that ginseng limited the harmful effects of gentamicin. Our findings support those of Qadir et al. (2011) who discovered that ginseng reduced the harmful effects of gentamicin on renal tissue. [8]. Moreover, our findings support a prior study that revealed ginseng reduced the negative effects of ochratoxin and prophenophos on kidney tissue that had been severely changed following treatment with these pesticides. [10,11]. According to reports, lipid peroxidation and oxidative injury are the most likely mechanisms by which gentamicin damages tubules. [12] As soon as gentamicin enters the proximal tubular cells, it interacts with the anionic phospholipids on the cell membrane to release iron from the renal cortical mitochondria and create an iron drug complex, which is a powerful catalyst for the creation of free radicals. [13] Reactive oxygen species (ROS) assault DNA and harm kidneys by causing contraction of mesenchymal cells and changing the filtration surface area, which lowers glomerular filtration rate. A gentamicin therapy prevented DNA replication and protein synthesis while also causing a significant buildup of oxidants in the kidney. [14] Since nephrotoxicity is gentamicin's most significant adverse effect and it is the therapy of choice for severe infections brought on by Streptococcus pyogenes, an inexpensive and efficient antidote should allow for its usage in situations when it seems necessary. Ginseng's antioxidant, anti-inflammatory, and anti-proliferative qualities play a significant role in the mechanisms behind its protective effects. [15] Ginseng has beneficial effects because it contains phenolic acids and flavonoids, which improve renal blood flow and eliminate free radicals, preventing oxidative harm brought on by gentamicin. Ginseng shields rat cell organelles against lipid peroxidation brought on by several toxins and increases the number of ribosomes in the rough endoplasmic reticulum, indicating that it can produce protein. These discoveries might result in improvements to renal function. [16] Another study showed that berberine reduces the nephrotoxicity caused by gentamicin. It is possible that berberine's antioxidant, anti-inflammatory, and anti-apoptosis action partially mediates its renoprotective efficacy against gentamicin-induced nephrotoxicity. [17] Additionally, a recent study showed that treatment with C. deserticola could lessen kidney damage and dysfunction in rats brought on by GM by reducing inflammation, oxidative stress, and apoptosis. [18] Our research clearly shows that gentamicin contributed to tubular necrosis and an increase in serum urea and creatinine. However, these effects were largely mitigated in the animals that received ginseng treatment concurrently, indicating that ginseng offers a significant amount of protection. However, further research is required to validate and understand the mechanism of action of ginseng in reducing nephropathy.

Conclusion

By reducing inflammation, oxidative stress, and apoptosis, the study showed that ginseng administration could lessen kidney dysfunction and structural damage in rats caused by gentamicin.

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Authors' Contributions

All authors contributed to the research and/or preparation of the manuscript. Mohammed Saad Alqahtani, Ali Hassan A. Ali, Kamal R. El Baz participated in the study design and wrote the first draft of the manuscript. Kamal R. El Baz, Saad Alqasem and Shaban Ragab Ibrahim collected and processed the samples. Ali Hassan A. Ali and Ali Al-Gonaim participated in the study design and performed the statistical analyses. All of the authors read and approved the final manuscript.

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Conflicts of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Availability of Data and Materials

The data are available upon request from the authors.

Ethics Approval

All series of steps that were implemented in this study that included animal models were in compliance with Ethics Committee of Prince Sattam bin Abdulaziz University Institutional Review Board. (SCBR-083-2023)..

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