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# Protective effect of ethanolic extract of *Elettaria Cardamomum* against gentamicin hepato-renal toxicity in male albino rats

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**Abstract. – OBJECTIVE: Cardamom is one of the spices containing a wide range of antioxidants and is used in medicinal preparations. Thus, in this study, we want to explore the protective effect of ethanolic cardamom extract on the liver-kidney toxicity caused by gentamicin in male albino rats.**

**MATERIALS AND METHODS: The experiment was applied to twenty-eight male albino rats divided randomly into four groups. The control group was given 1 ml/kg of saline orally. The gentamicin (GM) group was given a daily 80 mg/kg i.p of GM for seven days. Another group was given 100 or 200 mg/kg b.wt. p.o. ethanolic extract of *Elettaria Cardamomum* (EC) for seven days. Blood and liver-kidney samples were taken after the end of the study for analyses to test for liver-kidney function and lipid profile (LP).**

**RESULTS: Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin activities were higher in the GM group than in the control group. However, the groups' differences in globulin levels and total protein (TP) were not statistically significant. Compared to the control group, the albumin level in the gentamicin group was considerably lower. On the other hand, creatinine and urea levels, lipid, serum total cholesterol levels, and high-density lipoprotein (HDL) significantly increased in the gentamicin group but decreased in the control group and co-treated groups with gentamicin and ethanolic extract EC. Low-density lipoprotein (LDL) significantly dropped, while the control group showed high levels of lipid and serum total cholesterol.**

**CONCLUSIONS: EC ethanolic extract shields the liver-kidney against GM harmful effects in male rats. Recent research demonstrated that the effects of the plant cardamom were the same at both low-high doses. The phenolic elements in EC may be responsible for this protective effect.**

*Key Words:*
*Elettaria Cardamomum*, GM, Hepatotoxicity, Nephrotoxicity.

## Introduction

The well-known antibiotic gentamicin, created in 1963, has particular advantages for treating bacteria resistant to other antimicrobials[1]. It is also frequently used as an antibiotic against infections brought on by Gram-negative bacteria[2]. Aminoglycoside antibiotics used to treat tuberculosis, a persistent gram-negative infection, carry a risk of hearing loss and severe renal impairment[3]. Even though gentamicin has functional characteristics, its renal toxicity is a negative consequence. Numerous studies[2] have found that gentamicin medication administered for over seven days can affect the kidney's proximal tubular cell, resulting in renal damage. Moreover, according to research[4], nephrotoxicity may occur in about 25% of people taking aminoglycosides for their condition. Numerous studies[4] have also shown that acute kidney injury (AKI) can impair other organs, including the liver; this explains the phenomenon known as harm to distant organs.

Because gentamicin is used more frequently, it is to blame for 10-20% of all occurrences of acute kidney injury[5]. Approximately 90% of the gentamicin drug secretion remains intact near the renal tubules, which, at higher dosages, could result in severe renal necrosis tubular[6]. Regardless of cell injury, gentamicin inhibits many cell membrane transporters on the brush border and the basolateral membranes, leading to electrolyte imbalances. Transport blockage affects tubular reabsorption and jeopardizes cell life, resulting in necrosis or death[7]. In addition, proximal tubular cell death is the primary cause of gentamicin-induced AKI[8]. This rat study examined the effectiveness of date extract supplementation in preventing renal and liver damage brought on by gentamicin. This study discovered that GM significantly altered the indicators of liver and kidney function (transaminases, albumin, creatinine, and blood urea). Besides, it was found[9] that inflammation and free



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radical overproduction are linked to liver and kidney damage caused by gentamicin.

The kidney toxicity of aminoglycosides and how they cause acute renal injury were studied[10] in male Wistar rats. Eight male Wistar rats were divided into three groups for the study: Control, Genta, and Deh+Genta. The results showed that 100 mg/kg of gentamicin caused acute renal injury. Still, it did not affect the liver when administered to the gentamicin group in two daily doses for eight days[10]. Additional adverse effects of GM medicines were discovered in a different investigation[11]. For instance, it was found a connection between hearing loss and gentamicin medication.

*Elettaria Cardamom* plant is the dried fruit of the perennial herbaceous Zingiberaceae plant[12]. After saffron and vanilla, cardamom is the most expensive spice. It has a distinctively rich flavor and aroma[13]. Other names for it include "real cardamom" and "green cardamom[14]". Little green and huge black cardamom are the two available cardamom types. The most prevalent species of cardamom, *Elettaria Cardamomum*, is the biological source of small green cardamom. At the same time, black cardamom is primarily grown in India, the world's top cardamom producer[15]. Worldwide, *E. Cardamomum* plants are grown in high latitudes with humid weather. However, the origins of several types of this plant can also be found in the evergreen rainforests of southern India (Kerala, Karnataka, and Tamil Nadu) and Sri Lanka. With 70% of the country's total production, Kerala is India's most significant producer of cardamom. It is followed by Karnataka (20%) and Tamil Nadu (5%)[16].

One of nature's great gifts is plants, which contain a variety of biological effects, phytochemicals, or chemicals as part of their normal metabolic processes[17]. Recently, it has been determined[18] that plant extracts and parts are essential sources for treating many disorders. Moreover, this affluent exporter offers many advantages, including few adverse effects, widespread availability, and inexpensive cost. Many diseases can be treated or prevented with the complex that comes from plants[19]. The antiviral, antibacterial, and antifungal activities of phytochemicals are due to their antioxidant characteristics[17].

Another study[20] treated animals with alcohol-based *Elettaria Cardamomum* extract in two doses of 100 and 200 mg/kg once daily for twenty-eight days. This treatment began twenty-one days after administering paracetamol at 400 mg/kg orally for one week to induce hepatotoxicity. Rat livers were examined for histopathology as a consequence. The findings showed that, in comparison to groups receiving positive controls, cardamom alcoholic extract improved biological assessment, liver functions, and antioxidant enzymes. Cardamom consumption thus protects the liver against paracetamol's negative effects. After being administered for a week, studies[21] have shown that the hydro-alcoholic cardamom extract contains antioxidant and flavonoid components that shield the liver from the damaging effects of lead acetate poisoning on its liver enzymes.

This study demonstrates the anti-hypercholesterolemic benefits of cardamom[22] (*Elettaria Cardamomum*). Cardamom's antioxidant, anti-inflammatory, antibacterial, and immune-stimulating properties have been shown to offer anti-cancer advantages in various cancer types, including breast cancer. Cardamom spice has demonstrated potential in this investigation as a breast cancer treatment[23]. Cardamom oil was utilized in a different investigation[24] to treat aluminum-induced neurotoxicity by preventing acetylcholinesterase enzyme activity and reducing oxidative stress. In addition, it has been proven to have neuroprotective effects. Cardamom oil might be an excellent alternative as there are not many options for treating Alzheimer's. This research examines the protective impact of alcoholic cardamom extract on hepatotoxicity and nephrotoxicity induced by gentamicin in Wistar male albino rats.

## Materials and Methods

### Plant Materials

Dried cardamom (*Elettaria Cardamomum*) was purchased from an organic grocery (Buraydah, Al-Qassim, Saudi Arabia).

### Preparation of Alcohol Extract of Cardamom

To conduct this study, 800 ml of 70% ethanol provided by (the pharmaceutical solutions industry® Ltd (PSI), Jeedah, Saudi Arabia) and 200 g of ground herbs were steeped for three days at ambient temperature (23-25°C) with occasional shaking. After passing through a muslin cloth, it was first filtered using a Whatman qualitative grade 1 filter paper. The combined filtrates were evaporated in a rotary evaporator (Heidolph Instruments, Schwabach, Germany) is a manufacturer of laboratory equipment) under low pressure after this procedure was repeated twice (760 mmHg)[25].

### Gentamicin

Gentamicin 80 mg/2 ml ampoules were purchased from SPIMACO (Al- Qassim pharmaceutical plant in Saudi Arabia).

### Experimental Animals

In this investigation, 28 healthy male albino rats weighing 160 and 190 g were employed. They were obtained from King Saud University's College of Pharmacy, Riyadh, Saudi Arabia.

Rats were kept in clear plastic cages on a sawdust bed. They were used in the current investigation. The animals were maintained in the lab for two weeks before and during the experimental work under stable temperature conditions of 22-24°C.

The lab environment also featured a 12-hour light and dark cycle and a 40-60% humidity percentage. Water and well-balanced commercial food were freely available (General Organization for Grain Silos & Flour Mills, Riyadh, Saudi Arabia)[26].

### Experimental Design

After two weeks of acclimation, the animals were randomly separated into four groups of seven in each group.

- Control group was given saline 1 ml/kg orally as a control.
- The group receiving gentamicin obtained daily intraperitoneal injections at a dose level of 80 mg/kg for seven days.
- The group receiving gentamicin plus alcohol extract of cardamom (100 mg/kg) received an intraperitoneal injection of gentamicin at a dose level of 80 mg/kg for seven days. Besides, it received an alcohol extract of cardamom (100 mg/ kg) for seven days by oral gastric tube administration.
- The group receiving gentamicin plus alcohol extract of cardamom (200 mg/kg) received an intraperitoneal injection of gentamicin at a dose level of 80 mg/kg for seven days. Besides, it received an alcohol extract of cardamom (200 mg/ kg) daily for seven days *via* a gastric tube.

### Hematological Study

After the study, rats were administered 24 hours of light ether anesthesia using diethyl ether. Blood was then collected from their optic veins using a capillary tube (Figure 1). Following that, the rats were taken to the lab for further analysis. There, they underwent centrifugation (Thermo Science, Waltham, MA, USA) at 3,000 g for 10 minutes, using a serum to measure alanine aminotransferase (ANAT) and aspartate aminotransferase (AST) activities, alanine aminotransferase (ALT), albumin, bilirubin, cholesterol, triglycerides, high-density lipoprotein-cholesterol (HDL-Chol), and low-density lipoprotein cholesterol (LDL-Chol).

### Histological Examination

Liver and kidney samples were quickly obtained from all animal groups after being dissected

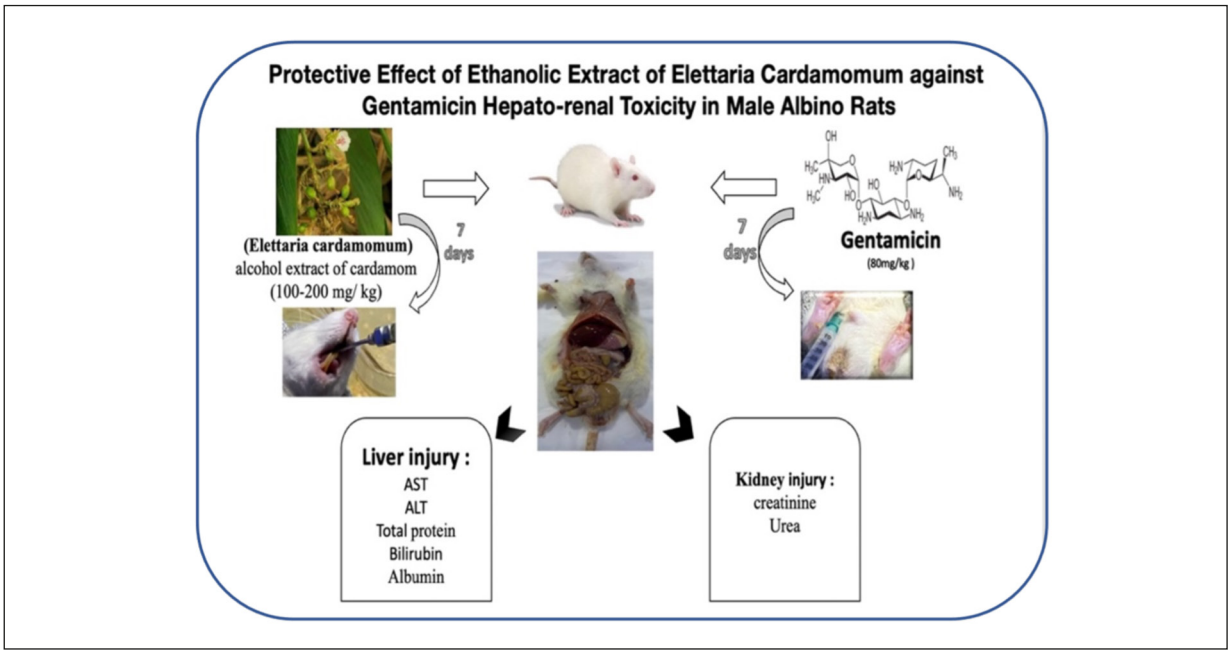


**Figure 1.** Flowchart illustrating the study.

for blood collection. Liver and kidney tissues were steeped in 10% natural buffered formalin for 24 hours to repair them. Later, they were washed with tap water. Tissues were dehydrated before being embedded in paraffin using a range of ethanol concentrations (70-100%) and xylene series. The tissue was sliced into sections that were five micrometers thick using a microtome (SLEE medical GmbH, Nieder-Olm, Germany). Slices were afterward deparaffinized, rehydrated, and stained with the hematoxylin-eosin solution to detect the presence of tissue damage[27].

### Statistical Analysis

Statistical Packages for Social Sciences (SPSS) data analysis was done using computer software (version 26, IBM Corp., Armonk, NY, USA). Following the LSD post-hoc test, means were compared using the (ANOVA) test at $p$=0.05. The results were deemed statistically significant.

## Results

### Physiological Results

#### One Glucose

Data in Figure 2 displays the effect of gentamicin on blood glucose levels. The impact of the gentamicin combination with ethanolic cardamom extract in two doses (100-200 mg/kg) is also shown after seven days of treatment. This study revealed insignificant differences in blood glucose levels across the various study groups.

### Kidney Function Result

This study revealed kidney functions in different studied groups, displayed in Figure 3. Serum creatinine and urea levels were significantly increased in the gentamicin group *vs.* the Control group.

In contrast, creatinine and urea levels decreased slightly in two groups of gentamicin combination with ethanolic cardamom extract of dose (100-200 mg/kg) compared to the gentamicin group ($p$<0.050). For this reason, the present results revealed that low and high doses of plant extract improved kidney function significantly compared with Group II (positive control).

### Lipid Profile Result

The lipid profile in different studied groups is shown in Figure 4. Serum total cholesterol levels were significantly increased in the gentamicin group compared to the control group ($p$<0.050). On the other hand, these levels decreased in the gentamicin combination with the ethanolic cardamom extract group at a dose of 100 mg/kg.

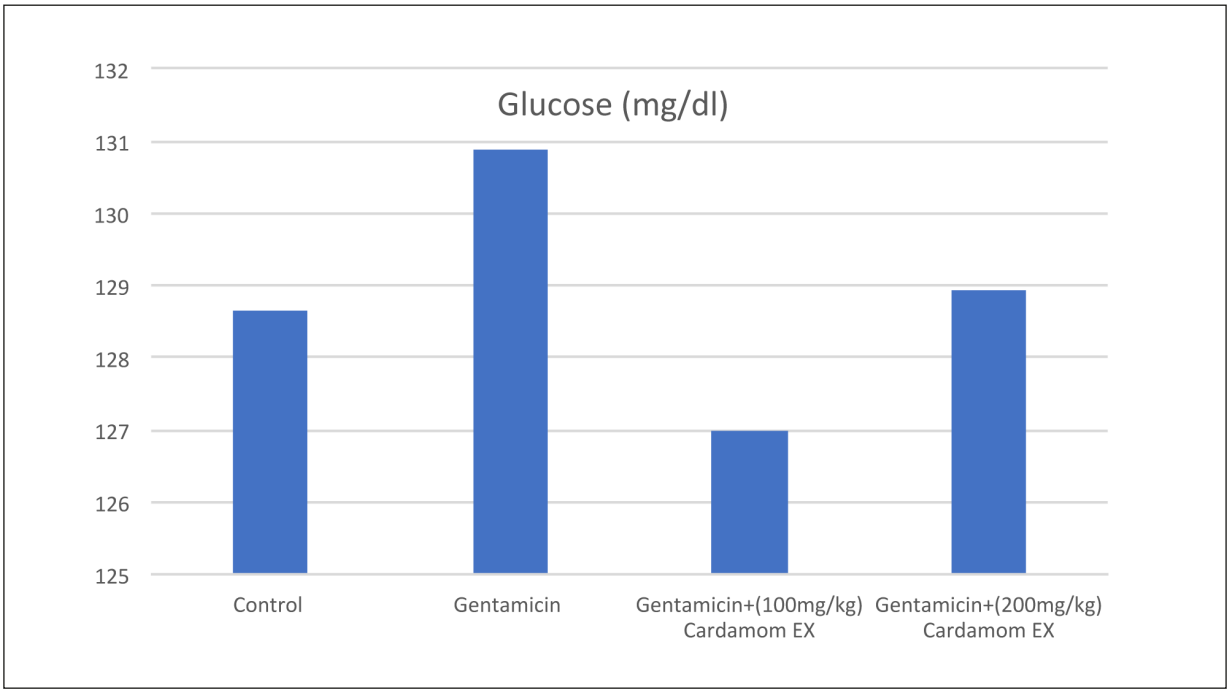


**Figure 2.** Effect of gentamicin and gentamicin combination with ethanolic cardamom extract group of doses 100 mg /kg and 200 mg/kg on glucose levels.

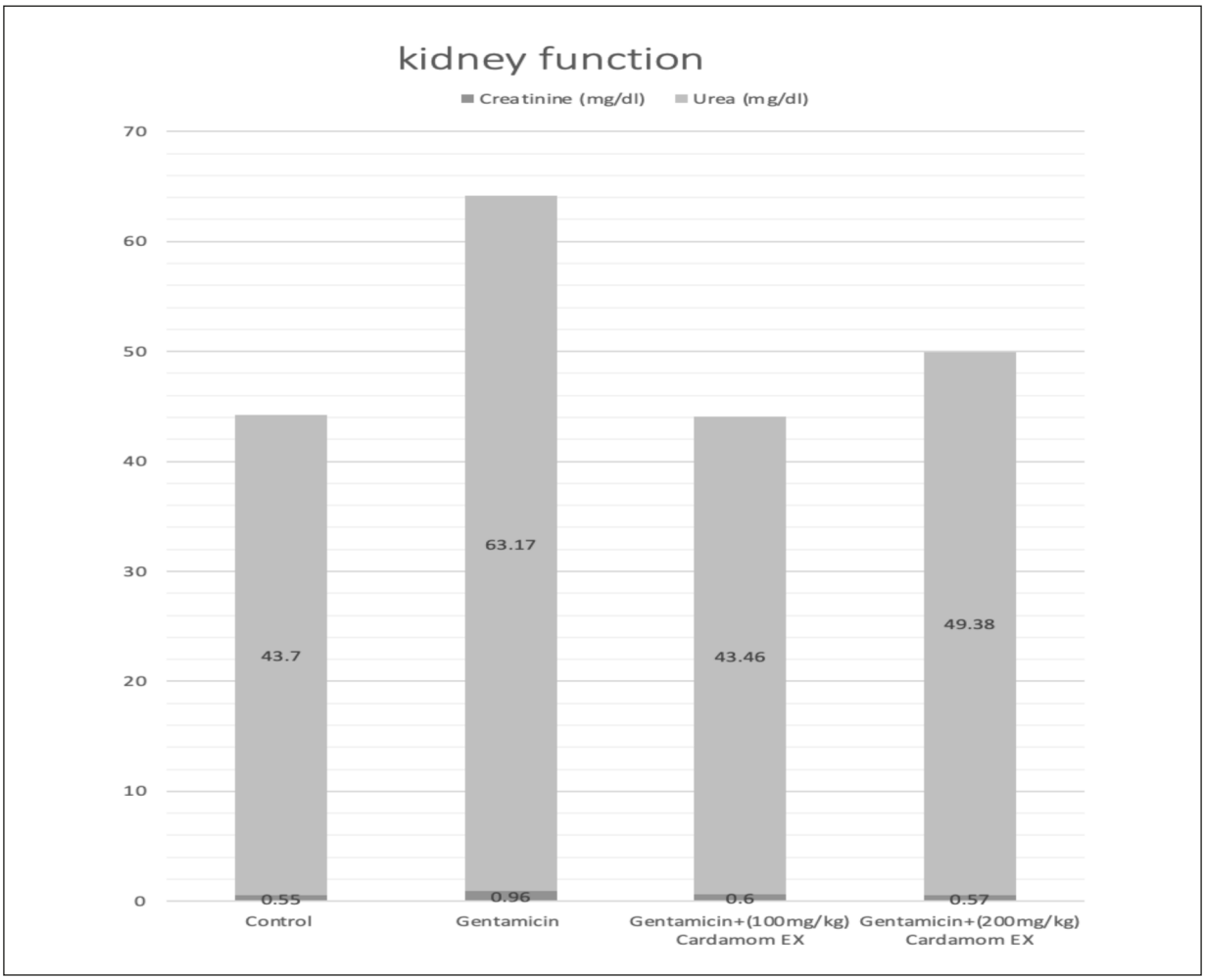


**Figure 3.** Effect of gentamicin and gentamicin combination with ethanolic cardamom extract group of doses 100 mg/kg and 200 mg/kg on kidney function.

Besides, the lipid profile in different studied groups is shown. High-density cholesterol levels were significantly higher in the gentamicin group than in the control group. In contrast, these levels were lower in the gentamicin combination with ethanolic cardamom extract group at 100 mg/kg and 200 mg/kg ($p<0.050$).

Low-density cholesterol levels were significantly decreased in the gentamicin group *vs.* the other three groups. In addition, oral administration of low and high doses of plant extract improved serum lipid profile with different degrees and serum triglycerides.

### Changes in Liver Activity

As displayed in Table I the liver functions are presented for the various groups studied. The results revealed that the activities of AST, ALT, and total bilirubin levels in serum were significantly increased in the group of gentamicin *vs.* the control group. On the other hand, the gentamicin combination with ethanolic cardamom extract group of doses (100 mg/kg and 200 mg/kg) showed decreased levels of AST, ALT, and total bilirubin. This decrease was significant, with a *p*-value lower than 0.050.

Meanwhile, the present results revealed that low and high doses of *Elettaria Cardamomum* ethanolic extract significantly reduced the elevation of transaminase enzymes (AST and ALT) and total bilirubin levels compared with the gentamicin group. This effect was also observed when compared with normal rats in the control group.

The serum albumin level was significantly decreased in the gentamicin group compared to the control group ($p<0.050$). In contrast, the albumin levels returned to normal in the groups where gentamicin was combined with ethanolic cardamom extract at doses of 100 mg/kg and

**Table I.** Changes in liver activity in experimental groups.

| Group | AST (IU/L) | ALT (IU/L) | Bilirubin (mg/dl) | Total protein (g/dl) | Albumin (g/dl) | Globulin (g/dl) | A/G ratio |
|---|---|---|---|---|---|---|---|
| **Control** | $37.43^{b}\pm3.34$ | $22.57^{b}\pm1.63$ | $0.60^{b}\pm0.05$ | $6.23^{a}\pm0.08$ | $3.40^{ab}\pm0.04$ | $2.91^{a}\pm0.06$ | $1.13^{a}\pm0.03$ |
| **Gentamicin** | $71.71^{a}\pm5.55$ | $30.71^{a}\pm2.70$ | $1.34^{a}\pm0.21$ | $6.12^{a}\pm0.13$ | $3.32^{b}\pm0.05$ | $2.59^{a}\pm0.17$ | $1.32^{a}\pm0.11$ |
| **Gentamicin + (100 mg/kg) cardamom EX** | $38.71^{b}\pm2.19$ | $22.14^{b}\pm1.14$ | $0.52^{b}\pm0.04$ | $6.25^{a}\pm0.21$ | $3.42^{ab}\pm0.07$ | $2.83^{a}\pm0.22$ | $1.27^{a}\pm0.13$ |
| **Gentamicin + (200 mg/kg) cardamom EX** | $40^{b}\pm3.22$ | $24.43^{b}\pm1.62$ | $0.51^{b}\pm0.05$ | $5.99^{a}\pm0.014$ | $3.40^{ab}\pm1.03$ | $2.59^{a}\pm0.12$ | $1.33^{a}\pm0.06$ |

All data are expressed as mean ± S.E. Means with different superscripted letters[a,b] are significantly different. Data were analyzed using SPSS software (version 26). Means were compared using the ANOVA test followed by the LSD post-hoc test.

200 mg/kg. It demonstrated liver function in various study groups.

Furthermore, the gentamicin group's serum albumin level was considerably lower than the control group. Still, in the gentamicin combination with ethanolic cardamom extract groups at doses of 100 mg/kg and 200 mg/kg, the levels approached those of the control group.

Additionally, there were no significant differences in total serum proteins, globulin, and A/G ratio levels between the different studied groups ($p>0.050$).

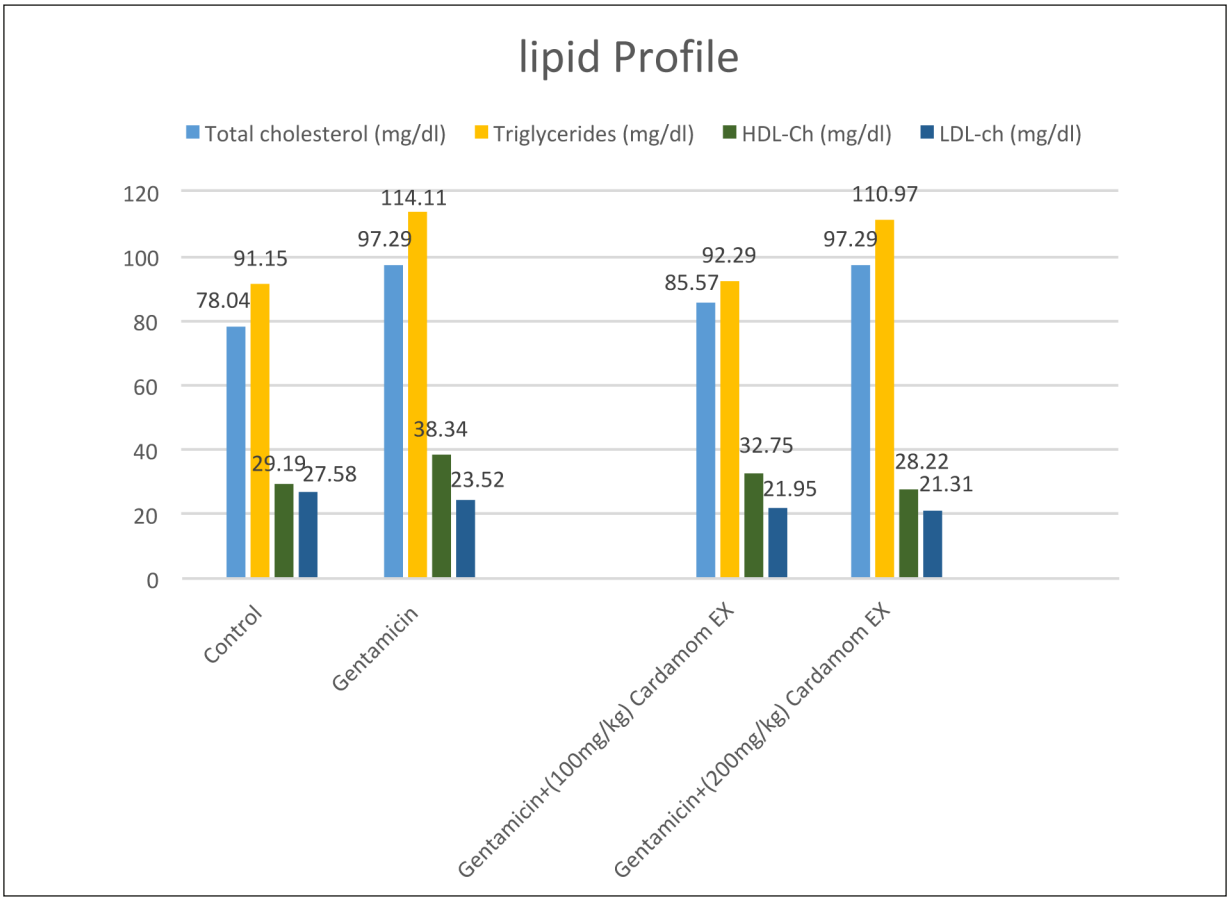


**Figure 4.** Effect of gentamicin and gentamicin combination with ethanolic cardamom extract group of doses 100 mg/kg and 200 mg/kg on lipid profile.

### *Histological Results*

The renal cortex of the control group was examined in hematoxylin and eosin-stained sections. It was discovered that the renal cortex was made up of renal corpuscles and renal tubules. The Bowman's capsule, which encircled the glomerular tuft of capillaries and had a parietal layer of simple squamous epithelial lines, comprised the renal corpuscles. The Bowman's gap separated the glomerulus and the parietal layer of the Bowman's capsule. Proximal-convoluted tubules had brush-bordered cuboidal cells with granular acidophilic cytoplasm. They rounded basal nuclei that seemed to have small lumens. Distal convoluted tubules had a larger lumen, no brush border, and were lined with light cuboidal cells with rounded nuclei in the center, as depicted in Figure 5.

In the gentamicin treated group, the distorted histological architecture of the renal cortex was observed. As shown in Figure 6, many renal corpuscles showed shrinkage with dilated renal spaces. The proximal and distal convoluted tubule lining cells displayed marked vacuolated cytoplasm and pyknotic nuclei. In Figure 7, some areas showed mononuclear cellular infiltration and hemorrhage between the renal tubules.

Figure 8 shows a slight improvement in kidney cortex histology in the rats co-treated with gentamicin and 100 mg/kg body weight of cardamom (Group III) compared to other groups. Still, some renal corpuscles and renal tubules showed mild degeneration.

The histopathological examination shown in Figure 9 reveals that the kidney structure in rats co-treated with gentamicin and 200 mg/kg of cardamom (Group IV) showed a notable improvement compared to Group III. The structure of most of the renal corpuscles and kidney tubules appeared more or less similar to normal.

In relation to the liver, an examination of the HX&E-stained sections from healthy control rats, as shown in Figure 10, revealed a normal hepatic structure. The rat's liver was divided into ill-defined classic hepatic lobules.

As depicted in Figure 11, treatment with gentamicin resulted in the loss of the liver's histological structure, as evidenced by degenerative changes in the liver hepatocytes. In addition, these hepatocytes appeared highly vacuolated with deeply stained pyknotic nuclei, indicative of fatty degeneration.

The histopathological analysis in Figure 12, which examines the liver of rats co-treated with gentamicin and cardamom (100 mg/kg B.W) in Group III, revealed a slight reduction in tissue damage caused by gentamicin. Some of the hepatocytes restore their normal structure with a normal appearance of the central vein. Still, others appeared with vacuolated cytoplasm (fatty degeneration) and deeply stained pyknotic nuclei.

In contrast, Figure 13 histopathological analysis of the liver in rats co-treated with gentamicin and cardamom (200 mg/kg B.W) in Group IV revealed a significant improvement in all previously mentioned

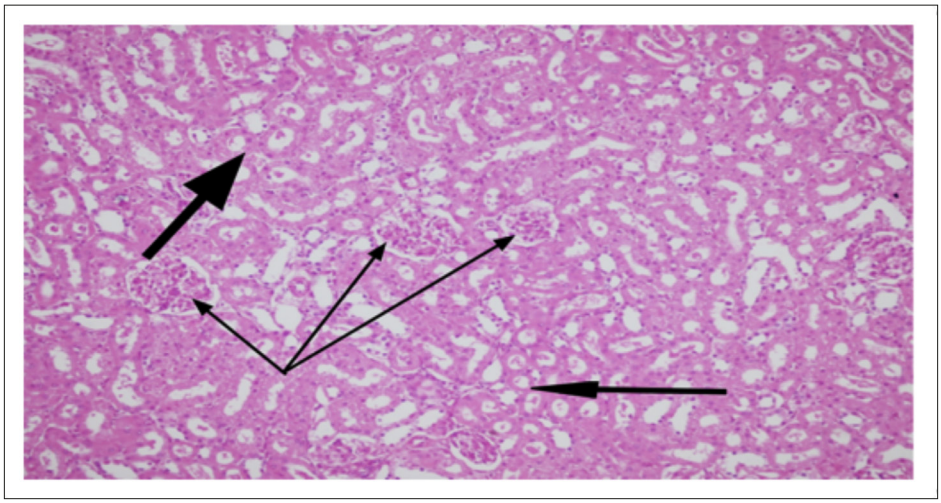

**Figure 5.** An image of a control rat kidney under a microscope stained with HX&E reveals that the renal cortex contains healthy renal corpuscles (thin arrow) and renal tubules (thick arrow) (HX&E X200).

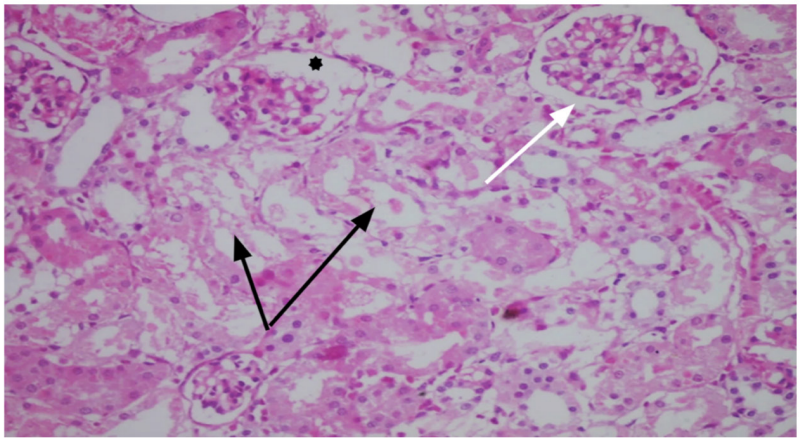

**Figure 6.** A photomicrograph of the gentamicin-treated rat kidney demonstrates the Bowman's space (*) being enlarged and the epithelial lining of the kidney tubules exhibiting noticeable degradation (black arrows) (HX&E X200).

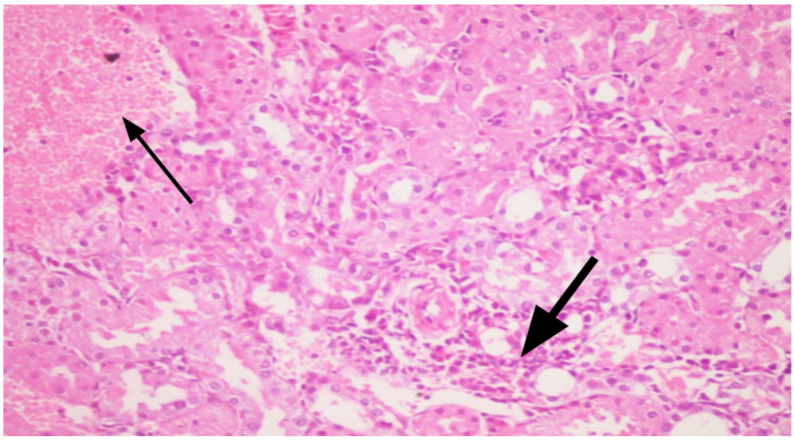

**Figure 7.** A photomicrograph of the gentamicin-treated kidney of the rat (HX&E X200).

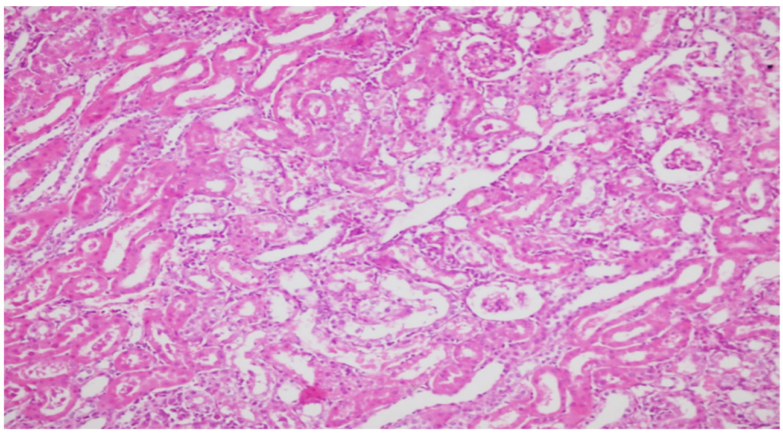

**Figure 8.** A photomicrograph in the rat kidney treated with gentamicin and cardamom (100 mg/kg BW) (HX&E X100).

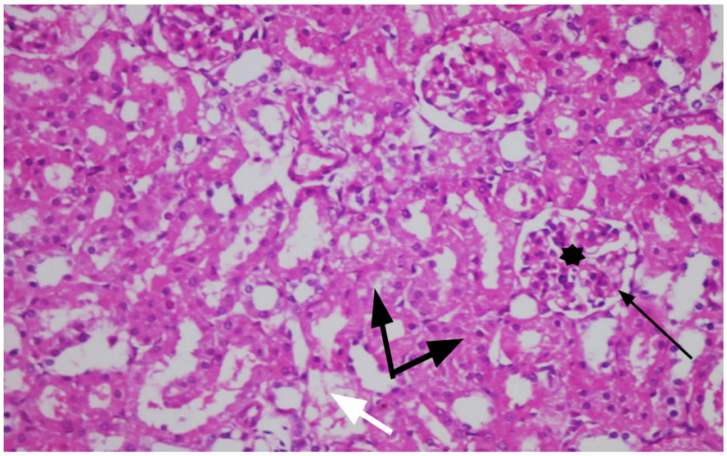

**Figure 9.** A photomicrograph in the rat kidney treated with gentamicin and cardamom (200 mg/kg BW) (HX&E X200).

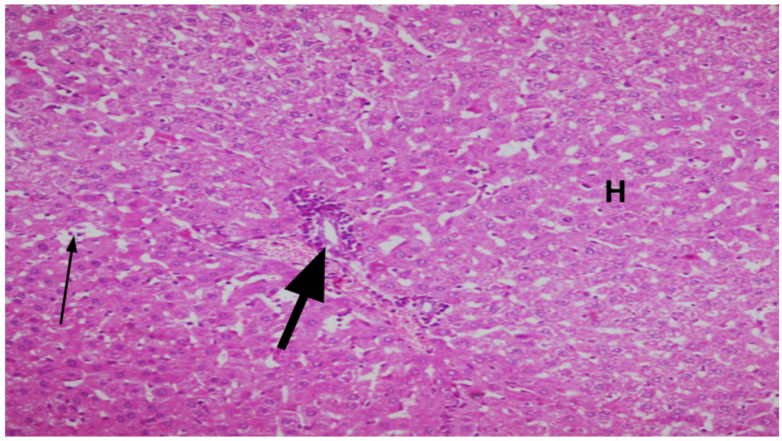


**Figure 10.** Photomicrograph from control rat liver showing the normal architecture of hepatic parenchyma (HX&E X200).

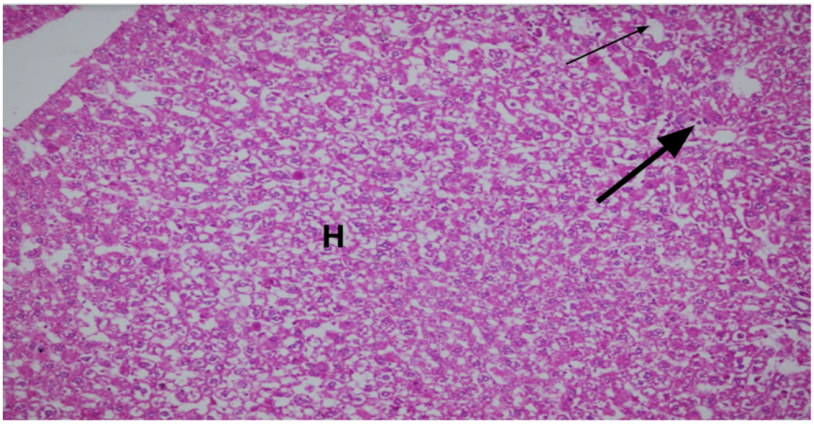


**Figure 11.** A photomicrograph of rat liver treated with gentamicin showing the degenerative changes in the liver hepatocytes (H), which appeared vacuolated with pyknotic nuclei. The central vein is a thin arrow, and the portal area is a thick arrow (HX&E X100).

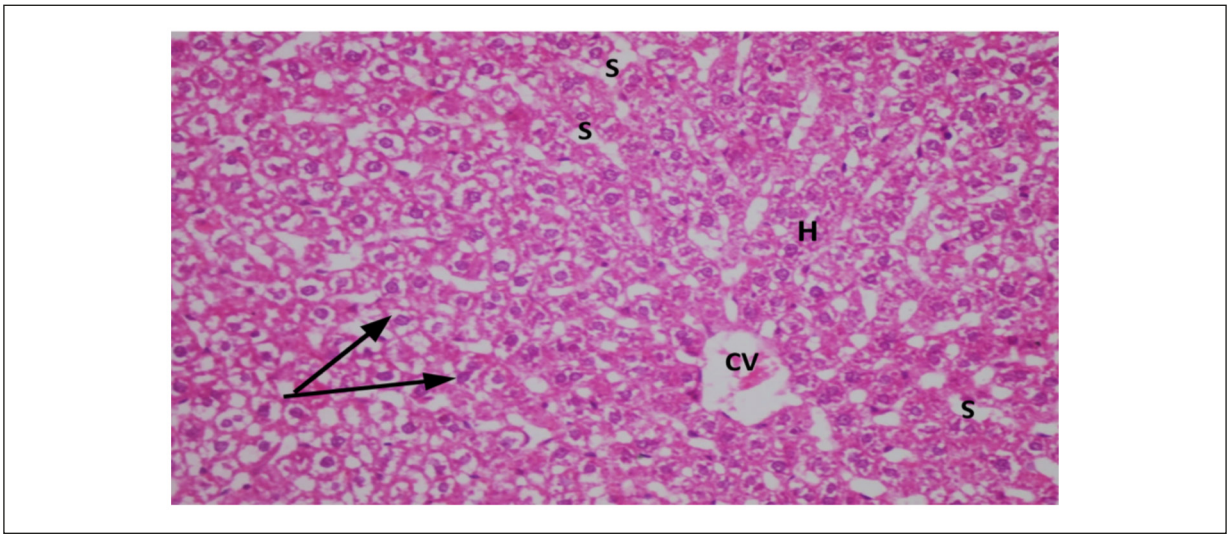


**Figure 12.** A photomicrograph of rat liver treated with gentamicin and cardamom (100 mg). Reduced tissue damage caused by gentamicin, and some of the hepatocytes restore their normal structure (H). Still, others appeared vacuolated with deeply stained pyknotic nuclei. Arrow: swelling of the blood (HX&E X100).

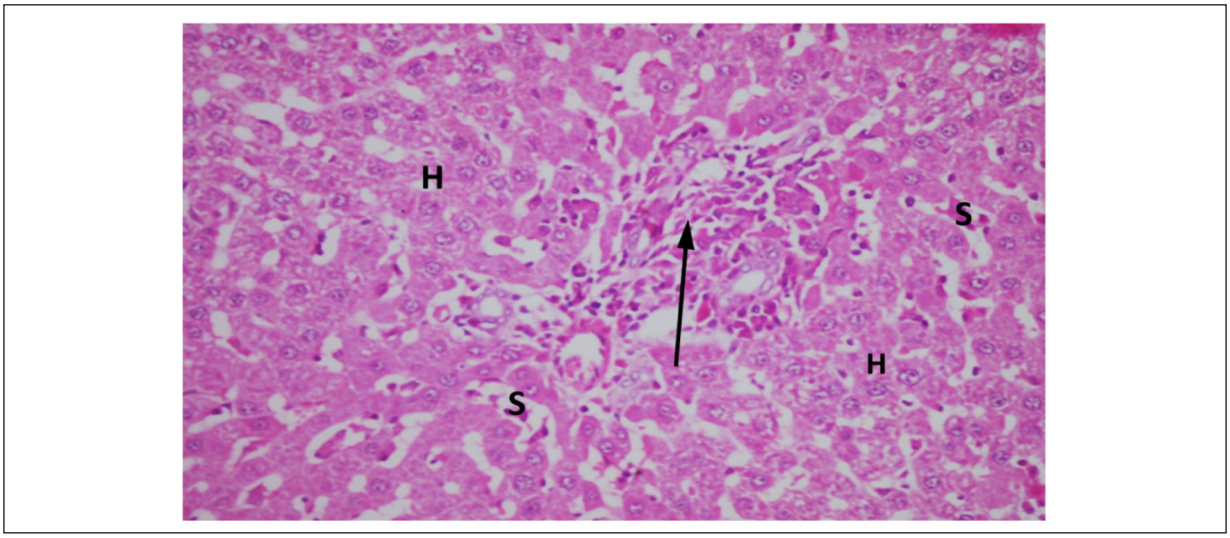


**Figure 13.** A photomicrograph of rat liver treated with gentamicin and cardamom (200 mg). It shows improvement in the histological structure and architecture of the hepatocytes. The hepatocytes have acidophilic cytoplasm with basophilic regions and rounded vesicular nuclei (H). (arrow) Still visible is the inflammatory cell infiltration in the portal region. (HX&E X200).

histopathological findings compared to the gentamicin-treated group.

## Discussion

The famous flavoring agent cardamom is widely utilized in both allopathic and ayurvedic medicine[28]. *Elettaria Cardamomum* Matan, a perennial herb native to India, Pakistan, Myanmar, and Sri Lanka, is frequently called "cardamom" and "elaichi" in different parts of the world. Cardamom is often used in cooking. Still, it is also prescribed by doctors to cure a number of ailments, such as asthma, constipation, colic, diarrhea, dyspepsia, hypertension, and epilepsy. It also functions well as a carminative, diuretic, antiviral, antifungal, antibacterial, and stoma-friendly remedy[29].

The ethanolic extract of *Elettaria Cardamomum* was analyzed using gas chromatography-mass spectrometry in this investigation[25]. The study found components of phytochemically active n-Hexadecanoic acid (1.87%), α-Farnesene

(1.46%), β-pinene (5.98%), p-Linalool (4.52%), Nerol (0.89%), α-Terpinyl acetate (41.24%), 1,8-Cineole (28.14%), Sabinene (4.24%), p-Cresol (1.12%), α-Terpineol (3.24%), Linalyl acetate (2.87%), p-Cymene (1.21%), Geranyl acetate (0.65%), Myrcene (2.57%)[25].

According to numerous studies, acute kidney injury (AKI) can affect the liver. Because of this, renal ischemia-reperfusion may increase hepatic enzymes, leukocyte infiltration, congestion, and cellular necrosis in the liver[4]. Harmful metabolites and some drugs are excreted as part of detoxification and equilibrium. Because of this, they are crucial in the processing of toxic medications. They are hence more vulnerable to dangerous compounds due to high renal blood flow. It transfers metabolites and absorbs toxic chemicals from the fluid around them[30].

Numerous studies[4] have shown that acute kidney damage (AKI) may impact the liver. As a result, renal ischemia-reperfusion may worsen liver congestion, cellular necrosis, leukocyte infiltration, and hepatic enzymes. Harmful metabolites and some medications are expelled as part of the detoxification and balance processes. They are, therefore, essential in the processing of dangerous drugs. Owing to their high renal blood flow, which transports metabolites and absorbs harmful substances from the surrounding fluid, kidneys are more susceptible to the effects of hazardous compounds[30]. gentamicin group in the current study showed significantly higher urea and creatinine serum values than the other groups.

Since kidney injury is the only significant factor that increases the blood creatinine level, creatinine and urea, which the kidney must excrete, have increased significantly in this study. It supports the idea that functional kidney damage has occurred[31]. Similar studies[32-34] showed that the group receiving gentamicin treatment had significantly greater urea and creatinine serum levels.

According to the study, taking cardamom ethanolic extract reduced the renal function changes caused by gentamicin treatment to levels that were close to average. Additionally, serum urea and creatinine levels were significantly lower in rats that received a combination treatment (gentamicin plus ethanolic cardamom extract at 100 mg/kg and gentamicin plus ethanolic cardamom extract at 200 mg/kg) for seven days compared to the rats that were only given the gentamicin group. These results indicate a significant reduction in the kidney's susceptibility to gentamicin-induced structural and functional changes in rats. Also, our findings showed that both low and high doses of plant extract enhanced kidney function.

According to past studies[31], taking a watery cardamom extract orally has a significant kidney-protective effect. Additionally, the antioxidant properties of gentamicin decrease kidney damage. The majority of the antioxidant capabilities of *Elettaria cardamom*, primarily attributed to its phenolic composition, which comprises polyphenols and flavonoids, are supported by these findings[35].

The histopathology of the tissue in the gentamicin-treated group revealed that the renal cortex's histological architecture had changed. This study backs up the conclusions we came to. It has been established[36] that the drug gentamicin decreased glomerular filtration rate (GFR), as shown by a steady decline in creatinine clearance.

Other tissues, however, showed partially desquamated or necrotic lining cells. In addition, the nuclei of these necrotic cells displayed apoptotic signals.

Significant increases in serum urea and creatinine suggest a decrease in glomerular filtration rate, and this investigation[33] demonstrated gentamicin-intoxicated mice. A high protein excretion rate may also be caused by GM-induced breakdown of the renal blood filtration barrier and impairment of proximal tubule protein absorption.

Rats treated with both gentamicin and cardamom concurrently showed a slight improvement in the histology of the renal cortex (Group III). Most of the renal corpuscle appeared practically normal, with some isolated injury to the proximal and distal convoluted tubules.

Rats in Group IV that received gentamicin and cardamom in combination had their kidneys histopathologically examined. The results showed a considerable improvement in the kidney's histological structure compared to Group III.

According to our research, using GM led to elevated serum levels of the enzymes AST and ALT and total bilirubin. This result is consistent with past studies[21] demonstrating that gentamicin produces significant hepatotoxicity when administered at a dose of 80 mg/kg, as seen by increased blood AST, ALT, and bilirubin.

Additionally, it has been established that elevated hepatic enzymes are a sign of liver cell damage. The results demonstrated that the two tested doses of the extract significantly reduced levels of liver enzymes AST, ALT, and bilirubin. This effect was observed when the groups receiving ethanolic cardamom extract were compared to the GM group.

The amounts of total serum proteins, globulin, and A/G ratio between the various study groups have shown to be incredibly small.

Other studies[20,31] have shown that cardamom-treated groups have higher protein and globulin serum levels. The Elettaria therapy group, for instance, had the highest total protein and globulin levels.

The results now prove that harm occurred because we demonstrated that the GEN group's serum albumin level dropped compared to those treated with cardamom extract.

This outcome is consistent with past studies[36]. This study supports the effect of gentamycin on albumin. It was discovered that gentamicin dramatically lowered serum albumin while considerably increasing serum creatinine, bilirubin, and protein compared to the control group.

In the gentamicin-treated group, clinical symptoms such as diarrhea were observed more frequently than those treated with cardamom extract and gentamicin. Diarrhea is a known side effect of gentamicin.

The study by Küçükler et al[37] agreed with what we found. The intestinal lumen's bacterial diversity was reduced after administering gentamicin and Cefradine. Besides, alterations in both composition and abundance made the gut microbiota's dysfunction worse[37]. Utilizing approaches, the efficacy of cardamom extract in treating hypertension, colic distress, diarrhea, and constipation was demonstrated. The current study assessed the impact of gentamicin use on blood sugar and lipid profile elevated levels of HDL-CH, triglycerides, and cholesterol. Additionally, after seven days, rats treated with gentamicin had low levels of LDL-CH[38].

Co-administration of gentamicin and cardamom extract (100-200 mg/kg) reduced blood serum levels of triglycerides, cholesterol, HDL-CH, and LDL-CH. According to these results from a recent study[35], *Elettaria Cardamom* and its extract have anti-inflammatory, anti-diabetic, hemolytic, and antioxidant activities.

The liver of the GM-treated group's histology showed degenerative changes in the liver hepatocytes. They were severely vacuolated and had deeply stained pyknotic nuclei. gentamicin therapy destroyed the histologic framework of the liver (fatty degeneration). As a result, hepatocytes in some regions had degenerated, leaving holes. In addition, the blood sinusoids had become more prominent, the principal vein's wall had been harmed, and mononuclear cells had invaded the region.

According to this study, gentamicin may be linked to severe oxidative stress. It is because it can generate moderately clogged portal blood vessels, hyperplasia of the bile ducts, congested intertubular blood vessels, and congested glomerular capillaries in the liver and kidney tissues[39].

GM damaged hepatic tissue in the current study, as shown by the histological changes in the liver tissues and increased serum levels of liver enzymes. During the co-treatment of gentamicin and cardamom, when tested histopathological, these caused reduced liver tissue damage (Group III). A typical central vein could be seen in some of the hepatocytes that had returned to normal, but others had vacuolated cytoplasm. The histological analysis of the liver tissue directly supported this assertion. The findings of this investigation support those of earlier studies[40]. Studies on tissues further demonstrate that GM causes lymphocyte release and hepatocyte destruction.

GM impacts the body's tissues by stimulating apoptosis, or deliberate cell death, and producing free radicals[40].

## Conclusions

Our results show that the oral dosing of *Elettaria Cardamomum* ethanolic extract has a beneficial protective effect against physiological disorders in different hematological parameters. Furthermore, the intake of gentamicin in combination with ethanolic cardamom extract has shown a protective action against GM toxicity-induced damage in the liver and kidney. This protective process is probably due to cardamom's pharmacological properties, including antioxidant, anti-diabetic, hepatoprotective, and neuroprotective activities of its phenolic compounds against GM toxicity.

The present study shows that using cardamom in daily food can protect the organs. However, further studies are required to assess the protective effects of cardamom ethanolic extract against toxins in different body organs.

### Informed Consent

Not applicable.

### Conflict of Interest

The authors affirm that they do not have any competing interests.

### Availability of Data and Materials

The authors attest that the publication and its supplemental materials have the data necessary to support the findings of this investigation.

### Funding

There was no external support for this research.

### Ethics Approval

The study protocol was approved by the Qassim University Committee for Scientific Research Ethics (protocol code: 21-24-03; date of approval: 31-7-2022).

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## References

1) Hayward RS, Harding J, Molloy R, Land L, Longcroft-Neal K, Moore D, Ross JDC. Adverse effects of a single dose of gentamicin in adults: A systematic review. Br J Clin Pharmacol 2018; 84: 223-238.
2) Solank S, Modi CM, Patel HB, Patel UD, Singh V. Protective Effect of Polyherbal Extract on gentamicin-Induced Renal Injury in Wistar Rats. Ind J of Pharmaceut S Scien 2022; 84: 369-379.
3) Jospe-Kaufman M, Siomin L, Fridman M. The relationship between the structure and toxicity of aminoglycoside antibiotics. Bioorganic Med Chem Let 2020; 30: 127218.
4) Yarijani ZM, Najafi H, Shackebaei D, Madani SH, Modarresi M, Jassemi SV. Amelioration of renal and hepatic function, oxidative stress, inflammation and histopathologic damages by Malva sylvestris extract in gentamicin induced renal toxicity. Biomed Pharmacother 2019; 112: 108635.
5) Rizwana K, Mohammad A, Shah CS, Fahamiya N, Shiffa M. Nephroprotective Activity of the Hydro-alcoholic, Ethanolic Extract and its Fractions of Tukhme Soya (Anethum sowa Roxb.) against gentamicin Induced Nephrotoxicity in Albino Rats. J Young Pharm 2022; 14: 50-55.
6) Al-Kuraishy HM, Al-Gareeb AI, Al-Nami MS. Irbesartan attenuates gentamicin-induced nephrotoxicity in rats through modulation of oxidative stress and endogenous antioxidant capacity. Int J Prev Med 2020; 11: 16.
7) Govindappa PK, Gautam V, Tripathi SM, Sahni YP, Raghavendra HLS. Effect of Withania somnifera on gentamicin induced renal lesions in rats. Braz J Pharm 2019; 29: 234-240.
8) Huang H, Jin WW, Huang M, Ji H, Capen DE, Xia Y, Lu HAJ. gentamicin-induced acute kidney injury in an animal model involves programmed necrosis of the collecting duct. JASN 2020; 31: 2097-2115.
9) Abdeen A, Samir A, Elkomy A, Aboubaker M, Habotta OA, Gaber A, Abdelkader A. The potential antioxidant bioactivity of date palm fruit against gentamicin-mediated hepato-renal injury in male albino rats. Biomed Pharmacother 2021; 143: 112154.
10) Queiroz Lima AC, Rodrigues Godinho ABF, Bueno Dias CV, Rocha VN, Jerdy H. Laboratory changes inherent to acute kidney injury induced by aminoglycosides in wistar rats. Ciência Animal Brasil 2022; 23: e-70110.
11) Tanaka M, Matsumoto K, Satake R, Yoshida Y, Inoue M, Hasegawa S, Nakamura M. gentamicin-induced hearing loss: A retrospective study using the Food and Drug Administration Adverse Event Reporting System and a toxicological study using drug– gene network analysis. Heliyon 2021; 7: e07429.
12) Sharma B, Vasudeva N, Sharma S. Chemical composition and anti-scabies activity of essential oil of Elettaria Cardamomum Maton. Leaves. ACTA Pharma Sci 2020; 58: 2.
13) Ashokkumar K, Murugan M, Dhanya MK, Warkentin TD. Botany, traditional uses, phytochemistry and biological activities of cardamom [Elettaria cardamomum (L.) Maton] - A critical review. J Ethnopharmacol 2020; 246: 112244
14) Ivanović M, Makoter K, Razboršek MI. Comparative study of chemical composition and antioxidant activity of essential oils and crude extracts of four characteristic zingiberaceae herbs. Plants (Basel) 2021; 10: 501.
15) Kumar Singhal P, Gautam GK, Kumar R, Kumar GA. Review on Amomum subulatum and Elettaria Cardamomum with their Pharmacological Activity. MAT J 2022; 4: 1-6.
16) Alam A, Majumdar RS, Alam P. Systematics evaluations of morphological traits, chemical composition, and antimicrobial properties of selected varieties of Elettaria cardamomum (L.) Maton. Natur Produ Communic 2019; 14: 1934578X19892688.
17) Oluwafemi RA, Olawale I, Alagbe JO. Recent trends in the utilization of medicinal plants as growth promoters in poultry nutrition-A review. Research in: Agricult and Veteri Sci 2020; 4: 5-11.
18) Masoumi-Ardakani, Mahmoudvand H, Mirzaei A, Esmaeilpour K, Ghazvini H, Khalifeh S, Sepehri G. The effect of Elettaria cardamomum extract on anxiety-like behavior in a rat model of post-traumatic stress disorder. Biomed Pharmacother 2017; 87: 489-495.
19) Mohamed AS, El Sayed HF, Moftha NSH, Al Shawoush AM. Naja nubiae venom ameliorate hepatorenal toxicity induced by gentamicin in rats. GSC Advan Res Rev 2021; 9: 030-038.
20) EL-Gawish AM, EL-Gezawy ES, Zeima NM. The potential protective effect of alcoholic extracts of some herbs on hepatotoxicity induced by paracetamol in experimental rats. Jedu J 2021; 7: 1349-1378.
21) Aboubakr M, Abdelazem AM. Hepatoprotective effect of aqueous extract cardamom against gen-

tamicin induced hepatic damage in rats. Int J Basic Appl Sci 2016; 5: 1-4.

22) Nagashree S, Archana KK, Srinivas P, Srinivasan K, Sowbhagya HB. Anti-hypercholesterolemic influence of the spice cardamom (Elettaria cardamomum) in experimental rats. J Sci Food Agric 2017; 97: 3204-3210.

23) Vutakuri N, Somara S. Natural and herbal medicine for breast cancer using Elettaria cardamomum (L.) Maton. Int J Herbal Med 2018; 6: 91-96.

24) Auti ST, Kulkarni YA. Neuroprotective effect of cardamom oil against aluminum induced neurotoxicity in rats. Front Neurol 2019; 10: 399.

25) Yassin MT, Mostafa AAF, Al-Askar AA, Alkhelaif AS. In vitro antimicrobial potency of Elettaria cardamomum ethanolic extract against multidrug resistant of food poisoning bacterial strains. J King Saud Univ Sci 2022; 34: 102167.

26) Noorani AA, Gupta KA, Bhadada K, Kale MK. Protective effect of methanolic leaf extract of Caesalpinia bonduc (L.) on gentamicin-induced hepatotoxicity and nephrotoxicity in rats. IJPT 2011; 10: 21-25.

27) Küçükler S, Kandemir FM, Özdemir S, Çomaklı S, Caglayan C. Protective effects of rutin against deltamethrin-induced hepatotoxicity and nephrotoxicity in rats via regulation of oxidative stress, inflammation, and apoptosis. Envir Sci Pollution Res 2021; 28: 62975-62990.

28) Sunil CK, Jaidhar CD, Patil N. Cardamom plant disease detection approach using EfficientNetV2. IEEE Access 2021; 10: 789-804.

29) Khan AU, Khan QJ, Gilani AH. Pharmacological basis for the medicinal use of cardamom in asthma. Bangla J Pharm 2011; 6: 34-37.

30) Abouzed TK, Sherif EAE, Barakat MES, Sadek KM, Aldhahrani A, Nasr NE, Dorghamm DA. Assessment of gentamicin and cisplatin-induced kidney damage mediated via necrotic and apoptosis genes in albino rats. BMC Veterin Resear 2021; 17: 1-9.

31) Elkomy A, Aboubakr M, Elsawaf N. Renal protective effect of cardamom against nephrotoxicity induced by gentamicin in rats. Benha Veterin Med J 2015; 29: 100-105.

32) Elgazzar D, Aboubakr M, Bayoumi H, Ibrahim AN, Sorour SM, El-Hewaity M, Abdeen A. Tigecycline and gentamicin-combined treatment enhances renal damage: Oxidative stress, inflammatory reaction, and apoptosis interplay. Pharm MDPI J 2022; 15: 736.

33) Babaeenezhad E, Nouryazdan N, Nasri M, Ahmadvand H, Sarabi MM. Cinnamic acid ameliorate gentamicin-induced liver dysfunctions and nephrotoxicity in rats through induction of antioxidant activities. Heliyon 2021; 7: e07465.

34) Liu KZ, Shi M, Man A, Dembinski TC, Shaw RA. Quantitative determination of serum LDL cholesterol by near-infrared spectroscopy. Vibra Spectroscopy 2005; 38: 203-208.

35) Nadeem F, Hussain F. Green Nanosuspensions of Elettaria Cardamomum Seeds–Comparative Data Analysis for Enhanced Bioactivities. Pakist J Biochem Biotech 2022; 3: 80-90.

36) El-Kashef DH, El-Kenawi AE, Suddek GM, Salem HA. Flavocoxid attenuates gentamicin-induced nephrotoxicity in rats. Naunyn Schmiedebergs Arch Pharmacol 2015; 388: 1305-1315.

37) Shao H, Zhang C, Xiao N, Tan Z. Gut microbiota characteristics in mice with antibiotic-associated diarrhea. BMC Microbiol 2020; 20: 1-9.

38) Mehvish S, Barkat MQ. Phytochemical and antioxidant screening of Amomum subulatum, Elettaria cardamomum, Emblica officinalis, Rosa damascene, Santalum album and Valeriana officinalis and their effect on stomach, liver and heart. Matrix Sci Med 2018; 2: 28-33.

39) Mohamed AS, El Sayed HF, Moftha NSH, Al Shawoush AM. Naja nubiae venom ameliorate hepatorenal toxicity induced by gentamicin in rats. GSC Advan Res Rev 2021; 9: 030-038.

40) Mirazi N, Baharvand F, Moghadasali R, Nourian A, Hosseini A. Human umbilical cord blood serum attenuates gentamicin-induced liver toxicity by restoring peripheral oxidative damage and inflammation in rats. BCPT 2021; 128: 268-274.