Egypt. J. of Nutrition and Health Vol. 16 No. 2 July (2021)

The Prophylactic Effect of some herbs extract on Gentamicin Induced Nephrotoxicity in Albino Rats

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Abstract

Nephropathies and particularlynephrotoxicity have been recognized as powerful reasonsof life-threatening illnesses due to frequent exposure to xenobiotic whether by environmental contaminationor by drugs misuse. This study aimed to investigatethe protectingimpacts of alcoholic extract of *Cinnamomum zeylanicum* and *Zingiber officinale* on gentamicin induced nephrotoxicity. Thirty six healthy adult albino male rats weighing (170±10 g), were bought for the study. They were grouped into 6 equal groups; group (G-) was kept as a negative control, group (G+) was fed on basal diet and treated with gentamicin as a positive control group. Group 1 and group 2 were also fed on basal diet + oral doses of herbal extract of *Cinnamomum zeylanicum* (100 and 200 mg kg^{-1}b.w. respectively), while group 3 and 4 were fed with *Zingiber officinale* extracts (100 and 200 mg kg^{-1}b.w respectively) once a day, for a period of 28 day. On the 22^{nd} day of the administration, all groups except (G-)group (normal rats) were injected with gentamicin (80 mg kg^{-1}. b.wt. i.p.) dailyfor 8 consecutive days. Assessment of hemogram, some serum biochemical parameters, and histopathology of kidneys were assessed. Chemical composition of Cinnamon and Ginger were analysed by High Performance Liquid Chromatography (HPLC). The results revealed that cinnamon and ginger alcoholic extracts improved the biological evaluation, kidney functions, and antioxidant enzyme activity compared to control+ group. The study showed that feeding rats with cinnamon and ginger have markedly protected them against the harmful impacts of gentamicin on kidney.

Keywords : *Cinnamomum zeylanicum;Zingiber officinale*; Gentamicin, kidney functions; antioxidant enzymes.

Introduction

The kidney is the body's major organ for extracellular fluid management, detoxification, toxic metabolite excretion,and homeostasis maintenance***(Stevens et al., 2006)***. Because of frequent exposure to xenobiotics, whether through environmental pollution or drug misuse, nephropathies and especially nephrotoxicity are now one of the greatest reasons of life-threatening illnesses ***(Atsamoet al., 2021).*** Nephrotoxicity is the term that depictsdrug-induced kidney injury. Some medications may commonly have variable impacts on kidney function. Nephrotoxins are materials that can negatively affect the kidney and cause structural and functional transformsin the kidney. Nephrotoxicity is

triggeredby variable processes involving inflammatory, kidney tubulotoxicity, crystall nephropathy, coagulant microangiopathy and glomerular destruction.

Many medications, including gentamicin (GM), have nephrotoxic effects **(*Safa et al., 2010; Khan et al., 2011)*.** It is proved that the GM renal toxicity is caused by its accumulation in the kidney proximal tubule is selective, which thenresults in a tubule brush boundary stability loss, acute degeneration, necrosis in proximal tubule epithelial cells, and mononuclear cell infiltration in intertubular areas***(Raju et al., 2011).***In clinical practices, GM is a wide spread amino glycoside antibiotic utilized for treatment of Gram-negative infection ***(Ullah et al., 2014).*** There is a possibility that 10 to 30% of patients who take this medication will suffer renal impairment, particularly with long-term usage***(Safa et al., 2010; Khan et al., 2011).*** The GM triggers renal injury by accumulation in the renal glomerulus, causing deterioration in a brushing barrier integrity in the proximal tubule ***(Lopez-Novoa et al., 2011).*** Furthermore, higher lipid peroxidation, free radical creation and diminishedantioxidant activity, renal inflammation distinguishedby subsequent activity and macrophage infiltration, of pro-inflammatory cytokines correlatedstress-induced NF-B, glomerular crammingand serioustubular necrosis which together cause reducedkidneys function, have been concernedas pathwaysof nephrotoxic impacts of GM ***(Lee et al., 2012).***

Herbs have a widespreadvariabilityof phytochemicals with antioxidants activity that are potential medicines preventing gentamicin toxicity because of their low adverse effects, inexpensive costs, and efficacy. Cinnamon (*cinnamomum zeylanicum*) is a popular plant that has a broadrange of bioactive properties. It works as a natural antioxidant, improving human health. Cinnamon has a high content of polyphenolic chemicals, which acts as potent antioxidants(**Su *et al*., 2007)**. Cinnamon has numerous pharmacological characteristics like anti-diabetic, antioxidant, anti-inflammatory and antibacterial characteristics***(Elkomy et al., 2017; Dorri et al., 2018).*** Total extract of cinnamon may protect from extraction, bisphenol, cadmium (Cd) and GM-simulated oxidative damage***(Hafizur et al., 2015) and (Abdeen et al., 2019).***

Ginger (*Zingiber officinale*) belongs to the Zingiberaceae family and is regularly used in the meals in many countries in Asia ***(Demin and Yingying, 2010).*** Ginger has anticlotting, anti-cancer, anti-inflammatory features and pain-relievingactivities ***(Yiminget al., 2012).*** Ginger extract has a high content of gingerols and shagaols exhibiting anti-cancer, anti-inflammation and antioxidant proprieties in both of *vivo* and *in vitro* settings ***(Surh, 2002).***

This study aims to examine the influences of alcohol extractions of both of cinnamon and gingeron the toxicity of kidney and hematological parameters of rats that suffer from nephrotoxicity simulated by GM.

Materials and Methods

***Materials*:**

Cinnamon bark and fresh ginger roots were bought from the Ministry of Agriculture; Giza, Egypt. A total of 36 adult male albino rats (*Sprague Dawley* strain) were obtained from the laboratory of animal colony, Ministry of Health and Population, in Egypt. Gentamicin sulfate, be presentas Epigent (80 mg 2 ml^{-1}) ampoules were obtained from private pharmacy, which is manufactured by the Egyptian International Pharmaceutical Industries Company (EIPICO, Egypt). Casein, minerals, vitamins, choline chloride, cellulose and all essentialchemicals were obtained from El-Gomhoria Company for Trading Drugs, Chemicals, and Medical Appliances, Cairo, Egypt.

Methods:

Herbs chemical analysis:

The polyphenolic components of herbal extracts were separated and classifiedfor phenolic components using HPLC***(Tarola et al., 2013).***

Herbs preparation:

Roots of ginger were washed by water many times, sheared into small pieces, and dried by oven at 50°C for two hours ***(Abdu et al., 2017),*** the dryginger roots and cinnamon barks were crushedto powder using the mill and saved until preparing alcohol extract.

Preparation of alcohol herbsextract:

About 24 g of each powdered herbs was dissolved in ethyl alcohol 96%. The solutions were kept for 24 hrs. at room temperature (25℃). The mixture was then thoroughly mixed for 4 minutes with a magnetic stirring before being filtrated and dried at 50℃ for 30 minutes by an Avon devise. The extract was putin a non-polluting environment for 48 hrs. Therefore the extra alcohol evaporates and is reached to the smallest quantity practicable ***(Jahromi et al., 2014).***

Experimental design and groups:

Thirty-six male adult Sprague Dawley rats weighing (170± 10 g) were kept in well-aerated cages in hygienic conditions for one week and fed basic diet ***(Reeves et al., 1993)*** for one week for adaption. Then the rats were distributedrandomly into six groups (each group has six rats) the study continued for four weeks, according to the following groups:

Negative control group (G-) was fed on basal diet for the whole period.

Positive control group (G+) that treated with gentamycin and fed on basal diet for the whole study period.

Groups 1 and **2:** were fed on the basal diet and daily treated orally with the cinnamon extract (100 and 200 mg kg^{-1} body weight respectively) (G1 and G2).

Groups 3 and **4:** had been fed also on the basal diet and also daily treated orally with the ginger extract (100 and 200 mg kg^{-1} body weight respectively) (G3 and G4). On the 22 day, throughoutthe administration period of the respective treatments, all animal groups 1,2, 3 and 4 were given a GM (80 mg kg^{-1}. b.wt. i.p.) every day for 8 successivedays***(Elkomy et al., 2015).*** Body weight and feed intake were noticed once a week. After the end of the four weeks, rats were weighted, fasted overnight, and sacrificed. Blood samples were taken, and experimental measurements were determined.

Biological assessment:

Body weight gain, feed intake, feed efficiency percentages and relative kidney weight were assessed at the final day of the experiment ***(Chapman et al., 1959).***

Serum Biochemical analysis:

After the rats being sacrificed, blood samples were obtained from rat's hepatic portal vein. The first tube was clean centrifuge tube and the second contain EDTA. After centrifugation Serum and plasma were kept frozen at - 20 C for subsequent analysis. The following markers were determined: urea ***(Chaney and Marbach, 1962)*;** creatinine forms colored complex when reacted with alkaline picrate ***(Faulkner and King, 1976)***and uric acid ***(Barham and Trinder, 1972) and Fossati et al., 1980)***; alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ***(Bergmeyer et al.,***

1986),serum (ALP) was determined according to the colorimetric method ***(Roy, 1970);***Albumin ***(Drupt, 1974)***andtotal protein ***(Sonnenwirth and Jaret, 1980).***Globulin was calculated according to ***Busher, (1990)*** by the following equation:
Globulin = Total protein – Albumin ***(Busher, (1990))***

Blood picture determination of rats:
Blood samples were collected from all rats and put in dipotassium EDTA for the typicalhemogram (CBC) usingthe counter of Animal Blood Cell (ABC Vet, France) ***(Feldman et al., 2000).***

Organs sampling:
Kidneys were carefully separated from all rats, washed by saline solution (0.9%), dried byfilter paper and individuallyweighted. A specimen from kidneys was freezed at (-20 °C) for preparing tissues homogenate to determine antioxidant activities. The homogenation was centrifuged at 1000 rpm for 10 min.

Assessment of antioxidant activities in the kidney tissues:
Antioxidant indications were assessed such as Lipid peroxide (LPO) as malondialdehyde (MDA) ***(Buege and Aust, 1978),*** Superoxide dismutase (SOD)***(Nishikimi et al., 1972),*** Catalase (CAT) was assessed by colorimetric assay ***(Sinha, 1972),*** and GPX ***(Lawrence and Burk, 1976).***

Assessment of inflammatory indicators was indicated by definingthe level of Tumor Necrosis Factor α (TNF-α) in the tissues of kidney ***(Lisowski et al., 2008).***

Histopathological examination:
The kidney of each sacrificed rat was removed and fixed in a 10% neutral buffering formaldehyde solution with a pH of 7.5, then cleaned in xylol before being fixedin paraffin. For histological analysis, a 4-5 µm thick piece was cut and spottedwith Hematoxylin and Eosin (H&E) ***(Bancroft and Gamble, 2008).***

Statistical analysis:
One-way analysis of variance (ANOVA) was used, following by the Duncan test, in SPSS software (18) to know the difference between means at $P< 0.05$. The data was presented as a mean ± standard deviation (SD) ***(Snedecor and Cochran, 1989).***

Results

Defining phenolic components of both cinnamon and ginger extracts
The HPLC analysis of phenolic substances in both cinnamon and ginger showed that cinnamic, p-coumaric, protocatechuic acids, and cateachin has recorded the highercontents in cinnamon, while ginger has higher phenolic substances ferulic acids, cinnamic acid, vanillic acid and Apigenin-7-glucoside).In contrast, the phenolic substances of kaempferol, chrysin, qurecetin, and chlorogenic acid are the minimum in cinnamon, while protocatechuic acid, caffeic acid, kaempferol, and p-coumaric acid recorded the minimum contents of phenolic substances in ginger (Table 1).

Table (1):

Phenolic substances in cinnamon and ginger extract (µg g^{-1})

Compound	Cinnamon	Ginger
Gallic acid	159.45	19.62
Protocatechuic acid	234.43	0.32
p-hydroxybenzoic acid	80.36	3.01
Gentisic acid	46.82	0.0
Cateachin	581.08	23.45
Chlorogenic acid	7.68	0.0
Caffeic acid	16.32	1.28
Syringic acid	18.39	22.41
Vanillic acid	14.87	69.97
Ferulic acid	221.66	636.01
Sinapic acid	109.02	3.91
p-coumaric acid	576.92	2.57
Rutin	58.28	0.0
Rosmarinic acid	58.92	45.86
Apigenin-7-glucoside	9.56	55.54
Cinnamic acid	873.39	74.41
Qurecetin	6.59	2.65
Apigenin	-	6.65
Kaempferol	3.77	2.10
Chrysin	4.78	3.96

Biological evaluation:

Feed intake (FI), body weight gain (BWG) % and feed efficiency ratio (FER) have significantly decreased in G+group compared to normal group (G-) (Table 2). However, the other treated groups have revealed a significant rise in all of them compared with G+group.

Table (2):

Effects of cinnamon and ginger extracts on feed intake (FI), body weight gain (BWG %) and feed efficiency ratio (FER) in rats

Parameter / Groups	FI (g per 28 day)	BWG (%)	FER
G- (- ve)	407.00 ± 2.91a	78.84 ± 4.84a	0.193 ±0.01a
G+ (+ve)	284.00 ± 2.91e	42.91 ±5.12d	0.151 ± 0.02c
G1	387.00 ±2.23c	62.99 ± 6.76bc	0.162 ± 0.01bc
G2	397.20 ± 2.23b	70.20 ±3.27b	0.176 ± 0.01ab
G3	371.00 ± 2.23d	60.49 ±7.28c	0.163 ±0.02bc
G4	370.00 ±2.23d	66.84 ± 5.55bc	0.180 ± 0.01ab

Means in the same column with completely different letters are significantly different at $p<0.05$.

Relative kidney weight:

As shown in (Table 3), relative kidney weight has been increased in G+ group compared with G- group. However, it was significantly decreased in all treated groups compared with G+ Group. The best results were recorded in G3 group (i.e. 100 mg kg^{-1}) as it recorded a significant decline in relative kidney weight compared with other investigated groups.

Table (3):
Effects of cinnamon and ginger extractson relative kidney weight in investigated rats (mean ± SD)

Parameter / Groups	Relative kidney weight%
G- (- ve)	1.68 ± 0.02e
G+ (+ve)	1.88 ± 0.01a
G1	1.84 ± 0.02b
G2	1.77 ± 0.02cd
G3	1.75 ± 0.02d
G4	1.79 ± 0.01c

Means in the same column with completely different letters are significantly different at p<0.05.

Erythrogram parameters (table 4):

The results of RBCs, Hb, PCV, MCV, MCH and MCHC has been significantly decreased in G+ compared with G- group. However, in the other examined groups, there was an increase when compared with G+. The best results in RBCs, Hb and PCV were found in groups treated with G3 and G4, while the best ones in MCV, MCH and MCHC were observed in G4.

Table (4):
Effects of cinnamon and ginger extract on erythrogram parameters in rats (mean ± SD)

Parameter / Groups	RBCs x 106 ul^{-1}	Hb g dl^{-1}	PCV %	MCV fl	MCH pg	MCHC %
G- (- ve)	4.86 ±0.02^{a}	14.95 ± 0.04^{a}	44.84 ± 0.01^{a}	92.26 ± 0.13^{a}	35.10 ± 2.55^{a}	38.37 ± 1.94^{a}
G+ (+ve)	3.58 ±0.05^{d}	9.00 ± 0.05^{d}	26.98 ± 0.02^{e}	75.36 ±0.83^{d}	26.74 ± 0.09^{c}	28.32 ± 4.07^{c}
G1	4.05 ± 0.01^{c}	11.01 ± 0.02^{c}	33.03 ± 0.02^{d}	81.52 ± 0.46^{c}	28.83± 0.94^{bc}	30.62 ± 1.24^{bc}
G2	4.35 ±0.23^{b}	12.30 ± 0.05^{b}	36.96 ± 0.03^{b}	84.79 ± 4.25^{bc}	29.20 ± 1.91^{bc}	30.46 ± 1.25^{bc}
G3	3.87 ±0.11^{c}	11.03 ± 0.01^{c}	33.12 ± 0.03^{c}	85.37 ± 2.49^{bc}	29.50 ±1.60^{bc}	31.48 ± 1.55^{bc}
G4	4.32 ±0.06^{b}	12.33 ± 0.02^{b}	36.99 ± 0.01^{b}	85.63 ± 1.15^{b}	30.72 ± 1.27^{b}	32.03 ± 2.09^{b}

Means in the same column with completely different letters are significantly different at p<0.05

Kidney functions:

The data in Table (5) indicated that mean values of urea, creatinine and uric acid in the G+ group were significantly higher compared with G- group. All parameters in (G1, G2, G3 and G4) groups significantly decreased (P<0.05) compared to G+ group. The best findings in creatinine and uric acid were found in G4, while G2 and G4 recorded the best result in urea.

Table (5):

Effects of cinnamon and ginger extract on kidney functions in rats (mean ± SD)

Parameter / Groups	Urea (mg dl^{-1})	Creatinine (mg dl^{-1})	Uric acid (mg dl^{-1})
G- (- ve)	29.26 ± 2.97d	0.42 ± 0.01e	2.76 ± 0.05e
G+ (+ve)	97.32 ± 1.45a	1.24 ± 0.02a	6.75 ± 0.39a
G1	47.13 ± 2.71b	0.83 ± 0.02b	5.68 ± 0.42b
G2	41.20 ± 2.68c	0.74 ± 0.01c	4.29 ± 0.24c
G3	49.30 ± 1.51b	0.82 ± 0.01b	5.60 ± 0.49b
G4	39.28 ± 2.92c	0.55 ± 0.02d	3.23 ± 0.37d

Means in the same column with completely different letters are significantly different at p<0.05.

Liver functions:

The data in Table (6) revealed that the mean values of ALT, AST and ALP in G+ were significantly higher compared with the G- group, whereas all other groups were significantly decreased compared with G+ group. The best findings of ALT and AST were observed in G2, while G3 and G4 recorded the best result in ALP

Table (6):

Effects of cinnamon and gingerextracton Liver functions in rats (mean ± SD)

Parameter / Groups	ALT (U l-1)	AST (Ul^{-1})	ALP (U l^{-1})
G- (- ve)	38.86 ± 2.015e	78.00 ± 2.00e	125.00 ± 2.00e
G+ (+ve)	96.00 ± 3.00a	99.33 ± 2.51a	149.66 ± 2.52a
G1	53.00 ± 3.00c	88.00 ± 2.00bc	143.00 ± 1.00b
G2	44.76 ± 2.45d	83.00 ± 3.00d	140.00 ± 3.00bc
G3	60.00 ± 3.00b	90.00 ± 3.00b	137.00 ± 2.00c
G4	55.00 ± 2.00c	84.00 ± 1.00cd	130.00 ± 4.00d

Means in the same column with completely different letters are significantly different at p<0.05.

Serum Albumin, Globulin and Total protein

The data in Table (7) demonstrated that the mean value of total protein (TP), albumin (Alp) and globulin (Glob) in (G+ group) were significantly declined compared with G- group. However, all other examined groups recorded a significant increament compared to G+ group. The maximum total protein and globulin levels were noticed in the treated G4 group, while the maximum albumin were recorded in groups G2 and G4.

Table (7):
Effects of cinnamon and ginger extracton total protein, albumin and globulin in rats (mean ± SD)

Parameter / Groups	TP (mg dl^{-1})	Alb (mg dl^{-1})	Glob (mg dl^{-1})
G- (- ve)	5.32±0.044a	3.72±0.11a	1.60± 0.14a
G+ (+ve)	2.54± 0.044e	1.99 ±0.01d	0.54 ±0.11d
G1	4.50±0.158cd	3.50 ±0.07bc	1.00±0.20c
G2	4.66±0.20c	3.60 ±0.16ab	1.06±0.19bc
G3	4.36± 0.11d	3.38 ±0.08c	0.98 ±0.08c
G4	4.95±0.015b	3.68 ±0.19a	1.27±0.20b

Means in the same column with completely different letters are significantly different at p<0.05.

Table (8):
Effects of cinnamon and ginger extracton GPX, SOD lipids peroxidation MDA, CAT and tumor necrosis factor -α in kidney tissue of rats (mean ± SD)

Parameter / Groups	GPx (ngmg-1)	SOD (uml-1)	MDA (mmolml-1)	CAT (ngmg-1)	TNF (pgmg-1)
G- (- ve)	100.00 ± 3.00a	202.00 ± 2.00a	2.23 ± 0.05e	11.40 ± 0.03a	46.00 ± 4.00e
G+ (+ve)	23.00 ± 2.00e	37.16 ± 3.01e	19.50 ± 1.00a	0.59 ± 0.00e	146.00 ± 2.00a
G1	45.00 ± 3.00d	84.16 ± 4.01d	13.00 ± 1.00b	2.80 ± 0.05d	70.00 ± 2.00b
G2	86.00 ± 3.00b	191.00 ± 3.00b	8.42 ± 1.05c	9.16 ± 0.02b	60.33 ± 2.50cd
G3	55.00 ± 1.00c	105.00 ± 3.00c	12.00 ± 1.00b	3.65 ± 0.05c	65.00 ± 2.00c
G4	90.00 ± 5.00b	190.50 ± 3.50b	6.48 ± 0.87d	9.16 ± 0.02b	56.00 ± 1.00d

Means in the same column with completely different letters are significantly different at p<0.05.

Antioxidant enzymes (GP_X, SOD, CAT, Lipid peroxidation (LPO) parameter malondialdehyed (MDA) and tumor necrosis factor -α (α –TNF) in kidney tissue.

Table 8 illustrated the activities of kidney glutathione peroxidase (GPX), superoxide dismutase (SOD) and catalase (CAT) were significantly declined in G+ group compared with G-, while they rose in other groups compared with G+. The best finding were noticed in G2 and G4.Table (8) also revealed that the mean value of MDA and TNF-α were significantly higher in G+ group increase in compared with G-, however, their values were significantly lower in other groups compared with G+ group. The best findings were recorded in G4.

Histological assessment

The histological kidney sections stained with H & EX 400 are shown in Fig.1 (A – F). The rats' kidney in G- group (Fig.1-A) revealed the normal histological structure of renal parenchyma, while the rats' kidneys in G+ group exhibited glomerular tufts congestion, cytoplasm epithelial lining renal tubules vacuolize, and epithelial lining renal tubules necrobiosis(Fig.1-B).Conversely, mild glomerular tuft congestions, and cytoplasm vacuolization of epithelial lining some renal tubules were shown in G1 group (Fig.1-C) compared to no histopathological alterations except slight congestions of glomerular tufts and some renal blood vessels that were observed in G2 group (Fig.1-D).While, rats' kidney displayedno histopathological changes in G3 and G4 groups (Fig.1-E and F).

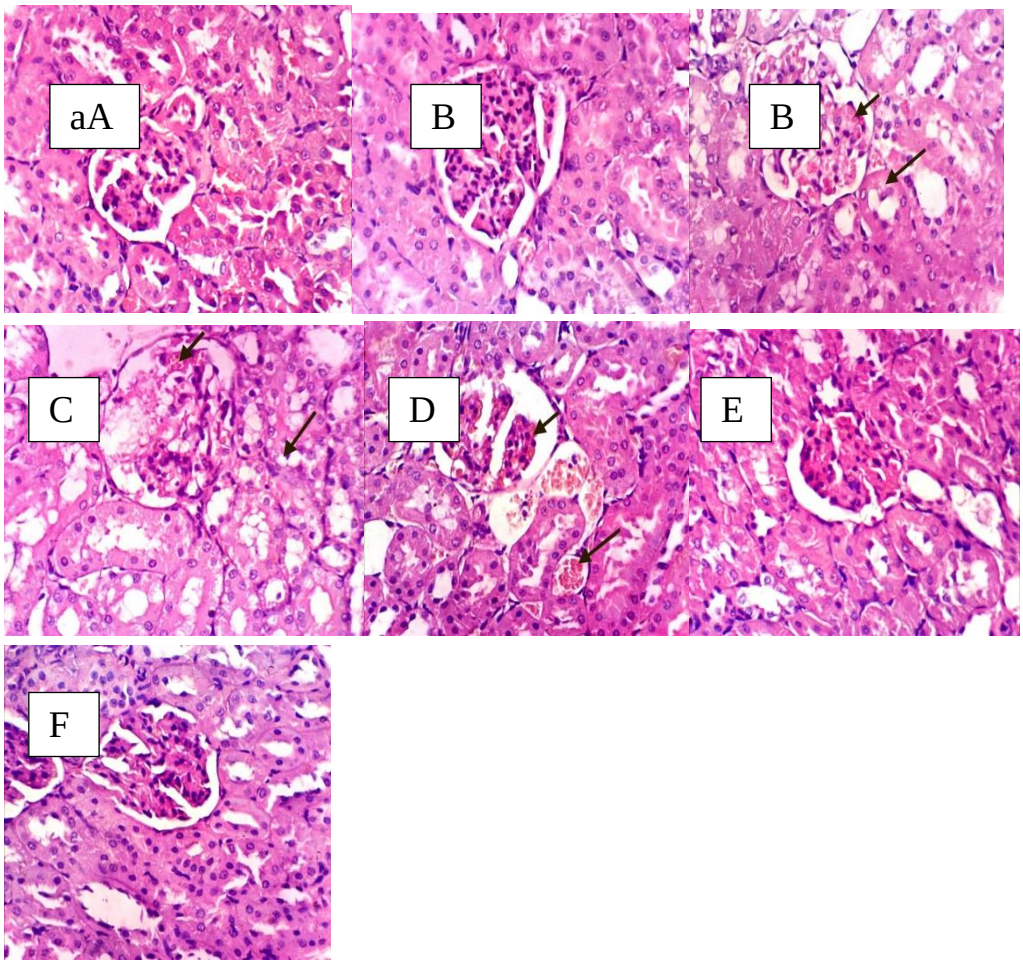

Fig. 1: Microscopic images of hematoxylin and eosin (H & E X 400) stained kidney sections showing (A): G-, (B): G+, (C): G1; (D): G2, (E): G3, and (F): G4 groups.

Discussion

The cinnamon barks comprise mainly of cinnamaldehyde, as well from trans-cinnamic acid, volatile oils, and euginol, phenolic substances, tannin, monoterpines, catechins, proanthocyanidians, sesquiterpines, mucilage. Furthermore, these barks contain sugar, starch, resin, and coumadin traces ***(Uma et al., 2009). Tohmaet al., (2017) and Joel et al., (2021)*** added that HPLC analysis indicatedthe existence of at least eight divers ephenolic acidic substances that were defined in ginger (e.g pyrogallol p-hydroxybenzoic acid, ferulic acid) and p-coumaric acid which were abundantly detected in the extract.

This study agreed with that of ***Adil et al., (2016)*** who reported that GM injection decreased BWG and increased the relative weight of rats' kidney. The decline in BWG might be ascribedto greater proteolysis and lesser proteins synthesis. The findings are supported by***Songmeneet al., (2021)*** who reported that GM decreased BWG and serum total proteins, however, it increased kidneys' relative weight, serum, urea, uric acid, and creatinine. Furthermore, the levels of reduced glutathione, catalase, and superoxide dismutase activities were declined.

Tanomand and Najafian, (2013) noticedthatcinnamon barks extract can protect from the GM-induced nephrotoxicity. Cinnamon extract's antioxidant capabilities may be responsible for the protective impact. ***Hussain et al. (2019)*** study explained that treating with aqueous extract of cinnamon against acetaminophen (APAP) has a highly substantial preventative capability by reducing blood creatinine and urea levels, which are both raised by APAP. These findings were confirmed with **Elkomy*et al.,* (2020)** who revealed that pretreatment of GM in the rats administered with cinnamon oil has significantly declined urea and serum creatinine. This accorded with***Quamuddinet al., (2021)*** who reported thatthe treatments of rats with cinnamon aqueous extract against paracetamol-induced nephrotoxicity in rats has significantly diminishedthe levels of urea, uric acid, and creatinine in serum compared with paracetamol treated rats. Previously, ***Sudhakar and Lakshmi (2010)*** proved that the extracts of ethyl acetate and fresh juice of ginger renormalized the GM-induced increment in the serum contents of creatinine, uric acid, urea and confirmed by the histopathological results. Similar results were reported by ***Policegoudraet al. (2011)*** who found marked decrease in blood urea levels in rats that have taken ginger.

Eidi et al., (2012)indicated that treatment with cinnamonextracts for 28 days had significantly declined the CC14 toxicity impact in the serum indicatorsof liver injury, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase. These findings were reinforcedby ***Hussain et al., (2019)*** who studied on mouse model and found that aqueous cinnamon extract revealed that APAP-induced higher contents of serum alanine aminotransferase, aspartate aminotransferase, and macroscopic and histological alterations in kidney had a significantly substantial preventative potential. Pre-administration of cinnamon inhibitedthe toxic alterations that happened by acetaminophen which provedby histopathological evaluation, more likely due to its antioxidant properties. In cisplatin-treated rats, ginger treatment was demonstrated to diminished,the increased activity of AST and ALT ***(Attyah and Ismail, 2012)***. Also, according to ***Kalaiselviet al. (2015),*** ginger extract ameliorated liver function enzymes in the ginger provided group of rats, compared to groups treated with aluminium. ***Quamuddinet al., (2021) and Zainab et al., (2016)*** found that the use of cinnamonaqueous extract against paracetamol induced nephrotoxicity in rats has significantly restored the total protein to normal

levels, also demonestratedthat rats treated with ginger ethanolic extract has significant higher increase in total protein content.

Elkomyet al., (2020) noticed that pretreatment of GM treated rats with cinnamon oil reduced kidney MDA levels substantially more effectively than GM alone treated rats. In comparison to GM-treated rats, it also boosted SOD, GSH, and CAT activity in kidney tissues. These effects are likely attributed to their powerful antioxidant properties as well as their capacity to maintain permeability of the cell membrane and decline the inflammation***. (Dorriet al., 2018)*** reported that cinnamon and its main components can decreasethe toxicity of toxicants in the hepatic, kidney, plasma, reproductive organs, heart, and central nervous system in portion by acting as antioxidants, radical scavengers, lowering lipid peroxidation, anti-inflammatory, fungistatic and fungicidal agents, and modulating TNF- and IL-6 levels. Those findings was confirmed with ***Quyamuddinet al., (2020)*** who noticed that treatment with cinnamon bark ethanolic extract (100, 200 mg kg^{-1}, bw) has significantly recovered the changedlevels of SOD, CAT and GSH in kidney tissues. These results were highlighted by ***Al-Azhary, (2011)***where ginger decreased the lipid peroxidation, subsequently MDA levels, by affectingthe levels of enzymatic blood of superoxide dismutase, catalase, and glutathione peroxidase.***Ademiluyiet al., (2012)*** conducted that pre-administration with ginger before GM administration has significantly ($p < 0.05$) protected the kidney and decreasedoxidative stress by controllingrenal damage and antioxidant markers. As a result, including ginger rhizomes in someone's diet may protect from GM-induced renal damage and oxidative stress. Ginger includes polyphenols and flavonoids, which have antioxidant and nephroprotective properties and aid in regular nephron function***(Lebdaet al., 2012).*** According to ***Rodrigues et al., (2014)***, nephrotoxicity is the most frequentside effect of GM therapy. Gingerols (i.e. phenolic substances in ginger) have antioxidant and anti-inflammatory properties. In rats treated with GM and gingerol fraction, renal function indices were improved, lipid peroxidation and nitrosative stress were decreased, and glutathione and superoxide dismutase activity were increased. The present study was supported by the findings of ***Zainab et al., (2016),*** who discovered that ginger ethanolic extract may significantly lower MDA levels while significantly increased GSH levels.

Rodrigues et al., (2014) reported that nephrotoxicity is the principalcomplication of GM treatment. The GM damages the kidneys by producing too many reactive oxygen species and causing inflammation in the proximal tubular cells. In the GM-treated group, histological investigation of the kidney indicated tubule necrosis, glomerular degradation, and macrophages infiltration, according to ***Songmene et al., (2021).*** This study is in a line with ***Tanomandet al., (2014)*** who studied the histological effects of cinnamon on the nephrotoxicity caused by GM in rats is attributed to its antioxidant characteristics. It was revealed that the Hydro-alcoholic extract of cinnamon partially contains phenolic substances and antioxidant activities that may be able to treat tubular damage caused by GM. The histological analysis of kidney from rats treated with cinnamon Hydro-alcoholic extract has significantly decreased kidney damage. ***Gunawardena et al. (2015)***found thatthe major constituents of cinnamon bark such as cinnamaldehyde that has a long list of medicinal values, including antioxidative and anti-inflammatory functionalities, as well as nephroprotective benefits. Thus, the nephroprotective benefits observed in this study might be attributed toits presence. These results are confirmed by***Quyamuddinet al., (2020)*** who observed that the treatment with cinnamon bark ethanolic extract, of 100 and 200 mg kg^{-1}, bw, has declined the renal histopathological alterations caused by acetaminophen. Previously, ***Sudhakar and Lakshmi (2010)***reported that the two ginger extracts (ethyl acetate and fresh juice) have significantly protected rats' kidneys against GM-induced histopathological alterations. The GM-induced glomerular, peritubular, and blood vascular congestions, epithelium ulcerations, inflammatory cell buildup, and kidney cell necrosiswere decreased in the rats'

groups treated with both ginger extract along with GM. ***Nasriet al. (2013)*** also stated that ginger may prevent degeneration of the renal cells and decrease the severe tubular damage resulted from GM. It was, however, unable to reverse the GM degeneration. However they suggested that ginger may be used as a prophylactic agent.

Conclusion

Gentamicin has toxic side effects on experimental animals proved by biochemical and histological results. The results concluded that using high doses of alcoholic extracts of cinnamon and ginger has improved kidney functions, their tissues and hematological parameters.

Recommendation: It is worthy trial to use cinnamon and ginger as spices or drinks to patients of nephrotoxicity may help the medical treatment.

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الثأثير الوقائي لبعض مستخلصات الأعشاب علي الجينتاميسين المحدث للتسمم الكلوي في فئران الألبينو

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أصبحت أمراض الكلى وخاصة السمية الكلوية أحد الأسباب الخطيرة التي تهدد الحياة بسبب التعرض الشديد للمواد الكميائيه سواء عن طريق التلوث البيئي أو عن طريق تناول الأدوية. أجريت الدراسة الحالية لتقييم التأثير الوقائي للمستخلصات الكحولية للقرفة والزنجبيل علي السمية الكلوية التي يسببها الجنتاميسين. تم استخدام 36 فأر بالغ سليم من سلالة الألبينو تتراوح أوزانهم بين (170 ± 10 جم). وتم تقسيم الفئران إلى 6 مجموعات متساوية، تركت أحد المجموعات كمجموعة ضابطه سالبه ، المجموعة (2) تم تغذيتها علي الغذاء القياسي كمجموعة ضابطه موجبة، جميع المجموعات الأخري تم تغذيتها علي الغذاء القياسي بالإضافه إلي جرعات من الأعشاب عن طريق الفم كالاتي : (3 و 4) تمت معالجتهم بمستخلص القرفة(100و 200 مجم / كجم من وزن الجسم) على التوالى , (5 و 6) تمت معالجتهم بمستخلص الزنجبيل(100و 200 مجم / كجم من وزن الجسم) على التوالى مرة واحدة في اليوم لمدة 28 يومًا وفي اليوم 22 أثناء إدارة العلاج السابق، تم حقن جميع مجموعات الحيوانات دون المجموعه الأولي(-G) بالجنتاميسين (80 مجم / كجم من وزن الجسم) يوميا لمدة 8 أيام متتالية. تم إجراء تقييم للدم وبعض المتغيرات البيوكيميائية في السيرم كما أجري الفحص الهيستوباثولوجي لأنسجة الكلى. تم تقدير المركبات الفينولية للقرفة والزنجبيل بواسطة الجهاز الكروماتوغرافي السائل عالي الأداء. أظهرت النتائج أن المستخلص الكحولي للقرفة والزنجبيل أدي إلي تحسين في التقييم البيولوجي ووظائف الكلى والإنزيمات المضادة للأكسدة مقارنة بالمجموعة الضابطة الموجبة. يمكن أن نستنتج أن تناول القرفة والزنجبيل يحميان بشكل ملحوظ من الآثار الضارة للجنتاميسين على الكلى في حيوانات التجارب.

الكلمات المفتاحية: القرفة، الزنجبيل, الجنتاميسين، وظائف الكلى ,الأنزيمات المضادة للأكسدة.