Studying Effect of Aqueous Extract of Cinnamon Stem Bark and Stevia Leaves and Their Combination on Gentamicin-Induced Nephrotoxicity in Rats

By

Aml F. Elgazar

Department of Nutrition and Food Sciences,
Faculty of Home Economics, Helwan University, Cairo, Egypt
Email:dr_aml_fawzy@yahoo.com

Research Journal Specific Education

Faculty of Specific Education

Mansoura University

ISSUE NO. 67, MAY , 2022

مجلة بحوث التربية النوعية - جامعة المنصورة

العدد السابع والستون - مايو ٢٠٢٢

Studying Effect of Aqueous Extract of Cinnamon Stem Bark and Stevia Leaves and Their Combination on Gentamicin-Induced Nephrotoxicity in Rats

*Aml F. Elgazar**

The principle aim of the present study was to assess the potential effect of aqueous extract (AE) of cinnamon stem bark (CSB) and stevia leaves (SL); and their combination against gentamicin (GM)-induced nephrotoxicity in rats. Rats were grouped into five rats each in five groups. Group one kept as healthy control group; the other four groups were intraperitoneal injected with 100 mg/kg b.wt of GM for 10 days to induce nephrotoxicity. Rats of groups 3, 4 and 5 were administered daily 200 mg/kg of b.wt of AE of CSB & SL; and their combination, respectively. GM significantly ($P<0.05$) induced an elevation in relative weight of liver and kidney; serum biochemical markers of liver and kidney functions; and imbalance in oxidative parameters of kidney tissues, as well as morphological changes in the kidney, along with decreased body weight and total of serum albumin and protein levels, compared with that of normal rats. Co-administration AE of CSB, SL, or their combination significantly ameliorates all of the tested parameters; and histopathological changes, as well as the activities of antioxidant enzymes in kidney tissues were reconditioned. Effect of CSB or CSB + SL ameliorate all of the parameters more than that of SL. Finally, the present work demonstrated that AE of CSB and SL, or CSB + SL ameliorate the changes in liver or kidney functions and oxidative markers in the kidney induced by GM in rats. Thus, CSB and SL can be used within of the nutritional plan for kidney patients.

Keywords: Gentamicin; Renal toxicity; Liver Function; Antioxidant Enzymes; Histopathological; Stevia, Cinnamon

* Department of Nutrition and Food Sciences, Faculty of Home Economics, Helwan University, Cairo, Egypt

Introduction

The kidneys are highly vulnerable to injury caused by a high volume of blood flowing through it, and infiltration large amounts of toxins, which can converge in kidney tubules (**Begum *et al*., 2011**). The kidneys variability in the reaction to toxic substances by various morphological patterns starting with tubular changes to nephropathy (**Silva, 2004**). Kidney diseases are considered one of the main causes an increased grade of mortality in the worldwide, especially due to side effects manifested by artificial drugs (**Singh *et al*., 2016**). Furthermore, the increase of pollutions in the environment, some the diseases (hyperuricaemia, high blood pressure, diabetes mellitus, and obesity) and misuse of drugs, as well as family history of kidney failure are the main factors contributing to the prevalence of chronic kidney diseases (CKD) (**Himmelfarb, 2004**).

Gentamicin (GM) is a type of the aminoglycoside antibiotic drug, which used widely against life-menacing infections caused by Gram-negative bacteria (**Randjelovic *et al*., 2012**). Proximal renal tubules are the main place for excretion and reabsorption of GM. Ordinarily GM is accumulated within renal tubules causing renal deterioration (**Ghaznavi *et al*., 2016**). Therefore, the total dose of GM and duration of treatment should be decreased, and limits the therapeutic prescribing of especially in patients with renal insufficiency (**Acharya *et al*., 2013**). GM-triggered the renal failure is usually accompanied by the announced release of reactive oxygen (ROS) and nitrogen species (RNS), superoxide anions, hydrogen peroxide and hydroxyl radicals by kidney mitochondria (**Tavafi and Ahmadvand, 2011**).

Stem barks of cinnamon are used as a spice in culinary for several centuries in many countries. In addition to its culinary uses, cinnamon has been used for the treatment of gastrointestinal disorders (**Teuscher, 2003**); antidiabetic effect (**Verspohl *et al*., 2005**); rheumatism, muscular pain and typhoid fever (**Dongmo *et al*., 2007**); immunomodulatory activity (**Niphade *et al*., 2009**); vasorelaxant and antihypertensive effect (**Nyadjeu *et al*., 2011**); and ant-atherosclerosis (**Nayak *et al*., 2017**).

Stevia (*Stevia rebaudiana Bertoni*) is a sweet herb domestic in South America, plays an important role as a non-nutritive natural sweetener, safe sugar substitute and does not possess any threat to human health (**Savita *et a*l., 2004**). Also, stevia has been established hopeful results as the remedy of diabetes, hypertension, sexual dysfunction and other metabolic disorders (**Ghaheri *et a*l., 2019**). The most common effects of stevia are antioxidant and anti-inflammatory; and support to decrease of the cardiovascular and metabolic disorders (**Boonkaewwan *et a*l., 2006**). The main active constituents of stevia are stevioside and rebaudioside, which are responsible for antidiabetic, antihypertensive and antioxidant activity (**Ghaheri *et a*l., 2018**). According to the strong and consistent relationship between oxidative stress and nephrotoxicity a number of studies, the present study was conducted to evaluate the potential effect of aqueous extract of cinnamon stem bark and stevia leaves; and their combination against GM-induced nephrotoxicity in rats.

Materials and Methods

Materials

Plant Materials: Dried **s**tevia leaves were obtained from Sugar Crops Research Institute, Agricultural Research Center, Giza, Egypt. Stem barks of cinnamon were purchased from Khedr El Attar shop for herbs, medicinal plants, spices, seeds and oils, Cairo, Egypt.

Rats and Diet: Twenty-five adult male albino rats Sprague-Dawley strain, aged 10-12 weeks and weighting 180±10 gm were used. Rats were purchased from the Laboratory Animal Colony, Helwan, Egypt. Basal diet constituents were purchased from the El Gomhouria Company for Trading Drugs, Chemicals and Medical Appliances, Cairo, Egypt.

Chemicals and Drug: Gentamicin sulfate was obtained from the Memphis Pharm and Chemical Ind., Cairo, Egypt. Reagents for biochemical reactions and other chemicals used in the present study were purchased from the Gamma Trade Company for Pharmaceutical and Chemical, Dokki, Egypt.

Methods

Preparation of Aqueous Extract: Dried stevia leaves and stem barks of cinnamon were cleaned from dust and remove all worthless parts. Then, both plants materials were ground into a grinder and sieves were used to take out a fine powder particle size of less than 0.4mm. One kilogram of each plant powders were soaked into 10 L of distilled water for 48 hours, and heating at 50º C for 20 minutes. The solutions mixture was then filtered using Whatman filter paper no. 4. The filtrate solutions were concentrated under vacuum to obtain on concentrated aqueous extracts of stevia leaves and cinnamon, which were 65 and 50 g of stevia leaves and cinnamon, respectively.

Preparation of Basal Diet: Diet (AIN-93M) was ready as depicted by **Reeves *et al.*, (1993)** to meet the reasonable suggested supplements levels of nutrients for keeping up with wellbeing rats as shown in Table 1.

Table 1: Components of Basal diet (AIN-93M)

Components	**Amount (g/kg)**
Casein	140.00
Corn starch	620.69
Sucrose	100.00
Soybean oil	40.00
Fibers	50.00
Mineral mix.	35.00
Vitamin mix.	10.00
L-Cystine	1·80
Choline chloride	2.50
Tert-Butylhydroquinone	0.008

Experimental Plan and Grouping of Rats: All rats were adapted in the animal house setting at the Faculty of Home Economics for one-week prior to the start of the study. The animal house was maintained at a temperature of (20 ± 3 °C) and a humidity of 50 ± 5% with a 12 –hr dark/light cycle. Basal diet and drinking water ad *libitum* were provided to

the rats during the experimental period (180 days). Rats were randomly divided into five groups, and five rats in each group. Group (I) healthy control group (HCG), fed on a basal diet and orally administered distilled water. Groups II, III, IV and V were intraperitoneal injected by GM at a dose of 100 mg/kg body weight for 10 days as reported by **Sadeghi *et al.*, (2015)** to induce nephrotoxicity. Then, the group (II) was kept as nephrotoxicity control group (NCG), nephrotoxicity rats in groups (III) and (IV) were given orally the aqueous extract of cinnamon (NRTC) and stevia leaves (NRTS) at levels of 200 mg/kg of b.w/day, respectively. Group (V) nephrotoxicity rats giving orally the combination of both cinnamon and stevia (NRTCS) leaves aqueous extracts (1:1) in a dose of 200 mg/kg of b.w/day.

After the accomplishment of the experimental period, rats were fasted for 12 hr but had free access to water and weighed. Body weight was measured using a digital scale. Then, the rats were anesthetized using light diethyl ether and the blood samples were withdrawn from the portal vein into dry clean centrifuge tubes. Blood serum was obtained by centrifuging blood samples at 3000 rpm for 10 min and stored in a deep freezer even used for biochemical analysis. Carefully, kidneys, liver and heart were taken away from the sacrificed animals and weighed. Then, the kidneys were prepared for histopathological study.

Biochemical Assay: The biochemical markers were assayed quantitatively in the serum of rats using Automatic biochemistry analyzer (Humastar 200, Wiesbaden Germany). Serum activities of glutamic pyruvic transaminase (SGPT), glutamic oxaloacetic transaminase (SGOT), gamma-glutamyl transferase (GGT) and alkaline phosphates (ALP) enzymes; and concentrations of albumin, total protein (TP) and total bilirubin (TBr) were analyzed using the instructions of commercial diagnostic kits (Diamond Co, Hannover, Germany) as indicators of liver functions. Blood urea nitrogen (BUN), serum creatinine (Cr) and uric acid (UA) levels were determined by using commercially obtainable test kits (Diamond Co, Hannover, Germany) as indicators of renal functions according to the methods of **Lamb and Jones, (2019)**.

Preparation of Kidney Tissues Homogenates: One gram of the frozen kidney samples was washed by ice-cold NaCl solution (0.9%). Then, samples were homogenized in 10 ml ice-cold phosphate buffer solution (pH: 7.4). The homogenates tissues were centrifuged at 4000 rpm for 15 min at 4°C and the supernatant was collected into sample bottles and kept on -80°C until analysis as described by **Oyedemi *et al.*, (2011)**.

Determination of Malondialdehyde and Actives of Antioxidant Enzymes in Kidney Tissues: The oxidative status in kidney tissues was evaluated by the determination of malondialdehyde (MDA) level, activates of catalase (CAT), superoxide dismutase (SOD) and reduced glutathione (GSH) enzymes as described by **Uchiyama and Mihara, (1978), Aebi, (1984), Nishikimi *et al.*, (1972)** and **Habig *et al.*, (1974)**, respectively.

Histopathological Examination: The kidney of scarified rats was taken and immersed in formalin solution (10%). Then, the specific specimens were trimmed, washed and dehydrated in ascending grades of alcohol. Specimens were then cleared in xylol, implanted in paraffin, sectioned at 4-6 microns thickness, and splotchy with Hematoxylin and Eosin stain for examination, according to **Bancroft and Stevens, (1996).**

Statistical Analysis: Statistical analysis of data was performed using one-way analysis of variance (ANOVA) using the Origin Lab (SPSS Ver. 20) software. The obtained results were expressed as mean ± standard deviation (mean ± SD). Significant differences among experimental groups were taken into account at $P < 0.05$.

Results

As shown in Table 2, gentamicin treated rats (NCG: positive rats) have a significant reduction ($P<0.05$) in final body weight (FBW) and relative body weight gain (RBWG), compared to that of the healthy control group (HCG: normal rats). Gentamycin-induced nephrotoxicity groups treated with aqueous extracts of cinnamon (NRTC) or stevia (NRTS) and/or their combination (NRTCS) showed significant higher in FBW and RBWG, compared to that of the NCG ($P<0.05$). However, NRTS had a significant reduction in FBW and RBWG, compared to that of the NRTC and NRTCS.

Table 2: Effect of AE of CSB, SL and their combination on body weight in nephrotoxicity rats.

Parameters / Groups	IBW (g)	FBW (g)	BWG (g)	RBWG (%)
Group (I): HCG	185.00 ± 0.71	227.80 ± 0.84^{a}	42.80 ± 0.84^{a}	23.14 ± 0.84^{a}
Groups II: NCG	185.80 ± 0.84	201.40 ± 0.55^{d}	15.60 ± 0.89^{d}	8.40±0.89^{d}
Groups III: NRTC	185.40 ± 0.55	225.00 ± 0.71^{b}	39.60 ± 0.55^{b}	21.38 ± 0.37^{b}
Groups IV: NRTS	185.80 ± 0.84	216.40 ± 0.55^{c}	30.60 ± 0.55^{c}	16.47 ± 0.39^{c}
Groups V: NRTCS	186.00 ± 0.71	225.40 ± 0.55^{b}	39.40 ± 0.98^{b}	20.75 ± 0.79^{b}

Means ± SD with the different letters superscripts in the same column are significant at $P < 0.05$. IBW = Initial body weight; FBW = Final body weight; BWG = Body weight gain; RBWG = Relative body weight gain; HCG = Healthy control group; NCG = Nephrotoxicity control group; NRTC = Nephrotoxicity rats treated with cinnamon; NRTS = Nephrotoxicity rats treated with stevia; NRTCS = Nephrotoxicity rats treated with cinnamon + stevia.

Comparing the relative organs weight of gentamicin-induced nephrotoxicity rats with those treated with the aqueous extracts of cinnamon, stevia and their combination is shown in Table 3. The tabled results revealed gentamicin induced significant ($P<0.05$) increase in relative liver and kidneys weight and there is no significant changes in relative heart weight to body weight, compared to that of normal rats. In contrast, the nephrotoxicity-treated rats with the aqueous extracts of cinnamon and stevia; and their combination caused significant ($P <0.05$) reduction in relative weight of liver, kidneys and heart to body weight, compared to that of the untreated positive rats. There was non-significant ($P<0.05$) changes in relative organs weight (liver, kidneys and heart) among nephrotoxicity–treated rats with aqueous extracts of cinnamon and the mixture of cinnamon with stevia.

To investigate the effect of gentamicin-induced nephrotoxicity and treated rats with aqueous extracts of cinnamon, stevia and their combination on liver function; the serum levels of SGPT, SGOT, GGT and ALP were

measured. The obtained results showed that liver enzymes were significantly elevated in nephrotoxicity rats, compared to that of the normal control rats. Treatment of nephrotoxicity rats by administration of aqueous extracts of cinnamon, stevia and their combination significantly ($P<0.05$) lowered serum activities of SGPT, SGOT, GGT and ALP enzymes, compared to that of untreated nephrotoxicity rats. Furthermore, by comparing the liver functions in both cinnamon-treated nephrotoxicity rats and stevia-treated rats, the present study found that cinnamon treated rats had a significantly prominent reduction in serum activities of SGPT, SGOT and ALP enzymes ($P<0.05$) as compared to that of the stevia-treated nephrotoxicity rats. In addition to, aqueous extracts combination of cinnamon with stevia ameliorates the elevated level in serum activities of SGPT, SGOT, GGT and ALP enzymes, compared to that of cinnamon or stevia alone (Table 4).

Table 3: Effect of AE of CSB, SL and their combination on relative organs weight in nephrotoxicity rats.

Parameters / Groups	Liver		Kidneys		Heart	
	Weight (g)	RW (%)	Weight (g)	RW (%)	Weight (g)	RW (%)
Group (I): HCG	5.90±0.16b	2.59±0.09 c	1.42±0.04b	0.62±0.01d	0.86±0.05a	0.38±0.03a
Groups II: NCG	6.66±0.27a	3.34±0.13a	1.62±0.08a	0.80±0.02a	0.72±0.04b	0.36±0.02a
Groups III: NRTC	6.04±0.11b	2.67±0.05bc	1.46±0.05b	0.65±0.01c	0.72±0.04b	0.32±0.01 b
Groups IV: NRTS	5.88±0.13b	2.72±0.05b	1.50±0.07b	0.69±0.01b	0.74±0.05b	0.33±0.01 b
Groups V: NRTCS	5.90±0.10b	2.62±0.05bc	1.44±0.05b	0.64±0.01c	0.74±0.05b	0.32±0.02 b

Means ± SD with the different letters superscripts in the same column are significant at $P < 0.05$. RW = Relative organ weight to body weight; HCG = Healthy control group; NCG = Nephrotoxicity control group; NRTC = Nephrotoxicity rats treated with cinnamon; NRTS = Nephrotoxicity rats treated with stevia; NRTCS = Nephrotoxicity rats treated with cinnamon + stevia.

Table 4: Effect of AE of CSB, SL and their combination on serum activities of liver enzymes in nephrotoxicity rats

Parameters / Groups	SGPT (U/L)	SGOT (U/L)	GGT (U/L)	ALP (U/L)
Group (I): HCG	77.80 ± 0.21d	129.34 ± 0.71 c	21.90 ± 0.42 c	129.30 ± 0.84d
Groups II: NCG	136.40 ± 0.55a	197.00 ± 0.61a	95.80 ± 0.27a	196.00 ± 1.00a
Groups III: NRTC	78.60 ± 0.42c	129.80 ± 0.76 c	24.00 ± 1.00b	130.40 ± 0.55c
Groups IV: NRTS	79.90 ± 0.26 b	132.50 ± 0.35b	24.20 ± 0.84b	132.40 ± 0.89b
Groups V: NRTCS	78.40 ± 0.55 c	129.20 ± 0.45 c	21.70 ± 0.54 c	128.60 ± 0.55d

Means ± SD with the different letters superscripts in the same column are significant at $P < 0.05$. SGPT = Serum activities of glutamic pyruvic transaminase; SGOT = Glutamic oxaloacetic transaminase; GGT = ɣ-glutamyl transferase; ALP = Alkaline phosphatase; HCG = Healthy control group; NCG = Nephrotoxicity control group; NRTC = Nephrotoxicity rats treated with cinnamon; NRTS = Nephrotoxicity rats treated with stevia; NRTCS = Nephrotoxicity rats treated with cinnamon + stevia.

As shown in Table 5, the results indicated that gentamicin caused significantly ($P<0.05$) decreases in serum levels of albumin and total protein (TP) and increased in total bilirubin (TBr), compared to that of the healthy rats. However, administration of aqueous extracts of cinnamon, stevia or their combination to nephrotoxicity rats caused significantly ($P<0.05$) ameliorates in the serum levels of albumin, TP and TBr. These changes tend to improved towards normal levels with normal rats when compared to that of the nephrotoxicity rats. By comparing the effect of aqueous extracts of cinnamon, stevia and their combination in treating nephrotoxicity rats, results showed that there are no significant changes in the serum levels of albumin, TP and TBr.

Effects of gentamicin and administration of aqueous extract of cinnamon and stevia; and their combination on the renal biomarkers are recorded in Table 6. The presented data showed that there was statistically

significant (P< 0.05) increase in the serum concentrations of BUN, Cr and UA (58.30±0.67, 1.46±0.11 and 5.76±0.25) respectively in gentamicin group, compared to that of the normal group (27.70±0.57, 0.67±0.02 and 2.64±0.22), respectively. While, there is a significant reduction in the serum levels of BUN, Cr and UA in nephrotoxicity rats treated with aqueous extract of both cinnamon and stevia; and their combination, compared to that of the untreated nephrotoxicity rats. In addition, comparison of different variables between nephrotoxicity rats treated with cinnamon and stevia, the present results showed that there was statistically non-significant (P<0.05) reduction of the two treated groups. In contrast, combination of cinnamon and stevia aqueous extract significantly reduced serum BUN as compared to administration stevia aqueous extract alone, and there was no significant reduction, compared to that of treated with cinnamon, while there are no significant changes in the serum levels of Cr and UA.

Table 5: Effect of AE of CSB, SL and their combination on serum albumin, TP and TBr concentrations in nephrotoxicity rats

Parameters / Groups	Albumin (g/dL)	TP (g/dL)	TBr (mg/dL)
Group (I): HCG	6.76±0.42a	12.81±0.65a	0.31±0.01b
Groups II: NCG	5.83±0.84b	10.37±0.84c	1.16±0.11a
Groups III: NRTC	6.70±0.79 a	12.52±0.91 b	0.38±0.03 b
Groups IV: NRTS	6.69±0.74 a	12.59±0.74b	0.38±0.03 b
Groups V: NRTCS	6.76±0.65 a	12.52±0.76 b	0.35±0.03 b

Means ± SD with the different letters superscripts in the same column are significant at P < 0.05. TP= Total proteins; TBr = Total bilirubin; HCG = Healthy control group; NCG = Nephrotoxicity control group; NRTC = Nephrotoxicity rats treated with cinnamon; NRTS = Nephrotoxicity rats treated with stevia; NRTCS = Nephrotoxicity rats treated with cinnamon + stevia.

Table 6: Effect of AE of CSB, SL and their combination on serum BUN, Cr and UA concentrations in nephrotoxicity rats

Parameters / Groups	BUN (mg/dl)	Cr (mg/dl)	UA (mg/dl)
Group (I): HCG	27.70 ± 0.57d	0.67 ± 0.02b	2.64 ± 0.22 c
Groups II: NCG	58.30 ± 0.67a	1.46 ± 0.11a	5.76 ± 0.25a
Groups III: NRTC	28.90 ± 0.89bc	0.69 ± 0.01 b	2.92 ± 0.08b
Groups IV: NRTS	29.50 ± 0.50b	0.69 ± 0.11 b	2.94 ± 0.09 b
Groups V: NRTCS	28.50 ± 0.50cd	0.68 ± 0.32 b	2.88 ± 0.10 b

Means ± SD with the different letters superscripts in the same column are significant at $P < 0.05$. BUN= Blood urea nitrogen; Cr = creatinine; UA = Uric acid; HCG = Healthy control group; NCG = Nephrotoxicity control group; NRTC = Nephrotoxicity rats treated with cinnamon; NRTS = Nephrotoxicity rats treated with stevia; NRTCS = Nephrotoxicity rats treated with cinnamon + stevia.

Administration effect of aqueous extract of cinnamon or stevia and their combination on kidney MDA, CAT, SOD and GSH in gentamicin-induced nephrotoxicity rats are showed in Table 7. It revealed that, gentamicin significantly elevated the MDA level and lower the activities of CAT, SOD and GSH enzymes in the kidney tissues, compared to that of the normal rats. While, treatment of nephrotoxicity rats with aqueous extract of cinnamon or stevia or their combination significantly ($P <0.05$) reduced the MDA level and increased activities of CAT, SOD and GSH enzymes in the kidney tissues, compared to that of untreated nephrotoxicity rats. These changes tend to be improved towards normal levels when compared to that of the nephrotoxicity group. Also, there are no significant ($P<0.05$) changes in the level of MDA and serum activities of CAT, SOD and GSH enzymes in the kidney tissues of nephrotoxicity rats treated with cinnamon and stevia

Table 7: Effect of AE of CSB, SL and their combination on MDA level and activates of CAT, SOD and GSH enzymes in kidney tissues in nephrotoxicity rats

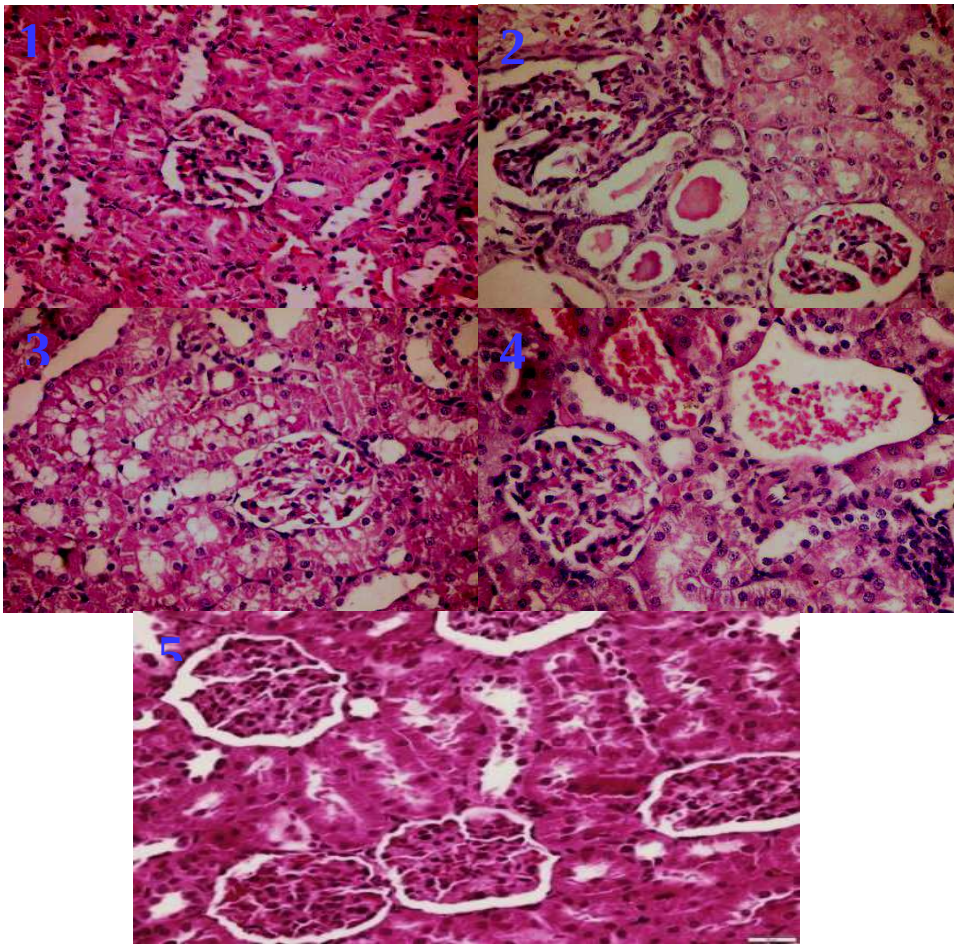
Parameters / Groups	MDA nmol/g tissues	CAT u/g tissues	SOD u/g tissues	GSH mg/ g tissues
Group (I): HCG	55.26 ± 0.34b	4.20 ± 0.27a	30.30 ± 0.45a	66.10 ± 0.74a
Groups II: NCG	118.70 ± 0.84a	1.80 ± 0.22b	16.00 ± 0.35b	34.50 ± 0.50c
Groups III: NRTC	55.10 ± 0.42 b	4.50 ± 0.35a	30.20 ± 0.27a	65.30 ± 0.76ab
Groups IV: NRTS	55.70 ± 0.27 b	4.20 ± 0.27a	30.20 ± 0.27a	64.90 ± 0.22b
Groups V: NRTCS	55.10 ± 0.42 b	4.60 ± 0.22a	30.60 ± 0.42a	65.62 ± 0.48ab

Means ± SD with the different letters superscripts in the same column are significant at $P < 0.05$. MDA = Malondialdehyde; CAT= catalase; SOD = superoxide dismutase; GSH = reduced glutathione; HCG = Healthy control group; NCG = Nephrotoxicity control group; NRTC = Nephrotoxicity rats treated with cinnamon; NRTS = Nephrotoxicity rats treated with stevia; NRTCS = Nephrotoxicity rats treated with cinnamon + stevia.

Histopathological examination of kidney

In gentamicin-induced nephrotoxicity rats and treated with aqueous extract of cinnamon or stevia and their combination, histopathology changes in kidney were examined. It showed that a taken light photograph by a microscope of kidney sections from normal rats observed no histopathological changes of glomeruli and renal tubules as shown in Picture 1. However, specify that gentamicin-induced nephrotoxicity showed noticeable structural changes of the kidney including thickening of glomerular basement membrane and dilatation of renal tubules with eosinophilic protein lost as shown in Picture 2. In contrast, administrations of aqueous extract of cinnamon or stevia to nephrotoxicity rats induced a partial improvement in renal tissues, which revealed as a slight congestion of renal blood vessels (Picture 3) and small focal leucocytes cells

aggregation (Picture 4), respectively. However, mixture of aqueous extract of cinnamon with stevia caused totally improvement in glomeruli and renal tubules as shown in Picture 5.



Picture 1: Photomicrograph of kidney sections from the normal rats showing apparently healthy glomeruli and renal tubules (H&E X 400).

Picture 2: Photomicrograph of kidney sections of gentamycin-induced nephrotoxicity rats (positive control) showing thickening of glomerular basement membrane and dilatation of renal tubules with eosinophilic protein lost (H & E X 200).

Picture 3: Photomicrograph of Kidney sections of treated gentamycin-induced nephrotoxicity rats with cinnamon aqueous extract showing slight congestion of renal blood vessels (H&E X 200).

Picture 4: Photomicrograph of Kidney sections of treated gentamycin-induced nephrotoxicity rats with stevia aqueous extract showing small focal leucocytes cells aggregation (H & E x 200).

Picture 5: Photomicrograph for kidneys sections of treated gentamycin-induced nephrotoxicity rats with the mixture of cinnamon with stevia aqueous extract showing apparently healthy glomeruli and renal tubules (H&E X 400).

Discussion

Drug-induced nephrotoxicity is one of the main common problems and can lead to kidney injury with the alterations in kidney structural and functional **(Khan *et al.*, 2011)**. Gentamicin (GM) is intensely used as an experimental typical for the induction of nephrotoxicity as it completely reflects the clinical findings. The purpose of the present work was to assess the potential nephroprotective activity of aqueous extract (AE) of cinnamon stem bark (CSB) and stevia leaves (SL) and/ or their combination in gentamicin-induced nephrotoxicity in rats.

In the present study, 10 days of GM intraperitoneal injection at a dose of 100 mg/kg b.wt significantly ($P<0.05$) lowered body weight gain and serum levels of albumin and total protein (TP). The decrease in body weight gain might be related to the increases in proteolysis and the reduced in protein synthesis as reported by **Adil *et al.*, (2016).** In the present study, the reduced in protein synthesis and the increased proteolysis are confirmed by the decrease in serum level of albumin and total proteins of gentamicin-treated rats. Also, GM significantly increased relative liver and kidneys weight. The increase of liver and kidney relative weight might be resulted from the edema that caused by GM-induced acute tubular necrosis. The obtained results agreed with **Dhodi *et al.*, (2015)** who reported that any toxic matter that provokes kidney tissue causing inflammatory response as well as its hypertrophy.

Co-treatment of AE of CSB or SL and their combination significantly ameliorated gentamicin's deleterious effects such as a decrease in body weight gain, serum total albumin and proteins, and the increase in liver and kidneys' relative weight. The present findings are consistent with earlier reports by **Atsamo *et al.*, (2021)** who mentioned that AE of CSB at the doses of 200 and 400 mg/kg significantly prevented the decrease of weight gain and the increase of relative kidney weight. It could be suggested that AE of CSB or SL and their combination prevents proteolysis or even potentiate protein synthesis. The hypothesis of inhibition of proteolysis is supported by the fact that AE of CSB or SL and their combination significantly prevented the drop in serum protein and albumin content induced by gentamicin. The plant extract as well as their combination significantly mitigated the liver and kidney hypertrophy. This may result from the anti-inflammatory potential of AE of CSB or SL and their combination. Interestingly, the two major constituents of CSB are cinnamaldehyde and eugenol. It has been completely notarized that they have various curative properties such as anti-inflammatory, antioxidative and nephroprotective effects (**Barboza et al., 2018**). In addition, **Gupta and Sparsh, (2019)** demonstrated that the antiinflammatory effect of the alcoholic extract of cinnamon stem bark was ascribed to trans-cinnamaldehyde components of cinnamon. Several studies have revealed the antiinflammatory properties of stevia and its components using both in vitro and in vivo models. For instance, **Latha *et al.*, (2017)** demonstrated that an alcoholic extract of SL can prohibit inflammation and lowered oxidative damage in the liver by altering the level of proinflammatory cytokines such as TNF-α, IL-1β and IL-6. Recently, **Casas-Grajales *et al.*, (2019)** reported that steviol glycosides present as an aglycone (steviol) in stevia leaves have anti-cancer, immunomodulatory and anti-inflammatory effects.

Serum activities of SGPT, SGOT, GGT and ALP enzymes and total serum bilirubin are the specific indicators of liver function. Administration of gentamicin caused significantly ($P<0.05$) increase in the serum activities of SGPT, SGOT, GGT and ALP enzymes and total serum bilirubin as an indicator of impairment of hepatic functions. The obtained results agreed

with **Rizwana *et al*., (2019**) who mentioned that administration of GM at a dose of 100 or 150 mg/kg b. wt significantly increased SGPT, SGOT, and total serum bilirubin in experimental animals. Also, **Masakazu *et al*., (2014)** reported that, despite the use of gentamicin as a therapeutic agent against infections, the longer period of use of gentamicin may encourage hepatorenal toxicity in about 30% of patients. The deterioration of liver functions might be correlated with increased production of reactive oxygen species (ROS), after the use of gentamicin, which is effective in inducing toxic impacts on the structure and function of tissues **(Wojciech and Vincent, 2005)**. In extension to that, **Nayma *et al*., (2014)** demonstrated that hepatocytes are hexagonal cell and have many metabolic enzymes. Liver cell damage may emerge these enzymes into plasma and can be used as an indicator in the statement of liver damage. GM is accountable for increased production of ROS associated with an increase in lipid peroxidation (LP) which takes place in the cell membranes. LP progresses an imbalance between oxidant and antioxidant status and essentially leading to cellular damage.

In addition, GM injection significantly increases the serum levels of blood urea nitrogen, creatinine and uric acid, which are indicated for renal necrosis and dysfunction. The present results were confirmed by the histopathological examination, which mentioned that GM induced thickening of glomerular basement membrane and dilatation of renal tubules with eosinophilic protein lost. The present results agreed with **Safa *et al*., (2010).** In addition to, **Rizwana *et al*., (2019)** reported that administration of 100 mg gentamicin/kg/day over a five-day to experimental animals significantly increased BUN, Cr and UA. The renal accumulation of a toxic metabolite of gentamicin could be leading to a sequence of biochemical responses that sustain kidney damage. **Ajami *et al*., (2010)** reported that the increase in free radicals production as a side effect of GM changes the filtration grade and area, so these factors might reduce the filtration in the glomerular resulting in aggregation of blood urea nitrogen, creatinine and uric acid in the serum and tissues. In reality, GM causes tubular deterioration through necrosis of tubular epithelial cells and amendment the

function of main cellular components participated in transport of water and solutes (**Randjelovi´c *et al*., 2017**). As indicated **Gupta and Sparsh, (2019)** that the renal toxicity of GM is due to its eclectic aggregation in the renal involutes tubules, which thence leads to the loss of the tubule safety, severe degradation, necrosis in epithelial cells of the proximal tubules, and infiltration of mononuclear cells in inter-tubular extent. The present findings confirmed that by oxidative stress activation as a major side effect of GM-induced nephrotoxicity. GM elicited a magnificent rise in the level of renal MDA with a significant reduction in CAT, SOD and GSH in the kidney tissues as an indicator for kidney deterioration. Some previous studies have indicated that an elevated level of lipid peroxidation (LPO) leads to tissue injury (**Reshi *et al*., 2020**). Antioxidative enzymes (CAT, SOD, GPx and GSH) are the responsible for weakening reactive molecules and protect kidney from oxidative damage (**Whidden *et al*., 2011**). In addition, **Sahu *et al*., (2014)** revealed that nephrotoxicity induced by GM was correlated to the mitochondrial dysfunction in renal tubular cells. It causes a marked impairment in the activity of mitochondrial respiratory enzymes, including NADH dehydrogenase resulting in the excessive ROS generation. In addition, **Paquette *et al*., (2015)** showed that GM stimulates O2– and NO• generation by the activation of inducible isoform of NO• synthase (iNOS) in kidney tissue. Reactive free radicals result in the lipid peroxidation, leading to the modulation in the arrangement of membrane lipid bilayer and reduction in the mechanisms of antioxidant defense, causing kidney cellular damage and necrosis.

The present study indicates that co-treatment with AE of CSB or SL and their combination shows a significant ($P<0.05$) amelioration in the serum activities of liver enzymes as well as serum levels of total bilirubin, BUN, Cr and UA. In addition to, the improvement in MDA level in kidney tissues accompanied by increased activities of all tested antioxidant enzymes (CAT, SOD, GPx and GSH) in the treatment groups. The present findings were also confirmed by histopathological examination of the kidney that showed rehabilitation cellular architect owing to robust antioxidant activity. These results may be elucidated that co-treatment of

AE of CSB or SL and their combination against GM-induced nephrotoxicity significantly reduced the renal toxicity. Based on these findings, the protective activities AE of CSB or SL and their combination may be through the ameliorating effect on antioxidative and its anti-inflammatory effects. Also, the nephroprotective activity of the ethanolic extract of cinnamon stem barks has been reported by **Ullah *et al.*, (2013)**. These results are in agreement with **Barboza et al., (2018)** who showed that the treatment with AE of CSB prevented the damage of renal tissues induced by gentamicin. Also, **Singh *et al.*, (2013)** indicated that stevia had the potential to increase the biosynthesis of GSH, which herewith reduces the oxidative stress and/or inhibit the formation of lipid peroxidation.

The cinnamon stem barks contain high amount of cinnamaldehyde, eugenol, and small amounts of 2′-hydroxycinnamaldehyde and 2′-benzoyloxycinnamaldehyde. Cinnamaldehyde as a phenolic component mostly detected as the main phytochemical presented in cinnamon bark and is responsible for the nearly of the biological effects of cinnamon (**Vangalapati *et al.*, 2012**). Several studies take in their suggested extracts and oils obtained from cinnamon have strong free radical scavenging or antioxidant activity related to the presence of flavonoids and polyphenolic compounds (**Khuwijitjaru *et al.*, 2012**). Recently, **Gupta and Sparsh, (2019)** observed that the nephroprotective effect of CSB might be due to the being of cinnamaldehyde and eugenol compounds. In the case of treatment with stevia, **Yesmine *et al.*, (2013)** showed that stevia significant protective effects against renal failure by reducing the serum creatinine level, blood urea, bilirubin, SGPT and SGOT levels. Antioxidant and anti-inflammatory effects of stevia may be related to its content of stevioside and rebaudioside, which are the main active components of stevia (**Ghaheri *et al.*, 2018**).

Conclusion

Results from the present study evidenced the nephroprotective effect of AE of CSB, SL and Their combination against GM toxicity and furthermore corroboration the use of these plants by populations in the management of kidney diseases. The nephroprotective effect of CSB or SL

is more probable by its antioxidant and anti-inflammatory properties. The combination of both CSB and SL might be a good candidate for protecting against nephrotoxicity effect.

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دراسة تأثير المستخلص المائي للحاء جذوع القرفة وأوراق الاستيفيا وخليطهما على السمية الكلوية التي يسببها الجنتاميسين في الفئران

امل فوزي الجزار*

المستخلص:

الهدف الأساسي من هذه الدراسة هو تقييم التأثيرالمحتمل للمستخلص المائي للحاء جذع القرفة وأوراق الستيفيا ومزيجهما ضد السمية الكلوية المُستحثة في الفئران. تم تقسيم الفئران إلي خمس مجموعات، تحتوي كل مجموعة علي خمس فئران. تم الاحتفاظ بالمجموعة الأولى كمجموعة ضابطة صحية. بينما تم حقن المجموعات الأربع الأخرى داخل الغشاء البرتوني بجرعة ١٠٠ مجم / كجم من وزن الجسم لمدة ١٠ أيام من الجنتاميسين لاحداث السمية الكلوية. تم معالجة الفئران في المجموعات ٣ و ٤ و ٥ يومياً بـ ٢٠٠ ملجم / كجم من وزن الجسم بالمستخلص المائي للقرفة واوراق الاستيفيا وخليطهما علي التوالي. أظهرت نتائج الدراسة ان الجنتاميسن تسبب بشكل كبير في ارتفاع الوزن النسبي للكبد والكلى وكذلك ارتفاع في مؤشرات سيرم الدم لوظائف الكبد والكلى. كما ادي إلي عدم التوازن في العوامل المؤكسدة لأنسجة الكلى، وكذلك التغيرات المورفولوجية في أنسجة الكلى مع انخفاض في وزن الجسم وإجمالي مستويات الألبومين والبروتين في الدم كمقارنة بالمجموعة الطبيعية. وعلي الجانب الاخر اظهرت نتائج المجموعات المصابة والمتناولة لكل من المستخلص المائي للقرفة واوراق الاستيفيا وخليطهما إلى تحسين جميع المؤشرات البيوكيميائية والتغيرات النسيجية المرضية وأنشطة الإنزيمات المضادة للأكسدة في أنسجة الكلى كمقارنة بالمجموعة المصابة والغير معالجة. كما أظهرت النتائج ان تناول الفئران المُصابه للمستخلص المائي للقرفة او خليط القرفة مع الاستيفيا إلي تحسين جميع المؤشرات المختبرة كمقارنة بتلك الفئران التي تناولت المستخلص المائي لاوراق الاستفيا وحده. في النهاية، أظهر العمل الحالي أن المستخلص المائي للقرفة واوراق الاستيفيا وخليطهما يحسن التغيرات في وظائف الكبد أو الكلى وعلامات الأكسدة في الكلى التي يسببها الجنتاميسين في الفئران. وبالتالي، يمكن استخدام القرفة والاستيفيا ضمن الخطة الغذائية لمرضى الكلى .

الكلمات المفتاحية: جنتاميسين، السمية الكلوية، وظائف الكبد، الانزيمات المضادة للأكسدة، الفحص الهستوباثولوجي، الاسيفيا، القرفة.

* قسم التغذية وعلوم الاطعمه – كلية الاقتصاد المنزلي – جامعة حلوان – القاهرة - مصر