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Nutraceutical Effects of Curcuma, Ginger, Celery, Yeast and Honey on Side Effects of Gentamicin Induced Nephrotoxicity in Rats

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Abstract: The study was carried out on 35 adult albino male rats Sprague-Dawley strain. 5 rats served as normal control group and 30 rats were injected with gentamicin (100 mg/kg/day for 7 days i.p) to induce renal damage. Then, rats reclassified into control positive group and 5 treated rat groups which administered curcuma, ginger, celery, yeast and honey. The treatment period was designed for eight weeks. The results revealed that, there was a significant increase in final weight, weight gain, weight gain percent, food intake, food efficiency ratio, protein efficiency ratio, hemoglobin, packed cell volume, serum total protein, globulin, calcium, erythropoietin hormone and vitamin D and serum and kidney superoxide dismutase, glutathione peroxidase and catalase antioxidant enzymes. There was a significant decrease in serum alanine and aspartate amino transferase and alkaline phosphatase enzymes activity, creatinine, urea, phosphor, sodium and potassium, pH and albumin to globulin ratio in all treated rat groups compared with control positive group. Rat groups which administered gentamicin with curcuma or celery or yeast showed a significant increase in protein intake and a significant decrease in rennin hormone while rat groups which administered gentamicin with curcuma or celery showed a significant increase in red blood cells but rat groups which administered gentamicin with celery and honey showed a significant decrease in white blood cells compared with control positive group. All treated rat groups revealed no histopathological changes. In conclusion, feeding rats with curcuma, ginger, celery, yeast and honey may significantly reduce nephrotoxicity.

Key words: Nephrotoxicity · Curcuma · Ginger · Celery · Yeast · Honey · Gentamicin · Rats

INTRODUCTION

Gentamicin belongs to a class of aminoglycoside antibiotics, is very effective antibiotic well suited to the treatment of severe infections and widely used in the treatment and prevention of Gram-negative bacterial infections [1]. Gentamicin, like other aminoglycosides, causes nephrotoxicity by inhibiting protein synthesis in renal cells. This mechanism specifically causes necrosis of cells in the proximal tubule, resulting in acute tubular necrosis which can lead to acute renal failure [2, 3]. This effect is related to duration of dose and the condition of the kidneys prior to treatment. Gentamicin can also be highly nephrotoxic, particularly if multiple doses accumulate over a course of treatment [4]. Nephrotoxicity is a major complication characterized by functional alterations including inhibition of protein synthesis, reduced glutathione depletion, lipid peroxidation and mitochondrial damage. Oxidative damage is thought to be one of the main mechanisms involved in nearly all chronic renal pathologies. Administration of gentamicin to rats induced a marked renal failure, characterized with a significant increase in plasma creatinine and urea concentrations. A significant increase in kidney MDA and a decrease in GSH concentrations were observed in gentamicin-treated rats [5]. The goal of reducing or protecting against aminoglycoside nephrotoxicity has attracted much effort and attention over the last decade. One means of protection is antioxidants [6]. The average diet contains a great number of antioxidant activities, such as polyphenols that are plant metabolites occurring widely in plant food and possess outstanding antioxidant and free radical scavenging properties [7, 8].

The aim of the present study was to evaluate and to compare the influence of curcuma, ginger, dried yeast, celery and honey on the side effects of gentamicin induced renal damage in rats.

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MATERIALS AND METHODS

Materials

Gentamicin: Gentamicin was purchased from El-Gomhoria Co., El-Mansoura city, Egypt. Gentamicin is given to rats in dose a 100 mg/kg/day for 7 days intraperitoneal for inducing renal damage according to previous studies as reported by Farombi and Ekor [9].

Natural Foods and Herbs: Curcuma powder (*Curcuma longa*), ginger powder (*Zingiber officinale*), celery (Apium graveolens rapaceum), yeast *(Saccharomyces cerevisiae)* and honey were obtained from the market of Ministry of Agriculture in Cairo city, Egypt. Celery was dried at hot oven then crushed to powder. Curcuma, ginger and celery were added to standard diet at 5% as constituents of fiber. Honey was added as instead of sucrose but yeast was added to standard diet as 50% of casein.

Experimental Animals: Thirty-five adult female rats of Sprague Dawely strain weighing 133 ± 8g were purchased from the Agricultural Research Center, Giza, Egypt.

Standard Diet: Standard diet was prepared according to NRC [10].

Methods

Experimental Rats Design: Rats were kept under observation for five days for adaptation and fed on standard diet. 5 rats served as normal control group and 30 rats were injected with gentamicin in dose a 100 mg/kg/day for 7 days intraperitoneal to induce renal damage which classified into control positive group and 5 treated rat groups that treated with curcuma, ginger, celery, yeast and honey. Food and water was provided *ad-libtum*. Food intake was recorded daily and body weight of rats was measured once weekly. At the end of the experimental period (eight weeks), the rats were anaesthetized by diethyl ether and sacrificed. Blood samples of each rat were withdrawn in two test tubes. The first was heparenized tube for estimation of some biochemical analysis and also to obtain blood pictures. The other tubes of blood were left for coagulation then centrifuged at 3000 rpm for 15 minutes to obtain serum for further analysis. Kidneys for every rat were collected. One kidney is used for antioxidant enzymes determination and the other was immersed in 10 % neutral buffered formalin as fixative and then sent to Pathological Department of Veterinary Medicine, Cairo University for histopathological examination.

Laboratory Analysis: Blood hemoglobin (HGB), packed cell volume (PCV), red blood cells (RBCs) and white blood cells (WBCs) were estimated according to Drabkin [11], MC Inory [12] and Cynthia *et al.* [13], respectively. Serum alanine and aspartate amino transferase (ALT and AST) and alkaline phosphatas (ALP) enzymes activity were performed according to the method of Bergmeyer and Horder [14] and Kind and King [15], respectively. Serum creatinine, urea, uric acid, total protein and albumin were enzymetically determined according to Bonsens and Taussky [16], Kanter [17], Fossati *et al.* [18], Henry [19] and Bartholomev and Delany [20], respectively. Superoxide dismutase (SOD), glutathione-peroxidase (GPX) and catalase (CAT) enzymes activity were determined by enzymatic colorimetric procedures in serum according to Dechatelet *et al.* [21], Habig *et al.* [22] and Sinha [23], respectively and in kidney according to Misra and Fridovich [24], Rotruck *et al*. [25] and Lueck [26], respectively. Serum Ca, P, Na and K were estimated according to Pupsa *et al.* [27]. Rennin and erythropoietin (EPO) renal hormones, vitamin D and pH were estimated according to Van-Kats *et al.* [28], Vale´rie *et al.* [29], Wilkie *et al.* [30] and Benjamin *et al.* [31], respectively.

Histopathological Examination: The fixed samples of kidney in 10 % neutral buffered formalin were cleared in xylol and embeded in paraffin 4-5 µm thick section and stained with Hematoxylin and Eosin (H and E) for subsequent histopathological examination [32].

Calculation of Some Parameters: Food efficiency ratio was determined according to the method of Chapman *et al.* [33]. Serum globulin value was determined according to Coles [34], while albumin/globulin (A/G) ratio was calculated according to the methods of Friedewald *et al.* [35].

Statistical Analysis: All the obtained data were statistically analyzed by SPSS computer soft ware. The calculated occurred by analysis of variance ANOVA and follow up test LSD by SPSS ver.11 according to Abo-Allam [36].

RESULTS

Nutritional Results: Data in Table 1 showed that the control positive rat group which administered gentamicin showed a significant decrease in final weight, weight gain, weight gain percent, food intake, food efficiency ratio (FER) and protein efficiency ratio (PER) ($P<0.01$ and 0.001) compared with normal control group.

Table 1: Nutritional indicators of normal control and renal damage rat groups treated with some natural foods and herbs

Groups			Variables							
			Initial weight (g)	Final weight(g)	Weight gain(g)	Weight gain(%)	Food intake(g)	FER	Protein intake(g)	PER
Normal control			134.55±7.14 ^{a}	186.85±14.89 ^{a}	52.34±5.37 ^{cd}	38.92±5.78 ^{c}	14.34±1.69 ^{a}	0.061±0.01 ^{a}	2.86±0.22^{b}	18.30±1.71^{a}
Renal damage	Control positive		135.63±8.45 ^{a}	150.61±11.77 ^{b**}	14.98±1.42 ^{e***}	11.04±1.81 ^{d***}	13.33±1.003 ^{a}	0.018±0.003^{e***}	2.66±0.13 ^{b}	15.63±0.43^{e***}
	Treated	Curcuma	134.61±8.37 ^{a}	195.80±13.09 ^{a}	61.21±4.10^{b*}	45.38±7.69 ^{b*}	16.31±2.56 ^{a}	0.062±0.003 ^{a}	3.26±0.19 ^{a*}	18.77±1.71^{a}
	groups	Ginger	135.01±17.99 ^{a}	181.60±18.19 ^{a}	46.61±6.62^{d}	34.58±6.21 ^{c}	14.87±1.69 ^{a}	0.052±0.002 ^{b*}	3.97±0.32 ^{b}	15.69±1.12^{b*}
		Celery	135.01±8.12 ^{a}	205.61±9.34 ^{a}	70.11±7.69^{a**}	53.73±5.60 ^{a**}	16.96±1.19 ^{a}	0.068±0.003 ^{a}	3.39±0.33 ^{a*}	20.68±2.11^{a}
		Yeast	134.81±8.32 ^{a}	189.41±16.29^{a}	54.6±9.99^{cd}	42.05±8.15^{b*}	15.94±1.35^{a}	0.057±0.004 ^{b*}	3.18±0.32^{a*}	17.16±1.16^{a}
		Honey	134.41±7.37^{a}	191.80±18.64^{a}	57.41±9.19 ^{cd}	42.70±5.81^{b*}	14.23±2.63^{a}	0.067±0.001 ^{a}	2.84±0.13 ^{b}	20.21±2.11^{a}

Each value is the mean ±SD

Significant with normal control group * P < 0.05 * * P < 0.01 * * * P < 0.001

Mean values in each column having different superscript (a, b, c and d) are significantly different at P <0.05

Table 2: Blood levels of HGB, RBC_s, PCV and WBC_s in control and renal damage rat groups treated with some experimental natural foods and herbs

Groups			Variables			
			HGB	RBCs	PCV	WBCs
Normal control			10.66±0.20 ^{a}	4.10±0.14 ^{a}	32.33±3.14^{a}	8701±122.67^{a}
Renal damage	Control positive		8.94±0.03 ^{c**}	3.51±0.17 ^{b*}	27.60±2.11 ^{b**}	1060±126.41 ^{c***}
	Treated groups	Curcuma	10.43±0.01 ^{a}	4.08±0.08 ^{a}	32.40±4.61 ^{a}	1030±155.36 ^{c***}
		Ginger	9.85±0.01 ^{b*}	3.64±0.11 ^{b*}	31.42±3.60 ^{a}	1020±147.21 ^{c***}
		Celery	10.58±0.55 ^{a}	4.14±0.11 ^{a}	35.36±3.21 ^{a}	6560±154.77 ^{b*}
		Yeast	10.07±0.01 ^{a}	3.44±0.27 ^{b*}	31.47±2.26 ^{a}	1220±147.21 ^{c***}
		Honey	10.17±0.03 ^{a}	3.71±0.12 ^{b*}	32.45±4.31 ^{a}	8200±147.21 ^{a}

Each value is the mean ±SD

Significant with normal control group * P < 0.05 * * P < 0.01 * * * P < 0.001

Mean values in each column having different superscript (a, b, c and d) are significantly different at P <0.05

The rat groups which administered gentamicin with curcuma or celery showed a significant increase (P<0.05) in weight gain, weight gain percent and protein intake while the rat group which administered gentamicin with ginger showed a significant decrease in FER and PER (P<0.05) compared with normal control group. The rat group which administered gentamicin with yeast showed a significant decrease (P<0.05) in FER and increase in weight gain and protein intake while the rat group which administered gentamicin with honey showed a significant increase (P<0.05) in weight gain (%) compared with normal control group. There was a significant increases in final weight, weight gain, weight gain percent, FER and PER in rat groups which administered gentamicin with tested food and herbs compared with control positive group. There was a significant increase protein intake in rat groups which administered gentamicin with curcuma or celery or yeast compared with control positive group.

Biochemical Analysis: Data in Table 2 showed that the control positive rat group showed a significant decrease in blood levels of hemoglobin (HGB), red blood cells (RBC_s), packed cell volume (PCV) and white blood cells (WBC_s) (P< 0.05 and 0.01 and 0.001) compared with normal control group. The rat groups which administered gentamicin with curcuma or celery showed a significant decrease (in WBC_s P< 0.001 and 0.05) while the rat group which administered gentamicin with ginger showed a significant decrease in blood levels of HGB, RBC_s and WBC_s (P<0.05 and 0.001) compared with normal control group. The rat group which administered gentamicin with yeast showed a significant decrease in RBC_s and WBC_s (P<0.05 and 0.001) but the rat group which administered gentamicin with honey showed a significant decrease (P<0.05) in RBC_s compared with normal control group. There was a significant increase in HGB and PCV in rat groups which administered gentamicin with tested food and herbs compared with control positive group. There was a significant increase in red blood cells (RBC_s) in rat groups which administered gentamicin with curcuma or celery and also significant increase in WBC_s in rat groups which administered gentamicin with celery and honey compared with control positive group.

Table 3: Effect of experimental natural foods on AST, ALT and ALP of control and renal damage rat groups at the end of study

Groups			Variables: AST(µ/ml)	ALT(µ/ml)	ALP(µ/ml)
Normal control			32.41±3.51 [b]	13.62±2.70 [c]	82.41±12.50 [b]
Renal damage	Control positive		59.11±2.11 [a***]	30.20±3.70 [a***]	114.4±17.50 [a***]
	Treated groups	Curcuma	17.36±2.11 [d***]	18.43±1.52 [b*]	84.31±11.33 [b]
		Ginger	37.51±4.30 [b]	12.43±2.07 [c]	83.66±12.70 [b]
		Celery	15.6±2.19 [d***]	19.21±2.92 [b*]	83.67±11.52 [b]
		Yeast	21.6±4.14 [c*]	19.44±1.58 [b*]	99.20±16.20 [b]
		Honey	37.21±3.58 [b]	18.36±1.58 [b*]	96.36±17.12 [b]

Each value is the mean ±SD

Significant with normal control group * P < 0.05 * * P < 0.01 * * * P < 0.001

Mean values in each column having different superscript (a, b, c and d) are significantly different at P <0.05

Table 4: Effect of tested natural foods on some renal functions parameters of control and renal damage rat groups

Groups			Variables: Creatinine (mg/dl)	Urea (mg/dl)	Uric acid (mg/dl)	Total protein (g/dl	Albumin (g/dl)	Globulin (g/dl)	A/G ratio
Normal control			0.51±0.07 [c]	36.42±4.51 [b]	3.21±0.16 [b]	7.92±0.62 [a]	3.54±0.27 [a]	4.38±0.68 [a]	0.80±0.01 [c]
Renal damage	Control positive		2.62±0.08 [a***]	77.42±4.93 [a***]	6.92±1.57 [a***]	4.95±1.14 [b**]	3.12±0.63 [a]	1.83±0.11 [c***]	1.70±0.12 [a**]
	Treated groups	Curcuma	0.65±0.15 [b*]	40.81±7.12 [b]	6.53±0.9 [a***]	6.53±0.96 [a]	3.41±0.51 [a]	3.12±0.25 [b*]	1.09±0.15 [b*]
		Ginger	0.57±0.05 [c]	39.4±3.51 [b]	3.33±0.1 [b]	6.86±0.38 [a]	3.74±0.11 [a]	3.12±0.35 [b*]	1.19±0.16 [b*]
		Celery	0.61±0.20 [b*]	39.22±6.20 [b]	3.06±0.72 [b]	6.68±1.23 [a]	3.58±1.63 [a]	3.10±0.24 [b*]	1.15±0.14 [b*]
		Yeast	0.68±0.08 [b*]	32.12±1.01 [bc]	3.22±0.01 [b]	7.08±0.91 [a]	3.52±0.0 [a]	3.56±0.52 [b*]	0.98±0.02 [b*]
		Honey	0.55±0.04 [c]	30.13±3.58 [bc]	3.14±0.11 [b]	6.66±0.11 [a]	3.48±0.08 [a]	3.18±0.43 [b*]	1.09±0.45 [b*]

Each value is the mean ±SD

Significant with normal control group * P < 0.05 * * P < 0.01 * * * P < 0.001

Mean values in each column having different superscript (a, b, c and d) are significantly different at P <0.05

Data in Table 3 showed that the control positive rat group showed a significant increase in AST, ALT and ALP (P< 0.001) compared with normal control group. The rat groups which administered gentamicin with curcuma or celery, or yeast showed a significant decrease in AST and a significant increase in ALT (p< 0.001 and 0.05) but the rat group which administered gentamicin with honey showed significant increase in ALT (P< 0.05) compared with normal control group. There was a significant decrease AST, ALT and ALP in rat groups which administered gentamicin with tested food and herbs compared with control positive group.

Data in Table 4 showed that the control positive rat group showed a significant increase in creatinine, urea, uric acid and A/G ratio (P< 0.01 and 0.001) and showed a significant decrease in total protein and globulin (P< 0.01 and 0.001) but showed non significant decrease (P> 0.05) in albumin compared with normal control group. The rat group which administered gentamicin with curcuma showed a significant increase (P< 0.05 and 0.001) in creatinine, uric acid and A/G ratio and a significant decrease (P< 0.05) in globulin while the rat group which administered gentamicin with ginger or honey showed a significant decrease (p <0.05) in globulin and a significant increase (P< 0.05) in A/G ratio compared with normal control group. The rat group which administered gentamicin with celery or yeast showed a significant increase (P< 0.05) in creatinine and A/G ratio and a significant decrease (P< 0.05) in globulin compared with normal control group. There was a significant decrease in creatinine, urea and A/G ratio and a significant increase in total protein and globulin in rat group which administered gentamicin with tested food and herbs compared with control positive group.

Data in Table 5 showed that the control positive rat group showed a significant decrease in SOD, GPX and CAT (P< 0.01 and 0.001) in serum and kidney compared with normal control group. The rat group which administered gentamicin with curcuma or ginger showed a significant decrease in serum SOD, GPX and CAT and also kidney SOD and GPX (P< 0.05 and 0.01) while the rat group which administered gentamicin with celery showed a significant decrease (P< 0.05 and 0.01) in both serum and kidney SOD and GPX compared with normal control group. The rat group which administered gentamicin with yeast showed a significant decrease in SOD, GPX and CAT and kidney GPX (P< 0.05 and 0.01) while the rat group which administered gentamicin with honey showed significant decrease in serum SOD and kidney GPX (P< 0.05) compared with normal control group. There was a significant increase in serum and kidney antioxidant enzymes (SOD, GPX and CAT) in rat groups which administered gentamicin with tested food and herbs compared with control positive group.

Table 5: Effect of experimental natural foods on SOD, GPX and CAT in serum and kidney of control and renal damage rat groups

Groups			Variables: Serum antioxidant enzymes (μ/ml) SOD	GPX	CAT	Kidney antioxidant enzymes (μ/mg) SOD	GPX	CAT
Normal control			0.53±0.03 ^{a}	0.88±0.04 ^{a}	1.49±0.12 ^{a}	2.21±0.38 ^{a}	1.06±0.13 ^{a}	3.78±0.53 ^{a}
Renal damage	Control positive		0.21±0.02 ^{c***}	0.30±0.07 ^{d***}	0.67±0.04 ^{c***}	1.09±0.15 ^{c**}	0.49±0.03 ^{c***}	1.99±0.05 ^{b**}
	Treated groups	Curcuma	0.37±0.01 ^{b*}	0.62±0.01 ^{b*}	0.86±0.02 ^{b*}	1.59±0.07 ^{b*}	0.76±0.06 ^{b*}	2.86±0.20 ^{a}
		Ginger	0.39±0.05 ^{b*}	0.41±0.02 ^{c**}	0.80±0.12 ^{b**}	1.34±0.07 ^{b*}	0.54±0.18 ^{d*}	2.31±0.43 ^{a}
		Celery	0.31±0.03 ^{b*}	0.44±0.07 ^{c**}	1.01±0.02 ^{a}	1.35±0.36 ^{b*}	0.62±0.15 ^{c*}	2.92±0.08 ^{a}
		Yeast	0.38±0.13 ^{b*}	0.45±0.08 ^{c**}	0.89±0.08 ^{b*}	1.99±0.05 ^{a}	0.57±0.05 ^{d**}	2.45±0.53 ^{a}
		Honey	0.39±0.01 ^{b*}	0.72±0.10 ^{a}	1.11±0.02 ^{a}	1.74±0.34 ^{a}	0.78±0.05 ^{b*}	2.19±0.08 ^{a}

Each value is the mean ±SD

Significant with normal control group * P < 0.05 * * P < 0.01 * * * P < 0.001

Mean values in each column having different superscript (a, b, c and d) are significantly different at P <0.05

Table 6: Effect of tested natural foods and herbs on serum Ca, P, Na and K of control and renal damage rat groups

Groups			Variables: Ca (mg/dl)	P (mg/dl)	Na (mg/dl)	K (mg/dl)
Normal control			9.36±1.80 ^{a}	3.82±0.98 ^{c}	506.40±119.70 ^{b}	47.72±3.87 ^{b}
Renal damage	Control positive		6.27±0.81 ^{b**}	7.06 ±0.91 ^{a***}	700.06±94.41 ^{a**}	61.78±9.40 ^{a***}
	Treated groups	Curcuma	8.17±1.92 ^{a}	5.82±0.35 ^{b*}	551.82±30.97 ^{b}	40.36±3.64 ^{b}
		Ginger	8.95±1.21 ^{a}	3.94±0.15 ^{c}	518.38±25.57 ^{b}	30.82±1.71 ^{c**}
		Celery	8.78±1.65 ^{a}	4.88±0.18 ^{c}	549.14±44.93 ^{b}	38.64±4.85 ^{b}
		Yeast	9.24±1.07 ^{a}	5.02±0.26 ^{b*}	483.38±36.65 ^{b}	48.26±2.05 ^{b}
		Honey	9.46±0.25 ^{a}	5.06±0.15 ^{b*}	504.94±26.12 ^{b}	29.94±0.15 ^{c**}

Each value is the mean ±SD

Significant with normal control group * P < 0.05 * * P < 0.01 * * * P < 0.001

Mean values in each column having different superscript (a, b, c and d) are significantly different at P <0.05

Table 7: Effect of tested food and herbs on serum rennin, EPO, vitamin D and pH of control and renal damage rat groups

Groups			Variables: Rennin (ng/ml/h)	EPO (ng/ml/h)	vitamin D (nmol/L)	pH
Normal control			2.01± 0.21 ^{b}	4.14±0.44 ^{a}	56.64± 3.20 ^{a}	7.71± 0.36 ^{b}
Renal damage	Control positive		4.21±0.27 ^{a**}	1.06± 0.11 ^{c**}	29.78±0.45 ^{d***}	10.03±0.25 ^{a***}
	Treated groups	Curcuma	2.92± 0.45 ^{b}	2.36± 0.09 ^{b*}	54.12± 2.83 ^{a}	5.32± 0.94 ^{c*}
		Ginger	1.65± 0.29 ^{c*}	3.08±0.04 ^{b*}	47.74± 3.22 ^{b*}	7.13± 0.75 ^{b}
		Celery	1.93± 0.10 ^{c*}	2.97±0.06 ^{b*}	43.32± 3.28 ^{b*}	7.86± 0.65 ^{b}
		Yeast	2.41± 0.27 ^{b}	2.55±1.26 ^{b*}	38.42±21.74 ^{b*}	6.26± 1.46 ^{b}
		Honey	3.95± 0.13 ^{a*}	2.55± 0.56 ^{b*}	33.06± 0.71 ^{c**}	4.78± 0.55 ^{c*}

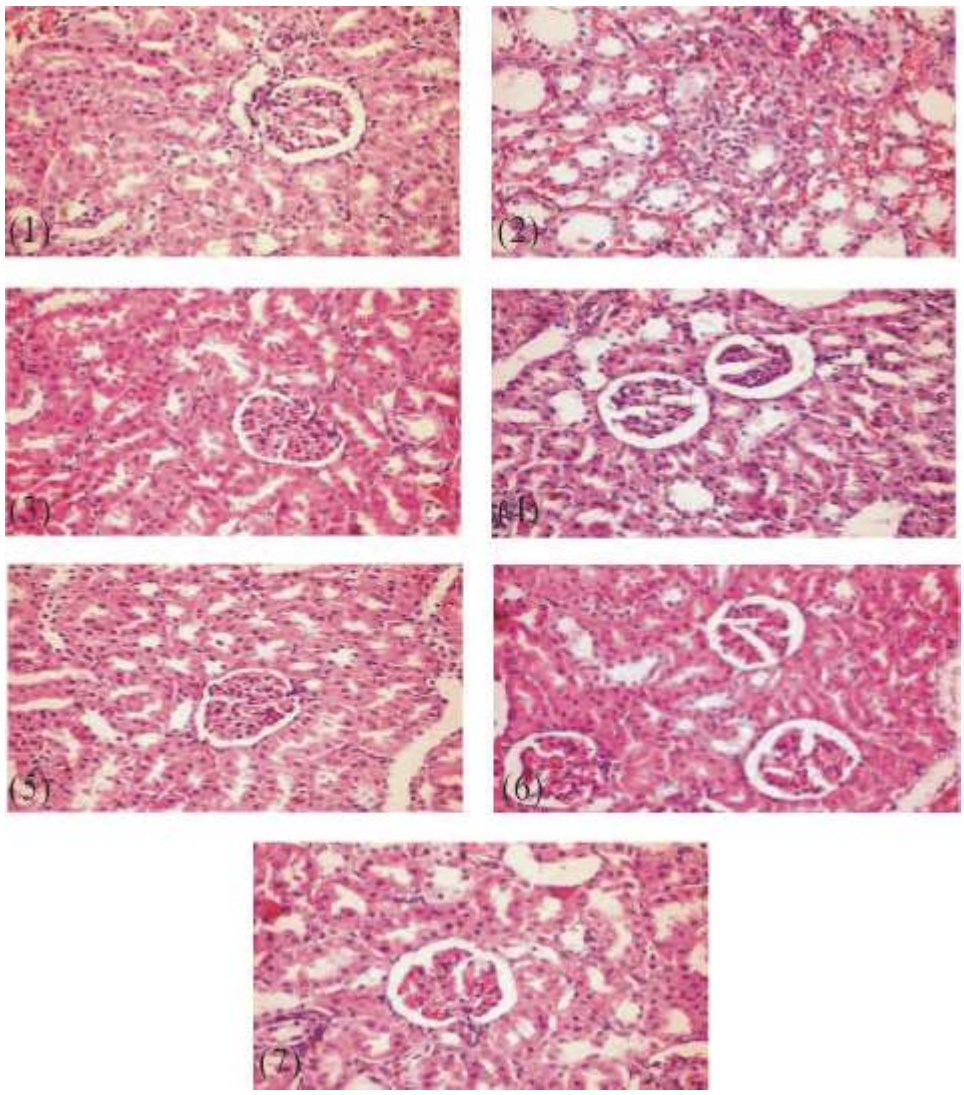
Each value is the mean ±SD

Significant with normal control group * P < 0.05 * * P < 0.01 * * * P < 0.001

Mean values in each column having different superscript (a, b, c and d) are significantly different at P <0.05

Data in Table (6) showed that the control positive rat group showed a significant decrease in serum Ca (P< 0.01) and a significant increase in serum P, Na and K (P< 0.01 and 0.001) compared with normal control group. The rat group which administered gentamicin with curcuma showed a significant increase in serum P (P< 0.05) while the rat group which administered gentamicin with ginger showed a significant decrease in serum K (P<0.01) compared with normal control group. The rat group which administered gentamicin with yeast showed a significant increase in serum P (P< 0.05) while the rat group which administered gentamicin with honey showed a significant increase in serum P (P<0.05) and significant decrease in K (P< 0.01)compared with normal control group. There was a significant increase in serum calcium (Ca) and significant decrease in phosphorus, sodium and potassium in rat groups which administered gentamicin with tested food and herbs compared with control positive group.

Data in Table 7 showed that the control positive rat group showed a significant decrease in serum EPO and vitamin D (P< 0.01 and 0.001) and a significant increase in serum rennin and pH (P< 0.01 and 0.001) compared with normal control group. The rat group which administered gentamicin with curcuma showed a significant decrease in serum EPO and pH (P< 0.05) while the rat group which



Pics. 1-7:

administered gentamicin with ginger or celery showed a significant decrease in serum rennin, EPO and vitamin D ($P< 0.05$) compared with normal control group. The rat group which administered gentamicin with yeast showed a significant decrease ($P< 0.05$) in serum EPO and vitamin D while the rat group which administered gentamicin with honey showed significant decrease ($P< 0.05$ and 0,01) in serum EPO, vitamin D and pH and showed a significant increase ($P< 0.05$) in serum rennin hormone compared with normal control group. There was a significant increase in EPO hormone and vitamin D and a significant decrease in serum pH in rat groups which administered gentamicin with tested food and herbs compared with control positive group. There was a significant decrease in rennin hormone in rat groups which administered gentamicin with curcuma or ginger or celery or yeast compared with control positive group compared with control positive group.

Kidney Histopathological Results: Microscopically, kidney of control negative rat revealed the normal histopathological structure of renal parenchyma (pict.1). Meanwhile, kidney of rat from control positive rat group showed vacuolations of renal tubular epithelium, congestion of intertubuler blood vessels, focal tubular necrosis associated with leucocytic cells infiltration (pict. 2). Kidney of rat from group administered gentamicin with curcuma or ginger or celery or yeast or honey revealed no histopathological changes (pict. 3, 4, 5, 6 and 7).

DISCUSSION

Our results of gentamicin side effects either nutritional or biochemical were reported by several researchers. It has been demonstrated that gentamicin reduced cellular protein synthesis after 2 d of treatment. This inhibition increased to 50% on the third day. Total cellular proteins synthesis was inhibited to the same extent as brush border membrane protein synthesis. Inhibition of phospholipid degradation was quantitatively the major contributor to the effects of gentamicin on phospholipid metabolism. The inhibition of phospholipases activities accumulates phospholipids and formation of lysosomal myeloid bodies [1, 37]. Gentamicin inhibits mitochondrial respiration and Ca^{2+} transport or lipid peroxidation that causes irreversible cell damage. Gentamicin was shown to chelate mitochondrial iron to catalyze the formation of free oxygen radicals, forming a very oxidant Fe (II)-gentamicin complex capable of causing cell death [38, 39]. Administration of gentamicin induced a marked renal failure, characterized with a significant increase in plasma creatinine and urea concentrations. A significant increase in kidney MDA and a decrease in glutathion concentrations were observed in gentamicin treated rats and severe proximal renal tubular necrosis followed by renal failure [4, 5].

Many studies have focused on the effects of gentamicin nephrotoxicity that associated with hypocalcemia, hyperkalemia and hyperphosphatemia due to decreased glomerular filtration rate. Alterations in sodium depend on the amount of urine production. Acute renal failure present with hypernatremia due to decreased glomerular filtration rate and excess uremic acids as the products of protein metabolism are unable to be adequately excreted. Bicarbonate ions buffer by converting to salts of the excess organic acids. The decrease in bicarbonate along with the increase in unmeasured ions (uremic acids) results in metabolic acidosis [40, 41]. Activation of the renin angiotensin system appears to be primarily responsible for the decrease in glomerular filtration [42]. Recent studies suggest healthy benefits associated with several natural herbs. Curcumin (diferuloylmethane), an active ingredient of turmeric, obtained from the powdered rhizomes of *Curcuma longa* Linn. Curcumin is claimed to be a potent anti-inflammatory and antioxidant agent. In addition, it is a powerful scavenger of the superoxide anion, hydroxyl radicals and nitrogen dioxide and protects DNA against singlet oxygen-induced strand breaks [43]. Turmeric has hepatoprotective and nephroprotective effects of pharmaceutical drugs as cisplatin or doxorubicin-induced nephrotoxicity that improves creatinine and urea clearance as well as uric acid and protects the chronic renal allograft nephropathy. These beneficial effects have been explained by the induction of antioxidative enzymes [44, 45].

Zingiber officinalis is widely used as culinary herb and herbal remedy for some common ailments. The volatile oil of ginger contains monoterpenes, sesquiterpenes and sesquiterpene alcohol zingiberol, gingerol and shagoals. Gingerols have cardio tonic analgesic, anti-inflammatory; antipyretic [46]. Shagoal is also used for conditions such as anti-oxidant and antihepatotoxic activities [47, 48]. Dried fresh juice extract of *Zingiber officinale* along with gentamicin normalized the gentamicin-induced increase in serum creatinine, serum uric acid and blood urea nitrogen and serum urea levels. Ethyl acetate extract and dried fresh juice of fresh rhizomes of Z. officinale extracts possess a significant nephroprotective activity and significantly protect rat kidneys from gentamicin-induced histopathological changes [49]. *Z. officinale* extracts contain phytoconstituents-flavonoids which could enhance renal mitochondrial antioxidant system, thereby protecting against gentamicin nephrotoxicity [50]. Ethanol extract of *Z. officinale* alone and in combination with vitamin E partially ameliorated cisplatin-induced nephrotoxicity as the activities of SOD, CAT GPx and level of GSH were elevated and level of MDA declined significantly. This protection is mediated either by preventing the cisplatin-induced decline of renal antioxidant defense system [51].

Because of the significant amount of bioactive compounds in celery as rich source of vitamin C, phalides and coumarins which can offer multiple unique health benefits. Celery also contains a variety of various minerals and nutrients such as tryptophan, folate, dietary fiber, molybdenum, manganese, phosphorus, calcium, magnesium, iron and vitamins B6, B1, B2 and A. Celery contains a large amount of vitamin C which is antioxidant to prevent the free radical damage that triggers the inflammatory cascade. Thus, it helps reduce the severity of inflammatory conditions [52]. Celery is a natural electrolyte balance and also helps to drain uric acid out of the system. Because of diuretic action upon the kidneys that assists in the elimination of toxins and excess fluid. Celery roots and leaves juices influenced the examined biochemical parameters and showed protective effects when applied with doxorubicine [53].Yeast is traditionally used as a source of vitamin B, selenium and chromium, especially by vegetarians. Clinical trials have evaluated yeast for a role in immunomodulation, respiratory infections, prevention of post surgical infections and as

a source of dietary fiber to improve the lipid profile [54]. *S. cerevisiae* serves as an abundant source of the protein and B-complex vitamins except vitamin B_{12} and these vitamins help break down carbohydrates, fats and proteins, which provide the body with energy. They also support the nervous system; help maintain the muscles used for digestion and keep skin, hair, eyes, mouth and liver healthy. Minerals provided by brewer's yeast include selenium, chromium and zinc. Additionally, the cell wall of yeast provides a better source of beta-glucan fiber [55]. Studies have also focused on selenium-and chromium-enriched yeast preparations used in diabetes and cancer patients [56]. Chromium may lower blood sugar levels as well, improving glucose tolerance. Chromium may help reduce body fat lesser than exercise so it may help maintain a healthy weight [57]. *S. cerevisiae*-derived beta-glucan has been shown to enhance neutrophil antimicrobial functions *in vitro* and in animal studies and to reduce staphylococcal abscess formation. Yeast has effective role on lowering the side effects of anti rheumatic drug. Serum triacylglycerol, total cholesterol was decreased in a study among 15 obese hypercholesterolemic men, as well as improvements in the glucose tolerance test [58, 59]. Administration of honey significantly prevented rise in the levels of serum creatinine, blood urea and plasma MDA as compared to the gentamicin treated group. It also significantly prevented the histological damage caused by gentamicin [60]. The protective effect of honey may be mediated through sulfhydryl-sensitive processes and it may also possess antioxidant properties. It is also suggested that endogenous sulfhydryl may facilate and mediate beneficial effects of gastroprotective and antioxidant drugs [61]. Honey is dermoprotective activity and protect the stomach of the rat against ethanol-induced increased vascular permeability, which may be correlated with the ascorbic acid content [62,63]. Consumption of these tested herbs and food improve the biochemical and histopathological results in gentamicin nephrotoxicity. It is recommended to consume curcuma, ginger, celery, yeast and honey as sources of antioxidant to reduce and protect nephrotoxicity. This preliminary study needs further investigation before the herbs can be used as an adjunct to pharmacological therapy.

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