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Full Length Research Paper

Investigation of antihypertensive effect of Nigerian varieties of *Solanum lycopersicon* on rats

Celestine O. Ani[1*], Agu U. Francis[2], Nworgu C. Chinemerem[2] Uzoigwe U. Jide[2], Okorie O. Pamela[2], Adugba O. Augustine[3], Ediale R. Joshua[3], Egharevba E. Jovita[2], and Nwachukwu C. Daniel[2]

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Hypertension remains a global challenge even in the 21st century with attendant increase in mortality rate. The quest for alternative management medications suffixed this investigation using three varieties. Thirty male hypertension induced wistar rats divided into 6 groups of 5 rats each were used. Group A served as the normal control group and was administered 0.9% normal saline as placebo. Group B, C and D were fed with Jos, UTC, Gboko varieties, respectively. Group E was treated with lisinopril at 2.5 mg/kg orally, while group F served as the hypertensive untreated group. Administration lasted for 28 days and all animals were allowed access to food and water ad libitium. Standard methods of non-invasive blood pressure assessment was used to access systolic blood pressure, diastolic blood pressure, heart rate, while the lipid panel was assessed using Cardiocheck test meter (lipidocare) in all the groups. ANOVA was used to analyze data and probability level of $p<0.05$ considered significant. Results show that rats given Jos and UTC tomatoes performed better as compared to those given Gboko tomatoes but the 3 groups did less well as compared to the Lisinopril group. Groups A and F, the Normotensive and hypertensive controls remained status quo. Groups B and C also did better in having an improvement in the lipid profile, as compared to all the other groups. All these indices put together suggest that the Jos and UTC varieties of tomatoes show a better antihypertensive effect as compared to the Gboko variety and could be used in the management of hypertension owing to the presence of high concentration of antioxidants in them. And if these results are applicable to man, the consumption of Jos and UTC varieties of tomatoes should be encouraged.

Key words: Tomatoes, systolic blood pressure, diastolic blood pressure, heart rates, lipid profile.

INTRODUCTION

Hypertension is defined as a persistent increase in blood pressure of >140 mmHg (systolic) and or ≥ 90 mmHg (diastolic) (Onwubere et al., 2012). Not less than 46.4% Nigerian over 15 years of age has hypertension'' (Ogah et al., 2012) and it is positively and independently associated with high morbidity and mortality rates in Africa (Ediale, 2011). Hypertension and overweight places an excessive financial burden on population and health systems consuming a scarce resources and thus places a lot of economic burden on the individual, loss of productivity and pre-mature death at younger age (Macmahon et al., 2005). Hypertension remains a global challenge even in the 21st century with attendant increase mortality rate. Considering the uncomfortable

side effects of antihypertensive drugs and the fact that many hypertensive patients need more than two kinds of drugs per day, alternative and supplementary treatment for blood pressure control has been suggested such as life style modification, especially dietary intervention. Thus, the quest for alternative management medications suffixed our investigation using different varieties of *Solanum lycopersicon* (tomatoes) commonly consumed within Makurdi, Benue State, Nigeria. Tomatoes outside its juiciness and rich flavor are quietly gaining a place in the prevention and management of hypertension. This attribute is suggestive of the presence of lycopene, potassium, beta carotene and antioxidants in tomatoes (Xinli and Jiuhong, 2013).

Tomatoes play an active role in the management of hypertension, coronary heart disease, Ischemic stroke, type II diabetes and certain diseases. Worldwide, about 58% of diabetic mellitus and 21% of Ischemic heart disease are attributed to high blood pressure (Onwubere, 2012). Blood pressure (BP) is the pressure exerted by circulating blood upon the walls of blood vessels and is one of the principal vital signs. During each heartbeat, blood pressure varies between maximum (systolic) and minimum (diastolic) pressure. The mean BP, due to pumping by the heart and resistance to flow in the blood vessels decreases as the circulating blood moves away from the heart. Though that of healthy adult human is 120 (systolic) and 80 mmHg diastolic (written $^{120}/_{80}$ mmHg, and called {in US and UK} one twenty over eighty), systolic and diastolic arterial BPs are not static but undergo natural variations from one heart beat to another and throughout the day in a circadian rhythm, they also change in response to stress, nutritional factors, drugs, diseases, exercise and momentarily from standing up. Persistently raised blood pressure exceeding about 120 (systolic) and 90 mmHg (diastolic) at rest is called hypertension. Cardiovascular diseases are associated with oxidative stress, inflammatory processes and vascular dysfunction. Lycopene, a carotenoid found in tomatoes is an antioxidant with protective effect on lipid peroxidation and antiatherosclerotic capacity (Ried and Fakler, 2011). A meta-analysis suggest that lycopenetaken in dosage ≥25 mg daily is effective in reducing LDL cholesterol by about 10% which is comparable to the effect of low dose of statins in patients with slightly elevated cholesterol levels.

MATERIALS AND METHODS

Plant collection and identification

The samples used for this research were fresh and ripe tomato fruits which include these three varieties (*Lycopersicon hiresitium* (LH) called Jos tomatoes, *Lycopersicon perivianum* (LP), UTC variety and *Lycopersicon cheesmani* (Gboko variety) and were purchased from railway market in Makurdi Nigeria. Identified and authenticated at the Herbarium Unit of the Department of Plant Science and Animal Breeding of the Federal University of Agriculture, Makurdi, Benue State, Nigeria and their samples were collected after identification and kept at their herbarium units with voucher number UAM/1773.

Phytochemical screening

In order to determine the presence and the concentrations of the alkaloids, glycosides, flavonoids, tannins, soluble carbohydrates, steroids, saponin, reducing sugar, standard methods of Harbone (1983) were used, while for vitamin C, beta-carotene and lycopene, method of Alexander and Griffiths (1993) were used. A preliminary study was performed with the blended ripe tomato fruits using the standard methods for various phytoconstituents as stated in Table 1.

Lipid profile assessment

The total cholesterol level (TC), high density lipoprotein (HDL-C) and triglycerides (TG) for all the experimental animals were determined using the hand held cardiocheck self-test meter (lipidocare), a device made by SD Biosensor Inc USA, and was used for the determination of the lipid profiles in the experimental animals using whole blood collected from the tail vein using Insulin syringe. The equipment has already being calibrated prior to its use after purchase. The memo clips was inserted and the device switched ON, the test strip for each sample was inserted after which two drops (0.2 ml) of blood samples were placed on the strips and within few seconds that the blood samples were dropped, a pink coloration was observed respectively and the automatic button was pressed which led to the instant display of the result (TC, TG, HDL-C, etc) and were recorded in milligram per deciliter (mg/dl).

Determination of body weights

The body weights of the experimental animals were determined prior to the commencement of the research and during the experiments on weekly basis (7 days interval) throughout the experimental periods for 28 days. Their weights were taken using the digital top loading weighing balances by Harvard Apparatus Ltd. A cylindrical transparent glass rat restrainer was weighed and the weight tarred to zero before introducing the rats individually and their weights were recorded in gram (g).

Determination of the systolic, diastolic and the heart rate

Non-invasive blood pressure meter (NIBP) (LE 5001) by PANLAB Equipment was used for the determination of the cardiovascular parameters (systolic, diastolic and pulse rates). The sensitive blood pressure meter was switched on and allowed to acclimatize for about 20 min; the selector switch located at the back of the equipment was switched to area marked for rats. The rats' tail was briefly immersed in water at temperature of 45°C with a thermostat and allowed for about 30 s for the dilatation of the tail veins to

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increase blood flow to the tail region. Before this, the rats were introduced into the transparent glass restrainer before the immersion of the tails into the hot water. The animals were covered with pieces of dark clothes for reduction of anxiety. The tail cuff/transducer were introduced into the base of the tail region and the selector switch turned on immediately the pulse waves indicated “ready”, the readings were displayed on the screen of the apparatus. The foot control switch was matched to save the reading and then recorded.

Preparation of tomato sauce

The tomato fruits were washed thoroughly with clean water to reduce the microbial load and other contaminants that might adhere to the surface of the tomatoes. The tomato fruits were chopped into smaller sizes with a kitchen knife and were blended and homogenized using a homogenizer. After which it was mixed with the normal rats chow and dried using an oven in the ratio of 92:8 g and kept for the animals *ad libitum.*

Induction of hypertension

Hypertension was induced in the rats after their initial baseline physical and cardiovascular parameters were assessed. For a rough estimation, a typical young male adult rats weighing between 300 and 350 g consumes around 20 g of normal rats chow per day, that is, about 48 g/kg body weights per day and this is equivalent to 1.6 g NaCl per 325 g of body weights per day or about 5 g of NaCl per kilogram weight for day. Based on this, 8 g of NaCl (Uncle Palm Iodized salt with Batch No; FT 256) was weighed using a digital weighing balance by Ohaus USA and transferred to a 500 ml beaker and made up to 100 ml of clean water using a delivery pipette to prepare sodium chloride solution and was mixed with approximately 92 g of normal rats chow and 1% NaCl in drinking water and was kept for them *ad libitum* (Sofola et al., 2002). They were allowed to feed on the diet for 28 days followed by blood pressure measurements on weekly basis till there was sustained increased in blood pressure to a hypertensive state before the treatment with the different varieties of *L. esculentum* commenced and lasted for another 28 days. The values were also reported and tabulated in the results.

Experimental animals

A total of thirty hypertensive male Albino rats of 3 to 4 months of age weighing between 100 and 200 g were used for the experiment. They were procured from the Animal House Unit, Department of Pharmacology, and College of Health Sciences of the Benue State University, Makurdi and kept in well aerated laboratory cages in a room with 12 h and dark cycle in clean disinfected cages in the animal house with free access to feed (standard pelletized growers feed from UAC- vital feed Jos, Plateau State) and clean drinking water *ad libitium.* The animals were treated according to the international guidelines for the care and maintenance of laboratory animals and allowed to acclimatize to the environment for one week (7 days) before commencement of the experiment. The animals were handled according to the protocols approved by the Research Ethics Committee of the Benue State University, Makurdi with protocol number, NHREC/BSUM/2016/00234b.

Experimental design

The thirty male hypertensive wistar rats after acclimatization were divided into six (6) groups each and their basal parameters measured and recorded before the commencement of the experiment.

Group A (n=5) Normotensive (control group); Group B (n=5) hypertensive and treated with Jos variety; Group C (n=5) hypertensive and treated with UTC variety; Group D (n=5) hypertensive and treated with Gboko variety; Group E (n=5) hypertensive and treated with standard angiotensin converting enzyme inhibitor (lisinopril) 2.5 mg/kg body weight P.O; Group F (n=5) hypertensive untreated but received water and feed *ad libitium*.

Method of data analysis

The data are presented as mean±standard deviation and were analyzed using one-way analysis of variance (one-way ANOVA) then multiple comparison with post hoc Tukey test (least standard deviation) to compare their means using computer software (SPSS version 21.0) and Excel for windows. $P < 0.05$ was considered to be statistically significant.

Table 1 shows the results of the qualitative and quantitative analysis of the phytochemical present in the three varieties of *Solanum lycopersicon*. The table shows the different concentration of the phytochemical present in Nigerian tomatoes. Jos variety of tomatoes has the highest concentration of antioxidants (flavonoids, lycopene, beta-carotenes and vitamin C) as compared to UTC and Gboko varieties, respectively.

Table 2 shows the result of the mean±SD of the SBP of the baseline values and the final treatment values. There was a decrease in their SBP (E>B>C>D), that is, A (-1.0±1.2 mmHg), B (-32.0±1.5 mmHg), C (-21.8±1.3 mmHg), representing 0.8, 19.6, 14.5 and 20.1%, respectively when compared with that of lisinopril (33.4±0.1 mmHg), representing 20.1% with the exception of group D (18.4±4.9 mmHg) and F (16.4±12.2 mmHg) that increased instead of decrease with 11.3 and 16.2%, respectively. They were compared statistically and found that there was a significant difference ($P<0.05$) between Groups B, C, and F when compared with A. Also, Groups B, C and E were significantly difference ($P<0.05$) when compared with Group D. Groups B, C, D and E were also significantly different ($P<0.05$) when compared with Group F. The group treated with the Jos variety was found to be more potent in SBP reduction than the UTC and Gboko varieties, respectively.

Table 3 also shows a decrease in their DBP, A (0.00±2.2), B (-25.8±15.5),C (31.0±2.6), E (-30.2±1.1) representing 0, 23.3, 29.9 and 27.7% decrease, respectively while Group D increased (7.8±3.0) representing 27.7% increase rather than decrease. They were compared statistically and found that there was a significant difference between Groups B, C and D when compared with Group E.

Table 4 shows the changes in their TCL. Groups B, C and E decreased significantly by B (-13.1±0.2), C (-6.8±2.3) and E (-8.8±0.5) representing 21.3, 11.7 and 15.7%, respectively, while D (9.4±0.1) and F (92.2±4.5) represents 18.0 and 150.4% increase in the TCL. They were compared statistically and found that there was a significant difference ($P<0.05$) among all the groups compared with Group F.

Table 5 shows the results of the high density lipoprotein (HDL-C). All the groups showed a significant increase in their HDL-C levels after treatment period with the exception of group F (HPT-U) that decreased and there was a significant difference ($P<0.05$) among Groups A, B, C, D and E as compared to Group F .

Table 6 represents the result of the triglycerides (TG-C) levels. After treatment, tomatoes treated groups showed a significant decrease in their TG-C levels when compared with the control Groups A and F that increased significantly with more significant increase seen in HPT-U groups. Groups B, C and D were

Table 1. The phytochemical screening (mg/100 ml).

Phytochemical	Test plant A (Jos)	Test plant B (UTC)	Test plant C (Gboko)
Carbohydrates	3.5	2.7	1.8
Saponin	0.7	1.1	0.8
Steroids	9.0	5.8	3.0
Tannin	0.5	3.0	3.6
Glycosides	4.4	3.6	3.8
Beta-carotene	0.9	0.9	0.7
Flavonoids	180	75	50
Lycopene	4.5	4.0	4.2
Vitamin- C	35	11	21
Alkaloid	0.05	0.08	0.07

Table 2. The mean± standard deviation of the systolic blood pressure (mmHg).

Group	Treatment stage (Day 1)	Treatment stage (Day 14)	Change in SBP (mmHg)	Change (%)
A (n=5)	123.8±3.9	122.8±2.7	-1.0±1.2	0.8
B(n=5)	163.6±5.3	131.6±3.8*$^{€ β¥}$	-32.0±1.5	19.6
C(n=5)	150.8±2.9	129.0±1.6*$^{€ β¥}$	-21.8±1.3	14.5
D(n=5)	163.4±4.9	145.0±4.8$^{β¥}$	-18.4±4.9	11.3
E(n=5)	166.0±5.2	119.4±5.1$^{€¥}$	-33.4±0.1	20.1
F (n=5)	162.0±4.7	194.7±6.2*^{β}	32.7±2.4	20.8

Values are expressed as mean ±SD. **P<0.05* compared with A; ^{μ}*P<0.05* compared with B; $^{£}$*P<0.05* compared with C; $^{€}$P<0.05 compared with D; ^{β} *P<0.05* compared with E; $^{¥}$*P<0.05* compared with F.

Table 3. The mean± standard deviation of the diastolic blood pressure (DBP) (mmHg).

Group	Treatment stage (Day 1)	Treatment stage (Day 14)	Change in DBP (mmHg)	Change (%)
A (n-5)	81.2±3.7	81.2±1.5	0.00±2.2	0.0
B(n-5)	110.6±6.8	84.8±22.3$^{β¥}$	-25.8±15.5	23.3
C(n-5)	103.4±7.7	72.4±5.1$^{β¥}$	-31.0±2.6	29.9
D(n-5)	96.2±3.0	104.0±6.0$^{β¥}$	7.8±3.0	8.1
E(n-5)	109.2±3.3	79.0±2.2$^{¥}$	-30.2±1.1	27.7
F(n-5)	101.4±5.5	117.8±4.8*^{β}	16.4±12.2	16.2

Values are expressed as mean ±SD. **P<0.05* compared with A; ^{β}*P<0.05* compared with E; $^{¥}$*P<0.05* compared with F.

significantly difference (P<0.05) when compared with HPT-U also, all the groups showed a significant difference with the control group A.

Table 7 similarly show the HR decrease by 1.4±16.27 beats/min, 20.2±0.3, 11.0±2.0, 30.6±8.9 representing 0.4, 5.9, 3.2 and 8.8%, respectively for Groups A, B, C and D. While Group E (15.0±1.3 mmHg) and F (19.1±1.6mmHg) represent 4.4 and 5.6% increase in the HR. They were also compared statistically and observed that there were significant differences between groups B, C and D when compared with Groups F and B, C significantly different (P<0.05) when compared with Group E. Also, Group D was significantly difference (P<0.05) when compared with group A.

In Table 8, body weights decreased in Groups B, C and D with 8.0±3.1 g, 3.8±0.1 and 4.6±0.8 g representing 5.2, 2.6 and 3.5%, respectively. Groups A, E and F increased in their body weights with 9.76±2.2 and 3.7±3.7 and 20.7±1.7 g representing 6.5, 2.6 and 13.2%, respectively and there was no statistical significant difference (P>0.05) among all the groups at the end of the experimental period. At the end of the treatments, the blood pressures returned to normal in Groups B (132/85), C (129/72) and E (119/79 mmHg), whereas this was not achieved in group D (145/85) and F (195/118). No death/sickness was reported during this study which shows that tomatoes fruits do not have any adverse effect on the body.

RESULTS AND DISCUSSION

This study investigated the antihypertensive effects of three varieties of ripe tomato fruits *(Solanum lycopersicon)* procured from Makurdi, North-central

Table 4. The mean± standard deviation of the total cholesterol level (TCL) (mg/dl).

Group	Treatment stage (Day 1)	Treatment stage (Day 14)	Change in TCL (mg/dl)	Change (%)
A	51.3±3.0	52.0±2.3	0.7±0.7	1.4
B	61.6±1.6	48.5±1.8[¥]	-13.1±0.2	21.3
C	57.9±3.8	51.1±6.1[¥]	-6.8±2.3	11.7
D	52.1±5.4	61.5±5.5[¥]	9.4±0.1	18.0
E	56.1±5.4	47.3±5.9[¥]	-8.8±0.5	15.7
F	61.3± 3.3	153.5±7.8*	92.2±4.5	150.4

Values are expressed as mean ±SD. **P<0.05* compared with A; [¥]*P<0.05* compared with F.

Table 5. The mean± standard deviation of the high density lipoprotein cholesterol (HDL-C) (mg/dl).

Group	Treatment stage (Day 1)	Treatment stage (Day 14)	Changes in HR (beats/min)	Change (%)
A	55.1±1.8	57.2±0.5[¥]	2.1±1.3	3.8
B	35.6±1.8	62.5±4.2[¥]	26.9±2.4	75.6
C	38.5±2.1	56.2±1.8[¥]	17.7±0.3	45.9
D	39.2±4.2	51.2±0.2[¥]	12.0±3.0	30.6
E	37.6±3.2	65.2±1.5[¥]	27.6±1.7	73.4
F	35.1±1.2	22.5±1.3	12.6±0.1	-35.9

[¥]*P<0.05* compared with F

Table 6. The mean± standard deviation of the triglyceride level (TG) (mg/dl).

Group	Treatment stage (Day 1)	Treatment stage (Day 14)	Changes in TG level (mg/dl)	Change (%)
A (n=5)	12.2±1.8	14.5±2.8	2.3±1.0	18.9
B(n=5)	135.2±4.8	90.2±3.7*[¥]	-45.0±1.1	33.3
C(n=5)	132.5±2.9	95.4±3.2[¥]	-37.1±0.3	28.0
D(n=5)	136.1±4.3	101.2±5.3*[¥]	-34.9±1.0	25.6
E(n=5)	127.1±2.4	60.5±1.8*[¥]	-66.6±0.6	52.4
F(n=5)	132.1±4.4	155.6±4.2*	23.5±0.2	17.8

Values are expressed as mean ±SD. **P<0.05* compared with A; [µ]*P<0.05* compared with B; [£]*P<0.05* compared with C; [€]P<0.05 compared with D; [β] *P<0.05* compared with E; [¥]*P<0.05* compared with F.

Nigeria. In this study, the experimental animals were induced to hypertension by salt loading method (Sofola et al., 2002). The five different cardiovascular parameters and non-cardiovascular parameters which include systolic blood pressure, diastolic blood pressure, total cholesterol, high density lipoprotein and triglycerides, heart rates and body weights were assessed. In this research work, the researcher discovered that the three varieties of the *Solanum lycopersicon* were found to have antihypertensive effects through their lowering effects on the parameters assessed but the most antihypertensive effect was observed in the Jos variety of tomatoes accompanied by the UTC and Gboko varieties, respectively, the standard antihypertensive drug (lisinopril) performed better than the three varieties of *Solanum lycopersicon.*

The significant increase in body weights of Groups A and F may be an indication of an increase in fluid volume. The decreased body weights in Groups B, C and D on the last day of treatment could be as a result of the antioxidant properties of some of the phytochemical present in ripe tomato fruits like the flavonoid, lycopene, etc. Dietary flavonoid protect against cardiovascular diseases. Emerging and largely consistent evidence suggests that flavonoids can improve human endothelial functions and may reduce blood pressure (Hodgson and Croft, 2006) through its vasorelaxative effect on isolated arteries from rats as there is evidence those flavonoids metabolism is an important factor influencing the biological activity and effect of dietary flavonoids. Lycopene, flavonoids, beta-carotenes, etc, are known as powerful antioxidants and free radical quenchers which have received attention for its pivotal role in inhibiting oxidative stress which is found to inactivate nitric oxide,

Table 7. The mean± standard deviation of the heart rates (HR) (beats/minute).

Group	Treatment stage (Day 1)	Treatment stage (Day 14)	Changes in HR (beats/min)	Change (%)
A(n=5)	342.0±45.9	340.6±29.63	-1.4±16.27	0.4
B(n=5)	345.2±13.7	325.0±13.4 $^{\beta¥}$	-20.2±0.3	5.9
C(n=5)	339.4±13.8	328.4±15.8 $^{\beta¥}$	-11.0±2.0	3.2
D(n=5)	346.0±22.3	315.4±13.4$^{*¥}$	-30.6±8.9	8.8
E(n=5)	339.0±12.6	354.0±11.3$^{¥}$	15.0±1.3	4.4
F(n=5)	340.2±14.2	359.3±12.6	19.1±1.6	5.6

Values are expressed as mean ±SD. *$P<0.0$5 compared with A; $^{\mu}P<0.05$ compared with B; $^{£}P<0.05$ compared with C; $^{€}$P<0.05 compared with D; $^{\beta}$ $P<0.05$ compared with E; $^{¥}P<0.05$ compared with F.

Table 8. The mean± standard deviation of the body weights (gram).

Group	Treatment stage (Day 1)	Treatment stage (Day 14)	Changes in weights (g)	Change (%)
A(n=5)	148.14±14.0	157.9±11.8	9.76±2.2	6.5
B(n=5)	151.5±24.5	143.5±21.4	-8.0±3.1	5.2
C(n=5)	142.7±23.0	138.9±23.1	-3.8±0.1	2.6
D(n=5)	141.7±20.3	137.1±19.5	-4.6±0.8	3.2
E(n=5)	141.5±16.3	145.2±12.6	3.7±3.7	2.6
F (n=5)	156.6± 15.7	177.3±17.4	20.7±1.7	13.2

Values are expressed as mean ±SD. *$P<0.0$5 compared with A; $^{\mu}P<0.05$ compared with B; $^{£}P<0.05$ compared with C; $^{€}$P<0.05 compared with D; $^{\beta}$ $P<0.05$ compared with E; $^{¥}P<0.05$ compared with F.

impairing endothelium dependent vasodilatation, improving vascular function and preventing cardiovascular diseases in humans (Xinl and Jiuhong, 2013).

The reduction in most of the cardiovascular parameters like systolic blood pressure etc could also be a protective effect of the saponin present in the ripe tomato fruits (Liu et al., 2012). The presence of saponin resulted in the lowering of total cholesterol and reduction in inflammation (Peter et al., 1997). Saponin if regularly included in the diets may help the body itself from cancer and other cardiovascular diseases as saponin and saponin like compounds have shown evidence that they can buttress the body's ability to fight cancer and cardiovascular diseases. The lipid profile obtained in this study showed a significant decrease in the triglyceride level and an increase in the high density lipoprotein cholesterol of the tomatoes treated groups when compared with the hypertensive untreated group. Lipidemia observed in the hypertensive untreated group may be as a result of an increase in visceral adipose mass (Brown and Dunmore, 2013) or may be due to a low activity of cholesterol biosynthesis enzymes (Tanko et al., 2016). Though anabolic steroids may increase blood pressure due to the sodium retention property, high dose of steroids use inhibits the enzyme 11-beta hydroxylase which leads to excessive production of deoxycortisterone, a mineralocorticoids in the adrenal glands and in due course a water and sodium retention. This mechanism of action of anabolic steroids towards increasing blood pressure was inhibited probably because of the high concentration of the antioxidants present in the Jos, UTC and Gboko varieties, respectively. Also, the high concentration of glycosides found in Jos variety could be a contributive factor that enhanced the the best blood pressure lowering effect observed in the research due to the fact that glycosides acts as a calcium channel blocking agent in the treatment of hypertension and other cardiovascular disorders and it is a potent dilator of peripheral arteries and in isolated tissue preparation exerts potent negative chronotropic, inotropic and dromotropic effect (Peter et al., 1980). Moreover, the limitations such as interrupted power supply, tail cuff bursting, etc were overcome successfully.

CONCLUSION AND RECOMMENDATION

This study showed that SL **can** effectively reduce blood pressure in hypertensive rats and it authenticates the various animal antihypertensive studies in SL. This also provides evidence that daily consumption of SE especially the Jos variety has no side effect. Therefore, these findings in addition to its cheapness and availability attenuate its desirability as an alternative blood pressure reducing agent in both mild to moderate hypertensive subjects. Though, its blood pressure reducing property is not commensurable to a standard antihypertensive drug (lisinopril). It further recommends that consumption of more of the Jos variety be encouraged and patronized in

the early management of hypertension. Also, further investigation should be carried out on the mild, moderate and severe hypertensive rats with the duration and dosages properly put into consideration. The researcher also suggests that the effect of these plants be assessed in urine microscopy, protein and creatinine ratio, etc to find out the effect of this plant in renal function. Also, method of preparation/consumption (cooked, fresh and thermoxidized) should be considered in order to achieve a better therapeutic effect.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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Full Length Research Paper

Administration of gentamicin-induced hematobiochemical and renal morphological alterations in Swiss albino mice

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Gentamicin is widely used as an effective antibiotic. A study was conducted to investigate the effects of intramuscular administration of gentamicin on 20, 5 to 6 weeks male Swiss albino mice weighing 25 to 30 g. The mice were divided into 4 groups: Group A (kept as control); groups B, C and D (treated with gentamicin intramuscularly daily at the dose rate of 5 mg/kg for 7 days, 5 mg/kg for 30 days, and 10 mg/kg for 30 days, respectively). The mice of treated groups showed specific clinical signs such as dullness, roughness of the body coat, anorexia and weakness. Blood was collected by cardiac puncture for estimation of various blood chemical parameters, such as total erythrocyte count (TEC), total leucocyte count (TLC), hemoglobin percentage (Hb%), alanine amino transferase (ALT), and serum creatinine. Kidneys were collected for gross and histological study. Body weight (P<0.01) and kidney weight (P<0.05) decreased significantly in gentamicin treated group. In hematological study, TEC, TLC, and Hb% values decreased significantly (P<0.01), whereas in biochemical study, serum creatinine and ALT values increased significantly (P<0.01) in treated group when compared with control group. Gross study of kidneys showed abnormal characteristics, such as, soft, flabby, brownish color with decreased size of left kidney in treated group. Histological study revealed desquamation of glomerulus, loss of glomerular architecture, distortion of renal tubules and hemorrhage in tubules of treated group. These data supports the view that gentamicin has a toxic effect on the morphology of kidney after long term treatment with higher dose.

Key words: Gentamicin, kidney, toxic effect, morphology, mice.

INTRODUCTION

The kidney is a vital organ for animal and it regulates the water and salt concentration of the body. It plays an important role to remove foreign substances from the blood. Many environmental contaminants and chemical

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variables including drugs alter the function of kidney (Mahmood and Waters, 1994).

To date, among the antibiotics, gentamicin is the most widely studied aminoglycoside antibiotic. The aminoglycoside antibiotic, gentamicin, synthesized by *Micromonospora purpurea*, is used for the treatment of various bacterial infections including both gram-negative and gram-positive bacteria (Gilbert et al., 2000). The action on bacteria is bactericidal and gentamicin has increased activity at alkaline pH. In case of gentamicin, oral absorption is minimal and for systemic use, gentamicin must be given by the parenteral route. Uptake is rapid after intramuscular injection and has a serum half- life of 75 to 110 min (Gonzelman, 1980). Whole animal isolated perfused rat kidney and human renal clearance and micropuncture studies have clearly demonstrated that aminoglycosides are eliminated in nonmetabolized form from the body in all animal species, primarily by renal glomerular filtration (Chiu et al., 1976). The inhibition of protein synthesis is mediated through aminoglycosides energy-dependent, sometimes irreversible binding to the cytocolic, and membrane-associated bacterial ribosome (Levison, 2012).

The use of gentamicin has tremendously increased in human and veterinary practice due to their greater effectiveness against human, livestock, and poultry diseases (Craig et al., 1998) but, most of the people of Bangladesh are inexperienced about the taking of antibiotic. They purchase antibiotics without any prescription from physician or even when the practice is not legal. For treatment purposes, they use overdose of antibiotic for a long time which may cause adverse effects in human beings. In rural Bangladesh, 95% of the people consume drugs without any prescription and purchase drugs from local pharmacies; only 8% of them consume drugs according to the prescription from physicians (Hossain et al., 1982). Drug takers usually have little or no knowledge of the required dosage, regimen, indications or contraindications (Dua et al., 1994).

Like many other antibiotics, gentamicin is not free from toxic effects both in human beings and livestock. Gentamicin can induce ototoxicity and nephrotoxicity, because both organs have higher than normal concentration of phospholipids in their cellular matrices (Ali et al., 1992). Nephrotoxic effects are found in 10 to 15% of cases due to over dosage or accumulation of gentamicin in renal cortical tubular epithelial cells. Necrosis of cells in the proximal tubule occurred due to over dose of gentamicin, leading to acute renal failure (Leehey et al., 1993). Gentamicin acts by binding to anionic phospholipids of plasma lemma and decreasing the permeability of the glycerol moiety of phosphatidylinositol, membrane fluidity and promoting membrane aggregation. For that reason, renal proximal tubules take up gentamicin and concentration in the renal cortex is far greater than those observed concurrently in the serum and other tissues (Lopez et al., 2011). Additionally, blood chemical investigation was conducted for more elucidation of the effects of tissue damage which could be provoked by gentamicin.

Therefore, in the toxicity of gentamicin problems relating to their hazardous effects upon human beings, animals, and birds must be taken into account. In the present study, the short and long term effects of gentamicin on kidney in mice were investigated histochemically.

MATERIALS AND METHODS

Chemicals

Inj. Gentaren 10% (Reneta, Bangladesh Ltd.) 100 ml bottle is a broad spectrum aminoglycoside antibiotic preparation which was purchased from the local market. Buffered neutral formalin, ethanol, xylene, hematoxylin, eosin, acetic acid, glycerin, and DPX were purchased from Merck Company, India.

Animals and treatments

The experimental male Swiss albino mice were collected from International Center for Diarrheal Disease Research (icddr'b), Mohakhali, Dhaka. All the mice possessed good health and devoid of any external deformities certified by the registered veterinarian from icddr'b. After procurement, all the mice were kept under close observation in order to acclimatize to the new environment for a period of one week prior to commencement of the experiment. All mice were raised under confinement as an intensive system. Twenty male mice aged 5 to 6 weeks old, weighing 25 to 30 g were used for this experiment. The rats were housed five per one plastic cage, maintained on a 12 h light/dark cycle at a constant temperature (70 to 74°F) and humidity (45 to 60%) and provided water and rodent pellets *ad libitum.* For each individual under study a record sheet with full details of each parameter were maintained. For the experimental purpose, the mice were randomly divided into four groups and each group contained five mice. Group A was kept as control, group B was treated with 5 mg/kg for 7 days, group C was treated with 5 mg/kg for 30 days and group D was treated with 10 mg/kg for 30 days.

Body weights of all mice were recorded before starting the treatment. Among the four groups, group A was kept as control without giving any treatment. The other 3 groups of mice (B, C, D) were treated with gentamicin (Gentaren 10%) intramuscularly. After administration of gentamicin, all the mice were kept under close observation for the entire 35 days (30 days of treatment period and 5 days of post treatment). The body weight of each animal was recorded twice weekly.

Clinical examination

All the mice were kept under close observation up to 7 and 35 days for investigation of any clinical signs.

Blood chemical

Each animal was euthanized under chloroform before 2 ml of blood was taken in 5 ml disposable syringe using anticoagulant (sodium citrate 3.8% w/v, Merck, India) by cardiac puncture for estimation of various blood chemical parameters, such as total erythrocyte count (TEC), total leucocyte count (TLC), hemoglobin percentage (Hb%),

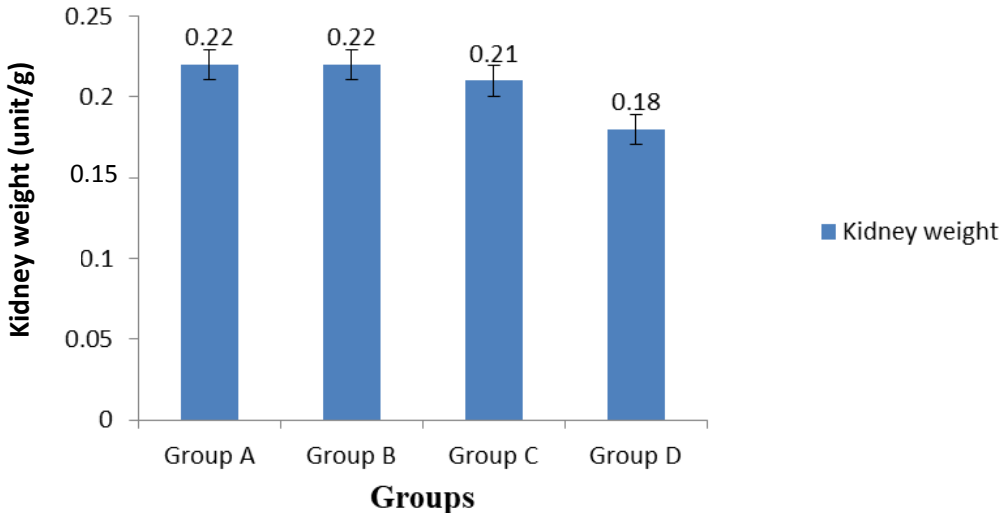

Figure 1. Changes of weight of kidney in control and treated mice.

alanine amino transferase (ALT) and serum creatinine. The blood sample was allowed to stand for 1 h and centrifuged at 3000 rpm for 15 min. Eppenorf tubes were used for collection of serum and stored in freeze at -20°C. Serum creatinine and ALT were measured by using auto-analyzer machine (ERBA-Smart lab SL-10304) and commercially available kits.

Gross and histology

After sacrifice of each animal sequentially, kidney was collected from each animal and examined for gross study. For gross study, color, weight and size of kidney were taken into consideration.

For histological observation, 5 mm^2 pieces were collected from different side of kidney and immersed in 10% formalin for 48 h. Then, the sample was washed in 10% phosphate buffer solution for 3 h, dehydration was done by passing the tissue in the ascending grade of alcohol, such as 70, 80, 90, 95, 100 (1), and 100% (2) each for 2 h and finally 100% (3) for overnight, cleared in xylene and embedded in paraffin. Sections from the paraffin blocks were cut in 5 µm in thickness by using rotatory microtome. Then, the sections were stained with Meyer's Hematoxylin and Eosin (H&E). The sections were protected by a thin cover slip attached to the slide with a mounting medium 'DPX' (Luna, 1968). The samples were studied with the aid of light microscope.

Data analysis

A statistical software package (SPSS, version 20) was used for data analysis. The descriptive data is given as mean ± standard deviation (SD). Chi-squared test was used for the analytical assessment. The differences were considered statistically significant when P values were less than 0.05 and 0.01.

RESULTS

All the mice of group A were healthy and active without any abnormal signs during the whole experimental period. Mice of group B were apparently normal without any abnormal sign up to 7 days of intramuscular administration of gentamicin at a recommended dose (5 mg/kg). Mice of group C (5 mg/kg for 30 days) showed fear with less appetite, roughness of the body, apathy and weakness. However, in group D (10 mg/kg for 30 days), all the mice produced irritable behavior, roughness of the hair coat, dullness, less appetite and weakness. Mortality of the animals was found in groups C and D, but the highest concentration was found in group D treated with 10 mg/kg for 30 days.

The mean body weight of the mice of group A at the start and at the end of the experiment was 27.18±0.217 and 28.50±0.274 g, respectively. Total body weight was not significantly affected due to short duration of administration of gentamicin in group B. However, after the end of the experimental period, the body weight was more significantly ($P<0.01$) decreased in group D (10 mg/kg for 30 days) in comparison to control group (Figure 1).

In group A (Control), the mean value of TEC, TLC and Hb% was 891.80±1.304 ml/m^3, 8.14±0.018 $thousand/m^3$ and 8.99±0.013. The value of TEC, TLC and Hb% decreased significantly ($P<0.01$) in group C (5 mg/kg for 30 days) and group D (10 mg/kg for 30 days) in comparison to the control group (Table 1). In group A (control), the mean value of serum creatinine and ALT were 0.54±0.035 mg/dl and 17.28±0.130 U/L. These values increased significantly ($P<0.01$) in group D (10 mg/kg for 30 days).

Gross examination of kidney

Reddish brown with smooth and shiny surface kidney was found in group A (Control) whereas, brownish color, soft and flabby kidneys were found in group C (5 mg/kg

Table 1. Blood chemical parameters estimated for all experimental groups (Data are given by Mean ± SD).

Name of group	TEC (ml/m^3)	TLC (thousand/m^3)	Hb%	Serum creatinine (mg/dl)	ALT (U/L)
Group A (Control)	891.80±1.304	8.14±0.018	8.99±0.013	0.54±0.035	17.28±0.130
Group B	876.80±1.304	7.98±0.017	8.08±0.084	0.53±0.010	21.68±0.415
Group C	802.60±1.140**	7.77±0.016**	8.22±0.084**	0.62±0.009*	25.18±0.164 **
Group D	587.80±0.837**	8.00±0.027**	7.40±0.071**	0.75±0.009**	33.82±0.512**

**Significant at 1% level (*P*<0.01); *significant at 5% level (*P*<0.05); NS, not significant (*P*<0.01).

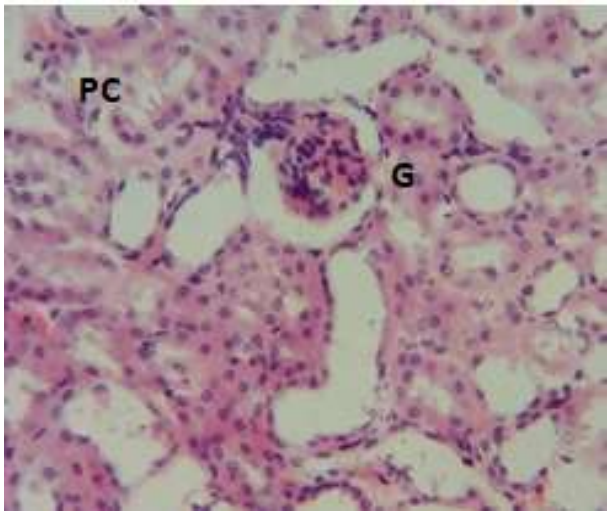

Figure 2. Photomicrograph of histological section of kidney of group A, showing renal corpuscle with glomerulus (G) surrounded by Bowman's capsule, proximal convoluted tubule (PC) and vessel.

for 35 days) and group D (10 mg/kg for 35 days). The mean weight of kidney of control group was 0.22±0.001 g. The weight of kidney decreased (0.18±0.001**) significantly (P<0.01) in group D.

Histological examination of kidney

Long term administration of gentamicin with higher dose induced marked glomerular, tubular and interstitial alterations in treated mice.

Kidney of group A (control), renal corpuscles appeared as dense rounded structure with glomeruli, surrounded by double walled epithelial Bowman's capsule and lined by simple squamous cells, having an outer parietal and inner visceral layers with a urinary space in between two layers (Figure 2). No deviation was found in glomerulus as well as tubules of the control group. In the experimental group B, there was no histological alterations observed in glomerulus and tubules of kidney treated with 5 mg/kg for 7 days. Desquamation of glomerulus, loss of glomerular architecture and marked lymphocytic infiltration were found in tubules of kidney in group C (5 mg/kg for 30 days) (Figure 3). Distortion of renal tubules (Figure 4), dilatation of tubule and tubular heammorhage were found in group D (10 mg/kg for 30 days) (Figure 5).

DISCUSSION

In the present study, behavioral changes, blood chemical and morphological alteration of kidney were observed after gentamicin administration.

Gentamicin in recommended (5 mg/kg for 30 days) and >recommended (10 mg/kg for 30 days) doses showed roughness of the body, apathy, loss of appetite and weakness. Similar findings were observed by Dantas et al. (1997) and Aguiar et al. (1997) when 10 dogs received gentamicin 10 mg/kg intramuscular (IM) 3 times a day for 14 days. However, they also found diarrhea and vomiting following administration of gentamicin in dog. In the current study, mortality was found in the highest concentration in group D (10 mg/kg for 30 days) whereas, Lichthorn (1985) reported death of new born rabbit

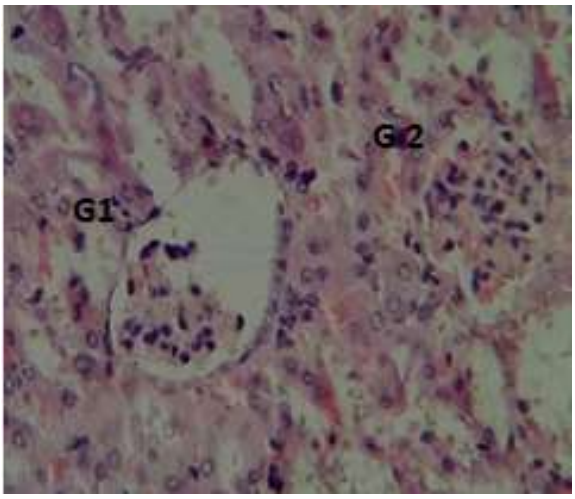

Figure 3. Photomicrograph of histological section of kidney of group C, showing desquamation of glomerulus (G1) and loss of glomerular architecture (G2). Stained with H&E, 40X.

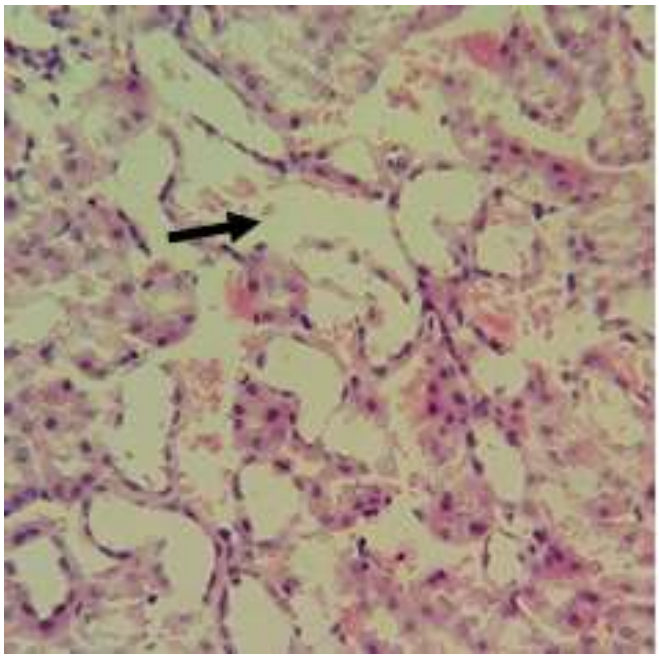

Figure 4. Photomicrograph of histological section of kidney of group D, showing distortion of renal tubules (black arrow); stained with H&E, 40X.

following low dose (20 mg/kg) of intramuscular injection of gentamicin during gestation period. Gentamicin is known to generate reactive oxygen species associated with an increase in lipid peroxidation and decrease in antioxidant enzyme activity in the kidney (Banday et al., 2008). Gentamicin treatment for long term produced statistically significant ($p<0.01$) loss of body weight and

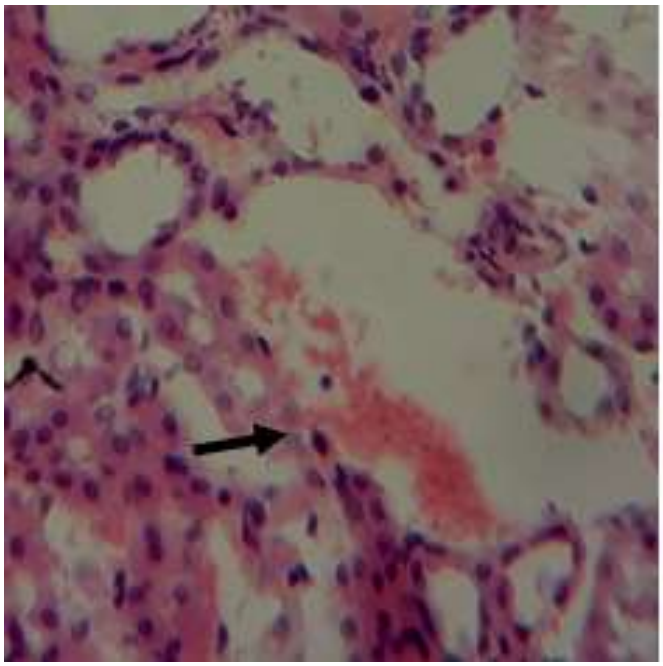

Figure 5. Photomicrograph of histological section of kidney of group D, showing hemorrhage with dilatation of renal tubule (black arrow); stained with H&E, 40X.

kidney weight in treated group as compared to control group. Houghton and Ali (1997) observed that renal failure due to gentamicin treatment in rats resulted in acidosis associated with anorexia and leading to decrease in body weight and kidney weight. Various blood chemical parameters were tested for the evaluation of the function of organs such as serum creatinine and ALT. In the present study, a significant increase of serum creatinine was observed and an increased serum creatinine indicates that kidney function was affected by gentamicin treatment. The presently recorded significant increase in blood creatinine was associated with distinct renal structural damage in rats (Chaware et al., 2011). Blood level of ALT increased significantly in the treated group. The blood level of ALT is indicative of the functional efficacy of liver and kidney. The level of these enzymes is very sensitive to any disease conditions of such organs (Tietz, 1996). Increased level of serum creatinine and ALT due to gentamicin treatment induced oxidative injury causing tubular damage and renal impairment. This finding is in accordance with that of Lipsky et al (1980) who also reported similar results. The presently observed necrotic changes of the renal tubules confirm the concept that significant structural changes of the kidney led to significant increase in the blood level of ALT (Smith et al., 1988). In the present study, intramuscular administration of gentamicin in 3 different doses (5 mg/kg for 7 days, 5 mg/kg for 35 days and 10 mg/kg for 35 days) significantly reduced the TEC, TLC and Hb%. Similar findings were reported by Smith et al.

(1988) that long term exposure of gentamicin in high dose affects the haemopoietic cells in the bone marrow and decrease erythrocyte production. In the present study, soft with brownish colored kidney was found in treated group (5 mg/kg for 30 days and 10 mg/kg for 30 days). Intramuscular administration of 10 mg gentamicin/ kg in 10 dogs, 3 times a day for 14 days, showed paled and soft kidney (Dantas et al., 1997) which is similar to the findings of the present study. For histological study, mice treated with gentamicin with high doses for long term showed progressive tubular, glomerular and interstitial alterations. The tubular damage and degenerative changes seen in the present work confirm with the findings of previous work (Ali et al., 2011; Dehghani et al., 2011; Kalayarasan et al., 2009).

The results of the present work show that the cortex of the kidney was more affected than the medulla as a result of long term administration of gentamicin. This might indicate that a relatively higher concentration of gentamicin reaches the cortex via the bloodstream than that entering the medulla. This is in agreement with the findings of Houghton et al. (1975). Kacew (1989) reported that gentamicin caused tubular necrosis, loss of brush borders and accumulation in renal cortex due to its reabsorption in proximal convoluted tubules causing necrosis and degenerative changes.

Conclusion

It is concluded that long term treatment with gentamicin in Swiss albino mice showed a fair degree of reduced food intake and body weight, increased mortality, induced significant blood chemical changes and caused derangement of kidney function with concomitant changes in the histological structures of that organ, which occurred mostly at highly gentamicin exposed group. The findings of the present study also revealed that treatment with gentamicin for 7 days is safe for human and animals. So, a physician prescription is needed before taking antibiotic to avoid the hazardous effects on kidney. People of Bangladesh should be conscious about taking antibiotic in major or minor issues. The present study may be considered as an experimental base of the relevant human studies.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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