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Determination of plasma Reactive Oxygen Species in young male albino rats after treatment with Gentamicin and Renadyl

Kanwal Zahra[1], Sohaib Aslam[2], Hamza Nazeer[1], Umair Rasool[1], Muhammad Umair[3], Ghazia Zahid[4], Arslan[4]
[1]Institute of Pharmacy, Physiology and Pharmacology, University of Agriculture Faisalabad, Pakistan
[2]Department of Theriogenology, Faculty of Veterinary Sciences, University of Agriculture Faisalabad, Pakistan
[3]Department of Parasitology, University of Agriculture Faisalabad, Pakistan
[4]Center of Agricultural Biochemistry and Biotechnology, University of Agriculture, Faisalabad, Pakistan.
*Corresponding author's email: zahraawan75@gmail.com

ABSTRACT

Kidney is important organ for controlling blood pressure and hypertension due to elevated level of salts. Gentamicin is aminoglycoside which is used for treatment of gram negative bacterial infection. Gentamicin is considered as nephrotoxic agent and cause cell death due to inflammation, free radical and renal blood flow. Renadyl is probiotic dietry supplement used in patient with chronic kidney disease. Experimental study had been conducted that Gentamicin was used for altering the kidney and Renadyl used for treatment of altered kidney. Thirty healthy male albino rats were divided into three (3) groups. Two groups were treated and one was controled. Equally divided ten (10) rats in each group. Gentamicin was given to rats intraperitoneally from 1st to 8th days for altering the kidney and 3rd group was treated by Renadyl orally from 9th to 18th days interval at regular basis for treatment. Blood sample was drawn out after administration of drug at 8th and 18th day and used for determination of total antioxidant, total oxidant status, glutathione reductase, glutathione peroxidase, catalase, arylestrase, and paraoxonase. All the required parameter was increased except total oxidant status (TOS), its level was decreased in the treated rats. The data was examined statistically by two way analysis of variance and DMR.

Introduction

Kidney is organ that contain many physiological functions. Vital function of kidney is to excretion of metabolic waste and retain the fluid in body. Kidney has important role in formation of urine and filtered the blood, related with regulation of blood pressure, levels of electrolyte and acid base balance. Blood filtration, metabolite secretion and reabsorption are function of nephron. Nephron dysfunctioning is due to abnormal structure of nephron and different types in injuries (Mccampbell *et al*., 2014). Kidney is imperative for nursing blood pressure and hypertension due to high level of salt. Hypertension indicates to disfunctioning of mitochondria during energy breakdown in kidney (Wang *et al*., 2017). The kidneys function containing excretory, biosynthetic, and metabolic organs, potent for retaining normal physiology. Although dialysis can change some kidney functions, it cannot imitate the biosynthetic and metabolic activities of the functional kidney (Peter., 2007). Kidney has two enzymes, cyclooxygenase I and cyclooxygenase II. COX-I is immunoreactive or non immunoreactive. Immmunoreactive are located in arteries and arterioles, glomeruli and collecting duct. While non immunoreactive are present in distal or proximal tubules, loop of Henle and macula densa (Harris *et al*., 1994).

In kidney, podocytes are available which are recognizing from epithelial cell. Some clinically utilized medications may influence the capacity of podocytes which prompts urinary protein discharge which demonstrates damage of kidney (Azeloglu *et al*., 2014). Teslariu *et al*., (2016) detailed that kidneys are crucial organs which keep up the electrolyte and water balance, discharge from blood and corrosive base adjust. Capacity of filtration is changed because of aggregated waste material and stagnated renal structure because of cell rot or apoptosis. No of medications, ecological elements and different risk synthetic compounds modify the morphology of kidney (Alarifi *et al*., 2011). Collected epithelial cell of renal proximal tubules prompts nephrotoxicity after glomerular filtration (Romero *et al*., 2009).

Ozbek (2012) detailed that oxidative pressure has a basic part in the malfunctioning of a few kidney infections, and numerous entanglements of maladies are interceded by oxidative pressure, which is related go between, and irritation. Hypertension is one of the significant reasons for advancement of renal disappointment. Key controller of this pathology is OS. Renal conduit stenosis is the most well-known reason for auxiliary hypertension and may prompt crumbling of renal capacity and ischemic disfunctioning of kidney. Chade *et al* (2002) demonstrated that a cross-talk amongst hypoperfusion and atherosclerosis to intelligently expanded OS, irritation, and tubular damage in the stenosis of kidney. Noeman *et al* (2011) demonstrated that high-fat eating regimen actuated weight is joined by expanded hepatic, heart, and kidney tissue oxidative stress, which is portrayed by diminishment in the cancer prevention agent compounds exercises and level of GSH, that associate to the expansion in MDA and protein carbonyl (PCO) points. Percy *et al* (2008) announced that extensive quantities of mitochondria present in proximal tubular cells and are the most dependent upon oxidative phosphorylation and most vulnerable to oxidant-instigated apoptosis and changes.

Nephrotoxicity or renal harmfulness can be a consequence of hemodynamic changes, guide damage to cells and tissue, fiery tissue damage, or potentially hindrance of renal discharge. Nephrotoxicity is oftentimes actuated by a wide range of restorative medications and natural toxins (Zhao *et al*., 2014). Medications are a typical wellspring of intense kidney damage. Medications appeared to cause nephrotoxicity apply their harmful impacts by at least one regular pathogenic components. Medication instigated nephrotoxicity has a tendency to be more typical among specific patients and in particular clinical circumstances (Naughton., 2008). Nephrotoxicity is ordinarily observed after intravenous acyclovir organization and might be because of direct tubular cell lethality and the arrangement of intratubular acyclovir gems, which show up as birefringent needle-formed precious stones on pee microscopy (Jefferson *et al*.,2011).

Gentamicin is an aminoglycoside anti-toxin that is utilized for treatment of gram negative bacterial disease (Randjelovic *et al*., 2012). *Micromonospora purpurea* is gram-positive microscopic organisms, which is available in soil and utilized for treatment in gram negative microorganisms. Acceptance of gentamcin is through intramasculary and intravenously and it is discharged out from body through pee (Balakumar *et al*., 2010). Utilization of gentamicin prompts ototoxicity, skin rash, neuromascular blockage, hepatotoxicity, genatotoxicity, oxidative harm and auxiliary chromosomal changes. Because of gentamicin, histological changes are analyzed (Alarifi *et al*., 2011). Gentamicin is utilized for the treatment of gram negative microorganism. Repeated utilization of medication causes nephrotoxicity (Romero *et al*., 2009). Randjelovic *et al*., (2011) announced that gentamicin is utilized as a part of facilities against perilous contaminations. Gentamicin indicates bactriacidal activity, wide range movement and substance steadiness. System of medication causes cell damage because of anomalous generation of ROS.

Renadyl is probiotic, named as Kibow which is framed with nourishment review with gram positive microscopic organisms. Container which is enteric covered, contains blend of various microorganisms like *Streptococcus thermophilus, Lactobacillus acidophilus* and *Bifidobacteriumlongum. Streptococcus thermophilus* utilizes urea and creatinine for development and survival, Lactobacillus acidophilus diminishes the centralization of poisons in circulation system and decreases the development of pathogen in little entrail while *Bifidobacteriumlongum* utilizes diverse phenolic and indole containing poisonous compound for development in colon locale (Awn and Fibms., 2016). Probiotics are portrayed as 'alive microorganisms which is directed in satisfactory sums, having wellbeing profits on the host, through their effect on the intestinal part. Probiotics are currently widely devoured as aged drain items, for example, stop dehydrated culture. The primary probiotic microscopic organisms identified with dairy items incorporate bacteria (Mazidi *et al*., 2017).

Glutathione is imperative for upkeep of cell honesty amid cell digestion. Glutathione is oxidative pressure marker which is decreased because of renal nephrotoxicity (Mehan *et al*., 2017). Glutathione peroxidase is that glycoprotein which has selenium (Gallo and Martino., 2009). Glutathione reductase and peroxidase diminished because of gentamicin (Kandemir *et al*., 2015). Creature regulated with gentamicin shows expanding level in glutathione peroxidase yet having no impact on glutathione. MDA diminished the substance of polyunsaturated unsaturated fat which go about as substrate with the expectation of complimentary radicals (Karahan *et al*., 2005). MDA levels expanded because of gentamicin (Mehan *et al*., 2017). Gentamicin organization demonstrates huge diminishing in SOD and CAT which demonstrates that medication lessened the impact of cancer prevention agent catalyst and increment level of MDA. Cell reinforcement properties decreased the level of oxidative worry with gentamicin drafted rats (Meky *et al*., 2016). Harmfulness of

gentamicin in pale skinned person rats shows the diminishing level of TOS and expanding level of TAC. These outcomes assessed the generation of hydrogen peroxide in renal cortical mitochondria which increment creation of superoxide (Meky *et al*., 2016).

Objectives

- To determine the alteration in plasma total oxidant, total antioxidant status, glutathione peroxidase, glutathione reductase, paraoxonase, arylestrase, and catalase by Gentamicin on day 8th and 18th of treatment.
- To determine reactive oxygen species on day 18th after Renadyl treatment.

Materials and methods

Experimental Animals

Eighteen (18) young 8-10 months old albino rats took from house of animals, Institute of Pharmacy, Physiology and Pharmacology, with the 150-200g body weight, taken from Institute of Pharmacy, Physiology and Pharmacology, University of Agriculture Faisalabad. The rats were provided with routine feed until experiment was completed. The available feed was made two time a day. Gentamicin was purchased from market in injection form, 80mg/kg. Gentamicin was given intraperitoneally to two groups of rats. One group was decapitated after 8th days while other was given treatment for rest of 10 days. Rats were preserved in Institute of Pharmacy, Physiology and Pharmacology, University of Agriculture Faisalabad, under 12 hours light and dark cycle at room temperature. Animals were given normal feed, water and medicine. Gentamicin was injected to 12 rats and at 8th day six rats were executed and from remaining rats, three were given by renadyl which was treated drug and decapitated at 18th days of experiment and three were as control for treated drug. (Table 3.1).

Table 3.1: Feed and medicine administration schedule of healthy and treated albino rats during the experimental period.

Groups	Treatment
Control	Routine diet and water (n=6)
Gentamicin	Routine diet+ water+ 80 mg/kg Gentamicin injected intraperitoneally (n=12)
Renadyl	Routine diet+ water+ Renadyl given through oral route (n=3)

Water and food intake of rats was detected from 1-18th days. Body weight was also detected during experimental duration. The blood sample was taken for purpose of ROS at 8th and 18th days respectively after the initiation of drug intraperitoneally. After using EDTA, sample of blood has been drained out at 8th and 18th days and plasma was divided and at -4°C, used for measuring ROS. Plasma sample was calculated for measurement of total oxidant status (Erel ., 2005) and total antioxidant capacity by following reference method (Erel., 2004). Glutathione (Nurrochmad *et al*., 2010), glutathione peroxidase (Frederik *et al*., 1986), glutathione reductase (Karaman *et al*., 2012), catalase (Nurrochmad *et al*., 2010), arylesterase (Ahmadvand *et al*., 2013) and paraoxonase (Caroline *et al*., 1995) was also be measured.

Statistical Analysis

The collected information was confirmed statistically by two way anova (Steel *et al.,* 1997). The importance of distinction between information esteems was broke down by Duncan's Multiple Range test (Duncan, 1955).

Results and discussion

4.1. Measurement of Body weight

Examination of fluctuation of body weight of control with that of treated male rats at various time interims has been offered in table 4.1. There was a non-huge distinction amongst control and treated gatherings at various time interims. In fig. 4.1, the body weight of control, and treated gatherings for day 8 and 18 was given. Gatherings on

treatment with medicate on day 18 showed non noteworthy high body weight when contrasted with control and rats treated for day 8.

Table. 4.1. Analysis of variance of Body Weight (g) of control, gentamicin and renadyl treated male rats on daily basis of 1-18th day

Weight	Sum of Squares	Df	Mean Square	F	Sig.
Between Groups	1143.750	2	571.875	.668	.523
Within Groups	17973.875	21	855.899		
Total	19117.625	23			

NS = Non-significant

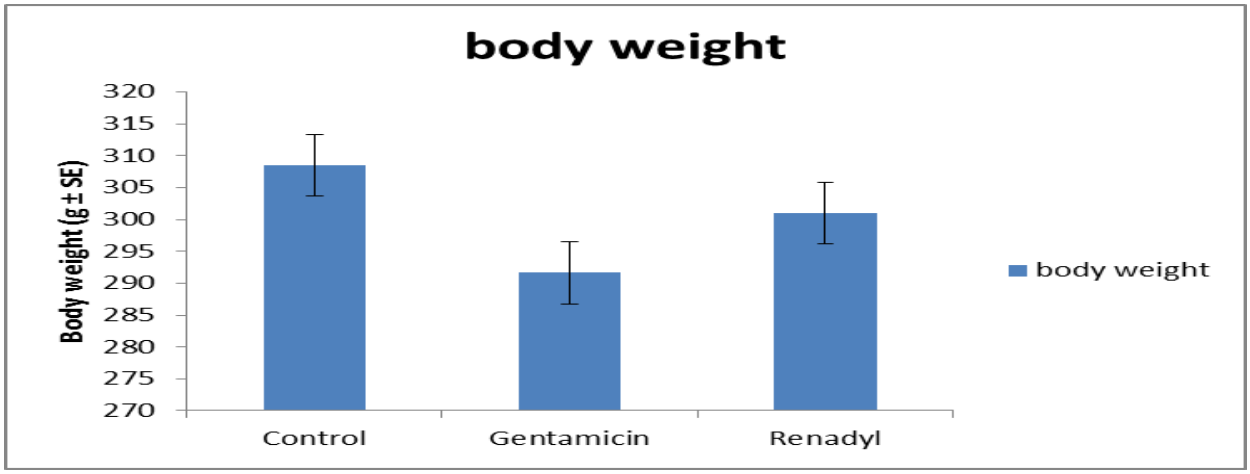

Figure. 4.1. Body Weight (Mean±SEM. g) of control and Gentamicn treated male rats at day 1-18th

4.2. Measurement of Feed intake

Feed admission of treated and control rats at adjusted time interims were analyzed by investigation of fluctuation and the outcome has been given in table 4.2. Feed admission of treated rats were non altogether extraordinary when it was contrasted with control gather at various time interims. In fig. 4.2, the feed admission of control, and treated gatherings for day 8 and 18 is open. Gatherings on treatment with sedate on day 18 showed non huge low feed allow when contrasted with control and rats treated for day 8.

Table. 4.2. Analysis of variance of Feed intake (g) of control and gentamicin treated male rats at different time intervals

Feed intake	Sum of Squares	Df	Mean Square	F	Sig.
Between Groups	10147.000	2	5073.500	10.672	.001
Within Groups	9983.500	21	475.405		
Total	20130.500	23			

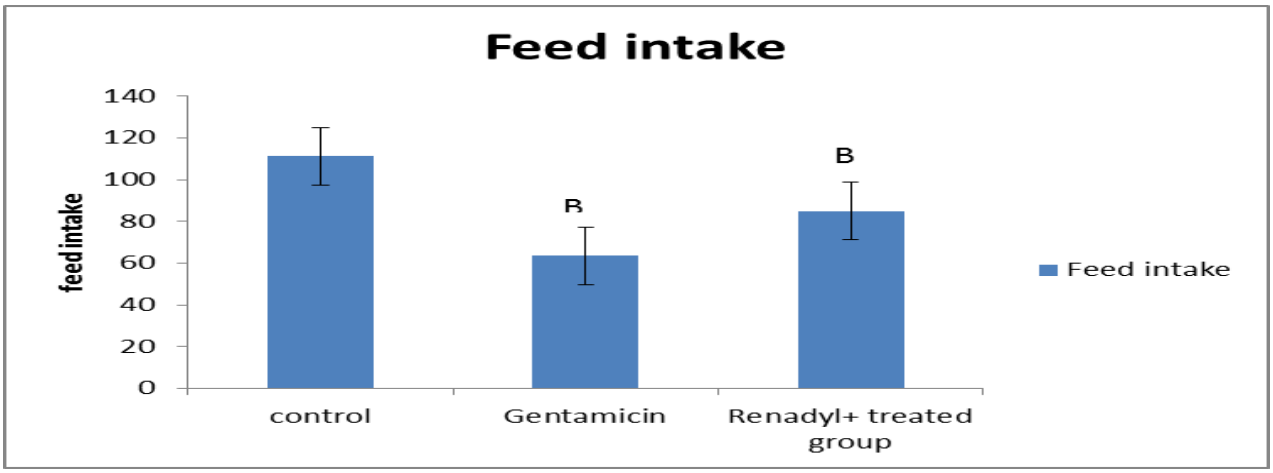

Figure 4.2. Feed intake (Mean±S.E.M.: g) of control and gentamicin treated male rats at different time intervals

4.3. Measurement of Water intake

In table 4.3, investigation of difference of water admission of control and medication treated male rats at various time interims have been uncovered. Water admission of male rats of control and medication treated gatherings were non essentially extraordinary at various time interims. In fig. 4.3, the feed admission of control, and treated gatherings for day eighth and eighteenth is displayed. Gatherings on treatment with sedate on day 18 showed non critical high water allow when contrasted with control and rats treated for day 8.

Table. 4.3. Analysis of variance of Water intake (ml) of control and gentamicn treated male rats at different time intervals

Water intake	Sum of Squares	Df	Mean Square	F	Sig.
Between Groups	11284.000	2	5642.000	17.979	.000
Within Groups	6590.000	21	313.810		
Total	17874.000	23			

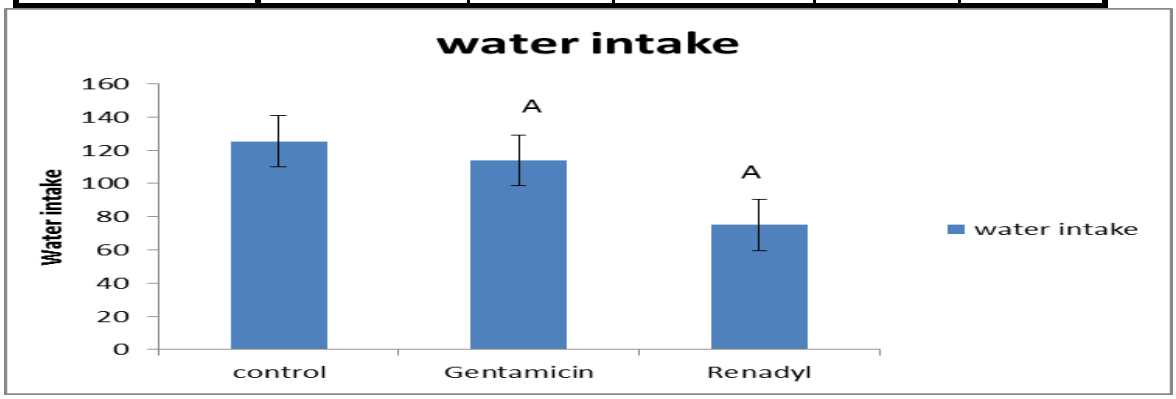

Figure 4.3. Water intake (Mean±S.E.M.: ml) of control and gentamicin treated male rats at different time intervals.

4.4 Analysis of liver weight

In table 4.4, investigation of change of liver weight of control and medication treated male rats at various time interims have been appeared. Water admission of male rats of control and medication treated gatherings were non essentially

extraordinary at various time interims. In fig. 4.4, the feed admission of control, and treated gatherings for day eighth and eighteenth is exhibited. Gatherings on treatment with medicate on day 18 showed non noteworthy high water allow when contrasted with control and rats treated for day 8.

Table. 4.4. Analysis of variance of liver weight of control and gentamicn treated male rats at different time intervals

Liver weight	Sum of Squares	Df	Mean Square	F	Sig.
Between Groups	60.718	2	30.359	13.119	.006
Within Groups	13.885	6	2.314		
Total	74.603	8			

NS = Non-significant

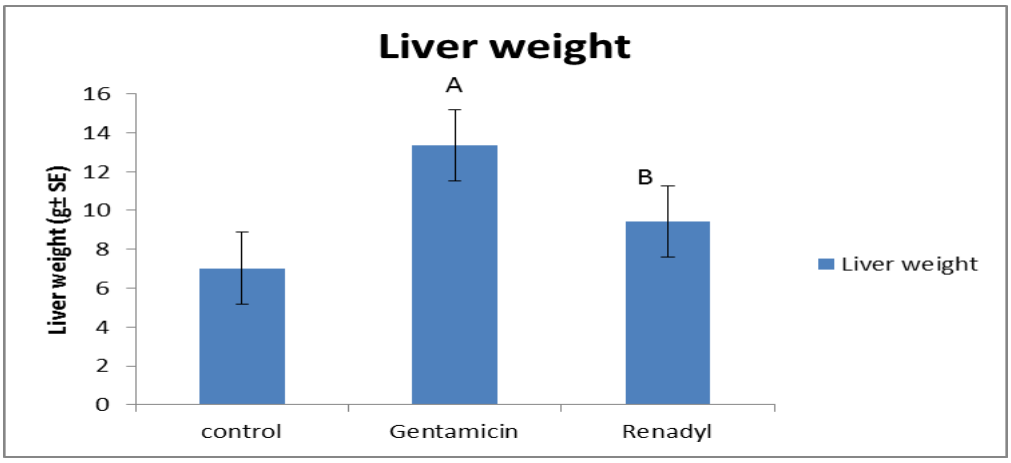

Figure 4.4. Liver Weight (Mean±S.E.M.: ml) of control and gentamicin treated male rats at different time intervals.

4.5. Analysis of kidney weight

In table 4.5, examination of change of kidney weight of control and medication treated male rats at various time interims have been appeared. Water admission of male rats of control and medication treated gatherings were non fundamentally extraordinary at various time interims. In fig. 4.5, the feed admission of control, and treated gatherings for day eighth and eighteenth is displayed. Gatherings on treatment with medicate on day 18 showed non noteworthy high water allow when contrasted with control and rats treated for day 8.

Table. 4.5. Analysis of variance of kidney weight of control and gentamicn treated male rats at different time intervals

Kidney weight		Sum of Squares	df	Mean Square	F	Sig.
Left kidney weight	Between Groups	.182	2	.091	58.550	.000
	Within Groups	.009	6	.002		
	Total	.191	8			
Right kidney weight	Between Groups	.079	2	.040	5.912	.038
	Within Groups	.040	6	.007		
	Total	.120	8			

Significant

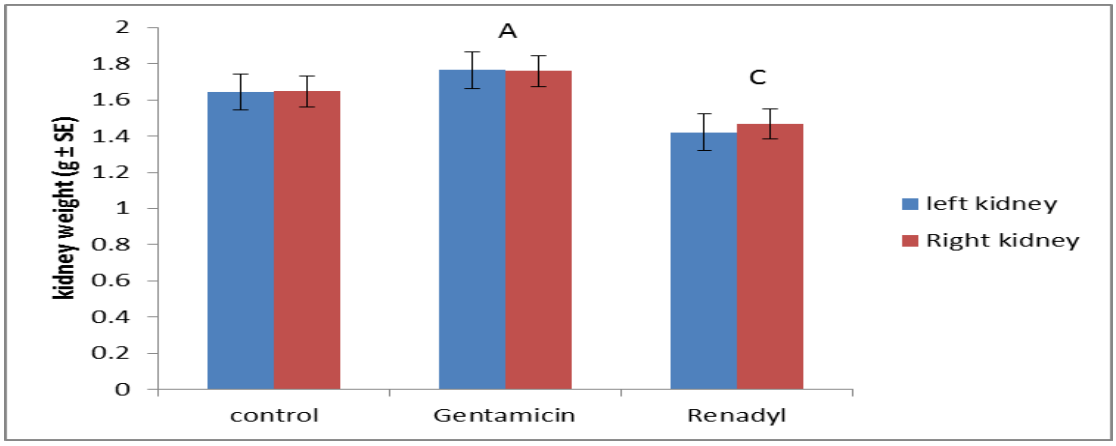

Figure 4.5. Kidney Weight (Mean±S.E.M.: ml) of control and gentamicin + renadyl treated male rats at different time intervals.

4.6. Measurement of Total Antioxidant Capacity

Analysis of variance of TAC of control with that of treated male rats at different time intervals has been offered in table 4.6. There was a non significant difference between control and treated groups at different time intervals. In fig. 4.6, the value of TAC for control, and treated groups for day 8 and 18 was given. Groups on treatment with drug on day 18 did show non significant high body weight as compared to control and rats treated for day 8**.**

Table. 4.6. Analysis of variance of TAC (µmol/L) for control, gentamicin and renadyl treated male rat on daily basis of 1-18th day

TOS	Sum of Squares	Df	Mean Square	F	Sig.
Between Groups	2.326	2	1.163	5.031	.052
Within Groups	1.387	6	.231		
Total	3.713	8			

Non-Significant

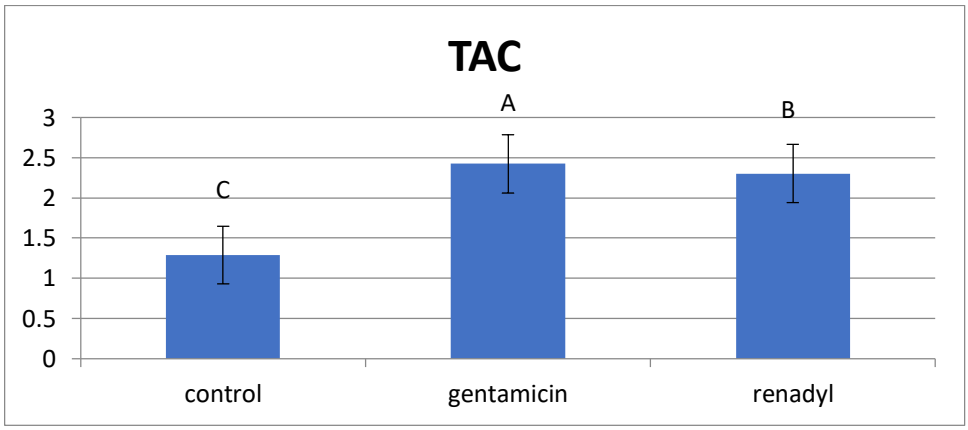

Fig. 4.6. Total antioxidant capacity (Mean ± SEM: µmol/L) in control, gentamicin and renadyl treated male rats at different time intervals

4.7. Measurement of Total Oxidant Status

Analysis of variance of TOS for control with that of treated male rats with gentamicin and renadyl at different time intervals has been offered in table 4.7. There was a non significant difference between control and treated groups at different time intervals. In fig. 4.7, the value of TOS for control, and treated groups for day 8 and 18 was given. Groups

on treatment with drug on day 18 did show non significant high body weight as compared to control and rats treated for day 8.

Table. 4.7. Analysis of variance of TOS (µmol/L) for control, gentamicin and renadyl treated male rats on daily basis of 1-18th day

TAC	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	3.230	2	1.615	20.134	.002
Within Groups	.481	6	.080		
Total	3.712	8			

Non Significant

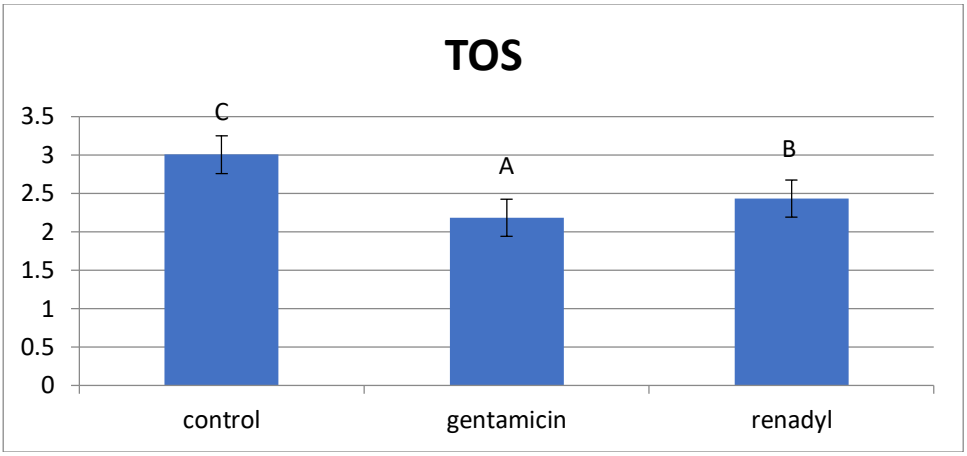

Fig. 4.7. Total oxidant status (Mean ± SEM: µmol/L) in control, gentamicin and renadyl treated male rats at different time intervals

4.8. Measurement of Glutathione Reductase

Analysis of variance of glutathione reductase for control with that of treated male rats with gentamicin and renadyl at different time intervals has been offered in table 4.8. There was a non significant difference between control and treated groups at different time intervals. In fig. 4.8, the value of glutathione reductase for control, and treated groups for day 8 and 18 was given. Groups on treatment with drug on day 18 did show non significant high body weight as compared to control and rats treated for day 8.

Table. 4.8. Analysis of variance of glutathione reductase (unit/ml) for control, gentamicin and renadyl treated male rats on daily basis of 1-18th day

G.reductase	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	1.954	2	.977	138.241	.000
Within Groups	.042	6	.007		
Total	1.996	8			

Non Significant

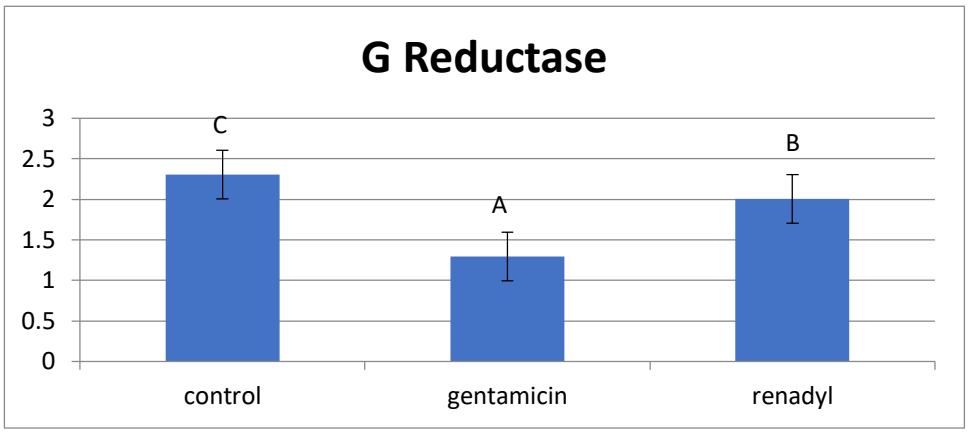

Fig. 4.8. Glutathione Reductase (Mean ± SEM: unit/ml) in control, gentamicin and renadyl treated male rats at different time intervals

4.9. Measurement of Glutathione Peroxidase

Analysis of variance of glutathione peroxidase for control with that of treated male rats with gentamicin and renadyl at different time intervals has been offered in table 4.9. There was a non significant difference between control and treated groups at different time intervals. In fig. 4.9, the value of glutathione reductase for control, and treated groups for day 8 and 18 was given. Groups on treatment with drug on day 18 did show non significant high body weight as compared to control and rats treated for day 8.

Table. 4.9. Analysis of variance of glutathione peroxidase (unit/ml) for control, gentamicin and renadyl treated male rats on daily basis of 1-18th day

G.peroxidase	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	2.091	2	1.046	91.358	.000
Within Groups	.069	6	.011		
Total	2.160	8			

Non-Significant

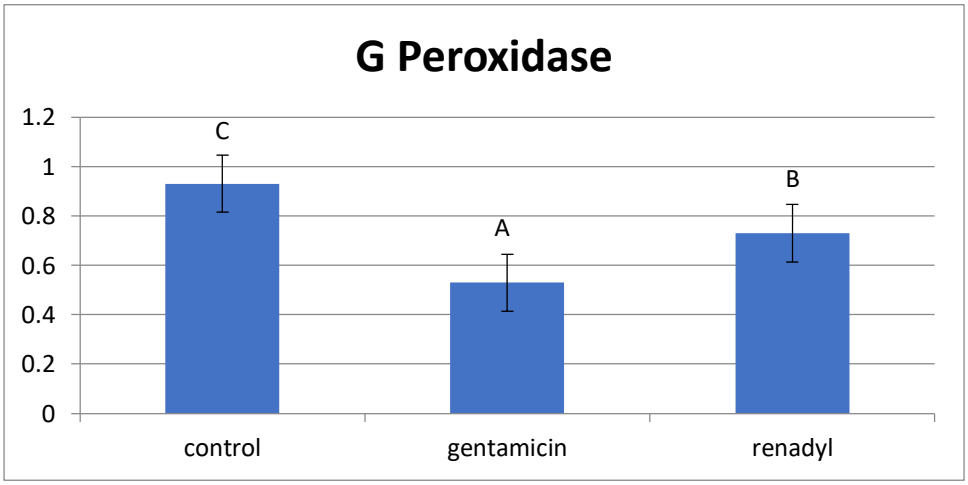

Fig. 4.9. Glutathione Peroxidase (Mean ± SEM: unit/ml) in control, gentamicin and renadyl treated male rats at different time intervals

4.10. Measurement of Catalase

Analysis of variance of catalase for control with that of treated male rats with gentamicin and renadyl at different time intervals has been offered in table 4.10. There was a non significant difference between control and treated groups at different time intervals. In fig. 4.10, the value of catalase for control, and treated groups for day 8 and 18 was given. Groups on treatment with drug on day 18 did show non significant high body weight as compared to control and rats treated for day 8.

Table. 4.10. Analysis of variance of catalase (unit/ml) for control, gentamicin and renadyl treated male rats on daily basis of 1-18th day

Catalase	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	.008	2	.004	.371	.705
Within Groups	.062	6	.010		
Total	.069	8			

Non Significant

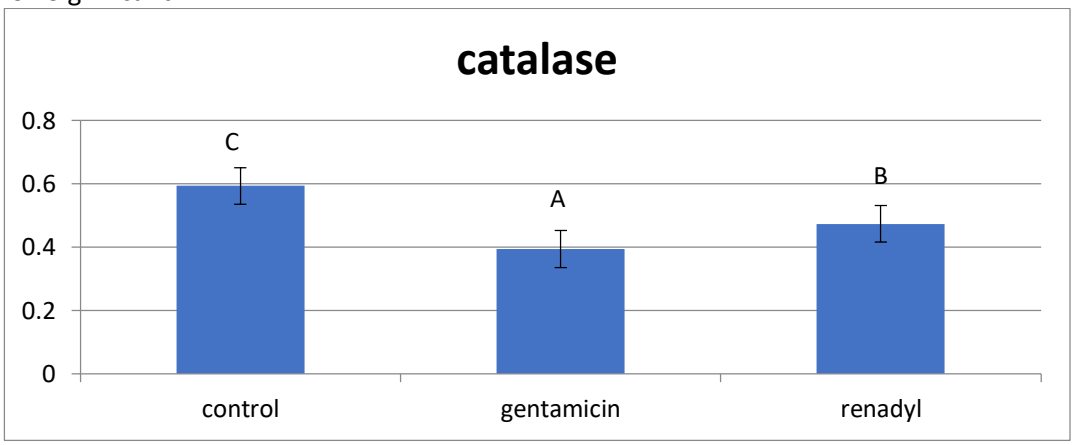

Fig. 4.10. Catalase (Mean ± SEM: unit/ml) in control, gentamicin and renadyl treated male rats at different time intervals

Discussion

Kidney is organ that contain many physiological functions. Vital function of kidney is to excretion of metabolic waste and retain the fluid in body. Kidney has important role in formation of urine and filtered the blood, related with regulation of blood pressure, levels of electrolyte and acid base balance. Blood filtration, metabolite secretion and reabsorption are function of nephron. Nephron dysfunctioning is due to abnormal structure of nephron and different types in injuries (Mccampbell *et al*., 2014). Kidney is imperative for nursing blood pressure and hypertension due to high level of salt. Hypertension indicates to disfunctioning of mitochondria during energy breakdown in kidney (Wang *et al*., 2017).

Gentamicin (GM) is an aminoglycoside anti-toxin generally utilized as a part of clinical practice for the treatment of dangerous Gram-negative bacterial diseases. The medicine has been limited because of genuine nephrotoxicity reaction. Despite the fact that the correct system fundamental GM-instigated nephrotoxicity are not totally explained, renal proximal tubule cells are the essential target site for the aminoglycoside anti-infection agents where it aggregates and cause nephrotoxicity through particular transporter. Nonetheless, a few different instruments that add to the pathogenesis of GM-prompted nephrotoxicity incorporate the abundance creation of receptive oxygen species (ROS, for example, superoxide anions, hydroxyl radicles, and hydrogen peroxide, Na+– K+– ATPase hindrance, and restraint of mitochondrial oxidative phosphorylation (Adil *et al*., 2016).

Renadyl is probiotic, named as Kibow which is bordered with nourishment analysis with gram positive microorganisms. Container which is enteric covered, contains blend of various microscopic organisms like Streptococcus thermophilus, Lactobacillus acidophilus and Bifidobacteriumlongum. Streptococcus thermophilus utilizes urea and creatinine for development and survival, Lactobacillus acidophilus diminishes the centralization of poisons in circulatory system and lessens the development of pathogen in little entrail while Bifidobacteriumlongum uses different phenolic and indole having harmful compound for development in colon area (Awn and Fibms., 2016).

Oxidative pressure is defined as a "state in which oxidation surpasses the cancer prevention agent frameworks in the body optional to lost the harmony between them. It not just purposes risky occasions, for example, lipid peroxidation and oxidative DNA harm, yet additionally physiologic adjustment marvels and control of intracellular flag transduction. Oxidative pressure is notable to be engaged with the pathogenesis of way of life related ailments, including atherosclerosis, hypertension, diabetes mellitus, ischemic maladies , and malignancies (Yoshikawa and Naito., 2002). Oxidative pressure has a basic part in the pathophysiology of a few kidney illnesses, and numerous difficulties of these maladies are interceded by oxidative pressure, oxidative pressure related middle people, and inflammation. A few fundamental sicknesses, for example, hypertension, diabetes mellitus, and hypercholesterolemia; disease; anti-toxins, chemotherapeutics, and radiocontrast specialists; and ecological poisons, word related synthetics, radiation, smoking, and liquor utilization incite oxidative worry in kidney (Ozbek., 2012).

It has been demonstrated that some side effects of certain drugs would be related to their ability to increase intracellular production of ROS and to induce oxidative stress in different cell types including human cells, causing damage that may affect health. Some of the toxic effects produced for certain antibiotics are related to the capacity to generate free radicals reaction producing damage in the human system for example, in leukocytes (Bustos *et al*., 2016). GEN-induced nephrotoxicity was associated with low activity of GSH-Px, CAT, SOD and levels of GSH in the renal cortex. These decreases in renal antioxidant enzymatic protection could aggravate the oxidative damage. The increased production of ROS in GEN-induced nephrotoxicity may cause inactivation of antioxidant enzymes such as GSH-Px, CAT and SOD (Karahan *et al*., 2005). Poisonous quality of gentamicin in pale skinned being rats demonstrates the diminishing level of TOS and expanding level of TAC. These outcomes assessed the creation of hydrogen peroxide in renal cortical mitochondria which increment generation of superoxide (Meky *et al*., 2016). Treatment with gentamicin caused significant reduction of GPx GR and TAC activity with following values as compare to control group, 840 ± 43, 47 ± 1.6 1.04 ± 0.03 respectively (Acharya *et al*., 2013).

According to my results, gentamicin effect the oxidative stress and form increasing and decreasing level in reactive oxygen species (ROS). Gentamicin effect the weight of kidney as compared to control group. Weight of kidney was increased as compare to control group due to nephrotoxicity. Gentamicin also effect the body weight of rat which was decrease due to poisonous effect of drug as compare to control group. In oxidative stress, the effect of total oxidant status decreased as compared to control group but effect of total antioxidant activity, glutathione peroxidase, glutathione reductase and catalase was increased due to induction of gentamicin in rats as compared to control group.

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