Nephroprotective Effects of Pentoxifylline and Captopril against Vancomycin Induced Nephrotoxicity in Male Rat Model

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Abstract
Background: Vancomycin, an antibacterial agent indicated to manage severe infections, it has been accompanying with nephrotoxicity, which restrict its use. Pentoxifylline, a methyl xanthine derivative with anti-inflammatory and antioxidant properties, and Captopril, a member of the angiotensin-converting enzyme inhibitor family that is used to treat hypertension and congestive heart failure. Objective: The purpose of this study was to evaluate the nephroprotective effects of pentoxifylline, and Captopril against vancomycin-induced nephrotoxicity in male rats. Methods: Forty albino male rats has been randomized assigned into four groups, each with ten rats, and were treated daily for 10 days as follows: Group 1; rats were orally administered (0.5 ml/kg) dimethyl sulfoxide. Group 2: rats were treated with vancomycin (200 mg/kg/day IP). Group 3: rats were treated with (100 mg/kg/d) captopril orally and vancomycin (200 mg/kg/day IP). Group 4: rats were treated with (50 mg/kg/day IP) pentoxifylline and vancomycin (200 mg/kg/day IP). All treatments were maintained until day 10. On the eleventh day rats were euthanized and serum urea, creatinine, and tumor Necrosis Factor-alpha levels, and also tissue malondialdehyde and interlukin-6 levels, were estimated. Results: Pentoxifylline and Captopril highly significant reduced the serum urea, creatinine, tumor necrosis factor-alpha, tissue malondialdehyde and interlukin-6 levels in comparison with vancomycin group. Conclusion: The present study shows that Pentoxifylline and Captopril exhibited nephroprotective effects. However, Pentoxifylline exhibited superior nephroprotective properties than Captopril.
Keywords: nephrotoxicity, vancomycin, pentoxifylline, captopril, nephroprotective.

1. Introduction

Nephrotoxicity is the harmful action of many compounds on the kidneys, comprising endogenous and exogenous compounds, as well as numerous medications (Kashyap *et al.*, 2019).Vancomycin (VCM), is kind of glycopeptide antimicrobial drug, with good activity versus G+ve bacteria. It has been utilized to manage *Staphylococcus aurous* and enterococcal infections that are resistant to methicillin (Öktem *et al.*, 2005; Elyasi, Khalili and Hatamkhani, 2012). Vancomycin is the antibiotic of choice for MRSA(Deepigaa and Gopinath, 2018). Since VCM was authorized for medical use in 1958, it has produced side effects such as nephrotoxicity (Elyasi, Khalili and Hatamkhani, 2012). Kidney damage caused by VCM has been observed in 5–25% of patients, although this may rise to 20–35% when taken with other nephrotoxic drug (Humanes *et al.*, 2015). The mechanism of VCM causing renal toxicity is not completely understood (Uckun *et al.*, 2020). Even so, it is frequently linked to acute kidney injury (Wen *et al.*, 2018). VCM is primarily removed via glomerular filtration and partially by tubular secretion. VCM-induced renal toxicity is caused by VCM accumulation, which leads to proximal renal tubular cell necrosis, as illustrated in animal studies (Gupta, Biyani and Khaira, 2011). Numerous studies have found that oxidative stress, apoptosis, and inflammation perform an important part in its pathophysiology, inducing acute tubule-interstitial injury and renal tubular ischemia in renal proximal tubular epithelial cells (Gupta, Biyani and Khaira, 2011; Arimura *et al.*, 2012; Mergenhagen and Borton, 2014; Humanes *et al.*, 2015). The mechanisms of VCM caused renal toxicity include raised production of reactive oxygen species (ROS), inflammatory cytokines and chemokines, elevated membrane lipid peroxidation, as well as antioxidant protection consumption (Fouad *et al.*, 2014)

Pentoxifylline (PTX) is employed for mange intermittent claudication as well as vascular dementia(Jeswani *et al.*, 2009). It's a nonspecific phosphodiesterase inhibitor that suppresses the production of many pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) (Zabel, Schade and Schlaak, 1993). PTX inhibits additional discharge of superoxide and hydrogen-peroxide ions, and it is confirmed that PTX posse anti-oxidant properties (Asvadi *et al.*, 2011). PTX has been shown to inhibit (TNF-α) development and regulate the development of other mediator like interlukin-6, interleukin -1, and interleukin -12 (Ji *et al.*, 2004).

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Captopril is an active inhibitor of ACE enzyme (Daharwal and Singh, 2015). it is used to treat hypertension and congestive heart failure (El-shanawany *et al.*, 2014; Vahidirad *et al.*, 2017) . Captopril reduce the concentration of angiotensin II in the circulation and tissue. Also, Captopril, as a thiol-containing molecule, has strong antioxidant activates, as well as inhibits lipid peroxidation (Fouad *et al.*, 2014). Anti-inflammatory action and antioxidant activity are also found in captopril (Miguel-carrasco *et al.*, 2010).
Based on previous research that show nephroprotective effect by inhibiting oxidative stress and inflammatory response. It is postulated that pentoxifylline and captopril may enhance renal function via their antioxidant and ant inflammatory activity. So in this study we investigate their protective effect against vancomycin induced nephrotoxicity in rat model.

2. Materials and Methods

Drugs and chemicals

Vancomycin (Julphar,UAE), Pentoxifylline ampule (Alex. Co. for Egypharma, Egypt), Captopril (Medochemie, Cyprus). Rat IL-6, malondialdehyde and tumor necrosis factor α ELISA kit (Sunlong Biotech Co., LTD).Urea kit (Abbott, USA). Creatinine kit (Randox, England).

Animals

The current research protocol was authorized by the College of Medicine/Al-Nahrain University's Institutional Board review. Forty albino male rats weighing (200-220 gram) were randomly chosen from the animal house of the College of Veterinary Medicine/Tikirit University. Before the study began, the animals were housed in the animal house of the College of Veterinary Medicine/Tikirit University; they were given two days to acclimate with environment of controlled temperature as well as 12-hour light/dark cycle. Each rat was provided with unrestricted access to food and tap water.

Experimental design

Forty albino male rats has been randomized assigned into four groups, each with ten rats, and were treated daily for 10 days as follows: group 1: rats were maintained on standard food and water, and orally administered (0.5 ml/kg/day) (DMSO) for 10 days. Group 2: rats were treated with (0.5 ml/kg/day) DMSO orally and on the 4th day, vancomycin (200 mg/kg/day IP) (Ahmida, 2012) was given. All treatments were maintained until day 10. Group 3: rats were treated with (100 mg/kg/d) (Hrenák *et al.*, 2013) captopril orally and on the 4th day, vancomycin (200 mg/kg/day IP) was given. All treatments were maintained until day 10. Group 4: rats were treated with (50 mg/kg/day IP) (Asvadi *et al.*, 2011) pentoxifylline and on the 4th day, vancomycin (200 mg/kg/day IP) was given. All treatments were maintained until day 10.

Preparation of serum samples

On the eleventh day, all of the animals were euthanized. Blood was taken from the animals prior euthanasia through an intracardiac puncture and promptly transported to plastic test tubes that did not contain anticoagulant. With the aid of glass rod the clot was removed and centrifuged for 15-20 minutes at 3000 rpm. The supernatant was then utilized to measure serum urea, creatinine and tumor necrosis factor alpha (TNF-α).

Estimation of serum urea concentration.

A ready-made auto analyzer kit for measuring serum urea concentrations was used to evaluate serum urea levels via a urease-modified Berthelot reaction (Fawcett and Scott, 1960). The concentrations of urea in the blood were determined and represented in milligrams per deciliter.

Estimation of serum creatinine concentration.

The level of serum creatinine were calculated utilizing a ready-made auto analyzer kit for this purpose, which can be evaluated in serum according to the Jaffe reaction (Acta and Chemistry, 1973). The serum creatinine concentrations were represented in milligrams per deciliter.

Assessment of serum (TNF-α).

Measurement of serum TNF-α concentration was done using the Sandwich ELISA method, utilizing a commercially available TNF-α assay kit following the manufacturer's instructions (Yin *et al.*, 2008). The result was represented in (ng/l).

Preparation of Kidney Tissue Homogenate

It prepared by homogenizing 1 gram of renal tissue with ten ml phosphate buffer saline via homogenizer (Bhattacharyya, Pandit and Mukherjee, 2003). For one minute at 4°C, then stored at-20°C overnight. In order to break the cell membrane two freezing-thaw cycle were done. After that homogenate were centrifuge for five minutes at 5000 x at 2-8 C. collect the supernatant and kept at – 20 to estimated tissue MDA and IL-6.

Estimation of tissue malondialdehyde concentration.

The level of MDA in kidney tissue was determined through using ELISA technique, which is based on the competitive inhibition enzyme immunoassay concept (Diskapi *et al.*, 2013). The result was represented as (ng/ml).

Estimation of tissue interlukin-6 concentration

The tissue interlukin-6 (IL-6) levels was estimated using the Sandwich ELISA method, utilizing a commercially available IL-6 assay kit following the manufacturer's instructions. The result was represented in (ng/l).

Estimation of histopathological change in the kidney (Dabak and Kuloglu, 2009).

The slides from every animal were labelled and investigated under a light microscope by a blind investigator searching for microscopic signs of renal toxicity. Tubular epithelial changes (swelling,

vacuolation, cell desquamation, and necrosis), inflammatory cell infiltration, and vascular congestion were all investigated in the kidneys. The damage were restricted to the tubule-interstitial regions.

Statistical analysis

An independent Student's t-test was employed for analyzing the numerical data. The Mann-Whitney U test was used to compare histological scores between the two groups in SPSS 23.0, which was used to determine statistical significance. At the $P < 0.05$ level, the difference was considered significant.

3. Result

Captopril and PTX effects on serum urea and creatinine levels

The mean serum urea and creatinine levels (±SEM) were highly significant elevated in the VCM group ($P < 0.001$) in comparison with the control group. When compared with VCM group, mean serum urea and creatinine in the groups treated with captopril and PTX were highly significant reduced ($P< 0.001$). In the PTX group, serum urea and creatinine levels were decreased to a near normal level, in comparison with control group and there is no significantly different ($p > 0.05$). The group of PTX had closest mean of urea and creatinine to that of the control group. The mean serum creatinine of PTX was no significant difference compared to that of the captopril group ($p > 0.05$) but the mean serum urea of pentoxifylline was significantly different compared to that of the captopril group ($p < 0.05$) as shown in table 1.

Table 1. Serum urea and creatinine levels (mg/ml) of study groups.

Group N=10	Serum Creatinine (Mean ±SEM) (mg/ml)	Serum Urea (Mean ±SEM) (mg/ml)
Control	0.79 ± 0.03	33.30 ± 1.03
Vancomycin	1.66 ± 0.04 a**	87.5 ± 0.95 a**
Captopril	0.87 ± 0.03 aNS ,b**	41.9 ± 3.16 a*. b**
Pentoxifylline	0.84±0.02aNS, b**, cNS	32.9 ± 2.83 aNS , b** , c*

N= Animals number, SEM= standard error of mean, a= when compare with that of control group, b= when compare with that of vancomycin group, c= when compare with that of Captopril group, NS= No different statistically ($p>0.05$), *= significantly different ($p<0.05$), **= high significantly different ($p<0.001$).

Captopril and PTX effects on serum TNF-α, renal tissue IL-6 and renal tissue MDA levels.

In the group of VCM the mean serum TNF-α, renal tissue IL-6 and tissue MDA levels (±SEM) when compared to that of control group were highly significant increased ($p<0.001$). Mean serum TNF-α, renal tissue IL-6 and tissue MDA levels in the groups treated with captopril and PTX were highly significance reduced when compared to that of VCM ($p<0.001$).In group treated with captopril and PTX mean serum TNF-α, renal tissue IL-6 and tissue MDA levels were decreased closed to that of normal group and there is no difference when compared to that of control group ($p>0.05$). PTX had closest mean serum TNF-α, renal tissue IL-6 and tissue MDA levels to that of the control group. The mean serum TNF-α, renal tissue IL-6 and tissue MDA levels of PTX had no significant difference compared to those of the captopril group ($p > 0.05$) as shown in table 2.

Table 2. Serum TNF-α, renal tissue IL-6 and renal tissue MDA levels of study groups.

Group N=10	Serum TNF-α level (Mean ±SEM) (ng/l)	Tissue IL-6 level (Mean ±SEM) (ng/l)	Tissue MDA level (Mean ±SEM) (ng/ml)
Control	49.85 ± 2.55	24.67 ± 0.88	57.16 ± 2.54
Vancomycin	96.49 ± 1.45 a**	47.96 ± 1.27 a**	105.87± 3.27 a**
Captopril	55.11 ± 2.14 aNS, b**	26.78 ± 0.77 aNS, b**	62.77 ± 1.22 aNS, b**
Pentoxifylline	53.01 ± 2.25 aNS, b**, cNS	25.91 ± 1.30 aNS, b**, cNS.	61.90 ± 2.84 aNS, b**, cNS

N= Animals number, SEM= standard error of mean, a= when compare with that of control group, b= when compare with that of vancomycin, group, c= when compare with that of Captopril group, NS= No statistical difference ($p>0.05$), *= significantly different ($p<0.05$), **= high significantly different ($p<0.001$).

Captopril and PTX effects on histopathological scores

The mean histopathological score (±SEM) in group of VCM when compared to that of control group were highly significant increased ($p<0.001$). Comparison of VCM mean histopathological score with groups treated with captopril and PTX show highly significant reduction in histopathological score ($p<0.001$). The mean histopathological score of PTX had no significant difference compared to those of the captopril group ($p > 0.05$) as shown in table 3. Figures 1 clarify histopathological examinations of renal sections from different groups.

Table 3. Histopathological scores of study groups

Group N=10	Histopathological score
Control	0.00 ± 0.00
Vancomycin	3.40 ± 0.16 a**
Captopril	1.60 ± 0.22 a**, b**
Pentoxifylline	1.40 ± 0.16 a**, b**, cNS.

N= Animals number, SEM= standard error of mean, a= when compare with that of control group, b= when compare with that of vancomycin, group, c= when compare with that of Captopril group, NS= No statistical difference ($p>0.05$), *= significantly different ($p<0.05$), **= high significantly different ($p<0.001$).

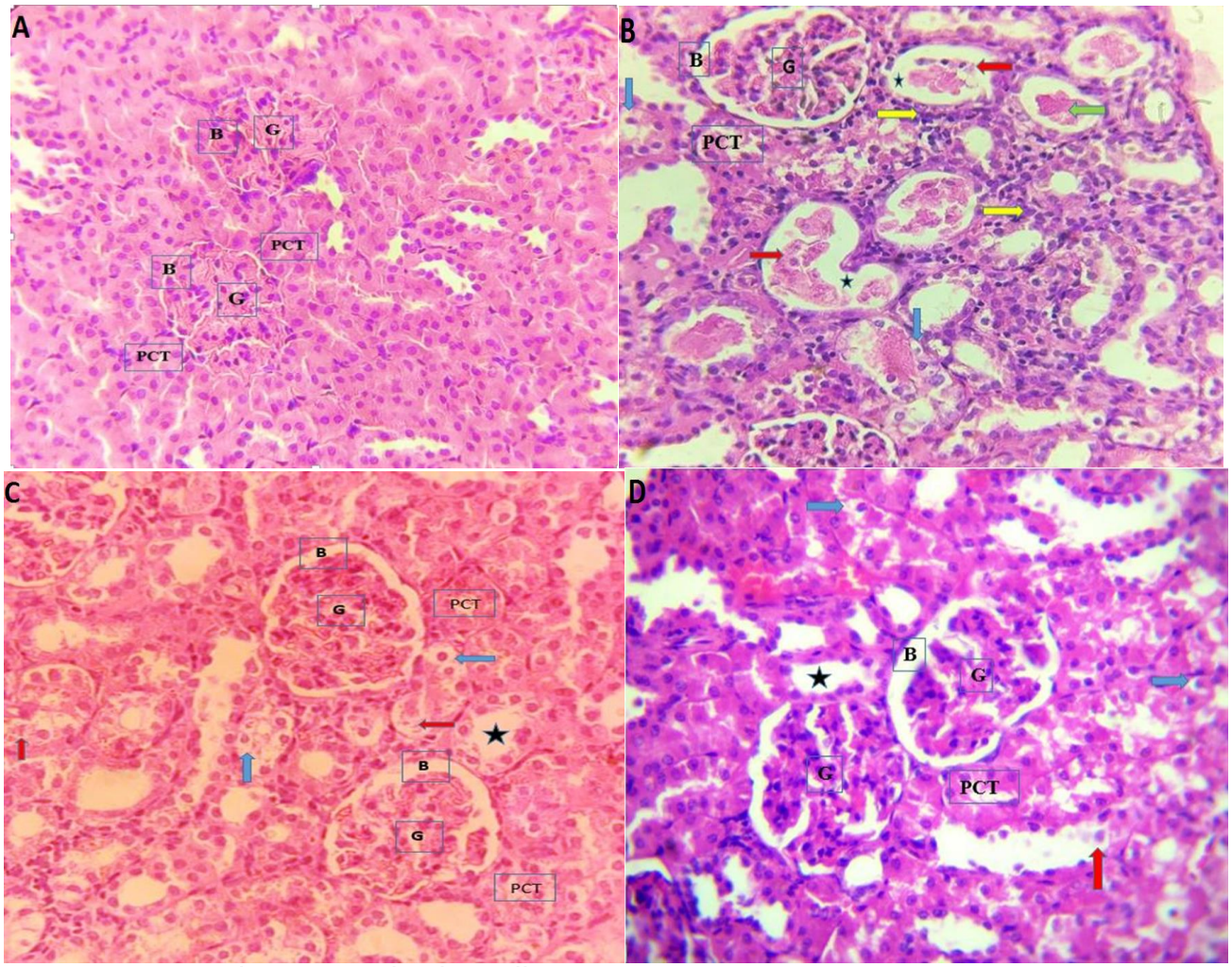

Figure 1. Sections of renal tissue of rat from different groups. (A) Control group showing normal kidney tissue. (B) Vancomycin treated group show changes involving (50 - 75) % of renal tubules. (C) Captopril treated group show changes involving (25) % of renal tubules. (D) Pentoxifylline treated group show changes involving (25) % of renal tubules. Cellular necrosis desquamated in the lumen of convoluted tubules, with vacuolated clear cytoplasm, interstitial infiltration, tubular cast and tubular dilatation are shown by red arrows, blue arrows, yellow arrows, green arrows and star, respectively.(G) Glomerulus, (B) Bowman's capsule, (PCT) Proximal convoluted tubule. H&E (40X).

4. Discussion

Vancomycin-induced nephrotoxicity

Nephrotoxicity caused by drugs represents approximately 18–27% of all acute renal damage cases. Though there's no specialized therapy for renal toxicity, it may be alleviated via supportive therapy(Thomas *et al.*, 2019).VCM, one of the effective therapy for MRSA infection, but it has potential to cause nephrotoxicity as a side effects (Mehmet *et al.*, 2018). Pathophysiology of VCM - caused renal toxicity may be linked to oxidative stress, in vivo VCM toxicity may be triggered by the drug's generation ROS linked with inflammatory reactions (Nishino *et al.*, 2003). Along with the action of inflammatory mediators, it has been shown that VCM increases oxidative stress and its related toxic consequences are caused by a decrease in free radical scavenging activity and the elevation of ROS (Elyasi, Khalili and Hatamkhani, 2012). The findings of this study show that VCM causes elevated serum urea and creatinine levels, which are biochemical indicators of kidney injury. Muscle metabolic activity generates creatinine. The kidneys eliminate the majority of the creatinine and keep it at a normal level, so kidney dysfunction raises serum creatinine values due to inefficient elimination(Yadav, Momin and Panjwani, 2020). May be attributed to the generation of ROS, which plays a crucial part in the mechanisms that cause tubular necrosis and reduced glomerular filtration rate (GFR). vasoactive substance which generated in response to oxidative stress , which may directly alter kidney function by causing renal blood vessel to constricted or reducing the glomerular capillary ultrafiltration coefficient, and so lowering the (GFR) (Choi *et al.*, 2012). In this study, VCM caused highly significantly elevated MDA level in renal tissue, oxidative stress have a major role in vancomycin-induced tissue injury (Elyasi, Khalili and Hatamkhani, 2012). VCM induces the production of ROS that can cause peroxidation of membrane lipid, and so result in compromising the function of membrane (Ahmida, 2012). MDA is a well-established parameter associated with peroxidation of lipid membrane and its levels represent the extent of occurrence of peroxidation (Basarslan *et al.*, 2014).In this study, VCM induced renal toxicity via causing serum TNF-α to be highly significant

increase in comparison with control group. The increased TNF-α value are considered to be linked to the event that oxidative damage appear to promote leukocyte aggregation in the tissues implicated, thereby exacerbating tissue damage indirectly via neutrophil stimulation. Stimulated neutrophils are thought to release enzymes like TNF-α, myeloperoxidase (MPO), elastase, and proteases and to release oxygen free radicals. Additionally, free radicals directly damage these tissues (Abd *et al.*, 2016). In this study, VCM caused a highly significant increase in the interlukin-6 level in renal tissue. IL-6 is a multifunctional cytokine and it is associated with pro-inflammatory activity. IL-6 is generated in large quantities by endothelial cells in response to pro-inflammatory signals such as TNF-α and hypoxia, and it's also a common reaction to tissue damage and organ failure (Nechemia-arbely *et al.*, 2008). Interleukin -6 is associated with a pro-inflammatory event that might be due to formation of free radicals during the inflammatory response (Frossi *et al.*, 2003). Ischemia, toxic, and autoimmune reactions all cause inflammatory responses. This involves soluble factors and cells interacting. TNF-α, IL-1b, and IL-6 are all produced by stimulated macrophages(Nadimohamed *et al.*, 2020).In the current study, VCM induced severe histopathological alterations with elevation of histopathological scores and these changes affecting between 50% and 75% of renal tubules.

Protective effect of pentoxifylline against vancomycin-induced nephrotoxicity

PTX causes a highly significant reduction in the elevated serum urea and creatinine levels, so it indicates its nephroprotective action. The protective effect of PTX achieved because PTX exerts a significant influence on the vascular endothelium, increasing the production of vasodilator prostaglandins, thus increasing blood flow and maintaining vascular integrity. It has been shown to enhance the actions of Endothelium-derived relaxing factor (EDRF), a well-known vasodilator, anti-aggregator, and anti-adhesive (Kaputlu *et al.*, 1997). PTX pretreatment effectively decreased serum creatinine, Blood urea nitrogen levels and reduced the decline in GFR in post-ischemic kidneys injury (Kim *et al.*, 2001). PTX caused a highly significant reduction in renal MDA tissue level. Increased ROS generation accelerates lipid peroxidation, elevating the amounts of lipid peroxidation products such as MDA as well as various TBARS that result in the destruction of cellular macromolecules(Rani, Sudhakar and Ramesh, 2017). PTX behaves as an efficient antioxidant, preventing lipid peroxidation by suppressing free oxygen radicals and, consequently, lowering MDA levels. This study shows that the use of PTX causes a highly significant reduction in serum TNF-α level. It is a nonselective PDE inhibitor that inhibits the production of a number of pro-inflammatory cytokines, such as TNF-α (Zabel, Schade and Schlaak, 1993). TNF-α is a pro - inflammatory cytokines that attracts a slew of tissue-damage-related mediators(Sherif, Abas and Zaitoun, 2018). PTX inhibits the elevated generation of TNF- α, which enhance cell apoptosis, and other cytotoxins that are essential elements of cellular proliferation (Kim *et al.*, 2003). In this study, PTX caused a highly significant reduction in renal IL-6 tissue level. It inhibits the production of a number of pro-inflammatory cytokines, such as tumor necrosis factor, interleukin-6, and interleukin-1 (Neuner *et al.*, 1994). PTX has demonstrated a nephroprotective effect by regulating inflammatory cytokines and nitric oxide production and correcting the oxidant/antioxidant equilibrium (Abo-Salem, 2013).

Protective effect of captopril against vancomycin-induced nephrotoxicity

Captopril is a useful nephroprotective agent because it causes a highly significant decrease in elevated serum urea and creatinine levels. Captopril may reduce efferent arteriolar resistance and mesangial cell contractility by inhibiting the rennin-angiotensin system (RAS).Other probable mechanisms involved in angiotensin converting enzyme inhibitors involve impaired vasodilator kinis breakdown and enhanced synthesis of vasodilator prostaglandin (Gotoh S, Ogihara T, Nakamaru M, Higaki J, Ohde H, Tabuchi Y, Kumahara Y, 1983). The present study documented that captopril caused a highly significant reduction in the renal MDA tissue level. MDA is used to measure lipid peroxidation, which happens due to free radicals that cause injury to the cell membranes (Nielsen *et al.*, 1997). Captopril, which contains sulphydryl group, seems to be a scavenger of oxygen-derived free radicals. Captopril reduced MDA levels as well as glutathione reductase and peroxidase activities (Ackerman Z, Oron-Herman M, Rosenthal T, Pappo O, Link G, Sela BA, 2009). Sulfhydryl compounds can counteract (ROS) via a hydrogen-donating or electron-transferring process (Ward, Loscalzo and Napoli, 2003). Bernstein et al report that captopril has been shown to block the conversion of angiotensin I to angiotensin II. Via its activities on the AngII-AT1 receptors, the peptide angiotensin II has a major effect on oxidative stress-related diseases. In many cells, AngII is a powerful stimulator of ROS, oxidative stress, and inflammation (Bernstein *et al.*, 2012). The enzymatic activity of superoxide dismutase and selenium-dependent glutathione-peroxidase was reported to be enhanced by captopril (Cavanagh *et al.*, 1995). Captopril caused highly significant reductions in the serum TNF-α level and tissue IL-6 level in comparison with the vancomycin group. Captopril's anti-inflammatory activity has already been demonstrated in various conditions associated with a rise in the inflammatory process, including

nephropathy (Tang *et al*., 2008), arthritis (Agha and Mansour, 2000), colitis (Jahovic *et al*., 2005), and uveitis (Jin *et al*., 2006). Angiotensin II triggers inflammatory responses, resulting in elevated the generation of pro-inflammatory cytokine TNF-α, which causes more tissue damage (Hayashi, Takai and Yamashita, 2010). Captopril suppresses the stimulation of the Nuclear Factor Kappa B (NF-kB) signaling pathway, which stimulates transcription of TNF-α and Inducible nitric oxide synthase (iNOS) genes (Jin *et al*., 2006; He *et al*., 2007). Captopril mediates its antioxidant and anti-inflammatory properties via blocking the angiotensin-converting enzyme (Ward, Loscalzo and Napoli, 2003). Captopril suppresses the inflammatory cytokine TNF-α and promotes the anti-inflammatory cytokine IL-10 production. These actions are achieved in part by captopril's direct impact on cytokine secretion and in part by captopril's antioxidant activity (Palmblad, 2002). Captopril previously demonstrated in animal models that it decreased interlukein-6 generation by preventing NF-kB, which is primary transcription factor responsible for the transcription of pro-inflammatory cytokines such as IL-6 (Miguel-carrasco *et al*., 2010).

5. Conclusion

From the correction of biochemical and histopathological parameter that altered via vancomycin we conclude that pentoxifylline and captopril exhibit nephroprotective activity and pentoxifylline have superior activity than captopril against vancomycin induced renal toxicity in male rat model.

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