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Original Research Article

Nephroprotective Effect of a Combination of Probiotics, Tender Coconut Water, and Vitamin E in Gentamicin-Induced Acute Kidney Injury in Rats

Siti T Zulaikhah[1*], Ratnawati Ratnawati[1], Atina Hussaana[2]

[1]*Department of Public Health, Faculty of Medicine, Universitas Islam Sultan Agung, Semarang, Central Java, Indonesia*
[2]*Department of Pharmacology, Faculty of Medicine, Universitas Islam Sultan Agung, Semarang, Central Java, Indonesia*

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ABSTRACT

Gentamicin increases Reactive Oxygen Species (ROS), leading to cell damage and kidney necrosis. The body counteracts free radicals by producing endogenous antioxidants. Natural antioxidants such as probiotics, vitamin E, and phenolic compounds are known to protect the kidneys. This study aims to evaluate the nephroprotective effect of a combination of probiotics, tender coconut water, and vitamin E on endogenous antioxidants in rats with an Acute Kidney Injury (AKI) model induced by gentamicin. The parameters measured were superoxide dismutase (SOD) and glutathione peroxidase (GPx). The study used a posttest-only control group design with 30 male Wistar rats divided into five groups: K1 (normal); K2 (gentamicin-induced); K3 (gentamicin + tender coconut water 8 mL/200 g BW); K4 (gentamicin + tender coconut water + probiotics); and K5 (gentamicin + tender coconut water + probiotics + vitamin E 1.8 IU/200 g BW). Gentamicin was administered at 20 mg/200 g BW/day via intraperitoneal injection. Data were analyzed using One-way ANOVA. The mean SOD levels in K2 were 23.77 ± 3.07%, increasing to 66.39 ± 3.07% in K5. The mean GPx levels in K2 were 23.77 ± 0.75 u/mg, rising to 61.94 ± 0.72 u/mg in K5. SOD and GPx levels were significantly higher in K5 compared to K2. The combination of probiotics, tender coconut water, and vitamin E exerts a nephroprotective effect in AKI model rats induced by gentamicin, as indicated by increased SOD and GPx levels compared to the negative control.

Keywords: Probiotics, tender coconut water, vitamin E, nephroprotective, endogenous antioxidants.

Introduction

Gentamicin is an aminoglycoside antibiotic used for infections caused by gram-negative bacteria. In addition to being useful as an antibiotic, gentamicin also has side effects if given in excessive doses, namely damage to the kidneys (nephrotoxic).[1] Kidney damage due to gentamicin in high doses will accumulate in the proximal tubule after being filtered in the glomerulus.[2] Accumulation of gentamicin in cells can cause an increase in reactive oxygen species (ROS), which can then trigger an increase in free radicals, causing cell damage and kidney necrosis.[3] Gentamicin can reduce endogenous antioxidants and increase ROS production, which can trigger oxidative stress. Gentamicin increases the formation of superoxide anions, hydrogen peroxide, and hydroxyl radicals and releases iron (Fe) from the mitochondria of the renal cortex, which causes lipid peroxidation *in vitro* and is a strong catalyst for the formation of free radicals.[4] Nephrotoxicity caused by gentamicin can be through oxidative stress with excessive ROS production.[5]The body's response to counteract free radicals is to produce endogenous antioxidants such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). Still, if the free radicals formed exceed endogenous antioxidants, exogenous antioxidants are needed to create a balance. Exogenous antioxidants from natural sources obtained from plants are essential.[6]

*Corresponding author. Email: sitithomas@unissula.ac.id,
Tel: +62 81390277161

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Several natural exogenous antioxidants such as probiotics, vitamin E, and phenolic compounds found in tender coconut water are known to protect against nephrotoxicity (nephroprotective). Research conducted by Zulaikhah *et al*.[7] showed that coconut water has an antioxidant effect on kidney cell damage caused by increased free radicals triggered by exposure to lead. Kunle-Alabi *et al*.[8] reported that coconut water has a protective effect on the kidneys and liver caused by exposure to monosodium glutamate in mothers and their offspring. Ekezie *et al*.[9] reported that tender coconut water protects against tetrachloride-induced kidney damage in Wistar rats. Research conducted by Nwangwa [10] showed that giving coconut water can prevent kidney damage in a rat model of alloxan-induced diabetes mellitus. Chrisanto[11] reported that probiotic drinks from tender coconut water have a strong antioxidant effect. Vitamin E has an antioxidant effect by eradicating peroxyl radicals, regulating oxidative changes in cell organelles, preventing lipid peroxidation, and preventing the destruction of kidney cells.[12] Nugraha *et al*.[13] also reported that Vitamin E exerts a protective effect on kidney damage in white rats induced with ethinyl estradiol. This study aims to evaluate the nephroprotective effect of a combination of probiotics, tender coconut water, and Vitamin E on endogenous antioxidants in rat models of Acute Kidney Injury due to Gentamicin.

Materials and Methods

Experimental animal

Ethical clearance for this study was obtained from the Medical/Health Research Bioethics Commission of the Faculty of Medicine, Unissula Semarang, with reference number 380/IX/2024/Komisi-Bioetik. The treatment of experimental animals and the examination of SOD and GPx, levels were conducted at the Center for Food & Nutrition Studies (PSPG) Gadjah Mada University Yogyakarta.

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Gentamicin induction
Gentamicin administration was carried out simultaneously with the administration of probiotics made from tender coconut water and vitamin E, with a dose of 100 mg/kg BW/day via Intraperitoneal injection.[14]

Administration of tender coconut water
Tender coconut water from green coconuts around 5-7 months old was obtained from the Yogyakarta area and its surroundings. The tender coconut water was given to the treatment group at 8 mL/200 g BB/day two times and administered for 14 days. The dose was adjusted to previous research and given orally by sonde for 2 weeks.[15]

Probiotic administration
Probiotics from product X containing *Lactobacillus* were added to tender coconut water at a dose of 18 mg/200 g BW for every 8 mL of tender coconut water, given orally using a tube for 2 weeks.[15]

Administration of vitamin
The dose of vitamin E was 1.8 IU/200 g BW, given orally for 2 weeks.[16]

Provision of treatment
Healthy Male Wistar rats (2 months old, 180-220 g) were used in this experiment. A total of 30 rats were randomly divided into 5 groups of 6 rats each.

Blood collection
Blood was withdrawn by inserting the microhematocrit tube into the ophthalmic vein in the corner of the mouse's eyeball periorbital, then rotated slowly until blood flowed and collected in 2 mL of Eppendorf tubes.[17]

Antioxidant assays
Examination of endogenous antioxidants by measuring SOD and GPx levels using the Elisa method.[17]

Statistical analysis
All values are expressed as mean ± SD. Data between groups were first tested by one-way ANOVA and then between two groups were analyzed by Pots Hoc Least Significant Different **(**LSD). Statistical analyses were performed using SPSS-26. A P value < 0.05 was considered statistically significant.[18]

Results and Discussion

The effect of the combination of probiotics, tender coconut water, and vitamin E on endogenous antioxidants is presented in Table 2. Indicators of endogenous antioxidants measured in this study were glutathione peroxidase (GPx) and Superoxide dismutase (SOD) levels. Data presented in Table 2 shows that the results of the normality test with Shapiro Wilk and homogeneity with Levene test for SOD and GPx levels have values >0.05. This indicates that both variables have normal and homogeneous data distribution, so the data were analyzed using the One-way ANOVA test. The lowest average SOD level in K2 was 23.77%, and the highest level in K1 was 77.59%. The average SOD level in K3 was 40.16%, K4 was 58.20, and K5 was 66.39%. The results of the ANOVA test showed a p-value: 0.0001, meaning that there was a significant difference in SOD levels in the five groups. The average GPx level observed in K2 was 23.77 u/mg, and the highest level observed in K1 was 72.41 u/mg. The average level of GPx in K3 was 39.73 u/mg, K4 was 51.43 u/mg, and K5 was 61.94 u/mg. The results of the ANOVA test showed a p-value of 0.0001, meaning there was a significant difference in GPx levels in the five groups. The results of this analysis indicate that the combination of probiotics, tender coconut water, and Vitamin E enhanced the activity of the endogenous antioxidants in gentamicin-induced acute kidney injury. Hence, combining probiotics, tender coconut water, and Vitamin E exerted a nephroprotective effect.

Table 1: Groups and treatments

Group	Treatment [a]
Group 1 (K1):	The healthy rat group, namely male albino rats of the Wistar strain, received a standard feed diet and drinking ad libitum
Group 2 (K2):	The negative control group was male albino Wistar rats induced by gentamicin and given a standard feed diet and drinking ad libitum
Group 3 (K3):	Treatment group 1, namely male albino Wistar rats induced by gentamicin and given a standard feed diet, drinking *ad libitum* and being given tender coconut water at a dose of 8 mL/200 g BW for 2 weeks
Group 4 (K4):	Treatment group 2, namely male albino Wistar rats induced by gentamicin and given a standard feed diet, drinking *ad libitum* and being given tender coconut water at a dose of 8 mL/200 g BW mixed with probiotics at a dose of 18 mg for 2 weeks.
Group 5 (K4):	Treatment group 3, namely male albino Wistar rats induced by gentamicin and given a standard feed diet, drinking *ad libitum*, tender coconut water at a dose of 8 mL/200 g BW mixed with probiotics at a dose of 18 mg and vitamin E at a dose of 1.8 IU/200 g BW for 2 weeks.[15]

After the treatment is complete, blood is taken to measure endogenous antioxidants, namely SOD and GPx levels.

Analysis of Figure 1 shows that the highest average levels of both SOD and GPx were seen in the group of mice induced by gentamicin and given tender coconut water with probiotics and vitamin E. This was also observed in the the group of mice induced by gentamicin and given tender coconut water with probiotics and vitamin E.

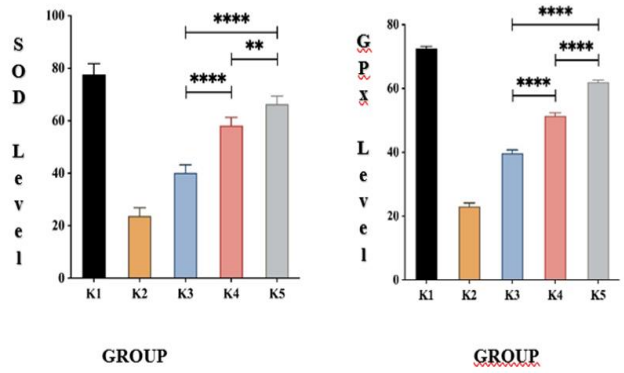

Figure 1: Results of the analysis of differences in mean SOD and GPx levels between groups using the LSD Post Hoc Test**.**

Table 2: Average, normality test, homogeneity test, and anova test for SOD and GPx levels in 5 groups

Variable (oxidative stress)	Group					
	K1[a] Average ± SD	K2[b] Average ± SD	K3[c] Average ± SD	K4[d] Average ± SD	K5[e] Average ± SD	p value
Levels of SOD (%)	77.59± 4.23	23.77 ± 3.07	40.16 ± 3.07	58.20 ± 3.07	66.39 ±3.07	
Shapiro-Wilk Test	0.964	0.961	0.910	0.961	0.960	>0.05*
Levene's Test						>0.05*
One way ANOVA						0.0001**
Level of GPx (u/mg	72.41 ± 0.75	23.77 ± 0.75	39.73 ± 1.02	51.43 ± 0.92	61.94 ± 0.72	
Shapiro-Wilk Test	0.796	0.459	0.649	0.849	0.976	>0.05*
Levene's Test						>0.05*
One way ANOVA						0.0001**

*: **Significant**

a: Healthy rat group, namely male white rats of the Wistar strain that received a standard feed diet and drink ed libitum, b: Negative control group, namely male white rats of the Wistar strain that were induced by gentamicin and received a standard feed diet and drink et libitum, c: Treatment group 1, namely male white rats of the Wistar strain that were induced by gentamicin and received a standard feed diet, drink et libitum and were given tender coconut water at a dose of 8 mL/200g BW for 2 weeks, d: Treatment group 2, namely male white rats of the Wistar strain that were induced by gentamicin and received a standard feed diet, drink et libitum and were given tender coconut water at a dose of 8 mL/200g BW mixed with probiotics at a dose of 18 mg for 2 weeks, e: Treatment group 3, namely male white rats of the Wistar strain that were induced by gentamicin and received a standard feed diet, drink et libitum, tender coconut water at a dose of 8 mL/200g BW mixed with probiotics at dose of 18 mg and vitamin E at a dose of 1.8 IU/200 g BB for 2 weeks.

This was also observed in the group of mice induced by gentamicin and given tender coconut water at a dose of 8 mL/200 g BW only (K3). There were significant differences in SOD and GPx levels between treatment groups 1 and 2, treatment group 1 with treatment group 3, and treatment group 2 with treatment group 3, meaning as follows: There was a significant difference in the average levels of SOD and GPx between group 1, group 2, and 3. There was a significant difference in the average levels of SOD and GPx between treatment 2 (Wistar rats induced by gentamicin) receiving tender coconut water at a dose of 8 mL/200 g BW mixed with probiotics at a dose of 18 mg and vitamin (K4) with treatment group 3, receiving tender coconut water with probiotics at a dose of 8 mL/200 g BW (18 mg) and vitamin E at a dose of 1.8 IU/200 g BW for 2 weeks (K5). The combination of probiotics, tender coconut water, and Vitamin E exhibited a nephroprotective effect in a gentamicin-induced Acute Kidney Injury. The combination exerted an antioxidant effect via an increase in endogenous (SOD and GPx) antioxidant activity. The average levels of SOD and GPx in K5 were the highest, followed by K4 and K3. The lowest levels of SOD and GPx were in group K2 (the group that was only induced by gentamicin). Gentamicin can induce kidney damage and accumulate in the proximal tubule after being filtered in the glomerulus.[2] Accumulation of gentamicin in cells can cause an increase in reactive oxygen species (ROS), which can trigger an increase in free radicals, causing cell damage and kidney necrosis.[3] ROS compounds that act as oxidants are hydrogen peroxide (H2O2), superoxide ion (O2•-), peroxyl radical (•OOH), hydroxyl radical (•OH), and singlet oxygen ($^1O2$).[19] Gentamicin increases the formation of superoxide ions (O2•-), hydrogen peroxide (H2O2), and hydroxyl radicals (•OH) and releases iron (Fe) from the mitochondria of the renal cortex. This condition causes *in vitro* lipid peroxidation and is a strong catalyst for forming free radicals. The finding of Patil *et al.* showed an increase in the production of hydrogen peroxide (H2O2) in the renal cortex of rats induced by gentamicin.[1]

Recently, gentamicin has also been shown to increase the formation of superoxide ions (O2•-) and hydroxyl radicals (•OH) in the mitochondria of the renal cortex. Superoxide ions (O2•-) are deleterious when present with H_2O_2 because they will form hydroxyl radicals (•OH), which is the most reactive and hazardous compound.[4] Increased free radicals can cause decreased endogenous antioxidant activity or antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione (GSH) and glutathione reductase (GR). Endogenous antioxidant activity such as catalase (CAT), superoxide dismutase (SOD), glutathione (GSH), glutathione reductase (GR), and glutathione peroxidase (GPx) can be decreased due to increased ROS formation by gentamicin.[20] Low levels of endogenous antioxidants can be used as a marker for high free radical levels in the body. The mechanism of gentamicin involves the increase in ROS, triggering oxidative stress and causing a decrease in endogenous antioxidants, as shown in Figure 2.

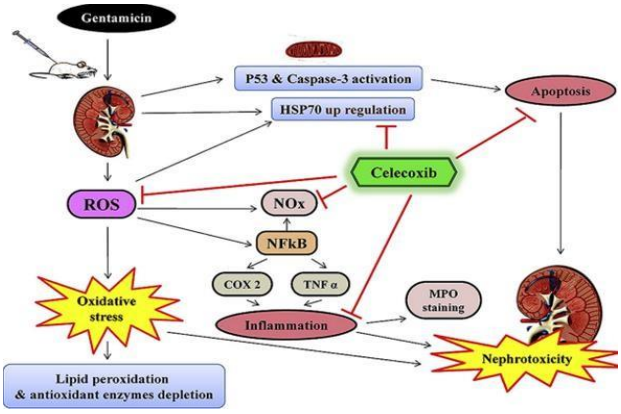

Figure 2: Mechanism of gentamicin against ROS, oxidative stress and antioxidant enzymes that trigger Nephrotoxicity.[21]

The body's response to counteract free radicals is by producing endogenous antioxidants. Still, if the free radicals formed exceed endogenous antioxidants, exogenous sources of antioxidants are needed to maintain a physiological balance. Foods containing natural exogenous antioxidants can reduce morbidity and mortality rates, primarily due to oxidative stress, and suppress the high prevalence of degenerative diseases.[19] This study proves that the combination of

probiotics, tender coconut water, and Vitamin E can increase SOD and GPx levels in rats with gentamicin-induced AKI. This effect was observed in the group of rats induced by gentamicin and given tender coconut water at a dose of 8 mL/200 g BW mixed with probiotics at a dose of 18 mg and vitamin E at 1.8 IU/200 g BW (K5) which gave a higher protection (SOD: 66.39% and GPx: 61.94 u/mg levels) when compared to the group of rats induced only by gentamicin (SOD: 23.77% and GPx: 23.77 u/mg) (K2). The group of rats induced by gentamicin and given tender coconut water at a dose of 8 mL/200 g BW mixed with probiotics (K4) showed higher SOD and GPx levels (SOD: 58.20% and GPx: 51.43 u/mg) when compared to the group of rats induced only by gentamicin (K2). The group of rats induced by gentamicin and given tender coconut water at a dose of 8 mL/200 g BW only (K3) showed higher levels of SOD and GPx (SOD: 40.16% and GPx: 39.73 u/mg) when compared to the group of rats induced by gentamicin alone (K2). The highest levels of both SOD and GPx were seen in group (K5), followed by (K4) and (K3). The combination of tender coconut water, probiotics, and vitamin E has a nephroprotective effect on rats in the Acute Kidney Injury model due to gentamicin induction.

A study by Kunle *et al*.[8] stated that tender coconut water protects against kidney and liver damage due to exposure to monosodium glutamate. Zulaikhah *et al*.[17] stated that tender coconut water can increase the levels of antioxidants SOD and GPx in gold miners exposed to mercury. Tender coconut water can increase SOD levels in mice exposed to cigarette smoke.[22] Tender coconut water made into powder and enriched with vitamin E can increase SOD and GPx levels in type 2 DM mice.[23] The active compounds found in tender coconut water and related to antioxidant status are methionine, L-arginine, selenium, vitamin C, and the minerals Zn, Mn, and Cu.[19,24] Methionine is an essential amino acid that contains sulfur. This compound is vital in protein synthesis. Methionine is a sulfur donor for cysteine. Cysteine is a compound the body needs to produce glutathione (GSH). GSH is the most critical antioxidant in the body.[19] The study's results by Azad *et al*. indicate that methionine can prevent nephrotoxicity and eliminate oxidative stress due to gentamicin.[25] Also, in a study Bashan *et al*. stated that administration of L-arginine can protect against kidney damage caused by gentamicin through protection against NO Synthase.[26] L-arginine is a non-essential amino acid in nitric oxide synthase (NO Synthase), a substrate producing citrulline and nitric oxide (NO). NO can inhibit xanthine oxidase (XO), increase SOD levels, total thiol levels (T-SH), vitamin C, and total antioxidants (TAC), and inhibit free radical chain reactions through lipid peroxidation. One of the processes of superoxide formation in the body is the oxidation of xanthine or hypoxanthine catalyzed by xanthine oxidase (XO), producing uric acid and superoxide. Hence, inhibiting the activity of XO by L-arginine leads to superoxide production decrease because the need for SOD to break down superoxide into H2O2 also decreases.[19] In a healthy organism, the endogenous antioxidant system consisting of SOD, CAT, GPx, and GR is responsible for homeostatic metabolism. It controls excess free radicals, but in the nephrotoxic condition caused by gentamicin induction, this system is eroded so that the conversion of H2O2 to hydroxyl radicals (OH•) increases. L-arginine indirectly triggers the activity of the antioxidant enzyme SOD by controlling the formation of H2O2, which inhibits the accumulation of H2O2.

Tender coconut water contains selenium at 0.001 mg/100 g. Selenium plays an essential role in protein synthesis and the activity of the enzyme glutathione peroxidase (GPx). GPx activity is greatly influenced by the presence of selenium. Selenium deficiency in the body can reduce GPx activity by up to 90%.[19] The body's selenium needs under normal conditions are met by food, but when the body experiences kidney damage, a greater supply of selenium is needed from exogenous sources. Selenium can protect against kidney damage induced by gentamicin.[4] The effectiveness of SOD enzymes can be increased by the presence of mineral nutrients such as copper (Cu) and zinc (Zn) and manganese (Mn).[19] Increased free radicals due to gentamicin induction can cause decreased SOD activity. The high nutrient content of tender coconut water can be utilized as an essential source of minerals, one of which is as an antioxidant cofactor of SOD. Zulaikhah *et al*. reported that deficiencies of Cu, Zn, and Mn minerals can reduce the activity of Cu-Zn SOD and Mn-SOD. Mn-SOD is a catalyst for the dismutase reaction of superoxide anion to hydrogen peroxide (H2O2) and oxygen (O2) in mitochondria. In contrast, Cu-Zn SOD functions as a catalyst for the dismutase reaction of superoxide anion to hydrogen peroxide (H2O2) and oxygen (O2) in the cytosol.[19]

The vitamin C content in tender coconut water makes it effective for increasing antioxidant levels because vitamin C can reduce superoxide radicals, hydrogen peroxide, and reactive oxygen species. The action of vitamin C as an antioxidant indirectly regenerates membrane antioxidant bonds, such as vitamin E, by lifting peroxyl radicals and singlet oxygen. Vitamin C works synergistically with vitamin E. Vitamin E, which is oxidized by free radicals into tocopheroxyl radicals, can react with vitamin C after receiving hydrogen ions from vitamin C; it metabolizes to tocopherol (vitamin E) and monodehydroascorbate. Monodehydroascorbate can spontaneously undergo dismutase into ascorbate (vitamin C) and dehydroascorbate.[27] Nugraha *et al*.[13] stated that Vitamin E protects against kidney damage in white mice given ethinyl estradiol. Vitamin E plays a role in preventing ROS and oxidative stress.[28]

Probiotics have antioxidant effects by preventing endothelial cell death caused by oxidants.[29] Probiotics can modulate the immune system, resistance to colonization, repair the intestinal barrier, and produce metabolites that can work locally, such as antimicrobials, enzymes, and organic acids. Probiotics have a role in increasing the production of short-chain fatty acids (SCFAs) and inhibiting the production of GDUT (*Gut-Derived Uremic Toxins*) and endotoxins so that probiotics can play a role in maintaining the integrity of the intestinal barrier, reducing the incidence of inflammation, oxidative stress and modulating immunity, thus playing a role in kidney protection.[30] Probiotic strain *Lactobacillus* sp can also repair the small intestine mucosa and increase energy efficiency.[31] Research by Cecilia *et al*. shows that the administration of probiotics can help to sustain healthy intestinal homeostasis, decrease obesity, and promote wellness.[32]

Conclusion

In this study, rats induced with gentamicin caused Acute Kidney Injury. The combination of probiotics, tender coconut water and Vitamin E has a nephroprotective effect in Acute Kidney Injury model mice due to gentamicin. The combination increased endogenous antioxidants, SOD and GPx levels compared to negative controls. Further studies are needed to evaluate its effectiveness in humans and to explore the underlying biochemical mechanisms in more detail.

Conflict of Interest

Authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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