

## RESEARCH ARTICLE

## ***Ganoderma lucidum* Polysaccharide Peptide Reduces Oxidative Stress and Improves Renal Function in Patient with Cardiometabolic Syndrome**

Syanindita Puspa Wardhani<sup>1</sup>, Khilmi Ainun Nadliroh<sup>1</sup>, Al Mazida Fauzil Aishaqena<sup>1</sup>, Fahriza Abid Sonia<sup>1</sup>, Achmad Guntur Hermawan Suryo Adji<sup>1</sup>, Intan Masyufah Hanim<sup>1</sup>, Rizkia Milladina Hidayatulloh<sup>1</sup>, Anna Fuji Rahimah<sup>2</sup>, Ardian Rizal<sup>2</sup>, Peter Sugita<sup>3</sup>, Ferry Sandra<sup>4,\*</sup>, Djanggan Sargowo<sup>2</sup>

<sup>1</sup>Master of Biomedical Science, Faculty of Medicine, Universitas Brawijaya, Jl. Veteran, Malang 65145, Indonesia

<sup>2</sup>Department of Cardiology, Faculty of Medicine, Universitas Brawijaya, Jl. Veteran, Malang 65145, Indonesia

<sup>3</sup>PT Sahabat Lingkungan Hidup, Jl. Embong Malang, Surabaya 60261, Indonesia

<sup>4</sup>Department of Biochemistry and Molecular Biology, Division of Oral Biology, Faculty of Dentistry, Universitas Trisakti, Jl. Kyai Tapa No. 260, Jakarta 11440, Indonesia

\*Corresponding author. Email: ferry@trisakti.ac.id

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### Abstract

**BACKGROUND:** Cardiometabolic syndrome is a risk factor for the development of diseases related to cardiovascular disease and decreased renal function. *Ganoderma lucidum* polysaccharide peptide (GLPP) has been reported to have anti-inflammatory and antioxidant properties. The current study was conducted to investigate the role of GLPP in inflammatory, oxidative stress and renal function markers of cardiometabolic subjects.

**METHODS:** A randomized double-blinded perspective control trial with pre-post design was conducted. Cardiometabolic syndrome subjects were treated with placebo or GLPP for 60 days. Blood serum was collected from each subject before the first capsule consumption and one day after the last capsule consumption. Serum tumor necrosis factor (TNF)- $\alpha$ , high-sensitivity-C-Reactive Protein (hs-CRP) and malondialdehyde (MDA) levels were

measured using enzyme-linked immunosorbent assay, while superoxide dismutase (SOD) level was measured using colorimetric assay. Serum urea and creatinine levels were measured using a clinical analyzer. The Cockcroft-Gault formula was used to calculate estimated glomerular filtration rate (eGFR).

**RESULTS:** Compared with the control group, the MDA level was significantly reduced, while the SOD level was significantly increased in the GLPP treatment group. Furthermore, serum urea and creatinine were lowered, while eGFR was increased in the GLPP treatment group.

**CONCLUSION:** Treatment of GLPP for 60 days could be beneficial for lowering oxidative stress and improving renal function of patients with cardiometabolic syndrome.

**KEYWORDS:** *Ganoderma lucidum*, cardiometabolic syndrome, inflammation, oxidative stress, renal function

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### Introduction

Cardiometabolic syndrome is a collection of pathological conditions which then become a major risk for the development of diseases related to cardiovascular disease.

(1) Cardiometabolic syndrome is also a risk factor for decreased renal function.(2,3) Cardiometabolic syndrome causes damage to the vascular endothelium which then causes the release of pro-inflammatory cytokines.(4) This can be a predisposing factor for decreased renal function through the process of endothelial dysfunction.(1)

Cardiometabolic syndrome can stimulate the recruitment of pro-inflammatory cells, one of which is macrophages. Macrophages can release pro-inflammatory cytokines, one of which is tumor necrosis factor (TNF)- $\alpha$ . (5,6) In addition, there is C-Reactive Protein (CRP) which also plays an important role as a promoter in pro-inflammatory and pro-atherogenic processes.(7) CRP has been known as a stable marker group that is not affected by circadian variations. These pro-inflammatory cytokines are related with the occurrence of endothelial dysfunction in the cardiometabolic syndrome which can affect renal vasculature leading to the decreased renal function.(8)

Free radicals and other prooxidants were significantly increased as renal failure progressed to its severe stages. The progress of renal failure is influenced by oxidative stress as one of the non-hemodynamic variables, either directly through renal ischemia and glomerular damage or indirectly through inflammation, hypertension, and endothelial dysfunction.(9-12) Depleted antioxidant enzymes, such as superoxide dismutase (SOD), catalase, and glutathione reductase, as well as proteinuria, inflammation, and electrolyte abnormalities, increased oxidative stress in chronic kidney disease (CKD) which has been linked to higher mitochondrial reactive oxygen species (ROS) and impaired mitochondrial activity.(11-13)

The renal function profile can be characterized by several biomarkers, including urea and serum creatinine. Urea is a metabolic waste product that comes from the breakdown of proteins. While creatinine is the end product of phosphocreatine catabolism which is mostly filtered by the kidneys.(14) Examination of renal function by examining serum urea-creatinine levels is a practical and inexpensive method.(15,16)

*Ganoderma lucidum* has been reported to have many benefits such as anticancer, antidiabetic, antihypertensive, antilipidemic, antimicrobial, anti-inflammatory and hypoglycemic effects as well as reducing insulin resistance. (17) Administration of *G. lucidum* can prevent cell injury due to oxidative stress by reducing intracellular ROS production and maintaining endothelial function.(18) The main active compounds in *G. lucidum* mycelia are triterpenes, polysaccharides, and proteins.(19) Polysaccharide peptide with high quality has been produced from *G. lucidum*, whose main bioactive compound is 1,3/1,6-D-Glucan.(20) The polysaccharide peptide induces antioxidant property by synthesizing superoxide dismutase (SOD), so that can protect the vascular endothelium.(21) Since the *G. lucidum* polysaccharide peptide (GLPP) could be potential for managing cardiometabolic syndrome, current study was

conducted to investigate the role of GLPP in inflammatory (TNF- $\alpha$  and high-sensitivity (hs)-CRP), oxidative stress (malondialdehyde (MDA) and SOD) and renal function (urea, creatinine, and estimated glomerular filtration rate (eGFR)) markers of cardiometabolic subjects.

## Methods

### Study Design and Subjects Recruitment

A randomized double-blinded perspective control trial with pre-post design was conducted. Subjects were recruited at the Cardiology Polyclinic of Saiful Anwar Hospital, Universitas Brawijaya Hospital and Lavalette Hospital in Malang from September to December 2021. The inclusion criteria were >18 years old patients with cardiometabolic syndrome based on The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) criteria, who were in stable condition for at least 2 weeks and routinely controlled. The exclusion criteria were patients with liver disease, renal failure, haematological disorder, rheumatological disorder, acute neurologic disorder, anaphylactic disorder, chronic obstructive pulmonary, systemic infection, malignancy, organ transplant, pregnancy, breastfeeding, heavy alcohol consumption and drug addiction.

### Intervention and Sample Collection

Included subjects consumed 1 capsule of 250-mg-freeze-dried-GLPP (PT. Sahabat Lingkungan Hidup, Surabaya, Indonesia) or placebo 3-times/day for 60 days. Each 250-mg-freeze-dried-GLPP capsule contained 180 mg  $\beta$ -1,3/1,6-D-glucan, meanwhile placebo contained inactive substance. Twenty mL blood sample was drawn from the medial vein of each subject on day 1 (before the first capsule consumption) and day 61 (one day after the last capsule consumption). The blood serum was collected and kept for the further assays. The study protocol was approved by the Ethics Committee of Faculty of Medicine, Universitas Brawijaya (No. 179/EC/KEPK/06/2021) and informed consents were signed by all subjects.

### TNF- $\alpha$ , hs-CRP and MDA Enzyme-linked Immunosorbent Assay (ELISA)

Human TNF- $\alpha$  (Biolegend, San Diego, CA, USA) and hs-CRP (Elabscience, Wuhan, China) ELISA kits were used to quantitatively measure the serum TNF- $\alpha$  and hs-CRP levels. Briefly, the sandwich-ELISA principle was used for both kits. The plates provided in these kits had been pre-coated with a specific antibody. Biotinylated detection antibody specific

for TNF- $\alpha$  or hs-CRP, avidin-horseradish peroxidase (HRP) conjugate and substrate were added and incubated in turn. Enzyme-substrate reaction was terminated and measured spectrophotometrically at a wavelength of 450 nm.

Meanwhile for MDA, MDA ELISA kit (Elabscience) with competitive-ELISA principle was used. Briefly, the plate provided in this kit had been pre-coated with MDA as well. Then MDA in the sample competed with a fixed amount of MDA bound with the biotinylated antibody. Avidin-HRP conjugate were added and incubated. Then a substrate solution was added, terminated and measured spectrophotometrically at a wavelength of 450 nm.

### SOD Colorimetric Assay

Total Superoxide Dismutase Activity (Elabscience) colorimetric assay kit was used. Briefly, SOD could inhibit O<sub>2</sub>- in oxidizing hydroxylamine to form nitrite. The activity of SOD could be determined by the colorimetric analysis with the OD value at 550 nm.

### Urea, Creatinine and eGFR Analyses

A Hitachi Analyzer (Hitachi, Tokyo, Japan) was used to measure serum urea and creatinine levels. Serum urea and creatinine levels were measured at wavelengths of 620 and 505 nm, respectively. To determine the required serum creatinine level, creatinine diluent and creatinine picrate reagent were used as standards. To calculate eGFR, the Cockcroft-Gault formula (22) was used.

### Statistical Analysis

Data was analyzed with SPSS version 20 (IBM, Corporation, Armonk, NY, USA). Data were displayed as mean $\pm$ standard deviation (SD). Normality and homogeneity tests were performed. Pre-post significant analyses were performed with Wilcoxon non normal and non-homogeneous results. In addition, for asymmetric delta value distributions, sign test was used.

## Results

In total, 62 cardiometabolic patients were included in the study. Subjects were randomly and equally grouped in control and treatment groups. As mentioned in Methods, subjects in control group consumed placebo capsule, while subjects in treatment group consumed 250-mg-freeze-dried-GLPP capsule. Slight and insignificant differences of age, blood pressure, weight, height body mass index (BMI) and heart rate variables were observed in both groups (Table 1).

### Role of GLPP towards Inflammatory Markers

All inflammatory markers including TNF- $\alpha$  and hs-CRP were decreased in both groups at 60-days post-treatment (Figure 1). The decreases of TNF- $\alpha$  pre-post mean level of both control (Sign Test,  $p=0.000$ ) and treatment groups were significant (Sign Test,  $p=0.000$ ) (Figure 1A). The decreases of hs-CRP pre-post mean level of both control (Wilcoxon,  $p=0.000$ ) and treatment (Wilcoxon,  $p=0.000$ ) groups were also significant (Figure 1B).

### Role of GLPP towards Oxidative Stress Markers

Oxidative stress markers were decreased for MDA and increased for SOD in both groups at 60-days post-treatment (Figure 2). The decrease of MDA pre-post mean level of treatment group was significant (Wilcoxon,  $p=0.004$ ), but decrease of MDA pre-post mean level of control group was not significant (Wilcoxon,  $p=0.906$ ) (Figure 2A). Meanwhile increase of SOD pre-post mean level of treatment group was significant (Wilcoxon,  $p=0.000$ ), but the increase of SOD pre-post mean level of control group was not significant (Wilcoxon,  $p=0.652$ ) as well (Figure 2B).

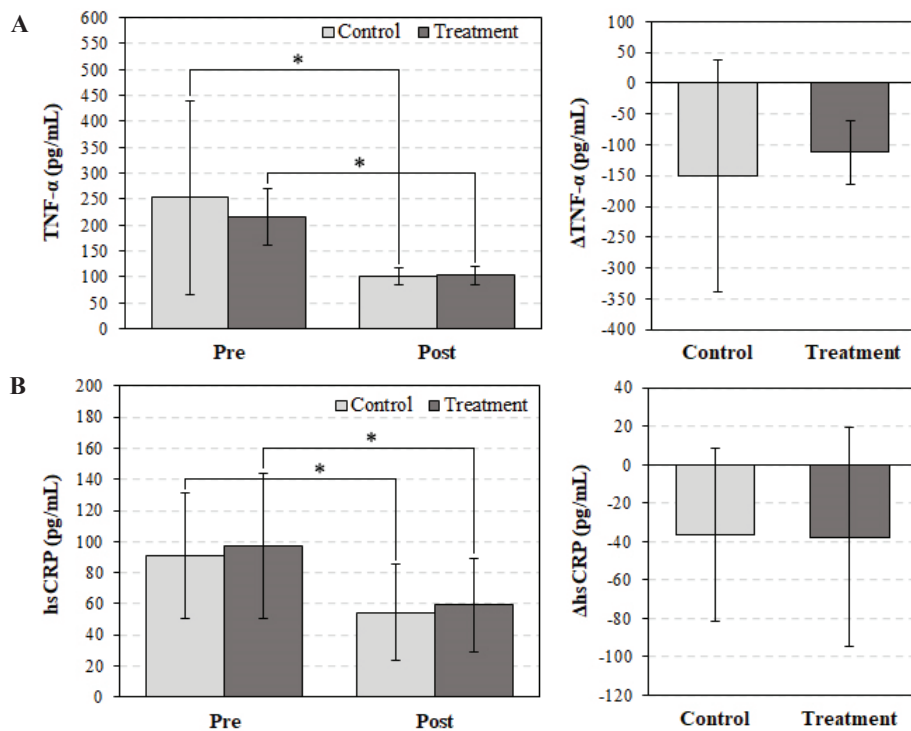
### Role of GLPP towards Renal Function Markers

Renal function markers for urea and creatinine were increased in control group, while the markers were decreased

**Table 1. Subject characteristics of control (n=31) and GLPP (n=31) groups.**

Variable	Control Group (Mean $\pm$ SD)	GLPP Group (Mean $\pm$ SD)	<i>p</i> -value*
Age (years)	59.50 $\pm$ 2.10	58.27 $\pm$ 2.50	0.721
Systolic blood pressure (mmHg)	133.27 $\pm$ 2.70	130.18 $\pm$ 2.70	0.421
Diastolic blood pressure (mmHg)	83.64 $\pm$ 1.70	81.64 $\pm$ 1.50	0.370
Weight (kg)	74.87 $\pm$ 1.42	75.53 $\pm$ 13.76	0.975
Height (cm)	155.96 $\pm$ 9.52	158.69 $\pm$ 8.13	0.301
BMI (kg/m <sup>2</sup> )	32.01 $\pm$ 11.85	31.02 $\pm$ 6.20	0.506
Heart rate	81 $\pm$ 14.41	76.96 $\pm$ 11.37	0.652

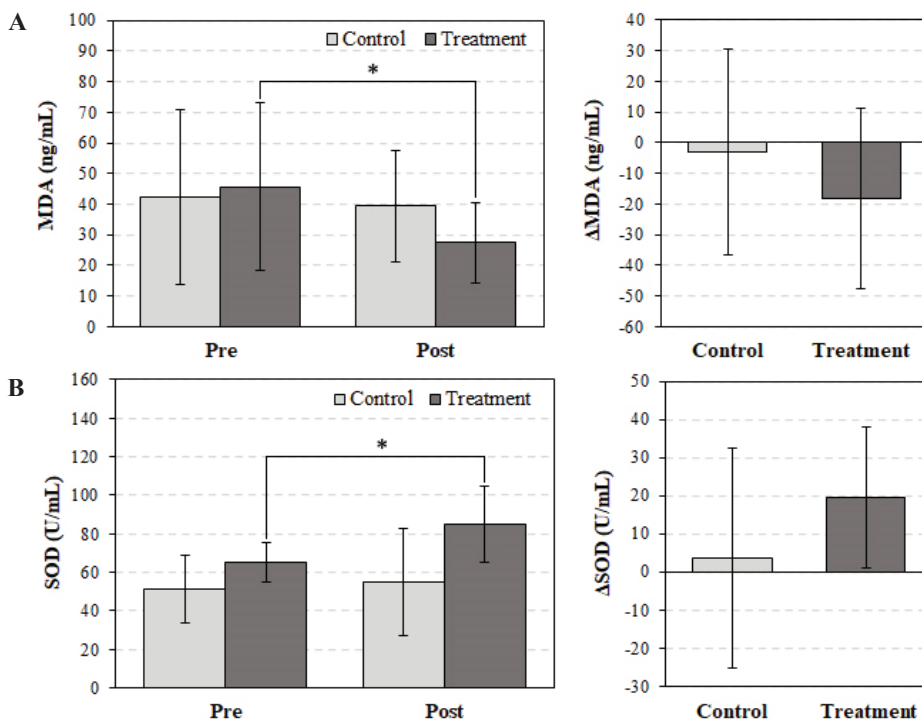
\*Tested with paired t-test.



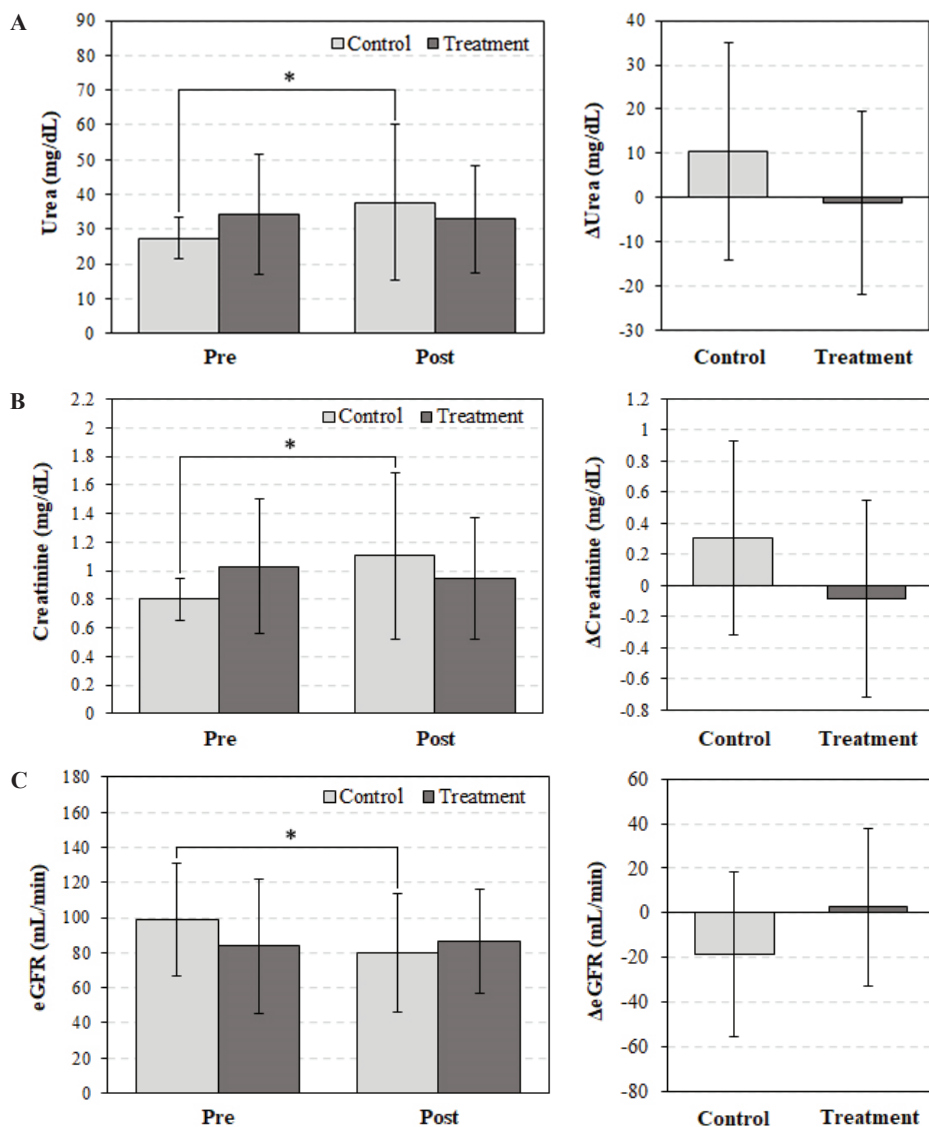
**Figure 1. Role of GLPP towards Inflammatory Markers.** Pre-post blood serum of subjects in control and treatment groups were collected and processed for TNF- $\alpha$  (A) and hs-CRP (B) ELISA as described in Methods. TNF- $\alpha$  and hs-CRP pre-post mean levels were shown on the left panel while the  $\Delta$  values of TNF- $\alpha$  and hs-CRP were shown on the right panel. \* $p < 0.05$ .

in treatment groups at 60-days post-treatment (Figure 3). The increase of urea pre-post mean level of control group was significant for both urea (Wilcoxon,  $p=0.015$ ) and creatinine (Sign Test,  $p=0.026$ ) (Figure 3A). Meanwhile, the decrease of urea pre-post mean level of control group was not significant for both urea (Wilcoxon,  $p=0.806$ ) and creatinine (Sign Test,  $p=0.472$ ) (Figure 3B).

Based on Cockcroft-Gault formula, eGFR was decreased in control group, while the eGFR were increased in treatment groups at 60-days post-treatment (Figure 3C). The decrease of eGFR pre-post mean level of control group was significant (Wilcoxon,  $p=0.004$ ). The increase of eGFR pre-post mean level of treatment group was not significant (Wilcoxon,  $p=0.590$ ).



**Figure 2. Role of GLPP towards Oxidative Stress Markers.** Pre-post blood serum of subjects in control and treatment groups were collected and processed for MDA ELISA (A) and SOD colorimetric assay (B) as described in Methods. MDA and SOD pre-post mean levels were shown on the left panel while the  $\Delta$  values of MDA and SOD were shown on the right panel. \* $p < 0.05$ .



**Figure 3. Role of GLPP towards Renal Function Markers.** Pre-post blood serum of subjects in control and treatment groups were collected and processed for urea (A) and creatinine (B) measurements as described in Methods. C: eGFR calculation with Cockcroft-Gault formula. Urea, creatinine and eGFR pre-post mean levels were shown on the left panel while the Δ values of urea, creatinine and eGFR were shown on the right panel. \**p*<0.05.

## Discussion

Studies in GLPP has shown that treatment of GLPP decreased the levels of inflammatory cytokines in atherosclerotic mice model (23), atrial fibrillation (24), dyslipidemic and high risk coronary heart disease patients (25). Current results showed that hsCRP, and TNF- $\alpha$  were significantly decreased in both control and treatment groups. These results suggested that with current selective inclusion and exclusion criteria, included subjects were optimally treated and routinely controlled, hence the inflammations in both subject groups were managed well and in stable condition.

However, when the risk of oxidative stress parameters were evaluated, current results showed that MDA level of the control group remained high after 60 days treatment, only slight nonsignificant decrease of MDA was observed.

Meanwhile, the MDA level of the treatment group was significantly decreased. Aligned with the MDA results, the SOD level of the control group was not increased significantly after 60 days treatment. Meanwhile the SOD level of the control group was increased significantly. These results showed that GLPP-treated subjects had lower oxidative stress suggesting the GLPP could be potential for preventing development of oxygen stress-induced inflammation. The decrease of MDA and significant increase of SOD in the GLPP treatment group were also reported in atherosclerotic (26) and type 2 diabetes mellitus rats studies (27,28). In human, with the treatment of GLPP, subjects with atrial fibrillation (24) and stable angina pectoris (17) showed a decrease of MDA level. It has been suggested that Dectin-1, a C-type lectin-like receptor, binds to  $\beta$ -D-glucan. Histone acetylation is a mechanism through which Dectin-1 engagement with  $\beta$ -D-glucan promotes manganese SOD (MnSOD) production.(29)

In renal function, current results showed that serum urea and creatinine levels were increased significantly in the control group while the urea and creatinine levels were decreased in the treatment group. Meanwhile eGFR was decreased significantly in the control group while the eGFR were increased in the treatment group. These results suggested that GLPP could improve the renal function of the subjects. Administration of GLPP has been reported to support the defense of glomerular vascular endothelial cells, increase reperfusion ability in cell injury condition (30), decreased mesangial matrix proliferation and extracellular matrix deposition in renal tubules of diabetic nephropathy-modified rats (31).

Despite current cardiometabolic results, earlier study in obese subjects also showed a decrease in serum urea and creatinine levels after administration of GLPP.(32) In the current study, although GLPP treatment did not reduce serum urea and creatinine as well as induce eGFR significantly, by comparing the control group, these improvements have shown remarkable results. Longer GLPP treatment and observation should be conducted to investigate possible role of GLPP to further increase the renal function in cardiometabolic subjects. In addition, investigation with large number of subjects numbers should be pursued.

## Conclusion

Compared with the control group, the MDA level was reduced as well as the SOD level was increased in the GLPP treatment group. Furthermore, serum urea and creatinine were lowered, while eGFR was increased in the GLPP treatment group. Taken together, treatment of GLPP for 60 days could be beneficial for lowering oxidative stress and improving renal function of patients with cardiometabolic syndrome.

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## Authors Contribution

SPW, KAN, AMFA, FAS, AGHSA, IMH, RMH, AFR, AR, DS, and PS were involved in planning the work. AFR, AR, and DS were involved in supervising the work. PS was involved in supporting the drug production and supervising the work. SPW, KAN, AMFA, and FS performed the measurements, processed the experimental data, performed the analysis, drafted the manuscript and designed the figures. SPW, KAN, AMFA and FS also performed the statistical analysis and aided in interpreting the results and worked on the manuscript. All authors discussed the results and commented on the manuscript.

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