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Original Article

Effect of β-1,3-1,6-D-glukan (*polysaccharide peptide*) from miselia ganoderma lucidum extract as antioxidant and antiinflammation towards left ventricular systolic function in cardiometabolic patients

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ABSTRACT

Background: Cardiometabolic disease (CMD) describes a metabolic condition often associated with cardiovascular disease. It has been revealed that the Ganoderma lucidum polysaccharide peptide (GLPP) possesses anti-inflammatory and antioxidant qualities.
Objective: This study aimed to find out how GLPP affected oxidative stress, inflammation, and left ventricular function in individuals with cardiometabolic syndrome.
Methods: A multicenter double-blinded randomized controlled trial was carried out. Subjects with cardiometabolic syndrome received either GLPP or a placebo for ninety days. Before taking the initial treatment and one day following the last treatment intake, blood samples were taken from every participant. The enzyme-linked immunosorbent assay was used to evaluate the levels of serum tumor necrosis factor (TNF)-α, interleukin-6 (IL-6), malondialdehyde (MDA), and high-sensitivity-C-Reactive Protein (hs-CRP) while the colorimetric test was used to measure the levels of superoxide dismutase (SOD). Global longitudinal strain (GLS) and Left ventricle ejection fraction (LVEF) were measured by single echocardiographer expert validation.
Results: The MDA level was decreased in the GLPP treatment group (mean 56.0 ± 71.4 ng/mL to 27.7 ± 12.0 ng/mL, p= 0.023) compared to the control group (mean 39.3 ± 29.2 ng/mL to 38.3 ± 17.7 ng/mL, p= 0.719). However, the SOD level remained constant in the GLPP treatment (mean 122.2 ± 176.1 U/mL to 93.0 ± 40.9 U/mL, p=0.925) instead of significantly declining in the control group (mean 102.0 ± 67.3 U/mL to 64.0 ± 52.0 U/mL, p=0.016). The marker of TNF-α and hsCRP were significantly decreased in all groups (both p<0.05), but IL-6 was only significantly decreased in the control group (mean 1149.3 ± 581.7 pg/mL to 744.8 ± 336.5 pg/mL, p=0.010). The GLS was significantly decreased in the GLPP treatment group (-16.1 ± 4.1 to -17.5 ± 4.8, p=0.048) but there was no difference in LVEF in both groups (p>0.05).
Conclusion: Patients with cardiometabolic syndrome may benefit from GLPP treatment for 90 days in terms of reduced inflammation, oxidative stress, and improved systolic left ventricular performance.

1. Introduction

Cardiovascular diseases (CVDs) that are associated with metabolic diseases (diabetes mellitus, genetic metabolic diseases, atherosclerosis, obesity, etc.) are Cardiometabolic Diseases (CMDs).[1] Patients with CMD are also at risk for impaired left ventricular function.[2] Many studies have been conducted on the processes of hypertension, atherosclerosis, and CVDs, including coronary artery disease (CAD) and cerebrovascular illness. A complicated mechanism of metabolic and molecular alterations in oxidative stress, inflammation, endothelial dysfunction, and lipid metabolism plays a significant role in the development of various disease processes.[1] Endothelial damage is the first stage in the pathophysiology of CVDs. It exposes the cell layers to potentially harmful inflammatory processes, which result in the formation of lesions.[3]

Because endothelial cells and vascular smooth muscle cells release damaging free radicals, cellular oxidative stress (OxS) is a factor in the pathogenesis of CMDs. Free radicals are unpaired free electrons that are found in the outermost orbital of reactive oxygen species (ROS). To become stabilized, they interact with elements of the cell, such as protein, DNA, or lipid. The two main oxidants that significantly affect cardiovascular disease are superoxide and nitric oxide. Oxidative stress was brought on by an imbalance in the body's defensive mechanisms against ROS generation. Antioxidants reduce the damage produced by oxidative stress by squelching reactive oxygen radicals.[3] The term "meta-inflammation" has been used to characterize the low-grade, persistent inflammatory response associated with metabolic illnesses such as diabetes, obesity, and other conditions generated by metabolism. When a metabolic syndrome is present, there is metainflammation in several tissues, including the heart that impairs it further.[4] Thus anti-inflammatory therapies may benefit CVDs. [2]

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Numerous health benefits of Ganoderma lucidum had been documented, including reduced insulin resistance and anticancer, antidiabetic, antihypertensive, antilipidemic, antibacterial, and anti-inflammatory properties.[5] Ganoderma lucidum administration could stop oxidative stress-induced cell damage by lowering intracellular ROS generation and preserving endothelial function. In Ganoderma lucidum triterpenes, mycelia, polysaccharides, and proteins are the primary active ingredients.[6] High-quality polysaccharide peptide has been extracted from Ganoderma lucidum. Its primary bioactive ingredient is 1,3/1,6-D-glucan. By producing superoxide dismutase (SOD), the polysaccharide peptide generates antioxidant properties that can shield the vascular endothelium.[7] The study aimed to find out how G. lucidum polysaccharide peptide (GLPP) affected oxidative stress (superoxide dismutase (SOD) and (malondialdehyde (MDA)), inflammation (IL-6, TNF-α and high-sensitivity-CRP), and left ventricular function (LVEF by Teich, LVEF by Biplane, GLS) in individuals with cardiometabolic syndrome.

2. Materials and Method

The study design and subject was a multicenter double-blinded randomized controlled trial. From September 2021 to January 2022, subjects were recruited at the Lavalette Hospital, Universitas Brawijaya Hospital, and Saiful Anwar General Hospital, Malang, Indonesia. Patients with cardiometabolic syndrome according to The National Cholesterol Education Program (NCEP) and Adult Treatment Panel III (ATP III) criteria[8] (three or more of the following five criteria were met: waist circumference over 40 inches (men) or 35 inches (women), blood pressure over 130/85 mmHg, fasting triglyceride (TG) level over 150 mg/dl, fasting high-density lipoprotein (HDL) cholesterol level less than 40 mg/dl (men) or 50 mg/dl (women) and fasting blood sugar over 100 mg/dl.), routinely controlled, older than eighteen, and in stable condition for at least two weeks met the inclusion criteria. Patients with a history of malignancy, heavy alcohol consumption, drug addiction, heart failure NYHA Class IV, malignant arrhythmia, pregnancy, breastfeeding, acute inflammation, acute coronary syndrome, percutaneous coronary intervention history, bypass history, inadherence to treatment, organ transplant acute neurologic disorder, anaphylactic disorder, acute hepatitis, renal failure, hematological disorder, rheumatological disorder, acute inflammation, dyspnea, and poor echocardiogram image quality were among the exclusion criteria.

Intervention and Sample Collection

For ninety days, the participants were given three times a day either a placebo or treatment. It contained a 250 mg freeze-dried GLPP (PT. Sahabat Lingkungan Hidup, Surabaya, Indonesia). Each capsule included 180 mg of β-1,3/1,6-D-glucan, on the other hand, the placebo contained an inert component. A 20 mL blood sample was drawn from each subject's medial vein on day 1 and day 91 (before to the first capsule ingestion and one day after the last capsule consumption). The serum from the blood was stored for the additional tests. All subjects completed informed consent forms, and The Ethics Committee approved the study protocol Committee of the Faculty of Medicine, Universitas Brawijaya (No. 179/EC/KEPK/06/2021). Serum IL-6, TNF-α, and hs-CRP levels were quantitatively measured using Enzyme-linked Immuno-sorbent Assay (ELISA) kits for human TNF-α (Biolegend, San Diego, CA, USA) and hs-CRP (Elabscience, Wuhan, China). In short, for both kits, the sandwich-ELISA principle was applied.

These kits included pre-coated plates with a particular antibody. Avagin-horseradish peroxidase (HRP) conjugate, substrate, and biotinylated detection antibody specific for hs-CRP or TNF-α were added and incubated sequentially. The enzyme-substrate reaction was stopped, and its wavelength (450 nm) was determined spectrophotometrically. In the meanwhile, the competitive-ELISA approach was applied with an MDA ELISA kit from Elbscience. In a nutshell, this package included a plate that had already been pre-coated with MDA. Following that, the sample was mixed with a predetermined amount of MDA conjugated to the biotinylated antibody Avidin-HRP conjugate, and it was then incubated. Following that, a substrate solution was added, the reaction was halted, and a spectrophotometric measurement of 450 nm was made.

SOD Colorimetric Assay

A colorimetric test kit from Labscience was utilized to measure total superoxide dismutase activity. In summary, SOD may prevent O2 from oxidizing hydroxylamine and forming nitrite. With an OD value of 550 nm, colorimetric analysis might be used to evaluate the activity of SOD.

Left ventricular function

Left ventricular function was examined at Saiful Anwar General Hospital on day 1 and day 91. LVEF was measured by Teich and Biplane (modified Simpson) methods, as well as GLS at GEhealthcare Vivid S70. Echocardiography was performed by one expert echocardiographer to minimize interobserver variability.

Statistical Analysis

SPSS version 26 (IBM, Corporation Armonk, NY, USA) was used to analyze the data. The information was shown as mean ± standard deviation (SD). Kolmogorov Smirnov test for homogeneity and normality was run. The paired t-test was used for pre-post significant analyses in either normal or Wilcoxon non-normal and non-homogeneous data. Furthermore, in cases of normal homogeneity the independent t-test and in cases of non-homogenous results, the Mann-Whitney test was calculated.

3. Results

Table 1. Subject characteristics of control and GLPP groups

Variable	Placebo (n=27) (Mean ± SD)	GLPP (n=25) (Mean ± SD)	p-value
Age (years)	60.22 ± 10.6	61.96 ± 8.438	0.518
Systolic blood pressure (mmHg)	138.3 ± 14.0	137.6 ± 15.6	0.580
Diastolic blood pressure (mmHg)	88.1 ± 9.3	84.8 ± 8.5	0.240
Weight (kg)	61.96 ± 8.4	62.0±8.4	0.732
Height (cm)	157.7 ± 7.8	156.8±10.1	0.719
BMI (kg/m²)	32.6 ± 12.6	29.8±3.8	0.614

BMI: Body Mass Index

Table 2. Subject characteristics medication of control and GLPP groups

Medication	Placebo (total n=27)	GLPP (total n=25)	P value
RAS Inihibitor	21 (77.8%)	18 (72%)	0.631
β Blocker	14 (51.9%)	13 (52%)	0.991
CCB	5 (18.5%)	4 (16%)	0.810
MRA	5 (18.5%)	4 (16%)	0.810
Statin	22 (81.5%)	21 (84%)	0.810
Diabetic Drug	5 (18.5%)	5 (20%)	0.892

RAS Inhibitor: Renin-Angiotensin System (Angiotensin Converting Enzyme (ACE) Inhibitor or Angiotensin Receptor Blocker), CCB: Calcium Channel Blocker, MRA: mineralocorticoid receptor antagonist, Diabetic drug: Oral Antidiabetic Drug or/and insulin

Table 3. Subject characteristics cardiometabolic criteria of control and GLPP groups

Variable	Placebo (total n=27)	GLPP (total n=25)	P value
TG ≥ 150 mg/dL or pharmacologic treatment	17 (63%)	16 (64%)	0.938
HDL < 40 mg/dL (men) < 50 mg/dL (women) or pharmacologic treatment	24 (88.9%)	23 (92%)	0.704
Blood Pressure ≥ 130/85 mmHg or pharmacologic treatment	22 (81.5%)	18 (72%)	0.417
FBG ≥ 100 mg/dL or pharmacologic treatment	19 (70.4%)	11 (44%)	0.054
Waist Circumference >102 cm (men) > 88 cm (women)	23 (85.2%)	24 (96%)	0.186

Baseline Characteristics

The study comprised 52 cardiometabolic patients in total. The control and treatment groups were randomly assigned to the subjects. According to the protocols, subjects in the treatment group took a 250 mg freeze-dried GLPP capsule, while those in the control group had a placebo capsule. Blood pressure, age, weight, height, and body mass index (BMI) factors were found to differ insignificantly between the two groups. (Table 1). Patients also consumed their routine medication and had insignificant results in both groups. (Table 2). From The NCEP-ATP III criteria for metabolic syndrome, a comparison of both groups showed insignificant results (Table 3). The data analysis results in Tables 1, 2, and 3 demonstrated that at baseline, there was no significant difference (p≥0.05) between the features of the treatment group and the placebo group. This suggests that at the outset of the clinical trial, participant homogeneity existed.

Role of GLPP towards Inflammatory Markers

Ninety days prior to therapy, levels of the inflammatory markers IL-6, TNF-α, and hs-CRP were observed (Table 4). The treatment group's pre-post mean IL-6 level was not statistically significant (p = 0.427), whereas it was significantly lower (p = 0.010) in the control group. Pre-post mean levels of TNF-α and hs-CRP decreased significantly (p=0.000) in both the treatment and control groups.

Role of GLPP towards Oxidative Stress Markers

Oxidative stress marker after treatment was decreased in the GLPP group (p=0.023) but insignificant in the control group in MDA (p=0.719). Meanwhile, the pre-post SOD in the GLPP group was insignificant (p=0.925), but the pre-post mean level of the control group was decreased significantly (p=0.016) (Table 4).

Role of GLPP towards Left Ventricular Systolic Function

Left ventricular function measured by echocardiography was LVEF by Teich, LVEF by Biplane, and GLS. Insignificant pre and post-tests were measured in both groups in LVEF by Teich (GLPP, p=0.756; Placebo, p=0.247) and LVEF by Biplane (GLPP, p=0.716; Placebo, p=0.159). Significant improvement in pre-post value was noted by GLS in the GLPP group (p=0.048) but insignificant in the control group (p=0.679) (Table 4).

4. Discussion

Our results showed that the MDA level was decreased in the GLPP treatment group compared to the control group. However, the SOD level remained constant in the GLPP treatment instead of significantly declining in the control group. Markers of TNF-α and hsCRP were significantly decreased in all groups, but IL-6 was significantly decreased in the control group. The GLS was significantly decreased in the GLPP treatment group, but there was no difference in LVEF in both groups.

The current results demonstrated that the treatment group's MDA level was decreased significantly than that of the control group when the risk of oxidative stress parameters was assessed. Consistent with the MDA findings, the treatment group's SOD level did not significantly change following a 90-day course of therapy. In the meantime, the control group's SOD level decreased significantly. According to these findings, individuals treated with GLPP exhibited reduced oxidative stress as indicated by declining levels of MDA, a lipid peroxidation product, and maintained endogenous antioxidant levels of SOD. These findings imply that GLPP may had the ability to inhibit the development of inflammation caused by oxygen stress. Atherosclerotic patients also showed a significant rise in SOD and a decrease in MDA in the GLPP therapy group [9] and studies on rats with type 2 diabetes [10].

Table 4. Laboratory and echocardiography findings of control and GLPP groups pre and post-test results

Variables	Baseline	3 Months	P-value (Paired)	Δ mean	P-value (Independent)
IL-6 (pg/mL)					
GLPP	852.6 ± 400.1	934.3 ± 474.0	0.427	81.7 ± 517.0	0.007
Placebo	1149.3 ± 581.7	744.8 ± 336.5	0.010	404.5 ± 707.4.	
p-value	0.990	0.140			
TNF-α (pg/mL)					
GLPP	209.1 ± 59.7	100.4 ± 17.8	0.000	108.7 ± 56.7	0.252
Placebo	261.2 ± 199.3	101.0 ± 17.1	0.000	160.2 ± 200.0	
p-value	0.360	0.897			
hsCRP (pg/mL)					
GLPP	950.6 ± 471.7	532.7 ± 274.4	0.001	418.0 ± 552.7	0.970
Placebo	950.9 ± 399.8	528.0 ±284.1	0.000	423.0 ± 383.2	
p-value	0.826	0.952			
MDA (ng/mL)					
GLPP	56.0 ± 71.4	27.7 ± 12.0	0.023	28.3 ± 73.6	0.041
Placebo	39.3 ± 29.2	38.3 ± 17.7	0.719	1.1 ± 35.0	
p-value	0.323	0.100			
SOD (U/mL)					
GLPP	122.2 ± 176.1	93.0 ± 40.9	0.925	29.2 ± 175.7	0.167
Placebo	102.0 ± 67.3	64.0 ± 52.0	0.016	38.0 ± 78.7	
p-value	0.978	0.107			
EF By TEICH (%)					
GLPP	62.2 ± 11.9	61.4 ± 11.8	0.756	0.8 ± 7.5	0.179
Placebo	60.0 ± 13.2	62.2 ± 13.5	0.247	2.3 ± 8.8	
p-value	0.369	0.776			
EF By BP (%)					
GLPP	61.1 ± 11.1	61.4 ± 9.8	0.716	0.3 ± 8.2	0.601
Placebo	58.8 ± 12.3	60.4 ± 13.6	0.159	1.7 ± 8.7	
p-value	0.490	0.666			
GLS					
GLPP	-16.1 ± 4.1	-17.5 ± 4.8	0.048	1.3 ± 3.2	0.453
Placebo	-15.2 ± 5.4	-15.8 ± 5.5	0.679	0.6 ± 2.4	
p-value	0.488	0.447			

In humans, with the treatment of GLPP, subjects with atrial fibrillation [11] and stable angina pectoris [5] showed a decreased MDA level.

The research on GLPP demonstrated that in an atherosclerotic mouse model, GLPP treatment reduced the levels of inflammatory cytokines [12], atrial fibrillation [11], and dyslipidemic and high-risk coronary heart disease patients [13]. The present findings demonstrated a considerable reduction in TNF-α and hsCRP in both the treatment and control groups. However, the IL-6 level pre-post mean level was insignificant in the treatment group but the control group decreased significantly. The discordant effect of the medication on TNF-α, hsCRP, and IL-6 may considered of several factors. GLPP might possessed a stronger suppressive effect on hsCRP and TNF-α compared to IL-6, leading to their significant decrease or indirectly stimulating IL-6 production as a compensatory mechanism for suppressing hsCRP and TNF-α. Drug interaction could also be a confounding factor because of the multipharmacy consumed by subjects. However, it indicated that both subject groups' inflammations were effectively treated and remained stable. Another clinical trial involving 48 patients with breast cancer revealed that administration of G. lucidum spore powder for four weeks significantly improved physical well-being, physical functioning, and psychological outcomes, reduced anxiety, and improved quality of life, as taken from quality of life questionnaires. Additionally, there was an improvement in immune markers such as IL-6 and TNF-α. [14] It has been proposed that β-D-glucan is bound by Dectin-1, a C-type lectin-like receptor. Manganese SOD (MnSOD) synthesis is stimulated by Dectin-1 association with β-D-glucan through a process involving histone acetylation.[15]

In left ventricular systolic function, current results showed left ventricular function was insignificant while measured LVEF by Teich and LVEF by Biplane by echocardiography. However, significant improvement in pre-post value was measured by GLS in the GLPP group. These results suggested that GLPP could improve the left ventricular systolic function. GLS has proven to be the most accurate and reproducible measure by strain techniques and is defined as the average peak regional systolic strain from all LV segments from the apical views. Assessment of strain has been shown to detect early signs of heart failure in cancer patients at risk of having chemotherapy-induced cardiomyopathy. Longitudinal strain analyses can reveal subclinical LV dysfunction before a decline in EF. A relative decrease of 15% in GLS raises the suspicion of subtle LV dysfunction and can guide the cardiologist in their strategic choices of heart failure treatment.[16]

In vitro studies demonstrated that Nox4 is associated with fibroblast activation and transformation into myofibroblasts in TGF-β1-stimulated human cardiac fibroblast.[17] Administration of GLPP was reported to attenuate post-myocardial infarction fibrosis via down-regulating TGF-β1/SMAD and relieving oxidative stress [18] and in the pressure-boosting irradiated cardiomyopathy mice model, one extract of spore oil was confirmed for the modification of cardiac function improvement through the circle RNA-FOXO3 axis, an important pathway associated with heart failure. [18]

Limitations of this study were a small sample, subjects taking multi-pharmaceutical drugs, patients having a variety of activities and diets so that there could be bias in concluding and a short period of follow-up. In future studies, a large number of subjects and longer observation should be done. In addition, equalizing medications taken, lifestyle, and diet. More investigation could be conducted on subjects in preserved LVEF, mid-ranged LVEF, and reduced LVEF.

5. Conclusion

In the GLPP treatment group, the SOD level remained stable but hsCRP and MDA levels were lower than in the control group. Moreover, GLS was getting better in the group receiving GLPP medication. When combined, GLPP therapy for 90 days may help individuals with cardiometabolic syndrome by reducing oxidative stress and inflammation and enhancing left ventricular performance.

6. Declaration

6.1 Ethics Approval and Consent to participate
Committee of the Faculty of Medicine, Universitas Brawijaya (No. 179/EC/KEPK/06/2021)

6.2. Consent for publication
Not applicable.

6.3 Availibility of data and materials
Data used in our study were presented in the main text.

6.4 Competing interests
Not applicable.

6.5 Funding Source
Not applicable.

6.6 Authors contributions
Idea/concept: TA. Design: TA. Control/supervision: DS, AF. Data collection/processing: TA. Analysis/interpretation: DS, AF. Literature review: TA, DS, AF. Writing the article: TA. Critical review: DS, AF. All authors have critically reviewed and approved the final draft and are possible for the content and similarity index of the manuscript.

6.7 Acknowledgements
Not applicable.

References

1. Banez MJ, Geluz MI, Chandra A, et al. A systemic review on the antioxidant and anti-inflammatory effects of resveratrol, curcumin, and dietary nitric oxide supplementation on human cardiovascular health. Nutr Res 2020;78:11–26. https://doi.org/10.1016/j.nutres.2020.03.002. 10.1016/j.nutres.2020.03.002

2. Schiattarella GG, Rodolico D, Hill JA. Metabolic inflammation in heart failure with preserved ejection fraction. 2021;423–34. 10.1093/cvr/cvaa217

3. Taleb A, Ahmad KA, Ihsan AU, et al. Antioxidant effects and mechanism of silymarin in oxidative stress induced cardiovascular diseases. Biomed. Pharmacother. 2018;102:689–98. 10.1016/j.biopha.2018.03.140

4. Hotamisligil GS. Inflammation and metabolic disorders. Nature 2006;444(7121):860–7. 10.1038/nature05485

5. Sargowo D, Ovianti N, Susilowati E, et al. The role of polysaccharide peptide of Ganoderma lucidum as a potent antioxidant against atherosclerosis in high risk and stable angina patients. Indian Heart J 2018;70(5):608–14. 10.1016/j.ihj.2017.12.007

6. Ahmad MF. Ganoderma lucidum: Persuasive biologically active constituents and their health endorsement. Biomed Pharmacother 2018;107(August):507–19. https://doi.org/10.1016/j.biopha.2018.08.036. 10.1016/j.biopha.2018.08.036

7. Seweryn E, Ziała A, Gamian A. Health-promoting of polysaccharides extracted from ganoderma lucidum. Nutrients 2021;13(8). 10.3390/nu13082725

8. Huang PL. A comprehensive definition for metabolic syndrome. DMM Dis Model Mech 2009;2(5–6):231–7. 10.1242/dmm.001180

9. Prasetya I, Ashriyah R, Setyawati I, et al. Polysaccharide Peptide: A promising Anti Inflammation and Anti Oxidant in Atherosclerosis. Indones J Cardiol 2015;36(1):22–7. 10.30701/ijc.v36i1.437

10. Shaher F, Wang S, Qiu H, et al. Effect and mechanism of Ganoderma lucidum spores on alleviation of diabetic cardiomyopathy in a pilot in vivo study. Diabetes, Metab Syndr Obes 2020;13:4809–22. 10.2147/DMSO.S281527

11. Rizal A, Sandra F, Fadlan MR, Sargowo D. Ganoderma lucidum Polysaccharide Peptide Reduce Inflammation and Oxidative Stress in Patient with Atrial Fibrillation. Indones Biomed J 2020;12(4):384–9. 10.18585/INABJ.V12I4.1244

12. Sargowo D, Wihastuti TA, Sukotjo CT, Anjani PM, Handayani O, Adrian LH. The effect of polysaccharides peptides ganoderma lucidum to aortic foam cell count and lipid profile in type 2 diabetic model Rattus norvegicus strain Wistar. Indones Biomed J 2017;9(3):153–9. 10.18585/inabj.v9i3.298

13. Farikh A. Pemberian Peptida Polisakarida (Psp) Suatu Senyawa Aktif Dari Ganoderma Lucidum (B-D-Glucan) Berpengaruh Terhadap Dislipidemia Dan Inflamasi Pada Pasien Resiko Tinggi Penyakit Jantung Koroner. Care J Ilm Ilmu Kesehat 2017;(Vol 5, No 1 (2017)):102–11. https://jurnal.unitri.ac.id/index.php/care/article/view/395.

14. Zhao H, Zhang Q, Zhao L, Huang X, Wang J, Kang X. Spore powder of Ganoderma lucidum improves cancer-related fatigue in breast cancer patients undergoing endocrine therapy: A pilot clinical trial. Evidence-based Complement Altern Med 2012;2012. 10.1155/2012/809614

15. Kao PF, Wang SH, Hung WT, Liao YH, Lin CM, Yang W Bin. Structural characterization and antioxidative activity of low-molecular-weights beta-1,3-glucan from the residue of extracted Ganoderma lucidum fruiting bodies. J Biomed Biotechnol 2012;2012:3–10. 10.1155/2012/673764

16. Cosyns B, Edvardsen T, Hristova K, Kim H-K. Left ventricle: systolic function. EACVI Textb Echocardiogr 2016;131–46. https://doi.org/10.1093/med/9780198726012.001.0001.

17. Chakraborti S, Dhalla NS, Dikshit M, Ganguly NK. Modulation of Oxidative Stress in Heart Disease. 2019. 10.1007/978-981-13-8946-7

18. Meng J, Ma A, Zhang S, et al. Ganoderma Lucidum Polysaccharide Peptide attenuates post myocardial infarction fibrosis via down-regulating TGF-β1/SMAD and relieving oxidative stress. Pharmacol Res - Mod Chinese Med 2022;4(August):100152. https://doi.org/10.1016/j.prmcm.2022.100152. 10.1016/j.prmcm.2022.100152