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OPEN ACCESS JOURNAL ISSN: 2148-6832

MSD Medical Science and Discovery
2020; 7(11):696-702

Research Article Doi: 10.36472/msd.v7i11.439

The Role of Ganoderma Lucidum Polysaccharide Peptide in Endothelial Progenitor Cells and Circulating Endothelial Cells as anti Endothelial Dysfunction from Stable Angina Pectoris Patients

Nizamuddin Ubaidillah[1]* , Djanggan Sargowo[1,2], Setyasih Anjarwani [1,2]

Abstract

Objective: Endothelial dysfunction is the primary initial step for atherogenesis in cardiovascular disease. Stable angina pectoris is a stable form of cardiovascular disease that profoundly alters Endothelial Progenitor Cells (EPC) and Circulating Endothelial Cells (CEC). Both CEC and EPC have a significant role as native homeostasis biomarker of endothelial, which could initiate cytokine storm when homeostasis was altering. Ganoderma Lucidum is known for the antioxidative, anti-inflammatory, and anti-cancer properties and indirect anti endothelial dysfunction. The previous study has proven the Polysaccharide Peptide (PsP) of Ganoderma Lucidum as an effective antioxidant and anti-endothelial dysfunction in atherosclerosis rats and shows no toxicity in an animal model. This study goals to prove the effect of PsP in CEC and EPC in stable angina patients.

Methods: This is a quasi-experimental trial of 35 Stable Angina patients, determined based on ESC Stable CAD Guidelines with pre and post-test design without a control group. The parameters are CEC and EPC counts. The patients were given PsP 750mg/day in 3 divided doses for 90 days. A paired t-test perform for normally distributed data, and the Wilcoxon test for not normally distributed data, and a significant level of $p \leqslant 0,05$.

Results: CEC significantly reduced in stable angina patients, with p=0,001. EPC count significantly reduced in stable angina with p=0,001.

Conclusion: Ganoderma Lucidum PsP is a potent anti-endothelial dysfunction against atherosclerosis's pathogenesis in stable angina.

Keywords: Polysaccharide Peptide (PsP), Ganoderma Lucidum, anti-endothelial dysfunction, stable angina, CEC, EPC.

Introduction

The primary leading cause of mortality and morbidity in the western world and project to be the first killer globally in 2020 is cardiovascular disease. It is responsible for 45% of deaths or equivalent to 4 million deaths per year and remains the most common reason for Europe's mortality. The Sample Registration System (SRS) survey in Indonesia in 2014 showed that cardiovascular disease was the highest etiology of death at all ages after stroke, 12.9% (1,2).

Atherosclerosis act as a primary backbone of coronary heart disease pathomechanism, which relies on endothelial dysfunction as a significant phase of its development. Endothelial dysfunction cause by inflammation, oxidative stress, metabolic abnormality, and risk factors (hypertension, diabetes, and dyslipidemia) (3).

Risk factors like smoking, hyperlipidemia, hypertension, and high blood sugar are the source for vascular failure, which initiates direct simultaneous deterioration effect in endothelial function and exaggerates inflammation, oxidative stress, and other factors metabolic pathway. Nevertheless, Inflammation and Oxidative stress will lead to other endothelial dysfunction with dysfunction of the respiration chain inside mitochondria, causing tissue damage (4).

Injured endothelium will activate detachment sequences of endothelium cells and release circulating endothelial cells (CEC) to circulation and derived endothelial progenitor cells (EPC) subsequently to restore endothelial integrity.

Received 07-11-2020 **Accepted** 25-11-2020 **Available Online** 25-11-2020 **Published** 30-11-2020
1 Universitas Brawijaya, Faculty of Medicine, Department of Cardiology and Vascular Medicine, Malang, Indonesia
2 Dr. Saiful Anwar General Hospital, Malang, Indonesia
*** Corresponding Author:** Nizamuddin Ubaidillah **E-mail:** nizamuddin_ubaidillah@yahoo.com.au

There are several potential mechanisms for detachment of endothelial lining cells, partially attenuating adhesive properties in endothelial cells because of protease and cytokine and mechanical injury (5).

EPC first describes and isolated from the peripheral circulation, which studies by Asahara and colleagues. EPC derives from bone marrow, significantly influencing tissue neovascularization in ischemic tissue and re-endothelialization of the injured vessel (6). In general, EPC's working mechanism will divide into mobilization, homing, differentiation, and survival or regeneration (7).

A Higher CEC count finds in stable CAD than in a healthy person. Contrarily, lower EPC count observes in stable CAD, cardiovascular risk factor, and a sedentary lifestyle than a healthy person (8,9). Thus, it is essential to find a potent anti-endothelial dysfunction agent that can prevent or improve atherosclerotic cardiovascular disease.

Lingzhi in China or Reishi in Japan names for Ganoderma Lucidum has antioxidative, anti-inflammatory, and anti-cancer properties (10). Scientists have studied Ganoderma Lucidum since the end of the century due to its beneficial health effects and found β-D-Glucan as the main active component in polysaccharide peptide (PsP).

The previous PSP study has proven Ganoderma Lucidum as an effective anti-inflammatory and antioxidant in atherosclerotic rats and revealed subchronic toxicity in animal doses with no toxic effect immunologic, blood test, and histopathologic (11). This study goals to prove the effect of PsP on CEC and EPC as anti-endothelial dysfunction in stable angina patients.

Material and Methods

Quasi-experimental research with pre-and post-test design, single-blinded, to know the effect of Polysaccharide Peptide (PsP) on 35 Stable Angina patients determined based on ESC Stable CAD Guidelines without a control group. The research was held at Saiful Anwar General Hospital Malang, assisted by Indonesia Heart Association (YJI), Lavalette Hospital Malang, and geriatric foundation in Malang, Indonesia, cooperations with Biomedical Laboratory and Physiology Laboratory of Faculty of Medicine, Brawijaya University Malang and Prodia and Proclinic Laboratories for the blood sampling for each patient. Participated patients in this research were patients that come to the Cardiology outpatient clinic at Saiful Anwar General Hospital Malang and Indonesian Heart Foundation Malang branch, without ischemic symptoms and classified as stable angina, and who are willing to participate in research and filled the informed consent. Criteria for stable angina patients are patients with ischemic symptoms at exercises or activities and emotional stress but resolved at rest. Patients who did not consume PSP for three months, and patients with new cardiac symptoms during the study dropped out of the research.

All of the protocols in this research has already approved through informed consents by the Ethical Committee of Saiful Anwar General Hospital Malang, Indonesia, and by the patients (no. 400/ 79/ K.3/302/ 2015)

Polysaccharide Peptide – Sahabat Lingkungan Hidup company supplied PsP that contained Ganoderma Lucidum extract. Each preparation was in the form of freeze-dried preparations in which each capsule 250 mg PSP contains about 180 mg β-D glucan. The PsP 750 mg/day in 3 divided doses for 90 days given in patients. Stable angina patients continued their previous medications besides PsP.

Flow cytometry—CECs (Circulating Endothelial Cells) assays using CD45 and CD146 antibodies and EPCs (Endothelial Progenitor Cells) tests using CD133 and CD34 antibodies Plasma was freshly collected from the blood samples and assayed using PE anti-human antibodies (BioLegend, USA). ELISA- TNF alfa, CRP, IL-6 (anti-inflammatory marker), SOD and MDA (oxidative marker), and adiponectin were collected from blood samples (Pre- and post-intervention) and then assayed with an ELISA kit (Elabscience, Wuhan)

Statistical Analysis - The Data give in mean ± SD. A paired t-test perform to see the differences between pre-test and post-test of stable angina patients. Wilcoxon would use If the normality test indicated the data was not homogeneous. The statistical calculation uses SPSS version 22 (SPSS Inc). The $p \leqslant 0.05$ were considered statistically significant.

Results

Subject characteristics-The study conduct for three months at Dr. Saiful Anwar Malang. The samples of the 45 patients with stable angina pectoris were studied. Of this amount, for three months, PsP Ganoderma Lucidum 3 x 200 mg was given periodically every one month. Of the 45 patients (ten patients excluded from the study, Two patients due to the effects of nausea due to consumption of PsP Ganoderma Lucidum, five patients due to moving domicile, one patient due to death, while two patients for no apparent reason). In total, up to the end of the study, samples of 35 patients with stable angina pectoris were studied.

Patients have an average age of 62.25 ± 9.28 years (Table 1). Patients with male gender as many as 8 (22%) patients while female sex as many as 27 (78%) patients. This group of patients had a bodyweight of 65.35 ± 10.87 kg and a BMI of 27.00 ± 4.06.

Tabel 1: Baseline characteristic

Age > 65 year	11 (31%)
Male	12 (34%)
Hypertension	16 (46%)
TDS (mmHg)	118.42 ± 47.07
TDD (mmHg)	72.85 ± 28.55
DM	18 (51%)
GDP (mg/dl)	113.09 ± 68.63
HbA1c	6.59 ± 2.00
Dyslipidemia	7 (20%)
Total Cholesterol (mg/dl)	205.49 ± 48.49
LDL (mg/dl)	126.17 ± 38.87
TG (mg/dl)	122.37 ± 62.04
HDL (mg/dl)	46.20 ± 12.55
Obesity/overweight	22 (62%)
Smoking	9 (25%)

http://dx.doi.org/10.36472/msd.v7i11.439

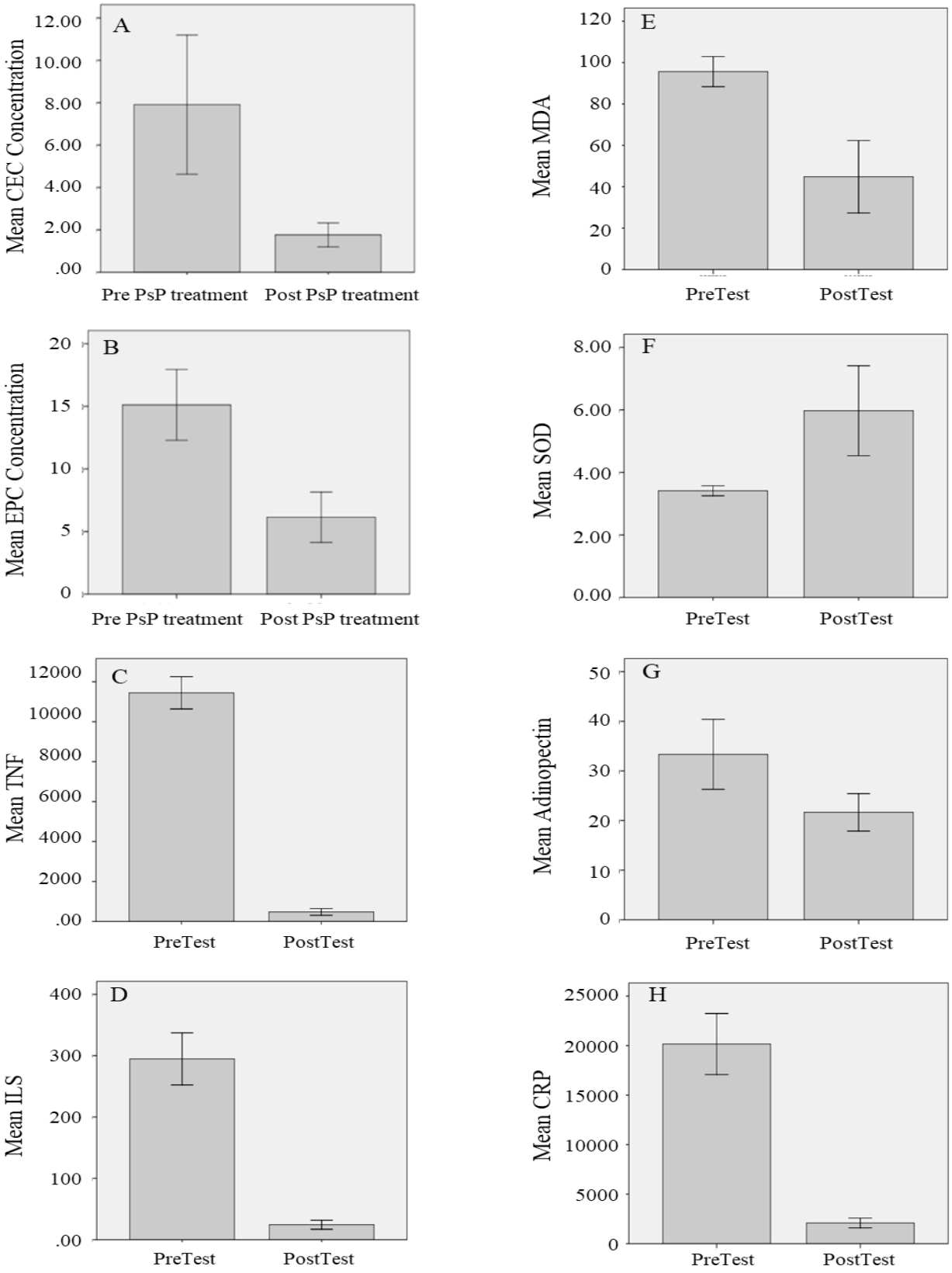

Figure 1. Biomarkers value pre and Post-test. A) CEC, B) EPC, C) TNF-alfa, D) IL-6, E) MDA, F) SOD, G) Adiponectin, H) CRP. CEC: circulating endothelial cells, EPC: endothelial progenitor cells, TNF-alfa: tumor necrosis factor-alfa, IL-6: interleukin-6, MDA: malondialdehyde, SOD: superoxide dismutase, CRP: c-reactive protein. ‘’Error Bars %95 Cl’’

Biomarkers endothelial dysfunction such as CEC found reduced with p=0.01 from 7.91 ± 9.11 cells/µl to 1.76 ± 1.56 cells/µl. Unfortunately, EPC as restorative endothelial markers found reduced too with p=0.001 from 15.11 ± 7.44 cells/µl to 6.14 ± 5.30 cells/µl. Improvement of endothelial function also mark with significantly reduced of ant-inflammatory biomarkers such as TNF-α with p=0.001 from 2094.70 ± 123.28 U/ml to 24.41 ± 21.45 U/ml, Il-6 with p=0.001 from 11444.00 ± 123.28 U/ml to 476.13 ± 482.99 U/ml, and CRP with p=0.001 from 20158.88 ± 8969.08 U/ml to 2092.00 ± 1437.16 U/ml. The antioxidant biomarker shown better improvement as SOD increased with p=0.001 from 3.41 ± 0.46 U/ml to 5.79 ± 4.19 U/ml and MDA decreased with p =0.001 from 95.63 ± 21.27 U/mL to 44,84 ± 50.95 U/mL. Interestingly, adiponectin as glucose and lipid metabolism hormone reduced with p=0.001 from 15.01 ± 8.39 U/ml to 5.43 ± 5.36 U/ml. (Figure 1)

Discussion

β-Glucans extracted from many resources such as barley or oats and black yeast. There are differences from the type of β-Glucans where β-(1,3-1,4)-D-glucan from barley or oat and β-(1,3-1,6)-D-glucan from the black yeast. The molecular weight of β-glucan extracted from barley with warm water is 40,000–100,000 Da; the oligomer prepared from the macromolecule β-glucan by enzymatic degradation with lichenase has a molecular weight of approximately 2,000 Da. In this study, the molecular weight of immunomodulatory protein in PsP, from Ganoderma Lucidum, was between 14.000-17.000 Da through SDS PAGE method (12).

In this study, the administration of PsP Ganoderma Lucidum for three months found a significant decrease in CEC, which showed an improvement in endothelial function. CEC itself is a marker of vascular damage. The administration of beta-glucans will reduce the gene expression of CDH13, which is cadherin, a Cyclin-Dependent Kinase Inhibitor 1C as a negative regulator of cell proliferation, another name is T-Cadherin; which generally provide stimuli for the release of epithelial cells. The research conducted by O'Hara stated that beta-glucan affects cadherin expression (13-14) The mechanism for involving other cadherins, especially E-cadherin through the inactivated immune receptors in the form of CLR receptors (C-type Lectin Receptor) and signal pathways Syk (15)

Wu revealed that dectin-1 receptors located in endothelial cells exposed to beta-glucan would express CD8 + T cells, which would then express CD103, a ligand for E-cadherin (16). Upregulation of E-cadherin would increase endothelial cell adhesion, which led to a decline in the CEC. Several studies also found that activation via the MAPK pathway will increase E-cadherin and increase inter-cell adhesion and activation of growth factors (17,18)

The hypothesis that establishes for EPC is restorative/regenerative cells, which the primary function as replacing/renew the damage of endothelial cells in parallel for this significant reduction in CEC from this study that suggests improvement of endothelial function after PsP administration

Besides examining CEC as a marker of endothelial dysfunction, EPC examination also carries out. EPC itself is a potential cell source that contributes to neovascularization through postnatal vasculogenesis. Several clinical studies show evidence that EPC in the circulation regenerates damaged endothelial cells. The amount of EPC in circulation also reports being inversely proportional to the risk of coronary heart disease. It shows that EPC status in blood circulation presents endothelial dysfunction and impaired vascular health. EPC capacity in repairing vascular damage shows an essential role in maintaining endothelial homeostasis.

As stated above, the atherosclerosis risk factor plays a vital role in EPC reduction. These perspectives indicate that endothelial dysfunction may involve many components of a risk factor. So, handling coronary heart disease management must be comprehensive in all risk factors (4)

In all form cardiovascular disease either acute or chronic, damage of endothelial cells become a source for CEC (elevated) and decreasing EPC. However, it more complicated process than a usual situation. For example, acute myocardial infarction has shown increases in both CEC and EPC. Furthermore, statins and endurance training in CAD patients lead to an improvement in endothelial function. Endothelial turnover in individuals is different. The low shear stress area with high endothelial death rates could make cells need a high turnover rate for maintaining vessel homeostasis (19). This study result shows a significant reduction of CEC but also EPC. CEC reduces, so a detachment of endothelial lining cell decreases, low turnover rate and will not induce EPC mobilization. The other study shows that EPC and CEC count were higher at baseline after 7, 30, and 180 days than healthy controls in AMI events.20,21 This enhance by Lee reported a decrease in EPC inpatient CAD mainly derived from EPC's exhaustion (22). Also, based on the study population in the form of patients with stable CAD found that the chronic inflammatory process will underlie the occurrence of EPC exhaustion (23)

Alessio et al., in their study for DVT patients revealed, CEC levels were increased significantly 24 hours after induction and decreased after 72 hours. The same phenomenon occurred for EPC levels, which markedly increased on day seven and returned to baseline within 60 days in AMI (Acute Myocardial Infarction) (24). It shows a process of mobilization and homing to the injured area; Wojakowski, in his study, showed an increase of fewer than 12 hours at AMI and decreased in 7 days, which was by the decrease in reduced levels of cytokines, especially inflammatory cytokines. Mobilization in AMI conditions involves EPC and affects hematopoietic cells, non-hematopoietic cells, and mesenchymal cells (25).

Research conducted by Mikirova et al. found that beta-glucan supplementation will increase EPC levels through VEGF upregulation (23). Cramer et al. showed that beta-glucan would improve mobilization of EPC from both

hematopoietic and non-hematopoietic types through MMP-9, definitely through CR3 receptor activation (26)

Mobilization of EPC has a complex mechanism. The majority of EPC remain quiescent in the bone marrow. The sequencing process involves migration of HSC (hematopoietic stem cells), translocation of SDF1 (stromal-derived factor 1), and activates MMP 9 (matrix metalloproteinase 9) that release sKitL (soluble Kit Ligand), which allow EPC to exit. Other factors involved are VEGF (vascular endothelial growth factor), IL-8 Groβ, nitric oxide (NO), erythropoietin, and other inflammatory agents or pharmacological modulation (24).

Morrone's research showed a low EPC level in patients with stable CAD (chronic ischemic heart disease) compared with patients without CAD. Besides, the value of the EPC density is higher for patients with CAD than for non-CAD; this emphasizes that EPC's mobilization and homing occur in CAD patients (26). From a prospective study by Morrow, it is shown that the decrease of EPC increased mobilization and homing to the site of vascular injury that occurs in CAD.

As reported from the previous study, SOD activity in a patient with CAD decreased by 17% compared to healthy (27). In this study, there is a significant increase in SOD, which could derive from the effect of β-Glucan as an antioxidant, whereas the patient still on medication consumption (28). The mechanism was involved in the increased activity of SOD was modulate via MnSOD-related angiogenesis. Dectin-1 was expressed by endothelial cells engaged with β-Glucan and induce MnSOD expression via histone acetylation.29 Furthermore, common risk factors such as diabetes mellitus, hyperlipidemia, hypertension, aging, and smoking increase free radicals from endothelial cells, which trigger lipid oxidation, apoptosis of endothelial cells, expression of adhesion molecules, and alteration vasomotor activity (30). Subjects in this study may have atherosclerotic risk factors.

SOD, as an antioxidant enzyme, works to detoxify hydrogen peroxide and convert it to lipid hydro-peroxides to become non-toxic substances (31). Catalyzation was the first process in SOD, which initiates the dismutation of superoxide anion to hydrogen peroxide in the vascular wall to reduce oxidative stress damage. the Previous study has revealed β-Glucan can improve SOD and inhibits lipid peroxidation in animal models (32) and from in-vitro studies revealed a protective effect against damage induced by H2O2 and Trp-P-2 (33).

MDA was one of the lipid peroxidation products and one of the oxidative markers. Increasing MDA levels will enhance the production of free radicals and a reduction of antioxidant activity. In this study, there are significantly reduced MDA levels, following the study by Sener et al. showed that β-Glucan could lower MDA level (34). Therefore, β-Glucan could be considered therapeutic agents because they can attenuate the oxidant's deterioration effect.

The marker's inflammatory study results show a significant decrease in pre-test IL-6, TNF-α, and CRP. It is probably due to the polysaccharide peptide (PSP) originating from the mycelium Ganoderma Lucidum acting as an anti-inflammatory, inhibiting the NF-kB activation pathway. This study supported several results of previous studies that stated that polysaccharide peptides derived from Ganoderma Lucidum could be anti-inflammatory (35,36).

Previous research has shown that β-glucan has a good effect on innate and adaptive immunity — the innate immune system can quickly recognize and respond to pathogens' entry, useful for controlling the infection. Dectin-1 is a type 2 transmembrane protein receptor that binds to β-1,3 and β-1,6 glucan, which can initiate and regulate the immune response. Dectin-1 express in cells responsible for innate immune responses found in macrophages, neutrophils, and dendritic cells. The dectin-1 working mechanism through ITAM, TLR-2/6, and Syk pathway will activate T cells, which will cause the release of cytokines. Cytoplasmic. In this study, it proved that the PSP extract of Ganoderma Lucidum through the active compound β-glucan was able to inhibit Dectin-1 in macrophages and thus inhibit activation of the Nuclear Factor kappa B (NF-kB) transcription factor, which can then inhibit activation of inflammatory cytokines such as IL-6, TNF-α, and hs-CRP. Overall, by inhibiting NF-ƙB and the inflammatory process, administration of PsP can ultimately prevent and slow down the process of atherogenesis (36).

In general, beta-glucan activates via the NF-kB pathway, JNK-MAPK, PI3K / Akt, JAK-STAT, TLR 2/6, and ITAM, while from the receptor side are dectin-1, CR-3, lactoseril ceramide, and Langerin receptor (37)

Research conducted by Verma et al. Shows that increasing CRP (C Reactive Protein) direct reduces differentiation, function, and survival of EPC, which is a critical component of angiogenesis and the response to chronic ischemia by significantly increasing EPC apoptosis and disrupting EPC induces angiogenesis. It also inhibits the expression of specific endothelial markers such as Tie-2, EC-lectin, and VE-Cadherin. This mechanism of CRP through CRP decreases eNOS expression by EPC and interferes with EPC antioxidant defense, antioxidant sensitivity EPC, and telomerase inactivation (38,39). Contrary to this, a study conducted by Fasing et al. found that there was no relationship between changes in CRP levels in EPC dysfunction in healthy people.40 What is interesting is that EPC levels increased in patients with unstable angina, but there is no adhesion disorder compared to patients with stable coronary heart disease (Stable CAD) (41).

Witztum et al., In their study, demonstrated that CRP increases the uptake of ox-LDL and not LDL native (42). Correlated with this, especially in LDL, from several studies it has shown that LDL native will bind to T-cadherin protein and activate intracellular pathways via ca (2 +) - tyrosine kinase-ERK1 / 2 and activation of small G-proteins by further reorganizing actin and affecting the interaction of epithelial cell attachments. T cadherin finds to increase atherosclerotic lesions and post-angioplasty restenosis associated with pathological angiogenesis (43).

Interestingly, LDL binds to T-cadherin and adiponectin, which activates NF-kappa B through AdipoR1 and AdipoR2 receptor paths (44).

This study revealed better improvement in endothelial function, which decreased CEC, which was strengthened by a better profile of anti-inflammatory and antioxidant properties, either adiponectin but unfortunately, EPC decreased.

Conclusion

Polysaccharide Peptide of Ganoderma Lucidum acts as a potent anti-endothelial dysfunction against atherosclerosis's pathogenesis in stable angina with proof from this study showed decreased CEC value, but unfortunately, EPC decreased too.

Acknowledgements, Funding: None.

Conflict of interest and financial disclosure: The authors declare that they have no conflict of interest and financial relationships.

Author's contributions: NU, DS, SA; Literature search, study design and patient selection, data collection and analyzes, **NU;** Article preparation and revisions

Ethical issues: All authors declare originality and ethical approval of research. The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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