Heart Sci J 2021; 2(1): 25-29

Contents list available at www.heartscience.ub.ac.id

Heart Science Journal

Journal Homepage : www.heartscience.ub.ac.id

Original Article

# The Role of Garcinia Mangostana Pericarp Extract as Antioxidant to Inhibit Atherosclerosis Process in High-Risk Framingham Score Patient

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ARTICLE INFO

*Keywords*:
Garcinia mangostana;
Antioxidant;
Atherosclerosis;
Framingham score

ABSTRACT

*Background* : Atherosclerosis is the pivotal role in cardiovascular disease (CVD) involving oxidative stress dan inflammation. Garcia Mangostana has been proven to have an antioxidant property for years; however, the application of this compound in the case of atherosclerosis has not been performed.
*Objectives* : This study was performed to explore the role of α-Mangostin of Garcia Mangostana Pericarp Extract as an antioxidant to inhibit atherosclerotic process in patients with high-risk Framingham score.
*Methods* : This prospective cohort study was conducted in patients with high-risk Framingham score. The patients were divided into two groups. The first group was administered 2520 mg/day of Garcinia mangostana Linn extracts (GMLE) in 3 divided doses for 90 days. The second group was administered a placebo. The outcome measures in our study were Nitric Oxide (NO), Superoxide Dismutase (SOD), and Malondialdehyde (MDA). They were measured at baseline and 90 days after treatment. The independent T-test was performed to assess the homogeneity of data, and the multiple logistic regression was used to assess the association.
*Results*: Among the 77 subjects, we found that the plasma MDA concentration was significantly decreased compared with placebo 0,29±0.5 vs -0.04±0.25, respectively p = 0.011). SOD level significantly decreased in GMLE patients compared with placebo (0,17±0.79 vs -0.27±0.67, respectively, p=0.010) and we found that there was slightly increased of nitric oxide (NO), but no significantly compared with placebo 4.34±10.01 and 2.35±7.39, respectively, p = 0.37).
*Conclusion*: *Garcinia mangostana* pericarp extract has an antioxidant effect that significantly inhibits atherosclerosis process in high-risk Framingham score patients.

## 1. Introduction

Cardiovascular disease (CVD) is a general term for heart and blood vessel disease.[1] Cardiovascular disease is the primary cause of death worldwide, with more than 17.3 million death annually in 2013, and predicted to grow more than 23.6 million in 2030.[2] Among them, 7.4 million death were estimated caused by coronary heart disease and 6.7 million by stroke.[3] Coronary heart disease manifests the atherosclerosis process and may involve many pathologic processes, including chronic inflammation, endothelial dysfunction, and lipid accumulation.[4]

Chronic inflammation in atherosclerosis was occurred by lipid accumulation and intracellular formation of reactive oxygen species (ROS). On physiological conditions, there is a balance between the formation of oxygen free radical and antioxidant mechanisms.[5] One of the natural antioxidant substances is superoxide dismutase (SOD) in whichcatalyzing superoxide anion to form hydrogen peroxide.[6] The increase of ROS, in turn, would lead to endothelial dysfunction, as indicated by the level of nitric oxide (NO)[7] and circulating endothelial cells (CEC). Therefore, the discovery of the antioxidant agent has a critical role in reversing the mechanism, lowering oxidative stress, and preventing atherosclerosis process.[8]

MDA is a profoundly responsive compound which is the last result of lipid peroxidation and is typically utilized as a biological lipid peroxidation biomarker to assess oxidative stress. Free radicals have a very short half-life that is difficult to measure in a laboratory. Lipid tissue damage due to ROS can be assessed by measuring the MDA compounds, in which they are lipid peroxidation products.

Garcinia mangostana, commonly known as mangosteen, has

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https://doi.org/10.21776/ub.hsj.2021.002.01.04
Received 25 January 2021; Received in revised form 1 February 2021; Accepted 25 January 2021
Available online 28 February 2021

the potency as the antioxidant agent. Mangosteen is frequently used in many Asian countries as traditional medicine for healing wounds, antimicrobial in dysentery, and eczema. Several studies have been conducted to investigate mangosteen potency, which has active metabolite xanthone, antioxidant properties. Fifty xanthone derivates could be extracted from pericarp of mangosteen, and the principal constituent is α-mangosteen. [9]

The previous study had proven the pericarp extract of Garcinia mangostana as an effective antioxidant and anti-inflammation in atherosclerotic rats after five weeks of treatment.[10] Another previous study for the toxicity of pericarp extract of Garcinia mangostana in animal models had shown no toxic effect in blood tests and internal organs, including liver and kidney.[11] Therefore, our study aimed to assess the potency of pericarp extract of Garcinia mangostana as an antioxidant in high-risk Framingham Score patients

## 2. Methods

### *2.1. Study Design and Patient*

A prospective cohort study was conducted at the Cardiology outpatient clinic at Saiful Anwar General Hospital Malang, Indonesian Heart Association and geriatric association in Malang, Indonesia. All patients with high-risk Framingham Score (score more than 14 for a male patient and 17 for female) were included in our study. Patients with the following criteria: increased transaminase, renal failure, prolonged coagulation, history of Non-Steroid Anti Inflammation drugs (NSAID) consumption, history of Cerebrovascular Attack (CVA), history of drug allergic, heart failure NYHA III-IV, and history of narcotics consumption were excluded from our study. Subsequently, patients who died and who did not complete follow-up were classified into drop-out criteria. The information related to the risk, benefit and purpose of our study was provided to patients before the study. All patients had provided written informed consent. The Ethical Committee had approved our Faculty of Medicine study protocols, Brawijaya University, Malang Indonesia (no. 64/EC/KEPK/03/2018).

### *2.2. Laboratory Parameters*

The laboratory parameters in our present study were the levels of MDA, SOD, and NO. All laboratory parameters were performed in Biomedical and Physiological laboratory of Brawijaya University and Pattimura® laboratory. Our study's laboratory parameters were performed before and after the administration of Garcinia mangostana L for three months.

### *2.3. Garcinia Mangostana Linn Extract*

Garcinia mangostana Linn extract was supplied by Zena Nirmala Sentosa (Garcia) company in Bogor. Each capsule contains 420 mg extract of Garcinia mangostana L. The patients were given Garcia 2520 mg/day in 6 divided doses for 90 days.

### *2.4. Statistics*

All data were presented in mean ± standard deviation (SD). A paired T-test was used to perform statistical analysis for the parametric data. If data were not homogenous, the Mann Whitney and Wilcoxon rank test was used. For subgroup analysis, we used one-way ANOVA. All data were analyzed by SPSS version 22 (SPSS Inc). P-value $<0.05$ was considered statistically significant.

## 3. Results

### *3.1. Subject characteristics*

Patients were divided into two groups. The first group received GMLE, and the second group received placebo in addition to statin and a combination of several drugs (ACE inhibitors/ ARB or Oral antidiabetic). Blood samples were obtained from patients before and after received GMLE and placebo for 90 days. All of the baseline characteristics were homogenous between groups ($p>0.05$) (Table 1).

### *3.2. Comparison of antioxidant parameters between groups*

After administering Garcia Mangostana Pericarp Extract therapy for three months, a significant change in MDA levels was observed between the treatment groups compared to the controls (-0.29 ± 0.5 and -0.04 ± 0.25, respectively P = 0.011). The levels of SOD was significantly higher in the treatment group compared to the placebo (0.17 ± 0.79 and -0.27 ± 0.67, respectively P = 0.010). However, the levels of NO between the treatment and control groups were similar (4.34 ± 10.01 and 2.35 ± 7.39, respectively P = 0.37, respectively (figure1).

### *3.3 Sub-group analysis*

In the sub-group analysis, in the combination of high-intensity statins and Garcinia Mangostana Linn extract, lower MDA levels were found in the treatment group compared to placebo. The summary of our findings is outlined in Table 2.

Tabel 1. Baseline characteristics of the patients.

| Charateristics | G. Mangostana extract (n=47) | Control (n=47) | P-Value |
|---|---|---|---|
| Age | 63.7±8.4 | 62.5±10.5 | 0.74 |
| Sex (Male) | 41.7% | 58.3% | 0.84 |
| BMI (kg/m$^2$) | 26.3±5.4 | 26.4±4.06 | 0.62 |
| Hypertension | 45.1% | 54.9% | 0.81 |
| Hipertrigliseridemia | 34.3% | 26.2% | 0.60 |
| Diabetes melitus | 42.9% | 57.9% | 0.71 |
| Systolic BP (mmHg) | 154.4±18.7 | 146.9±15.2 | 0.058 |
| Distolic BP (mmHg) | 86.6±14.02 | 88.3±10.6 | 0.54 |
| Total cholesterol (mg/dl) | 218.2±35.6 | 217.3±25.6 | 0.71 |
| Trygliserides (mg/dl) | 154.1±86.2 | 158.05±100.7 | 0.47 |
| HDL cholesterol (mg/dl) | 49.4±13.49 | 45.09±11.52 | 0.70 |
| LDL cholesterol (mg/dl) | 118.09±43.76 | 138.2±62.33 | 0.86 |
| Fasting blood glucose | 123.71±52.13 | 136.25±63.5 | 0.36 |
| HbA1C (%) | 6.55±1.58 | 7.25±1.95 | 0.10 |
| Nytric Oxide | 29.15±12.16 | 35.83±14.40 | 0.55 |
| HsCRP | 2992±86.6 | 2852±115.8 | 0.32 |
| IL1 | 14.82±18.82 | 13.75±1.29 | 0.12 |
| IL6 | 15.6±2.17 | 14.15±1.73 | 0.14 |
| SOD | 3.07±0.6 | 2.88±0.57 | 0.38 |
| MDA | 1.53±0.56 | 1.66±0.44 | 0.19 |

Note; BMI, Body Mass Index BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lip-oprotein; bpm, beats per minute; IL-1, interleukin-1; IL-6, interleukin-6; SOD, Superoxide Dismutase; MDA, Malondialdehyde.

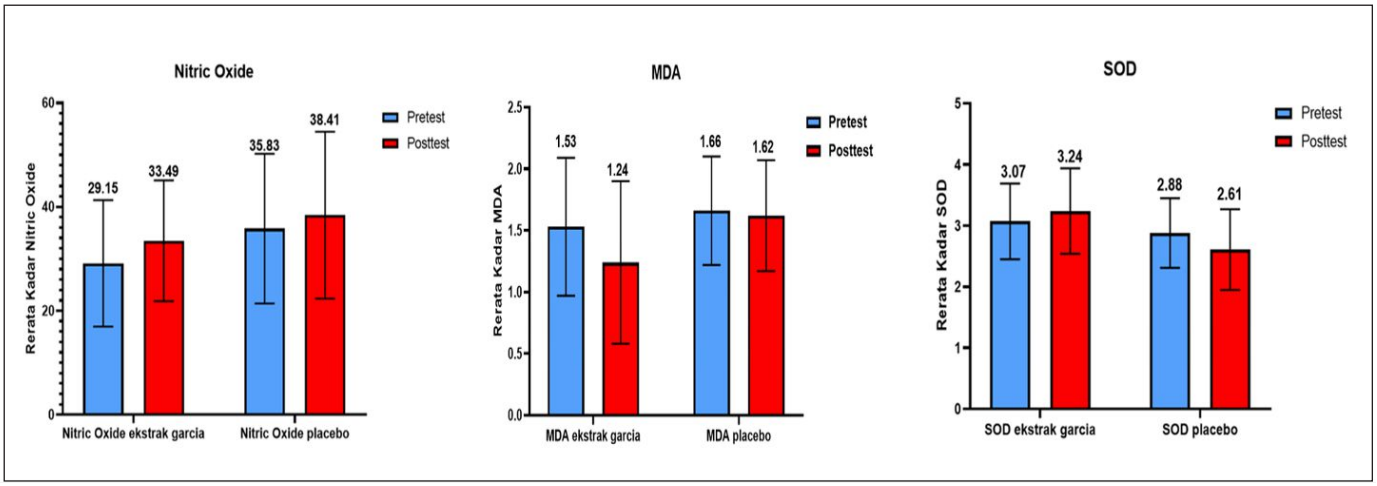


Figure 1. The levels of NO, MDA, SOD between treatment and control groups.

Table 2. Summary of the findings in our study.

| Group Interventions | G. Mangostana extract | Mean | P-Value |
|---|---|---|---|
| Delta SOD | Moderate Statin | -0.22±0.75 | 0.070 |
| | High Statin | -0.32±0.57 | |
| | Moderate Statin + GMLE | 0.25±0.98 | |
| | High statin + GMLE | 0.13±0.74 | |
| SOD post test | Moderate Statin | 2.62±0.62 | 0.001 |
| | High Statin | 2.59±0.73 | |
| | Moderate Statin + GMLE | 3.47±1.13 | |
| | High statin + GMLE | 3.16±0.48 | |
| MDA post test | Moderate Statin | 1.60±0.42 | 0.003 |
| | High Statin | 1.63±0.48 | |
| | Moderate Statin + GMLE | 1.63±0.71 | |
| | High statin + GMLE | 1.10±0.60 | |
| Delta MDA | Moderate Statin | -0.12±0.28 | 0.008 |
| | High Statin | 0.04±0.16 | |
| | Moderate Statin + GMLE | -0.11±0.35 | |
| | High statin + GMLE | -0.36±0.55 | |
| NO post test | Moderate Statin | 36.63±12.78 | 0.388 |
| | High Statin | 40.36±19.18 | |
| | Moderate Statin + GMLE | 32.13±9.57 | |
| | High statin + GMLE | 33.97±12.39 | |
| Delta NO | Moderate Statin | 1.39±4.63 | 0.626 |
| | High Statin | 3.87±9.53 | |
| | Moderate Statin + GMLE | 5.27±7.59 | |
| | High statin + GMLE | 4.02±10.83 | |

Note; SOD, Superoxide Dismutase; MDA, Malondialdehyde; DMLE, Garcinia mangostana Linn extracts

## 4. Discussion

This investigation was conducted to demonstrate the use of Garcinia mangostana Linn pericarp extract as an antioxidant agent in high-risk patients according to the Framingham score. Atherosclerosis is a chronic and progressive disease, caused by various molecular activities, leading to structural disruption and vascular homeostasis. The atherosclerosis was caused by dyslipidemia, chronic inflammation, free radical production, and endothelial dysfunction.[12] This study was mainly focused on the role of free radicals and endothelial dysfunction, leading to direct implications of building up atherosclerotic plaque. The association between Garcia Mangostana Pericarp Extract and atherosclerosis was investigated by measuring SOD, MDA, and NO levels.

Pathogenesis of atherosclerosis in endothelial dysfunction caused by ox-LDL is through the activation of lectin-like ox-LDL receptors (LOX-1).[13] LOX-1 is an ox-LDL receptor in endothelial cells. Ox-LDL may bound to LOX-1 to enter the cell and induce ROS formation. Excessive formation of ROS may trigger the emergence of MDA as a result of lipid peroxidation. Endogenous antioxidants, one of them is SOD, will respond to the emergence of MDA. This imbalance levels between MDA and SOD may increase free radicals, which may worsen the atherogenesis state.

The observation was carried out for 90 days on Garcia Mangostana Pericarp Extract's administration, and the following results were obtained: by administering Garcia Mangostana Pericarp Extract at a dose of 2520 mg/day there was a decrease in MDA levels, increased levels of SOD and NO levels. Our study's findings supported the results of previous studies evaluating the activity of Garcia Mangostana Pericarp Extract as an antioxidant. They showed that Garcia Mangostana Pericarp Extract significantly reduced intracellular ROS production measured using 2,7-dichlorofluorescein diacetate (DCFH-DA) SKRBR cells.[14] In our study, the antioxidant activity was measured using SOD and MDA as parameters of free radicals.

The SOD enzyme parameters were used to elucidate the antioxidant effect of Garcia Mangostana Pericarp Extract. In our study, there is a meaningful differentiation between the SOD levels of the Garcia Mangostana Pericarp Extract group patients compared to the placebo group patients, with a p-value = 0.010. SOD levels increased in the treatment group, and vice versa decreased in the placebo group.

The conditions of high free radicals are frequently causing interference with SOD formation, especially in MnSOD and EC SOD. MnSOD is formed in the mitochondria, which require mitochondrial import machines to circulate in the cytosol and carry out their functions. In high conditions, free radical can reduce the level of cytosolic MnSOD. Besides, SOD scavenges metabolites, defined as H2O2, can also reduce the amount of functional SOD2 protein, although it does

not affect mRNA expression from SOD2.[15] The results in this study are consistent with previous studies from Wang et al., 2015 which reported that xanthones from Garcinia mangostana increased the levels of antioxidant enzymes, such as SOD and GSH.[16]

Oxidized LDL is the initial stage of atherosclerosis. Free radicals are atoms or molecules that contain unpaired electrons, and are unstable and may trigger the damage cells by taking one hydrogen atom from other molecules of the body.[17] Free radicals are found in the body through daily metabolism and will soon be converted into substances that are not harmful to the body, namely H2O and CO2. However, if free radicals exceed the antioxidant protection limit and then meet with polyunsaturated fatty acids, lipid peroxidation may occur, a chain reaction of lipid oxidation by free radicals. Lipid peroxidation reaction will eventually produce aldehyde compounds, one of which is MDA, commonly used as a biological biomarker of lipid peroxidation and describes the degree of oxidative stress. To prevent lipid peroxidation, antioxidants are needed to stabilize free radicals not to be harmful to the body.[18]

This study found that lower MDA levels in patients in the Garcia Mangostana Pericarp Extract extract group were observed compared to placebo, with $p = 0.011$. The results of this study are consistent with the previous study. They reported that Garcia Mangostana Pericarp Extract could reduce MDA levels, derived from xanthones' effects as antioxidants that inhibit lipid peroxidation. [19]

Homeostasis between antioxidants and free radicals determines vascular endothelial cells' function, which may produce NO mediators. NO is produced by vascular endothelial cells, via the NO-synthase (NOS) enzyme, from the L-arginine substrate and oxygen. NO has various roles in vascular, counting guidelines of vascular tone and restrains platelet aggregation and vascular smooth muscle cell proliferation. In atherosclerotic conditions, this function is disrupted by high levels of free radicals, such as O2- which react NO to form peroxynitrites (ONOO-.[20] In this study, there was an increase in NO levels, but not significantly in the Garcia Mangostana Pericarp Extract group patients, with $p = 0.37$. This study's results are slightly different from previous studies where there was a significant increase in NO levels. This increase in NO levels may come from the effect of xanthones that inhibit the activity of iNOS, whose activity is induced by inflammation and free radicals and will activate eNOS.[21] The insignificant findings in our study might be caused by the potency of bias, either from the study period or the small sample size.

## 5. Conclusion

*Garcinia mangostana Linn* pericarp is proven to inhibit the atherosclerosis process through free radical scavenging and endothelial function improvement.

## 6. Declarations

*6.1. Ethics Approval and Consent to participate*
This study was approved by local Institutional Review Board, and all participants have provided written informed consent prior to involve in the study.

*6.2. Consent for publication*
Not applicable.

*6.3. Availability 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: AMZI. Design: AMZI. Control/supervision: DS, CT, SW,AR. Data collection/processing: AMZI. Extraction/Analysis/interpretation: DS, CT, CW, AR. Literature review: DS, CT, CW, AR. Writing the article: AMZI. Critical review: DS, CT, CW, AR. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

*6.7. Acknowledgements*
We thank to Brawijaya Cardiovascular Research Center.

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