Original Article

The Effect of *Garcinia Mangostana* Linn Extract to The Levels of Circulating Endothelial Cells and Endothelial Progenitor Cells in Patients with High Framingham Score

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ABSTRACT

Background: Recently, studies have focused on the use of xanthones for treating patients with cardiovascular diseases. In our country, xanthones were found in *Garcinia Mangostana* Linn.

OBJECTIVES: To assess the effect of *Garcinia Mangostana* Linn Extract (GMLE) to the levels of Circulating Endothelial Cells (CEC) and Endothelial Progenitor Cells (EPC) in patients with high Framingham score.

METHODS: A prospective cohort study was conducted from November 2018 to January 2019. The patients were divided into two groups. The first group was given 2520 mg/day of GMLE for 90 days and the second group was given placebo. In sub-group analyses, patients were divided based on previous medication, including statin, statin and angiotensin-converting-enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB), statin and oral antidiabetic drugs (OAD), and statin and ACEI or ARB and OAD. The outcome measures were CEC and EPC levels, measured at baseline and after 90 days of treatment. We used multiple linear regression to analyze the correlation and effect estimates.

RESULTS: A total of 72 patients was included in our study. All of the patients baseline characteristics were distributed homogeneously (p>0.05). Our findings confirmed that GMLE administration was associated with decreased CEC level compared to placebo. On other hands, increased EPC level compared to placebo was observed after GMLE administration. In sub-group analyses, our study found that the combination of GMLE with statin and ACEI or ARB and the combination of GMLE with statin and ACEI or ARB and OAD were associated with decreased level of CEC compared to placebo, with the odd ratios were 0.12 and 0.18, respectively. Conversely, increased level of EPC was observed in subjects receiving the combination of GMLE with statin and ACEI or ARB and the combination of GMLE with statin.

CONCLUSION: Administration of GMLE as adjuvant therapy is associated with the improvement of CEC and EPC levels in patients with high Framingham scores.

1. Introduction

Cardiovascular diseases remain the leading cause of mortality worldwide. It was reported that the global mortality caused by cardiovascular disease was ranging from 59.9 to 120.4 per 100,000 population. This number was estimated to increase about 3-fold in 2030. In our country, the reports revealed that the mortality was about 37%. However, the precise number was estimated due to limited reports while the risk factors of cardiovascular disease in Indonesia are complicated. Moreover, the risk factors of cardiovascular disease in our country including dyslipidemia, hypertension, and diabetes mellitus were reported to have increased trend over periods. Therefore, an approach to resolve this problem is required through both pre-clinical and clinical approach.

Recently, studies have focused on the inflammation as the target of endothelial dysfunction therapy. The process of inflammation in endothelial dysfunction is complex, and involves several
In our country, it has been widely known that a large amount of plants is existed. The used of active compound from plants had been shown to have benefits effects in some diseases, especially in cardiovascular diseases.17 In the context of cardiovascular diseases, studies had shown several compounds to have anti-inflammatory effects including xanthones,13 Tribulus terrestris extrac, Aqueous extract of Ocimum basilicum, salvianolic acid B, and Ethanol extract of Cynanchum wilfordii.14 However, recent studies showed that plants containing xanthones (α and γ mangosteen) were associated with better outcome in several cardiovascular diseases including ischemic heart disease, atherosclerosis, hypertension and thrombosis.13,15 Moreover, xanthones were also reported to provide decreased level of oxidant and the number of foam cells.15 Interestingly, studies also found that xanthones had no toxicity, suggesting that xanthones were safe for patients with cardiovascular diseases.17,18 In our country, xanthones are widely found in Garcinia Mangostana Linn. Therefore, Garcinia Mangostana Linn Extract (GMLE) might provide beneficial effects in patients with cardiovascular diseases, especially in patients with high framingham score.

Our present study, therefore, aimed to assess the correlation between the administration of GMLE and the levels of CEC and EPC in patients with cardiovascular diseases.19,20 In our study, patients were divided into two groups, GMLE and placebo, and data regarding the levels of CEC and EPC were collected at baseline and 90 days after treatment. To assess the correlation and effect estimates, data were analyzed using multiple linear regression.

2. Methods

2.1. Study Design

A prospective cohort study was conducted during November 2018 to January 2019 in dr. Saiful Anwar Hospital, Malang, Indonesia. To assess the correlation between the administration of GMLE and the levels of CEC and EPC in patients with high framingham score, study participants were divided into two groups, GMLE and placebo, and data regarding the levels of CEC and EPC were collected at baseline and 90 days after treatment. To assess the correlation and effect estimates, data were analyzed using multiple linear regression.

2.2. Ethical approval

The study protocols were conducted in accordance with the Declarations of Helsinki and were approved by the Institutional Review Board, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia (No: 64/EC/KEPK/03/2018). The aims, risks, and benefits of the study were explained to each participant, and they were asked to sign a consent form prior to enrolment in the study. Participants were also informed that they could quit at any time during the study session. Participations in this study were voluntary and no incentive was given.

2.3. Participants & eligibility criteria

To represent the total population, 30 participants were required as the minimum sample size based on the assumption that the prevalence of cardiovascular disease patients with high framingham score was 30% with a 5% margin of error and 95% confidence level. Data of sample frame was obtained from medical record in our Hospital. The recruitment of participants was conducted using a simple random sampling procedure. Inclusion criteria were (1) diagnosis having cardiovascular disease with high framingham score on the basis of clinical, biochemical, and electrocardiographic criteria for more than three months, (2) clinically stable and recovered, (3) having ability to communicate in Bahasa Indonesia. Patients with the following conditions: elevated levels of serum glutamic oxaloacetic transaminase (SGOT) / serum glutamic pyruvic transaminase (SGPT), urea, creatinine, prolonged blood coagulation, on routine therapy of Nonsteroidal anti-inflammatory drugs (NSAIDs), and patient with drug or narcotic abuse were excluded from the study. The study population was all high risk group patients according to the framingham cardiovascular risk score criteria. A total of 72 patients were divided into the treatment group (GMLE) and the control group with a combination of routine treatment that has been consumed previously. For GMLE group, three patients received GMLE, 13 patients received GMLE and Angiotension-converting-enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARBs), three patients received GMLE and oral anti diabetic, and 14 patients received a combination of GMLE and ACEI or ARB and oral anti diabetic. The GMLE administration was conducted for 90 days.

2.4. Measure

The baseline data, measured prior to GMLE administration, included age, gender, blood pressure, complete blood count, coagulation factors, SGOT/SGPT, urea, creatinine, lipid profile, blood glucose, and lipid profile. The outcome measures in our present study were the levels of CEC and EPC, measured before and after GMLE administration. All laboratory tests in our present study were conducted in Pattimura Laboratorium.

2.5. Statistical Analysis

To determine the correlation and effect estimates between the administration of GMLE and the levels of CEC and EPC in patients with high framingham score, data were analyzed using multiple linear regression. The p value of less than 0.05 was considered statistically significant. Prior to determine the correlation, data were assessed for homogeneity by using paired t-test and chi-square. All statistical analyses in our present study were conducted using the Statistical Package for Social Sciences software (SPSS for Windows, version 16, Chicago, USA).

3. Results

3.1. Patients Selections

During March to May 2017, a total of 123 patients with high framingham score was identified. Of those, a total of 51 patients was excluded because of elevated levels of SGOT and SGPT (12), urea and creatinine (26), prolonged blood coagulation (7), and on routine therapy with NSAID (18). Finally, we included 72 patients in our study, divided into 33 patients given GMLE and 39 patients given placebo. A flowchart describing eligibility pathway in our study is provided in Fig 1.

3.2. Baseline Characteristics

Approximately one-third of the participants were men (58.9%) with mean age and body mass index were 63.35 years and 25.79 kg/m2, respectively. Other baseline characteristics of patients included in our present study are summarized in Table 1. The baseline characteristics between patients receiving GMLE and placebo had p value of more than 0.05, suggesting that data were distributed homogeneously between groups.

3.2. Main Findings

A total of 33 patients receiving GMLE and 39 patients receiving placebo was enrolled in our study. Our overall analysis found that
A total of 123 patients with high Framingham score were included in our study. A total of 51 patients were excluded because of elevated levels of SGOT and SGPT. A total of 72 patients were included in our study. 1. 12 patients were excluded because of elevated levels of SGOT and SGPT. 2. 26 patients were excluded because of elevated levels of urea and creatinine. 3. 7 patients were excluded because of prolonged blood coagulation. 4. 18 patients were excluded because of on routine therapy with NSAID.

Table 1. Baseline characteristics of patients included in our study before treatment

| Variables               | GMLE (n=33) | Placebo (n=39) | p     |
|-------------------------|-------------|----------------|-------|
| Age                     | 64.21 ± 8.40 | 62.50 ± 10.30  | 0.6400|
| Sex (Male)              | 10 (30.3%)  | 13 (33.3%)     | 0.8060|
| Body mass index         | 25.18 ± 5.34 | 26.4 ± 4.06    | 0.3470|
| Framingham score        | 29.6 ± 17.38 | 35.09 ± 22.02  | 0.2890|
| Sistolic blood pressure | 155 ± 8.80   | 147 ± 15.30    | 0.0090|
| Diastolic blood pressure| 87 ± 14.30   | 88.5 ± 10.90   | 0.4980|
| Total cholesterol       | 227.00 ± 24.97 | 221.60 ± 34.71 | 0.4940|
| Triglyceride            | 156.50 ± 88.07 | 152.90 ± 102.40 | 0.8600|
| HDL                     | 48.45 ± 13.12 | 45.56 ± 11.66  | 0.4980|
| LDL                     | 116.05 ± 34.26 | 115.4 ± 34.18  | 0.9010|
| Fasting blood glucose   | 115.64 ± 42.39 | 138.49 ± 63.86 | 0.0940|
| CEC                     | 1.23 ± 72.89  | 1.07 ± 82.05   | 0.9140|
| EPC                     | 100.81 ± 46.79 | 99.34 ± 45.03  | 0.9270|

Note. Data were presented in mean ± SD or n[%]; GMLE, Garcinia Mangostana Linn Extract; HDL, High-density lipoprotein; LDL, Low-density lipoprotein; HbA1C, hemoglobin A1c; CEC, Circulating endothelial cells; EPC, Endothelial progenitor cells.

GMLE administration was associated with decreased level of CEC compared to placebo (OR95%CI = 0.17 [0.07 - 0.41], p<0.0001). Conversely, 15-fold elevated level of EPC was found in patients receiving GMLE compared to placebo (OR95%CI = 15.83 [6.10 - 41.09], p<0.0001). The summary of CEC and EPC levels between patients receiving GMLE and placebo is described in Table 2.

Table 2. The comparison of ∆ CEC and ∆ EPC between groups

| Parameters            | GMLE (n=33) | Placebo (n=39) | OR     | 95%CI      | p     |
|-----------------------|-------------|----------------|--------|------------|-------|
| ∆ CEC (cells/µL)      | -62.53 ± 70.63 | -3.97 ± 49.11  | 0.17   | 0.07 - 0.41 | <0.0001|
| ∆ EPC (cells/µL)      | 16.77 ± 20.81 | -22.90 ± 30.35 | 15.83  | 6.10 - 41.09 | <0.0001|

Note. Data were presented in mean ± SD; GMLE, Garcinia Mangostana Linn Extract; OR, odds ratio; CI, confidence interval.
In sub-group analysis, for CEC level, our findings found that the combination of GMLE with statin and ACEI or ARB was associated with decreased level of EPC compared to placebo (OR95%CI = 0.12 [0.05 - 0.29], p<0.0001). Subsequently, compared to placebo, decreased level of CEC was also observed in patients receiving the combination of GMLE with statin and ACEI or ARB and OAD (OR95%CI = 0.18 [0.07 - 0.43], p<0.0001). The summary of the comparison of CEC level between groups with drugs combination is provided in Table 3. Furthermore, for EPC level, we revealed that increased level of EPC was found in patients receiving the combination of GMLE with statin and ACEI or ARB (OR95%CI = 22.04 [8.27 - 58.79], p<0.0001). We also found that elevated level of EPC was also observed significantly higher in patient receiving the combination of GMLE with statin and OAD (OR95%CI = 13.18 [5.14 - 33.74], p<0.0001). We summarized the comparison of EPC level between groups with drugs combination in Table 4.

| Combination with | GMLE | Placebo | OR | 95% CI | p     |
|------------------|------|---------|----|--------|-------|
| Statin           | -39.50 ± 19.24 | 24.41 ± 93.09 | 0.66 | 0.28 - 1.53 | 0.3330 |
| Statin + ACEI / ARB | -48.00 ± 63.89 | 12.24 ± 36.08 | 0.12 | 0.05 - 0.29 | <0.0001 |
| Statin + OAD      | -18.00 ± 27.66 | 34.79 ± 81.78 | 1.63 | 0.70 - 3.79 | 0.2580 |
| Statin + ACEI / ARB + OAD | -90.44 ± 81.91 | 35.0 ± 20.49 | 0.18 | 0.07 - 0.43 | <0.0001 |

Note, data were presented in mean ± SD; GMLE, Garcinia Mangostana Linn Extract; OR, odds ratio; CI, confidence interval; ACEI, Angiotensin-converting-enzyme inhibitors; ARB, Angiotensin II receptor blockers; OAD, Oral anti diabetic drugs.

| Combination with | GMLE | Placebo | OR | 95% CI | p     |
|------------------|------|---------|----|--------|-------|
| Statin           | 15.80 ± 35.63 | -12.48 ± 16.32 | 0.14 | 0.06 - 0.35 | <0.0001 |
| Statin + ACEI / ARB | 20.11 ± 17.46 | -27.45 ± 34.19 | 22.04 | 8.27 - 58.79 | <0.0001 |
| Statin + OAD      | 4.30 ± 11.75 | -18.90 ± 18.95 | 13.18 | 5.14 - 33.74 | <0.0001 |
| Statin + ACEI / ARB + OAD | 26.56 ± 22.82 | -24.12 ± 34.24 | 23.04 | 8.61 - 61.68 | 0.9270 |

Note, data were presented in mean ± SD; GMLE, Garcinia Mangostana Linn Extract; OR, odds ratio; CI, confidence interval; ACEI, Angiotensin-converting-enzyme inhibitors; ARB, Angiotensin II receptor blockers; OAD, Oral anti diabetic drugs.

4. Discussion

Our results found that the administration of GMLE as an adjuvant therapy in patients with high framingham score was associated with decreased level of CEC. During this time, no study reported the effect of GMLE as an adjuvant therapy in patients with high framingham score. However, in other disease settings, studies had found that decreased level of CEC was observed in patients with hypertension, diabetes mellitus, and dyslipidemia after administration of GMLE as adjuvant therapy. The theory explaining this correlation was arduous to explain. However, some speculations regarding the role of CEC in the process of atherosclerosis have been proposed. A study revealed that the level of CEC in circulation was closely related to the severity of endothelial dysfunction, the higher CEC level the higher degree of endothelial dysfunction severity. Another study also supported the speculation. They showed that the positive correlation regarding the number of CEC and carotid plaque score was found, suggesting that CEC might play a pivotal role as one of the biomarkers of endothelial dysfunction severity. Subsequently, previous studies had found that GMLE contained xanthones (α and γ mangosteen). The precise mechanism of GMLE in the pathogenesis of endothelial dysfunction had not been clearly elucidated. However, the evidence revealed that xanthones administration as an adjuvant therapy was associated with better outcome in several cardiovascular diseases including atherosclerosis, hypertension, and dyslipidemia. Moreover, xanthones were also found to provide decreased level of oxidant and the number of foam cells. Therefore, implicitly, the lower level of CEC after administration of GMLE as an adjuvant therapy in patients with high framingham score was made sense. This explanation might describe the probable mechanism between GMLE administration as an adjuvant therapy and the level of CEC in patients with high framingham score.

We found that increased level of EPC was observed in patients with high framingham score receiving GMLE compared to placebo. Until now, we found no study evaluating the role of GMLE to the level of EPC in patients with high framingham score. However, in the case of hypertension, diabetes mellitus, and dyslipidemia, studies had found the correlation between the administration of GMLE and the level of EPC, indicating that GMLE is the important component involved in the development of endothelial dysfunction. Moreover, it was also revealed that EPC had a negative correlation with the progression of atherosclerosis by playing a role in regenerating damaged vascular endothelium. While it had been proposed that GMLE had an important role in the process of endothelial dysfunction, further studies are required to elucidate the precise mechanism on how GMLE affect the level of EPC in patients with high framingham score.

In sub-group analysis, we tried to identify in specific conditions the role of GMLE to the levels of CEC and EPC in patients with high framingham score, including in patients with diabetes mellitus, hypertension, and dyslipidemia. Overall, our results conformed with our main findings, showing that GMLE was associated with decreased level of CEC, and vise versa, GMLE was correlated with increased level of EPC in patients with high framingham score. Our findings were consistent with the previous study in the case of diabetes mellitus. They also found that GMLE administration was associated with increased and decreased levels of EPC and CEC, respectively, in...
patients with diabetes mellitus. Moreover, in the case of hypertension, studies had also reported that the improvement of CEC and EPC levels was observed after GMLE administration in hypertensive patients. Furthermore, in the case of dyslipidemia, alteration of EPC and CEC levels was also found in dyslipidemia patients after GMLE administration. Those evidences suggested that GMLE might play a crucial role in the development of endothelial dysfunction and its associated diseases. However, further investigations are needed to determine the precise role of GMLE in each endothelial dysfunction associated disease.

To the best of our knowledge, our findings were the first study evaluating the effect of GMLE to the levels of CEC and EPC in patients with high Framingham score. Our current study might provide the initial data in evaluating the effect of GMLE on endothelial dysfunction, assessed by the levels of CEC and EPC in patients with high Framingham score. We expected that up-coming studies might be existed to investigate further regarding the effect of GMLE on endothelial dysfunction by using the findings of our study as the basic data.

In our current study, we had several limitations. First, several factors that might affect the severity of endothelial dysfunction including tobacco use, family history of premature coronary events, and activity status were not controlled for. Second, our findings should be interpreted with caution due to relatively small sample size. Third, in our study, the measure outcomes were only limited to the levels of CEC and EPC. Further studies evaluating clinical outcomes after GMLE administration might be required. Fourth, data retrieved in our current study were obtained from single center. Further studies involving multiple centers might be needed to achieve findings with better evidence.

5. Conclusion

Administration of GMLE as adjuvant therapy is associated with the improvement of CEC and EPC levels in patients with high Framingham scores. In addition, GMLE administration is also associated with the improvement of CEC and EPC levels in combination with optimal routine treatment including statin, ACEI or ARB, and oral antidiabetic drugs for the underlying disease.

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: ASM. Design: ASM. Control/supervision: DS, AR, HM. Data collection/processing: AR. Extraction/Analysis/interpretation: ASM, DS, AR. Literature review: HM. Writing the article: ASM. Critical review: DS, AR, HM, MSR, AFR, JKE. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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