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Antioxidative activities of alpha-mangostin in high-fat/high-glucose diet and streptozotocin-induced insulin-resistant rodents

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ABSTRACT

Insulin resistance (IR), of which pathomechanism is mainly mediated by oxidative stress, leads to impaired insulin secretion and multisystem damages. Recent evidence suggests that alpha-mangostin (α-MG) is a potential candidate to ameliorate oxidative stress; hence, this study aims to evaluate the antioxidative properties of α-MG in IR-induced rats. A total of 36 male Wistar rats were divided into six groups, i.e., control, control + α-MG (200 mg/kg), IR, IR + metformin, and IR + various doses of α-MG (100 and 200 mg/kg) which were administered via oral gavage for 8 weeks. IR was induced by administering high-fat/high-glucose diet for 11 weeks followed by a single streptozotocin injection (35 mg/kg, i.p.). Malondialdehyde (MDA), superoxide dismutase (SOD), and glutathione (GSH) activities were assayed to assess the oxidative stress between groups. Welch's analysis of variance and Kruskal–Wallis test were used to compare the data. This study demonstrated that α-MG remarkably decreased MDA and increased SOD as well as GSH activities in the heart, liver, and kidney tissues of IR model. Furthermore, α-MG also upregulated SOD activity in heart tissues in a dose-dependent manner. Besides its antioxidative effects, the administration of α-MG at 200 mg/kg was also associated with the upregulation of skeletal glucose transporter type 4 expression (2.50 ± 0.43 *vs.* control, 3.65 ± 0.36 ng/ml; $p < 0.05$). These findings suggest that α-MG yielded the potent antioxidative properties against IR rats.

INTRODUCTION

Type 2 diabetes mellitus as caused by insulin resistance (IR) is the ninth leading cause of death, afflicting approximately one-tenth of adult population worldwide. The high mortality rate of this disease may be explained by the amplified risk of multisystemic complications, including cardiovascular disease, stroke, nephropathy, retinopathy, and neuropathy (Zheng *et al*., 2018). The pathomechanism of this disease involves impairment in insulin secretion and/or action as characterized by decreased glucose transporter type 4 (GLUT4) expression, both of which are mediated by oxidative stress (Asmat *et al*., 2016). Oxidative damages are evident in IR, illustrated by a decreased antioxidant protection including superoxide dismutase (SOD) and glutathione (GSH) (Asmat *et al*., 2016), as well as increased malondialdehyde (MDA) levels (Tiwari *et al*., 2013). Oxidative stress in IR is mainly associated with cellular injury and endothelial dysfunction, which play major roles in the development of cardiovascular diseases through DNA, lipid, and protein damages (Asmat *et al*., 2016).

The treatment of IR involves blood glucose control through pharmacotherapies as well as lifestyle and diet changes (Ladeiras-Lopes *et al*., 2015). However, several concerns regarding the use of pharmacotherapies, particularly allopathic drugs, have been reported as they may induce severe adverse effects leading to treatment discontinuation (Karimi *et al*., 2015). Hence, the recent development of IR treatments has favored herbal medicines, which may yield similar efficacy with potentially fewer side effects (WHO, 1980). Alpha-mangostin (α-MG), a major mangostin-purified xanthone, is known for its antioxidative properties by scavenging free radicals, inhibiting apolipoprotein B-100 oxidation, and ultimately preventing cellular deaths (Xu *et al*., 2017). Furthermore, research works have also shown that α-MG yields potent anti-inflammatory, anticancer, antimicrobial,

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and antiplasmodial activities (Asasutjarit *et al*., 2019; Ibrahim *et al*., 2016; Larson *et al*., 2010). Although recent evidence suggests that α-MG yielded potent antioxidative potentials, little is known regarding its effects on the oxidative markers of various organs and skeletal GLUT4 expressions in IR. Hence, this study aims to evaluate the effects of α-MG in oxidative stress and skeletal GLUT4 expressions in IR model rats.

MATERIALS AND METHODS

Animals

A total of 36 male Wistar rats with age ranging from 10 to 12 months (150–250 g) were bred and handled at the Institute of Health Research and Development, Faculty of Medicine, Universitas Indonesia, Jakarta. This study's protocol was approved by the Institute of Animal Studies Ethics Committee (Guo *et al*., 2018). Animals were housed in standard condition (12 hours light/dark cycle; 23°C ± 2°C) and were provided with *ad libitum* access to food and water.

Study protocol

The details on experiment procedures have been previously discussed elsewhere (Soetikno *et al*., 2020). In brief, the animals were randomly allocated to the following six groups of six rats each: (1) normal group, serving as control (C); (2) healthy rats supplemented by α-MG 200 mg/kg (C + α-MG 200) (Aktin Chemicals Inc., Chengdu, China); (3) untreated IR-induced rats; (4) IR-induced rats treated with metformin 200 mg/kg (IR + metformin); (5) IR-induced rats treated with α-MG 100 mg/kg (IR + α-MG 100); and (6) IR-induced rats treated with α-MG 200 mg/kg (IR + α-MG 200). Experimental rats were induced with IR by *ad libitum* high-fat/high-glucose [high-fat/high-glucose (HF/HG), high-fat diet (HFD), 46.1% energy as fat, 18.1% protein, and 35.8% carbohydrate, 58V8, TestDiet, St. Louis, MO] diet for 11 weeks as well as single intraperitoneal streptozotocin [streptozotocin (STZ), 35 mg/kg, Santa Cruz, Dallas, TX; catalog number sc-200719A] injection at week 3. On sacrifice, tissue samples were excised and stored at −80°C until further measurements.

Homeostasis model assessment-IR (HOMA-IR) index measurement

The HOMA index was measured using the steady-state blood glucose level along with insulin concentrations and was calculated using the following formula: HOMA-IR = blood glucose concentration (mM) × insulin (μU/l)/22.5.

Oxidative stress marker assays

The following oxidative stress markers were assessed in this study: MDA, SOD, and GSH. MDA level was measured using lipid peroxidation assay kit (Sigma-Aldrich, Singapore; catalog number MAK085), SOD activity using colorimetric activity kit (Invitrogen, Carlsbad, CA; catalog number EIASODC), and GSH level with colorimetric detection kit (Invitrogen, Carlsbad, CA; catalog number EIAGSHC), all of which were performed to the manufacturers' instructions. The obtained concentration for each oxidative stress marker was normalized for tissue protein content, and MDA level and GSH and SOD concentrations were expressed as nmol/mg protein, μmol/mg protein, and U/mg protein, respectively.

Estimation of GLUT4 expression in homogenized skeletal muscle

The effects of α-MG on GLUT4 expression in skeletal muscle tissue were analyzed by using the sandwich-ELISA kit for GLUT4 (Cusabio, Houston, TX; catalog number CSB-E13908r), carried out per manufacturer's instructions.

Statistical analysis

The findings are presented as mean ± standard deviation (SD) or as median (interquartile range (IQR)), whichever appropriate. The distribution and homogeneity of the data were analyzed with the Shapiro–Wilk test and Levene's test, respectively. Normally distributed and homogenous data were analyzed using the one-way analysis of variance (ANOVA) followed by Tukey's HSD test which was used to compare significance among groups, whereas the analysis of normal heteroscedastic data was performed with Welch's ANOVA followed by Games–Howell *post hoc* test. Otherwise, Kruskal–Wallis H-test followed by Mann–Whitney U *post hoc* test was utilized. All statistical analyses were performed using the Statistical Package for the Social Sciences 21.0 (IBM, Armonk, NY) and GraphPad Prism (version 8.4.2), and a p-value of <0.05 was considered to be statistical significance.

RESULTS

Effects of α-MG on body weight and HOMA-IR

Following HF/HG/STZ induction, the mean body weight of the IR group was lower than of other groups. Although α-MG administration did not show changes in the body weight of control group, its administration was able to prevent weight loss within the IR groups, and this effect was not significantly different among groups (Fig. 1A). The measurement of HOMA-IR revealed

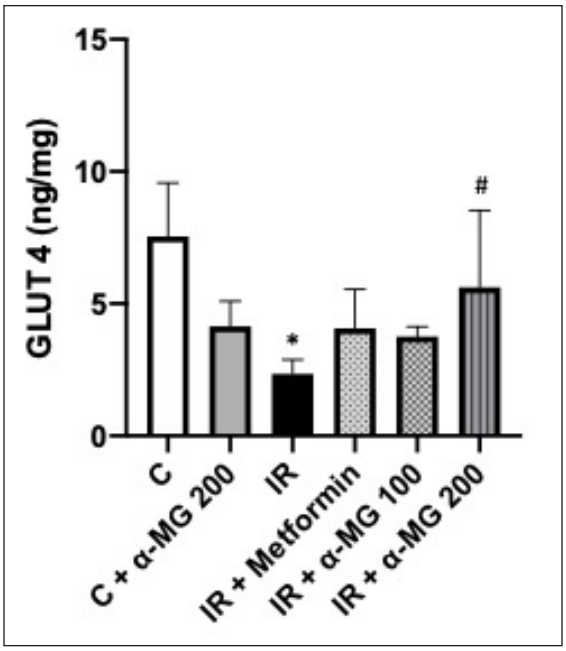

Figure 2. Effect of alpha-mangostin in both doses (100 and 200 mg/kg) and metformin on GLUT4 expression in the skeletal muscle of HF/HG/STZ-induced IR rats. Data were analyzed with one-way ANOVA using GraphPad Prism software and presented in mean ± SD (n = 6). $^{*}p < 0.05$ versus C and C + α-MG 200. $^{\#}p < 0.05$ versus IR.

that the administration of α-MG in both doses (i.e., 100 and 200 mg/kg) significantly increased insulin sensitivity, evident in the decreased HOMA-IR index when compared to untreated IR group (Fig. 1B).

Effects of α-MG on MDA levels

In this study, we demonstrated that oxidative stress ensues after HF/HG/STZ-induced IR, as shown in Table 1, where MDA concentration was higher in IR-induced diabetic rats than in control. The administration of α-MG in both doses on the heart and kidney tissues resulted in decreased MDA levels when compared to IR groups. Although the administration of α-MG at both 100 and 200 mg/kg resulted in significantly lower MDA concentrations, the desired effect was not observed in a dose-dependent manner. Nonetheless, the administration of α-MG at 200 mg/kg in heart tissues substantially ameliorated MDA concentrations better than metformin; however, this was not the case for kidney and liver tissues.

Effects of α-MG on antioxidants activity

The upregulation of the activities of antioxidant enzymes (i.e., SOD and GSH) was also observed with the administration of α-MG. Alpha-mangostin 200 mg/kg successfully ameliorated SOD activities in heart and kidney tissues ($p < 0.001$), whereas its improvement following α-MG administration at 100 mg/kg was only significant for heart tissues ($p < 0.001$). Similarly, the administration of α-MG at both 100 and 200 mg/kg also upregulated GSH activities (both at $p = 0.029$) (Table 1).

Effects of α-MG on GLUT4 expression

In terms of GLUT4 expression, the downregulation of GLUT4 expression in the skeletal muscle tissues following IR induction was also observed (2.50 ± 0.43 ng/ml), as compared to control (9.24 ± 2.24 ng/ml, $p = 0.039$). Subsequently, the administration of α-MG at 200 mg/kg significantly improved GLUT4 expression ($p = 0.045$) (Fig. 2).

DISCUSSION

The correlation between oxidative stress and IR has been well established. The reciprocal amplification between these two components may lead to deteriorations in body function and quality of life. While it may be true that oxidative stress is the root cause of IR, it is also the leading cause of pathophysiological changes in IR, including reduced nitric oxide as well as increased inflammatory cytokines and acute-phase reactants, which may lead to massive glycation and oxidation resulting in multiorgan failure, including atherosclerosis and major adverse cardiac events, kidney failure, and severe liver disorders (Wright *et al*., 2006), therefore, intensifying the need to develop alternative modalities to ameliorate oxidative stress and reduce its disease burden.

This study demonstrated that α-MG yielded protective effects against oxidative stress and GLUT4 expression in IR-induced rats. Although the antioxidative properties of α-MG are well established, to the best of authors' knowledge, its effect on skeletal GLUT4 expression as well as its potential antioxidative activities against IR, particularly on heart and liver tissues, has yet to be investigated. Overall, α-MG improved oxidative stress in diabetic organs, evident in the increase of SOD and GSH activities as well as decrease in MDA level. Its antioxidative effect on heart tissues was better augmented following the administration of α-MG 200 mg/kg. However, this was not the case for kidney and liver tissues, where the administration of α-MG 200 mg/kg resulted in lesser improvements of oxidative stress when compared to those of 100 mg/kg although insignificant, which may be explained by the different responses of various organs to oxidative stress and antioxidative mechanism (Liu *et al*., 2000).

The results corroborated findings of the previous studies, where α-MG exhibited cardioprotective effects on isoproterenol-induced myocardial infarction (Sampath *et al*., 2007), renoprotective effects on cisplatin-induced nephrotoxicity (Pérez-Rojas *et al*., 2009), and hepatoprotective effects on acute liver failure (Fu *et al*., 2018). The antioxidative properties of α-MG are mediated by its phenol-rich content, which may act as a free radical

Table 1. Study outcomes.

Variable	C ($n = 6$)	C + α-MG 200 ($n = 6$)	IR ($n = 6$)	IR + metformin ($n = 6$)	IR + α-MG 100 ($n = 6$)	IR + α-MG 200 ($n = 6$)
MDA (nmol/mg)						
Heart	2.29 ± 0.78	2.44 ± 0.50	6.46 ± 1.03*	2.44 ± 0.36**	2.05 ± 0.23**	± 0.15**
Liver	0.24 ± 0.00	0.02±0.01	0.078 ± 0.05*	0.05 ± 0.02	0.04 ± 0.01	± 0.01
Kidney	0.11 ± 0.52	0.09 ± 0.03	0.92 ± 0.33*	0.05 ± 0.02**	0.15 ± 0.08**	0.26 ± 0.10**
SOD (U/ml)						
Heart	1.06 ± 0.15	1.39 ± 0.36	0.14 ± 0.08*	1.61 ± 0.35**	2.01 ± 0.17**	± 0.29**
Kidney	0.61 ± 0.27	0.26 ± 0.18	0.21 ± 0.07*	0.29 ± 0.12	0.45 ± 0.18	0.54 ± 0.16**
GSH (μM)						
Liver	0.36 ± 0.06	0.35 ± 0.23	0.26 ± 0.04*	0.30 ± 0.01**	0.36 ± 0.11**	0.29 ± 0.04**
Skeletal GLUT4 (ng/ml)	9.24 ± 2.24	4.40 ± 0.10	2.50 ± 0.43*	3.63 ± 0.29**	6.11 ± 2.22	3.65 ± 0.36**

Results are presented as mean ± SD or median (IQR), whichever appropriate. Values are considered statistically significant at $p < 0.05$. AM = alpha-mangostin; HF/HG/STZ = high-fat/high-glucose diet + streptozotocin injection i.p.; MDA = malondialdehyde; SOD = superoxide dismutase; GSH = glutathione; GLUT4 = glucose transporter type 4. *$p < 0.05$ versus control. **$p < 0.05$ versus IR.

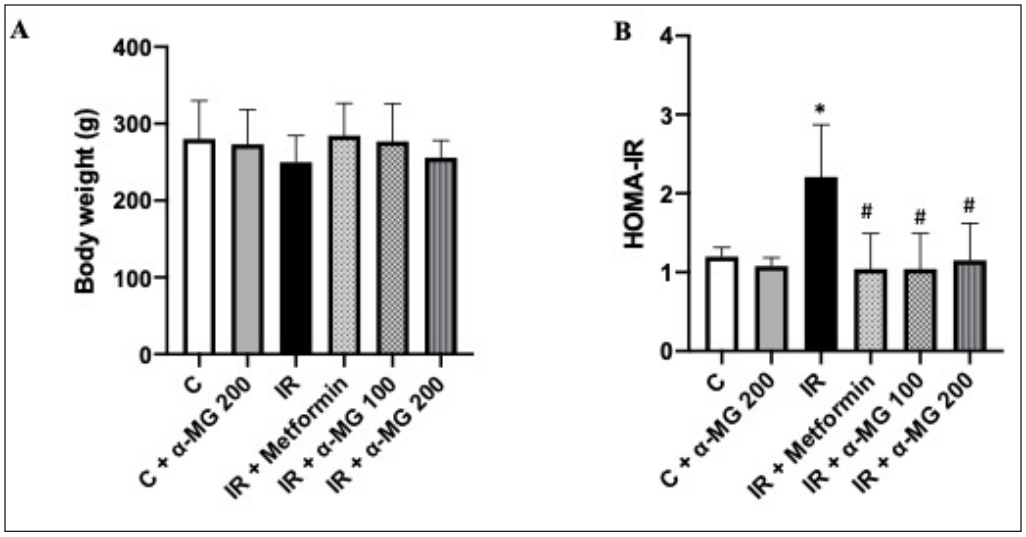

Figure 1. Effect of alpha-mangostin in both doses (100 and 200 mg/kg) and metformin on body weight (A) and HOMA-IR (B) in HF/HG/STZ-induced IR rats. Data were analyzed with one-way ANOVA using GraphPad Prism software and presented in mean ± SD ($n = 6$). $^{*}p < 0.05$ versus C and C + α-MG 200. $^{\#}p < 0.05$ versus IR.

scavenger as well as a modulator for several antioxidant enzymes (Ibrahim *et al*., 2016). Furthermore, α-MG may also downregulate peroxisome proliferator-activated receptor-γ expression, thereby inhibiting adipo/lipogenesis on 3T3-L1 cells and subsequently reducing lipid peroxidation (Taher *et al*., 2015).

The supplementation of α-MG on healthy rats did not yield positive results. On the contrary, it even reduced SOD and GSH activities on renal and liver tissues, respectively. This may be explained by the potentials of -MG to act as a pro-oxidant in oxidative balance state. Kosem *et al*. (2013) stated that the overdose of α-MG may induce severe hepatotoxicity and renotoxicity. Furthermore, the administration of high-dose α-MG may also cause hypoactivity, lethargy, decreased appetite, and piloerection, which were observed in this study.

In addition to the improvements in oxidative stress, α-MG was also associated with increased skeletal GLUT4 expression, suggesting that α-MG may also yield antidiabetic effects. This is, especially, true as skeletal GLUT4 expression was severely diminished in T2DM patients, thus worsening IR and the disease progression (Shan *et al*., 2011). The antidiabetic property of α-MG observed in this study may be related to its ability to stimulate insulin secretion by activating the insulin receptor and to inhibit the phosphorylation of insulin receptor substrate-1 (Lee *et al*., 2018). This study added that, besides increased GLUT4 expression in adipocyte (Taher *et al*., 2015), liver (Kim *et al*., 2017), and cardiac tissues (Ratwita *et al*., 2017), α-MG was also able to upregulate GLUT4 expression in skeletal muscles.

In this study, we used experimental animals that were administered with high-fat diet for 11 weeks and a single low-dose STZ injection at week 3 to induce IR. The method that we used is able to cause IR in all experimental animals, and this is in accordance with research conducted by Al-Trad *et al*. (2019) who analyzed the effects of eugenol on oxidative stress and inflammatory processes in rats with T2DM. IR which is commonly followed by obesity can be induced in experimental animals by providing a high-fat diet for several weeks to months. However, there are several studies that prove that IR can be detected in rodents only after 1–3 weeks of high-fat diet before an increase in body mass (Castorena *et al*., 2014; Hancock *et al*., 2008; Turner *et al*., 2013).

CONCLUSION

To summarize, this study confirmed the antioxidative properties of α-MG on heart, liver, and kidney tissues, evident in the decreased MDA levels as well as increased SOD and GSH activities. Furthermore, α-MG was also capable of upregulating skeletal GLUT4 expression, yielding potent antidiabetic effects in addition to its antioxidative activities. Future studies investigating the molecular mechanism of α-MG are required to better elucidate our findings.

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CONFLICT OF INTEREST

Authors declared that they do not have any conflicts of interest.

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