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Alpha-mangostin counteracts hyperuricemia and renal dysfunction by inhibiting URAT1 renal transporter in insulin resistance rat model

Vivian Soetikno^{1*} , Andriyani Murwantara², Ahmad Aulia Jusuf³ and Melva Louisa¹

Abstract

Background: Alpha-mangostin (AM) has been shown to have hypoglycemic activity. This study aimed to analyze the effects of AM at a dose of 100 mg/kg and 200 mg/kg to alleviate hyperuricemia and renal dysfunction on high-fat/high-glucose diet and low dose streptozotocin (HF/HG/STZ) injection-induced IR rat model. IR was induced in male Wistar rats by giving a HF/HG diet for 11 weeks and single injection of STZ (35 mg/kg, i.p.), then divided randomly into IR rats, IR rats treated with AM 100 and 200 mg/kgBW given by gavage for 8 weeks. At the end of the 11th week, all rats were killed, and the kidneys were taken to be analyzed for urate transporters 1 (URAT1) and glucose transporters 9 (GLUT9). We also assessed serum uric acid, proteinuria, BUN, creatinine clearance, HOMA-IR, and fasting blood glucose (FBG).

Results: We have found the significant increase in HOMA-IR and FBG levels of the IR rats, in comparison with its control groups, which were decreased significantly after AM administration at both doses. URAT1 and GLUT9 mRNA and protein expressions in kidney in the IR + AM at both doses groups also decreased compared those in the IR without treatment group, though the decrease in GLUT9 did not appear to be statistically significant. Consequently, hyperuricemia and renal dysfunction were attenuated by AM treatment at both doses.

Conclusion: After considering all findings, AM might be a potential candidate to ameliorate IR-induced hyperuricemia and renal dysfunction at least in part by modulating the renal URAT1.

Keywords: Insulin sensitivity, Urate transporters, Hypouricosuria, Kidney, Proximal tubule

1 Background

Previous studies have demonstrated that increasing serum uric acid (SUA) levels often occur in patients with insulin resistance (IR) [6, 9]. Uric acid (UA) has also been reported to be one of the important factors in the occurrence of impaired kidney function [24]. Previous study has reported that in healthy normotensive adults, increase in SUA level was linked to subsequent deteriorating of kidney function [4]. Basically, the levels

of SUA are governed by the UA transporters system in the proximal tubules of the kidney [10]. Briefly, UA after filtration process in the glomeruli is reabsorbed in the proximal tubules through URAT1 transporter on the apical side of the proximal tubules and then transcellularly transported through GLUT9 transporter which is on the basolateral membrane side which will then enter the systemic circulation [1, 22]. Previous study has reported that in metabolic syndrome rats there was an increase in the expression of UA transporters, namely URAT1 and GLUT9 which lead to hyperuricemia [19].

At present, herbal medicine get full attention as protector of IR complications, one of which is alpha mangostin (AM) [8]. The main xanthone isolated from the bark and dried sap of the *Garcinia mangostana* plants was AM.

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Multiple reports have shown that AM has several biological effects, including anti-oxidants, anti-inflammatory, pro-apoptotic, anti-proliferative, neuroprotective, hypoglycemic, and anti-obesity [15, 20]. We also previously reported that AM treatment has significant beneficial effects on High-Fat/High-Glucose/streptozotocin (HF/HG/STZ)-induced IR rats, which are obtained by decreasing plasma glucose, improving cardiac hypertrophy and fibrosis [23]. Even though recent evidence proposes that AM yielded potent anti-oxidative, anti-inflammatory, and hypoglycemic properties, not widely known regarding its effect on ameliorating hyperuricemia and renal dysfunction in IR. Therefore, the aim of this study is to evaluate the effects of AM to overcome hyperuricemia and renal dysfunction in rat model of IR.

2 Methods

2.1 Materials

All reagents used were of analytical grade and purchased from Sigma (CA, USA). High-fat diet (TestDiet, 58V8 rat chow) containing 46.1% fat, 35.8% carbohydrate, and 18.1% protein with total energy 4.60 kcal/g was purchased from Richmond, USA. Alpha mangostin was obtained from Aktin Chemical, Inc., Chengdu, China. Primary antibody against URAT1 was obtained from Abbotec, USA (cat. # 250521), and GLUT9 was obtained from Invitrogen (cat. # PA5-22966).

2.2 Animal

Male Wistar rats (150–250 g; obtained from Animal Laboratory of National Institute of Health Research and Development, Indonesian Ministry of Health Indonesia) were housed in colony cages, maintained on a 12-h light/12-dark cycle. Rats in IR group were fed with high-fat (HF) diet along with 20% high-glucose (HG) drinking water for 3 weeks. Low-dose streptozotocin (STZ) (35 mg/kg) was injected by intraperitoneal (*i.p.*) after 3 weeks of giving a HF and HG diet. Streptozotocin was freshly prepared by dissolved in 0.01 M citrate buffer, pH 4.5. Fasting blood glucose (FBG) levels were measured 72 h after STZ injection, rats that have FBG levels ≥ 250 mg/dL can be included in the study. If the FBG has not reached the target, the injection of STZ can be repeated once with a half-dose of the initial dose. Then, the HF and HG diet were continued until the 11th week. As a result, thirty rats were allocated into control (C, $n=6$), control+AM 200 (C+AM 200, $n=6$), IR ($n=6$), IR+AM100 ($n=6$), and IR+AM 200 ($n=6$). Alpha mangostin was dissolved in 1 mL of corn oil and administered orally for 8 weeks. The C and C+AM 200 rats were received 0.5 mL of distilled water alone. In addition, rats in the C and C+AM 200 groups received a standard diet and drinking water without glucose throughout the study

and at Week 3 were given NaCl injection to mimic the actions performed in the treatment groups. At 11 weeks, all rats were anesthetized with a single *i.p.* injection of ketamine/xylazine 0.15 mL/100 g body weight, and euthanized by cervical dislocation, and their kidneys were excised and decapsulated. Protein analysis was performed on a portion of the kidney which has been frozen immediately in liquid nitrogen and stored at -80°C . Half of the kidneys were fixed in 10% formalin, and some were unfixed for morphological studies.

2.3 Estimation of biochemical parameters

Blood samples of all rats were withdrawn from the heart via heart puncture at the time of sacrifice and placed in a serum separator vacutainer tube. To separate serum sample, the blood was sit for 30 min at room temperature to clot, and then, blood was centrifuged at 1000 g, 4°C , for 10 min. The serum, then, was used for the estimation of glucose, uric acid, urea, creatinine, and insulin. Twenty-four hours urine was also collected for each rat prior to killing by placing each rat in the metabolic cages for the measurement of creatinine using Jaffe method and protein concentration using Bradford method. Blood glucose was measured using Glucometer 4 Accu-check, CA, and was done at baseline, week-3, 5, 8, and 11, whereas serum uric acid (SUA) and urea were analyzed using the respective spectrophotometric diagnostic kit obtained from Diasys, Diagnostic Systems GmbH, Germany. Calculation of blood urea nitrogen (BUN) was done by multiplying the urea levels (mg/dL) by 0.467 [3]. Insulin was quantified with rat-specific ELISA kit (Mercodia, Uppsala, Sweden; Linco Research, St. Charles, MO, USA). HOMA-IR (homeostasis model assessment insulin resistance) was done using the following formula: $\text{HOMA-IR} = \text{blood glucose (mM)} \times \text{insulin (mU/L)} / 22.5$ [18]. The spectrophotometric analysis was performed using a UV-Vis Optizen. The calculation of creatinine clearance was carried out by the following formula: $\text{clearance creatinine (mL/min)} = \frac{\text{urine creatinine (mg/dL)} \times \text{urine volume (mL)}}{\text{plasma creatinine (mg/dL)} \times \text{time (1440 min)}}$ [2].

2.4 Histopathological analysis

The kidney tissues were cut transversely with a thickness of 2-mm and then fixed in 10% formalin and stained with hematoxylin and eosin (HE) to demonstrate nucleus pyknotic and thickening of capillary wall in the kidney. Formalin-fixed, paraffin-embedded kidney tissues were used for immunohistochemical staining. The slides, then, were deparaffinized and hydrated and followed by washed in Tris-buffered saline (TBS; 10 mM/L Tris HCl, 0.85% NaCl, pH 7.5) which contain 0.1% bovine serum albumin. Activity of endogenous peroxidase was quelled by incubating the slides in methanol and 0.3% H_2O_2 in methanol.

After being incubated overnight with primary antibodies, that are, URAT1 and GLUT9 (1:50 dilution) at 4 °C, the slides were washed in TBS buffer, added HRP conjugated secondary antibody (Santa Cruz), and incubated at room temperature for 45 min. Hematoxylin was used to counterstained the slides, and diaminobenzidine tetrahydrochloride (DAB) was used to visualize immunostaining. Twenty-five random fields per section were checked for all sections, and 3 animals per groups were used to assess immunostaining results.

2.5 Polymerase chain reaction

Kidney tissues were maintained by immersion in RNAlater (ThermoFisher, USA) immediately after sampling. Total RNA extraction was accomplished after homogenization using Ultra TurraxT8 (IKA Labortechnik, Staufen, Germany) in Quick-RNA Miniprep Plus Kit (Zymo Research) in accordance with the standard protocol. The total level of RNA is measured using a NanoDrop spectrophotometer at a wavelength of 260/280 nm and is considered pure if the purity index >2.0. cDNA synthesis was carried out from equal quantities of RNA using ReverTra Ace™ qPCR Master Mix with gDNA Remover (Toyobo).

To analyze the URAT1 and GLUT9 mRNA, splicing polymerase chain reaction was performed in a qRT-PCR

Light Cycler 480 using Thunderbird SYBR qPCR Mix kit (Toyobo). The total number of DNA templates used in each sample was 100 ng. Table 1 is the primer list used in this study. The conditions of PCR were as follows: pre-denaturation at 95 °C for 1 min, 40 cycles at 95 °C for 3 s, and 60 °C for 20 s. The quantity of mRNA was calculated via the cycle threshold (Ct) values, and the mRNA expression levels were measured according to the Livak method [16].

2.6 Statistical analysis

Data were reported as means ± standard error of the mean (SEM). Differences between groups were analyzed using one-way analysis of variance (ANOVA), followed by multiple comparisons using Tukey’s test. All data were analyzed using SPSS 20.0 software, and the results were said to be statistically significant when *p* value <0.05.

3 Results

3.1 Beneficial effect of AM on HOMA-IR and fasting blood glucose in HF/HG/STZ-induced IR rats

In order to determine the occurrence of IR, we assessed the HOMA-IR and FBG in HF/HG/STZ-induced IR rats. The vehicle-treated IR rats were noticed to have raised HOMA-IR (Fig. 1A) in comparison with control and control + AM 200 rats. The AM dose-dependently and significantly attenuated the HOMA-IR (*p*=0.03) in HF/HG/STZ-induced IR rats. These results suggest that AM improves IR in HF/HG/STZ-induced IR rats. At week 3, the baseline value of FBG revealed that there were no significant changes among groups (Fig. 1B). From the week 5, after the injection of STZ, the HF/HG/STZ rats were shown significant changes in FBG in comparison with

Table 1 List of primer sets used in this study

Gene	Forward (5’-3’)	Reverse (3’-5’)
URAT 1	TTACGACCACAGTACCTT	ACACAGACACCAGAAGAT
GLUT9	CTACACCAACAGCATCTT	CAATGACTAAGCCAGAGAA
Beta-actin	TTCACCACCACAGCTGAGAGG	GAACCGCTCGTTGCCAATAG

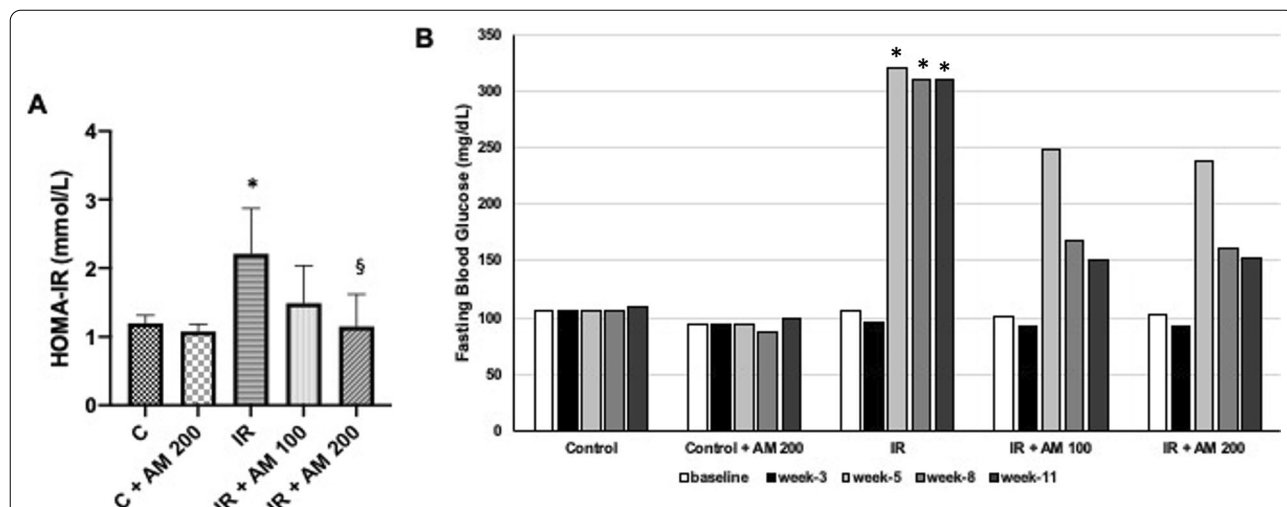


Fig. 1 Effect of AM on **A** HOMA-IR and **B** Fasting blood glucose. All values are expressed as the mean ± S.E.M.; *n* = 5; **p* < 0.05 versus C and C + a-MG 200; [§]*p* < 0.05 versus IR

control and control+AM 200 rats. Interestingly, there were decreased in the FBG of rats that were given AM at both doses at week 8 and 11, even though it did not reach a statistically significant ($p=0.22$) as compared to that of vehicle-treated IR rats.

3.2 Effect of AM on renal dysfunction in HF/HG/STZ-induced IR rats

In order to investigate the role of AM on renal dysfunction in HF/HG/STZ-induced IR rats, we examined proteinuria, BUN, and creatinine clearance. At 8 weeks after HF/HG/STZ administration, the vehicle-treated IR rats were shown significantly elevated in the proteinuria ($p<0.01$) (Fig. 2A) and BUN ($p<0.01$) (Fig. 2C) levels in comparison with control and control+AM 200 rats. The AM-treated IR rats showed significant changes in proteinuria (Fig. 2A) and BUN (Fig. 2C) in comparison with

vehicle-treated IR rats. In contrary, our vehicle-treated IR rats did not significantly affect the creatinine clearance level, and AM had no effect as well on the creatinine clearance in IR rats (Fig. 2B).

3.3 Effect of AM on SUA in HF/HG/STZ-induced IR rats

We next focused on renal UA handling. Interestingly, SUA in the vehicle-treated IR rats was significantly increased compared with that of the control and control+AM 200 rats ($p<0.001$) (Fig. 2D). The SUA levels of AM-treated IR rats were decreased significantly both at a dose of 100 mg/kg/day ($p<0.03$) and of 200 mg/kg/day as compared to that of vehicle-treated IR rats ($p<0.001$) (Fig. 2D).

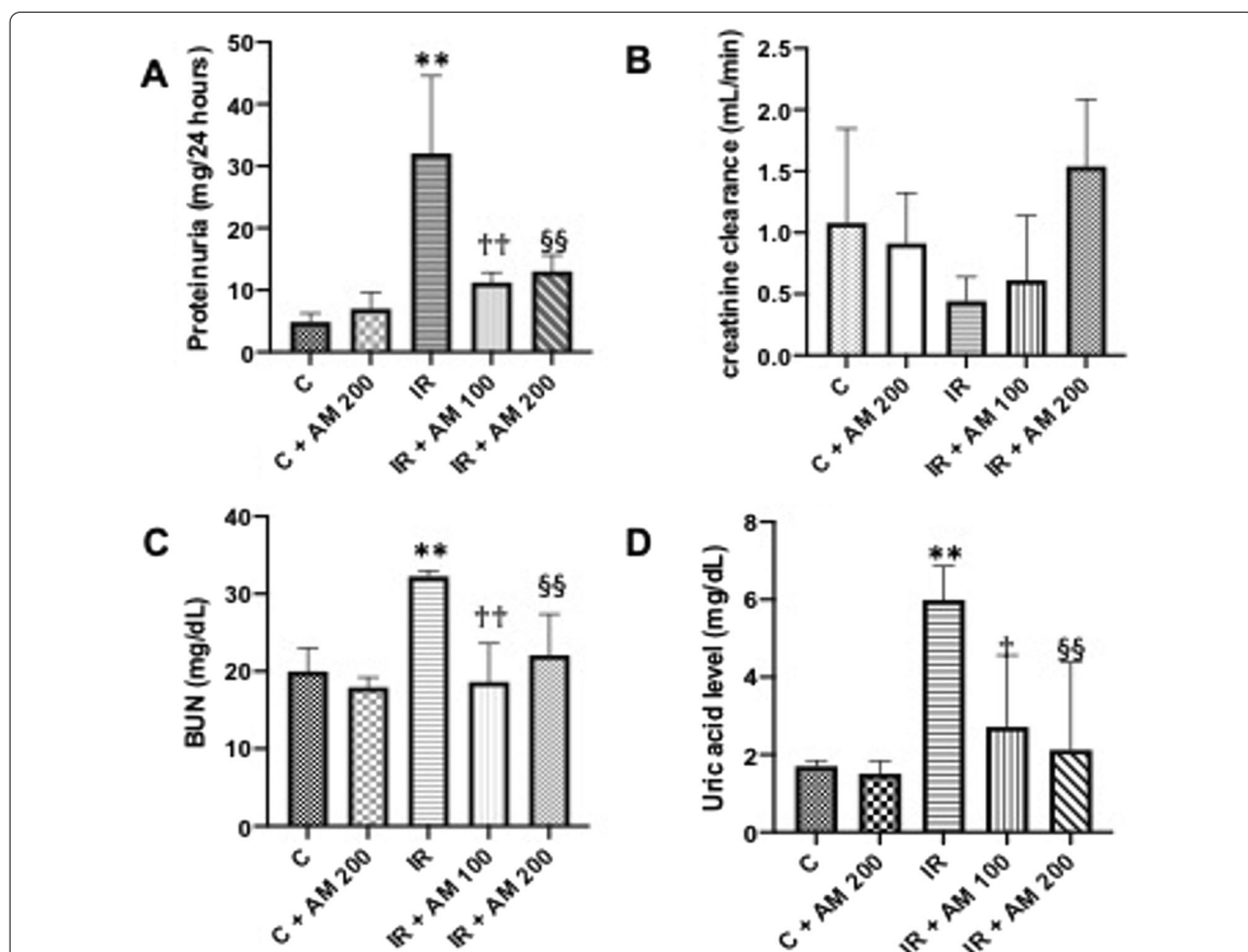


Fig. 2 Effect of AM on **A** proteinuria, **B** creatinine clearance, **C** BUN, and **D** uric acid level. All values are expressed as the mean \pm S.E.M; $n=5$; ** $p<0.01$ versus C and C+a-MG 200; † $p<0.05$ versus IR; †† $p<0.01$ versus IR; §§ $p<0.01$ versus IR

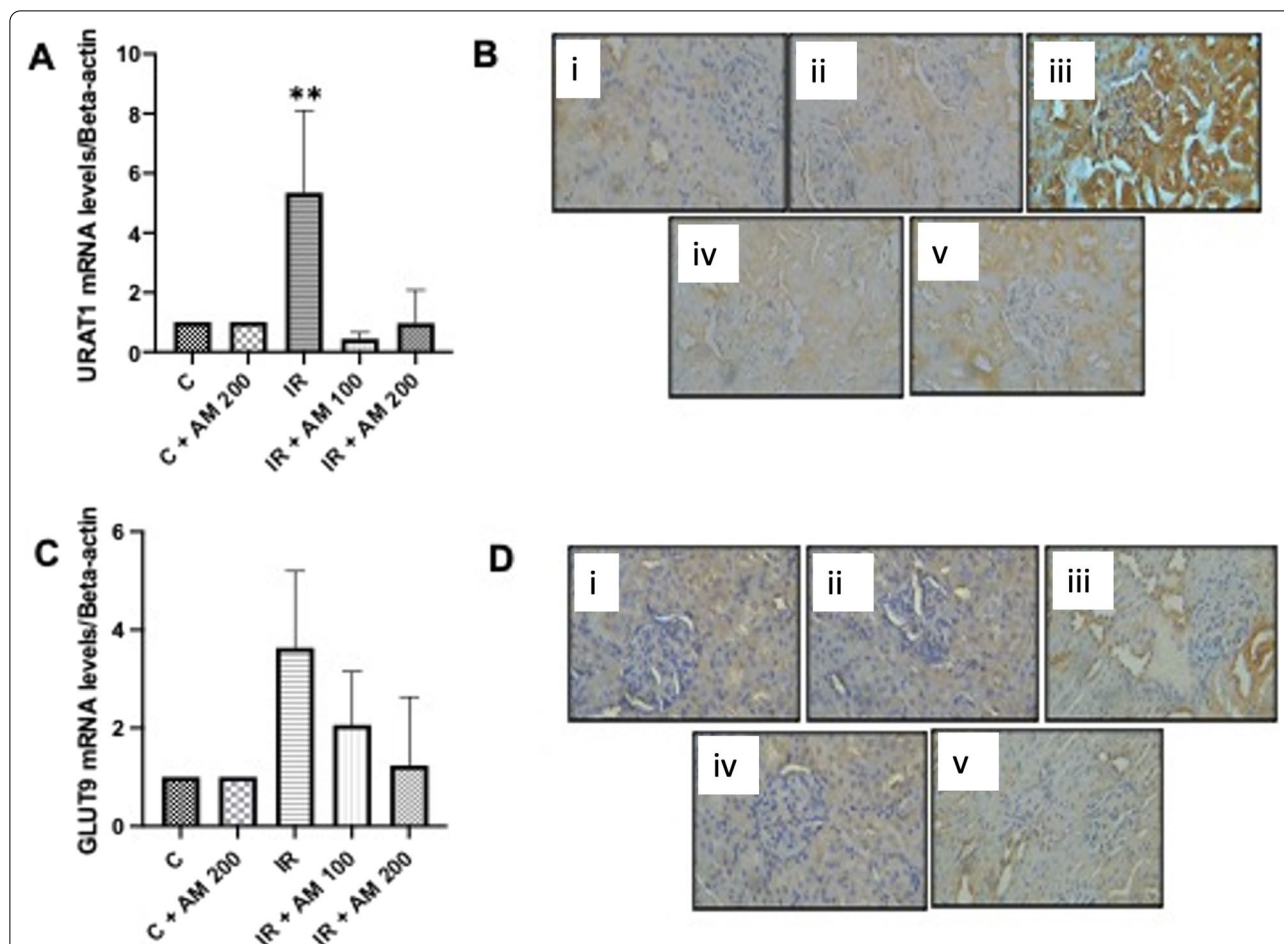


Fig. 3 Effect of AM on **A** URAT1 mRNA expression, **B** URAT1 performed by IHC in kidney sections, **C** GLUT9 mRNA expression, and **D** GLUT9 performed by IHC. Both expression of URAT1 and GLUT9 mRNA and protein were upregulated in animals fed with HF/HG/STZ injection. ** $p < 0.01$ versus C and C + a-MG 200; † $p < 0.01$ versus IR; †† $p < 0.01$ versus IR. (**B** and **D**, magnification $\times 200$)

3.4 Effect of AM on the mRNA expression of URAT1 and GLUT9 in HF/HG/STZ-induced IR rats

As shown in Fig. 3A, the levels of renal mRNA expression of URAT1 were significantly increased in the vehicle-treated IR rats as compared to that of control and control + AM 200 rats. In line with the mRNA expression, the protein expression of URAT1 was increased in the vehicle-treated IR rats (Fig. 3B), and AM at both doses evidently decreased the expression of URAT1 in the HF/HG/STZ-induced IR rats (Fig. 3A, B). In contrary, mRNA expression of GLUT9 did not show any difference between groups (Fig. 3C, D).

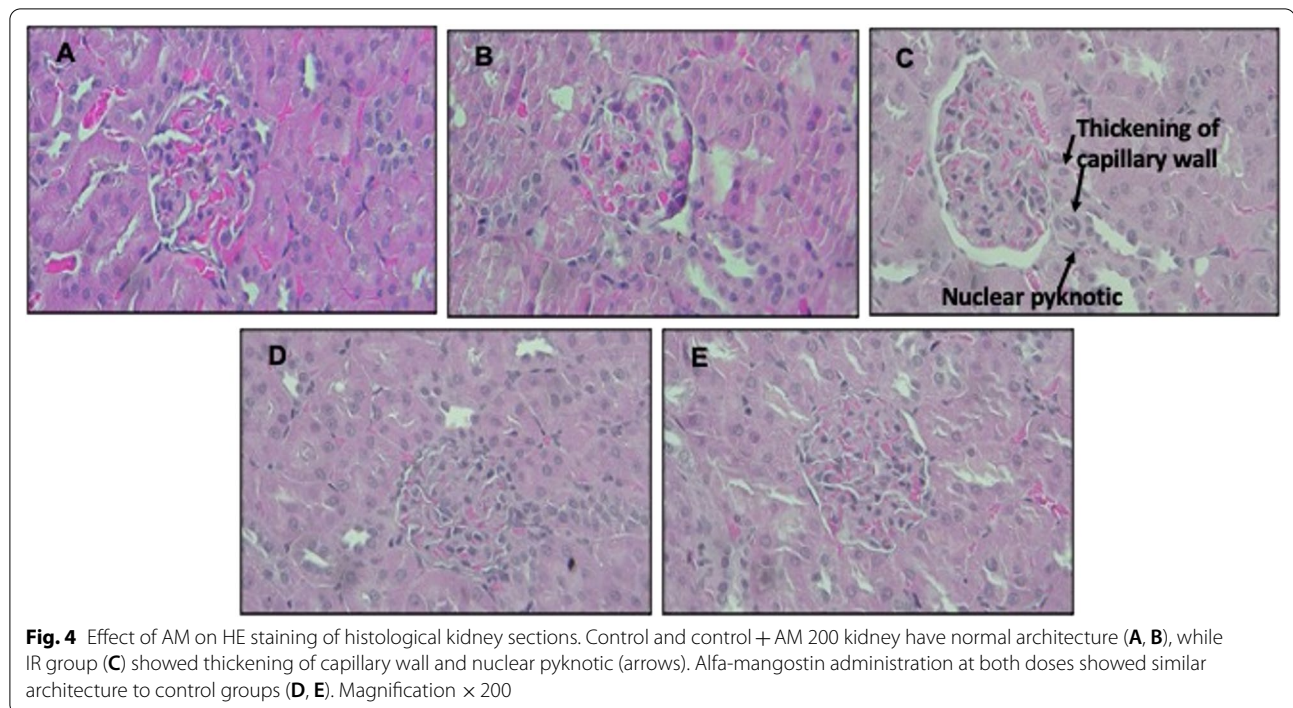
3.5 Effect of AM on tubulointerstitial injury in HF/HG/STZ-induced IR rats

To assess changes in the kidneys after HF/HG/STZ administration and AM intervention, we performed kidney histological analysis in HF/HG/STZ-induced IR rats.

As shown in Fig. 4, vehicle-treated IR rats demonstrated thickening of capillary wall in renal artery and pyknosis of the nuclei tubules (Fig. 4C). AM administration prevented the occurrence of these lesions as indicated by a decrease in the percentage of tubular damage in HF/HG/STZ-induced IR rats (Fig. 4D, E).

4 Discussion

In this study, we investigated the effects of AM to alleviate hyperuricemia and renal dysfunction in the HF/HG/STZ-induced IR rat model. It has been demonstrated that hyperuricemia and IR influence each other based on pathophysiological and metabolic point of view. Hyperuricemia can cause IR at least in part by reducing the bioavailability of nitric oxide and generation of mitochondrial oxidative stress through several mechanisms [12, 14]. Conversely, IR can induce hyperuricemia by increasing the reabsorption of UA in the renal tubules as manifested by up-regulation URAT1 expression [25]. The



current study firstly demonstrated that IR has occurred as evidenced by an increase in HOMA-IR and FBG in experimental animals receiving a HF/HG diet and low-dose STZ injection for 11 weeks. Our results also indicate that treating IR rat with AM at doses of 100 and 200 mg/kg/day for 8 weeks significantly reduced HOMA-IR and FBG and led not only to improved hyperuricemia but also ameliorated renal dysfunction and pathological changes with attenuated of nuclear pyknosis of tubules and thickening of capillary wall of renal artery compared with those in vehicle-treated IR rats. In the kidney, we found that the URAT1 and GLUT9 transporters were upregulated in the vehicle-treated IR rats. Interestingly, administration of AM at both doses could decrease them as compared to that of vehicle-treated rats.

IR and hyperuricemia are positively correlated with the progression of cardiorenal and metabolic diseases. In fact, hyperuricemia can arise due to reduced renal or extrarenal excretion or overproduction of UA [5]. However, more than 90% of all cases of hyperuricemia are the result of the diminished renal excretion of UA. Facchini et al., demonstrated that the extent of IR is associated with increased urinary UA reabsorption in human [30]. Through a genome-wide association studies, it is known that urate transporters in the kidneys play an important role in UA handling in the kidneys [21, 28]. In fact, UA is filtered in the glomeruli followed by its reabsorption in the proximal tubules through URAT1 at the apical membrane of proximal tubules and transcellularly transported

via GLUT9 at the basolateral membrane [17]. Wu et al. have reported that on hyperuricemia mice there was an increased in plasma UA levels, mRNA expression of renal URAT1, and GLUT9 [29]. Also, Ng et al. have demonstrated that the hyperglycemia and hyperuricemia greatly linked with the increase in renal glucose and UA transporters [19]. In line with the previous studies, we have shown that the IR kidney rats had significant increase in the mRNA expression of kidney URAT1 (Fig. 3A), whereas although there was an increase in mRNA expression of kidney GLUT9 (Fig. 3C), the increase was not significant. Our present study is in accordance with previously reported data that HF diet increased the protein level of URAT1 kidney transporter without any changes in the protein level of GLUT9 kidney transporter in mice, whereas in leptin-deficient mice, both of the kidney transporters, URAT1 and GLUT9, were increased. In fact, hyperuricemia was associated with the increased protein expression of URAT1 transporter without increased expression of GLUT9, which was enhanced by fat [26], similar to our study that used HF diet to induce IR. In this study, we also observed that the administration of AM at both doses has significant favorable effects on HF/HG/STZ-induced IR, which are obtained by blocking the upregulation of urate transporter. Previous study has demonstrated that AM administration to obese mice could improve insulin sensitivity and glucose tolerance, as well as ameliorated adipose inflammation and hepatic steatosis through inhibition of C-C chemokine receptor

2 [13]. In line with the previous study, we also showed that AM could improve insulin sensitivity and reduce the levels of FBG. However, to the best of our knowledge, our study was the first to evaluate the effects of AM in alleviating hyperuricemia and kidney dysfunction in the IR rat model.

IR, obesity, hypertension, and diuretics used have been shown to decrease renal excretion of UA which leads to elevated SUA level. A prospective cohort study involving 900 healthy and normotensive adults showed that high SUA levels were related with worsening renal function [4]. In addition, it has been demonstrated that the activation of the renin-angiotensin system as well as cyclooxygenase-2 pathways is strongly correlated with increased SUA level as shown by preglomerular arterial disease, renal inflammation, and hypertension [11]. In the present study, the HF/HG/STZ-induced IR rats displayed significantly increased proteinuria, as well as a decreased creatinine clearance compared with the normal rats, and AM at both doses treatment significantly reduced the proteinuria and elevated creatinine clearance, though it was not significantly different with the HF/HG/STZ-induced IR rats (Fig. 2A, B). Moreover, we observed significant decreases in the levels of BUN and SUA, after AM treatment in these rats (Fig. 2C, D). Chae et al. have shown that in diet-induced obesity mice, AM administration was able to attenuate hepatic steatosis, reduced serum glucose, induced weight loss, and improved lipid profile through sirtuin 1-AMP-activated protein kinase and peroxisome proliferator-activated receptor (PPAR) gamma pathways [7]. Moreover, Watanabe et al. reported that mangosteen extract which contained alpha and gamma mangostins could potentially represent a treatment of obesity and insulin resistance in obese female patients [27].

5 Conclusion

Given the promising results we showed, we suggest possible role of AM in selectively decreasing renal transporter URAT1 which leads to ameliorate hyperuricemia in the rat model of IR, though we failed to demonstrate a statistically significant difference of GLUT9, creatinine clearance as well as dose-dependency of AM doses as compared to that of control group.

Abbreviations

AM: Alpha mangostin; BUN: Blood urea nitrogen; DAB: Diaminobenzidine tetrahydrochloride; FBG: Fasting blood glucose; HE: Hematoxylin and eosin; HF/HG/STZ: High-fat/high-glucose/streptozotocin; HG: High-glucose; HOMA-IR: Homeostasis model assessment insulin resistance; IR: Insulin resistance; i.p: Intraperitoneal; SUA: Serum uric acid; STZ: Streptozotocin; TBS: Tris-buffered saline; UA: Uric acid.

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Author contributions

VS participated in the design of the study, performed statistical analysis, drafted the manuscript, and carried out the qRT-PCR studies. AM carried out the qRT-PCR and histopathology studies and helped the statistical analysis. AAJ participated in histopathological studies and helped drafted the manuscript. ML performed statistical analysis, helped drafted the manuscript, and participated in the design of the study. All authors read and approved the final manuscript.

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Availability of data and materials

Not applicable.

Declarations

Ethics approval and Consent to participate

Animal studies have been approved by the Ethics Committee of Universitas Indonesia (ethical clearance # 0084/UN2.F1/ETIK/2018), and all efforts were made to minimize suffering. Consent to participate is not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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