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Regular paper

Alpha-Mangostin ameliorates acute kidney injury *via* modifying levels of circulating TNF-α and IL-6 in glycerol-induced rhabdomyolysis animal model

Heba M. Eltahir[1]✉, Hossein M. Elbadawy[2], Ali Alalawi[2], Ahmed J. Aldhafiri[2], Sabrin R.M. Ibrahim[3,4], Gamal A. Mohamed[5,6], Abdel-Gawad S. Shalkami[7,8], Mohannad A. Almikhlafi[2], Muayad Albadrani[9], Yaser Alahmadi[10], Mekky M. Abouzied[1,11] and Maiiada H. Nazmy[11]

[1]Department of Pharmacology and Toxicology, Division of Biochemistry, Taibah University, Medina, Kingdom of Saudi Arabia; [2]Department of Pharmacology and Toxicology, Taibah University, Medina, Kingdom of Saudi Arabia; [3]Preparatory Year Program, Batterjee Medical College, Jeddah 21442, Saudi Arabia; [4]Department of Pharmacognosy, Faculty of Pharmacy, Assiut University, Assiut 71526, Egypt; [5]Department of Natural Products and Alternative Medicine, Faculty of Pharmacy, King Abdulaziz University, Jeddah, Saudi Arabia; [6]Department of Pharmacognosy, Faculty of Pharmacy, Al-Azhar University, Assiut Branch, Assiut, Egypt; [7]Department of Pharmacology and Toxicology, Faculty of Pharmacy, Al-Azhar University, Assiut, Egypt; [8]Clinical Pharmacy Program, Faculty of Health Science and Nursing, Al-Rayan Colleges, Medina, Kingdom of Saudi Arabia; [9]Department of Family and Community Medicine, College of Medicine, Taibah University, Medina, Kingdom of Saudi Arabia; [10]Department of Clinical and Hospital pharmacy, Taibah University, Medina, Kingdom of Saudi Arabia; [11]Department of Biochemistry, Faculty of Pharmacy, Minia University, Minia, Egypt

Alpha mangostin (AM), isolated from G. mangostana, showed beneficial effects in several disorders due to its antioxidant and anti-inflammatory properties. Acute kidney injury (AKI) due to different etiologies can develop into severe complications, resulting in high mortality rates. In this work, AM is tested for its ability to alleviate AKI in glycerol-induced AKI rat model, where 30 Male Sprague-Dawley rats were assigned to a healthy group, glycerol-treated group and AM-treated group. Glycerol- and AM groups received a single dose of glycerol (per IM, 50% glycerol in saline, 8 ml/kg), whereas control group was injected with saline. AM treatment (a single daily dose, per IP, 175mg/kg) was accomplished for three days. Animals were executed to collect blood samples and kidney tissue for biochemical and histological examination. It was found that glycerol induced increase in serum creatinine, blood urea nitrogen (BUN), lipid peroxidation, serum magnesium, TNF-α and IL-6. It also induced renal edema and hypocalcemia along with histopathological renal damage. AM treatment improved renal histological features and alleviated increase in serum creatinine, BUN, serum magnesium, TNF-α and IL-6 levels, as well as renal edema and lipid peroxidation but did not affect serum calcium levels. This suggests AM as a potential therapeutic agent for treating AKI mainly via its antioxidant and anti-inflammatory properties.

Keywords: AKI, alpha mangostin, rhabdomyolysis, antioxidant, TNF-α, IL-6, anti-inflammatory

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✉e-mail: Heba_m.eltahir@yahoo.com

Abbreviations: AKI, Acute kidney injury; AM, alpha mangostin; Il-6, interleukin-6; NF-α, tumor necrosis factor-α; BUN, blood urea nitrogen; MDA, malodialdehyde; TBARS, thiobarbituric acid reactive substances; Ca^{+2}, calcium ion; Mg^{+2}, magnesium ion; iNOS, inducible nitric oxide synthase; SOD, superoxide dismutase; NFκB, Nuclear factor κB; ROS, reactive oxygen species; TGF-β, transforming growth factor-β; KW/BW, kidney weight to body weight ratio

INTRODUCTION

Fruits are highly consumed and largely appreciated throughout the world. They represent a wealthy pool of diverse bioactive compounds, which have shown variable health benefits in reducing the incidence of various diseases such as hyperlipidemia, cancer, oxidative stress, inflammation and heart disease in addition to their effects as anti-diabetic, antimicrobial, neuroprotective, immune-stimulant and anticonvulsant (Karasawa & Mohan, 2018). *Garcinia mangostana* together with nearly 400 other species belongs to *Garcinia* genus; the biggest genus of the *Clusiaceae* family (Magadula, 2010). *G. mangostana's* round, reddish- to dark purple fruits have a sweet, slightly acidic flavor and have been used to treat a wide variety of medical conditions (Ovalle-Magallanes *et al.*, 2017). *G. mangostana* fruit is reported to be rich in xanthones; tricyclic oxygenated compounds (Fig. 1) that exhibit numerous bioactivities such as α-amylase inhibitory, anti-HIV, antimicrobial, antioxidant, anti-inflammatory, antimalarial, and antihypertensive effects in addition to its cytotoxic effect on various tumor cell lines (Mohamed *et al.*, 2017; Ibrahim *et al.*, 2019a; Ibrahim *et al.*, 2019b; Gutierrez-Orozco & Failla, 2013). α-Mangostin (AM, Fig. 1) is one of the major xanthones isolated from *G. mangostana* that has antioxidant properties and possesses diverse bio-activities, such as anti-tumor, anti-inflammatory, cardio-protective, anti-diabetic, larvicidal, antifungal, α-amylase inhibitory, anti-parasitic, anti-obesity, and antioxidant (Chen *et al.*, 2008; Devi Sampath & Vijayaraghavan, 2007; Watanabe *et al.*, 2018; Larson *et al.*, 2010; Perez-Rojas *et al.*, 2016; Chen *et al.*, 2018).

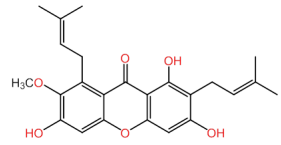

Figure 1. Structure of α-mangostin (AM).

Despite the number of reports suggesting a beneficial effect for AM in alleviating nephropathy (Perez-Rojas *et al*., 2009; Sanchez-Perez *et al*., 2010), no reports investigating its role in the management of acute kidney injury (AKI) are yet available. AKI is a high mortality rate clinical condition characterized by a sudden renal impairment; with multiple complicated underlying causes including hemorrhagic shock, infection, rhabdomyolysis, and urethral obstruction (Chawla *et al*., 2014; Bosch *et al*., 2009). Epidemiological screening showed that the incidence rate in ICU for AKI-patients was 30–50% and the mortality rate among those patients was 63% (Glodowski & Wagener, 2015). Surviving patients need 6–12 months to completely recover their kidney functions (Li *et al*., 2020a), whereas 19-31% of AKI patients reach end-stage renal failure (Goldberg & Dennen, 2008; Venkatachalam *et al*., 2015). Therefore, early intervention to improve kidney functions and treat AKI plays a key role to ameliorate the progression to chronic nephropathy (Homsi *et al*., 2010).

Intramuscular Glycerol injection is one of the most common protocols used in rats to induce rhabdomyolysis (RM) that ends by AKI, one of the most severe complications of RM (Al Asmari *et al*., 2017; Sun *et al*., 2018). RM is a condition caused by extensive skeletal muscle breakdown due to ischemia, toxins, physical effects and infections, resulting in leakage of overwhelming amounts of intracellular contents including myoglobin accessing the blood circulation. Myoglobin exerts toxic effect on the kidneys, where it induces oxidative stress due to production of ROS and inflammation ending by apoptosis. When myoglobin becomes filtered through the kidneys, it is engulfed into the tubular cells via endocytosis, where the ferrous-myoglobin is converted to ferric-myoglobin releasing highly reactive hydroxyl radicals. These radicals induce lipid peroxidation and affect membrane integrity, resulting in AKI (Panizo *et al*., 2015). ROS-induced inflammation results in infiltration of immune cells to the site of inflammation, where these cells start producing proinflammatory mediators, such as TNF-α and different interleukins that further aggravate the inflammatory response. Both TNF-α and IL-6 have been linked to disease severity in case of AKI and are used as markers for predicting the clinical outcome and mortality (Shimazui *et al*., 2019; Ramesh & Reeves, 2004).

In the current work, we aimed at evaluating the therapeutic potential of AM against glycerol-induced AKI via assessing its anti-inflammatory, antioxidant and tissue protective effects.

METHODS

Materials

All materials utilized in the current study were of analytical grade and were purchased from local suppliers unless otherwise stated. AM was isolated and purified from fruit bulb and purity was estimated to be 98% (see supplementary data).

Animals and Treatment

Thirty Male Sprague-Dawley rats, 8 weeks-old (180–200 g), were housed in controlled temperature under 12hrs light/dark cycle with free access to food and water and were allowed to accommodate for one week before initiating the experimental procedure. Animals were assigned randomly into three groups with 10 animals in each; a healthy control group, a positive control group (AKI-group) and AKI-AM treated group.

To induce the AKI model in the second and third groups, rats in these groups were deprived of water for 24 hrs before being injected with a calculated dose of 50%, v/v glycerol/saline divided equally on both hind limbs (IM, 8 ml/kg body weight). Healthy control animals were treated similarly to AKI animals but received an equivalent volume of sterile saline instead of glycerol. One hour before inducing the AKI model, animals of AKI-AM group received AM (175 mg/kg in DMSO, IP injection), and the AKI group animals received a corresponding amount of DMSO, and the treatment was repeated once a day for three consecutive days.

Twenty four hours after the last dose of AM, animals were weighed then sacrificed under anesthesia. Blood was collected by cardiac puncture and kidneys were promptly collected, rinsed in ice-cold saline and weighed individually and the recorded weight was used for calculating KW/BW ratio. The right kidney from each animal was stored in 10% neutral formalin solution for further histological examination, whereas the left one was homogenized in Tris-buffer and frozen for further biochemical evaluation.

All animal handling protocols were approved by the local Institutional Animal Care and Use Committee, faculty of pharmacy, Minia university (project code number: ES10/2022), and were in compliance with the International Guidelines for the Care and Use of Laboratory Animals.

Kidney weight-to-body weight ratio

The average weight of the freshly isolated kidneys was divided by the corresponding animal body weight and the value was multiplied by 100 to represent it as a percentage.

Biochemical analysis

Renal parameters. Collected blood samples were allowed to clot at room temperature for 15–20 minutes before being centrifuged at 3000 rpm at 4°C for 10 min to separate the serum. Assessment of blood urea nitrogen (BUN), creatinine, calcium (Ca^{2+}), and magnesium (Mg^{2+}) levels were performed spectrophotometrically using the commercially available kits according to the manufacturer's instructions (Randox®, UK).

Lipid peroxidation. Kidney homogenates were centrifuged at 5000 rpm for 15 minutes and the supernatants were collected for the quantification of thiobarbituric acid reactive substances (TBARS) in an attempt to assess lipid peroxidation based on the earlier established protocol (Ohkawa *et al*., 1979) and according to the manufacturer's instructions (Lipid peroxidation (MDA) assay kit, Sigma Aldrich, USA). Kidney lipid peroxidation in tissue was calculated as μmole MDA/g of tissue.

Assessment of TNF-α and ILs using enzyme-linked immunosorbent assay (ELISA). Levels of circulating proinflammatory markers TNF-α and interleukin-6 (IL-6) were evaluated in serum using commercially available ELISA kits according to the manufacturer's instructions (Sigma Aldrich, USA).

Assessment of relative gene expression using qRT-PCR

In brief, primers specific to the genes of interest: glutathione peroxidase (GPx), glutathione reductase (GRs) and superoxide dismutase (SOD) along with that of ribosomal protein S-18 (RPS-18) as a house keeping gene were utilized (as shown in primers list, Table 1) to perform, quantitative RT-PCR analyses. Freshly isolated kidney tissues were homogenized, and RNA was isolated using

Table 1. sequence of the primers used for quantitative evaluation of GPx, GRS, TSOD expression

Gene	Sense	Anti-sense
GPx	GTCCACCGTGTATGCCTTCT	TCTGCAGATCGTTCATCTCG
GRs	CAATTGGCATGTCATCAAGG	CCATCTCGAAATGTTGCGTA
TSOD	TGGTGAACCAGTTGTGGTGT	AAAATGAGGTCCTGCAGTGG
RPS-18	AGTTGGTGGAGCGATTTGTC	GAACGCCACTTGTCCCTCTA

miRNeasy Mini (Qiagen, Germany), followed by reverse transcription to create the cDNA using ImProm-II™ reverse transcription system according to the manufacturer's instructions (Promega, USA). Expression level of target genes mRNA was evaluated based on the cDNA, then the relative target gene expression was calculated by comparative Ct ($2^{-\Delta Ct}$) method using RPS-18 as a house keeping gene. Data were presented as mean ± standard error of means for three independent experiments.

Histopathological examination

After being excised, kidneys were rinsed in saline then fixed in 10% neutral formalin solution for 24 hrs followed by dehydration in a series of increasing alcohol concentrations. Finally, they were embedded in paraffin, and 5-microns sections were cut on a microtome and mounted on glass slides for histological investigation. After being deparaffinized, the sections were rehydrated and stained with Hematoxylin & Eosin to evaluate and quantify the extent of tubular injury, dilatation, vacuolation and necrosis in kidney tissues as previously described (Wu *et al.*, 2017).

Data and Statistical Analysis

All data are expressed as means ± S.E.M. (n=10) for all the experiments. Multiple comparisons of data were analyzed by one-way analysis of variance, as appropriate, and group means were compared using Tukey Kramer post hoc test. *p*-values less than 0.05 were considered as statistically significant.

RESULTS

Effect of glycerol and AM on serum biochemical parameters and lipid peroxidation

Injection of glycerol into the animals resulted in signs of renal injury that was characterized by a significant three-fold elevation of serum creatinine when comparing these animals to healthy control group ($p<0.05$). Glycerol administration also resulted in significant increase in blood urea nitrogen (BUN) compared to healthy control animals ($p<0.05$) (Fig. 2A and B).

Acute renal injury induced by glycerol also resulted in a significant increase in lipid peroxidation ($p<0.05$) in comparison to healthy control animals. Interestingly, administration of AM in glycerol-induced AKI animals effectively ameliorated the signs of renal injury. It significantly decreased serum creatinine as well as BUN levels to values that are comparable to normal healthy group (1.2±0.01 mg/dL and 43.66±25.66mg/dL respectively, $p<0.05$) (Fig. 2A and B)

In addition, AM was significantly capable of ameliorating glycerol-induced lipid peroxidation when compared to animals receiving glycerol alone ($p<0.05$) as shown in Fig. 2C.

Effect of glycerol and AM on serum calcium and magnesium levels

Analysis of electrolytes in the sera of test animals revealed a significant elevation in serum magnesium (Mg^{2+}) in AKI group compared to the healthy control group (4.1±0.02 mg/dl *vs.* 2.48±0.14 mg/dl, $p<0.05$). In contrast, a significant reduction in serum calcium (Ca^{+2}) was observed in this group compared to the healthy control (2.39±mg/dl *vs.* 8.56±0.31 mg/dl, $p<0.05$) as seen in Fig. 3A and B. It is worth to note that the treatment with AM significantly ameliorated the increase in serum Mg^{2+} levels induced by glycerol compared to glycerol-treated animals which didn't receive AM ($p<0.05$). In the same time, serum Mg^{2+} levels were significantly indistinguishable when comparing AM-treated animals with the healthy control ones ($p>0.05$). On the other hand, depleted (Ca^{+2}) levels in response to glycerol treatment were not replenished upon AM treatment ($p>0.05$) and remained significantly less than the healthy control ($p<0.05$, Fig. 3).

Effect of glycerol and AM on endogenous antioxidants

The relative expression of GPx, GRs and SOD was assessed to investigate the effect of the different treatments. Glycerol injection resulted in a significant reduction in the relative gene expression of all three enzymes compared to control animals ($p<0.05$; Figs 4A, B and C). Interestingly, treating AKI animals with AM significantly ameliorated the glycerol-induced reduction in GPx, GRs and SOD compared to animals that received glycerol only ($p<0.05$; Figs 4A, B and C). It is to be mentioned that relative gene expression of GPx and GRs was indistinguishable from that of healthy control animals upon AM treatment ($p>0.2$), whereas the relative expression of

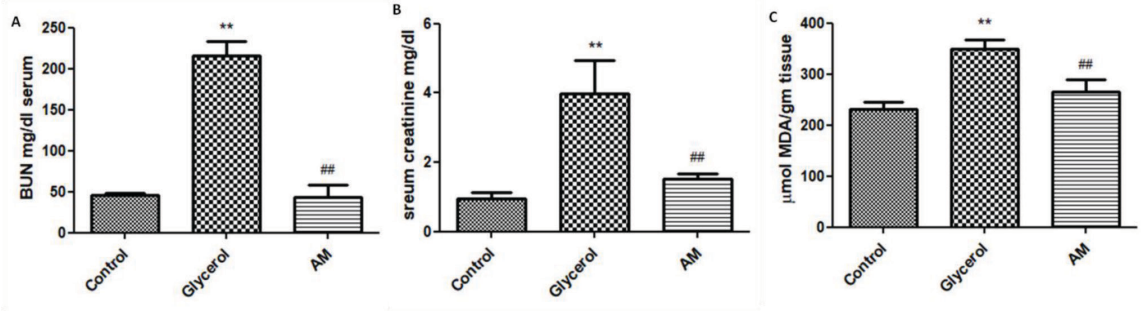

Figure 2. effect of glycerol and AM on biochemical parameters.
Glycerol administration induced a significant increase in serum urea (**A**), creatinine (**B**) and lipid peroxidation compared to healthy control (**$p<0.05$). Animals treated with AM show significant reduction in all three parameters compared to glycerol treated animals (##). Values are expressed as mean ± S.E.M., n=10, **/##$p<0.001$, */#$p<0.01$.

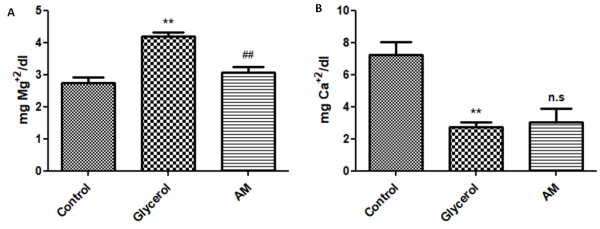

Figure 3. effect of glycerol and AM treatments on serum calcium and magnesium.
Glycerol administration induced a significant increase in serum Mg^{2+} (**A**, $p<0.05$) and reduction in serum Ca^{2+} (**B**, $p<0.001$) compared to healthy control. Animals treated with AM showed a significant reduction in magnesium levels compared to the glycerol treated group ($p<0.05$) but no significant changes in serum calcium levels ($p>0.0.05$) was achieved compared to the glycerol treated group. In AM treated animals, Mg^{2+} levels are comparable to control but Ca^{2+} levels are significantly lower than control ($p>0.26$ and $p<0.001$ respectively). Values are expressed as mean ± S.E.M., n=10, **/##$p<0.001$, */#$p<0.05$

SOD was still significantly less than that of control after AM treatment ($p<0.05$).

Effect of glycerol and AM on circulating inflammatory markers level

Animals exposed to glycerol treatment revealed a significant increase in levels of circulating TNF-α and IL-6 when compared to healthy control animals (Fig. 5A and B, $p<0.05$). Interestingly, treating animals with AM resulted in significant amelioration in serum levels of both proinflammatory cytokines ($p<0.05$).

Effect of glycerol and AM on kidney index

As expected, glycerol-treated animals suffered from renal edema as observed by a significant increase in kidney index (KW/BW ratio) when compared to the healthy group (0.57% *vs.* 0.31% respectively, $p<0.05$). Interestingly, treating the animals with AM was capable of reducing KW/BW ratio in the corresponding animals compared to the AKI group animals; however, this reduction was not statistically significant (0.42% *vs.* 0.57%, $p>0.05$) (Fig. 6).

Histopathological findings

Administration of glycerol effectively induced AKI as observed in the form of severe degenerative changes in renal corpuscles accompanied with accumulation of protein casts in the mesangial tissue when compared to control group animals (Fig. 7C and D, arrow head). In addition, marked degeneration of the renal tubules could be detected (arrow) where the lumen of such tubules was obliterated by protein casts. These changes were accompanied by severe congestion of the renal blood vessels (Fig. 7C and D).

Interestingly, treating AKI animals with AM resulted in marked alleviation of the degenerative changes induced by glycerol. Figures 6E and F show normal renal corpuscles (C) and glomerular capillaries. Despite the mild degree of hydropic degeneration that can be detected in some renal tubules (arrow), the majority of the tubules showed normal morphological features (T). It is to be noted that some protein materials can be detected in few tubules but less than that observed in the glycerol-treated animals. A comparison among the test groups regarding these morphological changes is presented in Table 2.

DISCUSSION

AKI is a renal dysfunction that is characterized by prompt loss of renal filtration rate and accumulation of protein debris within the renal tissues, where rhabdomyolysis (RM) is a main cause of AKI (Parekh *et al.*, 2012). Glycerol-induced rhabdomyolysis is an established model that mimics AKI in human as it induces a myoglobinuric condition and a significant reduction in filtration rate that result mainly from oxidative stress, which induces inflammation and consequently apoptosis (Zager, 1996).

In the current study, glycerol injection induced a significant increase in serum creatinine and BUN, indicating renal dysfunction that was associated with renal edema in response to the toxic levels of myoglobin reaching the kidneys as observed by the increased KW/BW ratio. These pathological changes were confirmed by the histological examination that showed signs of tubular necrosis, congestion and protein casts accumulation within the tubules and mesangial tissue. The observed effects of glycerol were reported earlier by several research groups (Al Asmari *et al.*, 2017; Ustundag *et al.*, 2009; Korrapati *et al.*, 2012).

Despite the possibility of recovering the renal functions affected by RM within few months, some reports have shown that structural changes, including fibrosis, possibly take place as a result of excessive extracellular matrix deposition and the released pro-inflammatory and pro-fibrotic factors (Wen *et al.*, 2011). This causes RM-induced AKI to be a serious condition that needs rapid intervention to improve the prognosis and to prevent long term complications.

RM can result from muscle damage caused by direct traumatic insults or excessive muscular effort that dam-

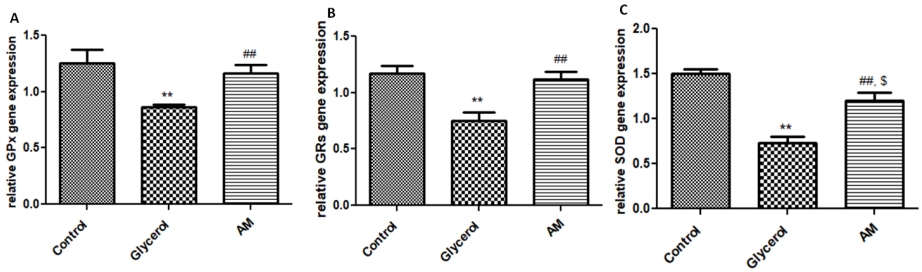

Figure 4. effect of glycerol and AM treatments on endogenous antioxidant enzyme gene expression.
Administration of glycerol significantly reduced the relative expression of GPx (**A**, $p<0.01$), GRs (**B**, $p<0.01$) and SOD (**C**, $p<0.001$) compared to healthy control animals. Treating animals with AM significantly increased gene expression of GPx (**A**, $p<0.05$), GRs (**B**, $p<0.05$) and SOD (**C**, $p<0.05$) compared to glycerol treated animals. No significant difference in relative gene expression of GPx and GRs could be detected between AM treated animals and control ones. Values are expressed as mean ± S.E.M., n=10, **/##/$$$p<0.001$, */#/$$p<0.05$.

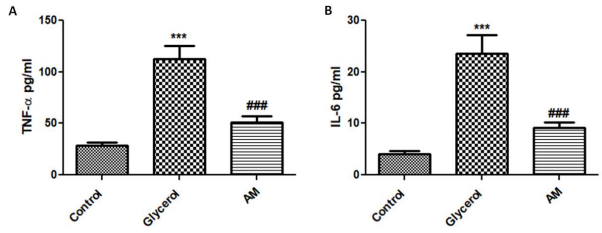

Figure 5. effect of glycerol and AM treatments on circulating proinflammatory cytokines.
Glycerol treatment induced a significant increase in both TNF-α (**A**, $p<0.001$), and IL-6 (**B**, $p<0.001$) compared to healthy control. AM treatment significantly ameliorated the increase in serum levels of both TNF-α (**A**, $p<0.001$) and IL-6 (**B**, $p<0.001$) compared to glycerol treated group. Values are expressed as mean ±S.E.M., n=10, **/##$p<0.001$, */#$p<0.05$

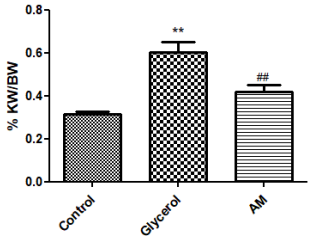

Figure 6. kidney index of the different test groups.
Glycerol administration induced a significant increase in kidney-to-body weight ratio compared to healthy control group ($p<0.01$). AM treatment resulted in reduction in kidney index compared to glycerol treated group ($p<0.05$). Values are expressed as mean ±S.E.M., n=10, **/##$p<0.001$, */#$p<0.01$

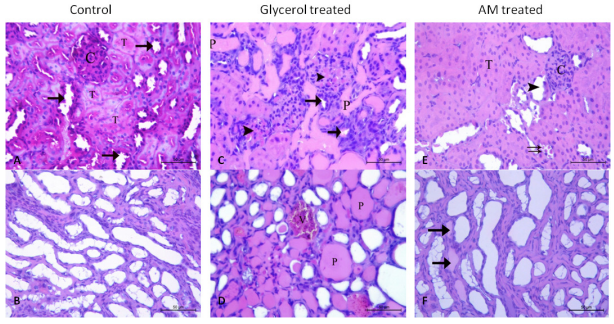

Figure 7. Photomicrographs of kidney sections from the different test groups.
A&B: sections from healthy control showing normal renal corpuscles with normal glomerular capillaries (C) and normal renal tubules (T) as well as normal collecting tubules (arrow, H&E stain, x400). B: renal medulla showing normal collecting tubules with cuboidal lining epithelium and normal loop of Henle's (H&E stain, x400). **C&D**: sections from glycerol treated group showing degenerative changes in renal corpuscles (C) with accumulation of protein materials in the mesangial tissue and renal tubules (arrowheads) with protein casts (arrow) and protein casts in the renal tubules' lumen (P). D: renal medulla showing sever congestion of the renal blood vessels (V) and protein casts (P). **E&F**: sections from AM-treated group with normal renal corpuscles (C), almost normal renal tubules (T) and collecting tubules (arrowhead) with few ones showing mild degree of hydropic degeneration (arrow). Scanty amounts of protein are present in few tubules (double arrow). F: renal medulla showing normal renal tubules. Protein casts present in few tubules (arrow). (H&E stain, X400)

ages muscle cells, some metabolic disorders, bacterial and viral infections, alcohol intake and exposure to various types of drugs like statins, heroine and cocaine as well as prolonged immobilization (Holt & Moore, 2001).

Table 2. Effect of glycerol and AM on the kidney morphological features

	Control group	AKI group	AKI-AM group
Degenerated corpuscles	–	+++	–
Congestion	–	++	–
Protein casts	–	+++	+
Necrosis	–	+++	–
Hydropic degeneration	–	+++	+

Key: – no pathological change, +mild degree pathological change, ++moderate pathological change, +++severe pathological change

As these factors induce RM, damaged muscle cells start to release unexpectedly large amounts of myoglobin which becomes filtered through the renal tubules, but instead of being excreted, myoglobin is mostly endocytosed inside the renal tubules' cells. These endocytosed myoglobin molecules undergo several oxidation reactions releasing hydroxyl free radicals among other ROS, initiating a cascade of oxidation and peroxidation reactions to generate a condition of oxidative stress (Boutaud & Roberts, 2011). As observed in the current study, glycerol treatment significantly induced peroxidation as one of oxidative stress outcomes that can be evaluated by MDA tissue content, in agreement with several studies reporting lipid peroxidation in AKI models (Al Asmari *et al.*, 2017).

In rodents, it is believed that glycerol-induced AKI is a result of myoglobinuric nephrotoxicity and renal ischemia (Parekh *et al.*, 2012; Zager, 1996), where the molecular events observed in this model are similar to those observed clinically, which causes the glycerol-induced RM a very common model to study AKI (Stein *et al.*, 1978). In other words, pathophysiology of RM-induced AKI includes oxidative stress, cast formation in renal tubules, vasoconstriction and inflammation of renal tissues (Shanu *et al.*, 2013).

In response to oxidative stress, pro-inflammatory cytokines are released activating macrophages and T-lymphocytes at the site of inflammation, which in turn produces various cytokines e.g. TGF-β and TNF-α to propagate the inflammation condition. Released proinflammatory TNF-α interacts with various cell types and induces NFκB activation and nuclear translocation. This activates the transcription of NFκB downstream proinflammatory target genes, resulting in the release of increased amounts of proinflammatory cytokines e.g. Il-6 (Moreno *et al.*, 2012).

Several reports have shown that antioxidants are capable of protecting against myoglobin-induced oxidative stress via scavenging the released ROS, improving the endogenous antioxidant defense mechanisms, preventing lipid peroxidation or ameliorating the inflammatory response, and hence protecting against the renal damage. These molecules included ascorbic acid, vitamin E, polyphenols, suramin, curcumin and quinacrine among others (Al Asmari *et al.*, 2017; Korrapati *et al.*, 2012; Ustundag *et al.*, 2009).

AM, a xanthone isolated from *G. mangostana* fruit, has been implicated in a lot of studies for its wide range of therapeutic effects as previously mentioned (Sanchez-Perez *et al.*, 2010; Devi Sampath and Vijayaraghavan, 2007; Jung *et al.*, 2006). It has been shown to exert its action via its positive effects on the endogenous antioxidant defense mechanisms, as it was previously reported to improve the superoxide dismutase and glu-

tathione peroxidase activity, in addition to replenishing glutathione tissue content (Fang *et al*., 2016). In addition, AM was shown to combat inflammation and suppress the production of various inflammatory mediators and fibrogenic mediators via scavenging different free radicals like superoxide and peroxynitrite according to *in vivo* and *in vitro* studies investigating its potential effects in nephrotoxicity models (Perez-Rojas *et al*., 2009; Li *et al*., 2020b; Muhamad Adyab *et al*., 2019; Sanchez-Perez *et al*., 2010). Some reports related the anti-inflammatory effect of AM to its ability to activate SIRT-1, a nuclear histone deacetylase, which inhibits NFκB signaling and consequently its downstream pro-inflammatory effectors (Franceschelli *et al*., 2016), whereas others reported the ability of AM to inhibit leukocyte migration as well as the production and secretion of inflammatory mediators e.g Il-2, Il-6 and TNF-α from different cell types (Kim *et al*., 2021; John *et al*., 2022). Despite these positive effects of AM, its effect on RM-induced AKI in glycerol model is not yet investigated.

In the current research, we found that AM administration to glycerol-induced AKI rats could efficiently alleviate signs of AKI as it normalized BUN and creatinine levels and alleviated renal edema. It also alleviated the oxidative stress induced by glycerol administration as observed in ameliorating MDA tissue content. It significantly reduced serum magnesium levels, however, serum calcium levels were not improved upon treatment. AM treatment also normalized the relative gene expression of the antioxidant enzymes SOD, GPx and GRs, and ameliorated the expected increase in circulating TNF-α and IL-6, which were upregulated upon AKI induction. On the cellular level, AM could reverse most of the histopathological changes induced by glycerol injection, regaining normal corpuscles and renal tubules with minimal protein deposition indicating good signs of recovery from tissue damage.

These effects can be explained by the previously reported ROS scavenging activity of AM and its ability to replenish the endogenous antioxidant mechanism (Fang *et al*., 2016; Martinez *et al*., 2011). In this context, AM was reported to achieve its antioxidant effect via increasing the activity of various antioxidant enzymes including SOD and GPx, and retrieving the gene expression of endogenous antioxidant enzymes as well (Perez-Rojas *et al*., 2009). In addition, its previously reported mitochondrial-stabilizing, antiapoptotic effect prevents cell death and protects against tissue damage, enabling the recovery of renal functions upon its use (Perez-Rojas *et al*., 2009; Sanchez-Perez *et al*., 2010). AM has been also reported previously for its anti-inflammatory effect and its ability to reduce/ameliorate TNF-α and other inflammatory cytokines e.g. IL-6 II-1β and IL-8 in several models including kidney disease models via its inhibitory effect on NFκB and TLR-4 signaling in addition to other signaling pathways linked to inflammation in renal tissues (Tewtrakul *et al*., 2009; Xu *et al*., 2017; Zou *et al*., 2019).

Hypocalcemia is expected in the early stage of AKI where calcium becomes deposited within the cells as a result of Ca^{2+}-ATPase pumps dysfunction and the damaged sarcoplasmic reticulum, leading to a significant decrease in serum calcium levels. In a later response, proteases and phospholipases attack the cell membranes resulting in leakage of cellular contents, which consequently destroy cells in the near proximity. It is to be noted that renal injury-induced hypocalcemia is observed only in the early oliguric phase of AKI (Graziani *et al*., 2011; Edelstein *et al*., 1997).

In contrast, the increase in serum magnesium level in AKI could be attributed to the expected hypovolemic condition that may affect magnesium concentrations, and the impaired tubular filtration mechanisms following AKI that could affect its excretion. It is well established that the decline in renal functions is commonly associated with increased serum magnesium levels (Swaminathan, 2003; Quamme, 1989). The observed effect of AM on serum magnesium levels could be attributed to its ability to retrieve the renal functions and hence improved filtration rate leading to decreasing magnesium levels.

TNF-α is a proinflammatory cytokine that is produced by infiltrating immune cells in addition to various cell types within the renal tissue i.e. mesangial cells, podocytes, and endothelial cells of the proximal tubules, collecting ducts and thick ascending limbs (Ramseyer & Garvin, 2013). It is produced in response to different stimuli such as oxidative stress, infections, complement reaction and exposure to lipopolysaccharides. It has been reported earlier that normalizing the oxidative stress levels using superoxide dismutase (SOD) mimics ameliorated TNF-α production and renal pathological changes in a diabetic nephropathy animal model (Ebenezer *et al*., 2009). TNF-α aggravates the inflammatory process via its effect on activating nuclear translocation of the transcriptional factor NFκB with the subsequent activation of the transcribing its downstream proinflammatory target genes (e.g. TNF-α, IL-6, inducible nitric oxide synthase (iNOS) and adhesion molecules). A large body of evidence has confirmed the role of TNF-α in inducing renal damage (Shahid *et al*., 2008; Sun & Kanwar, 2015; Mehaffey & Majid, 2017). It has been reported that TNF-α can enhance the expression of the pro-fibrotic factor TGF-β *via* activating ERK signaling. This cross talking between both cytokines causes both to be crucial players in the process of tissue remodeling and fibrosis as reported earlier (Sullivan *et al*., 2005; Liu *et al*., 2021). IL-6 is a proinflammatory cytokine that is produced by immune- as well as renal cells in response to inflammation. Previous reports have correlated its serum levels with the severity of organ failure and dysfunction in ICU-admitted systemic inflammatory conditions (Shimazui *et al*., 2019). The previously reported ability of AM to reduce the gene expression level of TNF-α, TGF-β and IL-6 allows it to break the vicious circle of oxidative stress- inflammation-tissue damage-remodeling and fibrosis (Yiemwattana & Kaomongkolgit, 2015), resulting in a significant improvement in the renal functions and histology and preventing fibrosis, which is a main complication of AKI as observed in the current study.

In conclusion, this work represents AM as a safe natural product that can be potentially used to ameliorate the devastating renal effects of RM on kidneys directly via its antioxidant and anti-inflammatory effects and indirectly by preventing fibrosis. It can modulate the inflammatory process through its effect on the proinflammatory cytokines, TNF-α and IL-6, bringing the inflammation to a halt and achieve better recovery in the renal tissue. This may provide a medicinal tool to combat the transition of these acute effects into chronic, long lasting damages and hence decrease AKI-related mortality rates.

LIMITATIONS

Despite the interesting findings, there are some limitations to this study. Serum creatinine and blood urea nitrogen were used as biochemical markers to evaluate re-

nal function, and these data were confirmed by the histopathological examination of renal tissue sections. Urine analysis based studies including urine volume, urine creatinine and creatinine clearance tests could have supported the findings that AM attenuates glycerol-induced renal impairment. In addition, further studies are required to understand the molecular mechanism by which AM exerts its nephroprotective effect and to confirm the efficacy of AM to improve kidney functions in AKI.

Declarations

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