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The Impact of *Monolluma quadrangula* Extracts on Oxidative Stress in Diabetic Male Rats

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Abstract:
Diabetes is a metabolic disease described as an excess of blood glucose that occurs as a result of lack of insulin secretion or because of insufficient cell absorption of insulin. *Monolluma quadrangula* (MQ) is an important medicinal plant used as a drug for diabetes mellitus in traditional medicine. This study investigated the impact of *M. quadrangula* extract as the protective and curative plant against diabetes mellitus. Thirty male rats aged 3-4 months and weighing (150-200g) were divided into five groups (each group consists of six rats). The first group received only normal saline and serve as a negative control (NC), whereas, the second group received 150 mg/kg alloxan to induce DM and serve as diabetic control (DC). Each of the third fourth and fifth groups received 150, mg/kg of alloxan to induce DM then treated with 100, 200, 300 mg/kg of *M. quadrangula* extract respectively. *M. quadrangula* extract significantly decreased oxidative stress and in turn, the blood glucose level in diabetic induced rats. This may be due to the fact that the plant extract increases glucose removal from the blood, decrease the release of glucagon, or increase that of insulin, directly stimulate glycolysis in peripheral tissues or reduce glucose absorption from the gastrointestinal tract.

Keywords: Alloxan, Oxidative stress, Diabetes mellitus, *Monolluma quadrangula*.

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease characterized by hyperglycemia due to insufficient or inefficient insulin secretory response (Al-Ofairi *et al.,* 2018; Hajiaghaalipour *et al.,* 2015; Muhammad *et al.,* 2013). It represents a chronic metabolic disorder of the beta cells in islets of Langerhans that continues to be a major health care problem worldwide. Diabetes is the most devastating and serious of all metabolic diseases (Ullah *et al.,* 2018). The prevalence of DM is expected to rise from the current 382 million individuals to 471 million in 2035 (Forouhi and Wareham, 2014). DM descriptions have been found in the Egyptian papyri, in ancient Indian and Chinese medical literature, as well as, in the work of ancient Greek and Arab physicians (Karamanou *et al.,* 2016). DM is a combination of two words, “diabetes” Greek word derivative, means siphon - to pass through and the Latin word “Mellitus” means honeyed or sweet. In 1776, excess sugar in blood and urine as a cause of their sweetness was first confirmed in the United Kingdom (Reece and Homko 1998; Ahmed, 2002). Diabetes is an important cause of blindness, kidney failure, lower limb amputation, and other long-term consequences that impact significantly on the quality of life (World Health Organization, 2016). On the other hand, DM can arise from other diseases or due to drugs such as genetic syndromes, surgery, malnutrition, infections, and corticosteroids intake (Narayan *et al.,* 2006; Jamison *et al.,* 2006; Whiting *et al.,* 2011).

DM is clinically characterized by hyperglycemia and the disturbance of carbohydrates, proteins, and fats metabolism due to chronic and relative insufficiency in insulin secretion and action (American Diabetes Association 2013). Furthermore, uncontrolled diabetes can cause many complications and affect the eyes, nerves, kidneys, and blood vessels, and even lead to premature death (Abbott *et al.,* 2011; Hirai *et al.,* 2011; Vincent *et al.,* 2011).

DM is associated with the increased production of free radicals or decreased activity of the antioxidant systems, which leads to the development of oxidative stress (OS) (Oberley, 1988; Bashan *et al.,* 2009). Brownlee (2001) examined OS markers in diabetic rats and found increased ROS levels in pancreatic islets. It was suggested that oxidative stress plays a role in the pathogenesis of diabetes mellitus and its complications. Furthermore, Tangvarasittichai (2015) found that OS has a deleterious factor leading to insulin resistance, β-cell dysfunction, impaired glucose tolerance and ultimately leading to type 2 diabetes.

On the other hand, diabetes is a prime risk factor for cardiovascular diseases (CVD) such as vascular disorders, peripheral vascular disease (PVD), stroke, and coronary artery disease (CAD). Diabetes also affects the heart muscle, causing both systolic and diastolic heart failure. Evidence suggests that although hyperglycemia, the hallmark of diabetes, contributes to myocardial damage after ischemic events, it is not the only factor, because both pre-diabetes and the presence of the metabolic syndrome, even in normoglycemic patients, increase the risk of most types of CVD (Muhlestein *et al.,* 2003; Thrainsdottir *et al.,* 2005; Nielson and Lange, 2005; The Decode study group, 1999). Diabetes increase CAD risk three to eight-fold (Norhammar *et al.,* 2002).

Hyperglycemia causes tissue damage through five major mechanisms: Increased flux of glucose and other sugars through the polyol pathway, increased intracellular formation of advanced glycation end-products (AGEs), increased expression of the receptor for advanced glycation end products and its activating ligands, activation of protein kinase C (PKC) isoforms and overactivity of the hexosamine pathway. Several lines of evidence indicate that all five mechanisms are activated by a single upstream event (Brownlee, 2005).

On the other hand, Poitout et al. (2006) and Paul (2015) reported that chronic

hyperglycemia caused an impairment of insulin biosynthesis and secretion. This process is called β-cell glucose toxicity, which is often observed under diabetic conditions.

Monolluma quadrangula (MQ) is a succulent bush with a yellow flower and irregularly branched and a compressed stem (Albers and Meve, 2013). It is known that *M. quadrangula* has been used in folk medicine for the treatment of DM and peptic ulcer (Ibrahim *et al*., 2015; Bin-Jumah, 2019), and high-cholesterol diet (HCD) fed rats as well as ameliorated serum lipids, hepatic and cardiac oxidative stress (Bin-Jumah, 2018). Plant parts are a good source of valuable therapeutic agents that are used to treat various disorders (Ali *et al.,* 2017; Iqbal and Ashraf, 2019a,b; Kalim *et al.,* 2016; Shahzad *et al.,* 2017; Shuaib *et al.,* 2019). Many vaccines and therapeutic compounds can be obtained from plants in many ways in the greenhouse, in the field, and cell or root cultures (Iqbal and Ashraf, 2018; Zaynab *et al.,* 2018).

M. quadrangula increased peripheral glucose uptake, improved lipid profile, suppressed hepatic glucose output, and prevented oxidative stress and inflammation in diabetic rats (Bin-Jumah 2019). Furthermore, Abdel-Sattar et al. (2017), showed decreased blood glucose, insulin, and glucose-phosphatase in streptozotocin-induced diabetic rats fed *M. quadrangula*. This work aimed to investigate the antioxidant and antidiabetic effect of *M. quadrangula* extract on diabetic rats.

MATERIAL AND METHODS

Plant collection and authentication

Monolluma quadrangula plants were collected from the Thamar governorate in Yemen and were identified and authenticated by a plant taxonomist at the Faculty of Science, Sana`a, University of Yemen. The plant was carefully washed with tap water to remove particles and adhered debris, rinsed with distilled water, and air-dried; it was cut into uniformly small pieces and shade dried at room temperature for two weeks, then they were ground into a fine powder. The powdered material was stored to use for animal treatments.

Preparation of the extract

The dried powder was extracted sequentially by hot continuous percolation method with Soxhlet apparatus, using ethanol. About 100 gm of dried powder was packed in the Soxhlet apparatus and successively extracted with 600 ml of ethanol (96%) for 24 hrs at 40-50 °C. The extracts were concentrated by using a rotary evaporator and subjected to freeze-drying in a lyophilizer until the dry powder was obtained (Ahmed *et al*., 2014).

Induction of diabetes mellitus

A single dose of freshly prepared alloxan monohydrate of 150mg/kg BW (dissolved in 0.9% sterile NaCl at pH 7) was injected intraperitoneally according to the method by Verma et al. (2010). This dose was administered to rats in groups II to V to induced diabetes. Before this, their blood glucose level was determined. After 48hrs, rats that had a blood glucose level above 400 mgdL-1 were considered diabetic and selected for the study. Thereafter extract of *M. quadrangula* was administered orally for 21 days.

Biochemical analysis of plant extracts

Biochemical analysis of extracts was done in the Physical and Biochemistry Research Laboratory Chemistry Department, Faculty of Science, Sana'a University. The spectrophotometer (Specord 200, Analytik Jena, Germany) was used to measure the absorbance of all samples.

Total phenolic content

The total phenolic content in the tested extracts was measured by using Folin-

Ciocalteu's reagent (FCR). This method depends on the reduction of FCR by phenols in each plant extract to a mixture of blue oxides. The experiments were performed according to the method by Parajule et al. (2012).

Animals

This study was performed on male albino rats, initially weighing (150-200 gm). Rats obtained from Science Faculty, Sana'a University were housed in stainless steel cages at a well-ventilated animal house. Tap water was given *ad libitum* and they were kept in individual cages at 12 h light: 12 h dark cycle. Animals were fed on the following diet formula, which was kindly supplied by the Department of Animal Production, Faculty of Agriculture, Sana'a University.

Diet Experimental design

In this experiment, thirty animals were fed the standard diet and were divided into five groups of six rats in each group as follows: Negative control (NC), received only normal saline, diabetic control (DC), received 150 mg/kg alloxan. Each of the other three groups received150 mg/kg alloxan and 100 mg/kg of *M. quadrangula* extraction; 200 mg/kg of *M. quadrangula* extraction and 300 mg/kg extraction respectively. The extracts were administered orally using an intragastric tube daily for three weeks. After three weeks of treatment, the rats have fasted overnight and the blood samples were collected for the testes.

Collection of blood

The blood was collected from the eye canthus of rats using microhematocrit capillary tubes. Blood samples were collected in EDTA tubes for blood glucose and antioxidant assays and plain tubes for biochemical marker analyses.

Preparation of hemolysate

Blood plasma was separated by centrifugation at 1000 rpm for 15 mins. After centrifugation, the buffy coat was removed and the packed cells washed thrice with physiological saline. A volume of 0.5 ml of erythrocytes was lysed with 4.5 ml of hypotonic (9%) phosphate buffer, pH 7.4. The hemolysate was separated by centrifuging at 2500 rpm for 15 min at 25°C. Plasma was used for the determination of biochemical parameters and MDA, Hemolysate was used for the antioxidant status study (Mansouri *et al*., 2011).

Biochemical analysis of plasma

Estimation of blood glucose

Fasting blood glucose was determined by the glucose oxidase method using Accu chek glucometer (Contour T-S diagnostics, Germany). The tail of the rat was cut swiftly with a sterile scalpel and a drop of blood was squeezed onto the test area of the strip that was inserted into the glucometer. The animals were fasted for 12 hrs before each glucose determination, which was repeated every 48 hrs till the end of the experiment at 21 days.

Estimation of lipid peroxidation (LPO)

Lipid peroxidation (LPO) in terms of malondialdehyde which is an end product of LPO was estimated using the method obtained by Buege and Aust (1978).

Estimation of total protein (TP)

Total protein (TP) was determined by a chemical analyzer at AL-Thbhani Specialized Medical Laboratory, Sana'a, by TP kit (Biuret Method) following the method of Thomas (1998).

Estimation Ascorbic acid (AsA)

Plasma vitamin C was estimated by the method of Omaye et al. (1979).

Biochemical analysis of hemolysate

Estimation of antioxidant biomarkers

Reduced glutathione (GSH)

The determination of GSH content was performed according to the method of Moron et al. (1979).

Superoxide dismutase (SOD)

This assay was performed according to Dhindsa et al. (1981), based on the inhibition of the production of nitroblue tetrazolium (NBT) formazon of the O_2^- by the enzyme extract. SOD activity was expressed as U/ mg hemolysate.

Catalase (CAT)

Catalase **(**CAT) activity was determined according to the method of Aebi (1984). The level of CAT was expressed in terms of µ moles H_2O_2 consumed/min/gm of hemoglobin.

Peroxidase (POD)

Peroxidase (POD) activity was estimated by the method of Reddy et al. (1995) with some modification by Venkatesh et al. (2003). One unit of peroxidase is defined as the change in absorbance/min at 430 nm.

Glutathione S-transferase (GST)

This activity was determined spectrophotometrically by the method of Habig et al. (1974).

Statistical analysis

All presented data were expressed as a mean ± SD. The statistical significance between groups was analyzed using a one-way analysis of variance (ANOVA) followed by Tukey Multiple Comparison methods using Prism 6. (Graph Pad, San Diego, CA, USA). A value of $p < .05$ was considered significant.

RESULTS

Bodyweight (BW)

The initial and final body weights of the normal and diabetic rats are given in table (1). A significant decrease in the body weight of diabetic control rats (50 gm) was observed when compared with normal control rats. After 21 days of alloxan challenge, the *M. quadrangula* extracts in treated groups (group IV and V) decreased their body weight as compared with the normal control group but the weights were better than in DC. The result also, showed that the *M. quadrangula* extracts treated group (III) showing better efficacy in maintaining body weights in comparison with groups IV and V. Furthermore, the gradual increase in the body weights of the *M. quadrangula* extracts treated group III was near to than in normal control rats.

Food and water intake

The food and water intake in the experimental groups are presented in table (2). DC rats showed a significant increase ($P<0.05$) in the intake of food and water when compared with the NC group. Whereas, the food and water intake increased significantly ($P<0.05$) in IV and V groups, respectively when compared with the NC group. While the food and water intake were decreased significantly ($P<0.05$) observed in group III when compared with DC rats.

Biochemical results of *M. quadrangula* extract

As shown in table (3) a comparison of the antioxidant capacities of lyophilized powder of *M. quadrangula* extract showed high scavenging significantly higher ($p<0.05$) ability against DPPH and O^{2-}. The *M. quadrangula* extract showed greater scavenging ability toward H_2O_2, which was near to the scavenging ability of AsA that commonly used as a standard antioxidant.

On the other hand, Table 4 showed that TPC in *M. quadrangula* was significantly higher ($p<0.05$) as compared to gallic acid that commonly used as a standard.

Table 1. Effect of plant extract management on the body weight (gm) of control and experimental groups.

Groups	Initial	Final
I (NC)	156.00±5.86	259.50±6.28 [a]
II (DC)	193.00±9.71	106.00±8.64870 [b]
III (D-MQ 100 mg/kg)	164.33±8.18	261.50±16.24 [a]
IV (D-MQ200 mg/kg)	175.66±16.21	200.00±18.49 [a]
V (D-MQ 300 mg/kg)	160.66±5.71	205.33±17.97 [a]

Values are expressed as mean ± SD (n= 6); a Values are statistically significant at p<0.05 compared to normal control rats; Values that have a different superscript letter (a, b, c, d) differ significantly with each other.

Table 2. Effect of plant extract on food intake and water intake in normal and diabetic rats.

Groups	Food intake (g/day)	Water intake (ml/day)
I (NC)	43.68±2.35 [a]	213.51±10.34 [a]
II (DC)	58.23±3.92 [b]	361.66±23.71 [b]
III (D-MQ 100 mg/kg)	49.41±3.12 [cd]	224.56±20.43 [cd]
IV (D-MQ200 mg/kg)	55.72±1.85 [b]	251.92±14.87 [b]
V (D-MQ 300 mg/kg)	53.94±1.38 [b]	217.75±15.34 [a]

Each value is mean ± SD. Values are given for each group that rats (n=6); Values that have a different superscript letter (a,b,) differ significantly with each other (P<0.05).

Table 3. The scavenging ability of *M. quadrangula* (MQ) extracts against different oxidants.

	% of Scavenging activity		
	DPPH	H_2O_2	$O_2^{\cdot-}$
AsA (Control)	98.13± 0.92	99.16±0.67	61.11±1.23
MQ Extract	84.88±0.72	95.99±0.76	31.00±1.83

Each value presented is means ± SD of 4 times of repeated sets of *M. quadrangula* extracts. are statistically significant at p<0.05 compared to AsA that commonly used as a standard antioxidant.

Table 4. Level of total Phenol Continent of *Monolluma quadrangula* (MQ) extracts.

	MQ extracts
TPC mg GAE/100 mg	69.52±2.34

Each value presented is means ± SD of 4 times of repeated sets of MQ extracts. are statistically significant at p<0.05 compared to gallic acid that is commonly used as standard.

Blood glucose level changes

The results of blood glucose level changes in normal, alloxan-induced diabetic rats and diabetic rats treated with *M. quadrangula* were shown in table (5). After 3 days of alloxan injection, a modest increase in the blood glucose levels was observed in II, III, IV, and V groups that reaching an optimum level on the 5th day. Administration of *M. quadrangula* in IV and V groups showed results of not a significant in decrease the blood glucose level then comparison with NC group. While was in group III showed better efficacy in the blood glucose level than comparison with DC groups, in which the decreasing of the blood glucose level, was near to the levels of NC rats.

Biochemical results of plasma

The levels of MDA in plasma were significantly increased in alloxan-induced diabetic rats as

compared to normal control rats, while is the level of MDA decreased to near than normal values in group III, daily for the 21 days as compared to the DC group, whereas these levels MDA increased significantly in IV and V groups, receptively as compared with NC group, as shown in table (5).

The level of AsA was significantly decreased in alloxan-induced diabetic as compared to normal control rats, while its level increased significantly in groups III and IV, respectively, as compared with DC rats. However, the significant decrease of AsA level in-group V was near than the DC group, too (0.88±0.07 mg/ml) as shown in table (5).

A significant decrease in the TP level was observed in the plasma of alloxan-induced diabetic rats when compared with that of NC rats. Administration of *M. quadrangula* showed results of a significant increase in the TP level with all groups treatment than compared with that of NC rats, as shown in table (5).

Table 5. Effect of *M. quadrangula* (MQ) extracts on the levels of plasma glucose**,** MDA, AsA, and TP in normal and experimental groups.

	Groups				
Parameters	(NC)	DC	D-MQ 100mg/kg	D-MQ 200 mg/kg	D-MQ 300mg/kg
Glucose (mg/dl)	101.00±8.83[a]	488.33±72.75 [b]	135.66±17.99 [a]	220.00±42.28 [b]	310.66±53.07 [b]
MDA(nmol/ml)	1.24±0.02[a]	3.41±0.25 [b]	1.59±0.13 [a]	2.53±0.33[ab]	3.55±0.33 [b]
AsA (mg/dl)	2.12±0.17[a]	0.62±0.08 [b]	1.71±0.15 [a]	1.30±0.21 [b]	0.88±0.07 [b]
TP (g/L)	54.16±1.26[a]	30.68±1.34 [b]	84.10±4.66 [ab]	74.96±4.32 [ab]	68.58±4.60 [a]

Each value is expressed as mean ± SD (n = 6), differences at $p < 0.05$ were considered significant. a –compared to NC group; b – compared to DC group.

Biochemical of antioxidant enzymes in hemolysate

In the present study, a significant decrease in the activities of the following antioxidant enzymes (SOD, CAT, POD, GST) and GSH level was observed in the erythrocytes of alloxan-induced diabetic rats when compared to that of NC. Upon administration of *M. quadrangula* extract in group III the activities of SOD, POD, and CAT was significantly increased reversed towards the normal levels. Whereas, the levels of GSH and GST were significantly increased in groups IV and V when compared to that of diabetic control rats. Generally, in the present study, treatment with ethanol extract of *M. quadrangula* significantly increased the levels of these antioxidants in diabetic rats, as in table (6).

DISCUSSION

Our results reported changes in experimental animal body weight, food consumption, and water intake as important parameters for the pathophysiology. In the experimental animal, alloxan-induced DM and appeared a significant decrease in body weight. The same results were observed by the results of Ajiboye et al. (2014) and Tian et al. (2010). In the present study, alloxan administration inhibited weight gain and induced an increase in water and food consumption as compared to the normal control animals. The decrease in body weight of diabetic rats is due to the catabolism of fats and proteins that occur by insulin deficiency. This result agreed with Babu et al. (2007), who reported that the protein content decreased in muscular tissue by proteolysis.

Table 6. Prevalence of HBV infection according to the duration on hemodialysis

Parameters	Groups				
	NC	DC	D+(100mg/k)	D+(200mg/k)	D+(300mg/k)
GSH (mg/gHb)	6.81±0.75[a]	2.62±0.4 [b]	6.08±0.51 [a]	7.12±0.48 [a]	8.72±0.52 [ab]
SOD (U/mgHb)	83.71±3.38[a]	51.40±3.28[b]	80.82±8.65 [a]	63.76±5.75 [ab]	61.63±11.94 [b]
CAT (U/gHb)	293.37±31.10[a]	148.98±45.37[b]	252.39±20.7[b]	169.93±30.01[a]	127.59±27.48[a]
POX(U/mgHb/min)	97.37±0.94[a]	38.29±1.44[b]	88.83±2.90 [b]	68.16±2.62 [ab]	46.46±3.32 [a]
GST (U/mgHb	2.72±0.35 [a]	1.77±0.26[b]	1.94±0.38 [a]	2.85±0.40[b]	3.98±0.32[b]

Each value is mean± S.D. (n=6) rats in each group. a – different than the normal control group; b – different than the diabetic control group.

As expected, in the present study, the alloxan-induced rats rapidly developed and maintained the physical symptoms and exhibited over 50% weight loss during 3 weeks of the experiment. On the other hand, the increase of body weight in group III was the best and revealed a marked positive effect on other physical parameters because of improved polydipsia and polyphagia in this group, whereas, in groups, IV and V did not their weights as compared to the normal control group. The failure of both groups IV and V, to restore the decreased body weight may be due to the appetite suppressant effect of pregnane glycoside (Liu et al. 2013). It was reported that pregnane glycosides are marketed as a supplement for weight loss, as well as pregnane glycosides are known to act at the level of the hypothalamus to control appetite (Priya *et al*., 2012). Similar results have been reported by Kiran et al. (2012); Abdallah et al. (2013) and Ajiboye et al. (2014).

In this study, the antioxidants activities of stem extracts of *M. quadrangula* against DPPH, H2O2, and $O^{-}2$ radicals showed that significant activity as an antioxidant when compared to the standard AsA at the same concentrations.

These results indicated that the *M. quadrangula* extract exhibited a higher inhibition percentage, (about 84 .88%) whereas the inhibition produced by AsA (standard) was 98.13%. The effect of the antioxidant on DPPH that serves as a stable free radical is thought to be due to hydrogen donating ability (Mir et al. 2013).

Antioxidants interact with DPPH, either transfer electrons or hydrogen atoms to DPPH leading to neutralize free radical character (Kumawat et al. 2012).

Our results revealed that *M. quadrangula* extract is a strong electron donor and could react with free radicals to convert them to more stable products and terminate radical chain reaction. This study was agreed with Abdallah et al. (2013) and disagreed with Ruchi et al. (2006).

Although H_2O_2 is not a radical species, it plays a role to contribute OS. The generation of even low levels of H_2O_2 in biological systems may be important. Naturally occurring iron complexes inside the cell are believed to react with H_2O_2 *in vivo* to generate highly reactive OH^{-} and this may be the origin of many of its toxic effects (Shahriar et al. 2015).

Potential sources of antioxidant compounds have been searched from stems of plant material by using some different methods. Phenolic is especially common in stems. The antioxidant activity of phenolic is mainly due to their redox properties which allow them to act as reducing agents, hydrogen donors, and singlet oxygen quenchers (Adnan et al. 2014; Ruchi et al. 2006). The purpose of this study was to screen the total phenolic compound content and antioxidant activity of extract made from *M.*

quadrangula extraction. The results obtained in the determination of total phenolic and the test of antioxidant activity were used as a basis for selecting the type of stem extract used in further studies for determining its biological activity. This study was agreed with Adnan et al. 2014 and disagreed with Ruchi et al. (2006).

Elevation of glucose levels has been observed in diabetic control rats in comparison with normal control rats in this experiment. Alloxan has been used to induce diabetic rats and the complications associated with the diabetic disorder (Ahmed *et al*., 2014). It has been shown that the toxic effect of alloxan in the pancreas is created by its rapid uptake by the beta-cells and ROS generation (Das et al. 2012).

The results of the present study showed that alloxan at a dose of 150 mg/kg body weight caused considerable damage to regulate blood glucose. This damage may be due to an increase in the mobilization of free fatty acids from peripheral tissue as a result of activation hormone-sensitive lipase during insulin insufficiency, resulting in a significant increase in blood glucose concentrations. The increasing glucose level in alloxan-induced rats made it unable to enter the cells due to a lack of insulin that leads to a deficiency of energy. As well as, abnormally high concentration of serum lipids profile which is likely to increase the risk of heart diseases (Ahmed *et al*., 2010).

Administration of *M. quadrangula* extract in group III showed a significantly decrease blood glucose level compared with the DC group. This may be since the plant extract increases glucose removal from the blood, decreases the release of glucagon, or increases insulin, stimulate directly glycolysis in peripheral tissues, or reduce glucose absorption from the gastrointestinal tract as reported by Alamgeer et al. (2012). Furthermore, it may be due to the presence of saponins, pregnane glycosides, and flavonoids that possess hypoglycemic activity by acting on insulin or by stimulating insulin secretion by the beta cells of the islets of Langerhans as reported by Abdalla et al. (2013) and Abdel-Sattar et al. (2016). Furthermore, pregnane glycoside was found to down-regulate the production of corticosteroid, one of the insulin antagonists, in human adrenocortical cells (Komarnytsky *et al*., 2013). The results of our study are similar to the work of Izuddin et al. (2016) and Abdel-Sattar et al. (2011) as well as, agreement with the study reported by Abdalla et al. (2013).

The present study revealed a significant increase in plasma TBARS levels in diabetic rats, which may be due to elevating OS. The increased levels of plasma LPO products observed in alloxan-induced diabetes may be due to pathological changes in tissues that increase the production and liberation of LPO into the blood circulation (Likidlilid *et al*., 2010). The decrease levels of plasma TBARS observed in the third group are due to the *M. quadrangula* extract anti-LPO effect. This suggested that ROS may exert their cytotoxic effects in this early clinical stage of the disease, but intake of 100 mg of *M. quadrangula* for 3 weeks improved the OS and inhibited the LPO process so the levels of MDA was low in comparison with diabetic control rats (Adnan *et al*., 2014). Administration of plant extracts significantly reduced MDA content in plasma probably due to their polyphenol content.

LPO of the membrane, associated with increased membrane rigidity and reduced cell survival has been implicated in DM (Coskun *et al*., 2013). Polyphenol-rich extract of *M. quadrangula* has significantly reduced the level of hydroperoxide compared to normal and diabetic controls of treated diabetic rats (Ruchi et al. 2006; Abdel-Sattar *et al*., 2011; Ibrahim *et al*., 2015). Our study agreed with Abdel-Sattar et al. (2011); Adnan *et al*. (2014) and Ibrahim *et al*., 2015).

This study demonstrated a significant decrease in the plasma TP content in alloxan-induced diabetic rats as compared to NC rats. The greater decrease of plasma TP in diabetic rats might be ascribed to liver

damage (Coskun *et al*., 2013). The decreased amino acid uptake or hepatic protein synthesis has been reported to be depressed due to liver damage (Kalender *et al*., 2015).

On the other hand, *M. quadrangula* extract significantly increased plasma TP concentration as compared to DC, which may have been due to increased serum insulin levels. These results may be attributed to that *M. quadrangula* extract, accelerated amino acid transporting through cells, and stimulated the protein manufacturing machinery of the cells. Our results agreed with Hemalatha et al. (2016) and Ibrahim et al. (2015) who reported that the plant extract administration increased the protein level in plasma for all groups' treatments, and suggested that may be due to present proteins in the plant.

Reduced glutathione (GSH) is the most important non-protein compound containing the thiol group which acts as a substrate for GST and GPx involved in preventing the deleterious effect of oxygen radicals (Hemalatha *et al*., 2016). Therefore, GSH is an important molecule involved in cellular defense against ROS. GSH is a scavenger of free radicals as well as a co-substrate for peroxide detoxification by GPx (Ejtahed *et al*., 2012). In the present study, diabetic rats showed a significant decrease in the level of GSH in the erythrocytes and AsA in plasma, which may be due to increasing utilization for scavenging free radicals, as well as increased consumption by GPx and GST (Shinde *et al*., 2011). These results were in agreement with the previous study, which showed that the glutathione level was decreased in different phases of diabetes (Abdel- Sattar *et al*., 2016). On the other hand, the administration of *M. quadrangula* extract by 300mg/kg dose increased the GSH level in erythrocytes and AsA in plasma of treated groups' diabetic rats. The elevation at the GSH level may be due to an increase in the biosynthesis of GSH or a reduction in OS or maybe both (Rohilla and Ali, 2012).

Activities of antioxidant enzymes (SOD, POD, GST, and CAT) significantly reduced in alloxan-induced diabetic rats (Izuddin *et al.,* 2016; Rohilla and Ali, 2012). In our study, depletion of total antioxidant capacity in diabetic rats compared to the normal control group. This may be due to the generation of ROS and may be due to poor glycemic regulation in diabetic untreated rats (Kasperczyk *et al.,* 2012). The results in this study suggested that the oxidative effects of DPPH scavenging activity in alloxan-induced diabetic rats have significantly affected by MQEt on DPPH levels that lead to decreased SOD, POD, GST, and CAT activity after the treatment with *M. quadrangula* extract. This could be due to the phenolic compound found in the *M. quadrangula* plant.

In the present study, the treatment of rats with 100 mg/kg *M. quadrangula* extract induced significant increases in the antioxidant enzyme activities as compared to diabetic control. These results are similar to a previous study reported by Ibrahim *et al*. (2015). In our study, the administration of *M. quadrangula* extract (100mg/kg) to diabetic rats showed the best significant increase in activity of SOD, GST, CAT, and POD levels in the erythrocyte. This increase may be due to the reduction of glycation of these enzymes or the reduction of ROS.

The ability of *M. quadrangula* extract to prevent the alteration of antioxidant status explained their protective role. This may be due to the presence of phenolic content and reducing substances as reported from the phytochemical screening. This finding agreed with Abdel-Sattar *et al*. (2016) and Adnan et al. 2014 and disagreed with Al-Yahya *et al.* (2000).

CONCLUSION

Based on the above experiments of *Monolluma quandragula* extraction, it is concluded that extract *Monolluma quandragula* contains a large number of

antioxidants and that decreased oxidative stress and in turn, blood glucose level in diabetic induced rats. This may be because the plant extract increases glucose removal from the blood, decrease glucagon releasing, or increase the insulin stimulation that leads to glycolysis in peripheral tissues or reduce glucose absorption from the gastrointestinal tract.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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