

*Full Length Research Paper*

## **Lycopene attenuates diabetes-induced oxidative stress in Wistar rats**

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Received 8 February, 2018; Accepted 15 May, 2018

**The purpose of this study is to evaluate the capacity of lycopene against diabetes-induced oxidative damage in Wistar rats. Thirty Wistar rats of both sexes, twenty-five of which were diabetic, were used. Diabetes was induced by a single intraperitoneal injection of streptozotocin (STZ) 60 mg/kg body weight and it was confirmed by the elevated blood glucose  $\geq 200$  mg/dl after three days. The rats were divided randomly into groups 1 to 6, each containing 5 rats. Group 1 (Normal control) and Group 2 (Diabetic control) rats were administered 0.5 ml of olive oil; Groups 3, 4, and 5 rats were respectively administered 10, 20 and 40 mg/kg body weight of lycopene, while Group 6 rats were administered 2 mg/kg body weight of Glibenclamide. All administrations were done orally and once daily for twenty-eight days. At the end of the treatment, serum levels of antioxidant enzymes, cortisol and malondialdehyde (MDA) were determined. Administration of graded doses of lycopene to diabetic animals significantly ( $P < 0.05$ ) decreased the blood glucose concentration after four weeks of treatment when compared to diabetic untreated animals. Serum levels of cortisol and MDA (index of oxidative stress) were reduced while there were up-regulated activities of serum endogenous enzymes (superoxide dismutase, catalase and glutathione peroxidase) in diabetic animals treated with all doses of lycopene when compared with diabetic untreated animals. Overall, lycopene attenuated the biomedical alterations in STZ-induced diabetic Wistar rats. Lycopene therefore possesses antioxidant activity at the doses tested in this study.**

**Key words:** Lycopene, diabetes mellitus, oxidative stress, cortisol, malondialdehyde, catalase, glutathione peroxidase.

### **INTRODUCTION**

Diabetes mellitus (DM) is a metabolic disorder that features hyperglycemia and deficiency of secretion or action of insulin (Sailaja et al., 2003). Increased free radicals coupled with the reduction of antioxidant defence

mechanisms, caused by diabetes mellitus, may result in insult to cellular organelles, alteration in biomolecules, and increased lipid peroxidation (Maritim et al., 2003; Rajasekaran et al., 2005). In diabetics, sustained

hyperglycemia causes increased generation of free radicals especially reactive oxygen species due to glucose auto-oxidation and protein glycosylation which results in diabetes-induced oxidative stress (He and King, 2004; Moussa, 2008; Al-Faris et al., 2010). Diabetes-induced oxidative stress is associated with diabetic complications (Negi et al., 2011). The sustained rise in reactive oxygen species (ROS) and reactive nitrogen species (RNS) coupled with a decline in antioxidant activity leads to the occurrence of oxidative and nitrosative stress that can result in endothelial dysfunction, insulin resistance as well as alteration in the number and function of pancreatic  $\beta$ -cells, contributing to diabetic microvascular and macrovascular complications (Baynes and Thorpe, 1999; Bandeira et al., 2013).

Lycopene is reported as one of the most powerful antioxidants which contain carotenoids found in foods particularly tomatoes (Gartner et al., 1997). It has gained increased attention for its health-enhancing properties (Bramley, 2000; Yang et al., 2006; Madhava et al., 2011). It is a member of the carotenoid family of phytochemicals that gives plants its characteristics red color (Blum et al., 2005; Tadmor et al., 2005). Lycopene is also found in watermelon, papaya, pink grapefruit and pink guava (Tadmor et al., 2005). Its high antioxidant capacity has been attributed to the open  $\beta$ -cycle in its structure (Yegin et al., 2013). Lycopene is the most predominant carotenoid in tomatoes and has the highest antioxidant property among all dietary carotenoids (Rao and Agrawal, 1999). Studies reported on lycopene's effects in STZ-induced diabetic animals included altered thyroid profile (Eze et al., 2015a), atherogenic cardiovascular risk (Eze et al., 2015b), kidney antioxidant enzyme activity (Eze et al., 2015c), a hypoglycemic effect (Eze et al., 2015d), altered liver markers and glucokinase activity of diabetic animals (Eze et al., 2016) as well as histological changes (Soleymaninejad et al., 2017). Haribabu et al. (2013) found that lycopene at 2 and 4 mg/kg body weight in combination with glipizide and metformin had anti-diabetic activity on the 21st day of treatment in alloxan-induced diabetic rats. Kuhad and Chopra (2008), Duzguner et al. (2008) and Ali and Agha (2009) reported that 90 mg/kg body weight of tomato extract of lycopene reduced elevated blood glucose, lowered free radicals and improved serum lipids in STZ-induced diabetic rats. Dalbeni et al. (2016) reported increased nitric oxide bioavailability and inhibition of endothelial cells migration by lycopene. Petyaev (2016) and Chen et al. (2015), respectively, reported lycopene deficiency in ageing and prostate cancer in human. Zigangirova et al. (2017) reported that lycopene inhibits propagation of Chlamydia red blood cells (RBC) osmotic fragility and lipid peroxidation in animals by lycopene. Moreover, Pandir et

al. (2016) reported the effect of lycopene at 4 and 40 mg/kg body weight against oxidative damage induced by furan. Karahan et al. (2005) reported the protective capacity of lycopene at 4 mg/kg infection, while Eze et al. (2017) reported differences in body weight on gentamicin-induced oxidative stress. Aydin and Celik (2012) reported the ability of lycopene at 4 mg/kg body weight on reduction of oxidative stress in STZ-induced diabetic rats. Furthermore, Duzguner et al. (2008) assessed the activity of lycopene at 10 mg/kg body weight on oxidative stress in STZ-induced diabetic rats. However, there are no studies on the antioxidant activity of lycopene especially at the unique and therapeutic doses of 10, 20 and 40 mg/kg body weight on diabetes-induced oxidative stress in rats. This work therefore aimed to study the activity of lycopene against diabetes-induced alterations of serum endogenous enzymes, cortisol and malondialdehyde (MDA) concentrations in Wistar rats at 10, 20 and 40 mg/kg body weight.

## MATERIALS AND METHODS

### Experimental animal model and care

Apparently healthy Wistar rats of both sexes (20 males and 10 females) weighing 150 to 200 g were procured from the Department of Human Physiology Animal House, Ahmadu Bello University, Zaria, Nigeria. The rats were kept under the laboratory condition. The rats were housed five in each cage, fed with standard commercial feeds and allowed to access drinking water. The study protocol was approved by the Institutional Animal Ethics Committee of the Ahmadu Bello University, Zaria, Nigeria.

### Induction of experimental diabetes mellitus

Diabetes mellitus was induced by a single intraperitoneal injection of 60 mg/kg body weight dose of STZ (Sigma Chemicals, St Louis, U.S.A.) dissolved in fresh 0.1M cold citrate buffer of pH 4.5 into 18 h-fasted rats. Because STZ has the capacity to produce severe and chronic hypoglycemia as a result of massive pancreatic insulin release, the rats were treated with 20% glucose solution orally after 6 h. For the next 24h, the diabetic rats were given 5% glucose solution bottles in their cages to prevent hypoglycemia (Dhandapani, 2007). Three days after STZ injection, the blood was collected from the tail artery of the animals. Rats having fasting blood glucose concentration  $\geq 200$  mg/dl were considered diabetic and recruited for the study.

### Experimental design

Thirty Wistar rats were used and randomly divided into six groups of five animals each as follows:

- Group 1: Non-diabetic rats (Normal Control) treated with 0.5 ml/kg olive oil;
- Group 2: Diabetic rats treated with 0.45 ml/kg olive oil;

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Group 3: Diabetic rats treated with 10 mg/kg of lycopene;  
 Group 4: Diabetic rats treated with 20 mg/kg of lycopene;  
 Group 5: Diabetic rats treated with 40 mg/kg of lycopene;  
 Group 6: Diabetic rats treated with glibenclamide 2 mg/kg.

All animals were treated orally once per day for four weeks.

#### **Determination of fasting blood glucose concentration**

Blood samples were collected from the tail artery of the animals before the commencement of treatment indicated as week 0 and weeks 1, 2, 3, and 4 after the treatment. Fasting blood glucose concentration was determined with glucometer (Accu-chek Advantage) and results were expressed as mg/dl.

#### **Collection of erythrocytes and serum preparation**

After the last day of treatment (28th day), all the animals were slayed using light chloroform after 24 h and 5 mL of blood was collected through the cardiac puncture into specimen bottles and allowed to clot. The blood was separated by centrifugation at 2,000 g for 10 min using Hettich Centrifuge (Universal 32, Made in Germany). The supernatant was used for the determination of serum cortisol level, MDA and antioxidant enzyme activity.

#### **Determination of serum cortisol, malondialdehyde concentration and antioxidant enzyme activities**

##### ***Determination of serum cortisol level***

Serum was collected in the morning hours before the noon time. Cortisol was determined using the standard laboratory of BLK diagnostics kit (BLK Cortisol Enzyme-linked Immunosorbent Assay (ELISA) kit, Badalona, which was based on the principle of competitive binding (Tietz et al., 1994).

##### **Estimation of serum malondialdehyde (MDA) concentration**

Malondialdehyde is one of many low molecular weight end-products of lipid hydroperoxide decomposition and is the most often measured as an index of lipid peroxidation. Serum MDA concentration was evaluated using the NWLSS™ Malondialdehyde assay kits (Northwest Life Sciences Specialties, Product NWK-MDA01, Vancouver WA. The assay is based on the principle that MDA reacts with thiobarbituric acid (TBA); forming an MDA-TBA2 adduct that absorbs strongly at 532 nm.

##### **Determination of serum superoxide dismutase (SOD) activity**

superoxide dismutase activity was assessed using the North West Life Science Specialties (NWLSS™) SOD assays kit (Product NWK-SOD02). The method is based on the principle of superoxide inhibition of auto-oxidation rate of hematoxylin as previously described by Martin et al. (1987) with modification to increase robustness and reliability of the method. Briefly, 920 µL of assay buffer was added to each cuvette. This was subsequently followed by addition of 40 µL of assay buffer (for blank) and 40 µL of the sample. The mixture was incubated for two minutes, after which 40 µL hematoxylin reagent was added and mixed quickly to start the auto-oxidation reaction. Absorbance was read at 560 nm for every 10 s for 5 min.

#### **Determination of serum catalase (CAT) activity**

The activity of catalase was evaluated using North West Life Science Specialties (NWLSS™) Catalase assay kits (Product NWK-CATO1) based on the method of Beers and Sizer (1952) with little adjustment in order to increase robustness and convenience of the method. The method is relied on monitoring the consumption of H<sub>2</sub>O<sub>2</sub> substrate at 240 nm. Briefly, to a clean cuvette, 1000 µL of sample dilution buffer was added and placed in the reference cuvette holder and the wavelength of spectrophotometer was set to 240 nm. To a clean semi-micro UV cuvette, 950 µL of working assay buffer was added. The 50 µL of diluted standard or sample was pipetted to the cuvette and mixed as quickly as possible by repeated pipetting (About 10 times) with the same pipette tip. Absorbance was measured immediately at 240 nm.

#### **Estimation of serum glutathione peroxidase (GPx) activity**

The activity of GPx was assessed by adopting the protocol of North West Life Science Specialties (NWLSS™) cGPx (GPX1) ELISA kit (Product NWK-GPX02) based on the method described by Avissar et al (1994). Estimation of GPx activity follows the sandwich Enzyme-Linked Immunosorbent Assay, where sample GPx concentration was determined by comparing the 450 nm absorbance sample wells to the absorbance of known standards.

#### **Data analysis**

The data were expressed as mean ±SEM. The data were analyzed using one-way ANOVA with Tukey's post-hoc test. All data analyses were evaluated using SPSS version 17.0 software and Microsoft Office Excel (2007). The values of P≤0.05 were considered statistically significant.

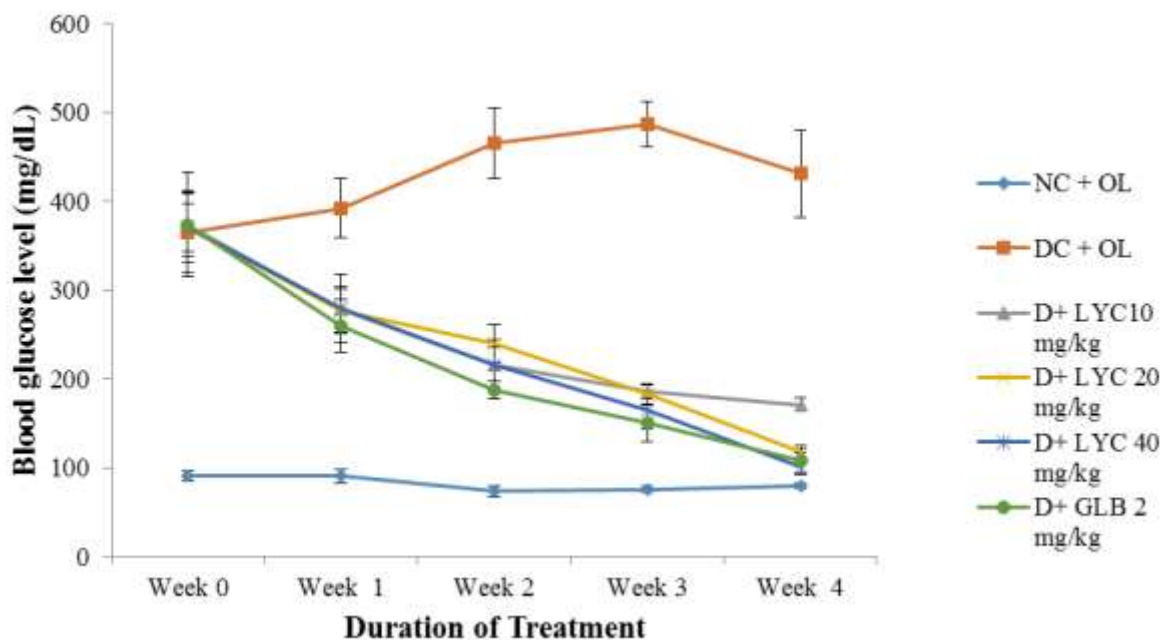
## **RESULTS**

### **Fasting blood glucose level following oral administration of lycopene**

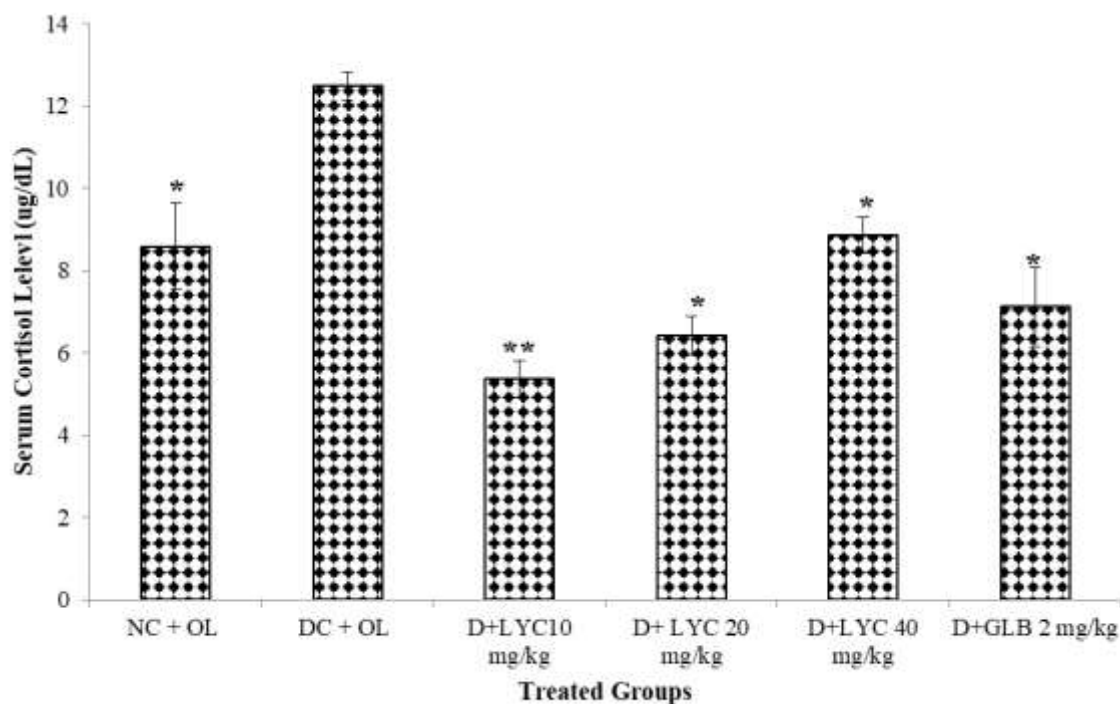
STZ significantly (P<0.05) increased blood glucose level of the animals on week 0. However, treatment of the experimental diabetic animals with graded doses of lycopene (10, 20 and 40 mg/kg body weight) and glibenclamide (2 mg/kg body weight) significantly (P<0.05) decreased blood glucose concentration when compared with the diabetic untreated animals (Figure 1).

### **Serum cortisol concentration following oral administration of lycopene**

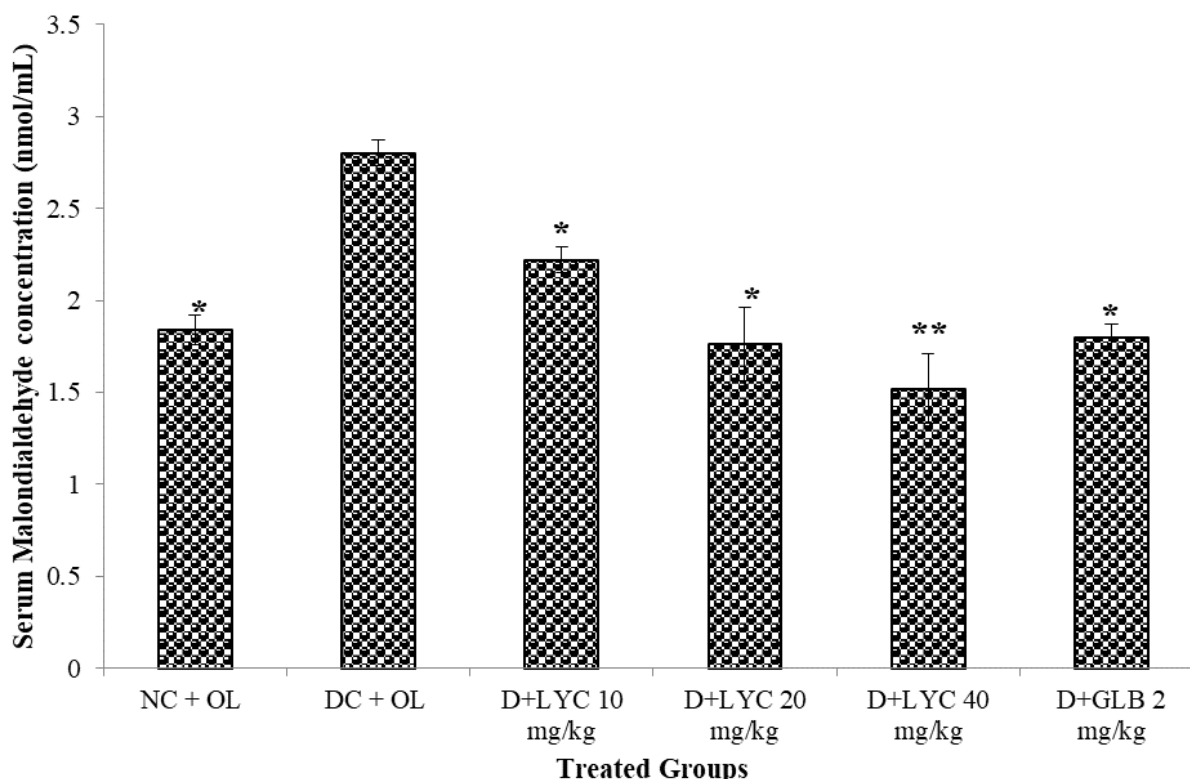
STZ substantially (P<0.05) increased serum cortisol levels in the diabetic untreated animals when compared with normal control. Lycopene at all doses significantly (P<0.05) reduced the serum cortisol levels in a manner not comparable with the glibenclamide (2 mg/kg body weight) treated diabetic animals. The greatest reduction was obtained with the 10 mg/kg body weight of lycopene (Figure 2).



**Figure 1.** Blood glucose levels after oral administration of lycopene in diabetic Wistar rats. Results are represented as mean  $\pm$  SEM. DC+OL: diabetic untreated animals treated with olive oil; NC+OL: normal control animals treated with olive oil; D+LYC10 mg/kg: diabetic animals treated with 10 mg/kg of lycopene; D+LYC 20 mg/kg: diabetic animals treated with 20 mg/kg of lycopene; D+LYC 40 mg/kg: diabetic animals treated with 40 mg/kg of lycopene; D+GLB 2 mg/kg: diabetic animals treated with 2 mg/kg of glibenclamide.



**Figure 2.** Results of lycopene on serum cortisol levels in diabetic Wistar rats. Data are presented as mean  $\pm$  SEM. \* $P < 0.05$  versus diabetic control group; \*\* $P < 0.05$  versus diabetic control group; DC+OL: Diabetic animals treated with olive oil; NC+OL: normal control animals that received only olive oil; D+LYC 10 mg/kg: diabetic animals treated with 10 mg/kg of lycopene; D+LYC 20 mg/kg: diabetic animals treated with 20 mg/kg of lycopene; D+LYC 40 mg/kg: diabetic animals treated with 40 mg/kg of lycopene; D+GLB 2 mg/kg: diabetic animals treated with 2 mg/kg of glibenclamide.



**Figure 3.** Serum malondialdehyde levels in diabetic Wistar rats after treatment with lycopene. Data are presented as mean  $\pm$  SEM. \* $P < 0.05$  versus diabetic control group; \*\* $P < 0.05$  versus diabetic control group; DC+OL: diabetic animals treated with olive oil; NC+OL: normal control animals that received only olive oil; D+LYC 10 mg/kg: diabetic animals treated with 10 mg/kg of lycopene; D+LYC 20 mg/kg: diabetic animals treated with 20 mg/kg of lycopene; D+LYC 40 mg/kg: diabetic animals treated with 40 mg/kg of lycopene; D+GLB 2 mg/kg: diabetic animals treated with 2 mg/kg of glibenclamide.

#### Serum MDA concentration following oral administration of lycopene

STZ significantly ( $P < 0.05$ ) elevated the serum MDA levels when compared with the normal control animals. Lycopene at all doses and glibenclamide significantly ( $P < 0.05$ ) reduced the serum MDA levels. The greatest decrease was observed in diabetic animals treated with 40 mg/kg body weight of a lycopene (Figure 3).

#### Serum SOD activity following oral administration of lycopene

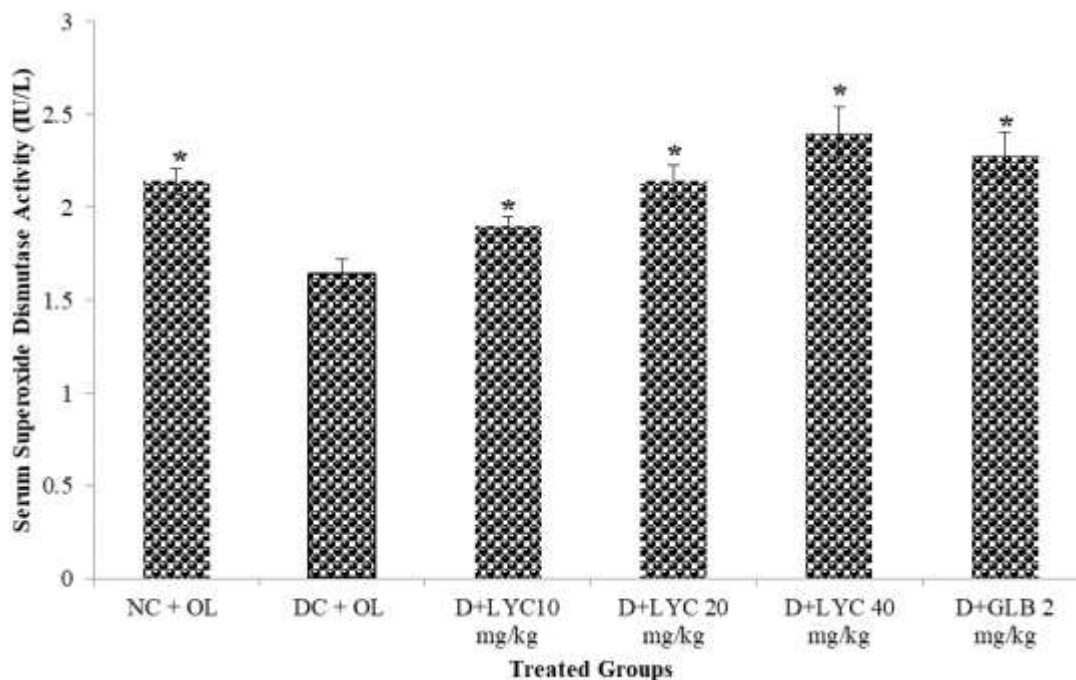
Compared with the non-diabetic rats, STZ significantly ( $P < 0.05$ ) decreased the activity of serum superoxide dismutase in untreated diabetic animals. Administration of lycopene to diabetic animals significantly ( $P < 0.05$ ) and dose-dependently increased SOD activity when compared with the diabetic untreated animals. The 40 mg/kg body weight of lycopene increased SOD activity comparable to ( $P > 0.05$ ) glibenclamide (2 mg/kg body weight) (Figure 4).

#### Serum CAT activity following oral administration of lycopene

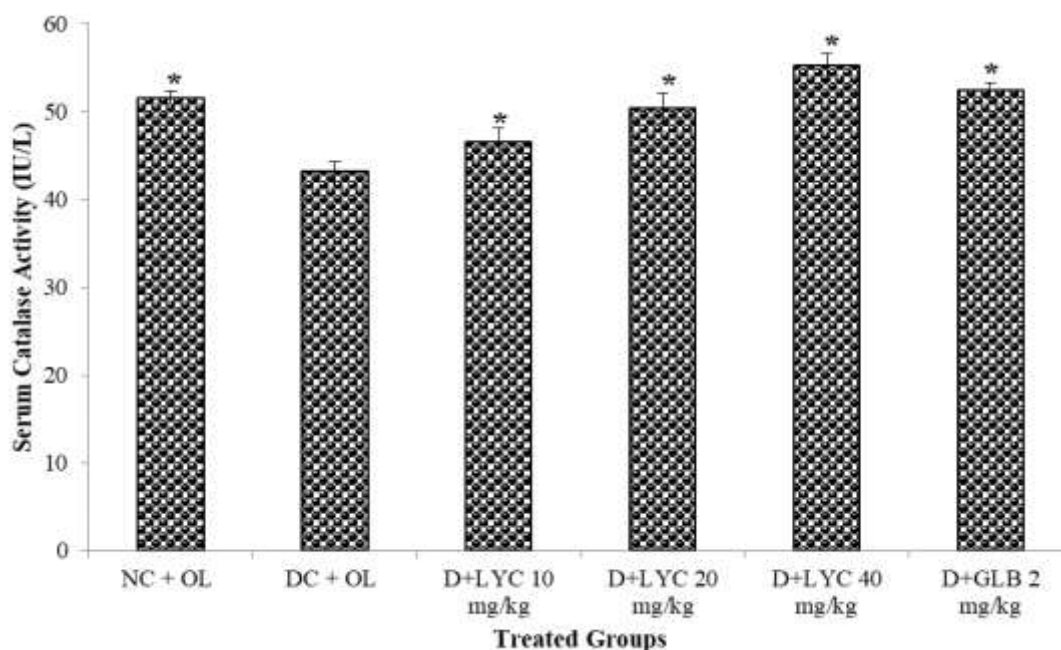
STZ significantly ( $P < 0.05$ ) reduced the activity of serum CAT in the diabetic untreated group when compared with nondiabetic animals ( $P < 0.05$ ). Lycopene at all doses notably ( $P < 0.05$ ) increased CAT activity in the serum of the diabetic animals when compared with the diabetic untreated group. The effect of glibenclamide (2 mg/kg body weight) was comparable to those with the 20 mg/kg body weight of lycopene. The highest serum CAT activity was obtained with the 40 mg/kg body weight of lycopene (Figure 5).

#### Serum GPx activity following oral administration of lycopene

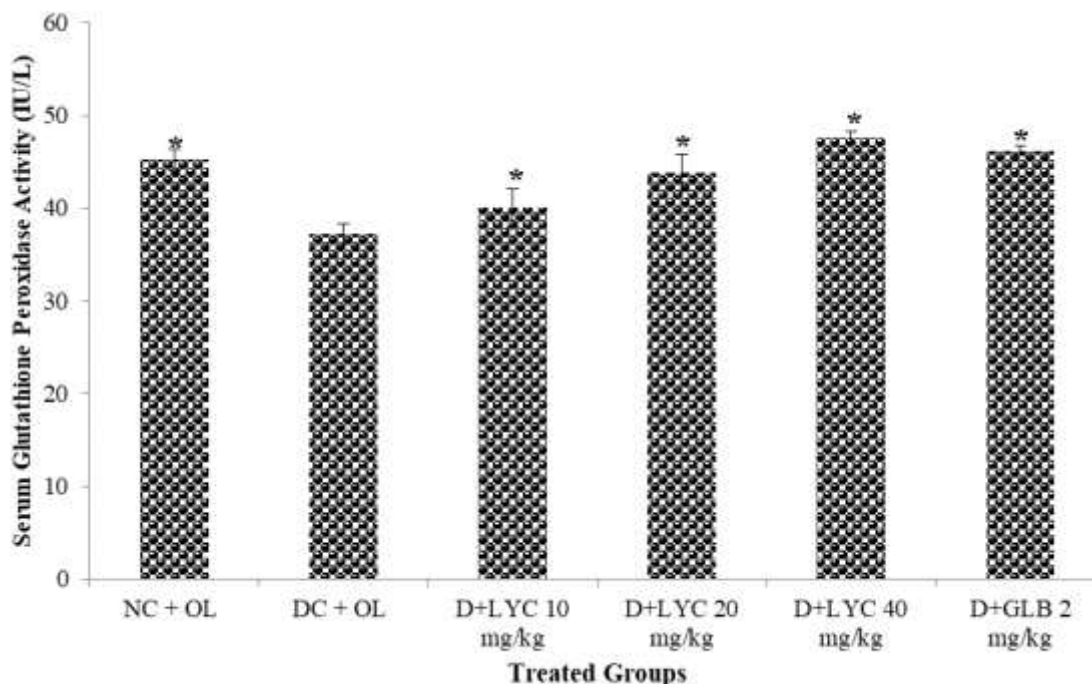
Serum GPx activity was lower ( $P < 0.05$ ) in the diabetic untreated group when compared with nondiabetic animals. Treatment of diabetic rats with lycopene significantly ( $P < 0.05$ ) increased serum GPx activity in a dose-dependent manner, the 20 mg/kg body of lycopene



**Figure 4.** Serum superoxide dismutase activity in diabetic Wistar rats after treatment with lycopene. Data are presented as mean  $\pm$  SEM. \* $P < 0.05$  versus diabetic control group; DC+OL: diabetic animals treated with olive oil; NC+OL: normal control animals that received only olive oil; D+LYC 10 mg/kg: diabetic animals treated with 10 mg/kg of lycopene; D+LYC 20 mg/kg: diabetic animals treated with 20 mg/kg of lycopene; D+LYC 40 mg/kg: diabetic animals treated with 40 mg/kg of lycopene; D+GLB 2 mg/kg: diabetic animals treated with 2 mg/kg of glibenclamide.



**Figure 5.** Activity of serum catalase in diabetic Wistar rats after oral treatment with lycopene. Data are presented as mean  $\pm$  SEM. \* $P < 0.05$  versus diabetic control group; DC+OL: diabetic animals treated with olive oil; NC+OL: normal control animals that received only olive oil; D+LYC 10 mg/kg: diabetic animals treated with 10 mg/kg of lycopene; D+LYC 20 mg/kg: diabetic animals treated with 20 mg/kg of lycopene; D+LYC 40 mg/kg: diabetic animals treated with 40 mg/kg of lycopene; D+GLB 2 mg/kg: diabetic animals treated with 2 mg/kg of glibenclamide.



**Figure 6.** Activity of glutathione peroxidase in diabetic Wistar rats after treatment with lycopene. Data are presented as mean  $\pm$  SEM. \* $P < 0.05$  versus diabetic control group; DC+OL: diabetic animals treated with olive oil; NC+OL: normal control animals that received only olive oil; D+LYC10 mg/kg: diabetic animals treated with 10 mg/kg of lycopene; D+LYC 20 mg/kg: diabetic animals treated with 20 mg/kg of lycopene; D+LYC 40 mg/kg: diabetic animals treated with 40 mg/kg of lycopene; D+GLB 2 mg/kg: diabetic animals treated with 2 mg/kg of glibenclamide.

increased serum GPx activity comparable to ( $P > 0.05$ ) that of the glibenclamide (Figure 6).

## DISCUSSION

This study showed the ameliorative effect of lycopene at 10, 20, and 40 mg/kg body weight on oxidative stress indicators in diabetic rats. Following treatment of diabetic rats with lycopene at all doses, the blood glucose levels were significantly reduced. This finding agrees with the previously reported investigations on glucose-lowering effect on lycopene by (Ali and Agha, 2009); (Haribabu et al., 2013) as well as (Aydin and Celik, 2012). Hyperglycemia is mediated largely in part, by a state of enhanced oxidative stress which results in the increased production of reactive oxygen species which can cause adverse structural and functional changes in tissues (Mehta et al., 2006). In addition, various mechanisms have been associated with hyperglycemia which includes glucose autooxidation, stimulation of the polyol pathway, activation of the reduced form of nicotinamide adenine dinucleotide phosphate oxidase, and generation of advanced glycation end-products which results in increased production of reactive oxygen species (Bonnefont-Rousselot et al., 2000). Therefore, the ability of lycopene to lower blood glucose levels in diabetic rats

may be as a result of its capacity to protect vital biomolecules including lipids, protein and DNA of beta cells from free radicals or as a result of its antioxidant activity through scavenging of free radicals released from glucose autooxidation resulting from sustained hyperglycemia (Ashwani and Prachi, 2013). More so, lycopene may also have acted by stimulating glucose utilization by peripheral tissues or increasing insulin production by the pancreas from regenerated  $\beta$ -cells (Suganya et al., 2012).

The present study showed that serum cortisol levels were significantly elevated in the diabetic untreated rats when matched with those of normal control animals. This effect is consistent with reports of Bitar (1998) and Radahmadi et al. (2006) which showed that diabetes is closely linked with heightened status of glucocorticoids and elevated adrenal function. The ability of lycopene to significantly reduce the elevated serum cortisol level in diabetic treated rats indicates that lycopene could be exerting ameliorative effects in diabetes-induced hypercortisolism in the animals. Administration of lycopene considerably lowered MDA concentration in the serum of the diabetic treated rats. This finding corroborates the report of Singh et al. (2012) which demonstrated that treatment of diabetics with lycopene given once daily for three months attenuated oxidative stress by significantly decreasing serum MDA level. The

activity of lycopene observed in the present study may be due to its various antioxidant defense strategies, most especially the scavenging of two of the ROS: singlet molecular oxygen and peroxy radicals (Atessahin et al., 2006).

Lycopene has been reported to act as a chain-breaking antioxidant (Singh et al., 2012). The combination of peroxy radicals formed in the propagation phase of lipid peroxidation with lycopene yield carbon-centered radicals. These carbon-centered radicals then react readily and reversibly with oxygen to form new chain carrying peroxy radicals which are stable than reactive oxygen species (Singh et al., 2012). The potent free-radical scavenging capacity of lycopene, owing to its unique structure (high number of conjugated double bonds), might have quenched the superoxide and other free radical anions, which are highly released in chronic diseases like diabetes mellitus (Rao and Agrawal, 1999; Upritchard et al., 2000; Khachik et al., 2002). Hence, the observed effects of lycopene in this study may be attributed to this property. In this study, serum anti-free radical enzymes (GPx, CAT and SOD) activities were significantly decreased in diabetic treated rats. These findings are consistent with the reports of various researchers (Balasubashini et al., 2004; Al-Azzawie and Alhamdani, 2006; Cheng and Kong, 2011; Singh et al., 2012; Cheng et al., 2013). Overproduction of free radicals from increased oxidative stress may result in diabetic complications (neuropathy, nephropathy, retinopathy, and vascular disorders) (Al-Azzawie and Alhamdani, 2006). However, whether anti-oxidative effects of lycopene can reduce those complications is unknown.

## Conclusion

Lycopene ameliorated diabetes-induced hypercortisolism, increased serum lipid peroxidation (MDA) and reduced serum antioxidant enzyme (SOD, CAT and GPx) reserves. The ability of lycopene to restore depleted serum enzymatic antioxidant activities in the diabetic animals could represent its antioxidant property.

## CONFLICT OF INTERESTS

The authors have not declared any conflict of interest

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