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Balanites aegyptiaca Modulates the Lipid Profile and Testicular Histopathology in Streptozotocin-Induced Diabetic Rats through an Antioxidant Mechanism

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ABSTRACT

Background: Hyperlipidemia is a confirmed consequence of diabetes mellitus that follows hyperglycemia. Moreover, diabetes plays a crucial role in testicular malfunction pathogenesis. **Objective:** The aim of this research is to examine the possible antihyperlipidemic and testicular protective action of *Balanites aegyptiaca* (*B. aegyptiaca*) fruit (flesh, kernel, and their mix) extracts in STZ-induced diabetic rats. **Results:** Diabetic rats treated with *B. aegyptiaca* showed significant decrease in the serum TG, LDL, and VLDL levels compared to the nontreated diabetic rats. *B. aegyptiaca* significantly increased the serum HDL levels compared to the nontreated diabetic rats. Furthermore, *B. aegyptiaca* extracts protected against STZ-induced diabetic testicular changes. *B. aegyptiaca* treatment increased level of GSH while decreased MDA level. **Conclusion:** *B. aegyptiaca* extract may be utilized as a preventive treatment for hyperlipidemia and testicular disruption linked with diabetes.

Keywords: Hyperlipidemia, testicular dysfunction, *Balanites aegyptiaca*, reduced glutathione, lipid peroxidation.

INTRODUCTION

Hyperlipidaemia is a documented diabetes mellitus complication that aligns with hyperglycemia, marked by increased levels of cholesterol, triglycerides, and phospholipids, as well as shifts in lipoproteins (Bagdade *et al.*, 1991; Sheu *et al.*, 2001). There are significant defects in lipid metabolism and lipoproteins during diabetes, which in turn rely on the level of insulin deficiency, insulin resistance, overweight, lifestyle, and concurrent essential triggers of hyperlipemia. Emerging data support the crucial role of hyperlipemia in the progression of the atherosclerosis-related disease, primarily increased blood cholesterol, low-density lipoprotein (LDL), and very-low-density lipoprotein (VLDL) (Andallu *et al.*, 2009). Different therapeutic approaches currently available for diabetes treatment achieve temporarily controlled hyperglycemia but do not avoid alterations in lipid and lipoprotein and eventually introduce diabetic people to cardiovascular risks (Grant *et al.*, 2002). In addition, many of these medications have serious side effects and/or toxicity such as liver toxicity (troglitazone) and cardiac insufficiency [rosiglitazone] (Gale, 2001).

Male sexual and reproductive complications of diabetes mellitus have recently gained a lot of interest in both animals and humans (Zha *et al.*, 2018). Decreased testosterone concentrations and testicular injury in the context of diabetes mellitus can result in erectile dysfunction, impaired sperm motility and lowered seminal fluid amount (Feyli *et al.*, 2017). Much research has shown that diabetes plays a crucial role in testicular malfunction pathogenesis by inducing seminiferous tubules atrophy and the destruction of spermatogenetic cells, which act as morphological indicators of spermatogenesis dysfunction (Cameron *et al.*, 1985; Sisman *et al.*, 2014). In a model of animal diabetes, streptozotocin (STZ) was found to produced testicular dysfunction via increased testosterone secretion, reactive oxygen species formation, and apoptosis induction (Zha *et al.*, 2018).

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Phytochemicals extracted from natural medicinal herbs present a new source for new medicines to be established. The quest for natural dietary therapeutic approaches for diabetes management has been very active (Hagura, 2000). *Balanites aegyptiaca (B. aegyptiaca)* is commonly used in rural areas in several communities by herbalists (Al-thobaiti and Zeid, 2018; Rashad *et al.*, 2017). *B. aegyptiaca* fruits are also well-known herbal medicines in traditional Egyptian medicine to minimize blood glucose levels and cure diabetes (Chothani and Vaghasiya, 2011). The antidiabetic impact of *B. aegyptiaca* fruit was claimed by Al-Malki *et al.* (2015) that may be related to its antioxidant molecules, particularly vanillic acid, syringic acid, and β-sitosterol. Recently, our lab documented that *B. aegyptiaca* kernel and flesh extracts could have a hypoglycemic effect equivalent to the effect of the standard antidiabetic agent, metformin in a model of STZ-induced diabetic rats (Al-Thobaiti and Zeid, 2019). This research aims to examine the possible antihyperlipidemic and testicular protective action of *B. aegyptiaca* fruit (flesh, kernel, and their mix) extracts in STZ-induced diabetic rats. Moreover, the possible antioxidant effect of *B. aegyptiaca* extracts will be tested.

MATERIALS AND METHODS

Plant material:
The fruits of *B. aegyptiaca* were picked up from the regional market, Jeddah, Saudi Arabia. The fruit was identified and validated by Dr Abdalla Elfeel, Faculty of Meteorology, Environment and Arid Land Agriculture, King Abdulaziz University, Jeddah, Saudi Arabia.

Drugs and chemicals:
STZ was obtained from Sigma, USA. Metformin (Glucophage, 500 mg metformin) Merck Santé, France.

Experimental animals:
Male Wister rats (180–240 g) were purchased from Mansour Scientific Research and Development Foundation, Jeddah, SA. Rats were kept at room temperature with a light cycle of 12 hours and free access to food and water ad libitum. The research procedure was accepted by the King Fahd Medical Research Centre's Research Ethics Committee.

Preparation of methanolic extract of B. aegyptiaca fruit (kernel, flesh and their mix):
The method of Al-Malki *et al.* (2015) was adopted with some modifications. Briefly, the crude powder of *B. aegyptiaca* (either kernel, flesh or their mixture) was put in a stoppered container with methanol. Allowstanding at room temperature for a period of at least 3 days until the soluble matter was dissolved. The rotary evaporator was employed for the efficient and gentle removal of solvents from samples. Then the mixture was strained, the marc (the damp solid material) was pressed, and the combined liquids were clarified by filtration or decantation after standing. The water bath was employed in order to evaporate the solvent at higher percentage (in fume hood). Finally, the complete dryness of the methanolic extract was carried out by freeze-drying.

Experimental protocol:
Rats were divided into 6 groups (n = 10): Rats in the control group were I.P. injected with 0.05 M citrate buffer (pH 4.5). Induction of diabetes was implicated in 5 groups of rats via I.P. injection of a single dose of STZ in a dose of 45 mg/kg (Zafar *et al.*, 2009). In three of the diabetic groups, rats were either orally administered with the methanolic extract of either *B. aegyptiaca* kernel extract, flesh, or their mixture in a dose of 650 mg/kg (based on preliminary trial). In one diabetic group, rats were orally treated with metformin in a dose of 200 mg/kg (Li *et al.*, 2014). The treatment protocol was continued for a period of 6 weeks.

Samples collection:
Rats were euthanized with deep ether anaesthesia at the completion of the experimental phase. Blood samples were obtained from the orbital vein plexus, permitted to be coagulated, and centrifuged for serum isolation at 3000 rpm. The sera were then preserved at -80 °C until used to test the lipid profile. Testis was picked out, cleaned with normal saline, and stored in 10 percent buffered formalin solution until subjected to Haematoxylin and Eosin (H & E) histological staining.

Assessment of serum triglyceride (TG), cholesterol, high-density lipoprotein (HDL), LDL, and VLDL:
The serum concentration of TG, cholesterol, HDL, LDL, and VLDL was determined using sandwich enzyme-linked immunosorbent assay (ELISA) rat specific kits of My BioSource, USA. Briefly, 96-well plates coated with specific antibodies against TG, cholesterol, HDL, LDL, and VLDL which will bind to the TG, cholesterol, HDL, LDL, and VLDL present in the serum and this is detected by a biotin-conjugated antibody. The biotin moiety is subsequently detected, by the addition of streptavidin coupled horseradish peroxidase (HRP). ELISA detection substrate (3, 3', 5, 5'-Tetramethylbenzidine, TMB) was used to visualize HRP enzymatic reaction. TMB was catalyzed by HRP to produce a blue colour product that changed into yellow after adding acidic stop solution. The density of yellow colour is directly proportional to the concentration of TG.

Statistical analysis:
Data were expressed as mean ± SEM. Statistical analysis was conducted using Windows SPSS software version 22, Armonk, NY. To determine the significant difference between different groups ANOVA followed by Tukey's posthoc test was carried out.

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RESULTS AND DISCUSSION

Antihyperlipidemic activity of B. aegyptiaca kernel, flesh and their mixture extracts:

The results of this study clearly showed that, after 6 weeks of STZ injection, the diabetic rats exhibited a highly significant increase in serum TG, LDL, and VLDL levels ($p < 0.001$) in comparison to the control rats. Diabetic rats treated with metformin showed a significant decrease ($p < 0.001$) in the serum TG, LDL, and VLDL levels compared to the nontreated diabetic rats. Similarly, diabetic rats treated with *B. aegyptiaca* kernel, flesh and their mix showed a significant decrease ($p < 0.001$) in the serum TG, LDL, and VLDL levels compared to the nontreated diabetic rats.

On the other hand, the results of this study clearly showed that, after 6 weeks of STZ injection, the diabetic rats exhibited a highly significant decrease in serum HDL level ($p < 0.001$) in comparison to the control rats. Diabetic rats treated with metformin showed a significant increase ($p < 0.001$) in the serum HDL level compared to the nontreated diabetic rats. Similarly, diabetic rats treated with *B. aegyptiaca* kernel, flesh and their mix showed a significant increase ($p < 0.001$) in the serum HDL level compared to the nontreated diabetic rats. The effectiveness of *B. aegyptiaca* kernel, flesh and their mix extracts on serum TG, LDL, and VLDL levels obtained in this study is similar to that of standard antidiabetic drug metformin (Figure 1 a, b, c, d). The hypertriglyceridemia was always accompanied by an increased level of LDL and VLDL and decreased HDL level (Helal *et al.*, 2013). This increase may be due to the inhibition of lipoprotein lipase activity concomitant to hypoinsulinemia (Minnich and Zilversmit, 1989). Similar to this study data several recent studies reported that *B. aegyptiaca* fruit extract significantly decreased TG, LDL and VLDL levels while increased HDL level in STZ-induced diabetic rats (Deib and Ali, 2018; Hassanin *et al.*, 2018). Furthermore, Rashad *et al.* (2017) concluded that in humans the treatment of type-2 diabetic patients with *B. aegyptiaca* capsules for 6 weeks produced a significant reduction in the plasma TG, LDL, and increase the HDL. This could be explained by the elevation in serum leptin, insulin concentration and sensitivity which cause inhibition of cholesterol biosynthesis enzymes and lipolysis (Ghanem *et al.*, 2016; Helal *et al.*, 2013). This could also attribute to *B. aegyptiaca* saponin and diosgenin content (Roman *et al.*, 1995; S. N. Abd El-Rahman and H. Al-ahmari, 2013).

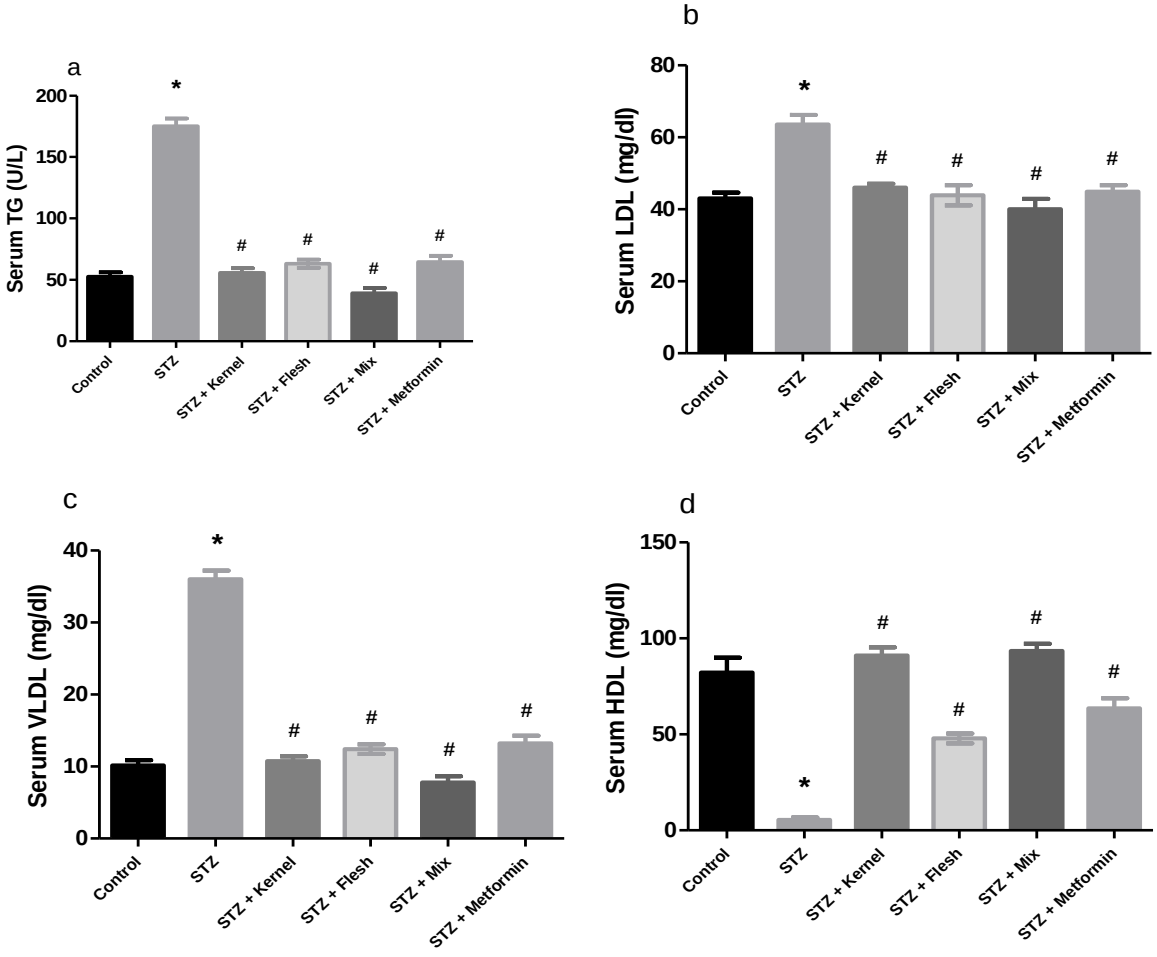

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Figure 1: Effect of metformin, methanolic extract of *B. aegypiaca* kernel, flesh and their mix on STZ-induced changes in serum TG (a), LDL (b), VLDL (c), and HDL (d) measured after 6 weeks of STZ injection. Results are expressed as mean ± SEM (n = 10). * indicates a significant difference compared to the control group at $p \leq 0.05$. # indicates a significant difference compared to the STZ group at $p \leq 0.05$.

B. aegyptiaca kernel, flesh and their mix ameliorated STZ-induced testicular histopathological changes:

Normal control testis showed seminiferous tubules (ST) with regular outlines and full-thickness germ layers. It also showed narrow interstitial spaces that contain Leydig testosterone secreting cells (Figure 2 a). Each seminiferous tubule showed full-thickness germ layers, narrow lumen and sperm tails. The interstitial tissue contains a normal population of Leydig cells (Figure 2 b). In STZ diabetic rats (hyperglycemic group), the testis sections showed shrunken tubules with, irregular outlines, wide lumen and decreased thickness of germ cell layers. Numerous tubules exhibited loss of most germ cell layers appeared empty except of the basal spermatogenic stem cells (Figure 2 c). These sections are also characterized by degenerated Leydig cells (Figure 2 d). In STZ diabetic rats treated with metformin, marked protection against STZ-induced testicular changes was observed. The seminiferous tubules showed regular outlines and full-thickness germ layers. Interstitial spaces are narrow and contain normal population Leydig cells, however, some Leydig cells showed slightly degenerated nuclei near congested blood vessels (Figure 2 e and f).

In STZ diabetic rats treated with *B. aegyptiaca* kernel extract the testis showed preservation of normal seminiferous tubules structure, where each showed the full thickness of germ layer with narrow interstitial spaces that contain Leydig testosterone secreting cells. The lumen also contains mature sperm heads (Figure 2 g and h). In STZ diabetic rats treated with *B. aegyptiaca flesh extract*, the seminiferous tubules showed regular outlines and full-thickness germ layers. However, the interstitial spaces are slightly widened contain congested blood vessels and few Leydig cells (Figure 2 i and j). In STZ diabetic rats treated with kernel/flesh mix extract, the testis showed preservation of most seminiferous tubules. However, few tubules showed degenerated germ cell layers. In addition, the interstitial tissue contains slightly dilated vessels and Leydig cells with dark degenerated nuclei (Figure 2 k and l).

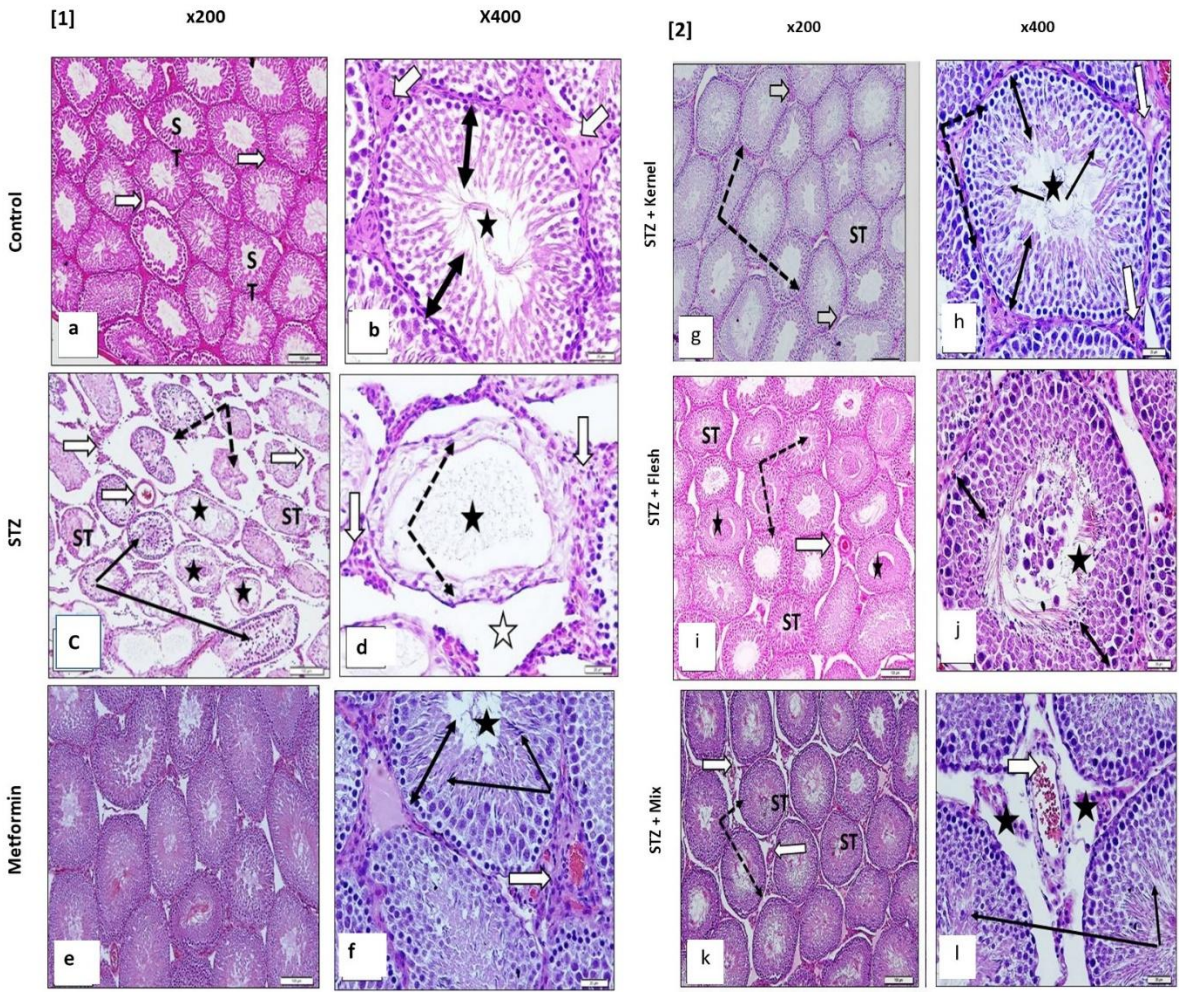

Figure 2: Effect of metformin, methanolic extract of *B. aegypiaca* kernel, flesh and their mix on STZ-induced histopathological changes determined after 6 weeks of STZ injection. Panel 1 contains control (a, b), STZ (c, d), and STZ + metformin (e, f) sections. Panel 2 contains STZ + kernel (g, h), STZ + flesh (I, j), and STZ + mix (k, l) sections. Slides were stained with H & E.

Antioxidant activity of B. aegyptiaca kernel, flesh and their mixture extracts:

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The results of this study clearly showed that, after 6 weeks of STZ injection, the diabetic rats exhibited a highly significant increase in serum MDA level ($p < 0.001$) in comparison to the control rats. Diabetic rats treated with *B. aegyptiaca* flesh extract showed a significant decrease ($p < 0.001$) in the serum MDA level compared to the nontreated diabetic rats. On the other hand, diabetic rats treated with metformin, *B. aegyptiaca* flesh and mix extract showed the non-significant change in the serum MDA level compared to the nontreated diabetic rats (Figure 3 a).
The results of this study clearly showed that, after 6 weeks of STZ injection, the diabetic rats exhibited a significant decrease in serum GSH level ($p < 0.05$) in comparison to the control rats. Diabetic rats treated with metformin showed a significant increase ($p < 0.001$) in the serum GSH level compared to the nontreated diabetic rats. Similarly, diabetic rats treated with *B. aegyptiaca* kernel, flesh and their mix showed a significant increase ($p < 0.001$) in the serum GSH level compared to the nontreated diabetic rats (Figure 3 b).

Amassing data has shown that increased serum glucose has an important role in testicular malfunction pathology via triggering seminiferous tubules necrosis and destruction of spermatogenetic cells, that act as morphological signs of spermatogenesis dysfunction (Cameron *et al.*, 1985; Sisman *et al.*, 2014). Testicular damage caused by hyperglycemia is suspected to result from the induction of oxidative stress (Zha *et al.*, 2018). Oxidative stress causes damage to the gonads in several ways. Production of oxygen free radicals causes germ cells lipid peroxidation and mitochondrial damages, resulting in spermatogenesis and steroidogenesis impairment (Aitken *et al.*, 1993; Diemer *et al.*, 2003). In addition, increased oxygen free radicals production causes DNA degradation and germ cell damage (Rajesh Kumar *et al.*, 2002). Consequently, reducing oxidative stress in diabetic rats is a form of attenuating testicular damage. In this work, endogenous antioxidant molecule, GSH, has been decreased, whereas the marker of lipid peroxidation, MDA, has been substantially increased in diabetic rats. Thus, *B. aegyptiaca* treatment may be contributed to increased levels of antioxidant molecule, GSH and inhibition of membrane lipid peroxidation, MDA and hence protect the testis against hyperglycemia-induced damage. *B. aegyptiaca* extracts may either raise GSH formation or decrease the oxidative stress causing minimal GSH consumption or have both actions (Valko *et al.*, 2007).

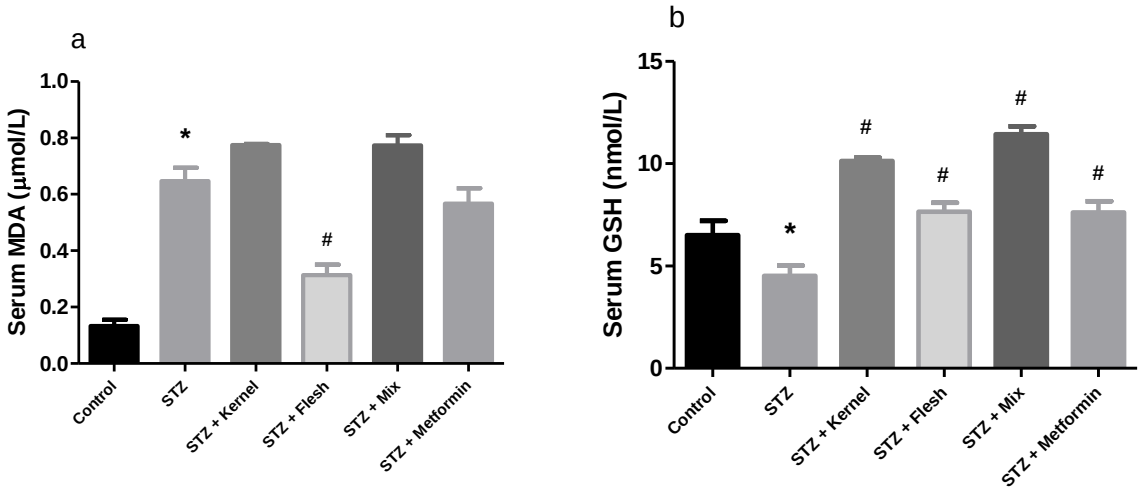

Figure 3: Effect of metformin, methanolic extract of *B. aegypiaca* kernel, flesh and their mix on STZ-induced changes in serum MDA (a), and GSH (b) measured after 6 weeks of STZ injection. Results are expressed as mean ± SEM (n = 10). * indicates significant difference compared to the control group at $p \leq 0.05$. # indicates significant difference compared to the STZ group at $p \leq 0.05$.

CONCLUSION

B. aegyptiaca extract can be used as a complementary therapy for diabetes-associated hyperlipidemia and testicular damage. *B. aegyptiaca* extract augments the body antioxidants besides decreasing the harms associated with the free radicals.

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