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Assessment of the Antidiabetic and Antihyperlipidemic Effects of Aqueous Extract from *Zanthoxylum armatum* DC. in High-Fat Diet and Streptozotocin-Induced Type 2 Diabetic Rats

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Diabetes mellitus refers to a collection of metabolic illnesses that are distinguished by elevated levels of sugar in the blood. This occurs due to inadequate synthesis of insulin, impaired functioning of insulin, or a combination of both factors. Owing to inactive lifestyles and little knowledge about the illness, it has emerged as a noteworthy socioeconomic concern. India has a wealth of historical knowledge in the field of natural medicine. *Zanthoxylum armatum* DC., a plant with a long history of usage in Indian medicine, is the subject of this study. This research sought to investigate whether or not a water-based extract of *Zanthoxylum armatum* DC. had any antidiabetic benefits in Wistar albino rats that had been streptozotocin high-fat diet-induced diabetics. Both those with normal glucose tolerance and those tested for glucose tolerance showed a drop in blood glucose levels after a glucose load. Insulin sensitivity was also shown to be higher in the insulin tolerance test. Blood glucose, triglyceride, total cholesterol, and free fatty acid levels were significantly reduced after 45 days of therapy with the water-based extract of *Z. armatum* DC. Furthermore, there was a documented rise in plasma insulin and liver glycogen concentrations. These findings indicate that the selected plant has properties that may help manage diabetes and reduce high levels of lipids in the blood.

Keywords: Diabetes mellitus; Streptozotocin (STZ); Antihyperlipidemic; high-fat diet; antidiabetic; Zanthoxylum armatum DC.

1. INTRODUCTION

Diabetes mellitus (DM) is a long-term metabolic illness caused by several factors, characterised by consistently high blood sugar levels due to changes in the metabolism of carbohydrates, fats, and proteins, as well as decreased insulin production and function [1]. Insulin insufficiency or insulin resistance are the main factors that lead to diabetes. Diabetes, when it reaches advanced stages, may result in issues that include the eyes, kidneys, blood vessels, and nerves. Diabetes is becoming more widespread, affecting around 422 million people worldwide, primarily in nations with low or middle incomes [2]. Diabetes is directly responsible for causing 1.6 million fatalities per year [3]. Diabetes diagnoses and prevalence have been consistently rising in recent decades. Access to cost-effective medical care, particularly insulin, is crucial for the survival of those suffering from diabetes. There exists a globally accepted objective to cease the increase in diabetes and obesity by the year 2025 [4]. Diabetes is quite prevalent in India, with 21.4% of the population classified as overweight and 4.7% as obese [5]. The standard treatment for Type 2 Diabetes Mellitus (T2DM) generally involves implementing Changes in one's way of living (such as dietary adjustments and increased physical activity), administering oral medications like sulfonylureas, α-glucosidase and biguanides inhibitors, using injectable drugs such as insulin and GLP-1 agonists, considering clinical interventions, and exploring balancing and alternate treatments [6]. Although diabetes is becoming more common, finding a successful therapy is still difficult to achieve. Due to the adverse consequences and constraints of contemporary medicine, there is an increasing worldwide fascination with alternative treatments for Type 2 Diabetes Mellitus [7]. (T2DM). Herbs and phytochemicals are recognised for their potential as antioxidants, hypoglycemic agents, and antihyperlipidemic agents. As documented in Siddha and Ayurvedic medicine, traditional medicinal herbs have been used as antidiabetic medicines and are still being employed [8]. These conventional remedies are often based on sociocultural customs and can potentially alleviate disease-related problems [9]. Numerous conventional remedies include familiar edibles such as vegetables, flowers, fruits, seeds, spices, and herbs. These items not only provide nourishment but also provide health advantages that extend beyond their nutritional content. Moreover, they have proven efficacy in both illness prevention and treatment [10].

Current studies have concentrated on the pharmacological characteristics of plants and plant-derived substances for treating diverse ailments, such as diabetes. The plant species used for this investigation is *Zanthoxylum armatum* DC., a member of the Rutaceae family and frequently referred to as prickly ash or Timur [11]. Traditionally, this plant has been used to treat fever, toothache, and cholera. The seeds of this plant are utilised as spices, while the essential oil is harvested. The plant has demonstrated antifertility, antiseptic, in vitro antidiabetic, disinfectant, and antidiabetic properties [12]. This research aims to assess the antidiabetic properties of the aqueous extract of *Z. armatum* DC. in albino Wistar rats induced with diabetes using a diet high in fat and streptozotocin.

2. MATERIALS AND METHODS

2.1 Collection of Plants

Zanthoxylum armatum DC., a plant species, was obtained from the Palampur region in Himachal Pradesh. The identification and authentication of the subject were conducted at the Institute of Himalayan Bioresource Technology (CSIR) in Himachal Pradesh, India.

2.2 Aqueous Extract Preparation

After precise identification and verification, selected portions of the gathered plant specimens were thoroughly cleansed, dried in the shade, and ground into a coarse powder. A quantity of 200 grammes of this powder was combined with 1,200 millilitres of liquid and heated till the volume decreased to one-third of its original amount. The resulting mix was filtered and subjected to evaporation until it reached a state of full dryness. The viscous extract produced was kept in an airtight container at 4ºC.

2.3 Animals Used in Research

The research included male Wistar rats with a weight range of 160 to 200 grams. The rats were acquired and kept in the PG and Research Department of Biochemistry, Srimad Andavan Arts and Science College (Autonomous), affiliated with Bharathidasan University. The college is in Thiruvanaikovil, Tiruchirappalli, Tamilnadu, India, with a postal code 620005. The rats were given a nutritious pellet meal (Biogen, Bangalore, India) and unlimited access to water. The research received approval from the Institutional Ethical Committee of Srimad Andavan Arts and Science College (SAC/IAEC/BC/2017/May RP-001).

2.4 Induction of Diabetes Mellitus

Diabetes mellitus was produced in rats that had fasted for 12 hours by injecting them intraperitoneally with STZ, which is at a dosage of 40 mg/kg of body weight. The STZ was suspended in a cold citrate buffer with a pH of 4.5 and a concentration of 0.1M. Following the treatment of STZ, the rats were provided with a 10% blood glucose solution for the subsequent 24 hours to avoid low blood sugar levels. No deaths or negative responses were detected. Rats exhibiting moderate diabetic symptoms, characterised by glucose levels above 260 mg/dl, together with the presence of glycosuria and hyperglycemia, were chosen for experimental research after one week of diabetes onset and progression.

2.5 Experimental Design

Group I: Normal Control (NC)
Group II: High Fat Diet and Low Dose STZ treated DC
Group III: STZ treated + AEZA 200mg/kg bw
Group IV: STZ treated + AEZA 400mg/kg bw
Group V: STZ treated + AEZA 800mg/kg bw
Group VI: STZ treated + Metformin treated 100mg/kg bw [13].

Following the 45-day administration period, the rats underwent fasting and were then euthanised by cervical dislocation while under anaesthesia. Blood samples were obtained, and serum was isolated using centrifugation.

2.6 Collection of Blood and Estimation of Biochemical Parameters

Blood samples were collected from the rats' tail veins and analysed for blood sugar levels utilising an Accu-Chek Active™ Test metre. Extra blood samples were collected via the rats' retro-orbital plexus while under mild ether anaesthesia to evaluate plasma profiles. A heparin-containing Eppendorf tube was used to transfer the blood obtained via capillary tubes. After 5 minutes of centrifugation at 5,000 rpm, the plasma was extracted. The lipid profiles were checked, including LDL cholesterol, glycosylated haemoglobin, HDL cholesterol, serum total cholesterol, and triglycerides. A colourimetric method was used to quantify glycosylated haemoglobin, whereas traditional enzymatic methods with an automated analyser were used to evaluate plasma profiles [14].

2.7 Statistical Analysis

The data were presented as mean values, with or without a standard error. The statistical differences were assessed utilising Dunnett's multiple comparisons test after doing a one-way analysis of variances (ANOVA). A p-value below 0.05 was deemed to be statistically significant.

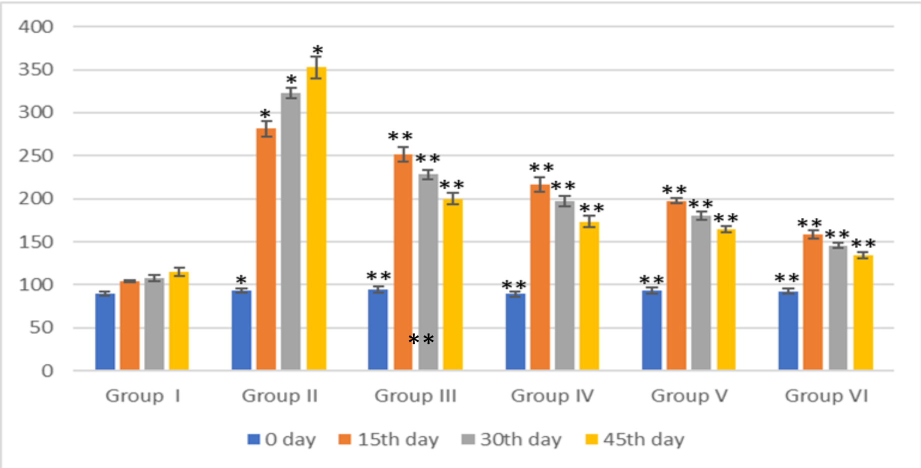
3. RESULTS

3.1 Effect of a Water-Based *Z. armatum* DC. (Stem Bark) Extract on Fasting Blood Glucose Levels in Mice with Type II Diabetes Caused by a High-Fat Diet and STZ

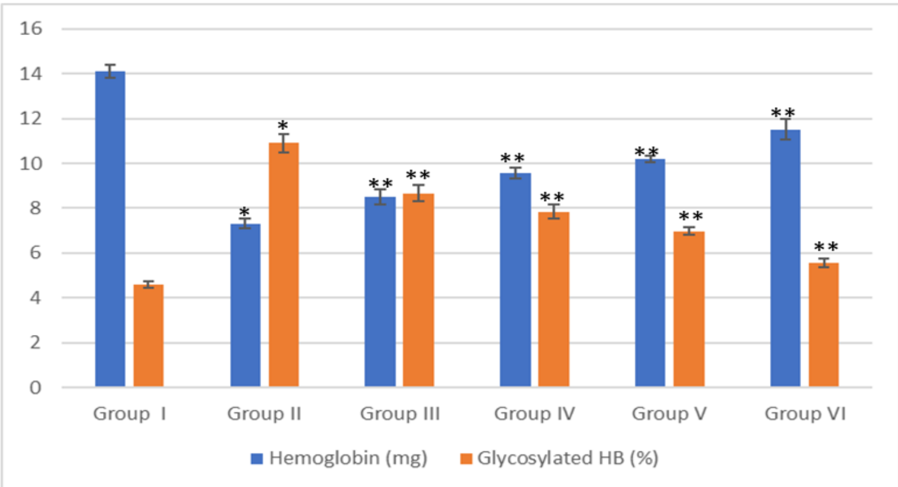
In the study, diabetic rats induced with STZ and fed a high-fat diet were orally administered based on water extraction of *Zanthoxylum armatum* DC (stem bark) at 200, 400, and 800 mg for 45 days. Graph 1 showed greater overnight blood glucose levels in the control group. However, the 400 mg and 800 mg groups exhibited a significant reduction in blood glucose levels following treatment with the AEZA stem bark extract.

3.2 The Effect of a Water-Based Extract from *Z. armatum* DC. (Stem Bark) on Haemoglobin and Glycosylated Haemoglobin (HbA1c) Levels in Rats with Type II Diabetes Induced by a High-Fat Diet and STZ Injection

The treated groups exhibited substantially reduced glycosylated haemoglobin (HbA1c) levels compared to the diabetic control group, as seen in Graph 2.



Graph 1. Level of fasting blood glucose (mg/dl)
The data indicate the average ± standard error (SE) of six rats in each group.
**P < 0.05, when compared to the values of a normal group.*
***P < 0.05, when compared to the values of a group with diabetes.*



Graph 2. Level of hemoglobin and glycosylated hemoglobin
The data indicate the average ± standard error (SE) of six rats in each group.
**P < 0.05, when compared to the values of a normal group.*
***P < 0.05, when compared to the values of a group with diabetes.*

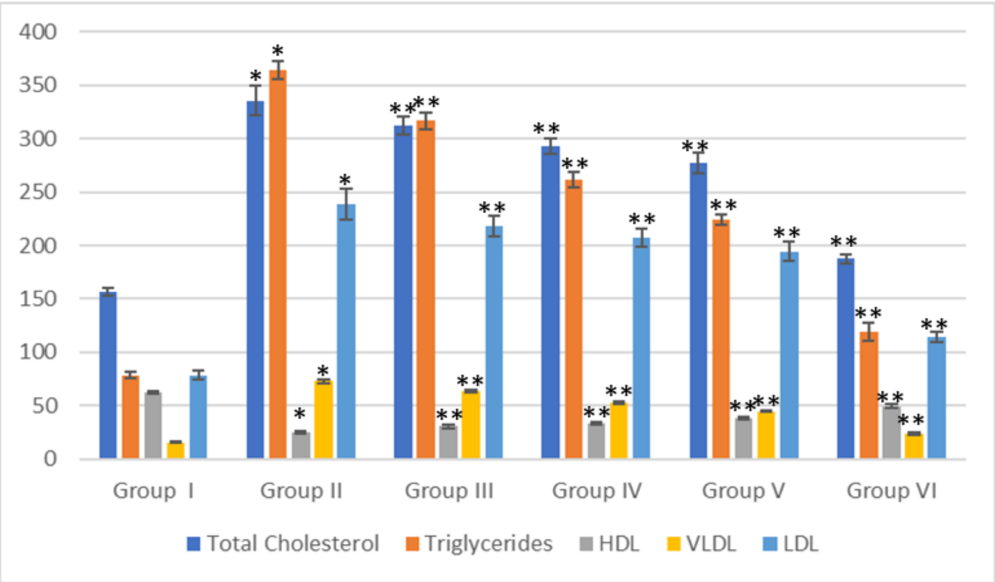
3.3 Effect of a Water-Based *Z. armatum* DC. (Stem Bark) Extract on Glucose and Lipid Profiles in Rats with Type II Diabetes Induced by STZ and a High-Fat Diet

The levels of very low-density lipoprotein (VLDL), low-density lipoprotein (LDL), triglycerides (TG), and total cholesterol were all considerably higher in diabetic control rats compared to normal control animals. In contrast, the group of individuals with diabetes had lower levels of HDL compared to the group of individuals without diabetes. The administration of AEZA at doses of 200, 400, and 800 mg/kg, in combination with Metformin, resulted in a significant decrease in the number of triglycerides (TG), low-density lipoprotein (LDL), and total cholesterol (TC) while simultaneously raising the levels of high-density lipoprotein (HDL) compared to the diabetic control group. The findings are shown in Graph 3.

4. DISCUSSION

T2DM is anticipated to emerge as a significant contributor to both morbidity and death in the 21st century. Prior studies have shown that when rats are fed a diet rich in fat and simultaneously administered a low dosage of streptozotocin (STZ) at 40 mg/kg, they develop insulin resistance, resulting in increased levels of lipids in their bloodstream [15]. Botanical compounds are a prominent reservoir for identifying efficacious remedies for diabetes. Despite the availability of different allopathic treatments, the adverse effects and high expenses associated with them have prompted a significant number of individuals worldwide to pursue alternative medicine. The Ayurvedic and traditional plant-based therapeutic systems are well acknowledged for their extensive historical lineage. High-fat diets cause insulin resistance by promoting the buildup of lipids, such as free fatty acids, triglycerides and their CoA esters, skeletal muscle, adipose tissue, and the liver. This process is accompanied by oxidative stress. The administration of a small amount of STZ leads to the partial death of β-cells, contributing to long-term imbalances in glycemic control [16].

A recent study discovered that the aqueous extract derived from the stem bark of Zanthoxylum armatum DC., which is rich in alkaloids, terpenoids, and flavonoids, successfully decreased glucose levels in rats with streptozotocin-induced diabetes that were given a high-fat diet. Compared to the conventional antidiabetic medication metformin, the extract enhanced glucose absorption in peripheral tissues, perhaps by promoting insulin production through the regeneration of β-cells [17].



Graph 3. Level of lipid parameters

The data indicate the average ± standard error (SE) of six rats in each group.
**P < 0.05, when compared to the values of a normal group.*
***P < 0.05, when compared to the values of a group with diabetes.*

Diabetes causes extended periods of high blood sugar levels, which impact plasma proteins. Glucose interacts with haemoglobin to produce HbA1c. HbA1c values are believed to correlate directly with fasting blood glucose levels. They are considered a dependable indicator of diabetes status because they remain stable throughout the lifetime of red blood cells. HbA1c readings are unaltered by food, exercise, or insulin administration on the test day, making it a reliable indicator for evaluating diabetes treatment [18]. The research found that administering *Z. armatum* DC. Orally administered stem bark extracts to diabetic rats for 45 days substantially reduced HbA1c levels. The observed outcome is most likely a result of increased insulin production, which reduces plasma glucose levels and subsequently lowers HbA1c [19].

Untreated diabetic rats had elevated levels of plasma triacylglycerol, total cholesterol, VLDL cholesterol, and LDL cholesterol, accompanied by reduced HDL cholesterol, suggesting significant dyslipidaemia in their lipid profile. These results are consistent with prior investigations conducted on diabetic models. The heightened functioning of hormone-sensitive lipase causes hypertriglyceridemia in diabetes [20]. This enzyme releases fatty acids from stored triglycerides, resulting in more fatty acids being sent back to the liver to be converted into triglycerides and then released into the bloodstream as very low-density lipoproteins (VLDL). Moreover, the diminished functioning of lipoprotein lipase, an enzyme responsible for breaking down triglycerides in VLDL and chylomicrons, contributes to diabetic hypertriglyceridemia [21].

In a study conducted on rats, it was shown that a water-based extract of *Z. armatum* DC. (stem bark) reduced levels of VLDL, LDL, and triacylglycerols while increasing levels of HDL. The enhancement of the lipid profile is related to improving glycaemic management and promoting increased insulin action by the extract. The decrease in serum triacylglycerols and VLDL might be attributed to the extract's ability to safeguard lipoprotein lipase against lipid peroxidation [22].

The extract from the stem bark of *Z. armatum* DC. Possesses both antidiabetic and antihyperlipidemic properties, potentially reducing low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) levels [23]. Improved blood sugar regulation also positively affects oxidised LDL levels, which are associated with the development of atherosclerosis. The extract had a preventive impact on decreasing HDL levels in STZ-induced mice throughout the study period, indicating possible protective properties against atherosclerosis and cardiovascular disease [24]. The rise in HDL levels after extract therapy may be attributed to the augmentation of lecithin acyltransferase (LCAT) activity. LCAT facilitates the transfer of cholesterol esters inside HDL lipoproteins, enhancing cholesterol transportation from peripheral tissues to the liver. The plant extract has encouraging hypolipidemic and antidiabetic effects in a high-fat diet. Rats with type 2 diabetes caused by STZ

5. CONCLUSION

The current investigation showcased that the aqueous extract of *Zanthoxylum armatum* DC. (stem bark) shown notable effectiveness in reducing blood glucose levels and addressing several diabetes-related issues, demonstrating strong antidiabetic properties. This study provides evidence of this herb's effectiveness in traditional medicine for managing diabetes.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Scheen AJ. Drug treatment of non-insulin-dependent diabetes mellitus in the 1990s. Drugs. 1997;54(3):355-68.
2. Reaven GM, Bernstein R, Davis B, Olefsky JM. Nonketotic diabetes mellitus: insulin

deficiency or insulin resistance?. The American journal of medicine. 1976; 60(1):80-8.
3. Balakumar P, Maung-U K, Jagadeesh G. Prevalence and prevention of cardiovascular disease and diabetes mellitus. Pharmacological research. 2016; 113:600-9.
4. Roth GA, Nguyen G, Forouzanfar MH, Mokdad AH, Naghavi M, Murray CJ. Estimates of global and regional premature cardiovascular mortality in 2025. Circulation. 2015;132(13):1270-82.
5. Jagadesan S, Harish R, Miranda P, Unnikrishnan R, Anjana RM, Mohan V. Prevalence of overweight and obesity among school children and adolescents in Chennai. Indian pediatrics. 2014;51(7): 544-9.
6. Pang GM, Li FX, Yan Y, Zhang Y, Kong LL, Zhu P, Wang KF, Zhang F, Liu B, Lu C. Herbal medicine in the treatment of patients with type 2 diabetes mellitus. Chinese Medical Journal. 2019;132(1):78.
7. Lan J, Zhao Y, Dong F, Yan Z, Zheng W, Fan J, Sun G. Meta-analysis of the effect and safety of berberine in the treatment of type 2 diabetes mellitus, hyperlipemia and hypertension. Journal of ethnopharmacology. 2015;161:69-81.
8. Nabi SA, Kasetti RB, Sirasanagandla S, Tilak TK, Kumar MV, Rao CA. Antidiabetic and antihyperlipidemic activity of Piper longum root aqueous extract in STZ induced diabetic rats. BMC complementary and alternative medicine. 2013;13(1):37.
9. Shakya AK. Medicinal plants: future source of new drugs. International Journal of Herbal Medicine. 2016;4(4):59-64.
10. Kasole R, Martin HD, Kimiywe J. Traditional medicine and its role in the management of diabetes mellitus: patients' and herbalists' perspectives. Evidence-Based Complementary and Alternative Medicine. 2019;2019.
11. Keerthana K, Jothi G. Determination of In vitro antidiabetic potential of Aqueous and Ethanol extracts and isolated fraction of Zanthoxylum armatum DC stem bark. Research Journal of Pharmacy and Technology. 2020;13(8):3681-4.
12. Jothi G, Keerthana K, Sridharan G. Pharmacognostic, physicochemical, and phytochemical studies on stem bark of Zanthoxylum armatum DC. Asian Journal of Pharmaceutical and Clinical Research. 2019;12(2):1-5.
13. Le PM, Benhaddou-Andaloussi A, Elimadi A, Settaf A, Cherrah Y, Haddad PS. The petroleum ether extract of Nigella sativa exerts lipid-lowering and insulin-sensitising actions in the rat. Journal of ethnopharmacology. 2004;94(2-3): 251-9.
14. Maroo J, Vasu VT, Gupta S. Dose dependent hypoglycemic effect of aqueous extract of Enicostemma littorale Blume in alloxan induced diabetic rats. Phytomedicine. 2003;10(2-3):196-9.
15. Srinivasan K, Viswanad B, Asrat L, Kaul CL, Ramarao P. Combination of high-fat diet-fed and low-dose streptozotocin-treated rat: a model for type 2 diabetes and pharmacological screening. Pharmacological research. 2005;52(4): 313-20.
16. Zhang L, Yang J, Chen XQ, Zan K, Wen XD, Chen H, Wang Q, Lai MX. Antidiabetic and antioxidant effects of extracts from Potentilla discolor Bunge on diabetic rats induced by high fat diet and streptozotocin. Journal of Ethnopharmacology. 2010;132 (2):518-24.
17. Jackson RL, Hess RL, England JD. Hemoglobin A1c values in children with overt diabetes maintained in varying degrees of control. Diabetes care. 1979;2 (5):391-5.
18. Zhang JF. Records of bizarre Jurassic brachycerans in the Daohugou biota, China (Diptera, Brachycera, Archisargidae and Rhagionemestriidae). Palaeontology. 2010;53(2):307-17.
19. Ylonen K, Saloranta C, Kronberg-Kippila C, Groop L. Associations of dietary fiber with glucose metabolism in nondiabetic relatives of subjects with type 2 diabetes: the Botnia Dietary Study. Diabetes care. 2003;26(7): 1979.
20. Stefater MA, Inge TH. Bariatric surgery for adolescents with type 2 diabetes: an emerging therapeutic strategy. Current diabetes reports. 2017;17(8):62.
21. Almeida DA, Braga CP, Novelli EL, Fernandes AA. Evaluation of lipid profile and oxidative stress in STZ-induced rats treated with antioxidant vitamin. Brazilian Archives of Biology and Technology. 2012; 55(4):527-36.
22. Mendez JD, Balderas F. Regulation of hyperglycemia and dyslipidemia by exogenous L-arginine in diabetic rats. Biochimie. 2001;83(5):453-8.

23. Bonnefont-Rousselot D, Bastard JP, Jaudon MC, Delattre J. Consequences of the diabetic status on the oxidant/ antioxidant balance. Diabetes and metabolism. 2000;26(3): 163-77.

24. Price KD, Price CS, Reynolds RD. Hyperglycemia-induced ascorbic acid deficiency promotes endothelial dysfunction and the development of atherosclerosis. Atherosclerosis. 2001;158 (1):1-2.

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