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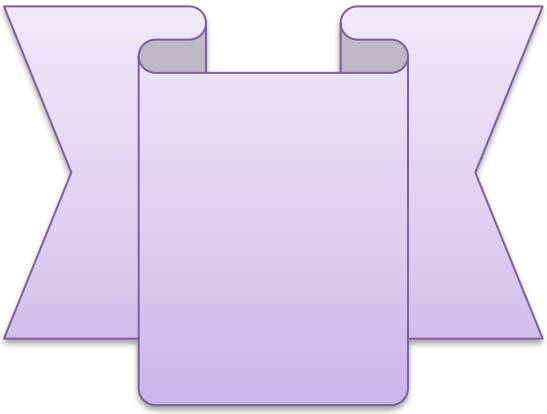

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Original Article

Impact of Antioxidants on Pancreatic B-Cell Damage Caused by Streptozotocin in Adult Male Albino Rats

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ABSTRACT

Aim of the Work: To evaluate the effect of streptozotocin on the endocrinal functions of the pancreatic gland, and the potential protective effects of vitamin-E in adult male albino rats.

Materials and Methods: The Al-Azhar University of Medicine in Cairo's animal house, where this investigation was carried out, between March and May 2022. 50 adult male albino rats were randomly assigned to one of five equal groups: normal control group I, olive oil-treated control group II, vitamin-E-treated control group III, and streptozotocin-treated control group IV and streptozotocin-vitamin E-treated group V.

Results: Streptozotocin-treated group [group IV] was connected to significantly higher serum glucose levels, Malondialdehyde [MDA], interleukin-1b, and interleukin-6 levels and decreased level of serum insulin and glutathione [GSH] in comparison to the normal control groups. This was supported by the islets of Langerhans exhibiting areas of necrosis, vacuolation, and deformation of the pancreatic tissue's typical architecture. Lipid peroxidation was significantly reduced in the group that received vitamin E and streptozotocin. [group V] represented by a significant decrease of serum glucose, MDA, interleukin-1b, and interleukin-6 levels. Histopathological changes were improved after receiving vitamin E.

Conclusion: In adult male albino rats, streptozotocin-induced changes to the pancreas might be prevented by vitamin E.

Keywords: Streptozotocin; Vitamin- E; Insulin; Pancreas; Diabetes.

INTRODUCTION

Streptomyces achromogenes is used to produce streptozotocin [STZ]. It is a DNA alkylating agent and glucosamine-nitrosourea that only enters cells through the glucose transport protein [GLUT2]. The pancreatic islet beta-cells that produce insulin are extremely toxic to the diabetogen streptozotocin. Neuroendocrine tumor cells that are GLUT2 expressing are poisonous to it. For scientific purposes, type I diabetes is induced with streptozotocin. It is applied clinically to treat pancreatic -cell cancer [1].

Vitamin E [x-Tocopherol] is referred to as a membrane antioxidant since it is one of the main fat-soluble antioxidant vitamins found in membrane lipoproteins. Through the scavenging of intermediate peroxyl radicals, it halts the chain reaction of lipid peroxidation [2].

In a dose-dependent way, vitamin E supplements may shield the pancreas, liver, kidney, and other organs against environmental toxins including ozone, chemotherapy, and radiotherapy [3].

Inhibiting platelet aggregation, protecting against polyunsaturated fatty acid oxidation, and supporting neurological processes are all actions of vitamin E [2].

The goal of the current investigation was to determine whether vitamin E would have any protective effects against Streptozotocin-induced pancreatic beta cells damage in adult male albino rats.

PATIENTS AND METHODS

Vitamin-E

A gelatin capsule of vitamin E was obtained from El Kahira Pharmaceutical Company in Cairo, Egypt. Each capsule contained 600 mg vitamin-E which dissolved in olive oil solvent to obtain a concentration of 6000 mg/100 ml [each 1 ml containing 60 mg of vitamin-E]. Each rat was administered vitamin-E [600 mg/kg/day] orally through gastric gavage [4].

Streptozotocin

Streptozotocin [40 mg/kg body weight] was administered intraperitoneally [IP] to each rat in a single dose from Sigma-Aldrich, USA [1].

Using olive oil as a solvent for vitamin-E [Sekem, Cairo, Egypt].

For anesthesia, In Egypt, we bought isoflurine from Nile Pharmaceutical.

Animals

The Al-Azhar Faculty of Medicine's Medical Physiology Department conducted an experimental study in Cairo between March and May of 2022. A local breed of 50 adult male albino rats weighing between 90 and 110 grams served as the study's animal model [average weight: 100 g]. The animals were kept in cages that met environmental standards and were suitable for their needs [40 x 32 x 40 cm for every 5 rats]. The cages also had wide-meshed elevated flooring to prevent coprophagia. In order to give the rats time to acclimatise, they were kept in a room with free access to food and tap water for ten days. Animals were allocated evenly and randomly into 5 groups:

Group I [Negative control Group] Each rat received normal saline intraperitoneally [i.p.], equivalent amounts to STZ-treated group.

Group II [Positive control Group]: For four weeks, each rat got just one oral dose of 0.7 cc of an oily solvent as a carrier for vitamin-E. [1].

Group III [Vitamin-E-treated group]: Throughout the course of four weeks, each rat received vitamin E once daily through a stomach tube at a dose of 600 mg/kg body weight dissolved in olive oil [4].

Group IV [Streptozotocin-treated group]: STZ [40 mg/kg body weight] was injected intraperitoneally [IP] into each rat once. **[1].** After three days, blood glucose levels were checked. Diabetes was defined as a fasting blood glucose level greater than 250 mg/dL in animals, and these animals were used in the experiment.

Group V [**Streptozotocin-Vitamin E-treated group]:** each rat received both streptozotocin and vitamin-E daily for 4 weeks in the same pervious doses.

Blood sampling and biochemical estimation

Blood was obtained from each site after the retro-orbital plexus was punctured with a

capillary tube that had been heparinized and had an internal diameter of 0.75 to 1.0 mm [approximately 3.5 ml of blood total]. Serum was obtained by drawing blood into a graded, dry, clean glass centrifuge tube. It was quickly placed in a centrifuge and spun at 5000 rpm for 15 minutes.

To quantify the serum levels of interleukin -1B, interleukin-6, Malondialdehyde, and glutathione-peroxidase, as well as serum insulin and serum glucose, a little less than half of the supernatant serum was taken out into Eppendorf tubes and kept frozen at -20 °C till the time of analysis.

Histopathological examination

The pancreas was removed for histological research at the end of the fourth week. Quickly removed tissue samples were examined under a light microscope after being stained with hematoxylin and eosin [H and E] [5, 6].

Ethical Approval

Institutional Research Board received a request for approval of the study protocol. [IRB00012367-22-010-005] of Damietta Faculty of Medicine, Al-Azhar University.

Statistical Analysis

The results were gathered, plotted and statistically examined. The mean and Standard Deviation [SD]. Using the Kolmogorov-Smirnov test of normalcy, data were examined for normality. Tukey's post hoc tests and one-way analysis of variance [ANOVA] were carried out for comparison because the results of the Kolmogorov-Smirnov test indicated that the data were normally distributed [parametric data]. When p < [less than] 0.05, the significance level was established. SPSS 22.0 for Windows was used to conduct the statistical analysis.

RESULTS

In groups I, II, III, IV, and V, respectively, the mean and standard deviation of fasting serum glucose levels were 116.170.73, 118.110.65, 110.140.44, 267.935.75, and 149.563.83 mg/dl. Insignificant changes were seen between Groups II and III and Group I. [control group]. Although group V's raised fasting serum glucose was lower after receiving vitamin E treatment compared to the untreated streptozotocin-treated group, it was still substantially higher than that of the control groups I, II, and III. When compared to the control group I, the streptozotocin treatment resulted in a considerable increase in group IV's fasting serum glucose [FSG] levels [Table 1].

In groups I, II, III, IV, and V, respectively, the mean and standard deviation of serum insulin were 2.480.02, 2.880.01, 2.430.05, 1.680.026, and 2.520.04 mIU /dl. Insignificant changes were seen between Groups II and III and Group I. [control group]. While the therapy with vitamin E increased the serum insulin in group V compared to the untreated strepto-zotocin-treated group, the streptozotocin-treated group significantly reduced the levels of blood insulin in group IV compared to control group I [table 1].

The mean ± standard deviation of MDA was 0.42± 0.05, 0.51± 0.07, 0.39± 0.03, 2.09 ± 0.26 and 0.49 ±0.07 nmol/L in groups I, II, III, IV and V respectively. Group II and III showed insignificant changes in respect to the group I [control group]. The blood MDA levels in group IV of the streptozotocin-treated group were significantly higher than those in group I of the control group, whereas group V of the vitamin-E-treated group had their raised MDA levels significantly lower than those in group IV of the streptozotocin-treated group [table 1].

The mean ± standard deviation of serum GSH was 1.37±0.997, 1.29±0.779, 1.46±0.988, 0.57±0.076 and 1.02±0.075 nmol/L in groups I, II, III, IV and V respectively. Group II and III showed insignificant changes in respect to the group I [control group]. While the treatment with Vitamin-E elevated the decreased serum GSH in group V compared to the untreated streptozotocin-treated group, it was still not statistically different from that of the control groups I, II, and III. The serum GSH levels in group IV were significantly lower than those in group I when streptozotocin was used as the treatment [table 2]

The mean ± standard deviation of Interleukin-1B was 22.82 ± 6.04, 20.74 ± 5.05, 19.99 ± 7.07, 92.80 ± 8.29, and 37.90 ± 8.74 pg/ml in groups I, II, III, IV and V respectively. The mean ± standard deviation of Interleukin-6 was 16.42 ± 4.17, 17.22 ± 3.15, 16.33 ± 5.13, 75.12 ± 12.08, and 36.42 ± 12.73 pg/ml in groups I, II, III, IV and V respectively.

Interleukin -1B and 6 in group II and group III did not differ significantly from group I in any way [control group]. In comparison to control group I, interleukin-1B and 6 levels were significantly higher in the streptozotocin-treated groups. However, the levels of interleukin-1B and 6 were significantly lower in the vitamin-E-treated groups, although they were still significantly higher than those of the control groups I, II, and III [table 3].

When the control groups' [groups I, II, and III] pancreatic tissue was examined under a light microscope, it revealed normal pancreatic structure in the form of normal islets of Langerhans enclosed by normal pancreatic acini with normal interlobular connective tissue [figure 1a and 1b].

In the streptozotocin-treated group [group IV], pancreatic slices revealed acini cell degradation, enlargement of the interlobular gaps with blood vessels, and infiltration by inflammatory cells. Islet of Langerhans cells have degraded [figure 2].

Due to the little inflammatory response and slight acinar cell degradation, vitamin-E therapy only partially improved the histological abnormalities. Mild degenerative changes were visible in the islet of Langerhans cells, and the intercellular septa were still spreading [figure 3].

Table [1]: Comparing several study groups' serum glucose, insulin, and HOMA-IR readings

	Control normal [Group I]	Control group received oil [Group II]	Vitamin-E treated group [Group III]	Streptozotocin-treated group [Group IV]	Streptozotocin-Vitamin-E treated group [Group V]
Fasting serum glucose [mg/dl]	116.17±0.73	118.11±0.65*	110.14±0.44*®	267.93±5.75*≠ Ω	149.56±3.83*¶@
Insulin [mIU/ml]	2.48±0.02	2.88±0.01*	2.43±0.05*®	1.68±0.026*≠ Ω	2.52±0.04*¶@
HOMA- IR	0.71	0.83	0.66	1.11	0.93

Number of rats in each group, number of them = 10; ® Groups III and II were contrasted; **@** The comparison between groups V and group III; ¶ Groups V and IV were contrasted; ***** Each group was contrasted with the control group I; **Ω** Group III and Group IV were contrasted.

Table [2]: Different study groups' serum MDA and GSH enzyme concentrations

	Control normal [Group I]	Control group received oil [Group II]	Vitamin-E treated group [Group III]	Streptozotocin-treated group [Group IV]	Streptozotocin-Vitamin-E treated group [Group V]
MDA [nmol/L]	0.42± 0.05	0.51± 0.07*	0.39± 0.03*®	2.09 ± 0.26*≠ Ω	0.49 ±0.0*¶@
GSH [nmol/L]	1.37±0.997	1.29±0.779*	1.46±0.988*®	0.57±0.076*≠ Ω	1.02±0.075*¶@

Number of rats in each group, number of them = 10; ® Groups III and II were contrasted; **@** The comparison between groups V and group III; ¶ Groups V and IV were contrasted; ***** Each group was contrasted with the control group I; **Ω** Group III and Group IV were contrasted.

Table [3]: Serum levels of interleukin-1B and interleukin-6 in the various study groups

	Control normal [Group I]	Control group received oil [Group II]	Vitamin-E treated group [Group III]	Streptozotocin-treated group [Group IV]	Streptozotocin-Vitamin-E treated group [Group V]
Interleukin-1B [pg/ml]	22.82±6.04	20.74±5.05*	19.99±7.07*®	92.80±8.29*≠ Ω	37.90±8.74*¶@
Interleukin-6 [pg/ml]	16.42±4.17	17.22±3.15*	16.33±5.13*®	75.12±12.08*≠ Ω	36.42±12.73*¶@

Number of rats in each group, number of them = 10; ® Groups III and II were contrasted; **@** The comparison between groups V and group III; ¶ Groups V and IV were contrasted; ***** Each group was contrasted with the control group I; **Ω** Group III and Group IV were contrasted.

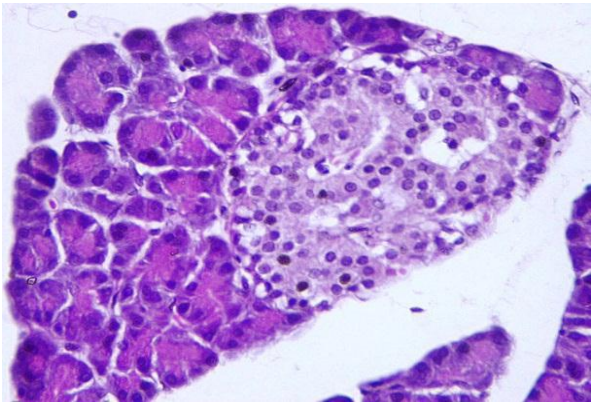

Figure [1a]: The control groups [I, II, and III] showed typical pancreatic architectures, including islets of Langerhans and sparsely spaced acini lobules divided by thin interlobular septa [Hx & E, 400X].

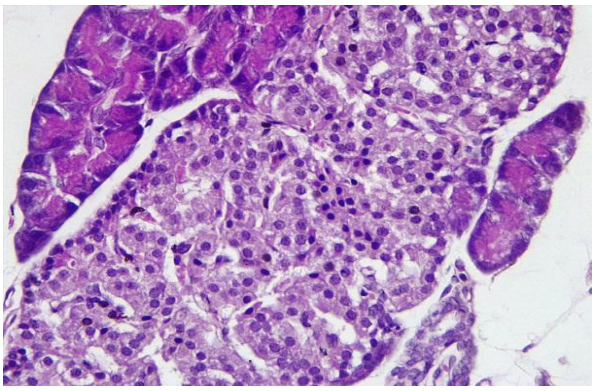

Figure [1b]: control groups [I, II, and III] Another slice showed typical pancreatic features, including thin interlobular septa dividing the tightly packed acini lobules and islets of Langerhans [Hx & E, 400X]

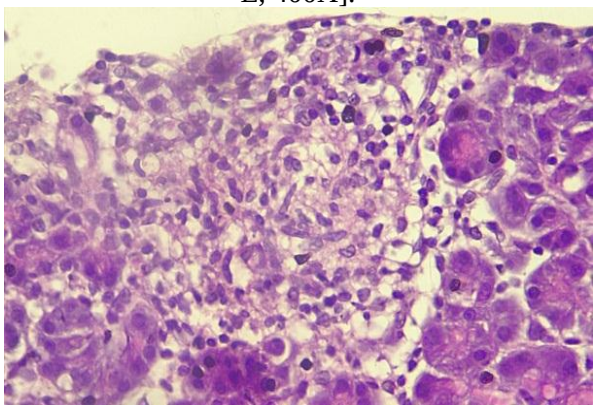

Figure [2]: Group IV displayed acini cell degeneration, enlargement of the interlobular gaps, and inflammatory cell infiltration. [Hx & E, 400X]

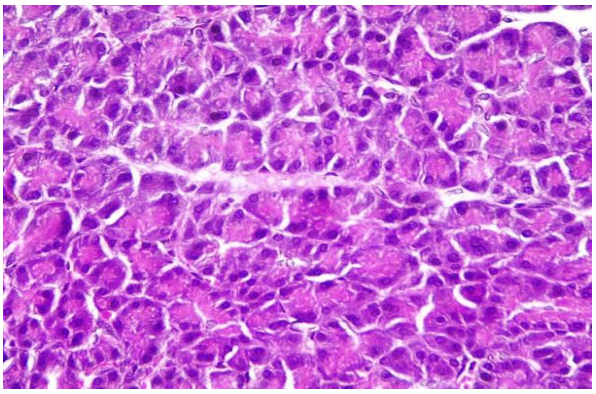

Figure [3]: With minor inflammatory responses, group V demonstrated a partial improvement in the histological abnormalities. Mild degenerative changes were visible in the islet of Langerhans cells, and intercellular septa continued to enlarge. [Hx & E 400X]

DISCUSSION

This study was been establish how damage caused by STZ affected pancreatic beta-cells. A naturally occurring nitrosamide called streptozotocin is used to cause cytotoxicity in pancreatic beta-cells, possibly by producing excessive reactive oxygen species [ROS] and lipid peroxides, interfering with the glucose transporter GLUT2, and damaging DNA either through alkylation or peroxynitrite formation. [7]. Streptozotocin's DNA strand breaking activates poly ADP-ribose polymerase [PARP], which depletes ATP and causes cell death and a reduction in insulin levels [8].

The current study made it clear that streptozotocin significantly changed the pancreatic shape and had negative histological effects on the pancreas of adult albino rats. Alteration of the pancreatic tissue's normal architecture due to areas of hemorrhage, vacuolation, and Langerhans islet necrosis. These findings are in accordance with those of other studies that noted pancreatic vacuolar degeneration following streptozotocin administration [9].

Treatment with vitamin-E in the current study's group V significantly decreased fasting blood glucose when compared to the group IV that did not get any streptozotocin. and significantly increased serum insulin levels. These results might be explained by increased hepatic insulin sensitivity, which would lead to less hepatic glucose generation [10]. Vitamin E may improve insulin sensitivity or release, and it may protect more pancreatic beta-cells by increasing the availability of insulin. By enhancing membrane mobility, vitamin E supplementation may modify insulin receptors in muscle or adipose tissue. Additionally, vitamin E might improve the diaphragm's ability

to absorb glucose [2, 3, 10]. Inflammatory pathways of pancreatic damage enhance oxidant stress indicators, which are important factors [11]. Due to the presence of three types of phytochemicals, including flavonoides [quercetin and kaempferol] and phenolic acids, vitamin E possesses antioxidant properties [2].

Vitamin-E-treated normal rats revealed negligible modifications in MDA and GSH levels in the serum.

The antioxidant that is easily available is GSH. It participates in the catalytic sequences of antioxidant enzymes, acting as an antioxidant either directly or indirectly. Glutathione's thiol group releases the hydrogen atom from free radicals, protecting the cell membrane [11]. A marker of oxidative stress, serum GSH, was reported to be lowered by streptozotocin treatment [12]. The MDA in the untreated streptozotocin rat increased dramatically [13], and the GSH activity significantly decreased in comparison to the control groups [14].

Improvement in pancreatic structure was evident in group V, possibly as a result of vitamin E's antioxidant properties, which reduce oxidative stress and shield pancreatic cells from the creation of free radicals while promoting cellular regeneration and proliferation [15]. The body naturally produces antioxidants that are needed for defense against free radicals and protection from oxidative stress, and vitamin-E was thought to augment these levels [3]. Other harmful stimuli including hypoxia, TNF-, and oxidative stresses like nitric oxide, hydrogen peroxide, and superoxide can also induce apoptosis, which antioxidants can prevent [16]. Antioxidants' therapeutic role in the reduction of inflammatory cytokines in necrotizing tissues [17].

In the current study, group IV demonstrated a considerable rise in pancreatic IL-1B and IL-6 levels, indicating a marked inflammatory cellular infiltration. This increase was caused by the action of streptozotocin, which increased the release of all inflammatory mediators and produced targeted inflammatory responses that released TNF, IL-1, IL-6, and IL-10, indicating that pancreatic acinar cells are the primary source of proinflammatory and anti-inflammatory cytokines [18].

Nuclear factor B, activator protein-1, triggering pancreatitis, and infiltration of inflammatory cells to lymphocytes—all of which play crucial roles in the course of pancreatic damage—are only a few of the transcription factors that streptozotocin regulates [19, 20].

In the current investigation, group V had significantly lower serum levels of IL-1B and IL-6. Inhibiting proinflammatory cytokines including TNF-, IL-1B, IL-6, and IL-1 is made possible by antioxidants [15].

Conclusions: It could be concluded that vitamin E considerably lessened Strepto-zotocin's ability to cause changes in the pancreas of adult male Albino rats.

Connections and Activities of Interest, both Economic and Non-Financial: Nothing

Author contributions: The work was produced with equal contributions from all authors. They planned and carried out the study. They conducted research and wrote the paper.

REFERENCES

1. Sun P, Ortega G, Tan Y, Hua Q, Riederer PF, Deckert J, Schmitt-Böhrer AG. Streptozotocin Impairs Proliferation and Differentiation of Adult Hippocampal Neural Stem Cells *in Vitro*-Correlation With Alterations in the Expression of Proteins Associated With the Insulin System. Front Aging Neurosci. 2018 May 18;10:145. doi: 10.3389/fnagi.2018.00145.
2. Elshafy SA, Abd Elhameed SM, Mohamed HH. The Possible Protective Effect of Vitamin E on Pancreas of Adult Male Albino Rats Treated with Bleomycin Sulfate. Med J Cairo Univ. 2021;89 [1]:363-372.
3. El-Hak HNG, ELaraby EE, Hassan AK, Abbas OA. Study of the toxic effect and safety of vitamin E supplement in male albino rats after 30 days of repeated treatment. Heliyon. 2019 Oct 12;5[10]:e02645. doi: 10.1016/j.heliyon.2019. e02645.
4. Ramah A, EL-shwarby R, MA N, El-shewey EA. The effect of lead toxicity on male albino rats reproduction with ameliorate by vitamin E and pumpkin seeds oil. Benha Veterin Med J. 2015 Mar 1;28[1]:43-52.
5. Masamune A, Watanabe T, Kikuta K, Satoh K, Shimosegawa T. NADPH oxidase plays a crucial role in the activation of pancreatic stellate cells. Am J Physiol Gastrointest Liver Physiol. 2008 Jan;294[1]:G99-G108. doi: 10.1152/ajpgi.00272. 2007.

6. Shalbueva N, Mareninova OA, Gerloff A, Yuan J, Waldron RT, Pandol SJ, Gukovskaya AS. Effects of oxidative alcohol metabolism on the mitochondrial permeability transition pore and necrosis in a mouse model of alcoholic pancreatitis. Gastroenterology. 2013 Feb;144[2]: 437-446.e6. doi: 10.1053/j.gastro.2012.10.037.

7. Balamash KS, Alkreathy HM, Al Gahdali EH, Khoja SO, Ahmad A. Comparative Biochemical and Histopathological Studies on the Efficacy of Metformin and Virgin Olive Oil against Streptozotocin-Induced Diabetes in Sprague-Dawley Rats. J Diabetes Res. 2018 Nov 18;2018:4692197. doi: 10.1155/2018/4692197.

8. Soliman GA. Effect of vitamin c and/or vitamin e on kidney, liver and brain functions of streptozotocin-induced diabetic rats. Egyptian J Hosp Med. 2013;53:799-808. doi: 10.12816/ 0001642.

9. Anastasiou IA, Eleftheriadou I, Tentolouris A, Koliaki C, Kosta OA, Tentolouris N. CDATA[The Effect of Oxidative Stress and Antioxidant Therapies on Pancreatic β-cell Dysfunction: Results from in Vitro and in Vivo Studies. Curr Med Chem. 2021;28[7]:1328-1346. doi: 10.2174/0929867327666200526135642.

10. Rizk AA, Fattah SA, El Sebaie M. Can vitamin E protect the pancreas against ethanol-induced alterations in adult male albino rats? A histomorphometric and immunohistochemical study. Kasr Al Ainy Med J. 2017 Jan 1;23[1]:43. doi: 10.4103/kamj.kamj_6_17.

11. Akbarzadeh A, Norouzian D, Mehrabi MR, Jamshidi Sh, Farhangi A, Verdi AA, Mofidian SM, Rad BL. Induction of diabetes by Streptozotocin in rats. Indian J Clin Biochem. 2007 Sep;22[2]:60-4. doi: 10.1007/BF02913315.

12. Sellamuthu PS, Arulselvan P, Kamalraj S, Fakurazi S, Kandasamy M. Protective nature of mangiferin on oxidative stress and antioxidant status in tissues of streptozotocin-induced diabetic rats. ISRN Pharmacol. 2013 Sep 12; 2013:750109. doi: 10.1155/2013/750109.

13. Khorsand M, Akmali M, Akhzari M. Efficacy of melatonin in restoring the antioxidant status in the lens of diabetic rats induced by streptozotocin. J Diabetes Metab Disord. 2019 Dec 2;18[2]:543-549. doi: 10.1007/s40200-019-00445-8.

14. Serino A, Salazar G. Protective Role of Polyphenols against Vascular Inflammation, Aging and Cardiovascular Disease. Nutrients. 2018 Dec 28;11[1]:53. doi: 10.3390/nu11010053.

15. Kurutas EB. The importance of antioxidants which play the role in cellular response against oxidative/nitrosative stress: current state. Nutr J. 2016 Jul 25;15[1]:71. doi: 10.1186/s12937-016-0186-5.

16. Wallert M, Börmel L, Lorkowski S. Inflammatory Diseases and Vitamin E-What Do We Know and Where Do We Go? Mol Nutr Food Res. 2021 Jan;65[1]:e2000097. doi: 10. 1002/mnfr.202000097.

17. Liu W, Jiang HL, Cai LL, Yan M, Dong SJ, Mao B. Tanreqing Injection Attenuates Lipopoly-saccharide-Induced Airway Inflammation through MAPK/NF-κB Signaling Pathways in Rats Model. Evid Based Complement Alternat Med. 2016;2016:5292346. doi: 10.1155/2016/ 5292346.

18. Mangan MSJ, Olhava EJ, Roush WR, Seidel HM, Glick GD, Latz E. Targeting the NLRP3 inflammasome in inflammatory diseases. Nat Rev Drug Discov. 2018 Sep;17[9]:688. doi: 10.1038/ nrd.2018.149.

19. Ziegler M, Wallert M, Lorkowski S, Peter K. Cardiovascular and Metabolic Protection by Vitamin E: A Matter of Treatment Strategy? Antioxidants [Basel]. 2020 Sep 29;9[10]:935. doi: 10.3390/antiox9100935.

20. Zhu BT. Pathogenic Mechanism of Autoimmune Diabetes Mellitus in Humans: Potential Role of Streptozotocin-Induced Selective Autoimmunity against Human Islet *β*-Cells. Cells. 2022 Jan 31; 11[3]:492. doi: 10.3390/cells11030492.

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