

Effect of Saxagliptin on Oxidative Stress Parameters in Streptozotocin-Induced Diabetic Testicular Damage

Tuba KARAARSLAN¹

¹Department of Biochemistry,
Faculty of Veterinary Medicine,
Atatürk University, Erzurum, Türkiye



Esra AKTAŞ ŞENOCAK²

²Department of Animal Science, Horasan
Vocational College, Atatürk University,
Erzurum, Türkiye



Elif DALKILIÇ KILIÇLIOĞLU¹

¹Department of Biochemistry, Faculty of
Veterinary Medicine, Atatürk University,
Erzurum, Türkiye



ABSTRACT

Objective: The present study aimed to evaluate the effects of the dipeptidyl peptidase-4 (DPP-4) inhibitor saxagliptin on streptozotocin (STZ)-induced testicular injury in rats by assessing biochemical markers of oxidative and nitrosative stress and antioxidant status.

Methods: Male rats were randomly divided into four experimental groups: Control, Sax, Diabetes Mellitus (DM), and DM + Sax. Diabetes was induced by streptozotocin administration. Oxidative and nitrosative stress were assessed by measuring malondialdehyde (MDA), advanced oxidation protein products (AOPP), ischemia-modified albumin (IMA), and nitrate/nitrite levels. Antioxidant status was evaluated by determining reduced glutathione (GSH) and ceruloplasmin levels, as well as the activities of superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) using standard biochemical methods.

Results: Diabetes induction resulted in a significant decrease in SOD and CAT activities, GPx activity, and GSH levels, accompanied by a marked increase in MDA, AOPP, IMA, and nitrate/nitrite concentrations, indicating enhanced oxidative and nitrosative stress in testicular tissue. Treatment with saxagliptin significantly restored SOD, CAT, and GPx activities, increased GSH levels, and normalized ceruloplasmin concentrations, reflecting an improvement in antioxidant defense capacity. Moreover, saxagliptin administration significantly reduced MDA levels, AOPP and IMA levels, and nitrate/nitrite concentrations, demonstrating its effectiveness in attenuating lipid peroxidation, protein oxidation, ischemia-related modification, and nitrosative stress.

Conclusion: Saxagliptin exerts a protective effect against STZ-induced testicular damage by reducing oxidative and nitrosative stress and enhancing the antioxidant defense system. These findings suggest that saxagliptin may play a beneficial role in preserving testicular tissue integrity and cellular function in diabetes-related testicular injury.

Keywords: Antioxidant, diabetes mellitus oxidative stress, saxagliptin, testicular toxicity.

Received 28.01.2026
Accepted 05.03.2026
Publication Date 09.07.2026

Corresponding author: Tuba Karaarslan
E-mail: tuba.dogan@atauni.edu.tr

Cite this article: Karaarslan T, Aktaş Şenocak E, Dalkılıç Kılıçlıoğlu E. Effect of Saxagliptin on Oxidative Stress Parameters in Streptozotocin-Induced Diabetic Testicular Damage. *Pharmata*. 2026;6(2):54-59

INTRODUCTION

Infertility is a significant health concern in both developed and developing countries.¹ The underlying complex mechanisms of male infertility, including congenital genetic defects, oxidative stress, diabetes, environmental factors, and endocrine disruptions, can lead to dysfunctional spermatogenesis and impaired sperm maturation.² Male infertility is among the most common complications of diabetes mellitus.³ The World Health Organization reported that in 2021, 463 million adults were diagnosed with diabetes.⁴



Content of this journal is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

Diabetes mellitus is a long-term condition that profoundly compromises the quality of life for millions worldwide, primarily due to its complications associated with chronic hyperglycemia.⁵ Prolonged exposure to chronic hyperglycemia damages the reproductive system, leading to dysfunction, which results in the production of reactive oxygen species (ROS) and an imbalance between antioxidant and oxidant enzymes in testicular tissue.⁶ Studies have shown that increased oxidative stress and hyperglycemic conditions can cause changes in glucose and lipid metabolism in the testes, leading to reduced sperm motility and count, decreased seminal fluid volume, reduced testosterone levels, and histological alterations in testicular tissue. These changes ultimately result in abnormal sperm production and testicular dysfunction.⁷ Uncontrolled hyperglycemia plays a crucial role in triggering complications associated with diabetes and male infertility.⁸ Therefore, compounds that help regulate blood glucose levels are often the focus of scientific research.⁹

Saxagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor approved by the FDA for the treatment of type 2 diabetes, enhances pancreatic insulin secretion indirectly. Commonly utilized in clinical practice for glycemic management, saxagliptin has also been shown to exert anti-inflammatory properties and positively influence metabolic parameters in experimental models of diabetes.⁸ Furthermore, it has been reported to reduce oxidative stress and promote cellular survival.⁹ The supplementary advantages of saxagliptin may play a role in safeguarding testicular tissue in the context of diabetes, positioning it as a potential therapeutic option for managing both glycemic regulation and diabetes-associated reproductive complications.

Streptozotocin-induced diabetes is a widely employed model in experimental research to explore the impact of diabetes on various organs, including the testes. The observed alterations in the male reproductive system are attributed not to the direct effects of streptozotocin but rather to insulin deficiency. Despite this, research on the protective role of saxagliptin in mitigating testicular damage remains limited. Consequently, this study seeks to evaluate the potential effects of saxagliptin on oxidative stress within the testicular tissue of streptozotocin-induced diabetic rats.

We hypothesized that DPP-4 inhibition with saxagliptin protects diabetic testicular tissue by modulating redox homeostasis—reducing lipid peroxidation (MDA) and nitric oxide—derived reactive species (nitrate/nitrite) while

enhancing endogenous antioxidant capacity (SOD, CAT, GPx activity and GSH levels).

MATERIALS

Chemicals

Saxagliptin (Onglyza 5 mg/kg) was purchased from AstraZeneca Pharmaceuticals Industry and Trade Co. Ltd. (Mt. Vernon, USA). Streptozotocin (STZ) was obtained from Sigma-Aldrich Chemicals (St. Louis, MO, USA). All other chemicals were also procured from Sigma-Aldrich Chemicals (St. Louis, MO, USA).

Experimental Animals

The study utilized twenty-four male Sprague Dawley rats weighing between 250 and 300 grams. The rats were housed under standard laboratory conditions ($24 \pm 2^\circ\text{C}$, $55 \pm 5\%$ humidity, and a 12-hour light/dark cycle). Throughout the experiment, the rats were provided with a balanced diet and ad libitum access to tap water. The experimental protocol was approved in accordance with the procedures established by the Atatürk University Local Ethics Committee for Animal Experiments (Approval Number: July 23, 2024/169).

Experimental Design

The rats were randomly divided into groups, ensuring that the average weights of the groups were similar. Each group consisted of six rats. The experimental protocol was designed based on reference doses from previous studies for saxagliptin and diabetes mellitus.^{10,11}

1. Control Group (C): Physiological saline was administered orally to the rats for 14 days.

2. Saxagliptin Group (Sax): Rats were administered saxagliptin orally at a dose of 10 mg/kg body weight for 14 days.

3. Diabetes Group (DM): Rats received a single intraperitoneal (i.p.) dose of streptozotocin (60 mg/kg). Diabetes was confirmed on day 7 by measuring blood glucose levels. Following confirmation, physiological saline was administered orally for 14 days.

4. Diabetes+Saxagliptin Group (DM+Sax): Rats received a single intraperitoneal (i.p.) dose of streptozotocin (60 mg/kg). After confirming the development of diabetes on day 7, saxagliptin was administered orally via gavage at a dose of 10 mg/kg body weight for 14 days.

Twenty-four hours after the final administration (day 15), the rats were decapitated under mild sevoflurane

anesthesia, and testicular tissues were collected. The collected testicular tissues were stored at -80°C for subsequent biochemical analyses.

Determination of the blood glucose levels

Rats were considered diabetic when their blood glucose values reached ≥ 250 mg/dL based on glucometer measurements obtained on the 7th day following STZ injection. Blood glucose (mg/100 mL) was determined using a Glucometer Elite device (Bayer), employing a glucose oxidase-based assay system.

Measurement of MDA, Nitrite, and Nitrate Levels in Testicular Tissue

The measurement of MDA in testicular tissue was performed using the manual method described by Placer et al.¹². Briefly, MDA levels (nmol/g tissue) were determined by adding thiobarbituric acid to the tissue homogenate, followed by boiling in a water bath. The resulting color was extracted with n-butanol and measured at 532 nm.

The determination of nitrate and nitrite levels in testicular tissue was conducted using the method described by Oehme.¹³ The results were read at 520 nm.

Measurement of GSH and Ceruloplasmin Levels in Testicular Tissue

GSH levels in testicular tissue were measured using the spectrophotometric method.¹⁴ Tissue homogenates were prepared and GSH content was determined based on the reaction with 5,5'-dithiobis-(2-nitrobenzoic acid) (DTNB) at 412 nm. Ceruloplasmin activity was measured spectrophotometrically by assessing the ability to oxidize o-dianisidine at 540 nm in acetate buffer (pH 5.4). Tissue homogenates were prepared, centrifuged and the reaction was carried out at 37°C for 5 min, followed by the addition of sodium azide to terminate the reaction.¹⁵

Measurement of SOD and CAT Activities in Testicular Tissue

Testicular tissues stored at -80°C were ground into a powder using liquid nitrogen, and up to 0.1 g was weighed. The weighed tissues were homogenized in 0.1 mL of phosphate buffer (pH 7.4) at a 1:10 (w/v) ratio using a QIAGEN TissueLyser LT. The homogenates were centrifuged at 11,000 rpm for 30 minutes at 4°C , and the supernatant was collected for the measurement of SOD and CAT activities. SOD activity in testicular tissue was determined according to the method described by Sun et al.¹⁶ and expressed as U/g tissue. CAT activity was measured following the method of Goth¹⁷ and also expressed as U/g tissue.

Statistical Analysis

Statistical significance was determined using one-way analysis of variance (ANOVA), followed by Tukey's multiple range post hoc test for pairwise comparisons, after verifying the normal distribution of the data. Results were expressed as mean $\pm$ standard error of the mean (mean $\pm$ SEM), and a P -value of $<.05$ was considered statistically significant.

Effects of Saxagliptin on MDA, Nitrite, and Nitrate Levels in Testicular Tissue

In this study, the protective effects of saxagliptin on testicular damage induced by DM were investigated, with a focus on its impact on MDA, nitrite, and nitrate levels. Testicular damage caused by diabetes in rats significantly increased MDA, nitrite, and nitrate levels in the DM group compared to control values ($P=.001$) (Figure 1). However, saxagliptin administration was observed to significantly reduce MDA, nitrite, and nitrate levels.

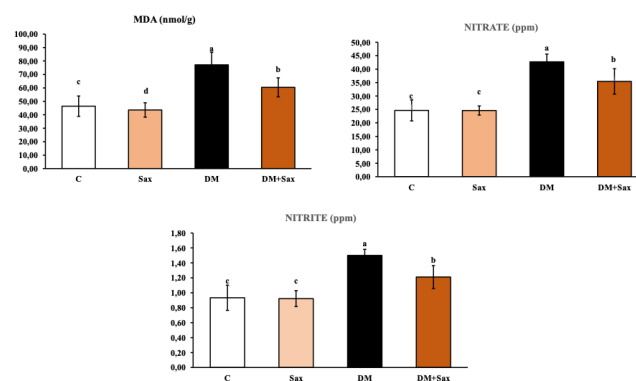


Figure 1. Effects of Sax and STZ applications on MDA, Nitrate and Nitrite levels in rat testicular tissue. Values are given as mean $\pm$ SE. Abbreviations: C, control rats; Sax, saxagliptin; DM, Diabetes Mellitus; DM+Sax. a, b, c, d: Significant differences between means indicated with different letters in the same column.

Effects of Saxagliptin on GSH and Ceruloplasmin Levels in Testicular Tissue

This study evaluated the protective effects of saxagliptin on DM-induced testicular damage through its influence on GSH and ceruloplasmin levels. The findings revealed that DM reduced GSH levels in testicular tissue, but saxagliptin treatment did not lead to significant changes in these levels (Figure 2).

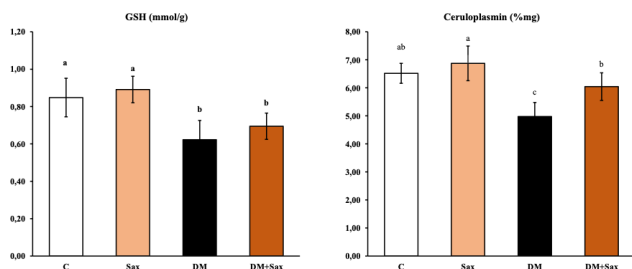


Figure 2. Effects of Sax and STZ applications on GSH and Ceruloplasmin levels in rat testicular tissue. Values are given as mean $\pm$ SE. Abbreviations: C, control rats; Sax, saxagliptin; DM, Diabetes Mellitus; DM+Sax. ^{a, b, c}: Significant differences between means indicated with different letters in the same column.

Effects of Saxagliptin on SOD and CAT Activities in Testicular Tissue

This study investigated the protective effects of saxagliptin against DM-induced testicular damage by evaluating SOD and CAT enzyme levels. It was determined that DM increased oxidative stress in testicular tissue, leading to the suppression of antioxidant defense enzymes such as SOD and CAT. Saxagliptin treatment was observed to significantly enhance the activities of these enzymes (Figure 3).

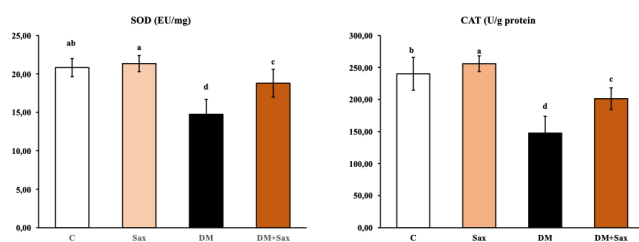


Figure 3. Effects of Sax and STZ applications on SOD and CAT activity in rat testicular tissue. Values are given as mean $\pm$ SE. Abbreviations: C, control rats; Sax, saxagliptin; DM, Diabetes Mellitus; DM+Sax. ^{a, b, c, d}: Significant differences between means indicated with different letters in the same column.

DISCUSSION

This study was conducted to evaluate the protective effects of saxagliptin on diabetes-induced testicular damage. Diabetes not only leads to metabolic disorders but also adversely affects reproductive health, causing

structural and functional damage to testicular tissue.¹⁸ Factors such as hyperglycemia, oxidative stress, inflammation, and microvascular dysfunction associated with diabetes can disrupt the spermatogenesis process in the testes, potentially resulting in fertility loss.^{1,10,19,20} Saxagliptin, as a DPP-4 inhibitor, emerges as a therapeutic option that may offer protective effects against these pathological processes.

The study aimed to assess the protective effects of saxagliptin on markers of oxidative and nitrosative stress in diabetes-induced testicular damage. Hyperglycemia caused by diabetes triggers excessive production of ROS and reactive nitrogen species, leading to oxidative and nitrosative stress.²¹ This process results in various adverse outcomes in testicular tissue, including lipid peroxidation, protein damage, and cellular dysfunction.²² In this study, the levels of MDA, nitrite, and nitrate were evaluated as key biochemical indicators of these pathological processes. The findings suggest that saxagliptin administration reduces MDA levels, indicating its role in protecting against lipid peroxidation and oxidative damage in testicular tissue.

Additionally, the observed modulation of nitrite and nitrate levels implies that saxagliptin may influence nitric oxide pathways, potentially improving vascular and cellular function in testicular tissue. These effects might be attributed to the drug's ability to enhance antioxidant defenses and reduce inflammatory responses.²³

Our study aimed to evaluate the protective effects of saxagliptin on the antioxidant defense system in diabetes-induced testicular damage. Diabetes is associated with increased oxidative stress, which can lead to significant structural and functional impairments in testicular tissue. Antioxidant enzymes such as SOD and CAT, along with GSH and ceruloplasmin, are critical components of cellular defense mechanisms that play a key role in limiting the harmful effects of oxidative stress.²⁴

Saxagliptin, by increasing GLP-1 levels, not only improves glycemic control but also supports antioxidant defense systems in combating oxidative stress.²⁵ In our study, saxagliptin treatment was observed to enhance SOD and CAT enzyme activities, elevate GSH levels, and regulate ceruloplasmin levels, thereby mitigating the adverse effects of diabetes on testicular tissue. These findings suggest that saxagliptin may play a protective role in diabetic testicular damage and help preserve the physiological structure of the tissue through antioxidant mechanisms. The results of our study provide significant

contributions to the literature regarding the effects of saxagliptin on oxidative stress and related mechanisms.

As a DPP-4 inhibitor, saxagliptin effectively contributes to glycemic control and suppresses oxidative stress mechanisms by increasing GLP-1 levels.^{25,26} In this context, our study observed that saxagliptin reduces MDA levels, preventing lipid peroxidation, and modulates nitrite/nitrate levels, alleviating the adverse effects of nitrosative stress. The findings of our study offer important evidence of the protective effects of saxagliptin in diabetes-induced testicular damage and underscore the need for further research to investigate these mechanisms in greater detail.

The main limitation of this study is the lack of histopathological assessment of testicular tissue. Although the biochemical findings suggest that saxagliptin attenuates oxidative and nitrosative stress, we cannot substantiate morphological protection (seminiferous tubule integrity, spermatogenic epithelium layers, and interstitial alterations) without microscopic evaluation. Future studies combining histology with functional reproductive endpoints are warranted.

CONCLUSION

Saxagliptin treatment in STZ-induced diabetic rats was associated with a significant reduction in biochemical markers of oxidative and nitrosative stress (e.g., MDA and nitrate/nitrite) and a partial restoration of antioxidant defense parameters (e.g., SOD, CAT, GPx, GSH, and ceruloplasmin) in testicular tissue. These findings suggest that DPP-4 inhibition may contribute to improving testicular redox balance under diabetic conditions; however, the present conclusions are limited to biochemical outcomes. Because no histopathological evaluation, fertility/functional assessments, or inflammatory marker measurements were performed, structural or reproductive benefits and specific mechanistic pathways cannot be confirmed. Further studies incorporating histological and functional endpoints, direct inflammatory profiling, and detailed molecular analyses—followed by long-term investigations and clinical studies—are needed to clarify the translational relevance of these results.

Ethics Committee Approval: Ethics committee approval was obtained from Atatürk University Local Ethics Committee (Date: July 23, 2024, Number:169)

Peer-review: Externally peer-reviewed.

Author Contributions: Concept -TK; Design-TK, EAS, EDK; Supervision-TK; Resources-TK and EAS; Data Collection and/or Processing-TK EAS; Analysis and/or Interpretation-TK; Literature Search-TK; Writing

Manuscript-TK; Critical Review-EAS.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Use of Artificial Intelligence: Artificial intelligence tools were used only for English language editing (grammar, spelling, and clarity).

REFERENCES

1. Agbaje IM, Rogers DA, McVicar CM, et al. Insulin dependant diabetes mellitus: implications for male reproductive function. *Human Reproduction*. 2007;22(7):1871–1877. [\[CrossRef\]](#)
2. Virtanen HE, Jørgensen N, Toppari J. Semen quality in the 21st century. *Nature Reviews Urol*. 2017;14(2):120–130. [\[CrossRef\]](#)
3. Jin Z, Cao Y, Wen Q, et al. Dapagliflozin ameliorates diabetes-induced spermatogenic dysfunction by modulating the adenosine metabolism along the gut microbiota-testis axis. *Scientific Reports*. 2024;(14):1. [\[CrossRef\]](#)
4. Saeedi P, Petersohn I, Salpea P, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. *Diabetes Res Clin Pract*. 2019;157:107843.
5. Oltulu C, Ersoy O, Akinci M, Cevikelli-Yakut ZA, Dasman M, Bakar E. Effects of sitagliptin and L-theanine combination therapy on testicular tissue in rats with experimental diabetes. *Toxicol Appl Pharmacol*. 2024;492:117119.
6. Kiani M, Soleimani Mehranjan M, Ali Shariatzadeh M. Empagliflozin reduces the adverse effects of diabetes mellitus on testicular tissue in type 2 diabetic Rats: A stereological and biochemical study. *Biochem Pharmacol*. 2024;223:116135.
7. Mao CF, Sudirman S, Lee CC, Tsou D, Kong ZL. Echinacea purpurea Ethanol Extract Improves Male Reproductive Dysfunction with Streptozotocin–Nicotinamide-Induced Diabetic Rats. *Front Vet Sci*. 2021;8:651286.
8. Mega C, Vala H, Rodrigues-Santos P, et al. Sitagliptin prevents aggravation of endocrine and exocrine pancreatic damage in the Zucker Diabetic Fatty rat - Focus on amelioration of metabolic profile and tissue cytoprotective properties. *Diabetol Metab Syndr*. 2014;6(1):1–14. [\[CrossRef\]](#)
9. Cobble ME, Frederick R. Saxagliptin for the treatment of type 2 diabetes mellitus: Assessing cardiovascular data. *Cardiovasc Diabetol*. 2024;(26);11(1):1–8. [\[CrossRef\]](#)
10. Nephani G. Fruktöz ile oluşturulan insülin direnci sıçan modelinde saksagliptin tedavisi. 2024://acikbilim.yok.gov.tr/handle/20.500.12812/146491
11. Apaydin Yildirim B, Dogan T, Aktas Senocak E, Yildirim S, Kordali S, Yildirim F. Punica granatum L. peel extract protects diabetic nephropathy by activating the Nrf-2/HO-1 pathway. *Acta Diabetol*. 2024;26;1–12. [\[CrossRef\]](#)
12. Placer ZA, Cushman LL, Johnson BC. Estimation of product of lipid peroxidation (malonyl dialdehyde) in biochemical systems. *Anal Biochem*. 1966;16(2):359–364. [\[CrossRef\]](#)
13. Oehme f.w. *Analytical toxicology methods manual* 1977;38(9):1453. [\[CrossRef\]](#)
14. Stahl HM, ed. *Analytical Toxicology Methods Manual*. Ames, IA: Iowa State University Press; 1977.
15. Ravin HA. Rapid test for hepatolenticular degeneration. *Lancet*. 1956;270(6925):726–727. [\[CrossRef\]](#)
16. Sun Y, Oberley LW, Li Y. A simple method for clinical assay of superoxide dismutase. *Clin Chem*. 1988;34(3):497–500. [\[CrossRef\]](#)

17. Góth L. A simple method for determination of serum catalase activity and revision of reference range. *Clinica Chimica Acta*. 1991;196(2–3):143–151. [\[CrossRef\]](#)
18. Pavlova E, Ivanov R, Abadjieva D, et al. Evaluation of Rat Testicular Cell Populations in Experimental Condition of Diabetes Induced in Early Postnatal Life. *Cells*. 2025;14(21):1714. <https://www.mdpi.com/20734409/14/21/1714/htm>
19. Kiani M, Soleimani Mehranjani M, Ali Shariatzadeh M. Empagliflozin reduces the adverse effects of diabetes mellitus on testicular tissue in type 2 diabetic Rats: A stereological and biochemical study. *Biochem Pharmacol*. 2024;223(4):116135. [\[CrossRef\]](#)
20. Kucuk Baloglu F, Guldag Tas D, Yilmaz O, Severcan F. The recovery effect of Vitamin C on structural alterations due to Streptozotocin-Induced diabetes in rat testicular tissues. *Spectrochim Acta A Mol Biomol Spectrosc*. 2023;288(6):122149. [\[CrossRef\]](#)
21. Elsherbiny NM, Maysarah NM, El-Sherbiny M, Al-Gayyar MM. Renal protective effects of thymoquinone against sodium nitrite-induced chronic toxicity in rats: Impact on inflammation and apoptosis. *Life Sci*. 2017;180:1–8. [\[CrossRef\]](#)
22. Chilukoti SR, Sahu C, Jena G. Protective role of eugenol against diabetes-induced oxidative stress, DNA damage, and apoptosis in rat testes. *J Biochem Mol Toxicol*. 2024;38(1):e23593. [\[CrossRef\]](#)
23. Owembabazi E, Nkomozepi P, Mbajjorgu EF. Potential role of inducible nitric oxide synthase (iNOS) activity in testicular dysfunction following co-administration of alcohol and combination antiretroviral therapy (cART) in diabetic rats: an immunohistochemistry study. *Toxicol Res*. 2024;40(1):3143. [\[CrossRef\]](#)
24. John Aitken R, Roman SD. Antioxidant Systems and Oxidative Stress in the Testes. *Adv Exp Med Biol*. 2009;636:154–171. [\[CrossRef\]](#)
25. Srour L, Ismail J, Njeim R, Eid AA. Exploring the Evolving Role of SGLT-2 Inhibitors and GLP-1 Receptor Agonists in Managing Cardiovascular Injury Induced by Obesity: *Spotlight on ROS as a Key Mediator*. 2024;207–226. [\[CrossRef\]](#)
26. Fathy MA, Alsemeh AE, Habib MA, et al. Liraglutide ameliorates diabetic-induced testicular dysfunction in male rats: role of GLP-1/Kiss1/GnRH and TGF- β /Smad signaling pathways. *Front Pharmacol*. 2023;14:1224985. [\[CrossRef\]](#)