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Original Research Article

Urolithin A safeguards against diabetes-induced pathospermia and embryotoxicity in rats

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Abstract

Objective: Diabetes mellitus (DM) as a chronic disease can negatively affect male fertility due to endocrine and metabolic pathways disruption. This study was implemented to appraise the possible beneficial effects of urolithin A (UA), a natural polyphenol produced by the gut microbiota, against DM adverse effects on epididymal sperms and pre-implantation embryo development in mature rats.

Materials and Methods: Forty mature male Wistar rats were randomly allocated to five equal groups including non-treated control group, DM group administered with intra-peritoneal streptozotocin (50 mg/kg), and three treated diabetic groups which received 25, 100, and 400 mg/kg of UA for 60 days orally. Thereafter, serum levels of testosterone, follicle-stimulating hormone (FSH), and luteinizing hormone (LH), and testicular total anti-oxidant capacity (TTAC) and malondialdehyde (TMDA), as well as sperm quantity and quality, *in vivo* fertility, and *in vitro* fertilization (IVF) success rate were rigorously assessed.

Results: The UA exerted dose-dependent protective effects against DM-related negative impacts on biochemical (testosterone, FSH, LH, TTAC, and TMDA), spermatological (sperm count, motility, viability, and chromatin and DNA qualities), *in vivo* fertility, and embryological (IVF, and two-cell embryos, morulae, and blastocysts formation rates) parameters.

Conclusion: This study's outcomes spotlighted the promising protective functions of UA in DM-associated male reproductive disorders in rats, owing its weighty anti-oxidative properties.

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Introduction

The prevalence of diabetes mellitus (DM) as a common and chronic metabolic disease has been estimated to be 10.00% of the population, and the number of people with DM is expected to rise to 783 million in 2045 (Graziani et al. 2024; Huang et al. 2024). A growing body of clinical and epidemiological evidence points out that DM is pronouncedly associated with female reproductive disorders, including delayed

menarche, menstrual disorders, hormonal disturbances, polycystic ovarian syndrome, decreased ovarian reserve, and early menopause, all of which negatively affect fertility (Qin et al. 2023). Accordingly, DM has also been deemed a major risk factor for male factor infertility; some degrees of infertility have been found in about half of the male patients with DM (Graziani et al. 2024).

Manifold *in vivo* and *in vitro* studies have illustrated that DM can cause male infertility through multi-layered and multi-faceted pathophysiological mechanisms including endocrine imbalance due to the hypothalamic-pituitary-gonadal axis dysfunction, glucose metabolism disorders, mitochondrial dysfunction, endoplasmic reticulum stress, chronic inflammation, and oxidative stress (OS), leading to testicular dysfunction (Huang et al. 2024; Jiang et al. 2022).

In light of these challenges, steady endeavors have been made by researchers to establish therapeutic strategies to counteract DM-mediated OS through exogenous anti-oxidant supplementation (Shrivastav et al. 2023).

Urolithin A ($C_{13}H_8O_4$; UA), a natural polyphenol produced by gut microbiota from ingested ellagitannins and ellagic acid, has been found to boast anti-oxidant, anti-inflammatory, anti-apoptotic, anti-aging, neuro-protective, nephro-protective, and cardio-protective properties (D'Amico et al. 2021). Empirical evidence has also evinced that UA improves systemic insulin sensitivity in male mice through mitochondrial function and biogenesis promotion (Toney et al. 2019). Correspondingly, it has been reported that UA exerts anti-diabetic and pancreas-protective effects in a murine model of type 2 DM *via* autophagy and AKT/mTOR signaling pathway regulation (Tuohetaerbaike et al. 2020), and cardio-protective activities in a streptozotocin (STZ)-induced rat model of diabetic cardiomyopathy (Savi et al. 2017).

In the wake of this concept, in a rat model of STZ-induced DM, we gauged whether UA oral administration can remediate DM-evoked spermatotoxicity and embryotoxicity.

Materials and Methods

Animals

Forty mature male Wistar rats (weight: 195±20 g; age: 90±10 days) were supplied from the Animal Resource Center, Faculty of Veterinary Medicine, Urmia University, Urmia, Iran. Animal were positioned in a controlled environment having well ventilation (12 hr/12 hr light/dark cycle; temperature: 24 ± 1°C; humidity: 58 ± 2%) with free access to the rodent laboratory chow and tap water. All experimental procedures performed in this study were carried out ethically according to the ethical guidelines of the Animal Research Ethics Board, Faculty of Veterinary Medicine, Urmia University, Urmia, Iran (IR-UU-AEC-3/75).

Experimental protocol

Following two-week acclimation, animals were randomly assigned into five equal groups including non-treated control group, DM group received intra-peritoneal (IP) STZ (Sigma-Aldrich, St. Louis, USA; 50 mg/kg), and three STZ-induced diabetic groups (Sigma-Aldrich; 50 mg/kg) administered with 25, 100, and 400 mg/kg of UA (Sigma-Aldrich) for 60 days orally, (Li et al. 2022; Furman 2021).

In vivo fertility

Three male rats per each experimental group were mated on day 60 with sexually mature females unfamiliar with the males at a ratio of 1:2. The presence of sperm in the vaginal smear was considered a pregnancy initiation. At the end of pregnancy, the pregnancy index (PI: percentage of pregnant females) and fertility index (FI: percentage of males impregnated females) were recorded (Mostahsan et al. 2024).

Sampling

At the end of the experimental period (60 days), following anesthesia induced by IP injection of 40 mg/kg ketamine (Alfasan, Woerden, The Netherlands) and 5 mg/kg xylazine (Alfasan), blood and tissue samples were collected (Valizadeh et al. 2025).

Biochemical assessments

Hormones

The serum levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were determined using rat/mouse enzyme-linked immuno-sorbent assay kits (Monobind Inc., USA) according to the manufacturer's instructions, same as the testosterone hormone (Cosmo Bio Co., Tokyo, Japan).

Testicular malondialdehyde (TMDA) and total anti-oxidant capacity (TTAC)

The TMDA and TTAC levels in homogenized testicular tissues were determined based on Tappel and Zalkin (Tappel and Zalkin 1959), and Katalinic et al. (Katalinic et al. 2005) methods, respectively.

Spermatological examinations

Epididymal sperms concentration was enumerated using Neubauer hemocytometer (Brand™, Berlin, Germany), as detailed previously (Shalizar Jalali et al. 2012).

Rapid progressive forward, slow progressive forward, and circumferential motilities of epididymal sperms were quantified in 10 microscopic fields of view using light microscopy (Model CHT, Olympus Optics Co. Ltd., Tokyo, Japan), (Shalizar Jalali et al. 2015).

Eosin-nigrosin staining was used to compute the percentage of live epididymal sperms under a light microscope (Olympus) at 400X magnification (Figure 1A), (Heydari et al. 2022).

The aniline blue and acridine orange staining techniques were also employed to surveil sperm cells chromatin and DNA qualities, respectively (Figures 1B and 1C), (Azad et al. 2018).

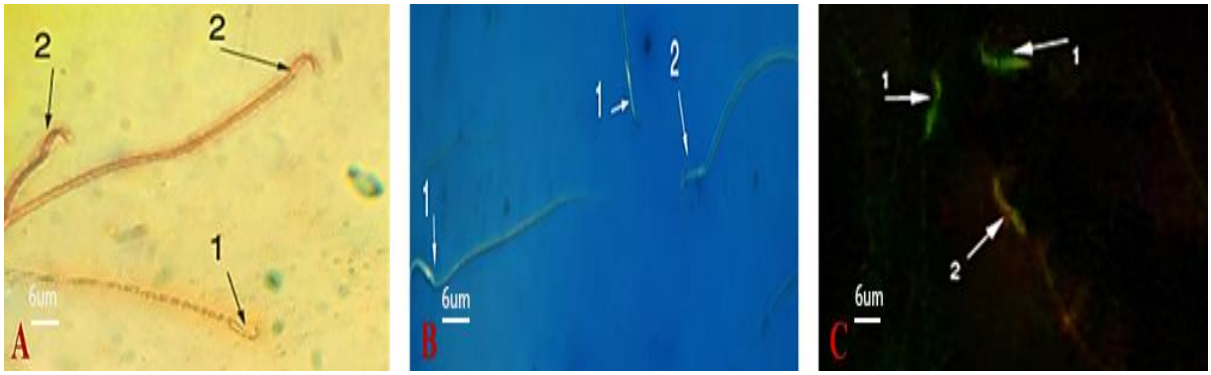

Figure 1. Sperm viability, and chromatin and DNA qualities analyses. A) Eosin-nigrosin staining: Viable sperm (1) with uncolored head and non-viable sperms (2) with pink-red head can be observed (X400); B) Aniline blue staining: Sperm heads with mature nuclear chromatin (1) appear light blue and sperm head containing immature nuclear chromatin (2) is dark blue (X400); C) Acridine orange staining: Sperm cells with normal DNA integrity (1) exhibit green fluorescence and sperm with single-stranded DNA (2) appears orange-red (X1000).

Early embryonic development follow-up

Super-ovulatory regime and ovulated oocytes collection

Sexually mature female Wistar rats (age: 3-4 months) received pregnant mare's serum gonadotropin (15.00 IU, IP; Folligon®, Intervet, Boxmeer, The Netherlands), followed by human chorionic gonadotropin (hCG; 15.00 IU, IP; Intervet) after 48 hr. Afterwards (12 hr post-hCG injection), oviduct ampullae were cautiously excised following animals euthanasia (ketamine-xylazine over-dose) and located into a Petri dish containing 5.00 ml of modified rat 1-cell embryo culture medium (mR1ECM) being supplemented

with 4.00 mg/ml bovine serum albumin (BSA; Sigma-Aldrich). The ovulated oocytes were then dissected out and transferred into fertilization droplets under mineral oil in the mR1ECM + BSA medium (Hosseinchi et al. 2013).

In vitro embryo development

The capacitated sperms (1.00×10^6 per 1.00 ml mR1ECM) were introduced into the fertilization medium. Fertilization rate was determined 10 hr after co-culture *via* observation of male and female pronuclei. Thereafter, zygotes were transferred to the fresh, pre-equilibrated medium and cultured for 120 hr to record two-cell embryos, morulae, and blastocysts formation rates (Figure 2), (Oh et al. 1998).

Statistics

The results are presented as mean ± standard deviation. Differences in quantitative data were analyzed using one-way analysis of variance, followed by Tukey test using SPSS Software (version 22.0; IBM Corp, Armonk, USA), and a $p<0.05$ was considered statistically significant.

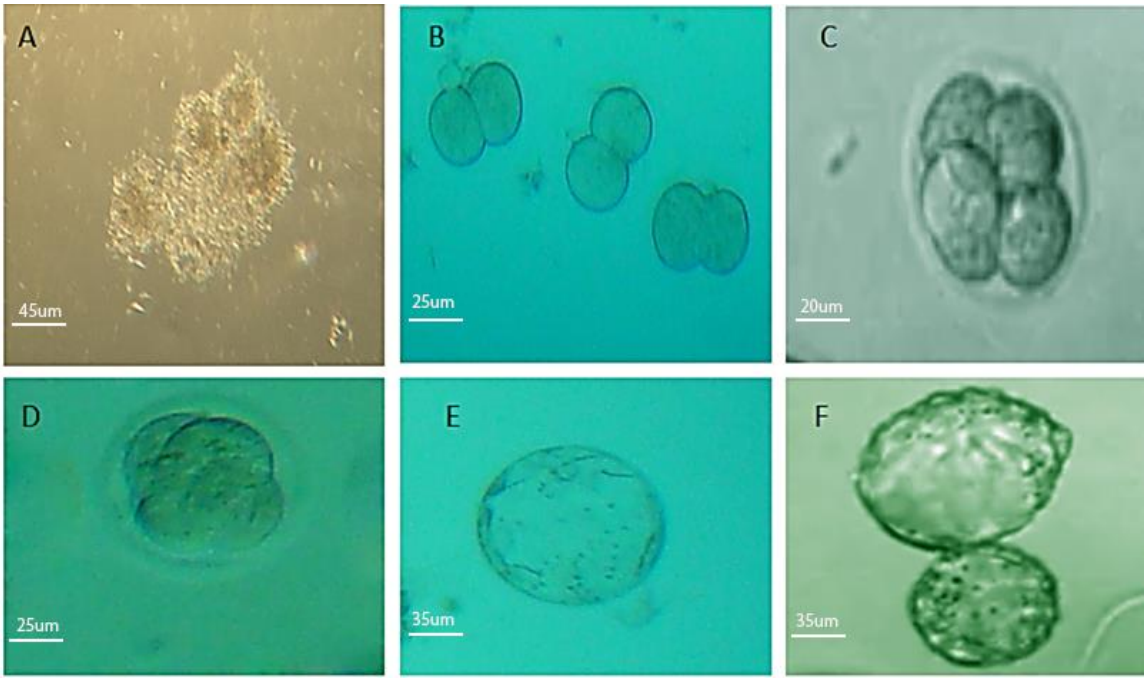

Figure 2. Photomicrographs of *in vitro* embryo development. A) Oocytes; B) Two-cell embryos; C) Four-cell embryo; D) Morula; E) Blastocyst; F) Hatched blastocyst (X200).

Results

Biochemical findings

Hormones

A significant ($p<0.05$) reduction was observed in the testosterone levels of the DM group in comparison with control group. Whereas, pronounced ($p<0.05$) escalations were found in the serums levels of FSH and LH in the DM group rats compared to the controls.

Treatment of diabetic rats with 100 and 400 mg/kg of UA caused marked ($p<0.05$) increases in the testosterone levels, as well as significant ($p<0.05$) reductions in the FSH and LH levels compared to the DM group (Table 1).

Testicular MDA and TAC

As depicted in Table 1, diabetic animals exhibited pronounced ($p<0.05$) elevation in TMDA level, as well as significant ($p<0.05$) TTAC decrease compared to the control group. While, administration of UA at the doses of 100 and 400 mg/kg resulted in statistically significant ($p<0.05$) reductions in TMDA levels, along with increases in TTAC levels compared to the non-treated diabetic rats.

Table 1. Biochemical parameters in different experimental groups.

Groups	TMDA (nmol per mg protein)	TTAC (nmol per mg protein)	Testosterone (ng/ml)	FSH (mIU/ml)	LH (mIU/ml)
Control	11.48±083[a]	18.05±1.66[a]	2.37±0.32[a]	0.23±0.02[a]	0.26±0.01[a]
DM	23.01±1.69[b]	7.49±0.59[b]	1.02±0.42[b]	0.48±0.06[b]	0.51±0.03[b]
DM + UA (25 mg/kg)	20.38±1.31[b]	8.95±0.93[b]	1.18±0.33[b]	0.42±0.03[b]	0.47±0.02[b]
DM + UA (100 mg/kg)	15.02±1.17[c]	11.01±1.05[c]	1.78±0.86[c]	0.33±0.01[c]	0.38±0.04[c]
DM + UA (400 mg/kg)	14.14±0.93[c]	14.22±0.48[c]	1.93±0.14[c]	0.30±0.05[c]	0.36±0.05[c]

DM; Diabetes; UA: Urolithin A; TMDA: Testicular malondialdehyde; TTAC: Testicular total anti-oxidant capacity; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone. [abc] Values with different superscripts within one column differ significantly at $p<0.05$.

Spermatological findings

As shown in Table 2, DM led to marked ($p<0.05$) reductions in epididymal sperms count, motility, and viability, as well as significant ($p<0.05$) escalations in percentages of epididymal sperms with damaged DNA and immature nuclear chromatin compared to the control group. Interestingly, STZ-induced diabetic groups administered with 100 and 400 mg/kg of UA showed pronounced ($p<0.05$) improvements in the epididymal sperms quantity and quality compared to the DM group.

In vivo fertility

The PI and FI showed marked ($p<0.05$) rises in DM group compared to the control group. While, evident improvements in the *in vivo* fertility indices were seen in the STZ-induced diabetic groups administered with 100 and 400 mg/kg of UA ($p<0.05$; Table 3).

Embryological findings

In vitro fertilization, as well as two-cell embryos, morulae, and blastocysts formation rates were reduced significantly ($p<0.05$) in DM group compared to the control group. Whereas, distinct higher percentages of two-cell embryos, morulae, and blastocysts than DM group were found in the STZ-induced diabetic groups administered with 100 and 400 mg/kg of UA ($p<0.05$; Table 3).

Table 2. Spermatological findings in different experimental groups.

Groups	Sperm count (10^6 *per* ml)	Sperm motility (%)	Sperm viability (%)	DNA-damaged Sperms (%)	Immature sperms (%)
Control	39.14±6.11[a]	77.41±3.10[a]	84.37±3.1 4[a]	5.07±0.85[a]	8.70±0.52[a]
DM	22.68±5.09[b]	46.72±6.91[b]	46.33±6.83[b]	21.08±1.66[b]	17.38±1.06[b]
DM + UA (25 mg/kg)	23.31±3.93[b]	51.36±4.66[b]	60.13±4.60[c]	19.53±0.48[b]	15.98±0.97[b]
DM + UA (100 mg/kg)	29.43±2.87[c]	65.57±6.07[c]	63.08±4.33[c]	13.69±0.58[c]	11.12±0.64[c]
DM + UA (400 mg/kg)	34.25±2.19[c]	73.11±3.84[c]	67.86±7.05[c]	10.22±0.95[c]	9.20±0.83[c]

DM; Diabetes; UA: Urolithin A. [abc] Values with different superscripts within one column differ significantly at $p<0.05$.

Table 3. *In vivo* fertility indices, *in vitro* fertilization rate, and two-cell embryos, morulae, and blastocysts percentages in different experimental groups.

Groups	Pregnancy index (%)	Fertility index (%)	*In vitro* fertilization rate (%)	Two-cell embryos (%)	Morulae (%)	Blastocysts (%)
Control	100[a]	100[a]	91.16±7.96[a]	77.59±3.18[a]	72.48±5.93[a]	48.14±3.96[a]
DM	16.66[b]	33.33[b]	58.12±6.33[b]	32.29±5.60[b]	42.68±3.27[b]	21.05±1.55[b]
DM + UA (25 mg/kg)	16.66[b]	33.33[b]	61.59±6.03[b]	44.91±2.83[b]	46.81±3.09[b]	25.19±2.90[b]
DM + UA (100 mg/kg)	66.66[c]	66.66[c]	76.68±3.11[c]	59.20±7.11[c]	57.20±4.01[c]	37.27±2.33[c]
DM + UA (400 mg/kg)	66.66[c]	66.66[c]	78.02±5.43[c]	63.51±4.83[c]	57.84±4.77[c]	39.97±2.40[c]

DM; Diabetes; UA: Urolithin A. [abc] Values with different superscripts within one column differ significantly at $p<0.05$.

Discussion

In the current STZ-induced rat model of DM, epididymal sperms quantity and quality, as well as testicular anti-oxidant defense machinery, androgens synthesis, *in vivo* fertility, and *in vitro* pre-implantation embryonic development were negatively influenced by DM. Consistently, there is an increasing amount of evidence underscoring that DM in men and male animals is linked with impaired spermatogenesis, testicular germ cells degeneration and apoptosis, testicular micro-environment disruption, and lower testosterone synthesis (Barkabi-Zanjani et al. 2020). Accordingly, based on a large number of reports, DM-related OS causes sperm cells dysfunction through affecting material transport, energy flow, and immune defense due to the sperm cell membrane fluidity disruption, leading to male fertility disorders (Huang et al. 2024). Besides, it is well-defined that OS-mediated damages to the sperm DNA integrity surge spermatozoa apoptosis, resulting in reduced sperm quantity and quality (Agarwal et al. 2003). Furthermore, it has been detailed that DM-elicited OS can result in abnormal testicular cells autophagy, leading to Leydig cells malfunction, serum testosterone levels reduction, higher levels of FSH and LH, testicular germ cells proliferation impairment, blood-testis barrier integrity and reconstruction disruption, sperm morphology and motility disorders, and even epididymal dysfunction (Musa et al. 2021; Tian et al. 2020). Also, extensive evidence has delineated that DM-associated sperm glucose metabolism impairment can lead to low fertility and/or infertility (Huang et al. 2024). Additionally, there is an overwhelming body of evidence indicating that DM-connected inflammation can negatively affect male reproductive function through androgen synthesis inhibition, Leydig cells apoptosis induction, and sperm quality reduction (Jiang et al. 2022). Accordingly, it has been reported that elevated FSH in males is associated with sperm abnormalities (Fantus et al. 2023). Relatedly, it has been reported that couples with a diabetic male partner undergoing assisted reproduction techniques show lower pregnancy rates than controls (Lotti and Maggi 2023). Also, it is well-grounded that damaged sperms as a source of reactive oxygen species negatively affect embryo development after *in vitro* fertilization and intra-cytoplasmic sperm injection, leading to fertilization failure or impaired embryo development due to the oxidative damage of the oocytes (Armand et al. 2013).

Alternatively, anti-oxidants have shown promise in managing diabetic complications affecting multiple organ systems regarding anti-oxidant defense systems re-regulation (Dilworth et al. 2024). In concordance with preceding reports emphasizing UA potent therapeutic efficacies (D'Amico et al. 2021; Tuohetaerbaike et al. 2020; Toney et al. 2019; Savi et al. 2017), our findings illustrated that UA shielded against DM-related negative effects on biochemical, spermatological, *in vivo* fertility, and embryological parameters in a dose-dependent manner. In a parallel manner, it has been demonstrated that UA alleviates acetaminophen-induced OS and hepatic necrosis by activating Nrf2/ARE signaling pathway (Gao et al. 2022). Likewise, it was found that UA prevented bone loss in ovariectomy-induced osteoporotic mice (Zhou et al. 2024). Correspondingly, it has also been shown that UA safeguards against cisplatin-induced nephrotoxicity in mice *via* down-regulation of inflammatory responses and oxidative/nitrative stress suppression (Jing et al. 2019). Similarly, UA has also been reported to be protective against human Aβ peptide-induced toxicities, owing its anti-inflammatory and anti-oxidant properties (Kshirsagar et al. 2022).

Altogether, it can be inferred that UA may exert dose-dependent protective activities in DM-associated male reproductive failure in rats regarding its

well-founded anti-oxidative properties, positioning it as an encouraging candidate to manage DM-induced organopathies (Figure 3).

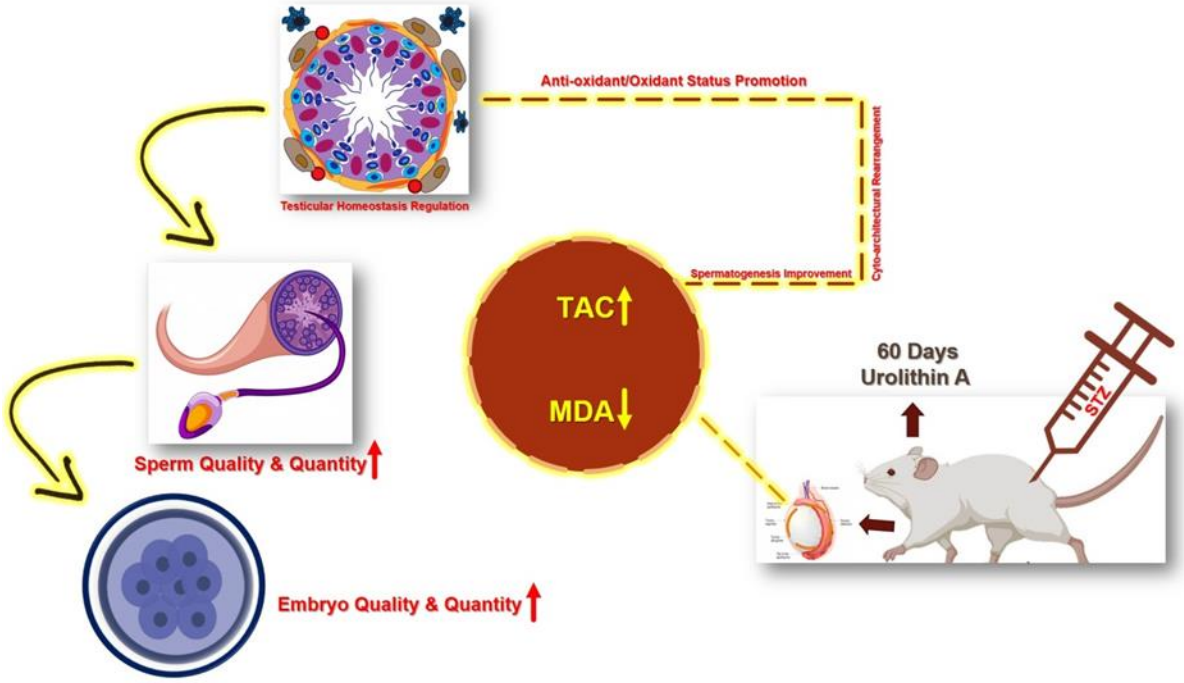

Figure 3. Urolithin A exerts protective activities in diabetes-associated male reproductive failure in rats regarding anti-oxidant defense systems re-regulation. TAC: Total anti-oxidant capacity; MDA: Malondialdehyde; STZ: Streptozotocin.

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Conflicts of interest

There are no competing financial or non-financial interests or personal relationships to declare.

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Ethical Considerations

All experimental procedures performed in this study were carried out ethically according to the ethical guidelines of the Animal Research Ethics Board, Faculty of Veterinary Medicine, Urmia University, Urmia, Iran.

Code of Ethics

IR-UU-AEC-3/75

Authors' Contributions

Reza Haddadi-Salmasi performed the experiments, obtained the data, and prepared the original draft. Ahmad Gharekhani conceptualized the study, analyzed the data, and revised the manuscript. Ali Shalizar-Jalali conceptualized and supervised the study, analyzed the data, revised the manuscript, and helped in data curation. Gholamreza Najafi conceptualized the study, analyzed the data, and revised the manuscript.

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