Impact of Quercetin on Sperm Parameters, Testicular Tissue and Sex Hormone: a Systematic Review

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Abstract

Background and Objective: Quercetin is a polyphenolic flavonoid compound with a potent antioxidant impact, proposed to make a drastic contribution in treating male infertility. The current systematic review aimed to provide an overview of previous studies about quercetin’s impact on male infertility.

Material and Methods: Electronic search with MeSH words including Quercetin, Infertility, Sperm, Testicular tissue, and Sex hormones was accomplished in databases Web of Science, Scopus, Science Direct, Wiley, NCBI, and Google Scholar. Finally, 296 articles were recognized during the primary search. A total of 144 papers, passing the analysis stage containing Identification, Screening, and Eligibility were selected for assessment.

Results: Quercetin prevents damage to the testicular germinal epithelium and facilitates the spermatogenesis process by strengthening the antioxidant system, reducing lipid peroxidation and oxidative stress, preventing the expression of pro-apoptotic genes, increasing testosterone and gonadotropins.

Conclusion: In conclusion, the present review showed that quercetin by its antioxidant impacts, can counteract various toxins that induce oxidative stress in the male reproductive system.

Keywords: Quercetin[MeSH]; Fertility[MeSH]; Spermatogenesis[MeSH]; Testosterone [MeSH]
Introduction

Quercetin as an antioxidant has an anti-cancer and anti-tumor role, also it contributes to the treatment of cardiovascular diseases and male infertility (1-6). Quercetin is a plant molecule that is classified as a flavonol category (polyphenolic flavonoid compound), which it has 2-(3,4-dihydroxy phenyl)-3,5,7-trihydroxychromen-4-one, and C15H10O7 chemical structure (fig. 1). Quercetin is a yellow crystalline powder with 302.236 g/mole molar mass that can be found in tea, red wine, onions, potato, and so on (1, 7, 8, 9).

Quercetin reduces oxidative stress through various mechanisms, which are briefly mentioned. Vitamins, non-enzymatic antioxidants including glutathione (GSH), and enzymatic defense systems including glutathione peroxidase (GPx), superoxide dismutase (SOD), and catalase naturally in cells occupy an axial role to remove excess ROS (CAT, 10). Researchers have shown that quercetin by increasing levels of SOD, CAT, GSH, and GPx can prevent oxidative stress (6, 11-18).

![Figure 1. Chemical structure depiction of Quercetin](image)

Extensive studies have been done on quercetin's role in male infertility, but according to our knowledge, a complete, comprehensive, and specialized review is not reported so far (1, 2). Andres (2018) and Seddiki (2017) in some paragraphs have mentioned this matter (7, 8), Although, in male infertility treatment, these studies are very limited and non-specialized. Based on the above mention, a vast majority of researchers agree on the affirmative role of quercetin rooted in its antioxidant feature.

One of the important factors in infertility is the oxidative stress induction in the male reproductive system, especially sperm. Also, the most common way to deal with oxidative stress is to use antioxidants today. Hence, the present review intended to contribute a summary of prior researches regarding quercetin antioxidant role upon male reproduction disorder carried out.

Materials and Methods

In the present review, multifold electronic searches were accomplished in databases of Science Direct, Web of Science, Scopus, Wiley, NCBI, and Google Scholar. The inclusion criteria...
of this study were contained andrological studies (spermatogenesis, spermiogenesis, and sperm parameters), histological and morphometrical studies (testicular tissue), and endocrinological studies (Gonadal Steroid Hormones) in quercetin users such as human and laboratory animals (1979 to 2020). Firstly, the MeSH words including Quercetin, Infertility, Sperm, Testicular tissue, Oxidative stress, and Sex hormones were applied. In total, 296 articles were found in the primary search. These articles were dwindled to 144 after passing the analysis stage containing Identification, Screening, and Eligibility. This study was performed for 6 months and 23 months. As seen in Figure 2, invalid articles were denied and considered exclusion criteria. They were involved in short comments, duplication, unreliable journals, and no access to full-text (due to global sanctions on Iran for accessing and purchasing some publications; fig. 2). Besides, three researchers independently participated in data extracting and evaluation. Finally, if there was a difference in the special case, it would be referred to the fourth researcher.

Figure 2. PRISMA diagram

**Results**

The results of 66 studies in table 1 present that various toxins can reduce sperm parameters such as motility, viability, count, chromatin quality, morphology, antioxidant enzymes capacity, membrane integrity, fertility rates, and mitochondrial activity. Besides, they can increase oxidative stress and MDA level. Although, quercetin in different doses and treatment time compensate for mentioned disorders and upregulate sperm parameters (Table 1).
The results of 53 studies in table 2 present that various toxins can degenerate seminiferous tubules and reduce antioxidant enzymes capacity, Bcl-XL, StAR, and NF-κB expression, 3β-HSD, 17β-HSD, and NR5A1 mRNA transcripts, MSTD, MTBS, PCNA, testes and epididymis weight, the thickness of the tunica albuginea, tubular diameter, and epithelial height, number of spermatogonia, spermatocytes, and spermatids, spermatogenesis, and also tissue testosterone level. Besides, they can increase Bax, caspase-3, FasL, and HSP expression, MDA levels, necrosis in germinal cells, interstitial edema and congestion, apoptotic index, vacuolization and detachment, DNA fragmentation, the percentages of chromosomal aberrations in primary spermatocytes. Although, quercetin in different doses and treatment time compensate for mentioned disorders and upregulate spermatogenesis (Table 2).

The results of 23 studies in table 3 present that various toxins can reduce levels of testosterone, LH, FSH, estradiol, glutathione peroxidase, and total antioxidant capacity in the blood. Besides, they can increase lipid peroxidation and oxidative stress. Although, quercetin in different doses and treatment time compensate for mentioned disorders in the blood and upregulate gonadotropins (Table 3).

| Species      | Type of response                      | Dose of QE & Duration of treatment | Mot | Abn | Cou | Vi | Other Parameters | T & D | Reference |
|--------------|---------------------------------------|-----------------------------------|-----|-----|-----|----|------------------|-------|-----------|
| Ram          |                                       | 0.1 mM - 5 hours                   | ↑   |     |     |    | ↓ LPO            |       | (40)      |
| Human        |                                       | 100, 500 µM – 1 hour               |     |     |     |    | ↓ DNA damage     |       | (111)     |
| Chicken      |                                       | 0.01, 0.1 and 1 µg/ml - 48 hours   |     |     |     |    | ↓ LDH, ↑ TBARS, ↑ SOD, ↑ GSH, ↑ spermatogonial cell number |       | (11)      |
| Stallion     |                                       | 0.05, 0.1, 0.2 and 0.3 mM – 3, 5 and 21 hours |     |     |     |    | ↓ LPO            |       | (112)     |
| Chicken      |                                       | 0.01-1 µg/ml - 48 hours            | ↑   |     |     |    | ↑ SOD, ↑ GSH, ↑ spermatogonial cell number, ↓ MDA, ↓ LDH |       | (12)      |
| Sprague-Dawley rat |                             | 30, 90, or 270 mg/kg - 3, 7 and 14 days |     |     |     |    | ↑ Weights of testes, epididymis and vas deferens |       | (113)     |
| Wistar Albino rat |                               | 15 mg/kg - 4 weeks                  |     |     |     |    |                  |       | (41)      |
| Wistar rat   |                                       | 100 µM and 200 µM - 3 hours         | ↑   | ↓   | ↑   |    | ↑ SOD, ↑ CAT, ↑ GPx, ↓ MDA |       | (66)      |
| Wistar albino rat |                               | 20 mg kg⁻¹ - 60 days                | ↑   | ↓   | ↑   |    |                  |       | (73)      |
| Wistar rat   |                                       | 10 mg/kg⁻¹ - 5 days                 | ↑   | ↓   | ↑   |    | ↑ MDA, ↓ H₂O₂, ↑ SOD, ↑ CAT, ↑ GPx, ↑ sperm concentration, sperm viability, sperm number and DSP were not significantly different |       | (100)     |
| Human        |                                       | 30 µM – 1 hours                     |     |     |     |    | ↓ LPO, preserving sperm membranes and chromatin texture |       | (19)      |
| Human        |                                       | 50 µM                               |     |     |     |    | ↑ DNA fragmentation and oxidation, no effects on caspase 3 activation |       | (33)      |
| Wistar albino rat |                               | 10 mg/kg – 8 weeks                  | ↑   | ↓   | ↑   |    | ↑ CAT, ↑ ascorbic acid, ↓ MDA, ↑ DSP |       | (100)     |
| Wistar rat   |                                       | 50 mg/kg - 28                       | ↑   | ↓   | ↑   |    |                  |       | (114)     |

Table 1. Evaluation of the effect of quercetin on men and different species of animals (Spermatogenesis)
| Treatment           | Time Duration | Effect | Impact | Reference |
|---------------------|---------------|--------|--------|-----------|
| *Wistar albino* rats | 150 mg/kg – 10 weeks | ↓ | ↑ Sperm motility and epididymal sperm concentration (nonsignificant) | Carbon tetrachloride (68) |
| *Wistar albino* rats | 50 mg/kg – 10 days | ↑ ↓ | ↑ Sperm count (nonsignificant), ↑ thickness of the germinal cell layer | Cisplatin (102) |
| *Pony* stallion     | 0.15 mM       | ↑    | ↓ DNA damage, ↑ zona binding ability | Sex-sorting and cryopreservation (34) |
| *Bull*              | 1, 5, 10, 50, 100 and 200 μmol/l – 2, 6, 12 and 24 hours | ↑ ↑ | ↑ Superoxide production | | |
| *Boar*              | 1, 50 and 100 μM – 3 and 6 hours | ↑ ↑ | ↑ Motility (nonsignificant), ↑ membrane integrity, ↑ IVF embryo development | | |
| *Rabbit*            | 0, 25, 50 and 200 μM – 48, 72 and 95 hours | ↓ LPO, ↓ H2O2 | | | |
| *Wistar albino* rats | 20 mg/kg – 21 days | ↑ ↓ | ↑ Sperm concentration, amelioration in the histological alterations in the seminiferous tubules, germ cells and Leydig cells (not significant) | Docetaxel (42) |
| *Wistar* rat        | 10 mg/kg – 6 weeks | ↑ ↓ ↑ ↑ | ↑ GSH, ↑ SOD, ↑ CAT, ↑ GST, ↓ LPO, ↓ XO | BLCO (15) |
| *Wistar* rat        | 5, 10, 15 and 20 mg/kg – 2 weeks | ↑ ↑ | | | |
| *Wistar* rat        | 25 mg/kg – 3 weeks | ↑ ↑ | ↑ Sialic acid | Cadmium (75) |
| *Albino* rat        | 100 mg/kg – 12 weeks | ↑ ↓ ↑ ↑ | | ZnONPs (76) |
| *Sprague-Dawley* rat| 50 mg/kg – 70 days | ↑ ↓ ↑ | | Fenitrothion (84) |
| *Wistar* rat        | 10 mg/kg – 16 days | ↑ ↓ ↑ ↑ | ↑ DSP | Atrazine (103) |
| *Wistar* rat        | 90 mg/kg – 15 days (pretreatment) | ↑ ↑ | | DEHP (117) |
| *Sprague-Dawley* rat| 50 mg/kg – 49 days | ↑ DSP, ↓ DNA damage, ↑ diameter of epididymis | | | |
| *Human*             | 30 mM – 60 and 180 min | ↑ | improvement in the number of intact acrosomes, ↓ ROS (not significant) | Cotinine (43) |
| *Bovine*            | 7.5, 25, 50 and 100 μmol/l – 2 and 6 hours | ↑ | ↑ ROS & superoxide Concentration, ↑ SOD, ↑ GSH, ↑ CAT, ↑ GPs, ↓ MDA, ↓ LPO | Ferrous ascorbate (16) |
| *Stallion*          | 0.1, 0.2, and 0.3 mM | ↑ | At 0.1 mM did not have any significant effect on sperm viability, abnormality, or MDA. This parameters were adversely affected by higher concentrations | Cryopreservation (55) |
| *Human*             | 30, 50 and 100 μM – 1 hour | ↓ LPO, ↓ acrosome reacted sperm and broken plasma membrane | | TBHP (56) |
| *NMRI mice*         | 75 mg/kg – 42 days | ↑ ↓ ↑ | | NITiO2 (118) |
| *Wistar* rat        | 10 and 20 mg/kg – 52 days | ↑ ↓ ↑ | | Manganese (92) |
| *Wistar albino* rats| 25 and 50 mg/kg – 5 weeks | ↑ ↑ ↑ | | Streptozotocin (99) |
| *Wistar albino* rats| 20 mg/kg – 4 weeks | ↑ ↓ ↑ ↑ | ↑ RPFM | Cadmium chloride (81) |
| Species | Concentration | Duration | Parameters | Treatments |
|---------|---------------|----------|------------|------------|
| Equine  | 0.25, 0.5, 0.75 and 1 mM | | Did not affect the seminal parameters analyzed (Mot, Via, DFI, …) | Cryopreservation [119] |
| Albino rat | 50 mg/kg – 4 weeks | ↑ ↓ ↑ | ↑ Spermatogenesis | Lead acetate [44] |
| Ram     | 5 μg/ml | ↑ ↑ | ↓ MDA (not significant) | Cryopreservation [120] |
| Goat    | 10 and 20 μM | ↑ ↑ | ↓ MDA, ↑ progressive motility | Cryopreservation [36] |
| Mice    | 10, 50 and 100 μg/ml | ↑ | ↑ Fertilization rates, ↑ mitochondrial Activity, ↑ Protein tyrosine phosphorylation, birth rates were similar with fresh sperm | Cryopreservation [21] |
| Mice    | 10 mg/kg – 6 weeks | ↑ ↓ ↑ ↑ | | BPA [106] |
| Wistar albino rat | 80 mg/kg - 2 weeks | ↑ ↓ | ↑ | Doxorubicin [121] |
| Albino rat | 10 and 50 mg/kg - 21 days | ↓ | ↑ Live –Dead ratio | Atrazine [96] |
| Wistar rat | 100 mg/kg – 45 days | ↑ ↓ ↑ | | Cypermethrin and Deltamethrin [64] |
| Wistar rat | 20 mg/kg – 14 days | | ↑ Motility (not significant), ↑ acrosome reaction, ↑ GST, ↑ GPX, ↑ GSH, ↓ MDA, ↑ SOD | Sulphasafazine [17] |
| Rabbit  | 30 mg/kg - 8 weeks | ↑ ↓ | ↑ Progressive motility, ↑ VCL, VSL, and VAP ↑ Via (not significant), ↑ sperm concentration, ↑ sperm mitochondrial Potential, ↓ MDA | Heat stress [2] |
| Goat    | 10 μM – 4, 8 and 12 hours | ↑ | ↑ ↓ MDA, ↑ ROS, ↑ membrane integrity, ↑ mitochondria activity | Cadmium chloride [3] |
| NMRI mice | 50 mg/kg – 7 days | ↑ ↓ ↑ | ↑ DSP | Dexamethasone [97] |
| Albino rat | 50 mg/kg – 4 weeks | ↑ ↓ ↑ | | Cadmium chloride [101] |
| Wistar albino rat | 50 mg/Kg - 4 weeks | ↑ | ↑ Progressive motility | L-NAME [91] |
| Rooster | 20, 40 and 80 μM – 48 hours | ↑ | ↑ ↓ MDA, ↑ SOD, ↓ NO, ↓ HPO, ↑ plasma membrane integrity | H2O2 [18] |
| Buffalo bull | 50, 100, 150 and 200 μM | ↓ | ↑ Progressive motility, ↑ plasma membrane integrity, ↑ supra vital plasma membrane integrity, ↑ acrosome integrity, ↑ DNA integrity, ↑ in vivo fertility | Cryopreservation [39] |
| Sprague-Dawley rat | 10, 25 and 50 mg/kg – 28 days | ↑ ↓ ↑ | ↑ HOS tail coiled sperm percentage, ↓ DFI, ↑ SOD, ↑ CAT, ↑ GPX, ↓ NF-κβ and TNF-α | STZ-nicotinamide [4] |
| Human   | 10 μmol – 2 hours | | ↑ Progressive motility, ↓ H2O2, ↓ sperm mtDNA damage, ↑ cytochrome B, ↑ NADH 5, up regulate hyperactivation and acrosome reaction | Leukocytospermia [109] |
| Rabbit  | 30 mg/kg – 60 days | ↑ | ↑ ↑ Progressive motility ↑ concentration, ↑ VCL , ↑ VSL, ↑ VAP, ↑ mitochondrial potential, ↑ acrosome integrity | Heat stress [22] |
| Boar    | 5, 10, 25 and 50 μM – 24, 48 and 72 hours | ↑ | | |
Table 2. Evaluation of the effect of quercetin on men and different species of animals (testicular tissue)

| Species | Dose of QE & Duration of treatment | Type of Response | T & D | Oxidative stress & Apoptosis | Histology, Testicular biochemistry & PCR | Reference |
|---------|-----------------------------------|-----------------|------|------------------------------|----------------------------------------|-----------|
| ICR mice | 75 mg/kg - 2 weeks | Cadmium | ↓ AP, ↓ OS | ↓ MDA, ↓ H2O2, ↑ SOD, ↑ GPx, ↑ GSH, downregulated of Bax expression, decreased expression of caspase-3 and upregulated Bcl-XL expression | (72) |
| Albino rat | 90 mg/kg - 8 weeks | BPA | ↓ OS | ↑ Glutathione reductase, ↑ sperm concentration, ↑ percentage of normal sperm forms, ↑ serum testosterone | (105) |
| Mice | 75 mg/kg – 3 days | PNMC | ↓ AP, ↓ OS | ↓ H2O2, ↓ OH, ↓ MDA, ↑ GSH, ↑ SOD, ↑ GHSPx, ↓ Bax, ↑ Bcl-XL, ↓ caspase-3 activity, ↓ damage to the seminiferous tubules, ↓ atrophy | (71) |
| ICR mice | 75 mg/kg – 6 weeks | PNP | ↓ AP, ↓ OS | ↓ MDA, ↓ hydroxyl radical, ↑ SOD, ↑ GHSPx, ↓ caspase-3 activity, ↓ Bax, ↑ Bcl-xl | (79) |
| Wistar albino rats | 150 mg/kg - 10 weeks | Carbon tetrachloride | ↓ AP, ↓ OS | ↑ Tests weight, ↓ MDA, ↑ GHSPx and CAT (nonsignificant), ↑ diameter of seminiferous tubules, ↓ atrophy in seminiferous tubules, ↓ necrosis in germinal cells, ↓ interstitial oedema and congestion, ↓ spermatogenic arrest | (68) |
| Wistar rat | 50 mg/kg - 28 days | LTC | ↓ OS | ↑ Tests weight (nonsignificant), ↓ MDA, ↑ GSH, ↑ SOD, ↑ GPX, ↑ CAT, ↑ GST, ↓ interstitial oedema and congestion | (114) |
| Albino rat | 50 mg/kg – 10 days | Letrozole | ↓ OS | ↑ Body weight, ↑ testicular weight, ↑ NO, ↑ GHSPx, ↓ MDA, ↓ normal appearance of testicular tissue | (124) |
| Wistar albino rat | 270 mg/kg - 1 - 8 weeks | Ethanol | ↓ OS | ↑ SOD, ↑ GHSPx, ↑ CAT, ↓ NO, ↓ MDA | (125) |
| Albino rat | 15 mg/kg – 30 | Estradiol-3- | ↓ AP, ↓ | ↑ Tests weight, ↑ spermatoocyte, ↑ round spermatid | (126) |
Impact of Quercetin on Sperm parameters, Testicular Tissue and Sex Hormone

| Treatment Group | Days | Compound | Effect on Sperm parameters | Effect on Testicular Tissue | Effect on Sex Hormone |
|-----------------|------|----------|----------------------------|---------------------------|----------------------|
| Wistar albino rats | 20 mg/kg - 21 days | Docetaxel | ↓ LPO, ↑ TBARS, ↑ SOD, ↑ CAT, ↑ GPX, ↑ GSH, ↑ testes weight and epididymis | ↑ Thickness of the tunica albuginea, ↓ interstitial space, ↑ number of spermatogonia, spermatocytes, and spermatids, ↑ CAT, ↑ SOD & POD, ↑ GSR, ↓ TBARS, ↓ plasma and intra-testicular testosterone | ↑ Testis weight (nonsignificant), ↑ number of primary spermatocytes, spermatids and Spermatozoa |
| Sprague-Dawley rats | 50 mg/kg - 49 days | Sodium arsenite | ↓ OS | ↑ Spermatogenesis, thickness, ↑ seminiferous epithelium, ↑ thickness of the tunica albuginea, ↓ interstitial space, ↑ number of spermatogonia, spermatocytes, and spermatids, ↑ CAT, ↓ TBARS | ↑ Testis weight (nonsignificant), ↑ number of primary spermatocytes, spermatids and Spermatozoa |
| Albino rats | 50 mg/kg - 21 days (pre-treatment) | Lead nitrate | ↓ OS | ↑ Numbers of spermatozoa, partial recovery in the germinal epithelium, improvement early spermatid with acrosomal formation, well developed Golgi apparatus and peripheral arrangement of mitochondria | ↑ Testis weight (nonsignificant), ↑ number of primary spermatocytes, spermatids and Spermatozoa |
| Wistar rats | 5, 10, 15 and 20 mg/kg - 2 weeks | BLCO | ↓ caspase 3, ↓ FasL, ↓ HSP, ↑ STAR, ↑ NF-κB and ↓ Clusterin (to near control level) | ↑ Numbers of spermatozoa, partial recovery in the germinal epithelium, improvement early spermatid with acrosomal formation, well developed Golgi apparatus and peripheral arrangement of mitochondria | ↑ Testis weight (nonsignificant), ↑ number of primary spermatocytes, spermatids and Spermatozoa |
| Wistar rats | 25 mg/kg - 3 weeks (pre-treatment) | Cadmium | ↓ OS | ↑ GSH, ↑ GPx, ↑ GST, ↑ CAT, ↑ SOD, ↑ cholesterol | ↑ Numbers of spermatozoa, partial recovery in the germinal epithelium, improvement early spermatid with acrosomal formation, well developed Golgi apparatus and peripheral arrangement of mitochondria |
| Albino rats | 100 mg/kg - 12 weeks | ZnONPs | ↓ OS | ↑ GSH, ↑ GPx, ↑ CAT, ↑ SOD, ↓ MDA, ↑ CAT and SOD mRNA transcripts, ↑ serum testosterone, ↑ 3β-HSD, 17β-HSD and NR5A1 mRNA transcripts, ↑ intact seminiferous tubules and regular basement membrane and normal spermatocytes and spermatids | ↑ Numbers of spermatozoa, partial recovery in the germinal epithelium, improvement early spermatid with acrosomal formation, well developed Golgi apparatus and peripheral arrangement of mitochondria |
| Sprague-Dawley rats | 50 mg/kg - 70 days | Fenitrothion | ↓ OS | ↑ Steroidogenic genes (3β-HSD6, 17β-HSD3 and Nr5A1), ↑ CAT and SOD mRNA levels, ↓ edema in the interstitial tissue | ↑ Numbers of spermatozoa, partial recovery in the germinal epithelium, improvement early spermatid with acrosomal formation, well developed Golgi apparatus and peripheral arrangement of mitochondria |
| Wistar rats | 10 mg/kg - 16 days | Atrazine | ↓ OS | ↓ MDA, ↑ SOD, ↓ LDH, ↑ 3 β-HSD and 17 β-HSD | ↑ Numbers of spermatozoa, partial recovery in the germinal epithelium, improvement early spermatid with acrosomal formation, well developed Golgi apparatus and peripheral arrangement of mitochondria |
| Wistar rats | 90 mg/kg - 15 days (Pre-treatment) | DEHP | ↓ OS | ↑ Relative testes Weight, ↑ DSP, ↑ LPO, ↑ SOD, ↑ GSH, ↑ CAT, amelioration of LDH-X activity | ↑ Numbers of spermatozoa, partial recovery in the germinal epithelium, improvement early spermatid with acrosomal formation, well developed Golgi apparatus and peripheral arrangement of mitochondria |
| Sprague-Dawley rats | 50 mg/kg - 52 days | BPA | ↓ Vacuolation and cellular lesion, ↑ spermatozoa differentiation, ↑ tunica albuginea thickness, ↑ tubular diameter and epithelial height, ↓ interstitial space, ↑ secondary spermatocyte & spermatid | ↑ Numbers of spermatozoa, partial recovery in the germinal epithelium, improvement early spermatid with acrosomal formation, well developed Golgi apparatus and peripheral arrangement of mitochondria | ↑ Numbers of spermatozoa, partial recovery in the germinal epithelium, improvement early spermatid with acrosomal formation, well developed Golgi apparatus and peripheral arrangement of mitochondria |
| Sprague-Dawley rats | 50 mg/kg - 15 days | Arsenic | ↓ AP, ↓ OS | ↑ MSTD, ↑ MTBS, ↓ apoptotic index, ↑ PCNA index, ↑ SOD, ↑ CAT, ↑ GSH-Px, ↑ serum testosterone (nonsignificant) | ↑ Numbers of spermatozoa, partial recovery in the germinal epithelium, improvement early spermatid with acrosomal formation, well developed Golgi apparatus and peripheral arrangement of mitochondria |
| Wistar albino rats | 20 mg/kg - 30 min before detorsion | I/R | ↓ MDA, ↓ NO, ↑ TAC, ↓ TOC, ↓ abnormal germinal cells, ↓ vacuolization, ↓ tissue lesions | ↑ Numbers of spermatozoa, partial recovery in the germinal epithelium, improvement early spermatid with acrosomal formation, well developed Golgi apparatus and peripheral arrangement of mitochondria | ↑ Numbers of spermatozoa, partial recovery in the germinal epithelium, improvement early spermatid with acrosomal formation, well developed Golgi apparatus and peripheral arrangement of mitochondria |
| Wistar rats | 10 and 20 mg/kg - 52 days | Manganese | ↓ AP, ↓ OS | ↑ SOD, ↑ CAT, ↑ GSH, ↓ H2O2, ↓ MPO, ↓ NO, ↑ TNFα, ↑ LPO, ↓ caspase-3 activity, ↑ ACP, ↑ ALP, ↑ LDH | ↑ Numbers of spermatozoa, partial recovery in the germinal epithelium, improvement early spermatid with acrosomal formation, well developed Golgi apparatus and peripheral arrangement of mitochondria |
| NMRI mice | 75 mg/kg - 42 days | NTiO2 | ↑ Serum and tissue testosterone, ↑ testicular weights, ↑ vacuolization & detachment, ↑ SOD, ↑ CAT, ↓ MDA | ↑ Numbers of spermatozoa, partial recovery in the germinal epithelium, improvement early spermatid with acrosomal formation, well developed Golgi apparatus and peripheral arrangement of mitochondria | ↑ Numbers of spermatozoa, partial recovery in the germinal epithelium, improvement early spermatid with acrosomal formation, well developed Golgi apparatus and peripheral arrangement of mitochondria |
| Wistar albino rats | 20 mg/kg - 4 weeks | Cadmium chloride | ↑ AP, ↓ OS | ↑ Body weight, ↑ testes and epididymis weights, ↓ LDH, ↓ Lactate, ↓ glucose, ↑ SOD, ↑ CAT, ↑ GPx, ↑ GSH, ↑ Vitamin C, ↑ Vitamin E, ↑ TAC, ↓ MDA, ↓ H2O2, ↓ Bax, ↓ BCL-2, ↑ Cleaved caspase-3 activity | ↑ Numbers of spermatozoa, partial recovery in the germinal epithelium, improvement early spermatid with acrosomal formation, well developed Golgi apparatus and peripheral arrangement of mitochondria |
| Mice | 75 mg/kg - 21 days | PFOA | ↑ AP, ↓ OS | ↑ Testes weights, ↓ atrophy of seminiferous tubules, ↑ epididymal sperm count ↑ expression of NRF2, HO-1, SOD and CAT, ↓ MDA, ↓ BCL-2, ↓ p53, ↓ Bax | ↑ Numbers of spermatozoa, partial recovery in the germinal epithelium, improvement early spermatid with acrosomal formation, well developed Golgi apparatus and peripheral arrangement of mitochondria |
| Wistar rats | 20 mg/kg - 4 weeks | Cadmium chloride | ↑ AP, ↓ OS | ↑ 3 β-HSD and 17 β-HSD, ↓ cholesterol (but was significantly high compared to the control) | ↑ Numbers of spermatozoa, partial recovery in the germinal epithelium, improvement early spermatid with acrosomal formation, well developed Golgi apparatus and peripheral arrangement of mitochondria |
| Wistar albino rats | 25 mg/kg - 30 days | I/R | ↓ AP, ↓ OS | ↓ MDA, ↓ NO, ↓ GSH, ↑ TAC, ↑ TOC, ↑ JTBS | ↑ Numbers of spermatozoa, partial recovery in the germinal epithelium, improvement early spermatid with acrosomal formation, well developed Golgi apparatus and peripheral arrangement of mitochondria |
| animal       | treatment                  | OS                                  | effects of quercetin in different species of animals |
|--------------|----------------------------|-------------------------------------|-----------------------------------------------------|
| Mice         | 10 mg/kg – 6 weeks BPA     | ↓ AP, ↓ OS                          | ↓ MDA, ↑ CAT, ↑ TAA, ↑ BCL-2, ↓ caspase-3, ↑ serum  |
|              |                            |                                     | testosterone, ↓ the percentages of chromosomal    |
|              |                            |                                     | aberrations in primary spermatocytes, ↑ relative  |
|              |                            |                                     | testis weights, ↓ DNA fragmentation, ↓ vacuolization|
| Albino rat   | 10 and 50 mg/kg - 21 days  | Atrazine                            | ↑ Body weights, ↓ DNA fragmentation, ↑ expression  |
|              |                            |                                     | level of CYP17A1 mRNA, ↓ vacuolization and edema    |
|              |                            |                                     | in the interstitial regions, ↑ spermatogenesis, ↓ |
|              |                            |                                     | sperm abnormalities                                |
| Wistar albino rat | 50 mg/kg - 15 days Di-Butyl Phtalate | ↓ OS | ↑ Tubular diameter & epithelial height, ↑ germinal epithelial |
|              |                            |                                     | cell number, ↓ MDA, ↓ SOD (nonsignificant), ↓ CAT  |
| Wistar rat   | 100 mg/kg – 45 days        | Cypermethri n and Deltamethri n     | ↑ Tests and epididymis weights (nonsignificant), ↑ |
|              |                            |                                     | α- and β-HSD and 17 β-HSD, ↓ LPO, ↑ GSH, ↑ SOD, ↑ |
|              |                            |                                     | CAT, ↑ GPs, ↑ GR, ↑ GST, ↓ necrosis, ↓ vacuolization|
| Wistar rat   | 20 mg/kg – 14 days         | Sulphasalazine ne                   | ↑ 3 β-HSD and 17 β-HSD, ↑ cholesterol (nonsignificant), |
|              |                            |                                     | ↑ JTBS, ↓ atrophied tubules, ↓ germ cell degeneration, |
|              |                            |                                     | ↓ interstitial edema and congestion                |
| Albino rat   | 50 mg/kg – 4 weeks         | Cadmium chloride                    | ↓ Degenerative and apoptotic spermatogenic cells, ↑ |
|              |                            |                                     | regeneration in most seminiferous tubular germinal |
| Wistar rat   | 80 mg/kg – 21 days         | Doxorubicin                         | ↓ AP                                               |
|              |                            |                                     | ↓ Tubular diameter, ↓ epithelial height, ↓ germinal |
|              |                            |                                     | epithelial cell number, ↓ MDA, ↓ SOD (nonsignificant), |
|              |                            |                                     | ↓ CAT                                               |
| Wistar albino rat | 50 mg/Kg - 4 weeks L-NAME | ↓ OS | ↑ NO, ↑ T-SHs, ↑ GSH, ↓ MDA, ↓ ROS, improvement of |
|              |                            |                                     | the seminiferous tubular structure, ↓ the interstitial |
| NMRI mice    | 50 mg/kg – 7 days          | Dexamethas one                      | ↑ Volume and diameter of the seminiferous tubules, ↑ |
|              |                            |                                     | volume of interstitial tissue, ↑ germinal epithelium |
|              |                            |                                     | height, ↑ spermatogenesis                          |
| Rabbit       | 30 mg/kg – 60 days         | Heat stress                         | ↑ Epididymis weight, ↑ testicular length, ↑ apoptotic |
|              |                            |                                     | germ cell, improvement in testicular architecture  |
| Wistar albino rat | 50 mg/kg -65 days Vanadium pentoxide | ↓ OS | ↑ Acid phosphatase, ↑ glutathione, ↑ CAT, ↓ MDA, ↓ |
|              |                            |                                     | vacuolization, ↑ spermocytes, ↓ atrophy            |
| NMRI mice    | 75 mg/kg - 34.5 days       | Lead acetate                        | ↑ Number of round spermatids and long spermatids, ↑ |
|              |                            |                                     | ↓ interstitial spaces, ↑ BCL-2, ↑ caspase-3, 3 β- |
| Wistar rat   | 0, 100 µm/L - 24 hours     | ↑ AP                                | ↑ Number of round spermatids and long spermatids, ↑ |
|              |                            |                                     | ↑ MDA, ↓ ROS, ↓ protein carbonyl                   |
| Sprague-Dawley rat | 50 mg/kg – 4 weeks Cadmium | ↓ OS | ↑ Body weight, ↑ relative testicular weight, ↓ MDA, ↑ |
|              |                            |                                     | ↑ GSH, ↑ SOD, ↑ CAT, ↑ GPs, ↓ P62 and LC3B expression, ↑ |
|              |                            |                                     | ↑ atrophy and degeneration, ↑ number of sperm      |
| Wistar rat   | 5, 10 and 20 mg/kg – 3 days | Rotenone                       | ↑ SOD, ↑ GST, ↑ GSH, ↑ FRAP, ↓ PC, ↓ MDA, ↓ XO, ↓ |
|              |                            |                                     | MPO, ↓ LDH                                         |

QE: Quercetin; NMRI: Naval Medical Research Institute; Ap: Apoptosis; OS: Oxidative Stress; TTC: α cyhalothrin; GSH: Glutathione; CAT: Catalase; SOD: Superoxide dismutase; PNP: 4-nitrophenol; JTBS: Johnsen’s Tubular Biopsy Score; BLC: Bladder; PNM: 4-nitro-m-cresol; I/R: Ischemia/Reperfusion; NaF: Sodium fluoride; BPA: Bisphenol A; NITO2: Titanium dioxide nanoparticle; DEHP: di-(2-ethylhexyl) phthalate; HSP: Heat shock protein; TCD: 2,3,7,8-tetrachlorodibenzo-p-dioxin; PFOA: Perfluorooctane acid; LDH: Lactate dehydrogenase; MPO: Myeloperoxidase; ZnONPs: Zinc oxide nanoparticles; XO: xanthine oxidase; PC: Protein carbonyl; PCNA: Proliferating cell nuclear antigen; LPO: Lipid peroxidation; HO-1: Heme oxygenase-1; POD: peroxidase; T-SHS: Glutathione-S-transferase; GSR: Glutathione Reductase; TOC: Total antioxidant capacity; TAC: Total antioxidant capacity; GRx: Glutathione reductase; GSH-Px: Glutathione peroxidase; NO: Nitric oxide; TAA: total antioxidant activity; MDA: Malondialdehyde; GST: Glutathione S Transferase; FRAP: Ferric-reducing antioxidant power; ROS: Reactive oxygen species; T & D: Against Toxin & Diseases; MTBS: mean testicular biopsy score; MSTD: Mean seminiferous tubule diameter; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; TBARS: Thiobarbituric Acid Reactive Substances; eNOS: endothelial nitric oxide synthase; H2O2: Hydrogen peroxide; HSD: 17β hydroxysteroid dehydrogenase; L-NAME: N-nitro-l-arginine methyl ester; Gps: Glutathione peroxidase; ↑: Increase or Improve; ↓: Decrease. (Comparison in the toxin/disease group with quercetin + toxin/disease group).

**Table 3.** Evaluation of the effect of quercetin on men and different species of animals (Endocrinology and Blood biochemistry)

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### Discussion

Quercetin as an antioxidant can protect the male reproductive system from damage by various factors. The table below summarizes the effects of quercetin on different species and conditions, highlighting its protective role on sperm parameters, testicular tissue, and sex hormone levels.

| Species                  | Dose of QE & Duration of treatment | Type of Response                                                                 | T & D                  | Reference |
|--------------------------|------------------------------------|-----------------------------------------------------------------------------------|-----------------------|-----------|
| **Wistar albino rat**    | 15 mg/kg - 4 weeks                 | ↑ T                                                                               | ↑ MDA, ↑ TAC, ↓ ox-LDL, ↓ glucose | Streptozotocin (95) |
|                          |                                    |                                                                                   |                       |           |
| **Wistar rat**           | 10 mg/kg - 5 Days                  | ↑ T, ↑ LH, ↑ FSH                                                                   | Cadmium (100)         |           |
|                          |                                    |                                                                                   |                       |           |
| **Albino rat**           | 50 mg/kg – 10 days                 | ↑ T, ↑ LH, ↑ FSH, ↑ estradiol                                                      | Letrozole (124)       |           |
|                          |                                    |                                                                                   |                       |           |
| **Wistar rat**           | 5, 10, 15 and 20 mg/kg – 2 weeks   | ↑ LH & ↑ FSH (nonsignificant), ↑ T                                               | (62)                  |           |
|                          |                                    |                                                                                   |                       |           |
| **Wistar rat**           | 10 mg/kg – 6 weeks                 | ↑ T, ↑ LH                                                                          | BLCO (15)             |           |
|                          |                                    |                                                                                   |                       |           |
| **Wistar rat**           | 25 mg/kg – 3 weeks                 | ↑ FSH & T (nonsignificant), ↑ LH                                                  | Cadmium (75)          |           |
|                          |                                    |                                                                                   |                       |           |
| **Sprague-Dawley rat**  | 50 mg/kg – 70 days                 | ↑ T, ↑ LH                                                                          | Fenitrothion (84)     |           |
|                          |                                    |                                                                                   |                       |           |
| **Wistar rat**           | 90 mg/kg – 15 days (pretreatment)  | ↑ T                                                                                | DEHP (116)            |           |
|                          |                                    |                                                                                   |                       |           |
| **Sprague-Dawley rat**  | 50 mg/kg – 52 days                 | ↑ T                                                                                | BPA (63)              |           |
|                          |                                    |                                                                                   |                       |           |
| **Wistar rat**           | 10 and 20 mg/kg - 52 days          | ↑ T, ↑ LH, ↑ FSH                                                                   | Manganese (92)        |           |
|                          |                                    |                                                                                   |                       |           |
| **Wistar albino rats**   | 25 and 50 mg/kg – 5 weeks          | ↑ T                                                                                | Streptozotocin (99)   |           |
|                          |                                    |                                                                                   |                       |           |
| **Wistar albino rat**    | 20 mg/kg – 4 weeks                 | ↑ T, ↑ LH, ↑ FSH                                                                   | Cadmium chloride (81) |           |
|                          |                                    |                                                                                   |                       |           |
| **Wistar rat**           | 20 mg/kg - 4 weeks                 | ↑ T                                                                                | Cadmium chloride (83) |           |
|                          |                                    |                                                                                   |                       |           |
| **Albino rat**           | 50 mg/kg – 4 weeks                 | ↑ T, ↑ LH, ↑ FSH                                                                   | Lead acetate (44)     |           |
|                          |                                    |                                                                                   |                       |           |
| **Albino rat**           | 10 and 50 mg/kg - 21 days          | ↑ T                                                                                | Atrazine (96)         |           |
|                          |                                    |                                                                                   |                       |           |
| **Wistar rat**           | 100 mg/kg – 45 days                | ↑ T, ↑ LH                                                                         | Cypermethrin and deltamethrin (64) |           |
|                          |                                    |                                                                                   |                       |           |
| **Wistar rat**           | 20 mg/kg – 14 days                 | ↑ T                                                                                | Sulphasalazine (17)   |           |
|                          |                                    |                                                                                   |                       |           |
| **NMRI mice**            | 50 mg/kg – 7 days                  | ↑ T                                                                                | Dexamethasone (97)    |           |
|                          |                                    |                                                                                   |                       |           |
| **Albino rat**           | 50 mg/kg – 4 weeks                 | ↑ T, ↑ LH, ↑ FSH                                                                   | Cadmium chloride (101) |           |
|                          |                                    |                                                                                   |                       |           |
| **Wistar rat**           | 80 mg/kg – 21 days                 | ↑ T, ↑ LH (nonsignificant)                                                        | Doxorubicin (93)      |           |
|                          |                                    |                                                                                   |                       |           |
| **Wistar albino rat**    | 50 mg/Kg - 4 weeks                 | ↑ T, ↑ LH                                                                         | L-NAME (91)           |           |
|                          |                                    |                                                                                   |                       |           |
| **Rabbit**               | 30 mg/kg – 60 days                 | ↓ MDA                                                                             | Heat stress (22)      |           |
|                          |                                    |                                                                                   |                       |           |
| **Wistar albino rat**    | 50 mg/kg - 65 days                 | ↑ T, ↑ LH                                                                         | Vanadium pentoxide (94) |           |

QE: Quercetin; NMRI: Naval Medical Research Institute; T: Testosterone; NO: Nitric Oxide; MDA: Malondialdehyde; GSH-Px: Gluthathione peroxidase; TAC: Total antioxidant capacity; LH: Luteinizing hormone; GnRH: Gonadotropin-releasing hormone; FSH: Follicle-stimulating hormone; TACP: total acid phosphatase; PACP: prostatic acid phosphatase; DEHP: di-(2-ethylhexyl) phthalate; L-NAME: N-nitro-l-arginine methyl ester; BLCO: Nigerian Bonny Light crude oil; BPA: Bisphenol A; ↑: Increase or Improve; ↓: Decrease; T&D: Against Toxin & Diseases, (Comparison in the toxin/disease group with quercetin + toxin/disease group).
toxins. Toxins mainly disrupt the testicular tissue and spermatogenesis process by causing oxidative stress, so the use of this antioxidant by boosting antioxidant enzymes and by scavenging free radicals can prevent their toxicity. Spermatogenesis is an arduous and high organized process. Germinal cells are affected by three evolutionary phases: mitosis (spermatogonia evolution), meiosis (recombination, reduction, and division of DNA), and spermiogenesis (spermatid differentiation), which leads to the conversion of undifferentiated spermatogonia into specialized spermatozoa (27, 135).

 Plenty of conditions can disrupt spermatogenesis and reduce sperm quantity and quality (28). Moreover, germinal cells are also vulnerable to high ROS levels owing to their unique structure, an abundance of substrate for oxidation, and limited intracellular antioxidant defense (29, 136). ROS such as hydroxyl, superoxide, nitric oxide, and hydrogen peroxide interacts with the plasma membrane of sperm and lead to lipid peroxidation (LPO, 30). Yet, MDA is an important product of the unsaturated fatty acids peroxidation that is often applied as an indicator of oxidative stress damage (31). On the other hand, many studies have shown that quercetin can reduce MDA levels (2-6, 12, 14, 32-38).

 Oxidative stress is an imbalance between ROS and antioxidant defense mechanisms that can damage sperm structure and function such as motility, the integrity of the membrane, and acrosome. Also, it can harm mitochondrial function, DNA integrity, and the metabolism of sperm (39, 40). On the other hand, numerous studies have shown that the volume, count, motility, viability, and morphology of sperm are improved by quercetin supplementation (3, 24, 33, 34, 38, 40-46). Some studies have illustrated that in sperm freezing, quercetin supplementation can increase progressive motility, membrane and acrosome integrity, mitochondrial activity, and fertilization rate, it can prevent lipid peroxidation and DNA fragmentation (21, 24, 40, 47, 48).

 There is some truth in the argument that quercetin cannot positive role in male reproduction, but it is no denying the fact that the advantages of the ameliorative effect of quercetin outweigh its disadvantages (49-57). Besides, Ranawat attributed the paradoxical biologic effects of quercetin to the prescribed dose and cell redox position (58). Also, spermatogenesis is a highly active proliferative process that is capable of producing approximately 1000 sperm per second in seminiferous tubules. The high rate of intrinsic cell division of this process indicates the high rate of mitochondrial oxygen consumption by the germinal epithelium (59). The germinal epithelium in each seminiferous tubule contains two main cell types, which include Sertoli and Spermatogenic cells. Yet, Sertoli cells monitor spermatogenesis as physical and metabolic supporters for germ cells (60, 61). In some studies, quercetin has shown an increase in the population of spermatogonia, spermatocyte, spermatid, and sperm cells as well as testis weight (62-66). Besides, it can improve the seminiferous tubule structure by a reduction in vacuolation and interstitial space (62-69).

 ROS has a remarkable effect on spermatogenesis and sperm function. Also, oxidative stress occurs when the production of oxygen radicals be more than the antioxidant capacity in tissue (70). Inducers of oxidative stress are one of the important factors in male infertility. Yet, the testes contain a set of antioxidant enzymes and free radical scavengers so that the spermatogenic and steroidogenic functions of this organ not be affected by oxidative stress (59). Moreover, exposure to environmental toxins, X-rays, cryopreservation, varicocele, and cryptorchidism increase testicular oxidative stress which, leads to increased germinal cell apoptosis and hypospermatogenesis (71). Besides, many studies firmly maintain that quercetin increases total antioxidant capacity versus it can decrease MDA and DNA fragmentation (15, 33, 43, 50, 72-78). Quercetin can also reduce apoptosis in testicular tissue by reducing the expression of the proapoptotic genes including caspase-3 and Bax and increasing the expression of the anti-apoptotic genes including Bcl-xl and BCL-2 (71, 72, 79-82). On the other hand, cholesterol is a major
substrate for testosterone biosynthesis, which requires the presence of 3β-HSD and 17β-HSD enzymes (83). Research has shown that quercetin increases the expression of steroidogenic genes 3β-HSD and 17β-HSD in testicular tissue, which preserves it (64, 83, 84). Moreover, nowadays it is proven that one of the major reasons for infertility in men can be a disorder in the sex hormones levels, especially, LH is an important factor for spermatogenesis (85), which play as the main regulator for androgenic enzyme activity in the testis also it is responsible for maintaining testosterone levels (86). Moreover, testosterone and FSH also are essential for normal spermatogenesis as far as reducing their levels leads to fertility defects (87, 88). Many studies have shown that quercetin increases sex hormones such as LH, FSH, GnRH, and testosterone (44, 62, 64, 81, 89-91). On the other hand, alkaline phosphatase is an anti-inflammatory mediator that can prevent tissue damage. Also, lactate dehydrogenase is important for spermatogenesis and testicular metabolism. Therefore, disruption of the levels of these enzymes may cause testicular damage and quercetin can bring the levels of these two enzymes to near normalized (92, 93, 94). Also, there is no denying the fact that quercetin contributes to increasing total antioxidant capacity and reducing malondialdehyde (22, 95, 96, 97, 98). Researchers are of the same positive opinion about the quercetin effect that it serves as a remedy for various toxins such as streptozotocin (95, 99), 2, 4-dichlorophenoxyacetic (12), Aroclor (11), H2O2 (14, 18), cadmium (75, 81, 100, 101), quinine sulfate (100), cisplatin (102), docetaxel (42), atrazine (96, 103), cotinine (43), lead acetate (44, 104), bisphenol A (63, 105, 106), ethanol (107), sodium arsenite (61), acrylamide (108) on sperm parameters, testicular tissue, and sex hormones.

Quercetin may neutralize the adverse effects of these toxins by increasing total antioxidant capacity versus a decline in lipid peroxidation and DNA fragmentation. It also exerts similar beneficial effects on the side effects of diseases such as diabetes and leukocytospermia (41, 99, 109). In 2017, Ning evaluated the effect of varicocelectomy plus quercetin on varicocele in rats and concluded that they show quercetin could reduce apoptosis, but it reduced the protective effects of varicocelectomy (110). Finally, the findings have been illustrating that the advantage of quercetin strangely outweighs its poor disadvantages (Table 1, 2, and 3).

**Conclusion**

There is no denying that free radicals play a major role in the extension of male infertility due to the faint of antioxidant capacity on male reproductive disorders and spermatogenesis. Quercetin manages to act as an antioxidant by scavenging free radicals as well as chelating metal ions, thus it can increase total antioxidant capacity versus reducing lipid peroxidation. So far, studies have reported the positive effects of quercetin on reproductive system disorders. Therefore, the administration of quercetin as an antioxidant nutraceutical paves the way to boosting male reproductive health, and also it can protect of spermatogenesis process against various toxins.

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