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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]

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Highlights

- Investigation of the antioxidant capacity of quercetin
- The inhibitory impact of quercetin against various toxins
- The effect of toxins on the male reproductive system

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).

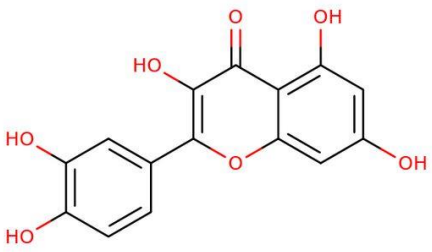

Figure 1. Chemical structure depiction of Quercetin

It is proven that oxidative stress induction manages to activate the transcription of inflammatory genes like NF-κβ. Yelumalai (2019) applied quercetin for downregulating levels of inflammatory marker proteins (TNF-α and NF-κβ) in STZ-nicotinamide-treated rats (4). Moreover, this polyphenolic flavonoid compound has an inhibitory effect on the p38MAPK/iNOS signaling pathway that can inhibit apoptosis (1). Yet, many articles have shown the quercetin therapy paves the way for the prevention of sperm inflammation by reducing oxidative stress (19). Since mitochondria are lack GSH, their structure is doubles sensitivity versus ROS during stress induction (20). Overproduction of ROS can reduce mitochondrial activity, Adenosine triphosphate levels, and sperm kinetics (5). Although quercetin can maintain the integrity and mitochondrial structure in the mid-piece of spermatozoa (2, 3, 21-24). Moreover, quercetin can stimulate sperm capacitation and acrosome response by increasing depolarization of channel Hv1 (voltage-gated proton) and activation of calcium-dependent CatSper (25, 26).

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.

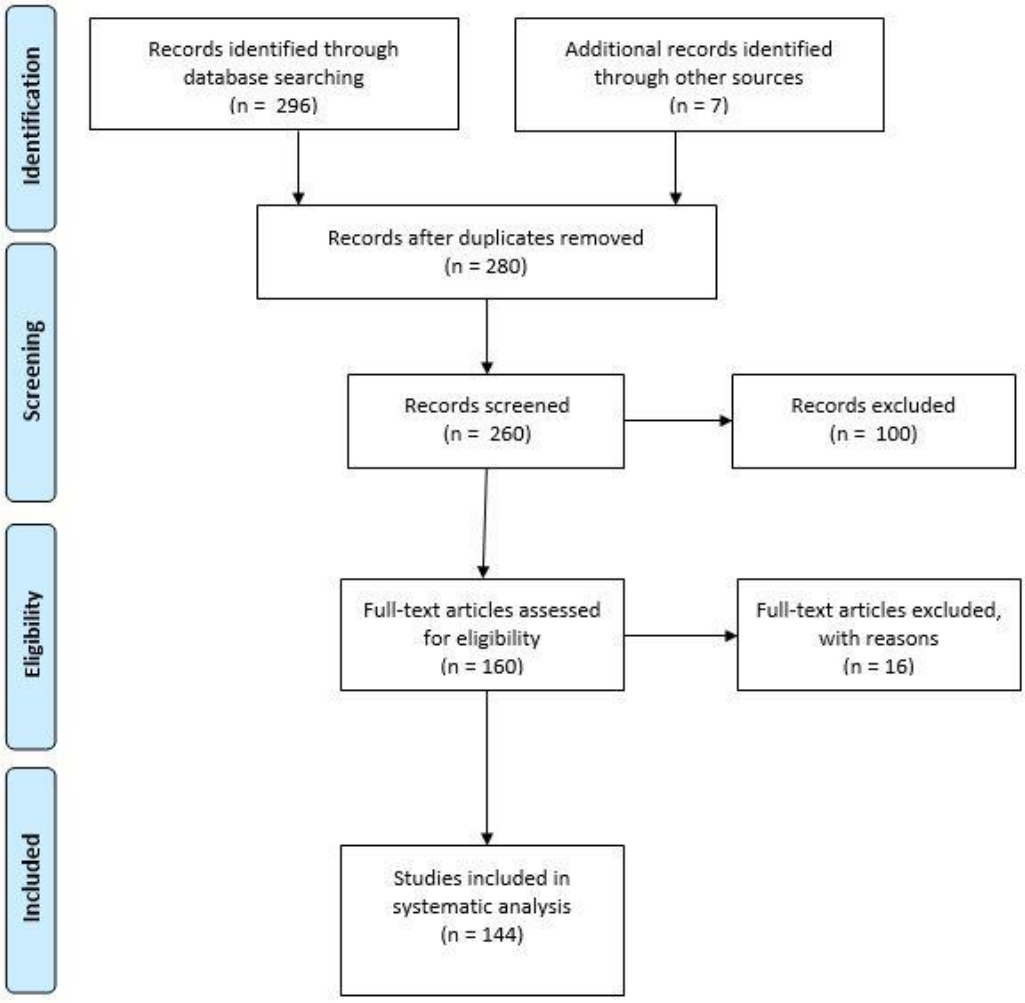

Figure 2. PRISMA diagram

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-kB expression, 3β-HSD, 17β-HSD, and NR5A1mRNA 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).

Table 1. Evaluation of the effect of quercetin on men and different species of animals (Spermatogenesis)

Species	**Type of response**							
	Dose of QE & Duration of treatment	Mot	Abn	Cou	Via	Other Parameters	T & D	Reference
Ram	0.1 mM - 5 hours	↑				↓ LPO		(40)
Human	100, 500 µM – 1 hour					↓ DNA damage	Thyroid hormone & noradrenaline	(111)
Chicken	0.01, 0.1 and 1 µg/ml - 48 hours					↓ LDH, ↓ TBARS, ↑ SOD, ↑ GSH, ↑ spermatogonial cell number	Aroclor 1254	(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	2, 4-dichlorophenoxyacetic	(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	↑		↑	↑		Streptozotocin	(41)
Wistar rat	100 µM and 200 µM - 3 hours	↑	↓		↑	↑ SOD, ↑ CAT, ↑ GPx, ↓ MDA	H_2O_2	(66)
Wistar albino rat	20 mg kg^{-1} - 60 days	↑	↓	↑			TCDD	(73)
Wistar rat	10 mg/kg^{-1} - 5 days	↑	↓			↓ MDA, ↓ H_2O_2, ↑ SOD, ↑ CAT, ↑ GPx, , ↑ sperm concentration, sperm viability, sperm number and DSP were not significantly different	Cadmium	(100)
Human	30 µM – 1 hours					↓ LPO, preserving sperm membranes and chromatin texture	TBHP	(19)
Human	50 µM	↑			↑	↓ DNA fragmentation and oxidation, no effects on caspase 3 activation	Cryopreservation	(33)
Wistar albino rat	10 mg/kg – 8 weeks	↑	↓	↑	↑	↑ CAT, ↑ ascorbic acid, ↓ MDA, ↑ DSP	Quinine sulfate	(100)
Wistar rat	50 mg/kg - 28	↑	↓	↑	↑		LTC	(114)

	days							
Wistar albino rats	150 mg/ kg^{-1} – 10 weeks		↓			↑ Sperm motility and epididymal sperm concentration (nonsignificant)	Carbon tetrachloride	(68)
Wistar albino rats	50 mg kg^{-1} – 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^{-1} - 2,6,12 and 24 hours	↑			↑	↓ Superoxide production		(23)
Boar	1, 50 and 100 µM – 3 and 6 hours				↑	↑ Motility (nonsignificant), ↑ membrane integrity, ↑ IVF embryo development		(115)
Rabbit	0, 25, 50, 100 and 200 µM - 48,72 and 95 hours					↓ LPO, ↓ H_2O_2		(116)
Wistar albino rats	20 mg/kg^{-1} - 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	↑		↑				(62)
Wistar rat	25 mg/kg^{-1} – 3 weeks	↑		↑		↑ Sialic acid	Cadmium	(75)
Albino rat	100 mg/kg – 12 weeks	↑	↓	↑	↑		ZnONPs	(76)
Sprague-Dawley rat	50 mg/kg^{-1} – 70 days	↑	↓	↑			Fenitrothion	(84)
Wistar rat	10 mg/kg^{-1} – 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		(35)
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, ↑ GPx, ↓ 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	↑	↓	↑			NTiO2	(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 rat	20 mg/kg – 4 weeks	↑	↓	↑	↑	↑ RPFM	Cadmium chloride	(81)

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	5µg/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	Sulphasalazine	(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	H_2O_2	(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	↑				↑ Mitochondrial activity, ↑ intact membranes, acrosome integrity, ↓ DNA fragmentation, ↓ ROS, ↓		(5)

						superoxide production, ↓ protein carbonyls		
Human	0.05, 0.1, 0.2, 0.5 and 1M – 1, 2 and 3 hours	↑				Sperm concentration, normal morphology and acrosomal index were not changed after the addition of quercetin	Asthenozoospermic	(122)
Wistar albino rat	50 mg/kg - 65 days	↑	↓	↑			Vanadium pentoxide	(94)
Canine	5 – 100 µg/ml	↑				↑ Fertility	Cryopreservation	(47)
Rooster	0.040, 0.020, 0.010 and 0.005 mg/mL	↑	↓		↑	↑ membrane intact, ↑ MMP, ↑ intact acrosome, ↑ CAT, ↑ SOD, ↑ GPx, ↓ DNA fragmentation, ↓ LPO, ↓ ROS	Cryopreservation	(6)
Red Jungle Fowl	5, 10, 15 and 20 mM	↑			↑	↑ Plasma membrane integrity, ↑ acrosome integrity, ↑ chromatin condensation, ↑ mitochondrial activity, ↓ damage to chromatin condensation, ↓ LPO, ↑ FRAP activity (total antioxidant potential)	Cryopreservation	(24)
Boar	0.25, 0.50 and 0.75 mM – 1,2, 4, 6, 8 and 10 hours after thawing	↑			↑	↓ LPO, ↓ polyspermic penetration, ↑ IVF efficiency, ↑ cleaved embryos	Thawing and incubation	(123)

QE: Quercetin; NIMRI: Naval Medical Research Institute; Mot: Motility; Abn: Abnormality; Cou: Count; Via: Viability; T&D: Against Toxin & Diseases; TCDD: 2,3,7,8-tetrachlorodibenzo-p-dioxin; LTC: ʎ cyhalothrin; FRAP: Ferric Reducing Antioxidant Power; VCL: Curvilinear velocity; VSL: Straight linear velocity; VAP: Average path velocity; XO: xanthine oxidase; SDF: Sperm DNA fragmentation; DEHP: di-(2-ethylhexyl) phthalate; TBHP: tert-butylhydroperoxide; HPO: total hydroperoxide; L-NAME: N-nitro-l-arginine methyl ester; BLCO: Nigerian Bonny Light crude oil; ZnONPs: Zinc oxide nanopartciles; BPA: Bisphenol A; RPFM: Rapid Progressive Forward Movement; NTiO2: Titanium dioxide nanoparticle; TAC: Total antioxidant capacity; MDA: Malondialdehyde; MMP: Mitochondrial Membrane Potential; ↑: Increase or Improve; ↓: Decrease, (Comparison in the toxin/disease group with quercetin + toxin/disease group).

Table 2. Evaluation of the effect of quercetin on men and different species of animals (testicular tissue)

Species	**Type of Response**				
	Dose of QE & Duration of treatment	T & D	Oxidative stress & Apoptosis	Histology, Testicular biochemistry & PCR	Reference
ICR mice	75 mg/kg - 2 weeks	Cadmium	↓ AP, ↓ OS	↓ MDA, ↓ H_2O_2, ↑ 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	↓ H_2O_2, ↓ OH, ↓ MDA, ↑ GSH, ↑ SOD, ↑ GSH-Px, ↓ 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, ↑ GSH-Px, ↓ caspase-3 activity, ↓ Bax, ↑ Bcl-xl	(79)
Wistar albino rats	150 mg/kg^{-1} – 10 weeks	Carbon tetrachloride	↓ AP, ↓ OS	↑ Testes weight, ↓ MDA, ↑ GSH-Px 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	↑ Testes weight (nonsignificant), ↓ MDA, ↑ GSH, ↑ SOD, ↑ GPX, ↑ CAT, ↑ GST, highly regular seminiferous tubules	(114)
Albino rat	50 mg/kg – 10 days	Letrozole	↓ OS	↑ Body weight, ↑ testicular weight, ↓ NO, ↑ GSH-Px, ↓ MDA, ↑ normal appearance of testicular tissue	(124)
Wistar albino rat	270 mg/kg_1 - 8 weeks	Ethanol	↓ OS	↑ SOD, ↑ GSH-Px, ↑ CAT, ↓ NO, ↑ MDA	(125)
Albino rat	15 mg/kg – 30	Estradiol-3-	↓ AP, ↓	↑ Testes weight, ↑ spermatocyte, ↑ round spermatid, ↓	(126)

	days	benzoate	OS	TBARS, ↑ SOD, ↑ GST, ↑ TAC, ↑ total glutathione, ↓ apoptotic index, ↓ caspase-3 activity, ↓ Bax, ↓ P53, ↓ FasL	
Wistar albino rats	20 mg/kg^{-1} - 21 days	Docetaxel	↓ OS	↓ LPO, ↓ TBARS, ↑ SOD, ↑ CAT, ↑ GPX, ↑ GSH, ↑ testes weight and epididymis	(42)
Wistar albino rat	75 mg/kg – 30 days	NaF		↑ SOD, ↑ GST, ↑ GRx, ↑ TCA, ↓ LPO, ↑ CAT & GPx (nonsignificant)	(127)
Wistar rat	10 mg/kg – 6 weeks	BLCO	↓ OS	↑ GSH, ↑ SOD, ↑ CAT, ↑ GST, ↓ LPO, ↓ XO	(15)
Sprague-Dawley rat	50 mg/kg – 49 days	Sodium arsenite	↓ OS	↑ Thickness of the tunica albuginea, ↓ interstitial space, ↑ number of spermatogonia, spermatocytes, and spermatids, , ↑ CAT, ↑ SOD & POD, ↑ GSR, ↓ TBARS, ↑ plasma and intra-testicular testosterone	(61)
Sprague-Dawley rat	50 mg/kg – 49 days		↓ OS	↑ Spermatogenesis, thickness ↑ seminiferous epithelium, ↑ thickness of the tunica albuginea, ↓ interstitial space, ↑ number of spermatogonia, spermatocytes, and spermatids, , ↑ CAT, ↓ TBARS	(61)
Albino rat	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	(128)
Wistar rat	5, 10, 15 and 20 mg/kg – 2 weeks			↑ Testis weight (nonsignificant), ↑ number of primary spermatocytes, spermatids and Spermatozoa	(62)
Wistar rat	10 mg/kg – 7 days	BLCO		↓ caspase 3, ↓ FasL, ↓ HSP, ↑ StAR, ↑ NF-kB and ↓ Clusterin (to near control level)	(129)
Wistar rat	25 mg/kg^{-1} – 3 weeks (pre-treatment)	Cadmium	↓ OS	↓ LPO, ↑ GSH, ↑ GPX, ↑ GST, ↑ CAT, ↑ SOD, ↑ cholesterol	(75)
Albino rat	100 mg/kg – 12 weeks	ZnONPs	↓ OS	↑ GSH, ↑ GPx, ↑ CAT, ↑ SOD, ↓ MDA, ↑ CAT and SOD mRNA transcripts, ↑ serum testosterone, ↑ 3β-HSD, 17β-HSD and NR5A1mRNA transcripts, ↑ intact seminiferous tubules and regular basement membrane and normal spermatocytes and spermatids	(76)
Sprague-Dawley rat	50 mg/kg^{-1} – 70 days	Fenitrothion	↓ OS	↑ Steroidogenic genes (3β-HSD6, 17 β-HSD3 and Nr5A1), ↑ CAT and SOD mRNA levels, ↓ edema in the interstitial tissue	(84)
Wistar rat	10 mg/kg^{-1} – 16 days	Atrazine	↓ OS	↓ MDA, ↑ SOD, ↓ LDH, ↑ 3 β-HSD and 17 β-HSD	(103)
Wistar rat	90 mg/kg – 15 days (Pre-treatment)	DEHP	↓ OS	↑ Relative testes Weight, ↑ DSP, ↓ LPO, ↑ SOD, ↑ GSH, ↑ CAT, amelioration of LDH-X activity	(117)
Sprague-Dawley rat	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	(62)
Sprague-Dawley rat	50 mg/kg^{-1} – 15 days	Arsenic	↓ AP, ↓ OS	↑ MSTD, ↑ MTBS, ↓ apoptotic index, ↑ PCNA index, ↑ SOD, ↑ CAT, ↑ GSH-Px, ↑ serum testosterone (nonsignificant),	(130)
Wistar albino rat	20 mg/kg^{-1} - 30 min before detorsion	I/R		↓ MDA, ↓ NO, ↑ TAC, ↓ TOC, ↓ abnormal germinal cells, ↓ vacuolization, ↓ tissue lesions	(131)
Wistar rat	10 and 20 mg/kg - 52 days	Manganese	↓ AP, ↓ OS	↑ SOD, ↑ CAT, ↑ GSH, ↑ GST, ↓ H_2O_2, ↓ MPO, ↓ NO, ↓ TNFα, ↓ LPO, ↓ caspase-3 activity, ↑ ACP, ↑ ALP, ↑ LDH	(92)
NMRI mice	75 mg/kg – 42 days	NTiO2		↑ Serum and tissue testosterone, ↑ testicular weights, ↓ vacuolization & detachment, ↑ SOD, ↑ CAT, ↓ MDA	(118)
Wistar albino rat	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, ↓ H_2O_2, ↓ Bax, ↑ BCL-2, ↓ Cleaved caspase-3 activity	(81)
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	(82)
Wistar rat	20 mg/kg - 4 weeks	Cadmium chloride		↑ 3 β-HSD and 17 β-HSD, ↓ cholesterol (but was significantly high compared to the control)	(83)
Wistar albino	25 mg/kg – 30	I/R	↓ AP, ↓	↓ MDA, ↓ NO, ↑ GSH, ↑ TAC, ↓ TOC, ↑ JTBS	(132)

rat	min before detorsion		OS		
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	(106)
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	(96)
Wistar albino rat	50 mg/kg - 15 days	Di-Butyl Phthalate	↓ OS	↑ Tubular diameter & epithelial height, ↑ germinal epithelial cell number, ↓ MDA, ↑ SOD (nonsignificant), ↓ CAT	(133)
Wistar rat	100 mg/kg – 45 days	Cypermethrin and Deltamethrin	↓ OS	↑ Testes and epididymis weights (nonsignificant), ↑ 3 β-HSD and 17 β-HSD, ↓ LPO, ↑ GSH, ↑ SOD, ↑ CAT, ↑ GPx, ↑ GR, ↑ GST, ↓ necrosis, ↓ vacuolization	(64)
Wistar rat	20 mg/kg – 14 days	Sulphasalazine	↓ OS	↑ 3 β-HSD and 17 β-HSD, ↑ cholesterol (nonsignificant), ↑ GST, ↑ GPX, ↑ GSH, ↓ MDA, ↑ SOD (nonsignificant)	(17)
Albino rat	50 mg/kg – 4 weeks	Cadmium chloride		↑ JTBS, ↓ atrophied tubules, ↓ germ cell degeneration, ↓ interstitial edema and congestion	(101)
Wistar rat	80 mg/kg – 21 days	Doxorubicin	↓ AP	↓ Degenerative and apoptotic spermatogenic cells, ↑ regeneration in most seminiferous tubular germinal epithelium	(93)
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 spaces	(91)
NMRI mice	50 mg/kg – 7 days	Dexamethasone		↑ Volume and diameter of the seminiferous tubules, ↓ volume of interstitial tissue, ↑ germinal epithelium height, ↑ spermatogenesis	(97)
Rabbit	30 mg/kg – 60 days	Heat stress	↓ AP	↑ Epididymis weight, ↑ testicular length, ↓ apoptotic germ cell, improvement in testicular architecture	(22)
Wistar albino rat	50 mg/kg - 65 days	Vanadium pentoxide	↓ OS	↓ Acid phosphatase, ↑ glutathione, ↑ CAT, ↓ MDA, ↓ vacuolization, ↑ spermatocytes, ↓ atrophy	(94)
NMRI mice	75 mg/kg - 34.5 days	Lead acetate	↓ AP	↑ Number of round spermatids and long spermatids, ↑ BCL, ↓ caspase-3, Bax and Bax/Bcl-2 (nonsignificant)	(104)
Wistar rat	1, 10 and 100 µmol/L - 24 hours		↓ OS	↑ TAC, ↓ MDA, ↓ ROS, ↓ protein carbonyls	(78)
Sprague-Dawley rat	50 mg/kg – 4 weeks	Cadmium	↓ OS	↑ Body weight, ↑ relative testicular weight, ↓ MDA, ↑ GSH, ↑ SOD, ↑ CAT, ↑ GPx, ↓ P62 and LC3B expression, ↓ atrophy and degeneration, ↑ number of sperm	(65)
Wistar rat	5, 10 and 20 mg/kg – 3 days	Rotenone	↓ OS	↑ SOD, ↑ GST, ↑ GSH, ↑ FRAP, ↓ PC, ↓ MDA, ↓ XO, ↓ MPO, ↓ LDH	(134)

QE: Quercetin; *NIMRI*: Naval Medical Research Institute; Ap: Apoptosis; OS: Oxidative Stress; LTC: ʎ cyhalothrin; GSH: Glutathione; CAT: Catalase; SOD: Superoxide dismutase; PNP: 4-nitrophenol; JTBS: Johnsen's Tubular Biopsy Score; BLCO: Nigerian Bonny Light crude oil; PNMC: 4-nitro-m-cresol; I/R: Ischemia/Reperfusion; NaF: Sodium fluoride; BPA: Bisphenol A; NTiO2: Titanium dioxide nanoparticle; DEHP: di-(2-ethylhexyl) phthalate; HSP: Heat shock protein; TCDD: 2,3,7,8-tetrachlorodibenzo-p-dioxin; PFOA: Perfluorooctane acid; LDH: Lactate dehydrogenase; MPO: Myeloperoxidase; ZnONPs: Zinc oxide nanopartciles; XO: xanthine oxidase; PC: Protein carbonyl; PCNA: Proliferating cell nuclear antigen; LPO: Lipid peroxidation; HO-1: Heme oxygenase-1; POD: peroxidise; T-SHS: Glutathione-S-transferase; GSR: Glutathione Reductase; TOC: Total oxidant 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: 17-β hydroxysteroid dehydrogenase; L-NAME: N-nitro-l-arginine methyl ester; Gpx: 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)

Species	Type of Response				
	Dose of QE & Duration of treatment	Endocrinology	Blood biochemistry	T & D	Reference
Wistar albino rat	15 mg/kg - 4 weeks	↑ T	↓ MDA, ↑ TAC, ↓ ox-LDL, ↓ glucose	Streptozotocin	(95)
Wistar rat	10 mg/kg^{-1} – 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^{-1} – 3 weeks	↑ FSH & T (nonsignificant), ↑ LH		Cadmium	(75)
Sprague-Dawley rat	50 mg/kg^{-1} – 70 days	↑ T, ↑ LH		Fenitrothion	(84)
Wistar rat	90 mg/kg – 15 days (pretreatment)	↑ T	↓ TACP, ↑ PACP	DEHP	(116)
Sprague-Dawley rat	50 mg/kg – 52 days	↑ T	↓ BUN, ↓ creatinine, ↓ cholesterol, ↓ triglyceride, ↑ HDL, ↑ LDL	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	↓ Glucose	Streptozotocin	(99)
Wistar albino rat	20 mg/kg – 4 weeks	↑ T, ↑ LH, ↑ FSH, ↑ GnRH		Cadmium chloride	(81)
Wistar rat	20 mg/kg - 4 weeks	↑ T	↓ NO	Cadmium chloride	(83)
Albino rat	50 mg/kg – 4 weeks	↑ T, ↑ LH, ↑ FSH	↑ Hb, ↑ PCV, ↓ WBC, ↑ RBC	Lead acetate	(44)
Albino rat	10 and 50 mg/kg - 21 days	↑ T	↓ MDA, ↑ TAC, ↑ IgA	Atrazine	(96)
Wistar rat	100 mg/kg – 45 days	↑ T, ↑ LH, ↑ FSH		Cypermethrin and deltamethrin	(64)
Wistar rat	20 mg/kg – 14 days		↑ Thyroidotropin (T3, T4), restored plasma hormone levels	Sulphasalazine	(17)
NMRI mice	50 mg/kg – 7 days	↑ T	↓ MDA, ↑ TAC	Dexamethasone	(97)
Albino rat	50 mg/kg – 4 weeks	↑ T, ↑ LH, ↑ FSH	↑ Hb, ↑ PCV, ↑ total WBC, ↑ RBC, ↑ TSH	Cadmium chloride	(101)
Wistar rat	80 mg/kg – 21 days	↑ T, ↑ LH (nonsignificant)	↓ ALP & LDH (nonsignificant), ↑ GSH-Px, ↑ TAC	Doxorubicin	(93)
Wistar albino rat	50 mg/Kg - 4 weeks	↑ T, ↑ LH, ↑ FSH		L-NAME	(91)
Rabbit	30 mg/kg – 60 days		↓ MDA	Heat stress	(22)
Wistar albino rat	50 mg/kg - 65 days	↑ T, ↑ LH	↓ LDH	Vanadium pentoxide	(94)

QE: Quercetin; *NIMRI:* Naval Medical Research Institute; T: Testosterone; NO: Nitric Oxide; MDA: Malondialdehyde; GSH-Px: Glutathione 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).

Discussion

Quercetin as an antioxidant can protect the male reproductive system from damage by various

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 reason 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), H202 (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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