

# Ameliorative Impact of Silymarin on the Male Reproductive System: An Updated Systematic Review

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## Abstract

**Background and objectives:** Numerous studies have evaluated the effects of silymarin on sperm quality and its neutralization impact of various toxins on the male reproductive system. However, these studies as a whole have not been summarized and categorized yet. Silymarin is a flavonoid and known as a powerful antioxidant compound in the treatment of many diseases including liver disorders, rhinitis, diabetes, and testis disorders. The study aimed to discuss the impact of silymarin on the male reproductive system.

**Material and Methods:** From Apr 1998 to Feb 2020, related articles were extracted from databases of Web of Science (WOS), PubMed, Google Scholar, Science Direct, Scopus, EBSCO, and grey literature by seeking MeSH words including Silymarin, Milk thistle, Silybum marianum, testis, Spermatogenesis, and Sex hormones.

**Results:** Silymarin withdraws damage to the testicular germinal epithelium and comforts the spermatogenesis process by amplification the antioxidant system, decreasing lipid peroxidation and oxidative stress, and preventing the expression of pro-apoptotic genes, increasing testosterone and gonadotropins.

**Conclusion:** In outcome, based on the results, silymarin can boost fertility in sterility males by its talented antioxidant features.

**Keywords:** Silymarin [[MeSH](#)], Spermatogenesis [[MeSH](#)], Gonadal Steroid Hormones [[MeSH](#)], Testis [[MeSH](#)]

**Highlights**

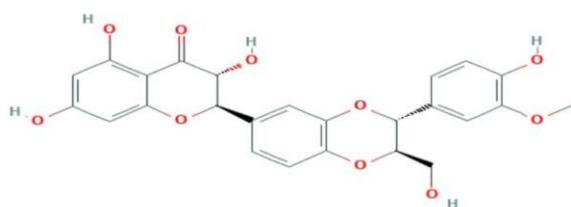
- Silymarin acts as a powerful antioxidant.
- This antioxidant protects the male reproductive system against various toxins that increase free radicals.
- Silymarin is able to prevent lipid peroxidation and expression of pro-apoptotic genes in testicular tissue.

**Introduction**

Silybum marianum is widely used in the treatment of many disorders ([Fig 1](#)) ([1](#)). Silymarin (C<sub>25</sub>H<sub>22</sub>O<sub>10</sub>), a flavonoid and polyphenolic molecule, is extracted from the seeds of Silybum marianum ([Fig 2](#)) ([1- 3](#)). Silymarin can be effective in many including infertility in men and women ([4](#)). In addition to having other biological properties, these compounds are recognized as antioxidants ([5, 6](#)). In 1959, silybin was discovered as the first member of a new family of natural compounds called flavonolignans and was known as the active and dominant compound in silymarin ([1, 7, 8](#)). Many studies have shown the protective and antioxidant properties of silymarin against the side effects of chemotherapy drugs and environmental toxins on sperm ([9-12](#)).



**Fig 1.** The species of Silybum Marianum



**Fig 2.** Chemical Structure Depiction (C<sub>25</sub>H<sub>22</sub>O<sub>10</sub>) of silymarin

One of the reasons for oxidative stress is the imbalance between ROS production and antioxidants ([13- 15](#)). Oxidative stress is involved in many pathological conditions and diseases ([16- 18](#)). Many studies have shown that there is a relationship between oxidative stress conditions in semen dysfunction ([15, 19- 21](#)). Antioxidant mechanisms of silymarin in the reproductive tissue are likely to suppress ROS and protect gonadal cells and spermatozoa from getting damaged. Studies show silymarin can improve semen parameters as an antioxidant ([1, 8, 9, 22, 23](#)). Silymarin affects the enzyme systems associated with glutathione and superoxide dismutase and increases them, silymarin can increase the amount of cellular content of glutathione by increasing the substrate (cysteine) and inhibits lipid peroxidation ([24- 26](#)) given that glutathione is the most abundant cellular antioxidant and be able to protect cells against the toxic effects of ROS ([7](#)) and also can inhibit lipid peroxidation ([26](#)). Moreover, silymarin can regulate membrane permeability and increase membrane stability in the presence of xenobiotic damage ([22](#)). Silymarin inhibits the uptake of toxins and prevents them from binding to the cell surface ([27](#)). Finally, silymarin can enter the nucleus and stimulate RNA polymerase enzymes, thereby increasing ribosome formation that, in turn, accelerates DNA and protein synthesis ([25](#)).

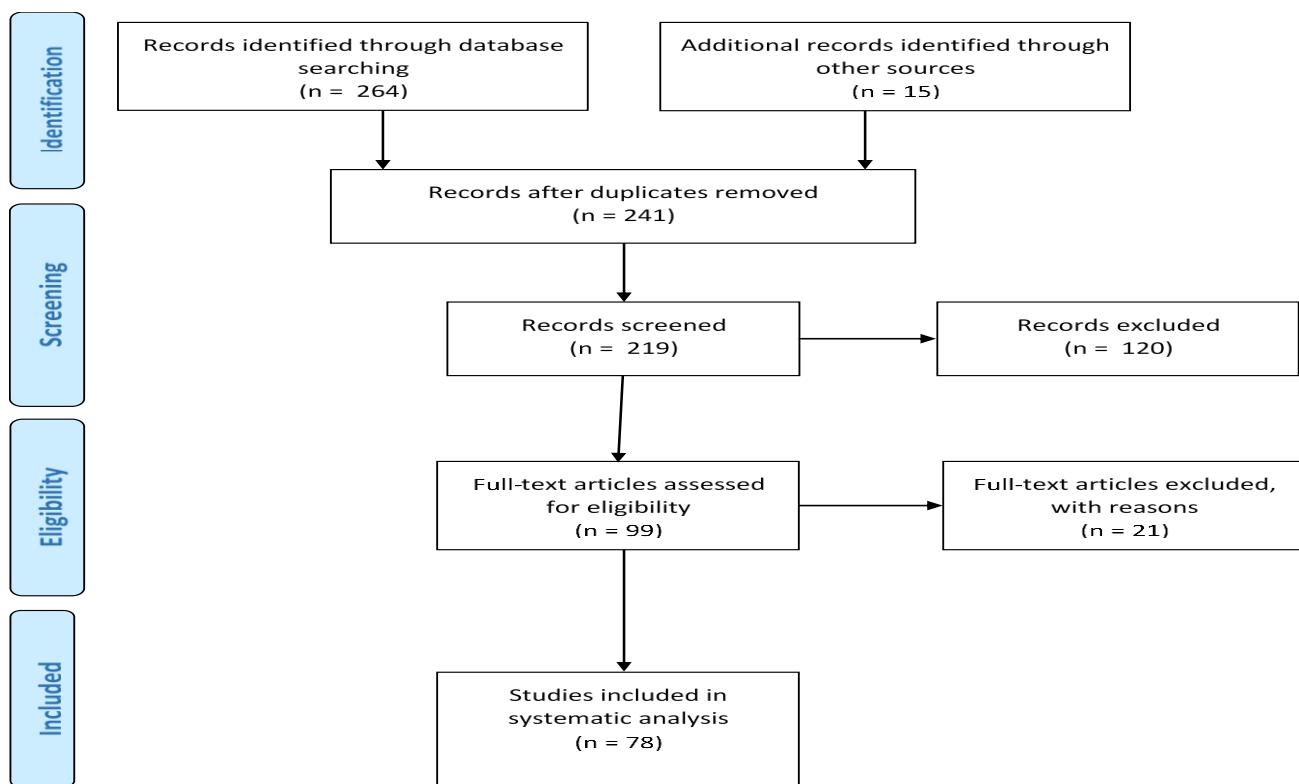
Oxidative stress is one of the important factors in male reproductive system disorders. Also, the most common way to deal with oxidative stress is to use antioxidants today. Hence, the present review intended to contribute a summary of prior research regarding silymarin antioxidant role in male reproduction disorder carried out.

**Materials and Methods**

Inclusion criteria in the present study included the evaluation of spermatogenesis, testicular tissue, blood hormones, and enzymes from Apr 1998 to Feb 2020. The electronic search was performed on the databases of WOS, PubMed, Science Direct, Scopus, EBSCO, and grey literature. Finally, the Google Scholar Database was used to ensure complete content and this study lasted

from Jan 2021 to Jul 2021. The inclusion criteria of this study were contained andrological studies (spermatogenesis, spermiogenesis, and sperm parameters), histological and morphometrical studies (testicular tissue), and endocrinological studies (sex hormone). The present study was performed using the words MeSH including Silymarin, Milk thistle, Silybum marianum, testis, spermatogenesis, and sex hormones. The search results of the databases involved a total of 264 articles. The number of these articles was reduced to 78 after passing the identification, screening, and eligibility stages. Exclusion criteria included invalid journals, duplication, and lack of access to the full text ([Fig 3](#)). The steps related to searching for articles, results, and extracting data were

performed independently by two researchers and in case of differences in each of the steps, they were reviewed by a third researcher. A search syntax was developed by using: Search (((("silymarin"[MeSH Terms] OR silymarin [Text Word]) OR ("milk thistle"[MeSH Terms] OR Milk thistle [Text Word])) OR ("milk thistle"[MeSH Terms] OR Silybum marianum [Text Word])) AND ("testis" [MeSH Terms] OR testis [Text Word])) OR ("spermatogenesis"[MeSH Terms] OR Spermatogenesis [Text Word])) AND ("gonadal steroid hormones"[MeSH Terms] OR sex hormones [Text Word]).



**Fig 3.** Preferred Reporting Items for Systematic Analysis (PRISMA) diagram: the flow of information through the different phases of a Systematic Review

## Results

Increased ROS during oxidative stress is known to impair oxidant-antioxidant balance and contribute to the peroxidation of unsaturated fatty acids in the sperm membrane and disorder in

spermatogenesis and sperm function ([16, 17, 28-31](#)). The quantity and quality of spermatogenesis are determined based on the evaluation of parameters such as count, motility, viability, DNA damage, normal morphology, and population of Sertoli and spermatogenic cells ([32- 34](#)).

Numerous studies have shown that silymarin compensates for the integrity of plasma membranes and acrosomes, motility, viability, and sperm DNA fragmentation (4, 30, 35-38).

Malondialdehyde (MDA) levels are considered an indicator of lipid peroxidase activity and the end product of lipid peroxidation (39). Studies have shown that silymarin increases total antioxidant capacity and decrease MDA (4, 36, 40, 41). Silymarin due to its antioxidant properties can prevent lipid peroxidation of cell membranes and maintain sperm membrane integrity (26).

Silymarin can also increase testosterone levels, which in turn promotes sperm health and maintains cell division (3, 42). It has been shown that silibinin may improve germinal epithelium function and spermatogenesis by preventing oxidative stress (3).

Moreover, silymarin as a potent antioxidant can eliminate free radicals including ROS, and subsequently reduce DNA fragmentation (1, 14). Research has shown that silymarin increases Bcl2 gene expression and decreases Bax and caspase 3 expression, thereby reducing apoptosis in testicular tissue (43).

Transcription factor E2F1 is one of the factors involved in the apoptosis, count, and viability of sperm. Silymarin can reduce E2F1 expression and thus prevents overstimulation of apoptosis in sperm cells (41) (Table 1).

Sperm are vulnerable to ROS at different stages of spermatogenesis (25). Several internal and

external factors can interact with lipids and proteins to cause oxidative stress and ROS production following that occur lipid peroxidation, DNA fragmentation, raise superoxide ions in mitochondria, decreased antioxidant activity, and ultimately spermatogenesis disorder (44- 46).

Numerous studies have shown that low testosterone levels reduce testicular function (32). Moreover, increased apoptosis is one of the results of oxidative stress that reduces motility and count of sperm (25, 46). Silymarin increases testicular weight, epithelial height, spermatogenesis, and total antioxidant capacity, and decreases MDA, apoptosis, and edema (3, 47- 53).

Numerous studies have shown that silymarin is a powerful antioxidant that can protect testicular tissue from the adverse effects of oxidative stress (3, 54). Table 2 evaluates and compares the effects of silymarin on testicular tissue (Table 2).

Many studies have illustrated that silymarin can increase LH, FSH, and GnRH hormones (43, 47, 55-57). Testosterone is important in the starting and continuing of spermatogenesis and its reduction contributes to defects in spermatogenesis (58). Silymarin can also increase testosterone levels, which in turn increases spermatogenesis (47, 56, 59). Moreover, silymarin can regulate serum levels of LH, FSH, inhibin B, and testosterone against toxins, and vis-a-vis can reduce lipid peroxidation and MDA (60-65, 71- 77).

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

Author, year (ref)	Species	Type of response							T & D
		Dose of SM & Duration of treatment	Mot	Abn	Cou	Via	Other Parameters		
Aghashahi et al., 2020 (9)	Human	1 µM – 180 min <i>in vitro</i>	↑			↑	↑ Acrosome and plasma membrane integrity, ↑ total antioxidant capacity, ↓ MDA	Aluminum	
Aghashahi et al., 2020 (9)	Human	1 µM – 180 min <i>in vitro</i>	↑			↑	↑ Acrosome and plasma membrane integrity, ↑ TAC, ↓ MDA		
Etemadi et al., 2020 (10)	Human	2 µM- 180 min <i>in vitro</i>					↓ SDF, ↑ nucleus diameter, ↑ MMP	Cadmium	

Rahimi-Madiseh et al., 2020 (11)	NMRI mice	100 and 200 mg/kg – 28 days	↑	↓	↑	↑		Nicotine
Fatehi et al., 2017 (30)	NMRI mice	50 mg/kg – 7 days	↑	↓	↑	↑	↓ Immotile sperm, ↑ Progressive motility, ↑ testes weight, ↓ SDF	
Fatehi et al., 2017 (30)	NMRI mice	50 mg/kg – 7 days	↑	↓	↑	↑	↓ SDF	γ-ray
Ali Mehr & Parisoush, 2016 (35)	Taleshi ram	0, 50, 100, 150 and 200 µg/ml – 72 hours <i>in vitro</i>	↑			↑	↑ Acrosome and plasma membrane integrity, ↓ MDA	
Ziaeirad et al., 2015 (36)	Rooster	100 µg/mL – 48, 72 hours	↑			↑	↓ MDA	
Eskandari et al., 2017 (37)	Ram	20 µM – 180 min <i>in vitro</i>					↓ SDF	Sodium arsenite
Eskandari et al., 2016 (38)	Ram	20 µM – 180 min					↑ Acrosome integrity	Sodium arsenite
Shafiei-Roudbari et al., 2017 (41)	Wistar rats	50 mg/kg – 10 days	↑	↓		↑	↓ Sperm DNA fragmentation, ↓ nitric oxide, ↑ TAC	Doxorubicin
Heidari Khoei et al., 2018 (43)	Wistar rats	100, 200 mg/kg - 5 weeks	↑		↑	↑	↓ SDF, ↑ Normal sperm morphology (non-significant)	Diabetic
Abo El-atta et al., 2020 (47)	SD rat	200 mg/kg – 30 days	↑		↑		↑ Spermatogenesis, ↓ Abnormal morphology (%)	Malathion
Hamid et al., 2016 (48)	Albino rat	150 mg/kg – 35 days			↑	↑	↑ Testis weight	CCl <sub>4</sub>
Yaman et al., 2018 (50)	Wistar albino rats	200 mg/kg – 6 weeks	↑	↓		↑	↓ MDA, ↑ Spermatogenesis	Methotrexate
Khalil, 2002 (51)	Albino rat	151.2 mg/kg – 1 month					↑ Spermatogenesis	
Chen et al., 2015 (53)	ICR mice	5, 10, 20 mg/mL – 120 min <i>in vitro</i>	↓				↓ Glucose-activated sperm motility, ↓ VAP & VCL	High glucose (HG)
Abedi et al., 2016 (55)	Wistar rats	150 mg/kg – 28 days					↑ Spermatids, ↑ spermatozoa cells	
Attia et al., 2017 (56)	Rabbit bucks	5 and 10 g/kg – 8 weeks	↑			↑	↑ Sperm concentration, ↑ total sperm output	
Al-Moziel MS et al., 2020 (57)	Albino rat	100 mg/kg – 30 days	↑	↓	↑	↑	↑ Spermatogenesis	Tadalafil
Sahreen et al., 2013 (59)	SD rat	50 mg/kg – twice a week for eight weeks					↓ SDF	CCl <sub>4</sub>
Malekinejad et al., 2012 (61)	Wistar rat	50 mg/kg – 4 weeks					↓ SDF, ↓ carbonyl stress	Doxorubicin
Eskandari et al., 2016 (66)	Ram	20 µM – 180 min <i>in vitro</i>	↑			↑	↑ Intact mitochondrial membrane	Sodium arsenite
Choobineh et al., 2018 (67)	Ram	0.05, 0.1 and 0.15 mM – 180 min <i>in vitro</i>					↓ SDF, ↓ apoptosis	lithium chloride
Choobineh et al., 2018 (68)	Ram	0.1 and 0.15 mM – 180 min <i>in vitro</i>				↑	↑ Acrosome integrity	lithium chloride
Momeni et al., 2018 (69)	Ram	0.5 µM – 180 min <i>in vitro</i>	↑			↑	↑ Intact mitochondrial membrane	Aluminum

Momeni et al., 2015 (70)	Ram	0.5µM – 180 min <i>in vitro</i>					↑ Sperm plasma membrane integrity, ↑ sperm acrosome integrity	Aluminum Chloride
Anderson et al., 1998 (72)	Human	100, 200, 300, and 500 µM					↓ DNA damage	Trp-P-2 & IQ
Zahra Z et al., 2020 (74)	SD rat	200 mg/kg – 30 days	↑	↓	↑	↑	↓ DNA damage	BPA
El-Sheshtawy et al., 2017 (77)	Bull	0.18, 0.36, 0.54 and 0.72 mg/ml <i>in vitro</i>	↑	↓		↑	↑ Intact spermatozoa membranes	Cryopreservation

SM: Silymarin; NIMRI: Naval Medical Research Institute; SD: Sprague-Dawley; Mot: Motility; Abn: Abnormality; Cou: Count; Via: Viability; T&D: Against Toxin & Diseases; SDF: Sperm DNA fragmentation; BPA: Bisphenol A; TAC: Total antioxidant capacity; MDA: Malondialdehyde; MMP: Mitochondrial Membrane Potential; Trp-P-2 & IQ: 3-amino-1-methyl-5H-pyrido (4,3-b) indole & 2-amino-3-methylimidazo-(4,5-f) quinolone; VAP: average pathway velocity; VCL: curvilinear velocity; ↑: Increase or Improve; ↓: Decrease, (Comparison in the toxin/disease group with Silymarin + toxin/disease group).

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

Author, year (ref)	Species	Type of Response				Histology, Testicular biochemistry & PCR
		Dose of SM & Duration of treatment	T & D	Oxidative stress & Apoptosis		
Moshtaghion et al., 2013 (40)	<i>Wistar</i> rat	50 mg/kg - 42 days	Varicocele	↓ Ap, ↓ OS	↓ MDA, Maintain TTM, ↓ E2f1, ↓ dissociated germinal epithelium in the seminiferous tubules, ↑ negative TDI ↓ edema of connective tissue, ↑ Number of Leydig cells & Sertoli cells, ↑ percentage of seminiferous tubules and spermiogenesis indices	
Shafiei-Roudbari et al., 2017 (41)	<i>Wistar</i> rats	50 mg/kg – 10 days	Doxorubicin	↓ Ap, ↓ OS	↓ NO, ↓ E2F1 expression, ↑ TAC	
Heidari Khoei et al., 2018 (43)	<i>Wistar</i> rats	100, 200 mg/kg – 5 wk	Diabetic	↓ Ap, ↓ OS	↓ MDA, ↑ SOD, ↑ CAT (non-significant), ↓ LPO ↑ Bcl-2, ↓ Bax, ↓ Caspase-3	
Abo El-atta et al., 2020 (47)	SD rat	200 mg/kg – 30 days	Malathion		↑ Spermatogenesis, ↓ necrotic seminiferous tubules, ↑ Testicular weight	
Hamid et al., 2018 (48)	<i>Albino</i> rat	150 mg/kg – 35 days	CCl <sub>4</sub>	↓ OS	↑ Testis weight, the tail of the sperm are thin and the sperm offspring are similar to the normal state	
Sheweita SA et al., 2016 (49)	Rat	25 mg/kg – 1 wk	B[a]P		↑ CAT, ↑ GPx, ↑ SOD, ↓ TBARS, ↓ edema, ↓ necrotic seminiferous tubule, ↑ 17 HSD activity	
Yaman et al., 2018 (50)	<i>Wistar albino</i> rats	200 mg/kg – 6 wks	Methotrexate	↓ OS	↓ Atrophy & degeneration of germinal cells, ↑ Spermatogenesis, ↓ pathomorphological changes in the spermatogonia, ↓ interstitial edema, ↑ SOD2, ↑ GPx1, ↑ CAT	
Yaman et al., 2018 (50)	<i>Wistar albino</i> rats	200 mg/kg – 6 wks		↓ OS	↑ GPx1, ↑ CAT, ↓ MDA	
Khalil, 2002 (51)	<i>Albino</i> rat	151.2 mg/kg – 1 month			↑ Spermatogenesis	
Çeribas et al., 2020 (52)	Japanese quail chicks	Diet including 1% MTS – 35 days	High energy diets (HED)	↓ OS	↑ Round spermatid & Elongated spermatid ↑ sperm count, ↓ MDA	
El-Hady A et al., 2015 (54)	<i>Albino</i> rat	18 mg/Kg - 3 times/week for 2 months	Mobile phone radiation	↓ OS	↑ Number of Leydig cells, ↑ seminiferous tubules diameter, ↑ total protein, ↑ DNA content of the nuclei of spermatogenic cells and Leydig cells, ↓ collagen fibers	
Sahreen et al., 2013 (59)	SD rat	50 mg/kg – twice a week for 8 wk	CCl <sub>4</sub>	↓ OS	↓ TBARS & H <sub>2</sub> O <sub>2</sub> , ↑ SOD, ↑ CAT ↑ GSH, ↑ GST, ↑ GPx, ↓ abnormality of germinative epithelium, ↓ sperm with abnormal shape	

Faraji et al., 2018 (60)	NMRI mice	100 mg/kg – 24 hr	Cadmium	↓ OS	↑ TAC, ↑ SOD, ↑ CAT, ↑ GPx, ↓ MDA, ↑ the testis diameter, wall thickness of the seminiferous tubules, and nucleus diameter of spermatogonia
Malekinejad et al., 2012 (61)	Wistar rat	50 mg/kg – 4 wk	Doxorubicin	↓ OS	↓ Interstitial edema, ↑ Depletion of the seminiferous tubules, ↓ c-myc expression
Rafiee et al., 2016 (62)	Wistar rat	50 mg/kg – 28 days	CCl <sub>4</sub>	↓ OS	↑ Spermiogenesis index, ↑ absolute testis weight, ↑ seminiferous tubules diameter, ↓ MDA, ↑ CAT, ↑ the thickness of the epithelium
Ali Shah et al., 2017 (71)	SD rat	200 mg/kg – 60 days	CCl <sub>4</sub>	↓ OS	↑ SOD, ↑ CAT, ↑ POD, ↑ GSH, ↑ GST, ↑ GPx, ↓ TBARS, ↑ the morphology of the seminiferous tubules & the density of germ cells
Zahra Z et al., 2020 (74)	SD rat	200 mg/kg – 30 days	BPA	↓ OS	↑ Seminiferous tubules diameter, ↑ testis weight, ↑ GSH, ↑ CAT, ↑ SOD, ↓ TBARS & H <sub>2</sub> O <sub>2</sub> , ↓ ROS
Sajedianfard et al., 2016 (75)	Wistar rat	175 mg/kg – 14 days	Busulfan	↓ OS	↑ SOD, ↑ GPx, ↓ MDA
Kashif Saleemi et al., 2019 (76)	Japanese quails	250 mg/kg – 60 days	Cadmium		↑ Spermatogenesis, ↑ testis volume, ↑ testis weight
Marzban et al., 2017 (78)	SD rat	100, 200 mg/kg – 24 hr	γ-ray	↓ Ap	↑ Tube diameter, ↑ the height of seminiferous epithelium, ↑ number of spermatogonia, primary spermatocyte, round spermatid, spermatozoa, ↓ Leydig cell apoptosis
Chen et al., 2019 (79)	SD rat	150 mg/kg – 20 wk	AGE		↑ Number of epididymal sperm, ↓ abnormal sperm rate, ↓ MDA

SM: Silymarin; NIMRI: Naval Medical Research Institute; SD: Sprague-Dawley; Ap: Apoptosis; OS: Oxidative Stress; CAT: Catalase; SOD: Superoxide dismutase; BPA: Bisphenol A; B[a]P: benzo[a]pyrene; LPO: Lipid peroxidation; TAC: Total antioxidant capacity; GSH-Px: Glutathione peroxidase; MDA: Malondialdehyde; GST: Glutathione S Transferase; ROS: Reactive oxygen species; T & D: Against Toxin & Diseases; AGE: Advanced glycation end products; TBARS: Thiobarbituric Acid Reactive Substances; H<sub>2</sub>O<sub>2</sub>: Hydrogen peroxide; HSD: 17-β hydroxysteroid dehydrogenase; NO: Nitric oxide; TDI: tubular differentiation index; Gpx: Glutathione peroxidase; ↑: Increase or Improve; ↓: Decrease, (Comparison in the toxin/disease group with Silymarin + toxin/disease group).

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

Author, year (ref)	Species	Type of Response			
		Dose of SM & Duration of treatment	Endocrinology	Blood biochemistry	T & D
Heidari Khoei et al., 2018 (43)	Wistar rats	100 and 200 mg/kg - 5 wk	↑ T		Diabetic
Abo El-atta et al., 2020 (47)	SD rat	200 mg/kg – 30 days	↑ FSH, ↑ LH		
Abo El-atta et al., 2020 (47)	SD rat	200 mg/kg – 30 days	↑ FSH, ↑ LH, ↑ T	↑ BuChE	Malathion
Khalil, 2002 (51)	Albino rat	151.2 mg/kg – 1 month	↑ T, ↑ LH, estradiol not changed		
Abedi et al., 2016 (55)	Wistar rat	150 mg/kg – 28 days	↑ FSH, ↑ LH, ↑ T, ↑ GnRH		
Attia et al., 2017 (56)	Rabbit bucks	5 and 10 g/kg - 8 wk	↑ T	↓ ALT, ↑ TAC (non-significant)	
Al-Moziel MS et al., 2020 (57)	Albino rat	100 mg/kg – 30 days	↑ FSH, ↑ LH, ↑ T		Tadalafil
Sahreen et al., 2013 (59)	SD rat	50 mg/kg – twice a week for 8 wk	↑ FSH, ↑ LH, ↑ T, ↓ Prolactin, ↓ Estradiol	↑ SOD, ↑ CAT, ↑ GSH, ↑ GST, ↑ GPx	CCl <sub>4</sub>
Faraji et al., 2018 (60)	NMRI mice	100 mg/kg – 24 hrs	↑ T	↓ MDA	Cadmium chloride
Malekinejad et al., 2012 (61)	Wistar rat	50 mg/kg – 4 wk	↑ FSH, ↑ LH, ↑ T, ↑ IB		Doxorubicin

Rafiee et al., 2016 <a href="#">(62)</a>	<i>Wistar</i> rat	50 mg/kg – 28 days	↑ T		CCl <sub>4</sub>
Ali Shah et al., 2017 <a href="#">(71)</a>	<i>SD</i> rat	200 mg/kg – 60 days	↑ T		CCl <sub>4</sub>
Zahra Z et al., 2020 <a href="#">(74)</a>	<i>SD</i> rat	200 mg/kg – 30 days	↑ FSH, ↑ LH, ↑ T		BPA

SM: Silymarin; NIMRI: Naval Medical Research Institute; SD: Sprague-Dawley; T: Testosterone; MDA: Malondialdehyde; CAT: Catalase; GSH-Px: Glutathione peroxidase; SOD: Superoxide dismutase; TAC: Total antioxidant capacity; LH: Luteinizing hormone; GnRH: Gonadotropin-releasing hormone; FSH: Follicle-stimulating hormone; ALT: Alanine aminotransferase activity; BPA: Bisphenol A; IB: Inhibin B; BuChE: butyryl Cholinesterase; ↑: Increase or Improve; ↓: Decrease; T&D: Against Toxin & Diseases, (Comparison in the toxin/disease group with Silimarin + toxin/disease group).

## Discussion

The present study was performed to investigate the antioxidant effect of silymarin in the male reproductive system that has been exposed to toxins and environmental pollutants.

Spermatogenesis is a coordinated, orderly, long, and complex process that takes place in the germinal epithelium [\(28, 29\)](#). On the Other hand, seminiferous tubules are very sensitive to endogenous and exogenous stresses and exposure of the testicle to such conditions affects the somatic cells or germ cells at various stages of differentiation and leads to temporary or permanent irreversible infertility [\(30\)](#).

Many studies based on human and animal exposure to environmental toxins showed the negative impact of toxins on sperm quality and quantity [\(63\)](#). These toxins may also damage the DNA of sperm [\(63- 65\)](#). Although silymarin therapy has an effective role in the improvement of sperm-related parameters and fertility against various toxins [\(68, 69, 71, 72\)](#). Research has shown that silymarin increases the concentration of norepinephrine. Norepinephrine is one of the factors that could influence the hypothalamus-pituitary-testis axis, and it increases GnRH and gonadotropins (LH and FSH hormones) through the synthesis of nitric oxide [\(48, 55\)](#). There is a relationship between the concentration of LH and the number of spermatogenic cells [\(48\)](#). LH by binding to Leydig cell increases the secretion of testosterone. Testosterone is an important factor in the spermatogenesis process [\(55\)](#). Also, FSH by binding to the Sertoli cell able to increase the concentration of ABP (androgen binding protein) and ABP can increase the concentration of

testosterone in the seminiferous tubule to promote spermatogenesis [\(8, 55\)](#). On the other hand, silymarin can illustrate its antioxidant properties in 5 ways, such as 1. Direct scavenging of free radicals, 2. Preventing the formation of free radicals by inhibiting the specific enzymes responsible for their production of them, or by maintaining the integrity of the mitochondrial electron transfer chain, 3. By participating in maintaining the optimal redox conditions (oxidation and reduction) of the cell by activating a range of antioxidant enzymes and non-enzymatic antioxidants, 4. Activation of protective genes, responsible for the synthesis of protective molecules, including HSP (Heat shock proteins) and thioredoxin, 5. Reducing inflammatory responses by inhibiting NF-κB (Nuclear Factor-κB) pathways [\(22, 23\)](#).

Silymarin with its antioxidant effect can counteract the effects of various toxins such as sodium arsenite [\(66\)](#), lithium chloride [\(67, 68\)](#), aluminum [\(69, 70\)](#), tetrachloride Carbon [\(48, 71\)](#), Trp-P-2 and IQ [\(72\)](#), malathion [\(47\)](#), doxorubicin [\(61\)](#), acetate [\(73\)](#), methotrexate [\(50\)](#), nicotine [\(6\)](#), bisphenol A [\(74\)](#), busulfan [\(75\)](#) and cadmium [\(5, 60, 76\)](#). Silymarin also exerts similar beneficial effects on the side effects of diseases such as diabetes and varicocele [\(40, 43\)](#).

Spermatogenesis is a dynamic and controlled process that involves spermatogonia proliferation, meiotic divisions of spermatocytes, and differentiation of spermatids into sperm [\(44\)](#).

Sertoli cells and the height of the germinal epithelium regulate spermatogenesis by providing structural and nutritional support to the germ cells. Sertoli cells also control germ cell populations through apoptotic pathways [\(39, 45\)](#).

In addition to the physiological apoptosis of germ cells that occurs continuously throughout life, external disorders such as radiation or exposure to toxic substances increase the apoptosis (39).

Besides, silymarin can be considered a promising plant protection agent in complementary medicine that may act an important role in protecting spermatocytes against the potential effects of freezing damage and  $\gamma$ -rays (30, 77, 78).

## Conclusion

The results of studies show that antioxidants in the male reproductive system reduce oxidative stress in the testis and improve spermatogenesis. Many studies have shown the protective and antioxidant properties of silymarin against damage from chemotherapeutic drugs and environmental toxins in sperm. Also, the main published studies show the positive effects of silymarin on increasing the quality and quantity of sperm. Therefore, it is recommended that silymarin be prescribed to treat diseases caused by the effects of oxidative stress on the male reproductive system and improve fertility.

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## Conflicts of Interest

There is no conflict of interest.

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