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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 withholds 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]

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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 (C25H22O10), 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 specie of Silybum Marianum

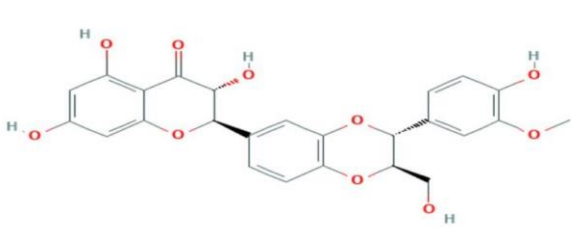

Fig 2. Chemical Structure Depiction (C25H22O10) of silymarin

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]).

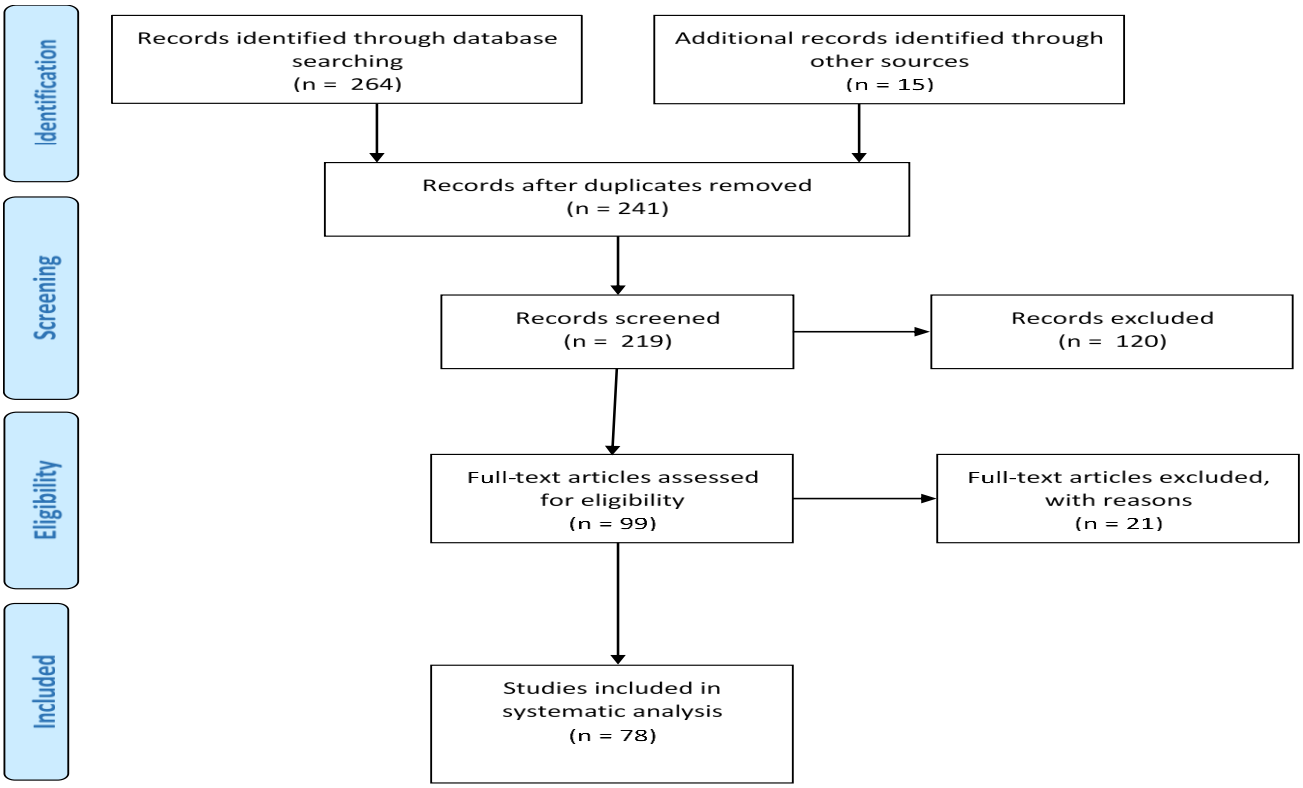

Fig 3. Preferred Reporting Items for Systematic Analysis (PRISMA) diagram: the flow of information through the different phases of a Systematic Review

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

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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 *in vitro*	↑			↑	↑ 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 *in vitro*					↓ 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_4
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 *in vitro*	↓				↓ 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_4
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 *in vitro*	↑			↑	↑ Intact mitochondrial membrane	Sodium arsenite
Choobineh et al., 2018 (67)	Ram	0.05, 0.1 and 0.15 mM – 180 min *in vitro*					↓ SDF, ↓ apoptosis	lithium chloride
Choobineh et al., 2018 (68)	Ram	0.1 and 0.15 mM – 180 min *in vitro*				↑	↑ Acrosome integrity	lithium chloride
Momeni et al., 2018 (69)	Ram	0.5 µM – 180 min *in vitro*	↑			↑	↑ Intact mitochondrial membrane	Aluminum

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Momeni et al., 2015 (70)	Ram	0.5µM – 180 min *in vitro*					↑ 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 in vitro	↑	↓		↑	↑ 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			
		Dose of SM & Duration of treatment	T & D	Oxidative stress & Apoptosis	Histology, Testicular biochemistry & PCR
Moshtaghion et al., 2013 (40)	*Wistar* 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)	*Wistar* rats	50 mg/kg – 10 days	Doxorubicin	↓ Ap, ↓ OS	↓ NO, ↓ E2F1 expression, ↑ TAC
Heidari Khoei et al., 2018 (43)	*Wistar* 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)	*Albino* rat	150 mg/kg – 35 days	CCl_4	↓ 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)	*Wistar albino* 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)	*Wistar albino* rats	200 mg/kg – 6 wks		↓ OS	↑ GPx1, ↑ CAT, ↓ MDA
Khalil, 2002 (51)	*Albino* 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)	*Albino* 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_4	↓ OS	↓ TBARS & H_2O_2, ↑ 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_4	↓ 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_4	↓ 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_2O_2, ↓ 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; H2O2: 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_4
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

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Rafiee et al., 2016 (62)	*Wistar* rat	50 mg/kg – 28 days	↑ T		CCl_4
Ali Shah et al., 2017 (71)	*SD* rat	200 mg/kg – 60 days	↑ T		CCl_4
Zahra Z et al., 2020 (74)	*SD* 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).

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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 γ-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.

References

1. Surai PF. Silymarin as a natural antioxidant: an overview of the current evidence and perspectives. Antioxidants. 2015 Mar;4(1):204-47. [view at publisher] [DOI] [PMID] [PMCID] [Google Scholar]

2. Soleimani V, Delghandi PS, Moallem SA, Karimi G. Safety and toxicity of silymarin, the major constituent of milk thistle extract: An updated review. Phytotherapy research. 2019 Jun;33(6):1627-38. [view at publisher] [DOI] [PMID] [Google Scholar]

3. Govind P, Sahni YP. A review on hepatoprotective activity of silymarin. Int J Res Ayurveda Pharm. 2011 Jan;2(1):75-9. [Google Scholar]

4. Zarif-Yeganeh M, Rastegarpanah M. Clinical role of silymarin in oxidative stress and infertility: A short review for pharmacy practitioners. Journal of research in pharmacy practice. 2019;8(4):181. [view at publisher] [DOI] [PMID] [PMCID] [Google Scholar]

5. Vahabzadeh M, Amiri N, Karimi G. Effects of silymarin on metabolic syndrome: a review. Journal of the Science of Food and Agriculture. 2018;98(13):4816-23. [view at publisher] [DOI] [PMID] [Google Scholar]

6. Mastron JK, Siveen KS, Sethi G, Bishayee A. Silymarin and hepatocellular carcinoma: a systematic, comprehensive, and critical review. Anti-Cancer Drugs. 2015;26(5):475-86. [view at publisher] [DOI] [PMID] [Google Scholar]

7. Gillessen A, Schmidt HH-J. Silymarin as supportive treatment in liver diseases: A narrative review. Advances in therapy. 2020;37(4):1279-301. [view at publisher] [DOI] [PMID] [PMCID] [Google Scholar]

8. Oufi HG, Al-Shawi NN, Hussain SA. What are the effects of silibinin on testicular tissue of mice? Journal of Applied Pharmaceutical Science.2012;2(11):9. [DOI] [Google Scholar]

9. Aghashahi M, Momeni HR, Darbandi N. Impact of aluminium toxicity on vital human sperm parameters-Protective effects of silymarin. Andrologia. 2020 Nov;52(10):e13742. [view at publisher] [DOI] [PMID] [Google Scholar]

10. Etemadi T, Momeni HR, Ghafarizadeh AA. Impact of silymarin on cadmium-induced apoptosis in human spermatozoa. Andrologia. 2020 Dec;52(11):e13795. [view at publisher] [DOI] [PMID] [Google Scholar]

11. Rahimi-Madiseh M, Mohammadi M, Hassanvand A, Ahmadi R, Shahmohammadi M, Rostamzadeh A. Assessment of the toxicity effects of nicotine on sperm and IVF and the potential protective role of silymarin-an

[DOR: 20.1001.1.26453509.2022.10.2.4.4]
[DOI: 10.52547/jorjanibiomedj.10.2.10]

experimental study in mice. Middle East Fertility Society Journal. 2020;25:1-9. [view at publisher] [DOI] [Google Scholar]

12. Xie Y, Zhang D, Zhang J, Yuan J. Metabolism, transport and drug-drug interactions of silymarin. Molecules. 2019 Jan;24(20):3693. [view at publisher] [DOI] [PMID] [PMCID] [Google Scholar]

13. Heyat F. Cellular and molecular mechanisms of the production of free radicals during exercise and their function on skeletal muscles. Journal of Fasa University of Medical Sciences. 2017 Jun 10;7(1):1-1. [view at publisher] [Google Scholar]

14. Fanaei H, Azizi Y, Khayat S. A review: role of oxidative stress in male infertility. Journal of Fasa University of Medical Sciences. 2013;3(2):93-103. [view at publisher] [Google Scholar]

15. Alahmar AT. Role of oxidative stress in male infertility: An updated review. Journal of human reproductive sciences. 2019;12(1):4. [view at publisher] [DOI] [PMID] [PMCID] [Google Scholar]

16. Crespy V, Williamson G. A review of the health effects of green tea catechins in in vivo animal models. The Journal of nutrition. 2004 Dec 1;134(12):3431S-40S. [view at publisher] [DOI] [PMID] [Google Scholar]

17. Birben E, Sahiner UM, Sackesen C, Erzurum S, Kalayci O. Oxidative stress and antioxidant defense. World Allergy Organization Journal. 2012;5(1):9-19. [view at publisher] [DOI] [PMID] [PMCID] [Google Scholar]

18. Liu Z, Ren Z, Zhang J, Chuang C-C, Kandaswamy E, Zhou T, et al. Role of ROS and nutritional antioxidants in human diseases. Frontiers in physiology. 2018;9:477. [DOI] [PMID] [PMCID] [Google Scholar]

19. Selvam MKP, Agarwal A, Henkel R, Finelli R, Robert KA, Iovine C, et al. The effect of oxidative and reductive stress on semen parameters and functions of physiologically normal human spermatozoa. Free Radical Biology and Medicine. 2020;152:375-85. [view at publisher] [DOI] [PMID] [Google Scholar]

20. Aitken RJ. Reactive oxygen species as mediators of sperm capacitation and pathological damage. Molecular reproduction and development. 2017;84(10):1039-52. [view at publisher] [DOI] [PMID] [Google Scholar]

21. Ramya T, Misro MM, Sinha D, Nandan D. Sperm function and seminal oxidative stress as tools to identify sperm pathologies in infertile men. Fertility and sterility. 2010 Jan 1;93(1):297-300. [view at publisher] [DOI] [PMID] [Google Scholar]

22. Pradhan SC, Girish C. Hepatoprotective herbal drug, silymarin from experimental pharmacology to clinical medicine. Indian journal of medical research. 2013 Feb 1;137(2). [view at publisher] [Google Scholar]

23. He L, He T, Farrar S, Ji L, Liu T, Ma X. Antioxidants maintain cellular redox homeostasis by elimination of reactive oxygen species. Cellular Physiology and Biochemistry. 2017;44(2):532-53. [view at publisher] [DOI] [PMID] [Google Scholar]

24. Dutta S, Majzoub A, Agarwal A. Oxidative stress and sperm function: A systematic review on evaluation and management. Arab journal of urology. 2019;17(2):87-97. [DOI] [PMID] [PMCID]

25. Saller R, Melzer J, Reichling J, Brignoli R, Meier R. An updated systematic review of the pharmacology of silymarin. Complementary Medicine Research. 2007;14(2):70-80. [view at publisher] [DOI] [PMID] [Google Scholar]

26. Jung YS, Kim SJ, Kim YS, Choi DW, Kim YC. Alterations in sulfur amino acid metabolism in mice treated with silymarin: a novel mechanism of its action involved in enhancement of the antioxidant defense in liver. Planta medica. 2013;79(12):997-1002. [view at publisher] [DOI] [PMID] [Google Scholar]

27. Fraschini F, Demartini G, Esposti D. Pharmacology of silymarin. Clinical drug

[DOR: 20.1001.1.26453509.2022.10.2.4.4]

[DOI: 10.52547/jorjanibiomedj.10.2.10]

investigation. 2002;22(1):51-65. [DOI] [Google Scholar]

28. Holstein AF, Schulze W, Davidoff M. Understanding spermatogenesis is a prerequisite for treatment. Reproductive Biology and Endocrinology. 2003 Dec;1(1):1-6. [view at publisher] [DOI] [PMID] [PMCID] [Google Scholar]

29. Junqueira LC, Carneiro J. Basic histologytext & atlas. 2005. [DOI] [PMCID] [ISI]

30. Fatehi D, Mohammadi M, Shekarchi B, Shabani A, Seify M, Rostamzadeh A. Radioprotective effects of Silymarin on the sperm parameters of NMRI mice irradiated with γ-rays. Journal of Photochemistry and Photobiology B:Biology.2018;178:489-95. [view at publisher] [DOI] [PMID] [Google Scholar]

31. Poljsak B, Šuput D, Milisav I. Achieving the balance between ROS and antioxidants: when to use the synthetic antioxidants. Oxidative medicine and cellular longevity. 2013;2013. [view at publisher] [DOI] [PMID] [PMCID] [Google Scholar]

32. Malmir M, Soleimani Mehranjani M, Naderi Noreini S, Faraji T. Protective antioxidant effects of N-acetylcysteine against impairment of spermatogenesis caused by paranonylphenol. Andrologia. 2018;50(10):e13114. [DOI] [PMID] [Google Scholar]

33. Rabaça A, Ferreira C, Bernardino R, Alves M, Oliveira P, Viana P, et al. Use of antioxidant could ameliorate the negative impact of etoposide on human sperm DNA during chemotherapy. Reproductive biomedicine online. 2020;40(6):856-66. [view at publisher] [DOI] [PMID] [Google Scholar]

34. Shahrzad E, Shariati M, Naimi S, Edalatmanesh MA. Protective effect of N-acetylcysteine on changes in serum levels of Pituitary-Gonadal axis hormones and testicular tissue in acrylamide-treated adult rats. Advances in Human Biology. 2020;10(1):16. [view at publisher] [DOI] [Google Scholar]

35. Roostaei-Ali Mehr M, Parisoush P. Effect of different levels of silymarin and caproic acid on storage of ram semen in liquid form. Reproduction in Domestic Animals. 2016;51(4):569-74. [DOI] [PMID] [Google Scholar]

36. Ziaei rad H, Rustaei Ali Mehr M, Mohammadi M. Effect of silymarin on rooster semen during storage at 4 C. Animal Science Researches. 2016;26(3):1-13. [Google Scholar]

37. Eskandari F, Momeni H. Effect of silymarin on DNA and nuclear integrity of ram sperm Treated with sodium arsenite. Journal of Cell & Tissue. 2016;7(4):429-36. [view at publisher] [Google Scholar]

38. Eskandari F, Momeni HR. Silymarin protects plasma membrane and acrosome integrity in sperm treated with sodium arsenite. International Journal of Reproductive BioMedicine. 2016;14(1):47. [DOI] [Google Scholar]

39. Asadi N, Bahmani M, Kheradmand A, Rafieian-Kopaei M. The impact of oxidative stress on testicular function and the role of antioxidants in improving it: a review. Journal of clinical and diagnostic research: JCDR. 2017;11(5):IE01. [DOI] [PMID] [PMCID] [Google Scholar]

40. Moshtaghion S-M, Malekinejad H, Razi M, Shafie-Irannejad V. Silymarin protects from varicocele-induced damages in testis and improves sperm quality: evidence for E2f1 involvement. Systems biology in reproductive medicine. 2013;59(5):270-80. [view at publisher] [DOI] [PMID] [Google Scholar]

41. Shafiei-Roudbari SK, Malekinejad H, Janbaz-Aciabar H, Razi M. Crosstalk between E2F1 and P53 transcription factors in doxorubicin-induced DNA damage: evidence for preventive/protective effects of silymarin. Journal of Pharmacy and Pharmacology. 2017;69(9):1116-24. [view at publisher] [DOI] [PMID] [Google Scholar]

42. Nashwa A, Kawkab A, Mouneir S. The protective effect of ginger and N-acetyl cysteine

[DOR: 20.1001.1.26453509.2022.10.2.4.4]

[DOI: 10.52547/jorjanibiomedj.10.2.10]

on ciprofloxacin-induced reproductive toxicity in male rats. Journal of American Science. 2011;7(7):741-52. [Google Scholar]

43. Heidari Khoei H, Fakhri S, Parvardeh S, Shams Mofarahe Z, Ghasemnejad-Berenji H, Nazarian H, et al. Testicular toxicity and reproductive performance of streptozotocin-induced diabetic male rats: the ameliorating role of silymarin as an antioxidant. Toxin reviews. 2019;38(3):223-33. [DOI] [Google Scholar]

44. Shaha C, Tripathi R, Mishra DP. Male germ cell apoptosis: regulation and biology. Philosophical Transactions of the Royal Society B: Biological Sciences. 2010;365(1546):1501-15. [view at publisher] [DOI] [PMID] [PMCID] [Google Scholar]

45. Boekelheide K, Fleming SL, Johnson KJ, Patel SR, Schoenfeld HA. Role of Sertoli cells in injury-associated testicular germ cell apoptosis. Proceedings of the Society for Experimental Biology and Medicine:Minireview.2000;225(2):105-15. [DOI] [Google Scholar]

46. Sabeti P, Pourmasumi S, Rahiminia T, Akyash F, Talebi AR. Etiologies of sperm oxidative stress. International Journal of Reproductive BioMedicine. 2016;14(4):231. [DOI] [Google Scholar]

47. Abo El-Atta H, Ahmed D. Testicular dysfunction in malathion induced toxicity in male rats: Protective role of NAC and Silymarin. Mansoura Journal of Forensic Medicine and Clinical Toxicology. 2020;28(2):33-45. [view at publisher] [DOI] [Google Scholar]

48. Hamid AK, Ahmed MA, Tayawi HM. Silymarin effect as an antioxidant to improve damages induced by CCl4 on some characteristics of male rats reproductive system. Tikrit Journal of Pure Science. 2018;23(2):60-5. [view at publisher] [DOI] [Google Scholar]

49. Sheweita SA, Al-Shora S, Hassan M. Effects of benzo [a] pyrene as an environmental pollutant and two natural antioxidants on biomarkers of reproductive dysfunction in male rats. Environmental Science and Pollution Research. 2016;23(17):17226-35. [DOI] [PMID] [Google Scholar]

50. Yaman T, Uyar A, Kaya MS, Keles ÖF, Uslu BA, Yener Z. Protective effects of silymarin on methotrexate-induced damages in rat testes. Brazilian Journal of Pharmaceutical Sciences. 2018;54(1). [view at publisher] [DOI] [Google Scholar]

51. Khalil EA. Hormonal profile and histopathological study on the influence of silymarin on both female and male albino rats. The Egyptian Journal of Hospital Medicine. 2003;13(1):112-22. [view at publisher] [DOI] [Google Scholar]

52. Çeribaşı S, Türk G, Özçelik M, Doğan G, Çeribaşı A, Mutlu Sİ, et al. Negative effect of feeding with high energy diets on testes and metabolic blood parameters of male Japanese quails, and positive role of milk thistle seed. Theriogenology. 2020;144:74-81. [DOI] [PMID] [Google Scholar]

53. Chen Y-C, Pan L-C, Lai C-W, Chien Y-S, Wu T-H. Silymarin and protein kinase A inhibitor modulate glucose-mediated mouse sperm motility: An in vitro study. Reproductive biology. 2015;15(3):172-7. [DOI] [PMID] [Google Scholar]

54. El-Hady A, Mahmoud A, El-Tahawy NAE-L. The possible protective effect of vitamin E and⁄or silymarin on rat testes exposed to 950MHz electromagnetic field. Journal of Bioscience and Applied Research. 2015;1(3):97-111. [view at publisher] [DOI] [Google Scholar]

55. Abedi H, Jahromi HK, Hashemi S, Jashni HK, Jahromi ZK, Pourahmadi M. The effect of silymarin on spermatogenesis process in rats. Int Sci J Med Res Health Sci. 2016;5:146-50. [Google Scholar]

56. Attia YA, Hamed RS, Bovera F, Abd El AE-HE, Al-Harthi MA, Shahba HA. Semen quality, antioxidant status and reproductive performance of rabbits bucks fed milk thistle seeds and rosemary leaves. Animal reproduction science. 2017;184:178-86. [DOI] [PMID] [Google Scholar]

[DOR: 20.1001.1.26453509.2022.10.2.4.4]
[DOI: 10.52547/jorjanibiomedj.10.2.10]

57. Al-Moziel Ms, Kadhum Hj, Ghanim Wk. Effects of Tadalafil and/or Silymarin On Gonadal Function in Adults Male Albino Rats. Basjvetres. 2018;17(2):147-60. [Google Scholar]

58. McBride JA, Coward RM. Recovery of spermatogenesis following testosterone replacement therapy or anabolic-androgenic steroid use. Asian journal of andrology. 2016;18(3):373. [DOI] [PMID] [PMCID] [Google Scholar]

59. Sahreen S, Khan MR, Khan RA. Ameliorating effect of various fractions of Rumex hastatus roots against hepato-and testicular toxicity caused by CCl4. Oxidative medicine and cellular longevity. 2013;2013. [view at publisher] [DOI] [PMID] [PMCID] [Google Scholar]

60. Faraji T, Momeni HR, Malmir M. Protective effects of silymarin on testis histopathology, oxidative stress indicators, antioxidant defence enzymes and serum testosterone in cadmium-treated mice. Andrologia. 2019;51(5):e13242. [DOI] [PMID] [Google Scholar]

61. Malekinejad H, Janbaz-Acyabar H, Razi M, Varasteh S. Preventive and protective effects of silymarin on doxorubicin-induced testicular damages correlate with changes in c-myc gene expression. Phytomedicine : international journal of phytotherapy and phytopharmacology. 2012;19(12):1077-84. [DOI] [PMID] [Google Scholar]

62. Rafiee F, Nejati V, Heidari R, Ashraf H. Protective effect of methanolic extract of Berberis integerrima Bunge. root on carbon tetrachloride-induced testicular injury in Wistar rats. International Journal of Reproductive BioMedicine. 2016;14(2):133. [DOI] [Google Scholar]

63. Mima M, Greenwald D, Ohlander S. Environmental toxins and male fertility. Current urology reports. 2018;19(7):1-8.doi: 10.1007/s11934-018-0804-1 [DOI] [PMID] [Google Scholar]

64. Goldstone AE, Chen Z, Perry MJ, Kannan K, Louis GMB. Urinary bisphenol A and semen quality, the LIFE Study. Reproductive Toxicology. 2015;51:7-13. [DOI] [PMID] [PMCID] [Google Scholar]

65. Wang Y-X, Zeng Q, Sun Y, You L, Wang P, Li M, et al. Phthalate exposure in association with serum hormone levels, sperm DNA damage and spermatozoa apoptosis: A cross-sectional study in China. Environmental research. 2016;150:557-65. [DOI] [PMID] [Google Scholar]

66. Eskandari F, Momeni HR. Protective effect of silymarin on viability, motility and mitochondrial membrane potential of ram sperm treated with sodium arsenite. International Journal of Reproductive BioMedicine. 2016;14(6):397. [DOI] [Google Scholar]

67. Choobineh T, Khodaei-Motlagh M, Momeni H, Darbandi N. Effect of silymarin and lithium chloride on DNA integrity in epididymal ram sperm. Journal of Cell & Tissue. 2018;9(1):76-85. [view at publisher] [Google Scholar]

68. Choobineh T, Momeni H, Khodaei Motlagh M, Darbandi N, Khavari A. Study of Antioxidant Properties of Silymarin in Dealing with the Toxicity of Lithium Chloride in Ram Sperm. Iranian Journal of Animal Science Research. 2018;9(4):498-506. [Google Scholar]

69. Momeni H, Sepehri H, Yosefi M, Eskandari N. Protective effect of silymarin on viability, motility and mitochondrial membrane potential in spermatozoa treated with alominium. Journal of Cell & Tissue. 2018;9(2):102-11. [view at publisher] [Google Scholar]

70. Momeni HR, Sepehri H, Yosefi M. Effect of Silymarin on Plasma Membrane and Acrosome of Sperm Treated with Aluminum Chloride. Journal of Arak University of Medical Sciences. 2015;18(4):71-80. [Google Scholar]

71. Shah NA, Khan MR. Increase of glutathione, testosterone and antioxidant effects of Jurenia dolomiaea on CCl 4 induced testicular toxicity in rat. BMC complementary and alternative medicine. 2017;17(1):1-9. [DOI] [PMID] [PMCID] [Google Scholar]

[DOR: 20.1001.1.26453509.2022.10.2.4.4]

[DOI: 10.52547/jorjanibiomedj.10.2.10]

72. Anderson D, Dobryńska M, Başaran N, Başaran A, Yu T-W. Flavonoids modulate comet assay responses to food mutagens in human lymphocytes and sperm. Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis. 1998;402(1-2):269-77. [DOI] [Google Scholar]

73. AL-Naimi RA. The therapeutic effect of Silybum marianum on the lead acetate induced-reproductive toxicity in both gender laboratory rats. Journal Of Wassit For Science & Medicine. 2012;5(1). [Google Scholar]

74. Zahra Z, Khan MR, Majid M, Maryam S, Sajid M. Gonadoprotective ability of Vincetoxicum arnottianum extract against bisphenol A-induced testicular toxicity and hormonal imbalance in male Sprague Dawley rats. Andrologia. 2020;52(6):e13590. [DOI] [PMID] [Google Scholar]

75. Sajedianfard J, Nazifi S, Izadi A, Chahardahcherik M, Honarmand M. Effect of various doses of silymarin on the oxidative stress induced by busulfan administration in the different organs of rats. Turkish Journal of Pharmaceutical Sciences. 2016;13(2). [DOI] [Google Scholar]

76. Saleemi MK, Tahir MW, Abbas RZ, Akhtar M, Ali A, Javed MT, et al. Amelioration of toxicopathological effects of cadmium with silymarin and milk thistle in male Japanese quail (Coturnix japonica). Environmental science and pollution research. 2019;26(21):21371-80. [DOI] [PMID] [Google Scholar]

77. El-Sheshtawy R, El-Nattat W. Impact of silymarin enriched semen extender on bull sperm preservability. Asian Pacific Journal of Reproduction. 2017;6(2):81. [view at publisher] [DOI] [Google Scholar]

78. Marzban M, Anjamshoa M, Jafari P, Masoumi H, Ahadi R, Fatehi D. Effects of gamma rays on rat testis tissue according to the morphological parameters and immunohistochemistry: radioprotective role of silymarin. Electronic physician. 2017;9(6):4524. [DOI] [PMID] [PMCID] [Google Scholar]

79. Chen M-C, Lin J-A, Lin H-T, Chen S-Y, Yen G-C. Potential effect of advanced glycation end products (AGEs) on spermatogenesis and sperm quality in rodents. Food & function. 2019;10(6):3324-33. [view at publisher] [DOI] [PMID] [Google Scholar]

.

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[DOR: 20.1001.1.26453509.2022.10.2.4.4]

[DOI: 10.52547/jorjanibiomedj.10.2.10]