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Original Article

Protective effects of phenolic phytochemicals on male fertility: a narrative review

Efeitos protetores dos compostos fitoquímicos fenólicos na fertilidade masculina

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Abstract

Infertility is a global health issue and is closely related to oxidative stress, which occurs when high concentrations of free radicals surpass the protective effects of antioxidant molecules and enzymes. Such imbalance causes damage to DNA, as well as cellular proteins and lipids, ultimately leading to the destruction of the blood-testis barrier. This, in turn, hinders spermatogenesis. Various plants and compounds have been employed in an attempt to reverse these damages, such as phenolic compounds. Therefore, this review aims to identify the main phytochemical phenolic compounds and their respective effects when used in the treatment of male infertility. Related information concerning phenolic phytochemical compounds was gathered from studies selected from PubMed, Scopus, and Web of Science databases. The search was conducted using the combination of six terms: “phenolic compounds”, “male infertility”, “testis”, “spermatozoa”, “testosterone” and “male fertility”. These compounds can raise testosterone levels, reduce lipid peroxidation, and improve tubular histoarchitecture in cases of subfertility associated with diabetes mellitus. They can also mitigate the damage caused by obesity by increasing serum testosterone, antioxidant activity, and sperm motility. When it comes to fertility problems caused by inorganic and organic pollutants, these compounds effectively restore the structure of the seminiferous tubules, increase testosterone levels, and improve sperm quality. Furthermore, phenolic phytochemical compounds have shown beneficial effects in countering the adverse impacts of certain drugs on testicular physiology by reducing apoptosis in testicular tissue, increasing the number of Leydig cells, and promoting spermatocyte production. However, while these compounds may have protective effects on sperm cryopreservation for in vitro fertilization, caution is needed as certain dosages can cause irreversible damage to sperm quality. Overall, plant extracts containing phenolic phytochemical compounds hold promise as a therapeutic avenue for treating infertility and subfertility caused by metabolic disorders and environmental pollutants.

Keywords: phenolic compounds, male infertility, phytotherapy, oxidative stress, antioxidants.

Resumo

A infertilidade é um problema de saúde global e está intimamente relacionada com o stress oxidativo, que ocorre quando elevadas concentrações de radicais livres ultrapassam os efeitos protetores das moléculas e enzimas antioxidantes. Este desequilíbrio provoca danos no DNA, bem como nas proteínas e lipídeos celulares, levando, em última instância, à destruição da barreira hemato-testicular. Isto, por sua vez, prejudica a espermatogênese. Diversas plantas e compostos têm sido utilizados na tentativa de reverter esses danos. Portanto, esta revisão tem o objetivo de identificar os principais compostos fitoquímicos fenólicos e seus respectivos efeitos quando utilizados no tratamento da infertilidade masculina. A informação relacionada aos compostos fitoquímicos fenólicos foi obtida a partir de estudos selecionados nas bases de dados PubMed, Scopus e Web of Science. A pesquisa foi efetuada utilizando a combinação de seis termos: “phenolic compounds” (compostos fenólicos), ‘male infertility’ (infertilidade masculina), ‘testis’ (testículos), ‘spermatozoa’ (espermatozóides), ‘testosterone’ (testosterona) e ‘male fertility’ (fertilidade masculina). Estes compostos podem aumentar os níveis de testosterona, reduzir a peroxidação lipídica e melhorar a histoarquitetura tubular em casos de subfertilidade associada à diabetes mellitus. Podem igualmente atenuar os danos causados pela obesidade, aumentando a testosterona sérica, a atividade antioxidante e a motilidade dos espermatozoides. Quando se trata de problemas de fertilidade causados por poluentes inorgânicos e orgânicos, estes compostos restauraram de forma eficaz a estrutura dos túbulos seminíferos, aumentam os níveis de testosterona e melhoram a qualidade espermática. Além disso, os compostos fitoquímicos fenólicos demonstraram efeitos benéficos no combate aos impactos adversos de certos medicamentos na fisiologia testicular, reduzindo a apoptose no tecido testicular, aumentando o número de células de Leydig e promovendo a produção de espermatócitos. No entanto, embora estes compostos possam ter efeitos protetores na criopreservação de esperma para fertilização *in vitro*, é necessário ter cautela, uma vez que certas dosagens podem causar danos

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irreversíveis na qualidade do esperma. Em geral, os extratos de plantas contendo compostos fitoquímicos fenólicos são promissores como via terapêutica para o tratamento da infertilidade e subfertilidade causadas por distúrbios metabólicos e poluentes ambientais.

Palavras-chave: compostos fenólicos, infertilidade masculina, fitoterapia, estresse oxidativo, antioxidants.

1. Introduction

Infertility is a prevalent worldwide health problem, characterized by the inability of a couple to achieve pregnancy without the use of contraceptive methods, after one year. It is estimated that infertility affects about 9% of couples worldwide, with male factor contributing to approximately 50% of cases (Fainberg and Kashanian, 2019). Male infertility takes place due to genetic, anatomical, physiological, and immunological factors, as well as due to infections, varicocele, age, and lifestyle. Regardless of the cause, many of these conditions induce oxidative stress, which plays an important role as the molecular basis of male infertility (Leaver, 2016; Noordin et al., 2020; Sengupta et al., 2018).

Oxidative stress results from an increase in the generation of free radicals, mainly reactive oxygen species (ROS), and a reduction in antioxidant defense mechanisms (Noordin et al., 2020; Tvrdá et al., 2016). Human semen contains endogenous antioxidants to protect sperm from oxidative stress, which can be enzymatic and non-enzymatic antioxidants (Sengupta et al., 2018). Although small amounts of ROS are essential for sperm capacitation, hyperactivation, acrosome reaction, and gamete fusion (Sengupta et al., 2018; Mani et al., 2021), problems such as lipid peroxidation of the sperm cell membrane, DNA fragmentation, and, thus, apoptosis, can occur when the level of ROS production becomes excessive, negatively affecting sperm parameters (Takeshima et al., 2020).

Several plants show therapeutic potential to increase sperm quality such as the *Eryngium caucasium*, native to northern Iran, *Mallotus roxburghianus* Müll, which is found in Nepal and China, *Euterpe oleracea Mart.,* which can be found in regions of the Amazon *Rainforest* and the *Eruca sativa var. eriocarpa* (Boiss.) that can be found in Spain. One feature that these plants have in common is the presence of phenolic phytochemical compounds that, in adequate amounts, help maintain the spermatogenic process, as will be discussed later in this review.

Phenolic phytochemicals are natural bioactive compounds with high antioxidant potential, which protect biomolecules, avoiding the deleterious effects caused by oxidative damage through the elimination of free radicals, in addition to inhibiting or delaying the oxidation of substrates (Mani et al., 2021; Mahfuz et al., 2021). Therefore, several studies have reported using phenolic phytochemical compounds, such as flavonoids, tannins, and phenolic acids, to treat male infertility (Noordin et al., 2020; Mani et al., 2021). Thus, such compounds could be used as a valuable tool for the treatment of male subfertility due to their antioxidant capacity.

This study aims to show the use of phenolic phytochemical compounds in several contexts, such as in the reversion of damage in male fertility due to (1) diabetes mellitus, (2) obesity, (3) inorganic and (4) organic pollutants, (5) adverse effects caused by medications, and their effects on (6) sperm cryopreservation. Besides, this review aims to answer the following questions: What are the effects of these compounds when used in treating male infertility? Can these compounds effectively reverse male infertility or improve fertility? In this way, it will be possible to provide an overview for future research that aims to use such compounds to improve male reproductive health.

2. Material and Methods

The search protocol was devised following the PICO (population, intervention, comparison, and outcomes) strategy (Methley et al., 2014). Different key terms such as "phenolic compounds", "male infertility", "testis", "spermatozoa", "testosterone" and "male fertility" were searched online using PubMed, Scopus, and Web of Science databases. The search was carried out in all chosen databases using the previously elaborated search strategy. The Boolean operator "AND" was used to combine the term "phenolic compounds" with each of the other terms, resulting in the following combinations: (phenolic compounds* AND male infertility*), (phenolic compounds* AND testis*), (phenolic compounds* AND spermatozoa*), (phenolic compounds* AND testosterone*) and (phenolic compounds* AND male fertility*). The generated database was organized using the "EndNote" software, through which duplicate articles were automatically and manually excluded (Table 1).

The articles were selected according to the eligibility criteria, answering the following questions: (1) Is this a randomized clinical trial or a pre-clinical study? (2) Does it have phenolic phytocompounds as the only intervention strategy if there is no simultaneous administration of compounds (i.e. the treatment of male infertility)?; (3) Was it written in English or Portuguese? The answer "yes" to all questions, which are inclusion criteria, is a necessary and sufficient condition for inclusion in the study. On the other hand, articles that answered affirmatively to the following questions were excluded: (1) Does it have a design different from that established?; (2) Performed any fertility analysis?; (3) Were phenolic compounds not extracted from plants?; (4) Is the abstract unavailable online? The answer "yes" to all these questions, which are exclusion criteria, is a necessary and sufficient condition for exclusion from the study.

3. Results

3.1. Identification of studies

From 1975 to 2024, 1559 articles were found, from which 830 duplicates were excluded, resulting in 724 articles.

Table 1. The action of phenolic compounds in the treatment of diseases of the male reproductive tract.

Reference	Pathology	Damage caused by pathology	Extract used	Animal	Dose administered	Principal effects of the compound
Afshari et al. (2019)	Diabetes *Mellitus*	* Decreased testosterone levels in diabetic subjects *Increased MDA levels	Hydroalcoholic extract of *Eryngium caucasium* Trautv.	Wistar rats	100, 200, and 300 mg/kg	*Increased serum testosterone levels in individual diabetics, * Decreased MDA, decreased NO
Akomolafe et al. (2015)	Erectile dysfunction	*Increased arginase activity *Increased AChE activity	Aqueous extract of *Tetracarpidium conophorum* (Müll. Arg.) Hutch. & Dalziel	Wistar rats	0-200 µL/mg	*Increased penile and testicular endothelial cell function *Inhibition of AChE activity
Eleazu et al. (2022)	Prostatic hyperplasia	*Increased prostate weight *Increased levels of pro-inflammatory cytokines *Increased lipid peroxidation and oxidative stress	Hydroalcoholic extract of *Colocasia esculenta* (L.) Schott.	Wistar rats	100, 200, and 400 mg/kg	*Attenuation of prostatic inflammation * Decreased concentration of swelling-related prostate proteins *Normalization of prostatic histological parameters
Jahromi et al. (2017)	Testicular torsion	*Increased severity of lesions in the testicular parenchyma * Increased MDA levels *Damage to spermatogenesis	Aqueous extract of *Phoenix acaulis* Roxb.	Spraque-Dawley	500 mg/kg	*Recovery from damage in spermatogenesis * Decreased plasma MDA level * Testicular protective effect *Inhibition of testicular oxidative stress
Luo et al. (2019)	Obesity	* Decreased sperm motility *Increased sperm malformations * Decreased sperm concentration * Decreased antioxidant defenses	Isolated isoflavones	Spraque-Dawley	0, 50, 150, and 450 mg/kg	*Increased sperm motility *Increased sperm density * Decreased spermatogenic abnormalities *Increased expression of antioxidant enzymes
Ourique et al. (2013)	Hyperthyroidism	* Decreased sperm motility *Increased lipid peroxidation * Significant decrease in antioxidant defenses	Isolated resveratrol	Wistar rats	1 and 10 mg/kg	*Protection of sperm motility *Increased GST activity
Refat et al. (2021)	Inflammation	*Increased pro-inflammatory cytokines *Increased oxidative stress * Decreased antioxidant enzymes	Quercetin isolated	Wistar rats	20mg/kg	*Combats testicular oxidative stress * Decreased inflammatory cytokines *Increased antioxidant activity
Roy et al. (2015)	Diabetes *Mellitus*	*Alteration in the histoarchitecture of the seminiferous tubules *Increased MDA levels *Reduced testosterone levels * Decreased levels of antioxidant enzymes	Methanolic extract of *Mallotus roxburghianus* Müll.Arg	Wistar rats	100 and 400 mg/kg	* Decreased MDA levels *Increased testosterone level *Increased antioxidant enzymes *Improvement of the structure of the seminiferous tubules
Buncharoen et al. (2016)	Prostatic hyperplasia	*Increased MDA levels * Decreased levels of antioxidant enzymes * Increased prostate weight *Increased expression of androgen receptors	Ethanolic extract of *Uvaria rufa* Blume	Wistar rats	10 and 20 mg/kg	*Reduction of benign prostatic hyperplasia *5α-reductase inhibition *Reduced expression of androgen receptors in prostate tissue

After the first selection stage, 652 articles were excluded because they did not meet the inclusion criteria, while 1 was not found, resulting in 71 articles. After the second selection stage, 5 articles were excluded for not meeting the inclusion criteria, and, therefore, 71 articles remained for analysis.

3.2. Mechanism of action of phenolic phytochemical compounds on the testicular parenchyma

Based on the results obtained in this review, it was possible to propose, in an unprecedented way, a comprehensive discussion on the use and various applications of phenolic phytochemical compounds in the recovery and protection of male reproductive health. The main protective mechanism of these compounds seems to lie primarily in the modulation of oxidative stress, as discussed below.

Several environmental and physiological stressors have oxidative stress as a way of causing testicular changes such as the reduction in the number and volume of germ and somatic cells, atrophy of the seminiferous tubules, decrease in testosterone synthesis, decrease in sperm motility and viability and fragmentation of the sperm DNA from these cells (Roy et al., 2015; Allai et al., 2016). The set of these changes is capable of inducing male infertility, and in this sense, antioxidant therapy with phenolic compounds is useful to attenuate this condition.

After hepatic metabolism, which involves the methylation and glucuronidation processes that give the amphipathic nature of the structure of phenolic compounds, the process of absorption through cell plasma membranes becomes facilitated (Hussain, 2019). In the testicular parenchyma, phenolic compounds have antioxidant mechanisms as their primary target; by increasing the activity of enzymes such as catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx), phenolic compounds can change the redox balance, in favor of antioxidant production, of the testicular environment.

By balancing antioxidant defenses in the testis, processes such as lipid peroxidation, DNA fragmentation, and cellular apoptosis are marked by decreased overexpression of proinflammatory molecules such as the NF-kB, TNF-α, and iNOS (Fahmy et al., 2020) The modulation of inflammation is an important protective mechanism of phenolic phytochemical compounds. In contexts of injury, immune system cells such as neutrophils respond to antigens by releasing considerable amounts of free radicals at a systemic level. In the testicular microenvironment, high levels of free radicals cause damage to the cell membranes of germ cells and somatic cells, which leads to cell death processes and consequently reduced fertility (Mega et al., 2022).

An example of this protective mechanism in action is the study by Tinco-Jayo et al. (2024), which administered increasing doses (25, 50, 100, and 150 mg/kg) of atomized extract from the trunk and leaves of *Cnidoscolus diacanthus* (Pax & K. Hoffm.) to male and female mice. In this study, male subjects who received a 100 mg/kg dose of the plant extract showed higher serum testosterone levels. The authors attribute the pro-steroidogenic capacity of the extract to its phenolic compound, quercetin, known for its antioxidant and anti-inflammatory properties.

3.3. Effects of phenolic phytochemicals on testicular damage caused by diabetes mellitus

Several diseases affect the male reproductive system and some of them, through different mechanisms, lead to infertility. Diabetes Mellitus (DM) is a disease that causes dysfunction in the metabolism of proteins, lipids, and carbohydrates, due to the absence or non-functioning of the insulin hormone, which in turn generates a constant condition of hyperglycemia (Kharroubi and Darwish, 2015). In the male reproductive system, DM is capable of producing effects such as decreased testosterone concentration, increased lipid peroxidation of cell membranes, decreased activity of antioxidant enzymes, and abnormalities in the morphology of the seminiferous tubules, which in the long term can generate infertility (Omolaoye and Du Plessis, 1990).

Plant extracts with significant amounts of phenolic compounds can help manage the harmful effects of diabetes on the male reproductive system, as these compounds show antioxidant and anti-inflammatory activity. As observed in the study carried out by Afshari et.al (2019), who induced DM in rats through the administration of nicotinamide and streptomycin, and used the hydroalcoholic extract of *Eryngium caucasium*, rich in flavonoids, as a treatment, at doses of 100, 200 and 300 mg/kg. As a result, the testosterone level was increased, while lipid peroxidation markers (such as malondialdehyde - MDA) and nitric oxide (NO) were lower in the treated animals. Similar results were verified by Roy et al. (Roy et al., 2015), who induced DM in adult Wistar rats, through the administration of alloxan, and used treatment with 100 and 400 mg/kg of *Mallotus roxburghianus* Müll. Arg methanolic extract. Several phenolic compounds such as malotoxin, myricetin, kaempferol, bergenine, hydroxybenzoic acid, and gallic acid, were described within the extract, which shows great antioxidant biological activity. The extract showed a mitigating effect on the damage caused by DM, such as decreased MDA levels, increased testosterone levels, and normalization of the histoarchitecture of the seminiferous tubules.

3.4. Effects of phenolic phytochemicals on testicular damage caused by obesity

Obesity is defined as the excessive accumulation of adipose tissue in the body, and as DM, it is a public health problem. Obesity represents a risk factor for several diseases, such as arterial hypertension, diabetes, acute myocardial infarction, and cerebrovascular accident. Among the harmful mechanisms generated by obesity, such as increased body temperature, insulin resistance, and increased estrogen concentration, it is possible to highlight oxidative stress as one of the main forms of injury, since adipose tissue has a pro-inflammatory action, which in turn facilitates the production and exacerbated release of reactive oxygen species in obese individuals (Katib, 2015).

Furthermore, in obese individuals there is an increase in the amount of adipose tissue, and consequently an increase in the aromatase enzyme, which converts androgens into estrogens. High levels of estrogens can inhibit the hypothalamic release of gonadotropin-releasing hormone (GnRH), and consequently inhibit the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Soon obesity can lead to problems such as decreased testosterone concentration, decreased sperm quality, and reduced male fertility (Service et al., 2023; Sallmén et al., 2006). On the other hand, isoflavones have antiestrogenic activity due to the affinity of the estrogen receptors (Messina and Wood, 2008). Because of that, these molecules compete for the same receptors, decreasing their bioavailability and estrogen activity. In the study of Luo et al. (2019), the administration of isoflavones increased the antioxidant defenses, leading to higher sperm motility, rates, and concentration, with lower gamete abnormalities. Table 1 shows that phenolic phytochemical compounds can be applied in various contexts of damage to the male reproductive tract. These compounds are effective in mitigating damage resulting from metabolic disorders such as diabetes mellitus, obesity, hyperthyroidism, and inflammation (Ourique et al., 2013; Luo et al., 2019; Refat et al., 2021), as well as mechanical damage to the structures of the male reproductive tract, such as testicular torsion (Jahromi et al., 2017).

Most studies have used Swiss mice as an experimental model. In addition, phenolic compounds have been used alone and in combination with plant extracts. In both cases, beneficial effects were observed, mainly by reducing the oxidative stress caused by the problems mentioned above. Finally, concerning dosages, the isolated compounds proved to be more effective in smaller quantities to achieve the therapeutic effect, when compared to the plant extracts.

3.5. Effects of phenolic phytochemical compounds against injuries caused by inorganic pollutants

Environmental pollutants represent a major threat to public health, being identified as one of the risk factors for male fertility. Metallic compounds such as iron sulfate, lead acetate, sodium arsenite, aluminum chloride, and cadmium chloride, have harmful effects on the testicular parenchyma, leading to lipid peroxidation of testicular and penile cells, atrophy of the seminiferous tubules, decreased testosterone levels, necrosis of spermatocytes and spermatids, decreased Leydig cells and decreased testicular cell viability (El-Demerdash et al., 2009; Akomolafe et al., 2015; Dewanjee et al., 2015; Aksu et al., 2017; Mohamed and Abd El-Moneim, 2017; Mouro et al., 2020).

The mechanism of heavy metal damage to testicular tissue involves increased lipid peroxidation, and decreased antioxidant defenses resulting in oxidative stress. Arsenite, for instance, leads to an increase in carbonylated protein, a decrease in GSH, as well as the inhibition of the enzymes 3β and 17β hydroxysteroid dehydrogenase. Similarly, cadmium can cause a decrease in antioxidant enzymes such as CAT, SOD, and GSH, as well as destroying the blood-testicular barrier (Aitken and Roman, 2009). The latter occurs due to cadmium's affinity for calcium-binding sites within cell adhesion regions.

The study conducted by Mouro et al. (2020), used the oil from *Euterpe oleracea* Mart. (50, 100, and 150mg/kg) to reverse the effects of cadmium chloride. The oil was able to restore testosterone levels and the seminiferous tubule architecture, as well as to increase antioxidant activity. Part of this effect can be explained by the content of anthocyanins present in *E. oleracea* oil, conferring an antioxidant capacity to the compound. Similar results were found when using the extract of *Ginkgo biloba* f. *aurea* (J.Nelson) Beissn to attenuate testicular lesions caused by aluminum chloride, with increased levels of testosterone and antioxidant enzymes being observed (Mohamed and Abd El-Moneim, 2017).

3.6. Effects of phenolic phytochemical compounds against injuries caused by organic pollutants

Some organic pollutants, such as bisphenol A (BPA) and di-ethylhexyl-phthalate, also have testicular harmful effects, compromising antioxidant activity, disorganizing the testicular histoarchitecture, and reducing testosterone and luteinizing hormone production. The study by Grami et al. (2018), used the aqueous extract of *Eruca sativa* var. *eriocarpa* (Boiss.) Post at dosages from 15.6 to 1000 µg/mL to mitigate the harmful effects of BPA. This extract has 5 different phenolic compounds (gallic acid, quercetin, kaempferol, cirisilineol, and acacetin) that reveal the antioxidant potential of the extract. The study showed that low doses of the extract could reverse the damage caused by BPA, restoring cell viability and sperm motility, however high doses of the same extract resulted in functional impairment of sperm. Male gametes need a minimum amount of reactive oxygen species for their capacitation, that is, excess antioxidant molecules are also toxic to sperm.

A study published by Shehab et al. (2024) evaluated the protective effects of alkaline extracts from plants such as *Lepidium meyenii, Trigonell foenum-graecum, Spirulina platebsus,* and *Tribullus arabica* against the damage caused by monosodium glutamate (MSG). MSG is a flavor enhancer capable of reducing sperm quality. In this study, the alcoholic extract of *L. meyenii* (500 mg/kg/day), showed greater antioxidant capacity, being able to reverse the damage caused by MSG. Due to the considerable amount of antioxidant phenolic phytochemical compounds, such as naringenin, quercetin, and kaempferol, this extract increased the total and progressive motility of the spermatozoa of the treated animals.

As shown in Table 2, phenolic phytochemical compounds were effective in mitigating the damage caused by contamination by organic and inorganic pollutants. Similarly to what was observed in the treatment of diseases (Table 1), these compounds, present in plant extracts or their isolated form, have shown promise in protecting against oxidative stress, as well as reversing the damage caused by contaminants.

Table 2. The action of phenolic compounds in the treatment of environmental contaminants on the male reproductive tract.

Reference	Environmental pollutant	Extract/ compound	Dose	Experimental model	Main effects of the compound
Abd El-Fattah et al. (2016)	Di-ethylhexyl-phthalate	Resveratrol and Curcumin	80mg/kg (RSV), 200mg/kg (Curcumin)	Wistar rats	*Testicular weight increase, normalization of GSH, MDA, LDH, and serum testosterone levels; *Increased ALP, ACP activity
Akomolafe et al. (2015)	Iron sulfate	Aqueous extract of *Tetracarpidium conophorum* (Müll.Arg.) Hutch. & Dalziel	(0-100)µL 1mL 100-400µL	Wistar rats	*The extract inhibited lipid peroxidation in the testes and epididymis by 50%.
Aksu et al. (2017)	Lead acetate	*Punica granatum* L.	30 and 60 µL	Wistar rats	*Increased amount of Zinc in the testes, *Attenuates the effects of lead contamination on the testes
Bakir et al. (2020)	Dimethoate	Methanolic extract of *Laurocerasus officinalis* M.Roem	4mg/kg	Wistar rats	* Improved oxidant/ antioxidant balance, sperm DNA integrity, and seminal parameters and decreased testicular apoptosis
Ben Salah-Abbès et al. (2009)	Zearalenone	Extract of *Raphanus raphanistrum subsp. sativus* (L.) Domin	15 mg/kg	Balb/c mice	*Increased testicular SOD and GPx, *Inhibition of lipid peroxidation * DNA repair
Dewanjee et al. (2015)	Lead	Aqueous extract of *Ipomoea aquatica* Forssk.	100 mg/kg	Swiss albino mice	* Decreased histological abnormalities in the testes caused by lead *Protection against oxidative stress through binding to metal ions
El-Demerdash et al. (2009)	Sodium arsenite	Curcumin	15 mg/kg	Sprague–Dawley rats	* Decreased testicular oxidative stress induced by sodium arsenite
Grami et al. (2018)	Bisphenol A	Aqueous extract of *Eruca sativa var. eriocarpa* (Boiss.) Post	15.6, 62.5, 250 and 1000 µg/mL	Human	*Restoration of sperm viability and progressive motility *Deleterious effects at high doses
Hanchinalmath and Londonkar (2014)	Carbon tetrachloride	*Feronia limonia* (L.) Swingle	100 and 400 mg/kg	Wistar rats	*Increased levels of intracellular antioxidants * Decreased reactive oxygen species and free radicals
Kaur and Sadwal (2020)	Bisphenol A	Aqueous extract of *Trigonella foenum-graecum* L.	200mg/kg	Balb/c mice	*Improves testicular histoarchitecture * Reduced serum MDA *Increased antioxidant enzymes

Table 2. Continued...

Reference	Environmental pollutant	Extract/ compound	Dose	Experimental model	Main effects of the compound
Li and Yang (2016)	Sulfur mustard	Extracts of *Salvia miltiorrhiza* Bunge and *Anemarrhena asphodeloides* Bunge	30, 60, and 120 mg/kg	Sprague-Dawley rats	*Increased production of GSH *Acts in the regulation of signaling pathways such as cancer, antigen processing, and presentation
Mi et al. (2010)	4-nitro-3-phenyl-phenol	Quercetin	1 µg/mL	Embryonic chicken spermatogonial cells	*Attenuation of oxidative stress * Decreased MDA production *Increased activity of antioxidant enzymes
Mi et al. (2007)	Polychlorinated biphenyl	Daidzein	0.1-10 µg/mL	Chicken testicular cells	*Increase in the number of germ cells, *Increased GSH level * Inhibition of cytotoxicity
Mohamed and Abd El-Moneim (2017)	Aluminum chloride	Extract of *Ginkgo biloba* L.	200 mg/kg	Wistar rats	* Protection against peroxidation *SOD increase *Protective effect on testicles
Mouro et al. (2020)	Cadmium chloride	*Euterpe oleracea* Mart. Oil	50,100, and 150 mg/kg	Balb/c mice	* Decreased damage to the seminiferous tubules *Increased testosterone levels *Recovery of the tubular architecture * Oxidizing activity
Olukole et al. (2020)	Bisphenol A	Galic acid	20 mg/kg	Wistar rats	*Improvement of antioxidant enzymes *Reduced MDA level *Maintenance of testicular architecture
Saalu et al. (2011)	Hydroxyurea	Aqueous extract of *Moringa oleifera* Lamarck	50 mg/kg	Sprague-Dawley rats	*Conservation of testicular weight and volume *Improvement of testicular histomorphometric profile
Seif et al. (2021)	Sodium arsenite	Ethanolic extract of *Zingiber officinale var. cholmondeleyi* F.M.Bailey	100 mg/kg	Sprague-Dawley	* MDA and ROS reduction *Protection from oxidative stress *Increased gene expression of steroidogenic enzymes *Increased levels of cholesterol, testosterone and LH *Increased sperm count and *Recovery of histological parameters

Table 2. Continued...

Reference	Environmental pollutant	Extract/ compound	Dose	Experimental model	Main effects of the compound
Wei et al. (2020)	Bisphenol A	*Cuscuta chinensis var. applanata* (Engelm.) Costea & Stefanov. oil	20, 30, and 40 mg/kg	Kunming mice	*Restrict BPA-induced hormone reduction *Regulation of ERα and ERβ expression *Reduced DNA methylation
Wei et al. (2019)	Bisphenol A	*Cuscuta chinensis var. applanata* (Engelm.) Costea & Stefanov. oil	20, 30, and 40 mg/kg	Kunming mice	*BPA-induced apoptosis inhibition
Yadav et al. (2005)	Cadmium chloride	Picroliv	12 mg/kg	Wistar rats	*Oxidative stress relief * Testicular protector
Yousaf et al. (2016)	Bisphenol A	Aqueous extract of *Adiantum capillus-veneris* L.	25 mg/kg	Wistar rats	*Increased testosterone levels *Improvement of testicular histological parameters * Antioxidant effects
Zahra et al. (2020)	Bisphenol A	Methanolic extract of *Vincetoxicum arnottianum* (Wight) Wight	150 and 300 mg/kg	Sprague-Dawley	*Protection against reproductive toxicity *Attenuation of ROS production *Prevention of lipid peroxidation *Maintenance of normal histological features * Protection of spermatogenesis * Decreased DNA damage

3.7. Role of phenolic phytochemical compounds in the control of adverse drug effects on the male reproductive system

Treatments for neoplasms that involve cytotoxic mechanisms are closely linked to adverse effects linked to testicular damage and male infertility on a temporary or permanent basis. Methotrexate, cisplatin, doxorubicin, and busulfan are chemotherapeutic drugs that have side effects on the testicular parenchyma, such as a decrease in the amount of sperm, germ, and somatic cells. When albino mice took 5 to 40mg/kg/day of methotrexate (MTX), a high number of abnormalities in the sperm head were noticed (Padmanabhan et al., 2008; Al-Ezzy et al., 2019). Such abnormalities were fully reversed after administration of *Achillea millefolium* extract at doses of 100 and 200 mg/kg in a dose-dependent way. In this study, the 100 mg/kg dose proved to be more effective, showing 31.33% of sperm abnormalities, compared to 52.56% of the animals that received the 200 mg/kg dose, while the animals that received the drug showed 68.76% of abnormal spermatozoa (Al-Ezzy et al., 2019). Part of the observed effect may be linked to the significant number of phenolic compounds such as caffeic and salicylic acids, which can inhibit the formation of free radicals and increase the activity of enzymes with GST and SOD, conferring great antioxidant capacity to the extract (Al-Ezzy et al., 2019).

Similar to the protective effects of *Achillea millefolium* on methotrexate-induced damage, other plant extracts like *Satureja hortensis* (L.) Kuntze (50, 100, and 200 mg/kg) and *Ficus carica* Linn (50, 100, and 200 mg/kg), have shown efficacy in reversing the reproductive damage caused by cisplatin (Boroja et al., 2018; Fahmy et al., 2020). In the study by Boroja et al. (2018), using the extract of *S. hortensis* L., the doses of 100 mg/kg and 200mg/kg proved to be more effective in reversing the damage caused by the administration of 7.45mg/kg of cisplatin for 10 days. These doses suppressed the testicular apoptotic process by increasing the Bcl-2/Bax ratio and raising testosterone levels, and they also showed fewer testicular histopathological changes compared to the positive control. The methanolic extract of *S. hortensis* contains 20 phenolic compounds, such as rosmarinic acid (24,900.67µg/g), caffeic acid (1,285.42µg/g), and naringenin (1,061.75µg/g) the most abundant ones, giving the extract anti-inflammatory and antioxidant status. Such extracts can increase testosterone levels and decrease apoptosis in the testicular tissue, thus attenuating the histological changes caused by cisplatin. Beneficial effects were also observed using the methanolic extract of *F. carica* Linn, which increased the number of sperm in the lumen of the seminiferous tubules.

Other extracts such as *Olea europaea subsp. africana* (Mill.) P.S. Green and the alcoholic extract of *Citrus paradisi Macfad* were also used to mitigate the deleterious effects of chemotherapeutics: busulfan and doxorubicin. *O. europaea subsp. africana* (Mill.) P.S.Green intake (250, 500, and 750 mg/kg) decreased the apoptotic process of spermatogenic cells, increasing the number of Leydig cells and primary spermatocytes, thus fertility (Hakemi et al., 2019). In this study, the administration of *O. europea* extract at doses of 250 and 500 mg/kg improved parameters such as the number of Leydig cells and decreased sperm abnormalities, which the modulation of oxidative stress can explain. On the other hand, the dose of 750mg/kg of the extract associated with cisplatin caused damage to the testicular parenchyma such as the reduction of the germinal epithelium and an increase in apoptosis of testicular parenchyma cells. Such effects were also described after the use of the alcoholic extract of *C. paradisi* Macfad, at a dose of 10 mg/kg (Saalu et al., 2011).

Plant extracts rich in phenolic phytochemical compounds can also attenuate the testicular toxic effects of dexamethasone, a corticosteroid with immunosuppressive and anti-inflammatory properties. Dexamethasone is capable of inducing effects such as vacuolization of the nucleus of the cytoplasm of germ cells, obliteration of the lumen of the seminiferous tubules, increase in sperm morphology abnormalities and degeneration of Leydig cells (El-Wassimy et al., 2014). However, the methanolic extract of *Moringa oleifera* (400 mg/kg) was effective in reverting such damage, improving the morphology of testicular germ cells, aiding in testicular antioxidant defense, inhibiting lipid peroxidation and DNA damage, decreasing sperm abnormalities, and androgenic effect. Table 3 shows that the phenolic phytochemical compounds were effective in reversing the adverse effects induced by drugs on the testicular parenchyma. By reducing oxidative stress, these compounds were able to promote benefits such as a reduction in sperm abnormalities and morphological restoration of germ cells. It is important to note that the doses administered in the studies varied according to the bioavailability of the compounds in each plant species. However, it is essential to consider the dose limits, as high concentrations of phytochemical compounds can induce toxicity.

Table 3. Effects of phenolic phytochemical compounds against injuries caused by medicines.

Reference	Drug	Drug damage	Extract/ compound	Dose	Experimental model	Main effects of the compound
Al-Ezzy et al. (2019)	Methotrexate	*Increased sperm head abnormalities	Extract of *Achillea millefolium* L.	100 and 200 mg/kg	Albino male mice (*Mus musculus*)	* Decreased spermatozoa head abnormalities at a moderate dose *Increased abnormalities in the sperm head at high doses
Boroja et al. (2018)	Cisplatin	* Decreased testosterone levels *Increased apoptosis in testicular tissue *Testicular histoarchitecture modification	Methanolic extract of *Clinopodium hortense* (L.) Kuntze.	50, 100, and 200 mg/kg,	Wistar rats	*Increased testosterone levels * Decreased apoptosis in testicular tissue *Attenuation of the histological changes caused by cisplatin
El-Newary et al. (2021)	Streptomycin	*Increased gonadal weight * Decreased activity of antioxidant enzymes	Ethanolic extract of *Launaea nudicaulis* (L.) Hook. f	250 mg/kg	Wistar rats	*Normalization of gonadal weight in diabetic subjects *Activation of serum antioxidant enzymes * Restoration of spermatogenic cells *Improvement of testicular histological parameters
El-Wassimy et al. (2014)	Dexamethasone	*Germ cells with a pyknotic nucleus and vacuolization of the cytoplasm *Obliteration of the lumen of the seminiferous tubules *Increased sperm abnormalities * Degeneration of Leydig cells	Methanolic extract of *Moringa oleifera* Lam. Lam.	400 mg/kg	Wistar rats	*Improved testicular germ cell morphology *Aid in testicular antioxidant defense *Inhibition of lipid peroxidation and DNA damage * Decreased sperm abnormalities *Androgenic effect

Table 3. Continued...

Reference	Drug	Drug damage	Extract/ compound	Dose	Experimental model	Main effects of the compound
Fahmy et al. (2020)	Cisplatin	*Reduction in the number of sperm in the lumen of the seminiferous tubules	Methanolic extract of *Ficus carica* Linn	200, 400, and 600 mg/kg	Swiss mice	* Dose-dependent increase in the number of sperm in the seminiferous tubules
Hakemi et al. (2019)	Busulfan	*Reduced sperm viability * Decreased number of primary spermatocytes and Leydig cells	*Olea europaea subsp. africana* (Mill.) P.S.Green. oil	250,500, and 750 mg/kg	Wistar rats	*Anti-apoptotic, antioxidant activity, increased fertility and spermatogenesis, increased number of Leydig cells and primary spermatocytes
Saalu et al. (2010)	Doxorubicin	* Decreased testicular weight and volume *Induction of oxidative stress	Alcoholic extract of *Citrus paradisi* Macfad	10 mg/kg	Wistar rats	*Improvement of testicular histomorphometric parameters *Overcoming oxidative stress

3.8. Use of medicinal plants to optimize the in vitro fertilization process

The effects of phenolic phytochemical compounds directly on testicular cells were, that the main cell types studied were sperm, germ cells, Leydig cells, and Sertoli cells. The most explored aspect was the protective effects of phenolic compounds on cryopreserved sperm. Sperm cryopreservation is routinely used to store gametes for future assisted reproduction processes. However, sperm freezing results in cellular damage such as DNA fragmentation, plasma membrane peroxidation, and decreased sperm motility and viability, making fertilization difficult.

Part of the damage induced by freezing is due to the imbalance between antioxidant and cellular pro-oxidant molecules, which generate oxidative stress (Hezavehei et al., 2018). Concerning oxidative stress, freezing sperm generates this problem from intra and extracellular aspects in male gametes. Considering intracellular aspects, it is important to mention that spermatozoa move due to high mitochondrial activity, and due to their high specialization and chromatin condensation, this cell type is unable to produce its antioxidant responses. In this context, the freezing process makes use of processes such as dehydration, which ends up absorbing part of the cytoplasm, reducing the amount of cytoplasmic antioxidants (Hai et al., 2024).

The extracellular aspects that lead to oxidative stress are due to the deregulation of the extracellular environment. The main purpose of the dehydration and cooling processes is to reduce the cellular metabolism of sperm during freezing, which increases the chances of sperm survival (Hai et al., 2024). However, while the freezing and reheating processes are taking place, sperm metabolism is re-established, as is the production of reactive oxygen species. Thus, administering extracts containing phenolic compounds or even these compounds in isolation can help recover parameters (Hezavehei et al., 2018)

The oil of *Origanum vulgare* var. *albidum* Bellynck was tested at doses of 2, 4, 8, 12, 16, and 20 mL/dL as a cryoprotectant during the cryopreservation process of sperm samples from Holstein bulls (Daghigh Kia et al., 2016). In this study, semen from healthy high-quality bulls was collected and assessed for motility and viability, then diluted in an extender containing the ethanolic extract of *O. vulgare*, only to be cooled slowly to 5 ºC in an extender containing glycerol for packaging and freezing. As a result, there was an increase in the activity of catalase and superoxide dismutase enzymes in the samples that received doses of 4 and 8 mL/dL of the oil, which showed a lower rate of lipid peroxidation. Concerning sperm parameters, the 2 and 4 mL/dL doses caused a significant increase in motility, especially the 4 mL/dL dose. In addition, the extract increased viability with values of 73.91% and 79.13% for the 2 and 4 mL/dL doses, respectively. On the other hand, the higher doses (12 and 16 mL/dL) inhibited all sperm oxidative activity, causing damage to sperm motility. Higher doses of the ethanolic extract of the same species (37.5, 75, 150, 300 μg/mL) caused the reduction of sperm motility, viability, and mitochondrial viability, causing irreversible damage to gamete structure and function (Ďuračka et al., 2019).

Reactive oxygen species (ROS) are naturally produced by sperm through the activity of the nicotinamide adenine dinucleotide phosphatase (NADPH) oxidase system and by electron leakage from the mitochondrial electron transport chain. In moderate amounts, ROS plays a crucial role in maintaining chromatin stability and protecting DNA during sperm maturation and capacitation. Additionally, ROS help to activate the cAMP pathway, essential for sperm capacitation and progressive motility (Hai et al., 2024). However, the adverse effects of high extract dosages may be linked to an excessive reduction in ROS levels, which subsequently impairs sperm quality. However, the studies only focus on sperm quality and do not address aspects related to the fertilization success rate, revealing the need for future studies that focus on the latter aspect (Figure 1).

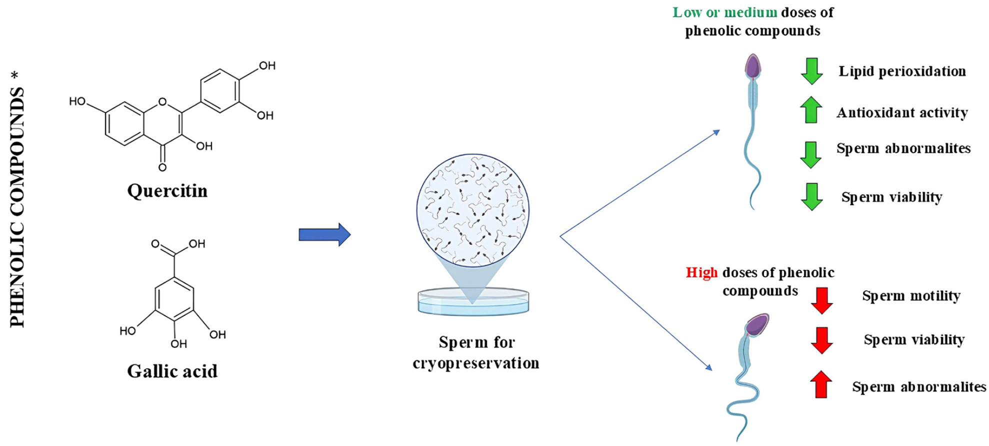

Figure 1. Effects of phenolic compounds in spermatozoa post cryopreservation. * = Most abundant phenolic compounds in the ethanolic extract of O. vulgare according to Daghigh Kia et al. (2016).

4. Conclusion and Perspectives

Male infertility extends beyond the biological domain, impacting individuals socially and psychologically, and has become a recognized public health issue. This review highlights the remarkable versatility and efficacy of phenolic phytochemical compounds in enhancing and protecting male fertility. Studies demonstrate that these compounds can elevate testosterone levels, reduce lipid peroxidation, and improve tubular histoarchitecture in cases of subfertility linked to diabetes mellitus. Additionally, phytochemical compounds mitigate damage due to obesity by boosting serum testosterone, enhancing antioxidant activity, and improving sperm motility. When addressing fertility impairment from inorganic pollutants like heavy metals, phytochemical compounds effectively restore seminiferous tubule structure and testosterone levels. Similarly, evidence shows their efficacy in contamination from organic contaminants, such as BPA, where they contribute to improved sperm quality.

Moreover, phenolic phytochemical compounds have shown beneficial effects in countering the adverse impacts of certain drugs on testicular physiology. Their administration can reduce apoptosis in testicular tissue, increase Leydig cell numbers, and promote spermatocyte production. Furthermore, phenolic phytochemical compounds are being investigated for their potential in sperm cryopreservation for *in vitro* fertilization. However, the findings here are mixed. While some studies support the protective effects of these compounds against freeze-related damage, others caution that certain dosages may cause irreversible harm to sperm quality.

Studies using plant extracts from diverse global regions have shown promising results in reversing or reducing testicular damage from metabolic disorders and environmental pollutants. This review emphasizes the potential of phenolic phytochemical compounds, derived from flora worldwide, as a therapeutic tool for addressing infertility and subfertility.

5. Limitations

It is worth mentioning that texts contained in dissertations, theses, annals of scientific events, book chapters, and journals were not considered, since this material is not indexed and therefore falls into the category of gray literature. The exclusion of this type of literature may have caused a possible publication bias. However, the studies did not include the possible transgenerational effects generated by paternal consumption of the extracts on the offspring, revealing the need for new studies to explore this effect.

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