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Review article

A comprehensive review on potential role of selenium, selenoproteins and selenium nanoparticles in male fertility

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ABSTRACT

Selenium (Se), a component of selenoproteins and selenocompounds in the human body, is crucial for the development of male reproductive organs, DNA synthesis, thyroid hormone, metabolism, and defence against infections and oxidative damage. In the testis, it must exceed a desirable level since either a shortage or an overabundance causes aberrant growth. The antioxidant properties of selenium are essential for preserving human reproductive health. Selenoproteins, which have important structural and enzymatic properties, control the biological activities of Se primarily. These proteins specifically have a role in metabolism and a variety of cellular processes, such as the control of selenium transport, thyroid hormone metabolism, immunity, and redox balance. Selenium nanoparticles (SeNPs) are less hazardous than selenium-based inorganic and organic materials. Upon being functionalized with active targeting ligands, they are both biocompatible and capable of efficiently delivering combinations of payloads to particular cells. In this review, we discuss briefly the chemistry, structure and functions of selenium and milestones of selenium and selenoproteins. Next we discuss the various factors influences male infertility, biological functions of selenium and selenoproteins, and role of selenium and selenoproteins in spermatogenesis and male fertility. Furthermore, we discuss the molecular mechanism of selenium transport and protective effects of selenium on oxidative stress, apoptosis and inflammation. We also highlight critical contribution of selenium nanoparticles on male fertility and spermatogenesis. Finally ends with conclusion and future perspectives.

1. Introduction

Selenium (Se) is an essential trace element with important roles in immune and reproductive function, reproductive health, gonadal development, gametogenesis and fertilisation, and maintenance of homeostasis; it is also involved in cancer chemoprevention

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[1–4]. According to several studies, a lack of selenium and selenoproteins can cause several issues with the reproductive system and pregnancy, such as infertility, preeclampsia, miscarriage, early labor, fetal development restriction, gestational diabetes, and obstetric cholestasis. Heart failure, nutrient-induced myodegeneration, and Keshan disease are all caused by se deficiency [5–7]. Selenium has a crucial function in the creation and usual growth of spermatozoa, as well as in the process of testosterone biosynthesis, which is essential for effective male reproduction, including spermatogenesis and male fertility [8]. Selenium controls the redox state, and either excess or insufficient amounts have detrimental effects on health. Selenium and selenoprotein availability is crucial for protecting DNA against genomic instability and mutations. Recent research suggests that when selenium is scarce, oxidative stress may also influence the expression of several antioxidant selenoproteins. When the expression of selenoprotein is downregulated, it is hypothesised that increased ROS generation from ER stress and oxidation-mediated DNA damage would occur, impairing cellular homeostasis and interfering with cell cycle progression [9]. According to studies, selenium exhibited protective antioxidant qualities and have a significant role in cell development, death, and the modulation of transcription factors and cell signalling networks [10].

Numerous proteins, known as selenoproteins, contain selenium, which is used for a variety of purposes, such as cancer prevention, redox state modulation, and antioxidant defense. Selenoproteins have a role in several metabolic processes. Selenoproteins have become possible biomarkers of various diseases and selenoproteins additionally provide some defense against heavy metals [11]. GPx1-8, the eight GPx isoforms, is important in several redox reactions. The other isoforms are cysteine-containing counterparts, whereas GPx1-4 and GPx6 are selenoproteins [12]. Selenium is a component of selenoproteins such as glutathione peroxidase 1 (GPx1), glutathione peroxidase 3, mitochondrial GPx4 (mGPx4), cytosolic GPx4 (cGPx4), and GPx5, which guard spermatozoa against oxidative damage as they mature. Among selenoproteins, mGPx4 and snGPx4 serve as essential parts of the mature spermatozoa's structural framework. The antioxidant GPx activity is said to be enhanced by increased dietary selenium consumption, which enhances male fertility [13]. GPx4 aids in sperm integrity and motility as well as protecting sperm from DNA damage brought on by oxidative stress during the early stages of spermatogenesis [14]. To protect spermatozoa against ROS and to ensure their viability, selenium, and selenoproteins are present in the body. Selenoprotein gene knock-out experiments have shown that their absence during spermatogenesis leads to aberrant spermatozoa, which in turn impairs the quality of the semen and fertility [15]. The male and female reproductive systems are negatively impacted by se insufficiency.

Specific selenoproteins are produced as a result of se dietary supplementation and have an impact on redox-regulated genes. These genes produce ROS-to-less reactive molecule conversion proteins [16]. Additionally, selenium can control redox-sensitive pathways and antioxidant defence systems. Mammals may reproduce most effectively when certain parameters are met, including genetics, diet, management, and the environment [17]. The biological activities of selenium are mostly carried out by selenoproteins; among them, trace mineral nutrition plays a crucial role in a variety of biological processes, including proper growth, development, and both male and female fertility [18]. For healthy spermatogenesis, sperm maturation, sperm motility, and general male reproductive function an appropriate quantity of selenium is necessary [15,19,20]. To maintain animal and human health, selenium performs a variety of vital tasks at the cellular and organism levels [7,21–23]. The pathophysiology linked to the development of cancer is more prone in transgenic mice that express lower amounts of selenoproteins. *In vivo* study demonstrated that the amelioration of xenotoxicity by selenium, in this study transgenic mice's cells were exposed to X-rays, DNA damage and the production of micronuclei were more prevalent than in the corresponding wild-type control cells. This study concluded that selenoprotein deficiency enhances radiation-induced micronuclei formation and treatment with selenoproteins protected DNA against deterioration [23,24]. Two ER-resident selenoproteins are expressed in mice by Qazi et al. (2020) who investigated the impact of dietary Se deficit and supplementation [25]. Selenoprotein K protein expression was much greater in the groups receiving selenium supplements compared to those receiving diets with low level selenium. In the ovaries of ageing mice, selenium supplementation raised the expression of selenoproteins K and M collectively, perhaps improving the developmental potential of in vitro-matured MII oocytes. By reducing antioxidant enzyme activity, modulating mitogen-activated protein kinase (MAPK) signalling, and controlling the expression of pro-apoptotic markers, semitigates the oxidative damage and apoptosis caused by the bisphenol A (BPA) in the mouse testes. Se supplementation

Table 1
Selenoproteins and their role in various health aspects.

SelPs Name	Abbreviation	Functions	Reference
Selenoprotein M	SelM	Maintenance of Ca^{2+} ions	Negro, 2008 [27]
Selenoprotein N	SelN	Growth and development of muscles	Negro, 2008 [27]
Selenoprotein K	SelK	Immunity & inflammation	Verma et al., 2011 [28]
Selenoprotein l	Sell	Phospholipid biosynthesis	Mangiapane et al., 2014 [29]
Selenoprotein O	SelO	Regulation of redox reactions	Mangiapane et al., 2014 [29]
lodothrionine Deiodinase 1-3	Dio1-3	Regulation of thyroid gland secre-tion, neuronhealth	Ogawa-Wong et al., 2016 [30]
Selenoprotein V	SelV	Expression of taste	Ogawa-Wong et al., 2016 [30]
Selenoprotein S	SelS	Regulation of inflammation & redox reactions	Yang and Liu, 2017 [31]
Selenoprotein H	SelH	Cell cycle regulation &cancer prevention	Bertz et al., 2018 [32]
Selenoprotein P	Sepp1	Transportation of Se to brain and other tissues of body	Saito, 2020 [33]
Selenoprotein T	SelT	Regulation of endocrine secretion	Pothion et al., 2020 [34]
Selenoprotein W	SelW	Oxidative stress regulation, Bone remolding	Pothion et al., 2020 [34]
Thioredoxin Reductase 1-3	TrxR1-3	Tumour cell apoptosis, oxidative stress, and reduction of disulfide bonds	Zhang et al., 2021 [35]
Glutathione Peroxidase	GPx	Prevents oxidative stress, regulation of antitumorimmunity	Andrade et al., 2021 [36]

significantly reduces the expression of stress-activated kinases and significantly increases antioxidant enzyme activity, which further down regulates apoptosis [26].

The role of selenium and selenoproteins in mammalian reproduction has been strongly implicated in several studies; however, to fully comprehend the role of selenium in male reproduction, it is still important to combine recent study findings with earlier findings. Selenoproteins are not only play major role human reproduction and also involved to regulate various health aspects (Table 1) [27–36]. Recently, selenium nanoparticles are less toxic than inorganic and organic Se. SeNPs are biocompatible and capable of effectively delivering combinations of payloads to specific cells.

Based on available literature, the main aim of this review is to present and discuss in detail the chemistry, structure and functions of selenium, and mile stones various functions on male infertility and spermatogenesis, Furthermore, we discuss the molecular mechanism of selenium transport and protective effects of selenium on oxidative stress, apoptosis and inflammation. In addition, we discuss the seminal role of selenium nanoparticles on fertility and spermatogenesis.

2. Chemistry, structure and functions of selenium

2.1. Chemical forms of selenium

The chemical element selenium belongs to group XVI of the periodic table and is non-metallic. It is similar to tellurium and sulphur in both chemical activity and physical characteristics. Selenium partially replaces sulphur in ore minerals found in nature. According to Butterman and Brown, selenium can exist in a variety of allotropes, or fundamentally separate molecular forms, each with a unique set of physical characteristics. Common oxidation states of selenium compounds are −2, +2, +4, and +6. Two oxides are formed by selenium: selenium trioxide (SeO_3) and selenium dioxide (SeO_2). In the gas phase, the polymeric solid transforms into monomeric SeO_2 molecules.

2.2. Selenium allotropes

There are several allotropes of selenium, which are essentially distinct molecular forms of the element with differing physical characteristics. In addition to adopting a crystalline hexagonal structure, selenium also forms a stable metallic gray allotrope. Trigonal selenium, which is likewise a gray solid, is the most thermodynamically stable allotrope of selenium. Both crystalline and amorphous forms of selenium exist [37]. The "vitreous" and finely split brick red forms of amorphous selenium are the most well-known types and are commonly referred to as two different allotropes. However, these forms are identical at the microscopic level, and the only reason they appear differently is because they were produced in a different way. The so-called "metallic" gray or black selenium is one of several monoclinic variants among the crystalline allotropes that range in colour from red to brown. Both of the primary monoclinic forms transition to the hexagonal, crystalline form, which is the most thermodynamically stable allotrope. Selenium is regarded as an essential trace element and is relatively harmless and also long half-life. The predominant form of selenium in organoselenium chemistry is selenium in the -2 oxidation state. Since it is the precursor of selenocysteine at the active centres of several selenoenzymes, selenide is a significant metabolite in animals and some microorganisms [38]. Comparing selenium compounds to their sulphur counterparts, selenium compounds are more acidic and nucleophilic.

The bioavailability, use, and toxicity of selenium to humans are all influenced by its various chemical forms. While selenites and selenates, which are inorganic forms of selenium, can be found in many minerals, selenoaminoacids, selenopeptides, and selenoproteins are the predominant organic forms [39]. As a result, the incorporation of organic selenium into selenoproteins primarily regulates its physiology or biochemistry. According to Dumont et al. [40], selenoaminoacids such selenomethionine and methylselenocysteine contain the majority of the selenium in plants, as depicted in Fig. 1.

2.3. Organic selenium compounds

Selenium and carbon-containing chemical compounds are known as organoselenium compounds. They frequently contain other elements as well, including halogens, oxygen, sulphur, or nitrogen. The bioavailability of organoselenium compounds is typically higher than that of inorganic selenium, and they are typically also less hazardous [41]. Organoselenium compounds have minimal

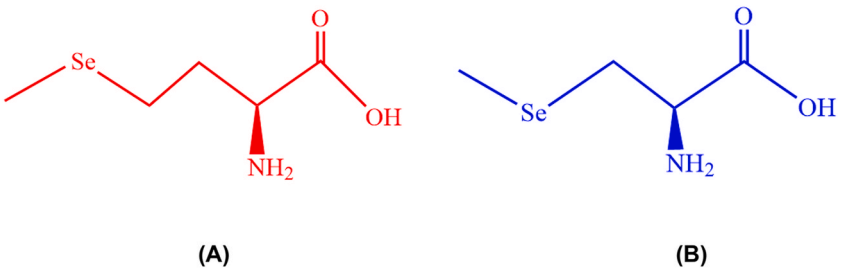

Fig. 1. The chemical structures of selenomethionine (A) and methylselenocysteine (B).

toxicity and are key biochemical activities such as antioxidants, anticancer, and antiviral agents [42,43]. Numerous innovative synthetic organoselenium compounds have been created as a result of the variety of applications. According to experimental data, altering organoselenium compounds may significantly change their chemistry and, as a result, their biological activity [44]. Selenols, diselenides, selenoxides, selenones, selenium acids, selenides, selenium halides, and selenaheterocyclic substances are the primary classes of organoselenium compounds. Organoselenium compounds can be categorized similarly to analogs based on their chemical characteristics. In light of this, thiols, sulphides, and sulfoxides are analogous to selenols, selenides, and selenoxides. Even though their structures are similar, the stability, chemical composition, and methods of production of sulphur and selenium compounds frequently differ. The cerium selenide (CeSe) bond is more readily destroyed by halogens and oxidizing chemicals than the cerium-sulphur (CeS) bond is due to selenium's higher metallic characteristics when compared to those of sulphur.

2.4. Therapeutic potential of selenium

Selenium play a significant role in various diseases including cancer, cardiovascular disease, cognitive decline and Alzheimer's disease, HIV infection, male fertility, and thyroid disease whereas trace elements also play an important role in various health aspects (Table 2) [45–48]. Selenium is believed to support the healthy environment of the body and brings in numerous other health benefits. Selenium mostly serves as a nutrient agent, rather than a special medication. Selenium's potential for therapeutic use is demonstrated not only by its nutritional benefits but also by its proven ability to treat Se-independent illnesses. The dose form of a medicinal substance has a significant influence on its pharmacological efficacy. The form of nano-Se, or SeNPs, is primarily utilized in the current utilization of selenium for a variety of medical applications. SeNPs foster the creation of Se-based nanomedicines and lay the groundwork for selenium's use in biological applications.

2.5. Milestones of selenium and selenoproteins

Jöns Jacob Berzelius discovered selenium for the first time in 1817 while looking for the compounds to blame for worker illness outbreaks at a Swedish sulphuric acid plant [49]. Large-scale studies conducted later in China on children and young people with Keshan illness showed that selenium supplementation had ameliorative benefits [50,51]. In the past fifty years, Klaus Schwarz and Calvin M. Foltz, who isolated substance containing selenium from hog kidneys, have come to understand selenium as a necessary trace

Table 2
Biological activities and health impacts of selenium versus trace element.

Elements	Biological Effects	Bioavailability	Health effects	References
Cr	Influences carbohydrate, lipid, and protein metabolism by potentiating insulin.	It involves processes other than simple diffusion and many factors change the bioavailability or absorption of Cr.	Limited to hospitalized patients with increased catabolism and metabolic demands in the setting of malnutrition.	Hua et al., 2012 [45] and Mehri et al., 2020 [46]
Cu	Major function involves oxidation-reduction reactions. It is an integral component of many enzymes.	Cu absorption occurs by active transport at lower levels of dietary copper and by passive diffusion at high levels of dietary copper.	Extreme form of copper deficiency is Menkes disease, or Menkes kinky (steely) hair syndrome.	Mehri et al., 2020 [46]
Zn	Zn involves in a large number of enzymes or is a stabilizer of the molecular structure of subcellular constituents and membranes. It plays an important role in cell proliferation, differentiation, and metabolic activity of the cell and supports normal growth and development. Also, it plays an essential role in the processes of genetic expression.	Zn absorption is concentration dependent and occurs throughout the small intestine. It is inhibited by the presence of phytates and fiber in the diet that bind to zinc, as well as dietary iron and cadmium.	Genetic disorder related with zinc metabolism is acrodermatitis enteropathica.	Costa et al., 2023 [47] and Mehri et al., 2020 [46]
Se	Se has antioxidant defense activity of glutathione peroxidase as a selenoprotein in regulation of immunity, thyroid function, and reproductive system. Se is present in foods mainly as the amino acids selenomethionine and selenocysteine. Se content decreases with age, smoking, inflammation, and some types of cancer.	Se is absorbed but the amount is affected by chemical form in the diet and other factors including intake of protein and the presence of any levels of toxic elements in the diet, such as mercury and arsenic.	Se deficiency is associated with the development of systemic connective tissue diseases such as sclerodermia, lupus, rheumatoid arthritis, and Raynaud's syndrome.	Ye et al., 2022 [48]
Mo	Functions as an enzymatic cofactor.	Mo is absorbed in GI tract depending on the ingested dose.	Mo deficiency is rare and is associated with impaired reproductive functions and growth retardation.	Mehri et al., 2020 [46]
I	It is an essential constitute of the thyroid hormone triiodothyronine (T3) and thyroxine (T4). Dietary iodine is converted into iodide ion before it is absorbed.	Iron is absorbed totally from food and water.	I deficiency is associated with goiter, hypothyroidism, increased risk of miscarriage, preterm birth, congenital fetal abnormalities, and elevated incidence of neonatal death.	Mehri et al., 2020 [46]

Cr═C, Cu=Copper, Zn = Zinc, Se=Selenium, Mo=Molybdenum, I=Iodine, GI=Gastrointestinal tract.

element for higher vertebrates as well as microorganisms. Indicating that the trace element may carry out its biological activity as an essential component of enzymes, the first selenoproteins were discovered in mammals and bacteria fifteen years later [52,53]. Furthermore, selenium protects against liver deterioration brought on by a vitamin E deficit, requires se as an essential component [52, 54].

The 21st proteinogenic amino acid, selenocysteine (Sec), is found in the active core of a novel family of unusual redox-active proteins known as selenoproteins. Research on the biochemistry and uses of selenoproteins was financed in 2000 by the German Research Council in three different categories: fundamental, applied, and clinical. The selenogenome was discovered in 2003 using brand-new methods. 25 genes make up the selenogenome of the human, which is at least partially translated into several proteins with unique roles. Based on this information, scientists have determined that selenium serves as more than just an antioxidant; it also regulates spermatogenesis, the insulin response, inflammatory mediator production, and numerous aspects of brain development and function [52,53]. Later research has concentrated heavily on figuring out selenium function in reproduction. According to Rosenfeld's initial investigation in 1964, significant selenium content was found in the rat testis [55]. The next year, a team of scientists discovered that after giving mice w75Sex, selenium increased over days in the testis and epididymis while declining in other tissues [56–59]. Then, Patrick et al. (1965) discovered for the first time that 75Se gets protein bound, at least in cock sperm, most likely in the form of Sec [60]. Later, a different group revealed that male rats deficient in selenium became sterile for two generations, and a mouse investigation supported this finding [61–64]. Brown and Burk (1973) discovered that an injected w75Sex label was only present in the middle of rat spermatozoa, and that the sperm of these rats had poor motility and morphological changes, such as the breaking of fibrils in the axial filaments [65]. GPx activity, on the other hand, did not correspond to the high selenium concentration of sperm [66].

Selenium also has a structural function; it is a component of the structural protein known as selenoflagellin, subsequently known as mitochondrial capsule protein [67,68]. The selenoprotein-encoding genes were cloned and described in 1992 [69,70]. Phospholipid-bound GPx4, which is abundantly expressed in rat testis, was identified by Ursini and colleagues in Padova, Italy [69,71]. According to research by Ursini et al. (1999), around 50 % of the capsule protein is made up of an inactive version of the enzyme GPx4, and these proteins can go from being an active peroxidase in spermatogenic cells to a structural protein in spermatozoa [72]. Selenoprotein P's structure was described by Kryukov and Gladyshev in 2000. Its size in humans ranges from 45 to 57 kDa and it includes up to 17 Sec residues [73]. To better understand the function of selenoproteins in health and development, many mouse models were created in the early 2000s [74–77]. With the use of these mouse models, it has been possible to ascertain that the production of selenoproteins is reliant on the presence of a single tRNA, Sec tRNA[Ser]Sec, and that this tRNA is encoded by a single gene known as Trsp [78].

2.6. *The biological functions of selenium and selenoproteins*

Selenium exerts a wide range of biological actions through selenoproteins, which have Secor selenomethionine as part of their main structure. The human genome can encode 25 selenoproteins, whereas rodents have 24 proteins that are known to exist. The micronutrient selenium is crucial for a number of cellular functions including DNA synthesis, the most fundamental biological process, and thyroid functions, which include preserving thyroid health, metabolizing thyroid hormones (TH), preventing thyroid disorders, and reducing inflammation [4,7,79,80]. It fundamentally impacts fertility and regulates a number of biological processes, such as growth and reproductive ability [18]. Furthermore, selenium and selenoproteins exhibited organ specific protective effects on male infertility and spermatogenesis (Fig. 2).

Selenoproteins have a major role in redox homeostasis, redox control of transcription factors, and signalling pathways connected to antioxidant response elements. Selenoproteins have a number of biological activities in the thyroid, including catalysing enzymatic

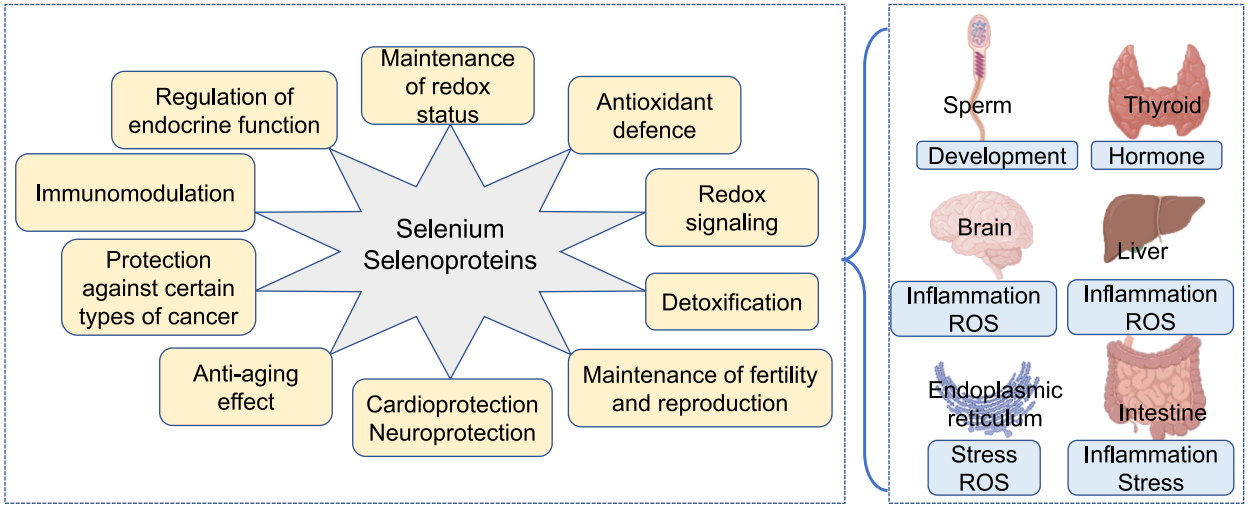

Fig. 2. The effects of Selenium and Selenoproteins on male infertility and organ specific protective effects.

redox reactions, controlling thyroid hormone metabolism, and preventing oxidative DNA damage brought on by inflammatory processes like lipid peroxidation (LPO) and hydrogen peroxide (H_2O_2) [81]. Selenium may be transported from the liver to peripheral tissues via selenomelanoprotein P, which also protects against oxidative damage. According to Burk et al. (2003), selenoproteins, are directly linked to protection against diquat-induced liver necrosis and LPO [82].

Selenium is more easily transported from peripheral organs like the brain to selenium-containing proteins. They also function as antioxidants, protecting endothelial cells from free radicals [82]. The ER is the home of seven selenoproteins. Numerous cellular activities they perform have been linked, directly or indirectly, to calcium (Ca2+) flow or homeostasis [83]. Sec is present in all of the catalytic sites of selenoenzymes and is more nucleophilic and electrophilic than cysteine. There may be some enzymatic activity in selenoproteins that is strongly related to thyroid-derived metabolism. They are the GPxs, iodothyronine deiodinase (DIO), and thioredoxin reductase (TXNRD) [80]. The GPxs are antioxidant enzymes that have a variety of biological tasks, such as regulating cellular redox homeostasis, catalysing the breakdown of hydroperoxides, and signalling through H_2O_2. The majority of selenoproteins are connected to signalling and redox processes [81]. The DIO1, DIO2 and DIO3 proteins are involved in the metabolism of thyroid hormones and have metabolic regulatory functions, such as regulating growth, differentiation, thermogenesis, and metabolism [84]. Transcriptional regulation, immunomodulation, and cell proliferation are all significantly influenced by the TXNRDs [85]. In mammals, the oxidoreductase activity of Trx-(SH)2 modulates downstream apoptotic signalling and promotes DNA synthesis while controlling transcription factors for a variety of inflammatory genes. The Trx system has a substantial impact on the host's ability to protect itself against oxidative and inflammatory stress and damage, as well as the accompanying disease processes such as metabolic disorders linked to diabetes and obesity [86,87]. In order to restore thyroid hormone production and reduce the oxidative stress brought on by too much iodide, the Trx system is also essential [88]. Together, Trx/TXNRD preserves the equilibrium between oxidant and antioxidant systems in thyroid tissues. Growth, development, thermogenesis, the basal metabolic rate, energy consumption, and body weight are only a few of the metabolic activities that affect TH levels throughout the body [89]. Selenium has a significant impact on keeping people healthy and preventing sickness.

In individuals with autoimmune thyroiditis, the combination of selenium and iodine lowers inflammatory markers. Selenium has been demonstrated to regulate granulosa cell growth and the *in vitro* manufacture of 17-oestradiol (E2), one of the main female sex hormones, during the folliculogenesis process. During follicular development and proliferation, it also plays an antioxidant role [90,91]. Different phases of pregnancy are impacted by lower selenium levels. In addition to impairing placental function and foetal development, selenium deficiency also lowers the amounts of selenoproteins involved in redox control [92,93]. This can result in miscarriage or difficult premature delivery. A healthy thyroid, proper TH metabolism, and defence against thyroid diseases all depend on the presence of selenium at the ideal amount. The homeostatic response to oxidative stress includes selenium, which also plays a vital function in antioxidant systems. Therefore, keeping a physiological concentration of selenium within an ideal range is crucial for ensuring optimal thyroid function and the subsequent generation of essential regulators crucial for metabolism.

Thyrocytes and immunological cells perform better when selenium is supplemented because selenium is necessary for the formation of TH-metabolizing enzymes [94]. Activated T cell proliferation, NKT cell activation, and tumour cytotoxicity are all increased by selenium supplementation [95,96]. The prevalence, virulence, and development of viral infections, on the other hand, are linked to selenium deficiency [97]. Cancer mortality and incidence are both more likely to occur in those who have selenium deficiencies or low selenium levels [98,99]. Selenium shortage is also marked by higher liver levels of oxidative stress indicators, which leads to oxidative stress that has negative consequences on joint development [100]. Sengupta et al. (2009) assessed the biological effects of selenium by knocked down the expression of selenoprotein T (SELT) in murine fibroblasts [101]. They discovered that SELT deficiency changes cell adhesion, increases the expression of a number of oxidoreductase genes, and lowers the expression of genes that are involved in organising cell structure, pointing to the role of SELT in redox regulation and cell anchoring. Additionally, the authors discovered that SELT depletion increases selenoprotein W (SEPW1) expression.

Studies conducted both *in vivo* and *in vitro* have shown that selenoprotein V protects against ER stress and oxidative damage brought on by prooxidants. Mice treated with *N*-acetyl-*para*-aminophenol (APAP) showed an increase in prooxidant markers such as serum alanine aminotransferase activity, hepatic malondialdehyde (MDA), protein carbonylation, ER stress-related proteins (BIP and CHOP), apoptosis-related proteins (FAK and caspase-9) and 3-nitrotyrosine, along with lower total anti oxidizing capability (T-AOC) and more severe hepatic necrosis. However, prooxidant levels were reduced in mice treated with selenium and APAP [102]. Khera et al. (2015) investigated Seto's capacity to shield the mitochondria of trophoblasts from oxidative stress [103]. Swan-71, JEG-3, and BeWo cells as well as placental tissue were treated with sodium selenite or selenomethionine, and mitochondrial activity was examined. In cells and tissues, selenium administration greatly increased mitochondrial respiration. Supplementing with selenium led to cells having more mitochondria and upregulating mediators of mitochondrial biogenesis. The host immune system can be stimulated and gastrointestinal inflammation can be controlled by selenoproteins. In order to effectively treat gut inflammation and restore the integrity of the epithelial barrier, alterations in selenoprotein levels can promote a transition from a proinflammatory to an anti-inflammatory phenotype in the cellular oxidative state [104]. Recent research suggests that dietary selenium influences host metabolism and immunity as well as the gut flora [105–108]. A high-fat diet increases gut dysbiosis, negatively impacts the health of the gastrointestinal system, encourages neurological diseases, and hinders spermatogenesis [109–111]. Male fertility is improved by an increase in dietary selenium intake because it boosts the antioxidant GPx activity. Selenium combined with other crucial micronutrients may increase men' reproductive efficiency [25]. Selenoproteins control immunological response and serve as redoxhomeostasis' gatekeepers. Researchers cultivated macrophages generated from murine bone marrow that had been stimulated by the inflammatory compound lipopolysaccharide (LPS) in the presence or absence of selenoprotein to examine the role of selenoproteins in metabolic reprogramming during inflammation and resolution. The authors found that the addition of selenium caused a significant reprogramming of cellular metabolism in response to LPS stimulation, enhancing the tricarboxylic acid cycle, pentose phosphate pathway, and oxidative

phosphorylation. This helped to facilitate the phenotypic shift towards alternatively activated macrophages, which are associated with the resolution of inflammation. In order to assist anti-inflammation and pro-resolution, the authors came to the final conclusion that selenium plays a crucial role in metabolic reprograming [112].

2.7. Recent advancements on selenium and selenium nanoparticles on therapeutic applications

Selenium play a significant role in various diseases including cancer, cardiovascular disease, cognitive decline and Alzheimer's disease, HIV infection, male fertility, and thyroid disease whereas trace elements also play an important role in various health aspects (Table 2). Selenium is believed to support the healthy environment of the body and brings in numerous other health benefits. Selenium mostly serves as a nutrient agent, rather than a special medication. Selenium's potential for therapeutic use is demonstrated not only by its nutritional benefits but also by its proven ability to treat Se-independent illnesses. The dose form of a medicinal substance has a significant influence on its pharmacological efficacy. The form of nano-Se, or SeNPs, is primarily utilized in the current utilization of selenium for a variety of medical applications. SeNPs foster the creation of Se-based nanomedicines and lay the groundwork for selenium's use in biological applications.

Due to its absorption into selenoproteins—a characteristic absent from other metal nanoparticles—selenium (Se) is an essential nutrient with potential medicinal and pharmacological effects. Thiol oxidation of signalling proteins is one of the most important ways that selenoproteins modify the activity of protein kinases, phosphatases, and regulatory genes like NF-κB [113–115]. SeNPs are significantly more effective in terms of anticancer, nontoxicity, and biocompatibility in the form of selenite (SeO3) and selenate (SeO4) molecules. The main mechanisms driving SeNPs' anti-cancer activities are the invasion of apoptotic cell death and cell cycle arrest (CCA), which eventually leads to blocking other pathways. SeNPs provide the ability to introduce novel and routine approaches for treating diseases such as cancer [116,117]. A study suggests that by modulating selenoproteins, active-form functionalized SeNPs may enhance cancer chemotherapy employing NK and CI-NK cells for various cancer types. Functionalized SeNPs may therefore prove to be an effective therapeutic option for a variety of illnesses; in fact, certain research teams have focused particularly on the therapeutic utility of SeNPs in inflammatory disorders [118–120]. In patients with IBD, selenium can strengthen the gut microbiota's defenses. For IBD therapy, selenium may be a suitable substitute for both short- and long-term measures [121]. The SeNPs exhibited anti-colitis effects in by decreasing the effect of IL-1 and TNF-α in a concentration-dependent manner [122]. It has been demonstrated that selenium analogs decrease mRNA in human keratinocytes, halting the *in vitro* generation of proinflammatory cytokines caused by UVB (NazIroğlu et al., 2012). SeNPs reduced vascular endothelial impairment and inflammatory processes [123]. SeNPs enhance the synthesis of insulin and promote cell division. It is thought that the anti-diabetes activity of SeNPs involves scavenging ROS and important modifications of HSP70 and SIRT1. SeNPs may prove to be a useful and efficient method in the future for creating nanomaterials intended to treat severe diabetes [124–126]. It was discovered that Se NPs could increase the decrease in blood testosterone brought on by hyperglycemia induced by STZ. SeNPs significantly decreased the testicular tissue's oxidative stress indicators, such as lipid peroxidation and NO. Additionally, it increased the testicular tissues' glutathione content and antioxidant enzyme activity. According to these results, SeNPs may be able to lessen the oxidative damage brought on by diabetes, especially in testicular tissue [124]. When treating with SeNPs, the most prevalent brain disorders are called neurodegenerative diseases (NDs), include dementia, Parkinson's disease, Alzheimer's disease, and Huntington's disease, SeNPs have demonstrated therapeutic success in contrast to traditional therapies [127]. Collectively, Se and SeNPs have shown immense potential of therapeutic potentials.

2.8. Factors influences male infertility

Infertility is defined as the inability to conceive a child after 12 months or more of continuous, unprotected sexual activity. With 15 % of all couples of reproductive age experiencing infertility, it has recently become a major clinical concern and a global public health issue. According to estimates by Boivin et al. [128], subfertility or infertility affects 70 million couples globally. Male variables, such as worse semen quality, account for about 25 % of cases of infertility [129,130],and 3.3–4.7 million men in the USA are thought to be seeking reproductive treatment at any given time [131,132]. Male infertility is caused by a variety of reasons, including iatrogenic, hormonal, genetic, behavioral, environmental, and lifestyle variables [133]. It has been suggested that environmental variables including air pollution, smoking, stress, chemicals, heat heavy metals, radiation, and other harmful substances in the diet may be to blame for the decline in semen quality seen in developed countries [134–136].

2.9. Air pollution

Air pollution causes significant effect on reproductive system make in both males and females. It has a significant impact on male's semen quality. According to recent study, sperm morphological alterations, increased DNA fragmentation, and decreased motility are all effects of air pollution [137]. According to a thorough meta-analysis, the rate of normal sperm morphology, progressive and total sperm motility, and semen volume were all significantly correlated with the amount of air pollution. Additionally, it causes sperm DNA fragmentation index to increase, which further reduces male fertility [138]. Gaseous pollutants like sulphur dioxide (SO_2) and nitrogen dioxide (NO_2) had a strong negative impact on sperm concentration and motility, which was found to be more aggressive in the early stages of spermatogenesis and during the sperm development period [139]. A vast range of chemicals are present in the daily lives of people all around the world. The functioning of the human body, especially the reproductive organs, is severely harmed by several of these substances. Injurious effects from exposure to environmental toxins that cause male infertility have been demonstrated in recent investigations to primarily affect the male reproductive system [140].

2.10. Heat

Exposure to severe heat is another important risk that may contribute to male infertility. The preservation of healthy spermatogenesis in the testes is highly dependent on temperature. The increasing temperature potentially affects scrotal temperature and affects the spermatogenesis process, which will lead to male infertility. Additionally, it was found that an increase in scrotal temperature of 1–1.5 °C can lead to aberrant sperm morphology and reduced sperm production [141,142]. Increasing temperature resulted in the activation of heat shock protein (HSP) and are responsible for the folding, assembly, and disassembly of other proteins, which are playing vital role in spermatogenesis [134,143].

2.11. Tobacco smoking

According to a WHO statistic, there are 1.3 billion smokers worldwide. This is equivalent to 37 % of males who are 15 years of age or older and around 20 % of the global population. According to several studies smoking has a detrimental impact on sperm capacitation, DNA integrity, motility, morphology, numeration, vitality, and semen volume through increased oxidative stress and inflammation [144–147]. Proteins involved in immunological and inflammatory responses were shown to be enriched in smokers, specifically protein S100A9, a biomarker of inflammation that was found to be able to identify the smoker group [148]. The findings of a different study point to the possibility that accessory gland and testis inflammation may be to responsibility for the lower mitochondrial activity and acrosome integrity as well as the higher DNA fragmentation seen in the spermatozoa of smokers [149]. Another proteome profiling investigation showed that isolated spermatozoa from the semen of control and smoke-exposed mice both displayed 22 differently expressed proteins; 10 of them were up-regulated and 12 of them were down-regulated. Superoxide dismutase (SOD), catalase (CAT), and glutathione-*S*-transferase (GST) activity in seminal plasma has been demonstrated to be decreased by smoking [150–152].

According to an intriguing study, Acrosin (ACR), a protease present in the sperm acrosome, had lower activity in males who smoked. The acrosome reaction's inducibility was also reduced as a result of this decrease [153]. In spermatozoa from men who smoke found that there was a correlation between higher cadmium concentrations in the seminal plasma and lower Ca^{2+}-ATPase (ATP2B4) function. The reduced motility seen in smoker's spermatozoa, they hypothesised, could be caused by this consequence. According to Cui et al. [154], increased sperm DNA fragmentation is caused by a decrease in the expression level of checkpoint kinase 1 (CHK1), an enzyme involved in DNA repair and cell cycle control. Creatine kinase (CK) activity and sperm motility were found to be negatively correlated with smoking duration in smoker semen by Ghaffari and Rostami (2013) [155]. TNF receptor superfamily member 6 (Fas) and caspase 3 (CASP3), two apoptosis markers, were identified in higher concentrations in the sperm of smoking men.

According to numerous studies [156–159], sperm quality, lower semen volume, decreased sperm concentration, motility and morphology, and increased sperm DNA damage are all affected by obesity and overweight. Additionally, chronic inflammation, elevated testicular heat, and oxidative stress are all factors in obesity and overweight that are linked to poor spermatogenesis. According to several studies [158,160], compared to healthy donors, obese patients either had higher or lower expression of the outer dense fibre protein 1 (ODF1). Spermatogenic glyceraldehyde 3-phosphate dehydrogenase (GAPDHS), a sperm-specific glycolytic enzyme was ten times more prevalent in obese males. According to a study by Paasch et al. (2011) [161], the eppin protein complex (EPC) has high levels of three distinct proteins, including clusterin (CLU), LTF, and SEMG1. According to Wang et al. (2007) [162], EPC is engaged in the motility and spermatozoa preservation processes. According to Paasch et al. the altered sperm functions in these people may be related to the elevated amounts of modified versions of SEMG1 and LTF identified in obese persons. Another study examined the proteome alterations linked to asthenospermia brought on by obesity. They analyzed the proteome of spermatozoa from three obese people with severe asthenospermia with three clinically healthy people using a label-free quantitative LC-MS/MS technique. They discovered 127 proteins, including 105 less abundant proteins and 22 more abundant proteins that were deregulated in the obesity-associated asthenospermic group in comparison to the control group. By using immunofluorescence, flow cytometry, and Western blotting, the researchers found that two proteins, endoplasmic reticulum protein 57 (ERp57) and actin-binding-related protein T2 (ACTRT2), were downregulated in a new cohort of obese asthenospermic people. In an *in vivo* experiment, mice or rats were fed either a control diet (CD group) or a high-fat diet (HFD group) for several weeks. Of the 160 proteins that were found to be differentially regulated between the two groups, 100 were found to be less abundant and 60 to be more abundant in the HFD group [163]. According to Peng et al. (2016), GO analysis assigned the majority of the differentially expressed proteins to the biological processes of transport, intracellular protein traffic, cell shape and motility, exocytosis, and endocytosis. In particular, centrin 1 (CETN1) and centrosome and spindle pole associated protein 1 (CSPP1), two proteins related to the cytoskeleton, were found to be reduced in obese and overweight males (Peng et al., 2019) [163]. According to research by Shi et al. (2014), both the level and activity of protein-tyrosinase phosphatase 1 B (PTP1B) were significantly higher in obese mice and males, and this increase was associated with changes in sperm acrosome response [164]. Interleukin-6 (IL-6) and tumour necrosis factor (TNF) levels in seminal plasma of obese patients were elevated, which affected the quality of the semen and the chronic inflammation of the male genital tract in the fertility of obese people [157]. Reduced fertility is brought on by SEMG1, a seminal protein that inhibits premature sperm capacitation. In seminal plasma and purified spermatozoa from obese patients, phospholipase A2 (PLA2B) expression was seen to be reduced [165–167]. The sterol acceptor apolipoprotein A1 (ApoA1), which is found in seminal fluid, has been demonstrated to stimulate sperm motility [106,140]. An essential mechanism that is frequently dysregulated in obese people is the oxidation-reduction process. According to several studies [158,168,169], oxidative stress, which is brought on by an imbalance between the production and neutralization of reactive oxygen species (ROS), is indeed responsible for the disruption of spermatogenesis and alteration of sperm quality in obese men. Higher amounts of ROS seem to harm DNA, oxidize membranes, and stop mitochondrial function in sperm.

Accordingly, the fluctuation in antioxidant protein abundance may work to reduce the harmful effects of ROS in obese males [170–172]. The chronic inflammatory condition of the obese male genital tract, which is characterized by the abnormal production of cytokines and has been shown to impair spermatogenesis in testicular tissues and sperm maturation in the epididymis, is undoubtedly linked to the immune response that has been highlighted in humans [157,173,174].

2.12. Diabetes

According to WHO, diabetes is a chronic condition that develops when the pancreas either generates insufficient amounts of the hormone insulin (type-1 diabetes) or when the body cannot properly sense the insulin it produces (type-2 diabetes). Due to reduced sperm count and motility, increased sperm apoptosis, and nuclear and mitochondrial DNA damage, men with diabetes have a greater risk of infertility than men without diabetes. Epigenetic dysregulation, oxidative stress, endocrine abnormalities, and diabetic neuropathy may all contribute to defective spermatogenesis, which in turn contributes to diabetes-related reproductive issues [134,175,176]. Kriegel et al. observed the effects of diabetes and obesity on the sperm proteome. Seven differentially expressed proteins were found after 2D-DIGE combined to MALDI-TOF-MS analysis of the proteomic profile of progressive normomorphic spermatozoa from two type-1 diabetic patients and five normospermic donors [166]. The altered mitochondrial structure was observed in spermatozoa from obese men, and it leads to alteration of sperm motility is a primary cause of diabetes-induced male infertility [177]. Serum amyloid *P*-component (APCS) and Ras-related protein Rab-2A (RAB2A) were more abundant in the spermatozoa from diabetic men [178]. Insulin shortage and hyperglycemia may contribute to pelvic neurological diseases and urogenital infections, both of which may have an impact on seminal parameters and fertility [179]. Sahu et al. (2020) reported that 8 weeks combined treatment of Zn (3 mg/kg, i. p.) and Se (0.5 mg/kg, i. p.) reduced diabetes-induced germ cell damage [180].

2.13. Bisphenol-A (BPA)

The U.S. Environmental Protection Agency (EPA) and the European Commission (EC) started researching the effects of endocrine disruptors, which are chemicals that affect the hormonal system and have an adverse impact on a person's ability to develop, reproduce, and maintain a healthy immune and nervous system. Male fertility has been studied in relation to a variety of endocrine disruptors, including phthalates, polychlorinated biphenyls, dioxins, pesticides, and parabens [181,182]. The chemical bisphenol-A (BPA) is present in a variety of products that contain food, including cans, metal lids for epoxy resins and home appliances, plastic bottles, and plastic wrapping for polycarbonate plastics. Therefore, people are having chances to expose to BPA. Exposure to BPA compromises DNA and acrosome integrity as well as sperm quality, motility, vitality, spermatozoa concentration, and ATP generation [183–185]. Furthermore, BPA has detrimental effects on the male reproductive system, impairing spermatogenesis and testicular development [186–189]. In order to understand the impact of BPA on the sperm proteome, Rahman et al. exposed mouse sperm to different concentrations of BPA (100 μM) for 6 h. The authors found that BPA treated group showed a down-regulation of β-actin (ACTB) and an up-regulation of peroxiredoxin-5 (PRDX5), glutathione peroxidase (GPX4), GAPDHS, and succinate dehydrogenase (SDHB) [189]. Rahman et al. showed that lactate dehydrogenase (LDH) levels were higher in the spermatozoa of male mice (F0) exposed to NOAEL and LOAEL dosages of BPA compared to controls. According to Barbonetti et al. findings, spermatozoa with activated caspase-3 (CASP3) and caspase-9 (CASP9), significantly increased after being exposed to 300 M BPA for 4 h. This showed how BPA was involved in the activation of the mitochondrial apoptosis pathway, which changed sperm motility and resulted in DNA damage. This was accompanied by an increase in ROS generation and a decrease in the mitochondrial membrane potential [190]. The expression of structural proteins such ACTB, ROPN1, FABP9, and ODF2 was shown to be altered when spermatozoa were exposed to BPA. Alteration in sperm morphology and/or motility results from altered expression. It has been suggested that the lower sperm ATP levels and motility seen after BPA exposure are caused by a decrease in ATP5O, an enzyme involved in oxidative phosphorylation [191–193]. BPA promotes the dysregulation of four antioxidant enzymes, GPX4, PRDX5, GSTM5, and SOD2, resulting in oxidative damage to sperm [134]. Similar to this, it has been demonstrated that BPA exposure decreases Prohibitin (PHB) expression, which increases ROS levels and reduces sperm motility [191,192]. BPA-treated animals significantly decreased antioxidant enzyme activities including superoxide dismutase, catalase, and increased the expressions of stress-activated kinases (c-Jun NH2-terminal kinase (JNK), extracellular signal-regulated kinase (ERK) and p38) and the expressions of pro-apoptotic markers (caspase-9, caspase-8 and caspase-3). Conversely, supplementation of selenium restored the antioxidant enzyme activities and lowered the expressions of stress activated kinases, which further down-regulated the apoptosis. Thus, selenium supplementation demonstrated to be effective against BPA provoked testicular damage.

2.14. Dietary elements

Since the 1980s, a number of dietary elements and nutrients have been investigated as potential influences on sperm function, fertility, or regular reproductive system operation [194]. Male obesity and specific dietary elements may be very important in regulating spermatogenesis, sperm maturation, and fertilizing potential, according to growing data from human *in vitro* and animal research. Because it affects the chemical and physical structure of sperm, male obesity, for instance, has been linked to reduced reproductivity [195–197]. Additionally, a number of foods and dietary elements that have been linked in animal models to poor sperm quality or function have also been linked to an increased risk of obesity, insulin resistance, and diabetes. For instance, diets high in calories [198], *trans*-fatty acids (TFAs), saturated fats [199], or cholesterol [200] have been linked to testicular disturbance, causing abnormalities in spermatogenesis potentially harming male fertility and the progeny. The impacts of environmental and lifestyle

factors on semen quality and male infertility was discussed in Table 3 [190,201–231].

2.15. Functions of selenium and selenoproteins in spermatogenesis

Selenium is a crucial trace element and both organic and inorganic forms of selenium are being used for the biology and wellness of humans. As more and more data come to light, it appears that this mineral is crucial for both human and animal reproduction and normal growth. Infertility in men and women, miscarriages, preeclampsia, foetal development restriction, premature labour, gestational diabetes, and obstetric cholestasis are among the reproductive and obstetric issues brought on by selenium deficiency. Selenium has a role in idiopathic infertility in addition to being engaged in spermatogenesis, sperm motility, and proper testicular growth [232].

Table 3
Comparative account of effect of environmental factors on male fertility in animal and human.

S. No	Predisposing factor	Source/cause	Human studies	Animal studies
1	Air Pollution	Motor vehicles exhaust, factories, fire, household, agriculture, waste treatment, oilrefneries, natural sources, such as volcaniceruptions, wind, etc.	$PM_{2.5}$ in the air is directly associated with total sperm number and concentration [201,202] PM_{10} is related to semen volume and typical forms and inversely related to atypical forms [201,203] SO_2 exposure at the time of sperm development causes oxidative damage to sperm [204] Air pollution negatively affects testosterone levels [203]	$PM_{2.5}$ exposure in mice causes a significant fall in sperm concentration, motility, serum testosterone levels, an increased percentage of morphological abnormalities in sperms [205] $PM_{2.5}$ causes severe testicular damage on histopat- hology [206]
2	Chemicals			
	i. Dioxins/ Furans	Produced as a by-product of industrial and natural processes, such as smelting, chlorine bleaching of paper and pulp, production of pesticides, biomedical and plastic waste incineration	Reduced sperm concentration and motility [207] Ejaculate of infertile men had 2.2–2.3 times higher content of dioxins and furans as compared to their fertile counterparts [208]	Reduced daily sperm production, epididymis sperm counts, and dose-dependent histological changes in the testes [209] Fall in plasma concentrations of testosterone, and LH [209]
	ii. Bisphenol A (BPA)	A major component of plastic and released during production, use, or disposal of plastics and breakdown of industrial plastic-related wastes	Pro-oxidative/apoptotic mitochondrial dysfunction [190] Inverse correlation between sperm concentration and urinary BPA levels [210]	Reduced sperm production, motility, increased sperm abnormalities, acrosomal and sperm plasma membrane damage, decreased mitochondrial activity and, increased defective spermatozoa [211,212]
	iii. Pesticides/ Herbicides	Used in agriculture, to control insects	Reduced sperm motility, sperm count, concentration, and increased sperm morphological abnormalities [213,214]	Reduced sperm motility, motion kinematic parameters, sperm ATP levels, and increased morphological modifcations [215,216]
	iv. Phthalates	Found in numerous consumer products, such as toys, pharmaceuticals, cosmetic products, building and construction materials, scent retainers, some medications, and personal care products	Reduced total sperm counts, sperm concentration, larger sperm head sizes, an increased number of morphologically abnormal sperm lead to reduced semen quality [217,218]	Reduced sperm motility, capacitation, and acrosome reaction, leading to poor fertilisation in mice [219] Increased DNA fragmentation and decreased sperm motility in dogs [220]
	v. Heavy Metals	Volcaniceruptions, Weathering of metal-bearing rocks, mining, andindustrial and agricultural activities	Increased blood Cadmium and Barium levels and higher seminal lead, Cadmium, Barium, and Uranium result in low sperm viability and increased immotile sperm [221,222] Uranium levels correlate with decreased sperm motility and abnormal sperm morphology [221] Exposure to high $CuSO_4$ (250 μg/mL) and $CdCl_2$ (500 μg/mL) results in reduced sperm motility [223]	Acute and chronic cadmium exposure causes reduced sperm motility, viability, and acrosome reaction both *in vivo* and *in vitro* [224] Heavy metals adversely affect testicular morphology, sperm production, and quality [225]
3	Heat Exposure	Occupational exposure in people working in furnaces, bakeries, welding, ceramic factories, laundries, dry cleaning shops, or drivers, hot climate, excessive use of hot tubs, Jacuzzi, or hot baths	Extremes of temperature result in decreased semen quality including reduced sperm concentration, total sperm count, total motility, progressive motility [226] Reduced sperm concentration and total amount per ejaculate in summers as compared to winters [227]	Heat stress causes a rise in sperm abnormalities, lipid peroxidation, altered mitochondrial function, decreased sperm motility, plasma membrane integrity, increased DNA fragmentation, and reduced sperm quality [228–230] Heatwave conditions (5–7 °C above the optimum temperature for 5 days) adversely affect male reproductive potential, halve male fertility, and severely affect sperm competitive ability [231]

Selenium has a crucial function in the development of mammalian sperm, and its presence in the male reproductive tract is necessary for proper spermatogenesis. X-ray fluorescence microscopy (XFM) was used in the first investigation to validate the existence of selenium in the involvement of selenium in spermatogenesis [233]. Selenium concentration in spermatogenic cells decreases and morphological abnormalities in spermatozoa result from selenoprotein P and ApoER2 deficiency during spermatogenesis. Selenium in the testis is reduced by up to 77 % when selenoprotein P is absent [233]. A protein that is a structural part of the mitochondrial capsule within the midpiece of mature spermatozoa has been hypothesised to include selenium in the form of Sec [65,234].

A study was done to compare rams fed with 0.5 ppm organic selenium to another group fed with 0.2 ppm organic selenium. The selenium concentration was significantly higher in rams fed a diet containing 0.5 ppm organic selenium. Selenium-deficient diets cause abnormalities in the tail, midpiece, mitochondrial gaps, and plasma membrane of boarspermatozoa [235,236].

Selenium is an essential component of selenoproteins and modifies their expression. Selenium is incorporate into selenoproteins and selenoenzymes, such as GPxs, via seleno-amino acids, replacing sulphur in proteins. These seleno-amino acids and selenoenzymes play an important role in sperm quality and male fertility. A low concentration of selenium-containing proteins in spermatozoa decreases the possibility of fertilisation and it is more vulnerable to oxidative stress [10]. Most soluble GPx4 is present in germ cells; in spermatids, it possesses active peroxidase activity and effectively shields cell membranes from free radicals. Through the formation of disulphide bridges in chromatin, the insoluble form of GPx4 affects sperm maturation and male fertility. Spermatozoa from GPx4 mutant mice had greater concentrations of the protein thiols. The presence of mGPx4 and its protein thiol peroxidase activity is necessary for the integrity of the sperm midpiece [237]. GPx4 that has been polymerized, on the other hand, results in low sperm numbers and subpar sperm quality.

A crucial micronutrient during spermatogenesis, selenium protects against oxidative damage. Selenium has a significant impact on the development of organisms and their ability to function, either positively or negatively, in terms of toxicological effects [238,239]. Redox active transcription factor activator protein 1 (AP-1) and testicular function were both examined by Shalini and Bansal in 2005 [240]. The inadequate, sufficient, and excess selenium statuses were all examined in male Balb/c mice. Selenium concentration had an impact on the mice's ability to reproduce. The activity of superoxide dismutase (SOD) and the concentrations of reduced (GSH) and oxidised (GSSG) glutathione were specifically affected by the selenium level. Further, the authors observed decreased *Jun*and*Fos* messenger RNA (mRNA) levels – encoding proteins that are part of AP-1 – when selenium was deficient or in excess. The lower fertility, changed differentiation, and decreased number of germ cells found at the altered selenium levels may be brought about by these mRNA alterations. Selenium deficiency causes modulation of Nuclear Factor Kappa B (NF-κB), AP-1, heat shock proteins, ERK signalling and eventually leads to enhanced level ROS, RNS, oxidative stress, lipoperoxidation, DNA damage and apoptosis As a result of all these changes causes impairment in steroidogenesis, spermatogenesis, and male fertility(Fig. 3).

In testes, GPx4 is prominently expressed; it is widely dispersed in late spermatocytes and spermatids and localised in the sperm midpiece, namely in the mitochondria [241]. The mitochondrial sheath that surrounds the flagellum, a crucial component for sperm stability and motility, is thought to be protected by GPx4 in order to prevent oxidative stress-related DNA damage to developing sperm [10,14,72,242]. When Gpx4 is disrupted, homozygous Gpx4 knockout mice have early embryonic mortality and prominent early developmental abnormalities [243]. Similar to other mammalian species, GPx4 is crucial for the proper growth and operation of bovine sperm and is also crucial for the proper functioning of male reproductive organs. Studies on mice lacking the gene for mGpx4 have shown that Se decrease significantly reduces spermatogenesis [233]. For sperm cells to mature normally, testosterone is necessary. Male fertility is harmed by excessive ROS generation during testosterone manufacture [244]. Leydig cells contain seleniproteinPmRNA, a protein that guards against oxidative damage [245]. In several animal species, se supplementation raises

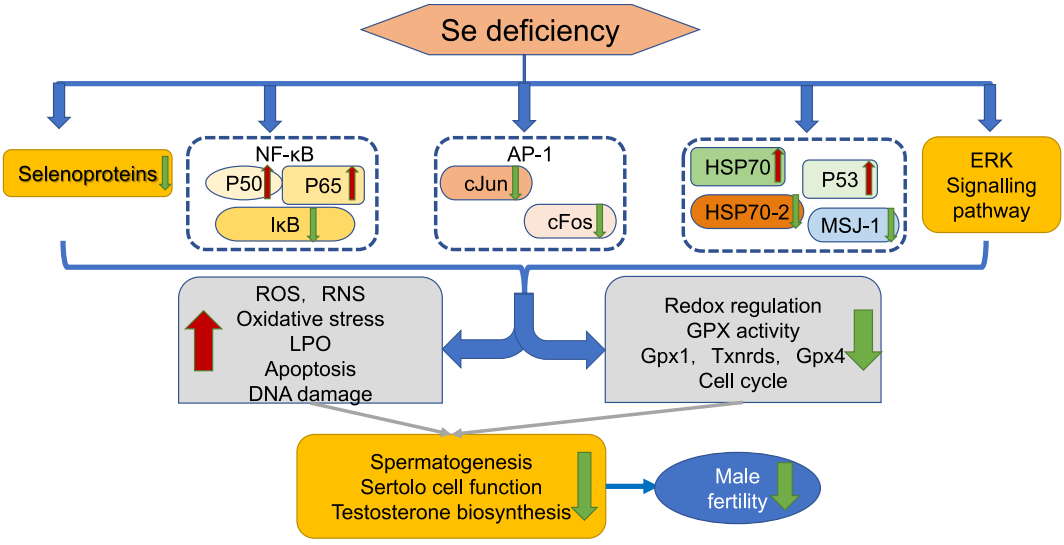

Fig. 3. Schematic illustrating the implication of Se-deficiency in steroidogenesis, spermatogenesis, and male fertility.

testosterone levels and enhances sperm quality [246–248].

As a result of extracellular signal-regulated kinase (ERK) signalling pathways being activated, selenium plays a crucial role in vital cellular activities [249]. In bovine Leydig cells, selenium influences cellular processes related to proliferation and apoptosis, while cellular processes related to proliferation and apoptosis in bovine Leydig cells influence these processes. The control of oxidative stress, the cell cycle, and apoptosis-related indicators subsequently modifies these processes [250].

Apolipoprotein E receptor-2 (ApoER2), a member of the lipoprotein receptor family, is responsible for selenoprotein P uptake in Sertoli cells, which enables selenium to be transported from the blood to spermatogenic cells to assist spermatogenesis [251]. In a research using ovine Leydig cells, the authors discovered that the 2.0 mol/L group had the lowest ROS level and the maximum GPx activity in comparison to the control (without Se) and high selenium-treated (4.0 and 8.0 mol/L) groups [252]. By triggering the ERK signalling pathway and the activation of its downstream genes, they also discovered that selenium boosted testosterone manufacture in Leydig cells. Selenium (2.0 mol/L) increased testosterone production by significantly upregulating the expression of downstream genes. Nuclear factor kappa B activation in cultured Sertoli cells was reduced by pre-treatment with inorganic selenium (0.50 mg/L). The genes that regulate testicular shape and function were upregulated in roosters administered selenium at doses of either 0.3 mg/kg feed as inorganic (sodium selenite) or organic (yeast-derived) selenium. Notably, roosters that received organic selenium had considerably greater testis selenium concentrations [253]. These data show that selenium is necessary for spermatogenesis. The mean number of spermatogonia, spermatocytes, spermatozoa, or spermatogenic cells did not change significantly between goats fed regular feed and those supplemented with 0.6 mg/kg sodium selenite in the diet or a selenium-deficient group [254]. Spermatozoa with aberrant head structures are produced by selenium-deficient mice [255]. Spermatozoa ROS can be protected when GPx1 and cGPx4 are expressed in the epididymal epithelium [256]. In order to protect spermatozoa from ROS, selenoproteins and selenoenzymes, which are involved in spermatogenesis, contain selenium.

The suppression of inflammatory cytokine activation in Sertoli cells exposed to MC-LR was evidence that selenium also shows certain immunomodulatory functions [257]. Additionally, this pre-treatment altered the expression of mitochondria-related genes, including cytochrome *c* oxidase subunit I (COX-1), cytochrome *c* oxidase subunit 2 (COX-2), acetyl-CoA acetyltransferase 1 (ACAT1), mitochondrial transcription factor A (mtTFA), and subunit 2 of NADH dehydrogenase (MT-ND2). Apoptosis-related genes are induced to express in Sertoli cells by selenium.

According to results from an *in vivo* investigation, selenium controls spermatogenesis via altering the expression of genes involved in cell cycle and death. For instance, CDC2/cyclin B1 is inhibited by selenium-induced oxidative stress during spermatogenesis [258]. The process of spermatogenesis and male fertility are eventually impacted by selenium deficit because it has a substantial effect on redox signalling and intracellular oxidative stress, which in turn causes the production of many redox-sensitive transcription and proliferation factors. Chicken Sertoli cell's phosphoinositide 3-kinase/AKT/mechanistic (or mammalian) target of rapamycin signalling pathway is significantly influenced by selenium protein U [259]. Two selenoproteins, specifically phospholipid hydroperoxide glutathione peroxidase (PHGPx), commonly known as GPx4, control mammalian spermatogenesis, sperm quality, and male infertility [260].

2.16. Impact of selenium on clinical studies and potential therapeutic interventions

A substantial portion of the world's population—between 500 million and 1 billion people—are deficient in selenium as a result of inadequate food consumption. Notably, selenium deficiency is more common in people with phenylketonuria and other diet-related disorders. Their dietary limitations, which frequently lead to inadequate ingestion of goods rich in this essential element, are the cause of this sensitivity. Interestingly, combinatory antioxidant therapy for three months does not improve the semen parameters and clinical outcomes in 174 couples suffering from male factor infertility, according to research by Steiner and colleagues, one of the largest adequately powered clinical trials of its kind conducted in the USA with a "well characterized" study population. Additionally, these authors showed that a number of previous clinical studies and trials that indicated improvements in sperm parameters due to antioxidant therapy were constrained by non-clinical endpoints, subject variability, small numbers of participants, and a range of antioxidants (Steiner et al., 2018).

According to Ref. [261], sperm were allegedly subjected to excessive oxidative insult in 28 Turkish men who suffered from idiopathic infertility. Despite this, the semen quality parameters were compromised because of increased ROS-related DNA damage in sperm. Additionally, the levels of MDA, protein carbonyl group, and nitrotyrosine were elevated in the idiopathic infertile males. The fact that males with idiopathic infertility had higher levels of oxidative stress in their seminal plasma suggests that their reproductive systems were not able to combat the oxidative stress. It was recently reported that cryopreserved semen from 42 clinically healthy Iranian men showed dramatically increased sperm quality and viability after receiving Se-treatment (5 μg/mL of sodium selenite) [262]. Another study with fifty asthenoteratozoospermic men found that the test group (treated with 2 μg/mL Se at 37 °C for two, four, and 6 h) had a significantly higher score for sperm quality criteria like motility, viability, and mitochondrial membrane potential. The Se-supplemented group showed noticeably decreased levels of DNA fragmentation and MDA [263].

Usually, a selenium deficit affects whole populations as opposed to being a problem with a single, isolated person. To tackle this issue, biofortification techniques—soil enriching through agricultural practices—have been put into place [6]. One further strategy is to add selenium compounds to animal feed in order to raise the selenium content of dietary sources. By using this technique, selenium-enriched eggs or egg yolks can be produced, which have a greater nutritional selenium content. Eggs, meat, and milk fortified with selenium have been effectively implemented in numerous nations. It's a novel approach to use microbes to create functional meals like selenium yeast. This strategy focuses on initiatives to address selenium deficiency and enhance nutrition and public health [264]. The best way to prevent selenium insufficiency, maintain good health, and minimize the need for excessive supplementation is

to emphasize a well-balanced diet [265].

2.17. Role of selenium and selenoproteins in male fertility

Sperm maturation, which is strongly correlated with the quality of the sperm and ejaculate as well as overall male reproductive efficiency, is a component of male fertility. Any anomaly during these processes results in insufficient and worse quality ejaculates, which eventually reduces male fertility. Selenium has been thought to have a significant role in male fertility in rats, mice, and sheep for a number of decades. Increasing the amount of dietary selenium may increase the antioxidant GPx activity and boost male fertility (Fig. 4).

Two generations of rats fed a diet lacking in selenium produced spermatozoa with abnormalities. Selenium deficit is so severe that it causes spermatogenesis to be stopped, the seminiferous epithelium to deteriorate, and aberrant sperm morphology to be seen. As a result, male rats and mice become infertile. When rats were given injections of 75Se, the majority of the selenium collected in the portion of the spermatozoon that houses the mitochondrial sheath, which is enclosed in a matrix resembling keratin [65,266].

According to Edens and Sefton (2009), selenite, also known as SelPlex, at a dose of 0.2 mg/kg in feed, has a significant role in the development of male sexuality. While roosters fed without selenium generated semen at 26 weeks, those fed with selenium did so at 19 weeks [267]. According to a research by elemental nano-selenium, male Boer goats' testes have altered ultrastructural morphology [268]. Selenium has been shown to work in conjunction with vitamin E in most cases. Rams produced more offspring when supplemented with vitamin E and selenium than when vitamin E was the only nutrient present [269]. Body weight, testicular and cauda-epididymal weight, and the number of spermatogenic cells were decreased in male rats fed diets high in excess selenium (6.0 and 8.0 ppm sodium selenite). In addition, the researchers found that the cauda-epididymal tubule diameter, lumen diameter, seminiferous epithelial height, and seminiferous tubule diameter were all decreased [270].

According to Maiorino et al. (1998), the age- or gonadotropin-dependent expression of PHGPx in testis is not caused by testosterone directly activating transcriptional genes; rather, it is caused by differentiation stage-specific expression in late spermatids [71]. Increased ROS generation led to membrane peroxidation, reduced sperm motility, and oxidative stress-induced DNA damage and/or death. Redox balancing is thus a critical step for the optimal operation of cells [3]. By changing antioxidant indicators and the activity of antioxidant enzymes, changes in the redox balance have a striking impact on male fertility. Heat shock protein 70 (HSP70) expression is disrupted by changes in selenium levels which ultimately leads to oxidative stress. These results are in favour of selenium involvement in redox equilibrium [271].

An investigation revealed that mature spermatozoa of Selenoprotein P knockout men have a particular collection of flagellar structural anomalies that develop sequentially throughout spermiogenesis and following testicular maturation in the epididymis. The flagellar abnormalities include creation of a hairpin-like bend at the midpiece-main piece junction, truncation of the mitochondrial sheath, and ejection of a particular set of axonemal microtubules and dense outer fibres from the principal piece. Collectively, these findings show that selenium is necessary for the growth of functional spermatozoa and suggest that the selenium delivery mechanism for germ cell development includes selenium protein P [272].

According to results from an *in vivo* investigation, low levels of selenium increase LPO and ROS while lowering GPx [273]. The antioxidant activity of GPx and SOD as well as the gross morphological and histomorphological indices in the testes of young male goats were all considerably enhanced by long-term food supplementation with organic selenium (0.3 mg/kg body weight) [274]. The authors assessed sperm quality, which was influenced by a number of factors including sperm concentration, vitality, progressive movement, and overall sperm morphology. Subfertility and infertility in males are caused by changes in biomarkers.

The redox state of thioredoxins is controlled by the crucial redox regulating enzymes known as thioredoxin reductases (TRs).

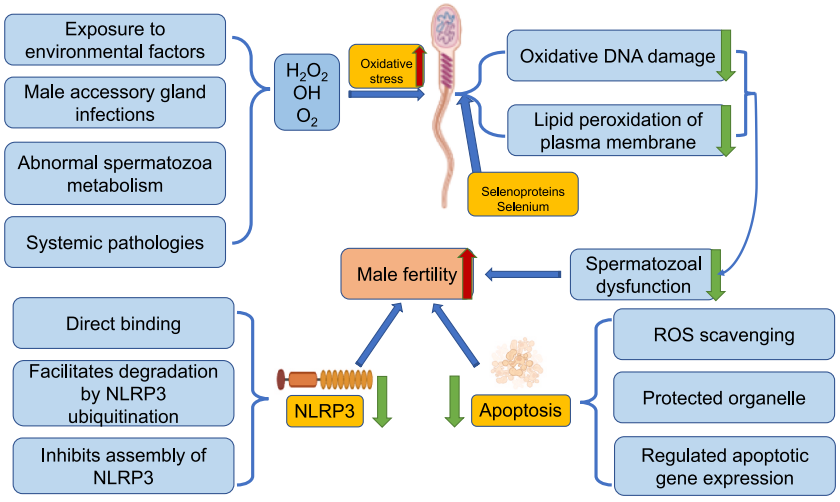

Fig. 4. Selenium and selenoproteins ameliorating male spermatogenesis fertility and reproductive efficiency in males.

Essential selenium residues are present in the cytosol and mitochondrial TRs, which also lower the cytosolic and mitochondrial thioredoxins. However, mature sperm do not contain the protein, which is more prevalent in elongating spermatids where the mitochondrial sheath is forming [275].

In terms of male fertility, oxidative damage is quite important. Selenium plays a crucial function in preserving male fertility by helping to shield spermatozoa from this damage and preventing further spermatozoa damage [276]. Sperm is susceptible to oxidative stress, in part because of its metabolic makeup, which includes a high concentration of polyunsaturated fatty acids and a low level of cytoplasmic antioxidant enzymes in comparison to somatic cells [277]. Selenium deficit results in increased ROS generation, LPO, loss of plasma membrane integrity, sperm DNA damage, and chromatin condensation, which is a necessary stage for both sperm maturation and the ability of men to reproduce [278]. Selenium shortage may result in oxidative injury, and decreased selenoprotein synthesis may affect the antioxidant state and sperm quality indicators in the male reproductive organs, lowering male fertility.

When compared to other traditional forms of selenium, selenium nanoparticles (SeNPs) have a higher bioavailability and lower toxicity. The motility, viability, and maintenance of mammalian sperm's capacity for fertilisation are significantly influenced by the serum concentration in plasma. A domestic cat *in vivo* study found significant correlations between serum selenium concentrations and sperm quality traits, testosterone levels, and testis morphology, as well as a negative correlation between serum selenium concentrations and total testicular weight and sperm morphological traits like total head defects [279,280]. According to a research done on male horses, sperm, seminal plasma, and semen selenium levels have an impact on fertility and sperm quality as a whole [281]. Dog's sperm qualities, including total sperm count, concentration, morphology, and motility scores, were increased by the combination of selenium and vitamin E [282]. In animals, combining selenium with either minerals or micronutrients improves fertility, semen quality, and antioxidant status [283]. Selenium and vitamin E together considerably raise testosterone levels and enhance sperm and ejaculate quality metrics [284]. When compared to mice consuming selenium-adequate diet (0.23 mg/kg), animals given a diet low in selenium showed greater endogenous levels of DNA damage in the testicular parenchyma [285]. According to a study conducted both human and animal models, increased oxidative stress brought on by varicocele has been linked to adverse effects on male testicular parenchyma and semen, [286]. When inorganic selenium was added to the diet of varicoceles male Wistar rats, the testicles' damage was lessened [286]. In rats, SeNPs improve the effectiveness of reproduction. By modifying the phosphorylation of ERK1/2, p38, and c-Jun NH2-terminal kinase (JNK)/MAPK pathway components for 14 days, different concentrations of SeNPs (0.5, 1.0, and 2.0 mg/kg) supplementation ameliorated nickel-induced testicular damage, DNA perturbations, and testosterone biosynthesis [287].

When compared to mice that were not treated with selenium (0.5 ppm sodium selenite/kg diet), selenium therapy reduced the oxidative damage and apoptosis that BPA exposure caused in mouse testes. Selenium treatment dramatically decreased ROS and LPO levels as well as the rate of apoptosis in the testes, while also improving sperm quality metrics including motility and concentration [288]. In addition, mice treated with selenium had more spermatogenic cells than the untreated, BPA-exposed group [288]. Zearalenone-induced damage to testicular tissue and sperm in mice was prevented by selenium therapy. The sperm's concentration and motility were also preserved. When compared to the group influenced by zearalenone, selenium also lowered MDA levels while raising GPx and SOD levels. Additionally, genes associated with apoptosis including Bax and caspase-3 had their relative mRNA expression altered [289].

Aktan et al. (2013) reported that excessive oxidative stress impaired semen quality parameters and increased DNA damage, MDA, protein carbonylation and nitrotyrosine in sperm of 28 Turkish men with idiopathic infertility [261]. Selenium (5 g/mL sodium selenite) treatment resulted in considerably increased sperm quality and viability in cryopreserved semen from 42 clinically healthy Iranian men. Additionally, the selenium-treated group outperformed the untreated control group in terms of the proportion of sperm with normal morphology and motility [262]. According to a research, selenium (2 g/mL) treatment dramatically improved sperm quality indicators like motility, viability, and mitochondrial membrane potential while also considerably lowering levels of MDA and DNA fragmentation in 50 males with asthenoteratozoospermia [263].

Sperm must have sufficient motility to reach and fertilise the female egg, making it one of the most important fertility characteristics. GPx4 is believed to protect sperm from DNA damage brought on by oxidative stress during the early stages of spermatogenesis. In both early embryo development and gametogenesis, GPx4 is a crucial prerequisite. The zona pellucida during fertilisation is significantly affected by GPx4 expression in the acrosomal area [10,14,72,242,290]. Male mice's testis selenium concentration was raised by intraperitoneal injections of sodium selenite and selenium nitrate daily for seven days [291].

The structural role that mGpx4 plays during spermatogenesis is essential for the midpiece of the sperm. The nonenzymatic structural role of mGpx4 is critical because male mice lacking this protein are infertile [292]. One gene encodes all three of the GPx4 isoforms, such as mGPx4, snGPx4, and cGPx4 and each isoform performs different tasks. Male fertility has been linked to mGPx4, which is found in the mitochondrial midpiece of spermatozoa [241,292,293]. Mammalian spermatids were used as a model for the study of GPx4 in order to assess male fertility, and it was shown that selenium deficit may result in decreased spermatozoa motility and production [294]. The overall content of selenium in the testis depends on GPx4 concentration. Selenium deficiency in the diet causes GPx activity to decrease. On the other hand, excessive selenium consumption (1.0 ppm in a yeast-based diet) raises GPx activity and reduces the ability of mice to reproduce male offspring [270,273,295]. At puberty, mGPx4 levels rise, neutralising ROS produced by redox processes in the mitochondrial electron transport chain. It's interesting to note that enhanced mGPx4 preserves the shape and structure of the mitochondrial capsule by forming cross-links with other proteins and with itself [20,241]. In addition to promoting significant morphological changes in spermatozoa, a decrease in mGPx4 reduces spermatozoa motility and causes gradual loss of motility over time [294]. Infertility in male mice is caused by low GPx4 levels. The inability of spermatozoa lacking mGPx4 to fertilise oocytes was revealed in an *in vitro* experiment [296]. Low levels of spermatogenic cells in seminiferous tubules and infertility are both caused by GPx4 deletion. Less spermatozoa are produced as a result of these modifications, and the epididymis produces less spermatozoa [243,296,297]. Spermatozoa lack forward motility mostly because of compromised mitochondrial activity, decreased

mitochondrial membrane potential, and hairpin-like tail bending. Se levels were 60 % lower and spermatogenesis was markedly decreased in mGPx4 knockout mice. This deletion resulted in a selenium level reduction of 77 % [233].

In GPx5 knockout mice, spontaneous miscarriages were more common, embryo abnormalities in the late phases of development, and early infant mortality were all seen. These mice had fewer developmental abnormalities, low sperm quality, deformity, abortion, and pupmortality [298]. The spermatozoa count, concentration, motility, and shape in mice, people, and farm animals with severe Se insufficiency are improved by oral supplementation of 1 g vitamin C/day, 1 g vitamin E/day, and 1.0 ppm sodium selenite [251,272, 299].

According to several studies, selenium can affect the testis's gross and histological morphology [19,270,300]. The length and circumference of the scrotum were shown to significantly increase when sodium selenate was present in the in mice [301]. LPO, MDA, and ROS levels were enhanced by the uptake of low selenium (0.2 ppm sodium selenite) or high selenium (1.0 ppm sodium selenite) [270,273]. The frequency of tailless and headless spermatozoa increases along with the proportion of motile spermatozoa, spermatozoa concentration, and motile spermatozoa count that is damaging to semen quality [95].

The male offspring of mice fed low amounts of dietary selenium (2–7 g/kg feed) had delayed testis development and puberty [19]. The testes of mice that received enough selenium (250–300 g/kg sodium selenite) were bilaterally atrophying and devoid of mitotic activity. The seminiferous tubules were also smaller, bordered with a sparse number of stem cells or Sertoli cells, and had incomplete or decreased spermatogenic activity [19]. In comparison to a control group given simply a baseline diet, testosterone output significantly increased in male Baladi goats when supplemented with 0.15 ppm organic selenium [302]. Dietary selenium supplementation in boars was studied by Marin-Guzman et al., in 1997. When compared to animals provided a basal diet supplemented with vitamin E, sodium selenite, or both, animals fed the basal diet without selenium demonstrated lower sperm motility and an increased percentage of morphologically aberrant spermatozoa [303]. In comparison to the boars fed the vitamin E-supplemented food, those provided a selenium supplemented diet shown notable differences. Animals receiving the diet without selenium supplementation also had a decrease in normal spermatozoa and fewer cytoplasmic droplets. Compared to boars fed a diet supplemented with vitamin E, those fed a diet high in selenium had reduced levels of spermatozoa tail deformation [303]. In comparison to pigs given 0.2 mg/kg of inorganic selenium, organic selenium-fed pigs showed considerably greater sperm concentration, total spermatozoa per ejaculation, and osmotic resistance of the acrosome membrane, as well as a reduced percentage of defective spermatozoa. According to the authors' findings, organic selenium is a superior source of selenium in terms of gastrointestinal absorption, performance, and tissue retention [304].

In comparison to controls that did not receive selenium supplementation, Gallo et al. found that roosters given selenium at 2.5 mg/kg live weight had significantly higher spermatozoa viability, concentration, and motility [305]. In comparison to control roosters given a diet lacking in selenium, dietary organic selenium dramatically increased spermatozoa motility and vitality as well as the percentage of normal spermatozoa at different storage durations [306]. Male fertility is largely dependent on the quality of the male sperm. According to a recent study, 0.1 ppm sodium selenate increased spermatozoa motility and concentration, increased semen volume per ejaculate, and reduced the proportion of dead spermatozoa, aberrant spermatozoa, and acrosome damage in rams' sperm [301]. The semen concentration, semen concentration per ejaculate, spermatozoa motility, motile spermatozoa per ejaculate, and total sperm count were all greater in Ossimi rams fed organic selenium at 0.5 mg/kg feed than they were in rams fed organic selenium at 0.2 ppm [235].

In comparison to a control group that received no treatment, boars fed with 0.5 ppm sodium selenite in the food had enhanced motility and morphology in their spermatozoa as well as a higher rate of fertilisation [236,255]. In one investigation, neither the spermatozoa motility in the ejaculate of boars given 0.3 or 0.6 mg/kg organic selenium (Sel-Plex) or 0.3 or 0.6 mg/kg feed inorganic selenium (sodium selenite) showed any discernible difference [307]. The spermatozoa concentration and count were dramatically reduced in the boars fed 0.3 mg/kg sodium selenite, whereas those fed 0.6 mg/kg sodium selenite showed a progressive decline in spermatozoa concentration but an increased ejaculate volume [307]. Another investigation found that selenium supplementation improved sperm quality, including motility and gross count, in the treatment group as compared to the control group by lowering oxidative stress [291]. ROS are necessary for normal physiological activity at a particular level. In fact, certain crucial sperm processes including capacitation and the acrosome response need to be supported by an ideal amount of ROS [3]. Excessive ROS, on the other hand, causes oxidative stress, sperm DNA damage and/or apoptosis, membrane peroxidation, and reduced sperm motility. The potential ameliorative effects of SeNPs on monosodium glutamate (MSG)-induced reproductive damage were assessed in an *in vivo* investigation. The effects of MSG—a drop in testosterone and higher oxidative stress markers—were significantly mitigated by the administration of SeNPs. In male mice, SeNPs reduced antioxidant status and reduced testicular damage [308]. A study looked at the possible connection between selenoproteins in the gut microbiota and the health of male reproduction. The interaction between gut microbiota and selenoproteins, which governs testicular function, is influenced by seleno supplementation, according to the authors [309].

Given the high concentration of selenium present in the gonads, particularly the testes, selenium plays a crucial role in healthy spermatogenesis, testicular growth, and sperm motility [310]. PHGPx and selenoprotein P, two antioxidative selenoproteins, control normal spermatogenesis [38]. When sperm mature, PHGPx serves two purposes: it alters the sperm's morphological features and biological processes. While PHGPx is present in mature spermatozoa as an inactive protein, it is present in spermatids as a soluble peroxidase. At least half of the capsule substance that encases the mitochondrial helix in mature spermatozoa's midpiece is made up of PHGPx [72]. As compared to mature semen, developing spermatids have higher levels of TrxR [38].

The increase in GPX4 that results from selenium being supplied by selenoprotein P causes selenium to be plentiful in late spermatids [233]. Selenium is a co-factor for antioxidant enzymes, which neutralise, get rid of, and stop the formation of ROS. Normal spermatogenesis, mitochondrial activity, and capacitation often generate ROS [233,311,312]. The oxidative degradation of polyunsaturated fatty acids and nucleic acids as well as mitochondrial dysfunction are caused by increased ROS. A protective impact is had

on the sperm by enzymes such PHGPx, catalase (CAT), and SOD. Additionally, sperm structural integrity and chromatin organisation are maintained by semenoproteins [312]. Researchers looked examined sperm quality in 107 males with asthenozoospermia and 235 age-matched controls to determine the impact of antioxidants, including selenium. A diet rich in antioxidants, according to the authors, was linked to a decreased likelihood of asthenozoospermia [312]. Lipovac et al. (2016) conducted a study with 156 infertile men who received 500 mg L-carnitine twice daily for 3 months and 143 infertile men who received 440 mg L-carnitine, 250 mg L-arginine, 40 mg zinc, 120 mg vitamin E, 80 mg glutathione, 60 μg Se, 15 mg coenzyme Q10 and 800 μg folic acid daily for 3 months [311]. The infertile group's semen concentration, volume, morphology, and overall progressive motility all significantly improved. Studies have been done on the impact of antioxidants like selenium and omega-3 fatty acids on male infertility. The researchers discovered that certain nutrients are linked to sperm quality [132]. A study was performed, to identify the role of selenium status and selenium intake in male subfertility. Sperm motility was boosted by receiving selenium alone or in combination with vitamins A, C, and E [313]. For males with idiopathic oligoasthenoteratozoospermia, Safarinejad et al. (2009) examined the effects of supplementation with 200 g of selenium per day, 600 mg of *N*-acetyl-cysteine per day, 200 g of selenium + 600 mg of *N*-acetyl-cysteine per day, or a placebo per day (n = 118). There was a noticeable improvement in the semen parameters overall.

The impact of nutrients, nutritional supplements, and foods on sperm parameters was evaluated in mice [314]. They comprised three RCTs that assessed selenium supplementation at doses of 100–300 g/day. They discovered that using selenium supplements had a positive effect. According to the research described above, selenium supplementation improves sperm parameters in infertile men. Selenium-mediated amelioration of BPA-induced oxidative stress and germ cell death in mice was examined by Kaur et al., in 2021 [26]. Groups I (C) (0.2 ppm selenium), Group II (selenium) (0.5 ppm selenium), Group III (BPA) (0.2 ppm selenium and BPA = 1 mg/kg orally), and Group IV (selenium + BPA) (0.5 ppm selenium and BPA = 1 mg/kg bodyweight orally) were the four groups used in the study. The antioxidant enzyme activities of BPA-treated mice significantly decreased, whereas the expression of stress-activated kinases (JNK, ERK, and p38) and pro-apoptotic markers significantly increased. The antioxidant enzyme activities were also dramatically restored by selenium supplementation, and stress-activated kinases were expressed less often, which further downregulated apoptosis. Therefore, selenium supplementation protected against testicular damage brought on by BPA. Paternal nutrition has been shown to have a part in controlling the sperm epigenome in mammals [315]. The authors propose that tRNA fragment biogenesis and function occur during mammalian sperm maturation and fertilisation. The investigators also discovered that the paternal diet can affect the phenotypic of the offspring through information in sperm. sRNA concentrations are influenced by diet, and tRNA fragments can control the production of transcripts that are regulated by endogenous retroelements. Supplementation of selenium decreases the level of oxidative stress markers and increases antioxidants markers and ultimately enhances male spermatogenesis, fertility and reproductive efficiency in males (Fig. 5).

2.18. Molecular mechanism of selenium transport

Selenoproteins play a major role in the biological function of selenium. Selenocysteine (Sec), a cysteine analogue that has selenium in place of sulphur, makes up these proteins. Human selenoproteins come in 25 different varieties, and they all have different functions in the body's redox homeostasis [316,317]. SELENOP was identified as a survival-promoting factor and a major transporter of

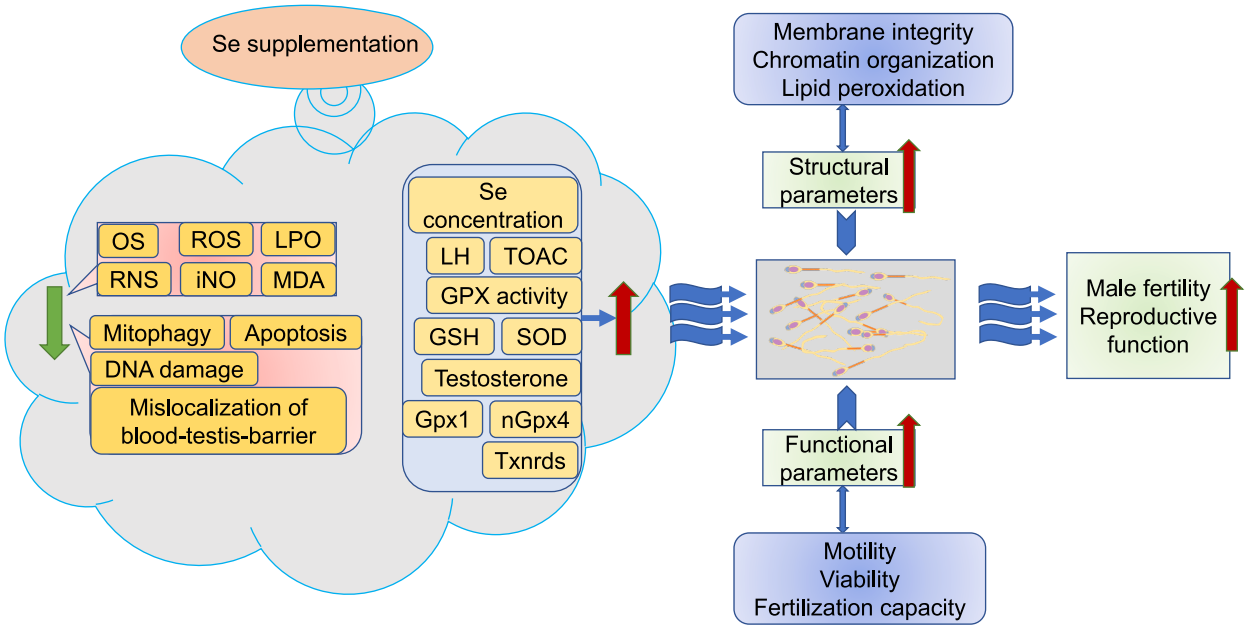

Fig. 5. Rescue of effects of selenium and selenoproteins on oxidative stress induced male infertility.

selenium using *in vitro* culture experiments in cultured neurons in serum free medium [318]. SELENOP is not only selenium transporter but also it functions as a multifunctional protein that controls cellular redox homeostasis and preserves cellular selenoproteins. Additionally, the selenium-independent function of SELENOP points to the protein's varied biological and pathological significance. *In vitro* and *in vivo* studies demonstrated that the effective selenium transport system involving SeP has been observed in the tissue selenium levels in the brain, kidney, testis, and bone of SeP KO mice [319–321]. Selenium transport in sertoli cells were shown in Fig. 6. Renko et al. confirmed that selenoprotein P (SePP) expression is essential to maintain fertility and restores selenium transport and prevents infertility and motor-in coordination in Sepp-knockout mice [322]. To fully comprehend the many roles played by SELENOP, more study is required. There are three different types of SELENOP receptors: ApoER2 (LRP8), megalin (LRP2), and LRP1. Immobilized SELENOP affinity column chromatography was used to identify ApoER2 and megalin for the first time [251,323]. SELENOP delivers selenium to many tissues through these receptors. ApoER2 is connected to SELENOP uptake in the brain, testis, and bone according to the phenotype of each receptor knockout (KO) mice, megalin is connected to the kidney and brain, and LRP1 is connected to the skeletal muscle. Megalin has been linked to brain selenium uptake, while Apoer2 has been linked to neuronal SELENOP uptake [324]. Selenium as Sec, which is covalently linked to the polypeptide chain, is present in SELENOP. A number of metabolic processes are required in order to utilize the selenium in SELENOP for selenoprotein production. According to earlier studies, it has been assumed that SELENOP enters the cell and subsequently undergoes lysosomal degradation to become an amino acid. It is noteworthy because included SELENOP has a long half-life, enabling *in vivo* and *in vitro* immunostaining to detect incorporated cellular SELENOP. Since SELENOP is a glycoprotein, its carbohydrate chains may work to stop proteolysis in lysosomes [325,326]. By using SeP, Mizuno et al. (2023) showed that a new, very effective selenium transport method is made possible by innovative molecular mechanisms. A high-affinity ApoER2 variation with the O-linked sugar domain was revealed to be involved in the SeP, a highly efficient selenium transport mechanism of Jurkat cells. According to the researchers, selenium is transported in a way that is not dependent on the Sec lyase. The testis expresses ApoER2 at extremely high levels, particularly in Sertoli cells [251]. These cells serve as the blood-testis barrier and absorb nutrients from the bloodstream so that they can be given to the germ cells. The presence of vesicles containing Sepp1 in wild-type mice's Sertoli cells but not in apoER2/animals suggests that Sepp1 is taken up by Sertoli cells through apoER2-mediated endocytosis [251]. It is consistent with the selenium absorbed by Sertoli cells as Sepp1 being used to synthesise Gpx4 and other selenoproteins required for the development of spermatozoa that late spermatids contain more selenium than do Sertoli cells [233]. Sertoli cells take up selenocysteine as Sepp1, which is then delivered to spermatids before being catabolized. Spermatids, but not sertoli cells, stain significantly with the anti-selenocysteine lyase antibody [327].

2.19. Selenium protects oxidative stress, apoptosis and inflammation

One crucial trace element, selenium has antioxidant and anti-inflammatory properties. Selenium deficiency affects male fertility and entirely prevents spermatogenesis [20,328,329]. Due to their inadequate antioxidant systems, spermatozoa are particularly vulnerable to high concentrations of reactive oxygen species (ROS). Lipids, proteins, and DNA oxidation are all caused by high ROS levels in spermatozoa. Low sperm quality and male infertility are related to oxidative stress. Selenoproteins of the GPxs family demonstrated effectiveness in preventing spermatozoa and its DNA from oxidative damage in a number of animal models. Notably, this serves as a fundamental foundation for developing more effective therapy approaches for male infertility [330]. Redox equilibrium and the preservation of male fertility have a long history of association. At physiological levels, ROS are crucial for sperm function and fertilisation because they play a key role in crucial processes like steroidogenesis and spermatozoa's oocyte fertilisation. Male reproductive function may be impaired by aberrant ROS generation under pathological situations. The redox homodynamic maintenance is mostly maintained by the internal antioxidant system; however exogenous antioxidants from the diet may be crucial if the internal activity is insufficient. On the other hand, uncontrolled supplementation can prevent the oxidative stress induced infertility.

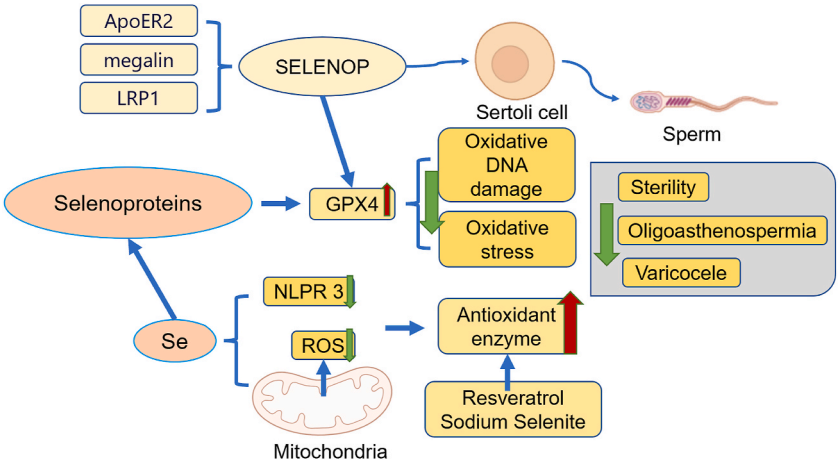

Fig. 6. Selenium transport in sertoli cells.

Thus, maintaining ROS at the right physiological concentration by balancing oxidants and antioxidants is the fundamental problem for ensuring adequate male fertility [172].

GPx4 inhibits protamine sulfoxidation, which is essential for sperm concentration, by reducing phospholipid hydroperoxides and H_2O_2. On the other hand, H_2O_2 and phospholipid hydroperoxides also contribute to oxidative stress in a way that harms spermatozoa's structure and motility. In order to prevent sperm cells from suffering oxidative damage during maturation, GPx4 logically plays a very delicate modulator role in male fertility [331]. GPx4 is converted back into its active state after reduction with GSH or other thiol reductants. The cytosolic form, known as cGPx4, and the nucleus form, known as nGPx4, has also been discovered in addition to the mitochondrial form, known as mGPx4. At first, it wasn't obvious if one of these types in particular was in charge of the role of selenium in male reproduction. GPx4 was found to reduce phospholipid hydroperoxides and H_2O_2 that are involved in protamine sulfoxidation, fundamental for sperm concentration [332,333]. On the other hand, phospholipid hydroperoxides and H_2O_2 also contribute to oxidative stress negatively affecting the structure and motility of spermatozoa. Thus, GPx4 reasonably performs an extremely fine modulator role for male fertility, protecting sperm cells from oxidative damage during maturation [334]. According to study conducted in 73 men, GPx4 expression is lowered in around 10 % of infertile men and about 35 % of men with oligoasthenozoospermia, with considerably decreased sperm motility and spermatozoa concentration [241]. In comparison to the controls, a different study revealed considerably decreased GPx4 levels in sperm samples from 75 infertile males associated with poor spermatozoa vitality, morphological integrity, and forward motility [294]. According to studies by O'Flaherty and Matsushita Fournier (2017) and Adeoye et al. (2018), increased levels of ROS have been seen in sperm and spermatozoa in 25–40 % of infertile males [335,336]. Infertile men's semen has been discovered to contain high levels of ROS as well as low levels of antioxidants [337].

Mitochondria are a major source of ROS, which is essential for both normal activity and apoptosis. The intrinsic pathway's core component, the mitochondria, may be involved in the triggering of apoptosis in spermatozoa. ROS are necessary for the activation of the intracellular pathways that support sperm activity under normal circumstances. They take part in chemotactic activities, acrosomal reactions, hyperactive motility, capacitation, and union with the oocyte [338,339]. According to Koppers et al. (2011), spermatozoa have the capacity to undergo a shorter form of apoptosis that is characterized by a rapid loss of motility, mitochondrial ROS generation, cytosolic caspase activation, cytoplasmic vacuolization, and oxidative DNA damage [340]. Oxidative stress occurs when the level of ROS rises above a particular limit. Oxidative stress has the ability to cause spermatozoa to go through a number of damaging processes. Polyunsaturated fatty acids (PUFA) at high concentrations are present in sperm's plasma membrane, making it more vulnerable to lipid peroxidation and reactive oxygen species (ROS) [341]. Oxidative stress lowers sperm motility, mitochondrial activity, and the capacity to fertilise the oocyte, and ROS also causes DNA damage and DNA base oxidation [342,343]. Sperm motility, mitochondrial activity, and the capacity to fertilise the oocyte are all decreased by oxidative stress [342,344]. It's interesting to note that electrophilic aldehydes like 4-hydroxynonenal and acrolein are produced by lipid peroxidation brought on by oxidative stress in human spermatozoa. These substances interact with the mitochondria by targeting succinate dehydrogenase, which changes the way the respiratory chain works and activates the intrinsic apoptotic pathway while also causing an excess of ROS to be produced in a self-reinforcing cycle [345]. Infertile patients or patients with spermatic abnormalities have been demonstrated to have a positive association between ROS levels, cytochrome-c release, and activation of caspases 9 and 3 [346,347]. These investigations also demonstrate a change from anti-apoptotic Bcl-2 protein expression to pro-apoptotic Bax expression. Males with asthenozoospermia have higher levels of NOX5 expression in their spermatozoa, which promotes DNA damage and O_2 and H_2O production [348]. Teratozoospermia instances have also been demonstrated to have increased NOX5 expression [349]. Additionally, protein kinase C, a recognized regulator of NOX activity, can be stimulated by phorbol esters, which in turn activates ROS generation [350]. NOX5's reliance on the tyrosine kinase c-Abl and the HvI voltage-regulated proton channel is a crucial characteristic [351]. The HvI proton channel, which prevents the cytoplasmic acidification (proton generation) that invariably follows NADPH oxidation, is necessary for optimum O_2 production. The male and female reproductive tracts include a number of prosurvival substances that keep spermatozoa alive and functionally active, such as insulin, prolactin, or angiotensin [352]. Phosphorylation of AKT by PI3K targets apoptosis regulator BCL2-associated-agonist-of-cell-death (BAD), inhibit Bax-triggered apoptosis, thereby maintaining spermatozoa in a viable motile state free from ROS generation. Disruption of phosphorylation of AKT leads to failure of phosphorylation of downstream target protein called BAD leads to apoptosis. Selenium supplements protect Ibuprofen induced oxidative stress through upregulation of antioxidant enzymes. As a result of Ibuprofen induced oxidative stress caused reduced seminal volume, sperm count, sperm motility. Furthermore, selenium deficiency significantly increased oxidative stress of ibuprofen. Selenium as essential antioxidant selenoproteins ameliorates Ibuprofen induced male reproductive toxicity [353]. Owumi et al. (2020) investigated the protective effects of selenium on diclofenac-induced testicular and epididymal toxicity in rats [354]. Diclofenac (10 mg/kg) or selenium (0.125 and 0.25 mg/kg body weight) was administered to rats for fourteen days straight. The findings demonstrated that selenium significantly reduced diclofenac-induced reductions in sperm count and motility, testicular function enzymes, and serum levels of luteinizing hormone and testosterone. Additionally, selenium co-administration at 0.125 and 0.25 mg/kg prevented the diclofenac-induced decline in antioxidant enzyme activities and elevated oxidative stress parameters—lipid peroxidation, reactive nitrogen, and oxygen species—in the rat epididymis and testes. To determine the effects of selenium excess or deficiency on mouse spermatogenesis, an *in vivo* investigation was carried out. Selenium deficient diet (selenium D, 0.02 mg selenium/kg), adequate-selenium diet (selenium A, 0.2 mg selenium/kg), and excess-selenium diet (selenium E, 2.0 mg selenium/kg) were given to three-week-old male mice ($n = 10$ animals/diet) for five months. Selenium decreased the mice's body weight by 10.4 % and sperm density by 84.3 %, however selenium increased sperm deformities by 32.8 % and decreased both sperm density (78.5 %) and sperm motility (35.9 %) when compared to selenium A. In contrast to selenium A, selenium D and selenium E both elevated serum FSH values (10.4–25.6 %) ($P < 0.05$) and caused testicular injury in mice. selenium D increased the 8-OHdG concentration by 25.5 % ($P < 0.05$) as compared to selenium A, while selenium E increased it by 0.10 ($P < 0.05$). When compared to selenium A, selenium D and selenium E caused testicular injury in mice and elevated

serum FSH values (10.4–25.6 %) ($P < 0.05$). selenium E increased the concentrations of MDA and 8-OHdG in the testis by 118.8–180.3 % and 25.5 %, respectively, as compared to selenium D and selenium A, respectively. Additionally, the testis of selenium D and selenium E, in comparison to selenium A, had 1325 and 858 transcripts changed ($P < 0.05$), respectively. These differentially expressed genes were mostly abundant in the PI3K-AKT signalling pathway, which is controlled by oxidative stress, according to the KEGG pathway analysis [355].

The ROS-dependent activation of the NLR pyrin domain-containing 3 (NLRP3) inflammasome prevented the ROS from being blocked by chemical scavengers. Multimolecular assemblies known as inflammasomes are produced intracellularly in response to various activators [356]. The adaptor protein "apoptosis-associated speck-like protein containing a caspase recruitment domain" (ASC) and the procaspase-1 combine to form the NLRP3 inflammasome. The NLRP3 inflammasome is a molecular apparatus that initiates the processing of pro IL1-beta and the activation of inflammatory caspases. Procaspase-1 cleaves to create the active caspase-1 when the NLRP3 inflammasome is activated, which causes the release of IL-1 and IL-18 and the rapid inflammatory form of cell death known as "pyroptosis" [356,357]. Plasma membrane rupture, cytoplasmic swelling, osmotic lysis, DNA cleavage, and the release of additional pro-inflammatory cellular components are the hallmarks of pyroptosis. Recently, an increase of NLRP3 inflammasome levels in an experimental model of varicocele were shown, which was lowered by the injection of resveratrol, a nutraceutical substance with anti-inflammatory characteristics. Additionally, research has demonstrated the presence of NLRP3 inflammasome components in the semen of varicocele patients [358]. When treating varicocele-related testicular injury, sodium selenite was able to boost the activity of antioxidant enzymes such CAT, SOD, and GPX and reduce lipid peroxidation [286]. In humans, varicocelectomy combined with antioxidant therapy (vitamin E-selenium-folic acid) improved sperm parameters by eliminating ROS from the environment [359]. In the testes and kidneys of chickens that had received Pb treatment, selenium dramatically decreased the mRNA expression of the NLRP3 inflammasome, caspase-1, and inflammatory cytokines and boosted the activity of antioxidant enzymes in rats with experimental varicocele [286,360,361]. In an experimental model of varicocele, Antonuccio and colleagues investigated the effects of selenium and Polydeoxyribonucleotide (PDRN) on the NLRP3 inflammasome. The interaction of selenium and PDRN dramatically enhanced all tube morphological parameters and their ultra structural characteristics, boosted testosterone levels, decreased NLRP3, caspase-1, and IL-1 expression, and raised the frequency of TUNEL-positive cells, demonstrating an overall significant effect on fertility.

2.20. Selenium nanoparticles and infertility

Metallic nanoparticles are nano sized metals with dimensions range between 1 and 100 nm have specialty with appropriate functional groups. Metallic nanoparticles have unique properties such as surface plasmon resonance and optical properties. For example, silver and gold nanoparticles are immensely used as antibacterial, antiviral and anticancer agent [362]. Although metal nanoparticles have shown significant beneficial effects, still it has toxic effects compared to SeNPs. For example, zinc oxide nanoparticles (ZnONPs) influences on mouse testicular cells growth and development [363]. Similarly, silver nanoparticles (AgNPs) cause complications in pregnant mice and exhibited detrimental effects on neonatal testis development in mice [364,365]. Contrast to metal nanoparticles, SeNPs exhibited remarkable beneficial effects in reproduction. Due to potential beneficial effects of SeNPs at the cellular and tissue levels, their biomedical applications have garnered the interest of several researchers on a global scale. For example, the results from the treatment of Huntington's disease with nano-Selenium are encouraging [366]. AgNPsinternalisation in mouse spermatozoa leads to poor fertilisation and impaired embryo development [367].

SeNPs have significant advantages over other selenium-containing compounds. Selenium-based nanoparticles (SeNPs) are less hazardous than selenium-based inorganic and organic materials. They are functionalized with active targeting ligands, making them biocompatible and capable of efficiently delivering combinations of payloads to targeted cells. SeNPs have been demonstrated to possess anti-inflammatory, anti-oxidant, immunomodulatory, and organ-protective qualities. SeNPs have lower toxicity than other forms of selenium, which has increased interest in their manufacture and bioactivity [368]. According to multiple studies (Jia et al., 2005; Zhang et al., 2005; Wang et al., 2007), SeNPs are also less hazardous and have improved bioefficacy and biocompatibility when compared to organic and inorganic selenocompounds [369,370]. SeNPs could be used as a reproductive preventive agent against the negative effects that bisphenol inflicted on male rats [371]. Furthermore, it has been demonstrated that SeNPs can protect male mice from the toxicity of monosodium glutamate [308]. Studies showed that SeNPs protected the male reproductive system against aflatoxin B1 induced toxicity by reducing the quantity of abnormal spermatozoa and the DNA fragmentation [372]. Histological studies showed that SeNPs improved the structural architecture of the testis, decreasing the atrophy brought on by aflatoxin B1 in the seminiferous tubules [373]. The treatment with SeNPs improved deltamethrin-induced reproductive toxicity and negative effects such as sperm characteristics, testosterone, and antioxidant biomarkers, as well as behavioral and histopathological alterations. The SeNPs treated group showed improved semen parameters, antioxidant status, and sexual performance [374]. SeNPs have been demonstrated to improve the quality of semen in rats and goat bucks [268,374,375]. Spermatogenesis and the quality of spermatozoa have been reported to be boosted by SeNPs. Dkhil et al. (2016) reported that SeNPs significantly ameliorated diabetes induced lower expression of PCNA, testicular dysfunctions, severe biochemical and histopathological changes in the testes of STZ-diabetic rats by the promotion of cell cycle progression and decreasing oxidative stress and apoptosis [376]. Hamza et al. (2020) reported that the administration of SeNPs diminished the effect of MSG induced decrease in testosterone hormone levels, testicular injury and elevated oxidative stress markers markedly by increasing antioxidant enzymes and decreases lipid peroxidation [308]. Gan et al. (2019) investigated the amelioration effect of nanoseleniumon nickel-induced disturbance of testosterone synthesis in sprague-dawley rats [287]. The results showed thatSeNPs improve the effectiveness of reproduction. By modifying the phosphorylation of ERK1/2, p38, and c-Jun NH2-terminal kinase (JNK)/MAPK pathway components for 14 days, different concentrations of SeNPs (0.5, 1.0, and 2.0 mg/kg)

supplementation ameliorated nickel-induced testicular damage, DNA perturbations, and testosterone biosynthesis. As a result of all these findings, SeNPs serve as potent antioxidant and anti-inflammatory agent.

2.21. Molecular effects of selenium, selenoproteins and selenium nanoparticles in male fertility

Selenium is necessary for both female and male reproduction [377]. Oxidative damage to sperm cells is the fundamental factor that maintains male fertility; selenium (Se) serves as a vital component in this process by protecting sperm cells from destruction [378]. Reduced selenium concentration may make sperm more vulnerable to free radicals, which could interfere with the acrosome's biological functions [379]. Lowering the concentration of Se was observed to cause damage to the center portion of the sperm whip, decrease sperm motility, and increase morphologically associated defects [380]. Se-deficient diet leads to a decrease in motility ability and poor-quality semen as compared to increased Se in the diet. Mice study demonstrated that Se deficiency leads to decreased production of spermatozoa and lipid peroxidation and eventually causes decrease in motility ability and poor-quality semen. Conversely, Se supplementation improves Se lacking effects in male mice [15,381]. Rat testis treated with a particular amount of selenium showed considerably higher mRNA levels of the selenoprotein GSH-PX [382]. Additionally, giving Se improves the control of CatSper family gene expression, which is crucial for enhancing spermatogenesis [383]. Sperm motility is significantly influenced by the CATSPER1 and 2 genes [384,385]. Selenium treatment dramatically raises the expression of CATSPER1 and 2 genes. As a result, supplementing with selenium may enhance the quality of sperm and cause the testes to overexpress genes that are essential for sperm to function properly [383]. Yeast-derived selenium (YS) or sodium selenite (SS) influences the patterns of gene expression in reproductive tissues. Canonical pathways that are critical to normal male reproductive function appear to be impacted by YS supplementation. For instance, the actin cytoskeleton and integrin-linked kinase (ILK) signalling pathways are impacted by this supplement. The production of mature sperm genes is therefore required for males to reproduce properly, and Se status may affect this process [253]. When Sertoli cells were pretreated with δ-9-tetrahydrocannabinol (THC) and selenium, it was found that THC administration significantly altered the testis tissue and Sertoli cells. These changes included a decrease in the viability of the Sertoli cells, an increase in p53, and a reduction in AKT expression, which are factors that are pro- and anti-apoptotic, respectively. Selenium pretreatment attenuated the effects of THC on Sertoli cells and testis tissue [386]. Furthermore, studies demonstrated that the PI3K/AKT signalling pathway is involved in the relaxin inducedproliferation of rat Sertoli cells and dibutyl phthalate(DBP)-induced Sertoli cell apoptosis [387,388]. Selenium nanoparticles functionalized with lectinan prevent TM3 cells from undergoing oxidative stress-induced apoptosis by inhibiting the JAK2/STAT-3 and p53 pathways. The viability and multiplication of TM3 cells are markedly enhanced by nano-selenium. In normal cells, SeNPs@LNT treatment raised the level of mitochondrial membrane potential and reduced the oxidative stress-induced decrease in mitochondrial membrane potential. Furthermore, SeNPs@LNT treatment reduced the oxidative stress-induced rise in reactive oxygen species and lessened the H2O2-induced necrosis and death of TM3 cells. By altering the P53 and Janus kinase 2/signal transducer and activator of transcription 3 signalling pathways, as well as the expression levels of other relevant proteins like protein kinase B (AKT) and C3, nanoselenium protects TM3 cells from oxidative H2O2-induced stress injury [389]. Serum-mediated oxidative stress may also play a role in the regulation of HSP70, HSP70-2, and MSJ-1 expression, which may compromise spermatogenesis and lower mouse fertility. Changes in Se-levels (excess or deficit) may cause a substantial increase in p53-meidated apoptosis in mouse spermatogenic cells [271]. The modulation of cfos gene expression has been associated with mitogen-activated protein kinase (MAPK), and the suppression of MAPK/c-Jun amino-terminal kinase (JNK) pathways has been linked to elevated Se levels. Accordingly, it is proposed that these two processes may be involved in reducing the expression of cjun and cfos under conditions of high selenium [390]. The study conducted by Keshta et al. (2023) examined the potential protective effects of selenium nanoparticles (SeNPs) against cisplatin testicular toxicity in male rats [391]. The authors measured the rats' body weight, testis weight, oxidative stress markers in testis homogenates, such as malondialdehyde (MDA), superoxide dismutase (SOD), glutathione reduced (GSH), glutathione peroxidase (GSH ~ PX), and catalase (CAT), gene expression, testosterone concentration (T), sperm characteristics (count, motility, and abnormality), and testicular histopathology. Body weight, testis weight, T concentration, steroidogenetic expression, antioxidant activities (SOD, GSH, GSH ~ PX and CAT), and MDA levels were all lower in the Cis group. In the meantime, testis sections' histopathology revealed degenerative changes in the seminiferous tubules. The negative effects of cisplatin were lessened by the concurrent delivery of selenium nanoparticles. Ehghaghi et al. (2022) used probiotics Lactobacillus casei (L. casei) and selenium nanoparticles (SeNPs) to study how X-ray radiation impacts testicular tissue and the spermatogenesis process [392]. The experiments were designed with 64 adult male Syrian mice. Eight groups were randomly assigned to the animals: probiotic (X-ray radiation), SeNPs, probiotic, SeNPs and probiotic, control group, and SeNPs and probiotic (X-ray). Examined were the histology parameters and the concentrations of oxidative stress indicators, including glutathione peroxidase, superoxide dismutase, catalase, and malondialdehyde. Furthermore, testicular cells treated with SeNPs and L. casei as a probiotic had their amount of apoptosis evaluated. The outcomes demonstrated that the effects of X-ray radiation were lessened when probiotics or SeNPs were administered. These substances caused a marked upregulation of the catalase, superoxide dismutase, and Catsper genes and a marked downregulation of the malondialdehyde, caspase 3, and caspase 9 gene levels. Probiotics and SeNPs increased sperm motility, spermatogenesis percentage, sperm cell count, and mean number of spermatogonia cells. They also had a strong antioxidant impact. With its capacity to lessen ionizing radiation's adverse impacts and safeguard healthy tissues, the recommended substance demonstrated the perfect radioprotective function. SeNPs and probiotics enhance the antioxidant status in male mice and prevent testicular damage.

3. Conclusion and future perspective

Numerous factors, such as hormonal, genetic, behavioral, environmental, and lifestyle factors, contribute to male infertility. There

has been ounting evidence suggest that dangerous compounds in the food and environmental factors such air pollution, smoking, stress, chemicals, heat, heavy metals, and radiation influences male fertility. A crucial dietary trace element called selenium is needed to maintain male fertility. According to a number of studies, selenium shortage results in GPx-4 depletion and structural defects in the spermatozoa, which impair motility and lower fertility. Two selenoproteins, phospholipid hydroperoxide glutathione peroxidase (PHGPx) and selenoprotein P, are thought to play a crucial role in mediating the key role that selenium plays in normal mammalian spermatogenesis. The primary selenoprotein expressed by germ cells in the testis is called PHGPx. It serves a variety of roles and serves as a vital link between selenium, healthy sperm, and male fertility. Selenium, selenoproteins and selenium nanoparticles have been discussed in relation to the impact they may have on spermatogenesis and male infertility in both human and animal models. The ideal physiological concentration of selenium is necessary to preserve both male and female reproductive potential and also to protect general health. Selenium supplementation is essential for maintaining mineral homeostasis and the selenoproteome in the testes. Additionally, selenium is necessary for the process of spermatogenesis. In specifically, folate and vitamin B12 are needed for the synthesis of RNA and DNA.

The processes of polymerization and transcription require co-factors, selenium and zinc. In order to produce mature, healthy spermatozoa, the process of spermatogenesis must be carried out under rigorous, controlled circumstances. Both men and women can become infertile due to oxidative stress, and protective effects of selenium have a significant impact on fertility. Selenium regulates antioxidant defence systems, other crucial biological pathways, and redox-sensitive transcription factors in addition to having a favourable impact on the development, maturity, and replication of oocytes. GPx4 is a crucial protein that cooperates with selenium to protect delicate germ cells from oxidative damage. Selenium performs critical functions in enhancing sperm motility, semen quality, the growth of Sertoli cells and Leydig cells, and the capacitation and fertilisation processes. In addition to being crucial for the synthesis of certain selenoproteins involved in spermatogenesis and steroid biosynthesis, GPx4 has a substantial impact on sperm motility, chromatin integrity, and fertility rate. Selenium deficiency/shortage finally results in male infertility by impairing spermatogenesis and reproductive potential. Considering all these literature into account, we discuss briefly chemistry, structure, and uses of selenium, as well as significant developments involving selenium and selenoproteins. The biological activities of selenium and selenoproteins are then covered, along with the causes of male infertility and the part selenium and selenoproteins play in spermatogenesis and male fertility. The molecular basis of selenium transport as well as selenium's anti-inflammatory, apoptotic, and protective effects on oxidative stress are also covered. Additionally, we emphasize the important role that selenium nanoparticles as potent antioxidant and anti-inflammatory agent against infertility.

The molecular processes of many dietary components implicated in spermatogenesis are still unclear, despite the fact that selenium and selenoproteins has been the subject of several researches on spermatogenesis and male infertility. Additionally, research is needed to determine the specific mechanism behind the negative effects of selenium and selenoprotein insufficiency. Subsequent research endeavors may concentrate on elucidating the particular molecular mechanisms via which selenium delivers its advantageous impacts on reproductive processes. To examine important processes of these nutrients in promoting spermatogenesis and the precise concentration of these dietary intakes required to achieve optimal testicular development and spermatogenesis with standard protocol, a dedicated consortium should be set up. Male infertility can be treated more effectively if the processes governing spermatogenesis and testicular functions are well understood. For the welfare of people, this knowledge would be useful. Furthermore, more research into the optimum amounts of selenium and selenoproteins for animals to grow sexually to their fullest potential would provide a solid framework for investigations into the best nutritional treatments for male infertility. To assess the relationship between bloods selenium levels and selenium concentrations in reproductive organs, research is necessary and most wanted. To find out whether selenium supplementation can improve male infertility, additional clinical trials are also necessary. More research is necessary to determine the ideal dietary selenium intake levels for enhancing spermatogenesis and sperm motility. The optimal amount and length of selenium supplementation in infertile persons must be established through controlled clinical trials that take genetic predispositions and environmental differences into account. Furthermore, studies that are carefully planned and randomised are required to investigate the protective and beneficial effects of selenium supplementation in both men and women seeking reproductive therapy. Studies should be planned to identify trustworthy and simple-to-measure biomarkers that could make it easier to diagnose selenium deficiency-related male infertility. Finding trustworthy biomarkers for male infertility caused by selenium insufficiency may make early diagnosis and treatment easier. In order to support the therapeutic management of infertility, future research should give priority to identifying easily measured biomarkers that link with selenium level and reproductive outcomes. Future investigations should pay particular attention to assessing selenium has possible effects under various experimental setups that might either impair or help male reproductive potential. In-depth analyses are required to comprehend the potential roles and mechanisms of selenium, selenoproteins and selenium nanoparticles in enhancing male reproductive capacity and health. Furthermore, research is necessary to comprehend the connection between dietary intake of selenium and the ideal seminal concentration of selenium for spermatogenesis and sperm motility under varied environmental circumstances. It is crucial to investigate possible connections between environmental variables and selenium supplementation on male reproductive health. Subsequent investigations ought to examine the ways in which fluctuations in environmental circumstances impact the effectiveness of selenium therapies, offering perspectives on customized methods for managing fertility. To assess selenium's effects under various experimental setups—taking into account both beneficial and harmful outcomes on male reproductive potential—in-depth experimental evaluations are required. Such research would change our knowledge of the role selenium plays in male fertility and help develop more specialized treatment plans.

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CRediT authorship contribution statement

Shuai Yuan: Writing – original draft. **Ye Zhang:** Writing – original draft. **Pei-Yu Dong:** Software. **Yu-Mei Chen Yan:** Conceptualization. **Jing Liu:** Conceptualization. **Bing-Qiang Zhang:** Methodology. **Meng-Meng Chen:** Validation. **Shu-Er Zhang:** Project administration. **Xi-Feng Zhang:** Writing – review & editing, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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