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Review Article

Effect of metallic and nonmetallic nanoparticles (NPs) and their salts in reproductive biotechnology

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ABSTRACT

In order to maintain or enhance genetic diversity, particularly in endangered species, essential procedures are applied in a variety of species, including humans, livestock, and aquatic vertebrates and invertebrates. These techniques include sperm cryopreservation and *in vitro* embryo creation. Reactive oxygen species (ROS), which are molecules made from oxygen, are frequently produced in greater amounts because of these techniques. ROS levels in cells can range from low to high, leading to a variety of effects including apoptosis, autophagy, and necrosis. To combat and neutralize ROS, cells have intrinsic antioxidant systems made up of enzymes and non-enzymatic antioxidants. Free radicals and oxidative stress have a big impact on *in vitro* operations. To develop solutions to lessen their impacts, this review focuses on analyzing how metallic and nonmetallic (NPs), as well as their salts, regulate oxidative stress during *in vitro* embryo formation and sperm cryopreservation.

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Introduction

The generation of *in vitro* embryos, sperm cryopreservation, and sperm sexing are only a few examples of assisted reproductive technologies (ART) that are known to produce significant amounts of reactive oxygen species (ROS). For instance, the freezing and thawing of semen samples during sperm cryopreservation increases the generation of ROS, which can result in lipid peroxidation from being exposed to oxygen and cold shock (Bansal and Bilaspuri 2009). The selection of an extender during sperm cryopreservation can also have an impact on the sperm's quality and oxidative stress, which will ultimately affect the result (Salehi et al. 2020). Enzymatic and non-enzymatic defenses against ROS buildup are present in cells. Non-enzymatic antioxidants can reduce ROS production and reduce inflammation, including the TNF-RI/P-60 receptor, which causes apoptosis, as well as vitamins C and E, glutathione, uric acid, and substances present in herbal medicines (Baghshahi et al. 2014; Mokhtari et al. 2020). Superoxide anions are transformed into hydrogen peroxide by enzyme antioxidants such as copper/zinc superoxide dismutase (Cu/ZnSOD) in the cytosol and mitochondrial Mn2+-dependent superoxide dismutase (MnSOD) (Zavareh et al. 2015). Another class of antioxidant enzymes called glutathione peroxidases (GPXs) uses reduced glutathione to destroy H_2O_2. H_2O_2 is broken down by the catalase enzyme into oxygen and water (Fardsadegh and Jafarizadeh-Malmiri 2019) Cofactors, including copper, zinc, manganese, selenium, iron, and selenium all contribute to the construction of these enzymes. Due of its uses and

developments, the science of nanotechnology has recently attracted a lot of interest. Because of their distinct characteristics from their bulk counterparts, metal and non-metal NPs have gained considerable interest (Farokhzad and Langer 2009). Nanotechnology is influenced by some scientific fields, including chemical, materials science, physical, biological, and engineering. Through Nano-bio interactions, NPs with sizes ranging from 1 to 100 nm can influence cell destiny and structure, potentially causing or avoiding mutations and promoting cell-cell communication (Khurana et al. 2019). NPs can promote the movement of water-soluble substances, amino acids, peptides, DNA, miRNA, siRNA, vaccines, and other treatments and the therapeutic efficacy of ionized medicines. The absorption of nanoparticles by cells and tissues is often greater than that of their salts (Gupta et al. 2010).

In recent years, oocyte, sperm, and embryo preservation in a variety of species, notably in cattle, have benefited significantly from advances in nanotechnology and nanomedicine. This study intends to investigate the functions of selenium, copper, zinc, iron, and other metal and nonmetal nanoparticles, together with their salts, which function as cofactors in the structure of antioxidant enzymes. These nanoparticles and their salts are essential for several procedures, including sperm cryopreservation, *in vitro* embryo development, sperm sexing, and sperm isolation.

***In Vitro* Oxidative Stress on Oocytes, Sperm and Embryos**

There are two basic sources of reactive oxygen species (ROS): 1) Internal sources coming from metabolic pathways and enzymes such as xanthine oxidase, NADPH oxidase, and oxidative phosphorylation; and 2) External sources coming from elements including light, culture media, energy supply, oxygen content, and cryopreservation (Torres-Osorio et al. 2019). Under normal circumstances, aerobic metabolism produces ROS such as hydrogen peroxide (H_2O_2), superoxide anion (O^{2-}), and hydroxyl radicals (OH^-), whereas the enzyme nitric oxide synthase (NOS) produces nitric oxide (NO) by converting L-arginine and L-citrulline (Halliwell 2006). When there is an imbalance between the generation and removal of ROS within the biological system, oxidative stress (OS) takes place. As a result of oxidizing proteins, destroying nucleic acids, and inducing lipid peroxidation, ROS can impair cellular activities when they are overcome by cells and the detoxification systems are unable to remove them (Halliwell 2000). Low amounts of ROS can increase cell survival while excessive concentrations can cause cell death, therefore ROS can have both positive and negative impacts on cellular life. Additionally, ROS can function as second messengers, inducing certain biological reactions (Aitken and Drevet 2020). Polyunsaturated fatty acids make sperm membranes extremely susceptible to lipid peroxidation, and oxidative stress raises the quantities of lipid peroxides in the body. Reduced sperm motility, impaired fusion with oocytes, and decreased electron efflux in sperm mitochondria have all been linked to this (Evans and Cooke 2009; Alahmar 2019). Free radical generation during cryopreservation and thawing has been shown to negatively affect DNA integrity and enzymatic repair procedures, according to studies (Prasad et al. 2016).

Additionally, ROS can lead to cell death, oocyte meiosis arrest, and embryonic developmental arrest. Increased amounts of ROS can cause maturation promoting factors (MPFs) to lose their stability, down the chance of viability, and cause mitochondria-stimulated death in oocytes (Tarin et al. 1996). Chromosome abnormalities brought on by oxidative stress in the process *in vitro* maturation may not be seen in live oocytes but may become obvious after fertilization (Sánchez-Ajofrín et al. 2020). Compared to the lower oxygen levels (5-8.5%) prevalent in vivo, mammalian embryos cultivated *in vitro* are exposed to greater oxygen concentrations (about 20%). The higher ROS levels in *in vitro*-produced embryos can cause DNA strand breaks and the raised oxygen levels in the environment can slow down embryonic development (Takeuchi et al. 1996; Ramamurthy et al. 2013).

Uses in gamete cryopreservation and *in vitro* embryo production

A highly valuable element in biology, chemistry, and medicine due to its special qualities and many uses is selenium. In addition to serving as a cofactor for the enzyme glutathione peroxidase (GSH-Px), it is essential for scavenging free radicals generated inside cells. Additionally, selenium plays important roles in the breakdown of exogenous compounds, the removal of certain amino acids via the kidneys, and the creation of hormones from arachidonic acid (Livingston et al. 2009; Aprioku 2013). GSH-Px activity is crucial for preserving the integrity of cell membranes and acrosomes, which contributes to fertilization (Sztrik 2016). Insufficient selenium levels have been linked to negative impacts on reproductive success in a variety of animals (Agarwal et al. 2012). Reduced sperm motility, mitochondrial instability, and morphological defects can all be caused by a lack of selenium (Dorostkar et al. 2012). In a study on buffalo semen extenders, sodium selenite was used in a range of concentrations (0, 0.5, 1, 2, 4, and 8 g/ml), and it was found that supplementing with 1 and 2 g/ml sodium selenite significantly improve sperm viability, membrane integrity, antioxidant capacity, motility, and lessen DNA damage. Higher selenium concentrations (8 g/ml) nonetheless exhibited negative impacts on sperm parameters (Hawkes and Turek 2001). High selenium concentrations

have a negative effect on the energetic area of sperm cells, impairing normal oxidation and cell respiration activities that take place in the mitochondria. This is thought to be the cause of selenium's harmful effects (Kaur and Parshad 1994). The midpiece area of the flagellum, which is responsible for producing energy, exhibits anomalies when dietary selenium at a concentration of 4 ppm is consumed, according to a study of different phases of spermatid differentiation in the testis (Siegel et al. 1980).

Bovine sperm motility has been reported to be improved by selenium via preventing oxidative damage (Ghafarizadeh et al. 2018). Selenium has been found to protect sperm from the damaging effects of reactive oxygen species (ROS) during sperm collection in males with asthenozoospermia by maintaining appropriate enzymatic and antioxidant activities (Tareq et al. 2010). Studies have shown that vitamin E and selenium in the form of selenomethionine (SeMet) and SeMet coupled with each other can reduce ammonia buildup and enhance glucose utilization in pig spermatozoa (Basini and Tamanini 2000). Selenium has also been shown to boost estradiol release and stimulate the proliferation of bovine granulosa cells (Tareq et al. 2012). *In vitro* maturation, fertilization, and culture of pig oocytes were all improved by SeMet and SeMet mixed with vitamin E, according to a Tareq et al. research (Hoshino 2018), which also demonstrated that SeMet's ammonia-reducing properties. The glutathione peroxidase enzyme in oocyte maturation, includes chemical compound production, protein phosphorylation, and activation of certain metabolic pathways (Soltani et al. 2023).

In research by Guimarães et al. (2016), it was shown that vit-E, although substantial effects were seen with selenium (Se) and Se plus vit-E, was more efficient than Se or a combination of Se and vit-E in correcting ROS-induced damage in mouse embryos. The combination of insulin, transferrin, selenium, and ascorbic acid did not, however, enhance the quality of oocytes generated from tiny follicles in bovine *in vitro* maturation (Boas et al. 2017).

Zinc deficiency has been found to have an impact on male fertility through altering the development of the testicles, spermatogenesis, and steroidogenesis through the release of gonadotropins (Meng et al. 2017). Additionally, testosterone production, the expression of steroid receptors, and the control of serum cholesterol levels all include zinc (Ebisch et al. 2007). It serves as a cofactor for a variety of metalloenzymes, such as DNA repair and antioxidant enzymes (Kotdawala et al. 2012). It has been shown that adding zinc to human semen extenders enhances sperm survival, DNA integrity, membrane integrity, and motility (Jeon et al. 2014). Parthenogenetic and *in vitro* fertilized embryos' embryonic development has been observed to benefit from the addition of 0.8 g/ml of zinc during *in vitro* maturation (Barros et al. 2018). The meiotic competence of developing oocytes and the subsequent development of bovine embryos are greatly influenced by the presence of zinc in the maturation and fertilization media (Jeon et al. 2015). The cytoskeleton is organized in part by zinc, and zinc shortage can change the distribution of microfilaments in oocytes during *in vitro* maturation, impacting somatic cell nuclear transfer embryos (Cheng et al. 2013). The identification of cytoskeleton-associated proteins as crucial determinants of early clone formation raises the possibility that oocyte cytoplasmic components play a role in nuclear reprogramming (Stephenson and Brackett 1999). However, research showing that high quantities of zinc (10 mg/mL) given to the maturation medium decreased fertilization and showed harmful consequences of zinc supplementation (Kincaid 2000). It was discovered that hazardous levels of zinc (3 to 15 mg/mL in plasma) existed. Since a suitable ROS concentration is necessary for normal development, excessive ROS reduction caused by high zinc dosages might harm embryonic development (Sakatani et al. 2007). Additionally, it has been demonstrated that too much ROS reduction is detrimental to the growth of embryo (Kim et al. 2010).

In a study by Kim et al. (2010), In mouse oocytes, copper concentrations below 10 M did not affect maturation, whereas concn. of 20 M or above were hazardous. For several enzymes, including tyrosinase, amino oxidase, cytochrome oxidase, and copper-dependent superoxide dismutase, copper functions as an important cofactor, similar to how selenium and zinc do. It participates in the processes of oxygenation, hydroxylation, and dismutation. High copper concentrations, however, can cause free radical generation, nucleic acid binding, oxidation of proteins and lipids, and protein and lipid oxidation (Cunninghamn et al. 1995). The bulk of the copper in the plasma is transported by ceruloplasmin, while the remainder is attached to other transporters such albumin, and transcuprein, copper-amino acid complexes. Because of its strong redox activity, which can result in redox imbalances, unbound copper is hazardous (Evans et al. 2002; Tabassomi and Alavi-Shoushtari 2013). Because of its strong redox activity, which can result in redox imbalances, unbound copper is hazardous (Gao et al. 2007). In contrast to the control group, the addition of Fe and Cu to the maturation media considerably decreased the frequency of apoptotic blastomeres while having no discernible effect on the maturation of bovine oocytes. The effective, morulae, and blastocysts also depends on iron and copper, and a chronic iron or copper deficit might increase the frequency of apoptotic blastomeres (Domínguez et al. 2004). High iron concentrations can produce extremely

reactive free radicals and hydro peroxides when combined with unsaturated fatty acids, which can result in oxidative damage (Picco et al. 2012). It has been discovered that copper enhances DNA integrity in cumulus cells and raises intracellular glutathione (GSH) levels during oocyte maturation (Cheema et al. 2009).

Bull semen extenders with $MnCl_2$ added have been proven to increase the quality of the semen, as seen by improvements in measures including motility, membrane integrity, and MDA generation (Singh et al. 2019). It is possible that Mn^{++} is involved in the quick quenching of these radicals by reactions like R-OO + Mn^{++} + H^+ $ROOH^+$ + Mn since it has peroxyl radical scavenging capability (Singh et al. 2019). Elbetieha et al. (2001) conducted a study to evaluate the detrimental effects of high $MnCl^2$ concentrations on fertility and reproduction in male and female mice Pelyhe and Mézes (2013) revealed that 0.1 mM $MnCl^2$ had a positive effect on sustaining sperm mobility without compromising mucus penetration or fertilizing effectiveness. They suggested that Mn^{++} may affect the activity of the enzyme sperm cyclase, causing a rise in calcium (Ca^{++}) concentration and improved motility.

Uses in gamete cryopreservation and *in vitro* embryo production

Nanotechnology offers a promising method to take use of the biological characteristics of several elements, including Nano selenium, for uses in cell freezing, digesting, and reproduction (Hosnedlova et al. 2018). Comparing selenium nanoparticles to sodium selenite and selenite, they show less toxicity (Safa et al. 2016). Researchers Abd-Allah and Hashem (2015) discovered that 1% selenium nanoparticles and 5 g/ml vitamin E added to the freezing diluent increased rooster sperm motility, viability, and oxidative variables. Additionally, Se-NPs have demonstrated an improvement in sperm quality and spermatogenesis rates (Talebi et al. 2014). Studies and clinical trials have looked at how Se-NPs effect on goat sperm (Khalil et al. 2019). Additionally, the addition of 1 g/ml of Se-NPs to Holstein bull semen extenders led to better semen quality and greater in vivo fertility rates (Mézes and Salyi 1994). However, Se-NPs at greater concentrations (1.5 g/ml) had detrimental effects on sperm viability, increased the amount of apoptotic and necrotic sperm, and interfered with the antioxidant system, causing lipid peroxidation and spermatozoa mortality (Flick and Kaiser 2012). More free radicals may be produced by Se-NPs at higher concentrations, which might contribute to lipid peroxidation and causes cellular stress marked by decreased protein production and lower protein breakdown (Stohs and Bagchi 1995). Due to the potential negative consequences, care should be taken when supplementing with greater doses of Se-NPs (Asri-Rezaei et al. 2018).

Selenium nanoparticles added to the diets of male mice dramatically increased antioxidant capacity and sperm quality in comparison to the control group (Khoram et al. 2017). In research including elderly and young rodents, older mice treated with 0.4 mg of selenium nanoparticles had greater rates of sperm motility and viability, as well as a lower percentage of dead and damaged sperm, than younger mice given with 0.2 to 0.4 mg/kg body weight (Talebi et al. 2014). In comparison to the control group, the addition of 4% selenium nanoparticles to the semen diluent increased sperm motility and membrane integrity (Abdel-Halim and Helmy 2017). *In vitro* bovine oocyte maturation media containing selenium nanoparticles (Se-NPs) and zinc oxide nanoparticles (Zn-NPs) resulted in a decrease in DNA damage and an increase in total intracellular glutathione. Expanded blastocysts treated with Se-NPs or Zn-NPs showed greater viability rates than the control group following freezing-thawing operations. The ram sperm parameters of progressive motility, viable sperm percentage, and plasma membrane integrity were all increased by 0.1 mg/ml of zinc oxide nanoparticles, whereas malondialdehyde (MDA) generation was decreased. However, at concentrations more than 0.1 mg/mL, sperm viability and motility were adversely reduced (Alavi-Shoushtari et al. 2009). Zinc imbalances in seminal plasma or spermatozoa may have a negative impact on seminal abnormalities and the onset of oxidative stress in rams, which might cause reproductive issues (Jahanbin et al. 2015). Bull semen extenders with Zn-NPs added to them increased sperm vitality, motility, mitochondrial integrity, and membrane integrity while lowering the proportion of defective sperm (Barkhordari et al. 2013).

Study results showed that cytotoxicity increased with increasing concentrations and longer incubation times, showing the maximum toxicity rate, when zinc oxide nanoparticles were infused into human semen at various concentrations and incubation times (Heng et al. 2010). Although the precise processes causing the toxicity of zinc oxide nanoparticles remain unclear, probable causes include mitochondrial malfunction, ion release, binding to proteins in the membrane or cytoplasm, and the creation of intracellular reactive oxygen species (ROS) (Isaac et al. 2017). Malondialdehyde (MDA) levels and sperm chromatin damage were significantly decreased when zinc oxide nanoparticles were introduced to human semen extenders in comparison to the control group, indicating that these particles did not impair human spermatozoa (Baek et al. 2011). The size and charge of zinc oxide nanoparticles likely affect their cytotoxicity (Abaspour Aporvari et al. 2018). Oral delivery of zinc oxide nanoparticles at a dose of 80 ppm increased sperm motility, vitality, membrane functioning, and decreased abnormalities in research on ram sperm quality and

antioxidant characteristics of seminal plasma. Additionally, it improved the antioxidant capacity of seminal plasma and superoxide dismutase enzyme activity (Jahanbin et al. 2021). Another investigation employing bull semen extenders discovered that the inclusion of zinc oxide nanoparticles enhanced mitochondrial activity and plasma membrane integrity decreased MDA levels, and had no discernible impact on motility, viability, or pregnancy rates. However, adding Zn-NPs during *in vitro* maturation increased blastocyst rates (Soltani et al. 2022). Liquid-maintained ram epididymal spermatozoa performed better when modest doses of ZnO-NPs were added, especially in terms of overall motility, viability, and membrane and DNA integrity at various incubation times (Odhiambo et al. 2014). Nanoparticles may be hazardous, according to some research, however, they have also been effectively used in biological applications including the treatment of cancer and *in vitro* fertilization (Gil et al. 2013). Magnetic nanoparticles coated with lectin or annexin V have shown promise in the separation of viable sperm cells from unhealthy or damaged ones. When exposed to heat stress, treatment of pig semen with lectin-coated magnetic nanoparticles boosted reproductive rates and sperm motility (Barkalina et al. 2014). By removing defective sperm cells during artificial insemination, lectin-coated magnetic nanoparticles have also been successful in increasing conception rates in bull semen samples (Feugang et al. 2015).

Feugang et al. (2015) enhanced motility by separating functional sperm from immotile or weakly motile sperm using lectin-coated magnetic iron oxide nanoparticles. Both the survival of newborn piglets and the fertility of boar semen were unaffected by these magnetic nanoparticles. The sperm plasma membrane contains lectin and carbohydrate receptors, which have a variety of functions, including causing sperm to clump together (Domínguez et al. 2018). In recent investigations, the use of magnetic nanoparticles for semen sexing in several species has been investigated. For instance, to differentiate sperm based on the changes in electrical potential between spermatozoa harboring the X and Y chromosomes, magnetic nanoparticles were introduced to donkey semen samples and subjected to a magnetic field. Using this method, spermatozoa may be separated based on the number of chromosomes they contained (Moradi et al. 2021). Similar techniques have been used for sperm sexing in sheep, where magnetic nanoparticles were successful in separating sperm carrying X and Y chromosomes (Moradi et al. 2022). After semen sexing, pretreating ram semen extenders with magnetic nanoparticles did not have a detrimental impact on the semen properties after cryopreservation (Ben-David Makhluf et al. 2006). Magnetic nanoparticles were used to treat spermatozoa, which showed that they could penetrate cells without compromising motility or acrosomal reactivity (Rajabi et al. 2019). The number of distinct cell types in testis tissue was decreased in Wistar rats after intraperitoneal injection of varied amounts of copper oxide nanoparticles. Bovine oocytes' *in vitro* maturation medium was supplemented with zinc/copper oxide nanoparticles at doses of 0.7 to 1 g/ml, which decreased DNA damage and raised the intracellular total glutathione level in both the oocytes and cumulus cells. However greater quantities of these nanoparticles (1.5 g/ml) had negative impacts on the viability of bovine oocytes (Abdel-Halim et al. 2018).

Fig. 1: An illustration of nanoparticles in different reproductive technologies

Conclusions

The critical elements selenium, copper, iron, and zinc play crucial roles in a variety of biological processes. Important enzymes including glutathione peroxidase, Cu/Zn superoxide dismutase, catalase, and mitochondrial Mn_2-dependent superoxide dismutase all contain them as essential parts. These substances, whether in salt or nanoparticle form, support the structure and operation of enzymatic antioxidants, reducing the generation of reactive oxygen species (ROS) and enhancing cellular processes. According to the research previously stated, Se, Cu, Fe, and Zn nanoparticles that function as cofactors for enzymatic antioxidants have a variety of impacts on sperm cryo-preservation and in-vitro embryo development. While several studies have noted the toxicity of NPs, it is vital to recognize that this might vary based on cell types, species, and concentration. Nevertheless, no harm has been shown in several tests

proposes encouraging pathways to conserve the threatened species and ensure the protection of biodiversity. Massive challenges like low genetic variety and reproductive problems can be dealt and overcome by the employment of advanced approaches. Assisted reproductive technologies can enhance conception rates, reduce the risk of genetic abnormalities, and help in the propagation of threatened species. Still, the ethical concerns and potential risks associated with their use must be kept under consideration. With continued studies, cooperation, and public support, we can take advantage of these technologies and strategies to protect our planet's intricate biodiversity.

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Ethical statement

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Availability of data and material

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All the authors gave their consent for equal participation.

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The authors declare that they have no relevant financial or non-financial interests to disclose.

Author Contribution

All the authors were involved in writing and editing the manuscript. KY finalized the article and proceeded with publication.

References

Felix A, Andrabi Abaspour Aporvari M, Mamoei M, Tabatabaei Vakili S, Zareei M and Dadashpour Davachi N, 2018. The effect of oral administration of zinc oxide nanoparticles on quantitative and qualitative properties of Arabic ram sperm and some antioxidant parameters of seminal plasma in the non-breeding season. Archives of Razi Institute 73(2):121-129.

Abd-Allah S and Hashem K, 2015. Selenium nanoparticles increase the testicular antioxidant activity and spermatogenesis in male rats as compared to ordinary selenium. Int J Adv Res 3(1):792-802.

Abdel-Halim B and Helmy NA, 2017. Effect of nano-selenium and nano-zinc particles during in vitro maturation on the developmental competence of bovine oocytes. Animal Production Science 58(11):2021-2028.

Abdel-Halim BR, Moselhy WA and Helmy NA, 2018. Developmental competence of bovine oocytes with increasing concentrations of nano-copper and nano-zinc particles during in vitro maturation. Asian Pacific Journal of Reproduction 7(4):161-166.

Agarwal A, Kashou AH and Sekhon LH, 2012. Oxidative stress and the use of antioxidants for idiopathic oats. Studies on Men's Health and Fertility:485-516.

Aitken RJ and Drevet JR, 2020. The importance of oxidative stress in determining the functionality of mammalian spermatozoa: A two-edged sword. Antioxidants 9(2):111.

Alahmar AT, 2019. Role of oxidative stress in male infertility: An updated review. Journal of Human Reproductive Sciences 12(1):4-18.

Alavi-Shoushtari S, Rezai SA, Ansari M and Khaki A, 2009. Effects of the seminal plasma zinc content and catalase activity on the semen quality of water buffalo (*Bubalus bubalis*) bulls. Pakistan journal of biological sciences: PJBS 12(2):134-139.

Aprioku JS, 2013. Pharmacology of free radicals and the impact of reactive oxygen species on the testis. Journal of Reproduction and Infertility 14(4):158.

Asri-Rezaei S, Nourian A, Shalizar-Jalali A, Najafi G, Nazarizadeh A, Koohestani M and Karimi A, 2018. Selenium supplementation in the form of selenium nanoparticles and selenite sodium improves mature male mice reproductive performances. Iranian Journal of Basic Medical Sciences 21(6):577.

Baek M, Kim M, Cho H, Lee J, Yu J, Chung H and Choi S, 2011. Factors influencing the cytotoxicity of zinc oxide nanoparticles: Particle size and surface charge. In: Journal of Physics: Conference Series; pp:012044

Baghshahi H, Riasi A, Mahdavi A and Shirazi A, 2014. Antioxidant effects of clove bud (Syzygium aromaticum) extract used with different extenders on ram spermatozoa during cryopreservation. Cryobiology 69(3):482-487.

Bansal AK and Bilaspuri GS, 2009. Antioxidant effect of vitamin e on motility, viability and lipid peroxidation of cattle spermatozoa under oxidative stress.

Barkalina N, Jones C, Kashir J, Coote S, Huang X, Morrison R, Townley H and Coward K, 2014. Effects of mesoporous silica nanoparticles upon the function of mammalian sperm in vitro. Nanomedicine: Nanotechnology, Biology and Medicine 10(4):859-870.

Barkhordari A, Hekmatimoghaddam S, Jebali A, Khalili MA, Talebi A and Noorani M, 2013. Effect of zinc oxide nanoparticles on viability of human spermatozoa. Iranian Journal of Reproductive Medicine 11(9):767.

Barros RG, Lodde V, Dieci C, Fraciosi F and Luciano AM, 2018. Study on the effects of zinc supplementation during in vitro embryo production technologies in cattle. International Journal of Health, Animal Science and Food Safety 5(1s)

Basini G and Tamanini C, 2000. Selenium stimulates estradiol production in bovine granulosa cells: Possible involvement of nitric oxide☆. Domestic Animal Endocrinology 18(1):1-17.

Ben-David Makhluf S, Qasem R, Rubinstein S, Gedanken A and Breitbart H, 2006. Loading magnetic nanoparticles into sperm cells does not affect their functionality. Langmuir 22(23):9480-9482.

Boas K, Gunn PJ, Hansen SL, Dohlman TM and Jahnke M, 2017. Effects of injectable trace mineral supplementation on embryo development and quality in superovulated dairy heifers—first year progress report. Iowa State University Animal Industry Report 14(1)

Cheema RS, Bansal AK and Bilaspuri GS, 2009. Manganese provides antioxidant protection for sperm cryopreservation that may offer new consideration for clinical fertility. Oxidative Medicine and Cellular Longevity 2(3):152-159.

Cheng Y, Gaughan J, Midic U, Han Z, Liang C-G, Patel BG and Latham KE, 2013. Systems genetics implicates cytoskeletal genes in oocyte control of cloned embryo quality. Genetics 193(3):877-896.

Cunninghamn J, Leffell M, Mearkle P and Harmatz P, 1995. Elevated plasma ceruloplasmin in insulin-dependent diabetes mellitus: Evidence for increased oxidative stress as a variable complication. Metabolism 44(8):996-999.

Domínguez E, Moreno-Irusta A, Castex HR, Bragulat AF, Ugaz C, Clemente H, Giojalas L and Losinno L, 2018. Sperm sexing mediated by magnetic nanoparticles in donkeys, a preliminary in vitro study. Journal of Equine Veterinary Science 65:123-127.

Domínguez R, Barreiro T, Sousa E, Bermejo A, Cocho JA, Fraga JM and Bermejo P, 2004. Study of the effect of different iron salts used to fortify infant formulas on the bioavailability of trace elements using icp-oes. International Dairy Journal 14(12):1081-1087.

Dorostkar K, Alavi-Shoushtari SM and Mokarizadeh A, 2012. Effects of in vitro selenium addition to the semen extender on the spermatozoa characteristics before and after freezing in water buffaloes (bubalus bubalis). In: Veterinary research forumpp:263

Ebisch I, Thomas C, Peters W, Braat D and Steegers-Theunissen R, 2007. The importance of folate, zinc and antioxidants in the pathogenesis and prevention of subfertility. Human Reproduction Update 13(2):163-174.

Elbetieha A, Bataineh H, Darmani H and Al-Hamood MH, 2001. Effects of long-term exposure to manganese chloride on fertility of male and female mice. Toxicology Letters 119(3):193-201.

Evans JL, Goldfine ID, Maddux BA and Grodsky GM, 2002. Oxidative stress and stress-activated signaling pathways: A unifying hypothesis of type 2 diabetes. Endocrine Reviews 23(5):599-622.

Evans MD and Cooke MS, 2009. Oxidative damage to nucleic acids. Springer Science & Business Media.

Fardsadegh B and Jafarizadeh-Malmiri H, 2019. Aloe vera leaf extract mediated green synthesis of selenium nanoparticles and assessment of their in vitro antimicrobial activity against spoilage fungi and pathogenic bacteria strains. Green Processing and Synthesis 8(1):399-407.

Farokhzad OC and Langer R, 2009. Impact of nanotechnology on drug delivery. ACS Nano 3(1):16-20.

Feugang J, Liao S, Crenshaw M, Clemente H, Willard S and Ryan P, 2015. Lectin-functionalized magnetic iron oxide nanoparticles for reproductive improvement. JFIV Reproductive Medicine, Genetics & Stem Cell Biology 3(145):17-19.

Flick K and Kaiser P, 2012. Protein degradation and the stress response. In: Seminars in cell & Developmental Biology; pp:515-522

Gao G, Yi J, Zhang M, Xiong J, Geng L, Mu C and Yang L, 2007. Effects of iron and copper in culture medium on bovine oocyte maturation, preimplantation embryo development, and apoptosis of blastocysts in vitro. Journal of Reproduction and Development 53(4):777-784.

Ghafarizadeh A, Vaezi G, Shariatzadeh M and Malekirad A, 2018. Effect of in vitro selenium supplementation on sperm quality in asthenoteratozoospermic men. Andrologia 50(2):e12869.

Gil M, Sar-Shalom V, Melendez Sivira Y, Carreras R and Checa MA, 2013. Sperm selection using magnetic activated cell sorting (macs) in assisted reproduction: A systematic review and meta-analysis. Journal of Assisted Reproduction And Genetics 30:479-485.

Guimarães A, Pereira S, Diógenes M and Dode M, 2016. Effect of insulin–transferrin–selenium (its) and l-ascorbic acid (aa) during in vitro maturation on in vitro bovine embryo development. Zygote 24(6):890-899.

Gupta S, Sekhon L, Kim Y and Agarwal A, 2010. The role of oxidative stress and antioxidants in assisted reproduction. Current Women's Health Reviews 6(3):227-238.

Halliwell B, 2000. The antioxidant paradox. The Lancet 355(9210):1179-1180.

Halliwell B, 2006. Reactive species and antioxidants. Redox biology is a fundamental theme of aerobic life. Plant Physiology 141(2):312-322.

Hawkes WC and Turek PJ, 2001. Effects of dietary selenium on sperm motility in healthy men. Journal of andrology 22(5):764-772.

Heng BC, Zhao X, Xiong S, Ng KW, Boey FY-C and Loo JS-C, 2010. Toxicity of zinc oxide (zno) nanoparticles on human bronchial epithelial cells (beas-2b) is accentuated by oxidative stress. Food and Chemical Toxicology 48(6):1762-1766.

Hoshino Y, 2018. Updating the markers for oocyte quality evaluation: Intracellular temperature as a new index. Reproductive Medicine and Biology 17(4):434-441.

Hosnedlova B, Kepinska M, Skalickova S, Fernandez C, Ruttkay-Nedecky B, Peng Q, Baron M, Melcova M, Opatrilova R and Zidkova J, 2018. Nano-selenium and its nanomedicine applications: A critical review. International Journal of Nanomedicine:2107-2128.

Isaac AV, Kumari S, Nair R, Urs DR, Salian SR, Kalthur G, Adiga SK, Manikkath J, Mutalik S and Sachdev D, 2017. Supplementing zinc oxide nanoparticles to cryopreservation medium minimizes the freeze-thaw-induced damage to spermatozoa. Biochemical and Biophysical Research Communications 494(3-4):656-662.

Jahanbin R, Yazdanshenas P, Amin Afshar M, Mohammadi Sangcheshmeh A, Varnaseri H, Chamani M, Nazaran MH and Bakhtiyarizadeh MR, 2015. Effect of zinc nano-complex on bull semen quality after freeze-thawing process. Animal Production 17(2):371-380.

Jahanbin R, Yazdanshenas P, Rahimi M, Hajarizadeh A, Tvrda E, Nazari SA, Mohammadi-Sangcheshmeh A and Ghanem N, 2021. In vivo and in vitro evaluation of bull semen processed with zinc (zn) nanoparticles. Biological Trace Element Research 199:126-135.

Jeon Y, Yoon JD, Cai L, Hwang S-U, Kim E, Zheng Z, Lee E, Kim DY and Hyun S-H, 2014. Supplementation of zinc on oocyte in vitro maturation improves preimplatation embryonic development in pigs. Theriogenology 82(6):866-874.

Jeon Y, Yoon JD, Cai L, Hwang SU, Kim E, Zheng Z, Jeung E, Lee E and Hyun SH, 2015. Zinc deficiency during in vitro maturation of porcine oocytes causes meiotic block and developmental failure. Molecular Medicine Reports 12(4):5973-5982.

Kaur R and Parshad V, 1994. Effects of dietary selenium on differentiation, morphology and functions of spermatozoa of the house rat, ratuus rattus l. Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis 309(1):29-35.

Khalil WA, El-Harairy MA, Zeidan AE and Hassan MA, 2019. Impact of selenium nano-particles in semen extender on bull sperm quality after cryopreservation. Theriogenology 126:121-127.

Khoram AF, khodaei MM and Moradi M, 2017. Effect of in vitro selenium nanoparticles addition to the semen extender on the spermatozoa parameters after freezing in Farahani ram. Journal of Animal Research 30(3): 0-0

Khurana A, Tekula S, Saifi MA, Venkatesh P and Godugu C, 2019. Therapeutic applications of selenium nanoparticles. Biomedicine & Pharmacotherapy 111:802-812.

Kim AM, Vogt S, O'halloran TV and Woodruff TK, 2010. Zinc availability regulates exit from meiosis in maturing mammalian oocytes. Nature Chemical Biology 6(9):674-681.

Kincaid R, 2000. Assessment of trace mineral status of ruminants: A review. Journal of Animal Science 77(Suppl E):1-10.

Kotdawala AP, Kumar S, Salian SR, Thankachan P, Govindraj K, Kumar P, Kalthur G and Adiga SK, 2012. Addition of zinc to human ejaculate prior to cryopreservation prevents freeze-

thaw-induced DNA damage and preserves sperm function. Journal of Assisted Reproduction and Genetics 29:1447-1453.

Livingston T, Rich K, MacKenzie S and Godkin JD, 2009. Glutathione content and antioxidant enzyme expression of in vivo matured sheep oocytes. Animal reproduction science 116(3-4):265-273.

Meng Z, Gao P, Chen L, Peng J, Huang J, Wu M, Chen K and Zhou Z, 2017. Artificial zinc-finger transcription factor of a20 suppresses restenosis in Sprague Dawley rats after carotid injury via the pparα pathway. Molecular Therapy-Nucleic Acids 8:123-131.

Mézes M and Salyi G, 1994. Effect of acute selenium toxicosis on the lipid peroxide status and the glutathione system of broiler chickens. Acta Veterinaria Hungarica 42(4):459-463.

Mokhtari S, Mahdavi AH, Hajian M, Kowsar R, Varnosfaderani SR and Nasr-Esfahani MH, 2020. The attenuation of the toxic effects of LPS on mouse pre-implantation development by alpha-lipoic acid. Theriogenology 143:139-147.

Moradi M, Hajarian H, Karamishabankareh H, Soltani L and Soleymani B, 2021. Recovery of sperms bearing x chromosomes with different concentrations of magnetic nanoparticles in ram. Reproduction in Domestic Animals 56(2):263-269.

Moradi M, Hajarian H, Karamishabankareh H, Soltani L and Soleymani B, 2022. Pre-treatment of ram semen extender with magnetic nanoparticles on freeze-thawed spermatozoa. Veterinary Medicine and Science 8(2):792-798.

Odhiambo JF, DeJarnette J, Geary TW, Kennedy CE, Suarez SS, Sutovsky M and Sutovsky P, 2014. Increased conception rates in beef cattle inseminated with nanopurified bull semen. Biology of Reproduction 91(4):97, 91-10.

Pelyhe C and Mézes M, 2013. Myths and facts about the effects of nano selenium in farm animals–mini-review. Eur Chem Bull 2(12):1049-1052.

Picco SJ, Rosa DE, Anchordoquy JP, Anchordoquy JM, Seoane A, Mattioli GA and Furnus CC, 2012. Effects of copper sulphate concentrations during in vitro maturation of bovine oocytes. Theriogenology 77(2):373-381.

Prasad S, Tiwari M, Pandey AN, Shrivastav TG and Chaube SK, 2016. Impact of stress on oocyte quality and reproductive outcome. Journal of Biomedical Science 23:1-5.

Rajabi S, Shahbazi F, Noori A and Karshenas R, 2019. Investigation of the toxic effects of copper oxide nanoparticles on the structure of gonadal tissue in male. Experimental Animal Biology 7(4):117-124.

Ramamurthy C, Sampath K, Arunkumar P, Kumar MS, Sujatha V, Premkumar K and Thirunavukkarasu C, 2013. Green synthesis and characterization of selenium nanoparticles and its augmented cytotoxicity with doxorubicin on cancer cells. Bioprocess and Biosystems Engineering 36:1131-1139.

Safa S, Moghaddam G, Jozani RJ, Kia HD and Janmohammadi H, 2016. Effect of vitamin e and selenium nanoparticles on post-thaw variables and oxidative status of rooster semen. Animal Reproduction Science 174:100-106.

Sakatani M, Suda I, Oki T, Kobayashi S-i, Kobayashi S and Takahashi M, 2007. Effects of purple sweet potato anthocyanins on development and intracellular redox status of bovine preimplantation embryos exposed to heat shock. Journal of Reproduction and Development 53(3):605-614.

Salehi M, Mahdavi AH, Sharafi M and Shahverdi A, 2020. Cryopreservation of rooster semen: Evidence for the epigenetic modifications of thawed sperm. Theriogenology 142:15-25.

Sánchez-Ajofrín I, Iniesta-Cuerda M, Sánchez-Calabuig MJ, Peris-Frau P, Martín-Maestro A, Ortiz JA, del Rocío Fernández-Santos M, Garde JJ, Gutiérrez-Adán A and Soler AJ, 2020. Oxygen tension during in vitro oocyte maturation and fertilization affects embryo quality in sheep and deer. Animal reproduction science 213:106279.

Siegel RB, Murray FA, Julien W, Moxon A and Conrad H, 1980. Effect of in vitro selenium supplementation on bovine sperm motility. Theriogenology 13(5):357-367.

Singh N, Savanur MA, Srivastava S, D'Silva P and Mugesh G, 2019. A manganese oxide nanozyme prevents the oxidative damage of biomolecules without affecting the endogenous antioxidant system. Nanoscale 11(9):3855-3863.

Soltani L, Ghaneialvar H and Mahdavi AH, 2023. An overview of the role of metallic and nonmetallic nanoparticles and their salts during sperm cryopreservation and in vitro embryo manipulation. Nucleosides, Nucleotides & Nucleic Acids 42(3):262-279.

Soltani L, Samereh S and Mohammadi T, 2022. Effects of different concentrations of zinc oxide nanoparticles on the quality of ram cauda epididymal spermatozoa during storage at 4 c. Reproduction in Domestic Animals 57(8):864-875.

Stephenson JL and Brackett B, 1999. Influences of zinc on fertilisation and development of bovine oocytes in vitro. Zygote 7(3):195-201.

Stohs SJ and Bagchi D, 1995. Oxidative mechanisms in the toxicity of metal ions. Free radical biology and medicine 18(2):321-336.

Sztrik A, 2016. Production of nano-size elemental selenium particles and its investigation in the soil-plant-animal system. 1-26. University of Debrecen Debrecen, Hungary.

Tabassomi M and Alavi-Shoushtari SM, 2013. Effects of in vitro copper sulphate supplementation on the ejaculated sperm characteristics in water buffaloes (*Bubalus bubalis*). Veterinary Research forum: an international quarterly journalpp:31

Takeuchi T, Nakajima M and Morimoto K, 1996. Accelerated paper: Relationship between the intracellular reactive oxygen species and the induction of oxidative DNA damage in human neutrophil-like cells. Carcinogenesis 17(8):1543-1548.

Talebi E, Ghasemi F and Haghigat Jahromi M, 2014. Effect of selenium nanoparticles antioxidant on sperm parameters in mature and adult rats. Journal of Advanced Biomedical Sciences 4(1):111-119.

Tareq K, Akter QS, MAM Y and Tsujii H, 2012. Selenium and vitamin E improve the in vitro maturation, fertilization and culture to blastocyst of porcine oocytes. Journal of Reproduction and Development 58(6):621-628.

Tareq K, Akter QS, Takagi Y, Hamano K-i, Sawada T and Tsujii H, 2010. Effect of selenium and vitamin E on acrosome reaction in porcine spermatozoa. Reproductive Medicine and Biology 9:73-81.

Tarin JJ, Vendrell FJ, Ten J, Blanes R, Van Blerkom J and Cano A, 1996. The oxidizing agent tertiary butyl hydroperoxide induces disturbances in spindle organization, c-meiosis, and aneuploidy in mouse oocytes. MHR: Basic science of Reproductive Medicine 2(12):895-901.

Torres-Osorio V, Urrego R, Echeverri-Zuluaga JJ and López-Herrera A, 2019. Estrés oxidativo y el uso de antioxidantes en la producción in vitro de embriones mamíferos. Revisión. Revista Mexicana de Ciencias Pecuarias 10(2):433-459.

Zavareh S, Talebi A and Hasanzadeh H, 2015. Amending in vitro culture condition to overcome oxidative stress in assisted reproduction techniques (art). Archives of Advances in Biosciences 6(2):135-148)