Chapter 2

Nanoparticles as Food Additives and their Possible Effects on Male Reproductive Systems

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Abstract

Nanoparticles (NPs) are substances that are used in many fields, especially in antimicrobial and food additives. Consumable nanoparticles, also known as food nanoparticles, are separated into organic and inorganic nanoparticles. Organic NPs can be classified as proteins, carbonates, phospholipids, and lipids, while inorganic NPs can be classified as silica (SiO_2, E571), zinc oxide (ZnO), titanium dioxide (TiO_2, E171), iron oxide (Fe_2O_3, E172), copper (Cu), gold (Au, E175) and silver (Ag, E174). Organic nanoparticles are not long lasting in the body. However, is it possible to make the same claim about inorganic nanoparticles? Inorganic nanoparticles are employed as food additives, vitamin supplements, and food packaging in the nutrition of both humans and animals. Food nanoparticles that make products brighter, tastier, more shelf-stable, and more antimicrobially resistant influence the liver, renal, digestive, respiratory, and genital systems once they enter the body. NPs can enter the male genital tract, adversely affect the testicles and sperm, and even affect the hypothalamo-pituitary axis, causing hormonal disorders. The effects of inorganic NPs on testes and spermatozoa vary depending on the diameter and composition of this NPS. Studies with some inorganic NPs show that low doses have positive effects on the antioxidant system and harmful effects occur when their concentrations are increased, while some have toxic effects even at very low concentrations. Given all of this information, might consumable nanoparticles be one of the causes of rising male infertility? The aim of this review is to explain how nanoparticles affect the male genital system and sperm quality and to provide insights into whether they might be one of the factors contributing to male infertility.

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1. Introduction

The term "nanotechnology" describes the interdisciplinary research and development activities that focus on the creation, design, and characterization of nanoscale materials and the systems that are made with these materials. Nanotechnology designs and synthesizes artificial structures which called nanoparticles (NPs) by processing known molecules with different atoms and molecules. Nanoparticles have a changeable surface structure and can be produced from a wide range of materials, including metals, proteins, polysaccharides, and lipids (Samrot, Sean et al. 2020). With nanotechnology, it has become possible to produce materials that are more functional, fast, take up less space, consume less energy, are more durable, cheap and have extraordinary new properties (Bayda, Adeel et al. 2019). Nanotechnology is used in many fields including manufacturing, electronics and computer technologies, the medical and health sector, aerospace researches, environment and energy, defense industry, biotechnology, agriculture and food technologies(Aithal and Aithal 2021) .

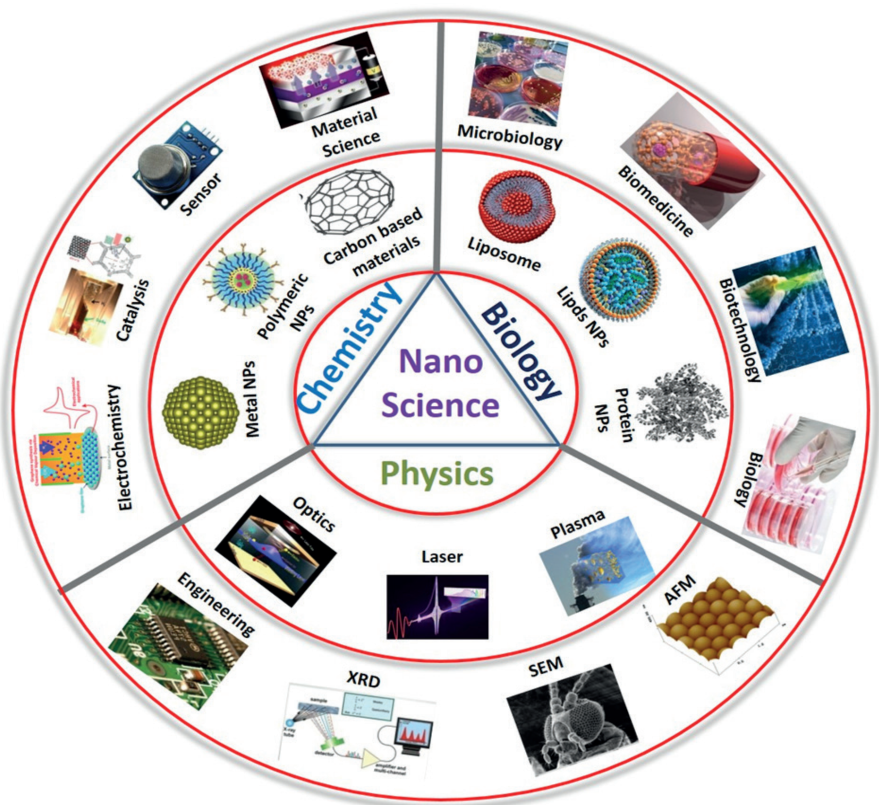

Figure 1. Nanoscience and related fields (Bayda, Adeel et al. 2019).

Nanoparticles (NPs) have various applications such as soil and groundwater remediation, air pollution control, drinking and wastewater treatment. Iron, silver, manganese, magnesium, aluminum and titanium nanomaterials are used in drinking water and wastewater treatment (Van Benschoten, Reed et al. 1994, Agrawal and Sahu 2006). Silver nanoparticles are mostly used for disinfection in the treatment of drinking water, and iron oxide nanoparticles are used to remove arsenic and other dangerous heavy metal pollutants from drinking water (Prathna, Sharma et al. 2018). Nanotechnology can be widely used in livestock and related enterprises. Foods not used for human consumption can be used as animal feed, and this includes important issues such as digestibility of feed, improvement of its quality and spread of diseases (Scott 2007). In the animal nutrition field of nanotechnology, it is mostly aimed at increasing the bioavailability of mineral nanoparticles. Nanoparticles are used to increase the rate of absorption in terms of specific surface area, surface activity, catalytic and efficiency. Thus, it makes it possible to increase the growth performance and utilization rate of the consumed feed in animals. Many nano-scale application systems such as micelles, liposomes, nano-emulsions, biopolymeric nanoparticles, protein-carbohydrate nano-scale complexes, solid nano-lipid particles have been developed in order to use nutrients effectively in the animal body (Chen, Weiss et al. 2006). From another point of view, nanobots that allow the study of the nervous system in animals have also been developed (Opara 2004).

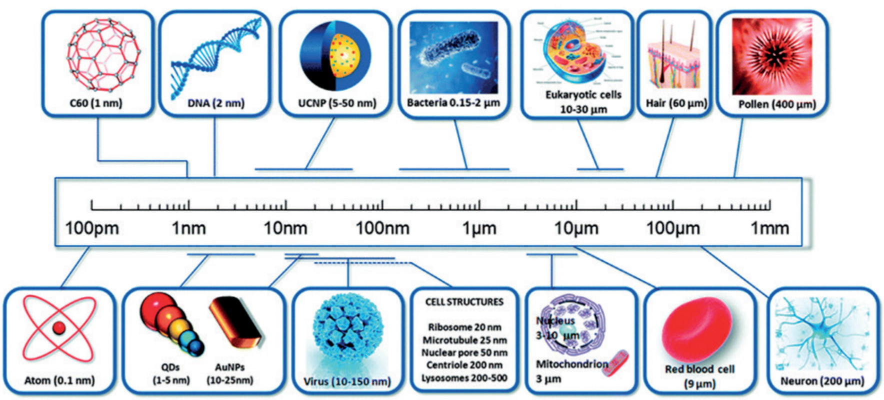

Figure 2. A basic comparison of nanomaterial sizes (Gnach, Lipinski et al. 2015).

Consumable nanoparticles can be classified as organic or inorganic nanoparticles (Moradi, Razavi et al. 2022). Organic NPs can be categorized as proteins, carbonates, phospholipids, and lipids. On the other hand, inorganic NPs can be classified as silica (SiO_2, E571), zinc oxide (ZnO), titanium dioxide (TiO_2, E171), iron oxide (Fe_2O_3, E172), copper (Cu), gold (Au, E175), and silver (Ag, E174). Organic nanoparticles can be digestable in gastrointestinal tract and they are not bio- persistent. Thats why they are more less toxic than the inorganic NPs. However, when it comes to inorganic nanoparticles both society and the scientific community are concerned about the potential risk associated with oral consumption of inorganic NPs (Aisen, Medina et al. 2002, Moradi, Razavi et al. 2022). Inorganic nanoparticles are implemented in human nutrition as food additives, vitamin supplements, and food packaging (Chaudhry, Scotter et al. 2008, Go, Bae et al. 2017). Nanoparticles are utilized in food technology to improve health, safety, quality, and shelf life. Nanoparticles employed in food technology have beneficial effects on the color, smell and flavor of the products. For instance, TiO_2's naturally white color makes food appear brighter (Setyawati, Zhao et al. 2020) whereas Fe_2O_3 and ZnO nanoparticles are employed as necessary minerals in foods (Voss, Hsiao et al. 2020, Kim, Viswanathan et al. 2022). Furthermore, Fe2O3 nanoparticles are employed as food color pigments, whereas ZnO nanoparticles are used in sunscreens due to their UV radiation protective capabilities. While SiO_2 NPs are used to avoid sediment development in beverages like beer and wine(Antony, Sivalingam et al. 2015), Ag NPs are used to prevent microbial contamination of foods (Wang, Du et al. 2013).

2. Food Nanoparticles in Male Reproductive System

The use of nanoparticles in food and beverages is increasing day by day. This increase exposes living organisms to increasing numbers of nanoparticles through various factors. Nanotechnological developments expose the male reproductive system to nanoparticles (NPs). These NPs are reported to have negative consequences on male germ and somatic cells. (Lee 1998, Brohi, Wang et al. 2017). The male reproductive system is considered susceptible to oxidative stress and inflammation, and both can be used as hallmarks of nanoparticle exposure in other organs (Walczak–Jedrzejowska, Wolski et al. 2013, Azenabor, Ekun et al. 2015). Various nanoparticles induce reactive oxygen species (ROS) as one of the main mechanisms of cytotoxicity (Risom, Møller et al. 2005).

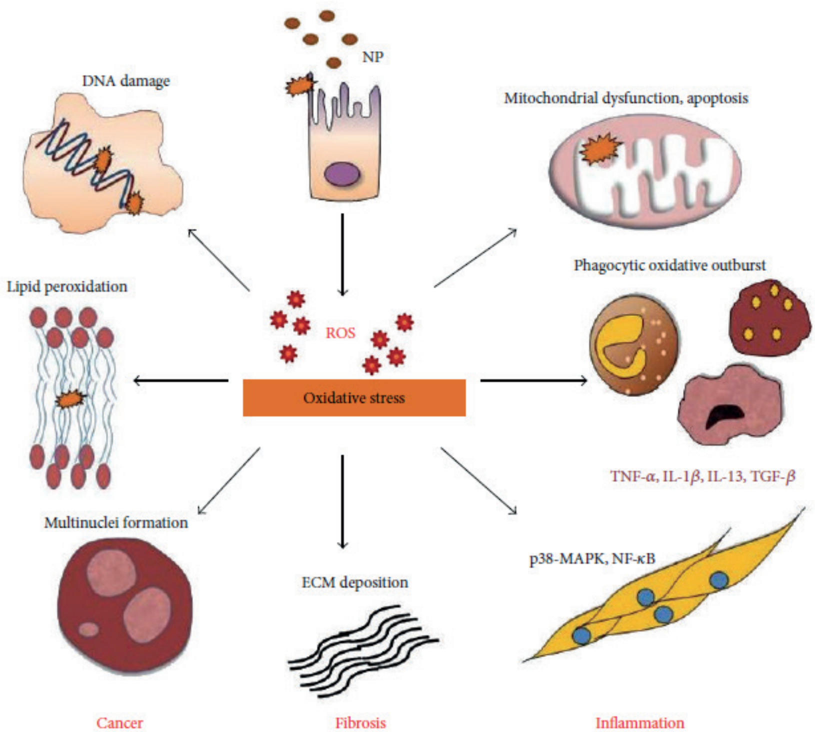

Figure 3. Prooxidant pathway for NP-induced toxicity (Manke, Wang et al. 2013).

It activates transcription factors by affecting intracellular calcium concentrations of nanoparticles and modulates cytokine production through free radical production. Cells exposed to nanoparticles respond to increased oxidative stress with antioxidant defense systems. Transcriptional activation of phase II antioxidant enzymes under mild oxidative stress conditions occurs via induction of erythroid-derived nuclear factor-like 2 (Nrf2). Moderately, the redox-sensitive mitogen-activated protein kinase (MAPK) and nuclear factor kappa-light chain enhancer (NF-κB) cascades of activated B cells produce a proinflammatory response. In addition, extremely toxic levels of oxidative stress lead to mitochondrial membrane damage and cell death (Huang, Aronstam et al. 2010). NP is oxidative in nature, inducing its pro-oxidant effects by reacting with cells and producing intracellular ROS, which includes activation of mitochondrial respiration and NADPH-like enzyme systems (Driscoll, Howard et al. 2001). The prooxidant effects of NP result in the activation of signaling pathways, transcription factors, and cytokine cascade contributing to a diverse range of cellular responses (Manke, Wang et al. 2013). NP-induced ROS induce changes in homeostatic redox state.

NPs activate nuclear factor kappa B (NF-kB) signaling by upregulating the transcription of various proinflammatory genes, including tumor necrosis factor-a and interleukins (IL)-1, IL-6 and IL-8, followed by severe DNA damage and apoptosis (Khanna, Ong et al. 2015).

Table 1. Effects of NPs on the male reproductive system.

Tissue, cell	Experimental Models	Nanoparticles	Authors
Sperm	*Fish*	TiO_2 and Silver NPs	**Carvalhais, Oliveira et al. (2022)**
Testicular tissue	Mouse	TiO_2 and Silver NPs	**Arslan, Keles et al. (2022)**
Sperm	Sea urchin	ZnO NPs	**Kukla, Chelomin et al. (2022)**
Epididymal sperm	Dog	ZnO NPs	**Fayez, El Sayed et al. (2022)**
Testicular tissue	Rat	ZnO NPs	**Hong, Shao et al. (2022)**
Epididymal sperm	Rat	Fe_2O_3 NPs	**Paskeh, Babaei et al. (2022)**
Testicular tissue	Mice	SiO_2 NPs	**Sun, Wang et al. (2022)**
Epididymal sperm	Mice	TiO_2	**Danafar, Khoradmehr et al. (2021)**
Sperm	Bull	Silver-Carbon NPs	**Yousef, Abdelhamid et al. (2021)**
Spermatocyte	Mouse	SiO_2 NPs	**Sang, Liu et al. (2021)**
Sperm	Rabbit	ZnO NPs	**Halo Jr, Bułka et al. (2021)**
Sperm	Bull	ZnO NPs	**Jahanbin, Yazdanshenas et al. (2021)**
Sperm	Human and Rat	CeO_2 NPs	**Cotena, Auffan et al. (2020)**
Sperm	*Fish*	TiO_2 NPs	**Özgür, Ulu et al. (2020)**
Sperm	Swine	Silver NPs	**Pérez-Duran, Acosta-Torres et al. (2020)**
Spermatogonia	Mouse	ZnO NPs	**Pinho, Martins et al. (2020)**
Sperm	*Fish*	SiO_2 NPs	**Özgür, Ulu et al. (2019)**
Sperm	Human	TiO_2 NPs	**Santonastaso, Mottola et al. (2019)**
Testicular tissue	Rat	Silver NPs	**Elsharkawy, Abd El-Nasser et al. (2019)**

Leydig cells	Mouse	ZnO NPs	**Shen, Yang et al. (2019)**
Sperm	Sea urchin	CuO NPs	**Gallo, Manfra et al. (2018)**
Spermatogenic ephitelium	Rat	TiO_2 NPs	**Sharafutdinova, Fedorova et al. (2018)**
Sperm	Buffalo bull	Silver NPs and Multiwalled carbon nanotubes	**Sanand, Kumar et al. (2018)**
Sperm	Bull	Fe_2O_3 NPs	**Caldeira, Paulini et al. (2018)**
Testicular tissue	Mice	CeO2 NPs	**Adebayo, Akinloye et al. (2018)**
Germ cell line		TiO_2 NPs	**Mao, Yao et al. (2017)**
Sperm	Human	Silver NPs	**Wang, Huang et al. (2017)**
Epididymal sperm	Mice	Silica NPs	**Ren, Zhang et al. (2016)**
Epididymal sperm	Mice	TiO_2 NPS	**Smith, Michael et al. (2015)**
Sperm	Rabbit	Silver NPs	**Castellini, Ruggeri et al. (2014)**
Sperm	Buffalo	TiO_2 NPs	**Pawar and Kaul (2014)**
Sperm	Mice	Mo NPs	**Zhai, Zhang et al. (2013)**
Sperm	Human	ZnO NPs	**Barkhordari, Hekmatimoghaddam et al. (2013)**
Sperm	Human	Gold and Silver NPs	**Moretti, Terzuoli et al. (2013)**

2.1. Titanium Dioxide Nanoparticles

Titanium Dioxide nanoparticles (TiO_2) occur naturally as anatase, rutile, and brookite. With its white, bright colors, anatase form is utilized as a preservative and coating in foods. (Irshad, Nawaz et al. 2021). Although the rutile form and the anatase form have similar characteristics, the rutile form is lighter and provides anti-corrosion capabilities and UV light protection. Brookite form, on the other hand, is a rare form and can transform into rutile form at high temperatures due to its unstable structure. (Vijayalakshmi and Rajendran 2012).

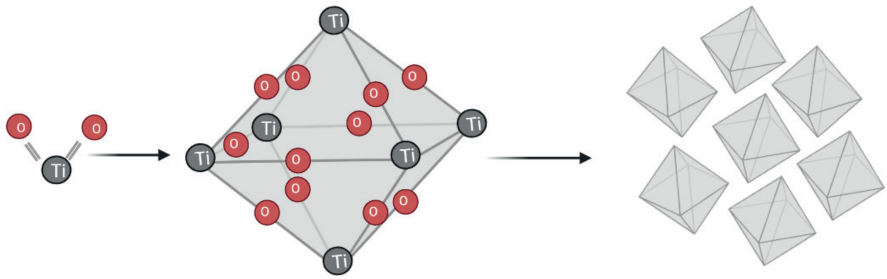

Figure 4. Structure of TiO_2 nanoparticles

On the other side, TiO_2 is used in infrastructure technologies including waterproof clothing, paint, glass coatings, and wallpapers. While it is used in agriculture to prevent pollution and pesticide residues, it is also used in electrical systems, solar panels, fluorescent lights, and refrigerators. It is used in the treatment of cancer and the manufacture of surgical instruments in medicine (Irshad, Nawaz et al. 2021). Although TiO_2 NPs, which helps to acquire a brighter color in meals and is commonly used in the cosmetics industry, is classified as a safe nanoparticle, the International Agency for Research on Cancer (Tsatsakis, Docea et al.) has warned that it can be carcinogenic when inhaled (Hong, Zhao et al. 2015).

TiO_2 nanoparticles are synthesized using a variety of techniques. According to production methods, it can be divided into two categories: physical/chemical method and biological method. The physical/chemical method can be classified as sol-gel method (Sharma, Sarkar et al. 2020), solvothermal method (Ramakrishnan, Natarajan et al. 2018) and hydrothermal method (Wang, Haidry et al. 2020). There are many different production techniques available when using the biological method. Various microorganisms, plants or plant wastes, fungi, and fruit extracts can all be used in this process, which is known as "green synthesis" (Singh, Kumar et al. 2019). While the chemical method is not preferred because it contains many toxic chemicals and can only produce a small number of TiO_2 nanoparticles, biological methods are far more preferred. As a result, TiO_2 nanoparticles, which are more easily and safely produced, are among the consumable nanoparticles. Many researchers have been studying the effects of TiO_2 nanoparticles on various tissues and organs, which can enter the body if foods such as fruit are eaten without washing. One example is research into the effects of TiO_2 nanoparticles on the male reproductive system. When the effects of these nanoparticles on the male reproductive system were investigated, it was discovered that motility decreased, DNA integrity was impaired, DNA damages were observed, genomic stability of sperm decreased, and intracellular ROS formation increased in human semen exposed to TiO_2 nanoparticles in vivo (Santonastaso, Mottola et al. 2021). Considering these changes in human semen and the damages of TiO_2 nanoparticles in vitro, their effects in vivo have also been a matter of curiosity. In one of the studies based on this curiosity, Hong et al. Administered TiO_2 nanoparticles orally at doses of 1.25, 2.5 and 5 mg/kg in mice during a period of six months. The applications led to the discovery that nanoparticles aggregated in the testis and drastically decreased the quality of semen (Hong, Zhao et al. 2015). Again, in a study where TiO_2 nanoparticles were injected intravenously into rats, they were administered at doses of 5, 25, and 50 mg/kg and at a size of 21 nm. It has been observed that when TiO_2 nanoparticles are used in high doses, they accumulate in the testicles, activate the apoptotic enzyme caspase-3, and alter spermatological parameters (Meena and Kajal 2015). It is quite remarkable that TiO_2 nanoparticles taken in increasing doses have harmful effects on the male reproductive system. Therefore, Jia et al demonstrated that TiO_2 nanoparticles taken in the period from the postnatal 28th day to puberty inhibit the release and conversion of testosterone hormone, which is indispensable in the male reproductive system (Jia, Sun et al. 2014). The effects of consumable nanoparticles on the environment are equally as important as the effects of TiO_2 nanoparticles on humans, which have been the subject of studies with laboratory animals. It is stated that TiO_2 nanoparticles also damage bull semen, decrease sperm viability, membrane integrity and increase DNA damage fragmentation (Pawar and Kaul 2014). TiO_2 nanoparticles' effects on the male reproductive system are not limited to terrestrial creatures. TiO_2 nanoparticles were found to be harmful to both *Capoe trutta* and *Sparus aurata* sperm (Özgür, Ulu et al. 2018, Carvalhais, Oliveira et al. 2022). Application of 400 μg of subcutaneous TiO_2 NPs (<300 nm diameter) during pregnancy leads to a decrease in the number of Sertoli cells and changes in the testicular morphology and changes in the seminiferous tubules in male offspring (Takeda, Suzuki et al. 2009). TiO_2-NPs (21 nm in diameter) in testis cause a decrease in the level of antioxidant enzymes, an increase in the level of caspase 3, which is one of the apoptosis markers, and an increase in the rate of DNA damage (Meena and Kajal 2015). In addition, microarray analysis produces changes in spermatogenesis and gene expression associated with steroid hormones in testes exposed to TiO_2 NPs (Gao, Ze et al. 2013). It has been reported that TiO_2 NPs in mice also activate the MAPK signaling pathways (p38, c-Jun N-terminal kinase (JNK) and extracellular signal-regulated kinase (ERK)) of testicular tissue of mice, leading to male reproductive dysfunction through this pathway (Lu, Ling et al. 2021). TiO_2 NPs cause germ cell apoptosis by downregulation of Bcl-2, upregulation of Bax, Cleaved Caspase 3 and Cleaved Caspase 9 (Meng, Li et al. 2022).

2.2. Silver Nanoparticles

Three processes are used to create silver nanoparticles: physical, chemical, and biological synthesis. Although the physical method, which uses techniques like spark discharge and pyrolysis, is quick and doesn't require harmful chemicals, but it has several disadvantages, including energy consumption, the possibility of solvent contamination, and less uniform distribution. (Zhang, Liu et al. 2016). Another method, the chemical method, includes methods such as cryochemical synthesis (Sergeev, Kasaikin et al. 1999), lithography (Hulteen, Treichel et al. 1999) and chemical reduction (Zhang, Li et al. 2011). Chemicals used in the synthesis of nanoparticles in the chemical method are toxic and harmful. (Mallick, Witcomb et al. 2004). As a result, while they are simple and inexpensive to produce, they can be harmful to living organisms. (Gurunathan, Han et al. 2015). Despite the disadvantages of the physical and chemical method, the biological method is a good alternative as it is simple, inexpensive and harmless. Along with different biomolecules, bacteria, fungi, and plant extracts are also used in the biological synthesis method. As an example of bacterial production, Ag nanoparticles in spherical, triangular and hexagonal form can be produced from *Pseudomonas stutzeri* isolated from silver mines in Africa. (Klaus, Joerger et al. 1999). In another biological method, *Verticilim sp*. and *Fusarium oxysporum* can produce 25 nm Ag nanoparticles. (Mukherjee, Ahmad et al. 2001, Sastry, Ahmad et al. 2003).

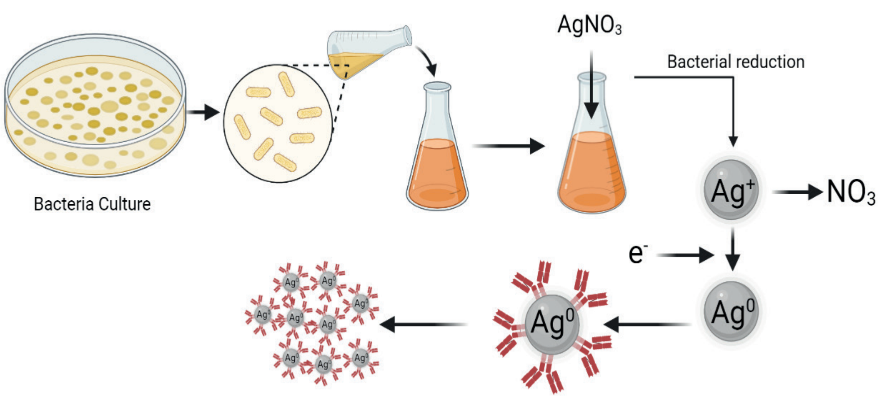

Figure 5. Biological production of silver nanoparticles.

Ag nanoparticles have found use in many areas such as toys, detergents, antibacterial chemicals, cosmetics, etc. Because of its antimicrobial properties, it is used in food packaging and as a food additive (Marambio-Jones and Hoek 2010, Abu-Taweel, Albetran et al. 2021). Antimicrobial effects of Ag nanoparticles are size dependent (Morones, Elechiguerra et al. 2005). When Ag nanoparticles come into contact with bacteria, they stick to the cell surface and alter it in various ways. It inhibits the enzymes that are part of the cellular respiratory chain, damages the cell membrane by forming pits and cracks, and alters the permeability of the cell as a result. (Morones, Elechiguerra et al. 2005, Pal, Dutta et al. 2007). In addition to these effects, metal ions form oxygen radicals and lead to oxidation of cellular structures. (Dastjerdi and Montazer 2010, Sweet and Singleton 2011). Silver nanoparticles are well known for their excellent antibacterial abilities and superior physical properties and are widely used in an increasing number of applications, from household disinfectants to medical devices and water purifiers. (Yu, Yin et al. 2013). The wide usage area of silver nanoparticles also causes increased exposure to it. For this reason, the effects of silver nanoparticle exposure on the reproductive systems of living things as a result of nano-pollution have also been a matter of interest. The effects of Ag nanoparticles, which we are exposed to at every stage of life, on the reproductive system are not different from TiO_2 nanoparticles. In a study, it was revealed that Ag nanoparticles administered intraperitoneally at a dose of 40 mg/kg decreased testicular weight in mice, reduced the antioxidative defense mechanism, and decreased motility in semen (Abu-Taweel, Albetran et al. 2021). While oral administration of 5.3 mg/kg and 13.4 mg/kg Ag nanoparticles to rats reduced testosterone levels, SOD levels, sperm viability, and DNA chromatin integrityi increase MDA levels, in electron density in the nucleus and cytoplasm of spermatogonia were observed (Elsharkawy, Abd El-Nasser et al. 2019). It was noted that 50 mg/kg Ag nanoparticles taken orally during the prepubertal period damaged the testicular tissue and slowed down reproductive development in addition to studies in adult rats (Sleiman, Romano et al. 2013, Mathias, Romano et al. 2015). The increase in ROS production by AgNPs stimulates insulin receptor substrate-1 (IRS-1), protein kinase B(AKT), mechanistic target of rapamycin (mTOR), p53, p21 and caspase 3 as well as SOD and CAT activity as defense mechanisms in the cell and preserves DNA integrity (Blanco, Tomás-Hernández et al. 2018). Furthermore, AgNPs significantly downregulated the hypothalamic–pituitary–gonadal axis (Arisha, Ahmed et al. 2019).

2.3. Zinc Nanoparticles

Along with silicon-based nanoparticles and titanium dioxide nanoparticles (TiO_2 NPs), zinc oxide nanoparticles (ZnO NPs) are thought to be among the three most produced nanoparticles. The production mechanisms of ZnO NPs are similar to other nanoparticles, and physical and chemical methods are widely used. This methods can be clasifies as chemical precipitation (Wang and Muhammed 1999), sol-gel method (Spanhel and Anderson 1991), solid-state pyrolytic method (Wang, Zhang et al. 2002) and solution free mechanochemical method (Shen, Bao et al. 2006). However, the environmental pollution problem that has emerged in recent years has led researchers to the biological production of ZnO NPs, which is much safer for the environment. For this reason, zinc oxide nanoparticles have been produced from many plant extracts and green synthesis studies are still continuing (Elumalai and Velmurugan 2015). Zinc oxide nanoparticles are used in industrial fields such as rubber, paints, coatings and cosmetics (Smijs and Pavel 2011). ZnO NPs were first used in the rubber industry (Kołodziejczak-Radzimska and Jesionowski 2014, Ruszkiewicz, Pinkas et al. 2017). Due to its UV absorption properties, ZnO is also used in personal care products such as cosmetics and sunscreen (Newman, Stotland et al. 2009). Zinc oxide nanoparticles are the form with low toxicity, which effectively overcomes cells and molecules in pathological conditions (Suri, Fenniri et al. 2007).

In general knowledge, zinc plays curicial roles in all body tissues such as bone, skin, brain and muscle. It is also the main component of various enzymatic systems and protein and nucleic acid synthesis mechanisms (Jiang, Pi et al. 2018). With so many important roles to play, ZnO NPs with very small particle sizes can be easily absorbed from the body. As a result, the effects of numerous consumable products and ZnO NPs entering the body on cell systems should be thoroughly explained.

ZnO NPs first bind to the cell membrane when they get to the target tissues and organs. The intracellular cytoplasmic structure leaks out of the cell as a result of ZnO NPs' damage to the cell membrane, which also compromises the integrity of the cell. In addition to the physical damage of the cell, ZnO NPs entering the cell damage the electron transport chain occurring in the mitochondrial membrane and inhibit respiratory dehydrogenase enzymes. ROS are produced when ATPase complexes are damaged and appear as H_2O_2, OH^- VE O_2^{-2}. These reactive oxygen species disrupt mitochondrial function, cause lipid peroxidation, and damage to plasmids and DNA. (Singh, Singh et al. 2018). For all nanomaterials, the mechanism shown below acts in a similar way (Figure 6).

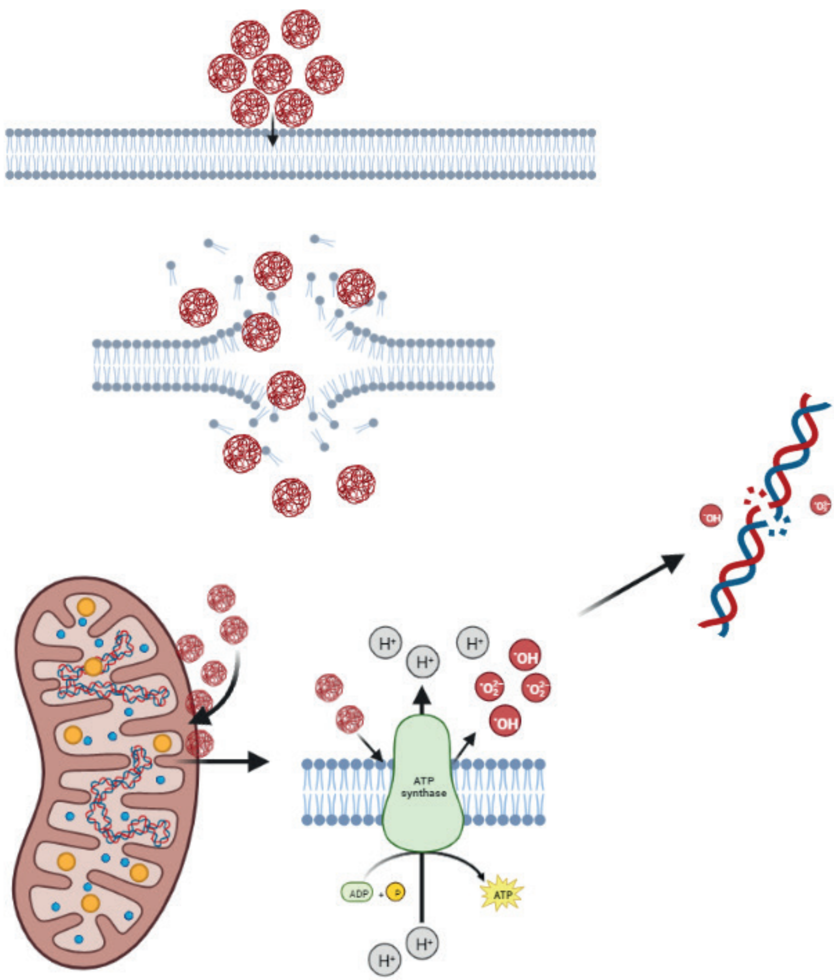

Figure 6. Cellular damage mechanism of ZnO nanoparticles.

This damage caused by high levels of ZnO NPs has drawn the attention of researchers, and numerous studies have been done to study the effects of ZnO NPs on various tissues and organs. ZnO NPs, which have low toxicity under normal conditions, increased sperm motility, antioxidant enzyme activity and mRNA expression level in diabetic rats (Afifi, Almaghrabi et al. 2015). However, when high-dose exposure occurs, ZnO NPs do not reveal such innocent results. YIn a study using high doses of ZnO NPs, different concentrations of ZnO NPs (10, 100, 500, and 1000 μg/mL) were reported to be cytotoxic at all time periods at the highest dose in human semen incubated (45, 90 and 180 min) (Barkhordari, Hekmatimoghaddam et al. 2013). In foods, ZnO serves as an antimicrobial agent as well as a mineral component. This nanoparticle, which is crucial in preventing microbial contamination, endangers both aquatic and terrestrial life. Similar to earlier studies, it was found that 350 mg/kg of ZnO nanoparticles caused damage to rat testicular tissue, altered epididymal weight, sperm motility, and changed hormone levels in a study in which ZnO nanoparticles were given orally to adult rats (Hong, Shao et al. 2022). Studies conducted both in vivo and in vitro have shown that ZnO nanoparticles have negative effects, including harm to testicular tissue and induction of apoptosis and autophagy in mouse Leydig cells (Liu, Xu et al. 2016, Shen, Yang et al. 2019, Pinho, Martins et al. 2020). ZnO nanoparticles have been shown to be toxic not only in laboratory animals, but also in aquatic organisms. One of these studies was conducted by Oliviera et al. DNA damage was discovered in the sperm of *Paracentroutus lividus* after 30 minutes of exposure to ZnO nanoparticles (Oliviero, Schiavo et al. 2019). ZnO damages the seminiferous epithelium in the testis, reduces the semen density in the cauda epididymis and lowers the serum testosterone level. In addition, caspase 8, caspase 3, Bax, LC3-II, Atg 5, and Beclin 1 levels increase, while Bcl-2 levels decrease (Shen, Yang et al. 2019).

2.4. Iron Oxide Nanoparticles

Iron oxide nanoparticles are found in nature as magnetite (Fe_3O_4), maghemite (γ-Fe_2O_3) and hematite (α-Fe_2O_3) (Ali, Zafar et al. 2016). The forms used in the food industry are maghemite, which has supraparamagnetic properties, and hematite, which can be used as a food dye. Maghemite nanoparticles, especially thanks to their high magnetic properties, bind to unwanted materials in foods and help them to precipitate in the magnetic environment and thus to purify foods (Dong, Chen et al. 2022). This process of purification allows foods to maintain their original flavor (Schwaminger, Fraga-García et al. 2019). In a study using this method, Mierczynska-Vasilev et al. succeeded in removing some proteins from wine (Mierczynska-Vasilev, Boyer et al. 2017). Maghemite nanoparticles (Fe_2O_3) are also widely used in clinical diagnosis for T2-weighted magnetic resonance imaging (Bansal and Bilaspuri) as a contrast agent (Yang, Wang et al. 2022). Fe_2O_3-NPs is also significant for its extensive uses, such as magnetic resonance imaging (Bansal and Bilaspuri) (Ha¨feli, Riffle et al. 2009). α-Fe_2O_3, which is known by the European Union with the code E172, is also used as a colorant in foods (Voss, Hsiao et al. 2020). The cytotoxic effect of iron oxide nanoparticles at high doses is similar to that of ZnO NPs. For this reason, there is a concern that they may have harmful effects on various tissues and organs when consumed in large amounts. In a study where this situation was sorely tested, mice given 25 and 50 mg/kg Fe_2O_3 nanoparticles experienced an increase in caspase 3 activity and Bax levels, which led to apoptosis in the testicular tissue (Sundarraj, Raghunath et al. 2017). Similar findings were also seen in mouse semen, where 40 mg/kg Fe_2O_3 nanoparticles given intraperitoneally for two weeks reduced motility and density (Nasri, Rezai-Zarchi et al. 2015). Comparable to terrestrial life, aquatic life experienced similar effects, causing destruction to the gonads of *Poecilia reticulata* (Gonçalves, Dias et al. 2021). Oxidative stress has been implicated as a central mechanism for damage caused by Fe_2O_3-NPs. Fe_2O_3-NPs cause a decrease in body weight, gonodo somatic index, sperm motility and viability in mice. In addition, it causes an increase in the level of MDA, which is a lipid peroxidation marker, while it causes a decrease in the levels of CAT, SOD, GSH and GPx and the relative mRNA level (Ahmed, Hussein et al. 2022). Fe_2O_3 NPs cause significant changes in gene expression of mitochondrial transcription factor-A (mtTFA) and dissociation protein 2 (UCP 2) in testicles (Younus, Yousef et al. 2020).

2.5. Copper Nanoparticles

Copper Nanoparticles (Cu NPs) are used as antimicrobial and anticancer agents along with their use in the textile, electronics and chemical industrie. Fertilizers and herbicides containing CuNP are used in various agricultural applications (Cometa, Iatta et al. 2013). Cu NPs are used in animal feeds because of their good antibacterial and growth promoting effects that reduce the incidence of animal diseases (Tamilvanan, Balamurugan et al. 2014). CuNPs show their toxic effect by increasing reactive oxygen species (ROS) (Lin and Xing 2007). CuNPs decrease sperm quality parameters, male hormones, cause testicular damage, increase oxidative stress and apoptosis, decrease antioxidant enzymes and germ cell proliferation, and increase 8-oxoguanine DNA glycosylase-1 (OGG1) and apelin receptor (APJ) expression (Nicy, Das et al. 2022). Cu NPs cause testicular damage, decrease in sperm quality and fructose content, increase in oxidative stress and sperm malformations, and changes in Bax, Beclin, Bcl-2 and p52 expression in rats. Cu NPs cause testicular damage, decrease in sperm quality and fructose content, increase in oxidative stress and sperm malformations, and changes in Bax, Beclin, Bcl-2 and p52 expression in rats (Chen, Wang et al. 2022).

CuO nanoparticles are another type of nanoparticle that can affect an aquatic animal's reproductive system. Gallo et al. discovered that CuO nanoparticles increased ROS formation, resulting in a decrease in sperm viability and mitochondrial membrane potential in *Paracentrotus lividus* semen (Gallo, Manfra et al. 2018). In a different study, researchers found that Cu nanoparticles in *Onchorynchus mykiss* semen were more harmful than CuO nanoparticles and emphasized that the toxicity or benefit of a nanoparticle depended on its particle diameter or its composition (Garncarek, Dziewulska et al. 2022). In a study conducted in laboratory animals, Cu nanoparticles applied at a dose of 40 mg/kg damaged the rat testicular tissue, causing a decrease in sperm viability and an increase in the amount of abnormal spermatozoa (Al-Bairuty, Taha et al. 2016).

2.6. Silicon Based Nanoparticles

Silicon is the second most abundant element in the earth's crust after oxygen and is used in agriculture because it is beneficial to plants (Epstein 1994). Silicon exists in nature as two forms, crystalline and amorphous, with the same molecular formula (Chen, Liu et al. 2018). SiO_2 nanoparticles are used in the fields of industry, biomedicine, food and environmental protection due to their properties such as good stability, excellent biocompatibility and easy modification (Xu, Wang et al. 2014).

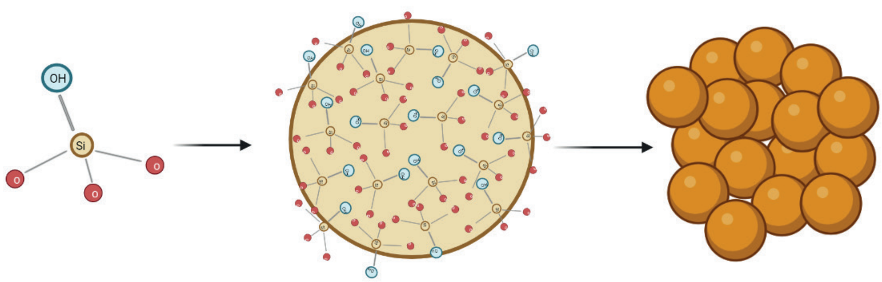

Figure 7. Nanostructure of Silica nanoparticles.

Silica used in foods is numbered with the code E551 and named as synthetic amorphous silica (Sastry, Ahmad et al.). The main usage of SAS are in noodles, soups, creams and coffee creamers as an anti caking agent (Dekkers, Krystek et al. 2011, Gubala, Giovannini et al. 2020). SiO_2 nanoparticles are used in pharmaceutical applications (Li, Barnes et al. 2012), medical diagnostics (Chen, Yin et al. 2012), in vivo imaging (Tu, Ma et al. 2010). When applied to semen, it reduced motility, viability, and DNA integrity; however, when applied to testicular tissue of lab animals, it induced apoptosis and oxidative stress-related cellular damage (Barkalina, Jones et al. 2015, Azouz, Korany et al. 2022, Sun, Wang et al. 2022). SiO_2 NPs cause histopathological changes in testis (Hassankhani, Esmaeillou et al. 2015). SiO_2 nanoparticles in water have a negative impact on marine organisms' reproductive systems, with exposure levels of 50 mg/L having toxic effects on rainbow trout sperm (Özgür, Ulu et al. 2019). SiO_2 NPs increased lipid peroxidation in rat and decreased the activities of antioxidant enzymes. SiO_2 NPs induced apoptosis, demonstrated by upregulation of Bax and caspase 3 and downregulation of Bcl-2, as well as induction of DNA damage. SiO_2 NPs also caused upregulation of inflammation-related genes such as; IL-1β, TNF-α, NF-κB, cyclooxygenase 2 (COX2) (El-Sayed, El-Demerdash et al. 2021).

2.7. Molybdenum Nanoparticles

Molybdenum is mentioned as an essential trace element for humans and microorganisms. However, adverse effects of high molybdenum content in the diet on metabolism have been reported (Yang, Cui et al. 2011). Mo NPs are used in the electron industry, cutting tools, hard alloys, textiles, microelectronic films, coatings, plastics, nanowire and X-ray tubes. However, these industrial activities negatively affect the lives of people and animals (Chen, Yin et al. 2012, Siddiqui, Saquib et al. 2015). Mo NPs reduce the serum testosterone level in rats and cause histopathological changes in the testis (Asadi, Mohseni et al. 2017). High dose molybdenum administration in rats affected sperm parameters negatively and decreased SOD and GPx levels while increasing MDA levels (Zhai, Zhang et al. 2013). In the in vitro study, Mo NPs showed cytotoxic effect in mouse spermatogonial stem cell line (Braydich-Stolle, Hussain et al. 2005). Molybdenum trioxide (MoO_3) NPs with high toxicity are mainly used in industry, glass and the production of cracking catalysts, hydrogenation catalysts and refractory alloys, and they can significantly threaten public health (Gawande, Goswami et al. 2016). In a study, it was stated that MoO_3 changed the biochemical parameters in the blood and caused histological changes in the uterus (Fazelipour, Assadi et al. 2020). In a study, it was reported that the application of MoO_3 anoparticle caused the irregularity of spermatogenic cells in the seminiferous tubules and a decrease in the number of sperm and sertoli cells (Mirza Mohamadi and Sohrabi 2015).

2.8. Cerium Nanoparticles

Cerium is a member of the lanthanide group and exhibits antioxidant properties as well as catalytic properties (Dahle and Arai 2015, Dhall and Self 2018). CeO_2 NPs are used in various biomedical applications such as protection against radiation damage, retinal neurodegeneration, anti-inflammatory and antioxidant activities (Tarnuzzer, Colon et al. 2005). In one study, CeO NPs decreased blood hemoglobin, PCV and RBC count compared to controls. Additionally, luteinizing hormone (LH) and follicle stimulating hormones (FSH), prolactin sperm quality parameters were significantly reduced in mice (Adebayo, Akinloye et al. 2018). In another study, it was stated that CeO_2 NPs improved testicular and sperm parameters in rats with diabetes (Artimani, Amiri et al. 2018). It was stated that the addition of CeO_2 NPs to the semen and the uptake of intracellular CeO_2 NPs did not affect the CASA parameters in the short-term storage of ram semen (Falchi, Bogliolo et al. 2016). It was stated that CeO_2 NPs improved sperm quality in rats treated with malathion (Moridi, Hosseini et al. 2018). CeO_2 NPs applied in the cryopreservation of human semen have been reported to improve sperm quality (Hosseinmardi, Siadat et al. 2022). A study in mice showed that CeO_2 NPs (20 mg/kg and 40 mg/kg) increased the Ce element content in the testis, testicular histopathological patterns and sperm DNA damage, while decreasing testicular weight, daily sperm production (DSP) and sperm motility. A remarkable reduction in testosterone levels and marker enzyme activities was noted, with downregulated mRNA expression levels of various steroidogenesis genes such as Star, P450scc, P450c17, 3β-Hsd and 17β-Hsd (Qin, Shen et al. 2019). Another study showed that the tubular diameter, epithelial height and spermiogenesis index were significantly reduced by CeO_2 NPs at 50 and 100 mg/kg doses. Sperm parameters were significantly reduced and also the percentages of immature sperm and sperm with DNA damage increased significantly compared to control. In addition, it was stated that in vitro fertilization and in vitro embryo development rates decreased (Hosseinalipour, Karimipour et al. 2021).

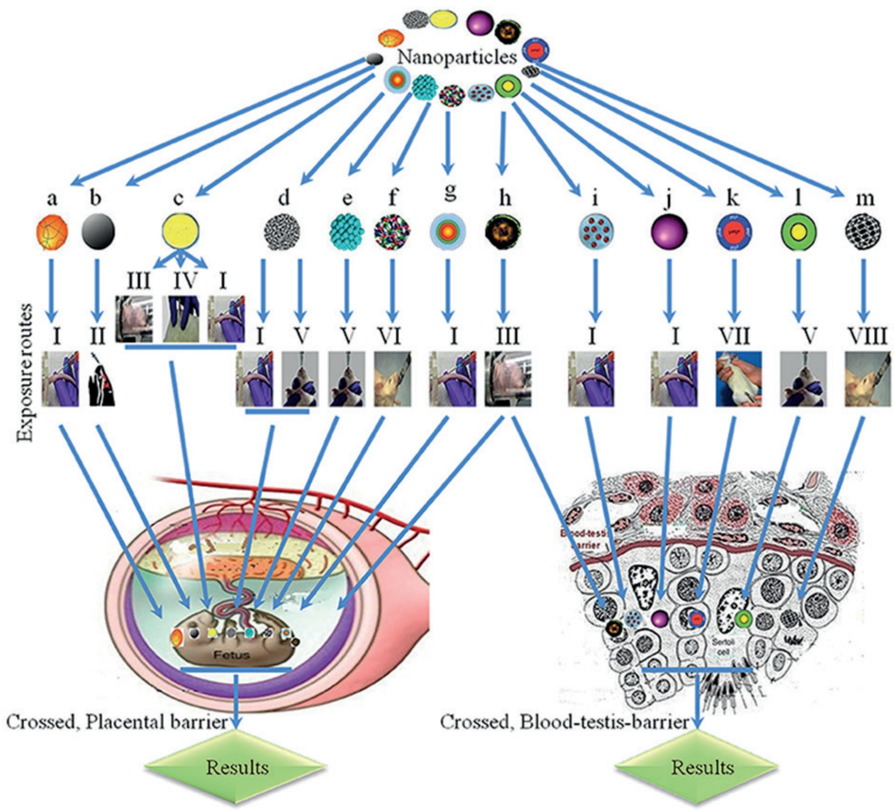

Figure 8. Effects of nanoparticles on male and female reproductive system (Brohi, Wang et al. 2017).

a,[198]Gold-nanoparticles(Semmler-Behnke, Fertsch et al. 2007); b, black carbons(Takahashi and Matsuoka 1981, Kubo-Irie, Oshio et al. 2011); c, titanium oxide(Wang, Zhou et al. 2007); d, single-walled carbon nanotubes(Sugamata, Ihara et al. 2006, Snyder, Fennell et al. 2015); e, platinum(Meng, Yang et al. 2010), f, multi-walled carbon nanotubes(Jackson, Vogel et al. 2011); g, cadmium telluride/cadmium sulfide quantum dots(Mattison, Plowchalk et al. 1990); h, diesel exhaust(Hamada, Suzaki et al. 2003, Hougaard, Jackson et al. 2010, Pietroiusti, Massimiani et al. 2011, Jackson, Halappanavar et al. 2013, Kyjovska, Boisen et al. 2013); i, sodium chloride-modified silica nanoparticles(Philbrook, Walker et al. 2011); j, silicon dioxide(Yoshida, Hiyoshi et al. 2009); k, silica-coated magnetite nanoparticles (rhodamine B isothiocyanate)(Bai, Zhang et al. 2010); l, metal-free polymethyl methacrylate(Kashiwada 2006); m, carbon(Kubo-Irie, Oshio et al. 2011); I, intravenous; II, intranasal; III, inhalation; IV, subcutaneous; V, oral exposure; VI, by gavage; VII, intraperitoneal; VIII, intragastric.

3. Conclusion & Future Prospects

Nanoparticles show their effects in the biological process in various ways. Basically, the following situations can be mentioned;

- direct association with the cell membrane (Buchman, Hudson-Smith et al. 2019),

- physical effect by removing/destroying the lipid membrane (Tu, Lv et al. 2013, Mensch, Hernandez et al. 2017),

- interaction based on electrostatic attraction (Dickson and Koohmaraie 1989),

- inducing internal signaling pathways that damage the cell (Hussain, Garantziotis et al. 2014),

- releasing toxic ions by binding to proteins and enzymes (Bondarenko, Ivask et al. 2013),

- effect of metal ions on the phospholipid membrane and genetic material (Stohs and Bagchi 1995),

- inhibiting cellular functions (Barras and Fontecave 2011, Macomber and Hausinger 2011).

- the occurrence of oxidative stress conditions in which different key enzymes such as mononuclear iron proteins can be targeted (Sobota and Imlay 2011, Anjem and Imlay 2012) and mutation formation in the organism by the oxidation of DNA bases and deoxyribose by ROS (Galhardo, Almeida et al. 2000, Imlay 2008).

Successful fertilization depends on the healthy production and functioning of reproductive cells. The harmful effects of nanoparticles disrupt the fertilization process. This situation is summarized in the image below.

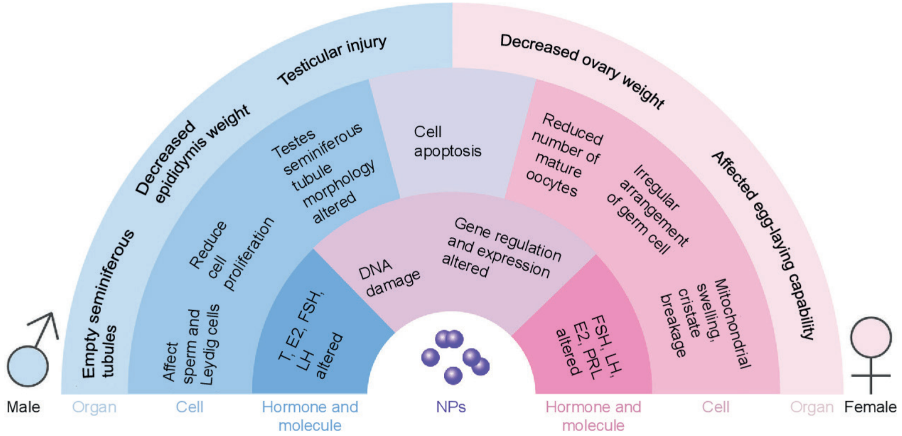

Figure 9. Negative effects of nanoparticles in the fertilization process (Wang, Song et al. 2018).

Consumable nanoparticles' benefits in the food industry have led to their widespread use, and various nanoparticles are involved in every stage of food processing. In vivo and in vitro studies show the effects of these nanoparticles on the reproductive system, which have passed many toxicity tests and have been approved for use. Toxicological studies on a wide range of animals, from laboratory animals to human experiments, aquatic creatures to farm animals, reveal that the reproductive toxicities of nanoparticles vary depending on the dose of use. The harmful effects of existing nanoparticles occur at high doses and frequent exposures. In the light of all this information, when taken in high quantities and on a continuous basis, consumable nanoparticles might be considered one of the major causes of male infertility.

Further advances in reproductive biotechnology may be possible with greater incorporation of nanoparticles into molecular biology techniques. Sperm-mediated gene transfer is an application in which nanoparticles can be loaded with nucleic acids and proteins (Barkalina, Jones et al. 2014). With continued research, it may be discovered that nanoparticles play a much more active role in the reproductive system. However, it should be kept in mind that some nanoparticles can lead to serious negative consequences due to their toxic effects.

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