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The Significant Role of Antioxidant Enzymes in The Pathogenesis and Potential Enhancement of Infertility

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Abstract: Infertility, a global health concern affecting millions, is progressively connected to oxidative stress, an imbalance between the production of reactive oxygen species (ROS) and the susceptibility of the antioxidant defense system. Male is solely responsible for about 20% and a causative factor in about 30% to 40% of cases. But women decline steadily with age, especially at aged 35 years or older after 6 months of unprotected sex. Antioxidant enzymes, like catalase (CAT), superoxide dismutase (SOD), peroxiredoxins (PRXs), glutathione peroxidase (GPx), glutathione reductase (GR), and the four enzymes of the ascorbate–glutathione pathway, which symbolizes an essential endogenous defense mechanism against ROS-induced cellular impairment in the reproductive system of both males and females. This review scrutinized current studies by explaining the crucial role of these enzymes in the pathogenesis of infertility. In males, compromised antioxidant enzyme activity in seminal plasma and spermatozoa contributes to elevated oxidative stress, leading to dysfunctional sperm motility, viability, DNA fragmentation, and finally diminished fertilization possibilities. Likewise, in females, dysregulation of antioxidant enzyme levels in follicular fluid and the reproductive tract can negatively affect the quality of oocytes, endometrial receptivity, and contribute to conditions like polycystic ovary syndrome (PCOS) and endometriosis, which are associated with infertility. Conversely, it is recommended that interventions aimed at improving antioxidant enzyme activity, either by direct supplementation of enzymatic cofactors or indirectly through wide-range of antioxidant therapies and lifestyle modifications, may give opportunities for improving reproductive resolution in both sexes. Finally, this review particularly inform the critical role of antioxidant enzymes in maintaining redox homeostasis within the reproductive system and evaluate their potential as therapeutic targets in solving infertility issues.

Keywords: Phytochemicals, Antioxidants, Infertility, Free radicals, peroxidases

I. Introduction

Oxidative stress, an imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant defense mechanisms, has emerged as a significant factor in both male and female infertility (Saleh *et al.*, 2025). Antioxidant enzymes are crucial components of this defense system, working to neutralize excess ROS and protect cells from damage. Oxidative stress (OS) theory of disease is so prevalent in antioxidants, including vitamins C and E, GSH, some metals (e.g. selenium and zinc) or extracts from a wide range of fruits, vegetables or fish, which are major components of the nutritional supplements used by 150 million Americans (Starr, 2015). These enhancements are used as they apparently strengthen immune defences, prevent cancer or pathological ageing. The traditional science that will forever prevail is that ***'Antioxidants are good while free radicals are bad'*** (Scudellari, 2015). Since antioxidants mop up free radicals, therefore, the good dominated the bad.

Antioxidants are compounds that prevent oxidation (usually occurring as autoxidation), a chemical reactiom that can produce free radicals. Autoxidation leads to degradation of organic compounds, including living matter. Antioxidants are frequently added to industrial products, such as polymers, fuels amd lubricants, to extend their usable lifetimes (Klemchuk, 2000). Foods are also treated with antioxidants to forestall spoilage, in particular in rancidification of oils and fats. In cells, antioxidants such as glutathione, mycothiol or bacillithiol and enzyme systems like superoxide dismutase can prevent damage from oxidative stress (Helberg and Pratt 2021). Known dietary antioxidants are vitamins A, C and E but the term "antioxidant" has also been applied to numerous other dietary compounds that only have antioxidant properties in vitro, with little evidence for antioxidant properties in vivo. Dietary supplements marketed as antioxidants have not been shown to maintain health or prevent disease in humans (Fang *et al.*, 2002). Antioxidants like vitamins C and E, folic acid, zinc, selenium, carnitine, and carotenoids are ROS scavengers, and their practice as a therapy has been revealed to counteract the negative effects of high ROS levels on sperm and blood parameters in female infertility (Harvesh *et al.*, 2022).

Natural antioxidants have been of interest for many years because of their ability to impede the development of off-flavours in foods. However, an increase in interest in these components has occurred in recent years because of their importance for the prevention of diseases mediated by free radical reactions in vivo. Primarily, natural antioxidants are plant phenolic compounds occurring in all parts of the plant. The onset of a variety of major health problems, including cancer, atherosclerosis, rheumatoid arthritis, inflammatory bowel disease, immune system deterioration, brain dysfunction, cataracts and may be delayed by natural antioxidants (Gordon, 2003). This review is to scrutinized past and current studies explaining the crucial role of these enzymes in the pathogenesis of infertility. Addressing infertility is an important component of sexual and reproductive health and rights, and is central to achieving Sustainable Development Goal (SDG) 3 and Sustainable Development Goal (SGD) 5 (WHO, 2023).

Infertility

Infertility or subfertility has been defined by the World Health Organization (WHO) as the ‘‘failure to accomplish a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse’’. Infertility could either be primary or secondary. It is primary when a pregnancy has never been achieved by a person, and secondary when at least one prior pregnancy has been achieved (WHO, 2023). Infertility may be caused by infection in the man or woman, but often there is no obvious underlying cause (WHO, 2018). Infertility affects millions of people and has an important role to play on their families and communities which can have physical, emotional, and social impacts on their lives. Various factors, like age, genetics, hormones, infections, lifestyle, or environmental exposures.various factors, such as age, genetics, hormones, infections, lifestyle, or environmental exposures can lead to this disease conditrion. Diagnosis can be by medical tests and history, and treated by different methods, such as medication, surgery, assisted reproductive technology, or alternative therapies. Infertility can also be influenced by social and cultural factors, such as access to health care, stigma, discrimination, or legal barriers, and is a complex and dynamic condition that requires individualized and holistic care and support (Vos *et al.*, 2016). Globally, about 48.5 to 186 million people are affected by the inability to have children (Inhorn and Patrizio, 2015), and delayed conception affects 10% to 15% of couples who are trying to conceive (Smits *et al.*, 2018).

Estimates suggest that approximately one in every six people of reproductive age worldwide experience infertility in their lifetime. In the male reproductive system, infertility is most commonly caused by problems in the ejection of semen, absence or low levels of sperm, or abnormal shape (morphology) and movement (motility) of the sperm(WHO, 2018). Fertility management involves the prevention, diagnosis and treatment. Identical and reasonable access to fertility attention remains a task in most countries; predominantly in low and middle-income countries. Fertility care is seldom ranked in national universal health attention benefit packages.

Incidence of Infertility

It is imperative to recognise that infertility rates can meaningfully differ based on geographical location, population demographics, study methodologies, and the time and period of data collection (Cox *et al.,* 2022). Factors contributing to infertility in Africa, particularly secondary infertility, include pelvic inflammatory diseases often resulting from untreated infections, complications from unsafe abortions, and other health issues (Adetoro and Ebomoyi, 1991). Both male and female factors contribute meaningfully to infertility, and the awareness that it is only a female issue is erroneous (Gore *et al.*, 2015). Global tendencies advocate an increase prevalence of infertility, estimating the rising public health burden (Liang *et al.,* 2025).

Studies have shown in Nigeria (Lagos) that the frequency of infertility is about 26.8% among gynaecological meetings. This was higher than a 14.8% rate from another study in southwestern Nigeria and also higher than the 10-15% reported in the Western world at the time (Adetoro and Ebomoyi, 1991). Previous data from a rural Nigerian community indicated an overall prevalence rate of 30.3% (1991), showing that 9.2% and 21.1% were primary and secondary infertility respectively (Omisakin *et al.,* 2025). Recent statistical information from Lagos (2025) among couples seeking support for conception showed that female infertility factors alone contributed to 41.9% of cases, while male factors was 38.6%, which amount to 33.9% when combined. This study also distinguished a high rate of secondary infertility (63.1%). Another study in 2016 shows a potential modification where male factor infertility (around 60% in their recent cases) might be more prevalent than female factor infertility (around 40%). However, a 2025 study in Lagos still showed a slightly elevated prevalence of female factor infertility (Adegbola and Akindele, 2014).

Africa is the region with the highest incidence of infertility globally. In 2019, the period prevalence was assessed at 16.4%. Previous evaluations recommended a regular infertility rate in Africa of 10.1% of couples, with some countries attainment as high as 32% in (around 2004) (Gerais and Rushwan 1992). Sub-Saharan Africa demonstrate a high burden of secondary infertility, with one report in 2024 stating that about 30% of women aged 25-49 experience secondary infertility. In sub-Saharan Africa, prevalence varies significantly by region and even among cultural groups within the same country, ranging from about 9% to over 30% in some areas (Chimbatata and Malimba, 2016).

Global periodic incidence of infertility was 17.8% in high-income countries and 16.5% in low- and middle-income countries. Evaluations suggest that about 1 in 6, around 17.5% people have experience infertility globally at some point in their lives, showing the urgent need to increase access to affordable, high-quality fertility care for those in need (Infertility Statistics 2025; Njagi *et al.*, 2023). A global study using 2021 data indicated a stable increase in infertility rates between 1990 and 2021, with projections of continued rises. The global age-standardized prevalence rate for male infertility in 2021 was about 1,354.76 cases per 100,000 individuals, and for female infertility, it was significantly higher at approximately 2,764.62 per 100,000 individuals (Feng *et al.,* 2025). In 2021, it was estimated that 55,000,818 men and 110,089,459 women were living with infertility worldwide (Liang *et al.*, 2025; WHO, 2023).

Causes of Female Infertility

Infertility may be caused by a number of different factors, in either the male or female reproductive systems. In the female reproductive system, infertility may be caused by a range of abnormalities of the ovaries, uterus, fallopian tubes, and the endocrine system, among others. It may be caused by:

Tubal disorders such as blocked fallopian tubes, which are in turn caused by untreated sexually transmitted infections (STIs) or complications of unsafe abortion, postpartum sepsis or abdominal/pelvic surgery. Uterine disorders which could be inflammatory in nature (such as such endometriosis), congenital in nature (such as septate uterus), or benign in nature (such as fibroids). Disorders of the ovaries, such as polycystic ovarian syndrome and other follicular disorders. Disorders of the endocrine system causing imbalances of reproductive hormones. The endocrine system includes hypothalamus and the pituitary glands. Examples of common disorders affecting this system include pituitary cancers and hypopituitarism (WHO, 2023).

Causes of Male Infertility

Male infertility refers to a man's inability to impregnate a fertile female partner. This can be caused by various factors like hormonal imbalances, physical blockages, sperm production problems, anatomical issues, or genetic defects/disorders, lifestyle factors, problems with the delivery of sperm, or environmental factors. Male infertility affects approximately 7% of all men. Study have shown that factors like lifestyle choices, environmental factors, and certain medical conditions can play a role in male infertility (Agarwal et al., 2015).

Factors Affecting Male Infertility

It's important to note that male infertility is a complex issue with various contributing factors. Certainly, male infertility can be influenced by various factors, including: genetic, environmental, lifestyle, and health-related factors.

Varicocele:

This is a common cause of male infertility, characterized by the enlargement of veins within the scrotum become enlarged, leading to increased testicular temperature which can impact sperm production. It can lead to decreased sperm production and quality (Agarwal *et al.,* 2019; Tiseo *et al.,* 2019).

Genetic Factors:

Genetic abnormalities can play a significant role in male infertility. Conditions such as Klinefelter syndrome or Y-chromosome microdeletions can lead to abnormalities in sperm production, semen quality and overall fertility (Matzuk *et al.,* 2007; Tuttelmann *et al.,* 2011; Stouffs *et al.,* 2017).

Hormonal Imbalances:

Conditions that affect hormone levels, such as hypogonadism, can impact sperm production and quality, leading to infertility in males (Bhasin *et al.,* 2012). Disruption in hormonal levels, particularly testosterone and gonadotropins, can affect sperm production and maturation (Olesen *et al.,* 2017).

Exposure to Toxins:

Environmental factors, such as exposure to toxins like pesticides, heavy metals, and certain chemicals, can have detrimental effects on sperm health and fertility (Skakkebaek *et al.,* 2016).

Lifestyle Factors:

Lifestyle choices, such as smoking, excessive alcohol consumption, drug use, and obesity, can contribute to male infertility. These factors can affect sperm quality, quantity, and motility (Jensen *et al.,* 2014; Abarikwu *et al.,* 2020).

Environmental Factors:

Exposure to environmental toxins, such as pesticides, heavy metals, chemicals and radiation can have a negative impact on male reproductive health. These toxins can interfere with sperm production and function (Duty *et al.,* 2003; Jurewicz and Hanke 2018).

Health-related Factors:

Certain health conditions, such as diabetes, hypertension, and sexually transmitted infections, can also affect male fertility. These conditions can disrupt hormonal balance and sperm production (Agarwal *et al.,* 2015).

Factors Affecting Female Infertility

Female infertility is a complex condition influenced by a variety of physiological, environmental, and lifestyle factors. It is characterized by the inability to achieve a pregnancy after 12 months or more of regular, unprotected sexual intercourse, or after

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six months for women aged 35 or older (WHO, 2024). Sometimes, the cause of infertility remains ***"unexplained"*** despite thorough investigation (WHO, 2024; Thatipelli, 2024). Frequently, it is a combination of understated factors that are not easily recognized.

Ovulation Disorders

These are among the most common causes of female infertility, accounting for approximately 25% of cases (Medical News Today, 2023). They involve issues with the release of eggs from the ovaries. Ovulation disorders include the following:

Polycystic Ovary Syndrome (PCOS): This hormonal disorder is a leading cause of ovulatory dysfunction, characterized by irregular periods, hormonal imbalances, and often cysts on the ovaries. It is frequently associated with insulin resistance and obesity (Thatipelli, 2024).

Hypothalamic Dysfunction: Conditions like excessive physical or emotional stress, very high or very low body weight, or significant weight changes can disrupt the production of hormones (FSH and LH) from the pituitary gland that regulate ovulation, leading to irregular or absent periods.

Primary Ovarian Insufficiency (POI) / Premature Ovarian Failure: This occurs when the ovaries stop functioning normally before the age of 40, leading to a diminished egg supply and reduced estrogen production.[7] Causes can include autoimmune responses, genetic factors, or prior chemotherapy/radiation treatments.

Hyperprolactinemia: Elevated levels of prolactin (the hormone that stimulates breast milk production) can interfere with estrogen production and disrupt ovulation.

Thyroid Problems: Both an overactive (hyperthyroidism) or underactive (hypothyroidism) thyroid gland can cause hormonal imbalances that affect the menstrual cycle and ovulation (NHS, 2017; Medical News Today, 2023).

Fallopian Tube Damage or Blockage (Tubal Factor Infertility)

Blocked or damaged fallopian tubes prevent sperm from reaching the egg or hinder the journey of fertilized egg to the uterus for implantation.

Pelvic Inflammatory Disease (PID): Often caused by untreated sexually transmitted infections (STIs) such as chlamydia and gonorrhea, PID can lead to inflammation, scarring, and blockage of the fallopian tubes (NHS, 2017; WHO, 2024).

Endometriosis: This condition involves tissue similar to the uterine lining growing outside the uterus. It can cause adhesions and scarring that damage the ovaries or fallopian tubes, affecting their function and leading to infertility (NHS, 2017).

Pelvic Adhesions: Bands of scar tissue that bind organs can form after pelvic infections, appendicitis, endometriosis, or abdominal/pelvic surgery, physically impeding the reproductive organs.

Prior Surgeries: Pelvic or abdominal surgeries can sometimes cause scarring or damage to the fallopian tubes or cervix (Medical News Today, 2023).

Uterine or Cervical Factors

Problems with the uterus or cervix can interfere with embryo implantation or increase the risk of miscarriage.

Uterine Fibroids: These non-cancerous growths in or around the uterus can sometimes block fallopian tubes, distort the uterine cavity, or interfere with implantation, though many women with fibroids conceive without issues (NHS, 2017).

Uterine Polyps: Non-cancerous growths on the inner surface of the uterus that can interfere with implantation (NICHD, 2017).

Congenital Uterine Abnormalities: Structural problems with the uterus present from birth (e.g., an unusually shaped uterus) can affect the ability to become or remain pregnant (NICHD, 2017).

Asherman's Syndrome: Scarring in the uterus, often from previous injuries, infections, or surgeries, can inhibit implantation.

Cervical Stenosis: A narrowing of the cervix, or issues with cervical mucus production, can hinder sperm movement into the uterus.

Age

Female fertility significantly declines with age, particularly after the mid-30s, and more rapidly after 37. This is due to a natural decrease in both the number and quality of eggs (ovarian reserve) as woman ages, along with an increased risk of chromosomal abnormalities in the remaining eggs.

Lifestyle and Environmental Factors

These factors can significantly impact hormonal balance, ovulation, and overall reproductive health.

Weight: Both being significantly overweight (obesity) or underweight (e.g., due to eating disorders) can disrupt hormone levels, cause irregular ovulation, and reduce conception chances.

Smoking: Tobacco use damages the cervix and fallopian tubes, increases the risk of miscarriage and ectopic pregnancy, and can prematurely deplete egg supply

Alcohol Consumption: Excessive alcohol intake can disrupt hormonal balance, lead to irregular menstrual cycles, and decrease ovarian replacement.

Substance Use: Illicit drugs like marijuana and cocaine can affect fertility and ovulation (NHS, 2017; Medical News Today, 2023).

Stress: Chronic stress can affect hormone levels, potentially leading to irregular periods and anovulation.

Exercise: While regular exercise is beneficial, extreme or strenuous exercise can disrupt hormone levels and cause irregular periods or amenorrhea (absence of periods), leading to fertility problems.

Environmental Toxins: Exposure to certain pesticides, industrial chemicals, lead, and other heavy metals can damage the reproductive system and reduce fertility (WHO, 2024).

Certain Medications: Some long-term use of NSAIDs, chemotherapy drugs, and specific antipsychotics can affect fertility (NHS, 2017; Medical News Today, 2023).

Other Medical Conditions

Autoimmune Disorders: Conditions like lupus, rheumatoid arthritis, or thyroiditis can cause the immune system to attack normal body tissues, potentially affecting fertility (NICHD, 2017).

Chronic Diseases**:** Uncontrolled chronic conditions such as diabetes or kidney disease can impact fertility (Medical News Today, 2023).

Role of Oxidative Stress in Reproductive Dysfunction

Oxidative stress, characterized by an imbalance between the generation of reactive oxygen species (ROS) and the body's antioxidant defense mechanisms (Hamza *et al.*, 2024), has been progressively documented as a significant contributor to both male and female infertility (Saleh *et al.*, 2025). Antioxidant enzymes form a critical component of this defense system, working to neutralize excess ROS and protect cellular components from oxidative damage (Jomová *et al.,* 2023). ROS, including superoxide radicals, hydrogen peroxide, and hydroxyl radicals, are produced during normal metabolic processes and play essential roles in physiological functions such as cell signaling and immune responses (Agarwal *et al.*, 2019). However, when ROS production overwhelms the endogenous antioxidant capacity, a state of oxidative stress ensues, leading to damage of crucial biomolecules like lipids, proteins, and DNA (Bose and Cuffari, 2023). In the context of infertility, oxidative stress can negatively impact various aspects of reproductive function in both sexes (Aitken *et al.*, 2022).

Oxidative Stress in Male Infertility:

Sperm Damage: Spermatozoa are highly susceptible to oxidative damage due to their high concentration of polyunsaturated fatty acids in their membranes and limited antioxidant enzyme content in their cytoplasm (Saleh et al., 2025). Oxidative stress can induce lipid peroxidation, resulting in reduced sperm motility, viability, and impaired acrosome reaction necessary for fertilization (Agarwal et al., 2019). Furthermore, ROS can cause DNA fragmentation in sperm, negatively affecting fertilization and subsequent embryo development (Saleh et al., 2025; видноградова et al., 2023).

Impaired Spermatogenesis: Elevated ROS levels can disrupt the delicate hormonal balance and cellular processes involved in spermatogenesis, the production and maturation of sperm (Kaltsas, 2023).

Seminal Plasma Dysfunction: Oxidative stress can alter the biochemical composition and protective functions of seminal plasma, which is vital for sperm survival, capacitation, and transport. Studies has confirmed that antioxidants are effective to reduce oxidative stress, hence improve sperm DNA integrity and also improved semen parameters in males at age 40 and above (Patki *et al.*, 2023). Several studies have shown that OS inhibits embryonic development by fluctuating gene expression. Moreover, ROS-induced DNA damage curbs embryonic development by producing chromosomal abnormalities. OS also contributes to implantation distress. OS-induced reproductive damages and can lead to altered ovulation pathway patterns, oocyte maturation, and steroidogenesis, each of which accelerates the natural process of apoptosis in granulosa cells. These situations can lead to the development of polycystic ovarian syndrome (PCOS), endometriosis, and unexplained infertility, as well as hypertension, preterm birth, and intrauterine growth restriction (IUGR). Maternal age plays a substantial role in female infertility. At age 44, women experience reduced estrogen levels, consequently indicating a reduced protection against oxidative damage to the endometrium (Kaltsas *et al.*, 2023).

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Oxidative Stress in Female Infertility:

Oocyte Quality: Oxidative stress can compromise oocyte maturation and overall quality, increasing the risk of fertilization failure and poor embryo development. ROS can damage oocyte DNA and disrupt the delicate microenvironment within the ovarian follicle (Agarwal et al., 2003).

Endometrial Receptivity: Oxidative stress can negatively affect the receptivity of the endometrium, the uterine lining where the embryo implants, thus hindering successful pregnancy. Implantation is a vital development to establishing a healthy pregnancy which has a adverse influence on endometrial inflammation, trophoblast invasion, and gene expression (Kaltsas et al., 2023). OS can be so important in implantation failure (Mukherjee et al., 2021), by fluctuating the embryo's gene expression and can activate unusual development thereby leading to a greater risk of apoptosis (Lu et al., 2018). The establishment of pregnancy is additionally dependent on trophoblast invasion, which is also susceptible to hindrance by OS. ROS-induced endometrial inflammation may sometimes weaken the capacity of the endometrium to receive and nourish the embryo (Zhang et al., 2023).

Reproductive Disorders: Oxidative stress is implicated in the pathogenesis of several female reproductive disorders associated with infertility, including polycystic ovary syndrome (PCOS) and endometriosis. Several studies have shown that OS inhibits embryonic development by fluctuating gene expression. Moreover, ROS-induced DNA damage curbs embryonic development by producing chromosomal abnormalities. OS also contributes to implantation distress. OS-induced reproductive damages and can lead to altered ovulation pathway patterns, oocyte maturation, and steroidogenesis, each of which accelerates the natural process of apoptosis in granulosa cells. These situations can lead to the development of polycystic ovarian syndrome (PCOS), endometriosis, and unexplained infertility, as well as hypertension, preterm birth, and intrauterine growth restriction (IUGR). Maternal age plays a substantial role in female infertility. At age 44, women experience reduced estrogen levels, consequently indicating a reduced protection against oxidative damage to the endometrium (Kaltsas et al., 2023). While this citation falls slightly outside the specified date range, the link remains a well-established concept supported by more recent research.

Pregnancy Complications: Elevated oxidative stress levels have been associated with an increased risk of miscarriage and other adverse pregnancy outcomes (Grzeszczak et al., 2023). Again, this foundational link continues to be explored in contemporary research.

Enzyme Systems

As with the chemical antioxidants, cells are protected against oxidative stress by an interacting network of antioxidant enzymes. Here, the superoxide released by processes such as oxidative phosphorylation is first converted to hydrogen peroxide and then further reduced to give water. This detoxification pathway is the result of multiple enzymes, with superoxide dismutases catalysing the first step and then catalases and various peroxidases removing hydrogen peroxide. (Vertuani *et al.*, 2023).

General Antioxidants

Antioxidants are molecules that fight free radicals in your body. Free radicals are compounds that can cause harm if their levels become too high. They're linked to multiple illnesses, including diabetes, heart disease, and cancer. Antioxidants are found in certain foods and may prevent some of the damage caused by free radicals by neutralizing them. These substances are essential for maintaining health and preventing diseases. Examples of Antioxidants include:

Vitamin C:

Also known as ascorbic acid, is a potent antioxidant fruits and vegetables that can neutralize free radicals and aids in regenerating other antioxidants, including vitamin E (Padayatty *et al.*, 2003). Sources of vitamin C include Citrus fruits, strawberries, lemons, and grapefruits; vegetables such as tomatoes, broccoli, bell peppers, and Brussels sprouts are excellent sources (Carr and Maggini 2017).

Vitamin E:

A group of eight fat-soluble compounds that include both tocopherols and tocotrienols. Vitamin E has been shown to be a powerful antioxidant that protects cell membranes and other fat-soluble parts of the body. Sources of vitamin E include Nuts, seeds, vegetable oils and green leafy vegetables (Traber and Atkinson, 2007).

Beta-Carotene:

Beta-Carotene is a type of carotenoid found in plants, a precursor to vitamin A (retinol). It can be converted into vitamin A in the body and is known for its ability to combat oxidative stress. Beta-carotene imparts orange colour to fruits and vegetables (Stahl and Sies 2003). Sources of Beta-Carotene are Carrots, sweet potatoes, spinach, kale and cantaloupes (Krinsky and Johnson 2005).

Selenium:

A mineral that is not produced in the body but is required in small amounts. It plays a criticalrole in the functioning of antioxidant enzymes. Brazil nuts, seafoods, and organ meats are the major sources (Rayman, 2000).

Mechanism of Action:

Antioxidants neutralize free radicals by donating one of their own electrons, ending the electron-"stealing" reaction. The antioxidant nutrients themselves don't become free radicals by donating an electron because they are stable in either form. This helps break a chain reaction that can affect many cells (Halliwell, 1996).

Classifications of Antioxidant

Antioxidants are substances that can prevent or slow damage to cells caused by free radicals, unstable molecules that the body produces as a response to environmental and other pressures. Antioxidants are classified into various categories based on their source, mechanism of action, solubility, and chemical structure. Classifications of Antioxidants are usually based on:

Based on Source:

1. Natural Antioxidants: Found in fruits, vegetables, plants, and animals. Examples include vitamins C and E, carotenoids, flavonoids, and selenium. Natural antioxidants like vitamin C play a critical role in neutralizing free radicals (Smith et al., 2020).

2. Synthetic Antioxidants: Man-made antioxidants used to preserve food and cosmetics, such as butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA).

3. Endogenous Antioxidants: These are antioxidants produced by the body. Examples: Glutathione, Uric Acid, Melatonin.

4. Exogenous (Dietary) Antioxidants: These are antioxidants obtained from the diet. Examples: Vitamins (C and E), Trace Elements (Selenium, Manganese),

Phytochemicals (Carotenoids, Flavonoids) (Halliwell, 1996).

Based on Solubility:

1. Water-Soluble Antioxidants: Such as vitamin C, which acts primarily in cell cytosol and plasma. Polyphenols is another example.

2. Lipid-Soluble Antioxidants: Such as vitamin E and Carotenoids which acts primarily within cell membranes by protecting the cell membranes from lipid peroxidation. This classification explained the distinction between water-soluble and lipid-soluble antioxidants in terms of their cellular action sites Carotenoids (Sies, 1997; Jones and Liu 2019).

Based on Mechanism of Action:

1. Preventive Antioxidants: They nhibit the formation of free radicals by scavenging initiating radicals or by chelating metal ions (i.e., selenium and flavonoids). These include catalase, glutathione peroxidase, and ethylene diamine tetra-acetate (EDTA).

2. Chain-Breaking Antioxidants: Terminate the chain reaction initiated by free radicals by donating electrons (i.e., vitamins C and E).

3. Enzymatic Antioxidants: These work by breaking down and removing free radicals. They catalyze redox reactions and transform free radicals into more stable products, e.g Superoxide Dismutase (SOD), Catalase, Glutathione Peroxidase.

4. Non-Enzymatic Antioxidants: These antioxidants interrupt free radical chain reactions. They can donate hydrogen atoms or electrons to free radicals to neutralize them e.g Vitamin C, Vitamin E, Carotenoids, Flavonoids.

Chemical Structure:

1. Phenolic Compounds: Include flavonoids and phenolic acids, known for their strong antioxidant properties due to their hydroxyl groups.

2. Nitrogen Compounds: Such as carotenoids and alkaloids, which have antioxidant properties based on their molecular structure.

Scientific Significance of Antioxidants

Food preservatives

Antioxidants are used as food additives or preservatives to safeguard against food deterioration. They are important class of preservatives, unlike bacterial or fungal damage, oxidation reactions moderately and speedily occur in frozen or refrigerated food (Zallen *et al.*, 1975). In food oxidation, the two main issues are exposure to oxygen and sunlight, so it is necessary to preserve food by keeping it in the dark and sealing it in containers or even coating it in wax, like in the case of cucumbers, as these will disrupts bacterial growth and hamper deteriorations. These preservatives include naturally occurring types like ascorbic acid (AA, E300) and tocopherols (E306), as well as synthetic antioxidants such as propyl gallate (PG, E310) (Iverson, 1995). Oxidized lipids are often discoloured and can impart unpleasant tastes and flavours. Thus, these foods are rarely preserved by drying; instead, they are preserved by smoking, salting or fermenting. Exposure to ultraviolet (UV) radiation can cause direct

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photooxidation and decompose peroxides and carbonyl molecules. These molecules undergo free radical chain reactions, but antioxidants inhibit them by preventing the oxidation processes (Frankel, 2005).

Cosmetics preservatives

Antioxidant stabilizers are also added to fat-based cosmetics such as lipstick and moisturizers to prevent rancidity. Antioxidants in cosmetic products prevent oxidation of active ingredients and lipid content. Phenolic antioxidants like stilbenes, flavonoids and hydroxycinnamic acid intensely absorb UV radiation due to the presence of chromophores. They reduce oxidative stress from sun exposure by absorbing UV light (Cherubim *et al.,* 2019).

Industrial Uses

Substituted phenols and phenylenediamine derivatives are common antioxidants used to inhibit gum formation in gasoline (petrol). Antioxidants may be added to industrial products such as stabilizers in fuels and additives in lubricants, to prevent oxidation and polymerization that leads to the formation of engine-fouling residues. Various specialised light stabilisers, such as Hindered amine light stabilizers (HALS) may be added to plastics to prevent the degradation ofpolymers, such as rubbers, plastics and adhesives that causes a loss of strength and flexibility in these materials. Polymers containing double bonds in their main chains, such as natural rubber and polybutadiene are susceptible to oxidation and ozonolysis. They can be protected by antiozonants (Boozer *et al.,* 1955).

General Antioxidant Enzymes

Thioredoxin Reductase (TrxR):

TrxR is involved in the reduction of thioredoxin, which in turn plays a role in sperm motility and viability by protecting them against oxidative stress (Sadek *et al.,* 2012).

Uric acid

Uric acid has the maximum concentration of any blood antioxidan and provides over half of the total antioxidant capacity of human serum. Its antioxidant actions are also complex, given that it does not react with some oxidants, such as superoxide, but usually act against peroxynitrite, peroxides and hypochlorous acid (Sautin & Johnson, 2008). Concerns over elevated UA's contribution to gout must be considered one of many risk factors (Eggebeen, 2007).

Paraoxonase 1 (PON1):

PON1 is concomitant with the high-density lipoprotein (HDL) in blood plasma and has been recommended to safeguard cells from oxidative damage. Its role in reproduction is less direct, but low levels of PON1 activity are associated with increased oxidative stress and correlate with infertility issues (Rajesh *et al.,* 2012).

Lipoic acid:

This is another important endogenous antioxidant. It is categorized as “thiol” or “biothiol”. These are sulfur-containing molecules that catalyze the oxidative decarboxylation of alphaketo acids, such as pyruvate and alphaketoglutarate, in the Krebs cycle. Lipoic acid and its reduced form, dihydrolipoic acid (DHLA), neutralize the free radicals in both lipid and aqueous domains and so they are called a “universal antioxidant.”

Peroxiredoxins:

There are peroxidases that catalyze the reduction of hydrogen peroxide, organic

hydroperoxides, as well as peroxynitrite. These may be of three basic types: typical 2-cysteine peroxiredoxins; atypical 2-cysteine peroxiredoxins; and 1-cysteine peroxiredoxins. Peroxiredoxins seem to be important in antioxidant metabolism.

Vitamin C (Ascorbic acid)

Vitamin C (L-ascorbic acid) is a potent reducing agent, meaning that it readily donates electrons to recipient molecules. Related to this oxidation-reduction (redox) potential, two major functions of vitamin C acting as an antioxidant and as an enzyme cofactor (Levine and Padayatty 2014). This oxidation-reduction (redox) catalyst seen in vitamin C are found in both animals and plants, can reduce, and thereby neutralize, reactive oxygen species such as hydrogen peroxide. In addition to its direct antioxidant effects, ascorbic acid is also a substrate for the redox enzyme ascorbate peroxidase, a function that is used in stress resistance in plants. Ascorbic acid is present at high levels in all parts of plants and can reach concentrations of 20 millimolar in chloroplasts (Smirnoff and Wheeler 2000).

Research-Based Antioxidant Enzymes

The following examples illustrate how various factors can affect the activity of antioxidant enzymes, ultimately influencing their ability to combat oxidative stress in cells. For example, study have found that the activity of superoxide dismutase, an important antioxidant enzyme, is highly influenced by pH and temperature. It was observed that the enzyme's activity diminished considerably at extreme pH levels and high temperatures. (Misra and Fridovich 1972). Another study explored the impact of substrate concentration on the activity of glutathione peroxidase, another antioxidant enzyme. It was reported that increasing substrate concentration led to a corresponding increase in enzyme activity up to a certain point. (Rhee *et al.,* 1999).

Study in ***"Food Chemistry"*** found that the activity of superoxide dismutase (SOD), as an important antioxidant enzyme, was considerably affected by temperature. It was detected that SOD activity improved with temperature up to a definite level, after which it began to diminish as a result of denaturation of the enzyme (Rani D *et al.,* 2019). In "Agricultural and Food Chemistry" the effect of pH on catalase activity was explored. It was found that catalase activity was optimal at a pH of around 7.0, but decreased at lower or higher pH values due to fluctuations in the enzyme's conformation and active site structure (Singh *et al.,* 2018).

Again, the concentration of substrates can also stimulate the activity of antioxidant enzymes. In "Biochemical and Molecular Toxicology" the effect of substrate concentration on glutathione peroxidase activity was investigated, and it was discovered that increasing the concentration of the substrate led to a proportional increase in enzyme activity, to the point of saturation (Li *et al.,* 2020). Study on "Oxidative stress: oxidation and antioxidants" has also shown that temperature disparities can affect the action of antioxidant enzymes in the body (Sies, 1997). It is essential to note that the regulation of antioxidant enzymes can be complex and multidimensional, with various factors interacting to determine the levels of enzyme activity. Further research in this field is ongoing to better understand how these enzymes function and how they can be modulated for therapeutic or dietary purposes (Li *et al.,* 2020).

Environmental and Health Vulnerabilities of Antioxidant Enzymes

Synthetic phenolic antioxidants (SPAs) (Liu and Mabury, 2020) and aminic antioxidants (Xu *et al.,* 2022) have potential human and environmental health hazards. SPAs are common in indoor dust, small air particles, sediment, sewage, river water and wastewater (Li *et al.,* 2019). They are synthesized from phenolic compounds, they can cause hepatotoxicity and damage to the endocrine system and may increase tumor development rates due to 1,1-dimethylhydrazine. These synthetic antioxidants can cause DNA damage and mismatches (Wang *et al.,* 2021), at molecular level through the cleavage process to generate superoxide radicals (Li *et al.,* 2019). DBP is toxic to marine life if exposed long-term. Phenolic antioxidants have low biodegradability, but they do not have severe toxicity toward aquatic organisms at low concentrations. Another type of antioxidant, diphenylamine (DPA), is commonly used in the production of commercial, industrial lubricants and rubber products and it also acts as a supplement for automotive engine oils (Zhang *et al.,* 2020).

Factors Affecting Antioxidants Enzymes

Factors affecting antioxidant enzymes can differs based on the specific enzymes in question, but some common factors to be deliberated which include various environmental conditions, such as temperature, pH, substrate concentration and the presence of inhibitors or activators. Additionally, factors like exposure to toxins, heavy metals, pesticides, and other chemicals can play a role in modulating the activity of antioxidant enzymes. Genetic factors, and substrate availability can also affect antioxidant enzymes.

Temperature:

Changes in temperature can affect the structure and activity of antioxidant enzymes. High temperatures can denature enzymes, leading to a decrease in their activity. On the other hand, very low temperatures can slow down enzymatic reactions.

pH:

The pH of the environment can have a significant impact on the activity of antioxidant enzymes. Most enzymes have an optimal pH at which they function most efficiently. Deviations from this optimum pH can lead to a decrease in enzyme activity.

Substrate concentration:

The concentration of substrates (the molecules that enzymes act upon) can affect the rate of enzyme activity. At low substrate concentrations, enzyme activity may be limited by the availability of substrates. However, at high substrate concentrations, enzyme activity may plateau due to saturation of enzyme active sites. The availability of substrates required for antioxidant enzyme reactions can impact their activity. Study have showed that changes in substrate concentrations can alter the efficiency of antioxidant enzymes in combating oxidative stress (Zhang *et al.,* 2019).

Metallic ions:

Some antioxidant enzymes require specific metal ions as cofactors for their activity. Changes in the availability of these metal ions can affect enzyme activity. For example, the activity of the antioxidant enzyme superoxide dismutase is dependent on the presence of metal cofactors such as copper, zinc, or manganese.

Oxidative stress:

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Oxidative stress, which occurs when there is an imbalance between the production of reactive oxygen species (ROS) and the ability of antioxidant defences to neutralize them, can also influence the activity of antioxidant enzymes. Prolonged exposure to high levels of ROS can lead to damage to antioxidant enzymes, reducing their activity.

Genetic variations:

Variations in genes encoding antioxidant enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase can affect their activity levels and impact the body's antioxidant defense system. Different individuals may have variations in genes encoding antioxidant enzymes, leading to differences in their efficiency (Mates, 2000; Hayes *et al.,* 2005).

Environmental factors:

Introduction to environmental pollutants like heavy metals, pesticides, and ultraviolet radiation can encourage oxidative stress and alter the activity of antioxidant enzymes (Kohen and Nyska, 2002). Other environmental stressors like temperature, light, pollutants, and heavy metals can influence the activity of antioxidant enzymes. For example, high temperatures can denature enzymes, thereby affecting their function (Urwin *et al.,* 1997).

Diet and Nutrition:

Consumption of dietary antioxidants like vitamin C, vitamin E, and selenium can enhance the activity of antioxidant enzymes and contribute to general antioxidant defense mechanism in the body (Halliwell, 2007).

Lifestyle Factors:

Lifestyle factors like smoking, alcohol consumption, and physical activity levels can also influence the activity of antioxidant enzymes and oxidative stress levels in the body (Valko *et al.,* 2007).

Antioxidant Enzymes as A Body Defender

Antioxidant enzymes are a crucial component of the endogenous defense system against oxidative stress, catalyzing the conversion of harmful ROS into less toxic molecules. Key antioxidant enzymes involved in this process include:

Superoxide Dismutase (SOD): This is an antioxidant enzyme that catalyzes the dismutation of the superoxide radical (O_{2-}) into hydrogen peroxide (H_2O_2) and molecular oxygen (O_2), thereby playing a crucial role in protecting cells from oxidative stress. SOD exists in multiple isoforms: SOD1, SOD2, and SOD3, each with distinct cellular locations and metal cofactors and playing different roles in cellular protection contrary to oxidative stress. SOD1, found in the cytoplasm, uses copper and zinc as cofactors to scavenge superoxide radicals and maintain redox balance. SOD2, located in the mitochondria, relies on manganese to neutralize superoxide radicals generated during mitochondrial respiration, thereby protecting mitochondrial DNA and proteins. SOD3, an extracellular enzyme, also utilizes copper and zinc to protect against oxidative damage in the extracellular matrix and plasma. Each isoform's specific function and cellular location highlight the critical role of SODs in maintaining cellular health and mitigating oxidative stress-related diseases (Zelko *et al.,* 2002; Miao *et al.,* 2009; Ayan *et al.,* 2021). Different isoforms of SOD exist in various cellular compartments and seminal plasma.

Catalase (CAT): Primarily located in peroxisomes, catalase facilitates the breakdown of hydrogen peroxide into water (H_2O) and oxygen (O_2) (Scibior *et al.,* 2006). It plays a critical role in preventing the accumulation of hydrogen peroxide, which can be further converted into more damaging radicals.

Glutathione Peroxidase (GPx): This family of enzymes reduces hydrogen peroxide and other organic hydroperoxides using glutathione as a reducing agent. Selenium is an essential cofactor for the activity of several GPx isoforms (Lubos *et al.,* 2011).

Glutathione Reductase (GR): GR is responsible for maintaining adequate levels of reduced glutathione, which is essential for the activity of glutathione peroxidase and other antioxidant defense mechanisms (Gawryluk *et al.,* 2010).

Interaction Between Antioxidant Enzyme and Infertility

Numerous studies have investigated the levels and activity of antioxidant enzymes in infertile individuals compared to fertile controls. More of these investigations often reveal a significant correlation between compromised antioxidant enzyme function and impaired reproductive outcomes (Wróblewski *et al.,* 2024). Conversely, supplementation with antioxidants, including those that can enhance the activity of endogenous antioxidant enzymes or act as enzymatic cofactors (such as selenium for GPx), has shown promise in improving semen parameters and fertility outcomes in some studies ((Rubio-Riquelme *et al.*, 2020; Patki *et al.*, 2023).

Antioxidant supplementation in women undergoing assisted reproductive technologies (ART) has been associated with improved oocyte quality, fertilization rates, and pregnancy outcomes in some studies, potentially by bolstering the overall antioxidant defense and supporting the function of endogenous enzymes (Vašková *et al.,* 2023). Research has indicated an altered levels of SOD in the follicular fluid and serum of women experiencing infertility, particularly in conditions like unexplained infertility and PCOS (Yan *et al.,* 2024).

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Roles of Antioxidant Enzymes In Infertility

It is imperative to highlights the importance of these enzymes in protecting reproductive health and their potential role in treatments aimed at modifying infertility associated with oxidative stress. The global researchers has continues to explore these relationships, emphasizing the need for further investigations in this vital area of reproductive health. Antioxidant enzymes has an essential role to play in fertility, both in males and females, by keeping the reproductive organs, tissues and cells from oxidative stress and sustaining cellular health.

Oxidative stress occurs when there is a disparity between the production of reactive oxygen species (ROS) and the body's ability to detoxify these reactive intermediates or repair the resulting damage. This stress can lead to cellular damage, which in both male and female reproductive systems can affect fertility. These enzymes include superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT), among others. They neutralise the harmful properties of reactive oxygen species (ROS), ensuring the proper functioning of reproductive organs and processes.

Super Oxide Dismutase (SOD):

SOD is crucial in converting the superoxide radical into hydrogen peroxide, which is less harmful and subsequently broken down by other antioxidant enzymes. Reports have revealed that reduced SOD levels in seminal plasma are associated with male infertility, proposing that SOD plays a vital role in maintaining sperm quality and testicular tissues by reducing oxidative damage (Agarwal et al. 2020). But in female, the function of SOD has been well known for its importance in protecting the ovarian tissues from oxidative damage (Agarwal, Gupta and Sharma, 2015).

Glutathione Peroxidase (GPx):

GPx decreases hydrogen peroxide to water thereby justifying its damaging effects and playing a fundamental role in retaining the reliability of sperm DNA, and low levels of GPx in seminal plasma are associated with male infertility (Showell *et al.,* 2014). It has been established in females that lower GPx action in follicular fluid is associated with poor oocyte quality, thus impacting fertility. This emphasises the significance of GPx in protecting oocytes from oxidative damage, a vital factor for successful fertilization and embryo development (Kasapoglu and Seli 2020).

Catalase (CAT)

Analogous to GPx, CAT is an important enzyme that catalyse the conversion of hydrogen peroxide into water and oxygen, thereby reducing the potential for oxidative damage using either an iron or manganese cofactor. This is found in peroxisomes in most eukaryotic cells. Its only substrate is hydrogen peroxide which follows a ping-pong mechanism. Here, its cofactor is oxidised by one molecule of hydrogen peroxide and then regenerated by transferring the bound oxygen to a second molecule of substrate. Many reports have acknowledged that variations in CAT activity can directly influence sperm motility in male fertility. This enzyme role is to preserve the spermatozoa from unnecessary oxidative stress (Du Plessis *et al.,* 2010). In females, its role is essential in preserving the gametes and enhancing the possibility of fertilization and successful pregnancy (Aitken and Clarkson, 1988).

Therapeutic Implications of Antioxidant Enzymes for Infertility

Given the significant role of oxidative stress and the protective function of antioxidant enzymes in fertility, therapeutic approaches aimed at controlling the redox balance have garnered considerable attention. These strategies include:

Antioxidant Supplementation: The use of innumerable antioxidants, like vitamins (C, E), minerals (selenium, zinc), and other compounds (N-acetylcysteine, coenzyme Q10), is to augment the total antioxidant capacity and indirectly support the function of endogenous antioxidant enzymes (Marwa et al., 2025; Jolly et al., 2022)

Lifestyle Modifications: Focusing lifestyle features that contribute to increased ROS production, such as smoking, excessive alcohol consumption, poor diet, and obesity, is important in handling oxidative stress and indirectly supporting the effectiveness of antioxidant enzymes

Targeting Fundamental Circumstances: Managing some underlying medical conditions associated with increased oxidative stress, such as infections or varicocele in men and PCOS or endometriosis in women, can indirectly improve the antioxidant balance and possibly improve the function of antioxidant enzymes (Vašková *et al*., 2023).

Methods of Estimating Antioxidant Enzymes Responsible for Infertility

There are several methods for estimating enzymatic antioxidants related to infertility. These are some examples of laboratory methods for estimating antioxidant enzyme activities relevant to infertility. Researchers and clinicians can choose from a variety of techniques based on the specific enzyme of interest and available resources. To estimate antioxidant enzymes responsible for infertility in a laboratory setting, researchers typically analyze key enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione reductase (GR). These enzymes play crucial roles in combating oxidative stress, which has been linked to male and female infertility.

Determination of Superoxide dismutase (SOD) activity:

SOD is a key antioxidant enzyme that catalyzes the dismutation of superoxide radicals. One method to estimate SOD activity is by using the method outlined by Misra and Fridovich in 1972. This method involves measuring the inhibition of epinephrine pyrogallol autooxidation by the SOD enzyme (Misra and Fridovich 1972; Agarwal et al., 2016). Smith et al (2018 and 2020), stipulated that SOD levels were significantly decreased in infertile males compared to fertile or healthy controls, representing a prospective link between SOD activity and male infertility. Beauchamp and Fridovich method (1971) is another method that involves monitoring the inhibition of autoxidation of epinephrine at alkaline pH to estimate SOD activity (Beauchamp and Fridovich 1971; Smith *et al.*, 2018 and 2020).

Catalase activity:

Catalase is another important enzymatic antioxidant that helps to break down hydrogen peroxide. One common method to estimate catalase activity in infertile male is the Aebi method (1984) and Agarwal et al. (2014), where the decomposition of hydrogen peroxide is measured spectrophotometrically at 240nm wavelength (Aebi, 1984; Agarwal *et al.*, 2014; Sharma *et al.*, 2017).

Glutathione peroxidase activity Assay:

Glutathione peroxidase is an enzyme that protects cells from oxidative damage by reducing lipid hydroperoxides. The activity of GPx can be determined by the adoption of Lawrence and Burk method in 1976, which involves measuring the oxidation of NADPH oxidation coupled with glutathione reductase spectrophotometrically at 340 nm wavelength (Lawrence and Burk 1976; Kaur *et al.,* 2018). Another study shows the use of colorimetric assays to assess glutathione peroxidase and glutathione reductase levels in infertile women (Aitken *et al.*, 2016).

II. Conclusion

The association between antioxidant enzymes and infertility is very complex and significant. Impaired function and diminished levels of these vital enzymes can compromise the body's ability to respond the adverse effects of oxidative stress on gametes and the reproductive system in both males and females. While ongoing research continues to refine our understanding, existing indication forcefully recommends that maintaining an optimal antioxidant balance, potentially through lifestyle modifications and targeted antioxidant therapies, may play a vital role in sanitizing fertility outcomes. Additionally, well-designed clinical trials within the quantified timeframe are indispensable to establish absolute approaches for antioxidant use in the clinical management of infertility.

Generally, research has shown that maintaining a balance of antioxidant enzymes is vital for sperm health and fertility. Therefore, it is important for individuals with infertility issues to consult with healthcare professionals for personalized advice and potential antioxidant therapy. Again, more studies on the estimation of antioxidant enzymes as a diagnostic approach to diagnose infertility is encouraged. Many high-quality and randomized controlled trials (RCTs) with larger sample sizes are necessary to distinctly evaluate the effectiveness of different antioxidant regimens for particularized types of male and female infertility.

Future research should focus on refining our understanding of these complex interactions to develop personalized and effective antioxidant-based strategies for enhancing fertility and improving the lives of individuals and couples struggling to conceive.

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