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Apoptosis, inflammation, and oxidative stress in infertility: A mini review

Oluwafemi Adeleke Ojo [a,1,*], Pearl Ifunanya Nwafor-Ezeh [a], Damilare Emmanuel Rotimi [b], Matthew Iyobhebhe [b], Akingbolabo Daniel Ogunlakin [a], Adebola Busola Ojo [c]

[a] Phytomedicine, Molecular Toxicology, and Computational Biochemistry Research Laboratory (PMTCB-RL), Department of Biochemistry, Bowen University, Iwo, Nigeria
[b] Department of Biochemistry, Landmark University, Omu-Aran, Nigeria
[c] Department of Biochemistry, Ekiti State University, Ado-Ekiti, Nigeria

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ABSTRACT

Infertility has been a major issue in our society for many years, and millions of couples all over the world are still experiencing it. There are several reasons for and causes of infertility in both men and women. Recent studies have shown that apoptosis, inflammation, and oxidative stress contribute immensely to infertility. The data regarding this report were obtained through a thorough review of scientific articles published in various databases, including Elsevier, Web of Science, PubMed, Scopus, and Google Scholar. Furthermore, PhD and MSc theses were also reviewed when compiling the data. Apoptosis, also known as "programmed cell death," is a natural and harmless process that occurs in human beings. Although it can become harmful if altered, Inflammation, on the other hand, is the body's reaction to detrimental stimuli caused by toxic substances or compounds, while oxidative stress is a phenomenon that results in an imbalance between the generation and aggregation of reactive oxygen species (ROS) in the cells against antioxidants. These three factors interchangeably bring about several reproductive disorders in the body, resulting in infertility. This review aims at discussing how apoptosis, inflammation, and oxidative stress play a role in human infertility.
Availability of data and material: The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

1. Introduction

Infertility is a medical condition that means you cannot have a baby after 12 months of frequent, unprotected sexual activity [1]. This disorder affects both the male and female reproductive systems. It causes physical, mental, and emotional stress for both the individual and the couple [2,3]. The rate of infertility globally suggests that about 48 million couples and 186 million people are affected by it [1]. Infertility can be categorized into primary and secondary infertility. The term "primary infertility" is used for a person who has never experienced pregnancy, while "secondary infertility" is used for someone who has previously experienced a successful pregnancy. In men, infertility is mostly the result of sperm ejaculation, oligozoospermia (low sperm count), weak sperm motility, and morphological differences in the sperm; in women, it could be the result of disorders or abnormalities in the ovaries, the uterus, and the fallopian tubes, hormonal imbalance,

and endocrine factors [1]. Infertility has also been associated with factors such as medical, physical, emotional, and environmental factors [3].

Apoptosis, also known as "programmed cell death," is a process that takes place in living organisms as well as humans and involves events leading to morphological changes and the death of damaged cells [4]. Apoptosis can be activated by a minor injury to the cell by several factors that could be inside or outside the cell and that is disposed of in a controlled manner. The mechanism of apoptosis is usually characterized by cell shrinkage, nuclear DNA fragmentation, chromatin condensation, dynamic membrane blebbing, and loss of adhesion to extracellular matrices [5]. The effect on apoptosis in female infertility begins right from the ovaries, which in turn affects the female ovarian cycle [6]. In the ovary, early apoptosis begins in the nucleus of the granulosa cells, avoiding the mitochondria until the next stage of apoptosis. In pathological settings, uncontrolled and excessive apoptosis in the male germ

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* Correspondence to: Phytomedicine, Molecular Toxicology, and Computational Biochemistry Research Laboratory (PMTCB-RL), Department of Biochemistry, Bowen University, Iwo 232101, Nigeria.
E-mail address: oluwafemiadeleke08@gmail.com (O.A. Ojo).
[1] +2347037824647.

cell can lead to alterations in sperm quality, which can lead to infertility. [7].

Inflammation is the body's response to harmful stimuli like toxic substances or compounds, pathogens, irritation, or cells that have been damaged [8]. Inflammation is a complicated defense mechanism that happens in response to harmful stimuli. It can cause abnormalities in the body's structure, which can lead to infertility and pelvic adhesions [9]. According to some research, inflammation is associated with reproductive tract disorders, which in turn affect fertility in both men and women. Oxidative stress is a condition that involves the imbalance between pro-oxidants such as reactive oxygen species (ROS) and reactive nitrogen species (RNS) and antioxidants [10]. These pathological changes could lead to the development of the following: Parkinson's disease, aging, cancer, heart failure, Alzheimer's disease, depression, and atherosclerosis [11]; In men, this could lead to damage to spermatozoa, defects in the sperm, sperm DNA fragmentation, and possible cases of varicocele and testicular torsion, while in females, it could lead to polycystic ovary syndrome (PCOS), premature ovarian failure, and endometriosis [10,11]. Apoptosis, inflammation, and oxidative stress are important factors in the pathophysiology of infertility in both males and females.

2. Methods

Using the keywords apoptosis, inflammation, oxidative stress, male infertility, female infertility, sperm, and ovary, a search was done in Google Scholar, Pubmed/Medline, and Scopus from the beginning of the databases to December 2022. The references of all papers were checked for cross-references that had not been found in the database search.

3. Infertility

After a period of 12 months of unprotected sexual activity, infertility is defined as the inability to carry a pregnancy to term. It is estimated that around 7% of couples throughout the globe are unable to have a child, with men being responsible for 50% of these cases [12]. The etiology of male infertility is complicated and involves several variables, one of which is oxidative stress (OS). The presence of reactive oxygen species (ROS) has been shown to have a significant correlation with male infertility [13]. Free radicals such as superoxide anions (O2), hydrogen peroxide (H2O2), peroxyl (ROO), and hydroxyl (OH) are examples of extremely reactive free radicals that are included in ROS [14]. Capacitation of sperm, hyperactivation of sperm, acrosomal response, and fertilization of ovules by sperm all need low amounts of reactive oxygen species (ROS). However, OS is caused when there is an imbalance between the quantities of ROS and antioxidants in the seminal plasma. Damage to sperm caused by reactive oxygen species (ROS) is the primary reason for male infertility in 30–80% of cases, and these circumstances eventually induce DNA damage in the nucleus and mitochondria of cells [15]. Sperm cells are very vulnerable to the effects of oxidative damage. On the other hand, these cells contain cytoplasmic membranes that are high in unsaturated fatty acids; as a result, they are susceptible to lipid peroxidation when exposed to ROS because of the presence of these membranes [13]. In addition, since these cells suffer from a lack of critical cytoplasmic enzymes, they are unable to repair the damage that has been caused by oxidative stress. Moreover. Finally, sperm lose their ability to move and die as a result of the depletion of adenosine triphosphate (ATP), which is brought on by lipid peroxidation and is then followed by axonemal damage [16]. OS has an indirect effect on the axis of the hypothalamus and has the potential to impair the production of sex hormones. ROS lowers the levels of male sex hormones and restores their equilibrium, but it also has the potential to wreak havoc on the reproductive system [17].

Infertility in women can be caused by an increase in the level of ovarian steroidogenesis (OS) in the body, which can be caused by a wide variety of factors, including genetic, epigenetic, and lifestyle-related

factors like excessive alcohol consumption, smoking, radiation, and obesity, as well as infections and varicoceles [18]. As a result, the function of the antioxidant system is very necessary to combat excessive ROS production. Plasma or natural sperm cells have a high concentration of antioxidant enzymes and compounds. Some examples of these are superoxide dismutase (SOD), glutathione (GSH), and catalase (CAT) [19]. The genes NRF2, SOD, CAT, glutathione S-transferase (GST), and glutathione peroxidase (GPx) are responsible for encoding the majority of these enzymes. In males, infertility caused by OS is caused by genetic abnormalities in these genes, which, in turn, induce infertility [20]. As a consequence of these injuries, the rates of fertilization and implantation are decreased, fetal development is disrupted, and the probability of abortion is raised. Because redox homeostasis is maintained by a balance between the levels of antioxidants and ROS, the use of oral antioxidants in conjunction with herbal medicine may be beneficial in the treatment of infertility in males. These antioxidants get rid of any additional ROS and keep the redox equilibrium in check [21]. To overcome infertility, it is important to focus more attention on the processes that cause harm to sperm as well as the treatment approaches related to these mechanisms. Recent months have seen the publication of a few research reviews that describe the impact that OS has on the male reproductive system. For example, Bui et al. found that high levels of ROS were responsible for genomic and mitochondrial DNA damage, as well as a reduction in telomere length, Y chromosomal microdeletions, and epigenetic shifts [15]. Additionally, Agarwal et al. explored infection- and inflammation-induced OS as well as male infertility in their study [22]. The mechanisms of ROS-mediated alteration of male hormonal profiles were elucidated by Darbandi et al. in a different publication [17]. However, in this study, we used a more all-encompassing approach and explored the many effects of OS on male infertility, including its pathophysiology and genetic components, with a primary focus on the therapeutic use of antioxidants.

3.1. Toxicity effects of xenobiotics on infertility

Xenobiotics have the potential to build up in the body, which may have detrimental effects on a variety of organs and tissues [23]. Mammalian testicles are responsible for the production of spermatozoa as well as the discharge of testosterone into the bloodstream. Hematotesticular barriers are among the most densely packed in any of the mammalian species [24]. Several different heavy metals cause organ and system damage because of their acute and chronic toxicities. Intestinal and urinary tract dysfunction, neurological and endocrine system diseases [25], immune system dysfunction, birth deformities, and cancer are some of the health problems that can be caused by exposure to radiation. They are caused by the toxicity of heavy metals [26]. The cumulative effects of exposure to two or more metals may be harmful to the body [26]. Lead pollution is a consequence of industrialization. Children living in areas of Idaho that are close to lead plants have blood lead levels of 25 mg/dl and severe anemia. Therefore, lead poisoning over an extended period may interfere with reproduction [27].

According to the findings of Wang et al. [28], lead is responsible for the death of and toxicity to spermatogenic cells in the seminal tubules of the testicles. Both Mariola et al. [29] and Patrick [30] hold the view that an excessive amount of reactive oxygen species causes lead to poison the testicles. They came to this conclusion independently. During the process of testicular cell death, levels of reactive oxygen species and caspase-3 grow [31].

Products containing cadmium are quite common in industrialized countries, which makes the risks associated with them much greater. In high enough concentrations, cadmium may cause osteomalacia, hepatotoxicity, renal toxicity, neurotoxicity, and infertility. It can also cause cancer [32]. According to Zhu Q [33], when male animals, including humans, consume cadmium, it is claimed to cause damage to the testicles. This includes both humans and other male animals (2020). It causes significant structural damage to the seminal tubules of Sertoli cells as

well as the hematotesticular barrier, which leads to the loss of sperm from the testicles as a final consequence. It prevents the production of Leydig cells, prevents these cells from performing their normal functions, and causes tumors to grow in these cells. In addition to this, it causes damage to the vascular system of the testicles.

Titanium dioxide nanoparticles have a detrimental effect on the morphological parameters of rat testicles, which affects important aspects of this structure, such as the proliferative activity of cells and their capacity to specialize into various parts of the male reproductive system. This study was conducted on rats [34].

According to a study that was carried out by Loebenstein et al. [35] exposure to xenobiotics is associated with abnormalities of the reproductive tract like cryptorchidism and hypospadias, as well as testicular cancer and hypo-fertility/infertility in men, which is known as testicular dysgenesis syndrome. Although its precise mechanism is not yet completely known, epigenetic regulation is assumed to be involved in testicular dysgenesis syndrome. This is even though there is no concrete evidence to support this hypothesis. This is related to the fact that male infertility in adulthood may be caused by toxicant exposure that occurred during the development of the fetus [36]. According to the findings of a study that was carried out by M.S. El-Neweshy [37], the manifestation of these changes was shown to be connected with a decline in testosterone levels. Heavy metal salts, as stated by Pandya C. et al. [38], have an effect on the spermatogenic and steroidogenic activities of the testicles, reduce male fertility and sperm quality, and promote degeneration of the testicles, which results in infertility. These negative effects of heavy metal salts on the testicles can be reversed by avoiding exposure to heavy metals. Intoxication with heavy metal salts is said to result in histological lesions of the testicles, interstitial edema, degeneration, and the development of intracellular giant cells, as stated by Manal M. Sayeda [39].

Compounds that are not naturally occurring may have harmful effects on the ovary, which can result in temporary or even permanent infertility. Because of the ovary's crucial function in the process of female reproduction, the presence of these substances is a cause for significant worry. The effect that temporary infertility has during a woman's prime reproductive years is a source of concern. It is estimated that 11% of women living in the United States have had problems with their fertility [40]. On the other hand, permanent infertility, often known as menopause in females, is a reason for concern because of the negative health implications that are known to be connected with ovarian failure [41,42].

Oocytes, which are immature germ cells, are present in a limited number in the primordial follicles of female animals at the time of their birth. The primordial follicle consists of one oocyte that is encircled by a single layer of pregranulosa cells that are shaped like squamous cells. Because the oocyte is stopped in the prophase of the first meiotic division when germ cells are being formed in the fetal ovary, the amount of germ cells available throughout a person's lifespan is restricted. Primordial follicles transform primary follicles when they become activated, and then continue their development into secondary and antral follicles [42]; If an environmental factor damages all populations of follicles, this results in both disrupted cyclicity (temporary infertility) and early ovarian failure (permanent infertility). The antral preovulatory follicle is the most mature developmental stage. It can become ovulated and is the site of many environmental factors. The mechanisms of selective targeting may change based on the kind of follicle that is being targeted. Because of their potential to disrupt cell cycle control, cell signaling pathways, steroidogenesis, and genomic DNA, xenobiotics have the potential to cause harm to larger follicles. In addition, the destruction of primordial follicles might potentially come from a disturbance of the delicate balance that exists between the survival and activation of follicular cells [43].

3.2. Apoptosis

Apoptosis, also known as "programmed cell death," is a process that takes place in living organisms as well as humans and involves events leading to morphological changes and the death of damaged cells [4]. For example, apoptosis occurs in fetal development during the separation of the webbed fingers and toes of a fetus (Fig. 1). The cells between the fingers undergo apoptosis and disintegrate, causing the fingers and toes to properly separate. The mechanism of apoptosis is usually characterized by cell shrinkage, nuclear DNA fragmentation, chromatin condensation, dynamic membrane blebbing, and loss of adhesion to extracellular matrices [5]. Apoptosis activates cell death with high specificity and efficiency, resulting in the proper development and protection of organisms from developmental abnormalities and diseases [44]. However, excess apoptosis could lead to neurodegenerative diseases or cases of infertility, whereas insufficient apoptosis could cause uncontrolled proliferation of the cells, which could lead to cancer and autoimmune diseases. The biochemical alterations in apoptosis include the externalization of phosphatidylserine and the activation of cysteine aspartyl protease, also known as caspases, which lead to cell death [5]. The cascade of events that leads to apoptosis does not initiate inflammatory responses and is ignored by the tissues around it [44]. The process of apoptosis is regulated by several stimuli. Although not all cells die in response to the same stimuli [45], The stimuli could be drugs, toxins, stressors, heat, radiation, or reactive oxygen species (ROS). Two mechanisms lead to the initiation of apoptosis: the extrinsic pathway and the intrinsic pathway. These pathways are closely related, as some molecules from one pathway affect the other [46].

3.2.1. Apoptotic pathways

3.2.1.1. The extrinsic apoptotic pathway. The death receptor pathways, which are part of the extrinsic apoptotic pathways (Fig. 2), are made up of transmembrane death receptors that depend on the interaction between the ligand and the receptor for cell death to happen [46]. Several receptors are part of the tumor necrosis factor (TNF) receptor genes involved in the extrinsic apoptotic pathways; however, FasL/Fas, TNF-α/TNF-1, and TRAIL receptors are the most studied [48]. When the ligands FasL and TRAIL bind to their respective receptors, it triggers their receptors to aggregate on the target cell, causing the recruitment of the adaptor proteins called Fas-associated death domain protein (FADD) on the cytoplasmic part of the receptors [48]. The FADD protein dimerizes with pro-caspase-8, leading to the formation of the Death-Inducing Signaling Complex (DISC), which activates pro-caspase-8, and this could either initiate apoptosis directly or activate the intrinsic apoptotic pathway to promote DNA fragmentation and cell death depending on the cell type [46].

3.2.1.2. The intrinsic apoptotic pathway. The mitochondria control the activities inside the cell that are part of the intrinsic apoptosis pathway (Fig. 2). This pathway involves a cascade of events that initiates apoptosis. The proteins that are mainly involved in the control of the intrinsic pathway are the Bcl-2 family proteins, which have both pro-apoptotic and anti-apoptotic proteins [46]. The constituents of the pro-apoptotic Bcl-2 protein family are Bax, Bak, Bok, Bim, Bik, Bad, Noxa, and Puma, and the main anti-apoptotic members of the Bcl-2 protein family are Bcl-2 and Bcl-XL; others include A1, Bcl-w, and Mcl1 [48]. These anti-apoptotic members hinder apoptosis by stopping the release of cytochrome C from the mitochondria. When cytochrome is released from the mitochondria, caspase-9 is activated, and then it activates caspase-3 and caspase-7, which are responsible for the cell death process. An imbalance in the proportion of the pro-apoptotic and anti-apoptotic members can trigger different reactions, which could either lead to the inhibition of apoptosis or excessive apoptosis [48]. The pro-apoptotic members, Bax and Bak, are activated by members of their
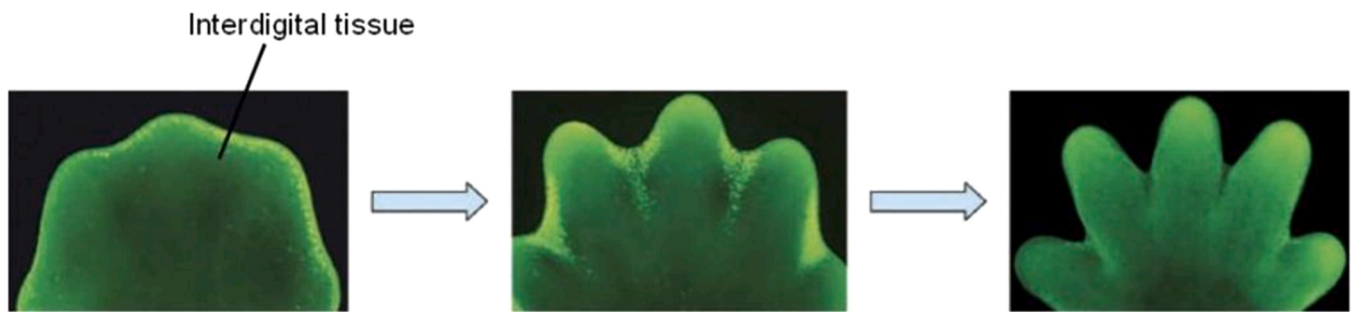
Fig. 1. Showing the process of apoptosis in between the developing fingers in a foetus. Modified from [47].
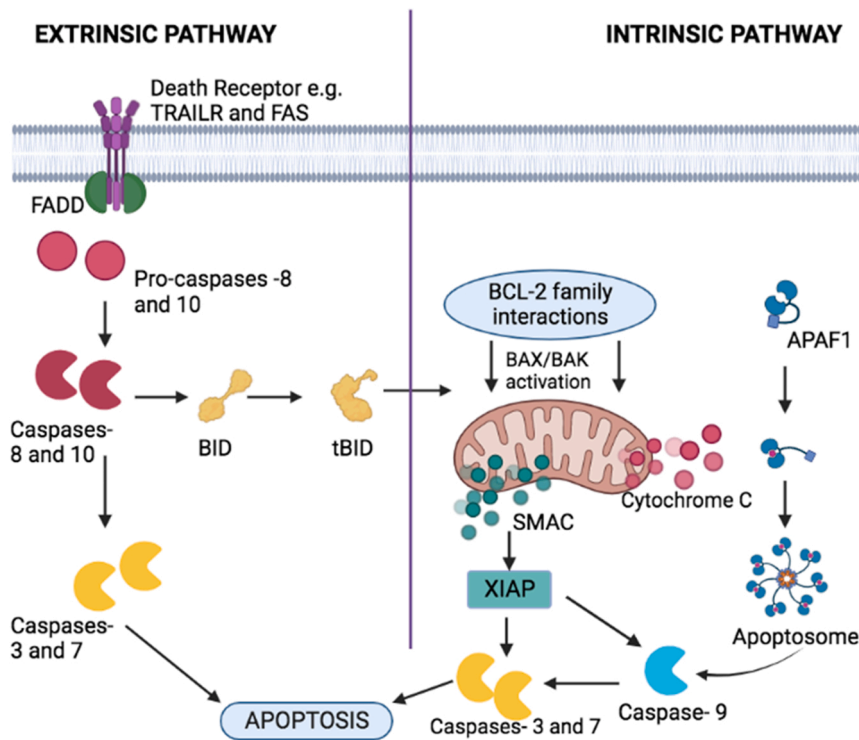

Fig. 2. Illustration of the extrinsic and intrinsic Pathways of apoptosis as modified from [49].

kind, such as Bid, which promotes the proteolytic activity that eventually leads to apoptosis, while other pro-apoptotic members such as Noxa and Puma, via the TP53 mediator, increase their response to chromosomal abnormalities. The absence of TP53 will not lead to apoptosis, which could cause several abnormalities in the male and female germ cells as well as some cancer diseases [49].

3.3. Apoptosis in the ovaries and female infertility

The effect of apoptosis in female infertility begins right in the ovaries, which in turn affects the female ovarian cycle. Early apoptosis in the ovary begins in the nucleus of the granulosa cells. Until the next phase of apoptosis [50], the mitochondria are not involved. Hormones like follicle-stimulating hormone (FSH), luteinizing hormone (LH), estrogen, progesterone, prolactin, laminin, leptin, glucocorticoids, and other growth factors like bone morphogenetic proteins (BMP), epidermal growth factors (EGF), and fibroblast growth factor (FGH) has anti-apoptotic factors that stop cells from dying at a certain time during folliculogenesis. Most of the time, apoptosis is stopped during the follicular phase [50] of the ovarian cycle. The follicular phase is the first phase in the ovarian cycle. It involves the growth of granulosa cells that

surround the follicles that contain the developing ovum. The granulosa cells continuously proliferate, causing the size of the follicle to increase as a result of the continuous secretion of follicle-stimulating hormone (FSH). As this process goes on, a sheath known as the capillary follicle begins to form around the growing follicle. The theca follicle consists of two layers: the theca interna and theca externa. The theca interna is responsible for the secretion of estrogen. The theca externa consists of several vesicular follicles, one of which develops into a mature follicle known as the dominant follicle or the Graffian follicle, which later, in response to the secretion of the luteinizing hormone, ruptures and expels the ovum. The remaining vesicular follicles degenerate through the process of apoptosis [51]. The hormones produced by the theca and granulosa cells give off an anti-apoptotic effect at a particular point during the development of the follicles. Once the Graffian follicle has been selected, cholesterol gets converted to pregnenolone by cytochrome P450 in the mitochondria of the theca cells. The newly formed pregnenolone is released from the mitochondria and is converted to progesterone, which undergoes a series of reactions to form testosterone. The testosterone formed is deposited in the granulosa cells from the theca cells, where estrogen is produced. Estrogen prevents granulosa cell apoptosis by the actions of the anti-apoptotic signaling pathways

[50]. If apoptosis does not occur or oxidative stress alters the apoptosis process (Fig. 3), there will be a continuous proliferation of the granulosa cells and vesicular follicles, leading to the development of several ovarian cystic disorders such as follicular cysts, corpus luteum cysts, polycystic syndrome, ovarian aging, or ovarian cancer, which are all associated with female infertility [52].

3.4. Apoptosis in the sperm and male infertility

The process of apoptosis is important in the male germ cell because it keeps the ratio of germ cells to Sertoli cells stable and gets rid of damaged or abnormal germ cells as they develop [7]. Uncontrolled and too much apoptosis in the male germ cell could change the quality of the sperm, which could make it impossible to get pregnant (Fig. 4). Apoptosis usually occurs in the spermatocytes and not infrequently in the spermatogonia and spermatids. The research carried out by Martinic and colleagues shows that in infertile males, uncontrolled apoptosis occurs in the germ cells while the Sertoli cells do not go through apoptosis. Usually, Sertoli cells show FasL, which stimulates apoptosis in germ cells that are Fas-positive and exhibits paracrine interactivity between Sertoli cells and the male germ cell. Also, apoptosis increases as one gets older, leading to a reduction of the germ cells; it could also be associated with oxidative stress.

4. Inflammation

Inflammation is the body's response to harmful stimuli like toxic substances or compounds, pathogens, irritation, or cells that have been damaged [8]. Inflammation is a complex defense mechanism that happens in response to harmful stimuli. It can cause abnormalities in the body's structure, which could be linked to infertility and pelvic adhesions [9]. Some research shows that inflammation is linked to problems with the reproductive tract, which in turn affect both men's and women's ability to have children. Some physiological processes, like ovulation, implantation, and pregnancy in women, and abnormal sperm production, function, and ejaculation [9,55], are largely caused by inflammation. Inflammation mediators usually come from damaged

tissue cells, the platelets, the leukocytes, the blood plasma, and the endothelial cells that line the blood vessels [56]. Infectious agent's Infectious agents like bacteria, viruses, and protozoa can cause inflammatory effects on the reproductive tracts. Bacteria such as Chlamydia trachomatis, Neisseria gonorrhea, Traponema pallidum, Mycoplasma, and Ureaplasma play a role in inflammation. In comparison to less developed countries, Chlamydia trachomatis infection is the most common cause of infertility as a result of inflammation in developed countries [9].

4.1. Inflammation and male infertility

4.1.1. Disorders caused by inflammation to infertility

4.1.1.1. Varicocele. Varicocele a condition that is characterized by an unusual enlargement of the vein in the scrotum that happens when the blood in the veins accumulates instead of flowing to all parts of the scrotum (Fig. 5) [57]. This condition is usually seen in cases of abnormally low sperm count and morphology as well as weak sperm motility. This is an endogenous cause of inflammation [58]. The restriction of blood flow in the testes causes an increase in the amounts of inflammatory cytokines and NO (nitric oxide) [58]. The functionality of the sperm cells in the testes is preserved by reasonable amounts of cytokines. Chemical mediators such as interleukin-1 (IL-1) also influence the function of the Leydig cells and Sertoli cells in the testes, while IL-37 and IL-18 are increased in the prostatic fluid of a patient diagnosed with varicocele, and this is also harmful to the function of the sperm cells in the testes. High amounts of endothelial NO synthase are used to improve the flow of blood into the tissues of the testicles. This makes up for the lack of oxygen in the accumulated blood pool in the veins, but if the required amount of NO is exceeded in this situation, it can become dangerous and react with the free radicals of superoxide, which could cause infertility [58].

4.1.1.2. Leukocytospermia. Leukocytospermia is also an endogenous cause of inflammation. Leukocytospermia, also known as pyospermia,
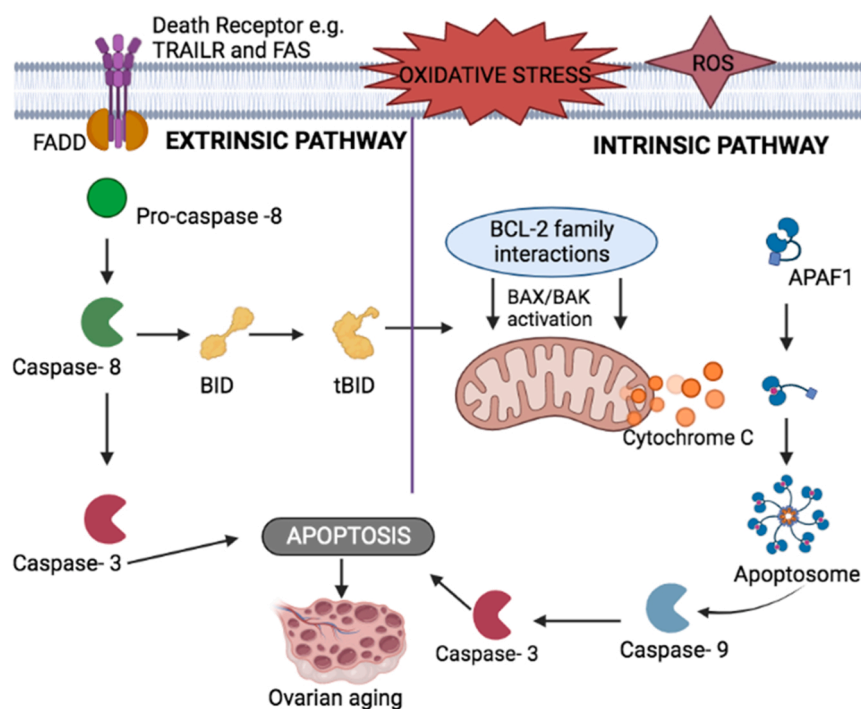

Fig. 3. The altered apoptotic pathway in the female ovarian cycle as a result of oxidative stress. Modified from [53].
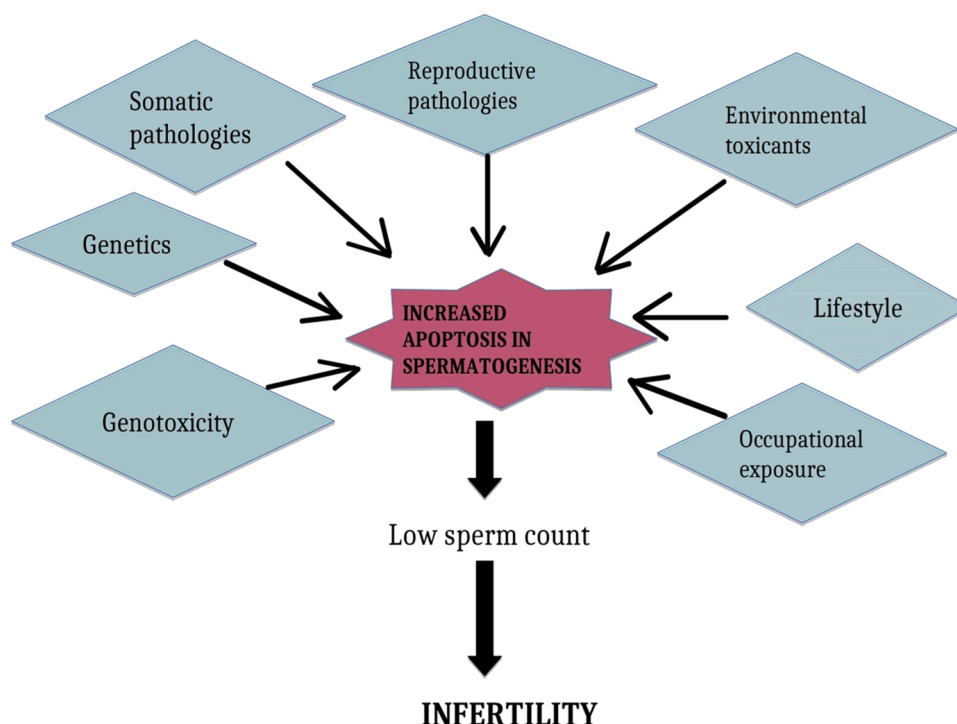
Fig. 4. Factors that trigger an increase in male germ cell apoptosis. Modified from [54].
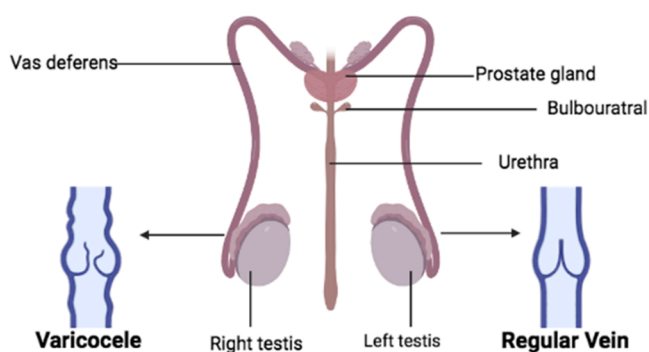

Fig. 5. Showing the difference between inflamed veins and normal veins in the testes as modified from [59].

can be defined as a condition in which there are over 1 million leukocytes found in 1 mL of sperm ejaculate and which occurs as a result of an infection in the urogenital system [60]. Leukocytospermia is a serious condition that can greatly affect the sperm's health and its genetic materials. In leukocytospermia, leukocytes generate high amounts of reactive oxygen species (ROS) that fight infections (Fig. 6). Its infectious agents increase the G6PDH process, which results in the production of reasonable amounts of NADPH [58]. NADPH oxidase from NADPH utilizes an electron to convert oxygen into toxic cells known as superoxide anion, which will give rise to a large amount of oxidative stress (OS) that will cause the chemotactic cytokines such as CXCL5, CXCL8, IL6, and IL8 to be activated. In pyospermia, the excess white blood cells begin to clump, resulting in a weakness in the motility of the sperm and making the process of impregnating a woman difficult and nearly impossible [60].

4.1.1.3. Urethritis. Urethritis is the inflammation of the urethra (Fig. 7). This inflammatory condition is usually linked with sexually transmitted infections, which are generally caused by infectious agents such as

Chlamydia trachomatis, Neisseria gonorrhea, Mycoplasma genitalium, Trichomonas vaginalis, adenoviruses, and herpes simplex virus (62; 57). During the ejaculation of sperm cells across the urethra, the sperm cells usually get infected, and this infection may lead to infertility in men [57]. Also, the cicatrical tissue along the urethra limits the amount and quality of sperm cells to be deposited in the female reproductive parts.

4.2. Inflammation and female infertility

Inflammation in the female reproductive tract can lead to several reproductive disorders and physiological conditions that could all be associated with infertility (Fig. 8).

4.2.1. Disorders caused by inflammation in relation to female infertility

4.2.1.1. Ovulatory abnormalities. Premature ovarian failure and anovulation are a few of the ovulatory abnormalities that are related to female infertility because of their connection to inflammation [9]. Premature ovarian failure usually affects women who are 40 years of age and older. This causes a problem with the fertility rate of such women. Several other factors that are linked to premature ovarian failure are genetic abnormalities and chromosomal diseases, radiation, toxins, and ovarian surgeries. There are several factors responsible for the inflammation in the ovaries, and they include cytokines, leukotrienes, histamines, and prostaglandins. These inflammation mediators affect the function and quality of the ovaries [9].

4.2.1.2. Endometriosis. Endometriosis is a common condition that is associated with infertility and is strongly linked to inflammation [9,63]. About 50% of infertile women suffer from endometriosis. It has been observed that the cytokines TNF-α, IL-1, IL-6, and IL-8 are all enhanced in women diagnosed with endometriosis. For instance, TNF-α takes part in the inflammatory process as its amount rises in the fluid in the peritoneal cavity. Also, pelvic inflammation occurs due to damage and adhesion as well as anatomical abnormalities in the female reproductive tract. Endometriosis creates an obstruction linked to endometriotic
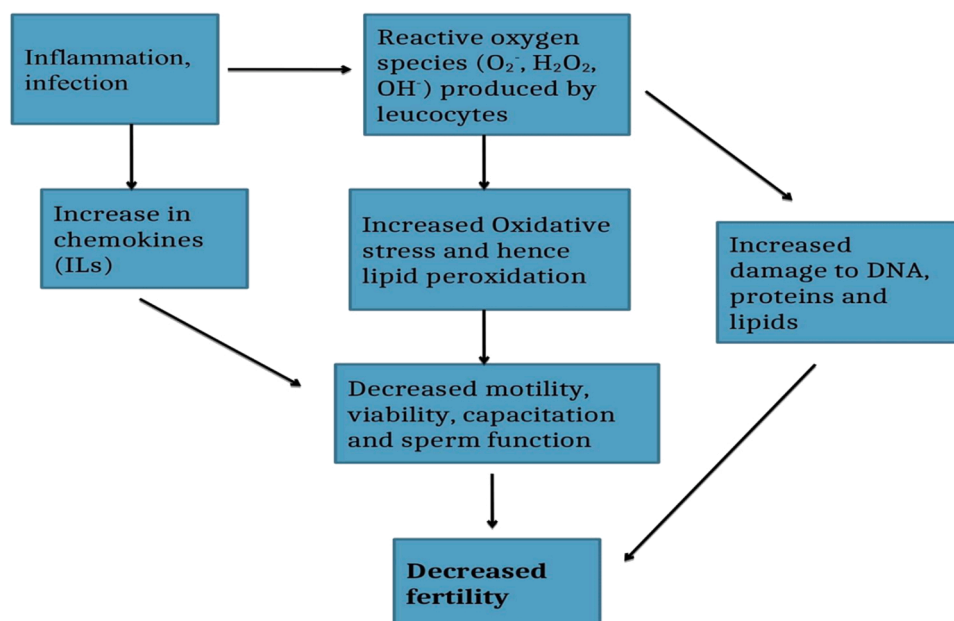
Fig. 6. Illustrating the role of Leukocytospermia in male infertility as modified from [61].
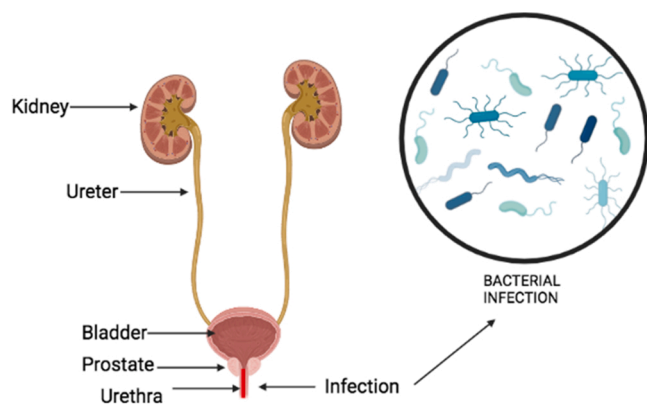

Fig. 7. Illustrating the infection and inflammation of the urethra as modified from [62].

lesions that could lead to the inability of the embryo to be implanted and miscarriage.

4.2.1.3. Polycystic ovary syndrome (PCOS). Polycystic ovary syndrome is a common endocrine disease that is linked to infertility as a result of anovulation [9]. During ovulation, deregulated inflammation could lead to PCOS. Some research has shown that the visceral adipose tissue in the uterine cavity contributes to inflammation in PCOS. Inflammation triggers the generation of larger amounts of androgen and hyper-androgenism, which can be linked to the low-chronic inflammation state. There are pro-inflammatory genotypes that encode cytokines such as IL-6 and TNF receptors that are also associated with PCOS and play a major role in inflammation.

5. Oxidative stress

Oxidative stress is the condition involving the imbalance between pro-oxidants such as reactive oxygen species (ROS) and antioxidants [10]. Oxidative stress occurs when a given cell, tissue, or fluid produces reactive oxygen species (ROS) that exceed the defensive capacity of the antioxidant system [11]. Usually, pro-oxidants and anti-oxidant mechanisms normally occur in a balanced state where biological oxidation reactions can cautiously take place, but if this balance is altered as a result of excess generation of ROS or a lack of antioxidant defense, it would lead to the oxidation of substrates in an uncontrolled manner and cause changes pathologically [11]; These pathological changes could lead to the development of the following: Parkinson's disease, aging, cancer, heart failure, Alzheimer's disease, depression, atherosclerosis, and vulnerability to both the male and female reproductive systems (Fig. 9). Cytotoxic substances and an exacerbated state of stress could be the causes of this type of oxidative vandalism. Oxidative stress as a result of the overproduction of ROS is a major cause of infertility in humans [10]. In men, this could lead to damage to spermatozoa, defects in the sperm, sperm DNA fragmentation, and possible cases of varicocele and testicular torsion, while in females, it could lead to polycystic ovary syndrome (PCOS), premature ovarian failure, and endometriosis [10, 11].

5.1. Oxidative stress in male

5.1.1. Precursor germ cells

Because ionizing radiation can kill cells, male fertility was one of the first reproductive functions that were vulnerable to oxidative stress [11]. The effect of testicular heating on reproduction can also be seen when the precursor cells of germ cells are put under oxidative stress. The testes are located outside of the body because, for them to function, they need to be heated at a lower temperature than the normal body temperature. Heating the testes above their normal temperature could kill the male germ cells at the spermatocyte and spermatid stages of development. This would make men sterile. Also, the spermatids are specifically sensitive to lipid peroxidation and the cytotoxic effect of lipid aldehydes (Fig. 10).

5.1.2. Spermatozoa

5.1.2.1. Damage or impairment of the spermatozoa. Damaged sperms are one of the major causes of infertility in men. The nucleohistone part of the sperm that consists of histone-bound DNA and the gene promoters for the development of the embryo is usually vulnerable to oxidative stress, which results in infertility [10] (Fig. 10). Also, the changes in the structure of the chromatin in the sperm as a result of mutations in the gene could also lead to infertility.
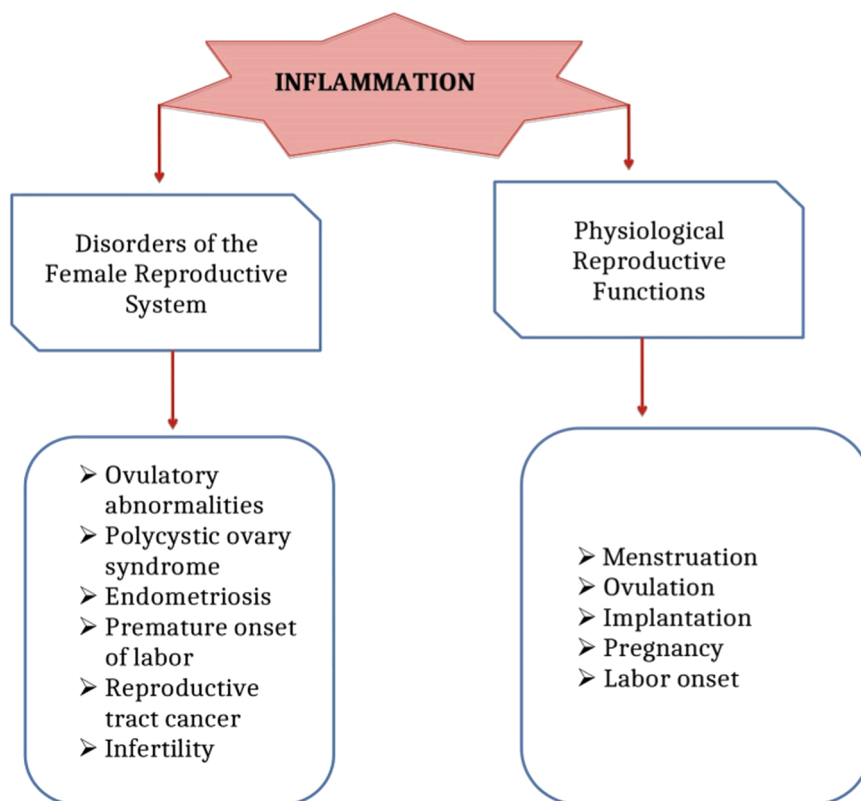
Fig. 8. Showing the effects of inflammation in the female reproductive tract and physiology as modified from [9].
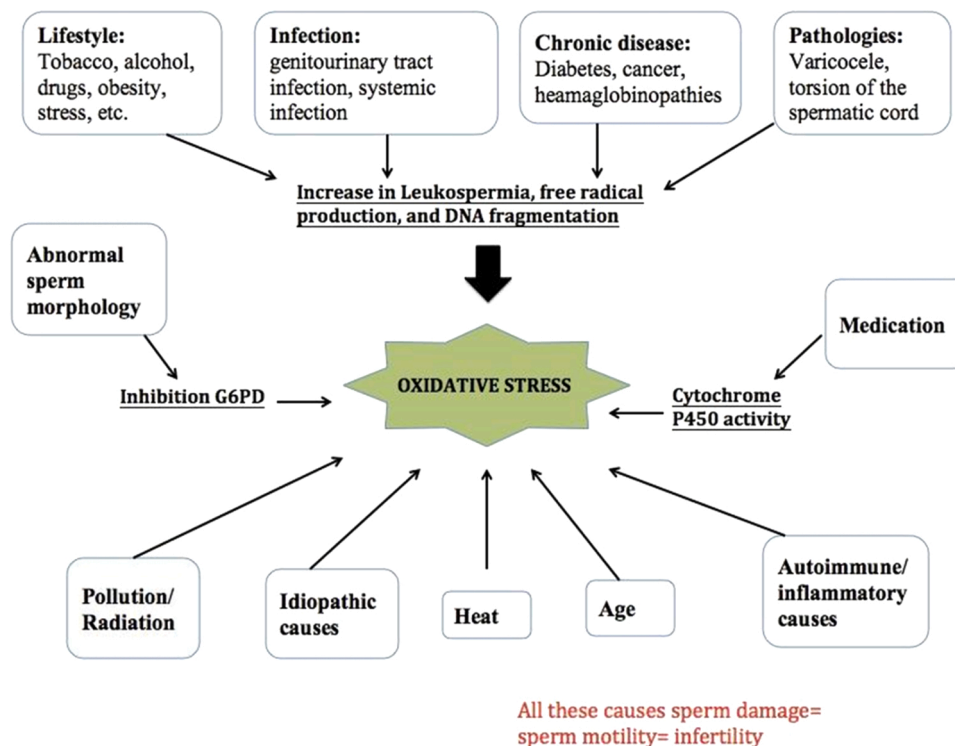
Fig. 9. Showing the relationship between oxidative stress and infertility as modified from [10].

5.1.2.2. Fragmentation of sperm DNA. Some research shows that free radicals are what cause sperm DNA to break up [10]. The systems responsible for sperm DNA fragmentation include DNA crosslinking and fragmentation, as well as the initiation of pyrimidine, purine, and deoxyribose. Once DNA fragmentation occurs in the sperm, the sperm is no longer functional, which results in infertility.

5.1.2.3. Sperm damage or dysfunction. Sperm dysfunction could be the
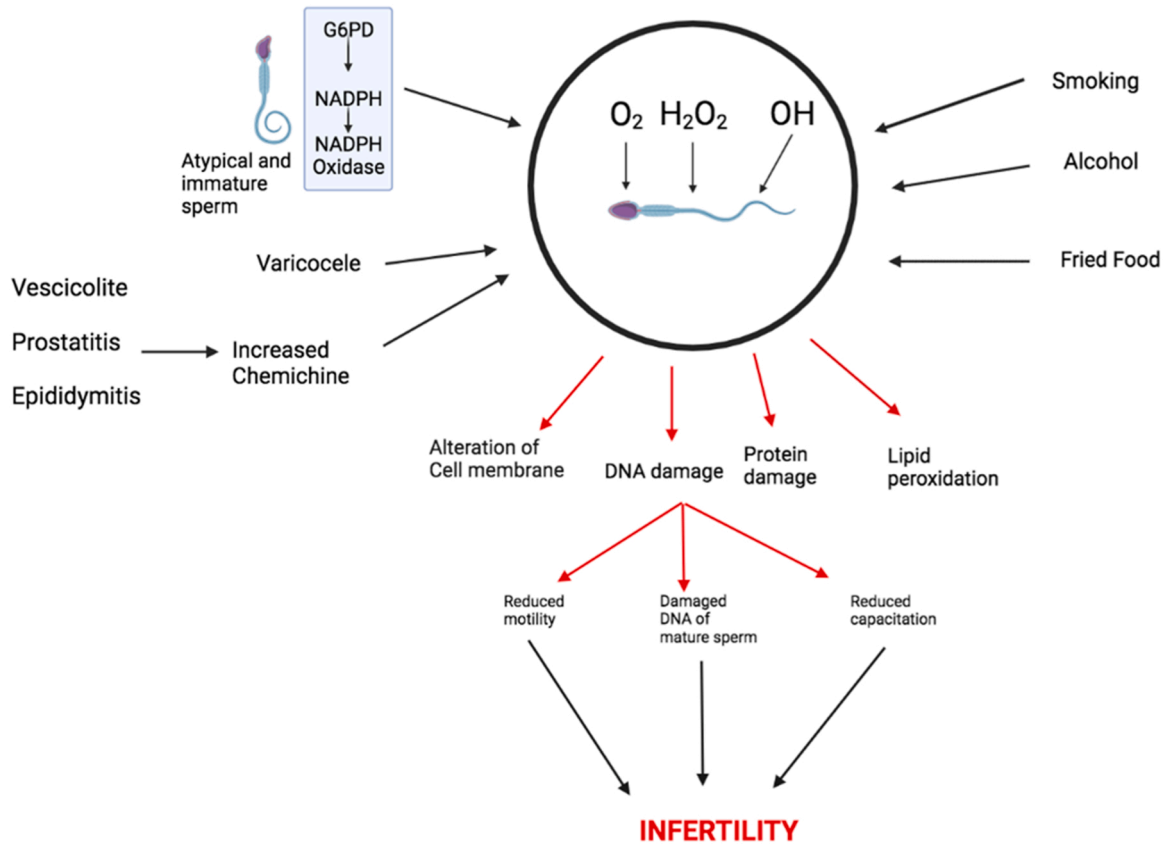
Fig. 10. The effects of oxidative stress on the sperm cell.
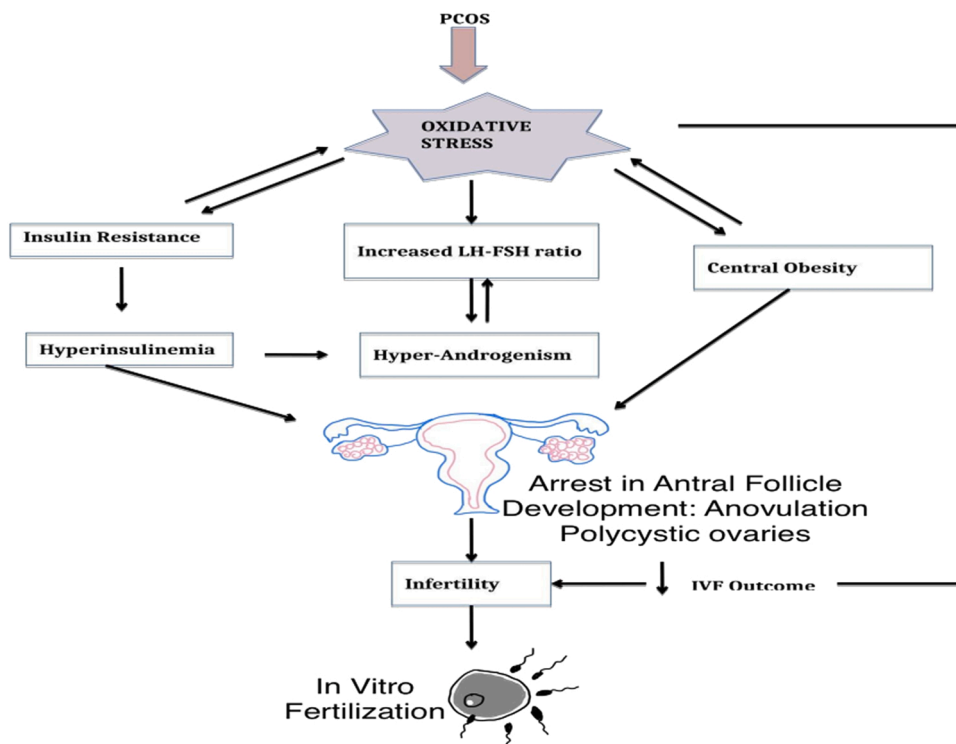Modified from [64].

Fig. 11. The relationship between oxidative stress and PCOS as modified from [65].

result of several reasons related to oxidative stress, such as damage to the integrity of the sperm DNA as a result of damage to the sperm cell membrane, leading to an adverse effect on the permeability and fluidity of the sperm cell, which results in infertility [10].

5.2. Oxidative stress in female

The female germ cells are more sensitive to oxidative stress compared to the male germ cells [11]. Oxidative stress is a major cause of Polycystic Ovary Syndrome (PCOS), endometriosis, and some other cases of infertility [10].

5.2.1. Oxidative stress and PCOS

PCOS refers to multiple cysts in the ovaries that occur as a result of oxidative stress [10]. Patients with PCOS undoubtedly have reactive oxygen species (ROS). Protein carbonyl (PC), which is a molecular marker of oxidative stress, and superoxide dismutase (SOD) are found to be more present in women with PCOS. The content of protein carbonyl in patients with PCOS possesses a positive correlation with fasting insulin and the connection between insulin resistance and protein oxidation. The higher levels of pro-inflammatory markers of oxidative stress, which are IL-6 and TNF-α are found in patients diagnosed with PCOS but are increased in PCOS-IR patients [10] (Fig. 11).

5.2.2. Endometriosis

Oxidative stress is thought to destroy the peritoneal cavity by making it easier for ectopic endometrium cells to stick together [66]. As we've already talked about, endometriosis is an inflammatory disease that causes endometrial tissue to grow on the outside of the uterus. No one knows for sure what causes endometriosis, but it is known that oxidative stress leads to general inflammation, which in turn leads to endometriosis. In women with endometriosis, the granulosa cells have oxidatively damaged DNA and display more occurrences of apoptotic bodies.

The ovarian cortex is also affected by endometriosis, which is also a result of oxidative stress. The ovarian cortex in women diagnosed with endometriosis exhibits high amounts of 8-hydroxy-2-deoxyguanosine, which is a marker for calculating the result of oxidative stress on DNA fragmentation [67,68].

5.3. The role of oxidative stress in apoptosis

Oxidative stress is the most common cause of infertility [7]. Oxidative stress takes place due to a disproportion in the generation of reactive oxygen species (ROS). When the mitochondrion of the sperm cell and ovaries is exposed to ROS, it triggers the apoptotic process, leading to disintegration. As one gets older, the production of ROS increases, and if the antioxidant capacity is low, it also triggers apoptosis and leads to oxidative damage. Research has highlighted the fact that infertile men have higher amounts of cytochrome C in the mitochondrion of their sperm cells.

6. Antioxidants in the treatment of male infertility

The antioxidant system plays an important role in maintaining reproductive and other biological tissues below a crucial threshold of ROS, hence minimizing deleterious effects on reproduction [69]. This is accomplished by keeping ROS levels below the threshold at which ROS becomes harmful. Antioxidant-containing herbal remedies were able to lower ROS levels, shielding germ cells from the effects of OS-mediated apoptosis [70]. They have the potential to be used in complementary and alternative medicine fields to facilitate pregnancy [71]. It has been shown that many plant-derived pure molecules and herbal extracts provide some degree of protection against a variety of illnesses [72], including those that are associated with the reproductive system [73]. Recent research has revealed that giving male plant extracts improves sperm quality, as well as sperm parameters, androgen status, and

Table 1
Plant derived natural products and male infertility (in vitro studies).

Classification	Compound/Extract	System	Source	Cell Line/Animal Model	Dose; Duration	Efficacy	Mechanism	Reference
Plant	Date palm pollen extract	*In vitro*	*Phoenix dactylifera* Linn.	Sertoli cells, spermatogonia stem cells from mice	0.06, 0.25, 0.62 mg/mL; 14 days	Increase in proliferation of spermatogonia		[84]
Plant	5 H-purin-6-amine, *Sedum sarmentosum* extract	*In vitro*	*Sedum sarmentosum*	Spermatogonial stem cells C57BL. 6-TG-EGFP	0.01, 0.1, 1, 10 mg/mL; 1 week	Increase of self-renewal in SSCs	$\uparrow$ PLZF, GFRα1, VASA, Lhx1 $\downarrow$ Pgk2	[85]
Plant	Licorice extract	*In vitro*	*Glycyrrhiza uralensis* Fisch.	Testis tissue from C57BL/6 N mice	0.2, 2, 20 µmol/L; 72 h	Increase in proliferation of spermatogonia	$\uparrow$ PCNA, SCP3, Spo11	[86]
Plant	*Lycium barbarum* polysaccharide	*In vitro*	*Lycium barbarum* Linn.	Leydig MLTC-1	50 µg/mL; 48 h	Increase in cell viability	$\uparrow$ Testosterone, $\downarrow$ p-PERK/PERK, p-elF2α/elF2α, ATF4/β-actin, apoptosis rate, LC3II/I, Atg5/β-actin	[87]
Plant	*Morindae* radix aqueous extract	*In vitro*	*Morinda officinalis*	TM3 cells, mouse Leydig cells	10, 50, 100, 250 mg/mL; 24 h	Increase in testosterone production. Decrease of H_2O_2 induced cytotoxicity, and lipid peroxidation	$\uparrow$ SOD, CAT $\downarrow$ MDA	[88]
Plant	*Taraxacum officinale* aqueous extract	*In vitro*	*Taraxacum officinale*	TM3, ATCCNoCRL	1, 10, 25, 50 mg/mL; 12, 48 h	Increase in the levels of steroidogenic enzymes	$\uparrow$ STAR, CYP11A1, CYP17A1	[89]
Plant	*Typha capensis* rhizome extract F1 fraction	*In vitro*	*Typha capensis* (*Rohrb.*) *N.E.Br.*	TM3-Leydig cells	10, 100 µg/mL; 96 h		$\uparrow$ Testosterone	[90]

PCNA, proliferating cell nuclear antigen; PERK, protein kinase-like endoplasmic reticulum kinase; p-PERK, phospho-PERK; elF2α, eukaryotic initiation factor 2; p-elF2α, phospho-elF2α; ATF4, activating transcription factor 4; SCP3, synaptonemal complex protein 3; SOD, superoxide dismutase; CAT, catalase; MDA, malondialdehyde; StAR, steroidogenic acute regulatory protein; CYP17A1, cytochrome P450 17A1; CYP11A1, cytochrome P450 11A1.

fertility index (Table 1) [74,75]. These findings demonstrate that plant extracts have a favorable impact on sperm quality. In female patients, herbal medication improves ovarian dysfunction and ovarian follicle [76] and increases endometrial receptivity [77,78]. It also affects the underlying molecular process and inhibits estrogen-dependent endometrial hyperplasia. Additionally, an herbal treatment that has activities on the hypothalamic–pituitary–gonadal axis may alter reproductive physiology and alleviate certain types of infertility disorders [79]. The gonadotrophic-like effects of the extracts were characterized by the following biological parameters: an increase in the weight of the ovary and the uterus; the induction of ovulation; an increase in the levels of estradiol, progesterone, and protein; a decrease in the level of cholesterol; and so forth [80]. Many other groups of phytocompounds, most notably flavonoids, and phenolic compounds have been suggested to be responsible for the antimutagenic or protective actions [81]. Natural antioxidants that can scavenge free radicals have garnered a lot of interest as possible treatments for oxidative stress and aberrant hormone functioning [82]. Antioxidants can directly scavenge reactive oxygen

species (ROS), therefore rendering them inactive and repairing the damage. In addition to this, they demonstrated a wide range of biological activities as a consequence of their capacity to imitate the effects of endogenous estrogen, block the actions of hormones, and modify the synthesis of hormones [82]. It has been shown time and time again, using a wide variety of in vitro and in vivo systems, that phenolic compounds, flavonoids, and foods rich in these compounds have powerful antioxidant activity. In the current research, our primary objective was to evaluate the impacts and underlying processes of several different plant extracts and natural products on the reproductive system. Around the globe, including in Korea, people have been using a broad variety of herbs for the treatment of infertility for thousands of years [83]. In addition, a wide variety of natural compounds, including extracts from plants, have been shown to have the capacity to operate as agents that may reverse the reproductive activity of both men and females (Table 2). The origin of natural goods may be traced back to plants, animals, or fungi, and their final forms can take the shape of compounds, extracts, or a variety of other recipes. The reproductive

Table 2
Plant derived natural products and male infertility (in vivo studies).

Classification	Compound/Extract	System	Source	Cell Line/Animal Model	Dose; Duration	Efficacy	Mechanism	Reference
Plant	*Acacia hydaspica* ethyl acetate extract	*In vivo*	*Acacia hydaspica* R. Parker	SD rats	400 mg/kg; 21 days	Increase of seminiferous tubule diameter, area, epithelial height Decrease of width of tubular lumen, interstitial space, DNA damage	[↑] Testosterone, LH, FSH, SOD, POD, CAT, QR, GSH, GR, GST, GPx, γ-GT[↓] H_2O_2, NO, MDA	[91]
Plant	*Achillea millefolium* inflorescences ethanol extract	*In vivo*	*Achillea millefolium* Linn.	Wistar mice	120 mg/kg; 48 days	Increase of sperm motility, capsule thickness, epithelial thickness, tubule differentiation index	[↑] SOD, LH [↓] LDH, NO, MDA	[92]
Plant	Aged garlic extract	*In vivo*	*Allium sativum* for. *pekinense MAKINO*	Wistar mice	250 mg/kg; 14 days	Increase of testis weight, sperm count, motility, recovery of seminiferous tubules Decrease of the death of sperm, sperm abnormality	[↑] Testosterone, GSH, GSH-Px, CAT, SOD,[↓] MDA	[93]
Plant	*Angelica keiskei* powder	*In vivo*	*Angelica keiskei* Koidz.	Self-breeding CD-1 mice	57.5 mg/kg; 7 days	Increase of density of sperm, motility, motile sperm density, progressive sperm velocity, progressive sperm density Decrease of abnormal seminiferous tubules, DNA fragmentation	[↑] GSS, HO-1, Hspa11, Hspa2 Hsf1, Hsf2	[94]
Plant	Banaba leaf and ginseng extract	*In vivo*	*Lagerstroemia speciosa* (L.) Pers.	Swiss mice	150 mg/kg; 30 days	Increase of testis weight, epididymis weight, seminal vesicle weight, sperm density, sperm viability, progressive sperm motility Decrease of nonprogressive sperm motility, abnormal sperm morphology (head, tail, twisted body)	[↑] Testis glycogen, testis protein, testis fructose, seminal vesicle fructose, Epididymal fructose, testis protein, seminal vesicle protein, epididymal protein [↓] Testis cholesterol	[82]
Plant	Bajijiasu	*In vivo*	*Morinda officinalis* F.C.	Normal Kunming mice kidney-yang-deficient Kunming mouse	20, 40, 80,160,320 mg/kg; 30 days 80, 160, 320 mg/kg; 18 days	Increase of the sexual behavior Decrease of DNA damage of sperm by H_2O_2	[↑] Testosterone, [↓] Cortisol, SOD, GPx, CAT, MAD	[95]
Plant	*Balanites aegyptiaca* sapogenin extract	*In vivo*	*Balanites aegyptiaca*	Albino rats	25, 50, 100 mg/kg; 70 days	Increase of semen quality	[↑] LH, Estradiol, Testosterone, Glucose[↓] FSH, Cholesterol, sAST, urea, creatinine	[96]

SOD, superoxide dismutase; GSH, glutathione; MDA, malondialdehyde; NO, nitric oxide, GSS, glutathione synthase, GST, glutathione-S-transferase; GPx, glutathione peroxidase; GSH-Px, glutathione peroxidase; Hsp70, heat shock protein 70, CAT, catalase; H_2O_2, hydrogen peroxide; POD, peroxidase; QR, quinone reductase; GR, glutathione reductase; γ-GT, γ-glutamyl transpeptidase; LH, luteinizing hormone; FSH, follicle-stimulating hormone; HO-1, heme oxygenase-1; LDH, lactate dehydrogenase

system has been shown to have undergone structural and functional changes, and studies have identified the particular processes responsible for the observed consequences.

6.1. Antioxidants in female infertility management

Since the beginning of time, people have been using plants as a source of medicine to prevent, protect against, and treat a wide variety of health conditions. This practice dates back to ancient times. Herbal remedies and other natural items, including the many chemical derivatives of these natural products, account for nearly half of all the medicine that is being utilized around the globe right now [97]. In addition, traditional herbal treatments play a significant part in the healthcare systems of underdeveloped nations as well as wealthy ones [98,99]. Medicinal herbs are used for the treatment of female infertility as an alternative therapy option to avoid the high costs and harmful health consequences connected with the many infertility treatment

procedures that are accessible in the form of assisted reproductive technology (ART). Kaadaaga and his colleagues [100] have only recently investigated the prevalence of the use of herbal medicine by infertile women as well as the parameters linked with its use. Researchers have carried out numerous ethnopharmacological surveys in various regions of the world to discover the various medicinal plants that are used for the treatment of infertility or pathologies in females that cause infertility [101,102]. Some of these medicinal plants are highlighted below (Table 3).

7. Conclusion

Apoptosis, which is a process that takes place in living organisms as well as humans, involves events leading to morphological changes and the death of damaged cells. From the discussions in the previous sections, it has been shown that increased apoptosis in both the sperm and ovaries gives off negative effects that contribute to the problem of

Table 3
Medicinal plant derived natural products and female infertility.

Plant species	Part used	Study candidate/animal	Treatment	Improved reproductive functions	References
Trigonella foenum-graecum	Seed	PCOS women	2 capsules of 500 mg each/day for 90 days	A reduction in both the volume of the ovary and the number of ovarian cysts The restoration of normal menstrual periods Observable rises in both LH and FSH levels	[103]
		Healthy women	600 mg/day seed extract for 2 menstrual cycles	Increases of both free testosterone and estradiol to a significant degree Enhancement of sexual desire as well as sexual arousal	[104]
Justicia insularis	Leaf	Immature rat	12.5, 50, and 100 mg/kg bw extract daily for 20 days	An earlier opening of the uterus. The quantity of hemorrhagic spots, the corpus luteum, the implantation sites, the weight of the ovary, and the uterine and ovarian proteins all increased (induces folliculogenesis) Decrease in the amount of cholesterol found in the ovary	[105]
Acmella oleracea	Flowers	Rat	88.91 mg/kg and 444.57 mg/kg daily for 21 days	Increased incidence of both the proestrous and the estrous phases Reduced incidence of the metaestrous and diestrus phases of the menstrual cycle	[106]
Cimicifuga racemosa	Rhizome	Infertile women	120 mg/day dry extract	increased levels of oestrogen and luteinizing hormone Increases in blood progesterone, endometrial thickness, and the percentage of clinical pregnancies	[107,108]
		PCOS women	20 mg dry extract daily for 10 days	A higher progesterone level, which indicates ovulation will be more successful Increased thickness of the endometrial layer Increased number of pregnancies	[109]
Zingiber officinale	Rhizome	Rat	100 mg ginger powder daily for 5 and 10 days	An increasing amount of antral follicles as well as ovarian stromal VEGF; an elevated number of endometrial VEGEF as well as ovarian stromal eNOS	[110]
			100 mg/kg/day of 6-gingerol-rich fraction for 35 days	Guarded from an increase in OS that was caused by chlorpyrifos (H_2O_2 and NO) GSH levels in ovarian and uterine tissue were shown to have increased, along with the activity of the antioxidant enzymes CAT, SOD, GPx, and GST.	[111]
Nigella sativa	Seed	Mice	0.2, 0.5, and 1.0 mL/100 g N. sativa oil for 5 days	Cyclophosphamide treatment led to an elevation in the amount of normal, primary, and secondary follicles as well as the diameter of the ovary in rats.	[112]
		Rat	0.5 and 1.0 g/kg daily from day 3 to day 15 of lactation	Lactation results in enhanced milk yield as well as enhanced weight in the puppies.	[113]
		PCOS women	2 g/day powdered seed as capsules for 16 weeks	A rise in both the average length of the menstrual cycle and the number of cycles that occur each month was observed. Reduced time between periods of menstruation	[114]
Hypericum perforatum	Flowering tops	Women with premenstrual syndrome	900 mg/day for 2 menstrual cycles	a reduction in the severity of the premenstrual syndrome's behavior and physical characteristics	[115]
Crocus sativus	Stigma	Women with premenstrual syndrome	30 mg/day for 2 menstrual cycles	Efficient in the treatment of the discomforts associated with premenstrual syndrome	[116]
Cinnamomum zeylanicum	Bark	PCOS women	3 cinnamon capsules (Each containing 500 mg cinnamon) for 8 weeks	an elevation in the capacity of total antioxidants (TAC) Reduced levels of MDA in the serum	[117]
			1500 mg/day for 6 months	Improved menstrual cyclicity	[118]
Urtica dioica	Leaves and root	Women with hyperandrogenism	300–600 mg dried extract daily for 4 months	Significant drop in complete testosterone level, free testosterone level, and DHEA level	[119]
Linum usitatissimum	Seed	PCOS women	15 g flaxseed powder for 3 months	a decrease in ovarian volume as well as the number of follicles Enhancement of the menstrual cycle and the likelihood of pregnancy	[120]

infertility in both men and women. To increase the rate of fertility, it is important to control the process of apoptosis. Furthermore, oxidative stress via ROS generation plays an important role in apoptosis by producing various reproductive abnormalities that lead to infertility. Inflammation, which plays a major role in some physiological processes such as ovulation, implantation, and pregnancy in women, as well as abnormal sperm production and function, and ejaculation of sperm, is the main contributor to inflammation. The mediators of inflammation, which are cytokines, chemokines, and growth factors, are the main contributors to inflammation. Reproductive tract diseases can be the result of excessive activation of inflammatory pathways. The overproduction of ROS is a result of an inflammatory injury in the reproductive tract. Infectious agents, which settle in the reproductive tract, also trigger the excessive generation of ROS and free radicals, which are associated with inflammation reactions. Xenobiotics are hazardous substances that people are exposed to in their environment and thus run the risk of developing infertility. They also contribute to the growing problem of infertility in both sexes. Additionally, antioxidants, when present in persons, they help to mop up the excess ROS generated by xenobiotic exposure. To maintain cell activity, antioxidants can regulate the excess generation of ROS.

Ethics approval and Consent to participate

Not applicable.

CRediT authorship contribution statement

All authors contributed to the study's conception and design. All authors read and approved the final manuscript.

Consent for publication

not applicable.

Declaration of Competing Interest

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

Data availability

Data will be made available on request.

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