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The consequences of climate change and male reproductive health: A review of the possible impact and mechanisms

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ABSTRACT

A global decline in male fertility has been reported, and climate change is considered a major cause of this. Climate change refers to long-term shifts in temperatures and weather patterns, and results from greenhouse gas emissions like carbon dioxide and methane that act as a blanket wrapped around the earth, trapping heat and elevating temperatures. Sad to say, the consequences of climatic variation are beyond the dramatic elevated temperature, they include cold stress, increased malnutrition, air pollution, cardiovascular diseases respiratory tract infections, cancer, sexually transmitted infections, mental stress, and heat waves. These negative effects of climate change impair male reproductive function through multiple pathways, like ROS-sensitive signaling, suppression of steroidogenic markers, and direct damage to testicular cells. The present study aimed to describe the impact of the consequences of climate change on male reproductive health with details of the various mechanisms involved. This will provide an in-depth understanding of the pathophysiological and molecular basis of the possible climatic variation-induced decline in male fertility, which will aid in the development of preventive measures to abate the negative effects of climate change on male reproductive function.

1. Introduction

Infertility is a global health challenge involving about 15 % of couples [1,2]. Male infertility solely accounts for about 20 % of the cases of infertility, while it contributes to about 50 % of the total cases of infertility [1–3]. Male infertility may be a consequence of the suppression of the hypothalamic-pituitary-testicular axis with resultant testicular dysfunction, which impairs testicular steroidogenesis and/or spermatogenesis [4]. Genetic disorders, endocrine pathologies, immunological disorders, and sperm antibodies, testicular disorders, reproductive tract obstruction, systemic disorders, and inflammatory conditions like epididymo-orchitis play a role in the pathogenesis of male infertility [1,5,6]. Causes of male infertility are classified as pre-testicular, testicular, and post-testicular [7]. Pre-testicular causes are extra-testicular factors that modulate hormonal stimulation, hence impairing spermatogenesis, and they include hypogonadotrophic hypogonadism (due to congenital Kallmann's syndrome or acquired cases like trauma or tumors), drugs, cigarette smoking, substance abuse, and chronic alcoholism. Testicular causes are primary pathologies of the testis, such as congenital anomalies (like Klinefelter's syndrome), orchitis, testicular torsion/detorsion injury, cryptorchidism, chemotherapy and radiotherapy. Post-testicular causes are defects of the genital tract and/or factors that alter ejaculation, such as obstruction or lack of the vas deferens, obstruction of the ejaculatory duct, hypospadias, and impotence.

Recently, environmental climatic change has begun to gain attention as a possible predisposing factor for male infertility [8,9]. The last few decades have witnessed rapid global environmental change that has

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been triggered by natural phenomena and human activities [10]. Climate change is the long-term variation in temperature and weather patterns (precipitation, and wind) that results from natural occurrences, such as variations in the solar cycle, and human activities, such as the burning of fossil fuels [11]. Recently, human activities have been identified as the primary driver of climate change. Domestic and industrial human activities generate greenhouse gas emissions such as carbon dioxide and methane that act like a blanket wrapped around the earth, trapping heat and elevating temperatures [11]. Climatic change affects the five components of the environment, viz., water, air, weather, ocean, and ecosystem [11,12], which directly or indirectly alter male reproductive function [13,14]. Unfortunately, the consequences of climatic change are beyond the dramatic rise in temperatures, they include cold stress, malnutrition, air pollution, increased cardiovascular diseases and respiratory tract infections, cancer and sexually transmitted infections, mental stress, and heat waves [15] (Fig. 1). These consequences of climatic change have reproductive health implications, such as male infertility, directly or indirectly.

Moreover, climate change has been thought to affect human health as well as the human reproductive function through a differenct range of direct and indirect exposures. This has been linked with obvious and visible extreme events of diverse environmental factors such as floods, forest fires, heat waves and cold stress. It has however been reported that some certain silent factors such as global warming has a chronic effects on health and fertility [16]. It has been established that the reproductive tissues function only within a range of ambient temperature in which when exceeded adversely affects the reproductive functions via common mechanisms of gonadal heat shock, oxidative stress (OS) and alterations in endocrine interplay [9,13,14]. Heat stress can be an environmental cause as well as an occupational hazard that can lead to chronic illnesses and even death right from the after effects of heat stroke (Mackay, 2007).

Besides temperature changes casues a wider range of accumulated toxic contaminants in the air which can also contribute to various reproductive disorders and can also induce OS [13,14]. These environmental factors can induce unregulated production of free radicals, reactive oxygen species (ROS) and reactive nitrogen species (RNS) which triggers the chain of oxidative damage severely affecting gonadal functions such as impairment of gametogenesis, gamete chromatin integrity, mitochondrial functions as well as increased germ cell apoptosis [16]. This consequenty leads to a decrease in semen quality and reduced oocyte quality and uterine receptivity in males and females respectively. The disruption in the hypothalamic–pituitary–gonadal (HPG) axis alter the release of gonadotropin releasing hormone (GnRH) and subsequent tropic hormones, luteinizing hormone (LH) and follicle stimulating hormone (FSH), thereby leading to decreased testosterone levels in males, oestrogenic and progesterone in females and impairing gonadal functions [13,14]. Intrestinglly, other natural desasters and calamities like storms, floods, draught and changes in rainfall pattern can affect socioeconomic status of an environment inflicting malnutrition, poor sanitation, increased food and water-borne diseases, emergence and spread of infectious diseases that can procure and affect the overall health and thereby indirectly posing threat to fertility [17].

Although several studies exist in the literature that document the impacts of environmental toxicants on male reproduction, studies reporting the direct and likely indirect effects of climatic change on male reproduction are scarce. In this review, with a more comprehensive approach, we discussed the direct and indirect impact of the consequences of climate change (such as heat stress, cold stress, malnutrition, air pollution, respiratory tract infection, sexually transmitted diseases, cardiovascular diseases, cancers, stress, and heat waves) on male reproductive health, including the associated pathophysiological and molecular basis. In addition, potential preentive and therapeutic strategies were also discussed.

2. Methods

The present study was based on the data from the scientific literature that were retrieved from a search performed on PubMed, EMBASE, Scopus and Google Scholar databases. The following keywords were

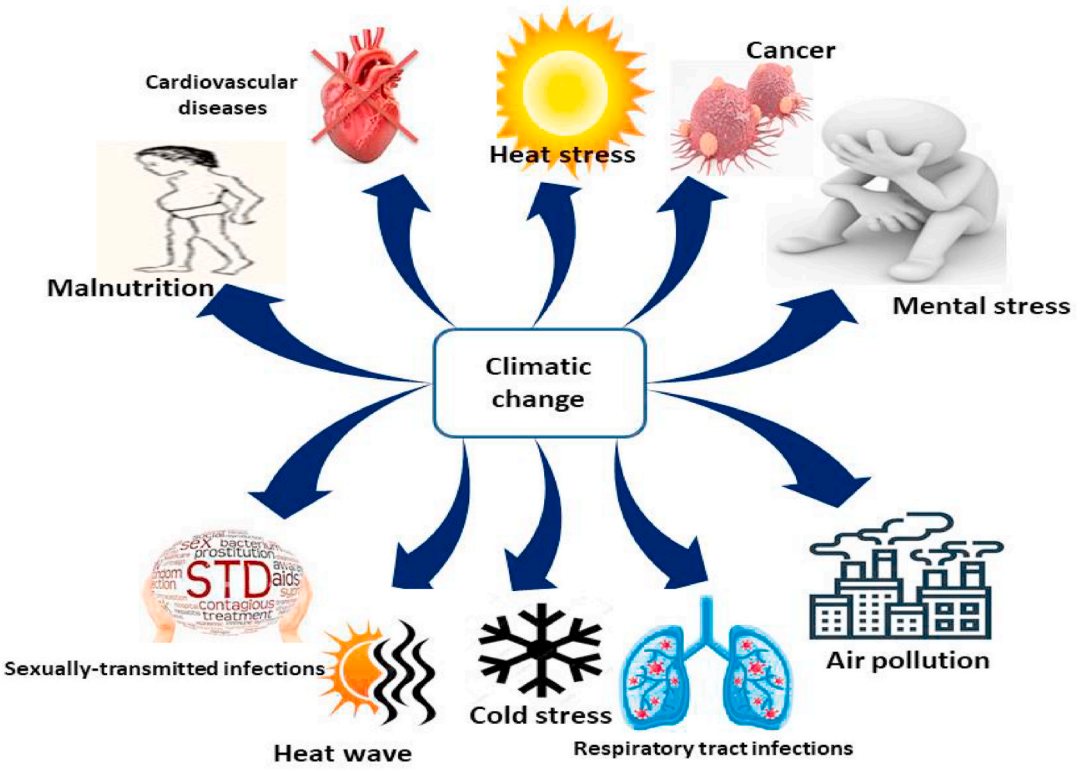

Fig. 1. Effects of climatic changes on human health.

used alone and in combination: “climate change”, “heat stress”, “cold stress”, “malnutrition”, “air pollution”, “respiratory tract infection”, “URTI”, “sexually transmitted infections”, “STI”, “STD”, “cardiovascular diseases”, “CVD”, “cancer”, “mental health”, “psychiatric”, “heat waves” “reproductive function:, “male reproduction”, “sperm”, “sperm cells”, “testis”, “germ cell”, “fertility”, and “infertility”. Searches were conducted without restrictions to the country of origin and year of publication.

2.1. Heat stress and male reproduction

Consequent upon anthropogenic climatic variation, the global mean temperatures are rising and would keep rising irrespective of greenhouse emissions [18]. Climatic change is expected to increase overall temperature distribution and contribute to a rise in the frequency of extreme heat waves [19]. Climate change in different parts of the world has led to a rise in temperature and occupational heat stress levels in outdoor and indoor workplaces [20,21]. Although there is a dearth of data on the impact of a rise in temperature from climate change on male fertility, the available experimental study used models of heat stress in animal models to mimic real-time events.

A study demonstrated a short and long term effects of elevated ambient temperature on testicular functions in boars shows that an elevated temperature causes a significant shift in androgen biosynthesis by testis slices incubated in vitro which clearly suggested that elevated ambient temperatures alter testicular endocrine activity [22]. However, heat stress had no apparent deleterious effects on the steroidogenic responses mediated by exogenous gonadotropins and also casues a decline in serum testosterone level after exposure to an elevated ambient heat. Taken together, it has been observed that the short and long term studies suggest that heat stress causes a transitory suppression in peripheral testosterone concentrations. The early effects of heat stress on circulating testosterone levels causes an alteration in androgen biosynthesis and about 50 % reduction in round spermatids seen after prolonged heat stress which establishes that whole body exposure to elevated ambient temperature exerts a suppressive effect on the steroidogenic and spermatogenic elements of the boar testis [22].

Leydig cells are more resistant to heat than germ cells (Setchell, 2006); however, their steroidogenic function, testosterone biosynthesis, can be impaired by adverse conditions like heat stress [22–24]. This may be due to the repression of the Steroidogenic Acute Regulatory Protein (StAR) gene and protein that occurs in response to heat stress [25]. Reduced activity of this enzyme will impair the translocation of cholesterol into the inner mitochondrial membrane of the testes for desmolase action, an essential rate-limiting step in steroidogenesis [1], resulting in reduced biosynthesis of testosterone that is essential for spermatogenesis and maintenance of testicular integrity [26]. In an animal model, Rizzoto et al. [27] observed a 10-fold reduction in the expression of gene encoding StAR and testicular testosterone level 48 h after scrotal insulation in *B. indicus* bulls, demonstrating the severity of the effect of heat stress on testosterone biosynthesis.

The production of steroid hormones is mediated by cAMP signaling [28] and is initiated by the transport of cholesterol from cellular stores to the mitochondrial inner membrane. The enzyme cytochrome P450 is located at this site and catalyzes the cholesterol-side-chain-cleavage process [28–31]. In addition, the intra-mitochondrial mobilization of cholesterol is mainly triggered by the StAR protein, a rapidly produced mitochondrial phosphoprotein whose expression, activation, and extinction are mediated by protein kinase A (PKA), PKC [32]. However, StAR activity is also influenced by factors that exert both acute and

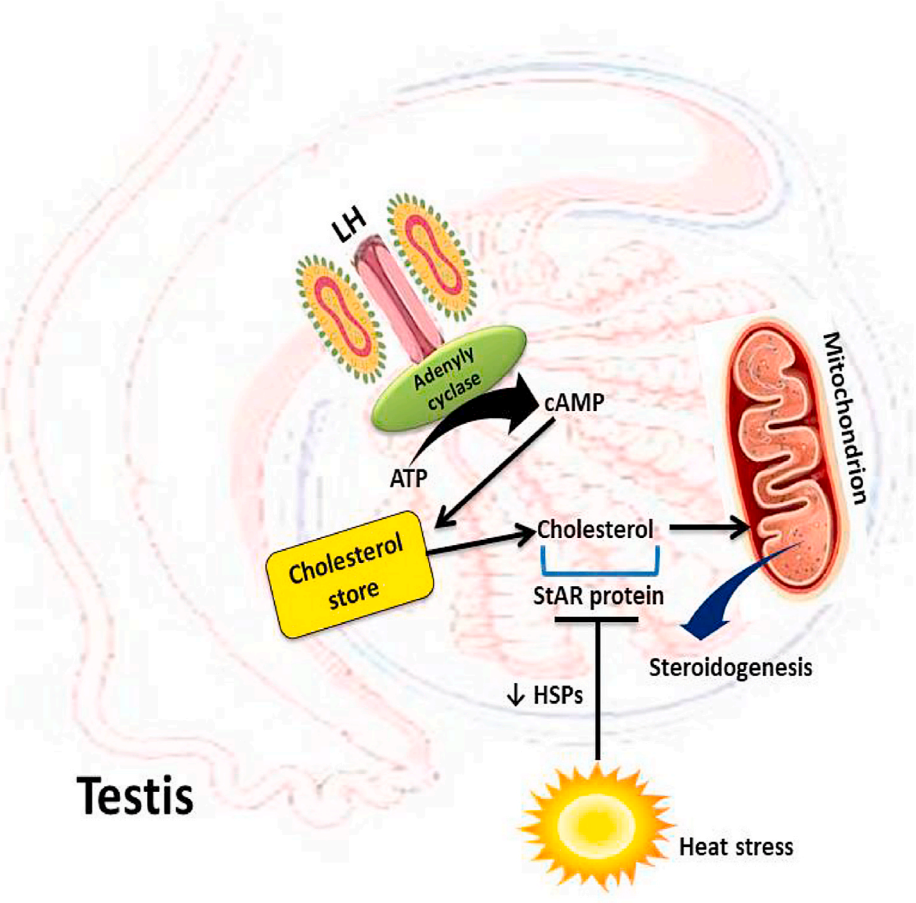

Fig. 2. Effect of heat stress on testicular steroidogenesis.

chronic effects on steroidogenesis ([30,32,33]; Manna and Bose, 2011; [34]). Therefore, heat stress-driven decline in StAR activity results in decreased mobilization of cholesterol needed for the steroidogenic process [25] (Fig. 2).

Spermatogenesis is a temperature-dependent process. In mammals, the scrotal temperature is about 2–4 °C lower than the core body temperature; this is essential for optimal spermatogenesis [35–38]. Garolla et al. [39] demonstrated that scrotal hyperthermia by exposure to increased environmental temperature may induce a significant alteration in spermatogenesis. The disruption of scrotal thermoregulation due to heat stress often results in testicular hyperthermia, generating genital heat stress [24,40], and resulting in the production of spermatozoa of low quality. In addition, epididymal sperm cells and testicular germ cells are highly susceptible to disruption of heat, with a characteristic reduction in testicular germ cell proliferative activity stress [41,42]. Studies have also revealed that exposure of sperm cells in mice to hyperthermia upregulates apoptosis [24,40], with disrupted DNA and RNA integrity [35,36], as well as impaired protein synthesis. These apoptosis-induced alterations often result in low fertilizing potential in sperm cells, both in vivo and in vitro [43].

Reportedly, reactive oxygen species (ROS) are involved in heat stress-induced apoptosis, thus revealing oxidative stress as a direct trigger of testicular germ cell apoptosis [44]. Further, evidence has indicated that heat stress-induced reproductive dysfunction may be secondary to enhanced ROS generation, lipid peroxidation, and suppressed testicular antioxidant defense capacity [45–47]. It is also likely that ROS activate heat shock proteins (HSP) via heat shock factor-1 (HSF-1)-sensitive signaling [48].

HSPs confer cellular protection through chaperoning activities such as polypeptide folding, assembling, and translocation of organelles across membranes, conducting repairs, and degradation of irreparable peptides [49,50], and inhibition of ROS-induced DNA fragmentation [51]. HSP 70 has also been shown to prevent inflammation by inhibiting the activation of NFkB, cyclo-oxygenase 2 (COX-2), and nitric oxide synthase (NOS) [48,52]. In addition HSPs prevent the activation of caspase 3 by apoptosis protease activating factor-1 (Apaf-1), thus preventing apoptosis [48,52]. Beyond these signaling and cytoprotective roles, HSF and HSPs have been demonstrated to promote spermatogenesis [53]. Thus, the short-term exposure of the testis and sperm cells to heat stress may activate HSF and HSPs to confer cytoprotection against oxidative injury; however, HSF and HSPs may be overwhelmed following persistent or chronic exposure, resulting in depletion of these protective molecules and increased susceptibility of the testis and sperm cells to ROS-induced damage. Decreased expression of HSPs, especially HSP 70, has been shown to be associated with impaired spermatogenesis [54]. The knock-out of HSP 70 gene in a mouse model has been shown to result in the arrest of maturation of the primary spermatocytes at stage I of meiosis, while a homogenous mutant of HSP 70 leads to infertility [54,55].

Although the findings of in vitro studies may not be obtainable in vivo due to the interconnections between several organs and systems that may tend to create a homeostatic environment, some human studies lend credence to this claim. Occupational heat exposure has been shown to lower semen quality and lead to subfertility [56]. In the study, temperature rise above 80 °F causes a decline in birth rates as a result of high temperature-induced impaired male and female gamete development [57]. Animal studies also demonstrated that exposure of bulls to high temperatures resulted in a decline in sperm motility after two weeks and a decline in other parameters after eight weeks [58]. In addition, mice that had testicular exposure to 42 °C for 30 min showed reduced sperm count, and motility and reduced sperm DNA integrity [38,59]. Moreover, testicular heat stress often leads to testicular tissue destruction and spermatogenesis disturbances thus, a slight increases in temperature can disrupt spermatogenesis which eventually leads to fertility issues [37,38]. Studies have established that HS is detrimental to spermatogenesis and results to a fall in semen quality, epididymal sperms and testicular germ cells in rats [41,42]. It is also evident that HS exposure leads to testicular dysfunctions including decreased in testicular weight, germ cell loss and increased rates of apoptosis in rats [35,36,38,59]. Studies have shown that HS exert toxic effect on the seminiferous tubular epithelium with concomitant reduction in the reproductive abilities of the male rats with concurrent exposure to heat [60].

Human studies have also shown that heat stress is one of the most common hazardous agents in workplaces [61]. It has been reported to impact most aspects of reproductive function in mammals, including humans [62]. Heat stress causes a transient decline in testicular endocrine function and spermatogenesis, which are likely restored a few weeks later [63]. A study by Zhang et al. [64] showed that exposure of the testes to transient scrotal heat at 43 °C in thirty proven-fertile men resulted in suppression of circulating testosterone. However, this effect may be reversible at the pre-treatment level three months after heat exposure [64]. Hou et al. [62] also reported a reduced testicular index.

Heat stress may also exert indirect effects on male reproduction by reducing access to medical supplies, expiration of heat-sensitive medication, migration and conflict, food shortages, and increased heat-related emergencies that may overburden the health system [65].

2.2. Cold stress and male reproduction

Cold stress is a condition characterized by the body's inability to maintain its normal temperature. It is the result of an imbalance between the heat generated in body tissues and the heat exchanged with the environment by various mechanisms [66]. Climate change forces upward wave activity which results in a stretched stratospheric polar vortex that sets up wave reflection, leading to a southward-shifted jet stream and a cold wave. Cold stress is usually characterized by a reduced ecological relevance with low temperature but above the super cooling point (SCP, i.e., "the temperature at which spontaneous nucleation of body water occurs), is referred to as a cold shock or direct chilling injury" [67].

Exposure to cold stress has been shown to cause a decrease in testosterone that is associated with impaired spermatogenesis and degeneration of testicular germ cells, primarily round spermatids and primary spermatocytes in adult Wistar rats [68] (Fig. 3). García-Díaz et al. [69] and Juarez-Rojas et al. [68] also demonstrated that exposure to cold stress led to suppression of circulating testosterone and increased corticosterone in Wistar rats. These findings are in agreement with earlier reports of Jain et al. [70] in Sprague-Dawley rats that documented that cold stress decreased serum testosterone and increased serum corticosterone, glucose and protein.

In a human study, Demir et al. [71] and Santi et al. [72] demonstrated seasonal variation in circulating testosterone and sexual behaviour. It was observed that the frequency of sexual activity and ejaculation was significantly reduced in winter (cold). This was associated with lower sexual function and a reduced serum testosterone level. Suppression of testosterone may be mediated by cold stress-induced upregulation of transcript mRNA that encodes pro-inflammatory cytokines like interleukins and interferon [73], which may in turn trigger testicular oxido-inflammatory injury and suppress testicular functions, viz., spermatogenesis and steroidogenesis [74–76]. In a pre-clinical study, Basha et al. [77] observed that cold stress significantly reduced sperm motility, viability, and count via an oxidative stress-mediated pathway. It was also noted to markedly reduce acrosome integrity and normal sperm morphology [77]. The study of Basha et al. [77] corroborated earlier findings of Graham and Hammerstedt [78] that revealed that cold stress induced sperm membrane lysis and sperm dysmotility.

2.3. Malnutrition and male reproduction

Extreme weather events and variations in temperature and precipitation patterns may directly reduce yield and yield products as well as the nutritional values of crops and destroy agricultural produce,

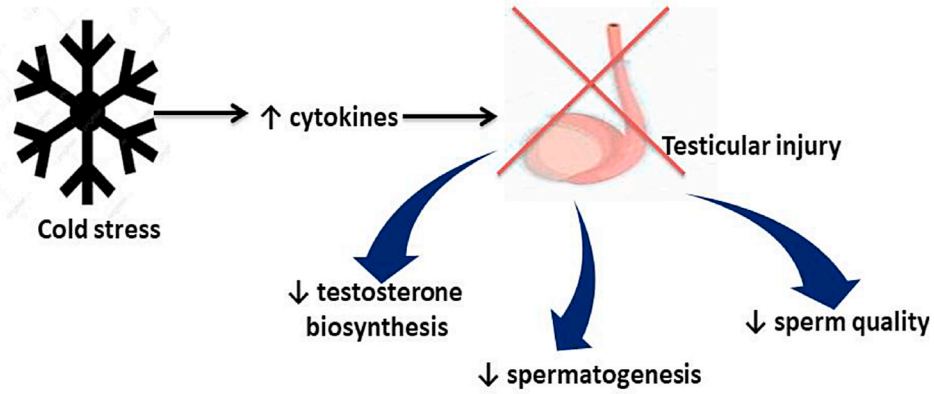

Fig. 3. Effect of cold stress on testicular steroidogenesis and sperm quality.

especially crops and food supplies. Transportation and distribution of food and other agricultural produce may also be affected by adverse weather conditions. In addition, climate change increases the spread of food-borne pathogens (Gambe et al., 2008), increases pesticide use with associated exposure to environmental toxicants [79–81], and increases exposure to heavy metals (Ebi et al., 2008). Although this may be a seasonal occurrence and not strictly related to malnutrition, it is worsened by climate change and poses a risk for malnutrition.

Compelling pieces of evidence show that malnutrition impairs testicular steroidogenesis and semen quality (Fig. 4). Clinical evidence revealing hypogonadism in severe malnutrition has been consistent long before now [82,83]. Smith et al. [84] demonstrated that hypogonadism in protein-energy malnutrition is mainly due to the suppression of Leydig cell function. Lado-Abeal et al. [85] also reported hypogonadism in men with protein-energy malnutrition, which was associated with low testosterone levels and normal or high gonadotropin levels, suggesting impaired Leydig cell function. In an experimental study, Rahma et al. [86] showed that malnutrition significantly reduced circulating testosterone and the diameter and epithelial thickness of the seminiferous tubule of the testes via upregulation of HSP70 expression.

Omirinde et al. [87] demonstrated in a Wistar rat model that low-protein-energy diets significantly reduced epididymal sperm quality. The findings of Omirinde et al. [87] corroborate those of Hassanein and Hamed [88], who revealed that malnutrition lowered sperm quality and led to distorted testicular and epididymal histoarchitecture. Martinez et al. [89] demonstrated that in utero malnutrition in F1 generation

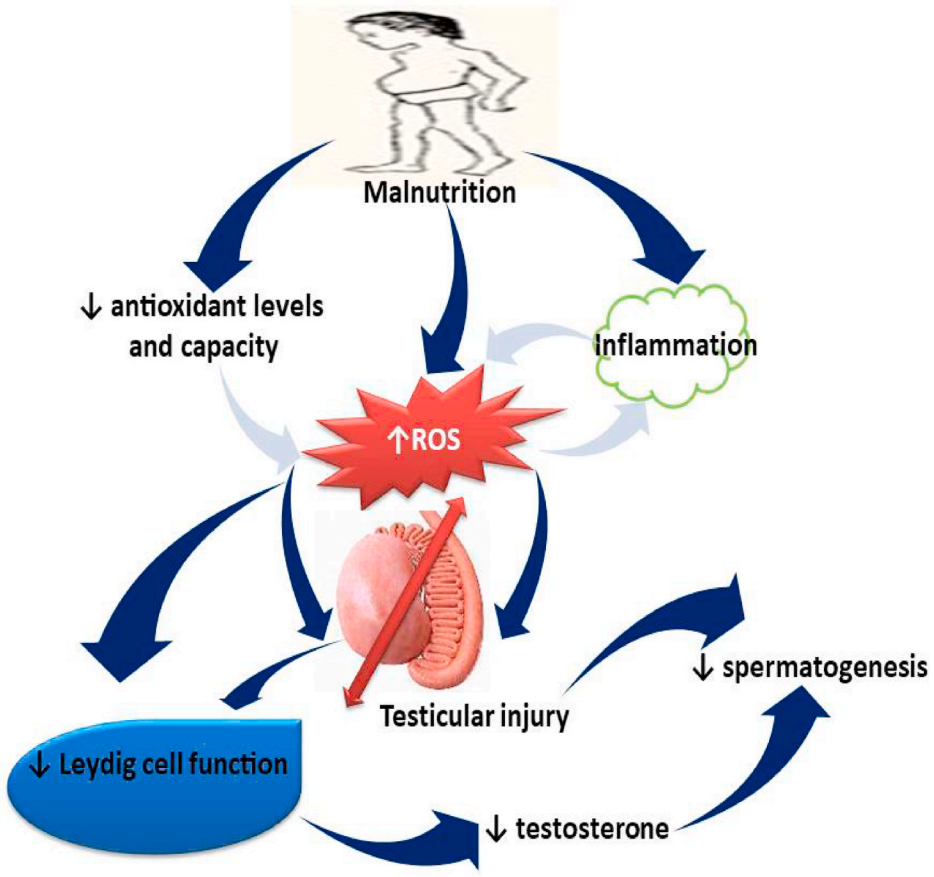

Fig. 4. Effect of malnutrition on testicular steroidogenesis and sperm quality.

male mice increased the risk of metabolic disorders in their own F2 offspring, as evidenced by glucose intolerance, obesity, reduced expression, and DNA methylation. This epigenetic modification may negatively impact on male reproductive functions [90,91].

2.4. Air pollution and male reproduction

Climatic change results in the emission of air pollutants such as carbon dioxide, methane, fine particulate matters ($PM_{2.5}$), and ozone. These pollutants are environmental toxicants and may cause cardiovascular disorders [92], pulmonary disease [93], and reproductive dysfunction [94], including low sperm quality [95] and adverse pregnancy outcomes [96]. Tallon et al. [97] and Zhao et al. [98] established a relationship between air pollutants and erectile dysfunction (ED). They revealed that exposure to $PM_{2.5}$, NO_2, and ozone was consistently associated with greater ED probabilities. Wang et al. [99,100], also demonstrated that $PM_{2.5}$ may impair erectile function via suppression of endothelial nitric oxide synthase (NOS) expression and activity in penile cavernous tissue. Santi et al. [101] and Santi et al. [102] also revealed that exposure to PM_{10} and $PM_{2.5}$ lowered sperm quality, which was associated with increased abnormal forms.

Greenhouse gases have also been shown to alter male reproductive hormones (Fig. 5). In a recent study by Wang et al. [103], long-term exposure to ambient ozone and residential greenness independently modulated hormone levels. It was reported that ozone exposure significantly reduced circulating testosterone, while higher greenness improved ozone-induced reduction in androgen levels, although this is not in agreement with the findings of Zhao et al. [104], who did not observe a significant relationship between ozone exposure and puberty onset that was determined by testosterone. Similar to the findings of Zhao et al. [104], Calogero et al. [105] reported unaltered serum levels of testosterone in individuals exposed to vehicle exhaust, a major source of ozone. However, Jedlinska-Krakowska et al. (2003) also reported a significant decline in serum levels of testosterone in rats exposed to ozone. The variation in the findings may be due to the concentration of ozone subjects were exposed to and the duration of exposure.

Greenhouse gas emissions have also been implicated to impair spermatogenesis and lower sperm quality. A decline in sperm concentration has been documented in many industrialized nations in recent times, and male infertility has surged from 7 to 8% in the 1960s to 20–30 % currently [106]. Epidemiological studies showed that air pollution negatively correlates with sperm quality [107,108]. Chronic exposure to NO_2 and SO_2 significantly reduced sperm count, motility, and testicular volume [109]. Also, with less SO_2 exposure, spermatogenesis improves [109]. These findings are consistent with reports that showed that air pollution negatively altered semen quality [94,95,110–112]. Rubes et al. [113] and Bosco et al. [114] also reported that these air pollutants induce sperm DNA fragmentation (SDF).

Human and experimental studies have established the role of testosterone in spermatogenesis [4,115,116]. Therefore, the reduced circulatory testosterone observed following exposure to these environmental pollutants contributes, at least in part, to the associated reduced semen quality. Radwan et al. [117] also observed significantly reduced sperm quality following exposure to PM_{10}, $PM_{2.5}$, NOx, SO_2, and CO.

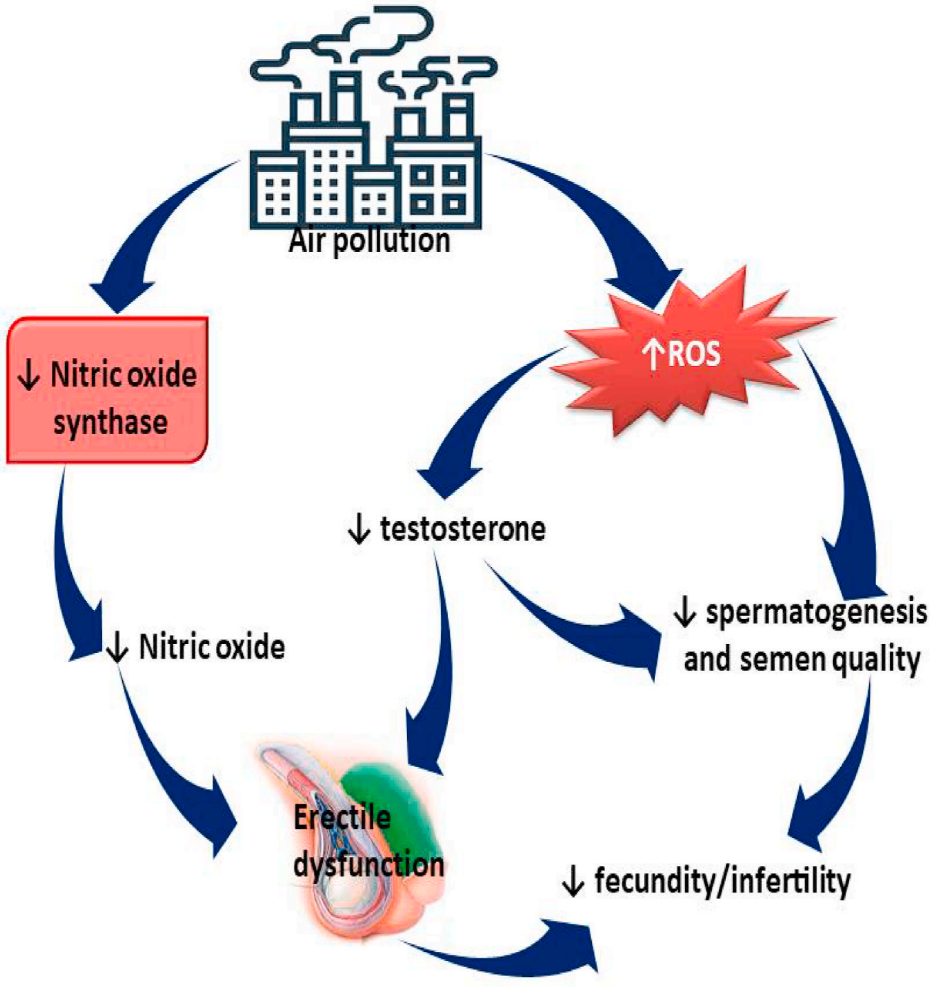

Fig. 5. Effect of air pollution on male fertility.

PM_{10}, $PM_{2.5}$, NOx, CO, and SO_2 were also associated with lower testosterone levels [117]. An experimental study also observed that $PM_{2.5}$ altered the blood-testis barrier (BTB) through excessive ROS-mediated autophagy [118]. These air pollutants may also induce hypoxia, thus contributing to their negative impacts on circulating testosterone, spermatogenesis, and sperm quality, and ED [4].

2.5. Respiratory tract infection and male reproduction

Air pollution has been projected to increase with climate warming and changing patterns of atmospheric circulation [119]. Several urbanized regions in the world are experiencing changing air pollution patterns with an adverse impact on pulmonary health [120]. Over time, pulmonary diseases are constantly increasing globally, especially allergic diseases such as asthma and rhinitis due to climate change [121,122]. It is well documented that a change in climate directly induces airway inflammation, leading to allergen-induced respiratory responses (allergic respiratory diseases) and/or indirectly increases susceptibility to risk factors for respiratory tract infections [123].

Patients with respiratory tract infections and COPD may have symptoms compatible with hypogonadism and a defective reproductive system. This could result in testicular dysfunction [4] and atrophy of the Leydig cells via hypoxic inhibition of pituitary gonadotropin secretion in patients with COPD [4,124]. The effects of hypoxia on steroidogenesis vary with the duration of exposure. Transient hypoxia may enhance testosterone synthesis through stimulation of autophagy [125] and upregulation of steroidogenic enzymes and voltage-gated L-type calcium channel [4,126]. Acute exposure to hypoxia drives cholesterol into the inner mitochondrial membrane, where it is converted by desmolase to pregnenolone, which is in turn acted upon by other steroidogenic enzymes at various stages to produce testosterone [126]. On the other hand, chronic exposure to hypoxia, as seen in COPD, impairs steroidogenesis via suppression of the hypothalamic-pituitary-testicular axis [4]. The impact of hypoxia on testosterone biosynthesis is attributable to hypoxia-induced atrophy of the Leydig cells that are responsible for testicular steroidogenesis.

Climatic variation increases predisposition to respiratory tract infections, including SARS-CoV-2 infection, which may impair testicular steroidogenesis and suppress circulating testosterone via multiple mechanisms [127,128] (Fig. 6). The evidence that SARS-CoV-2 infection induces orchitis suggests that testicular infections might damage the testis-blood-barrier and permit viral shedding into semen [128]. This impairs male fertility by disrupting the endocrine function of the testis, resulting in a reduction of serum testosterone [129]. SARS-CoV-2 infection may also induce inflammatory orchitis, resulting in fibrosis and further loss of testicular functions (Pan et al., 2019; [130,131]). Local inflammatory testis-blood barrier damage might potentially lead to indirect semen infection (Ediz et al., 2020) and a reduction in sperm quality.

The presence of low-grade systemic inflammation in COPD may trigger extra-pulmonary manifestations, including hypogonadism [132] and reduced testosterone level [133]. Moreover, testosterone deficiency can contribute to elevated levels of cytokines [134], which may trigger oxido-inflammatory injury to the testis and sperm cells [135]. Sergerie et al. [136] reported that a febrile episode could have marked effects on semen parameters and sperm DNA integrity, and this might be related to future infertility. The sperm abnormalities observed following infections are most likely the result of a combination of systemic fever and the direct DNA damage of the sperm cells, resulting in apoptosis and a sharp decline in fertility [137,138]. It has been reported that an episode of influenza and hyperthermia alters human sperm chromatin structure, thus impairing sperm integrity and function [139].

2.6. Sexually transmitted infections and male reproduction

Climate change influences the incidence of sexually transmitted infections via various means. In a study by Burke et al. [140] employing a study population of 2000 people across 19 African countries, a rain

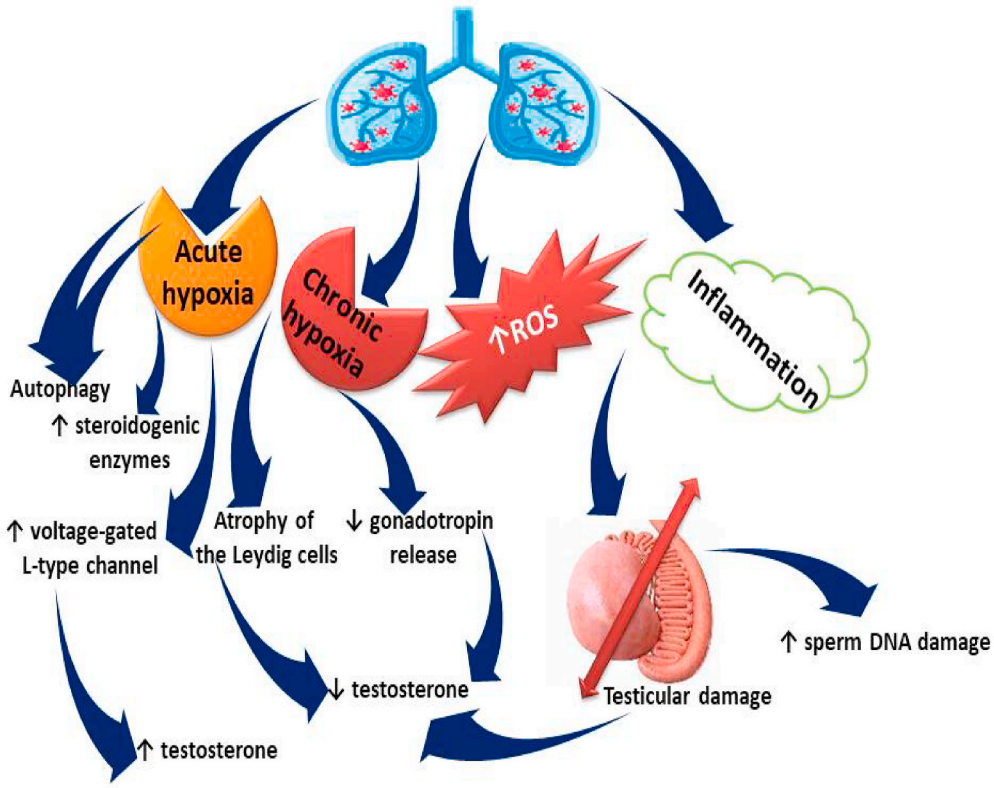

Fig. 6. Effect of pulmonary infections on testicular functions.

shock was linked with an 11 % increase in HIV prevalence. Similarly, a study conducted in Lesotho showed that drought occurring two years earlier was associated with higher HIV prevalence among adolescent girls in rural locations [141]. Food insecurity due to climate change is associated with HIV acquisition risks by increasing decisions to engage in transactional sex for survival [142]. Food insecurity has also been associated with increased sexual risk practices in HIV-positive youths in sub-Saharan Africa, and also decreases safer sex efficacy in HIV-positive women [143]. Food insecurity exacerbates health outcomes among HIV patients by weakening the immune defense, disrupting access to sexual health care, and compromising the adherence to and effectiveness of highly active antiretroviral therapy (HAART) [144,145]. In addition, climate change has been linked with reduced condom efficacy among adolescents [146] and reduced condom use among adults [147]. The report by Lancet Countdown published in 2020 shows that climate change causes extreme weather and rising sea levels, which lead to migration and displacement and pose risks to sexual health [148–150]. Climate change is also changing the distribution of infectious diseases such as malaria and diarrheal, which will make populations more susceptible to the acquisition of HIV and decrease health outcomes [151, 152].

There is enough scientific literature explaining the incidence of hypogonadism in HIV-infected patients though this is still a subject of debate due to the absence of a standardized consensual diagnostic method. Though the exact mechanism is not fully understood, HIV has been shown to impact male fertility by altering the levels of serum testosterone. Ochsendorf [153] explained that testicular function is impaired in HIV with the progression of immunodeficiency. HIV induces secondary hypogonadism and, as a result, decreases testosterone and LH levels. Although not as common as HIV-induced secondary hypogonadism, HIV also induces primary hypogonadism that is associated with a low level of testosterone and a high level of LH [154]. These demonstrate that HIV may directly induce toxicity to the testis, and impair testicular steroidogenesis despite optimal Leydig cell functions, and suppress the hypothalamic-pituitary-testicular axis, resulting in declining levels of LH and testosterone. Testosterone deficiency is observed in 50 % of HIV patients prior to receiving antiretroviral therapy and in 20–25 % of patients after receiving antiretroviral therapy [155–157].

Prior to the use of HAART, androgen deficiency was the most common hormonal abnormality detected [158–160]. In addition, this abnormality is usually not resolved during HAART [160] (Fig. 7). HIV causes testosterone deficiency by suppressing gonadotropin concentrations, which may be a result of hypothalamic-pituitary dysfunction [161]. The observed hypothalamo-pituitary dysfunction in HIV-positive men indicates suppressed secretion of gonadotropin releasing hormone (GnRH), which may lead to decreased secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). This may contribute to the decrease in testosterone and dihydrotestosterone (DHT) levels. Sex hormone-binding globulin (SHBG) levels are often reduced in HIV-positive patients [162]. Diabetes, obesity, and diabetes may contribute to the decrease in the concentration of SHBG in HIV-positive patients [161]. SHBG binds to testosterone, dihydrosterone, and estrogen, thus regulating the bioavailability of these sex hormones.

Cases of oligozoospermia and azoospermia have been reported in AIDS patients [163]. As the disease progresses, abnormal sperm morphology is increased [153], and grossly abnormal sperm cells and leukocytospermia have been reported when HIV develops into AIDS. Crum-Higher semen viscosity and low sperm count have been reported in retroactive patients. Cianflone et al. (2007) attributed the low sperm count in HIV-positive patients to low testosterone, while Van Leeuwen et al. [164] attributed the higher viscosity of the semen to the disruption of normal function of the seminal vesicles and the prostate gland.

It is surprising that despite the effectiveness of antiretroviral drugs in

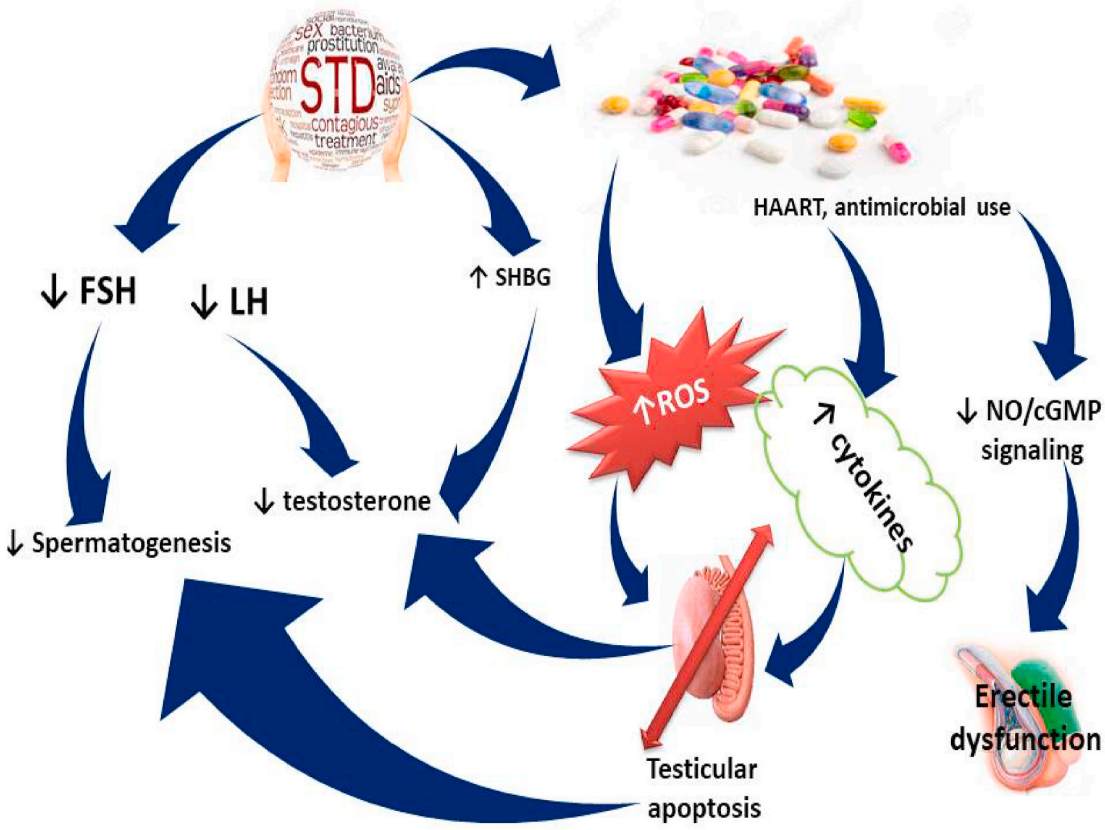

Fig. 7. Effect of sexually transmitted infections on male reproductive functions.

the management of HIV/AIDS, they exert similar effects like HIV infection on the male reproductive functions. Although this is an indirect impact of HIV/AIDS on male reproduction, the effects should not be downplayed. Some studies have reported alterations in the sperm quality of HIV-positive patients on non-nucleoside reverse transcriptase inhibitors [165–167]. Savasi et al. [168] also observed an increased SDF rate in HIV-infected patients on HAART. Findings in animal models revealed that HAART impaired male sexual competence via a testosterone-dependent mechanism [169] and through downregulation of NO/cGMP signaling [170]. This was associated with suppression of spermatogenic enzymes [171], low sperm quality with increased sperm DNA damage, and ROS-mediated testicular damage [172]. Studies have shown that HAART directly suppresses testicular function, which is accompanied by reduced testicular weight, and may also suppress the hypothalamic-pituitary-testicular axis, as evidenced by reduced circulating LH and testosterone [74,169].

Herpes simplex virus (HSV) has been associated with low sperm count and reduced sperm motility [173,174]. The ability of the virus to infect almost all organs of the male reproductive tract could facilitate its adverse effects on male reproductive function, including reduction in sperm quality. Similar to the Mumps virus, the Ebola virus was also shown to be associated with Sertoli cells and BTS disruption, which has dire consequences on endocrine and spermatogenic functions of the testes [175]. About 5–8% of the survivors of Ebola virus infection have reported complaints of erectile dysfunction and another 10–12 % of reduced sexual desire, possibly due to compromised endocrine function of the testes [176,177].

2.7. Cardiovascular disease and male reproduction

There is scientific evidence that increased temperature due to climate change may lead to a higher incidence of weather-related morbidity and mortality, largely through deaths from cardiovascular events [178]. Climate sensitivity for cardiovascular diseases increases the predisposition to cardiovascular diseases and also exacerbates existing cardiovascular disease. Bhaskaran et al. [179] showed that increased ambient temperature promotes acute myocardial infarction. Extremely high or low temperatures may lead to the development of cardiovascular disorders in susceptible, aging populations [180]. In addition, increase in death rate during heat waves is related to cardiovascular (13–90 %) and cerebrovascular diseases (6–52 %). High temperature can cause increased platelet and red cell count, blood viscosity, serum cholesterol levels, and mortality as a result of coronary and cerebral diseases [181]. Increased temperature induces physiologic changes such as elevated cardiac output (CO), leading to dehydration, hypotension, endothelial damage, and elevated peripheral resistance [182]. Low ambient temperatures can cause a rise in blood pressure, heart rate, and systemic vascular resistance, while raising the levels of plasma norepinephrine and vasoconstrictor peptides. Extremely low temperatures may trigger increased blood pressure due to increased CO and sympathetic muscle nerve activity, with consequent rise in peripheral resistance [183].

Studies demonstrating the link between the pathophysiology of cardiovascular diseases and its implication in infertility abound (Fig. 8). This relationship may be dependent on testosterone deficiency in male infertility. Cardiovascular diseases are associated with reduced

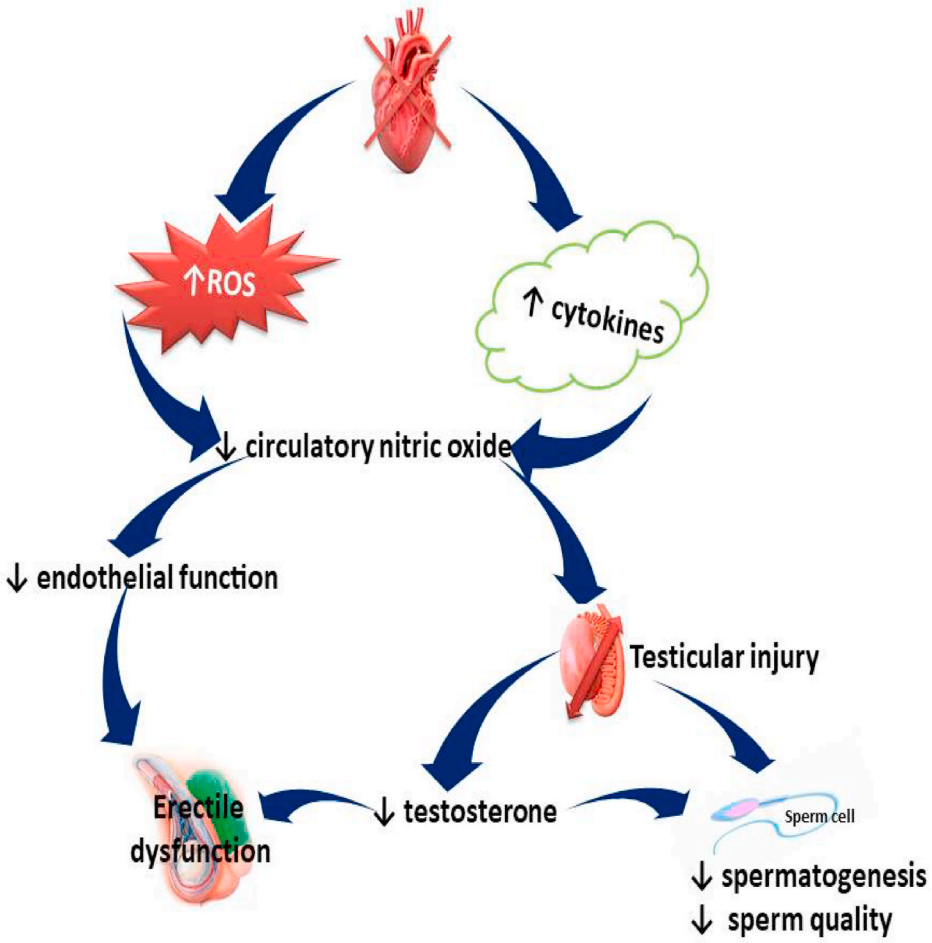

Fig. 8. Effect of cardiovascular disease on male reproductive functions.

testosterone levels [184]. Goodale et al. [185] also noted an inverse relationship between circulating testosterone levels and the severity of coronary artery disease (CAD). This implies that circulating testosterone levels decrease as the severity of CAD increases. Low testosterone levels have been associated with high triglyceride and low high-density lipoprotein levels, which are common features in cardiovascular diseases [134]. Reduction in testosterone concentration is associated with increased levels of inflammatory markers such as TNF-α, IL-6, and IL-1β [134], with resultant oxido-inflammatory injury to the testis [135] and promotion of atherosclerotic process [186] that may impair endothelial function and lead to erectile dysfunction [90,134]. Endothelial dysfunction may also impair testicular microcirculation, thus reducing testicular blood flow and increasing testicular and sperm cell DNA fragmentation.

Although the phenomenon is debated, decreased semen quality has been observed in cardiovascular disorders [187]. Hypertension is associated with lowered semen quality, including increased abnormal sperm morphology and sperm DNA fragmentation [188,189]. Hypertensive states may also decrease lumen/wall proportion of intratesticular arterioles, promote hyalinization, and increase vascular volumetric density [190]. Cardiovascular diseases may lead to the impairment of spermatogenesis via vascular mechanisms [187]. Colli et al. [187] reported increased ROS generation in the sperm cells of hypertensive rats. This may induce lipid peroxidation, mitochondrial dysfunction, and DNA damage of the sperm cells, resulting in reduced sperm count and concentration and impaired sperm function. Colli et al. [187] also revealed an increase in the population of sperm cells with damaged acrosomes in hypertensive rats.

Interestingly, some anti-hypertensives have also been shown to impair male fertility. Beta-blockers reduce sperm motility and increase sperm anomalies, which is associated with distorted testicular histoarchitecture and a decline in testosterone production ([191]; el-Sayed et al., 2017). Schlosser et al. [192] and Brezina et al. [193] also demonstrated that calcium blockers caused a marked reduction in sperm motility and viability, which was accompanied by impaired calcium transmembrane movement and spermatozoa-oocyte interaction. Spironolactone inhibits testicular and adrenal cytochrome P450, resulting in suppressed testosterone production [194]. Spironolactone and digoxin also impair libido and sexual function by inducing endothelial dysfunction ([195]; VIDAL Hoptimal, 2016). Methyldopa induces ejaculatory dysfunction by activating pre-synaptic α2-adrenergic receptors and impairing central sympathetic tone (VIDAL Hoptimal, 2016).

2.8. Cancer and male reproduction

Climate change creates a favorable condition for more production of carcinogens and exposure to carcinogens [196]. Extreme weather events increase the amount of carcinogens in human communities. Climate change is causing longer wildfire seasons and larger fires, which are sources of air pollutants such as particulate matter known to induce cancer [196]. Scientific literature presents projections of the future impact of climate change on the incidence of cancer among humans. For example, climate change has been projected to increase dietary exposure to aflatoxin [197], which is a potent carcinogen produced by fungi that can contaminate staple food crops [196]. Climate change has accelerated rapidly in the past half century, and the effects on the incidence of human diseases such as skin cancer have been established [198]. Climate change specifically increases the incidence of cutaneous malignancy due to increased ultraviolent radiation. According to Van der Leun and de Gruijl [199], the incidence of climate-related skin cancer would peak around 2050. For every 1 % reduction in the thickness of the ozone layer, there would be an increase in the incidence of melanoma by 1–2%, while the incidence of squamous cell carcinoma (SCC) would increase by 3–4.6 % and basal cell carcinoma (BCC) by up to 2.7 % [200]. Increased exposure to fine particles and other sources of air pollution contributes to the burden of lung cancer [201].

Chan et al. [202] demonstrated in a community-based study that increased incidence in any cancer was associated with low testosterone and dihydrotestosterone. This is an extension of the study by Kuper et al. [203] that showed that serum testosterone levels were significantly lower among patients with hepatocellular carcinoma and metastatic liver cancer, although serum hormone-binding globulin levels did not differ significantly. Interestingly, the long-held belief that high circulating level of testosterone promotes incident prostate cancer is rapidly losing credence. Current evidence demonstrates that maximal androgen-stimulated growth of prostate cancer is achieved at a relatively low level of serum testosterone [204]. However, these are not in agreement with the reports of Watts et al. [149,150], that showed that higher testosterone levels were associated with increased risks of melanoma, prostate cancer, and hepatocellular cancer.

Nonetheless, the impact of cancer on male fertility is beyond the disease itself (Fig. 9). The management of cancer, which includes chemotherapy, radiotherapy, and surgery, may negatively impact male fertility more than the cancer itself. Impaired spermatogenesis in the contralateral testis, resulting in azoospermia following unilateral orchidectomy, has been reported [205]. Also, Centola et al. [206] demonstrated a decrease in sperm count following exposure to megavoltage radiation with testicular doses between 28 and 90 cGy. Lampe et al. [205] observed that about 24 % of patients were oligospermic and another 24 % were azoospermic before the commencement of chemotherapy. However, after chemotherapy, only 64 % of the initially normozoospermic patients remained normozoospermic, while others were either oligozoospermic or azoospermic. However, some of these cases are reversible, and those with irreversible lowered sperm quality may benefit from sperm preservation facilities.

2.9. Mental health and stress-related disorders and male reproduction

In 2001, the average temperature had risen by 0.5 °C due to anthropogenic emissions [207], and it was predicted to further increase by 2.4–5.8 °C in 2100 AD [208]. Anderson [209] showed a relationship between an increase in ambient temperature and aggressive behaviour. Other studies also suggest a relationship between aggressive behaviours and high temperatures, especially in the summer [210–212]. Studies have also shown an increase in the rate of suicides with the recent rise in temperature [213–215]. In addition, Nitschke et al. [216] reported that heat waves are associated with an increase in admissions for mental and behavioral illnesses such as mood and anxiety disorders in Australia.

Furthermore, climate change is also responsible for natural disasters such as drought, bushfires, hurricanes, flood, and famine, with attendant economic woes that have negative psychological consequences [212]. Individuals exposed to these situations are at risk of suffering from posttraumatic stress disorder (PTSD) (McMillen et al., 2002; DeSalvo et al., 2007). Survivors of these natural disasters are usually at a greater risk of acute stress reaction and adjustment, and anxiety spectrum disorders (Viswanath et al., 2013; North, 2014). Other mental health effects may include the development of acute and transient psychosis, relapse of bipolar disorder, bereavement (grief reaction) or depression [212].

Specifically, drought caused by climate change has been reported to be associated with farmer suicides in developed countries like Australia and developing countries like India (Deshpande, 2002; Sarma, 2004; Hanigan et al., 2012; Guiney, 2012). Crop failure as a result of the unexpected drought can lead to economic hardships, and this may increase suicidal incidences. Prolonged droughts trigger migration and/or pursuit of alternative means of livelihood, which may induce acculturation stress and further increase suicide attempts [212].

According to Berry et al. [217] and Padhy et al. [212], adaptation and mitigation measures taken to acclimatize to the changing environment or to lessen the effect of environmental change in the future may aggravate mental health risks through various causal pathways. According to Padhy et al. [212], migrants are more prone to schizophrenia than the host population. Therefore, individuals forced to migrate as a

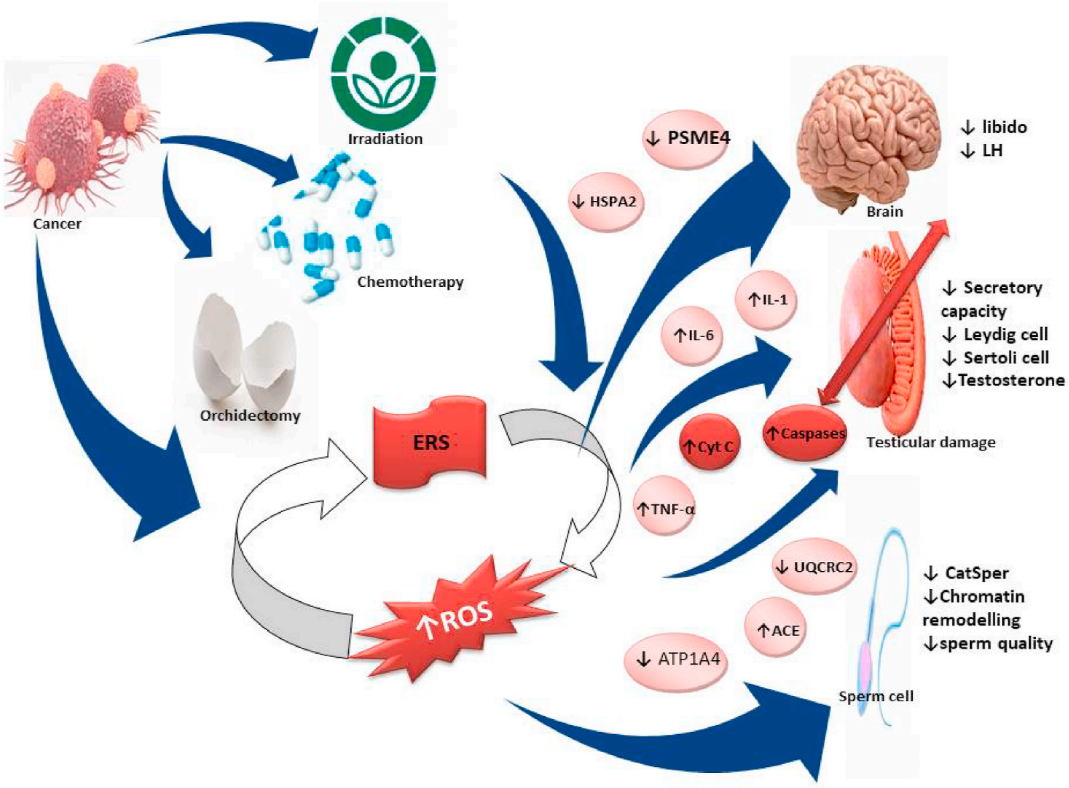

Fig. 9. Effect of cancer on male reproductive functions.

result of climate-related disasters are at a greater risk of developing psychological problems and psychiatric illnesses compared to those who choose to migrate voluntarily [212]. The cause of migration may also influence the susceptibility to incident psychological problems in individuals. Those individuals who have to migrate after strife and disasters are at a higher risk of serious psychiatric illnesses as compared to those who choose to migrate voluntarily [218].

Ilacqua et al. [219] showed that psychological stress may decrease the levels of LH and testosterone in male subjects (Fig. 10). Pre-clinical data revealed that *acute* stress impaired testicular function coupled with increased levels of cortisol, and apoptosis of the Leydig and germ cells [220,221]. Stress-induced testicular injury and Leydig and germ cell apoptosis may be due to the associated suppression of glutathione-dependent defense capacity in the testis [116].

Zou et al. [222] demonstrated an increased level of serum corticosterone and upregulation of glucocorticoid receptor (GR) expression in chronic mild stress exposure. The observed decrease in serum testosterone levels due to mental health disorders such as depression and anxiety in subfertile males may be a result of the decrease in the secretion of SHBG and dehydroepiandrosterone sulphate (DHEA-S), and the higher secretion of cortisol and prolactin [223].

The biochemical feminization of males (that is, a reduction in

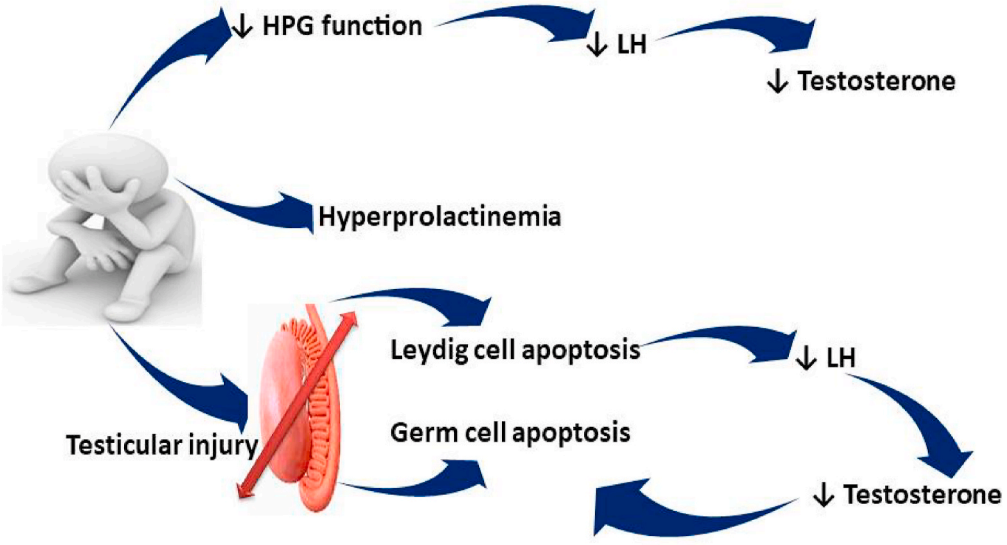

Fig. 10. Effect of mental stress on circulating testosterone and germ cells.

testosterone and LH) induced by climate-related mental health disorders is characterized by decreased semen parameters. Reduction in LH and testosterone levels results in a decrease in spermatogenesis and sperm quality [224,225]. According to Zou et al. [222], chronic mild stress reduced the spermatid population and increased the severity of apoptosis in seminiferous tubules. Stress may also induce sperm maturation arrest at the G_0/G_1 phase [222]. The findings of Zou et al. [222] are similar to those of Wdowiak et al. [223], who revealed that depression and anxiety induced a reduction in semen volume and sperm density in male patients.

2.10. Heat waves and transgenerational sperm damage

Heat waves are one of the extreme weather events that threaten human existence and continuity of life in the changing earth [226–228]. It is usually characterized by warm air masses and high temperatures in consecutive nights [229]. This extreme climatic condition is predicted to occur more frequently and likely to alter normal biological functions [19,230,231], including male reproductive function. The mammalian male reproductive system is sensitive to increases in temperature, and physiological adaptations that permits cooling of the testicular environment (2–8 °C below core body temperature) is important for normal reproductive function [232]. The warmer air occurring in heat waves due to climate change could impact sperm traits, their ability to fertilize, and the phenotypes of the offspring [233]. Typical of climate-related heat waves, the effects of an increase in temperature are abnormal spermatogenesis and sperm damage [234,235]. This is particularly interesting because sperm damage due to heat wave has transgenerational impacts, which include decreased life expectancy and poor reproductive potential of offspring fathered by males that had experienced heat waves [236].

The testes are suspended in a scrotum located outside the body so as to keep the temperature 2–4 °C lower than that of the core body temperature. This is necessary for optimal spermatogenesis [237]. Increased testicular temperature leads to a reduction in the circulating levels of testosterone, LH, FSH, and GnRH but an increase in serum cortisol levels [238]. The decreased levels of sex hormones have a negative effect on spermatogenesis with an attendant transgenerational impact. Exposure to increased ambient temperatures enhances ROS generation by directly affecting cellular metabolism, resulting in testicular germ cell damage and endocrine disruption [239]. This is associated with a decrease in inhibin B, a biomarker of spermatogenesis [240] and reduced sperm motility and density [241]. Exposure to heat stress does not only alter semen quality; it modifies the seminal plasma proteome [242].

Transgenerational epigenetic inheritance refers to the transmission of epigenetic information from one generation to the next through the germline. The main epigenetic mechanisms are DNA methylation, functional noncoding RNA, chromatin structure, histone modifications, and RNA methylation [243]. During spermiogenesis, transition proteins, then protamines replace the nuclear histones. During epididymal transit of spermatozoa, disulfide bonds formation aid chromatin stability ([244]; Gan et al., 2019). Protamine-induced sperm chromatin condensation is very important for normal sperm fertility potential, and subsequently embryonic development [245,246]. Sperm cells with abnormal morphology cannot complete the process of spermiogenesis ([247]; Sakkas et al., 2016) due to modifications in chromatin remodeling, abortive apoptosis, and oxidative stress [248,249], with consequent negative impacts on male offspring.

Exposure to heat induces sperm DNA damage [250], a major cause of defective sperm function, which includes DNA denaturation and SDF. This has been implicated in the aetiopathogenesis of infertility, recurrent spontaneous abortion (RSA), and pre- and post-implantation losses [251]. SDF also causes loss of integrity of both the mitochondrial and nuclear genomes [252], which may be consequential upon altered histone to protamine ratio and abortive apoptosis [252]. Sales et al. [236] also reported a significant reduction in the ability of males exposed to a single heat wave to sire offspring. The reproductive ability of male offspring sired by fathers exposed to heatwaves is also reduced [236].

Alterations in these epigenetic parameters can have short- or long-term effects on genome activity and then become transgenerational when the germline is involved [253] (Fig. 11). DNA methylation has significant implications for gamete integrity and the transmission of epigenetic information to the next generation [254,255]. More so, modification of the sperm methylation pattern can lead to widespread repercussions on chromatin integrity and gene expression [256].

2.11. Potential preventive and therapeutic approaches

Studies have revealed some preventive and therapeutic strategies that may alleviate the consequences of climate change on male reproductive health. These measures include the use of pharmacological drugs and nutraceuticals that directly target associated pathways linking the adverse events of climate change with reproductive dysfunction.

2.11.1. Heat stress-induced male reproductive dysfunction

Amino acids particularly glutamine, taurine and arginine, have been shown to possess antioxidant properties that can mitigate oxidative stress caused by heat exposure in the testes ([257,258]; Jiang et al., 2018). It has also been demonstrated that dietary supplementation with arginine improved antioxidant capacity in heat-stressed boars, leading to improved sperm quality and testicular function. Some certain amino acids can modulate the expression of heat shock proteins (HSP) which play a crucial role in cellular protection against heat stress (Zhao et al., 2017). It was investigated that leucine supplementation upregulated heat stress production (HSP) expression in heat-stressed boar testes contributing to improved spermatogenesis. It is evident that amino acids like carnitine and arginine can help maintain mitochondrial function in sperm cells under heat stress conditions [259]. A study carried out by Longobardi et al. [260] reported that L-carnitine supplementation improved mitochondrial function and sperm motility in heat-stressed rams. More so, some amino acids processes anti-apoptotic effects which have been shown to reduce heat-induced apoptosis in testicular cells, this was observed in taurine supplementation which reduces apoptosis in testicular germ cells of heat-stressed rats [261]. Certain amino acids can help maintain hormonal balance which are often disrupted by heat stress [262].

Also, antibiotics and antioxidants have been shown to alleviate heat stress-induced reproductive dysfunction. According to Durairajanayagam et al. [40,263], it was emphasized that heat stress can increase susceptibility to genital tract infections which may exacerbate reproductive dysfunction. However, some antibiotics have been shown to mitigate antioxidant properties which could help reduce oxidative stress associated with heat exposure [264]. The antioxidant and anti-inflammatory properties of some certain antibiotics, including tetracyclines and quinolones could potentially mitigate oxidative damage and reduce inflammation in reproductive tissues [265]. Antioxidants, particularly vitamin E and selenium help maintain the structural integrity of sperm cell membranes which are rich in polyunsaturated fatty acids and vulnerable to lipid peroxidation under heat stress conditions. Antioxidant decreases testicular damage caused by oxidative stress, apoptosis in germ cells [14,266]. Antibiotics can alter the gut microbiome and gut flora which may indirectly affect reproductive function through the gut-testis axis [267]. Agarwal et al. (2020) emphasized that certain antibiotics could affect sperm parameters, suggesting direct interactions with reproductive cells which prevented apoptosis and decrease total sperm defects [268]. Antioxidants like vitamins C and E protect sperm DNA from oxidative damage, reducing the risk of DNA fragmentation and potential genetic abnormalities in offspring [269].

In addition, enzyme inhibitors and hormones offers a multifaceted approach to ameliorating heat stress-induced male reproductive dysfunction. It is well established that certain enzyme inhibitors such as

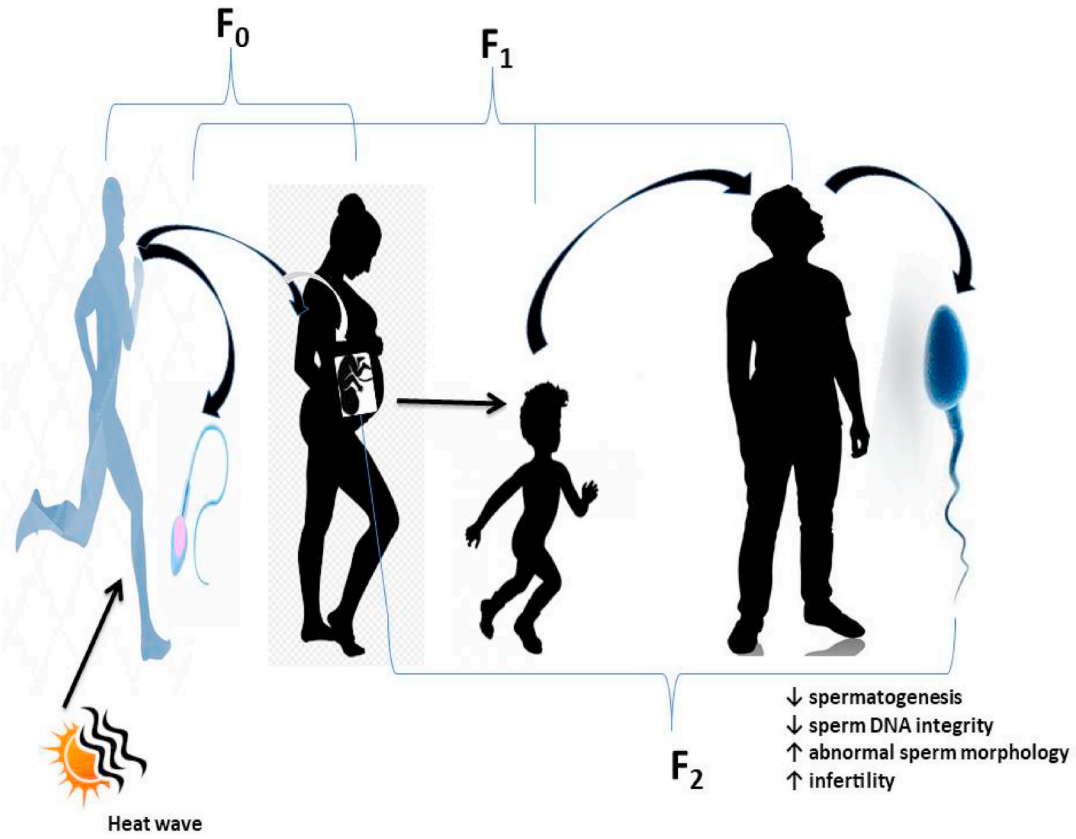

Fig. 11. Effect of heat wave on epigenetic modification of male reproduction.

allopurinol decrease apoptosis in germ cells [270]. Moreover, hormones such as melatonin Increases normal live sperm and decrease abnormal and dead sperm [271]. However, melatonin decrease vacuolization of seminiferous tubules and increase tubules with regular seminiferous epithelium and multiple layers of germ cells [272].

Furthermore, many minerals and natural substances act as antioxidants, neutralizing reactive oxygen species (ROS) produced during heat stress [239]. According to Xavier et al. [273], it was proven that minerals such as Selenium and Vitamin E improved tubular diameter and seminiferous epithelium. However, natural substance such as co enzyme Q10 improved semen quality and male fertility. It was further established that there was a decreased oxidative stress by increased main antioxidant testicular enzyme (GSH) and decreased MDA. Minerals such as selenium and zinc enhanced endogenous antioxidant systems and boost the activity of antioxidant enzymes such as glutathione peroxidase and superoxide dismutase [274]. Natural substances like omega-3 fatty acids and minerals like zinc help preserve sperm membrane integrity under heat stress conditions [275] Some natural substances like curcumin have been shown to help regulate testicular temperature and exhibit anti-inflammatory properties under heat stress conditions [276,277]. Minerals like zinc and natural substances like L-carnitine also support various stages of spermatogenesis under heat stress conditions [278].

More so, phenolic compounds are potent antioxidants that directly neutralize reactive oxygen species (ROS) generated during heat stress, protecting sperm membrane integrity and testicular cells from oxidative damage [279]. Moreover, it also upregulates endogenous antioxidant system through the expression of antioxidant enzymes such as superoxide dismutase (SOD), catalase and glutathione peroxidase [280,281]. Phenolic compounds prevent DNA fragmentation and oxidative DNA damage in sperm cells exposed to heat stress as well as the modulation of heat shock proteins (HSPs) ([282]; Shain et al., 2013). Phenolic compounds processes anti-inflammatory effects and it has been studied that resveratrol and quercetin exhibited potent anti-inflammatory properties potentially mitigating heat-induced inflammation in testicular tissue and also preventing excessive germ cell death induced by heat stress [283,284]. It is evident to know that certain phenolic compounds improve spermatogenesis, enzyme activity and potentially helping to maintain hormonal balance disrupted by heat stress as well as sperm motility [285,286]

Many vitamins such as vitamin E, C and herbs such as and Withania somnifera (Ashwagandha) boost the activity of antioxidant enzymes and also act as potent antioxidants, neutralizing reactive oxygen species (ROS) produced during heat stress [239,287]. However, it has also been shown to protect sperm membrane integrity and protect against DNA damage [249,288]. Mounting evidences have also shown that vitamin D can help to maintain hormonal balance [289]. Vitamins like E, A and herbs such as Curcuma longa (Turmeric) exhibit anti-inflammatory properties as well as supporting various stages of spermatogenesis potentially mitigating heat-induced inflammation in testicular tissue (Gonzales et al., 2014; [290]) (Table 1).

2.11.2. Cold stress-induced male reproductive dysfunction

Vitamins, particularly A, C and E act as powerful antioxidants that helps in neutralizing reactive oxygen species (ROS) generated during cold stress [274]. Vitamin E in particular helps in maintaining the structural integrity of sperm membranes and DNA protection which are vulnerable to lipid peroxidation under cold stress conditions [336,337]. It has also been noted to regulate testicular temperature and enhance spermatogenesis under stress conditions [338,339]. Vitamin D has been studied to modulate hormonal balance and regulate apoptotic signaling pathways which can be disrupted by cold stress [340,341].

Studies have shown that resveratrol and quercetin are potent antioxidants that directly neutralize reactive oxygen species (ROS) generated during cold stress, protecting sperm and testicular cells from oxidative damage and inflammation [280,342]. More so, phenolic compounds help in protecting sperm membrane integrity and DNA

Table 1
Preventive and therapeutic approaches on heat stress-induced reproductive dysfunction.

Reference	Model	Intervention	Dose/Route	Duration	Effects and Mechanisms
Amino Acids					
[257,258]	Pig	l-arginine	0.6, 0.8 or 1.0 % of basal diet	42 days	Increase semen quality and libido during hot weather. 1.0 % group had great semen quality and antioxidant capacity. 0.8 % group had better libido
[259]	Rat	l-arginine	15 mg/100 kg BW (oral)	8 weeks	Decreases testicular oxidative stress but did not improve outcomes with cryptorchidism
Antibiotics					
[291]	Rat	Minocycline (semisynthetic, 2nd generation tetracycline)	Spermatogenic cells cultured in vitro 45 mg/kg BW (i/p)	12 h	Suppressed release of cytochrome C which triggers HS-induced apoptosis from mitochondria (in vivo and in vitro). Significantly lowers number of TUNEL-positive cells (Terminal deoxynucleotidyl transferase-mediated deoxy-UTP end labelling).
[292]	Mouse	Minocycline (semisynthetic, 2nd generation tetracycline)	100 mg/kg BW (oral)	7 days	Inhibited germ cell apoptosis induced by dexamethasone. Increase Johnsen score and sperm/testis
[268]	Horse	Pentoxifylline	17 mg/kg BW, 2x/d (oral)	30 days	Increase total motility and rapid sperm within 14 days. Increase lipid peroxidation. Prevented apoptosis and decrease total sperm defects
Antioxidant Cocktail					
[269]	Pig	Mixed multi-antioxidant supplement	100 g/d for (oral)	42 or 84 days	Antioxidant supplementation for 42 or 84 days in tropical summer Decrease harmful effects of HS on DNA integrity, but not on sperm concentration or motion end points
[14,266]	Rat	Mixed multi-antioxidant supplement	One capsule in 10 mL saline; 1 mL i/p (once)	48 h	Decrease testicular damage caused by oxidative stress, apoptosis in germ cells and [spermatogenesis; protected fertility after irradiation.
Enzyme Inhibitors					
[270]	Rat	Xanthine oxidase inhibitors (**Allopurinol and BOF-4272**)	Allopurinol: 0.1e100 mg/kg BW (i/p) daily after surgery BOF-4272: 300 mg/kg	7 days	Both compounds attenuated weight reductions of cryptorchid testis. Decrease apoptosis in germ cells (in-situ staining of fragmented DNA). Potential treatment of male infertility due to HS
Hormones					
[293]	Rat	GnRH agonist and antiandrogen	Implant GnRH agonist + daily injections of anti-androgen.	14 days	Did not prevent initial decline in testicular mass or % abnormal sperm after heating (35 d post-heating), but lessened subsequent decreases in testicular mass and sperm count (182 d post-heating)
[271]	Chicken	Melatonin	Melatonin: 3 mg/kg BW (oral)	20 days	Increase normal live sperm Decrease abnormal and dead sperm. Melatonin had positive impact on hatch weight and relative spleen weight of chicks. Fertile eggs not affected
[294]	Rat	Melatonin	0.7 mg/kg BW (i/p)	56 days	Epididymis of ipsilateral testes and bilateral cryptorchid with melatonin were oligospermic compared to azoospermic control. No change in sperm concentration or motility, or testosterone concentrations.
[295]	Rat	Melatonin	Given 24 h of Melatonin (10 mg/kg), immediately before (20 mg/kg) and 24 h after irradiation (10 mg/kg) (i/p)	24 h	Decrease apoptosis Decrease immunoreactivity of caspase-3 (apoptosis marker). Based on electron microscopy, inhibited degenerative changes in spermatogenic cells after irradiation, especially spermatocytes
[272]	Mouse	Melatonin	20 mg/kg BW at 2 h before 42 °C treatment (i/p) 20 mg/kg BW daily (immediately after 42 °C treatment) (i/p)	14 days	**Melatonin pre-treatment** Decrease vacuolization of seminiferous tubules. Increase tubules with regular seminiferous epithelium and multiple layers of germ cells post-HS Decrease malondialdehyde (MDA) and hydrogen peroxide (H2O2) generation (markers of ROS).

(*continued on next page*)

Table 1 (*continued*)

Reference	Model	Intervention	Dose/Route	Duration	Effects and Mechanisms
					Increase SOD and catalase (CAT) activity; implied alleviation of heat-induced oxidative stress Suppressed activation of JNK and p38 mitogenactivated protein kinase (MAPK) (apoptosis-related signaling pathway) and increase HSPA2 and anti-apoptotic B-cell lymphoma 2 (BCL-2) in testes (mitigated heat-induced damage). Melatonin post-treatment Faster recovery of spermatogenesis post-heat treatment apparent at 7 versus 14 d without melatonin. Preserved integrity of Sertoli cell tight junction
Minerals					
[296]	Mouse	Selenium	0.5 ppm/kg (oral)	8 weeks	Decrease apoptotic index of spermatocytes, round and elongated spermatids. Increase motile sperm and decrease ROS generation.
[273]	Goat	Selenium and Vit E	Selenium (0.1 mg/kg BW) and vitamin E (0.3 IU/kg BW)	120 days and 60 days prior to Scrotal installation (SI) and 18 days during (SI) and 42 days post (SI)	Maintained scrotal circumference, but failed to protect testes against degenerative changes 18 d after insulation. Improved tubular diameter and seminiferous epithelium height at 42 d after SI supplementation
[297,298].	Mouse	Zinc	10 mg/kg of zinc sulphate (i/p)	Every 2 days for 60 days	Promoted restoration of normal testicular structure 15 d after HS. Sperm motility, concentration and hypo-osmotic sperm test (HOST) positive sperm maintained without further deterioration at 30 d post-HS. Maintained fetus weight obtained from paternal heat treatment
[299]	Mouse	Zinc	300 mg/kg BW zinc sulphate orally	1 month before HS	Maintained relatively intact testicular structure with slight degeneration. Increase Ca, Zn, SOD Decreased MDA, maintained Nrf2 protein
[300]	Pig	Zinc	Zinc sulphate 1500 mg/kg BW (oral)	30 days	Decrease MDA and glutathione (GSH) in epididymis (alleviated oxidative stress). Restored integrity of caput epididymis epithelium and Y stress response
Natural Substances					
[301]	Boar	Betaine (methylamine naturally occurring in plant and animal tissues; used as feed additive)	0.63 or 1.26 % (oral)	10 weeks	Increase total sperm in ejaculate by 6 or 13 % (0.63 and 1.26 %, respectively). * 1.26 % betaine Increase % sperm with distal midpiece reflex (DMR), but 0.63 % did not affect sperm
[302]	Mouse	Betaine (methylamine naturally occurring in plant and animal tissues; used as feed additive)	250 mg/kg BW/d	For 14 d, before or after testicular HS	Treatment before and after HS [antioxidant defense ([activity of CAT and GPX enzymes). * Accelerated germinal epithelium regeneration, no change in epididymal sperm. * Improved epididymal sperm in intact mice (no HS).
[303]	Boar	Betaine (methylamine naturally occurring in plant and animal tissues; used as feed additive)	BET; 0.63 % of 96 % betaine + 250 phytase units BET; 0.63 % of 96 % betaine + super-dosed Phytase (2500 phytase units)	For 16 wk (4 wk before HS, 4 wk during HS and 8 wk after HS)	Partially mitigated effects of HS on sperm morphology; minimal effects on total or progressive motility. No improvement in semen production.
[304]	Chicken	Betaine (methylamine naturally occurring in plant and animal tissues; used as feed additive)	BET only: 1000 mg/kg BW BET (1000 mg/kg BW) + Vit C (200 mg/kg BW BET (1000 mg/kg BW) + Vit E (150 mg/kg BW) BET (1000 mg/kg BW) þ Vit C (200 mg/kg BW + Vit E (150 mg/kg BW)	52 weeks	Antioxidants, either individually or combined, induced complete recovery in sperm concentration, % live, pH, and fertility. All treatments restored total protein, globulin, AST, ALT, TAC, and MDA. Enhanced semen quality of roosters in hot regions
[305]	Rabbit	Coenzyme Q10	10 or 20 mg/kg BW (oral)	8 weeks	Both doses improved semen quality and male fertility, but induced sperm DNA damage and altered testes histology. Decreased oxidative stress by increased main antioxidant testicular enzyme (GSH) and decreased MDA
[306]	Rat	Gherlin (endogenous antioxidant)	At onset of heating, 2 nmol s/c,	Every 2 days for 60 days	Partial recovery in miotic index, spermatogenesis rate, presence of

(*continued on next page*)

Table 1 (*continued*)

Reference	Model	Intervention	Dose/Route	Duration	Effects and Mechanisms
					spermatocytes. Hastened testicular regeneration by day 30
(Li et al., 2014)	Mouse	Hydrogen sulphide (H2S) (Endogenous gaseous transmitter)	Before HS, NaHS 5.6 mg/kg BW (i/p)	3 days	Attenuated apoptosis cultures of testicular germ cells (inhibited effects of H2S on release of cytochrome C and Bax/Bcl-2 ratio). Enhanced mitochondrial function by increasing O2 intake and increase in ATP and SOD activity and a decrease in ROS
Phenolic compounds					
([307]; Li et al., 2014)	Mouse	Tert-butylhydroquinone (tBHQ, synthetic phenolic antioxidant)	10 mg/g tBHQ diet for 1 wk and then treated with scrotal heat. Single i/p injection of 100 mg/kg BW tBHQ, scrotal heat 3 h later. Single intra-testis injection of 12.5 mg/kg BW tBHQ and were exposed to heat before injection. 1 % tBHQ (w/w) for 1 wk in die	25 min	Testes from oral and i/p tBHQ-treated mice had increase compact interstitial cells and decrease germ cell loss. Decrease testosterone and decrease expression of cytochrome P450 17a-hydroxylase/17,20-lyase (CYP 17), a microsomal enzyme used to assess androgen output. Decrease MDA and Induced mild oxidative stress and further enhanced ability of cellular antioxidants to protect testicular cells from HS via the Nrf2 antioxidant system
[308]	Rabbit	Quercetin	Quercetin hydrate in diet (30 mg/kg)	8 weeks	Maintained semen quality and decrease oxidative stress.
Vitamins					
[309]	Human	Ascorbic acid	Ascorbic acid (400 and 600 mmol/L) in sperm suspension	2–4 h	600 mmol/L had more pronounced Decrease in static oxidation reduction potential (sORP) compared to 400 mmol/L. Reduced heat-induced oxidative stress (in vitro)
[310]	Rat	Vit E (a-tocopherol)	30 or 100 mg/kg BW (I/P)	15 days	Long-term increase in seminiferous epithelium region and maturation and reduced apoptosis and histological alterations. α-tocopherol before orchidopexia, particularly 30 mg/kg, partially protected undescended testis from ROS damage
[296]	Mouse	Vit E (Alpha-tocopherol)	200 mg/kg diet (oral)	8 weeks	Increase apoptotic index of spermatocytes, round spermatids and elongated spermatids. Increase motile sperm and decrease ROS generation, Decrease caspases 3, 8, 9 and apoptosis Increase BCl2.
[311]	Mouse	Vit E (Alpha-tocopherol)	20 IU/kg BW/d (oral)	75 days	Decrease free radicals and increase Sperm velocity straight line (SVSL), sperm velocity curved line. (SVCL) and sperm velocity average path (SVAP). Normalized seminiferous epithelium
[312]	Chicken	Vit E + organic	200 mg α-tocopherol/kg diet 0.3 mg organic Se/kg diet 200 mg α-tocopherol/kg diet þ0.3 mg Se/kg diet		All treatments increase semen quality. The combination decrease seminal plasma thiobarbituric acid reactive substances (TBARS) to ~28 % of controls and doubled activity of seminal plasma glutathione peroxidase
[313]	Cattle	Retinol	6 μM retinol as an antioxidant added to storage extender	3 h	Increase live, active and progressive sperm with an increase % membrane integrity at 41.5 °C supplemented with retinol compared to control
Traditional herbs					
[314]	Rat	Lycium barbarum (LBP, Chinese medicinal herb)	10, 50, 100, and 200 mg/kg/d	14 days for 15 min	Increase testis and epididymis weights (first three doses). Increase SOD activity and decrease MDA (all doses). Most seminiferous tubules had intact structure (especially 10 mg/kg dose).
[315]	Bovine Sertoli cell culture	Radix Puerariae (Chinese herbal medicine)	15 μM	Bovine Sertoli cell culture exposed to HS (42 °C for 1 h)	Supressed ROS production and decrease oxidative damage. Prevented initiation of mitochondria-dependent apoptotic pathway and increase expression of HSP 72
[316]	Bovine Sertoli cell culture	Baicalin (extracted from the dried root of Scutellaria baicalensis Georgi)	0.1, 1, 10, 20 mg/mL of baicalin	Bovine Sertoli cell culture exposed to HS (43 °C for 1 h)	Mitigated HS-induced cell apoptosis by modulating cell survival rate by activating the Fas/FasL pathway.

(*continued on next page*)

Table 1 (*continued*)

Reference	Model	Intervention	Dose/Route	Duration	Effects and Mechanisms
[317]	Bovine Sertoli cell culture	Baicalin (extracted from the dried root of Scutellaria baicalensis Georgi)	50 mg/kg BW	7 days	Increase activities of SOD, CAT and GSH-Px enzymes. Decrease MDA content and cellular apoptosis by blocking Fas/FasL pathway
[318,319]	Rat	Panax ginseng (Korean red ginseng, KRG)	100 or 200 mg/kg/d orally for 8 wk (starting from 1 wk before HS) or 100 or 200 mg/kg/day orally for 25 wk	25 weeks	Protected antioxidant related enzymes, proteins associated with spermatogenesis, sex hormone receptors and sperm quality in heat-stressed rats
[320]	Mouse	Kyung-Ok-Ko (KOK), also known in China as Qiong-yugao (traditional Korean medicinal formula)	0.25, 0.50 or 2.0 g/kg/d	5 weeks	Increase testes weights, sperm concentration and motility. Morphological appearance of seminiferous tubules was restored. Increase antioxidant enzyme activity
[321]	Mouse	Platycodon grandiflorum (PGS) saponins (named Jiegeng in China, Kilkyong in Korea and Kikyo in Japan)	15 or 30 mg/kg)	14 days	Protein expressions of testicular apoptosis Restored testicular structure to normal standards, with well-preserved tubular morphology. Prevented activation of MAPK signaling pathway, which contributes to oxidative stress and apoptosis.
[322]	Mouse	Angelica keiskei (Ashitaba, contains two chalcones, xanthoangelol [XA] and 4-hydroxyder ricin [4HD])	Angelica keiskei (Ashitaba) powder (57.5 mg/kg) Xanthoangelol (functional component, 3 mg/kg)	Testes in 41 °C water for 15 min and 42 °C for 20 min	Prevented impairment in sperm densities, progressive motility and lateral head displacement amplitude. Prevented reduction of the expression of Hspa1l and Hspa2
[323]	Rat	Decursin (Angelica gigas Nakai, Apiaceae)	400 mg/kg orally	4 wk after unilateral cryptorchidism.	Increase mean weight of cryptorchid testis. Maintained sperm counts, motility, and spermatogenic cell density. Increase SOD, [Nrf2 and HMOX1 and decrease apoptosis
[324]	Mouse	Nigella sativa Linn (Black Seed)	10 and 20 % in diet	15 min	Enhanced spermatogenesis and increase testosterone. Decreases MDA and increase antioxidant enzyme activity.
[325]	Rat	Mallotus roxburghianus Muell	Methanol extract (400 mg/kg)	30 min	Suppressed lipid peroxidation. Restored antioxidant enzymes and testosterone, restored spermatogenesis.
[326,327]	Mouse	Apigenin (4, 5, 7-trihydroxyflavone)	10, 20 or 50 mg/kg once daily	35 days	Increase testosterone and inhibin B. Increase SOD and GSH-Px activity and decrease MDA and Preserved seminiferous tubule diameter
[328]	Japanese quail	Apigenin (4, 5, 7-trihydroxyflavone)	0.3, 0.6 and 0.9 mL Parsley oil/kg diet (Parsley oil contains Apigenin)		Improved semen end points and decreases negative alterations in seminiferous tubules. Positive effects of Parsley oil attributed to antioxidant activity
[329]	Mouse	Green tea (Camellia sinensis)	500 or 750 mg/kg orally	20 min for 49 days	Recovered adverse effects HS on sperm concentration, total and progressive motility and hypo-osmotic swelling test (HOST) within 28 d after HS, compared to 42 d in control.
[330]	Japanese quail	Cinnamon (Cinnamon bark oil, CBO)	250 or 500 ppm	8 h	Decrease testicular lipid peroxidation, MDA. Increase spermatids, sperm and Improved testicular histology
[331]	Mouse	β-carotene and curcumin	b-carotene (10 mg/kg) and curcumin (20 mg/kg) orally	14 days	Restored normal testes weight and structure. Decrease MDA and increase SOD. Decrease mRNA for BCL2-associated X protein and caspase-3 (antiapoptotic).
[332]	Guinea pig	Guava leaves essential oil (GLEO)	100 mL GLEO/kg BW	60 days	Decrease rate of free radical formation and thus lipid peroxidation.
[333]	Rat	Red grape (Vitis vinifera)	0.8 mL/rat/d of red grape juice (RGJ)	30minutefor 15 days	Restored antioxidant status of testis and intact testicular structure. Maintained normal serum testosterone, testicular SOD, catalase, glutathione and lipid peroxidase and the apoptotic enzyme caspase-3 of testis
[334]	Rabbit	Royal Jelly (RJ)	200, 400, or 800 mg/kg BW once a week	1 week	Increase testosterone, ejaculate volume, motility, sperm total output Decrease abnormal and dead sperm. Increase seminal plasma fructose
[335]	Rat	Royal Jelly (RJ)	100 mg/kg/d	20 min	Enhanced sperm characteristics. Decrease MDA and % of sperm with chromatin abnormality and DNA damage. increase numbers of zygote and 2-cell, blastocyst stage and hatched embryos and decrease % arrested embryos after IVF.

fragmentation and oxidative DNA damage in sperm cells exposed to cold stress [283,343]. However, resveratrol and quercetin can influence the expression and activity of Modulation of Heat Shock Proteins (HSPs) enhancing cellular resilience to cold stress [344]. These phenolic compounds can also modulate apoptotic pathways and steroidogenesis potentially preventing excessive germ cell death induced by cold stress [345,346]. According to Mojica-Villegas et al. [347], it was observed that Resveratrol and quercetin can protect sperm mitochondria and epigenetic regulation from cold-induced damage, helping to maintain energy production necessary for sperm function.

Minerals such as selenium, zinc and antioxidants such as vitamins C and E directly neutralize reactive oxygen species (ROS) generated during cold stress [239]. They also support spermatogenesis and protect against DNA damage [348,349]. Zinc and selenium play a crucial role in maintaining hormonal balance, thermoregulation and cellular membrane stabilization which is particularly important in cold conditions where membrane fluidity can be compromised (Bray et al., 1990; [350, 351]).

Many herbs and natural sources contain potent antioxidants as well as endogenous antioxidant such as Withania somnifera (Ashwagandha) and curcumin that boost and neutralize reactive oxygen species (ROS) generated during cold stress [280,352]. Studies have shown that natural substances and some herbs such as ginkgo-biloba has helped in the protection of sperm membrane integrity and enhance spermatogenesis [353,354]. Other herbs such as curcuma longa (Turmeric) have anti-inflammatory properties that can mitigate cold-induced inflammation in testicular tissue (Aktas et al., 2012). According to Panossian et al [355] many traditional herbs processes adaptogenic properties, such as Rhodiola-rosea, with properties that helps the body cope with various forms of stress including cold stress. However, natural sources like Coenzyme Q10 (found in organ meats and some plants) protect sperm mitochondria from cold-induced damage [356] (Table 2).

2.11.3. Malnutrition-induced male reproductive dysfunction

Malnutrition often leads to increased oxidative stress in the reproductive system. However, some antioxidants and certain vitamins combat this by neutralizing free radicals and protecting cellular membranes and preserving DNA integrity. Aly et al. [365] demonstrated that vitamin E supplementation in malnourished rats significantly improved sperm parameters and reduced oxidative stress markers in testicular tissue. The study showed increased glutathione peroxidase and catalase activity along with reduced malondialdehyde levels indicating improved antioxidant status. Certain vitamins are crucial for proper sperm production and maturation such as vitamin A which is essential for maintaining spermatogenesis and supporting energy metabolism [249,366]. However, a deficiency in these vitamins can lead to male sterility which has highlighted the role of vitamins in regulating gene expression necessary for spermatogonial differentiation.

Studies has reviewed how antioxidants including coenzyme Q10 can support mitochondrial function in sperm. This is crucial for energy production and motility which highlighted the role of CoQ10 in electron transport chain efficiency and protection against mitochondrial DNA damage [249]. A combination of antioxidants and vitamins can have synergistic effects on male reproductive health such as vitamin C, E and glutathione improved sperm quality in men with high levels of sperm DNA fragmentation [285].

Some minerals are essential for proper sperm production and function however, Zhao et al. (2016) conducted a study on the effects of zinc on male fertility and shows that zinc deficiency led to reduced sperm production and motility while zinc supplementation improved these parameters. Zinc was shown to support spermatogenesis through its role in DNA transcription and protein synthesis. Oteiza et al. [367] reviewed the role of zinc in endocrine function which shows that zinc is crucial for the production, storage and secretion of various hormones including testosterone. However, many natural food sources provide a combination of antioxidants and minerals that can support reproductive health such as selenium and nuts protects sperm membranes from lipid peroxidation which is a crutial indicator for maintaining sperm motility and fertilizing capacity [337,368] (Table 3).

2.11.4. Air pollution-induced male reproductive dysfunction

Air pollution generates reactive oxygen species (ROS) that can damage sperm and testicular cells. Vitamins and minerals with an antioxidant properties counteract this oxidative stress by reducing oxidative stress markers and inflammatory cytokines in testicular tissue (Xu et al., 2020). Certain vitamins and minerals help protect sperm DNA and enhance sperm motility from damage caused by air pollutants. Adedara et al. (2017) showed that zinc supplementation in rats exposed to diesel exhaust particles reduced sperm DNA fragmentation. Moreover, zinc plays an important role in DNA repair processes. Lafuente et al. (2016) also reviewed the protective effects of coenzyme Q10 against reproductive toxicity of environmental pollutants. CoQ10's role in the electron transport chain, anti-inflammatory effect and its antioxidant properties were highlighted as primary mechanisms (Hannan et al., 2020).

Many herbs and phenolic compounds exhibit potent antioxidant properties, neutralizing reactive oxygen species, free radicals and anti-inflammatory effect, this protection is crucial as malnutrition often

Table 2
Preventive and therapeutic approaches on cold stress-induced reproductive dysfunction.

Reference	Model	Intervention	Dosage	Duration	Effect	Mechanisms
[357]	Mouse	Melatonin	10 mg/kg body weight	60 days	Improved sperm count and motility	Antioxidant action, regulation of circadian rhythm
[358]	Mouse	Vitamin E	100 mg/kg body weight	4 weeks	Enhanced testicular function, increased testosterone levels	Antioxidant protection, maintenance of membrane integrity
[359]	Human	l-carnitine	150 mg/kg body weight	8 weeks	Improved sperm quality, reduced oxidative stress	Enhanced mitochondrial function, fatty acid metabolism
[360]	Mouse	Curcumin	100 mg/kg body weight	6 weeks	Protected against testicular damage, improved sperm parameters	Anti-inflammatory and antioxidant effects
[326,327]	Boars	Selenium	0.5 mg/kg diet	12 weeks	Increased antioxidant enzyme activity, improved sperm motility	Enhanced antioxidant defense system
[99,361]	Mice	Resveratrol	20 mg/kg body weight	4 weeks	Reduced oxidative stress, improved spermatogenesis	Activation of Sirt1 pathway, antioxidant effects
[257,258]	Rat	Zinc	30 mg/kg diet	8 weeks	Improved sperm quality, increased testosterone levels	Support of spermatogenesis, antioxidant enzyme cofactor
[362]	Mouse	Quercetin	50 mg/kg body weight	6 weeks	Protected against testicular damage, improved sperm count	Antioxidant and anti-inflammatory effects
[363]	Human	Coenzyme Q10	10 mg/kg body weight	60 days	Enhanced sperm motility, reduced lipid peroxidation	Improved mitochondrial energy production, antioxidant action
[364]	Human	Astaxanthin	25 mg/kg body weight	4 weeks	Improved semen quality, reduced oxidative stress	Potent antioxidant activity, membrane stabilization

Table 3
Preventive and therapeutic approaches on malnutrition-induced reproductive dysfunction.

Reference	Model	Intervention	Dosage	Duration	Effect	Mechanism
[369]	Human	Vitamin C	1000 mg/day	2 months	Increased sperm count and motility	Antioxidant protection, improved sperm quality
[370]	Human	Coenzyme Q10	300 mg/day	26 weeks	Enhanced sperm concentration and motility	Improved mitochondrial function and energy production
[371]	Human	Selenium	100 μg/day	3 months	Improved sperm motility	Antioxidant protection, essential for sperm formation
[372]	Human	Omega-3 fatty acids	1.84 g EPA + 1.52 g DHA/day	12 weeks	Improved sperm morphology	Improved sperm membrane fluidity and function
[373]	Human	Antioxidant combination (vitamins C, E, zinc, selenium, folate, garlic)	Various	3 months	Improved pregnancy rate	Reduced oxidative stress, improved sperm function
(Ebisch et al., 2006)	Human	Folic acid	5 mg/day	26 weeks	Increased sperm count	Improved DNA synthesis and cell division
[374]	Human	Vitamin E	600 mg/day	3 months	Improved sperm motility	Antioxidant protection, reduced lipid peroxidation
[375]	Human	l-carnitine	2 g/day	3 months	Improved sperm count and motility	Enhanced sperm energy metabolism
[376]	Human	Acetyl-l-carnitine	3 g/day	6 months	Increased sperm motility	Improved mitochondrial function

leads to increased oxidative stress in reproductive tissues [239,377]. However, they been shown to improve spermatogenesis by protecting against oxidative damage, these compounds can enhance sperm production and enhance testicular function [378,379]. Some herbs and phenolic compounds have tissue-protective properties which helps in improving blood flow (Table 4).

2.11.5. Respiratory tract infection-induced male reproductive dysfunction

Vitamins particularly A, C and E and minerals such as selenium and zinc act as potent antioxidants, neutralizing reactive oxygen species (ROS) and free radicals produced during respiratory infections [239]. Vitamins and minerals enhance immune function by helping the body combat respiratory infections more effectively. This reduces the duration and severity of infections, minimizing their impact on reproductive health. They are also crucial for maintaining the health of mucous membranes in both respiratory and reproductive tracts, providing a first line of defense against pathogens [380,381].

However, certain nutrients, particularly zinc and folate are essential for DNA synthesis and repair. They help maintain the genetic integrity of sperm cells which can be compromised during infections [351]. Several nutrients particularly vitamin A and zinc are essential for proper spermatogenesis by helping to maintain sperm production even under the stress of respiratory infections [285]. According to Salas-Huetos et al. [368] nutrients such as omega-3 fatty acids and vitamin E, have anti-inflammatory properties, potentially reducing inflammation in both the respiratory and reproductive systems during infections. More so, Vitamins E and C along with selenium help in maintaining the integrity of cell membranes, including those of sperm cells, protecting them from damage during infections [337]. Furthermore, studies have shown that some certain vitamins and minerals can modulate the production of inflammatory cytokines, potentially mitigating the negative impacts of respiratory infections on reproductive function [382].

Natural compounds like curcumin from turmeric and omega-3 fatty acids from fish oils have anti-inflammatory properties potentially reducing inflammation and modifies the immune system mitigating the negative impacts of respiratory infections on both respiratory and reproductive systems during infections [368,380]. Antibiotics directly combat bacterial infections and pathogen elimination in the respiratory tract, potentially preventing or reducing the severity of infection-induced reproductive dysfunction [383]. However, some antibiotics, particularly fluoroquinolones can induce oxidative stress and act as an anti-inflammatory effect that significantly reduces infection-induced inflammation in reproductive tissues (Kanoh et al., 2010; [384]) (Table 5).

2.11.6. Sexually transmitted infections-induced male reproductive dysfunction

Sexually transmitted infections (STIs) are a significant global health concern. Infections spread through this pathway afflict millions of individuals annually, resulting in severe detriment to male fertility and other crucial factors relevant to reproductive health. The dysfunction brought into the male reproductive system by STIs leads to various problems, such as infertility, erectile dysfunction, and intractable pain [173]. The medical treatment for ED was revolutionized by PDE5 inhibitors, since they are just about the sole orally active form of treatment. By inhibiting PDE5—a cGMP-specific degrading

Table 4
Preventive and therapeutic approaches on air pollution-induced reproductive dysfunction.

Reference	Model	Intervention	Dosage	Duration	Effect	Mechanism
(Xu et al., 2020)	Mice	Vitamin E	100 mg/kg/day	8 weeks	Improved sperm quality and testicular function	Reduced oxidative stress and inflammation
(Kurek-Górecka et al., 2021)	Rats	Bee pollen	250 mg/kg/day	4 weeks	Enhanced sperm motility and concentration	Antioxidant action and increased testosterone levels
(Liu et al., 2019)	Rats	Resveratrol	20 mg/kg/day	4 weeks	Improved sperm count and motility	Activated Nrf2 pathway, reducing oxidative stress
(Gong et al., 2017)	Mice	Curcumin	100 mg/kg/day	6 weeks	Protected against PM2.5-induced reproductive toxicity	Reduced oxidative stress and apoptosis in testes
(Mukherjee et al. (2018)	Rats	N-acetylcysteine	100 mg/kg/day	30 days	Improved sperm parameters and testicular histology	Enhanced antioxidant defense system
(Panahi et al. (2019)	Rats	Quercetin	50 mg/kg/day	8 weeks	Improved sperm quality and testicular function	Reduced inflammation and oxidative stress
(Zhang et al. [64]	Mice	Melatonin	10 mg/kg/day	16 weeks	Protected against PM2.5-induced sperm DNA damage	Antioxidant action and regulation of circadian rhythm
(Khosravi et al., 2019)	Rats	Zinc	10 mg/kg/day	8 weeks	Improved sperm parameters and reduced DNA damage	Enhanced antioxidant enzyme activity

Table 5
Preventive and therapeutic approaches on respiratory tract infection-induced reproductive dysfunction.

Reference	Model	Substance	Dosage	Duration	Effect	Mechanism
(Fraczek et al., 2016)	Human	Vitamin C	1000 mg/day	2 months	Improved sperm motility and morphology	Antioxidant activity, reduced oxidative stress
(Aitken et al., 2014)	Rat	Vitamin E	100 mg/kg/day	4 weeks	Enhanced sperm count and viability	Free radical scavenging, membrane protection
[249]	Human	Zinc	30 mg/day	3 months	Increased sperm concentration and motility	Supports antioxidant enzymes, DNA repair
[239]	Mouse	Selenium	0.5 mg/kg/day	5 weeks	Improved sperm quality and testicular function	Antioxidant activity, supports glutathione peroxidase
[349]	Human	N-acetylcysteine	600 mg/day	3 months	Enhanced sperm parameters and DNA integrity	Increases intracellular glutathione levels
(Walczak-Jedrzejowska et al., 2013)	Human	Coenzyme Q10	200 mg/day	6 months	Improved sperm concentration and motility	Mitochondrial energy production, antioxidant
(Mora-Esteves & Shin, 2013)	Rat	l-carnitine	500 mg/kg/day	8 weeks	Enhanced sperm motility and count	Supports sperm energy metabolism
[368]	Human	Omega-3 fatty acids	1.84 g/day	10 weeks	Improved sperm morphology	Anti-inflammatory, membrane fluidity

enzyme—PDE5-Is get entry into the smooth muscle cells, thereby enhancing the erectile function in the setting of sexual stimulation. It reduces the breakdown of cGMP, and thus both cellular levels of cGMP in corpus cavernosum and in the vessels that supply it are higher. Diminished degradation increases relaxation of the smooth muscle, thus making the corporeal sinusoids dilate and blood flow increase, finally allowing an erection. PDE5-Is possesses anti-inflammatory properties useful in reducing inflammatory reactions of the reproductive tract resulting from STIs. By reducing TNF-α, IL-1β, and IL-6 pro-inflammatory cytokines, PDE5-Is modulates the inflammatory response associated with infection [385]. PDE5-Is including Sildenafil (Viagra) (50–100 mg) and vardenafil, Levitra, 10–20 mg with a recommended duration of 1–12 h has proven to have very efficient therapeutic approaches. In contrast, 10–20 mg of Tadalafil (Cialis) with a recommended duration of One hour between dosing and intercourse is also a potent alternative [386].

Besides, bioactive compounds extracted from Zingiber officinale (ginger) attenuated steroidogenesis impairment induced by zearalenone in TM3 Leydig cell lines and elicited, in a dose-dependent manner, enhancement of fertility in male rats witnessed by increments in gonadal weights, sperm counts, and eliciting positive effects on folliculogenesis and implantation. Extract of Zingiber officinale inhibits the production of pro-inflammatory cytokines (for example, TNF-α, IL-1β, IL-6) and enzymes (for example, COX-2, 5-LOX), reducing inflammation in the reproductive tissues affected by STIs. Administration of gingerol-rich fraction of ginger at a dose of 50, 100, and 200 mg/kg to male rats with carbendazim-induced toxicity increased sperm motility and count but attenuated sperm abnormality [387].

The ethanol extract of Sesamum indicum seeds improved body weight gain, seminal parameters, antioxidant action, and testosterone level. Sesamin, a compound in this species, prevented the nuclear maturity of sperm and DNA damage caused by cyclophosphamide by increasing the expression levels of histones H2A and H2B in the testis [388]. Sesame seeds contain many antioxidants like sesamin, sesamolin and vitamin E, which neutralize ROS and decrease the rate of oxidative stress. STI-induced reproductive damage is caused by a number of key factors, including oxidative stress. Dosages have varied from 0.5 to 2 tablespoons (7–28 g) of sesame seeds per day for approximately 4–12 weeks in studies [389]. Studies conducted on Mondia whitei revealed that it increases sexual arousal and copulatory efficiency and improves sexual sensation in rats. A subsequent study using a polyherbal formulation of Mondia whitei,Bridelia ferruginea and Dracaena arborea plants concluded that the formula-treated groups showed increased sexual performances and mounting and intromission frequencies of normal and prediabetic rats [390]. The aqueous extract from root bark and roots of Mondia whitei exerts an anti-apoptotic activity by preventing apoptosis, that is, programmed cell death, in sperm cells and reproductive tissues, hence preserving their integrity and function. This consequently leads to increased sexual arousal, copulatory efficiency, and sexual sensation through nitric oxide synthase activity activation or stimulation, ultimately elevating the levels of cyclic guanosine monophosphate. Typical doses reported in studies are 500 mg to 2 g of Mondia whitei root powder or extract per day for 2–3 months [391].

200 mg/kg aqueous ethyl acetate extract derived from the bulb of Allium cepa L significantly improved copulatory behavior in male rats and also restored mating performance in male rats with drug-induced sexual dysfunction. Additionally, Quercetin isolated from the plant enhanced sperm motility. Extracts from Allium cepa L enhance semen quality and sperm parameters such as concentration, viability, motility, morphology, and DNA integrity by increasing gonadal hormone levels, neutralizing free radicals, and boosting nitric oxide production. Allium cepa L possesses anti-inflammatory substances that suppress inflammation in the reproductive system caused by sexually transmitted infections (STIs). These substances inhibit pro-inflammatory cytokines and enzymes, such as COX-2, thereby decreasing inflammation and enhancing tissue repair [387].

The powdered extract from the fruits of Kigelia Africana boosts sperm count, motility, and fertilization capability in African catfish, along with an increase in testicular weight, body weight, testosterone levels, and follicle-stimulating hormone [392]. Kigelia africana displays broad-spectrum antimicrobial properties against a variety of pathogens, including bacteria, fungi, and viruses. Compounds such as kigelinone and isopinnatal in the plant contribute to its antimicrobial effects by inhibiting the growth and proliferation of pathogens responsible for STIs. Research has utilized doses of Kigelia africana extract ranging from 100 mg to 500 mg per day for 4–12 weeks [393]. Aqueous and petroleum ether extracts from the bulb of Allium sativum L have been shown to increase the weight of seminal vesicles and epididymides in male rats. Additionally, S-allyl cysteine isolated from this species has been found to enhance fertility. Extracts from Allium sativum L improve semen quality and sperm parameters such as concentration, viability, motility, morphology, and DNA integrity by increasing gonadal hormone levels (testosterone and luteinizing hormone), neutralizing free radicals, and boosting nitric oxide production. Allium sativum L is abundant in antioxidants like allicin, selenium, and vitamins C and E, which neutralize reactive oxygen species (ROS) and mitigate oxidative stress, potentially harmful to sperm cells and reproductive tissues during infections. Consequently, Allium sativum L preserves the integrity and functionality of sperm by protecting cells from oxidative damage. Research has utilized doses ranging from 600 mg to 2000 mg of garlic extract per day for 4–12 weeks [387] (Table 6).

2.11.7. Cardiovascular diseases-induced male reproductive dysfunction

Cardiovascular diseases (CVDs) have huge effects on male

Table 6
Preventive and therapeutic approaches on sexually transmitted infection-induced reproductive dysfunction.

INTERVENTION	MODEL	MECHANISM OF ACTION	EFFECT	DOSAGE	REFERENCES
PDE5-Is (Sildenafil, vardenafil and Tadalafil. Zingiber officinale (ginger). Sesamum indicum Mondia whitei Allium cepa L Kigelia Africana Allium sativum L	Rats Rats Rats Rats Rats Catfish Rats	PDE5-Is possesses anti-inflammatory properties by reducing TNF-α, IL-1β, and IL-6 pro-inflammatory cytokines. Zingiber officinale inhibits the production of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) and enzymes (COX-2, 5-LOX) in the reproductive tissues. Sesamum indicum contain antioxidants which neutralize ROS and decrease the rate of oxidative stress. Mondia whitei exerts anti-apoptotic activity in sperm cells and reproductive tissues. Allium cepa L possesses anti-inflammatory substances that inhibit pro-inflammatory cytokines and enzymes, such as COX-2. Kigelia africana possesses antimicrobial properties against pathogens which contribute to inhibiting the growth and proliferation of pathogens responsible for STIs. Allium sativum L is abundant in antioxidants which neutralize reactive oxygen species (ROS) and mitigate oxidative stress.	PDE5-Is increases relaxation of the smooth muscle, dilation of corporeal sinusoids and blood flow increase into the smooth muscle cells, thereby enhancing the erectile function in the setting of sexual stimulation. Zingiber officinale enhance fertility in male rats evidenced by increments in gonadal weights, sperm counts, and eliciting positive effects on folliculogenesis. Sesamum indicum improves body weight gain, seminal parameters and testosterone level. It also prevents sperm and DNA damage. Mondia whitei increases sexual arousal, copulatory efficiency and improves sexual sensation in rats. Allium cepa L significantly improved copulatory behavior, mating performance, sperm motility and sperm parameters such as concentration, viability, motility, morphology, and DNA integrity. Kigelia Africana boosts sperm count, motility, and fertilization capability in along with an increase in testicular weight, body weight, testosterone levels, and follicle-stimulating hormone. Allium sativum L increases the weight of seminal vesicles and epididymis while also improving semen quality and sperm parameters such as concentration, viability, motility, morphology, and DNA integrity.	Sildenafil (50–100 mg), vardenafil (10–20 mg) for 1 h and (10–20 mg of Tadalafil) for 1–12 h). 50, 100, and 200 mg/kg. 7–28 g) of sesame seeds per day for approximately 4–12 weeks 500 mg to 2 g per day for 2–3 months. 200 mg/kg 100 mg–500 mg per day for 4–12 weeks. 600 mg to 2,000 mg per day for 4–12 weeks.	[385,386]. [387]. Sadogh et al., 2022, [389]. [390], [387] [387,392, 393]).

reproductive health, which includes erectile dysfunction (ED), low libido, and infertility. The relationship linking cardiovascular health with reproductive function is complex and involves vascular, hormonal, and neurological mechanisms. Various phytoconstituents such as alkaloids, flavonoids, tannins, xanthones, triterpenes, and quinones are components of the interventions that regulate reproductive activity. Herbal plants are commonly utilized for management because they offer vascular protection or oxygen radical scavenging by various mechanisms [394].

The ethanol solution extract from the roots of Anacyclus pyrethrum, when consumed in amounts of 50, 100, and 150 mg/kg for 28 days, had a marked influence on body and accessory sexual organ weights. Moreover, rats became more receptive and oriented to female rats and also increased pre-copulatory activities like licking and sniffing. The index of penile erection was enhanced significantly with a reduction in mount latency and intromission latency period, along with a 4-fold increase in mount and 3-fold increase in the frequency of intromission. Anacyclus pyrethrum consists of various antioxidant compounds, which reduce oxidative stress. As mentioned above, oxidative stress may be responsible for impairing endothelial function, and a reduced nitric oxide availability is considered to be essential for achieving and maintaining an erection. Anacyclus pyrethrum reduces oxidative stress and improves endothelial function and nitric oxide levels [394].

Moreover, consuming 150, 250 and 500 mg/kg hot water extract of alpinia calcarata roscoe for 3–6 months showed potent aphrodisiac action as evidenced by significant decrease in mounting and intromitting latencies; it also significantly increased latency for ejaculation, non-impairment in libido, sexual arousability, sexual vigour and sexual performance or penile erectability. Alpinia calcarata has anti-inflammatory properties, which can decrease inflammation in the body, including in the reproductive system. Inflammation can interfere with sexual function, and a decrease may benefit erectile function [395]. Moreover, 600 and 1200 mg/kg body weight of Arctum lappa L extracts, consumed for for 3–6 months significantly increased the MF (Mounting Frequency), IF (Intromission Frequency), and EF (Ejaculation Frequency), and reduced (ML) Mount Latency, IL (Intromission Latency), and also showed extended PEI (Post-Ejaculatory Interval) and EL (Ejaculation Latency). This extract also significantly increased all components of penile reflexes as well as the frequencies of serum testosterone levels. Arctium lappa consists of several compounds exhibiting antioxidant activity that are involved in reducing oxidative stress. Oxidative stress can hurt endothelial function and the production of nitric oxide, which are core for erection and maintaining that process. Arctium lappa reverses the oxidative stress and repairs endothelial functions, leading to an increased availability of nitric oxide. It also stimulates the increased production of nitric oxide. Nitric oxide is important in the relaxation of the smooth musculature of the penis, leading to vasodilatation and subsequent blood perfusion, which is a prerequisite for an erection [396].

The extract of ethanol solution from Asparagus adscendens Roxb consumed at 100, 200, and 300 mg/kg body weight for 30 days significantly increases the body weight, testes weight, testicular tubular diameter, and number of round/elongated spermatids, MF, IF, and EL. Therefore, A. adscendens possesses aphrodisiac activity which could be used for the treatment of sexual disorders as evidenced by results showing increased anabolic, reproductive, and sexual activities. Asparagus adscendens is endowed with anti-inflammatory properties that assist the body in reducing inflammation, which generally means even the inflammation in the genital or reproductive system. It may impact sexual function, and reduction in inflammation may improve erectile function [397].

Dichloromethane and methanolic-aqueous extracts from Chione venosa significantly improved mount frequency, penile erection, and ejaculation latency in experimental male rats. Chione venosa contains antioxidant compounds that help reduce oxidative stress. Oxidative stress impairs endothelial function and decrease the availability of nitric oxide, both of which play a very important role in achieving an erection and maintaining it. By reducing oxidative stress, Chione venosa may improve endothelial function and enhance nitric oxide production [398]. Also, 125 and 250 mg/kg dose of aqueous extract of

Chlorophytum borivilianum consumed for 14–60 days, significantly increase all parameters of sexual behavior, while it showed a saturation effect at high doses of 250 mg/kg, and the sperm count increased significantly. Therefore, the roots of C. borivilianum could be really useful in the treatment of certain forms of sexual inadequacies such as premature ejaculation, oligospermia [396].

In addition, Cinnamomum cassia's methanol extract significantly improved sexual function by increasing the smooth muscle level and reducing the collagen level within rat penile tissue. However, the use of 25 mg/ml in vitro and 400 mg/kg in vivo of methanol extract from Cinnamomum cassia's for 3–6 months significantly decreased ML, IL, PEI and III and significantly increased MF, IF, EL, serum testosterone levels, erections, quick flips, long flips and total reflex. Cinnamomum cassia possesses anti-inflammatory properties, which decrease inflammation in the body, including in the reproductive system. Inflammation inhibits sexual function, and decreasing it improves erectile function. Cinnamomum cassia regulates blood sugar levels and thus improves health on the whole, with a decreased level of risks of any conditions which may consequently impair erectile function, like diabetes. Cinnamomum cassia also enhances blood flow, which is vital to erection and sustaining it [398].

Treatment with 100, 200, and 400 mg/kg Garcinia kola extract daily for 56 days, led to an increase in the components of libido, erection, ejaculation, testicular weights, and sperm count. In addition, the serum testosterone in the treated rats also increased corresponding to increase in dose. Garcinia kola is rich in antioxidant compounds, of which kolaviron is a potent example. These antioxidants reduce oxidative stress, which impairs endothelial function and lowers nitric oxide availability. Garcinia kola reduces oxidative stress, thus improving endothelial function with enhanced nitric oxide necessary for attaining an erection and maintaining it. Garcinia kola from also improves the activities of the CNS which exhibits neurostimulant properties; the CNS has a role in sexual arousal and erection [399] (Table 7).

2.11.8. Cancer-induced male reproductive dysfunction

Cancer and its treatments, such as chemotherapy, radiation, and surgery, can significantly affect male reproductive health. These treatments impair spermatogenesis, reduce testosterone levels, and lead to erectile dysfunction (ED) [400]. Since prostate cancer mainly involves dysregulation of autophagy, modulators of autophagy are being tested for cancer treatment. For example, Icariside II, which inhibits PCa cell proliferation, invasion, and migration in vitro through enhanced autophagic activity via the PI3K/Akt/mTOR pathway. The use of Icariside II ranges from 200 mg to 600 mg per day for 3–6 months [401]. Further, treatment of PCa cells with benzyl isothiocyanate abrogated mTOR activity and resulted in the induction of autophagy, eventually leading to the death of the cancer cells [402]. Doses used in studies typically range from 10 mg to 50 mg per day for 3–6 months.

Similarly, reduced cell viability and tumor volume were noted in mice with human PCa cell xenografts treated with a traditional Chinese medicine, Qianlie Xiaozheng decoction, correlated with increased phosphorylation of Akt and mTOR and autophagic cell death. The exact dosage of Qianlie Xiaozheng would depend on the formulation (pill, powder, decoction) and the specific herbal combination used. Typically, the prescribed dosage for herbal pills might range from 3 to 6 g per day, taken in divided doses for 2–3 months [403]. Another promising anticancer agent is eriocalyxin B, which has a proven role in the induction of apoptosis and autophagy through the Akt/mTOR signaling pathway [404,361]. Another potent example is neuregulin, which induces autophagy while, at the same time, activating Akt and S6K. Neuregulin induces autophagy and cell death through a ROS-dependent rise in signaling pathways that activate JNK and Beclin 1. In animal studies, doses of Neuregulin can vary widely depending on the method of administration (e.g., intravenous, subcutaneous). For example, doses in mice can range from 0.1 mg/kg to several mg/kg for 1–2 months (Raee et al., 2023).

Further, in experimental rat models of CP-induced testicular dysfunction, therapy with L-carnitine not only improved the level of testosterone but also increased the motility and viability of sperm while decreasing apoptosis of germ cells. Furthermore, supplementation with L-carnitine gives rise to upregulation of the protein and mRNA levels of LC3 and Beclin 1, which in turn modulates autophagy. Some studies on male fertility have used doses around 1000 mg to 2000 mg per day for 2–3 months (Raee et al., 2023). A cellular study suggested that metformin inhibits the proliferation of benign prostate epithelial cells by reducing insulin-like growth factor 1 and IGF-1 receptor expression and by cell-cycle regulation. Metformin attenuated testosterone-induced or metabolically syndromic BPH (Benign Prostatic Hyperplasia) in male Sprague-Dawley rats by inhibiting the expressions of IGF-1 and IGF-1 receptor in the prostate gland [405] (Table 8).

Table 7
Preventive and therapeutic approaches on cardiovascular disease-induced reproductive dysfunction.

INTERVENTION	MODEL	MECHANISM OF ACTION	EFFECT	DOSAGE	REFERENCES
Anacyclus pyrethrum Alpinia calcarata Arctum lappa Asparagus adscendens. Chione venosa Cinnamomum cassia Garcinia kola	Rats Rats Rats Rats. Rats Rats	Anacyclus pyrethrum reduces oxidative stress and improves endothelial function and nitric oxide levels. Alpinia calcarata decreases inflammation in the body, including in the reproductive system. Arctium lappa reduces oxidative stress and repairs endothelial functions, leading to an increased availability of nitric oxide. Asparagus adscendens reduces inflammation in the reproductive system. Chione venosa significantly improved mount frequency, penile erection, and ejaculation latency. Cinnamomum cassia decreases inflammation in the reproductive system. Garcinia kola reduces oxidative stress, and enhances the production of nitric oxide.	The index of penile erection was enhanced significantly with a reduction in mount latency and intromission latency period, along with increase in mount and increase in the frequency of intromission. It significantly decreases mounting and intromitting latencies while significantly increasing latency for ejaculation, non-impairment in libido, sexual arousability and sexual vigour. Arctium lappa significantly increased the MF (mounting frequency), IF (intromission frequency), and EF (ejaculation frequency), while it reduces (ML) mount latency and IL (intromission latency). Asparagus adscendens significantly increases the body weight, testes weight, testicular tubular diameter, and number of round/elongated spermatids, mounting frequency, intromission frequency, and ejaculation frequency. Chione venosa reduces oxidative stress and enhance nitric oxide production. Cinnamomum cassia significantly increases mounting frequency, intromission frequency, ejaculation frequency. serum testosterone levels, erections, quick flips, long flips and total reflex. Garcinia kola increases the components of libido, erection, ejaculation, testicular weights, and sperm count.	50, 100, and 150 mg/kg for 28 days. 150, 250 and 500 mg/kg for 3–6 months. 600 and 1200 mg/kg body weight for 3–6 months. 100, 200, and 300 mg/kg body weight for 30 days 125 and 250 mg/kg for 3–6 months. 100, 200, and 400 mg/kg daily for 56 days,	[394]. [395]. [396]. [397]. [398]. [398]. [399]

Table 8
Preventive and therapeutic approaches on cancer-induced reproductive dysfunction.

INTERVENTION	MODEL	MECHANISM OF ACTION	EFFECT	DOSAGE/DURATION	REFERENCES
Icariside II.	Rats	Icariside II.enhances autophagic activity via the PI3K/Akt/mToR pathway.	Icariside II inhibits Prostate Cancer cells proliferation, invasion, and migration.	200 mg–600 mg per day for 3–6 months	[401].
Benzyl isothiocyanate.	Rats Mice	Benzyl isothiocyanate induces autophagy through abrogating mTOR activity.	Benzyl isothiocyanate induces death of the cancer cells.	10 mg–50 mg per day for 3–6 months.	[402]. [403].
Qianlie Xiaozheng	Rats.	Qianlie Xiaozheng	Qianlie Xiaozheng reduces cell viability and tumor volume.	3–6 g per day, for 2–3 months.	Raee et al., 2023.
Neuregulin	Rats	Increases phosphorylation of Akt and mTOR and autophagic cell death.	Neuregulin induces cell death.	0.1 mg/kg for 1–2 months.	[404,361].
Eriocalyxin B		Neuregulin induces autophagy cell death through a ROS-dependent rise in signaling pathways that activate JNK and Beclin 1.	Eriocalyxin B induces cell death.	1000 mg to 2000 mg per day for 2–3 months.	Raee et al., 2023.
l-carnitine		Eriocalyxin B induces apoptosis and autophagy through the Akt/mTOR signaling pathway	l-carnitine increases the level of testosterone, motility and viability of sperm.		[405].
Metformin		l-carnitine modulates autophagy by modulating protein and mRNA levels of LC3 and Beclin 1.	Metformin inhibits the proliferation of benign prostate epithelial cells.		
		Metformin inhibits the expressions of IGF-1 and IGF-1 receptor.			

2.11.9. Mental health and stress-related disorders-induced male reproductive dysfunction

Mental health and stress-related disorders, including anxiety, depression, and chronic stress, can significantly affect male reproductive health. These conditions impair libido, erectile function, and spermatogenesis [406]. The oral therapy of Phosphodiesterase Type 5 Inhibitor. (PDE5i) has been shown to be effective for the treatment of ED in terms of the safety and tolerability of the drug. The recent data support the ability of PDE5i drugs, besides promoting relaxation in smooth muscles along with the rigidity of the penis, to induce a correction in certain indicators of male sperm. PDE5i increases nitric oxide (NO)-mediated mechanisms within the prostate and testicular parenchyma, promotes sperm morphology changes, and enhances a positive effect on the smooth musculature in the seminal tract to result in an improvement of the final release of sperm from the seminiferous epithelium. In addition, PDE5i lead to a boost in testosterone levels through upregulation in the secretion of insulin-like 3-peptide by human Leydig cells within the testis—which could lead to epididymal sperm maturation processes and in turn result in an improvement of secretion by Sertoli cells [407].

However, compared with placebo, PDE5i improved erectile function and reduced psychosexual distress with positive effects on sperm parameters. Examples of Oral phosphodiesterase type 5 inhibitors include Sildenafil, more commonly known as Viagra, in amounts of 25 mg, 50 mg, or 100 mg about an hour before sexual activity; Tadalafil, known as Cialis, in doses of 2.5 mg or 5 mg once a day, or 10 mg or 20 mg; and Vardenafil, known as Levitra, in the recommended dose of 5 mg, 10 mg, or 20 mg, all before initiating sexual activity [408]. Also, Bupropion which is used to counteract SSRI (selective serotonin reuptake inhibitors) -induced sexual dysfunction facilitates noradrenergic and dopaminergic mechanisms NET and DAT inhibitor, and it exerts strong pro-sexual effect in mice-induced model. Bupropion is an antidepressant primarily used to treat major depressive disorder and seasonal affective disorder. Bupropion inhibits the reuptake of norepinephrine and dopamine, increasing their levels in the brain. These neurotransmitters modulate mood, motivation, and other activities that may improve symptoms of depression and anxiety, which often is the root cause of stress-related ED. Increased dopamine levels by bupropion may improve libido and sexual function, possibly compromised in patients with mental health issues. Typical dosages for the treatment of are between 150 mg and 450 mg daily [409].

Venlafaxine is an SNRI mainly indicated for the treatment of various mental health disorders, such as major depressive disorder, generalized anxiety disorder, social anxiety disorder, and panic disorder. All these disorders are contributors to stress-related male reproductive dysfunctions. Venlafaxine acts by increasing the levels of serotonin and norepinephrine in the brain by inhibiting their reuptake. It decreases symptoms of depression and anxiety and reduces stress, which indirectly has a positive effect on sexual function and fertility. Venlafaxine may restore the hormonal balance, increase libido, improve sexual performance, improve normal morphology, and viability of the sperm further to improve overall reproductive function. It exert its effect through neurotransmitters targets the hypothalamic-pituitary-gonadal axis that controls testosterone production and modulates sperm development. Usual dosages are between 37.5 mg and 225 mg daily [410].

For therapeutic management in male infertility due to psychological stress, a study result supported the dosage of 3 g of Withania somnifera, also known as "ashwagandha," to be used daily in a chronic manner for 3 months, as it is reported to increase fertility in normozoospermic psychologically stressed individuals. In that particular clinical study, ashwagandha significantly reduced plasma cortisol levels in psychologically stressed infertile men, and there were significant increases in the fertility rate of sperm motility, semen quality, and LH levels over untreated individuals. Thus, ashwagandha seems to be an effective antistress drug having therapeutic prospect in the management of psychologically stress-induced infertility. One of the active principles of this herb, withanolides, is believed to be responsible for its adaptogenic activity, supposedly by improving brain oxidative status in animal models of chronic stress [410] (Table 9).

2.11.10. Heat waves-induced male reproductive dysfunction

Some reviews have reported that heat waves, characterized by abnormally high temperatures for a long period, jeopardize male reproductive health. The deteriorating effects of HS on testicular functions are mainly due to the production of free radicals [reactive oxygen species, ROS; nitrogen species, RNS] originating from mitochondrial oxidative phosphorylation processes and loss of compensatory antioxidant defenses with resultant OS. El-Sherbiny et al. (2020) reported that in the summer months, there is a significant fall in blood and semen antioxidant enzymes (SOD, GPx, CAT] with an increased malondialdehyde MDA, which is a biomarker for lipid peroxidation and concomitant decline of TBF in rams [411]. In the recent past, the artificial mitochondria-targeted antioxidants like coenzyme Q10 have been involved in the improvement of OS-induced cell damage with better results than their cytosolic counterparts. CoQ10 supplementation improves testicular function and fertility in aged breeding roosters and heat-stressed rabbits by reducing OS, promoting total antioxidant capacity and testosterone level, and up-regulating testicular melatonin receptors. Common doses range from 100 mg to 300 mg per day for 3–6 months (Özcan et al., 2016).

Furthermore, it is considered that vitamins C and E act as critical factors which ameliorates the detrimental effects of HS and enhance thermotolerance that has been previously reported. Reduced mortality from HS and preservation of animal productivity can occur with

Table 9
Preventive and therapeutic approaches on mental health-induced reproductive dysfunction.

INTERVENTION	MODEL	MECHANISM OF ACTION	EFFECT	DOSAGE/DURATION	REFERENCES
PDE5i Sildenafil, Tadalafil and vardenafil. Bupropion Venlafaxine Withania somnifera	Rats Mice Rats Rats	PDE5i increases nitric oxide and upregulates the secretion of insulin-like 3-peptide. Bupropion inhibits the reuptake of norepinephrine and dopamine, increasing their levels in the brain. Venlafaxine increases the levels of serotonin and norepinephrine in the brain by inhibiting their reuptake. Withania somnifera adaptogenic properties improves brain oxidative status and significantly reduced plasma cortisol levels in psychologically stressed infertile men.	PDE5i lead to a boost in testosterone levels, promotes sperm morphology changes, and enhances a positive effect on the smooth musculature in the seminal tract. Bupropion improves libido and sexual functions. Venlafaxine restore the hormonal balance, increase libido, improves sexual performance, sperm morphology, and viability of the sperm. Withania somnifera significantly increases the fertility rate of sperm motility, semen quality, and LH levels.	Sildenafil (25 mg, 50 mg, or 100 mg), Tadalafil (2.5 mg, 5 mg, 10 mg or 20 mg) and vardenafil, dose of 5 mg, 10 mg, or 20 mg all before sexual intercourse. 150 mg–450 mg daily. 37.5 mg and 225 mg daily. 3 g daily for 3 months.	[407,408]. [409], [410]. [410].

enhanced thermotolerance. In general, HS increases the metabolism and the excretion of minerals and vitamins, thus aggravating a deficiency in vitamins and minerals [411]. VE enhances the functioning and multiplication of macrophages, lymphocytes, and plasma cells against such oxidative injury. It therefore enhances the quality of semen and fertility of boars during the high-temperature season. Hence, the enrichment of semen and spermatozoa with antioxidants is a prerequisite for improving male fertility. Administration of the diet containing 100–400 mg/kg VE significantly improved semen quality of roosters. Supplementation of 100 mg/kg VE and 200 mg/kg VE improved the status of antioxidants and reduced lipid peroxidation in seminal plasma of chicken males under HS [304].

Adequate dietary VC can reduce the metabolic signs of stress and can improve immunity and behavior in birds and their productive performance. VC showed improved semen quality in heat-stressed roosters and significantly increased serum total protein and globulin in laying hens exposed to HS. The VE and/or VC showed equal potential for elevating lymphocyte numbers and leucocytes and reduced the heterophil/lymphocyte ratio. Doses used in studies focusing on male reproductive health typically range from 500 mg to 1000 mg per day for 3–6 months. A combination of both VE and VC had a more significant effect on physiological traits than giving either one of the vitamins. Vitamins C + E caused an additional rise in basophil, serum total protein, and albumin than VC only. Additionally, the in vivo antioxidant activity of VE may be higher than that of VC (Abdel-Moneim et al., 2021) (Table 10).

3. Conclusion and future perspectives

Climate change is now considered a major cause of male infertility. Despite the need for a balanced ecosystem for the survival of man, greenhouse gas emissions following human activities and some natural occurrences cause climatic change with consequent heat stress, cold stress, malnutrition, air pollution, increased cardiovascular diseases and respiratory tract infections, increased risk of cancer and sexually transmitted infections, mental distress, and heat waves. These consequences of climate change promote male infertility through multiple mechanisms like ROS-sensitive signaling, suppression of steroidogenic markers, and direct damage to testicular cells. Preventive measures to abate the negative effects of climate change and the associated male reproductive health consequences is key in the present time to curtail the rapidly declining male fertility that is partly due to climatic variation.

CRediT authorship contribution statement

R.E. Akhigbe: Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Conceptualization. **P.A. Oyedokun:** Writing – review & editing, Writing – original draft, Project administration, Investigation. **T.M. Akhigbe:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation. **M.A. Hamed:** Writing – review & editing, Writing – original draft, Project administration. **F.B. Fidelis:** Writing – review & editing, Writing – original draft, Project administration, Investigation. **A.I. Omole:** Writing – review & editing, Writing – original draft, Project administration. **A.E. Adeogun:** Writing – review & editing, Writing – original draft, Project administration, Investigation. **M.D. Akangbe:** Writing – review & editing, Writing – original draft, Project administration, Investigation. **A.A. Oladipo:** Writing – review & editing, Writing – original draft, Project administration, Investigation.

Authors' contributions

ARE conceived the study. ARE, ATM and HMA designed the study. ARE, OPA, ATM, HMA, FFB, OAI, AAE, AMD, and OAA wrote the first draft of the manuscript. ARE, OPA, ATM, HMA, FFB, OAI, AAE, AMD, and OAA revised the manuscript for intellectual content. All authors read and approved the final manuscript.

Table 10
Preventive and therapeutic approaches on heat waves-induced reproductive dysfunction.

INTERVENTION	MODEL	MECHANISM OF ACTION	EFFECT	DOSAGE/ DURATION	REFERENCES
Coenzyme Q10 Vitamin E Vitamin C	Roosters and rabbits. Roosters Roosters and hens.	Coenzyme Q10 reduces oxidative stress, promoting total antioxidant capacity and up-regulating testicular melatonin receptors. Vitamin E improve status of antioxidants and reduced lipid peroxidation in seminal plasma. Vitamin C significantly increase serum total protein and globulin elevating lymphocyte and leucocytes and reduced the heterophil/lymphocyte ratio	CoQ10 supplementation improves testicular function and fertility. Vitamin E enhances the functioning of macrophages, lymphocytes and plasma cells, subsequently improving the quality of semen and fertility. Vitamin C improves semen quality and immunity.	100 mg–300 mg per day for 3–6 months. 100–400 mg/kg. 500 mg to 1000 mg per day for 3–6 months.	[411]. [304]. Abdel-Moneim et al., 2021

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Declaration of competing interest

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Data availability

Data will be made available on request.

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