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Article

Research progress on the role of lycopene in promoting mammalian spermatogenesis

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Abstract: A carotenoid called lycopene (LYC) is one of the most potent antioxidants. Superior physiological properties of LYC include cancer prevention, cholesterol reduction, antioxidant activity, scavenging of free radicals, immunity enhancement, prostate protection, and increased sperm viability. In recent times, male sperm quality has decreased. Following studies on LYC's function in spermatogenesis, the therapy of male infertility diseases has made extensive use of it. Here, we give an accurate theoretical foundation for the use of LYC in large animal breeding and the treatment of male infertility in humans by summarising the variables influencing spermatogenesis and the enhancing effect of LYC on mammalian spermatogenesis.

Keywords: lycopene; spermatogenesis; antioxidant; sperm cryopreservation

1. Introduction

Male infertility is one of the major illnesses impacting men's health and has become a very common medical ailment among contemporary men in recent years. Male reproductive health is influenced by a variety of circumstances, although infertility might result from a single condition, a combination of factors, or even the multiplier effect that lowers semen quality. The effects of the few medications that are now on the market for treating male infertility are unclear. Therefore, eugenics, male reproductive health, and even the healthy reproduction of humans depend greatly on the development of medications for treating male infertility. Numerous factors, such as radiation, extreme temperatures, hypoxia, prolonged exposure to harmful substances, long-term drinking, smoking, and drug use, have been demonstrated to impair male fertility [1]. A large number of studies have demonstrated that sperm damage from excessive reactive oxygen species (ROS) in semen is the main cause of infertility in 30% to 80% of infertile men [2]. In the normal physiological process of fertilization, there usually exists an oxidative stress balance between ROS family products and antioxidants/scavengers, while appropriate levels of ROS are related to physiological functions such as sperm hyperactive motility, capacitation, and acrosome reaction, and sperm-oocyte fusion(Antioxidants are divided into: such as superoxide dismutase (SOD), catalase and glutathione peroxidase (GPX) and non-enzymatic antioxidants (such as glutathione, Nacetyl-cysteine (NAC), vitamins A, E & C) [3]. When sperm are attacked by excessive ROS, it disrupts the fluidity and integrity of the sperm membrane, resulting in plasma membrane damage, rupture, and even cell death, which ultimately reduces sperm viability and fertilization capacity (2, 3). Lycopin, also known as lycopene, has a molecular formula of C40H56, with 11 conjugated C = C bonds, and is a non-cyclic planar conjugated polyunsaturated aliphatic hydrocarbon with a structure similar to carotenoids. Lycopene has cis- and

trans-isomers, which can be transformed into each other in the process of lighting, heating, processing, or cooking. Notably, lycopene present in natural plants exists mostly as all-trans lycopene. It is a fat-soluble unsaturated hydrocarbon that is widely found in a variety of red fruits and vegetables, such as tomatoes, watermelon, carrots, grapes, and strawberries, with the highest content in tomatoes. Moreover, lycopene is a potent antioxidant with strong free radical scavenging ability. Studies have shown that activation of the receptor for advanced glycation end products (RAGE) in human semen can elicit cellular responses and lead to the production of ROS, while lycopene can reduce the level of RAGE in human semen (4). Usually in humans, leukocytes are the main source of ROS production, whereas in animal semen we do not have any clear data on the role of leukocytes in ROS production. In animals, especially in cattle, sheep, goats and horses, live and dead spermatozoa are produced in semen [4,5]. It has also been reported that administration of lycopene can improve sperm quality in patients with idiopathic male infertility. Given the effects of lycopene on the reproductive system, spermatogenesis, and the protection of sperm viability, this study attempts to summarize factors affecting spermatogenesis and the mechanism underlying the role of lycopene in mammalian spermatogenesis in order to provide a reliable theoretical basis for its application in large animal breeding and male infertility in humans.

Spermatogenesis

Spermatogenesis is a highly efficient and coordinated process that requires the participation of a variety of cells, hormones, genes, and epigenetic regulators, as well as the interregulation of various signals [6]. This process can be subdivided into three stages based on functional differences, including multiplication, meiosis, and differentiation or spermiogenesis [7]. Primitive spermatogonia A (pSGA) and its daughter cells enter the seminiferous tubules during the multiplication stage, undergo many mitoses to differentiate into mature spermatogonia subtypes, and ultimately differentiate into spermatocytes. An essential stage of spermatogenesis is meiosis. During meiosis, a haploid secondary spermatocyte with half as many chromosomes is produced by the primary spermatocyte replicating its maternal and paternal chromosomes and then dividing twice in a row. The fundamental processes of meiosis include homologous chromosomal pairing, synapsis, and recombination exchange during the initial meiotic division [8]. The secondary spermatocytes divide further in the second meiotic division, eventually forming haploid round sperm cells [9]. In differentiation or spermiogenesis stage, haploid round sperm cells undergo morphological and protein changes to form spermatozoa [10]. This series of morphological changes results in the formation of a number of specific structures, as evidenced by nucleosome remodeling, acrosome generation, and flagellum and sperm tail formation [11]. Subsequently, the spermatozoa migrate from the testes into the epididymis, where they further develop into mature sperm with the capacity for sperm-egg binding.

2. Factors affecting sperm production

2.1. Environmental factors

Table 1. The environmental factors affecting reproductive.

Environmental factors affecting reproductive	pathway	Effects
environmental hormone	oxidative stress; antagonizing androgen receptors; damaging DNA	reduction in the number and quality of male sperm
Heavy metal chemicals	disrupts the function of the "hypothalamic- pituitary-testis axis"	degenerative changes in the testes, affects sperm production and development
Pesticides	enter the environment and accumulate in animals, plants, and even humans through bioconcentration and the food chain	sperm damage, reduced sperm viability, and an increasein malformed sperm

With the development of modern society, environmental pollution has become one of the key issues affecting human reproductive health, including air pollution, heavy metal pollution, and pesticide residue pollution [12]. There is growing evidence that some synthetic exotic chemical pollutants present in the environment affect normal endocrine functions in animals after entering the body through food or airways, particularly impairing reproductive functions [13]. In 1977, the concept of "environmental hormone" was introduced by NHK in Japan in the context of environmental issues [14]. These dangerous chemicals were classified as environmental hormones in May 1997 by Professor Taizumi Iguchi of Yokohama University in Japan because they disrupt the endocrine and reproductive systems of both humans and animals [15]. Environmental pollutants typically cause oxidative stress, antagonise androgen receptors, inhibit steroid synthesis, and damage DNA to induce epigenetic changes. These changes result in a decrease in the quantity and quality of male sperm, a notable drop in ejaculate volume, sperm viability, and the number of sperm per unit volume of semen, in addition to altered morphology and physiological states of sperm [16]. In contemporary agriculture, one of the key tools for increasing crop output is the use of pesticides. However, the long-term and large-scale use of pesticides allows some chemically stable and degradation-resistant pesticides, such as most organochlorine pesticides, enter the environment and accumulate in animals, plants, and even humans through bioconcentration and the food chain, causing serious pesticide residue problem [17]. It has been demonstrated that contaminated pesticides cause sperm damage, reduced sperm viability, and an increase in malformed sperm in mice, as well as decreased spleen and fetal weights and weakened fetal physical strength in pregnant rats [18]. Meanwhile, they can induce sperm deformities, reduce sperm density, and inhibit sperm motility in humans, possibly leading to infertility and miscarriage in pregnant women [19]. Heavy metal chemicals also have a greater impact on the reproductive system. For instances, lead pollution can lead to reproductive toxicity [20]. In this case, the pollution causes degenerative changes in the testes, affects sperm production and development, and disrupts the function of the "hypothalamic-pituitary-testis axis" as well as the binding of FSH to its receptors in Sertoli cells [21]. Arsenic can affect spermatogenesis, inhibit sperm swimming ability, and cause sperm deformities, thereby leading to decreased fertilization rates in male animals [22]. Likewise, mercury can cause structural damage to testicular tissue in male animals, affecting sperm production, mating and fertilization [23]. So, the environmental factors affecting reproductive as shown in

Table 1. Moreover, poor lifestyle habits such as high temperature, smoking, drug abuse, alcoholism, staying up late, and irregular work and rest, as well as exposure to external radiation can also lead to sperm disorders and reduced sperm quality in men [24–26].

2.2. Genetic factors leading to reproductive disorders

Genetically caused reproductive disorders are hereditary diseases that are determined by genes [27]. It has been shown that genetic abnormalities related to idiopathic male infertility include chromosomal abnormalities, sperm mRNA and DNA mutations, monogenic genetic diseases, and polygenic genetic diseases [28]. Studies have found that the incidence of chromosomal abnormalities in male infertility patients is 2%–5%, and that in azoospermia is as high as 15%. Meanwhile, chromosomal abnormalities can lead to male infertility, and Y-chromosome microdeletion is the second leading cause of male infertility [29]. The Y chromosome's long arm contains the azoospermia factor (AZF) gene, which is linked to spermatogenesis. AZF is broken into four sections, AZFa, AZFb, AZFc, and AZFd, all of which are crucial for sperm production [30]. Individuals who have AZFa deletion exhibit Sertoli cell only syndrome, which is characterised by variable degrees of testicular volume decrease and azoospermia. Patients with AZFc deletion, on the other hand, show a variety of testicular histological features and distinct clinical manifestations, such as normal sperm count, azoospermia, and oligozoospermia, while those with AZFb deletion present with azoospermia or severe oligozoospermia in the presence of spermatogenic arrest at the primary spermatocyte stage. [31]. Androgen receptor (AR) gene mutations are also one of the factors causing male infertility, and AR gene deficiency manifests as testicular feminization syndrome, also known as androgen insensitivity syndrome, which accounts for about 2% of all male infertility cases [32]. In addition, cystic fibrosis (CF), an autosomal recessive genetic disorder that can also lead to male infertility, is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Recent studies have demonstrated that mutations in CFTR gene cause congenital bilateral or unilateral absence of the vas deferens and low sperm quality in healthy men, thus resulting in infertility [33–34].

3. Beneficial effects of lycopene on reproduction in mammals

3.1. The promoting effect of lycopene on spermatogenesis

Spermatogenesis is a complex and precisely regulated process, and its abnormality leads to symptoms such as azoospermia, asthenozoospermia, and oligozoospermia, resulting in male infertility [35]. Lycopene contains many electrons due to the presence of eleven conjugated double bonds and these electrons can be assigned to free radicals, causing neutralization of the radicals. Thus, it can exert an antioxidant effect and play a protective role in the reproductive system [36–37]. General mechanisms of action of lycopene as shown in **Figure 1**, and Lycopene is a component of the body's anti-free radical redox defense mechanism and is present in high concentrations in the testes and seminal plasma [38]. Mohanty et al. found that

50 infertile men with oligozoospermia or asthenozoospermia showed a significant increase in sperm count and concentration after long-term administration of 8 mg lycopene [39]. Moreover, lycopene not only directly scavenges free radicals to protect spermatozoa, but also improves the body's antioxidant capacity by enhancing the activity of antioxidant enzymes, directly exerts antioxidant effects through capturing endogenous free radicals, and prevents spontaneous gene mutations caused by endogenous oxidants [40]. Türk et al. showed that lycopene administration led to a significant increase in sperm concentration and viability and a decrease in ROS production in rats treated with cyclosporine (CsA) [41]. Lycopene can also effectively inhibit the oxidation of lipids, proteins and DNA, maintain the balance of oxidation and antioxidation to keep the organism in a homeostasis, and induce gap junction intercellular communication (GJIC) to regulate the normal proliferation and differentiation of the cells and promote the sperm-egg binding [42]. Aly et al. found that lycopene supplementation prior to lipopolysaccharide treatment attenuates mitochondrial damage in male germ cells [43]. This finding can be explained by the fact that the lipophilicity of lycopene allows the accumulation of biomolecules in lipoproteins and membrane structures, thus stabilizing mitochondrial metabolism. Besides, the non-oxidative mechanisms by which lycopene exerts its effects also involve assisting in gap junction communication, regulating gene expression, modulating the cell cycle, and enhancing the immune system [44]. Tumor cells lack gap junction communication, which is notable for lycopene can improve cell-cell communication to prevent tumor formation, thereby preventing cancer, especially those in the prostate, breast, and lungs [45]. Lycopene has been shown to reduce the level of cholesterol due to its inhibition of hydroxymethylglutaryl coenzyme A reductase, an important rate-limiting enzyme in cholesterol production. In this case, the reduction in cholesterol contributes to the alleviation of cardiovascular disease [46]. The non-oxidizing mechanisms described above may also apply to male infertility.

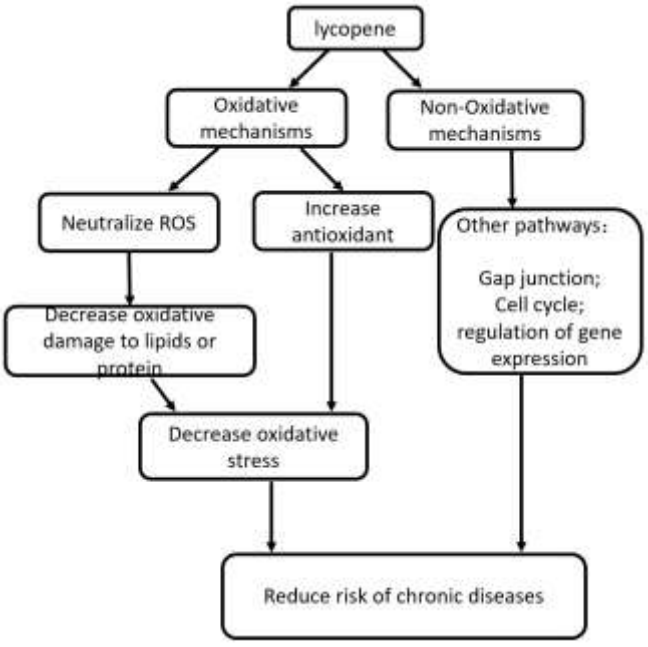

Figure 1. General mechanisms of action of lycopene.

3.2. The effects of lycopene on cryopreservation of sperm

Sperm freezing technology has become particularly important as male infertility is a growing problem. The sperm freezing is to freeze semen for providing an assisted reproduction method for male infertility patients due to external factors or diseases [47–48]. According to studies, the incubation of sperm with cryoprotectants, cooling and freezing, ultra-low-temperature storage, and thawing and rewarming can all produce physical and chemical effects that cause significant amounts of reactive oxygen species (ROS) to be produced in seminal plasma during the freezing process at low temperatures. This disturbs the equilibrium of oxidative stress between antioxidants and scavengers, causes oxidative stress damage, and destroys the microarchitecture of spermatozoa, leading to a sharp rise in the number of spermatozoa with abnormal morphology and function. Damage from ROS-induced oxidative stress can modify sperm's normal parameters and change the sperm DNA bases and deoxyribose backbone, which can result in chromosome breakage, DNA damage, and aneuploidy. Sperm are very sensitive to damage caused by oxidative stress. Thus, it is particularly important to balance oxidative stress through supplementing antioxidants to the freezing medium. Lycopene is a lipophilic substance that can act as a potent antioxidant to quench singlet oxygen and scavenge ROS for preventing lipoproteins and DNA from oxidative damage. Rosato et al. found that lycopene-containing semen extenders have a more significant protective effect on DNA molecules when the semen is refrigerated or frozen. It has also been shown that the sperm motility and activity in frozen-thawed semen supplemented with lycopene are increased as compared to the control group; this finding may have a microscopic impact on assisted reproduction. Therefore, lycopene can serve as an antioxidant and addition of a certain concentration of lycopene into the cryoprotective solution can lead to an improvement in the quality of frozen semen.

4. Summary and prospects

One of the primary causes of male infertility is the ever-growing environmental contamination that comes with society's ongoing development. Lycopene is a naturally occurring pigment with anti-cancer, blood lipid regulation, cardiovascular disease prevention, anti-aging, immune-boosting, and diabetes prevention properties. Additionally, biology and medicine use it extensively. Furthermore, lycopene has potent antioxidant qualities and the ability to scavenge reactive oxygen species. Because of this, it is crucial in treating male infertility because of the imbalance in oxidative stress brought on by an excess of ROS. Male reproductive issues are become more serious these days. Because of its exceptional physicochemical qualities, lycopene has a very broad development promise in the pharmaceutical and healthcare product industry for the treatment of male infertility.

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