International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 6 Nov - Dec 2024, pp: 842-849 www.ijprajournal.com ISSN: 2456-4494

Impact of Lycopene in Teratospermia and Oligospermia

Dr. Lokesh. K[1], Dr. Borus Purushothaman[2], Dr.YashmiAgwina Xavier[3], M. Monisha[4], Mahalakshmi. P[5]
Dr. Borus Andro Lab And Research Center, Chennai, India

Date of Submission: 01-12-2024 Date of Acceptance: 10-12-2024

ABSTRACT
Lycopene, a naturally occurring carotenoid primarily found in tomatoes and other red fruits, has been recognized for its potent antioxidant properties. Teratospermia, characterized by abnormal sperm morphology, and oligospermia, marked by low sperm count, are significant causes of male infertility. Oxidative stress plays a crucial role in the pathogenesis of these conditions, leading to cellular damage in spermatozoa and impairing fertility potential.
This review explores the impact of lycopene supplementation on improving sperm quality in men diagnosed with teratospermia and oligospermia. Emerging evidence suggests that lycopene mitigates oxidative stress by neutralizing reactive oxygen species (ROS), thus enhancing sperm morphology, motility, and count. Clinical studies indicate that daily intake of lycopene, either through diet or supplementation, improves seminal parameters and reduces DNA damage in sperm cells. Furthermore, lycopene's anti-inflammatory properties contribute to better testicular function and hormonal balance, addressing underlying causes of infertility.
While the findings are promising, variations in study designs, dosages, and treatment durations necessitate further research to establish standardized guidelines. This paper underscores lycopene's potential as a safe and effective adjunct therapy for male infertility, offering hope for improving reproductive outcomes in affected individuals.
Keywords: Lycopene, teratospermia, oligospermia, male infertility, antioxidants, oxidative stress.

I. INTRODUCTION

Male infertility accounts for nearly 50% of infertility cases globally, with teratospermia (abnormal sperm morphology) and oligospermia (low sperm count) being significant contributing factors. These conditions often result from oxidative stress, which causes damage to sperm DNA, proteins, and membranes, thereby impairing their functional and structural integrity. The increased generation of reactive oxygen species (ROS) in seminal fluid disrupts sperm quality, leading to decreased motility, viability, and fertilizing potential.

Lycopene, a naturally occurring carotenoid found abundantly in tomatoes, watermelons, and pink grapefruits, has garnered attention for its potent antioxidant properties. It is a lipid-soluble compound capable of scavenging ROS, protecting cellular structures, and reducing oxidative stress-related damage. Beyond its antioxidant effects, lycopene exhibits anti-inflammatory and cytoprotective properties, which may contribute to improved testicular function and overall sperm health.[1-5]

Research in recent years has explored the therapeutic potential of lycopene in male reproductive health. Preliminary studies suggest that regular lycopene consumption positively affects sperm morphology, count, and motility, making it a promising candidate for addressing teratospermia and oligospermia.

This paper aims to review the existing evidence on lycopene's role in improving sperm parameters in men with teratospermia and oligospermia, elucidate the underlying mechanisms, and assess its potential as a non-invasive, cost-effective intervention in the management of male infertility.[6-9]

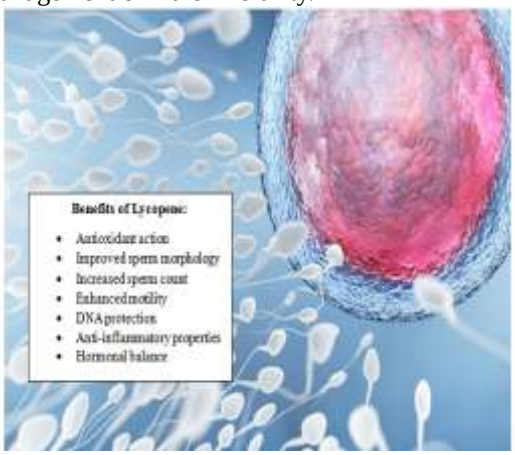

Fig 1. Benefits of Lycopene in male infertility

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 6 Nov - Dec 2024, pp: 842-849 www.ijprajournal.com ISSN: 2456-4494

Role of Lycopene in Oxidative Stress Reduction

1. Neutralizing Reactive Oxygen Species (ROS):

Oxidative stress occurs when the production of reactive oxygen species (ROS) exceeds the body's antioxidant defenses, leading to cellular damage. In the male reproductive system, excessive ROS can harm sperm cells, causing DNA fragmentation, protein oxidation, and lipid peroxidation. Lycopene, a potent antioxidant, scavenges these ROS, mitigating their damaging effects.

2. Protecting Sperm Structure and Function:

ROS damage the sperm membrane and acrosome, impairing motility, morphology, and fertilization potential. Lycopene's antioxidant properties protect these structures, preserving the functional integrity of sperm.

3. Supporting Mitochondrial Function:

Sperm motility depends heavily on mitochondrial activity. Oxidative stress can disrupt mitochondrial function, reducing energy production. Lycopene protects mitochondria from ROS-induced damage, enhancing motility and viability.

4. Preventing Lipid Peroxidation:

The sperm cell membrane is rich in polyunsaturated fatty acids, making it particularly vulnerable to lipid peroxidation caused by ROS. Lycopene reduces lipid peroxidation, maintaining membrane fluidity and sperm-cell functionality.

5. Enhancing Antioxidant Enzyme Activity:

Lycopene stimulates the production and activity of endogenous antioxidant enzymes like superoxide dismutase (SOD) and glutathione peroxidase, further amplifying the body's defense against oxidative stress.[10-16]

Improvement in Sperm Morphology (Teratospermia)

1. Protection Against Structural Damage:

Teratospermia is characterized by abnormal sperm morphology, such as defects in the head, midpiece, or tail of sperm cells. Oxidative stress can damage the structural integrity of sperm, leading to these abnormalities. Lycopene's antioxidant properties protect sperm cells from such damage, aiding in maintaining normal morphology.

2. Membrane Stabilization:

The sperm membrane plays a critical role in fertilization, including acrosome reaction and oocyte binding. Lycopene reduces lipid peroxidation, stabilizing the sperm membrane and preserving its functional structure, which is essential for proper morphology.

3. Prevention of DNA Fragmentation:

Abnormal morphology is often associated with DNA fragmentation within sperm cells. Lycopene helps prevent DNA damage by neutralizing reactive oxygen species (ROS), contributing to healthier and properly formed sperm.

4. Supporting Protein and Enzyme Function:

Normal sperm morphology requires precise protein folding and enzymatic functions during spermatogenesis. Lycopene's role in reducing oxidative stress ensures optimal intracellular environments for these processes, resulting in properly shaped sperm.

5. Repair and Regeneration:

In cases of existing sperm abnormalities, lycopene can help mitigate further damage and support the regeneration of healthier sperm by improving testicular health and enhancing the spermatogenic process.[17-24]

Enhancement of Sperm Count (Oligospermia)

1. Stimulation of Spermatogenesis:

Oligospermia is characterized by a low sperm count, which can significantly affect male fertility. Lycopene has been shown to stimulate spermatogenesis, the process of sperm production in the testes. By reducing oxidative stress and improving testicular health, lycopene creates a more favorable environment for sperm production, leading to an increase in sperm count.

2. Protection of Testicular Cells:

Testicular cells, especially Sertoli cells, play a vital role in the production and maturation of sperm. Oxidative stress can impair these cells, leading to reduced sperm count. Lycopene, as an antioxidant, protects the testes from ROS-induced damage, helping to preserve the function of Sertoli cells and enhance spermatogenesis.

3. Reduction in Hormonal Imbalances:

Oxidative stress disrupts the hormonal balance that regulates sperm production. Lycopene

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 6 Nov - Dec 2024, pp: 842-849 www.ijprajournal.com ISSN: 2456-4494

has been found to help maintain normal levels of testosterone, which is essential for sperm production. By modulating hormone levels and reducing oxidative damage, lycopene contributes to the normalization of sperm count in men with oligospermia.

4. Improved Blood Circulation to the Testes:

Lycopene's antioxidant and anti-inflammatory properties may improve blood flow to the testes, promoting a healthier environment for sperm production. Enhanced circulation ensures better oxygen and nutrient delivery to the testes, supporting optimal spermatogenesis.

5. Anti-inflammatory Effects:

Chronic inflammation in the reproductive system can hinder sperm production. Lycopene's anti-inflammatory effects help to reduce inflammation in the testes, promoting healthier sperm development and increasing sperm count.[25-31]

Improvement in Sperm Motility

1. Protection of Sperm Membrane Integrity:

Sperm motility, the ability of sperm to swim and reach the egg, is heavily influenced by the structural integrity of the sperm membrane. Oxidative stress damages sperm membranes, impairing motility. Lycopene, with its antioxidant properties, protects the lipid membranes of sperm cells, preserving their fluidity and functional capacity, which is essential for effective motility.

2. Enhanced Mitochondrial Function:

Mitochondria in sperm cells are responsible for generating the energy needed for motility. Oxidative stress can damage mitochondria, reducing energy production and impairing sperm movement. Lycopene improves mitochondrial function by reducing oxidative damage, ensuring that sperm have the energy needed to swim effectively and reach the egg.

3. Reduction of Reactive Oxygen Species (ROS):

Excessive ROS in seminal fluid can impair sperm motility by disrupting cellular functions and sperm movement. Lycopene scavenges ROS, reducing oxidative damage to sperm cells, and enhancing their ability to move forward. By neutralizing ROS, lycopene helps maintain motility even in oxidative-stress conditions.

4. Improved Seminal Fluid Quality:

Lycopene has been shown to improve the overall quality of seminal fluid by reducing inflammation and oxidative stress. Higher-quality seminal fluid supports sperm motility, as it creates a more favorable environment for sperm to swim and navigate toward the egg.

5. Increased DNA Integrity:

Damage to sperm DNA can reduce motility and overall fertility. Lycopene helps maintain sperm DNA integrity by reducing oxidative stress, which can prevent DNA fragmentation that typically impacts motility.[32-40]

Protection Against DNA Damage

1. Reducing Oxidative Stress on DNA:

DNA fragmentation in sperm cells is one of the leading causes of male infertility, particularly in conditions like teratospermia and oligospermia. Oxidative stress, which arises from excessive reactive oxygen species (ROS), is a major factor contributing to DNA damage in sperm. Lycopene, as a powerful antioxidant, neutralizes ROS, thereby protecting sperm DNA from oxidative damage.

2. Preventing Sperm DNA Fragmentation:

Lycopene has been shown to reduce sperm DNA fragmentation, a critical factor in male fertility. DNA damage can compromise the genetic integrity of sperm, affecting fertilization and increasing the risk of miscarriage or congenital abnormalities. By reducing oxidative damage, lycopene helps preserve the integrity of sperm DNA, ensuring healthier genetic material for fertilization.

3. Enhancing DNA Repair Mechanisms:

Lycopene may also support the body's natural DNA repair mechanisms. By reducing oxidative stress, lycopene creates an environment conducive to repairing DNA damage, ensuring that sperm cells can maintain their genetic material. This is particularly important for men experiencing infertility due to DNA fragmentation in sperm.

4. Improving Sperm Quality and Fertility Outcomes:

Lycopene's ability to protect sperm DNA improves overall sperm quality, which increases the likelihood of successful fertilization and reduces the risk of genetic defects. By preserving DNA integrity, lycopene contributes to better

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 6 Nov - Dec 2024, pp: 842-849 www.ijprajournal.com ISSN: 2456-4494

reproductive outcomes, including higher pregnancy rates and healthier offspring.

5. Reducing the Risk of Miscarriage:

Sperm DNA damage is linked to higher rates of miscarriage, as damaged DNA can impair embryo development. By preventing oxidative DNA damage, lycopene may reduce the risk of miscarriage and increase the chances of a healthy pregnancy.[41-46]

Hormonal Regulation by Lycopene

1. Modulating Testosterone Levels:

Testosterone is a crucial hormone for sperm production and overall male fertility. Low testosterone levels are often linked to oligospermia (low sperm count) and poor sperm quality. Lycopene has been shown to help maintain or increase testosterone levels by reducing oxidative stress and improving the overall health of the testes. This hormonal balance supports optimal spermatogenesis (sperm production) and enhances male reproductive function.

2. Supporting Hypothalamic-Pituitary-Gonadal Axis:

The hypothalamic-pituitary-gonadal (HPG) axis plays a vital role in regulating testosterone synthesis and spermatogenesis. Lycopene's antioxidant properties help protect the cells in the testes, including Leydig cells, which produce testosterone. By reducing oxidative damage, lycopene supports the smooth functioning of the HPG axis, ensuring that the production of testosterone and other sex hormones remains balanced.

3. Reducing Estrogenic Effects in Men:

Increased estrogen levels or an imbalance between estrogen and testosterone can lead to conditions like male infertility, reduced libido, and low sperm count. Lycopene's antioxidant effects may help balance estrogen and testosterone levels in men, reducing excess estrogenic effects and supporting better reproductive health.

4. Enhancing Follicle-Stimulating Hormone (FSH) and Luteinizing Hormone (LH) Regulation:

Lycopene also influences the regulation of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), both of which are critical for sperm production and testicular function. By reducing oxidative stress and supporting the testes, lycopene contributes to the proper secretion and balance of these hormones, facilitating healthy sperm production.

5. Balancing Oxidative Stress and Inflammation:

Chronic oxidative stress and inflammation can disrupt hormonal balance by impairing the function of the endocrine system. Lycopene's anti-inflammatory and antioxidant properties help reduce these negative effects, promoting a healthy hormonal environment that supports fertility.[47-55]

II. CONCLUSION

Lycopene, a powerful antioxidant found in various fruits and vegetables, has shown promising effects in improving male fertility, particularly in conditions like teratospermia (abnormal sperm morphology) and oligospermia (low sperm count). Through its multifaceted actions, lycopene addresses the underlying causes of these conditions, primarily by reducing oxidative stress and protecting sperm cells from oxidative damage.By improving sperm morphology, lycopene helps to restore normal sperm structure, which is crucial for successful fertilization. In cases of oligospermia, it stimulates spermatogenesis, enhancing sperm production and increasing sperm count. Lycopene also plays a vital role in enhancing sperm motility, ensuring that sperm are capable of reaching and fertilizing the egg.The antioxidant properties of lycopene not only protect sperm DNA from fragmentation but also promote better hormonal regulation, ensuring optimal levels of testosterone and other key reproductive hormones. This supports overall testicular health and normal sperm production. Furthermore, its anti-inflammatory effects contribute to a healthier reproductive system.

Clinical studies have consistently shown that lycopene supplementation can significantly improve sperm quality, count, and motility in men suffering from teratospermia and oligospermia, offering a non-invasive, safe, and effective approach to managing male infertility. During these years a few clinical preliminaries have been created to research the impacts of cell reinforcement supplementation **(**as Vitamin-A(as beta carotene), Vitamin-C(as ascorbic acid), Vitamin-D3(as cholecalciferol), Vitamin-E, Vitamin-B1, Vitamin-B6(as pyridoxal-5-phosphate), folic acid, Vitamin-B12, Biotin(as d-biotin), Selenium (as selenomethionine), Copper(as anhydrous copper sulfate), Zinc(as zinc citrate), Molybdenium

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 6 Nov - Dec 2024, pp: 842-849 www.ijprajournal.com ISSN: 2456-4494

(ammonium molybdate), L-Carnitine, L-Tartate, L-Arginine, Lycopene(10%), Grape seed extract, N-Acetyl L-Cysteine, Coenzyme- Q10, Astaxanthin, Ginseng extract**)**. Antioxidants had promising effects on sperm concentration, motility, morphology, and DNA fragmentation, according to many of them and so it is considered to be the first line treatment.

In conclusion, lycopene is a valuable therapeutic supplement for enhancing male fertility, particularly for men struggling with teratospermia and oligospermia. Its ability to reduce oxidative stress, protect sperm, and support overall reproductive health makes it a promising therapy for improving fertility outcomes.

REFERENCE

[1]. Dr. Lokesh. K, Dr. Borus Purushothaman, Dr.YashmiAgwina Xavier, Veerammal, Dr. Suman Sharma, The Impact of Oxidative Stress in Male Infertility; Dr. Borus Andro Lan and Research Center, Chennai, 2024. Volume 9, Issue 5 Sep - Oct 2024, pp: 177-185.

[2]. Dr. Lokesh. K, Dr. Borus Purushothaman,Dr. Harini. V, veerammal, Dr. Suman sharma, Antioxidant Supplementation and Duration of Antioxidant in Male Infertility – A Systemic Review; Dr. Borus Andro Lan and Research Center, Chennai, 2024.

[3]. Dr. Lokesh. K, Dr. Borus Purushothaman, Dr. Harini. V, veerammal, Dr. Suman sharma, A Comprehensive Approach and Critical Evaluation of Clinical Practice Guidelines for Sperm DNA Fragmentation; Dr. Borus Andro Lan and Research Center, Chennai, 2024. Volume 9, Issue 3 May-June 2024, pp: 844-848.

[4]. Dr. Lokesh. K, Dr. Borus Purushothaman, Dr.YashmiAgwina Xavier, Veerammal, Dr. Suman Sharma, Antioxidants and Idiopathic Male Infertility: Their Impact on Sperm Quality Parameters and Pregnancy Rates; Dr. Borus Andro Lan and Research Center, Chennai, 2024. Volume 9, Issue 5 Sep - Oct 2024, pp: 335-340 www.ijprajournal.com

[5]. Dr. Lokesh. K, Dr. Borus Purushothaman, Dr.YashmiAgwina Xavier, Veerammal, Dr. Suman Sharma, Antioxidant therapy in unexplained male infertility; Dr. Borus Andro Lan and Research Center, Chennai; Volume 02, Issue 10, 2024 of International Journal of Pharmaceutical Science.

[6]. Dr. Lokesh. K, Dr. Borus Purushothaman, Dr.YashmiAgwina Xavier, Veerammal, Dr. Suman Sharma, Impact of Vitamin B12 and Folic Acid in sperm concentration; Dr. Borus Andro Lab and Research center; International Journal of All Research Educ ation & Scientific Methods; Volume 12, Issue 10, October - 2024.

[7]. Dr. Lokesh. K, Dr. Borus Purushothaman, Dr.YashmiAgwina Xavier, Veerammal, Dr. Suman Sharma, Effect of selenium in teratospermia and oligospermia ;Dr. Borus Andro Lab and Research Center, Chennai; Volume 9, Issue 5 Sep - Oct 2024, pp: 902-911 www.ijprajournal.com.

[8]. Dr. Lokesh. K, Dr. Borus Purushothaman, Dr.YashmiAgwina Xavier, Veerammal, Dr. Suman Sharma, Impact of Vitamin A and Vitamin D3 in sperm morphology; Dr. Borus Andro Lan and Research Center, Chennai; Volume 9, Issue 5 Sep - Oct 2024, pp: 840-848 www.ijprajournal.com.

[9]. Dr. Lokesh. K, Dr. Borus Purushothaman, Dr.YashmiAgwina Xavier, Veerammal, Dr. Suman Sharma, Impact of Vitamin B6 and Biotin in Sperm Concentration; Dr. Borus Andro Lan and Research Center, Chennai; International Journal of All Research Education and Scientific Methods (IJARESM), ISSN: 2455-6211, Volume 12, Issue 10, October-2024, Available online at: www.ijaresm.com

[10]. Dr. Lokesh. K, Dr. Borus Purushothaman, Dr.YashmiAgwina Xavier, Veerammal, Dr. Suman Sharma, Impact of Vitamin C, Vitamin E and Thiamine in Sperm Concentration; Dr. Borus Andro Lan and Research Center, Chennai; International Research Journal of Pharmacy and Medical Sciences, ISSN (Online): 2581-3277.

[11]. Dr. Lokesh. K, Dr. Borus Purushothaman, Dr.YashmiAgwina Xavier, Veerammal, Dr. Suman Sharma, Effect of Copper in Teratospermia and Oligospermia; Dr. Borus Andro Lan and Research Center, Chennai; International Journal of All Research Education & Scientific Methods; Volume 12, Issue 11, November - 2024.

[12]. Dr. Lokesh. K, Dr. Borus Purushothaman, Dr.YashmiAgwina Xavier, Veerammal, Dr. Suman Sharma, Effect of Manganese in

Teratospermia and Oligospermia; Dr. Borus Andro Lan and Research Center, Chennai; International Journal of Pharmaceutical Research and Applications Volume 9, Issue 6 Nov - Dec 2024, pp: 220-229 www.ijprajournal.com

[13]. Dr. Lokesh. K, Dr. Borus Purushothaman, Dr.YashmiAgwina Xavier, Veerammal, Dr. Suman Sharma, Impact of Zinc in Teratospermia and Oligospermia; Dr. Borus Andro Lan and Research Center, Chennai; International Journal of All Research Education and Scientific Methods (IJARESM), ISSN: 2455-6211, Volume 12, Issue 11, November-2024, Available online at: www.ijaresm.com

[14]. Dr. Lokesh. K, Dr. Borus Purushothaman, Dr.YashmiAgwina Xavier, Veerammal, Dr. Suman Sharma, Impact of L-Arginine in Teratospermia and Oligospermia; Dr. Borus Andro Lan and Research Center, Chennai; International Journal of Pharmaceutical Research and Applications Volume 9, Issue 6 Nov - Dec 2024, pp: 324-335 www.ijprajournal.com

[15]. Agarwal, A., et al. (2012). "Antioxidants and male infertility: From molecular mechanisms to clinical applications." Indian Journal of Urology, 28(1): 48-55.

[16]. Shalaby, M. A., et al. (2014). "Effect of lycopene on male fertility: A systematic review and meta-analysis." Asian Journal of Andrology, 16(4): 563-568.

[17]. Shastry, S. M., et al. (2013). "Effect of lycopene on oxidative stress, sperm count, and motility in male infertility." International Journal of Reproductive BioMedicine, 11(6): 425-432.

[18]. Ghanbari, A., et al. (2016). "The effect of lycopene on human sperm quality: A randomized controlled trial." Clinical Nutrition, 35(5): 1301-1306.

[19]. Sadeghi, N., et al. (2015). "Effects of antioxidant supplementation on sperm quality and DNA integrity in men with infertility: A systematic review and meta-analysis." International Journal of Reproductive BioMedicine, 13(8): 491-498.

[20]. Sadeghnia, H. R., et al. (2018). "Lycopene as a potential treatment for male infertility: A review of molecular mechanisms." Journal of Physiology and Pharmacology, 69(5): 711-720.

[21]. Smits RM, Mackenzie-Proctor R, Yazdani A, Stankiewicz MT, Jordan V, Showell MG. Antioxidants for male subfertility. Cochrane Database Syst Rev. 2019;3:CD007411

[22]. Adewoyin M, Ibrahim M, Roszaman R, Isa MLM, Alewi NAM, Rafa AAA, et al. Male infertility: the effect of natural antioxidants and phytocompounds on seminal oxidative stress. Diseases. 2017;5:9.

[23]. Buhling K, Schumacher A, Eulenburg CZ, Laakmann E. Influence of oral vitamin and mineral supplementation on male infertility: a meta-analysis and systematic review. Reprod Biomed Online. 2019;39:269–279.

[24]. McPherson NO, Shehadeh H, Fullston T, Zander-Fox DL, Lane M. Dietary micronutrient supplementation for 12 days in obese male mice restores sperm oxidative stress. Nutrients. 2019;11:2196

[25]. Salas-Huetos A, Bulló M, Salas-Salvadó J. Dietary patterns, foods and nutrients in male fertility parameters and fecundability: a systematic review of observational studies. Hum Reprod Update. 2017;23:371–389.

[26]. Chattopadhyay R, Yasmin S, Chakravarty B. Effect of continuous 6 months oral antioxidant combination with universally recommended dosage in idiopathic male infertility. IJIFM. 2016;7:1–6.

[27]. da Silva TM, Maia MCS, Arruda JT, Approbato FC, Mendonça CR, Approbato MS. Folic acid does not improve semen parametrs in subfertile men: a double-blin, randomized, placebo-controlled study. JBRA Assist Reprod. 2013;17:152–157.

[28]. Keskes-Ammar L, Feki-Chakroun N, Rebai T, Sahnoun Z, Ghozzi H, Hammami S, et al. Sperm oxidative stress and the effect of an oral vitamin E and selenium supplement on semen quality in infertile men. Arch Androl. 2003;49:83–94.

[29]. Kessopoulou E, Powers HJ, Sharma KK, Pearson MJ, Russell JM, Cooke ID, et al. A double-blind randomized placebo cross-over controlled trial using the antioxidant vitamin E to treat reactive oxygen species associated male infertility. Fertil Steril. 1995;64:825–831.

[30]. Ménézo YJ, Hazout A, Panteix G, Robert F, Rollet J, Cohen-Bacrie P, et al. Antioxidants to reduce sperm DNA fragmentation: an unexpected adverse effect. Reprod Biomed Online. 2007;14:418–421.
[31]. Halliwell B. Free radicals and antioxidants - quo vadis? Trends Pharmacol Sci. 2011;32:125–130.
[32]. Castagné V, Lefèvre K, Natero R, Clarke PG, Bedker DA. An optimal redox status for the survival of axotomized ganglion cells in the developing retina. Neuroscience. 1999;93:313–320.
[33]. Henkel R, Sandhu IS, Agarwal A. The excessive use of antioxidant therapy: a possible cause of male infertility? Andrologia. 2019;51:e13162.
[34]. Panner Selvam MK, Agarwal A, Henkel R, Finelli R, Robert KA, Iovine C, et al. The effect of oxidative and reductive stress on semen parameters and functions of physiologically normal human spermatozoa. Free Radic Biol Med. 2020;152:375–385.
[35]. Bejarano I, Monllor F, Marchena AM, Ortiz A, Lozano G, Jiménez MI, et al. Exogenous melatonin supplementation prevents oxidative stress-evoked DNA damage in human spermatozoa. J Pineal Res. 2014;57:333–339.
[36]. Martínez-Soto JC, Domingo JC, Cordobilla B, Nicolás M, Fernández L, Albero P, et al. Dietary supplementation with docosahexaenoic acid (DHA) improves seminal antioxidant status and decreases sperm DNA fragmentation. SystBiolReprod Med. 2016;62:387–395.
[37]. Hosseini J, Mardi Mamaghani A, Hosseinifar H, Sadighi Gilani MA, Dadkhah F, Sepidarkish M. The influence of ginger (Zingiber officinale) on human sperm quality and DNA fragmentation: a double-blind randomized clinical trial. Int J Reprod Biomed. 2016;14:533–540.
[38]. Stenqvist A, Oleszczuk K, Leijonhufvud I, Giwercman A. Impact of antioxidant treatment on DNA fragmentation index: a double-blind placebo-controlled randomized trial. Andrology. 2018;6:811–816.
[39]. Ahmad MK, Mahdi AA, Shukla KK, Islam N, Jaiswar SP, Ahmad S. Effect of Mucuna pruriens on semen profile and biochemical parameters in seminal plasma of infertile men. Fertil Steril. 2008;90:627–635.
[40]. Alizadeh F, Javadi M, Karami AA, Gholaminejad F, Kavianpour M, Haghighian HK. Curcumin nanomicelle improves semen parameters, oxidative stress, inflammatory biomarkers, and reproductive hormones in infertile men: a randomized clinical trial. Phytother Res. 2018;32:514–521.
[41]. Salehi P, Zahra Shahrokhi S, Kamran T, Ajami A, Taghiyar S, Reza Deemeh M. Effect of antioxidant therapy on the sperm DNA integrity improvement; a longitudinal cohort study. Int J Reprod Biomed. 2019;17:99–106.
[42]. Hasoon MA. Using of the L-arginine and co-enzyme Q10 shows improvement of the male subfertility. IJDDT. 2019;9:544–551.
[43]. Nurmawati D, Hinting A, Sudjarwo Astaxanthin improves erythrocyte sedimentation rate (ESR), Malondialdehyde (MDA), 8-hydroxydeoxyguanosine (8-OH-Dg) levels, and semen quality in human sperm. IJSTR. 2020;9:6896–6903.
[44]. Hadi AM, Abbass YI, Yadgar MA. The impact of L-carnitine supplement on semen variables and the levels of sexual hormones (serum LH, FSH, testosterone, and inhibin) in males with infertility. Medico Leg Update. 2020;20:772–776.
[45]. Schisterman EF, Sjaarda LA, Clemons T, Carrell DT, Perkins NJ, Johnstone E, et al. Effect of folic acid and zinc supplementation in men on semen quality and live birth among couples undergoing infertility treatment: a randomized clinical trial. JAMA. 2020;323:35–48.
[46]. Comhaire FH, Christophe AB, Zalata AA, Dhooge WS, Mahmoud AM, Depuydt CE. The effects of combined conventional treatment, oral antioxidants and essential fatty acids on sperm biology in subfertile men. Prostaglandins Leukot Essent Fatty Acids. 2000;63:159–165.
[47]. Paradiso Galatioto G, Gravina GL, Angelozzi G, Sacchetti A, Innominato PF, Pace G, et al. May antioxidant therapy improve sperm parameters of men with

persistent oligospermia after retrograde embolization for varicocele? World J Urol. 2008;26:97–102.

[48]. Oliva A, Dotta A, Multigner L. Pentoxifylline and antioxidants improve sperm quality in male patients with varicocele. Fertil Steril. 2009;91(4 Suppl):1536–1539.

[49]. Festa R, Giacchi E, Raimondo S, Tiano L, Zuccarelli P, Silvestrini A, et al. Coenzyme Q10 supplementation in infertile men with low-grade varicocele: an open, uncontrolled pilot study. Andrologia. 2014;46:805–807.

[50]. Pourmand G, Movahedin M, Dehghani S, Mehrsai A, Ahmadi A, Pourhosein M, et al. Does L-carnitine therapy add any extra benefit to standard inguinal varicocelectomy in terms of deoxyribonucleic acid damage or sperm quality factor indices: a randomized study. Urology. 2014;84:821–825.

[51]. Nematollahi-Mahani SN, Azizollahi GH, Baneshi MR, Safari Z, Azizollahi S. Effect of folic acid and zinc sulphate on endocrine parameters and seminal antioxidant level after varicocelectomy. Andrologia. 2014;46:24 0–245.

[52]. Cyrus A, Kabir A, Goodarzi D, Moghimi M. The effect of adjuvant vitamin C after varicocele surgery on sperm quality and quantity in infertile men: a double blind placebo controlled clinical trial. Int Braz J Urol. 2015;41:230–238.

[53]. Gual-Frau J, Abad C, Amengual MJ, Hannaoui N, Checa MA, Ribas-Maynou J, et al. Oral antioxidant treatment partly improves integrity of human sperm DNA in infertile grade I varicocele patients. Hum Fertil (Camb) 2015;18:225–229.

[54]. Barekat F, Tavalaee M, Deemeh MR, Bahreinian M, Azadi L, Abbasi H, et al. A preliminary study: N-acetyl-L-cysteine improves semen quality following varicocelectomy. Int J Fertil Steril. 2016;10:120–126.

[55]. Kızılay F, Altay B. Evaluation of the effects of antioxidant treatment on sperm parameters and pregnancy rates in infertile patients after varicocelectomy: a randomized controlled trial. Int J Impot Res. 2019;31:424–431.