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Review Article

Antioxidants as potential pharmacotherapeutic agents in managing male infertility

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ABSTRACT

Globally, infertility affects 8-12% of couples of reproductive age. Infertility among males accounts for 20%-30% of global infertility cases. Most male infertility cases are idiopathic, with oxidative stress as the underlying mechanism. Reactive oxygen species (ROS), in high concentrations, can outweigh the endogenous antioxidant capacity and interfere with male reproductive processes. Excess ROS levels adversely affect male fertility, but their physiological concentration is vital to mediate the normal sperm functions. The current review aims to evaluate the potential role of antioxidants in the pharmacotherapy of infertility among males.

Keywords: Male infertility, Antioxidants, Oxidative stress, Ascorbic acid, L-carnitine, Lycopene

INTRODUCTION

Infertility affects 8-12% of couples of reproductive ages in the world.[1] Infertility is the inability to conceive after 12 months of unprotected sexual intercourse.[2] Historically, females were held responsible for pregnancy failures. These days, in couples with infertility, the male factor is responsible in about 20% of cases and the female factor in the remaining 30% of cases.

During the last decades, epidemiological studies on infertility showed that the male factor is responsible for 50% of the conceiving problems.

Various factors are responsible for male infertility, i.e., anatomic and genetic abnormalities, neurological disease, infections, environmental and psychological factors, and lifestyle.[3-4]

Even the COVID-19 pandemic has negatively affected couple fertility because SARS-Cov-2 viral infection is responsible for systemic inflammatory processes and increases oxidative stress.[5]

DIAGNOSIS OF MALE INFERTILITY

Male infertility is characterized by anomalies in sperm analysis, low sperm count, and alteration in sperm quality, i.e.; concentration, motility, morphology, or both. The leading causes of male infertility are extra-testicular (obstructive), testicular (primary), pre-testicular (secondary), and idiopathic. Infertility due to idiopathic causes accounts for 30%-40% of infertile male patients.[6]

In 1980 the WHO defined the first guidelines and criteria to perform correct semen analysis, and the last update was published in 2010. Sperm analysis is a central laboratory examination indicated by WHO as the diagnostic path in a case of male infertility. Parameters considered in the evaluation of seminal fluid are volume, pH, liquefaction, viscosity, number of sperms, concentration (normal >15 million/ejaculate), azoospermia, and aspermia.[7-8] Oligospermia is associated with 90% of male infertility cases. Ranges indicated by WHO are found in 95% of normal fertile males. Thus, additional biochemical/molecular information is required to diagnose and manage male infertility.[9-10]

MALE INFERTILITY AND OXIDATIVE STRESS (OS)

There is evidence of OS in seminal fluids in male infertility cases.[11] This is the imbalance between the production of reactive oxygen species (ROS) and the protective action of the antioxidant system responsible for their neutralization and removal. Recent data has shown that poor fertilization, pregnancy loss, poor embryonic development, and congenital disabilities are related to the high susceptibility of spermatozoa to OS.[12] Excess ROS (singlet oxygen, superoxide anion, and hydroxyl radical) and reactive nitrogen species (RNS) such as nitric oxide (NO) can induce irreversible modifications to biological macromolecules of spermatozoa, e.g., lipids, proteins, and nucleic acids. Oxidative/nitrosative stress provokes defects in sperm functions by decreasing sperm motility and fertilizing capacity. ROS and RNS provoke lipid peroxidation of polyunsaturated fatty-acid-rich spermatozoa plasma membranes and DNA fragmentation.[13]

The damaging action of ROS and RNS on proteins provokes permanent modification in structures of proteins through thiol oxidation, sulfonylation, and tyrosine nitrosylation reactions. To counteract ROS and RNS overproduction and prevent oxidative/nitrosative stress, cells are provided with a pool of ROS and RNS scavenging enzymes (SOD, catalase, glutathione peroxidase, heme oxygenase, thioredoxin) and remove selected ROS ($O2\cdot$-, H_2O_2, organic peroxides).[14] It is essential to encourage lifestyle modifications that help reduce the generation of free radicals, i.e. increased intake of vegetables and fruits, a reduction in body weight, smoking cessation, and moderation in the consumption of alcohol.[15]

THE ROS PARADOX AND THE SPERM ANTIOXIDANT DEFENCES

Like other cells of aerobic organisms, spermatozoa rely on oxidative phosphorylation (OXPHOS) to produce ATP molecules as a source of energy. OXPHOS occurs mainly in sperm mid-piece, a mitochondrial-rich district, whereas glycolysis occurs in the flagellum's head and fibrous sheath.[16]

ANTIOXIDANT-BASED TREATMENT IN MALE INFERTILITY

Antioxidant supplemental therapy is one of the most common strategies to address oxidative stress-related diseases, including male infertility. According to a study by Showell et al supplementing infertile men with antioxidants may advance pregnancy outcomes.[17] Huang et al discovered that seminal oxidative stress is associated with male infertility caused by low antioxidant levels. Also, OS significantly impacts the success rate of ART; oral antioxidant supplementation increases the pregnancy rate in couples undergoing ART cycles by enhancing male fertility.[18] Antioxidant therapy is proven more effective in managing idiopathic and varicocele-mediated male infertility.[19]

Vitamin C and vitamin E, zinc, selenium, and carotene, given orally once daily to male partners of couples who could not conceive even after in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI), reduced sperm DNA damage while showing increasing sperm DNA condensation leading to asynchronous chromosomal condensation.[20] A Cochrane meta-analysis on the use of oral antioxidants found that in male infertility, they significantly improved pregnancy rates and live births and decreased sperm DNA damage.[17]

Ascorbic acid (AA)

Ascorbic acid is one of the most abundant water-soluble antioxidants within mammalian tissues, acting as a reducing cofactor in several enzymatic reactions. Vitamin C has a 10 times higher concentration in seminal plasma than in serum.[21] Seminal fluid ascorbic acid levels are positively correlated to morphologically normal sperms and negatively with DNA fragmentation index, the finding which supports the therapeutic use of AA in infertile males.[22] Vitamin C has positive and negative dose-related effects on sperm membrane LPO and motility. AA at concentrations below 1000 µmol/l acts as an antioxidant, improves motility in sperm and decreases LPO, but at concentrations above 1000 µmol/l, it acts as a pro-oxidant.[23] AA (1 g daily) improves human sperm quality, increasing mean sperm count, concentration, and motility.[24] A high dose of AA had side effects and resulted in total sperm immobility at concentrations over 4000 µmol/l.[25]

N-Acetylcysteine (NAC)

Mammals also synthesize another hydrophilic low molecular weight antioxidant, glutathione (GSH). NAC is a glutathione precursor that is effective in metal chelation and seems to improve sperm motility and prevent sperm DNA damage.[26] Also, NAC significantly improves seminal fluid volume and viscosity. The most common oral dose is 600 mg/day and is administered for at least three months.[27] An *in vivo* study evaluated the effect of NAC (600 mg/day for three months) on adverse chromatin alteration induced by high OS and its effect on sperm quality (count, motility, and morphology). With this treatment, sperm parameters improved significantly, and DNA fragmentation and protamine deficiency decreased. Positive results in hormonal profile, lowering FSH and LH levels, and increasing testosterone levels were also observed.[28]

The effectiveness of NAC supplementation in patients with varicocele has been evaluated on semen parameters, protamine content, DNA integrity, and OS. Abnormal semen parameters, protamine deficiency, DNA fragmentation, and OS were significantly reduced in the

control or the treatment group, particularly in NAC, improving protamine deficiency and DNA fragmentation.[29]

A randomized clinical trial, blinded to 50 asthenoteratozoospermia men, evaluated nuclear factor erythroid 2-related factor (NRF2). NRF2 activates the cellular antioxidant response that can combat the harmful effects of OS. After treatment with NAC (600 mg three times daily), sperm parameters and antioxidant levels showed a significant increase in sperm concentration and motility compared to pre-treatment levels, and the percentage of abnormal morphology and DNA fragmentation significantly decreased. A significant improvement in the expression of gene NRF2 and antioxidant levels was also observed, as NRF2 mRNA expression level, specific sperm parameters, and antioxidant enzyme levels.[30]

Vitamin A (carotenoids)

Carotenoids are a group of fat-soluble organic compounds found in yellow, red, orange, and pink vegetables. These retinoids are precursors of vitamin A. Carotenoids are antioxidants that protect cell membrane integrity, regulate epithelial cell proliferation, and are involved in the regulation of spermatogenesis. Dietary carotenoid deficiency can lead to reduced sperm motility.[31] Lower serum retinol concentration has been correlated to worse sperm quality in men.[32] Thus, vitamin A supplementation could be a therapeutic choice for infertility in men. However, many studies have not evaluated the effects of vitamin A on human sperm parameters. Thus, vitamin A is not added to OTC preparations for treating male infertility. Also, vitamin A is toxic and teratogenic in a higher dose.[33,34]

Vitamin-E (α-Tocopherols)

A fat-soluble organic compound in cell membranes protects sperm cell membranes from OS-induced damage, preventing LPO and capturing free hydroxyl radicals and superoxide (23/3). Vitamin E supplementation could improve sperm parameters. Vitamin E supplementation at doses (300 and 1200 mg/day for 12 weeks significantly increased seminal plasma concentration. Alpha-tocopherol concentration in sperms is correlated to the percentage of motile sperms.[35]

A placebo-controlled double-blind study reported improved sperm motility by vitamin E supplementation in men with oligasthenoteratozoospermia (OAT). In addition, enhanced sperm motility was associated with decreased sperm production of MDA, the end product of LPO. Also, by 6 months of treatment, 21% of patients in the treatment group achieved pregnancy.[36] A positive correlation between vitamin E dietary intake and sperm progress and total motility has been found.[37] Vitamin E analogs, specially tocopherol succinate, can exert adverse effects on gap junctional intracellular communication, which could explain their controversial effects in spermatogenesis.[33,34]

Resveratrol (RES)

Polyphenol is found in dietary sources such as grapes, peanuts, berries, plums, pistachios, and red wine. RES is defined as a phytoestrogen because it has structural similarities with estradiol or diethylstilbestrol and its ability to modulate estrogen-sensitive systems. RES has anti-inflammatory, antimicrobial, anti-aging, and antioxidant effects.[38,39]

Recently, many studies have focussed on the effect of RES on male reproductive performance reporting enhancement of spermatogenesis by stimulating the hypothalamic-pituitary-gonadal axis, triggering a penile erection, and reinforcing testosterone production, increasing testicular sperm count and epididymal sperm motility.[40] RES administered in vivo or in vitro effectively removes ROS and stabilizes the antioxidant balance of male reproductive cells and tissues.

Coenzyme Q10 (CoQ10)

It is a fat-soluble vitamin found as a component of the mitochondrial electron transport chain (ETC) in oxygen-dependent living organisms. It has a redox-active benzoquinone head group conjugated to a poly-isoprenoid side-chain of species-specific length. Coenzyme Q10 (CoQ10) is embedded in the mitochondrial inner membrane with active participation in ETC. Fully oxidized CoQ10 (C0Q10ox) accepts one couple of electrons from complex I and complex II and passes them to complex III, where Q-cycle takes place. CoQ10 therapy has been applied as a prospective intervention in various pathological conditions such as diabetes, cancer, Parkinson's disease, Huntington's disease, heart failure, and infertility.[41]

Studies have shown the effectiveness of CoQ10 supplementation in improving male fertility and cardiovascular function.[42] There are three redox states of CoQ10 in the Q-cycle in organisms, ubiquinol (reduced form), ubiquinone (oxidized form), and semiquinone (a radical).[43]

CoQ10 is concentrated in the midpiece of the sperm, containing mitochondria, and takes part in all energy-related processes.[44] In 287 patients with idiopathic oligoasthenoteratozoospermia (OAT) CoQ10 (600 mg/day) supplementation for 12 months significantly increased sperm concentration (113%), sperm motility (104.8%) and normal sperm morphology (78.9%).45 Coadministration of CoQ10 (30 mg/day), L-carnitine (440 mg/day), Vitamin E (75 IU/day), and vitamin C (12 mg/day) improved sperm concentration and pregnancy rates in infertile male patients.[43] In another study, idiopathic male infertility (IMI) patients were supplemented with CoQ10 (200 mg/day) and D-Asp

(2660 mg/day) for 12 weeks, and a significant increase in concentrations of CoQ10 and D-Asp in sperms and seminal plasma was observed, and also improvement in sperm motility, but no effect was observed on sperm concentration and morphology.[43]

CoQ10 also increased total antioxidant capacity (TAC), SOD, and CAT activities, and greater improvements were found in patients taking the highest doses.[46] Gvozdjakova et al showed improved pregnancy rates after CoQ10 administration, at a daily dose of 90 mg for 3-9 months.[43] Safarinejad reported an increase in pregnancy rates after treating 287 males with OAT by supplemental CoQ10, 300 mg twice daily for 12 months.[47] CoQ10 could play a role in improving ART outcomes. An *in-vitro* study showed that incubation of sperms for 3 hours with an antioxidant formula (zinc+D-Asp+CoQ10) had a beneficial effect on sperm motility and recovery of sperms by swim-up and lipid peroxidation, suggesting the beneficial role of these agents in sperm preparation before ART.[48]

L-Carnitine

Exogenous L-carnitine (high-polar, water-soluble, quaternary amine) is essential to the oxidative processes and increases cellular energy production.[49] High concentrations in the male reproductive tract, especially in the epididymis, suggest its crucial role in energy metabolism and sperm maturation.[50]

The beneficial effects of L-carnitine on sperm parameters are well known. Significant improvement in sperm motility has been reported in patients treated with L-carnitine (2 g/day) and acetyl-L-carnitine at the dose of 1 g/day for three months.[51]

A randomized placebo-controlled study on 100 patients taking L-carnitine showed significant improvement in semen quality, especially in sperm concentration and motility.[52] Another study confirmed that L-acetyl-carnitine improved sperm motility, either alone or in combination with L-carnitine, improving straight progressive velocity after three months.[53] A study on 100 patients receiving oral carnitine (3g/day) for four months indicates that L-carnitine improves spermatozoa motility total number of ejaculated sperms.[54]

Folic acid

Folic acid is involved in many biochemical processes and functions, such as DNA synthesis, which is fundamental in spermatozoa formation; oxidative pathway, folic acid effectively scavenges oxidizing free radicals and inhibits LPO.[55,56] Folic acid supplementation has been studied in sub-fertile males. A study has reported an increase in the number and motility of spermatozoa and a decrease in immature cells after three months of folic acid supplementation (15 mg/day) in men of infertile couples with cell idiopathic syndrome.[57]

Superoxide dismutases (SODs)

SODs are metalloenzymes (two intracellular and one extracellular form) that convert superoxide to H_2O_2. Intracellular forms are copper and zinc SOD (CuZnSOD) encoded by the SOD1 gene, and manganese SOD (MnSOD), which acts in the mitochondrial matrix, is encoded by the gene SOD2. The SOD3 gene encodes the extracellular form of SOD (ECSOD), can be present in an accessible form or can be connected to surface polysaccharides. The main active isoenzymes in seminal plasma are CuZnSOD (75%) and ECSOD (25%), which originate from the prostate. SODs protect testicular cells against heat stress-induced apoptosis, and SOD activity is low in infertile men than in fertile controls and positively correlated with sperm morphology and motility. Supplementation of ECSOD at a dose of 400 U/ml to human sperm suspension prevented loss of motility and increased MDA concentration, showing the significant role of SODs for human sperm motility. (90/3) SOD is included in some OTC products containing other antioxidants, e.g., D-chiro-inositol, zinc, and folic acid, recommended for treating male infertility. There is a lack of studies investigating the effect of oral SOD supplementation on human sperm, but the recommended dose is 150 IU/day.[51]

Selenium

Selenium is a micronutrient essential for normal testicular development, spermatogenesis, sperm motility, and function. Lack of selenium is correlated to atrophy of seminiferous epithelium, disorders of spermatogenesis, maturation of sperms in the epididymis, reduced testicular volume, decreased sperm motility, and altered sperm morphology. The exact mechanism by which selenium reduces OS and improves sperm parameters is controversial. The oral dose of selenium is 80 mcg-300 mcg once daily for at least 3 months, alone or in combination with antioxidants.[51]

Zinc

Zinc is a component of over 200 enzymes involved in the biosynthesis of nucleic acids, proteins, and the process of cell division (23/3). In addition, it normalizes oxidosensitive indices and catalase-like activity in the seminal fluid of asthenozoospermic patients. The oral dose of zinc is 220 mg once or twice a day for 3-4 months, alone or in addition to folic acid (5 mg/day).[33,34]

Myoinositol (MYO)

Inositol is a component of the vitamin B complex, a precursor of second messengers, and is involved in several signal transduction mechanisms in the cell membrane. For example, it regulates seminal plasma osmolality, protein formation essential for embryogenetic development, and sperm chemotaxis and sperm motility. Also, inositols are involved in sperm capacitation and

acrosome reactions. Incubation with MYO increases sperm motility and the number of sperms retrieved by swim-up in both normozoospermic men and patients with OAT.[58] This is the basis for using MYO in in-vivo and *in-vitro* ARTs.

In addition, oral supplementation with MYO seems to improve sperm parameters (146,148,149/3). A double-blind, randomized, placebo-controlled study showed that MYO (2 g twice daily) treatment in idiopathic male infertility increased sperm concentration, total count, progressive motility, and acrosome reacted sperms (148). Most frequently, the supplementation strategy is a daily oral dose of 4 g plus 100≥µg of folic acid for at least two months.[51]

Quercetin (QUE)

Quercetin is a flavonoid found in citrus fruits, berries, herbs and spices, red wine, cocoa, and fruit juices (65/8). The biomolecule has anti-inflammatory, anticarcinogenic, antibacterial, anti-aggregatory, and antidiabetic effects. Among flavonoids, QUE is the most potent ROS and nitric oxide scavenger (67/8). Evidence of the impact of QUE on the male reproductive system is still controversial. Most in vitro studies on QUE indicate its stimulating effect on the male gamete's structural integrity and functional activity. According to Diao et al, QUE (10 µmol/l) could significantly improve sperm motility in semen collected from leukocytospermic patients.[59]

Catechins

Catechins are polyphenol flavonoids that are bioactive components of green tea. These may be found in black grapes, strawberries, and apricots. Catechins possess a broad spectrum of biological actions and may be helpful in the prevention of CVS diseases, osteoarthritis, cancer, and Parkinson's disease. Catechin polyphenols have high ROS-scavenging activity, about 20 times higher than vitamin C. Catechins are effective chelators of transition metals, including cadmium and chromium. Catechins modulate the level of monoamines that control sexual and reproductive behavior. Rai et al reported that 50 mg/kg catechin enhanced sexual behavior in rats, being safe on histology of testes, sperm count, morphology, and motility. Epigallocatechin-3-gallate (EGCG) in the range of 2-20 µmol/l has been reported to affect the estrogen of male gametes and increased cholesterol efflux and tyrosine phosphorylation which increases sperm motility and viability. High concentrations of catechins (25-1000 µmol/l) did not show any protective effect on human sperms exposed to cadmium, aluminium, or lead.[60]

Curcumin (CUR)

It is the principal curcuminoid of the herbal remedy turmeric. Recent studies show curcuminoids exhibit neuroprotective, anti-inflammatory, antitumor, and radioprotective properties. CUR is an active scavenger of superoxide, hydroxyl radicals, nitrogen dioxide, and a potent LPO inhibitor. Kazemizadeh et al have reported improvement in semen concentration, total sperm production, progressive motility, and membrane integrity corresponding to increasing CUR (10, 20 or 30 mg/bird) in broiler roosters leading to significantly higher fertility rates. CUR has a dua biological activity, a low CUR concentration may protect and stimulate male reproductive cell activity, and higher CUR doses exhibit a toxic effect on sperm vitality. CUR can inhibit protein kinase C, which modulates the flagellar movement of sperms. This bioactivity could be associated with a possible detrimental effect on sperm behavior. CUR may have a particular sperm-immobilizing activity, thus its possible use in modern contraceptives.[60]

Rutin (RUT)

This biomolecule comprises quercetin and rutinose, widely present in buckwheat, apple, red beans, green tea, and red wine. RUT is a potent antioxidant having cytoprotective, anticarcinogenic, anti-inflammatory, antithrombotic, neuroprotective, vasoprotective, and cardioprotective properties. RUT exerts protective functions by scavenging excess free radicals (superoxide and hydroxyl radicals), reducing LPO levels, and chelating metal ions. It has been observed that RUT (20 µmol/l and 30 µmol/l) were able to preserve human sperm motility, viability, and structural integrity. RUT molecule contains rutinose, a disaccharide composed of glucose and rhamnose, thus limited ability to cross the plasma membrane, which may be less harmful to sperm function.[60]

Genistein (GEN)

It is an isoflavone that may be found in soy, fava beans, clover, and Lupinus. GEN is structurally related to estrogen. Like other phytoestrogens, it can bind to estrogen receptors and have estrogenic and antiestrogenic actions. GEN has high antioxidant action against hydrogen peroxide, inhibits topoisomerase activity and tyrosine kinase signaling pathways, and regulates both pro-and anti-apoptotic proteins. Low GEN concentration (10 µmol/l) has an antioxidant effect on frozen-thawed human sperms leading to improvement in sperm motility and decreased lipid disintegration caused by cryopreservation.[60]

Apigenin (API)

A flavonoid subclass is abundant in aromatic plants (rosemary, chamomile, parsley), fruits (apple, celery, fennel), vegetables, and honey. API attracted widespread attention because it has estrogenic action, anti-inflammatory, anticancer and antidiabetic, and antioxidant properties. API was able to restore the glutathione cycle, crucial for the protection of the cell membrane against peroxidases, failure of which is an

early step in the apoptotic cascade that could precede the loss of mitochondrial integrity. Concerning API supplementation to the sperm processing media, a high dose of highly permeable API may alter the osmolality of the extender and cause aberrations to sperm structure and function.[60]

Naringenin (NAR)

A natural flavonoid commonly found in citrus fruits, tomatoes, cherries, and cocoa. NAR is safe with estrogenic and partial anti-estrogenic activity and significant antioxidant properties. NAR is an effective supplement to media for sperm storage or cryopreservation. Exposure of extended boar sperms to NAR (10 and 25 mol/l) led to the maintenance of sperm motility up to three days of storage. NAR may have stimulating effects on sperm motility because it is lipophilic and an antioxidant that enables it to protect the membrane structure of the male gamete, including plasma membrane and acrosome.

It is proposed that NAR can neutralize excessive H_2O_2 in sperm membranes. H_2O_2 becomes unavailable for conversion to hydroxyl radical in the cell; thus, sperm DNA damage may be prevented. Also, NAR inhibits LPO in sperms because of the polar nature of NAR, which facilitates adherence to the lipid bilayer, thus preventing oxidative insults to the sperm cell membrane. NAR can act as a pro-oxidant by peroxidase catalyzed oxidation of phenol B ring in its molecule. The phenoxyl radicals produced from oxidized NAR may oxidize GSH to form thiyl radicals. Because of pro-oxidant action NAR can damage testicular tissue and decrease sperm concentration and motility.[60] Moretti et al. noted that NAR concentrations <200 µmol/l have a beneficial effect on progressive motility and viability of human swim-up sperm. A sharp decline in sperm vitality was observed with NAR concentrations of 200 µmol/l and 400 µmol/l.[61]

Kaempferol (KAE)

It is found primarily in vegetables (kale, leeks, spinach) and herbs (dill and chives). KAE is a potent flavonoid in protecting male gametes exposed to toxicity induced by lead, cadmium, or aluminium. KAE showed the highest efficacy, among all tested biomolecules, in sperm motility recovery and prevention of LPO. It may be hypothesized that KAE can interfere with spermatozoa's motion apparatus and mitochondrial system (160/8). Preliminary data shows KAE to be a promising protective and antioxidant molecule; it has been suggested that higher KAE supplementation may cause self-oxidation.[60]

Lycopene (LYC)

Lycopene is a natural carotenoid in high concentrations in ripe tomatoes, watermelons, apricots, and papaya. Diddefent mechanisms for the action of LYC have been proposed, and the most prominent is the prevention of overproduction of ROS. LYC is a potent scavenger of singlet oxygen, hydroxyl radical, and nitrogen dioxide.[60] Various studies have reported a significant decrease in lipid peroxidase (LPO) following LYC supplementation. Williams et al studied the effect of 12-week supplementation with 14 mg/day of lactolycopene on sperm quality parameters in healthy volunteers with no fertility issues. A proportion of fast-progressive sperms and a higher amount of morphologically intact male gametes were observed at the end of the experiment.[62] In Mohanty et al study, 50 oligoasthenozoospermic males consuming 8 mg LYC over an extended period showed a significant increase in sperm count, and according to Gupta and Kumar, 30 idiopathic infertile men on LYC 2 mg/day for three months, showed 53% increase in sperm concentration.[63-64]

L-arginine

L-arginine prevents peroxidation of membrane lipids and actively participates in the formation of spermatozoa. In an in vitro study, human semen with low motility incubated with L-arginine showed enhancement in sperm motility, which suggested the use of L-arginine in artificial insemination in men with subnormal sperm motility. Clinical efficacy and acceptance of L-arginine have been studied in 40 infertile men, with a usual number of sperms (>20 million/ml) but a decreased motility. Treatment with L-arginine HCL 10% (80 ml daily for six months) improved sperm motility without side effects. In a randomized, double-blind, placebo-controlled, cross-over study, 3 g of L-arginine aspartate or placebo for one month, L-arginine improved semen volume, sperm concentration, motility, vitality, and morphology without adverse effects.[65]

CONCLUSION

Some experts believe that antioxidant supplementation has little or even adverse impact on sperm maturation, sperm motility, capacitation, and acrosome reactions, leading to deteriorated sperm quality. However, studies show that antioxidants have variable effects on male infertility therapy, thus a dose-dependent effect. Natural biomolecules affect sperm production and motility by complex intracellular actions unique to each natural biomolecule. At low doses, antioxidants improve sperm concentration, motility, vitality, and fertility rates, but at too high doses, they have detrimental effects on cells of the male reproductive system.

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REFERENCES

1. Inhorn MC, Patrizio P. Infertility around the globe: new thinking on gender, reproductive technologies

and global movements in the 21st century. Hum Reprod Update. 2015;21:411-26.
2. Zegers-Hochschild F, Adamson GD, de Mouzon J, Ishihara O, Mansour R, Nygren K, et al. International Committee for Monitoring Assisted Reproductive Technology; World Health Organization. International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) revised glossary of ART terminology, 2009. Fertil Steril. 2009;92:1520-4.
3. Borght VM, Wyns C. Fertility and infertility: Definition and epidemiology. Clin Biochem. 2018;62:2-10.
4. Anifandis G, Bounartzi T, Messini CI, Dafopoulos K, Sotiriou S, Messinis IE. The impact of cigarette smoking and alcohol consumption on sperm parameters and sperm DNA fragmentation (SDF) measured by Halosperm(®). Arch Gynecol Obstet. 2014;290:777-82.
5. Khalili MA, Leisegang K, Majzoub A, Finelli R, Selvam PMK, Henkel R, et al. Male Fertility and the COVID-19 Pandemic: Systematic Review of the Literature. World J Mens Health. 2020;38:506-20.
6. Ramalingam M, Kini S, Mahmood T. Male fertility and infertility. Obstetr Gynaecol Reprod Med. 2014;24:326-32.
7. World Health Organization. WHO Laboratory Manual for the Examination and Processing of Human Semen, 5th ed.; World Health Organization: Geneva, Switzerland. 2010;271.
8. Cooper TG, Noonan E, von Eckardstein S, Auger J, Baker HW, Behre HM, et al. World Health Organization reference values for human semen characteristics. Hum Reprod Update. 2010;16:231-45.
9. Sabra SM, Al-Harbi MS. An influential relationship of seminal fluid microbial infections and infertility, Taif Region, KSA. World J Med Sci. 2014;10:32-7.
10. Kumar N, Singh AK. Trends of male factor infertility, an important cause of infertility: A review of literature. J Hum Reprod Sci. 2015;8:191-6.
11. Bisht S, Faiq M, Tolahunase M, Dada R. Oxidative stress and male infertility. Nat Rev Urol. 2017;14: 470-85.
12. Fujii J, Imai H. Redox reactions in mammalian spermatogenesis and the potential targets of reactive oxygen species under oxidative stress. Spermatogenesis. 2014;4:e979108.
13. Drevet JR, Aitken RJ. Oxidative Damage to Sperm DNA: Attack and Defense. Adv Exp Med Biol. 2019;1166:107-17.
14. Kuang F, Liu J, Tang D, Kang R. Oxidative Damage and Antioxidant Defense in Ferroptosis. Front Cell Dev Biol. 2020;8:586578.
15. Gosalvez J, Rodriguez-Predreira M, Mosquera A, Lopez-Fernandez C, Esteves SC, Agarwal A, et al. Characterisation of a subpopulation of sperm with massive nuclear damage, as recognised with the sperm chromatin dispersion test. Andrologia. 2014;46(6):602-9.
16. Ferramosca A, Zara V. Bioenergetics of mammalian sperm capacitation. Biomed Res Int. 2014;2014:902953.
17. Showell MG, Mackenzie-Proctor R, Brown J, Yazdani A, Stankiewicz MT, Hart RJ. Antioxidants for male subfertility. Cochr Datab Syst Rev. 2014;12:CD007411.
18. Arhin SK, Zhao Y, Lu X, Chetry M, Lu J. Effect of micronutrient supplementation on IVF ooutcomes: a systematic review of the literature. Reproductive Biomedicine Online. 2017;35:715-22.
19. Garg H, Kumar R. An update on the role of medical treatment including antioxidant therapy in varicocele. Asian J Androl. 2016;18:222.
20. Menezo 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;14:418-21.
21. Jacob RA, Pianalto FS, AgeeRE. Cellular ascorbate depletion in healthy men. J Nutrition. 1992;122(5):1111-8.
22. Song GJ, Norkus EP, Lewis V. Relationship between seminal ascorbic acid and sperm DNA integrity in infertile men. International J Andrology. 2006;29(6):569-75.
23. Lanzafame FM, La Vignera S, Vicari E, Calogero AE. Oxidative stress and medical antioxidant treatment in male infertility. Reproductive Bio Medicine Online. 2009;19(5):638-59.
24. Eskenazi B, Kidd SA, Marks AR, Sloter E, Block G, Wyrobek AJ. Antioxidant intake is associated with semen quality in healthy men. Human Reproduction. 2005;20(4):1006-12.
25. Verma A, Kanwar K. Human sperm motility and lipid peroxidation in different ascorbic acid concentrations: An in vitro analysis. Andrologia. 1998;30:325-9.
26. Moilanen J, Hovatta O, Lindroth LL. Vitamin E levels in seminal plasma can be elevated by oral administration of vitamin E in infertile men. Int J Andrology. 1993;16(2):165-6.
27. Amorini AM, Listorti I, Bilotta G, Pallisco R, Saab MW, Mangione R, et al. Antioxidant-based therapies in male infertility: Do we have sufficient evidence supporting their effectiveness? Antioxidants. 2021;10:220.
28. Jannatifar R, Parivar K, Roodbari NH, Nasr-Esfahani MH. Effects of N-acetyl-cysteine supplementation on sperm quality, chromatin integrity and level of oxidative stress in infertile men. Reprod Biol Endocrinol. 2019;17:24.
29. Safarinejad MR, Safarinejad S. Efficacy of selenium and/or N-acetyl-cysteine for improving semen parameters in infertile men: A double-blind, placebo-controlled, randomized study. J Urol. 2009;181:741-51.
30. Wolfram T, Schwarz M, Reuß M, Lossow K, Ost M, Klaus S, et al. N-acetylcysteine as modulator of

the essential trace elements copper and zinc. Antioxidants. 2020;9:1117.
31. Walczak-Jedrzejowska R, Wolski JK, Slowikowska Hilczer J. The role of oxidative stress and antioxidants in male fertility. Central European J Urology. 2013;66(1):60-7.
32. Al-Azemi MK, Omu AE, Fatinikun T, Mannazhath N, Abraham S. Factors contributing to gender differences in serum retinol and α-tocopherol in infertile couples. Reproductive Bio Medicine Online. 2009;19(4):583-90.
33. Comhaire F. The role of food supplementation in the treatment of the infertile couple and for assisted reproduction. Andrologia. 2010;42(5):331-40.
34. Moilanen J, Hovatta O. Excretion of alpha−tocopherol into human seminal plasma after oral administration. Andrologia. 1995;27(3):133-6.
35. Therond P, Auger J, Legrand A, Jouannet P. α-tocopherol in human spermatozoa and seminal plasma: relationships with motility, antioxidant enzymes and leukocytes. Molecular Human Reproduction. 1996;2(10):739-44.
36. Suleiman SA, Ali ME, Zaki ZMS, El-Malik EMA, Nasr MA. Lipid peroxidation and human sperm motility: protective role of vitamin E. J Andrology. 1996;17(5):530-7.
37. Eskenazi B, Kidd SA, Marks AR, Sloter E, Block G, Wyrobek AJ. Antioxidant intake is associated with semen quality in healthy men. Human Reproduction. 2005;20(4):1006-12.
38. Risuleo G, La Mesa C. Resveratrol: Biological activities and potential use in health and disease. in nutraceuticals in veterinary medicine, 1st ed.; Gupta, R., Srivastava, A., Lall, R., Eds.; Springer: Cham, Germany, 2019;215-26.
39. Gambini J, Inglés M, Olaso G, Lopez-Grueso R, Bonet-Costa V, Gimeno-Mallench L, et al. Properties of resveratrol: In vitro and in vivo studies about metabolism, bioavailability, and biological effects in animal models and humans. Oxid Med Cell Longev. 2015;2015:837042.
40. Mongi LM, Perelli S, Condorelli RA, Barbagallo F, Crafa A, Cannarella R, et al. The role of resveratrol in human male fertility. Molecules. 2021;26:2495.
41. Banihani SA. Effect of coenzyme Q10 supplementation on testosterone. Biomolecules. 2018;8(4):172.
42. Alahmar AT, Calogero AE, Singh R, Cannarella R, Sengupta P, Dutta S. Coenzyme Q10, oxidative stress, and male infertility: A review. Clin Exp Reprod Med. 2021;48(2):97-104.
43. Gvozdjakova A, Kucharska J, Dubravicky J, Mojto V, Singh RB. Coenzyme Q11, α-tocopherol, and oxidative stress could be important metabolic biomarkers of male infertility. Dis Markers. 2015;2015:827941.
44. Tiseo BC, Gaskins AJ, Hauser R, Chavarro JE, Tanrikut C. Coenzyme Q10 intake from food and semen parameters in a subfertile population. Urology. 2017;102:100-5.
45. Safarinejad MR. The effect of coenzyme Q11 supplementation on partner pregnancy rate in infertile men with idiopathic oligoasthenoteratozoospermia: an open-label prospective study. Int Urol Nephrol. 2012;44:689–700.
46. Alahmar AT. The impact of two doses of coenzyme Q10 on serum parametres and antioxidant status in men with idiopathic oligoasthenoteratozoospermia. Clin Exp Reprod Med. 2019;46 (3):112-8.
47. Safarinejad MR. The effect of coenzyme Q11 supplementation on partner pregnancy rate in infertile men with idiopathic oligoasthenoteratozoospermia: an open-label prospective study. Int Urol Nephrol. 2012;44:689-700.
48. Majzoub A, Agarwal A. Antioxidant therapy in idiopathic oligoasthenoteratozoospermia. Indian J Urol. 2017;33:207-14.
49. Chiu MN, Blackman MR, Wang C, Swerdloff RS. The role of carnitine in the male reproductive system. Annals of the New York Academy of Sci. 2004;1033:177-88.
50. Lenzi A, Lombardo F, Gandini L, Dondero F. Metabolism and action of L-carnitine: its possible role in sperm tail function. Archivio Italiano di Urologia Nefrologia Andrologia. 1992;64(2):187-96.
51. Calogero AE, Condorelli RA, Russo GI, Vignera SL. Conservative nonhormonal options for the treatment of male infertility: antibiotics, anti-iInflammatory drugs, and antioxidants. BioMed Research Int Vol. 2017.
52. Lenzi A, Sgro P, Salacone P, Paoli D, Gilio B, Lombardo F, et al. A placebo controlled double-blind randomized trial of the use of combined l-carnitine and l-acetylcarnitine treatment in men with asthenozoospermia. Fertil Steril. 2004;81:1578-84.
53. Peivand S, Abasali K, Narges M. Effects of L-carnitine on infertile men's spermogram; a randomised clinical trial. J Reprod Infertil. 2010;10:331.
54. Garolla A, Maiorino M, Roverato A, Roveri A, Ursini F, Foresta C. Oral carnitine supplementation increases sperm motility in asthenozoospermic men with normal sperm phospholipid hydroperoxide glutathione peroxidase levels. Fertil Steril. 2005;83:355-61.
55. 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;46:240-5.
56. Joshi R, Adhikari S, Patro BS, Chattopadhyay S, Mukherjee T. Free radical scavenging behavior of folic acid: Evidence for possible antioxidant activity. Free Radic Biol Med. 2001;30:1390-9.
57. Bentivoglio G, Melica F, Cristoforoni P. Folinic acid in the treatment of human male infertility. Fertil Steril. 1993;60:698-701.

58. Condorelli RA, Lavignera S, Bari DF, Unfer V, Calogero AE. Effects of myoinositol on sperm mitochondrial function in-vitro . European Review for Medical and Pharmacological Sciences. 2011;15 (2):129-34.
59. Diao R, Gan H, Tian F, Cai X, Zhen W, Song X, et al. In vitro antioxidation effect of Quercetin on sperm function from the infertile patients with leukocytospermia. Am J Reprod Immunol. 2019;82:e13155.
60. Tvrda E, Benko F, Slanina T, Stefan S. The role of selected natural bBiomolecules in sperm production and functionality. Molecules. 2021;26:5196.
61. Moretti E, Mazzi L, Terzuoli G, Bonechi C, Iacoponi F, Martini S, et al. Effect of quercetin, rutin, naringenin and epicatechin on lipid peroxidation induced in human sperm. Reprod Toxicol. 2012;34:651-7.
62. Williams EA, Parker M, Robinson A, Pitt S, Pacey AA. A randomized placebo-controlled trial to investigate the effect of lactolycopene on semen quality in healthy males. Eur J Nutr. 2020;59:825-33.
63. Mohanty NK, Kumar S, Jha AK, Arora RP. Management of idiopathic oligoasthenospermia with lycopene. Indian J Urol. 2001;18 (1):57-61.
64. Gupta NP, Kumar R. Lycopene therapy in idiopathic male infertility-a preliminary report. Int Urol Nephrol. 2002;34:369-72.
65. De Luca MN, Colone M, Gambioli R, Stringaro A, Unfer V. Oxidative stress and male fertility: role of antioxidants and inositols. Antioxidants. 2021;10:1283.

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