J. Integr. Sci. Technol. 2024, 12(3), 751

Journal of Integrated
SCIENCE & TECHNOLOGY

Beneficial impacts and limitations of antioxidant supplements on Male Infertility

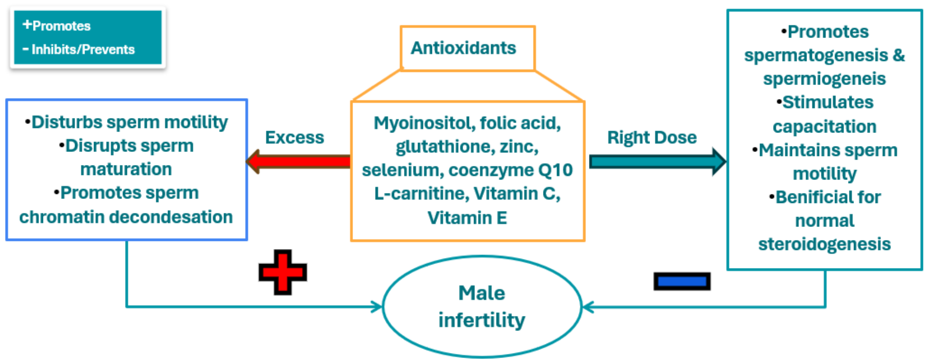
Suvendu Ghosh[1], Partha Sarathi Singha[2], Ankan Acharyaa[3], Debosree Ghosh[3*]

[1]*Department of Physiology, Hooghly Mohsin College, Chinsura, Hooghly, West Bengal, India.* [2]*Department of Chemistry, Government General Degree College, Kharagpur II, Paschim Medinipur, West Bengal, India.* [3]*Department of Physiology, Government General Degree College, Kharagpur II, Paschim Medinipur, West Bengal, India*

Received on: 16-Apr-2023, Accepted on: 28-Jul-2023 and Published on: 02-Nov-2023

Review Article

ABSTRACT



In general, there exists a balance between the free radicals and natural antioxidants in the human body. The human body exists in thermodynamic non equilibrium and remains in a steady state. The impacts of the free radicals generated indigenously or exposed to are constantly mitigated by the indigenous antioxidants. Supplementation of antioxidants in any form helps to combat the free radicals mediated oxidative stress (OS) induced health effects including infertility. Free radicals directly damage the histo-architecture of various reproductive organs and also the cyto-morphology of sperm. Antioxidants scavenge and neutralize the free radicals contributing to the beneficial effects of antioxidants on male infertility. Supplementation of antioxidants initially adds up to the beneficial effects but antioxidants in excess acts as pro-oxidants and contribute to further damaging effects on the male reproductive system, causing male infertility.

Keywords: Antioxidants, free radicals, infertility, sperm, oxidative stress

INTRODUCTION

Antioxidants are molecules and compounds that have the ability to scavenge or remove free radicals. These are essential for the maintenance of life. Normal physiological life process leads to continuous generation of several free radicals in the living system. Antioxidants constantly remove and neutralize those free radicals. Theses free radicals are highly reactive and have a tendency to react with whatever they find in their vicinity immediately after being formed. Thus if the free radicals are left unrevoked in living system they will react with almost all biomolecules and will cause tremendous damage and disruption of the living system which will cause various pathological conditions and may ultimately culminate to death. The damages caused by the oxygen derived free radicals like the superoxide anion radical, hydroxyl radical etc., is termed as oxidative damage. In such situation the only rescuers are the antioxidants. They are primarily of two categories. The indigenous ones are mostly enzymes like the catalase, superoxide dismutase etc., which are found in living cells or are biomoleules like the glutathione. These indigenous ones are synthesized in the living body naturally and are the natural defense of the body against free radicals induced damages. On the other hand, the exogenous antioxidants are the ones like vitamin C and E which are consumed or supplemented and removes the free radicals from living body thereby mitigating the free radicals induced damages of various biomolecules.[1-3]

Free radicals react with anything they find in their proximity and thus disrupt the normal biochemical composition of the biomolecules they react with. Free radicals lead to peroxidation of lipids and carbonylation of proteins. Lipid and protein being the main two components of plasma membrane, the cellular membrane integrity is thus damaged by free radical attack. All different types of cells in living body are susceptible to oxidative damage once the free radicals start accumulating in living body. There exists a fine balance between the generation and removal of free radicals.The balance is basically between free radicals and antioxidants. As long as the balance is perfect i.e., the antioxidants remain on the heavier

*Corresponding Author: Dr. Debosree Ghosh, Department of Physiology, Government General Degree College Kharagpur II, Madpur, Paschim Medinipur Pin: 721149, West Bengal, India. Email: ghoshdebosree@gmail.com

Cite as: *J. Integr. Sci. Technol., 2024, 12(3), 751. URN:NBN:sciencein.jist.2024.v12.751*

 ISSN: 2321-4635
HTTP://PUBS.THESCIENCEIN.ORG/JIST

side, there exists a physiological steady state. The moment the rate of formation of free radicals exceeds the rate of their removal, the living system falls vulnerable to damages starting from cellular and sub-cellular level.[4,5] Sperms being cellular entities are thus no exception of oxidative onslaught.[6]

Studies reveal that free radicals have significant deteriorative impact on the male reproductive system and thus adversely affect the fertility in male.[7] Generation of free radicals induced by ageing also leads to oxidative stress mediated damage of male reproductive system leading to decline in spermatogenesis and resulting in male infertility.[8] Also, oxidative stress is known to be associated with inflammation induced male infertility.[9] Oxidative stress is also known to be associated with infertility in female.[10] Antioxidants are reported to have beneficial effects on idiopathic male infertility and also are reported to improve pregnancy rates[11]. Studies also reports that use of antioxidants is recommended for the treatment of infertility in men as supportive therapy.[12] Oxidative stress is also recognized as an underlying mechanism for COVID-19 induced male infertility and supplementation of Vitamin C has been reported to be a possible remedy for the same by virtue of its antioxidant properties.[13] Also, use of antioxidants like Vitamin C, glutathione, Vitamin e N–acetyl–cysteine, and catalase in the semen reduces ROS levels and also prevents reduction in motility of sperm.[14, 15]

Antioxidants when use in excess may have reverse effects on male fertility. Certain antioxidants like Vitamin C(ascorbic acid) and vitamin E (tocoferol) gets converted to pro-oxidants when supplemented in excess. These pro-oxidants further enhance the generation of free radicals in the system and leads to increased oxidative damages.[16] Thus excess use of antioxidants as therapy of male infertility is reported to be associated with risks. These risks are oxidative stress mediated diseases like cancer and cardiomyopathy etc.,.[17] Hence, the risks, limitations and challenges associated with antioxidant induced stress needs to be recognized and considered cautiously while using antioxidants against male infertility issues induced by oxidative stress mediated oxidative damage.

Oxidative Stress Mediated Male Infertility

Male infertility is known to contribute to 50% of total infertility in couples. Reactive oxygen species (ROS) mediated damages leading to the condition of oxidative stress is known to be responsible extensively for male infertility in various ways[18,19]. These oxidative damages are accounted to be either due to increased generation of ROS or due to decreased level of antioxidants or both. Surprisingly, at normal physiological levels, ROS are known to be associated with promoting sort of good health of sperm. Studies report that physiological levels of ROS play some role in the development of fertilization properties of sperm. ROS at normal levels in body is associated with promoting motility and capacitation of sperm. Physiological levels of ROS promotes chromatin compaction in maturing spermatozoa , promotes hyperactivation, facilitates oocyte interaction and acrosome reaction etc.,.[20,21] ROS remains at moderate concentration in living system at their basic, physiological levels. And, at this moderate concentration ROS and other free radicals like the reactive nitrogen species (RNS) play important role in regulating various cellular signaling pathways, immune responses etc.,.[22]

Though, certain level of ROS is considered to be essential and beneficial for proper maturation, development of sperm and also plays significant role for sperm ovum interaction and the process of fertilization, yet, excess free radicals and subsequent redox imbalance cause several types of damages at cellular and sub-cellular level leading to deleterious impact on the homeostasis of sperm resulting in male infertility.[18,23,24] Studies show that Varicocele, which is considered as one of the most common cause of male infertility is associated with free radicals induced oxidative stress.[25] Primarily, ROS mediated damage of sperm DNA is the reason of varicocele.[25,26] Besides being produced naturally in living body as byproducts of various oxidative biochemical metabolic reactions, ROS generation is also induced by certain factors and agents.[26] Exposure to excess heat, heavy metals, certain chemicals, toxicants. smoking, alcohol etc. may induce generation of ROS.[2,27-29] These sources of ROS can be endogenous or exogenous.[26] Hyperglycaemic condition in diabetes and pre-diabetes induces generation of ROS which has been reported to be associated with changes in sperm parameters.[30] Infection induced elevated generation of ROS and ROS induced oxidative damage mediated elevation in infections and inflammations of the different organs and parts of the reproductive system leads to deteriorative changes in various parameters of the seminal fluid and the sperm and leads to male infertility.[31,32] Also, immuno-modulation induced by inflammation is often due to increased production of ROS and that is known to account for male infertility.[33] Smoking and alcohol consumption is known to cause generation of ROS which is associated with smoking and alcohol induced male infertility.[34,35] Both causes reduced spermatogenesis and ROS induced damages in sperm. Beside all these drugs used in chemotherapy, heavy metals like lead, cadmium , mercury etc., radiotherapy and all other possible causes of ROS generation may lead to oxidative stress induced damages to male reproductive tissues and sperm that may lead to male infertility.[36-38] ROS is known to directly damage and distort sperm morphology by interacting and altering the protein and lipid components of the cell.[39] Sperm is highly vulnerable to oxidative damages as it is rich in polyunsaturated fatty acids in its plasma membrane.[40] Such ROS induced damages may even lead to death of sperm.[26] Studies reveal that oxidative stress due to ROS imparts an adverse effect on sperm DNA that in turn leads to the formation of oxidative products like 8-oxo-7,8-dihydroxyguanosine. This oxidative product causes fragmentation of sperm DNA and results in mutagenic effect.[41]

Beneficial effects of Antioxidants on Male infertility

Antioxidants are known to fight back the condition of free radicals induced oxidative stress and oxidative damages by removing and neutralizing the free radicals.[42] There are several studies establishing the fact that supplementation of antioxidants are beneficial for improving male infertility.[43-46] Certain nutritional antioxidants like vitamins E,C, ß-Carotene and some micronutrients like folate, zinc etc., have been reported to have significant essential role for maintaining normal semen quality and assure reproductive function.[47]Also, antioxidant supplementation is reported to be beneficial in improving infertility treatments with Assisted reproductive technology (ART) .[47]

Myoinositol is identified as a molecule with potent antioxidant activity and is reported to have beneficial effects on male infertility.[48] Studies conducted in experimental fish reports that the molecule has ability to protect against oxidative damage, inhibits oxygen radical generation and also increases antioxidant enzyme.[49] Myoinositol is an important molecule that is a good buffer of oxidative stress in the male gonadal milieu.[48] Myoinisitol because of its molecular structure cannot invade the tight junctions at the testicular level and remains at a greater concentration in the seminiferous tubules rather than in other compartments of the male reproductive system. Myoinisitol controls intracellular calcium concentration of sperms and is a key regulator of sperm mitochondrial events related to free radical generation and is known to improve mitochondrial functions and motility of sperm.[50] It sustains a balanced oxidative stress and antioxidant milieu essential for sperm maturation events like capacitation, acrosomal reaction, and motility. It is reported to improve sperm parameters and serum reproductive hormones in male with idiopathic infertility.[51]

Alpha Lipoic acid, an eight-carbon endogenous cofactor is another potent antioxidant molecule that has been found to be beneficial for preventing oxidative stress mediated damage to sperms.[52] A study reveals that adding this antioxididant molecules to sperms which are cryopreserved for use in ART, causes reuction of cryopreservation induced oxidative stress mediated sperm damage.[52] Reduced form of this molecule prevents ROS mediated damage to sperms. It can prevent DNA fragmentation, improves sperm viability and motility.[53] It has also been reported to be beneficial in mitigating varicocele induced increased temperature and oxidative stress in murine testis.[54] Studies conducted in diabetic murine model establishes that supplementation of alpha lipoic acid is capable to delay testicular lesions and also to preserve the process of spermatogenesis in diabetes.[55] It quenches free radicals, reactive nitrogen species and restores glutathione, vitamin C and E levels in the testicular tissue.[56-58] It restores Leydig cell function in damaged testicular tissue and promotes androgenesis in rats.[56, 59]

Zinc is an antioxidant metal said to have potent beneficial effects on male reproduction. It hastens the process of spermatogenesis promoting production, storage, secretion, and function of several enzymes critical for meiosis and other steps of spermatogenesis. Seminal zinc conserves the integrity and stability of sperm membrane and the genetic material.[60] Studies reveal that zinc plays an important role in maintaining the normal functioning of the hypothalamus-pituitary-gonadal axis. Low Zn level is reported to have a negative impact on serum testosterone concentration.[61,62] Zinc is known to protect the testis against heavy metal, fluoride and heat induced stress.[60] Zn deficiency in men is known to cause primary testicular failure. Deficiency of Zn also is reported to lessen the function of the luteinizing hormone receptor, reduces steroid synthesis and damages Leydig cells by virtue of oxidative stress.[63]

Another interesting finding is that Coenzyme Q10 in subfertile men remains usually low. This cofactor is an important substrate in mitochondrial electron transport chain and is essential for energy generation in sperms. Mitochondrial oxidative phosphorylation leads to the generation of ROS and this coenzyme neutralizes the free radicals generated therein.[64] CoQ10 therapy in sub-fertile subjects increases sperm motility, restores normal sperm morphology and increases sperm density when supplemented in mixture of antioxidant supplements.[64,65] Studies report that supplementation of Coenzyme Q10 improves sperm kinetic features in male patients affected by idiopathic asthenozoospermia.[66] An extensive literature review reported by Salvio et al., in the year 2021 reveals that supplementation of Q10 alone or in combination with other antioxidants improves semen quality and various sperm parameters significantly establishing the fact that supplementation of this antioxidant molecule is beneficial to combat male infertility.[67]

Folic acid is an antioxidant molecule. Supplementation of this molecule is reported to combat oxidative stress and improve various sperm function parameters and enhance fertility in men.[68] The available literature reports that dihydrofolate and tetrahydrofolate are important for nucleic acid biosynthesis. This process is essential for germ cell development and maintaining the normal reproductive function in males. Folate scavenges free radicals and prevents oxidative membrane damage of membranes and the nucleic acids.[69].

Selenium in the form of selenoproteins are involved in metabolic pathways associated with the body's antioxidant defense.[70] Adequate quantities of selenoproteins are present within the testis and the seminal fluid. Selenium not only protects the sperms but also guides the successful passage of sperms across the genital tract during copulation until sperm oocyte interaction. Normal level of selenium assures proper sperm maturation, motility and spermatogenesis.[71,72] Selenium maintains the normal sperm density and sperm vitality. In males selenium enhances sperm volume, density and virility.[73]

Vitamin E is essential for normal spermatogenesis. Deficiency of this vitamin may hinder normal spermatogenesis. It helps to maintain normal testicular function and sperm health. Vitamin E is essential for cell membrane integrity and protects the cell for ROS mediated damage. Studies reveal that vitamin E can regulate the proteins associated with plasma membranes and biosyntheisis of protamines which in turn can promote the process of spermatogenesis.[74] Studies show that supplementation of Se and Vit E together have beneficial effects on semen quality and motility of sperm.[75] Supplementation of Vitamin E has also been found to be protective preventive against the mancozeb induced deleterious effects on sperm and testis parameters.[76] Vitamin C has beneficial effects on sperm motility and morphology. It scavenges free radicals and prevents oxidative damage. Vitamin C supplementation in infertile men has been reported to improve all parameters of sperm including, morphology, count and motility.[77]Semen quality has been reported to be improved with oral supplementation of vitamin C.[77].Other antioxidants like carnitine is also reported to have beneficial effects on male fertility by improving sperm motility.[43] [Table 1]. Thus supplementation of antioxidants like L-carnitine, vitamin C, vitamin E, or coenzyme Q10 has significant positive effects on semen quality including sperm DNA fragmentation, chromatin packaging, sperm concentration, and motility of sperm.[80,81] Combined antioxidant vitamins have been reported to be beneficial for treating male infertility in most cases. Bish et al., recommended that a mixed antioxidant diet of zinc and selenium decreases ROS production and that could be benefic for preventing oxidative stress mediated damage to testicular function.[78] Scaruffi et al., reported that combined antioxidant therapy enhance fertility rates in men.[79] Endogeneous antioxidant enzymes like glutathione peroxidase (GPX) and glutathione S-transferase (GST) haven been found to be essential for normal spermatogenesis and sperm functions.[80-82]

LIMITATIONS OF THE EFFECTS OF ANTIOXIDANTS ON MALE INFERTILITY

Antioxidants at right level are beneficial for living systems. Hence, antioxidants supplementation is used as a remedy to treat male infertility by mitigating oxidative stress. Antioxidants at higher level than normal are known to cause deleterious effects on the living system. Adverse effects high doses of antioxidants result due to altered balance in the physiological redox status. The phenomenon responsible for such redox imbalance is termed as “reductive stress” or the “antioxidant paradox”. [83] In a study the DNA fragmentation index and the degree of sperm decondensation was measured and for this the method of the sperm chromatin structure assay was used. The study revealed that treatment with antioxidant vitamins associated with zinc and selenium reduced the sperm DNA fragmentation but a negative impact of excess antioxidants on sperm DNA got reflected with an increase in sperm decondensation. [84] Studies also reveal that as a result of vitamin C supplementation increase in sperm nuclear decondensation was observed that is because of vitamin C-induced reduction of disulphide bonds in protamines.[85] Another study reveals that antioxidant supplementation in male patients with male factor infertility caused a significant increase in the risk of nausea, headache and dyspepsia in comparison to that of placebo.[86] Reports reveal that due to improper and definite detection of oxidative stress as the underlying reason for male infertility in certain cases may lead to inappropriate and overuse of antioxidant(s) which in turn may cause adverse effects on male reproductive system due to ‘reductive stress’.[7] Antioxidants like vitamin E has been reported to be fatal and life threatening for people who consume excess.[87] Similarly, excess vitamin C has been reported to have deleterious effects as that of oxidative stress.[88] The term paradoxical effect is termed to address the fact that excess supplementation of antioxidants often cause paradoxical results in case of certain diseases.[89] Though Zn supplementation is reported to restore normal level of hormones and improve sperm functions and facilitate spermatogenesis contributing immensely to improved male fertility[60-63,90] yet, excess Zn in semen is reported to cause reduced sperm motility and adversely effects male fertility.90. Also, studies show that high concentrations of Zn^{2+} (0.2 mM), is associated with compromised capacitation and hyper-activated motility of sperm and also is known to inhibit the voltage-gated H^+ channel Hv1 that is localized in the sperm tail. This Hv1is responsible for sperm cytoplasmic alkalization, [91] hyper-activated motility and the regulation of the rotation of human sperm tail.[92,93] Excess selenium is reported to impair male reproductive system by virtue of oxidative stress mediated damages in various components of the male reproductive system.[95] Like any other antioxidants, excess supplementation of alpha lipoic acid is strongly not recommended as it is evident from literature that excess dose of alpha lipoic acid may lead to fatal consequences.[96] High dose of Vitamin E has been reported to be detrimental for human health.[97] Vitamin E in high dose is considered to impose detrimental effects on male fertility.[7] Coenzyme Q10 is extensively prescribed and used as supplement to treat condition of male infertility. No specific adverse effect of Q10 coenzyme is well documented in scientific literature till date. Like all other antioxidants, it seems to be imposing harmful effects on male reproductive system and may adversely affect male fertility but extensive research is required to investigate the fact and to understand the underlying mechanism. Excess dose of Q10 coenzyme has been reported to be associated with side effects like nausea, vomiting, headache etc.,.[98] Excess supplementation of glutathione may disturb the indigenous balance of oxidized and reduced glutathione in our body and this may in turn disrupt the cycle of conversion of GSH and GSSG and the kinetics of the enzymes i.e., glutathione oxidase and glutathione reductase involved in the process may also get disturbed.[8] This as a whole may lead to excess reactive species generation and accumulation and contribute adversely to the male fertility condition. Studies reveal that high l-carnitine concentration (50 mg/mL) is toxic to sperm and is also reported to cause significant decrease in sperm motility.[99] Excess supplementation of folic acid may cause adverse health effects like retard brain development, may lead to other vitamin deficiency, may speed up mental ageing and even may cause prostate cancer in men.[100] Excess supplementation of folic acid is known to be detrimental for various systems of our body.[100] and the male reproductive system may not be an exception [Table 1].

Though there is extensive literature supporting the beneficial role of supplementation of antioxidants in treating conditions of infertility and sub-fertility, yet other additional evidences in vast number reveal that there remains a question in the free use of antioxidants for mitigating male infertility.[48]

Table 1. Beneficial abd detrimental effects of some antioxidants on male fertility

Sl. No.	Antioxidants	Effects on Male infertility	
		Beneficial Effects at right dose	**Detrimental effects at high/excess dose**
1.	Zinc	Promotes testicular development, sperm maturation and testosterone synthesis; Hastens the process of spermatogenesis[60];	Reported to cause reduced sperm motility anmd adversely effects male fertility;[90]
2.	Selenium	Protects the sperms but also guides the successful passage of sperms across the genital tract during copulation; Beneficial for	Impairs male reproductive system;[95]

		sperm maturation, motility and spermatogenesis;	
3.	Vitamin C	Benefial for sperm motility and morphology and improves semen quality [71,72];	Increases sperm nuclear decondensation ; [85]
4.	Vitamin E	Promotes spermatogenesis [76];	May have detrimental implications on male fertility and can be fatal;[7,97]
5.	Alpha Lipoic Acid	Prevents ROS mediated damage to sperms, DNA fragmentation, improves sperm viability and motility; Reported to delay testicular lesions and also to preserve the process of spermatogenesis in diabetes; Restores glutathione, vitamin C and E levels in the testicular tissue; Restores Leydig cell function in damaged testicular tissue and promotes androgenesis in rats[53,56-58];	Excess dose may lead to fatal consequences;[96]
6.	Coenzyme Q10	Increases sperm motility, restores normal sperm morphology and increases sperm density when supplemented in mixture of antioxidant supplements[63];	No reported exact adverse effects on male fertility but is reported to cause certain side-effects like headache and nausea when supplemented in overdose;[98]
7.	L-Carnitine	Improves sperm motility[43];	Toxic to sperm and is reported to reduce sperm motility;[99]
8.	Myoinositol	Reported to control intracellular calcium concentration of sperms and is a key regulator of sperm mitochondrial events related to free radical generation and is known to improve mitochondrial functions and motility of sperm; Improves sperm parameters and serum reproductive hormones in male with idiopathic infertility[50,51];	No significant literature available
9	Folic acid	Improves various sperm function parameters and improve fertility[68];	Reported to have detrimental effects on various systems of our body[100] and the male reproductive system may not be an exception. Though no specific literature report or data are available in the context.
10.	Glutathione	Reported to improve sperm motility patterns[94];	Excess supplementation may be detrimental for male fertility[101], No definite literature evidence available yet.

Conclusion

Thousands of work around the world establishes the fact that supplementation of antioxidants alone or in combination with other antioxidants or even anti-inflammatory agents are beneficial in significantly improving the condition of male infertility. The basic mechanism so far reported is removal of free radicals by the antioxidants and thus mitigating their damaging effects on various components of the male reproductive system including the sperm cytomorphology. Thus, protection and conservation of the structural integrity of the reproductive tissues by antioxidants in right level also assures restoration, protection and conservation of the normal function of the male reproductive system. Thus male infertility is effectively fought back with right dose of antioxidants. Whereas, excess of antioxidants in human body is detrimental by virtue of their pro-oxidant conversions. Following the similar rule, excess supplementation or overdose of antioxidants in male may lead to adverse effects and cause infertility / sub-firtility or may worsen the existing condition of infertility in man.

By considering the extent of good effects, beneficial role and therapeutic potential of antioxidant supplementations against male infertility when administered in right dose, the adverse effects by overdose of the same may be controlled by fixing the right dose and avoiding overdosing or excess supplementation of antioxidants. Studies conducted on human subjects show that antioxidants are helpful in improving the motility and count of sperm in sub-fertile men. Also, antioxidants are beneficial in improving DNA fragmentation in the sperm of sub-fertile men.[102] Natural herbal products rich in antioxidant phyto-constituents are safe to be consumed keeping in mind about avoiding their over consumption.[103-105] Along with antioxidants in right dose, a good lifestyle, eating health food, avoiding junk foods, regular exercise/ yoga, avoiding mental stress and tension, maintaining safe distance and precautions against exposure to radiations and to heat for long time may help to revert the condition of infertility in men.

Acknowledgments

Dr. SG acknowledges the Department of Physiology , Hooghly Mohsin College, Chinsurah, Hooghly, West Bengal, India. Dr. PSS acknowledges the Department of Chemistry, Govt. General Degree College, Kharagpur II, Paschim Midnapore, West Bengal, India. Mr. AA & Dr.DG acknowledges the Department of Physiology, Govt. General Degree College, Kharagpur II, Paschim Midnapore, West Bengal, India.

Conflict of Interest Statement

All authors declare no conflicts of interest in the paper.

REFERENCES AND NOTES

1. L. Saso, O. Firuzi. Pharmacological Applications of Antioxidants: Lights and Shadows. *Curr. Drug Targets* **2014**, 15 (13), 1177–1199.
2. E. Mitra, A.K. Ghosh, D. Ghosh, et al. Protective effect of aqueous Curry leaf (Murraya koenigii) extract against cadmium-induced oxidative stress in rat heart. *Food Chem. Toxicol.* **2012**, 50 (5), 1340–1353.
3. Mamta, K. Misra, G.S. Dhillon, S.K. Brar, M. Verma. Antioxidants. In *Biotransformation of Waste Biomass into High Value Biochemicals*; Springer New York, New York, NY, **2014**; pp 117–138.
4. D.J. Betteridge. What is oxidative stress? *Metabolism* **2000**, 49 (2), 3–8.
5. D. Bandyopadhyay, D. Ghosh, A. Chattopadhyay, et al. Lead induced oxidative stress: a health issue of global concern. *J. Pharm. Res.* **2014**, 8 (9), 1198–1207.
6. P. Sabeti, S. Pourmasumi, T. Rahiminia, F. Akyash, A.R. Talebi. Etiologies of sperm oxidative stress. *Int. J. Reprod. Biomed.* **2016**, 14 (4), 231–240.
7. S. Dutta, P. Sengupta, S. Roychoudhury, et al. Antioxidant Paradox in Male Infertility: 'A Blind Eye' on Inflammation. *Antioxidants* **2022**, 11 (1), 167.
8. S. Ghosh, D. Ghosh, P.S. Singha. Impact of altered Energy metabolism and Immune regulation in reproductive health of Aged Men. *Chem. Biol. Lett.* **2021**, 8 (4), 257–264.
9. S. Dutta, P. Sengupta, P. Slama, S. Roychoudhury. Oxidative stress, testicular inflammatory pathways, and male reproduction. *Int. J. Mol. Sci.* **2021**, 22 (18), 10043.
10. A. Agarwal, A. Aponte-Mellado, B.J. Premkumar, A. Shaman, S. Gupta. The effects of oxidative stress on female reproduction: A review. *Reprod. Biol. Endocrinol.* **2012**, 10.
11. K. Li, X. Yang, T. Wu. The Effect of Antioxidants on Sperm Quality Parameters and Pregnancy Rates for Idiopathic Male Infertility: A Network Meta-Analysis of Randomized Controlled Trials. *Front. Endocrinol. (Lausanne).* **2022**, 13.
12. R. Walczak–Jedrzejowska, J.K. Wolski, J. Slowikowska–Hilczer. The role of oxidative stress and antioxidants in male fertility. *Cent. Eur. J. Urol.* **2013**, 65 (1), 60–67.
13. P. Sengupta, S. Dutta, P. Slama, S. Roychoudhury. COVID-19, Oxidative Stress, and Male Reproductive Dysfunctions: Is Vitamin C a Potential Remedy? *Physiol. Res.* **2022**, 71 (1), 47–54.
14. B. Etensel, S. Özkisacik, E. Özkara, et al. Dexpanthenol attenuates lipid peroxidation and testicular damage at experimental ischemia and reperfusion injury; Pediatr Surg Int, **2007**; Vol. 23.
15. T. Oeda, R. Henkel, H. Ohmori, W.B. Schill. Scavenging effect of N-acetyl-L-cysteine against reactive oxygen species in human semen: A possible therapeutic modality for male factor infertility? *Andrologia*. 1997, pp 125–131.
16. C. Pal. Molecular mechanism facets of Oxidative stress mediated pathogenesis. *J. Mol. Chem.* **2023**, 3 (2 SE-Medicinal Chemistry), 587.
17. R. Henkel, I.S. Sandhu, A. Agarwal. The excessive use of antioxidant therapy: A possible cause of male infertility? *Andrologia* **2019**, 51 (1), e13162.
18. A. Mannucci, F.R. Argento, E. Fini, et al. The Impact of Oxidative Stress in Male Infertility; Front Mol Biosci, **2022**; Vol. 8.
19. G. Cito, M. Becatti, A. Natali, et al. Redox status assessment in infertile patients with non-obstructive azoospermia undergoing testicular sperm extraction: A prospective study. *Andrology* **2020**, 8 (2), 364–371.
20. S.S. Du Plessis, A. Agarwal, J. Halabi, E. Tvrda. Contemporary evidence on the physiological role of reactive oxygen species in human sperm function. *J. Assist. Reprod. Genet.* **2015**, 32 (4), 509–520.
21. S. Kothari, A. Thompson, A. Agarwal, S.S. du Plessis. Free radicals: Their beneficial and detrimental effects on sperm function. *Indian J. Exp. Biol.* **2010**, 48 (5), 425–435.
22. J. Kruk, H.Y. Aboul-Enein, A. Kładna, J.E. Bowser. Oxidative stress in biological systems and its relation with pathophysiological functions: the effect of physical activity on cellular redox homeostasis. *Free Radic. Res.* **2019**, 53 (5), 497–521.
23. A. Majzoub, A. Agarwal. Systematic review of antioxidant types and doses in male infertility: Benefits on semen parameters, advanced sperm function, assisted reproduction and live-birth rate. *Arab J. Urol.* **2018**, 16 (1), 113–124.
24. P. Sabeti, S. Pourmasumi, T. Rahiminia, F. Akyash, A.R. Talebi. Etiologies of sperm oxidative stress. *Int. J. Reprod. Biomed.* **2016**, 14 (4), 231–240.
25. C. Wright, S. Milne, H. Leeson. Sperm DNA damage caused by oxidative stress: Modifiable clinical, lifestyle and nutritional factors in male infertility. *Reprod. Biomed. Online* **2014**, 28 (6), 684–703.
26. N.B. Takalani, E.M. Monaneng, K. Mohlala, et al. Role of oxidative stress in male infertility. *Reprod. Fertil.* **2023**, 4 (3), ,12 1, 4–18.
27. D. Ghosh, S. Paul, S. Naaz, et al. Melatonin protects against lead acetate induced oxidative stress-mediated changes in morphology and metabolic status in rat red blood cells : a flow cytometric and biochemical analysis. *J. Pharm. Res.* **2016**, 10 (6), 381–402.
28. D. Ghosh, P.S. Singha, S.B. Firdaus, S. Ghosh. Metanil yellow: The toxic food colorant. *Asian Pacific J. Heal. Sci.* **2017**, 4 (4), 65–66.
29. M. Rao, X.L. Zhao, J. Yang, et al. Effect of transient scrotal hyperthermia on sperm parameters, seminal plasma biochemical markers, and oxidative stress in men. *Asian J. Androl.* **2015**, 17 (4), 668–675.
30. P.F. Oliveira, G.D. Tomás, T.R. Dias, et al. White tea consumption restores sperm quality in prediabetic rats preventing testicular oxidative damage. *Reprod. Biomed. Online* **2015**, 31 (4), 544–556.
31. J.W. Trum, B.W.J. Mol, Y. Pannekoek, et al. Value of detecting leukocytospermia in the diagnosis of genital tract infection in subfertile men. *Fertil. Steril.* **1998**, 70 (2), 315–319.
32. R.R. Henkel. Leukocytes and oxidative stress: Dilemma for sperm function and male fertility. *Asian J. Androl.* **2011**, 13 (1), 43–52.
33. S. Ghosh, D. Ghosh. Current perspectives of Male Infertility induced by Immunomodulation due to Reproductive Tract Infections. *Chem. Biol. Lett.* **2020**, 7 (2), 85–91.
34. R.A. Saleh, A. Agarwal, E. Kandirali, et al. Leukocytospermia is associated with increased reactive oxygen species production by human spermatozoa; Fertil Steril, **2002**; Vol. 78.
35. S. La Vignera, R.A. Condorelli, G. Balercia, E. Vicari, A.E. Calogero. Does alcohol have any effect on male reproductive function? A review of literature. *Asian J. Androl.* **2013**, 15 (2), 221–225.
36. E.K. Retto De Queiroz, W. Waissmann. Occupational exposure and effects on the male reproductive system. *Cadernos de Saude Publica*. Cad Saude Publica 2006, pp 485–493.
37. E. Tiligada. Chemotherapy: Induction of stress responses. *Endocr. Relat. Cancer* **2006**, 13 (SUPPL. 1), 1, 115–24.
38. N. Desai, R. Sharma, K. Makker, E. Sabanegh, A. Agarwal. Physiologic and pathologic levels of reactive oxygen species in neat semen of infertile men. *Fertility and Sterility*. 2009, pp 1626–1631.
39. A. Zini, M. San Gabriel, A. Baazeem. Antioxidants and sperm DNA damage: A clinical perspective. *J. Assist. Reprod. Genet.* **2009**, 26 (8), 427–432.
40. A. Agarwal, P. Sengupta. Oxidative Stress and Its Association with Male Infertility. In *Male Infertility: Contemporary Clinical Approaches, Andrology, ART and Antioxidants: Second Edition*; Parekattil, S., Esteves, S., Agarwal, A., Eds.; Springer, Cham, **2020**; pp 57–68.
41. Y.J.R. Ménézo, A. Hazout, G. Panteix, et al. Antioxidants to reduce sperm DNA fragmentation: An unexpected adverse effect. *Reprod. Biomed. Online* **2007**, 14 (4), 418–421.
42. D. Ghosh, E. Mitra, S.B. Firdaus, et al. Melatonin protects against lead-induced cardio toxicity: Involvement of antioxidant mechanism. *Int. J. Pharm. Pharm. Sci.* **2013**, 5 (3), 806–813.
43. S. Ahmadip, R. Bashirip, A. Ghadiri-Anarip, A. Nadjarzadehp. Antioxidant supplements and semen parameters: An evidence based review. *Int. J. Reprod. Biomed.* **2016**, 14 (12), 729–736.
44. F. Lombardo, A. Sansone, F. Romanelli, et al. The role of antioxidant therapy in the treatment of male infertility: An overview. *Asian J. Androl.* **2011**, 13 (5), 690–697.
45. W. de Ligny, R.M. Smits, R. Mackenzie-Proctor, et al. Antioxidants for male subfertility. *Cochrane Database Syst. Rev.* **2022**, 2022 (5).

46. P. Gharagozloo, A. Gutierrez-Adán, A. Champroux, et al. A novel antioxidant formulation designed to treat male infertility associated with oxidative stress: Promising preclinical evidence from animal models. *Hum. Reprod.* **2016**, 31 (2), 252–262.
47. H. Amor, N. Shelko, M. Mohammed, P. Michael Jankowski, M. Eid Hammadeh. Role of Antioxidants Supplementation in the Treatment of Male Infertility. In *Antioxidants - Benefits, Sources, Mechanisms of Action*; IntechOpen, **2021**.
48. R.A. Condorelli, S. Lavignera, F. Di Bari, V. Unfer, A.E. Calogero. Effects of myoinositol on sperm mitochondrial function in-vitro. *Eur. Rev. Med. Pharmacol. Sci.* **2011**, 15 (2), 129–134.
49. W.D. Jiang, L. Feng, Y. Liu, J. Jiang, X.Q. Zhou. Myo-inositol prevents oxidative damage, inhibits oxygen radical generation and increases antioxidant enzyme activities of juvenile Jian carp (Cyprinus carpio var. Jian). *Aquac. Res.* **2009**, 40 (15), 1770–1776.
50. R.A. Condorelli, S. La Vignera, S. Bellanca, E. Vicari, A.E. Calogero. Myoinositol: Does it improve sperm mitochondrial function and sperm motility? *Urology* **2012**, 79 (6), 1290–1295.
51. A.E. Calogero, G. Gullo, S. La Vignera, R.A. Condorelli, A. Vaiarelli. Myoinositol improves sperm parameters and serum reproductive hormones in patients with idiopathic infertility: A prospective double-blind randomized placebo-controlled study. *Andrology* **2015**, 3 (3), 491–495.
52. S.F. Ibrahim, K. Osman, S. Das, et al. A study of the antioxidant effect of alpha lipoic acids on sperm quality. In *Clinics*; Sao Paulo, **2008**; Vol. 63, pp 545–550.
53. S. Taherian, R. Khayamabed, M. Tavalaee, M.H. Nasr-Esfahani. Alpha-lipoic acid minimises reactive oxygen species- induced damages during sperm processing. *Andrologia* **2019**, 51 (8).
54. E. Shaygannia, M. Tavalaee, G.R. Akhavanfarid, et al. Alpha-Lipoic Acid improves the testicular dysfunction in rats induced by varicocele. *Andrologia* **2018**, 50 (9), e13085.
55. L.B.N.S. Corrêa, C.A.S. da Costa, J.A.S. Ribas, G.T. Boaventura, M.A. Chagas. Antioxidant action of alpha lipoic acid on the testis and epididymis of diabetic rats: morphological, sperm and immunohistochemical evaluation. *Int. braz j urol* **2019**, 45 (4), 815–824.
56. K.P. Shay, R.F. Moreau, E.J. Smith, A.R. Smith, T.M. Hagen. Alpha-lipoic acid as a dietary supplement: Molecular mechanisms and therapeutic potential. *Biochim. Biophys. Acta - Gen. Subj.* **2009**, 1790 (10), 1149–1160.
57. A. Behnamifar, S. Rahimi, M.A. Karimi Torshizi, M. Sharafi, J.L. Grimes. Effects of dietary alpha-lipoic acid supplementation on the seminal parameters and fertility potential in aging broiler breeder roosters. *Poult. Sci.* **2021**, 100 (2), 1221–1238.
58. A. Gorąca, H. Huk-Kolega, A. Piechota, et al. Lipoic acid – biological activity and therapeutic potential. *Pharmacol. Reports* **2011**, 63 (4), 849–858.
59. G. Vaos, N. Zavras. Antioxidants in experimental ischemia-reperfusion injury of the testis: Where are we heading towards? *World J. Methodol.* **2017**, 7 (2), 37.
60. A. Fallah, A. Mohammad-Hasani, A.H. Colagar. Zinc is an essential element for male fertility: A review of zn roles in men's health, germination, sperm quality, and fertilization. *J. Reprod. Infertil.* **2018**, 19 (2), 69–81.
61. C.D. Hunt, P.E. Johnson, J. Herbel, L.K. Mullen. Effects of dietary zinc depletion on seminal volume and zinc loss, serum testosterone concentrations, and sperm morphology in young men. *Am. J. Clin. Nutr.* **1992**, 56 (1), 148–157.
62. M. Yan, K. Hardin, E. Ho. Differential response to zinc-induced apoptosis in benign prostate hyperplasia and prostate cancer cells. *J. Nutr. Biochem.* **2010**, 21 (8), 687–694.
63. T.P. Croxford, N.H. McCormick, S.L. Kelleher. Moderate zinc deficiency reduces testicular Zip6 and Zip10 abundance and impairs spermatogenesis in mice. *J. Nutr.* **2011**, 141 (3), 359–365.
64. R. Lafuente, M. González-Comadrán, I. Solà, et al. Coenzyme Q10 and male infertility: A meta-analysis. *J. Assist. Reprod. Genet.* **2013**, 30 (9), 1147–1156.
65. G. Balercia, A. Mancini, F. Paggi, et al. Coenzyme Q10 and male infertility. *J. Endocrinol. Invest.* **2009**, 32 (7), 626–632.
66. G. Balercia, E. Buldreghini, A. Vignini, et al. Coenzyme Q10 treatment in infertile men with idiopathic asthenozoospermia: a placebo-controlled, double-blind randomized trial. *Fertility and Sterility*. 2009, pp 1785–1792.
67. G. Salvio, M. Cutini, A. Ciarloni, et al. Coenzyme Q10 and Male Infertility: A Systematic Review. *Antioxidants* **2021**, 10 (6), 874.
68. C. Niederberger. Re: The role of sperm oxidative stress in male infertility and the significance of oral antioxidant therapy. *J. Urol.* **2012**, 187 (4), 1377.
69. T.L.J. Kelly, O.R. Neaga, B.C. Schwahn, R. Rozen, J.M. Trasler. Infertility in 5,10-methylenetetrahydrofolate reductase (MTHFR)-deficient male mice is partially alleviated by lifetime dietary betaine supplementation. *Biology of Reproduction*. 2005, pp 667–677.
70. W.B. Minich. Selenium Metabolism and Biosynthesis of Selenoproteins in the Human Body. *Biochem.* **2022**, 87 (S1), S168–S177.
71. D. Behne, T. Hofer, R. Von Berswordt-Wallrabe, W. Elger. Selenium in the testis of the rat: Studies on its regulation and its importance for the organism. *J. Nutr.* **1982**, 112 (9), 1682–1687.
72. U. Ahsan, Z. Kamran, I. Raza, et al. Role of selenium in male reproduction-A review. *Anim. Reprod. Sci.* **2014**, 146 (1–2), 55–62.
73. I.H. Qazi, C. Angel, H. Yang, et al. Role of Selenium and Selenoproteins in Male Reproductive Function: A Review of Past and Present Evidences. *Antioxidants* **2019**, 8 (8), 268.
74. Y. Gao, L. Jian, W. Lu, et al. Vitamin E can promote spermatogenesis by regulating the expression of proteins associated with the plasma membranes and protamine biosynthesis. *Gene* **2021**, 773, 145364.
75. M.K. Moslemi, S. Tavanbakhsh. Selenium-vitamin E supplementation in infertile men: Effects on semen parameters and pregnancy rate. *Int. J. Gen. Med.* **2011**, 4, 99–104.
76. E. Saddein, T. Haghpanah, S.N. Nematollahi-Mahani, F. Seyedi, M. Ezzatabadipour. Preventative Effects of Vitamin E on Testicular Damage and Sperm Parameters in the First-Generation Mice Pups due to Pre- and Postnatal Mancozeb Exposure. *J. Toxicol.* **2019**, 2019, 1–12.
77. M. Akmal, J.Q. Qadri, N.S. Al-Waili, et al. Improvement in human semen quality after oral supplementation of vitamin C. *J. Med. Food* **2006**, 9 (3), 440–442.
78. T. Takeshima, K. Usui, K. Mori, et al. Oxidative stress and male infertility. *Reprod. Med. Biol.* **2021**, 20 (1), 41–52.
79. P. Scaruffi, E. Licata, E. Maccarini, et al. Oral antioxidant treatment of men significantly improves the reproductive outcome of ivf cycles. *J. Clin. Med.* **2021**, 10 (15).
80. C. Abad, M.J. Amengual, J. Gosálvez, et al. Effects of oral antioxidant treatment upon the dynamics of human sperm DNA fragmentation and subpopulations of sperm with highly degraded DNA. *Andrologia*. Andrologia 2013, pp 211–216.
81. F. Lanzafame, S. La Vignera, E. Vicari, A.E. Calogero. Oxidative stress and medical antioxidant treatment in male infertility. *Reprod. Biomed. Online* **2009**, 19 (5), 638–659.
82. O. Tunc, J. Thompson, K. Tremellen. Improvement in sperm DNA quality using an oral antioxidant therapy. *Reprod. Biomed. Online* **2009**, 18 (6), 761–768.
83. B. Yu, Z. Huang. Variations in Antioxidant Genes and Male Infertility. *Biomed Res. Int.* **2015**, 2015, 1–10.
84. E. Barati, H. Nikzad, M. Karimian. Oxidative stress and male infertility: current knowledge of pathophysiology and role of antioxidant therapy in disease management. *Cell. Mol. Life Sci.* **2020**, 77 (1), 93–113.
85. D. Giustarini, I. Dalle-Donne, R. Colombo, A. Milzani, R. Rossi. Is ascorbate able to reduce disulfide bridges? A cautionary note. *Nitric Oxide - Biol. Chem.* **2008**, 19 (3), 252–258.
86. M. Creta, D. Arcaniolo, G. Celentano, et al. Toxicity of Antioxidant Supplements in Patients with Male Factor Infertility: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Antioxidants* **2021**, 11 (1), 89.

87. E.Y. Chew, R. Milton. Meta-analysis: High-dosage vitamin E supplementation may increase all-cause mortality. *Evidence-Based Eye Care* **2005**, 6 (2), 88–89.
88. O.I. Aruoma, B. Halliwell, E. Gajewski, M. Dizdaroglu. Copper-ion-dependent damage to the bases in DNA in the presence of hydrogen peroxide. *Biochem. J.* **1991**, 273 (3), 601–604.
89. B. Halliwell. The antioxidant paradox; Lancet, **2000**; Vol. 355.
90. M. Ali, M. Martinez, N. Parekh. Are antioxidants a viable treatment option for male infertility? *Andrologia* **2021**, 53 (1).
91. Y. Ménézo, L. Pluntz, J. Chouteau, et al. Zinc concentrations in serum and follicular fluid during ovarian stimulation and expression of Zn 2+ transporters in human oocytes and cumulus cells. *Reprod. Biomed. Online* **2011**, 22 (6), 647–652.
92. P. V. Lishko, I.L. Botchkina, A. Fedorenko, Y. Kirichok. Acid Extrusion from Human Spermatozoa Is Mediated by Flagellar Voltage-Gated Proton Channel. *Cell* **2010**, 140 (3), 327–337.
93. M.R. Miller, S.J. Kenny, N. Mannowetz, et al. Asymmetrically Positioned Flagellar Control Units Regulate Human Sperm Rotation. *Cell Rep.* **2018**, 24 (10), 2606–2613.
94. A. Lenzi, F. Lombardo, L. Gandini, F. Culasso, F. Dondero. Glutathione therapy for Male infertility. *Syst. Biol. Reprod. Med.* **1992**, 29 (1), 65–68.
95. Z. jian Xu, M. Liu, Q.J. Niu, et al. Both selenium deficiency and excess impair male reproductive system via inducing oxidative stress-activated PI3K/AKT-mediated apoptosis and cell proliferation signaling in testis of mice. *Free Radical Biology and Medicine*. 2023, pp 15–22.
96. D.F. Emir, I.U. Ozturan, S. Yilmaz. Alpha lipoic acid intoxicatıon: An adult. *Am. J. Emerg. Med.* **2018**, 36 (6), 1125.e3-1125.e5.
97. A. Baltusnikiene, I. Staneviciene, E. Jansen. Beneficial and adverse effects of vitamin E on the kidney. *Front. Physiol.* **2023**, 14.
98. P.M. George, R.J. Mackay, S.L. Molyneux, et al. Coenzyme Q10 in health and disease. *Clin. Chim. Acta* **2010**, 411 (11–12), 907–908.
99. L. Mongioi, A.E. Calogero, E. Vicari, et al. The role of carnitine in male infertility. *Andrology* **2016**, 4 (5), 800–807.
100. K.R. Patel, A. Sobczyńska-Malefora. The adverse effects of an excessive folic acid intake. *Eur. J. Clin. Nutr.* **2017**, 71 (2), 159–163.
101. H. Bayram, Y. Donmez Cakil, M.E. Sitar, et al. The Effects of Glutathione on Clinically Essential Fertility Parameters in a Bleomycin Etoposide Cisplatin Chemotherapy Model. *Life* **2023**, 13 (3), 815.
102. A. Patki, R. Shelatkar, M. Singh, et al. Impact of antioxidants in improving semen parameters like count, motility and DNA fragmentation in sub-fertile males: a randomized, double-blind, placebo-controlled clinical trial. *Transl. Clin. Pharmacol.* **2023**, 31 (1), 28–39.
103. F. Dimitriadis, H. Borgmann, J.P. Struck, J. Salem, T.H. Kuru. Antioxidant Supplementation on Male Fertility—A Systematic Review. *Antioxidants* **2023**, 12 (4), 836.
104. N. Murugesan, D. Chandraprabha. Antioxidant activity of synergistic quercetin resveratrol. *J. Mol. Chem.* **2023**, 3 (1), 581.
105. P. Lakra, I.N. Gahlawat. Regular food chemicals as antioxidant towards prevention of diseases – An insight review. *J. Mol. Chem.* **2022**, 2 (2), 441.