

TetraSOD® and Fertility: maintenance and improvement

Both male and female infertility is associated with poor sperm or oocyte quality. Oxidative stress has been shown to be involved in the pathogenesis of male and female infertility (Figure 1). In fact, it is well known that antioxidants exhibit a beneficial effect in reversing oxidative stress-induced sperm dysfunction and in improving pregnancy rates in infertile couples. Oxidative stress is caused by an imbalance between the formation of reactive oxygen species (ROS) and the ability of the antioxidants to scavenge them (Agarwal *et al.*, 2008).

Thus, studies have shown that up to 25% of infertile men have significant levels of ROS in their semen, in contrast to low levels in fertile men. Moreover, significant negative correlations have been detected between oxidative stress and semen parameters, fertilisation rate, embryonic development and pregnancy rate (Agarwal and Majzoub, 2016).

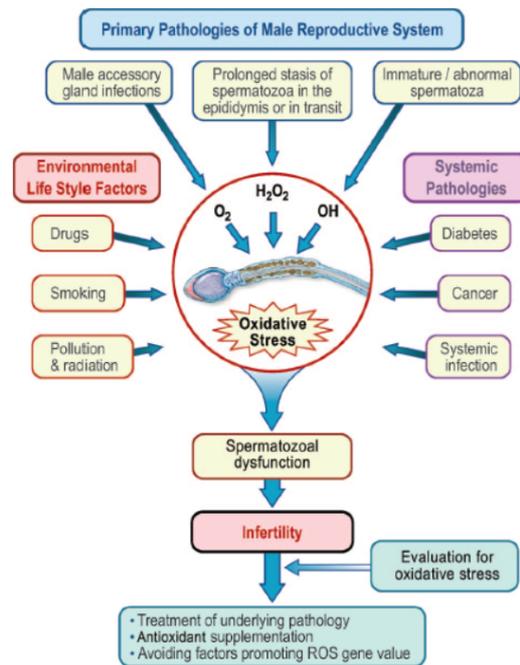


Figure 1. Factors contributing to oxidative stress-induced male infertility (Agarwal and Sekhon, 2010).

Among all the antioxidants studied, the role of Superoxide Dismutase (SOD) in influencing male and female fertility *in vivo* has been demonstrated by ‘knockout’ animals, both in female and male mice models.

SOD is critical to the maintenance of germ cell quality, decreasing ROS production in sperm. Moreover, SOD has demonstrated beneficial effects on quality of semen in animal models, with an improved sperm viability and favouring sperm-oocyte fusion. In addition, it has been demonstrated that SOD has an essential role in female fertility in a rat model.

SOD is among the most potent antioxidants known in nature and is a key constituent of cellular defense against oxidative stress. SOD improves the cell defense against ROS neutralizing the negative effects of free radicals in the same place they are generated.

TetraSOD® is the highest source of SOD on the market, with proven factor reducing oxidative stress.

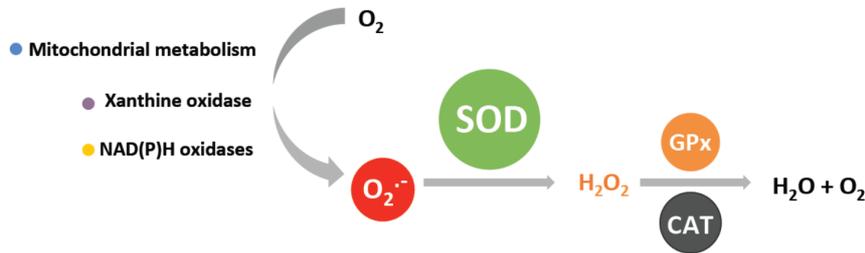


Figure 2. Action of SOD to control anion superoxide. Further reactions are needed to remove H_2O_2 derived from superoxide anion by catalase (CAT) and glutathione peroxidase (GPx) (TetraSOD® dossier, 2017).

1. SOD AND MALE FERTILITY

Globally, the incidence of infertility is estimated to be about 13-18% in the human population, regardless of race, ethnic group, etc. While certain cases of male infertility are due to anatomical abnormalities, an estimated 40-90% of cases are due to deficient sperm production of unidentifiable origin which are classified as idiopathic male infertility. Men with idiopathic infertility generally exhibit significantly higher seminal ROS levels and lower antioxidant potential than healthy fertile controls. In addition, high ROS levels have been detected in the semen samples of 25% to 40% of infertile men. Evidence now suggests that ROS-mediated damage to sperm is a significant contributing pathology in 30-80% of cases (Ghareeb and Sarhan, 2014).

To protect spermatozoa from oxidative damage, seminal plasma has a highly specialized ROS scavenger system, containing SOD, glutathione peroxidase (GPx) and catalase (CAT). Among them, SOD is known to be the most important antioxidant enzyme. SOD scavenges both extracellular and intracellular superoxide anion and prevents lipid peroxidation of the plasma membrane. SOD also prevents premature hyperactivation and capacitation induced by superoxide radicals before ejaculation (Agarwal, 2005).

Seminal SOD activity plays a role in determining sperm fertilization potential and male infertility. In this sense, Sertoli cells have been reported to produce SOD in the testis (Mruk *et al.*, 2002). Moreover, some studies showed a positive correlation between SOD activity in seminal plasma and semen quality parameters (sperm concentration and overall motility), whereas inversely with sperm DNA fragmentation (Yan *et al.*, 2014; Murawski *et al.*, 2007).

Significantly lower SOD activity in seminal plasma of infertile patients, comparing to healthy sperm donors, as well as positive correlation and beneficial impact of SOD activity on human semen quality parameters seem to confirm that decreased seminal plasma scavenger antioxidant capacity, particularly in the form of low SOD activity, can be responsible for male infertility (Murawski *et al.*, 2007).

In addition to these results, other study based on knockout mice concluded that SOD is critical to the maintenance of germ cell quality with aging (Selvaratnam and Robaire, 2016).



Vegan
TetraSOD® is a marine microalgae ingredient that is 100% Vegan.



Patent protected
TetraSOD® is a proprietary ingredient and is produced under a Patent Protected process.



Sustainable
TetraSOD® is cultivated in sustainable land and water media in recycled.



Green and natural
We monitor and Monitor Nature from our process is 100% Natural. No Chemicals, no additives.



Novel food approval
TetraSOD® is the only marine microalgae approved as a Novel Food (EU Reg. 258/97).



Maximum antioxidant activity
TetraSOD®, High ORAC and proved High GAA (Cellular Antioxidant Assay).



Marine source
TetraSOD® is sourced from the marine microalgae Tetraselmis (Chl).



Raw
TetraSOD® is 100% RAW, non-processed ingredient, no additives and no preservatives.



Non-GMO
The product doesn't contain Genetically Modified Organisms (GMO) as it is a wild type species.

In conclusion, an expanding body of evidence now supports a role for oxidative stress as a significant cause of male infertility (see Table 1).

Table 1. Summary of the evidences linking oxidative stress with male infertility (Tremellen, 2008).

Many infertile men have significantly higher levels of ROS within their semen compared
Many infertile men have significantly lower levels of protective antioxidants within their semen
The generation of sperm oxidative stress <i>in vitro</i> is associated with biochemical evidence of sperm lipid peroxidation and decreased sperm motility/oocyte fertilization capacity
The addition of antioxidants to culture media protects sperm from oxidative stress mediated impaired motility
Seminal oxidative stress in infertile men is correlated with impaired sperm motility/fertilization capacity and increased sperm membrane oxidation
Antioxidant treatment of infertile men can significantly improve sperm motility
The generation of sperm oxidative stress <i>in vitro</i> is associated with an increase in sperm DNA damage
Seminal oxidative stress in infertile men is correlated with an increase in sperm DNA damage
Antioxidant treatment of infertile men can significantly improve sperm DNA quality
The use of antioxidant supplements by infertile men can significantly increase their partners chances of spontaneous or IVF assisted pregnancy (randomized controlled trials only)

1.1. SOD increases sperm motility

Garrat *et al.* (2013) showed that various aspects of sperm motility and function are impaired in SOD1-deficient mice model. These authors also showed that SOD-deficient males have zero fertilisation success.

A positive correlation between SOD supplementation (50 U/ml), with or without the addition of CAT (100 IU/ml), and sperm motility has been reported in two studies (Amini *et al.*, 2015; Cocchia *et al.*, 2011).

Further studies have confirmed that the addition of SOD increases the sperm motility thanks to the inhibition of lipid peroxidation (Kobayashi *et al.*, 1991).

In an animal study, lead increased ROS production reduced sperm motility and sperm oocyte penetration rate and decreased seminal antioxidants (Xu *et al.*, 2003).

1.2. SOD decreases sperm oxidative stress

In a model of cryopreserved boar spermatozoa, SOD reduced sperm ROS production (ROS generation and lipid peroxidation model). The ROS generation was significantly reduced by the addition of SOD at concentrations of 150 and 300 IU/ml (Roca *et al.*, 2005).

1.3. SOD improves sperm viability

SOD plays a major role in maintaining sperm viability. Studies have reported that the addition of both SOD (100 IU/ml) and CAT (100 IU/ml) improved significantly human sperm recovery in human semen samples (Cocchia *et al.*, 2011). Other animal studies showed the same results only with the addition of SOD (100 U/ml). The authors claimed that improvements observed in sperm quality with the treatment of SOD may be attributed to prevention of excessive generation of free radicals (Perumal, 2014).

These results have been confirmed on boar spermatozoa with supplementation of SOD (at 150 and 200 IU/ml) and CAT (300 and 400 IU/ml) (Roca *et al.*, 2005). Because of their combined and



Vegan
TetraSOD® is a marine microalgae ingredient that is 100% Vegan.



Patent protected
TetraSOD® is a proprietary ingredient and is produced under a Patent Protected process.



Sustainable
TetraSOD® is cultivated in sustainable land and water made in recycled.



Green and natural
We produce under Marine Nature from our process is 100% Natural. No Chemicals, no additives.



Novel food approval
TetraSOD® is the only marine microalgae approved as a Novel Food (EU Reg. 258/97).



Maximum antioxidant activity
TetraSOD®, High ORAC and proved High CAA (Cellular Antioxidant Assay).



Marine source
TetraSOD® is sourced from the marine microalgae Tetraselmis (Chlorella).



Raw
TetraSOD® is 100% RAW, non-processed ingredient, no additives and no preservatives.



Non-GMO
The product doesn't contain Genetically Modified Organisms (GMO) & it is a wild type species.

simultaneous action on O_2^- and H_2O_2 , SOD and CAT contribute greatly to the prevention of sperm apoptosis. In this study, improvements observed in sperm quality may be attributed to prevention of excessive generation of free radicals, produced by spermatozoa themselves, by means of the antioxidant property of SOD. It was concluded that the possible protective effects of SOD supplementation are that it enhances the antioxidant enzymes content and prevents efflux of cholesterol and phospholipids from cell membrane and MDA production. Thus it may protect the spermatozoa during preservation, thus enhancing fertility in this species.

Several clinical studies have reported that levels of ROS within semen can be reduced by increasing the scavenging capacity of seminal plasma using oral antioxidant supplements, such as astaxanthin, carnitine, vitamins (E and C mainly), minerals (Se and Zn mainly), glutathione or coenzyme Q10 (Tremellen, 2008), although so far there is not any clinical trial that use an antioxidant enzyme to improve both, male or female fertility capacity.

2. SOD AND FEMALE FERTILITY

In women, several animal and *in vitro* studies suggest that oxidative stress may affect female fertility. ROS have been implicated in the development of premature rupture of the fetal membranes and evidence suggests that oxidative stress may be associated with preeclampsia (Ruder *et al.*, 2009).

The follicular fluid environment may also play an important role in oocyte development. A positive correlation has been found between level of ROS in the intrafollicular fluid and the pregnancy outcome in patients undergoing In Vitro Fertilization (IVF) (Agarwal *et al.*, 2008).

2.1. SOD improves embryo viability

Female homozygous knock-out SOD mice showed a markedly reduced fertility compared with that of wild-type and heterozygous knock-out mice. Further studies revealed that although these mice ovulated and conceived normally, they exhibited a marked increase in embryonic lethality (Ho *et al.*, 1998).

2.2. SOD improves luteal function

The study in a SOD1 knock-out model in female mice have pointed out that increased oxidative stress in the ovary could cause luteal insufficiency leading to miscarriage. The mutant mice showed decreased progesterone secretion even under the condition of superovulation, and displayed enhanced superoxide generation in the region surrounding the corpora lutea, which was associated with increased apoptotic cells and suppressed vasculature (Noda *et al.*, 2012).

CONCLUSION

Daily consumption of TetraSOD® increases significantly SOD, CAT and GPx levels, reducing ROS production. Therefore, it is a **recommended ingredient to reduce the effects of both, male and female, infertility.**

*TetraSOD® Daily recommended dose	150 - 400 IU	5 - 13.33 mg/day
--	--------------	------------------



Vegan
TetraSOD® is a marine microalgae ingredient that is 100% Vegan.



Patent protected
TetraSOD® is a proprietary ingredient and is produced under a Patent Protected process.



Sustainable
TetraSOD® is cultivated in sustainable land and water media in recycled.



Green and natural
We monitor and Monitor Nature from our process is 100% Natural. No Chemicals, no additives.



Novel food approval
TetraSOD® is the only marine microalgae approved as a Novel Food (EU Reg. 258/97).



Maximum antioxidant activity
TetraSOD®, High ORAC and proved High GAA (Cellular Antioxidant Assay).



Marine source
TetraSOD® is sourced from the marine microalgae Tetraselmis (Chl).



Raw
TetraSOD® is 100% RAW, non-processed ingredient, no additives and no preservatives.



Non-GMO
The product doesn't contain Genetically Modified Organisms (GMO) & it is a wild type species.

Bibliography

Agarwal, A. *Role of oxidative stress in male infertility and antioxidant supplementation*. US Kidney and Urological Disease, (2005), 122.

Agarwal, A., Cocuzza, M., Abdelrazik, H., & Sharma, R. K. (2008). 10 Oxidative stress measurement in patients with male or female factor infertility.

Agarwal, A., Cocuzza, M., Abdelrazik, H., Sharma, R. K. 10 Oxidative stress measurement in patients with male or female factor infertility, 2008.

Agarwal, A., Majzoub, A. *Role of antioxidants in male infertility*. BJUI Knowledge, 2016.

Agarwal, A., Sekhon, L.H. *The role of antioxidant therapy in the treatment of male infertility*. Human Fertility, 13 (2010), 217-225.

Amini, M. R., Kohram, H., Zare-Shahaneh, A., Zhandi, M., Sharideh, H., Nabi, M. M. *The effects of different levels of catalase and superoxide dismutase in modified Beltsville extender on rooster post-thawed sperm quality*. Cryobiology, 70 (2015), 226-232.

Cocchia, N., Pasolini, M. P., Mancini, R., Petrazzuolo, O., Cristofaro, I., Rosapane, I., Mancini, A. *Effect of sod (superoxide dismutase) protein supplementation in semen extenders on motility, viability, acrosome status and ERK (extracellular signal-regulated kinase) protein phosphorylation of chilled stallion spermatozoa*. Theriogenology, 75 (2011), 1201-1210.

Garratt, M., Bathgate, R., de Graaf, S.P., Brooks, R. C. *Copper-zinc superoxide dismutase deficiency impairs sperm motility and in vivo fertility*. Reproduction, 146 (2013), 297-304.

Ghareeb, D. A., Sarhan, E. M. E. *Role of Oxidative Stress in Male Fertility and Idiopathic Infertility: Causes and Treatment*. J Diagn Tech Biomed Anal 3: 1 (2014), 12.

Ho, Y. S., Gargano, M., Cao, J., Bronson, R. T., Heimler, I., Hutz, R.J. *Reduced fertility in female mice lacking copper-zinc superoxide dismutase*. Journal of Biological Chemistry, 273 (1998), 7765-7769.

Kobayashi, T., Miyazaki, T., Natori, M., Nozawa, S. *Protective role of superoxide dismutase in human sperm motility: superoxide dismutase activity and lipid peroxide in human seminal plasma and spermatozoa*. Human Reproduction, 6 (1991), 987-991. [Abstract available](#).

Mruk, D. D., Silvestrini, B., Mo, M. Y., Cheng, C. Y. *Antioxidant superoxide dismutase-a review: its function, regulation in the testis, and role in male fertility*. Contraception, 65 (2002), 305-311.

Murawski, M., Saczko, J., Marcinkowska, A., Chwiłkowska, A., Gryboś, M., Banaś, T. *Evaluation of superoxide dismutase activity and its impact on semen quality parameters of infertile men*. Folia Histochemica et cytobiologica, 45 (2007), 123-126.

Noda, Y., Ota, K., Shirasawa, T., Shimizu, T. *Copper/zinc superoxide dismutase insufficiency impairs progesterone secretion and fertility in female mice*. Biology of reproduction, 86 (2012), 16-1.

Perumal, P. *Effect of superoxide dismutase on semen parameters and antioxidant enzyme activities of liquid stored (5°C) Mithun (Bos frontalis) semen*. Journal of Animals, 2014.



Vegan
TetraSOD® is a marine microalgae ingredient that is 100% Vegan.



Patent protected
TetraSOD® is a proprietary ingredient and is produced under a Patent Protected process.



Sustainable
TetraSOD® is cultivated in sustainable land and water media in recycled.



Green and natural
We maintain total Member Nature items, our process is 100% Natural. No Chemicals, no additives.



Novel food approval
TetraSOD® is the only marine microalgae approved as a Novel Food (EU Reg. 258/97).



Maximum antioxidant activity
TetraSOD®, High ORAC and proved High GAA (Cellular Antioxidant Assay).



Marine source
TetraSOD® is sourced from the marine microalgae Tetraselmis (Chl).



Raw
TetraSOD® is 100% RAW, non-processed ingredient, no additives and no preservatives.



Non-GMO
The product doesn't contain Genetically Modified Organisms (GMO) & it is a wild type species.

Roca, J., Rodríguez, M. J., Gil, M. A., Carvajal, G., Garcia, E. M., Cuello, C., Martinez, E. A. *Survival and in vitro fertility of boar spermatozoa frozen in the presence of superoxide dismutase and/or catalase.* Journal of andrology, 26 (2005), 15-24.

Ruder, E.H., Hartman, T.J., Goldman, M.B. *Impact of oxidative stress on female fertility.* Current opinion in obstetrics & gynecology, 21 (2009), 219.

Selvaratnam, J.S., Robaire, B. *Effects of Aging and Oxidative Stress on Spermatozoa of Superoxide-Dismutase 1-and Catalase-Null Mice.* Biology of reproduction, 95 (2016).

Tremellen, K. *Oxidative stress and male infertility—a clinical perspective.* Human reproduction update, 14 (2008), 243-258.

Xu, D. X., Shen, H. M., Zhu, Q. X., Chua, L., Wang, Q. N., Chia, S. E., Ong, C. N. *The associations among semen quality, oxidative DNA damage in human spermatozoa and concentrations of cadmium, lead and selenium in seminal plasma.* Mutation Research/Genetic Toxicology and Environmental Mutagenesis, 534 (2003), 155-163.

Yan, L., Liu, J., Wu, S., Zhang, S., Ji, G., Gu, A. *Seminal superoxide dismutase activity and its relationship with semen quality and SOD gene polymorphism.* Journal of assisted reproduction and genetics, 31 (2014), 549-554.



Vegan
TetraSOD® is a marine microalgae ingredient that is 100% Vegan.



Patent protected
TetraSOD® is a proprietary ingredient and is produced under a Patent Protected process.



Sustainable
TetraSOD® is cultivated in sustainable land and water media in recycled.



Green and natural
We embrace what Mother Nature gives, our process is 100% natural. No Chemicals, no additives.



Novel food approval
TetraSOD® is the only marine microalgae approved as a Novel Food (EU Reg. 258/97).



Maximum antioxidant activity
TetraSOD®, High ORAC and proved, high CAA, (Cultured Antioxidant Assay).



Marine source
TetraSOD® is sourced from the marine microalgae Tetraselmis (Chl).



Raw
TetraSOD® is 100% RAW, non-processed ingredient, no additives and no preservatives.



Non-GMO
The product doesn't contain Genetically Modified Organisms (GMO) & it is a wild type species.