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Effect of herbs to protect oxidative stress in sperm and male fertility: A review

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Abstract
Male infertility is the major problem in livestock which causes economic loss as well as wastage of precious germ plasm. Kastelic and Thundathil (2008) stated that, in an unselected population, 20–40% of bulls are likely to have a reduced fertility due to impaired semen quality. Free radicals display both harmful as well as beneficial effects on semen production depending upon their concentration. Physiological concentration of free radicals are required to mediate normal process of reproduction (Gonçalves *et al.,* 2010). However, the higher concentration of free radicals disturb the endogenous antioxidant machinery of the spermatozoa resulting in oxidative stress. Free radical induced oxidative stress in animal reproduction causes great loss to the livestock industry. Less attention has been given in improving the semen production using exogenous plant derived antioxidants in feed supplementation in male animals than that of female animals. The application of exogenous plant derived antioxidant is likely to improve health status of male animal (Nantia *et al.,* 2000). Antioxidant therapy has been implicated to be effective in preventing diseases resulting from oxidative stress. Considering the advantages of lower side effects of natural antioxidants than those of synthetic antioxidants, plants and their extracts have been extensively used in improving the semen quality in human and lab animals. Limited literature is available on sheep, goat and cattle regarding the application of plant derived antioxidants for the improvement of semen quality as well as quantity. Further studies are required for identification of active principles in herbs and their application for the improvement of semen production in particularly livestock.

Keywords: Male, infertility, oxidative stress, free radicals, antioxidants, herbs

1. Introduction
Male infertility is the major problem in livestock which causes economic loss as well as wastage of precious germ plasm. It is usually said that male is "half of the herd" in dairy industry. For artificial insemination, animals of high genetic merit and high semen quality parameters are selected. Kastelic and Thundathil (2008) [19] stated that, in an unselected population, 20–40% of bulls are likely to have a reduced fertility due to impaired semen quality. There are many causes of male infertility, which is broadly divided into impotentia coeundi and impotentia generandi. There are many factors.

2. Oxidative stress
When there is an imbalance between formation and removal of free radicals then the condition called as oxidative stress (Shinde *et al*., 2012) [31]. The production of free radicals is a double-edged sword in reproduction system.

2.1 Free Radicals
Free radicals are a group of highly reactive chemical molecules with one or more unpaired electrons that can oxidatively modify biomolecules they encounter. It including reactive oxygen species (ROS) and reactive nitrogen species (RNS), are normal pro-oxidant molecules in aerobic metabolism. The three major types of ROS are superoxide, hydrogen peroxide, and hydroxyl ion, while nitric oxide is a main type of RNS (Agrawal *et al*., 2003) [1].

2.1.1 Advantages of free radicals
Low concentration of ROS is essential for normal physiological functions like gene expression, cellular growth and defense against infection. Macrophages and neutrophils generate ROS in order to kill the bacteria that may engulf by phagocytosis (Shinde *et al*., 2012) [31].

2.1.2 Disadvantages of free radicals

They can damage cell membranes and lipoproteins by a process called as lipid peroxidation. Proteins may also be damaged by ROS/NOS, leading to structural changes and loss of enzyme activity. Free radicals may cause DNA strand breaks which can cause cell mutation (Shinde *et al*., 2012) [31].

2.2 Oxidative stress in semen production

Physiological concentrations of free radicals are required to mediate normal process of capacitation, hyperactivation, acrosome reaction, fertilization and embryo development (Gonçalves *et al.*, 2010) [12]. However, above physiological levels of free radicals can result in oxidative stress which leads to sperm or ovum damage, deformity, endometriosis, preclampsia, miscarriage, intrauterine growth retardation, and infertility (Bansal and Bilasspuri, 2010) [4].

Spermatozoa membranes are vulnerable to free radical induced damage because they are not only rich in polyunsaturated fatty acids, but also contains low concentration of antioxidant enzymes (Maneesh and Jayalekshmi, 2006) [25]. Furthermore, spermatogenesis in testes is an extremely active replicative process to generate sperm at a high rate.

3. Natural antioxidant present in seminal fluid

To maintain normal cell function, endogenous antioxidants present in seminal plasma and spermatozoa, block the formation of new ROS or act as scavengers and remove ROS already generated. Metal chelators such as transferrin, lactoferrin and ceruloplasmin that are present in human semen also control lipid peroxidation of the sperm plasma membrane, protecting its integrity.

3.1 Characteristics of some natural antioxidants

a. **Coenzyme Q10:** It is a non-enzymatic antioxidant that is related to low-density lipoproteins and protects against peroxidative damage. Since it is an energy-promoting agent, it also enhances sperm motility. It is present in the sperm midpiece and recycles vitamin E and prevents its pro-oxidant activity (Lewin & Lavon, 1997) [22].
b. **Carnitines:** It is an antioxidant mostly derived from the human diet that may play a role in sperm energy metabolism and provide the primary fuel for sperm motility. Spermatozoa exhibit increased L-carnitine and L-acetyl carnitine content during epididymal passage and acquisition of motility (Jeulin and Lewin, 1996) [18].
c. **Vitamin C:** Vitamin C is found in concentrations 10-fold higher in seminal plasma than serum. It is protecting human spermatozoa against endogenous oxidative damage by neutralising hydroxyl, superoxide and hydrogen peroxide radicals and preventing sperm agglutination. Significantly reduced concentrations are seen in semen samples with excess ROS (Lewis *et al*., 1997) [23].
d. **Vitamin E:** It is an important lipid soluble antioxidant molecule in the cell membrane which interrupts lipid peroxidation and enhances the activity of various antioxidants. Vitamin E treatment decreased malondialdehyde concentrations in spermatozoa down to normospermic levels, improving motility and the probability of achieving pregnancy. Vitamin E may also be added to cryoprotectants to protect spermatozoa from increased exposure to OS during cryopreservation and thawing, which lead to reduced sperm motility (Suleiman *et al*., 1996) [33].
e. **Carotenoids:** Carotenoids work synergistically with Se and vitamin E. It has been found to have the highest ROS-quenching rate, with plasma levels higher than beta carotene. It is found in high concentrations in the testes and seminal plasma, with lower levels in infertile men (Klebanov *et al*., 1998) [21].
f. **Glutathione and N-acetyl cysteine:** It is found in the body, lipids, proteins and nucleic acids against oxidative damage. It combines with vitamin E and Se to form glutathione peroxidase.
g. **Pentoxifylline:** It is a competitive nonselective phosphodiesterase inhibitor that raises intracellular cAMP 220A. It has been shown to decrease ROS production sperm motility *in vitro* and improve semen parameters *in vivo* (Pang *et al*., 1993) [29].
h. **Selenium:** Selenium (Se) may protect against oxidative sperm DNA damage and is required for normal testicular development, spermatogenesis, sperm motility and function (Ursini *et al*., 1999) [35].
i. **Trace metals:** Adequate zinc and copper intake is needed to maintain the optimal functioning level of antioxidant enzymes, such as superoxide dismutase (Chia *et al*., 2000) [9].

4. Exogenous herbal antioxidants in animal reproduction

Under normal physiological conditions, living organisms possess a wide range of enzymatic antioxidants, such as superoxide dismutase (SOD), catalase and glutathione peroxidase (GPx) (Celino *et al.*, 2011) [6] and non-enzymatic antioxidants, including glutathione, uric acid, and coenzyme Q to scavenge excess free radicals (Agarwal *et al.*, 2003) [1]. Medicinal plants are a promising source for safe, natural anti-oxidant agents as they contain many bioactive constituents, especially anti-oxidant flavonoids and polyphenol compounds.

5. Role of natural plant derived antioxidants in semen production

To evaluate reproductive status of male animals, many factors must be considered, such as spermatogenesis, semen functions, sperm quality and fertility. Spermatogenesis depends on intratesticular and extratesticular hormonal regulatory processes and functions of the intertubular microvasculature (Holstein *et al.*, 2003) [16]. Semen parameters such as sperm count, concentration, viability, mobility, and morphology are indicator of semen functions (Rodriguez-Martinez, 2006) [30].

6. Beneficial effect of some plants on semen production:

1. **Ferula hermonis:** Hanafi *et al.*, (2010) [15]. demonstrated that F. hermonis extract added in freezing extender increased sperm motility and viability and decreased lipoxidation during boar sperm cryopreservation.
2. **Seaweed extract:** Trehalose is seaweed extract. It protect the sperm membrane structure against oxidative and cold shock damage during the freezing/thawing process. Trehalose supplementation in freezing medium could improve sperm quality in bovine (Hu *et al.*, 2010) [17].
3. **Rhodiola sacra:** It extract from Rhodiola rosea roots, has been used as an antioxidant (Ohsugi *et al.*, 1999) [28]. Zhao *et al.* (2009) [37] indicated that R. sacra aqueous

extract improved biochemical and sperm characteristics in cryopreserved boar sperm.

4. **Rosemary:** Malo *et al.* (2011) [24] reported that rosemary extract supplementation in freezing medium improved boar sperm motility and fertility after cryopreservation.
5. **Ginger:** Ginger is the rhizome of the plant consumed as a delicacy, medicine or spice. It increases sperm counts, motility, testosterone level and decrease malonhydialdehyde levels (Chaiyakunaprak *et al*., 2006) [7]. Ginger is a strong anti-oxidant substance and may either mitigate or prevent generation of free radicals (Ali *et al*., 2008) [3].
   Aqueous extract increase sperm counts, viability, and mobility in male rat (Morakinyo *et al.,* 2008). Rhizome powder increase sperm percentage, viability, motility and serum total testosterones in male rat (Khaki *et al.,* 2009a) [20].
6. **Pomegranate :** Turk *et al.* (2008) [34] demonstrated that the ingestion of a high amount of pomegranate juice (1mL/day) by adult male rats could have a beneficial effect on epididymal sperm concentration, sperm motility and the percentage of abnormal sperms. The authors suggest that the effects are due to the increase of plasma ascorbic acid (2.9-fold of control), which is active against ROS.
7. **Amaranthus:** The plant Amaranthus have higher protein, iron and calcium content. It is also called as Prince-of-Wales-feather an ornamental plant from Mexico, it might be promising to improve sperm quantity and quality (Singhal and Kulkarni, 1988) [32].
   Squalene is a natural organic compound the daily supplementation of which was shown to improve semen volume and sperm motility in boars by 33and 28%, respectively (Zhang *et al.,* 2008) [36].
8. **Tomato :** The red pigment contained in tomatoes is called lycopene. Lycopene is found in the testes and seminal plasma of male mammals and is considered to be part of the non enzymatic defence system of the semen used to cope with oxidative stress. Tomato also contains vitamin A, C and folic acid. The same authors found lycopene concentrations in the seminal plasma of subfertile men to be significantly lower by than concentrations in fertile men (Goyal *et al.*, 2006) [13].
   Dietary lycopene supplementation increased its concentration in the seminal plasma by 7–13% (Goyal *et al., 2*006) [13] and had positive effects on the concentration (+62%) and motility (+66%) of sperm from men suffering from sub fertility with unknown reason (Gupta and Kumar, 2002) [14].
9. **Sesbania :** Mekoya *et al.*(2009), supplementing sesbania to the diet at levels of up to 300 g/kg, found beneficial effects on the onset of puberty (−34 days), testicular growth (+13%) and sperm count (+17%) of male sheep.
10. **Alexandrian laurel**: It is also known as are Poet's laurel and has antioxidant and aphrodisiac activities. It has been reported to increase sperm mobility and viability in male rat (Khaki *et al.,* 2009a) [20].
11. **Wild Carrot:** It has got androgenic and antioxidant activities. It elevates testosterone level in rat (Nour *et al.,* 2009) [27].
12. **Lannea acida:** Its leaves and bark are used as febrifuge and have been described to be useful in gout, rheumatism, for wounds, swelling and burns. Bark of this plant has got antifertility activity. It protects morphology of testes and decrease sperm abnormality in male rat (Ahmed *et al.,* 2010) [2].
13. **Radish**: Seed of radish has free radical scavenging activity. It improves semen characteristic and nutritional performance in rabbit (El-Nattati *et al.,* 2007) [10].
14. **Mineral Pitch (**Shilajit**):** It is a potent rejuvenator, aphrodisiac and anti aging block buster**.** It support fertility & enhance testosterone level naturally. Today, in the United States, supplement companies are selling Shilajit as an ingredient in testosterone boosting supplements.
    It is a potent aphrodisiac and used to treat male sexual dysfunction. Animal and human studies indicate that shilajit enhances spermatogenesis. It has been reported that Shilajit increases serum testosterone level and sperm number in rat and man (Biswas *et al.,* 2009) [5].
15. **Black musli**: The rhizome of this plant is utilized extensively for medicinal purposes. Ayurveda also elaborates upon this herb's aphrodisiac properties. Black Musli preparations are widely used in treating erectile dysfunction, low libido, low sperm count, low sperm motility, gonorrhea, vigor, and male sterility. It has been reported that ethanolic extract of black musli enhances sexual activity in male rats (Chauhan and Dixit, 2008) [8].
16. **Winter Cherry (**Ashwagandha**)**: The roots, leaves and fruits (berry) possess tremendous medicinal value. The roots of Withania somnifera are alterative, aphrodisiac, deobstruent, diuretic, narcotic, sedative and restorative in nature. It is widely used to improve strength and stamina in various ayurvedic preparations. It contains active alkaloids in the form of withanoloids. It is also known as Indian ginseng has been described in folk medicine as an aphrodisiac and geriatric tonic (Ahmed *et al.,* 2010) [2].
17. **American Ginseng:** This hearty root is considered to be one of the best male sexual tonics. It supports healthy libido, erectile dysfunction and enhance male sexual performance. It has been found to provide excellent immune system support and strengthens the HPA axis. The HPA axis is vital to proper hormonal balance, stress management and immune system strength. The main active agent in are ginsenosides, which are triterpene, saponins (Ernst, 2002) [11].
18. **Tribulus fruit (**Gokharu): It increases virility, fertility and sperm production and rejuvenates the reproductive system. Ayurvedic practitioners have found Tribulus to be very effective in improving sperm count, motility, and morphology when combined with dietary and exercise changes. The main part of Tribulus that aids in fertility for men, is a constituent called protodioscin. This constituent improves dihydrotestosterone (DHT) and dihydroepiandrosterone sulphate (DHEAS), DHEA (Dihydroepiandrosterone) levels in the male body (Rajendar *et al*., 2011).
19. **Maca root**: Maca's main actions is to stimulate and nourish the hypothalamus which regulates the pituitary gland, acting as a tonic for the hormone system. When the pituitary gland functions optimally, the entire endocrine system becomes balanced, because the pituitary gland controls the hormone output of the other glands. Maca is a potent aphrodisiac and general health tonic containing Calcium, Magnesium, Manganese, Chromium, Selenium, EFA's, Vitamin A, B complex, C,

E and amino acids, that can improve libido, improve semen quality and increase ejaculate volume and stamina (Zheng *et al*., 2000).

20. **Saw Palmetto berry**: The most potent form is the standardized concentrated extract, derived from the active part of the berry. It contains steroids, saponins, estradiol, flavonoids, alkaloids, unsaturated fatty acids, vitamins, tannins, resins, aspartic acid and glutamic acid. Saw Palmetto has nourishing effect on entire endocrine system, which help to improve overall reproductive may function in men. It may increase low sperm count, supports stress and immune system response to treat chronic fatigue and improve libido.
21. **Yohimbe Bark**: Yohimbe has been found to increase circulation to the erectile tissues, aiding in physiological and psychogenic (mental) impotence. Yohimbine is the active component found in yohimbe bark. It has been shown to dilate the blood vessels and lower blood pressure, which enlarges the vessels in the sexual organs and increases reflex excitability in the lower spinal cord. In many cases, yohimbe has shown to make erections firmer.

7. Conclusion

The ROS are double edged swords and display dual functions in animal reproduction system. The adverse effect of oxidative stress on reproductive system involves damage to sperm and oocyte DNA and disruption of testicular functions. Role of various antioxidants such as vitamin E, C, and glutathione, has been well documented in animal reproduction and semen quality, however the side effects of synthetic antioxidants on animal production and reproduction is a matter of concern therefore, natural antioxidant from plant and their extract have occupied attention of scientists plants and their extracts as antioxidants are booming since last few years. In addition, exogenous antioxidants are also a double edged sword like ROS in reproduction system, because though some plant extracts have antioxidant activities, they also exhibit detrimental effects in animal reproduction, and the exact mechanism of actions are unclear.

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