Chapter

Antioxidant Strategies to Improve Female Reproduction

Tarique Hussain

Abstract

Animals are only productive once their reproductive cycle is continuously flown. There are several causes of stresses which interrupt animal physiology and make animal less productive. All factors involved in stress could eventually generate reactive oxygen species (ROS). Limited production of these reactive species performs several functions to maintain redox homeostasis. When these reactive oxidative metabolites are overwhelmed, it may generate oxidative stress. Disruption in oxidant/antioxidant mechanism leads to cause oxidative stress. Naturally, the body system is equipped with an antioxidant defense system. Once this system is broken-down due to the overproduction of ROS, it may have a detrimental effect on lipids, proteins, DNA, and carbohydrates and eventually influence animal fertility and productivity. Antioxidants available in nature are of two types: natural and synthetic. These compounds endowed several properties in the mitigation of various animal stresses, starting from physiology to molecular level. This chapter elucidates oxidative stress, natural and synthetic antioxidants, and particular focus are emphasized that how antioxidant supplementation can help to improve animal fertility and productivity. Moreover, the mechanism by which antioxidants produce fruitful effects will also be highlighted.

Keywords: reactive oxygen species, oxidative stress, animal fertility, productivity, antioxidants

1. Introduction

Oxidative stress is the condition in which the overproduction of free radicals is produced and the antioxidant system unable to neutralize them [1]. Limited quality of free radicals is compulsory to maintain physiological function, and accelerated production may lead to damage lipids, DNA, and proteins [2]. The efficacy of oxidative metabolites in female reproduction depends upon the site, amount and exposing levels to oxidant molecules [3].

In livestock, the appearance of the disease causes a reduction in the antioxidant status of the animals [4]. Oxidative stress is observed in several pathological conditions that influence animal health, welfare, and productive performance [5]. Indeed, in some productive phases, animals experience physiological alteration, such as farrowing and lactation, weaning, high temperature, and different stresses, that may decline antioxidant status [6–8].

Oxidative stress may influence physiological function of various reproductive events which thus involved in problems associated with pregnancy [9]. Antioxidants are chemical compounds is known to suppress autoxidation *via* reduction in free radicals' production using several different mechanisms. They can be categorized as primary antioxidants, chelators, $O_2^{\bullet-}$ quenchers, oxygen scavengers, and antioxidant regenerators [10]. The purpose of this chapter is to exploit the beneficial effect of antioxidant compounds various aspects of female reproduction and also discuss how antioxidant approaches improve animal productive performance and well-being.

2. Reactive oxygen species

Reactive oxygen species (ROS) encompasses of superoxide anion, hydrogen peroxide and hydroxyl radical. Their production is possible due to natural oxygen leakage [11]. Other origin of ROS production are metabolic reactions that are sustainable for life, the exogenous sources include X-rays, ozone, cigarette smoking, air pollutants, certain drugs and pesticides, and industrial chemicals [12]. The endogenous site of free radicals' production may be from mitochondria, xanthine oxidase, peroxisomes, inflammation, phagocytosis, arachidonate pathways, exercise, and ischemia/reperfusion injury [13]. Interestingly, the reactions of consists of enzymatic and nonenzymatic reactions within the body also produce free radicals. Many enzymatic reactions prevail in the respiratory chain, phagocytosis, prostaglandin synthesis, and cytochrome P-450 system [14], although nonenzymatic reactions are based on oxygen with organic compounds and ionizing reactions also generate free radicals [15].

ROS are comprised of oxygen ions, free radicals and peroxides. High level of ROS or reduce concentration of antioxidants induce oxidative stress that trigger cellular damage of macromolecules utilizing different ways. It has responsible for causing chronic diseases by interacting with molecular signaling pathways which alters gene expression [16]. The interaction between chemicals and signaling molecules are necessary to understand the involvement of ROS role in pathogenesis. Redox interaction with various proteins residues and ROS is the key component of inter-processes. Further reaction yields to produce reactive sulfenic acid and sulfonamide. Oxidation of these molecules leads to cause ultra-structural changes or functional alteration [17].

Pregnancy is a physiological phenomenon in which an ample amount of energy is required to balance the body's condition and combat fetal requirements. Thus, for this purpose more oxygen is required which in turn causes the overproduction of ROS. So, it is very crucial to maintain the balance between oxidative stress and the antioxidant system for perfect functioning of the body [18].

3. Antioxidants

Antioxidants are substances that overcome adverse effect of oxidative damages. They are available as natural and synthetic compounds. Natural antioxidants are derived from natural sources like food, cosmetics, and pharmaceutical industries. While the synthetic one is created artificially through chemical reactions [19].

The antioxidant system consists of enzymatic and non-enzymatic. The first one is also referred as natural antioxidants. They consist of superoxide dismutase (SOD) catalase and glutathione peroxidase (GSH-Px). Antioxidant enzymes are endowed to protect living cells against oxidant products. The SOD is an enzyme district superoxide anion radical into hydrogen peroxide. Another enzyme called catalase is in charge of catalysing the breakdown of hydrogen peroxide into water and oxygen. GSH-Px employs glutathione as a co-substrate and is composed of selenium. An enzyme found in the cytoplasm, it excludes hydrogen peroxide. However, in comparison with catalase, it has various ranges of substrates comprising lipid peroxides. The prime function of the Glutathione peroxidase is to decontaminate low levels of hydrogen peroxide in the cell.

Non-enzymatic antioxidants include dietary supplements or synthetic antioxidants. The complex nature of the body antioxidant system is impaired by consumption of dietary antioxidant such as vitamins and minerals [20]. Vitamin C, vitamin E, plant polyphenol, carotenoids, and glutathione are non-enzymatic antioxidants, they causes inhibition of free radicals reactions. Antioxidants can be classified as water-soluble or lipid-soluble depending on how potent they are. A water-soluble vitamin called vitamin C is found in cellular fluids such the cytosol and cytoplasmic matrix.

Antioxidants can be divided into small-molecule and large-molecule antioxidants depending on their size. The small one neutralizes ROS through scavenging process. The example includes Vitamin C, vitamin E, carotenoids, and glutathione (GSH). A large size of the molecule antioxidants comprises SOD, CAT, and GPx and albumin that captivate ROS and the attack form essential proteins. The mechanism by which antioxidants are utilized which offer protection against inhibition of free radical formation, scavenging free radicals, involved in repair-damage via free radicals, help to establish an environment that is conducive for the antioxidants to function effectively [21].

4. Synthetic antioxidants

Synthetic antioxidants are phenolic compounds responsible for eliminating free radicals and suppressing chain-reaction. They consist of butylated hydroxyl anisole (BHA), butylated hydroxyltoluene (BHT), propyl gallate (PG), metal chelating agent (EDTA), tertiary butyl hydroquinone (TBHQ), and nordihydroguaiaretic acid (NDGA) [21].

5. Oxidative stress and selenium

In commercial dairy and beef farming, various stresses influence economic benefit that is linked with declined productive and reproductive performance in cattle. It has been observed that diverse endogenous and exogenous sources of ROS lead to stresses that cause over generation of free radicals and eventually result in oxidative stress [22, 23]. It is well recognized that the consequences of oxidative stress have deleterious effects on immune system reproductive function, animal growth, development, and on general health [24, 25]. Hence, the antioxidant network is responsible for the preservation and maintenance of animal redox status in cells and tissues and is thus responsible for neglecting the harmful effect of stresses. In animals' body, the antioxidant system work either individually or in combination to exert particular function. Considering this mechanism, selenium has its own importance [26, 27]. It is noted that 25 selenoproteins have been identified in animal tissues; most of them are contributed in the conservation of body redox balance and antioxidant defense [27]. A deep theoretical knowledge of Se uptake toward the body/cells is required and its particular utilization for the balance of animal health. It is well-recognized in some animal species that the bioavailability of the Se relies on the dietary source of Se provided [28–30]. The Se integration relies on the rumen environment, which gradually declines depending upon the particular source of Se [31]. Selenium is present in two forms, inorganic and organic [32]. These forms may be a vital source of selenium [33].

It has been known that Se supplementation enhances female fertility but the exact mechanism is still not unknown. The progesterone hormone derived from the corpus luteum is a dominant hormone of pregnancy. This hormone is synthesized from cholesterol *via* several enzymatic reactions in which molecular oxygen is utilized for its reactions. These reactions generate oxygen radicals and different peroxides which are detrimental to cells [34]. In *in vivo* study, indicated that the inclusion of luteinizing hormone in luteal cells culture concurrently enhanced progesterone level in the medium and also the lipid peroxides in cells [35]. For luteal regression, the accretion of H_2O_2 [36] or lipid peroxides [37] in the corpus luteum has been documented. These findings show that corpus luteum requires antioxidant defense toward peroxides to stabilize normal functions. The significance of the corpus luteum has also been projected by Ref. [38]. Moreover, the inclusion of Se in luteal cells reduced the concentration of lipid peroxides in a cell [35]. Se as the part of glutathione peroxidase may destroy peroxides, in connection with superoxide dismutase, vitamin E, and beta-carotene.

6. Oxidative stress during pregnancy and antioxidants

Pregnancy is a normal mechanism in which overburden metabolic rate disrupts antioxidant status and energy balance. During first phase of pregnancy, 25% of the embryos die or reabsorbed within two weeks of pregnancy before implantation [39]. Once the zona pellucida is separated from the embryo, it enhances the production of ROS [40]. The imbalance between oxidant/antioxidant systems during early pregnancy may lead to disturbances in molecules which eventually compromise growth and development of embryo [41].

The nutritional requirement during early pregnancy is increased to maintain animal health and pregnancy, which is in turn generation of oxidative stress [42]. Although, malnutrition is also common around the globe in small ruminants because of the high price of the feed, especially in developing countries. Hence, small ruminants are easy to keep due to several reasons [43]. Malnutrition during pregnancy has deleterious effect on the conception rate and on fetus development [44]. Animal supplementation in a diet with plant source have sufficient nutrition and has been assumed to be the potential source of antioxidants to attenuate early pregnancy stress in goats [45, 46]. The plant compounds exert diverse nutrition comprises of rich source of antioxidants and immune-modulatory properties, which act as a potential feed supplement for ruminants [47, 48].

Moringa oleifera (MO) is a multifaceted medicinal tree with high nutritional values [49]. Its leaves are rich sources of several nutritious compounds, such as proteins, amino acids, minerals, and vitamins [50]. Apart of that, MO is also a rich source of antioxidant compounds, such as phenolic acids, vitamin E, vitamin C, selenium, zinc, and β carotene. These compounds have more robust antioxidant potential than synthetic ones [51]. The basal diet supplemented with 3.2% MOLP increased antioxidant index and blood biochemical in early pregnancy in Beetal goats. It also promoted progesterone profile, improved conception rate, and attenuated ROS production in early pregnancy of goats.

In another study, by Ref. [52] reported the use of herbal antioxidants during pregnancy and their effect on piglet performance. The supplementation profoundly enhanced number of live-born piglets, total litter weight, and reducing the chance of low-weight piglets. Moreover, supplementation declined MDA levels in sows and piglets. The mothers who had supplementation showed a higher trend of weaning weight. The results conclude from 1000 pregnancies that offering maternal supplementation with herbal antioxidants in pregnancy profoundly enhanced reproductive efficiency, litter traits, and piglet performance.

7. Oxidative stress during lactation and antioxidants

Reproductive performance is a main indicator related to maternal nutrition. The periparturient period causes reduced feed intake, and endocrine and metabolic alterations which disrupt energy balance and antioxidant index [22, 53]. In this period, increased nutritional requirements, such as digestion rate, mammary development, and fetus growth have been reported [54]. Pasture grazing and feeding on crop residues have a diverse nutritional profile and feeding on such sources is not adequate to meet the energy requirement of lactating animals [55]. In this scenario, pregnant animals are vulnerable to oxidative stress [56], which threatens to biomolecules and eventually affect productive and reproductive parameters [57]. Colostrum is the composition of immunoglobulins, minerals and other biological substances which transfer form colostrum to the young ones [58]. The quality of the colostrum depends upon maternal nutrition [59, 60]. The diet supplemented with phytobiotics has been assumed to be the main source of managing nutrition-induced oxidative stress in pregnancy and lactation in livestock [45, 46, 61]. In a recent study by Ali et al., (2022) using 2% and 3.5% *M. oleifera* leaf powder (MOLP) during periparturient period. He reported the increased biochemical and antioxidant indices of colostrum and milk. The milk yield, weight gain of the kids, and reproductive performance were enhanced with 2 and 3.5% MOLP. Further, the findings suggested that the diet supplemented with 3.5% MOLP promotes antioxidant index, milk yield, and reproductive performance in goats.

8. Effect of oxidants and antioxidants on embryo production

The *in vitro* embryo production (IVEP) technique is employed to combat infertility-related problems in mammalian species [62]. This tool has been known to be utilized for the production of large scale offspring from elite animals. The IVM prognosis relies on diverse factors consisting of oocyte quality and culture conditions [63]. The source of antioxidants from female organs has been reported to reduce ROS production [64]. The main hurdle which decides the fate of oocyte success during IVM is oxidative stress [64]. Accelerated ROS production might result in oocyte death and embryonic loss [65, 66]. An antioxidant approach during IVM has been proposed to govern oocytes from the deleterious effect of oxidative stress by maintaining a basal level of ROS [67, 68]. Presently, different antioxidants are utilized during IVM to confirm balanced intracellular redox status, resulting in good-quality of oocytes [69, 70]. The inclusion of antioxidants, such as thiols, polyphenols, melatonin, carotenoids, resveratrol, and vitamins C and E, to the IVM medium has been verified in different studies to increase oocyte quality and attenuate exceeding ROS damage [71, 72].

Previous evidence has reported that the balance amount of antioxidants and ROS in IVEP media which may be favorable for embryonic development [73, 74]. At present, the widely employed antioxidant in IVEP is cysteamine; its efficiency is mostly associated with the stage of IVM. It has been found to stimulate the embryonic process and secreting of glutathione (GSH), which is prevalent in male and female gametes from harmful effect of ROS [75]. Moreover, cysteine and glutathione have been implied in IVEP protocols with good results [73, 76]. The application of quercetin (2 μM), resveratrol (2 μM), vitamin C (50 μg/mL), carnitine (0.5 mg/mL), and cysteamine (100 μM) were determined to prove the vibrant antioxidant toward deleterious effects of ROS during IVM of bovine oocytes [71]. The positive effect of antioxidants is illustrated in **Table 1**.

Antioxidants	Dose	Animal species	Maturation vs. control rate	References
Melatonin	10^{-9} M 10^{-7} M 10^{-6} M	Bovine Sheep Mouse	82.3 (65.7) * 85.3 (75.3) * 85 (64) *	[77–79]
Lycopene	2×10^{-7} M	Bovine	76 (66.3) *	[80]
Beta-Mercaptoethanol (β-ME)	2×10^{-5} M	Buffalo	76.2 (66.7)ns	[81]
Cystamine	10^{-5} M	Mouse	80.1 (57.7) *	[82]
Vitamin C	2.3×10^{-3} M (1 mg/mL)	Bovine	~80 (~80)ns	[83]
Vitamin E	2.3×10^{-3} M (1 mg/mL)	Bovine	~80 (~80)ns	[83]
Vitamin E; Selenium (SeMet)	10^{-3} M; 2.5×10^{-8} M	Porcine	85.1 (67.6) *	[84]
Resveratrol	10^{-6} M	Bovine	93.4 (87.9) *	[85]
Quercetin	10^{-5} M	mouse	86.6 (79.7) *	[86]
Retinoic acid	10^{-8} M 2×10^{-5} M	Goat Camel	78.7 (65.1) * 69.4 (52.9) *	[87, 88]
Coenzyme Q10	5×10^{-5} M	Human	82.6 (63.0) *	[89]

**Shows the significant effects.*

Table 1.
The beneficial effect of antioxidant supplementation in different animal species.

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