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Antioxidant Signalling Pathways in Augmenting Reproductive Health and Production of Dairy Cows

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ABSTRACT

Oxidative stress (OS) occurs as the equilibrium shifts toward an excess of reactive oxygen species (ROS). A disproportion between free radical species or prooxidants and body's capacity to scavenge them causes OS. ROS and antioxidants sojourn a state of equilibrium in the body. ROS are vital indicator molecules in physiological, functional and pathological processes of the female reproductive tract. ROS have an outcome on various physiological and reproductive processes, including oocyte maturation, fertilisation, embryo formation, and pregnancy. The age-linked decrease in fertility is impacted by OS. Antioxidants can shield the ovarian epithelium from oxidative impairment and DNA loss. The pathophysiology of endometriosis, preeclampsia, unexplained infertility, abortions, free radical-induced birth defects are linked to the OS in female reproduction. The aetiology of female reproductive disorders shows composite interaction between OS and cytokines. The amount of OS biomarkers helps in detecting disorders in female reproduction. This review discusses the OS-associated female infertility, OS management and early action for the avoidance of reproductive disorders and the antioxidant interventions that can be prescribed as add-on to correct the female reproductive disorders.

HIGHLIGHTS

- Oxidative stress is caused by weakened antioxidant defence mechanism with the generation of free radicals.
- Antioxidant like Vitamin A, C and E, carotenoids, and selenium can assist in the prevention and treatment of female reproductive disorders.

Keywords: Free radicals, Reactive Oxygen Species, Oxidative stress, Antioxidants, Reproduction

The livestock sector suffers greatly due to oxidative stress (OS) brought by reactive oxygen species (ROS) and reactive nitrogen species (RNS) in animal reproduction. One of the major causes of decreased fertility in dairy animals is OS which causes several reproductive disorders such as placental retention, mastitis, and udder oedema (Folnozic, 2015; Turk *et al.,* 2017). The assessment of an animal's OS condition at various physiological states is critical for reducing economic losses caused by abortion, increasing calving intervals, and other reproductive diseases (Szczepanska *et al.*, 2003). The frequency of heat stress and high milk yield, as well as post-partum negative energy balance, affect the redox state of the cow and the extent of an antioxidant feature. Pregnancy and lactation are considered as the basis of metabolic stress in dairy cows (Drackley, 1999; Hyatt *et al.,* 2017) and, dairy cows go through OS, which are correlated to

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metabolic disorders in pregnancy (Pedernera *et al.,* 2009, Moolchandani and Sareen, 2018). The imbalance between the precursor and antioxidant species is called OS, which can cause molecular and cellular damage (Zuo, 2015; Tan *et al.,* 2018).

In the female reproductive system, free radicals play a vital physiological function, and excess free radicals contribute to diseases. OS is involved in a number of physiological processes of reproductive system from egg maturation to fertilisation and embryo development. Both ROS and RNS can cause infertility issues and various female reproductive diseases. When the production of free radicals exceeds the cell's ability to eliminate free radicals, the level of OS will increase, resulting in damage to cell biomolecules like DNA, proteins, sugars, and lipids. (Durackova, 2010; Poljsak, 2013, Sanz, 2016).

Antioxidants have an important role in physiological functions like milk yield, and the use of antioxidant-rich alternative feedstuffs in ruminant feeding is a unique management technique that is renewable, safe, ethical and very simple to implement (Gabai *et al.,* 2004; Martin, 2006). Female reproductive cells harbour wide arrays of antioxidants for limiting and inactivating ROS production, and repairing cell damage (Szczepanska *et al.*, 2003; Showell *et al.,* 2020). Antioxidants can control autoxidation by interrupting the spread of free radicals or by inhibiting the formation of free radicals, thereby reducing OS and improving immune function (Tan *et al.,* 2018). A good antioxidant therapy is one that enters reproductive tissues in high enough concentrations to be effective in decreasing damage caused by ROS.

In the last two decades, extensive research has shown the mechanism by which chronic OS generates chronic inflammation, which mediates the majority of chronic illnesses of the female reproductive system. The present review explores the different free radicals inducing OS that damages the female reproductive tract leading to various diseases and their containment through therapeutic interventions.

Classes of oxidants: bio-synthesis and chemistry

Free radicals are extremely reactive and unstable which can be stabilised by getting electrons from lipids, nucleic acids, sugars, proteins and similar molecules. OS results in DNA injury, lipid peroxidation, and protein damage (Halliwell, 2007; Durackova, 2010). The different classes oxidants are as follows:

Reactive Oxygen Species (ROS)

The critical function of free radicals, particularly ROS and RNS, in cellular physiology has been intensively investigated in recent decades (Droge, 2003). Both endogenous and external sources of oxygen free radicals cause substantial biomolecular damage. ROS, formed due to the electron receptivity of O_2, are highly reactive chemical molecules (Schieber and Chandel, 2014). ROS include hydroxyl radical, peroxides, singlet oxygen, and α-oxygen, superoxide. Radical ROS consist of superoxide anion and hydroxyl radical, while non-radical ROS take in hydrogen peroxide (H_2O_2) and hypochlorite ion. ROS, owing to the additional-unpaired electron at their outer shells, have high reactivity. The hydroxyl radical is the most harmful as it cannot be scavenged quickly in our systems. Neutrophils and activated macrophages generate substantial amounts of superoxide anion and its derivatives in the course of the NADPH oxidase pathway (Nunes-Silva and Freitas-Lima, 2014). Superoxide anion, H_2O_2, and hydroxyl anion are the three primary forms of ROS, while nitric oxide (NO) is a major form of RNS. In the replication method, free radical production is a double-edged sword (Silva *et al.,* 2010).

Free radicals include RNS and ROS in aerobic metabolism, which are common prooxidant chemicals that induce cumulative oxidative damage in macromolecules such as lipids, DNA, and proteins, eventually leading to cell death (Poljsak, 2013; Scheibye-Knudsen *et al*., 2015; Sanz, 2016), and affect the health span of numerous principal organ systems of the body (Dai *et al.,* 2014). The key class of ROS formed is the superoxide anion, which is an end result of NADPH oxidase reactions whereas the hydroxyl radical (OH^-) is formed by way of the spontaneous degeneration of H_2O_2, and is mostly concerned in their creation and breakdown. Accordingly, metallic cations, for example, copper and iron ions function as catalyst and add to ROS production (Agarwal *et al.,* 2012). Short electron chain of endoplasmic reticulum, cytochrome P_{450} in liver, and the enzyme xanthine oxidase are responsible for ROS production. The formation of H_2O_2 is the result of superoxide dismutation. The hydroxyl ion is a class of

ROS that may damage DNA strands by converting purines and pyrimidines (Agarwal *et al.,* 2005a). Endogenous ROS are produced in oocytes and embryos as a result of aerobic metabolism as well as the functioning of several metabolic pathways and enzymes. ROS can be generated either directly by embryos or indirectly by their environment.

Superoxide anion (O_2^-)

The formation of superoxide anion (O_2^-) results from the univalent reduction of oxygen. The reaction occurs in the mitochondrial electron transport chain without any enzymatic operation by the action of oxidation-reduction reactive intermediates like semi-ubiquinone. Enzymes namely, NADP oxidases and xanthine oxidase mediate this reaction and the activity of different isoforms of NADPH oxidase typically results in the discharge of large quantities of superoxide anions from neutrophils and macrophages. These O_2^- can subsequently be converted enzymatically using oxidative enzymes like SOD or nonenzymatically into non-radical species such as H_2O_2 and singlet oxygen (Droge, 2002).

Hydroxyl Radical (OH^-)

Hydroxyl radical (OH^-) is produced following reaction of hydrogen peroxide with metal ions such as Fe^{2+} and Cu^+ (Hayyan *et al*., 2016). Sometimes it could be produced as a by-product of the immunological activity. Macromolecules like carbohydrates, proteins, lipids and nucleic acids are damaged by hydroxyl radical. In contrary to superoxide which could be eliminated by SOD, hydroxyl radical could not be eliminated by enzymatic reactions. Mechanisms for its elimination include endogenous antioxidants such as melatonin and glutathione and nutritive antioxidants such as mannitol and vitamin E (Reiter *et al*., 1995).

The Fenton reaction occurs as H_2O_2 interacts with reduced transition metals like copper and iron, resulting in the development of hydroxyl radical (OH^-). Furthermore, revealing water molecules to ionising radiation forms hydroxyl radicals (Salmon *et al*., 2010).

Reactive Nitrogen Species (RNS)

Reactive Nitrogen species (RNS) are nitrogen-containing ROS (Doshi *et al*., 2012). RNS, like ROS, can take account of radicals similar to nitrous acid (HNO_2) and nitric oxide (NO) as well as non-radicals like dinitrogen tetraoxide (N_2O_4) and nitrogen dioxide (NO_2). With cofactors like calcium, calmodulin, NADPH, FMN, NOS and FAD, they can alter l-arginine and oxygen to NO and l-citrulline. Other types of RNS, such as nitrosonium cation (NO^+), peroxynitrite (ONOO), or nitroxyl anion (NO) are formed as a consequence of NO interactions with various substances (Semchyshyn and Lushchak, 2012).

Physiological status of animal and ROS production

Lactation, development, exercise, and heat stress are all physiological stages associated with increased metabolism, and thus with increased ROS generation (Belhadj Slimen *et al*., 2014). Following initiation of lactation, the levels of glutathione peroxidase in serum and glutathione peroxidase mRNA in mammary tissue scales up. High milk yielding cows have elevated serum lipid hydroperoxide concentrations. During pregnancy, the corpus luteum is required for progesterone synthesis and pregnancy maintenance; too much free radical production damages the luteal cell membrane and affects progesterone level. This disorder can result in embryo death, increasing calving periods, and significant economic loss. Owing to heat stress, the level of thiobarbituric acid reactive substances (TBARS) in the blood can be higher in the summer than in the winter (Tanaka *et al*., 2011; Kuru *et al*., 2018).

OS-mediated physiological alteration in the female reproductive tract

The controlled OS is thought to be essential in ovulation. ROS levels in follicular fluid can indicate role of ROS for usual oocyte and embryo development. The follicular fluid system includes leukocytes, macrophages, and cytokines, together with granulosa cells, growth factors, and steroid hormones that generates ROS (Attaram *et al*., 2000). Local paracrine and autocrine influences like the nitric oxide (NO) radical also play a role in ovarian folliculogenesis. Anovulation, behavioural anestrus, irregular oestrous cyclicity, abnormal preimplantation embryo development and placental incompetence are the four primary mechanisms that reduce lactating cow's fertility (Lucy *et al*., 2007). Advanced oxidation protein products are oxidised protein markers that have been

linked to reduced dairy cattle reproduction (Celi *et al*., 2011; Celi *et al*., 2012). As lipids are resistant to oxidation, the lipid peroxidation product, malondialdehyde (MDA) is thus measured as an OS biomarker (Castillo *et al*., 2006). Thiobarbituric acid reactive substances (TBARS) are the most widely used for measuring MDA in veterinary aspects (Tanaka *et al*., 2011). OS in the fallopian tubes may have a significant negative impact on the embryo. ROS and reduced antioxidants are related to luteal regression and insufficient luteal hormone cannot continue pregnancy (Agarwal *et al*., 2004). Other causes of infertility like recurring pregnancy failure, hydrosalpinx, endometriosis, polycystic ovarian disease and unexplained infertility are correlated to OS (Agarwal *et al*., 2006).

Endometritis in cow is the inflammation of the uterine endometrium over 21 days post-partum without any systemic signs of illness. The prooxidant/antioxidant balance can be disrupted by peritoneal ROS, macrophages, environmental hazards, resulting in enhanced tissue adhesion and proliferation (Conti *et al*., 2016). By producing vascular endothelial growth factor, OS stimulates angiogenesis in ectopic endometrial implants. The pathophysiology of endometriosis has been linked to activated peritoneal macrophages, which may be the source of elevated ROS generation. ROS promotes endometriosis adhesions and infertility by increasing endometrial cell growth and adhesion in the peritoneal cavity (Alpay *et al*., 2006; Park *et al*., 2006).

OS and inexplicable Infertility

Cellularly, OS is a chief contributor to infertility. Surplus reactive oxygen radicals can cause infertility in addition to pregnancy complications. High ROS levels in unsolved infertility patients proves deficiency in vitamin-E and glutathione like antioxidants diminishes scavenging of ROS neutralising its lethal effects. The antioxidant concentrations in unexplained infertility patients are considerably lower than fertile patients, showing antioxidant supplementation can control the elevated levels of ROS. OS causes irregular oestrous cycle, polycystic ovary syndrome, pregnancy failure, embryo development endometritis, infertility, etc. (Wong *et al*., 2010).

ROS may contribute to the age-related decrease in oestrogen production. Amplified OS in the follicular fluid causes ovarian senescence. Injury caused by free radicals partly causes age-associated deterioration of follicle reserves. This process causes oxidation of mitochondrial DNA, proteins, and lipids. In oocytes, ROS disrupt intracellular calcium homeostasis and cause oocyte ageing. This down regulation of genes involved in front-line ROS defence is connected to OS, which predominantly affects mitochondria (Takahashi *et al*., 2003). OS can be produced in sperm-mediated oocyte activation, sperms and embryonic genome activation. The maternofoetal oxygen diffusion tests show an embryo develops well in low oxygen concentrations during the first trimester (Jauniaux *et al*., 2003). During *in vitro* cultures, high O_2 concentrations trigger increased H_2O_2 levels, DNA separation, decreased embryo development competency. ROS like H_2O_2 causes apoptosis leading to preimplantation embryo death and blastocyst growth failure.

Molecular mechanism of antioxidant systems

Antioxidants, also known as “scavengers” are commonly used to detoxify waste reactive oxygen molecules and prevents occurrence of oxidation. Glutathione, lipoic acid, uric acid, taurine, keto acids, melatonin, coenzyme Q, and melanins are some of the chemicals generated in the animal and human bodies that have an antioxidant impact. In the body, both enzymatic and non-enzymatic antioxidants are present (Fig. 1) (Van Langendonckt *et al*., 2002; Pierce *et al*., 2004). Endogenous antioxidants are classified as enzymatic (SOD, GSH-Px), non-enzymatic (albumin sulfhydryl groups), and non-enzymatic low-molecular-weight (glutathione, α-tocopherol, β-carotene) (Li *et al*., 2021). The scavenging molecules transform ROS to H_2O to check overproduction of ROS. Glutathione, across all antioxidants, is one of the principal cellular antioxidants (Sifuentes-Franco *et al*., 2017).

Endogenous antioxidants play vital roles in the placenta and in the protection of trophoblast cells from OS. SOD plays a crucial role in cellular defence by converting two molecules of superoxide (O_2) into H_2O_2) and molecular oxygen (O_2). Catalase (found mostly in peroxisomes) catalyses the conversion of H_2O_2 to O_2 and water (H_2O). GSH-Px and GSH reductase are enzymes that take part in the oxidation of glutathione peroxides by eliminating H_2O_2 and lipid hydroperoxides (Rhee *et al*., 2005; Birben, 2012; Poljsak *et al*., 2013).

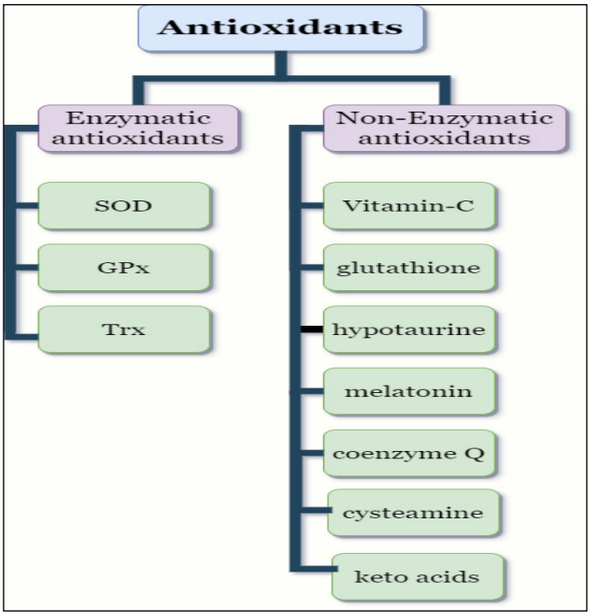

Fig. 1: Classification of antioxidants

Enzymatic antioxidants

SOD, Glutathione peroxidase, catalase and glutaredoxin are examples of enzymatic antioxidants. Endogenous antioxidants are more efficient than synthetic antioxidants. These antioxidants' centre is a transition metal with several valences, required throughout detoxification reactions for electron transfer (Burton and Jauniaux, 2011). These antioxidants aid in the maintenance of homeostatic oxidative balance.

Superoxide dismutase (SOD)

The superoxide anion, a free radical formed after oxygen reduction, the dismutation process and the subsequent proliferation of radical chains are catalysed by SOD (Wang *et al*., 2018). There are several isoforms, but the most common are SOD1, SOD2, and SOD3. Superoxide dismutase 1(Cu–Zn SOD), comprises a nucleus of two metal cofactors that form a copper–zinc enzyme, is mainly cytosolic (Fujii *et al*., 2005). SOD2 is activated in response to varying forms of inflammation and OS. SOD3, which is structurally related to SOD1, encodes an extracellular version of this enzyme and has not been connected to fertility or reproduction (Sah *et al*., 2020). As a result, SOD enzymes differ in form, location, and composition. Superoxide dismutase (SOD) protects cells from damaging effect of superoxide anion by its conversion to H_2O_2 (Laukkanen, 2016; Altobelli *et al*., 2020).

Glutathione Peroxidases (GPx)

This is a vast enzyme family that preferentially uses hydrogen peroxide as a substrate. Amongst these, GPx is one of the most important peroxidases. GPx is a tetrameric selenoprotein that needs reduced glutathione as a contributor of hydrogen molecules (Flohe, 2020). In reality, mammals have four isoforms, and it is a multisystem antioxidant defence mechanism. Catalase is one more important peroxidase that detoxifies H_2O_2 but does not necessitate an electron donor. It has an antiapoptotic effect (Sarıkaya and Dogan, 2020).

Thioredoxin (Trx) system

The thioredoxin mechanism controls a variety of enzymes and transactivating factors for genes. It plays a vital role in cell division, development, and death (Jia *et al*., 2019). It is also a recovery device, not just a defence system. Trx is a protein disulfide isomerase that corrects errors together with disulfide bridges and serves as a cofactor for the DNA-synthesizing enzyme ribonucleotide reductase (Boronat *et al*., 2005). Trx is essential to retain an oxidative equilibrium and bound oxidative damage and is also required for cell survival. The fact is that Trx-deficient mice are embryonically lethal (Hanschmann *et al*., 2013; Peoples *et al.,* 2019).

Non-enzymatic antioxidants

There are several low molecular weight non-enzymatic molecules that are synthesized in animal human body. They are Vitamin-C, glutathione, hypotaurine, taurine, cysteamine, lipoic acid, uric acid, keto acids, melatonin, coenzyme Q, and melanins taken as nutrients (Fujii *et al.,* 2005; Sifuentes-Franco *et al*. 2017). Two of the most essential compounds are Vitamin-C and Vitamin-E. Vitamin-C, also known as ascorbic acid, is one of the most ubiquitous hydrosoluble antioxidants. Vitamin-C remains mainly as an ascorbate anion in physiological pH condition (Camarena and Wang, 2016). Vitamin-C is required for vitamin-E regeneration and, therefore,

they serve as dual cofactors. Thiol compounds, such as thioredoxin, which degrades H_2O_2 are among the other molecules. Thioredoxin reductase can lessen and recycle the thiol compounds after they have been oxidised, thus retaining viable thiol levels. Ceruloplasmin and transferrin are two non-enzymatic antioxidants that help to seize free iron ions, which serve as a catalyst in Fenton reaction (Burton and Jauniaux, 2011). The existence of glutathione in various cellular compartments shows its role as an intricate intracellular transport mechanism.

Glutathione, a mixture of L-glutamate, L-cysteine, and glycine, is synthesised in the cytosol by glutathione synthetase and glutamate–cysteine ligase. The transfer of glutathione into the mitochondria is driven by a concentration gradient (Valko *et al*., 2007). Glutathione is a key antioxidant that protects cells against ROS such as peroxides, lipid peroxides, free radicals and heavy metals (Pisoschi and Pop, 2015). Through non-enzymatic antioxidant activity, glutathione can scavenge ROS given by the free thiol group of glutathione (Winterbourn, 2016). Moreover, involvement of glutathione reductase, glutathione peroxidase, and glutathione-S transferase help glutathione detoxify oxidants and electrophiles via enzymatic reactions (Farhat *et al*., 2018). Furthermore, glutathione may serve as a cofactor for many detoxifying GPx and glutathione transferase, as a signal between the interaction of enzymatic and non-enzymatic antioxidants. The reproductive system is susceptible to oxidative damage if any of these antioxidants is deficient.

OS in dairy cattle during the periparturient and early lactation phase relates to a variety of health problems (Hyatt *et al*., 2017). Selenium is a component of the 25 selenoproteins discovered in animals, making it one of the most important feed-derived antioxidants. Organic Selenium has been found to dramatically enhance selenium concentration in ruminant animal body tissues, suggesting that it might be used as a reserve in times of selenium deficiency or stress. Building selenium reserves in the body is a critical coping technique for dealing with stressful situations. Endogenous selenium reserve that can be used for increased selenoprotein production during times of stress. Improved selenium and antioxidant status, as well as enhanced selenium transfer via the colostrum, milk and placenta to the infant, are all advantages of organic selenium, especially in dairy and beef animals (Surai *et al.,* 2019). Glutathione and selenium enhanced the functional value and antioxidant activity of milk (Khan *et al.,* 2019). Heat stress is also linked to higher levels of SOD and intracellular thiols in circulating erythrocytes. Antioxidant supplementation in dairy animals will likely increase reproductive function by lowering the concentration of ROS in reproductive tissues and improving the redox state in reproductive tissues (Kukurt *et al.*, 2021).

Signalling pathways in reproductive cells affected by OS

The OS theory emphasises the importance of antioxidant defences as a component of the organism's overall redox balance (Perez *et al*., 2009). Aerobic metabolism involves the development of prooxidant molecules known as free radicals or ROS including $O_2^{\cdot -}$, OH^-, H_2O_2 and NO. ROS is associated with the modulation of all physiological reproductive functions like corpus luteal function, luteolysis, oocyte maturation, ovarian steroidogenesis (Ishikawa, 1993). The complex relationship of pro-oxidants and antioxidants preserves the intracellular homeostasis. An OS condition is initiated with an imbalance among pro-oxidants and antioxidants (Zuo, 2015). Under usual circumstances, paired electrons form stable bonds in biomolecules but in cases of weaker bonds, there is formation of free radicals.

ROS are considered as double-edged weapon as they are crucial signalling molecules in patho-physiological events in female reproductive system. The presence of appropriate levels of antioxidants maintains the equilibrium. The antioxidant capacity is determined by measuring the amounts of various antioxidants separately or as a whole (Ishikawa, 1993). Endogenous ROS are created as a normal by-product of aerobic metabolism and enzymes in oocytes and embryos and through various metabolic pathways activities. ROS may be produced directly by embryos or by their surroundings. Oxygen intake, visible light, amine oxidase, metallic cations, and spermatozoa are all exogenous factors that can upsurge the ROS amount released by embryos (Agarwal *et al*., 2005b). ROS may be generated by parenchymal steroidogenic cells, endothelial cells, leukocytes, phagocytes, etc. ROS-producing enzymes include oxidases of mitochondrial, microsomal, and peroxisomal origin, phagocyte plasma membrane NADPH oxidase and cytosolic NADPH oxidase.

Free radicals may affect the peritoneal fluid, tubal fluid, and follicular fluid microenvironments of sperm, oocytes, and embryos, thereby affecting reproductive outcome. However, under pathophysiological circumstances, endogenous antioxidants may be ineffective in combating excess free radicals. As a result, there is a constant need for exogenous antioxidant supplementation. The cellular free radicals' production is influenced by a dynamic interplay of cytokines, hormones, and other stressors. Free radicals then exert additional influence by modulating transcription factors and gene expression (Nath and Roy, 2021). ROS play critical parts in folliculogenesis, oocyte maturation, tissue remodelling, tubal function, endometrial cyclical shifts, hormone signalling, germ cell, and function ovarian steroidogenesis (Agarwal *et al*., 2005a). However, during periods of environmental stress, ROS levels will skyrocket damaging cell structures. Various antioxidants inhibit ROS formation, scavenge ROS, and repair the cell damage (Agarwal and Allamneni, 2004; Agarwal *et al*., 2006).

The complex interaction between OS and cytokines has indispensable role in female reproductive disorders. Leucocytes secrete cytokines into the extra cellular compartment (Bedaiwy and Falcone, 2003). The proteolytic cascade with vascular changes causes mammalian ovulation or follicular rupture and more importantly, cytokines, vascular endothelial growth factor (VEGF), ROS and RNS mediate these cascades (Tsafriri and Reich, 1999). In the ovary, OS and cytokines are connected and serve as intercellular messengers. Any imbalance between cytokine and angiogenesis factor might lead to implantation failure and pregnancy loss. ROS are important secondary messengers that activate downstream signal transduction pathways outside of the immune system. These pathways control the production and function of cytokines, ions, and growth factors. The activation of cytochrome-C and other proapoptotic cell mediators is the pathway's final consequence. In reaction to stress, the mitogen-activated protein (MAP) kinase c-Jun N-terminal kinase (a member of the MAP kinase family) is activated thereby phosphorylating and releasing Bcl-2-related proteins. This causes the protein Bax to uncouple and translocate within the mitochondria to oligomerize (Auten and Davis, 2009). The formation of the ultimate proapoptotic mediators is catalysed by the mitochondrial enzyme Bax. The mitochondrial apoptotic pathway involves the proteins Bax (proapoptotic) and Bcl-2 (antiapoptotic). Hormone signalling, ovulation, luteolysis, oocyte maturation, ovarian steroidogenesis, luteal maintenance in pregnancy, germ cell structure, implantation, compaction, blastocyst development and corpus luteum formation are all possible roles for ROS (Agarwal *et al*., 2003).

Therapeutic implications of antioxidants supplementation on female reproduction

Antioxidants are chemicals or biological compounds that contain minerals, vitamins and PUFA (polyunsaturated fatty acid) with omega-3, omega-6, and omega-9 fatty acids. Other researched antioxidants in female infertility include N-acetyl-cysteine, melatonin, myo-inositol, folic acid, selenium, copper and vitamins A, C, and E (Showell *et al*., 2018). Pentoxifylline, a trisubstituted xanthine derivative, and L-arginine are two other popular antioxidant supplements (Urman and Oktem, 2014). Antioxidant supplementation lifts up the function of antioxidant enzymes (SOD and GPx) diminishing OS indicators including malondialdehyde and lipid peroxides (Birben, 2012). The interplay between low antioxidant status and low fecundity indicates that antioxidant supplementation can treat augmented ROS levels in idiopathic infertility patients. OS has been accompanying to a variety of reproductive situations, including folliculogenesis, oocyte maturation, retained placenta, and endometriosis, all of which have an impact on natural fertility. To restrict the production of ROS, cells have evolved a variety of antioxidant systems to inactivate them and repair cell damage (Guerin *et al*., 2001; He *et al.,* 2017). Antioxidant supplements like vitamin C and vitamin E help to stop luteal phase deficiency, resulting in a higher conception rate (Henmi *et al*., 2003).

In dairy cows, OS can cause reproductive problems such as placental retention, mastitis, and udder edema (Folnozic, 2015; Turk *et al*., 2017). Placental retention appears to be linked to an overload of antioxidant and pro-oxidant enzymes. When lipid synthesis in late pregnancy is disrupted, there is a high frequency of placental retention. Selenium, vitamin-A and Vitamin-E treatment can reduce the happening of preserved placenta. The helpful benefits of antioxidant supplements are dependent on the intake of selenium and vitamin-E. Organic and inorganic

selenium sources are also involved in avoiding retained placenta (Cerri *et al*., 2009). Antioxidant supplementation enhances immune function while prenatal vitamin-E and selenium supplementation improve neutrophil function, and vitamin-A can boost lymphocyte proliferation ability (Spears and Weiss, 2008; Surai *et al*., 2019).

When evaluating the fertility status namely, estrous cycle, ovary functions and ovulation, embryo formation, conception, and foetal development, many histological, hormonal, morphological, and biochemical modifications occurring within the ovary during the estrous cycle are to be considered (Fig. 2).

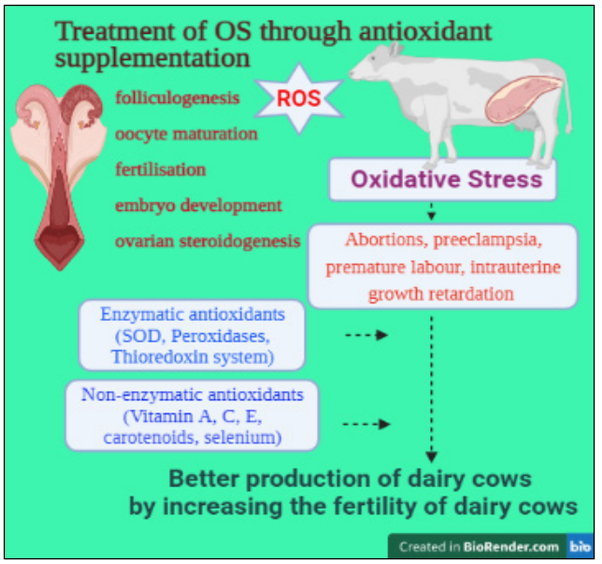

Fig. 2: Antioxidant supplementation can treat oxidative stress

Any disparity of oxidants and antioxidants results in ovary failure and an unusual estrous period (Gupta *et al*., 2011). SOD, present in the ovary, especially in theca interna cells in antral follicles has been studied in primordial, main, preantral, nondominant antral, dominant, and atretic follicles in follicular process (Sugino *et al*., 2000). As a result, theca interna cells have an essential role in oocyte maturation by shielding the oocyte from OS. The follicular fluid containing high levels of antioxidant systems allows an oocyte to be protected from oxidative damage (Jozwik *et al*., 1999). The antioxidant defence of the preovulatory follicle is robust, although it can be reduced by severe peroxidation (Aten *et al*., 1992). The antioxidant supplementation will lessen the incidence of infectious disease in the uterus by increasing the immune status of animals (Spears and Weiss, 2008). Feeding carotene for 8 weeks, starting 4 weeks before planned calving, lowered the proportion of cows diagnosed with metritis (Michal *et al*., 1994). An intramuscular injection vitamin-E 10 days before calving decreased the rate of metritis (Erskine *et al*., 1997). Transferrin, an iron-binding glycoprotein found in blood plasma, is known to reduce ROS production and has been linked to follicle growth (Briggs *et al*., 1999). Ascorbic acid, an antioxidant component, may be degraded through both oxidant scavenging and impaired vitamin-C cellular recycling. Ascorbic acid deficiency is characterised by ovarian atrophy, follicular atresia and premature meiosis, highlighting the significance of its anti-OS function. Synthetic antioxidants like vitamin C and E guard the ovum and embryo from OS (Nayyar and Jindal, 2010).

Antioxidants can have a two-fold effect on fertility. A decrease in the incidence of residual placentas or uterine diseases as a consequence of prepartum antioxidant administration. Second, ROS damage to the oocyte and pre-implantation embryo is a concern, and improving the antioxidant state of the reproductive tract in the postpartum period can improve oocyte or embryo production competence (Konvičná *et al*., 2015). Vitamin-E and selenium have an effect on uterine health, and cows with a second service were more likely to have an infectious uterine disease and respond to antioxidant care. The effect of vitamin-E, iron, zinc, selenium, and L-arginine supplementation resulted in an improvement in ovulation and pregnancy rates (Blavi *et al*., 2021). Furthermore, vitamin-E has been shown to shield cellular membranes from ROS by acting as a chain-breaking antioxidant, for example by protecting polyunsaturated fatty acids (PUFAs) from auto-oxidation (Traber and Atkinson, 2007). Dairy cows with preeclampsia have lower antioxidant response, lower antioxidant nutritional levels and higher lipid peroxidation. Preeclampsia is synonymous with a faulty placentation, resulting in an oxidative burst that generates ROS, inadequate antioxidant defences and high levels of ROS in preeclamptic cases (Gupta *et al*., 2009).

Vitamin-E and selenium are perhaps the most commonly used antioxidants in the diet, either individually or in combination in dairy cattle. Vitamin-E is a strong lipid-soluble antioxidant inhibiting the free radicals in

membranes and plasma lipoproteins (Traber and Stevens, 2011). Antioxidant levels of vitamin-E and selenium are related to udder health immunity. Increasing vitamin-E levels in the diet boosts per day milk production. Milk fat depression due to low crude fibre diets can be alleviated by vitamin-E supplementation as it improves ruminal flora (Naziroğlu *et al*., 2002). Supplementation of selenium alone has little effect on milk yield, but in combination with iodine and cobalt ion in the form of a ruminal bolus increased milk production (Cook and Green 2010; Sun *et al*., 2020). The antioxidant effects of selenium are due mainly to its role as a cofactor for selenoproteins, such as GSH-Px, which prevents OS and controls immunology in dairy calves during calving (Sordillo, 2013).

Future perspective

The underlying mechanism of ROS is still ill understood and a long way to go. Modulation of ROS or broadly redox homeostasis has the potential to improve OS with great specificity primarily targeting reproductive cells. Although recent studies have offered insight to the role of antioxidant to combat oxidative stress in dairy animals, but it is imperative to conduct future research to understand the underlying mechanism of antioxidants on the implications of OS for better and effective therapeutic interventions.

CONCLUSION

OS is concerned with diverse physiological processes of reproductive system like oocyte maturation, fertilisation, and embryo development influencing production of dairy cows. OS occurs due to impaired antioxidant defence mechanism and production of free radicals. Abortions, preeclampsia, premature labour, and intrauterine growth retardation are linked to OS. Infertility can be effectively treated with the right strategies. To successfully cure infertility, strategies for overcoming OS *in-vitro* issues and balancing both *in vivo* and *in vitro* environments can be used. The strategies for treatment of OS can be through antioxidant supplementation. Randomized clinical studies can be conducted to explore antioxidant supplementation treatment methods aimed at lowering OS. Many antioxidant treatments with Vitamin A, C and E, carotenoids, and selenium assist in the prevention and treatment of female reproductive disorders. An augmented employment of antioxidants, whether natural or synthetic, will lead to better production of dairy cows by increasing the fertility of dairy cows.

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