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Oxidative Stress: A Biomarker for Animal Health and Production: A Review

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ABSTRACT

Oxidative stress occurs when there is an imbalance between free radicals and antioxidants in body. Body produces free radicals during metabolic processes which are neutralized by antioxidants. However, too many free radicals produced can interfere with cell regeneration and repair, which over time can lead to accelerated aging and the development of certain diseases. Oxidative stress is defined as an imbalance between increased sources of oxidation and decreased or defective antioxidant mechanisms. This definition lends itself to the notion that a special type of mechanism exists and that deviations from this can affect the homeostasis and potentially cause or worsen disease. Oxidative stress plays an important role in the development of chronic diseases such as cardiovascular disease, diabetes, neurodegenerative diseases and cancer. Long-term exposure to high levels of pro-oxidant factors can lead to structural defects at the mitochondrial DNA level and functional changes in several enzymes and cellular structures leading to aberrations in gene expression. As such, many attempts has been made to restore this “balance” by providing antioxidants to animals and human beings to prevent the ill effects of these free radicles produced by the body tissues. Oxidative stress is a disease driver or an epiphenomenon; which worsen the condition in body and the use of antioxidants treatment may prevent some degree of oxidative stress from occurring, which could play an important role in controlling inflammation and cellular adaptive responses.

Key words: Defense mechanisms, Endogenous antioxidant, Natural antioxidants, Oxidative stress, Reactive oxygen species.

The term stress comes from the Latin word stringere, meaning “to draw.” In the 1920s and 1930s, the term was occasionally used for harmful environmental agent that could cause illness (Kumar *et al*., 2012). Oxidative stress is an imbalance between free radicals and antioxidants in the body. Free radicals are oxygen-containing molecules with an odd number of electrons. These uneven number allows them to easily react with other molecules and can cause large chain chemical reactions. These reactions are called oxidation and may be beneficial or harmful (Megan Dix, 2018). Oxidative stress occurs naturally and plays an important role in number of vital processes in the body. Long-term oxidative stress contributes to the development in a range of acute and chronic conditions such as neurodegenerative diseases (Liu *et al*., 2017), cancer (Reuter *et al.,* 2010), diabetes and heart disease due to molecular and cellular damage (Jamie Eske, 2019, Conti *et al.*, 2016). Mitochondria are the major organelles which are accountable for the generation of energy through oxidative phosphorylation to generate adenosine triphosphate (ATP), a molecule which is crucial for cellular actions (Weinberg *et al.*, 2015).

Antioxidants enzymes neutralize free radicals, however, during critical periods, imbalances can result in free radical generation beyond the neutralizing capacity of the antioxidants, It interferes with signal transduction and controls redox and/or damage to biomolecules such as DNA, proteins and lipids in a process known as oxidative stress. Oxidative stress is broadly defined as an imbalance between pro-oxidative and anti-oxidative processes. Enzymatic and non-enzymatic systems and other compounds with oxidative potential can buffer a wide range of reactive oxidative species. Oxidative stress has been linked to a wide range of adverse biological effects, like adaptive responses and resolution of inflammation. However, the therapeutic potential of antioxidants could be significantly improved through approaches that consider individual and environmental risk factors, rather than comprehensively treating respiratory oxidative stress.

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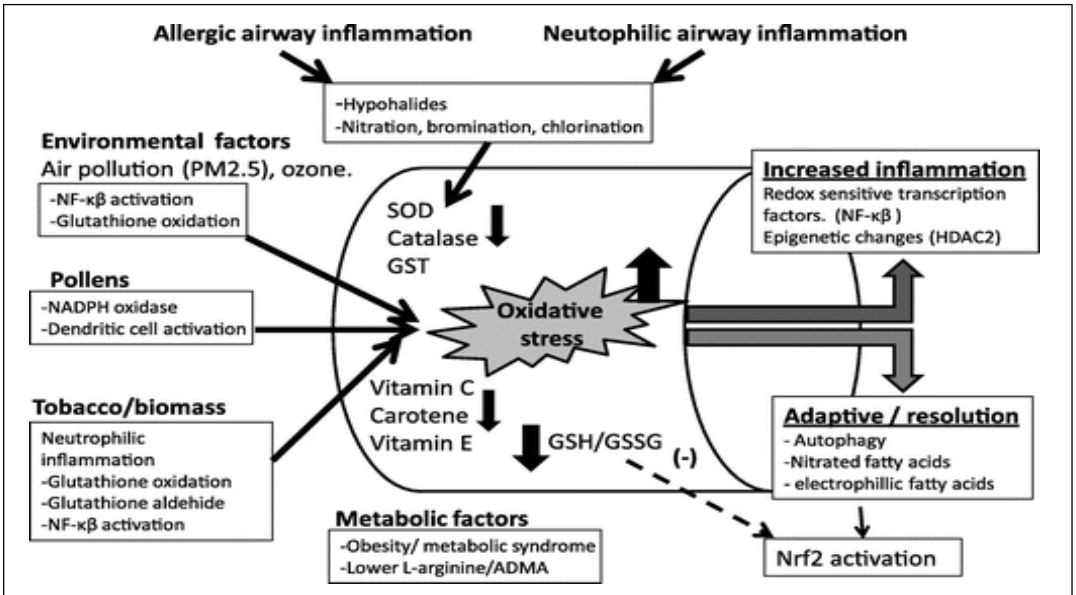
Sources of oxidative stress

One of the best sources for increased oxidative stress is the recruitment of inflammatory cells into the body tissues after exposure to trigger factors; these activated cells can generate anion superoxide (O2.”) through reduced

nicotinamide adenine dinucleotide phosphate (NADPH) oxidase pathway. Mitochondrial dysfunction in epithelial cells, which occurs in response to mechanical and environmental stimuli, can also contribute to the formation of anion superoxide and produced oxidative stress (Reddy, 2011). Anion superoxide is rapidly converted to hydrogen peroxide (H_2O_2) by superoxide dismutase enzymes (SOD). From here, H_2O_2 can react with transition metals to generate hydroxyl radicals (•OH) or, through the action of eosinophil or neutrophil peroxidases, interact with halides to respectively form hypobromous acid (HOBr) or hypochlorous acid (HOCl) (MacPherson *et al.,* 2001). In addition to the formation of these hypohalides, the amount of nitric oxide (NO) produced is increased by upregulation of epithelial-induced nitric oxide synthase (iNOS). In the presence of reactive oxygen species (ROS), NO rapidly forms reactive nitrogen species (RNS), such as peroxynitrite (van Dalen *et al*, 2006). Hypohalides can bromine, chlorinate, or nitrate tyrosine residues, thus affecting protein structure and function. Chlorine, bromine and nitrotyrosine compounds have been identified in many disease processes. These compounds have been shown to amplify the oxidative and inflammatory processes and have been associated with poor control (Wedes *et al*, 2011, Chen and Chiu, 2008,). Proteomic analysis and oxidative modification by nitro- and chlorotyrosine reduces catalase activity and allow more H2O2 to accumulate and further propagate the oxidative reactions (Ghosh *et al*, 2006) (Fig 1).

Oxidative stress results with the generation of ROS and antioxidant strategies *in vivo*. Reactive oxygen species are inevitable as they are formed during normal aerobic metabolic reactions within the mitochondrion. In this regard, spermatozoa, oocytes and embryos depend on mitochondrial oxidative phosphorylation for energy with ROS. Excess ROS distort the antioxidant capacity of cells leading to oxidative stress. Oxidative stress is also associated with detrimental effects of infertility in livestock. ROS have a positive correlation to any form of stress exerted on the animal. Stress has been implicated with the increase of ROS in the male reproductive tract (Agarwal *et al.,* 2005; Tsunoda *et al.*, 2014). Oxidative stress and antioxidant have become an integral part of the many scientific discussions with the issues related to the researches in biosciences. Oxidative stress, free radicals are due to disruption of redox signaling and control (Jones, 2006) which leads to damage of macromolecules such as lipids, proteins, DNA and disruption of normal metabolism and physiology (Trevisan *et al.,* 2001) leading to loss of cell function, cell death or necrosis (Lykkesfeldt and Svendsen, 2007; Nordberg and Arner, 2001).

High ambient temperature and humidity are the major constraint on animal productivity in tropical and subtropical areas. Oxidative stress is indicative of an imbalance between oxidants and antioxidants, methods for quantifying oxidative stress mostly include direct or indirect measures of oxidants and antioxidants (Miller *et al.*, 1993; Lykkesfeldt and Svendsen, 2007). Oxidative stress commonly occurs following heat stress in tropical regions and affects animals, which induces production of Reactive Oxygen Species (ROS). The high production of ROS and a decrease in antioxidant defense, leads to emergence of many diseases including respiratory problems like asthma etc. and onset of number of health disorders. The most abundant free radicals in biological systems are oxygen-centered free



ADMA= Asymmetric dimethylarginine; GSH= Reduced glutathione, GSSG= Oxidized glutathione, HDAC2= Histone deacetylase-2, NADPH= Nicotinamide adenine dinucleotide phosphate, NF-κB= Nuclear factor κB, Nrf2= Nuclear factor (erythroid-derived 2)-like 2, PM2.5= Particulate matter < 2.5 μm; SOD= Superoxide dismutase (Holguin, 2013).

Fig 1: Overview of oxidative stress sources and mechanisms of action.

radicals and their metabolites, commonly referred to as "reactive oxygen metabolites" (ROMs) (Miller *et al*., 1993). ROM is continuously formed as a normal byproduct of cellular metabolism, including protein phosphorylation, transcription factor activation, cell differentiation, apoptosis, oocyte maturation, steroidogenesis, cellular immunity and microbial cellular defense. It is essential at low concentrations for several physiological processes (Fig 2).

Types of free radicals

There are many types of free radicals, but for humans, the most important are oxygen free radicals (reactive oxygen species). Examples include singlet oxygen (when oxygen is "split" into single atoms with unpaired electrons), hydrogen peroxide, superoxides and hydroxyl anions.

Causes/Sources of free radicals

Free radicals can be produced by different ways like they may be generated from normal metabolic processes in the body, or by exposure to carcinogens (cancer causing substances) in the environment.

Free radicals due to normal metabolic processes

Production of free radicals in the process of breaking down nutrients to create the energy and allows body system to do function. The production of free radicals during these normal metabolic processes is one reason why the risk of cancer increases with age, even when there is little exposure to carcinogens (Fig 3).

Oxidative stress biomarkers

Oxidative stress is a condition associated with increased cellular damage caused by oxygen and oxygen-derived oxidants, commonly known as reactive oxygen species (ROS). Uncontrolled generation of ROS that exceeds the antioxidant capacity of cells causes oxidative stress. These ROS damage nucleic acids, proteins and lipids, causing tissue damage and cell death. Stress factors such as heat,

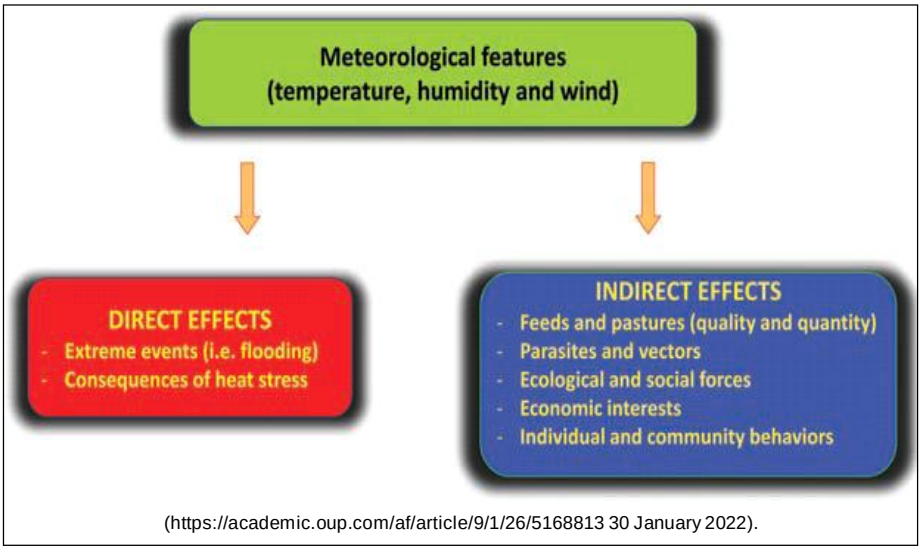


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Fig 2: Schematic representation of some mechanisms through which heat stress may cause metabolic disorders in farm animals.

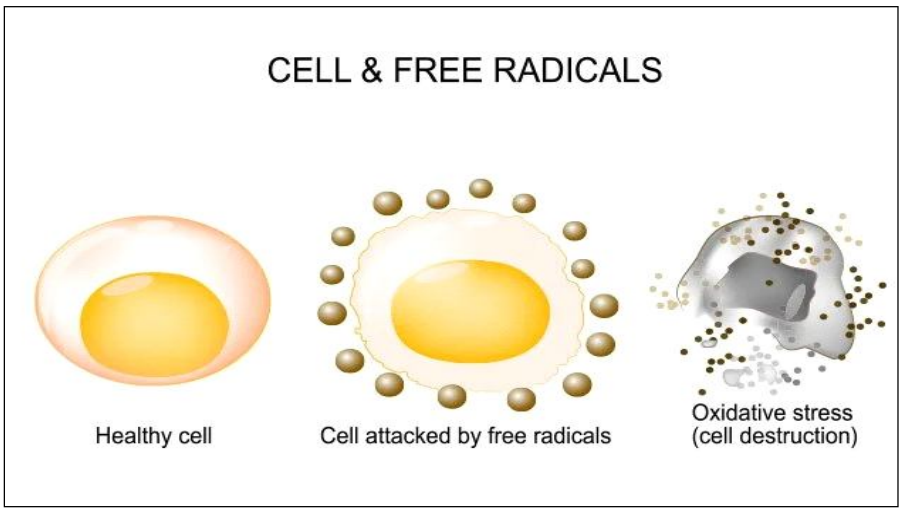

Fig 3: Measurement of oxidative damage.

toxins, UV radiation, inflammation and infections can cause oxidative stress, which can severely impact the function, life and death of affected cells. Oxidative stress can be assessed in three ways: quantification of reactive oxygen species (ROS) and estimation of antioxidant enzymes and redox molecules.

Quantification of oxidants and antioxidants

Oxidative stress represents an imbalance between oxidants and antioxidants. It occurs in the presence of ROS in excess of available antioxidant buffering capacity. A free radical has unpaired electrons in the outer orbital and thus makes the specie unstable with affinity to react with other molecules for stability. Oxidant and antioxidant action can be observed directly by electron spin resonance and indirectly by quantification of dichlorofluorescein, a fluorescent product formed by reaction of non-fluorescent diacetate dye with oxidants. It can be measured by using a fluorescence plate reader, by microscopy or by flow cytometry. Electron spin resonance is not routinely used (Fig 4).

Estimation of the antioxidant enzymes and redox molecules

Changes in oxidative stress biomarkers, including superoxide dismutase, catalase, glutathione reductase, glutathione peroxidase, glutathione levels, vitamins, lipid eroxidation, nitrite concentration, non-enzymatic glycosylated proteins can be estimated. The two most important antioxidant biomarkers are GSH and ascorbate which are capable of regenerating other antioxidants to their active state. Decreased redox ratios of GSH-GSSH or ascorbate-dehydroascorbic acid indicates increased oxidative stress and decreased antioxidant status. The changes in lipophilic antioxidants vitamin E and coenzyme Q may also be measured along with GSH and ascorbate which are also biomarkers of oxidative stress. These compounds can be measured directly by high-performance liquid chromatography (HPLC) and spectrophotometry. Assays are also available to determine the activity of some antioxidant enzymes, such as catalase and superoxide dismutase. The overall antioxidant capacity can be determined by performing various tests like total antioxidant status, total radical-trapping antioxidant parameter, Trolox equivalent antioxidant capacity, ferric reducing-antioxidant power colorimetric assays and cyclic voltammetry.

Measurement of oxidative damage

Measures of oxidative damage have typically focused on the three major macromolecules: DNA, proteins and lipids. Oxidative modifications to DNA include base disincorporation, mutations, DNA strand breaks and cell death. Quantification of oxidized DNA damage is done by COMET assay. It assesses the number of DNA strand breaks in single cells semi quantitatively using gel electrophoresis (Collins, 2004). Oxidized nucleotides and nucleosides can be quantified by HPLC or mass spectrometry. Protein oxidation leads to malfunctioning of enzymes incapable of performing their cellular tasks. Protein oxidation is estimated in terms of measurement of "protein carbonyls", which are produced by free radical mediated oxidation of amino acids. A crude homogenate or a microsomal fraction is reacted with dinitrophenylhydrazine, which gives strong absorbance upon reaction with carbonyl groups (Chevion *et al.,* 2000). Lipid oxidation can be assessed by either the malondialdehyde (MDA) or isoprostane assays. Malondialdehyde is a breakdown product of lipids which can be quantified as a measure of lipid hydroperoxides. Changes in oxidative stress biomarkers, including superoxide dismutase, catalase, glutathione reductase, glutathione peroxidase, glutathione levels, vitamins, lipid peroxidation, nitrite concentration, nonenzymatic glycosylated proteins and hyperglycemia in diabetes is also reported (Meritim *et al*., 2003).

Immunological markers

The immune system is highly sensitive to stress, so immune variables can be used as indicators of stress. Several aspects of immune function are affected by various

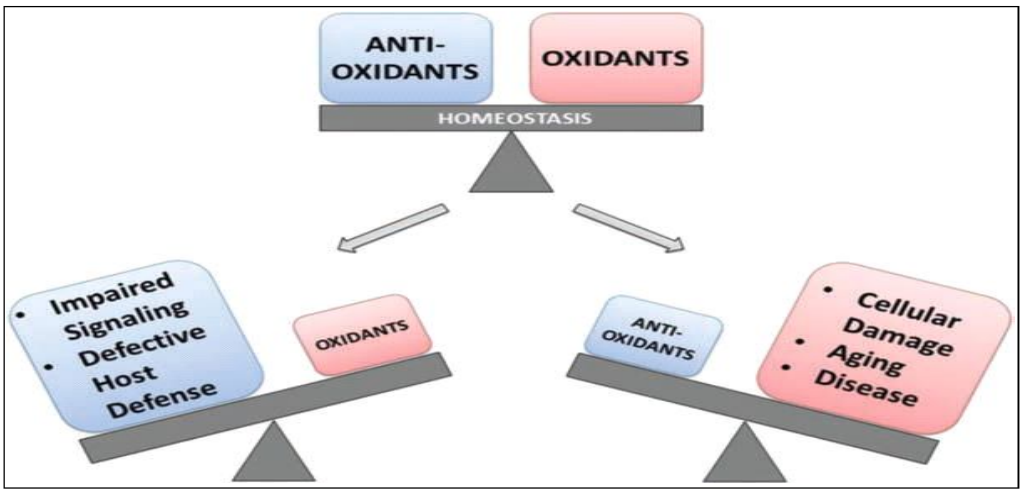

Fig 4: Balance between oxidants and antioxidants molecules in animal health and disease (Knoefler *et al.,* 2014).

stressors, including: B. Movement, transportation, tissue damage, infection, *etc*. Hormones induced response to stress have effect on immune system of animals either by inhibition or proliferation of immune cells. Hormonal changes in response to stress, such as increased plasma concentrations of adrenaline, cortisol, growth hormone and prolactin, are known to have immunomodulatory effects. After stressful events, cortisol levels are known to increase due to activation of the HPA. It has been observed that cortisol can inhibit the function of macrophages, mast cells, neutrophils, basophils and eosinophils. Glucocorticoids and ACTH have been shown to influence B and T cell proliferation, cytokine and antibody production, monocyte and neutrophil chemotaxis and NK cell cytotoxicity (Blalock, 1989). Potential immunological markers in response to stress include lecukocyte responses to antigens, salivary IgA, neutrophil/lymphocyte ratio, CD4/CD8 ratio and plasma cytokines. Strenuous exercise, like exhaustive endurance races in horses may cause detrimental effects on the immune system, by changing the cellular composition of peripheral blood.

Immunoglobulins such as salivary IgA and *in vitro* mitogen-stimulated lymphocyte proliferation are decreased in overtraining syndrome (Mackinnon, 1996, Gleeson, 2002). Neutrophilia and lymphopenia was also reported in cattle which have been transported (Fike and Spire, 2006). Researchers reported a decrease in antibody responses three days after transport and a decrease in lymphocyte blastogenesis in calves after transport. Macrophages and lymphocytes in bronchoalveolar fluid from young calves were changed in number and function after short-term transport (Ishizaki *et al.,* 2005). Neutrophils are also targets of the stress response and are important in lung defense. Neutrophils are also targets of stress responses and are important for lung defense. During weaning stress, neutrophilia was also observed along with changes in the neutrophil-to-lymphocyte ratio, with an increased proportion of neutrophils. Changes in the neutrophil-to-lymphocyte ratio are considered to be potential biological indicators of stress and disease susceptibility. Corticosteroids have been reported to reduce neutrophil accumulation at local sites of inflammation, as neutrophil accumulation is important for the clearance or resistance of bacterial infections. Increased susceptibility to infection and increased disease severity due to altered immune function during stress responses has been demonstrated in many species, including humans, cattle and mice (Mineur *et al*., 2006). The shift in cytokine production causes a shift in T-helper (Th) cells from Th1 cells to Th2 cells. A shift away from Th1 cell-mediated responses may lead to increased susceptibility to viral infection.

Genomic and proteomic markers

The involvement of genetic factors in neuroendocrine stress responses has been shown by selection studies. Different lines for HPA axis functioning have been obtained by genetic selection in poultry, pigs and turkeys (Satterlee and Johnson, 1988). Considerable differences between breeds of pigs have been observed in cortisol levels both in basal conditions and under stress. To understand multiple responses studies are underway to map genomic areas, identify candidate genes, mutations and underlying genetic pathways responsible for such responses. Genomic regions responsible for phenotypic variation in stress conditions have been detected by using Quantitative trait loci (QTL) approach. The gene encoding corticosteroid-binding globulin (CBG), carrier of cortisol in plasma, had been mapped at chromosome 7 in Meishan and Large White crosses (Desautes *et al*., 2002). Mutations in this gene have been found to influence cortisol levels, carcass composition and meat quality in pigs. Phenotypic variation is not only associated with mutations but significant differences are also attributed to alterations in expression levels of clusters of genes. Nowadays, microarrays, serial analysis of gene expression allow the measurement of expression of thousands of genes at the same time in different tissues and provide unique possibilities to expedite large-scale analyses of gene expression. Differential trends of protein, metabolite and element profiles were observed following a stress response by multivariate analysis. Proteomics profile analysis in rat liver has also been used to unravel the molecular mechanisms involved in the cellular responses to ionizing radiation (Marco *et al.,* 2011).

Prevention of oxidative stress

Everybody has natural defenses against oxidative stress and cell damage:

- Physical barrier (intact skin and epithelium) that protects against free radicals.
- Oxygen-neutralizing enzymes to counteract free radicals.
- Antioxidants that help repair damage caused by free radicals.
- An imbalance of free radicals in the body can cause damage that overwhelms the body's defenses. If left unchecked, oxidative stress can wreak havoc within the body and cause serious health problems. You can limit the damage caused by oxidative stress by:

• Avoid stressors

If possible, avoid situations that cause physical or mental stress. Avoid processed foods, air pollution and other toxins in your environment. Wash your hands especially during cold and flu season.

Reduce stress

If stressors cannot be avoided, try to reduce their impact on your body by practicing good sleep hygiene, practicing deep breathing and meditation and exercising regularly.

• Strengthen your immune system

Increase your intake of fresh fruits and vegetables, herbs, vitamins and phytonutrient supplements to stimulate your immune system and build your body's natural defenses.

To combat all these ill effects antioxidants are well known feed additives to elongate shelf life of feedstuffs via preventing lipid peroxidation. Dietary antioxidants and those circulating *in vivo* have their effect on scavenging free radicals and preventing the formation of ROS, hence combating oxidative stress in livestock production. This helps to promote health, wellbeing and efficiency of each livestock unit. The food industry has also acknowledged the significance of antioxidant supplementation in livestock. Nutritional, organoleptic properties and shelf life qualities of animal products from animals subjected to antioxidant supplementation showed an improvement compared to none antioxidant beneficiaries (Salami *et al.*, 2016).

Antioxidants

Antioxidant are broadly defined as substances which delays, prevents or removes the damage caused by the oxidative stress (Halliwell, 2007). The cellular antioxidant defense mechanism is divided into three levels according to their functions (a) quenching oxidants, (b) repairing/removing oxidative damage or (c) encapsulating non repairable damage (Lykkesfeldt and Svendsen, 2007). Antioxidants are molecules that can donate electrons to oxidants, thereby suppressing their reactivity and making them harmless to macromolecules. The whole antioxidant system is under homeostatic control. However, when metabolic reactions are overloaded, accumulation of free radicals may lead to disturbance of redox homeostasis resulting in oxidative stress (Celi, 2011) which will result in various diseases and reduced animal performance. Number of studies also support the concept that oxidative stress increases the susceptibility of animals like cows (Celi *et al*., 2012; Pedernera *et al*., 2010; Sharma *et al*., 2011), buffaloes (Dimri *et al*., 2010) and small ruminants (Po *et al.,* 2012) to many diseases (Bernabucci *et al.,* 2002, 2005; Castillo *et al*., 2005; Sordillo and Aitken, 2009), explained the importance of antioxidants for the ruminants during different physiological stages.

Antioxidant defenses

Antioxidant protection

Antioxidants interrupt radical chain reactions and prevent damage caused by oxidative stress (Da Pozzo *et al.,* 2018). Their chemical structure is highly heterogeneous as they need to function in both hydrophilic and hydrophobic cellular environments. There are enzymatic and non-enzymatic antioxidants, but from a nutritional perspective, a more informative classification can be made between endogenous and exogenous classes. All enzymatic antioxidants are endogenous, along with some non-enzymatic ones (thiols antioxidants and coenzyme Q10). Exogenous antioxidants are provided with the diet, since their synthesis is impossible in eukaryotic cells. Antioxidants can be classified into two categories depending on their solubility: water-soluble and fat-soluble. (Lazzarino *et al.,* 2019) (Fig 5).

Water-soluble antioxidants

Are best absorbed by the body because vegetables and fruits that contain water-soluble antioxidants also contain water. These are quickly excreted from the body through urine. Water-soluble antioxidants include polyphenols, vitamin C, uric acid and glutathione (Lazzarino *et al*., 2019).

Lipid-soluble antioxidants

Are absorbed in the presence of fat. Without fat, the body cannot absorb and use these antioxidants. These are difficult to remove from the body and can accumulate over time and exceed healthy levels. Vitamin E is an example of a fat-soluble antioxidant (Lazzarino *et al*., 2019).

Endogenous antioxidants

Endogenous antioxidants are divided into three major groups (Miller *et al.,* 1993). The first group comprises enzymatic antioxidants including superoxide dismutase (SOD) and glutathione-peroxidase (GSH-Px), are the main form of intracellular antioxidant defense. Plasma GSH-Px activity contributes to the oxidative defense of animal tissues by

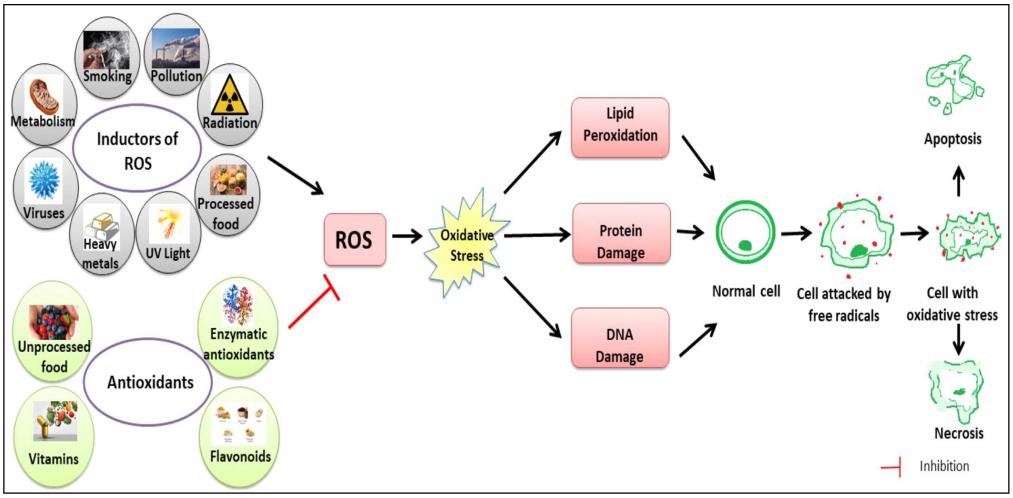

Fig 5: Link between ROS, oxidative stress and their effects (Da Pozzo *et al*., 2018).

catalyzing the reduction of hydrogen and lipid peroxides (Halliwell and Chirico, 1993, Cassia *et al*., 2018) and also an indicator of oxidative stress (Tüzün *et al*., 2002). GSH-Px functions in cellular oxidation–reduction reactions to protect the cell membrane from oxidative damage caused by free radicals (Lu *et al*., 2016). SOD catalyzes the dismutation of superoxide to hydrogen peroxide (H_2O_2) and it is considered the first defense against pro-oxidants (Halliwell and Chirico, 1993) (Fig 6).

The second group includes non-enzymatic protein antioxidants that are primarily found in plasma. They are mainly represented by sulfhydryl (SH) groups of albumin and are considered as a significant element of the extracellular antioxidant defense system against oxidative stress. The reducing properties of SH residue are known to be oxidized under oxidative stress and other physiological conditions. Total thiol groups of plasma represent the SH groups of albumin, L-cysteine and homocysteine. Under physiological conditions, SH groups are the most chemically reactive sites and have strong reducing properties (Tan *et al*., 2018, Deters and Hensen, 2020) (Fig 7).

The third group is represented by thenon-enzymatic low-molecular-weight antioxidants and it is found mainly in plasma but also in other extracellular and intracellular fluids. The main antioxidant capacity of serum is based on non-enzymatic antioxidants such as glutathione, α-tocopherol, β-carotene and uric acid. GSH plays a particularly important role in protecting cells from oxidative stress and toxic substances. It acts as substrate or co-substrate in enzymatic reactions and also reacts directly with free radicals and lipid peroxides (Briviba and Sies, 1994). Similarly, vitamin E being the major lipid soluble antioxidant in all cellular membranes, plays an important role in protection against lipid peroxidation by directly scavenging oxy-radicals, super-oxides and singlet oxygen, where as selenium, an integral component of glutathione peroxidase, is important for decomposition of hydrogen peroxide and lipid peroxides (Machlin and Bendich, 1987).

During different transition phases in dairy cows, they undergo substantial metabolic and physiological adaptations which contribute to the stress and immune responses of the host (Sordillo and Aitken, 2009). There is increased oxygen requirement to cope up with these physiological stresses. This increased utilization of oxygen leads to the production of free radicals and augments the oxidant status of the animal (Sordillo and Aitken, 2009). Heat stress accelerate the oxidative stress in transition dairy cows. Tanaka *et al.* (2011) investigated changes in plasma concentrations of oxidative stress markers in perinatal dairy cows under high temperature conditions and suggested that oxidative stress increases in cows after parturition under hot climatic conditions. In dairy goats also the redox homeostasis is impaired during the peripartum period, as they experience moderate oxidative stress (Celi *et al.,* 2008, 2010) and the summer season had a more pronounced effect on the oxidative stress markers than nutritional factors (Di Trana *et al.,* 2006). Environmentally induced periods of heat stress impairs production (growth, meat and milk yield and quality), reproductive performance, metabolic and health status and immune response of animals (Nardone *et al*., 2010). Heat stress induced economic losses, are not only associated with the declined milk production, but are also contributed by the poor health status, increased incidence of disease sand high mortality. Sheep exposed to heat stress

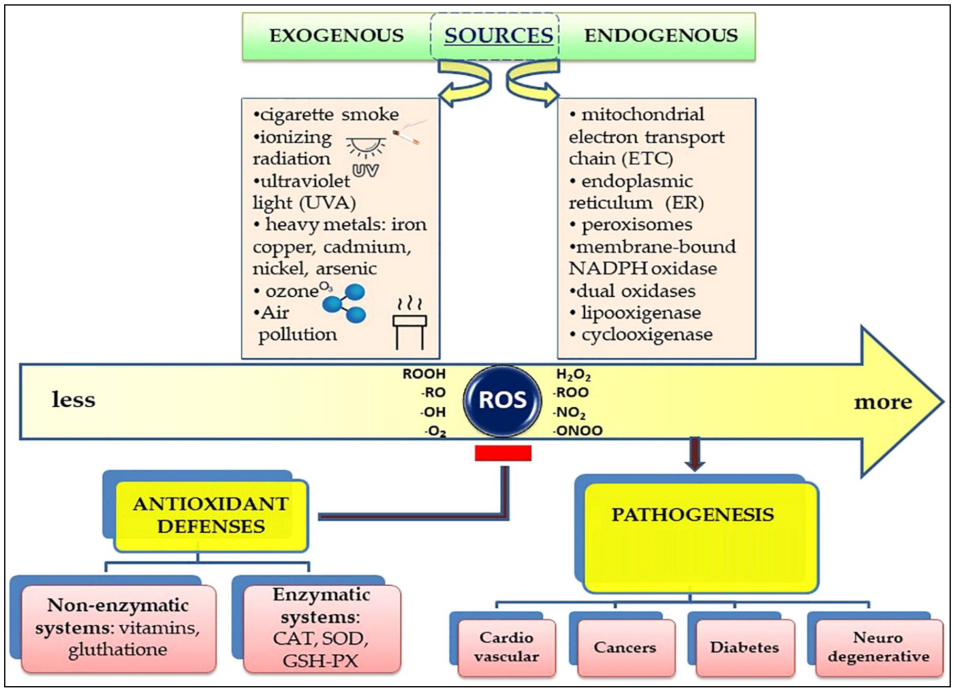

Fig 6: Schematic presentation of the sources of free radicals and their effects (Sharifi-Rad *et al.,* 2020).

in controlled climatic chambers, have demonstrated that heat stress induces oxidative stress and these effects can be ameliorated by supplementation of physiological doses of selenium and vitamin E (Chauhan *et al.,* 2014). Therefore, manipulation of oxidative stress during the transition period by supplementation of ruminants' diets with antioxidants under heat stress improved the health and productivity. Feeding of balanced diets to meet the specific requirements is necessary for efficient animal production. Supplementation of poultry diets with antioxidants and with selenium played an important role in maintaining bird's health and production (Surai, 2016). Growth is a trait that is affected by the intake of dietary antioxidants (Catoni *et al.,* 2008). The high metabolic rate of growing tissues produces large amounts of free radicals that if they are not safely removed by antioxidants, may lead to oxidative stress. Therefore antioxidant supplementation may help to counter negative effects of oxidative stress associated with growth also.

Antioxidant supplementation in farm animals

Some of the vitamins and minerals provided by grazing in herbivores has many health benefits. Fresh forages are considered to supply adequate levels of antioxidants for dairy cattle, but the availability of these compounds diminished when pasture is not adequately available to meet their energy requirements for lactating grazing cows. Silage is known to be low in antioxidants (Ballet *et al.,* 2000) and can therefore expose cows to oxidative stress. When sheep graze autumn pastures, wide spread subclinical vitamin E deficiency has been reported especially in weaner flocks (White and Rewell, 2007). The evaluation of oxidative stress in ruminants is significantly contributing to under-stand the fundamental processes involved in metabolic disorders. Oxidative stress is played an important role in the regulation of the metabolic activity of some organs and productivity in farm animals (Celi, 2011). However, it is not clear whether or not the level of oxidative stress during the peripartum period could compromise animal performance. For example, several studies have reported variable levels of oxidative stress during the peripartum period in dairy cows (Pedernera *et al.*, 2010) and goats (Celi *et al.*, 2010a). Reactive oxygen metabolites and antioxidants may be involved in some physiological functions (Gabai *et al*., 2004) and thus, the supplementation of cows' diets with antioxidants might result in an improvement of their oxidative status and productive performances.

Vitamin E and selenium supplementation

Vitamin E supplementation has been used in ruminants to improve reproductive performances (Horn *et al.,* 2010), antioxidant (Wang *et al*., 2023) and immune status (Spears and Weiss, 2008), to reduce the incidence of mastitis (Giadinis *et al*., 2011;) either in combination with selenium (Brozos *et al.,* 2009; Sathya *et al*., 2007) or alone (Bouwstra *et al*., 2008). Supplementation of vitamin E and selenium to calving buffaloes appears to help reduce oxidative stress (Dimri *et al.,* 2010). Dietary supplementation of vitamin E during heat stress, improved immune response (Niu *et al*., 2018), performance (Panda *et al.,* 2008) and reduce transportation stress in poultry (Ajakaiye *et al*., 2010). Supplementation with vitamins E and C during pregnancy in sheep reared at high altitudes prevents oxidative stress and improves pregnancy outcomes (Parraguez *et al*., 2011). Ali *et al*. (2021, 2017) and Bakar *et al.* (2021) reported that vitamin E alone or in combination with selenium improved semen characteristics and reproductive performance of Awassi rams during the hot season. Sivakumar *et al.* (2010) has been observed an improvement in acid base status and protection against heat stress in Vitamin E supplemented goats. Vitamin E supplementation can be achieved by adding synthetic (All-Rac-á-tocopherol acetate) or natural (RRR-á-tocopherol acetate) forms of vitamin E (Horn *et al*., 2010), either in diet or by parental route (Awawdeh *et al*., 2019).

The dietary of antioxidant nutrients is important in protecting tissues against free radical damage, since free radical reactions are the integral part of normal metabolism. The antioxidant function enhances immunity by maintaining the structural and functional integrity of immunity system. Antioxidant status provides complementary information about the metabolic status of the animal as well as metabolic

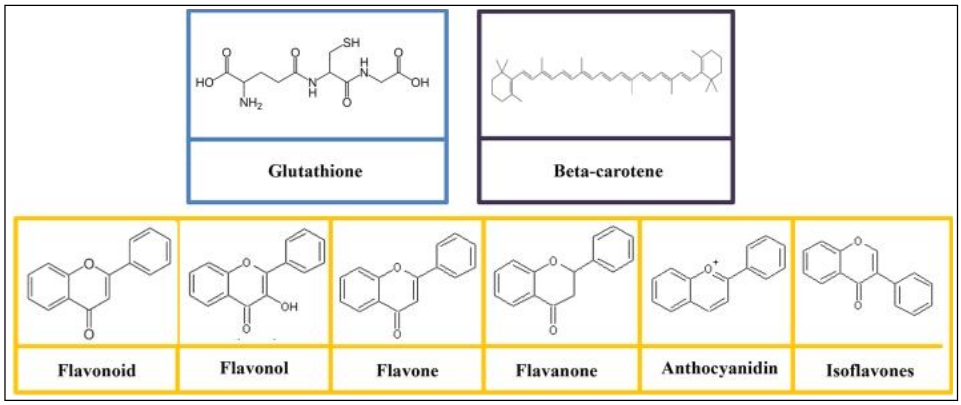

Fig 7: Molecular structures of glutathione, polyphenols (flavonoid, flavonol, flavone, flavanone, anthocyanidin and isoflavones) and beta-carotene (Tan *et al.*, 2018).

parameters. Oxidative stress markers can be divided into non enzymatic antioxidants and antioxidant enzymes such as Superoxide Dismutase (SOD), catalase and glutathione peroxidase. The important role of some antioxidants like glutathione, Adenosine-Tri Phosphate (ATP) and cholinesterase enzymes activities in relation to heat stressed animals was reviewed.

CONCLUSION

Antioxidants are a necessity, they scavenge and prevent the formation of ROS. Products of lipid peroxidation such as MDA are detoxified by antioxidants. Antioxidants play a key role in ensuring a positive animal reproductive function and efficacy. Use of enzymatic and non-enzymatic antioxidants in animal production has seen a positive increase in livestock fertility. There is evidence that ROS are a predominant cause of oxidative stress a challenging condition which is implicated in lowering a range of reproductive processes, they have some important roles that they play. Reactive oxygen species serve as key signal molecules in physiological processes up to a certain point beyond which they become toxic in the body hence commence pathological processes. It is therefore commended to optimally supplement antioxidants to control ROS as over supplementation tends to impair ROS positive functionality. To realize the full benefits of antioxidants in animal production, antioxidant dosage and timing of supplementation should be taken into consideration. For instance in reproductive females, antioxidant defense demands differ from gametogenesis up to the periparturient period. Therefore antioxidant supplementation is determined by a thread of genetic and non-genetic factors which influence the total antioxidant status in an animal system.

Conflict of interest

The authors declare that there is no conflict of interest.

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