CRIMSON PUBLISHERS
Wings to the Research

Advances in Complementary & Alternative medicine

ISSN 2637-7802

Opinion

Role of Antioxidants in Management of Mastitis in Dairy Cows

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Submission: : May 25, 2018; **Published:** January 03, 2019

Introduction

Mastitis (Greek, mastos- breast; itis- inflammation) is inflammation of parenchyma of mammary glands regardless of the cause and is characterized by a range of physical, chemical and bacteriological changes in milk and pathological changes in glandular tissues. It is the reaction of udder tissues to injury produced by physical force; chemicals introduced into the gland, most commonly from bacteria, their toxins and other microorganisms. The incidence of mastitis is an outcome of interplay between the infectious agents, poor management practices, genetic and environmental factors which stresses the defense of udder. Both clinical mastitis and subclinical mastitis produce great economic losses. At present mastitis is single, largest and the costliest disease of dairy animals in terms of economic losses in India. In India the economic loss due to mastitis is about 57.5 crore per annum which can be ascertained from the estimation that mastitis reduces milk yield (up to 70%) milk discard after treatment (9%), cost of veterinary services/care (7%) and premature culling (14%). In addition to the economic loss, the consumption of mastitis affected milk poses major public health hazard to the whole humanity. The diseases viz, Tuberculosis, streptococcal sore throat, brucellosis, and food poisoning may spread by consumption of raw (unpasteurized) milk.

Staphylococcus aureus and Streptococcus agalactiae are most common cause of contagious mastitis whereas; Mycoplasma bovis and coagulase- negative staphylococci are a less common. Environmental mastitis is mainly associated with three groups of pathogens, the coliforms (particularly E. coli, Enterobacter sp., Serratia sp. and Klebsiella spp.), environmental Streptococcus spp (Streptococcus uberis and Streptococcus dysgalactiae and Arcanobacterium pyogenes. Infection of the mammary gland always occurs via the teat canal and the development of mastitis is more complex. In clinical mastitis the most important changes in the milk include discoloration, the presence of clots and the presence of large numbers of leukocytes as well as swelling, heat, pain and edema in the mammary gland. However, subclinical mastitis has no apparent clinical signs but accompanied with elevation of somatic cells count (SCC) in milk. The incidence of subclinical mastitis is more in India than clinical mastitis; therefore the economic losses in terms of decreased/altered milk yield and quality cannot be directly visualized. The SCC in milk is considered as a well-known indicator that reflects milk quality and health status of mammary gland. Excessive amount of neutrophils, epithelial cells, macrophages, lymphocytes and eosinophils in milk is considered as indicative of response of mammary tissue to microorganisms.

Oxidative stress in mastitis

Oxidative stress is generally described as an imbalance between oxidant and antioxidant levels. When the production of oxidants exceeds the capacity of antioxidant defense, a condition of oxidative stress is produced resulting in oxidative damage to macromolecules such as lipids, DNA and proteins. Mastitis induces the increase of free radicals formation in milk and leading to oxidative stress, especially during the early lactation period of dairy cows. During lactation, mammary epithelial cells exhibit a high metabolic rate and thus produce large amounts of reactive oxygen species (ROS) and lipid peroxides in vivo. ROS is a collective term used for a group of oxidants, which are either free radicals or molecular species capable of generating free radicals. Intracellular generation of ROS mainly comprises superoxide ($O_{2}^{\cdot -}$) radicals and nitric oxide ($NO^{\cdot}$) radicals.

Milk with higher SCC is positively associated with malondialdehyde (MDA) level in milk, and the mean level of MDA is significantly higher in subclinical mastitis milk than in normal milk, consequently more free radicals being released and a stat of oxidative stress arise. Also, phagocytic granulocytes undergo respiratory bursts to produce oxygen radicals to destroy intracellular pathogens. However, these oxidative products can, in turn, damage healthy cells if they are not eliminated. Oxidative stress is initiated by reactive oxygen species (ROS), such as superoxide anion (O-2), perhydroxy radical (HOO-) and hydroxyl radical (HO·), as a byproduct of electron transport in mitochondria. The increase in ROS or decreased antioxidant availability can result in a net increase in intracellular ROS and hence cause extensive tissue damage leading to various degenerative diseases. The mechanism behind these diseases is lipid peroxidation of the membrane lipids, damage of DNA, lipoprotein, protein, etc. by excess ROS.

Nitric oxide (NO) is one of the most important reactive nitrogen intermediates, which operates in a variety of tissues to regulate a

diverse range of physiological processes including inflammatory response. During inflammation, epithelial cells and macrophage of mammary gland produce a significant amount of NO; this inducible NO mediates inflammation during mastitis. Another source for NO is the mammary epithelial cells and/or mononuclear phagocytes, which contribute to NO production upon stimulation with lipopolysaccharide and cytokines.

Role of vitamins and trace minerals as antioxidants in mastitis

The cells contain a variety of antioxidants that play an important role in the protection against excessive release of ROS in blood and tissues including the udder tissue and milk in mastitis. Antioxidants protect the body from free radicals either by directly scavenging free radicals or by inhibiting the activity of oxidizing enzymes. Due to the substantial background exposure to oxidants resulting from a life depending on molecular oxygen, aerobic organisms have adapted to constantly fighting a battle against oxidative stress. Advanced cellular defense strategies have evolved and gradually expanded the possible lifespan for the individual species. The cellular defense mechanisms can be divided into three levels according to their function of quenching oxidants, repairing/removing oxidative damage or encapsulating non-repairable damage.

As a first level of defense against oxidants, the cell is equipped with a so-called antioxidant network. Antioxidants are capable of donating electrons to oxidants, thus quenching their reactivity under controlled conditions and making them harmless to cellular macromolecules. A second and highly important level of defense is the ability to detect and repair or remove oxidized and damaged molecules. Finally, if the extent of the oxidative damage exceeds the capacity of repair and removal, the organism is equipped with one final weapon, controlled cell suicide or apoptosis. The ability to induce programmed cell death is of major importance in a variety of bodily functions, including control of tissue growth, and is apparently under control by several signaling pathways. However, one of these appears to be that apoptosis is induced by increased oxidative stress and thus constitutes a final resort to encapsulate and isolate the damaged cells.

Most living species have efficient defense systems to prevent themselves against oxidative stress. Innate defense system of the body some time may not be sufficient for curing the damage caused by continued oxidative stress. Thus, there is a need to supply the antioxidants exogenously to balance their levels in the body. External supplementation of antioxidants is recommended in such cases to protect cells from the deleterious effects of oxidative stress. Antioxidants are compounds that prevent the oxidation of essential biological macromolecules by inhibiting the propagation of the oxidizing chain reaction. Vitamins and minerals have long been recognized as antioxidants in the animal health and production. However, they also have specific roles in mastitis of dairy animals, such as vitamin A and β-carotene, vitamin C, vitamin E, vitamin D, selenium, Zinc and copper. Deficiency of them leads to increased incidence of mastitis with infection of longer duration and more severe clinical signs. Supplementation of antioxidant vitamins and trace elements stabilize the highly reactive free radicals generated as a result of oxidative stress during mastitis thereby they may reduce inflammatory response and; maintain the structural and functional integrity of cells.

Vitamin A and its precursor- β carotene play vital role in maintaining epithelial tissue health. They also help in maintenance of integrity and stability of mucosal surfaces; therefore build a resistance to the entry of pathogens into attenuating the mammary gland. Vitamin A as well as β carotene have stimulatory effects on immune cell, improving immune function, reduces the effect of oxidative stress. β carotene has an antioxidant property, reducing superoxide formation and it protects udder tissue and milk from the harmful effect of free radicals. It has been reported that the cows with higher California Mastitis Test (CMT) scores had significantly lower plasma Vitamin A and β carotene concentrations in comparison to the cows with CMT scores indicating no mastitis.

Ascorbic acid (vitamin C) is the most important water-soluble antioxidant for mammals. Though it can be synthesized in the body of most mammals except primates and guinea pigs, thus, it is not a required nutrient for dairy cows. In bovine mastitis, it has been identified as oxidative stress biomarkers. The cows suffering from mastitis have lower concentrations of vitamin C in their milk and plasma. The number of the leukocytes per milliliter blood is correlated positively with vitamin C content of plasma. The severity of clinical signs is related with magnitude of the decrease in concentrations. Ascorbic acid scavenges aqueous reactive oxygen species by rapid electron transfer, thus inhibiting lipid peroxidation. Decreased concentration of ascorbic acid has been recorded from mastitis milk of cows. Many studies had been reported that its milk concentration significantly decreased in acute mastitis and subclinical mastitis especially when the condition is accompanied by an increase in the levels of lipid hydroperoxide in erythrocytes. Ascorbic acid along with cupric ions has been found successful in prevention and treatment the mastitis of dairy cows as teat dip or intramammary infusion.

Vitamin E is the most important lipid soluble antioxidant, and its biologically active form is known as α-tocopherol. It is an integral component of lipid membrane and has an important role in protecting lipid membranes from damaging effect of reactive oxygen. It also enhances the functional efficiency of neutrophils by protecting them from oxidative damage following intracellular killing of ingested bacteria. The role of vitamin E in mastitis is that it acts as a lipid soluble cellular antioxidant, free radical scavenger, and protects against lipid peroxidation. The deficiency of vitamin E is frequently observed in peripartum dairy cows. Most cases of clinical mastitis occur during the first month of lactation and originate in the dry period and coincide with the lowest Vitamin E blood concentration. It is suggested that maintaining an optimal vitamin E level, together with low levels of oxidative stress is an important factor in dry cow management and improvement of udder health.

How to cite this article: Neelam K, Anand M. Role of Antioxidants in Management of Mastitis in Dairy Cows. Adv Complement Alt Med. 3(3). ACAM.000563.2019.DOI: 10.31031/ACAM.2019.03.000563

Selenium (Se) is an essential trace element for domestic animals; the majority of Se in body tissues and fluids is present as selenocysteine, which is incorporated into general proteins and acts as a biological pool for Se. It is an essential component of the glutathione peroxidase (GSH-Px), which is responsible for reduction of H_2O_2 and free O_2 to H_2O. It also plays a very important role in protecting both the intra- and extra-cellular lipid membranes against oxidative damage. The activity of GSH-Px in milk varies with the species and ration. GSH-Px catalyzes the reduction of various peroxides, protecting the cell against oxidative damage and protects milk lipids from oxidation. Vitamin E and Se supplements in ration have a preventive effects against acute mastitis in which high polymorphonuclear response occur. Se supplementation to periparturient cows reduces the incidence and severity of mastitis and it is thought to be due to the actions of certain antioxidant Se-dependent enzymes.

Zinc (Zn) is a vital trace mineral and an integral component of more than 300 enzymes involved in metabolism. It plays an important role in cell growth, cell replication, gene expression, bone formation, skin integrity, cell-mediated immunity and host defense. It is very much needed to maintain the integrity of the keratin that lines the streak canal of mammary gland. Cell mediated immunity has been found to be altered by Zn deficiency, as its deficiency is associated with reduced formation of both T and B lymphocytes, and phagocytes. Zn is also involved in the removal of free radicals by superoxide dismutase (SOD). Extracellular and cytosolic SOD requires both Zn and Cu. Zinc is required for the formation of Mn-Zn SOD. Deficiency of Zn affects the activity of SOD in blood and tissues, which results in increased superoxide radicals. It is also required for the hepatic synthesis of retinol-binding protein, which transports Vitamin A in the blood. It is well known fact that, mastitis is associated with increased SCC in milk, which acts as a source for free radicals and hence oxidative stress. Low level of Zn leads to low quality milk with high SCC and increased incidence of mastitis.

Copper (Cu) is an integral component of ceruloplasmin, which facilitates iron absorption and transport. It is also an important part of SOD, an enzyme that protects cells from the toxic effects of oxygen metabolites produced during phagocytosis. Its deficiency in cattle is generally due to the presence of dietary antagonists, such as sulfur, molybdenum and iron that reduce Cu bioavailability. As a modulator of the inflammatory process, ceruloplasmin serves as an acute-phase protein. Acute phase proteins rise in the blood with infection and other inflammatory events. In clinical mastitis there is significant decrease in blood SOD and catalase activities, reduced glutathione (GSH) concentration and an increase in erythrocytic lipid peroxides occurs. The enzyme SOD, present in the cytosol of cells and extracellularly, is Cu and Zn dependent. Without the presence of SOD, superoxide radicals can form more destructive hydroxyl radicals that damage both unsaturated double bonds in cell membranes, fatty acids, and other molecules in cells. Therefore, SOD assumes a very important protective function. Experimental studies have approved that Cu supplementation reduces the severity of clinical signs of E. coli mastitis.