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REVIEW ARTICLE

Use of Organic Minerals as Immune System Stimulants in Transition Dairy Cows: A Mini-Review

Abdur Rahman[1], Hafiz Muhammad Usman Siddiq[1,*], Abuzer Ali[2], Zafar Hayat[1], Akhtar Rasool Asif[1] and Ismail Bayram[3]
[1]Department of Animal Sciences, University of Veterinary and Animal Sciences, Lahore (Jhang Campus)-Pakistan
[2]Primary and Secondary Health Care Department, Jhang (Punjab), Pakistan
[3]Department of Animal Nutrition and Nutritional Diseases, Faculty of Veterinary Medicine, Afyon Kocatepe University, Turkey.

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***Corresponding Author:**
usmansiddiq923@yahoo.com

ABSTRACT

Dairy farming is based on high milk yield, efficient breeding performance, decreased morbidity rate and minimal health disorders. Once the animals suffer from any disorder, it takes much time to resume milk production and may lead to a higher incidence of reproductive failure. A lot of research work has been done to improve dairy animals' nutrition and management practices to minimize and/or prevent the occurrence of any disorder in dairy cows to make dairy farming a profitable business. Cow health during the transition period plays an important role in the future productivity and health status after calving. Physiological stress during the transition period may alter the immune status of the dairy cow which makes it more susceptible to infectious diseases, impairment of reproductive performance as well as milk production. In this connection, the use of humates and some organic minerals in dairy cow's feed proved to play a key role in enhancing the immune status which results in better performance and reduced incidence of diseases. This review focused on the perspective and advantages of organic minerals and humates feeding in dairy cattle.

INTRODUCTION

The transition period is defined as either side of calving (three weeks prepartum to three weeks postpartum). The term transition accentuates the importance of metabolic, physiological and nutritional transformations during this time frame, which endows them for lactational inception and peak milk yield. The occurrence of health issues during the transition period is a major complicating factor for impairment of subsequent reproductive efficiencies which emphasizes the management and nutritional practices. Three weeks prepartum to three weeks postpartum are critical periods characterized by tremendous suppression of the defense system leading to reduced ability of a cow to combat the diseases (Waldron, 2010). The constituents of immunosuppression incorporate oxidative stress, negative energy balance, non-esterified fatty acids, ketones and calcium status (Sordillo, 2009; Waldron, 2010). The pre-eminent process in which trace elements influence the defense status is through their activity as antioxidant nutrients alleviating oxidative stress. More precisely, trace minerals have a fundamental role in animal's ability to intercept free radical formation (hydrogen peroxide, superoxide, hydroxyl radical, fatty acid radicals) by assembling in the cell and motivating oxidative cell death.

The hormonal transformations lead to immunosuppression in the periparturient period and make them more susceptible to mastitis and other infectious disorders. Immunosuppression is more commonly manifested by a decline in T-cell population and function, lymphocyte receptivity towards mitogen activation, antibody response and cytokine production (Mallard et al., 1998; Kehrli et al., 2006). The three most common disorders associated with a weakened immune system are mastitis, metritis and retention of the placenta. Along with this, oxidative stress is a contributing factor in elevating the disease predisposition. Abrupt changes in metabolic parameters linked with transition from the dry period to calving and calving to early lactation enhance the formation of free radicals that generate oxidative stress. When reactive oxygen radicals inundate the antioxidant defense mechanism, they lead to oxidative stress. Polyunsaturated fatty acids present in cell membranes of immune cells make them oversensitive to oxidative stress, because of their oxidation by free radicals, leading to more reactive oxygen radicals.

Impact of minerals during the transition period

A mineral is a naturally occurring inorganic substance with definite chemical composition and a regular internal structure.

There are two divisions of minerals based on their requirement in the body of dairy cattle per day:

a. Major minerals (macrominerals >100ppm) including Calcium, Sodium, Chlorine, Magnesium, Potassium and Sulphur.
b. Trace minerals (microminerals <100ppm) including Copper, Iron, Manganese, Molybdenum, Zinc, Chromium, Selenium, Silicon.

During the transition period, the animal undergoes physiological transformations leading to mineral deficiencies that result in immunosuppression. Due to the increased demand for production on dairy cattle, some metabolic disorders may also occur such as milk fever, post-parturient hemoglobinuria. Moreover, mastitis, metritis, infertility issues can also be seen in neglected cases. These pathologies may be associated with deficiency of minerals during the transition period which is critical in dairy cattle production (Solda et al., 2017). Minerals maximize the immune response of dairy cows during the transition period and are critical in minimizing health problems during early lactation (spears and Weiss, 2008). For the integrity of the immune system, blood formation, structure of hormones, reproductive performance and enzyme formation, microminerals are required. These microminerals are added in dairy feed and their application is expressed in ppm per day of animal (Warken et al., 2018).

The accurate subsidiary of different macro and microminerals can elevate cow's defense systems to combat disorders like mastitis, milk fever, ketosis etc. both by increasing the resistance and reducing the extremity of infections/problems during occurrence (Bordignon et al., 2019).

Minerals and Immunity

The immune system is the animal's defense system against pathogens and any foreign molecules that may enter the body. The immune system is responsible for recognizing, resisting, and eliminating health challenges, including pathogens, injuries, parasites, and stress. A competent immune system is fundamental for optimal cattle performance. In general, the immune system can be separated into two components (Abbas et al., 2007).

1. Humoral immune response
2. Cell-mediated immune response

Changes and nutritional deficiencies during the transition period lead to immunosuppression by decreasing T- and B-lymphocytes population. Dairy animals who have encountered any kind of major or minor stress or who are at the risk of disease, having any reproductive issues are the bull's eye for minerals deficiencies.

Functions of trace minerals

Minerals as immunomodulators play a vital role in boosting cow's immunity during the transition period.

Selenium: is an important constituent of a wide domain of selenoproteins that consist of iodothyronine deiodinase, thioredoxin reductase and glutathione peroxidase. Selenium (Se) inclusion rate in the total mixed ration is 0.3 ppm in total diet of high producing cattle like Holstein Friesian (Faccenda et al., 2020).

Zinc: being crucial to catalytic and regulatory activity is the second most plenteous micromineral in mammalian and avian species. Zinc (Zn), being a fundamental part of the indispensable enzyme superoxide dismutase has a basic role in antioxidant defense (Underwood, 1999; NRC, 2001). The role of Zn has also been indicated in the release and working of the hormone Somatomedin-c. The Zn is included in the ration with 40 to 60 ppm in the total diet of Holstein Friesian cows (Adab et al., 2020). Functions of Zinc are

a. Cell division and formation of nucleic acids
b. Defensive role
c. Epithelial tissue maintenance and keratin formation
d. Fundamental constituent of calcified matrix
e. Synthesis of proteins
f. Engaged in carbohydrate, lipid and protein metabolism and have a structural, catalytic and regulatory role for different enzymes and transcription factors
g. Regulates the appetite through CNS
h. Has a role in spermatogenesis and sexual maturation.

Copper: Being part of functionally crucial metalloenzymes has been identified as a fundamental constituent of the defense system, Part of heart functions, Synthesis of bone tissue, Metabolism of carbohydrates and lipids, Defense mechanism, Formation of connective tissue, Keratinization of tissues, Spinal cord myelination and cell respiration. It is present 20 ppm in the total diet of dairy cows.

Iron: It is known for its performance in different biochemical reactions, it is a respiratory carrier of haem, a crucial part of catalase in the antioxidant defense system, role in redox reactions, role in the metabolism of carbohydrates and proteins and role in electron transport chain. The reduced form of iron (Fe) has a potent pro-oxidant function by acting as a catalyst for radical formation and lipid peroxidation (Halliwell, 2008) like Zn, reduced Fe concentration has been observed during an acute response to immunological problems in dairy animals, but Cu concentrations was increased (Nazari et al., 2019).

Table 1: Percent relative bio-availabilities of trace mineral sources

Zinc	***Copper***	***Selenium***
Proteinate: 100 percent relative bioavailability	Sulfate: 100 percent relative	Sodium selenite
Polysaccharide	bioavailability	100 percent relative bioavailability
100 percent relative bioavailability	Carbonate	Seleno methionine
Amino acid	85 percent relative bioavailability	150 percent relative bioavailability
100 percent relative bioavailability	Lysine	Seleno yeast
Oxide	100 percent relative bioavailability	100 percent relative bioavailability
50 percent relative	Methionine	Calcium selenite
bioavailability	110 percent relative bioavailability	100 percent relative bioavailability
Chloride	Oxide	
100 percent relative bioavailability	30 percent relative bioavailability	
Sulfate		
100 percent relative bioavailability		
Carbonate		
100 percent relative bioavailability		

Adopted from University of Missouri Extension (Anonymous, 2018).

Manganese: It has an essential role in dairy cows as a basic part of a wide variety of enzymes that play role in an antioxidant defense system, nervous and defensive functions, metabolism of lipids and carbohydrates and role in reproduction.

Above narrated all functions of microminerals express their key roles in defense system mainly through the anti-oxidative process. For an efficient antioxidant defense system, several trace minerals and vitamins are indispensable (Spears and Weiss, 2008). Trace elements show a particular role in regulating free radicals at the cellular level thus maintaining the antioxidant/free radical balance. A wide variety of trace minerals dependent antioxidant enzymes can be generated in the body that combats efficiently with free radicals but feeds derived mineral cofactor is a pre-requisite. For instance, Selenium (Se) is a fundamental constituent of a class of enzymes glutathione peroxidase (GSH-Px) and thioredoxin reductase (Jaaf et al., 2020). If their proper quantity is added to feed, sufficient anti-oxidant enzymes can be synthesized. Availability of dietary trace minerals throughout the gastrointestinal tract is a prerequisite for their absorption at the final site (small intestine). Their deficiencies or excessive quantities result in oxidative stress causing harm to the biological molecules like membranes and tissues. Certain components promote the assembling of free radicals, most common stressors like high physiological demands are contributing factors and leading to an increase in metabolic rate and free radicals assemblage (Bernabucci et al., 2002; Lohrke et al., 2005). Damage can result if anti-oxidants are absent or present in less amount to prevent free radical formation. Cattle experiencing immunosuppression are prone to infections or suffering from the increasing demand of lactation have more load of free radicals thus needs more supply of antioxidants (Bernabucci et al., 2002).

Due to iron deficiency, B-cells formation gets affected. Copper deficiency can cause severe immuno-suppression, as it affects cells of the immune system, so Cu-deficient animals are more prone to the infection as compared to healthy ones. A research study on lab animals showed that Zn deficiency can lead to immunosuppression (Shankar and Prasad, 1998). The Zn deficiency can cause a reduction in the weight of the thymus and the thymus is positively linked with lymphocytes, and so lymphocytes are also reduced. Young animals are more affected by this situation as compared to older animals.

Selenium deficiency in dairy cattle causes serious issues like loss of blood's ability to kill bacteria (Hogan et al., 1990). There are more chances of mastitis as neutrophils in the milk lose their working ability (Grasso et al., 1990). Migration of neutrophils chemotactically was reduced in Se-deficient goats (Meglia et al., 2018). In addition to this when selenium was added to the diet of bovines it enhanced the macrophages and neutrophils migration (Ndiweni and Finch, 1995, 1996). In one of the studies conducted by Maddox et al. (1999) mammary epithelial cells of bovine were grown in cell culture media deficient of selenium, it was observed that endothelial cells exhibit more neutrophil adherence because of activation of neutrophil with hydrogen peroxide and tumor necrosis factor-alpha and interleukine-1. This study proved whenever there is Se deficiency, it could lead to mastitis because endothelial cells form a complex with the neutrophils and hamper their function. There was a positive correlation between whole blood selenium concentration and neutrophil adhesion in dairy cows (Cebra et al., 2003).

One of the studies showed that in periparturient dairy cows supplemented with chromium (Cr), cell-mediated and humoral immunity got affected. Blastogenic response of lymphocytes was increased when the cow was offered 0.5mg/kg Cr in diet (Burton et al., 1993). In the control group of cows who were at 2 weeks, prepartum Cr supplementation stopped the blastogenic response. When the cow was fed with 0.5mg/kg chromium it leads to a decrease in the concentration of cytokines in the experimental group than in the control group when it was stimulated with Con A (Burton et al., 1996). Dietary Cr can alter the function of the neutrophil. (Chang et al., 1996; Faldyna et al., 2003).

Chelated minerals

As the enteric habitat reduces the absorption of the ionic minerals, there are possibilities of mineral antagonism which is overcome by increasing bioavailability of minerals with the help of chelation technology. Chelation means "firmly attached", usually to an amino acid or another organic component so that the two do not disassociate in the digestive system. It is required to enhance the absorption of minerals. Chelated minerals are used for supporting, stabilizing bipolar disorder, building strong muscles and bones, and improving immune system function and overall health. Chelated minerals are better absorbed within the body and their absorption can activate many physiological responses in the body. To provide the economic benefit to the dairy cow the product should bypass the rumen microflora and get digested in small intestine. Per milligram cost of chelated minerals are 10-15 times more than the inorganic sources and per cow cost of commercial chelated minerals ranges from 4 -18 cents per day.

Organic acids and immunity

Humic acid (HA) is a principal component of humic substances which are the major organic constituents of soil, coal, humus, peat, many upland streams, lakes and ocean water. It is produced by the biodegradation of dead organic matter.

Humic acid as an immune stimulant

Humic acids are well known for their immune stimulation, nutrient absorption and antibiotic effects. In general, efficiency is enhanced by adding Humic acid to feed. Humic acid has been used in pigs, poultry, and cattle. It is narrated that Humic acid reduces mycotoxins in feed because of its antibacterial and antifungal actions (Islam et al., 2005). Its most useful effects include antiviral, anti-inflammatory, immune system regulation, controlling the stress and protecting from intestinal problems mainly diarrhea in animals and humans (Islam et al., 2005).

Humic acid and its products promote gut health by enhancing nutrient utilization and improving immunity thus protecting against pathogens. HA (Humic acid) increases immune functions thus reduces intestinal problems like diarrhea and improve animal's defense against disease-causing organisms like *E. coli* (Taklimi et al., 2012). When Humic acid was used against bacteria so it caused abasement of rumen microbiota which are useful for protein synthesis. One of the functions of Humic acid is to decrease ammonia emission from the feedlot. Ammonia emission can be decreased from the feedlot of beef cattle using Humic acid and humates when used as soil amendments. Brown humates decrease ammonia emission by 67.6% as compared to black humate 60.2% (Shi et al., 2001). Chirase et al. (2000) showed that there were no adverse effects of humate when added to the diet and feed to gain ratio (F: G) along with dry matter intake (DMI) remained the same. This effect was observed after the 56th day of the study and it was also reported that liver functioning was not hampered due to supplementation of humates as there was no dramatic impact on rumen fermentation when high humic acid or humate products were used. The addition of 5.0g/kg of dietary humate reduced the ammonia emission and slightly altered the DMI.

Milk production was increased 1.9lb /day/animal, but no change was observed in butterfat and ther negative effect was seen in feed consumption from 38 to 36 lb. All these changes Were due to humates (Mosley, 1996). Another feeding trial of humates was conducted in dairy cattle in the Netherlands. When comparison was made between control and experimental group milk production, fat % and FPCM (fat and protein corrected milk) were increased in the experimental group but protein % was slightly decreased (Thomassen and Faust, 2000). In conclusion, during the transition period, minerals play a key role in overall performance of the animals. These minerals are essential for the normal growth, metabolism and functioning of the dairy cows during the transition period. Moreover, these minerals also protect dairy cows from different pathological conditions and lead to th e stimulation of the immune system in dairy cows.

Authors' Contribution

All authors contributed equally to write this manuscript. All authors read and approved the final draft before publication.

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