CODEN [USA]: IAJPBB **ISSN: 2349-7750**

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.1145736

Available online at: http://www.iajps.com ***Review Article***

NUTRACEUTICAL APPLICATIONS OF COPPER, MANGANESE AND ZINC IN RUMEN METABOLISM AND BODY IMMUNE PROCESSES

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Abstract:
The key component in striving towards optimum animal production are possible by the provision of essential nutrients such as protein, carbohydrates, fats, minerals and vitamins to livestock in a balance pattern. The important role of trace minerals in term of animal production is far away very much highlighted broadly, as the trace elements are recognized with the most significant functional components of numerous metabolic processes. The body has the basic needs of trace minerals in trace amounts, ranging from 0.10 to 50.0 mg/kg of dry matter in the feed of dairy animals. These trace elements are essential for all biochemical processes of the body that supports the growth and the appropriate maintenance. Such as, copper (Cu) is necessary for the function of the superoxide dismutase and in the removal of toxic by-products of metabolic pathways. The exclusion of these toxic by-products permits metabolism to perform efficiently, uninhibited by damaging oxygen free radicals. Manganese(Mn), an essential trace mineral, important for development, metabolism, in the antioxidant system and has a slight effect on stimulating the activity of the Urease. Zinc (Zn), a significant trace mineral for the enzymatic function, help in the regulation of the production of nucleic acid, the metabolism of carbohydrates and protein synthesis, thus providing a stable framework for the development. Generally, Legume forages, grains, dairy rations and dietary trace mineral complexes are the fair sources of these trace minerals to meet the requirements of livestock. The immune system is part of the defense of the host against the destructive forces from the outside of the body, such as bacteria, fungi, parasites and viruses, or of the Interior, such as the malignant cells or those who produce auto-antibodies. Trace minerals have an important role for normal immune function and disease resistance including zinc, copper and manganese. An insufficiency in atleast one of these components can compromise immunocompetence of an animal. The body immune framework is made of two branches: the innate or non-specific of the immune framework, and the adaptive or specific framework of immunity. In this review paper, an effort has been established to scrutinize the effects of minerals supplement in the rumen metabolism and their individual or joined effects on body immune processes in different species of animals.

Key words: *Trace Elements, Rumen Fermentation and Reproductive Health, Body Immune Processes.*

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Please cite this article in press as Habib-Ur-Rehman et al, ***Nutraceutical Applications of Copper, Manganese and Zinc in Rumen Metabolism and Body Immune Processes****, Indo Am. J. P. Sci, 2018; 05(01).*

1. INTRODUCTION:

The International Union of Pure and Applied Chemistry has officially accepted almost one hundred eleven chemical elements uptil now (1, 2 & 3). Out of them, ninety three are categorized as of natural origin, and approximately fifty have been recognized as functional to sustain a state of normal health in mammals. In addition to the six basic elements (C, H, N, O, S and P) that make up the nucleic acids, proteins, carbohydrates, lipids and other living matter in huge amount (4, 5), numerous other elements are essential for the nutritional needs of higher animals. Satisfactory trace mineral entrance and maintenance is required for an variety of metabolic capacities including immune response to pathogenic investigation, proliferation and growth. As animal trace mineral status decays, immunity and enzyme capacities are compromised first, at last followed by a diminishment in greatest growth and decrease in fertility (6). Stability among the trace minerals themselves is a serious consideration and frequently represents a huge challenge because of antagonist interactions that can happen between minerals. The minerals required in moderately huge amounts (g/d) are named "macro" minerals. In opposition, the minerals needed in mg or µg amounts are referred to as "micro" or "trace" minerals (1, 3 & 7). Minerals are generally classified into four broad categories according to their physiological roles:

Structural: Minerals constituting the elements of the structure of the organs and tissues which include Ca, P, Mg, Ca, and if in the bones and teeth and P and S in the muscle protein. **Physiological:** Minerals occurring in body fluids and tissues as electrolytes, involved in the maintenance of the osmotic pressure, the acid-base balance, membrane permeability and fabrics (e.g. stimuli Na, K, Cl, Ca and Mg in the blood and cerebrospinal fluid). **Catalytic:** Minerals acting as catalysts in the enzymatic systems, as an integral part of the structure of compounds or metalloenzymes as cofactors necessary for the enzyme activation (e.g. Fe, Cu, Zn, Mn, and is involved in the cytochromes, ceruloplasmin, carbonic anhydrase, pyruvate carboxylase and glutathione peroxidase, respectively). **Regulatory:** Minerals involved in the regulation of cell replication and differentiation (e.g. Ca, in the transduction of signals; Zn, transcript of the DNA). However, this classification is subjective and non-exclusive since the same element can fulfill more of a single function (5). Ideally, the supply of minerals for livestock must be sufficient to ensure the maintenance of body reserves, and provide adequate concentrations in the edible products. However, in some cases, drinking water may be sources of minerals are exceptionally rich, sometimes responsible of the mineral toxicity (8). The achievement of a sufficient supply of minerals is particularly difficult because the needs of most minerals are not constant, but affected by physiological factors, including genetics, age, sex, type of production (maintenance, growth, reproduction, and lactation), and the level of production (3, 6).

2. Minerals Accessibility to Livestock. The evaluation of foods and supplements of minerals for the host animal depends not only on the ingredient of minerals in the sources but also on the potential availability and the absorption of minerals from the gastro-intestinal tract and the use of the mineral by animal tissues (1, 5). However, the content of absorbable suture potentially mineral is strongly influenced by numerous factors including the age and species of animal, the involvement of metal by report to the amount compulsory, the chemical form of the mineral, and the quantity and the proportions of other food compounds involved in particular interactions with the mineral (1, 5). The diet of livestock are frequently supplemented by traces of minerals in the form of inorganic salts, generally of nitrogen, chlorides, sulphates and carbonates. In recent years there has been considerable interest in the use of organics trace minerals in the feeding of ruminants (3, 9). According to the Association of American Feed Control Officials (10), organics trace minerals in the United States are available in one of the following forms:

Metal Proteinate: The product coming about because of the chelation of a soluble salt with amino acids and/or incompletely hydrolyzed protein, e.g., proteinate copper, proteinate zinc, proteinate of Co and Mn proteinate. **Metal Amino Acid Chelate**: The product coming about because of the reaction of a metal ion from a metal salt soluble with the amino acids with a molar ratio of one mole of metal for one to three (preferably two) moles of amino acids forming coordinate the covalent bonds. For example, the Cu-lysine-Sulphate Sulphate is the salt of 2:1 molar ratio of L-lysine and Cu. Similarly Cu-methionine is the Salt bisulfate bisulfate to a 1:1 molar ratio of DL-methionine and Cu. Available in the trade of other metal amino acids are Cu amino acid chelate, Zn amino acid chelate and Mn amino acids chelate, in addition of minerals chelates for macro as Ca and Mg. **Metal Amino Acid Complex**: The product resulting from a complexation of soluble metals salt with an amino acid. The metal complexes, available in the trade are Zn-methionine, Zn-lysine, Mn methionine, Fe-methionine- and Cu-lysine (2). **Metal Polysaccharide Complex:** The product resulting from a complexation of soluble salt with a solution of polysaccharide declared as an ingredient of the formulation (e.g. Cu polysaccharide complex, Zn polysaccharide complex, etc). While the effectiveness of organic minerals for ruminants has been strongly criticized (3, 8). (1, 6) has established that the chelation process to be effective, the chelating agent should have greater stability for the metal than the metal binding substances, but smaller than the stability constant of the tissue system where the metal is necessary. In addition, other factors including, the balance of the metal ion, kinetic factors, gradients of pH and redox (in the case of Balance redox active metals such as Cu2+), can also influence the mechanism of absorption of metal ions (6). Several studies have been conducted to examine the benefits of the inclusion of organic sources of minerals on the productivity of ruminants. However, in many cases, a combination of several organic elements has been used, which makes it difficult to determine which is responsible for the effect noticed, as discussed later. The purpose of this review is to explore the factors involved in the bioavailability of Cu, Mn and Zn in the gastrointestinal tract, affecting the mineral status of the animal host. In addition, the role of Cu, Mn and Zn on rumenal physiology is presented ((1, 3).

3. Zinc

3.1. Interaction of Zinc with Nutritional Factors. The first studies from (12) have shown that in ruminants, the percentage of caloric intake Zn absorbed decreases as dietary Zn increases. (2, 13) showed a linear increase in the endogenous fecal Zn loss when rats were supplemented with the increase levels of dietary Zn ranging from 0 to 8400 ppm. Similarly, in a study conducted in the growing pigs receiving 67 Zn, the addition of phytase has increased the absorption of zinc but also resulted high endogenous faecal loss (1, 35). At the same time, the reduction in the excretion of urinary and faecal Zn by 48% and 46% respectively have been found in humans when the Zn has been reduced from 85 to 12 µmol/d. In spite of the influence of dietary levels, the requirement of Zn seems to be affected by other factors in food. However, all the factors and interactions that play a role on the bioavailability of zinc are not clearly defined (1). According to (6), the two main factors affecting the bioavailability Zn food products are the presence of Organic chelating agents and the interaction with the metal ions, with Cu and Ca being the most important of the antagonists (5,36 & 38).

3.2. Function of Zinc on Rumen Fermentation. The early studies from (11) have shown that the synthesis of microbial protein in vitro has been increased with a reduction of NH3-N, when the concentration of rumen fluid was incubated with additional Zn as ZnCl2 or ZnSO4. According to the authors, this response is due to an effect of Zn in the increasing microbial enzymatic activity. However, further study from (12) showed differences in the behavior of microbial populations in the rumen in the presence of Zn. Although the protozoa easily incorporated Zn and were tolerant to high concentrations of Zn (25 µg/mL), the degradation of cellulose from the rumen bacteria was very depressed, with the activity of bacterial urease. In Partial Agreement, with early study from (13) has shown that by addition more than 5 µg/mL of rumen fluid the digestion of the cellulose has increased by 24%, but addition of 20 µg/mL of Zn depressed it by 31%. (6) has shown that low levels of supplementation (10 to 15 ppm Zn in the incubation fluid) inhibits in vitro the hydrolysis of urea into ammonia and the delay of the accumulation. Similarly, when Zn was added in vivo at 250 ppm Zn on DM basis, molar proportion of propionate has been increased with the consequent decrease of the acetate: propionate ratio, and ammonia in the rumen was declined due to the inhibition of the Microbial urease (36). However, when Zn was added to reach a level of 470 ppm on DM basis, a downward trend of the DM digestibility has been noticed. In addition, (1, 2) showed a decrease of the total VFA when Zn has been provided to steers as Zn methionine or Zn glycine compared with ZnSO4 at concentrations closer to physiological concentrations (20 ppm). In the same study, the molar proportion of propionate has been increased by the Zn methionine and that of butyrate is reduced, resulting in a reduction of the acetate: propionate ratio. The authors conclude that the supplementation of Zn methionine may alter the rumen fermentation. Although these differences may be explained in part by the dose of Zn and the fermentation substrate used by different authors, another mechanism is proposed by (14), who have found that the addition of 50 µg/mL of Zn in the in vitro incubations, the digestion of cellulose decreased to 24 h, but not at 48 h, which results in a decrease in the rate, but not the magnitude of the digestion (1, 2). The authors conclude that the initial decrease in the digestion of cellulose is may be linked to a direct effect of Zn on the bacterial inactivation of cellulase, since the salts of heavy metals can precipitate and distort the soluble proteins and enzymes. However, enough cellulase activity may be present to overcome the negative effects of the high concentration of Zn (38). In addition, the accumulation of Zn in the Bacterial Cell Wall may have an impact on the adhesion of microbial cells for particles of cellulose, a step to the fermentation of cellulose as the previously established (12).

3.3. Zinc Accessibility from Organic and Inorganic Means. There is scientific evidence showing that the organic Zn is metabolized differently that inorganic sources. In the course of the many studies conducted by (2, 6 & 27), Zn is better retained when added as Zn methionine than ZnO in lambs and heifers. However, the improvement observed was not due to the higher absorption but due to the decline of the urinary excretion of Zn (38) in animals receiving Zn methionine, and only minor changes in blood parameters have been noticed (40). Similarly, in a study conducted by (1, 5 & 3) in calves, the organic or inorganic zinc supplementation does not affect the concentration of serum enzymes (alkaline phosphatases, glutamate oxaloacetate transaminase, glutamate pyruvate transaminase and super oxide dismutase) or of average concentrations of different vitamins (serum retinol, β-carotene, α-tocopherol) and hormones (triiodothyronine, thyroxine, insulin, and testosterone). In addition, blood parameters of supplemented groups were not different from unsupplement controls. In a comparative study, (15, 36) have found no difference in the liver and plasma Zn concentration of steers receiving ZnSO4 or Zn amino acid complex. However, the confounding effects could explain these results, given the differences in the minerals status of the animals at the beginning of the study. In Partial Agreement, no differences in the concentration of plasma Zn of steers, receiving ZnSO4, Zn methionine complex or Zn glycine were found by (11). Although large variations prevented from obtaining the differences in absorbed or retained Zn, Zn glycine at the origin of an increase in the Zn concentrations of the liver. Conversely, the use of organic and inorganic materials of Zn (37). (2, 5) found higher concentrations of Zn in the plasma of beef steers supplemented that among the witnesses, in spite of the Zn source. Interestingly, in animals receiving an implant containing estradiol benzoate and testosterone propionate, has resulted in a gain of weight more high when Zn has been completed on the basis of ZnSO4 than of Zn propionate (6). In a large production study of 250 dairy cows, only a trend to the improvement in the production of milk has been obtained when Cu, Zn, Mn, and Co as sulphate, have been replaced by organic forms of the mineral industry. The hepatic concentration of minerals is not affected by the mineral source, but the supplementation in organic minerals, milk solids has resulted an increase and a decrease in the incidence of sole ulcers (16). In another large scale study carried out on 573 dairy cows (1), supplementing 75% of the requirement of Zn, Zn methionine reached the same concentration of hepatic Zn than supplementing 100% of the requirement as ZnSO4. Based on the absence of differences in the health and performance of production, the authors suggest that the mineral content of liver is not an accurate indicator of cow's response to different sources and levels of trace elements. In agreement, (16, 2) suggest that the Zn, Mn and Cu content of liver is a poor indicator of the state of trace mineral. According to (11, 12), the supposed benefits of organic sources of Zn on Zn availability requested in the studies conducted in monogastric animals may not be adopted in the ruminants since the phytic acid, an antagonist of the Zn absorption, is largely hydrolyzed in the rumen. An additional difficulty in the assessment of the availability of Zn from different sources (37, 40) is based on the fact that the Zn is absorbed according to the animal needs and homoeostasis in ruminants is carried out mainly by the control of the intestinal absorption (1, 36).

4. Manganese

4.1. Manganese Interaction with Dietary Factors.

With reference to the (7), there is limited data concerning the maintenance requirements of Mn in dairy cattle. However, the coefficient of intestinal absorption of Mn in adult cattle (40) is known to be as low as 1% of the ingested Mn, but the absorption in the young calf is considerably higher (17). Despite the general idea of a partial absorption of Mn, (18) suggests that this situation is in part a reflection of the large surplus of Mn provided by most of the practical rations, since of the absorption coefficients were obtained when the diets to the animals have received marginal in Mn (17). For this reason, the (7) has adopted a coefficient of 0.75% conservative for Mn absorption. In agreement, (17) have noted a coefficient of 0.54% for Mn absorption in dairy cows. The study of dietary factors that influence the bioavailability of Mn has received little attention, probably because the deficiency in Mn is not considered a major problem in ruminants (1, 5). In addition, most of the available information has been generated in the monogastric animals models. (6, 3) observed a 10% and 13% increase of Mn in the bone and kidney, respectively of chicks receiving 12 ppm of virginiamycin in the diet. In the early study (17), the addition of 4 ppm of the lincomycin has given rise to higher concentrations of Mn in the bone. However, although virginiamycin and other antibiotics are currently used as additives in the feed of ruminants (19), their role in the uptake of Mn in the livestock remain unknown. According to (11), the intestinal absorption of Mn is negatively affected by the dietary levels of Ca and P. Similar results have been found by (17), which have found a 45% reduction in Mn in the tibia of chicks fed an excess of Ca and P. However, other evidence provided by (13) indicated that while P has a negative effect on the uptake of Mn, not of deleterious effects on the metabolism of Mn are obtained with the excess of level of Ca, but the effects of Ca and P are difficult to distinguish because the diets are usually enriched with the two minerals to maintain Ca:P physiological ratio (8, 5 & 39). There has been no report concerning the absorption of Mn with the composition of the forage in ruminants, but the phytate and fiber are known to be the main antagonists for monogastric animals species, including the human (1), pigs (20). Through microbial activity, phytate and fibers are decomposed into rumen (13). For this reason, it is suggested that the absorption of Mn in the ruminants may not be affected by the presence of phytate, being higher than that usually reported for monogastrics.

4.2. Manganese Play Important Role In Rumen Fermentation. The little information was available concerning the role of the Mn in rumen fermentation (1), but now Mn have a vast activity in rumen fermentation and digestion (17). Mn has a slight effect on stimulating the activity of the urease. In a previous study, (11) showed a reduction of cellulose digestion when Mn has been omitted in the in vitro incubations. However, it has reported that the digestion of cellulose culminated at Mn concentrations of 10 to 20 ppm, but has been completely abolished when Mn was added to 300 ppm. In using Mn, (6) observed that the accumulation of Mn was higher in the cell walls of the rumen bacteria that in the cytoplasm, and that the absorption was similar in bacteria and protozoa, but the biological implications of this fact are not established. (21) fed ram lambs diets that contain 13 to 45 mg Mn/kg DM during 84 days. While the number of rumen bacteria has not been affected by the Mn, the bulk of the rumen bacteria (identified as those of a diameter of 12.9 to 16.2 µm) resulted in the lowest with less admission Mn and the highest with the Mn provided to 30 mg/kg. This may be particularly relevant to the extent where the large rumen bacteria contain more protein than the small rumen bacteria (5, 39). However, despite this variation in microbial populations, no effect of Mn on DM digestibility has been observed. In experiment, it has suggested that the sheep with a diet rich in fiber and low in protein may respond to the Mn supplementation more than of 36 µg/g DM, but Mn requirements of the microbes in the rumen can be increased by consumption of forage of lower quality. In agreement, (21) suggest that the optimal content of Mn in the diets can be as high as 120 µg/g DM on the basis of the results of in vitro studies.

4.3. Accessibility of Manganese from Organic and Inorganic Sources. The objective of minerals supplement is to increase the biological availability of the target mineral(s), defined as the extent to which an item ingested is absorbed and may be used in the metabolism by the animal (6). Different sources of Mn are currently available as supplements for the feeding of the animals (39, 40). Among the inorganic sources, the most commonly used: manganese carbonate (MnCO3), hausmannite (Mn3O4), manganese oxide (MnO), manganese dioxide (MnO2), manganite (Mn2O3), manganous chloride (MnCl2-4H2O) and manganese sulphate (MnSO4) (1, 6). On the other hand, the sources of Mn classified as "organic" includes Mn methionine, Mn proteinate and Mn polysaccharide (19). Unfortunately, only a few studies have been conducted by comparing the relative bioavailability of Mn sources in the ruminants fed physiological concentrations of Mn. According to (22), some chelates and complexes can improve the bioavailability of minerals above that of soluble inorganic forms, as later shown by (19) in lambs comparing Mn-methionine with MnO. However, no difference was obtained in the same study when Mn-methionine was compared to the MnSO4. Similarly, (23) has compared the bioavailability of Mn of different organic sources and MnSO4 in broilers. The authors concluded that only organic Mn sources with moderate or strong chelation strength can provide the high pharmaceutical forms due to their ability to withstand the Ca antagonisms during the process of digestion. In addition, studies conducted on the females chicks showed an increase in the Mn retention of a Mn methionine chelate compared with MnO (17).

5. Copper

5.1. Copper Interaction with Dietary Factors. The amount of the necessary dietary Cu needed to supply Cu requirements for the maintenance, growth and lactation varies with the age of the animal, the chemical form of the dietary Cu and the presence of dietary substances that interfere with the Cu absorption (24). In relation to the monogastric animals, where the Cu is fairly well absorbed (30% - 75%), while the absorption in the adults ruminants is low, ranging from 1 per cent to 10 per cent of dietary Cu (25, 36). However, prior to the development of a functional rumen, the absorption of Cu in lambs can be as high as 70 to 85 per cent of the dietary supply (26). The reason for this decrease in the absorption of Cu appears to be related to interactions that occur in the rumen environment, including the Cu-S-Mo (8), Cu-S (24) and Cu-Fe (25) antagonisms. More recently, the results concerning the high Levels of Mn with dietary Cu deficiency have been reported (27, 28 & 1).

5.2. Copper Interaction with Molybdenum and Sulfur. In the presence of ruminal H+ ions, dietary S is reduced to sulfide, which then reacts with Mo (6) to form various thiomolybdates (mono-, di-, tri-, tetra-thiomolybdates (24). In the gastro-intestinal tract, thiomolybdates have been shown to bind the Cu preventing its absorption, while increasing the fraction of Cu associated with the solid phase of the rumen contents at the expense of a reduction of the fluid phase. Thiomolybdates associated with solid digesta in the rumen (bacteria, protozoa, and indigested food particles) form insoluble complexes which do not release of Cu, Even under acidic conditions, such as the abomasum environment (25, 36). In addition, the absorbed thiomolybdates have also been shown to cause systemic effects on the metabolism of copper, including the increase in the biliary excretion of Cu from the liver stores, a strong binding of Cu to plasma albumin, which reduced the availability for the biochemical processes, and the inhibition of Cu depending metallo-enzymes such as diamine oxidase, ceruloplasmin, cytochrome oxidase, ascorbate oxidase and tyrosine oxidase. According to (24), when concentrations of sulfide in the rumen are low, Mo has little effect on the formation of thiomolybdates. However, the bioavailability of Cu is very reduced (up to 70%) when the levels of Mo are not modified, but the concentrations of sulphide are increased (5).

5.3. Interaction of Copper with Sulfur. In addition to its role in the interaction, Cu-Mo-S, organic or inorganic S can also reduce the bioavailability of Cu. (26, 37) showed a reduction of 55% hepatic Cu when the sheep have been subject to high levels of S (2 g/kg ms) in feed. According to the authors, this reduction is due to the formation of the CuS in the digestive tract, since the diet has been very low in Mo. Similar results have been observed previously by (26) which have found a 39% - 56% reduction in the bioavailability of Cu when S was provided to ewes as methionine or NaSO4 as under low dietary concentrations of Mo, perhaps through the formation of insoluble CuS at sites beyond the rumen. However, the (24) assumption that it is the formation of the insoluble CUS and Cu2S in the rumen is exacerbated by the digestion of insoluble proteins by the protozoa, with the consequent increase in the available Sulfur. Despite the effect of the contribution the S has been previously mentioned, other S sources have also been responsible for the reduction in the bioavailability of Cu in the ruminants. Molasses, a by-product of sugar cane and sugar beet is a source of dietary sugar feed for dairy cows (7). Benefits of adding molasses to the diet includes the increase in the palatability, acting as a binder, and the reduction of dust to fine particles feeds (25). However, due to its high content of S, the liberal use of molasses may result in dietary S levels considerably in excess of requirements. (24) highlight a decrease of liver Cu at 29, 56 or 84 days after the supply of heifers with a supplement of the molasses. According to the authors, this observation was the result of a high concentration of S naturally in the molasses. In a review of the antagonists of the Cu in cattle (36), (25) describes other sources of S implicated in the Cu-Mo-S and Cu-S interactions, included fertilizers, high S water and S containing supplements. Cows grazing the Bahia Grass pasture fertilized with ammonium sulphate showed lower liver Cu concentrations by report to cows grazed on non fertilized pastures, or fertilized with ammonium nitrate. A study has shown that fertilization of gypsum (132 kg P/ha) has increased the S, from 0.33% to 0.40% and 0.29% to 0.37% of DM in tall fescue grass and in orchad-grass, respectively. However, the pastures for feeding those steers gave rise to no modification of the bioavailability of Cu, probably due to the high content of S of the non fertilized pastures. For this reason (1) suggest that the choice of fertilizer can be critical in areas where grazing cattle may be subject to a copper deficiency sulfur levels in drinking water can also be detrimental to the bioavailability of Cu. (29) have reported a decrease in the plasma concentration and hepatic Cu yearling steers provided with the high water-S (3651 mg SO4/L) compared to those receiving low S of the water (566 mg SO4/L). Similarly, a decrease of more and more hepatic Cu steers was found by (6, 3) When S content in drinking water has been increased from 404 to 4654 mg SO4/L. While the S concentrations are beyond what is commonly found in the water for the animals, high S-containing water has been reported in the United States and Canada (1).

5.4. Interaction of Copper with Iron. Ruminants consume the regimes to basis of forages are often exposed to high concentrations of Fe through the water, fodder, and exceptionally high quantities of the ingestion of soil (24, 36). Additional to 800 mg Fe/kg DM as FeO or FeSO4, decrease the absorption of Cu from 0.06 to 0.04 in sheep. In agreement with an early conducted study (40) have found a rapid decrease in the liver and plasma Cu, activities of superoxide dismutase and erythrocyte plasma ceruloplasmin of young heifers receiving 800 mg Fe/kg DM. However, after (26), The role of the Fe on Cu absorption is partially dependent of S. Indeed, an explanation is provided by (25) which show that the excess of Fe can compete with Cu for its absorption at the intestinal level, by saturating the DMT-1 Cu transporter (30).

5.5. Function of Copper on Rumen Fermentation. In a study conducted on the sector of the production of beef steers (26), the addition of 20 or 40 mg Cu/kg DM has decreased the yield of animals and animals performance against the animals receiving a basic diet containing 10.2 mg Cu/kg DM, suggesting that high dietary Cu can inhibit the rumen fermentation. Another study showed a decrease in the total concentration of post feeding VFA and VFA molar proportions of yearling steers receiving a high dose of supplemented Cu (57.3 mg/kg of MS), but average gain daily, the effectiveness of the feed efficiency, and carcass yield and quality class have not been affected. In agreement, (30) has shown in vitro, depression in rumen fermentation of concentrates to the result of the addition of high doses of CuSO4. Similarly, (24) showed a reduction of the molar proportion propionate when high doses of Cu have been added to the rumen in vitro incubations. A dose-response of another study has determined that 21 µg Cu/ml liquid of incubation was necessary in order to obtain an inhibition of 50% of the production of natural gas. However, great disparities have been obtained with regard to the sensitivity of the different bacterial populations to Cu. If the growth of Bacteroides succinogenes, Ruminococcus albus and Butyrivibrio fibrisolvens is inhibited by 10, 20 and 30 µg/mL of liquid of incubation, respectively, of highest concentrations have been required to inhibit Megasphaera elsdenii and Selenomonas ruminantium and Streptococcus bovis (100, 100, and 250 µg/mL, respectively). The opposite results were reported by (25, 5) who have found a reduction in the pH of the rumen and an increase of the total VFA concentrations when Cashmere whether goats received additional Cu in the diet. According to the authors, an increase of the NDF digestion may be responsible for these results. Conversely, subsequent studies conducted by (6) has shown that the digestion of NDF has not changed or enlarged by the addition of 10 mg Cu/kg DM, but supported at 30 mg Cu/kg DM have been added. Based on previous observations showing that 20 or 40 mg Cu/kg DM The increase of unsaturated fatty acids in adipose tissue of steers, a possible role of Cu as an inhibitor of lipids of the rumen biohydrogenation has been suggested. (30, 31) However, no study has been conducted to assess the validity of this hypothesis.

5.6. Copper Accessibility from Organic and Inorganic Sources. The effectiveness of organic sources of Cu to promote the animals benefits has been the subject of several controversies. (1, 30) reported a rate of maintenance of Cu in steers supplemented with Cu-lysine compared with the supplementation with CuSO4. In another two study (26, 24) the use of organic Cu materials (as Cu proteinate) has increased the hepatic retention of copper in the rearing of the multiparous beef cows, compared to inorganic Cu. However, no advantage on the performance of calves and cows have been obtained. Conversely, (32, 5) found an increase in body weight gain in goat kids supplemented with organic Cu, compared with inorganic Cu. In a recent meta-analysis (33). The assessment of the benefits of organic trace minerals, only marginal improvements in the production of milk, the fat content of the milk and milk proteins have been found. In the opposition, organic trace minerals do not affect the account of somatic cells, the interval of calving to first service, and 21-days rate of pregnancy. Similarly, no difference in the 60 days pregnancy rate, the health or the performance has not been found in 2 years old Cows receiving Cu as CuSO4 or as a complex of amino acids. In addition, (6) showed a decrease in pregnancy rate of primiparous cows receiving organic minerals and inorganic (Cu, Co, Mn, and Zn) compared to non-supplemented cows. According to the authors, beyond the excessive supplementation reduced the requirements of the performance of reproduction. In a previous study on the steers, the growth rate is higher when the animals have received of CuSO4 than when Cu-lysine have been provided during the initial period of 21 d, but no difference was obtained after 98 d. Other parameters, including the effectiveness of the diet, the index of consumption, the humoral and cell mediated immune response and the ceruloplasmin activity, have not been affected by the Cu source (25, 36). Organic sources of Cu have been seriously criticized by (33) who consider that the technologies of protection against the rumen antagonisms are extravagant and provide no any other advantage than conventional CuSO4. According to (30) led to commercial purposes, the continuation of benefits compared to insignificant cheap and effective to inorganic Cu sources must stop, and focus should be on the prediction of the necessary supplementation, rather than under-supply of Cu and its impact on the environment (24). In conclusion, Cu, Zn and Mn are required to maintain health and production status of livestock, but their functions at the gastrointestinal tract of ruminants are not fully elucidated. Like many other minerals, Cu, Zn, and Mn have the ability to interact with the organic compounds of the diet, macro minerals and micro minerals, usually resulting in a decrease in the availability for the host (3). Different technologies, including proteinates, amino acids chelates, amino acids complex and polysaccharides complex are currently available for mineral protection. However, these technologies seem to be more effective in monogastric animals that in ruminants. Mechanisms to ensure an optimal level of ruminally available minerals, and optimize the supply of minerals to the lower gastrointestinal tract without compromising the post-ruminal absorption require research further (33, 37).

6. Body Immune Function: Trace minerals that have been recognized as fundamental for normal invulnerable immune function and disease resistance include zinc, iron, copper, manganese and selenium (1, 6). An insufficiency in at least one of these elements can compromise immunocompetence of animal (5). The first level of defense in the immune system is the skin to protect the host against invasion of bacteria, fungi, parasite and viruses. Zinc and manganese (39) are key elements for maintaining epithelial tissue integrity. Further, the lining of the respiratory tract, lungs, gastro-intestinal tract and reproduction tract are also epithelial tissue. Maintaining the integrity and health of the tissue in these areas can result in a reduction of infiltration by pathogens (30).

6.1. Role of Cu, Mn and Zn In Body Immune Processes. Trace Minerals are necessary to the whole body organization in minute quantities (usually included in the diet in parts per million quantities). Several of these trace elements such as zinc, manganese, copper and cobalt are required for the functionality of many structural proteins, enzymes and cellular proteins (24, 1 & 6). Trace minerals can operate as cofactors, activators of enzymes, or stabilizers of secondary molecular structure and serve critical functions in the cell metabolism (24, 37). Many studies have shown that the feeding of amino acid complexes of the Zn, Mn, Cu, and Cobalt improved the performance of dairy cattle by the improvement in the rate of fertility and the reduction of the incidence of the disease (30, 6). These improvements in animal performance appear to be related to the increase in the availability of trace minerals for the metabolism (11). The ruminants are often subjected to serious nutritional deficiencies of trace elements such as copper, cobalt, selenium, iodine, manganese and zinc (24). These shortcomings have been linked to a decrease in the fertility of the enzyme malfunctions. In Hypocuprosis, dairy cattle and sheep has been linked to disorders of the reproduction, as the prevention of the implantation of the embryo and high prenatal mortality, in particular with the loss in early embryonic. Several studies conducted on rats and mice have shown that the two cells mediated and Humoral immunity are very depressed by copper deficiency (5). A study have shown that the marginal copper deficiency in dairy heifers reduces the ability of neutrophils to kill the S. aureus. The animals deficient in copper also show an increased sensitivity to pathogenic bacteria (40). This has been attributed to the role of the copper in the superoxide dismutase and cytochrome coxidase enzyme systems. (1) reported that the inadequacy of copper compromise the ability of macrophages to kill yeast cells. Another study has demonstrated that the copper-depleted calves exhibited impaired Phagocytic killing activity which has been reversed by the supplementation in copper. In another study, the low status in copper has been associated with a decrease in the response of peripheral blood lymphocytes to stimulation with T-cell mitogens. In spite of these studies, the general effect of the inadequacy of copper on the function of macrophages in cattle has not been studied in depth (34). Extensive research conducted on human subjects and laboratory animals suggest that zinc deficiency reduces the immune response and the resistance to diseases. Among children, a zinc deficiency has been shown to affect of neutrophils and lymphocytes T with function reduces the proliferation of lymphocytes in the presence of the mitogens and the slowdown of the chemotaxis of neutrophils (6). Zinc deficiency also produces a atrophy of lymphoid tissues the such as the thymus. A Zinc deficiency also has a negative impact on the function phagocyte which decreases the ingestion and phagocytosis. A study conducted on laboratory animals fed a diet deficient in moderately zinc has shown that the differentiation and function of B cells may be altered (5). In cattle, surprisingly little research has been conducted to examine the relationship between the intake of zinc and immune function. Marginal Zinc deficiency is seems to have marginal effects on immune function in ruminants, but the research also suggests that the addition of zinc to diets practices can have an impact on the resistance to diseases (34, 37). The zinc deficiency is more deleterious to the function of reproduction of male animals; however, the administration of a zinc supplement for cattle has been shown to increase the conception rate to 23 percent compared to the control, and the discontinuation of this supplement resulted in decreased conception rate (34). The manganese deficiency has been linked to the suppression of the estrus, the reduction of conception rate, increase in the incidence of abortions, and a low weight at birth (36). In dairy cattle, the main clinical sign of restricted manganese intake is anestrus or irregular return to estrus sometimes with extended periods of anestrus (40). This leads to the decline the conception rate. The animals fed with a diet deficient in manganese have demonstrated deficiencies the antibodies synthesis and secretion (6). After the addition of manganese to the diet, the improvement of the production of antibodies. The mechanism(s) by which the manganese affects the Synthesis of antibodies, or release has not been clearly elucidated and the continuation of studies in this area is necessary (5).

7. Conclusions. In this review paper, we conclude the following: **1.** Trace elements are very important for the health, their growth, production and reproduction. They are essential for the functioning of a number of mechanisms of the immune system. Thus, they play role in the maintenance of good health and immunity. They are important for the functioning of a numerous enzymes and proteins that are involved in several physiological and biochemical processes. **2.** Fundamental Trace minerals such as zinc, copper and manganese play a wide variety of biological and physiological roles in the development of the animals and their health. These minerals are involved in the antioxidant defense, development of the tissue, and immune function. **3.** There is almost a record that the trace elements have higher bioavailabilities, which enhance the performance of the animals, health, production and the immune response and the stress alleviation than their inorganic salts. **4.** Measuring the prerequisites of trace minerals for dairy cattle is extremely difficult and the techniques and models currently utilized may not be proper because of the unlike metabolic functions of trace components. Additionally, there is absence of proper laws and regulations to control and examine their quality for advertising and marketing purposes.

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