https://doi.org/10.47278/book.vpph/2021.016

PREVENTIVE MANAGEMENT OF THE PARASITIC DISEASES THROUGH TRACE ELEMENTS

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INTRODUCTION

Parasitism is still a serious threat to the livestock economy worldwide (Rashid et al. 2019). Gastrointestinal (GI) parasitic infections are considered among the major threats to livestock production all over the world due to retarded growth and productivity, and animal mortality (Githiori et al. 2004). A major impediment to maximizing production from livestock is the cumulative effects of parasitism on animals (Ahmad et al. 2017). GI tract parasitic infections of production animals have great economic impact, especially in developing countries. Helminths, especially GI nematodes and trematodes, impose severe threats to livestock in these areas in the form of morbidity, mortality, cost of treatment and control measures (Lashari and Tasawar 2011). Also, helminth infections in ruminants decrease natural resistance to diseases, result in poor weight gain and poor feed utilization (Pedreira et al. 2006). Apart from the importance of nematodes in ruminant populations, higher prevalence rates of cestodes and trematodes have also been reported (Rizwan et al. 2017; Ikurior et al. 2020).
In developing countries, antiparasitic drugs are used extensively for the control of parasitic infections, especially by smallholder farmers. This extensive use may lead to the development of resistance. Other factors responsible for the development of resistance are poor efficacy of antiparasitic agents, inappropriate dose, low protein diet and environmental toxicity (Smith and Sherman 2009; Khan et al. 2017). Development of resistance to antiparasitic agents and their residual effects in animal products have stimulated scientists and veterinarians to investigate alternative sources to prevent and control parasitic infections and to improve public health (Qadir et al. 2010; Badar et al. 2017). Keeping in view the limitations of chemotherapy, alternative solutions, such as biological control of parasites, use of vaccines, phytotherapy, use of trace elements (TEs) and development of resistant host genotypes, are being considered. These strategies, based on the holistic approaches, may substitute and/or augment existing prevention and control measures for parasitic infections, which have special significance in resource-poor communities due to their increased availability and cheaper prices.
The availability of trace elements (chemical elements required in minute quantities for normal growth of animals) in an appropriate quantity is a pre-requisite for the health and productivity (milk, meat, eggs, wool, hides) of livestock, while their insufficient intake or unavailability decreases productivity (Khan et al. 2007). Under natural grazing conditions, forages are among the major sources trace elements (TEs) for herbivores; however, water and soil also contribute to supply considerable quantities of TEs. Feed sources of TEs are largely separated into a variety of base feedstuffs, like harvested forages, concentrates, range or pasture plants, and mineral supplements (McDowell and Arthington 2005). The level of TEs consumption mainly depends upon forage intake. Factors responsible for the concentration of TEs in grazing forages are: plant species, plant developmental stage, dry matter yield, soil type, and climatic conditions (Mirzaei 2012). Determination of the abundance of TEs in grazing forages and their bioavailability to animals is important for meeting the requirements of animals (Qudoos et al. 2017; Rizwan et al. 2019; Ahmad et al. 2020).
In developing countries, data related on the association of TEs in the complex systems represented in the soil-plant-animal interface are poorly available, except for a few recent investigations (Qudoos et al. 2017; Rizwan et al. 2019; Ahmad et al. 2020). Other than this, a better understanding of the association of TEs with the burden of parasites in livestock is still needed. In this chapter, the role of TEs in animal health through their influence on physiological processes, and the development of non-specific and/or specific immunity against GI parasites, are discussed comprehensively.

Strategies to Control Parasites

For the control of parasites in livestock, especially those reared by resource-poor farmers, it is important to identify the burden and types of parasites along with specific risk factors associated with the parasitic infections in the specific area (Ayana and Ifa 2015). Breaking the life-cycles of parasites is the main goal in attempts to control parasitic infections. The use of antiparasitic drugs and appropriate management (of both animals and pastures) help to interrupt the life-cycle of parasites. The use of antiparasitic drugs for the control of parasitic infections is one of the best methods and is recommended globally (Grade et al. 2008). The strategic application of single or combination of two or more drugs for the control of parasites is very effective (Parr and Gray 2000). Integrated management through the combination of chemotherapy and other interventions usually results in the best parasite control (Atnafe and Melaku 2012). However, the development of resistance to almost all antiparasitic drug classes, due to their frequent use over the past few decades, has become a problem around the globe. In developing countries, most anthelmintics are used without registration and proper tests, which directly affect their efficacy (Atnafe and Melaku 2012).

Inadequate use of anthelmintics, poor efficacy of the commercially available products, and low protein diets result in development of resistance (Smith and Sherman 2009). Antiparasitic treatment of livestock in most countries is not practiced regularly in a systemic way, which may have a considerable effect on parasite prevalence and leads to resistance. Furthermore, sample size and the nature of sample sources (faecal or autopsies) are also important points in this regard (Githiori et al. 2004; Khan et al. 2017a).

Anthelmintic resistance is widespread, especially in nematode populations around the world (Kaplan 2004). The development of resistance to antiparasitic drugs and entrance of drug residues in the food chain have stimulated investigations into alternative ways to control parasitic infection and to improve public health. In this perspective, the search for alternative and/or augmenting tools to enhance antiparasitic activity gains currency. In Pakistan, some sheep breeds are resistant to *Haemonchus (H.) contortus* (e.g., native Lohi breed; Saddiqi et al., 2010). An alternative strategy to control resistance is manipulation of positive genetic variation. There are three ways through which one can introduce positive genetic variation: (a) selection of breeds, (b) cross-breeding and (c) selection among the breeds (Nicholas 1987). These methods are sustainable, efficient, safe and economical, but the only hindrance is the need of expertise in the field of genetics and the time needed to develop robust population of parasite-resistant sheep with suitable production value (Stear et al. 2007).

Another option is strategic grazing management, e.g., rotational grazing, which embraces stocking density and routine moving to clean pastures (Stear et al. 2007). Grazing management is related to the ecology of parasite larvae, plant species in grazing pasture, epidemiology of parasites, climatological status, schedule of using antiparasitic drugs and prevailing conditions (Hamad 2014). Another method to control parasitic infections is biological control, including the use of nematophagous fungi (e.g., *Duddingtonia flagrans*), which directly decreases the number of infective larvae (L3) in pasture (Waller et al. 2004). Addition of fungal spores to feed is also an effective method to control worms (Waller and Thamsborg 2005).

Plants have been used from ancient times for treatment of domesticated animals and humans. Plants are important sources of antibacterial, antiparasitic and insecticidal agents. Plants are being studied in different parts of the world for their ovicidal, adulticidal and larvicidal anthelmintic activities (Githiori et al. 2004; Masood et al. 2013; Tugume et al. 2016; Kebede et al. 2017). Antiparasitic agents extracted from plants have also been used in human and animal populations, but compared to commercial antiparasitic drugs, their scientific evaluation is limited (Masood et al. 2013; Badar et al. 2017). Use of botanical de-wormers is a good approach and is a possible augmentative solution to combat antiparasitic drug resistance (Jabbar et al. 2006).

Malnutrition and Parasitic Infections

Malnutrition and parasitic infections are directly related (Hailegebriel 2018). Malnutrition occurs in cases of GI parasitic infections due to induction of intestinal bleeding, impaired digestion and poor absorption of nutrients (Din et al. 2018). These parasites also lead to reduction in feed intake, fat absorption, protein usage and loss of nutrients in the form of diarrhea (Robertson et al. 1992). Likewise, malnutrition adversely affects local and systemic immune responses, resulting in increased susceptibility to parasitic infections (Koski and Scott 2001; Rajoo et al. 2017). GI parasites are one of the major risk factors which contribute to malnutrition, reduced performance and poor productivity in livestock and poultry (Yun et al. 2000). In human populations, malnourished people are primarily at risk of getting heavy parasitic infections, and helminthic infections with *Ascaris lumbricoides,* hookworms, *Trichuris trichiura* and *Schistosoma mansoni usually* cause malnutrition in humans (Papier et al. 2014; Mekonnen et al. 2014).

Among environmental factors, nutritional status plays an important role in affecting resistance to infection. Protein malnutrition in this regard is of prime consideration, as it leads to poor immunity and increased parasite burden (Clough et al. 2016). The public and veterinary health significance of helminth infections are often studied in the laboratory with the model roundworm, *Heligmosomoides (He.) polygyrus* in mice (Behnke et al. 2009). This parasitic infection may result in poor growth (Coltherd et al. 2011). The parasite load varies in different strains of the mice, representing genetic variation for resistance (Reynolds et al. 2012).

Immunity and Gastrointestinal Parasites

The GI tract of animals and humans harbors various species of nematodes, as these parasites have adapted themselves for nutrient uptake and evasion of local immune responses at the intestinal interface of the host. These parasites provide a strong challenge to the immune system of the host, leading to repeated exposure to infective stages, resulting in high endemicity of the parasitic infection (Sorobetea et al. 2018).

On entering the body of the host, first task for a parasite is to take over its immune system to reach its predilection site. This process depends upon the exact location and type of parasite and involves crossing host tissues, membranes and blood or lymphatic barriers. This is achieved by the wide variety of proteinases which are present in excretory/secretory (ES) products (Tort et al. 1999). The larval or adult forms produce these proteinases, which hydrolyze collagen, fibrinogen and hemoglobin. Metalloproteinases, serine, aspartic and cysteine proteases have been reported for GI nematodes. Most of them are related to zinc metalloproteinases and cathepsin B-type cysteine proteinases (Dezfuli et al. 2015).

Parasites play an important role in the adjustment and formation of the immune system in humans and animals. Strong mucosal Th2, Th1, and regulatory responses have been reported in hookworm infections, resulting in up-regulation of IL-15 and a complex, ALDH1A2. The juvenile stages of parasites in most helminth infections cause robust Th2 immune responses in their mammalian hosts. *Fasciola (F.) hepatica* (liver fluke) colonizes ruminants and can down-regulate the Th1 immune responses in mice, even in strains that are unable to produce IL-4 (O'Neill et al. 2000). This indicates that Th2 cells or cytokines are not the only factors to act against helminths, and the wide spectrum of proteins such as ES components are produced by these parasites, which assist them to evade host immune responses, including IFNγ production, invasion of tissue and feeding (Lucena et al. 2017). Infection with trematodes, like *F. hepatica* and/or *Dicrocoelium dendtriticum* in ewes, can lead to the development of mastitis after parturition. It has also been observed that ewes suffering from pregnancy toxemia are presented with increased β-hydroxybutyrate concentrations when infected with trematodes (Mavrogianni et al. 2014).

Deficiency of certain minerals in animals can be identified by alterations in metabolic activity (like enhanced cell proliferation) and alterations in rapidly growing tissues, which are badly affected due to mineral deficiency (Guthrie 1986). Mineral deficiency also has a profound effect on cells having shorter half-life and should be replaced frequently, such as lymphocytes. The intestinal immune responses induced by GI parasites are both physiologically complex and redundant in nature (McClure 2000). Mucous secretions, smooth muscle, nervous system and epithelium are the local protective barrier, in addition to innate and acquired immune systems. Among these, the mucosal immune system is substantial and more active metabolically; it is more profoundly affected due to mineral imbalance. Mucosal immune responses are acquired at the cost of higher requirements of nutrients; protein loss and malabsorption of nutrients may be enhanced due to disturbances in the integrity of GI tract due to worm infection (Humphrey et al. 2002). Therefore, trace minerals are essentially required for metabolic pathways involved in intestinal immunity (McClure 2008).

Role of Trace Elements in Animal Health

Even though animals require only very small amounts of TEs to maintain homeostasis, deficiencies of these elements may lead to deformities of the skeletal system, decreased growth rate, and immunodeficiency. Trace elements have been used as an immune-potentiating tool (to enhance the immune profile) of humans and animals all over the world. There are about 52 TEs required in animals; among these, 16 are categorized as macro {i.e. phosphorus (P), calcium (Ca), chlorine (Cl), sulfur (S), sodium (Na), magnesium (Mg), and potassium (K)} or micro minerals {i.e., zinc (Zn), cobalt (Co), manganese (Mn) selenium (Se), iron (Fe), copper (Cu), molybdenum (Mo), fluorine (F) and cadmium (Cd)}. These TEs are considered essential for the proper functioning of various physiological systems of the body. The possible functions and general mechanism of TEs to maintain the health of animals are shown in Fig. 1. Other TEs are also necessary, but are under less consideration because their excess and deficiency mostly do not show severe clinical signs (Spears 1999; McDowell 2003; McClure 2008). Following are some of the TEs that are essential for development of immunity in humans and animals: Na, Mg, S, K, P, Fe, Ca, Zn, Se and Mo (McClure 2008; Arthington and Havenga 2012). Table 1 summarizes the physiological and immunomodulating roles of some selected TEs in animals.

Imbalance in TEs ratio in feed is the main issue affecting livestock populations, mostly in grazing animals (Samanta and Samanta 2002). Deficiency of TEs is among the major causes of reduced and low-quality meat production, poor quality wool, poor quality hair and death of animals around the world (Grace and Knowles 2012). Minor TEs deficiency does not cause evidently harmful effects, and remains undetectable; however, clear signs and symptoms can be observed in severe deficiency. Deficiency may thus lead to severe diseases in animals (e.g., Cu deficiency causes swayback disease, deficiency of Mg causes grass tetany and that of Ca causes rumen stasis, blindness, and death; Suttle 2010). A high rate of mortality has been reported in animals reared in mineral deficient areas (Soetan et al. 2010). Skeletal disorders may not be directly related to Ca deficiency, but may also be attributable to an imbalance in the proportion of Ca and P in the diet (McClure 2008). In most cases, excess of one TE decreases bioavailability of another (e.g., Mg deficiency may be due to excess K (McClure 2008), and excess of Fe and Mo decreases absorption of Cu (Keen et al. 2003)). The mechanism of reducing resistance against diseases due to TE deficiency is shown in Fig. 2.

TE deficiency causes severe losses to the livestock industry to an extent similar to those caused by infections. These possess a special enzyme system that on activation helps to develop resistance against diseases (Suttle and Jones 1989; McClure 2003). Zn, Cu, Co, Fe, I, Mn, and Se are important for normal immune function (Radostits et al. 2007). These minerals play a role in: (a) defense against oxidative damage to tissues, (b) reduction of inflammatory reactions and (c) association with antioxidant enzymes (McClure 2008). Uncontrolled oxidation results in a weakened immune system in animals (Arthington and Havenga 2012). Trace elements can act as cofactors for certain enzymes (Hussein and Staufenbiel 2012), which act as antioxidants and are vital for maintaining livestock immunity (Gressley 2009). The list of TEs that act as cofactors and components of various enzymes is given in Fig. 3.

Table 1: Physiological and immunomodulatory roles of selected trace elements in animals

Sr. No.	Trace Element	Physiological role	Immunomodulatory role	Reference
1.	Sodium	absorption of different nutrients; increase appetite of animals; transmission of pulse; response to stimuli and peristalsis of gut	enhance production of granulocyte–macrophage colony-stimulating factor (GM-CSF), tumour necrosis factor-α (TNF-α) and enhances immunity.	McDowell, 2003; Wu et al., 2013
2.	Magnesium	production of vitamin B6; takes part in oxidative phosphorylation, and metabolism of lipids, carbohydrates, and protein	combines lymphocytes to target cells; provides energy to the cell for normal functioning and development of immunity.	Keen et al., 2003; Fekete and Kellems, 2007
3.	Phosphorus	component of protein (phosphoprotein), sugar phosphates, ATP and some enzymes; formation of microbial proteins in the rumen & increased appetite	maintaining the immune response and provide energy to the cell.	Keen et al., 2003
4.	Sulfur	present in amino acids, enzymes, hormones (insulin and corticosteroid) and vitamins (biotin and thiamin).	plays a role in replication, transcription, translation, antioxidant defense and immunity; maintains the mucosa of the intestine and controls inflammation.	Grimble, 2001
5.	Potassium	production of enzymes; nerve transmission and response to stimuli	modulation of macrophage physiology	McDowell, 2003; Villalonga et al., 2010
6.	Calcium	necessary for integrity of tissues and helps in muscle contraction	stimulates production of immune cells and provides energy for normal cell functioning and controls peristaltic movements	Fekete and Kellems, 2007
7.	Vanadium	used in protein, lipid and carbohydrate metabolism; controlling glucose level in the body	stimulates immune responses and enhances immunity by providing energy to the cells of the immune system	McDowell, 2003
8.	Manganese	part of many metalloenzymes and enzymes like kinases, hydrolases, transferases, and decarboxylases; neurotransmission, metabolism of lipids and carbohydrates	activation of inflammatory cells, i.e., neutrophils and macrophages	McDowell, 2003; Zhu and Richards, 2017
9.	Iron	cofactor of many enzymes; transportation of oxygen and carbon dioxide	activates the propagation of T and B cells, antibodies and compensates the amount of Fe in case of blood loss after worm infestation	Keen et al., 2003; Cassat and Skaar, 2013
10.	Cobalt	preparation of cyanocobalamin, methylcobalamin	enhanced anti-inflammatory properties	Nagabhushana et al., 2008
11.	Copper	formation of cytochrome C oxidase, ATP and monoamine oxidase; regulation of adrenal functions in neurotransmission and acts as an antioxidant; maintain the function of the body e.g. as cofactor, metalloprotein, and metalloenzymes.	epithelium repair, energy provision to cells, T cells and antibody formation,	Keen et al., 2003; Fekete and Kellems, 2007
12.	Zinc	part of many metalloenzymes and also regulates their functions; used in Vitamin A metabolism, replication, and transcription; increases appetite and plays a role in fetal growth	acts as an antioxidant and stimulator of thymulin; increases production of lymphocytes, provides energy for cell functioning and transcribes immune cells	Park et al., 2004
13.	Selenium	part of enzymes (glutathione peroxidase) and proteins; regulates reactions, energy and arachidonate metabolism; helps in cell integrity, brain functions and endocrine maintenance	limits tissue damage due to oxidation, controls immune response and inflammation	Hoffmann and Berry, 2008; McClure, 2008; Hefnawy and Tortora-perez, 2010
14.	Molybdenum	present in enzymes like xanthine oxidase, sulfite oxidase, and aldehyde oxidase; role in purine nucleotides, vitamin B6 functioning, and metabolism of lipids and carbohydrates	multiplication of immune cells and inhibition of anti-inflammatory mechanisms	Johnson et al., 1974
15.	Iodine	production of thyroid hormone in the form of thyroxin; starts ATP production and regulates oxidation rate and protein formation	cell growth and control of immune responses	McDowell, 2003; McClure, 2008

Role of Trace Elements against Gastrointestinal Parasites

Although some TEs are required in small amounts, their deficiency may cause problems, such as decreased resistance against bacterial and parasitic infections, decreased immunity, placenta retention, abortion, reduced growth and development (Suttle 2010). Limited information is available regarding any possible association between TE deficiency and GI parasitic infections in livestock. In the abomasum, parasites present in the growing stages can affect P and Ca absorption, resulting in skeletal defects. Sheep infected with larvae of *Ostertagia circumcincta* showed a deficiency of Ca and P, but in the case of *Trichostrongylus colubriformis* infected sheep, along with Ca and P deficiency, inhibition of skeletal development was also recorded (Fekete and Kellems 2007). Low levels of Co, Zn, and Fe in sheep infected with Fascioliasis have been observed (El-Sangary 1999). Rams infected with *H. contortus* showed a significant effect on the mean levels of Zn, Co, Se and Cu (Kozat et al. 2007). It has been stated that TEs may be used for effective and quick cure against GI parasitic infection. Administration of Cu, Se and vitamin E in sheep showed a significant increase in immunity against *H. contortus* (Camargo et al. 2010; Soli et al. 2010). The roles of some essential TEs for the development of immunity and their effects against GI parasites are discussed below:

Copper

Copper plays an important role in the maintenance of various biological processes, such as antioxidant protection mechanisms due to Cu/Zn superoxide dismutase (CuZnSOD) activity, Fe homeostasis, and energy metabolism (Whittaker 2010). Due to the role of Cu in oxidation mechanisms, its proper level is necessary for the appropriate function of defense against oxidative stress and infectious diseases (Huang et al. 2012).
Copper deficiency in animals may cause symptoms related to the immune system (Suttle and Jones 1989). Most prominent symptoms reported in Cu-deficient animals are: decreased T and B cell mitogens on splenic lymphocytes, decreased T cell numbers (most importantly T-helper cells), decreased response to antibodies, and increased susceptibility to infections, ataxia, growth reduction, diarrhea, anemia, abnormal pigmentation, decreased reproductive performance and increase in bone disorders (Suttle and Jones 1989).
The mode of action of Cu against GI parasites is not clear. It may act as an intraluminal anthelmintic or affect host immune response as a nutritional supplement (Langlands et al. 1989). The role of Cu in GI parasitic infections, especially in nematode infections, has been widely explored in animals (Frandsen 1982). Different methods were used to establish the Cu requirement to reduce GI nematode burdens in dairy animals infected with *Haemonchus* sp. (Chartier et al. 2000). Copper supplementation is reported to cause a reduction in

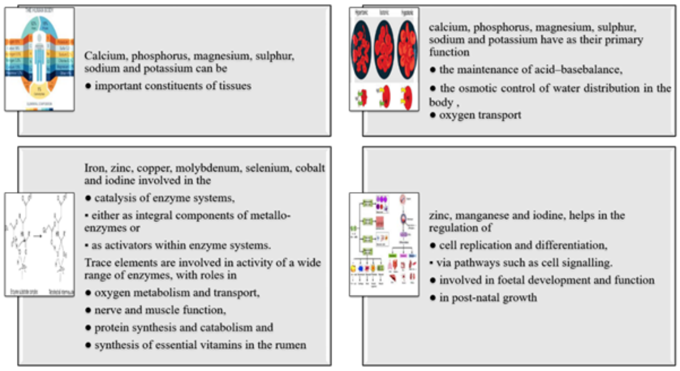

Figure 1: Possible functions and general mechanisms of trace elements in maintaining the health of animals.

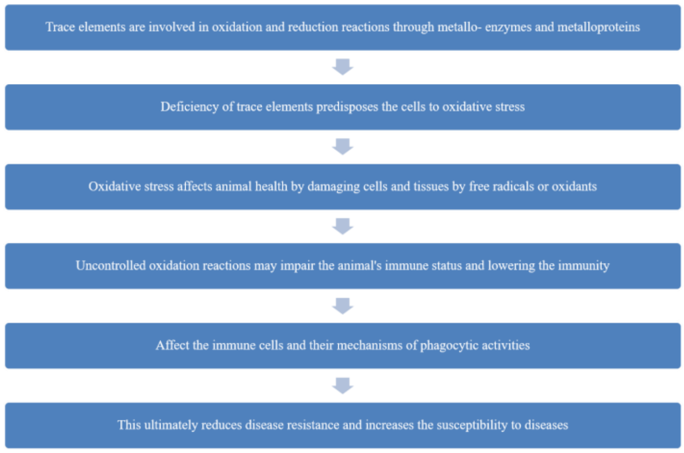

Figure 2: Showing how deficiency of trace elements impairs disease resistance.

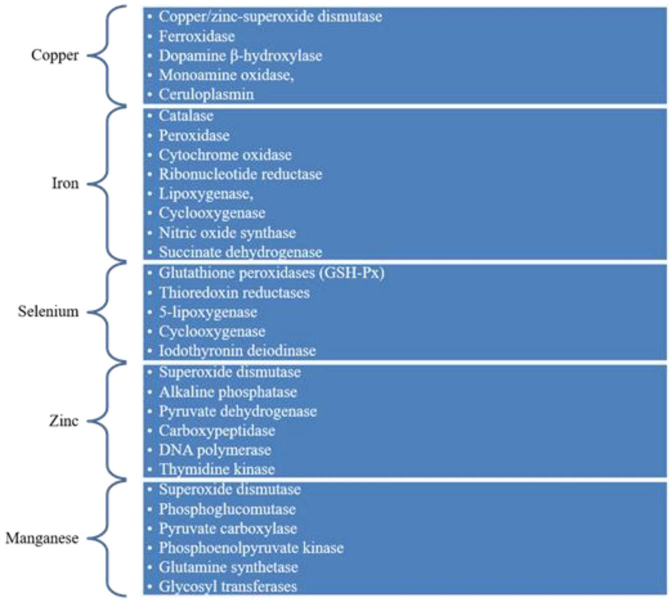

Figure 3: The list of trace elements which act as cofactors and components of enzymes in physiological processes.

abomasal nematodes (Burke and Miller 2006). Hucker and Yong (1986) noted higher worm burden and fecal eggs per gram (EPG) in Cu-deficient sheep compared to those with normal Cu levels. Animals with ostertagiasis showed a reduction in blood Cu level, probably because of interferencewith Cu metabolism due to increased pH of the abomasal and duodenal digesta (Bank et al. 1990). The effectiveness of oral Cu supplementation is related to a high concentration of soluble Cu in abomasal digesta. In case of nematode infections, reduction in blood Cu concentration is reported (Poppi et al. 1990). Cu availability is reduced in helminth-infected animals and the magnitude of effects is not related to the dietary Cu level. Animals with low Cu levels exposed to infective larvae of *Trichostrongylus (T.) axei* and *T. colubriformis* showed decreased ceruloplasmin activities, with decreased Cu levels in the plasma and liver.

The use of copper oxide wire particles (COWP) results in a significant reduction of *H. contortus* worm load (Vatta et al. 2009). Experimental infection trials also showed the persistent efficacy of COWP against *H. contortus* (Chartier et al. 2000); however, observations of Burke et al. (2007) and Vatta et al. (2009) showed a non-persistent effect of COWP. Oral administration of COWP to animals had a direct effect on parasites and resulted in lower EPG and worm burden in livestock (Soli et al. 2010). The effect of Cu level on the immune system and health of animals is shown in Fig. 4.

Selenium

Selenium is a vital element and plays an important role in increasing immune competence of the host by neutralizing oxidation reactions (Hoffmann and Berry 2008). Selenium-deficient diets decreased resistance to parasitic infection. Utilization of Se may provide effective antioxidant protection against the oxidative stress experienced during *H. contortus* infection (Burke and Miller 2008). Subclinical deficiency of Se results in reduced production and immunosuppression in animals (Hefnawy and Tortora-Perez 2010). In the case of parasitic infections, the host responds to the parasite by generating reactive oxygen species (hydroxyl radical, hydrogen peroxide, superoxide anion radical, peroxynitrite and nitric oxide) that damage the parasites but also enhances oxidative stress for the host (Sorg 2004; Rosenfeldt et al. 2013). Phagocytes, such as eosinophils, macrophages, and neutrophils, are responsible for the production of these reactive oxygen species, which may cause severe damage to the host through immunosuppression (Kotze 2003).

Neutralization of reactive species can occur by antioxidant defense systems, consisting of enzymatic (i.e., glutathione peroxidase,GPx), glutathione reductase, catalase (CAT), superoxide dismutase (SOD)) and non-enzymatic defenses such as reduced vitamins A, C and E and glutathione (Sorg 2004; Rosenfeldt et al. 2013).

GPx is involved in a chain of reactions catalyzing the formation of thromboxanes, prostacyclins, prostaglandins, and leukotrienes (Leal et al. 2010; Rosenfeldt et al. 2013). Selenium is a component of GPx and there is a strong association between the level of Se and enzyme activity. Deficiency of Se results in lower amounts of functional GPx, which may lead to severe cellular damage due to changes in the structure of proteins, polysaccharides, DNA and lipids (Hefnawy and

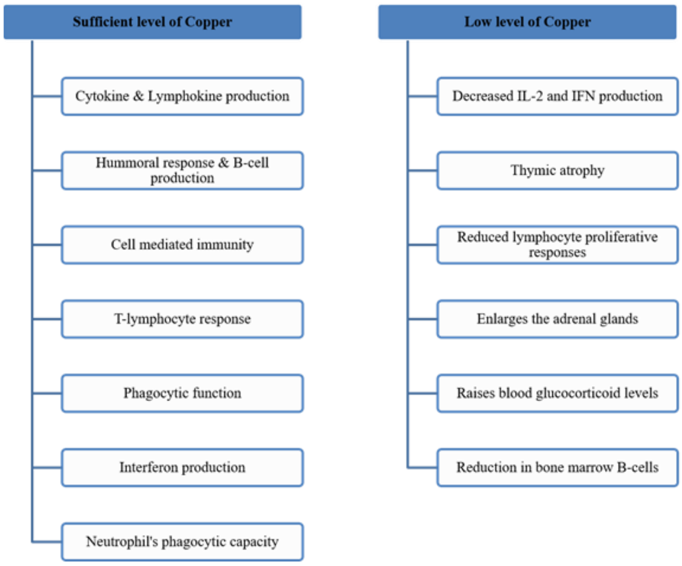

Figure 4: Effect of copper level on immune system and health of animals.

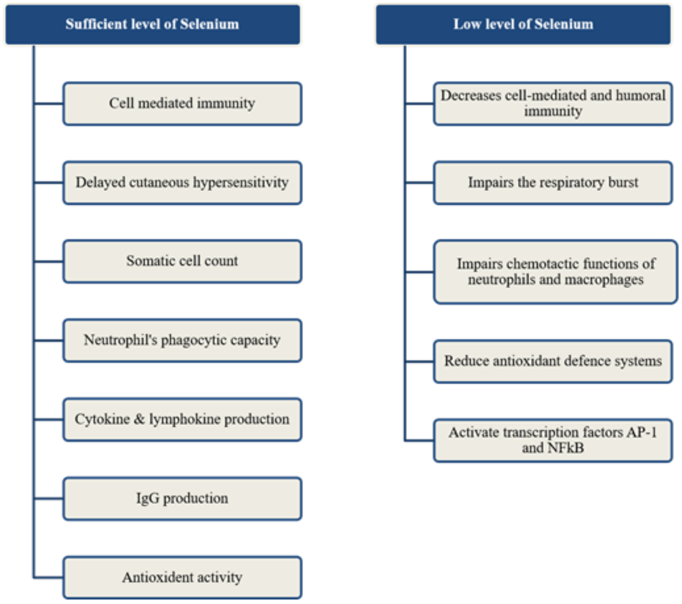

Figure 5: Effect of selenium level on immune system and health of animals.

Tórtora-Pérez 2010; Ferguson et al. 2012). Therefore, Se can be seen to be directly involved in proper working of the immune system, regulating phagocyte function, cell-mediated and humoral immune responses, and induction of pro-inflammatory cells that reduce oxidative cell production (McClure 2008; Leal et al. 2010).

Increased expression of TLR-4, L-selectin, selenocysteine-containing selenoproteins glutathione peroxidase-4 and IL-8R in animal neutrophils is related to supranutritional supplementation with Se-yeast. These genes are involved in the response against parasites and bacteria. Increased expression of the selenocysteine-containing selenoproteins GPx-4 leads to the lipid hydroperoxide free radicals detoxification in the intestinal mucosa (Speckmann et al. 2014). Deficiency of Se in *He. polygyrus*-infected mice led to an increase in adult worm numbers, parasitic egg production and fecal egg count

(Smith et al. 2005). Barium selenite injections in weaned Se-deficient lambs reduced fecal egg count and increased body weight (Celi et al. 2010), while use of intraruminal Se pellets in animals infected with *O. circumcincta* and *T. colubriformis* did not reduce worm counts or fecal egg counts (McDonald et al. 1989). According to Camargo et al. (2010), Se stimulates immunity of animals infected with *H. contortus*, resulting in a reduced number of parasites. The combination of Se and Cu had a significant effect on parasitic burden in terms of reduction in EPG and worm load in sheep infected with *H. contortus* (Silva et al. 2013). Celi et al. (2010) documented that the Se status of sheep has a vital role in resistance against parasitic infection. The Se supra-nutritional availability effects *H. contortus* infection and Se-yeast supra-nutritional supply helps to control the severity of infection (Hooper et al. 2014). A comprehensive outline of the effect of selenium level on the immune system and health of animals is shown in Fig. 5.

Molybdenum

The optimal range of Mo in feedstuff is 6-10 mg kg-1 dry matter, when the level of Cu is marginal, and this range is inconsistent with the maximal permissible concentration. Mo acts both as an essential nutrient and an immunity modulator, especially for mucosal immunity (Blood and Radostits 1989). Molybdenum is also vital for boosting the immune system and its deficiency predisposes an animal to primary and secondary infections. This element is necessary for the development of immune responses and normal functioning of the rumen microbial fauna, thus indirectly improving host nutrition (Ellis et al. 1958).

A low level of Mo in diets can reduce the ability of animals to reject challenges with *H. contortus* and *T. colubriformis* (Suttle et al. 1992; McClure et al. 1999). An optimum intake of about 4–8 mg/animal/day of Mo was found to be the greatest defense against parasites, as this level was linked to an increase in parasite-specific immune responses, i.e., jejunal mast cell numbers and antibody levels, proliferation of worm-specific lymphocytes, globule leucocyte numbers and eosinophil count.

Mo also plays a role in enhancing protection against inflammatory responses in nematodes, which is achieved through increased concentration of superoxide radicals in the mucosa, hence reducing the effectiveness of Cu-dependent inflammatory responses and the function of Mo as a co-factor for xanthine oxidation (Suttle et al. 1992). A similar mechanism is likely to be present in *T. colubriformis* rejection (Bendixsen et al. 1995). Another possibility is that the involvement of Mo in pyridoxal oxidase action mediated rejection of the parasites (Lee et al. 2002). Supplementation of Mo results in 78% reduction of *H. contortus* (Suttle et al. 1992) and 23% of *T. vitrines* (Suttle et al. 1992a). A low level of Mo in the diet reduces the ability of sheep to reject infection of *Trichostrongylus* sp. (McClure et al. 1999). Effects of Mo level on the immune system and health of animals are shown in Fig. 6.

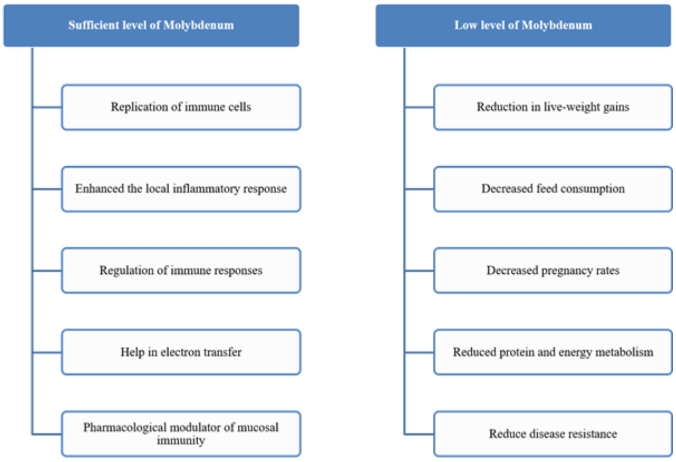

Figure 6: Effects of molybdenum levels on the immune system and health of animals.

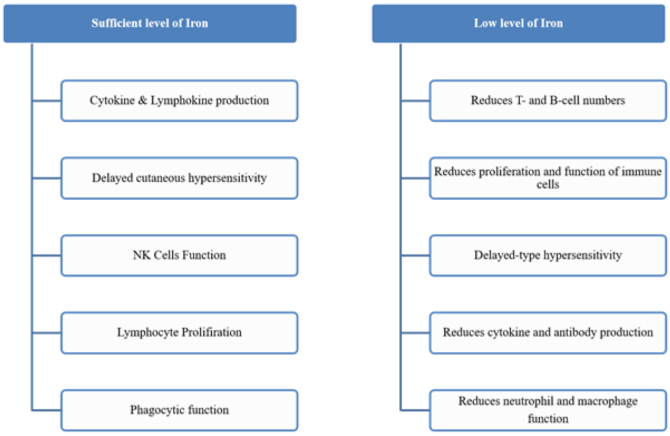

Figure 7: Effect of iron level on the immune system and health of animals.

Iron

Animals and humans are required to maintain optimum Fe concentration and Fe homeostasis based on its toxicity (Zhang et al. 2009). This mineral is a part of proteins, a cofactor for enzymes, iron-chelating proteins, and the heme group in hemoglobin and other hemoproteins (Dunn et al. 2007). Immunological processes in the host are regulated by minerals such as Fe, P, Co, and Zn, to make the immune system more responsive against parasites (Hughes and Kelly 2006).

Parasites need Fe to survive and reproduce and to produce disease in the body of vertebrate hosts, e.g., schistosomes (Jones et al. 2007). To cope with this situation, mammals have adapted themselves against these pathogens by activating iron-sequestering systems which minimize the concentration of free Fe in the body. Thus, lactoferrin and transferrin, Fe chelating proteins, lower the Fe concentration to levels below those needed for the parasite to survive (Nairz et al. 2010). Furthermore, infections are linked with hypoferremia, a host response in which free Fe in body fluids is reduced. Therefore, parasites have developed strategies to capture the Fe retained in proteins as in lactoferrin. In this way, lactoferrin acts as microbiostatic. In addition, Fe can also disturb the functional integrity of the parasite surface of *Giardia, Toxoplasma* and *Entamoeba,* thereby acting as a parasiticide (Ordaz-Pichardo et al. 2013).

Anemia due to Fe deficiency results in *G. intestinalis* and other protozoal infections due to destruction of intestinal mucosa, leading to malabsorption of micronutrients like Fe. Gastrointestinal parasitic infections can also lead to Fe deficiency and anemia (Le et al. 2007). Fe-deficiency anemia in helminth infections is attributable to malabsorption of Fe from intestine and direct feeding on blood, hindering Fe metabolism (Adebara et al. 2011). Fe and vitamin B_{12} have positive relation with respect to the host and its parasite (Marcelo et al. 2007). Effects of Fe levels on the immune system and health of animals are shown in Fig. 7.

Zinc

Zn plays an important role in minimizing pathogenesis by up-regulating the immune system through activating defensive mechanisms (Hughes and Kelly 2006; Ahmad et al. 2020). It is an essential element in cell-mediated cytotoxicity, T- and B-helper cell function, and other immune responses that enhance the efficiency of gut epithelial barriers and hence intestinal immunity against GI parasites, specifically nematodes. Zn deficiency can lead to down-regulation of these immune responses, resulting in increased susceptibility of animals to parasites (Scott and Koski 2000; Hughes and Kelly 2006). Zn is also necessary for the immune system and can reduce parasite numbers (Bundy and Golden 1987).

It has been reported for mouse models that parasites can better evade immune responses in Zn-deficient hosts than in healthy mice because IL4 production is suppressed in the spleen of the former, leading to lowered titers of IgE, IgG1, and eosinophils, as well as poor performance of APCs and T-cells (Scott and Koski 2000). Zinc supplementation can prevent lambs from infection with *H. contortus* by disturbing its life-cycle and causing oxidative stress. Zn has also been proposed to possess anthelmintic activity against nematodes (Váradyová et al. 2018; Rizwan et al. 2019).

Studies of the effect of Zn on intestinal nematodes in animals in laboratory setting have shown variable results. Rats given feed deficient in Zn at 3 mg kg^{-1} showed higher *Trichinella (Tr.) spiralis* burden for longer periods of time than those in the control group (Fenwick et al. 1990). Similar results were reported in Zn-deficient rats infected with *He. polygyrus* and *Strongyloides ratti* fed on the Zn-deficient diet with Zn concentration of 3 mg kg^{-1} (Fenwick et al. 1990a). On the contrary, mice fed Zn at 5 mg kg^{-1} efficiently controlled *H. polygyrus* infection. Although Zn at 3 mg kg^{-1} increased survivability of the above-mentioned helminths, *Nippostrongylus brasiliensis* remained unaffected in mice at this concentration (Minkus et al. 1992). However, *H. polygyrus* survival was enhanced in mice fed Zn in diet at 0.75 mg/kg. It indicates that Zn has a role in intestinal immunity against helminths in laboratory animals. Zinc also has been reported to play an important role in the activation of humoral immune response in mice infected with *Giardia* (Astiazarán-García et al. 2015).

A reduced level of serum Zn was observed in animals infected with GI parasites. Animals infected with *T. colubriformis* showed 17% Zn reduction in serum (Symons 1983). Zinc supplementation resulted in a reduction of the worm burden of *S. mansoni* in hamsters (Mansour et al. 1983). Severe deficiency of Zn resulted in increased worm burden of *Tr. spiralis* (Fenwick et al. 1990). This element laos has a positive impact on the immune system against GI parasites in livestock and laboratory animals (Koski and Scott 2001). Effects of Zn level on the immune system and health of animals are shown in Fig. 8.

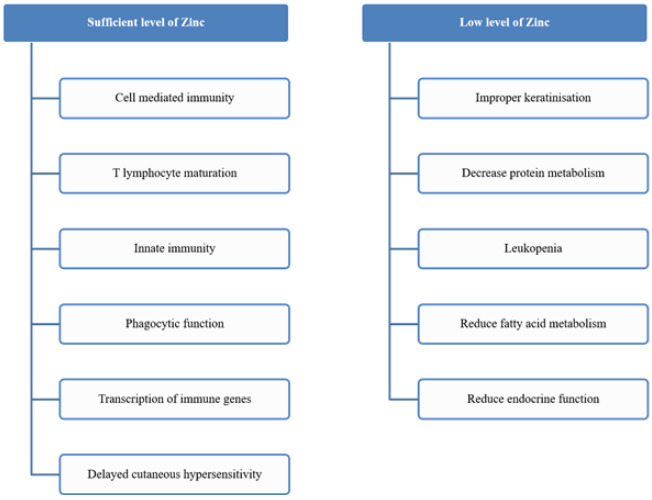

Figure 8: Effect of zinc level on the immune system and health of animals

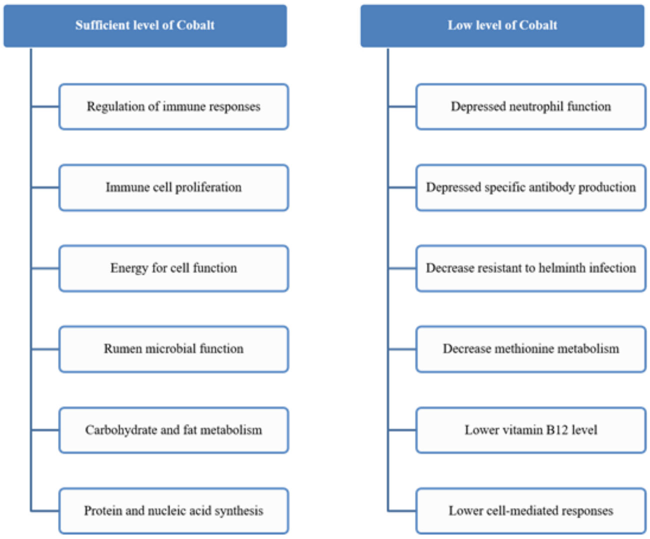

Figure 9: Effect of cobalt level on the immune system and health of animals

Cobalt

Cobalt (Co) is an important TE in the diet of ruminants, as it is required for vitamin B12 synthesis (National Academies of Sciences, Engineering, and Medicine 2016; Qudoos et al. 2017). Methylmalonyl-CoA mutase and 5-methyltetrahydrofolate homocysteine-methyltransferase are the two main enzymes which are dependent on vitamin B12 and play a major role in the formation of methionine and tetrahydrofolate (National Academies of Sciences, Engineering, and Medicine 2016). However, their relation to parasitic infection is not fully understood. Deficiency of Co results in a reduction of resistance against parasitic infections. Cobalt can help control parasitic infections, as cattle suffering from Co-deficiency are more prone to GI parasite infections (Silva et al. 2020). In a trial, lower cell-mediated responses to vaccination and higher EPG of nematodes were observed in animals fed low level of Co in the diet as compared to those having sufficient Co supplementation (Vellema et al. 1996). Effects of Co levels on the immune system and health of animals is shown in Fig. 9.

Molybdenum

The role of Mo in immunity is well-known and results in decreased *H. contortus* burden (McClure 2003). Parenteral administration of Mo results in worm rejection by the involvement of immune cells (Miller 1984).

Manganese

The relationship of Mn with parasitic infections in livestock is not well explored; however, excess Mn showed an increase in worm burdens in *Ascaridia galli*-infected chicks (Gabrashanska et al. 1999).

Conclusion

For the physiological functioning of the immune system, several micro and macro TEs are required. Essential TEs are important for cell metabolism and the immune system. Adequate levels of TEs, such as selenium, molybdenum, copper, iron, zinc and cobalt have significant effects on animal health through reduced GI parasitic infection. Other TEs are either directly or indirectly involved via physiological pathways that regulate mucosal immunity. The likelihood that minerals can affect gut immune responses of livestock against endoparasites can be predicted through implications generated in epidemiological and experimental studies in ruminants and monogastric species. Research is still needed to determine the effects of these minerals on mucosal immunity and determination of pathogenesis and control measures of already identified minerals and potentially involved minerals in humans and livestock species. Understanding immunity and nutrition is necessary for prevention of diseases. A systematic veterinary research approach is required to investigate the principles of mammalian resistance to gut diseases through epidemiological and clinical observation, followed by confirmation through experiments and elucidation of pathogenesis. This will allow the formulation of basic principles regarding physiological status and gut diseases across mammalian species.

It has been reported that deficiency of TEs in animals is directly associated with depressed immune system. Nutrition has the potential to affect GI parasites because it directly affects the degree of expression of the immunity and rate of acquisition of the infection, which can reduce the survival, fecundity, and establishment of GI parasites. A gap between TE deficiencies and parasitic infections in animals is reviewed in this chapter, which confirms the requirement for further research to explain their possible role against GI parasites. Due to sub-clinical deficiencies of TEs, animals use feed less efficiently, which may lead to a decrease in growth rate, low reproductive performance, and immunodeficiency. However, acute deficiencies of TEs cause huge economic losses in the sense of mortality. Therefore, it is important to identify TE-enriched pasture and soil to improve the immunity in animals.

Animals having inadequate supplies of nutrients are more prone to GI parasitic infections, which reduce their productivity. To determine the sufficient amount of TEs for animals, appropriate analyses of soil, forages, and animals are essential. Nutrition of animals depends upon soil-plant-animal complex, although season can strongly influence the dietary requirements for TEs. Deficiencies of TEs in soil and forages affect animal production adversely. Analysis of a particular area is imperative to assess its TE profile and to compare their availability for grazing animals.

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