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Immunity augmentation through nutritional approach in animals: A review

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Abstract
Immunity plays an important role to keep animals healthy and free from infectious diseases. Malnutrition may lead to decrease in immunity whereas, balanced supply of macronutrients like protein, carbohydrates, fat and micronutrients such as carotene, Vitamin E, Vitamin D, Selenium, Copper, Cobalt, Zinc, Chromium etc. along with feed additives such as prebiotics, probiotics, herbal extracts to animals leads to boosting the immunity of animals. Occurrence of diseases in animals leads to a minute to heavy economic losses due to a decrease in production and sometimes the death of animals. To keep animal healthy and productive, it is necessary to provide a balanced diet containing all essential nutrients in required quantity. Every nutrient contributes in development of immunity of animal directly or indirectly. Nutrients improves immunity of animals by provision of antioxidants, increase the number of immune cells or by improving the function of immune cells or organs.

Keywords: Nutrition, immunity, animals, macronutrients, micronutrients

Introduction

Dairy animals are routinely suffered from infectious, metabolic, parasitic diseases that have an effect on animal health, production and reproduction. An alteration in bovine immune mechanisms is a major contributing factor to increased health disorders (Sordillo, 2016) [39]. Increased incidence and severity of both metabolic and infectious diseases in dairy cattle is found mainly during the periparturient period. Health issues at the time of parturition have become problematic because they hamper the productive efficiency of cows in the coming lactation. Periparturient health disorders results in the decreased cow's productive capacity and increased mortality rates (Sordillo, (2016)) [39]. In dairy cattle, indirect economic losses due to diseases include the costs of antimicrobial drugs, vaccines, and surveillance measures, and the labour needed to implement treatment and control measures (Pritchett *et al.* (2005)) [33]. A many of the health disorders in the dairy cattle occur at the time of parturition are related with the difficulty in adapting to the nutrient needs for lactation. There is a relationship between metabolic status and immune function exists that leads to increase in the risk of disease. There is individual difference in physiological parameters in cows that experience problems in the periparturient period due to inadequate nutrient supply required for lactation. The imbalance in nutrients leads to decrease in immune function and increase the risk for disease as metabolites and nutrients, for example, Gln, glucose, BHBA and NEFA, can influence several important aspects of the immune response and thereby potentially disease resistance (Ingvartsen and Moyes, (2012)) [19]. From the data from various researches indicate that inadequate diets result in poor appetite, mal-absorption, and decreased growth. Thus, the consumption and absorption of nutrients that are critical for optimum immune responses (e.g., zinc, selenium, vitamin A, pyridoxine, vitamin E) are compromised (Chandra, (1996)) [9]. In cattle, nutritional status of cattle affects all physiological processes in the body, including the immune system. Therefore, the past and present nutritional status serves as an immune function modulator in cattle that can influence the performance and reproduction of beef cattle (Hersom, (2014)) [16].

Nutrition and immunity mechanism

The nutrients support the immune system via the provision of antioxidants. Immune cells are characterized by high levels of reactive oxygen species (ROS) that are used in part to kill ingested pathogens. In addition to high ROS generation, immune cell membranes are rich in the polyunsaturated fatty acids that are susceptible to ROS-mediated damage.

Table 1: Nutrients and their role in immunity

Nutrient	Role	Reference
Glucose/energy	Activation of immune system & phagocytic cells	Carroll and Forseberg, (2007) [7]; Van Eys and Moreland, (2016) [44]
Protein/amino acids	Reducing oxidative stress and improving immune function. Enhance antioxidant responses, increases the lymphocyte response to stimulation. Important in growth and development of immune cells. Maintenance of mucosal cells and improves the gut barrier function against bacterial infection. Role in Cytokine and ROM production, cell division; phagocytosis; CD4 Tcell abundance.	Coleman *et al.* (2020) [11]; Doepel *et al.* (2006) [12].
Buforin II	Stimulation of immune cell growth, stimulation of cell motility, induction of multicellular architecture and preventing bacteria from binding to mucosal epithelial cells.	Yamachika *et al.* (2002) [48]
Fat	Role in the synthesis of eicosanoids and cytokines (i.e., mediators of inflammatory response), signalling of T lymphocyte pathways by altering the molecular composition of lipid rafts	Bederska-Lojewska *et al.* (2013) [3]; Komprda, (2012) [20]; Swiatkiewicz *et al.* (2015) [41].
Carotenoids	Antioxidant activity, increased lymphocyte blastogenesis and increased neutrophil killing activity. Regulation of the differentiation, maturation, and function of cells of the innate immune system. Morphological formation of the epithelium, epithelial keratinization, stratification, differentiation, and functional maturation of epithelial cells and complete the indirect role of disease prevention, stimulated phagocytic and bacterial killing ability of neutrophils.	Huang, (2018) [17]; Michal *et al.* (1994) [25]; Tjoelker *et al.* (1988) [42].
Vitamin D	Role in the metabolism of foreign chemicals and in cellular development and differentiation.	Reinhardt and Hustmeyer, (1987) [35]
Selenium and Vitamin E	Antioxidant activity, enhanced neutrophil killing activity, improvement in the phagocytic activity of neutrophils, passive transfer of immunity from the dam to the calf	Hall *et al.* (2014) [15]; Mehdi and Dufrasne, (2016) [28].
Vitamin C/ Ascorbic acid	Lymphocyte proliferation, enhance neutrophil function and minimize free radical damage and protect the structural integrity of the cells of the immune system. Increase in antimicrobial and natural killer (NK) cell activities, lymphocyte proliferation, chemotaxis and delayed-type hypersensitivity. Scavenging reactive oxygen species (ROS) generated by stressors and prevents ROS-mediated cell damage by modulating gene expression.	Anderson *et al.* (1990) [1]; Behera *et al.* (2020) [4]; Bendich *et al.* (1986) [5]; Politis *et al*., (1995) [34]; Sontakke *et al* (2014) [43].
Vitamin B6	Role in cytokine production and NK cell activity.	Maggini *et al.* (2018) [27]
Folate	Maintains innate immunity by maintaining NK cell activity. Role in cell-mediated immunity.	Wu *et al.* (2019) [47]
Chromium	Improve cell-mediated and humoral response. Improve the proliferation of the T lymphocytes and enhance the cellular immunity. Improves cytokine production mainly IL-2, IL-4, IL-6, interferon$_{\gamma}$ etc. Regulating the activity of some immune-related enzymes and immunoglobulin content.	Shan *et al.* (2020) [37]; Wu, (2017) [46]
Copper	Enhances phagocytic activity of granulocytes, enhanced cell-mediated immunity (DTH response)	Forsberg *et al* (2010) [13]; Spears, (2000).
Zinc	Cofactor of superoxide dismutase (SOD) and proved the antioxidant activity through binding and stabilization of protein thiols. Modulates cytokine release and induces the proliferation of the CD8+ T cells that function as cytotoxic cells, able to recognize and kill pathogens.	Goselink and Jongbloed, (2012)
Cobalt	Required for synthesis of Vitamin B12. Vit.B12 is related with cell division and growth and thereby contributes in immune function. Maturation and proliferation of immune cells.	Spears, (2000) [40]; Sontakke *et al.* (2014) [43].
Iron	Increase of peripheral T-cells, enhanced phagocytic activity, natural killer activities, lymphocyte interleukin-2 production, delayed-type hypersensitivity	Sontakke *et al.* (2014) [43]
β-Glucans	Increased neutrophil functioning (i.e. production of reactive oxygen species, cytokine production)	Van Krimpen *et al.* (2014) [45]
Mannan-oligosaccharide (MOS)	Increased inflammatory response (i.e. phagocytosis and complement pathways)	Van Krimpen *et al.* (2014) [45]
Alfalfa	Increase heterophil functioning	Van Krimpen *et al.* (2014) [45]
Spray-dried animal plasma	Immune competence is mediated by the IgG component in the plasma. The IgG prevents viruses and bacteria from damaging the gut wall	Pierce *et al.* (2005) [32]
Probiotics	Increase in IgA and IgG levels of serum, increasing expression of toll-like receptors (TLRs), release of cytokines such as tumour necrosis factor-α (TNF-α), interleukin-4 (IL-4), and interferon-γ (IFN-γ).	Ashraf and Shah, (2014) [2].
Nucleotides	Stimulate the humoral immune response to T-dependent antigens and raise the total antibody level.	Ibrahim and EI-Sayed, (2016) [18]

Macronutrients and immunity

Carbohydrates (Energy), protein, fat these are the main macronutrients required to animal body for growth and to perform different body functions. Also, there is close interaction between these macronutrients and immunity of the animals.

1. Energy/carbohydrates

The maintenance of the immune system is dependent upon energy received from feedstuffs that are incorporated into the cattle's maintenance energy cost. For the activation of the immune system and the fever response requires energy expenditure to cattle (Carroll and Forseberg, (2007)) [7]. Effectiveness of the immune cells requires glucose and ketones that are affected by the changes in metabolism during the transition phase. This is especially happening due to lack of glucose during the transition phase, whose requirement has been demonstrated for phagocytic cells (Van Eys and Moreland, (2016)) [44].

2. Protein

In addition to their need for protein synthesis, AA serves as functional nutrients with a variety of roles in regulating key metabolic and immunological pathways such as one-carbon metabolism. These unique functions render the modulation of dietary AA supply during periods of stress such as the periparturient and preweaning periods a viable option for reducing oxidative stress and improving immune function. The data supporting the use of supplemental AA, particularly Met, Arg, and Gln, to enhance immune function and antioxidant responses during the periparturient period are strong (Coleman *et al.*, 2020) [11].

Protein concentrates should not be considered as a sole source in terms of their supply of indispensable and dispensable amino acids. Proteins have a role in the development of the immune system. Studies of protein-energy malnutrition showed that protein deficiency results in the impairment of cell-mediated immune responses. The role of individual amino acids is undetermined. Phenylalanine and tyrosine restricted diets enhance the cytotoxic immunity in tumour-bearing animals, reducing tumour growth and spread (metastasis). However, excess level of arginine in ration depressed tumour growth by 50 percent. Deficiency of branched-chain amino acids and of arginine + lysine increased splenocyte proliferation, but deficiency of sulphur amino acid leads to a decrease in splenocyte and lymphocyte proliferation. Increasing dietary methionine increases the lymphocyte response to stimulation with phytohaemagglutinin, with the maximum response at a greater level than needed.

Effects of glutamine and arginine in enhancing the immune system were recently studied by different researchers. Intestinal mucosa and lymphocytes have mainly responsible for metabolism of glutamine. Glutamine maintains mucosal cells and improves the gut barrier function against bacterial infection. Glutamine is a precursor for glutathione (GSH) that maintains the antioxidant status of cells, mainly the intestinal mucosa and lymphocytes. Glutamine is playing stimulatory role in immune response by Cytokine and ROM production, cell division; phagocytosis; CD4 Tcell abundance (Doepel *et al.*, 2006) [12]. Arginine can affect the immune system by increasing growth hormone with consequent effects on thymus weight and responsiveness and as the substrate for nitric oxide (NO) synthesis. Nitric oxide acts as a local messenger and as an endothelial relaxation factor, it involved in the maintenance of blood vessel dilatation and blood pressure control. Activated macrophages also produce the nitric oxide in much greater quantities (Miller, (2002)) [29].

Supplemental cysteine was also effective, having approximately 70 percent of the response to methionine (Konashi *et al.*, 2000) [21].

3. Buforin II

Buforin supplementation could decrease the jejunal and ileal mucosal lymphocyte amount as well as the calprotectin level. Calprotectin exerts antimicrobial effects through competition for zinc and by preventing bacteria from binding to mucosal epithelial cells. Buforin II significantly increased goblet cell amounts and the expression level of tight junction proteins (VEGF, HGH, Reg-3γ, TGF-β1, and TFF-3) in the jejunum and ileum. HGF acts on a wide variety of epithelial cells, as a mitogen (stimulation of cell growth), a mitogen (stimulation of cell motility), and a morphogen (induction of multicellular architecture), and is considered to be a key molecule for construction of structure during organ regeneration. TFF is a secretory protein expressed in gastrointestinal mucosa and may protect the mucosa from insults, stabilize the mucus layer and affect healing of epithelium (Yamachika *et al.*, 2002) [48].

4. Fat

The effects of dietary fatty acids on immunity are probably due to their role in the synthesis of eicosanoids and cytokines (i.e., mediators of inflammatory response), as well as in the signalling of T lymphocyte pathways by altering the molecular composition of lipid rafts (Komprda, (2012) [20]; Bederska-Lojewska *et al.*, (2013) [3]; Swiatkiewicz *et al.*, (2015)) [41]. A proper n-6: n-3 PUFAs balance in the diet may be important for optimal functioning of the immune system. It should be especially stressed that too high a n-6:n-3 PUFA ratio, often observed in livestock diets, can lead to an increase in the production of pro-inflammatory mediators (cytokines) such as tumour necrosis factor α (TNF), interleukin-1 (IL-811), and interleukin-6 (IL-6)and thus excessively enhance inflammatory response (Simopoulos, (2002)) [38].

Dietary n-3 PUFAs possess immunomodulatory properties, and that oils which are rich sources of n-3 PUFAs may beneficially modulate the immune systems of poultry and pigs. It should be stressed that the use of fish oil, as a direct source of n-3 PUFAs, yields better results in terms of immune response than the use of rapeseed or linseed oil rich in α-linolenic acid, a precursor of n-3 PUFAs. The dietary addition of 2-4% fish oil, decreasing n-6: n-3 ratio in the diet to 2-3, is the recommended level in terms of immunomodulation (Swiatkiewicz *et al.*, 2015) [41].

Micronutrients

Nutrients with antioxidant properties such as Carotenes, vitamin E, vitamin C, Zinc and Selenium supports the immune system.

1. Carotenoids

Carotenoids are plant pigments and antioxidants that include β -carotene, lurin, canthaxanthin, lycopene and astaxanthin. Carotenoids (i.e., β -carotene) have known source of vitamin A where, the cleavage of β -carotene precursor occurs that converts β -carotene into the active forms of vitamin A. However, carotenoids have immunostimulatory properties independent of their roles as precursors of vitamin A. In ruminants, supplementation with β -carotene at dry-off reduced mammary gland infections. β -carotene increased lymphocyte blastogenesis and increased neutrophil killing activity.

Retinoid acid plays crucial roles in the immune system by the regulation of the differentiation, maturation, and function of cells of the innate immune system. Innate immune cells are comprised of macrophages and neutrophils, which initiate immediate responses to pathogen invasion through phagocytosis and activation of natural killer T cells which perform immunoregulatory functions through cytotoxic activity (Michal *et al.*, (1994)) [25].

The epithelium lines all outer surface and most inner surfaces of organisms, and it functions as the “front line” of defence against pathogen invasion. Studies from recent years have shown that Vit. A plays a crucial role in the morphological formation of the epithelium, epithelial keratinization, stratification, differentiation, and functional maturation of epithelial cells and complete the indirect role of disease prevention. Research has shown that Vit. A improves the mechanistic defence of the oral mucosa, increases the integrity of intestinal mucus, and maintains the morphology and amount of urothelium cells. Also, crucial immune organs need constant dietary intake to maintain Vit. A-concentrations and RA was previously shown both to promote the proliferation and to regulate the apoptosis of thymocytes (Huang, (2018)) [17].

The increased bacterial killing could be accounted for partly by increased myeloperoxidase activity in the neutrophils. Tjoelker *et al.* (1988) [42] reported that dietary β-carotene stimulated phagocytic and bacterial killing ability of neutrophils from dairy cows during the stressful drying off period. However, retinol and retinoic acid generally had no effect on killing activity due to decreased phagocytosis.

Schwartz *et al.,* (1990) [30] reported increased cytochrome oxidase and peroxidase activities in macrophages incubated with canthaxanthin, β-carotene, and α-carotene compared with incubation with 13-*cis* retinoic acid. The stimulatory activity of canthaxanthin was greater than that observed with β-carotene and α-carotene. Phagocytosis also was stimulated by these carotenoids, even though to a lower degree.

2. Vitamin D

Vitamin D is not only important for bone mineralization but also plays a key role in the immune system, in the skin, cancer prevention, in the metabolism of foreign chemicals and in cellular development and differentiation. There is a regulatory role of vitamin D 1, 25- (OH) 2D3 in immune cell functions (Reinhardt and Hustmeyer, (1987)) [35].

Immune cells utilize 25 (OH) D3 independent of the kidneys, but the optimal 25 (OH) D3 concentration for immune function has yet to be determined (Nelson, (2014)) [31].

3. Vitamin E and selenium

Vitamin E and Selenium play very important roles in the maintenance of the immune system in ruminant animals. A large portion of the benefits of these nutrients is related to their functions as antioxidants. Feeding elevated levels of Selenium to ruminant animals reduces the incidence of diseases. Selenium enhanced neutrophil killing activity and Selenium deficiency increases neutrophil adherence and altered adherence could affect the ability of neutrophils to attack and sequester pathogen. Vitamin E prevented the peripartum reduction in neutrophil superoxide anion production and impaired IL-1 production by monocytes. Vitamin E supplementation increases lymphocyte proliferation and Selenium and vitamin E increased antibody responses of dairy cattle. Injectible Selenium alone or in combination with vitamin E resulted into markedly improvement in the production of specific antibodies against E.coli. These two nutrients have shown the most consistent effects on the ruminant immune system.

According to Hall *et al.,* (2014) [15], feeding selenium-replete cows during late gestation a supranutritional selenium yeast supplement improves antioxidant status and immune responses after calving. There is a relationship between selenium content in the diet and mastitis frequency in cows, knowing that the phagocytic activity of neutrophils is the primary defence mechanism against mastitis.

Selenium has an impact on the innate and the adaptive immune responses of the mammary gland via humoral and cellular activities. Increased expression of natural killer (NK) cells in the spleen cells found due to supplementation of selenium to animals. There is an effect of selenium supplementation on passive transfer of immunity from the dam to the calf. Due to supplementation of Selenium to cows, a high concentration of IgG in the cow and calf serum and colostrum was reported. Number of researchers reported that high levels of selenium may cause both the inhibition of tumour cell proliferation and improvement of *in vivo* and *in vitro* immunity (Mehdi and Dufrasne, (2016)) [28]. Nair and Stanley (1990) [30] reported that an excess of selenium can have a detrimental effect on some immunological functions.

4. Vitamin C/Ascorbic acid

Neutrophil has a prime role in the killing of invading pathogens. Due to the deficiency of ascorbic acid, the ability of the cell migration to the site of the inflammation is reduced, results in the increased oxidative damage to the neutrophils and major antimicrobial agent, hypochlorous acid. Hypochlorous acid production is reduced that exert a negative effect on lymphocyte proliferation. In the presence of adequate levels of ascorbic acid, lymphocyte proliferation occurs normally (Anderson *et al.,* 1990) [1]. Ascorbic acid and other antioxidant vitamins such as vitamin E have been shown to enhance neutrophil function and minimize free radical damage (Politis *et al*., (1995)) [34]. Vitamin C is a known antioxidant and in this capacity can quench free radicals and thereby protect the structural integrity of the cells of the immune system (Bendich *et al.,* 1986) [5].

As per Sontakke *et al.,* (2014) [34], Vitamin C an antioxidant is an excellent source of electrons; therefore, it "can donate electrons to free radicals such as hydroxyl and superoxide radicals and quench their reactivity. Supplementation of vitamin C results into increase in antimicrobial and natural killer (NK) cell activities, lymphocyte proliferation, chemotaxis and delayed-type hypersensitivity. Vitamin C stimulates the liver detoxifying enzymes and prevents the toxic, mutagenic and carcinogenic effects of environmental pollutants. Vitamin C protects cells from reactive oxygen species generated during the respiratory burst and in the inflammatory response by maintaining the redox integrity of cells.

In summer the bird's body attempts to maintain its body temperature which leads to increase the generation of reactive oxygen species (ROS) and results in the disturbance of the balance between the oxidation and antioxidant defence systems, causing oxidative damages and lowered plasma concentrations of antioxidant vitamins. Vitamin C has a protective effect on the superoxide dismutase activity and contributes to reduce the oxidative stress via transcriptional and post-translational mechanisms. Vitamin C contributes to the defence mechanism directly by scavenging reactive oxygen species (ROS) generated by stressors and prevents ROS-mediated cell damage by modulating gene expression (Behera *et al.,* 2020) [4].

5. Vitamin B6

Vitamin B6 regulates inflammation and has a role in cytokine production and NK cell activity (Maggini *et al.,* 2018) [27].

Transportation of animals leads to immunosuppression. However, supplementation of Vitamin C, E and chromium prevents immunosuppression by minimizing the number of free radicals in the body that arise as a result of stress during transportation (Bhatt *et al.,* 2021) [6].

6. Folate

Folate maintains innate immunity by maintaining NK cell activity. Has a role in cell-mediated immunity. Folate is Important for sufficient antibody response to antigens.

It supports Th 1-mediated immune response (Wu *et al.,* 2019) [47].

7. Chromium

Supplementation of Chromium to dairy cattle in a biologically available form (e.g., Chromium amino acid complex or Cr-yeast) benefits immunity. It may improve cell-mediated and humoral response as well as resistance to respiratory infections in stressed cattle. Chromium fed as a chelate increased IgG2 antibody response to tetanus toxoid. It is possible that stress and consequent immunosuppression are required for clear benefits of Chromium supplementation to be detected.

T cells are the main cells that participate in the cellular immunity. A lot of studies have been confirmed that the supplementation of the chromium has a positive effect on the cellular immunity. Chromium could increase the conversion of peripheral blood lymphocytes by interactivity with insulin and cortisol. Chromium can improve the proliferation of the T lymphocytes, and enhance the cellular immunity. B cells plays a key role in the development of humoral immunity and that is reflected by the production of antibodies by B cells. Animal studies have been proven that the chromium has significant effects on the humoral immunity. Chromium also improves cytokine production mainly IL-2, IL-4, IL-6, interferon$_{\gamma}$ etc. Some researchers reported that the rate of proliferation and the number of T and B lymphocytes were significantly increased after activation of the immune system by Chromium. Chromium contributes to the immune function by regulating the activity of some immune-related enzymes and immunoglobulin content. Chromium may also improve the immune function by enhancing the immune effect of the vaccine or by lowering cortisol level or other immune intermediates (Wu, (2017)) [46].

Supplementation with Chromium yeast containing organic form of chromium promoted the antioxidant status of dairy cows by increasing the activity of GSH-Px, SOD, T-AOC but decreasing the concentration of MDA in the serum. Supplementation with CY increased serum IgG and decreased serum IL-1β, IL-2, IL-4 and IL-10 concentrations of heat-stressed dairy cows (Shan *et al.*, 2020) [37].

8. Copper

Natural copper deficiency increases the susceptibility of ruminant animals to diseases. However, experimental models of Copper deficiency often fail to increase the incidence of diseases. Copper supports immunity as it is associated with many proteins. Copper enhanced cell-mediated immunity (DTH response). A copper deficiency reduces the amount of ceruloplasmin which release during the oxidative stress. Apart from this Copper maintain the normal osteoblastic activity, collagen and elastin formation, normal maturation of RBC's, normal hair and wool pigmentation (Forsberg *et al.*, 2010) [13].

Copper enhances phagocytic activity of granulocytes (primarily neutrophils) and improves Immune response. Limited research suggests that dietary Cu may affect cytokine production in cattle (Spears, (2000)) [40].

9. Zinc

Zn deficiency has an opportunity to impact a large number of cellular events which might compromise immunity. As one example, Zn plays an important role in transcriptional control through its action as a Zn-finger motif. Zn deficient in cells resulted in the reduction of the ability to proliferate. The immune response requires rapid proliferation of cells (e.g., T and B-lymphocytes) in response to specific antigens and therefore, Zn deficiency prevents this aspect of immunity from developing. Zn deficiency has little effect on immune function in ruminant animals but that Zn supplementation may be beneficial.

Zn acts as a cofactor of superoxide dismutase (SOD) and proved the antioxidant activity through binding and stabilization of protein thiols. Zn deficiency leads to hampered macrophage functions, neutrophil functions, NK cell activity and complement activity. For the synthesis of thymulin, the thymic hormone Zn acts as a cofactor that induces several T-cell markers, and promotes T-cell function. It also modulates cytokine release and induces the proliferation of the CD8 + T cells that function as cytotoxic cells, able to recognize and kill pathogens (Goselink and Jongbloed, (2012)) [14].

Zn improved immune response in peripartum Sahiwal cows by increasing the production of TIG, IgG and IL-2 (Chandra *et al.*, 2014) [8].

10. Cobalt

Few researchers reported that Co deficiency leads to reduced neutrophil function and resistance to parasitic infection. Neutrophils in Cobalt deficient calves had reduced ability to kill C. albicans. Co-deficient calves had a decreased prepatent period and increased faecal egg output following experimental infection with Ostertagia ostertagi. Higher faecal egg counts were also observed in Co-deficient lambs after natural infection with gastrointestinal nematodes (Spears, (2000)) [40].

Vit.B12 is related with cell division and growth and thereby contributes in immune function. Due to lack of B12 vitamin, white blood cells can't mature and multiply. Vit.B12 decreased white blood cell response and shrinkage of the critical immune system organ, the thymus (Sontakke *et al.*, 2014) [43].

11. Iron (Fe)

Low iron levels leads to the reduction of peripheral T-cells, impairment of phagocyte, natural killer activities, lymphocyte interleukin-2 production, decreased delayed-type hypersensitivity and the thymus atrophy. Impaired neutrophil bactericidal activities and cell-mediated immune functions were recorded due to deficiency of iron that effect becomes reversible after adequate iron supplementation (Sontakke *et al.*, 2014) [43].

12. Fungal and bacterial cell wall (β-glucans)

β-Glucans bind Dectin-1-like receptor on animal cells (e.g. neutrophils, monocytes). This supports the innate immunity by increased neutrophil functioning (i.e. production of reactive oxygen species, cytokine production), resulting in reduced susceptibility for pathogen invasion (e.g. *Salmonella enteritidis*) (Van Krimpen *et al.*, 2014) [45].

13. Mannan-oligosaccharide (MOS)

MOS acts as a competition molecule for the adhesion of certain bacterial species in the gut, thereby reducing the risk of diseases. Next to this, MOS also has an anti-inflammatory working, but the exact mode of action is not known. However, MOS was also reported to have an increased inflammatory response (i.e. phagocytosis and complement pathways) (Van Krimpen *et al.*, 2014) [45].

14. Alfalfa

Alfalfa was shown to increase heterophil functioning and was also shown to prevent *Salmonella enteritidis* infection in moulting chicken (Van Krimpen *et al.*, 2014)) [45].

15. Spray-dried animal plasma

The immune competence improving effects of spray-dried animal plasma in young pigs is most likely mediated by the IgG component in the plasma. The IgG prevents viruses and bacteria from damaging the gut wall, thereby resulting in a more functional intestinal wall, improves intestinal morphology and enzyme activity as evidenced by increased villus surface area, and increased mucosal maltase and lactase activities (Pierce *et al.*, 2005) [32].

16. Plant extracts

Plant extracts are able to reduce serum TNF-α and haptoglobin, white blood cells and lymphocytes, and to mitigate villus atrophy after an *E. coli* challenge, thereby modulating the systemic inflammation caused by *E. coli* infection (Liu *et al.*, 2013) [23]. TNF-α is one of the most important cytokines released especially form macrophages and monocytes, in response to bacterial cell wall products and bacterial toxins. The effects of plant extracts on white blood cells and TNF-α showed that they may alleviate the overstimulation of the systemic immunity and early immune response in E. coli infected pigs. Plant extracts could reduce the recruitment of macrophages and neutrophils in the ileum of *E. coli* infected pigs, indicating that these reduce both systemic and local inflammation (Van Krimpen *et al*., 2014) [45].

17. Probiotics

Liu *et al.* (2019) [19] reported an increase in IgA and IgG levels of serum of musk deer after feeding of probiotics. Probiotics produce antimicrobial compounds, such as organic acids, hydrogen peroxide, bacteriocins, and biosurfactants, all of which can inhibit the growth of pathogenic microorganisms (Chaucheyras-Durand and Durand, (2010)) [10]. Probiotics promote the innate immune system by increasing expression of toll-like receptors (TLRs), resulted in the release of cytokines such as tumour necrosis factor-α (TNF-α), interleukin-4 (IL-4), and interferon-γ (IFN-γ) (Ashraf and Shah, (2014)) [2].

18. Nucleotides

The potential role of exogenous nucleotides as regulators of the immune function is very well proven by different studies in which indicated that the dietary nucleotides stimulate the humoral immune response to T-dependent antigens and raise the total antibody level (Ibrahim and EI-Sayed, (2016)) [18].

Conclusion

Macro as well as micro nutrients are important to improve the immune status of the animal and to prevent health disorders. To make Animal Husbandry more profitable disease prevention by improving the immune status of an animal is essential and that could be achieved by providing a balanced diet to animals.

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