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AUTHORS: Merve Gündüz, Arda Sözcü, Üzeyir Çagirici

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Review

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NUTRITIONAL ASPECTS FOR MODULATION OF POULTRY IMMUNE STIMULATION

Merve GÜNDÜZ1*, Arda SÖZCÜ1, Üzeyir ÇAĞIRICI2

¹Bursa Uludağ University, Faculty of Agriculture, Department of Animal Science, 16059, Bursa, Türkiye ²Kaman Türk Telekom Osman Kulaksız Vocational and Technical Anatolian High School, 40300, Kırşehir, Türkiye

Abstract: The immune system's defense mechanism has been affected by the management and nutrition conditions in poultry production. In biological aspects, Bursa Fabricius and Thymus are primary lymphoid organs that defend the body against diseases. The spleen, cecal tonsils, immunoglobulins, and various forms of mucosal immunity, BALT (bronchus-associated lymphoid tissue), MALT (mucosa-associated lymphoid tissue), CALT (conjunctiva-associated lymphoid tissue), and GALT (gut-associated lymphoid tissue), are also vital to their overall health. The management program (environmental conditions, heating, lighting practices) and feed (feed ingredients, composition, and feed additives) significantly affect birds' immunity and performance. Dietary supplementation enhances immune system activation by improving the lymphoid tissues and beneficial immune modulators and responses. During the past fifteen years, alternative feed additives (amino acids, minerals, vitamins, probiotics, prebiotics, synbiotics, vitamins, minerals, and organic acids, are essential for sustaining hormonal, physiological, and immunological processes. These additives, probiotics, vitamins (A, C, D, E), mineral (selenium) supplementations, and organic acids boost the immune system's activity against microbial pathogens and physiological stress mechanisms. Finally, this paper aims to review the current improvement in the relationship between nutrition and immunity in poultry.

Keywords: Immune system, B and T cells, Vitamins, Minerals, Organic acids

*Corresponding author: Bursa Uludağ University, Faculty of Agriculture, Department of Animal Science, 16059, Bursa, Türkiye							
E mail: mervegunduz@uludag.edu.tr (M. GÜNDÜZ)							
Merve GÜNDÜZ 👘	https://orcid.org/0000-0002-5449-9893	Received: July 19, 2024					
Arda SÖZCÜ 👘 💼	https://orcid.org/0000-0002-0955-4371	Accepted: August 04, 2024					
Üzeyir ÇAĞIRICI 🛛 💼	https://orcid.org/0009-0001-2445-0933	Published: August 15, 2024					
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1. Introduction

The immune system is characterized by the innate (maternal) and adaptive immunological developmental processes against with inadequate defence mechanism and health issues, predisposing individuals to microbial infections (Wynn and Levy, 2010; Alkie et al., 2019). To prevent the spread of viral, bacterial, fungal, and parasitic diseases in the body, the immune system plays a major role with its activity. The body produces defense molecules called antibodies, which recognize and deactivate pathogens (Sarıca et al., 2009). Besides, different pathogens potentiate the cellular and humoral response by altering the immune system's reaction (Shaji et al., 2023).

The immune system consists of various organs and tissues, including the Bursa Fabricius, thymus, bone marrow, spleen, the harderian gland, lymph nodes, circulating lymphocytes, and lymphoid tissue in the alimentary tract in poultry (Panda et al., 2015). Lymphoid tissue may be specialized into two types: primary and secondary. The thymus and Bursa Fabricius are considered primary organs, whereas the spleen is a secondary type of lymphoid tissue. The Bursa Fabricius belongs to birds and is absent from mammals due to evolution. In both hens and mammals, primary lymphoid tissue reduces after puberty, with the effects of sex hormones (Junior et al., 2018).

Animals have a precise immune system mechanism that resists pathogens and adverse environmental conditions (Korver, 2023). Among the immunosuppressive components are management, feeding programs, and nutrition deficiencies, which cause health and welfare issues (Wlazlak et al., 2023). Also, immunosuppression decreases body weight gain and production performance and increases mortality and morbidity rates mainly due to secondary viral and bacterial infections (Fussell, 1998; Rehman et al., 2016). Immune system activation on metabolism has a significant impact on maintaining broiler health to optimize performance and cost-efficient production. Thus, acute activation of the immune system leads to inflammatory pathways with reduced feed intake. The hypothalamic-pituitary-adrenal axis is activated when the immune system detects a foreign substance and releases chemical messengers known as cytokines. These cytokines are responsible for initiating the production of acute phase proteins (APP) in the liver, transmitting feedback to the brain, resulting in common illness symptoms such as fever and decreased appetite

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(Silverman et al., 2005; Rochell et al., 2016). It has been stated that immunity and production performance in poultry are positively correlated. Antibody production and immunity regulation depend on non-genetic factors, which include nutritional concentrations in the diet. At the same time, it has been proven that imbalance between nutrients or toxicity, disorders in the bird's physiology may occur due to immunosuppression. The immune system's reaction to harmful microorganisms penetrating the animal's body is related to its nutritional condition. Immune system suppression may result in inadequate body weight gain and feed conversion ratio, high mortality rate, uniformity issues, secondary bacterial infections, and lymphoid organ atrophy (Aviagen, 2009; Abo-Al-Ela et al., 2021). Currently, modern broilers have a rapid growth rate, high body weight, and efficient feed conversion, which makes them vulnerable to high disease rates and necessitates strong immune function. Because the nutrients in the feed are utilized for muscle growth, fast-growing modern broilers tend to have low disease resistance and are susceptible to diseases (Song et al., 2021).

Numerous factors, including diseases, environmental conditions, management practices, vaccination programs, physical type of feed material, and nutrition-related stress, weaken the immune system, potentially increasing susceptibility to infections (Abo-Al-Ela et al., 2021; Wlazlak et al., 2023). Nutritional deficiencies in the feed supplementation may result in deterioration in the growth and development mechanism of the immune system. Additionally, insufficient vitamin levels may compromise the immune system, enhancing susceptibility to infection and inflammation. During metabolic processes, vitamins of A, D, E, and C have been shown to significantly impact immune system function (Khan et al., 2023). For this reason, the review focused on the relationship between nutrition and immune system modulation of poultry.

2. Primary Immune Organs

The formation of the immune system organs begins in the embryonic stage and entirely functions with advancing age. The immune system organs generate functional lymphocytes and release them into the peripheral immune system to actively participate in immune responses (Naukkarinen and Hippeläinen, 1989; Gordon and Manley, 2011). In the avian immune system, there are two primary organs. The first one is Bursa Fabricius, associated with B-cells, and the second is the Thymus, associated with T-cells. Both organs produce B and T cells to improve poultry immunity. The thymus is located in the neck's ventral region and under the thyroid gland in front of the chest cavity. This gland is surrounded by a thin capsule composed of connective tissue. The compartments of the thymus gland contain reticular cells and lymphocytes. The thymus gland's primary function is to protect the body from infection by activating lymphocytes before and immediately after

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birth. Autoreactive T cells are responsible for eliminating killing cells and synthesizing thymic hormones during the maturation of T lymphocytes in poultry (Sarıca et al., 2009). T and B cells progress to the secondary lymphoid tissue to provide a defense, which includes the spleen and mucosa-associated lymphoid tissue (MALT). The primary lymphoid tissue is crucial in selecting lymphocytes (including T-cells and B-cells) for a robust immune response while preventing autoimmunity (Yasuda et al., 2003).

The lymphoid stem cells in the bone marrow generate the T and B cell precursors (Ratcliffe and Jacobsen, 1994; Ratcliffe, 2006; Garcia et al., 2021). Bursa Fabricius is placed in the dorsal of the cloaca and is responsible for the maturation of B lymphocytes, the killing of autoreactive B cells, and the synthesis of hormones. The Bursa Fabricius produces B-cells, which are responsible for synthesizing antibodies. Moreover, bone marrowderived stem cells that resemble lymphoid cells mature in the thymus and Bursa Fabricius before proceeding via the bloodstream and lymphatic circulation to peripheral immune organs (Gordon and Manley, 2011; Davison, 2022). During the exposure to foreign antigens, the immune cells exhibit proliferation and differentiation. Additionally, in peripheral blood lymphocytes, the proliferative activity indicates a strengthening functional activity of T and B cells, reflecting an elevated cellular immune function (Dekruyff et al., 1980; Naukkarinen and Hippelãinen, 1989).

3. Secondary Lymphoid Organs

It has been stated that spleen, bone marrow, harderian gland (in orbit), pineal gland (in the brain), mucosaassociated lymphoid tissues (MALT), bronchuslymphoid tissue (BALT), gut-associated associated conjunctiva-associated lymphoid tissue (GALT), lymphoid tissue (CALT) are secondary lymphoid organs in birds. MALT, BALT, GALT, and CALT lymphoid tissues comprise approximately 50% of the cells in the spleen. These lymphoid tissues accumulate on the skin or mucosal surface, where foreign antigens enter the body (Gurjar, 2013). The spleen is the largest of the secondary lymphoid organs and is surrounded by a capsule composed of connective tissue. It has several functions for the aging erythrocytes, erythrocytes production in fetal life, and granulocytes in postnatal life, to contribute to the formation of antibodies through B lymphocytes, phagocytosis through macrophage, and for accumulation of red blood cells (Júnior et al., 2018). On the other hand, spleen size increases through hyperplasia tissue, known splenomegaly, after exposure to pathogens. as Lymphocyte hyperplasia has also been observed in MALT. The germinal center is where avian antibodies are effectively produced (Junior et al., 2018; Lewis et al., 2019). Additionally, chickens have three classes of immunoglobulins similar to mammals: IgA, IgM, and IgY (equivalent to IgG). Although it has been suggested that chickens also have antibodies similar to mammalian IgE and IgD, this has not been proven. Chicken IgY and mammalian IgG characterize immunological similarities, and the DNA sequence of chicken IgY is similar to human IgE (Shimizu et al., 1992; Aizenshtein et al., 2016; Pereira et al., 2019).

4. Nutrition and Immunity

Birds' immune systems benefit considerably from a wellbalanced nutrition program. The function of the immune system is to struggle with the negative impacts of stress and protect against pathogenic diseases. The regulation of the immune system in poultry involves the progress of anatomy in lymphoid tissues, mucus production, immunologically active substances synthesis, cellular proliferation, activation, movement, intracellular killing of pathogens, and modulation and regulation of the immune process. The nutritional intake may influence chickens' immune reactions, substantially benefiting their well-being and health. Therefore, a balanced diet could enhance chickens' overall health by preventing stress-related immune suppression (Butcher and Miles, 2002). The stimulation of immune system reactions in poultry nutrition has been revealed (Montout et al., 2021; Selim et al., 2021; Yu et al., 2021).

Poultry production has been focused on improving feed efficiency, decreasing disease risk, and increasing performance (Korver, 2023). Feed additives in poultry nutrition have been used as an alternative to antibiotics due to their potential positive effects on the growth rate, feed conversion, and resistance against pathogenic diseases (Fonseca et al., 2010; Ganan et al., 2012). It is widely known that antibiotics have extensively impacted poultry production in terms of maintaining gut microorganism balance and promotion (Selaledi et al., 2020). Due to food safety concerns and the public demand for antibiotic-free farm animal products, many countries have banned of antibiotics in poultry nutrition as a routine of growth promotion (Neveling and Dicks, 2021). So that, alternatives to antibiotics are needed to sustain poultry productivity and promote their performance and immunologic response (Wickramasuriya et al., 2024).

Nutraceuticals, including essential minerals and vitamins, are fundamental to animal nutrition. Nutritional components significantly benefit by preventing diseases, exhibiting immunomodulatory properties, promoting overall health, and enhancing productivity, regulating gut microbiota (Alagawany et al., 2021; Shehata et al., 2022). Feed additives essentially comprise amino acids, minerals, vitamins, fatty acids, enzymes, prebiotics, probiotics, synbiotics, pigments, medicinal herbs, herbal extracts, antioxidants, organic acids, and flavoring agents (Alagawany et al., 2018; Mohammed et al., 2019; Elgeddawy et al., 2020; Adhikari et al., 2020; Rehman et al., 2020; Shehata et al., 2022). Synthetic supplements include essential amino acids (such as lysine, methionine, threonine, and tryptophan), vitamins, and minerals. Besides, nutraceutical dietary elements may enhance digestion, absorption, utilization, metabolism, and positive health status (Ravindran, 2010; Haq at al., 2016; Alagawany et al., 2021) (Table 1).

The nutrients have been known to potentially affect embryonic development and hatchability with the prevention of musculoskeletal, immunological, and circulatory issues (Uni et al., 2012). During embryogenesis, nutrients are mainly acquired from yolk, which mainly contains lipids and low levels of carbohydrates (Santos et al., 2010). Supplementing with bioactive substances such as amino acids, polyphenols, and prebiotics will enhance the immune system, reduce osteoporosis, and lower the risk of heart diseases (Chalamaiah et al., 2018). The application of in-ovo injection for various biological agents has been recognized for its efficacy in poultry production. The application of in-ovo entails using nutritional supplements such as carbohydrates, proteins, amino acids, vitamins, and minerals (Ohta et al., 1999; Bhanja et al., 2005; Zhai et al., 2011; Bakyaraj et al., 2012). L-Arginine (100 μ g/ μ L/egg) in-ovo injection on the 14th day of the embryonic stage enhanced survival rates, body weight, and immune response (IgM) in Subramaniyan et al. (2019) research.

After hatching, the early feeding program has gained immense importance for the developmental process of immunity in birds. Firstly, innate immunity is considered the defense mechanism, and adaptive immunity is for the protection against specific pathogens by the functions of lymphoid cells and antibodies. It has been stated that innate immunity is essential to secure all living organisms' cellular integrity, homeostasis, and livability (Buchmann, 2014; Romo et al., 2016).

The formation of birds' defense mechanisms begins in embryogenesis and continues to function for several days after hatching (Yasuda et al., 2003). Maternal antibodies in the yolk protect embryos and chicks (approximately one month) against microbial infection during egg incubation and after hatching. The secondary lymphoid tissues complete their development one week after hatching, facilitating an effective immune response and specific antibody production in chick vaccination (Yasuda et al., 2003; Hamal et al., 2006). Additionally, the posthatching period is significant due to a lack of maternal immunity (approximately one week) (O'Neal and Ketterson, 2012).

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Dietary Supplementation	Species	Effects	Reference	Access Web
Probiotics Bacillus coagulans, Lactobacillus plantarum Probiotics	Broilers	The higher level of serum IgY, IgA, IgM concentration	Yu et al., 2022	https://pubmed.ncbi.nlm.ni h.gov/35265699/
Lactobacillus fermentum, Saccharomyces cerevisiae	Broilers	The higher proportions of CD3+, CD4+, and CD8+ T-lymphocytes	Bai et al., 2013	https://pubmed.ncbi.nlm.ni h.gov/23436517/
Probiotics DFM supplementation	Broilers	Regulation of gut microbiota by increasing the log concentrations of beneficial bacteria (Bacillus, Bifidobacterium, C. butyricum, and Lactobacillus)	Heak et al., 2018	https://www.ncbi.nlm.nih.g ov/pmc/articles/PMC6212 764/
Probiotics Bacillus subtilis, Lactic acid bacteria, Saccharomyces	Laying hens	Decreased the expression level of proinflammatory cytokines such as <i>IL-1</i> , <i>IL-6</i> and <i>TNF-α</i> in ovary	Xu et al., 2023	https://www.ncbi.nlm.nih.g ov/pmc/articles/PMC9902 371/
Prebiotics Mannan- oligosaccharides, Beta-d-alucan	Broilers	Improved the chicken gut microbiome and alleviated the negative effects of heat stress	Sayed et al., 2023	https://www.ncbi.nlm.nih.g ov/pmc/articles/PMC1046 0421/
Amino acids Glutamine, arginine, threonine	Broilers	Improve the immune response against an <i>Eimeria and E. coli</i> challenge	Gottardo et al., 2017	https://www.scielo.cl/sciel o.php?script=sci_arttextπ d=S0719- 81322017000300175
Aminoacids I-threonine	Laying hens	Linearly increasing levels of IgG and total Ig	Azzam et al., 2011	https://www.sciencedirect. com/science/article/pii/S1 056617119312589
Minerals Organic and inorganic Zinc, selenium, chromium	Broilers	Increased humoral immune response and upregulation of chTLR4 gene expression in bursa and spleen indicates a beneficial effect of OTM in augmentation of the immune system	Jain et al., 2021	https://pubmed.ncbi.nlm.ni h.gov/34220108/
Minerals Chelated form Manganese, selenium, copper, iron, zinc	Broiler Breeder	Significant increase in the antibody titre against Newcastle disease	Mohammadi et al., 2023	https://www.tandfonline.co m/doi/full/10.1080/18280 51X.2023.2215248
Minerals Zinc, copper, manganese chelated with the hydroxy analogue of methionine	Laying hens	Trace minerals in the chelated form improved bird immune response to antigenic challenge at wk 63	Manangi et al., 2015	https://www.sciencedirect. com/science/article/pii/S1 056617119303046
Vitamins Vitamin A and K3	Laying hens	Improved the intestine antioxidant capacity	Li et al., 2022	https://www.scielo.br/j/rb ca/a/FDydzRcrPkdG93B6m wKfSYq/?lang=en
Vitamins Vitamin E	Broilers	There was no increase in antibody titer against the IB virus with 300mg Vitamin E /kg feed additive	Sadiq et al., 2023	https://dx.doi.org/10.3638 0/jwpr.2023.13
Organic Acids SAS- Formic acid, propionic acid, soft acid SAP- Propionic acid, citric acid, soft acid	Laying hens	Significant increase in small intestinal villi with the addition of SAS and SAP	Gül et al., 2014	DOI: 10.1399/eps.2013.5
Organic acids and essential oil Sorbic acid, fumaric acid, thymol	Broilers	Higher villus height of the duodenum and jejunum and muscular layers of the duodenum and ileum (0.30 g/kg EOA during the grower period)	Yang et al., 2018	https://pubmed.ncbi.nlm.ni h.gov/30564758/

Table 1. Dietary supplementation in poultry immune stimulation

5. Nutritional Aspects in Poultry Immunity

5.1. Amino Acids

Dietary supplementation has been essential in optimizing poultry production due to obtaining better performance and health status with lower feed efficiency. The immune system consistently functions with sufficient levels of protein, energy, and micronutrients, vitamins, and minerals in nutrition (Butcher and Miles, 2002; Alagawany et al., 2021). Amino acids are the fundamental components of protein, the primary substances contributing to the growth of chickens and the production of eggs (Baker, 2009). The mechanism of lymphocyte activation, natural killer cells, and macrophages regulating intracellular redox balance, gene expression, and cytokine production related to amino acid supplementation. Therefore, appropriate dietary amino acids are critical for inhibiting infectious disorders, particularly viral infections (Chandra ve Kumari, 1994; Calder, 2013; Montout et al., 2021).

Several amino acids, such as methionine, threonine, and arginine, were studied to determine their contribution to a beneficial host immunological response (Montout et al., 2021). It has been indicated that different methionine supplementation levels of 0.60% and 0.90% in turkeys and broilers respectively resulted in increased methionine levels in the peripheral blood (Mirzaaghatabar et al., 2011; Kubinska et al., 2014). Also, in broilers, the dietary supplementation of %0.65 methionine and %0.13 choline may result in higher antibody levels (Swain and Johri, 2000).

Arginine has been characterized as a regulator of both innate and adaptive immunity (Lindez and Reith, 2021). Dietary arginine supplementation in metabolic processes may affect birds' immunological responses to physiological hemostasis under stressful conditions. A group of enzymes known as nitric oxide synthases are responsible for converting arginine into citrulline and nitric oxide as the sole route of nitric oxide synthesis (Förstermann et al., 1991; Fernandes et al., 2009). Nitric oxide exhibits cytotoxic effects on immuno-activated cells and regulates the immune system (Hibbs et al., 1988). Furthermore, arginine enhances interleukin production and T lymphocyte proliferation in broiler chickens (Rodriguez et al., 2017; Montout et al., 2021). Increasing dietary arginine over 0.45% may affect macrophage phagocytosis by stimulating the production of key cytokines, particularly IL-1, IL-2, INF, and TNF-a in broiler chickens (Emadi et al., 2010; Xu et al., 2018).

Supplementing lysine and methionine enhanced antibody production in broiler chickens against Newcastle and Gumboro infections (Bouyeh, 2012). A deficiency in dietary lysine inhibits protein synthesis, including cytokines, and lymphocyte proliferation, impairing immune responses in chickens and leading to morbidity and mortality in response to infection (Kidd, 2004). Insufficient dietary lysine levels may result in hen antibody responses and cell-mediated immunity (Chen et al., 2003). Several essential amino acids (leucine, isoleucine, and valine) have been used in poultry nutrition. These amino acids contribute to protein synthesis, immune response modulation, intestinal tract health, and villi development (Kim et al., 2022; Liu et al., 2023). Leucine, isoleucine, and valine amino acids provide the amino groups for the synthesis of glutamine and recreate a crucial role in maintaining the gut barrier functions for epithelial cells. Furthermore, the immune system considerably depends synthesis to produce cvtokines, on protein immunoglobulins, immune cells, and other essential immune molecules (Morgan, 2021; Montout et al., 2021). According to Liu et al. (2023), there were no significant differences between the effects of reduced-protein diets supplemented with arginine or branched-chain amino acids on the short-chain fatty acid profile in the cecal content of broiler chickens challenged with Eimeria spp on day 21.

L-carnitine is present in high lymphocyte concentrations for biological functions. Two essential amino acids (lysine and methionine), three vitamins (ascorbate, niacin in the form of nicotin amide adenine dinucleotide and vitamin B6), and reduced iron (Fe2+) are required as cofactors for the enzymes involved in the metabolic pathway of L-carnitine synthesis (Borum, 1983; Rebouche, 1992; Leibetseder, 1995; Adabi et al., 2011). These amino acids inhibit the apoptosis of immune cells and enhance their proliferative response to mitogens (Adabi et al., 2019). It has been reported that supplementing the diet of broiler chickens with 100 mg/kg of L-carnitine enhances the innate immune response by boosting acute phase protein production, and L-carnitine reveals glucocorticoid effects (Buyse et al., 2007). The supplementation of L-carnitine considerably enhanced total IgG and IgA responses but not IgM in broilers (Mast et al., 2000). In a study, the addition of 100 mg/kg L-carnitine supplementation indicated significantly effect on higher antibody response and Newcastle disease virus in broiler. Besides, 100 mg/kg L-carnitine supplementation group showed the highest Bursa Fabricius, spleen and thymus weight compared to 0, 25 and 75 mg/kg L-carnitine group (Golzar et al., 2007).

5.2. Probiotics, Prebiotics and Synbiotics

Bacterial population in the intestinal tract is necessary for appropriate immune function and obtaining better feed efficiency with probiotics in poultry. Primary, probiotics consist of live beneficial microorganisms for the host animal's health and welfare due to stimulating effects for intestinal microbial balance (Moreno et al., 2006). Probiotic species consist of Lactobacillus bulgaricus, Lactobacillus plantarum, Streptococcus thermophils, Bifidobacterim bifidum, Aspergillus oryzae (Khaksefidi and Rahimi, 2005; Ashayerizadeh et al., 2009; Kabir, 2009). Bacteria have a mutually beneficial relationship with the intestinal cells and microorganisms in the gastrointestinal tract. Probiotics significantly contribute to changes in the intestinal structure and digestive processes by stimulating the immune system. They also inhibit the growth of pathogenic bacteria, leading to an improvement in overall performance (Awad et al., 2009; El-Shenway and Soltan, 2015). Probiotics have importance for the immune system with including boosting the activity of macrophages, lymphocytes, and NK cells. They also enhance the oxidative burst of heterophils, resulting in increased production of immunoglobulins (IgG, IgM, and IgA). Also, probiotics have the potential effects to regulate the gastrointestinal tract and maintain an optimal balance between antiinflammatory and pro-inflammatory cytokines. Besides, the population of lamina propria lymphocytes (LPL) and intestinal epithelial lymphocytes (IEL) has increased with the probiotics activity in the small intestine while restricting the proliferation of detrimental microorganisms (Yeşilyurt et al., 2021).

Bacillus subtilis-based probiotic supplement has been approved to improve immune and oxidative responses in shackled broiler chickens under pre-slaughter stress challenge. The levels of IgG, IgA, and IgM of the shackled broiler chickens exposed to preslaughter stress were investigated. In the result of this study, IgG and IgA levels (mg/dL) in serum concentration were found similar between control, 0.25 g/kg feed, and 0.5 g/kg feed supplementation groups. In contrast, the level of IgM (mg/dL) in serum concentration was higher in the control group compared to 0.25 g/kg and 0.5 g/kg treatment groups (Mohammed et al., 2024).

Prebiotics are non-digestible feed ingredients that benefit by promoting the growth or activity of some bacterial species in the colon to improve host health (Ganguly, 2013). Prebiotics are small carbohydrate fragments, possibly commercially used as galactose, fructose, and mannose oligosaccharides. There are some prebiotics, such as fructooligosaccharide (FOS), (TOS), transgalactooligosaccharide inulin, glucooligosaccharide, xylooligosaccharide, isomaltooligosaccharide, soybean oligosaccharide, polydextrose, and lactosucrose (Vulevic et al., 2004; Propulla, 2008; Ganguly, 2013). Furthermore, mannan oligosaccharide (MOS) may be derived from the outer cell wall of Saccharomyces spp. yeast promotes gut health with pathogenic bacteria in type-I fimbriae or agglutinating various bacterial strains and increasing villi length, uniformity, and integrity (Spring et al., 2000; Loddi et al., 2004). Oligosaccharides are prebiotics that boost chickens' intestinal morphology and stimulate the activation of the immune system (Sayed et al., 2023). Oligosaccharides may be more active on macrophages to regulate the production of inflammatory cytokines and cytokines by T-helper cells (Th) during the immunological processes (Csernus et al., 2020).

Sittiya and Nii (2024) investigated the effects of oligosaccharides on the immune reactions in laying hens challenged with dextran sodium sulfate. Consequently, BOS (oligosaccharide extract from bamboo shoots) also increased *IFN-* γ in the liver and Th-17 cytokines in the

intestine in laying hens. In contrast, there are no significant differences in intestinal or liver morphology. On the other hand, BOS (oligosaccharide extract from bamboo shoots) suppressed an increase in leukocyte accumulation in the liver under DSS (dextran sodium sulfate treatment). These results approved that BOS (oligosaccharide extract from bamboo shoots) may enhance egg quality and Th-1 and Th-17 immune function without causing tissue damage under normal conditions, and it may suppress the excessive inflammatory responses during inflammation.

Synbiotics are a combination of probiotics and prebiotics that act as effective substitutes for antibiotics in feed (Dong et al., 2016; Mohammed et al., 2018; Ren et al., 2019). The beneficial effect of the synbiotics has impacted the gastrointestinal tract and health status in animals. Moreover, different synbiotics comprise probiotic strains, Lactobacillus plantarum, Lactobacillus reuteri, Lactobacillus pentosus, and Saccharomyces cerevisiae (Śliżewska et al., 2020). Due to the regulation of physiological balance and modifying both innate and adaptive immune responses against stress, synbiotics have gained immense importance in poultry nutrition (Seifert et al., 2011). It has been demonstrated that different levels of the synbiotic supplementation significantly changed plasma levels of the antioxidant enzyme GPx in heat-stressed broiler chickens (Mohammed et al., 2019).

5.3. Minerals

Minerals are essential micronutrients for activating optimal physiological processes and health status. The inclusion of microelements in poultry diets is common in commercial practice due to their importance in reproduction and immune function (Saripinar-Aksu et al., 2012). An adequate mineral supply in the diet is crucial for optimal poultry production. The lack of minerals in the diet may lead to various health issues in chicks (Pal, 2017). In poultry nutrition, optimizing animal health may be associated with adding zinc, selenium, chromium and zeolite to the diet program for rearing broilers and laying hens (Park et al., 2004; Tayeb and Qader, 2012; Jain et al., 2021; Elsherbeni et al., 2024).

Dietary zinc decreases feed intake and stimulates avian antibody production with plasma corticosterone levels (Onbasilar and Erol, 2007). It has been shown that dietary zinc supplementation of up to 80 ppm level enhances humoral and cell-mediated immune responses in broilers by Sunder et al. (2008). On the other hand, dietary zinc (up to 110 ppm) and higher doses (up to 10,000 mg/kg) in the diet result in inhibiting the colonization of Salmonella enteritidis (SE) in laying hens (Kubena et al., 2001).

Selenium is essential for optimal immune response and involves innate and acquired immune systems. This essential trace element is a component of selenoproteins, which are involved in various animal physiological processes. Although plants and fungi do not need selenium, they can convert mineral forms of selenium present in the soil into various organic forms, such as selenomethionine and methyl selenocysteine, as a strategy of adaptation. Selenoproteins influence immunity through multiple mechanisms, and nutrition could modulate the immune system to resist pathogens. Selenium regulates oxidative stress, redox, and other cellular processes in all tissues and cell types, including immune responses. Selenium interacts with vitamin E in tissues to protect biological membranes from oxidative damage (Allmang et al., 2009). On the otherside, in Jain et al. (2021) study, the plasma IgG concentrations (μ g/mL) showed significant differences between groups at 21, 28, 35 day age of broilers with feed different concentrations of organic and inorganic trace minerals (zinc, selenium, and chromium) supplementation.

Zeolite is a silicate mineral that is considered highly effective and non-toxic. Dietary supplementation of zeolite has been used as a feed additive. Additionally, the use of zeolite directly impacts on production performance and meat quality (Zhou et al., 2014; Abd El-Hady, 2020; Dashtestani et al., 2021). Zeolite has been used in biological processes to reduce ammonia and smell emissions from poultry production by absorbing nitrogenous metabolites such as ammonium (NH4⁺) and ammonia (NH₃) (Schneider et al., 2017). Elsherbeni et al. (2024) investigated the effects of using zeolite on lymphoid organs (%) in 42-day-old broiler chickens. In this study, thymus and Bursa Fabricus weights (%) were found to be higher in the 10g/kg zeolite diet supplementation group. In another study bv Abdelrahman et al. (2023), it was shown that dietary zeolite supplementation at levels of 0.5%, 1.0%, 1.5%, and 2.0% resulted in a statistically significant reduction in spleen weight of broiler chicks compared to the untreated group. However, the different zeolite treatments did not significantly affect the thymus and Bursa Fabricus weights.

5.4. Vitamins

The use of vitamins in nutrition is essential for maintaining a healthy immune system in poultry. It has been stated that vitamin level insufficiency has led to compromised immune function, increased susceptibility to infections, and inflammation. In poultry nutrition, vitamins (A, D, E, and C) significantly impact the activation immunologic process with various mechanisms. Firstly, vitamin A enhances mucosal immunity, reduces free radicals, and maintains epithelial cell integrity. Vitamin A comprises several brightly colored and fat-soluble molecules involving retinol, retinal, retinoic acid (RA), and pro-vitamin A carotenoids. Carotenoids have multiple functions: immune regulation and stimulation, antioxidant, antimutagenic, and anticarcinogenic properties. Avian and mammalian species may not synthesize carotenoids, unlike plants and microorganisms. Therefore, chickens must obtain carotenoids from their diet as the yolk initially provides vitamin A during embryonic development. However, after hatching, they require dietary sources of vitamin A

(Khan et al., 2023). Post-hatch immune system function improved with the addition of vitamin A to the diet (Shojadoost et al., 2021).

Vitamin D is a type of fat-soluble vitamin that is obtained through sunlight exposure or supplements. Vitamin D is absorbed by the small intestine and then taken up by the liver, where it is converted into 25-hydroxyvitamin D3 (25(OH)D3), the stored form of vitamin D in the body. Vitamin D3 (1,25(OH)2D3), the physiologically active form of the vitamin, is produced in the kidneys by the enzyme 1a-hydroxylase. This form is responsible for the biological actions of vitamin D, regulating bone and mineral metabolism and modulating immune responses (Fakhoury et al., 2020; Wei et al., 2024). It has been demonstrated that 25(OH)D3 increases the synthesis of nitric oxide, promotes the activity of innate immune cells, modifies adaptive immunity, and produces antimicrobial proteins and inflammatory cytokines in chickens (Shanmugasundaram et al., 2019; Fakhoury et al., 2020; Sharma et al., 2024).

Vitamin C, commonly known as L-ascorbic acid, is a water-soluble vitamin that the body converts from glucose. In the body, vitamin C does not accumulate, and excess levels are promptly excreted by the kidneys, resulting in decreased absorption (Johnston et al., 2006; Shojadoost et al., 2021; Hieu et al., 2022). Vitamin C is an antioxidant that protects cells from damage caused by free radicals generated by infection or toxins. Birds may produce vitamin C due to an enzyme called Lgulonolactone oxidase in their renal tissue, which converts l-gulono-g-lactone into ascorbic acid. However, vitamin C requirements increase when chickens experience stressful conditions such as beak trimming, vaccination, transportation, thermal stress, or infection. Therefore, supplementing vitamin C alleviates the adverse effects of these stressful conditions (Abidin and Khatoon, 2013).

Vitamin E is a fat-soluble antioxidant with four distinct functional forms. Among these forms, a-tocopherol is the most biologically active and naturally abundant. This vitamin is well-known for its potential to counteract the adverse effects of free radicals on cell integrity that can occur during normal cell metabolism and inflammation. In poultry, it is crucial to supplement the diet with vitamin E to maintain fertility and hatchability in parent stocks and to prevent nutritional encephalopathy and myopathies in chickens and turkeys. Vitamin E supplementation (or other antioxidants) becomes even more critical when oxidizable fats are included in the feed. The supplementation of vitamin E may prevent the oxidation of unsaturated fats. However, the level of active vitamin E and unsaturated fat used in poultry nutrition may be adequate in intestinal absorption, potentially decreasing the antioxidant status by increasing lipid peroxidation (Pompeua et al., 2018). Vitamin E boosts immune system activity by inhibiting the synthesis of prostaglandins, which may cause inflammation and hinder the immune response. Vitamin E also prevents

oxidation, which is responsible for the production of prostaglandins. Vitamin E is primarily known for its antioxidant properties, effectively reducing the damage caused by free radicals during metabolic stress and immunological disorders. Vitamin E regulates the production of free radicals and gene expression caused by free radical signaling gene expression (Packer and Suzuki, 1993). Deficiency of vitamin E and selenium may impair the immune response in poultry, as indicated in the research conducted by Lewis et al. (2019).

5.5. Organic Acids

Organic acids are a type of feed additives that may promote good health and stimulate immunity in poultry. These acids are categorized as organic chemical compounds that contain the carboxyl group COOH in their structure. It is also known that formic, acetic, propionic, malic, fumaric, and citric acids are commonly utilized in poultry nutrition (Hajati, 2018; Khan et al., 2022). Besides, organic acids upregulate harmful microorganisms' inhibition mechanism by reducing the environment's pH level. By penetrating the biological membranes of microorganisms and disrupting their cell function through electrolytic dissociation, organic acids may also restrict bacterial growth (Feye et al., 2021; Pope et al., 2022). It has been stated that formic acid supplementation has beneficially affected broiler chicken performance (body weight gain, feed intake, and feed conversion ratio). It may also enhance the growth of intestinal villi and increase the number of lymphocytes in the spleen and antibody levels for the prevention of disease (Tawfeeq and Al-Mashhdani, 2020).

Organic acids have been significantly effective in body growth rate, feed efficiency, nutrient digestibility, meat quality, immune response, and suppressing pathogenic bacteria (Yang et al., 2018; Adhikari et al., 2020). The enhancements may be completed by lowering the pH in the gastrointestinal tract, optimizing nutrient utilization in diets, inhibiting pathogen growth, and improving immune response in poultry (Alagawany et al., 2021). Recently, Liao et al. (2020) found a strong correlation between gut microbial communities and organic acids, contributing to the gut health status of broilers. The function of gut microbiota is known as an endocrine organ regulating the immune system through synthesizing interferon/cytokines and immunoglobulins (IgG, IgM, and IgA), activating white blood cells like lymphocytes and natural killer cells, and boosting the activity of macrophages and heterophils (Clarke et al., 2014; Abd El-Hack et al., 2020).

Moreover, acetic acid (0.30 g/kg of) may be responsible to prevent gastric apoptosis and stimulate mucin synthesis (Liu et al., 2017). Also, butyric acid plays a crucial role in promoting intestinal development and maintaining the integrity of intestinal epithelial cells (Sun and O'riordan, 2013). Numerous studies have shown that dietary organic acids can inhibit the growth and spread of harmful opportunistic pathogens such as Salmonella, E. Coli, and Clostridium while also promoting the growth of beneficial microorganisms such as Lactobacillus, Bacillus, and Bifidobacterium in the intestine (Lee et al., 2015; Nguyen et al., 2018; Gao et al., 2019). Additionally, in organic acids treatment group, the relative weights of lymphoid organs, such as Bursa Fabricius, thymus, and spleen, were found to be higher compared to the control treatment group, which is strongly related to immunological responses in chickens (Ghazala et al., 2011; Yang et al., 2018). These organic acids stimulate specific and non-specific immune responses in broiler chickens by activating macrophages, increasing cytokine production, and IgA, IgG, and IgM levels. Besides, organic acids inhibit bacterial infection growth, proliferation, and intestinal mucosa inflammation (Abd El-Hack et al., 2022).

5. Conclusion

A balanced diet with essential feed supplements (amino acids, probiotics, prebiotics, synbiotics, minerals, vitamins, and organic acids) stimulates the immune system. Dietary deficiencies may cause several health issues and economic losses in profitability for production. Besides, nutrition has been associated with immunologic processes in commercial production systems under various management conditions. Because of that, understanding the patterns of these feed additives is necessary for optimizing strong immunity.

Author Contributions

The percentage of the author(s) contributions is presented below. All authors reviewed and approved the final version of the manuscript.

	M.G	A.S	Ü.Ç
С	60	30	10
D	60	30	10
S	60	40	-
L	70	20	10
W	70	20	10
CR	70	20	10
SR	60	30	10

C=Concept, D= design, S= supervision, L= literature search, W= writing, CR= critical review, SR= submission and revision.

Conflict of Interest

The authors declared that there is no conflict of interest.

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