Poultry Science

Modulation of the immune system of chickens a key factor in maintaining poultry production—a review

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ABSTRACT The awareness of poultry production safety is constantly increasing. The safety of poultry production is defined as biosecurity and the health status of birds. Hence the constant pursuit of developing new strategies in this area is necessary. Biosecurity is an element of good production practices that ensures adequate hygiene and maintaining the health status of poultry production. Poultry production is the world leader among all livestock species. Producers face many challenges during rearing, which depend on the utility type, the direction of use, and consumer requirements. For many years, the aim was to increase production results. Increasing attention is paid to the quality of the raw material and its safety. Therefore, it is crucial to ensure hygiene status during production. It can affect the immune system's functioning and birds' health status. Feed, water, and environmental conditions, including light, gases, dust, and temperature, play an essential role in poultry production. This review aims to look for stimulators and modulators of the poultry immune system while affecting the biosecurity of poultry production. Such challenges in current research by scientists aim to respond to the challenges posed as part of the *One Health* concept. The reviewed issues are a massive potential for an innovative approach to poultry production and related risks as part of the interaction of the animal-human ecosystem.

Key words: immune response, biosecurity, environment, nutrition, poultry

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INTRODUCTION

Poultry production is the world leader among all livestock species. Producers face many challenges during rearing, which depend on the utility type, the direction of use, and consumer requirements. For many years, the aim was to increase production results, including weight gain (or the number of eggs), while trying to reduce feed intake. Therefore, it is crucial to ensure biosecurity during production. It can affect the immune system's functioning and birds' health status. Feed, water, as well as environmental conditions, including light, the presence of gases and dust, and temperature, play an essential role in poultry production (Nawab et al., 2018; Saeed et al., 2018; Hafez and Attia, 2020; Parolini et al., 2020; Abd El-Hack et al., 2021).

This review aims to look for stimulators and modulators of the poultry immune system while affecting the biosecurity of poultry production. Such challenges in current research by scientists aim to respond to the challenges posed as part of the *One Health* concept. The concept of *One Health* focuses on health and infectious disease in the context of the relationship between humans, animals, and the environment. It combines human and veterinary medicine in response to zoonose (Dunislawska et al., 2022). The reviewed issues are a huge potential for an innovative approach to poultry production and related risks as part of the interaction of the animal-human ecosystem.

IMMUNE SYSTEM OF THE CHICKEN

Basic Mechanisms of the Immune Response

Despite the significant evolutionary distance, many elements of birds' innate and adaptive immune responses are common. Leukocytes, macrophages, dendritic cells, and natural killer (**NK**) cells are involved in the action of the innate immune response. They recognize pathogen-associated molecular patterns (**PAMPs**) and then bind to pattern recognition receptors (**PRRs**) such as Toll receptors (**TLRs**) (Sebők et al., 2021). In chickens, 10 types of TLR have been identified

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(compared to 13 in mammals) (Turin and Riva, 2008). TLRs modulate signaling pathways in the host's defense system to control infection and repair damaged cells. After the appropriate TLR is bound to the microbial ligand, macrophages, various adapter proteins, transcription factors are activated, and cytokine genes are stimulated (Kawasaki and Kawai, 2014). Certain functions of the chicken TLRs depend on genetic polymorphism and are susceptible to dietary influence (Iqbal et al., 2005). Knowing the relationship between specific TLRs and pathogens provides a tool for improving chickens in terms of disease affinity (Iqbal et al., 2005). In the context of disease affinity, studies on the chicken HD11 cell line have demonstrated strong activation of TLR2t2/16, TLR4, and TLR21 by *Campylobacter* spp. derived lysate (De Zoete et al., 2010).

Another mechanism to defend the host is innate humoral factors, including cytokines and antimicrobial peptides (**AMP**). There is some similar functionality of individual cytokines in chickens and mammals despite the differences in their protein structures (Giansanti et al., 2006). The panel of proinflammatory cytokines released due to TLR binding to ligands includes interleukin-1 (**IL-1**), IL-6, IL-8, and tumor necrosis factor-alpha (**TNF-α**) (Xu et al., 2019).

Lymphocytes are the main tool of acquired immunity. In chickens, we distinguish B and T lymphocytes. B lymphocytes are generally responsible for the production of antibodies, while cytotoxic T lymphocytes actively destroy pathogens. Subtypes of T lymphocytes mediate cell killing. CD8+ T-cells are associated with the characteristic CD8 glycoprotein, which binds to the constant part of the MHC class I molecule. Their cytotoxic effect allows—this means them are able to kill cells infected with the pathogen and cancer cells directly. CD8+ T-cells use cytokines to engage other cell types, generating an immune response. CD4+ T-cells, also called helper cells (Th), are associated with a class of MHC II molecules. They express the CD4 glycoprotein on their surface. They activate B lymphocytes (inducing immune memory) and CD8+ T-cells (Petteri Arstila et al., 1994). Their role is, therefore, crucial in preventing/minimizing the effects of viral diseases that are dangerous for poultry production, both as a result of protective vaccinations and infections. For example, Collisson et al. (2000) showed that CD8+ T-cells play a significant role in eliminating infectious bronchitis virus (**IBV**). In comparison, another experiment discussed the role of CD4+ T-cells in this context. IBV antigens activate these after antigen presentation. Once activated, CD4+ T-cells interact with other T and B cells to enhance cytotoxic and humoral responses to IBV in chickens (Janse et al., 1994).

In chickens, the major histocompatibility complex (**MHC**) contains 46 genes. MHC I and MHC II genes are located on the same chromosome 16 in the MHC-B and MHC-Y regions. Their distribution in the genome is approximately 209 kb (da Silva and Gallardo, 2020). It proves a much simpler and more compact structure in the context of the MHC system of mammals (Trowsdale and Knight, 2013).

Organization of the Immune Organs in the Chicken

The immune system in chickens can be divided into primary immune organs and lymphoid tissue. The primary immune structures are the thymus, where T lymphocytes are produced and mature; the bursa of Fabricius, where B lymphocytes mature; and the bone marrow, where blood cell precursors are produced. In addition, during the embryonic development of chickens, the source of maternal antibodies is the yolk sec. Primary lymphoid organs mainly act as a center for the production and maturation of adaptive immune cells. Secondary lymphoid tissues specialize in controlling immune responses. They activate immune effector cells, such as lymphocytes (Boehm and Swann, 2014). After maturing in primary lymphoid organs, T and B lymphocytes re-enter the bloodstream and colonize secondary lymphoid tissues to facilitate antigen presentation to lymphoid cells and initiate and regulate the adaptive immune response.

The fundamental difference between the immune system in mammals and chickens is the lack of encapsulated lymph nodes. Instead, we find in them "diffuse" lymphoid tissue and its clusters in organizations such as Peyer patches, cecal tonsils, and Meckel's diverticulum (Peralta et al., 2017). Lymphoid tissues include the spleen and mucosa-associated lymphoid tissues (**MALT**), also classified as the mucosal immune system (**MIS**). Lymphoid tissues in mucous membranes lining systems associated with nutrition (gut-associated lymphoid tissue—**GALT**), respiration (nasal-associated lymphoid tissue—**NALT**, bronchus-associated lymphoid tissue—**BALT**), and vision (conjunctiva-associated lymphoid tissue—**CALT**). In chickens, these tissues are immunologically well-developed and are the first line of defense against pathogens (McGhee and Fujihashi, 2012). In about 20-wk-old chickens, the primary immune organs, that is, the bursa and thymus, are involuted, and it is in the MIS that the humoral immune response occurs.

Chickens have 3 immunoglobulins (**Ig**) classes: IgA, IgM, and IgY. The chicken IgA and IgM are similar in structure to mammalian IgA and IgM. There are no analogs to mammalian IgE and IgD in chickens (Zhang et al., 2017). IgM is associated with the primary immune response in chickens, and its monomer is a B-cell receptor (Morgan, 2021).

SHAPING THE IMMUNE RESPONSE

Development of Acquired Immunity in Poultry Practice

Good poultry production practices must be conducted in such a way as to ensure safety not only with consumers but also with epizootic protection. Some unique elements of the structure of the immune system of birds (discussed in this review) allow the widespread use of vaccination techniques that are impossible or ineffective in the animal production of mammalian species. Such methods include the delivery of in ovo vaccination during embryonic development and early postnatal stimulation of antibody production through spray and drop vaccines (Peebles, 2018). This technology stimulates innate and adaptive immune response from Harder's glands and local MALT (Mebrahtu et al., 2018). In addition, automatic whole-house vaccination by spraying can be used for both small- and large-scale poultry production. This is effective against poultry diseases such as Newcastle disease (**NDV**) and viral infectious bronchitis (**IBV**) (Mebrahtu et al., 2018; Purswell et al., 2019).

The Importance of Maternal Immune Status

The immune system is a complex that takes time to mature. This makes maternal antibodies critical for young bird health. To some extent, protection against potential pathogens is provided by maternal antibodies. In chickens, IgY transfer takes place via the yolk during in ovo nutrition (Brierley and Hemmings, 1956). In addition, it has recently been suggested that in chickens, there is a cross-generational influence of the maternal immune system on the specific antibody response in the next generation. An experiment was conducted to examine the effect of specific and nonspecific endotracheal (i.t.) immune activation of laying hens on the production of specific antibodies in the next generation. Two experimental designs were proposed in which laying dams received an intratracheal immune stimulus with human serum albumin (**HuSA**) or lipopolysaccharide (**LPS**). Maternal immune activation with LPS increased the offspring's HuSA-specific IgY and IgM responses. It suggests a cross-generational influence of the maternal immune system on the specific antibody response in the next generation.

Moreover, maternal immune stimulation with LPS reduced anti-HuSA IgY responses after HuSA immunization in chicks fed a diet supplemented with β-glucan (known for its prebiotic properties). This suggests a cross-generational link between the maternal innate immune system and specific antibody responses in the offspring. These results may indicate maternal innate immune system activation influences immune-modulating dietary interventions and vaccination strategies in next-generation poultry (Verwoolde et al., 2022). Despite the lack of direct evidence in the cited experiment for the intergenerational transmission of epigenetic patterns, there are indications of their impact on the activity of genes related to the immunity of offspring.

Ways to Stimulate Innate Immunity in Poultry

Microorganisms associated with poultry production directly impact the immune status of animals, food safety, and public health. The chicken has already been extensively studied, and the effect of gut microbiota composition on the chicken's performance and health has been demonstrated (Fathima et al., 2022). The composition of the intestinal microbiota of animals is shaped in the perinatal period. At this time, intensive intestinal development occurs (Iji et al., 2001). During this period, the chicks switch from utilizing the nutritional resources of the egg to being fed with starter feed, which brings several metabolic and physiological changes. This period coincides with the so-called hatching window (48−72 h) in the intensive poultry production system. During this time, chicks are at risk of delayed water and feed. An alternative to this system may be using a patio where the chickens receive water and feed. Chicks with a patio have increased body weight and immune organs, indicating advanced metabolism and physiological development, possibly due to early feeding (van de Ven et al., 2013). Reducing fasting after hatching chicks by providing feed and water promotes the development of intestinal microbiota (Proszkowiec-Weglarz et al., 2022).

Typical support for the development of the intestinal microbiota, and thus the immunological status of poultry, is the introduction of bioactive substances as an additive to feed/water or by in ovo injection. In recent years, many bioactive substances with immunomodulatory potential have been tested, which will be discussed in later chapters of this review. Nevertheless, when discussing the effect of bedding, the combined supplementation system and adding bioactive substances to the litter material is worth mentioning. For example, aluminosilicates as a feed additive and litter have a positive local immunomodulating effect in GALT and are beneficial in broiler performance (Biesek et al., 2021b).

In shaping the immune response of chickens, it is essential to protect them against immunosuppression caused by stress factors. Factors that cause stress in poultry include temperature (high and low) and light management. The flashing light program is effective during heat stress to down-regulate inflammation markers such as corticosterone, TNF-α, and malondialdehyde (**MDA**) in blood plasma (Alaqil et al., 2022). The immune status of poultry is also affected by the color of the light-emitting diodes (**LEDs**) used in the poultry house. Initially, light blue light and then bright blue light stimulates the production of macrophages in broilers (Seo et al., 2016).

As the immune system takes time to mature in fast-growing chickens, there is a greater sensitivity to pathogens. Intensive growth and the use of feed to meet growth needs may be at the expense of the development of the immune system. A study on broilers showed low levels of cytokines in peripheral blood and intestinal mucosa between 6 and 13 d of age. Moreover, it was established that the immune system of broilers did not mature until 30 to 34 d of age (Song et al., 2021). In such a system, boosting immunity is especially important.

IMMUNOSAFETY AND IMMUNE SECURITY

The Role of Feed in the Immunological Safety of Poultry

A high threat to the health of birds and the safety of animal products is the contamination of feed with fungi, particularly their secondary metabolites known as mycotoxins (Monson et al., 2015; Mehtab et al., 2022). Most of these substances are produced by the fungi *Aspergillus, Penicillium*, and *Fusarium*. Sixty percent of the identified fungi in feed samples could produce mycotoxins. In addition, the authors also found high feed contamination with fumonisin (100%), deoxynivalenol (90%), ochratoxin A (90%), aflatoxin (89.8%), and zearalenone (86%). The negative impact of mycotoxins in feed on poultry production results can be manifested by reducing body weight gain, feed conversion rate, and nutrient digestibility (Yang et al., 2014) and laying hens with lower egg quality (Murugesan et al., 2015).

The Aflatoxin B1 (**AFB1**) example also demonstrated the immunotoxic effect. AFB1 can activate extracellular heterophile traps (**HETs**), which are considered to be one of the basic mechanisms of the immune response. At the same time, active HETs increased biochemical liver indices such as alanine aminotransferase (**ALT**) and aspartate aminotransferase (**ASP**), and the histopathological study showed a harmful effect on liver and kidney cells (Gao et al., 2022). Adverse changes in the liver and kidneys depending on the dose of AFB1 were also found in the appearance of renal tubular necrosis and necrotic changes in the liver parenchyma (Naseem et al., 2018). The presence of AFB1 reduced the number of immune cells (IgA+) in the duodenum and jejunum and the level of mRNA expression, among others, IgA, IgM, and IgG on the 14th and 21st day of broiler chicken rearing (Jiang et al., 2015).

Another example is the cytotoxic activity of AFB1. According to Zimmermann et al. (2014), AFB1 at 10 and 20 μg/mL damaged lymphocytes and reduced their activity (Zimmermann et al., 2014). On the other hand, further research found contamination of poultry feed with *Salmonella* spp. from 0 to 3.5% in samples from 2007 to 2010, indicating an increase in hygienic status compared to previous years (Kukier et al., 2012).

The hygienic status of feed can be influenced by processes such as pelleting, extrusion, and expansion. They allow for the effective elimination of potentially harmful pathogenic microorganisms and also regulate the availability of nutrients, affect the intestinal microbiota (Goodarzi Boroojeni et al., 2016), and affect increased feed intake (**FI**), higher body weight gain (**BWG**) of birds, and feed conversion ratio (**FCR**) (Sibanda and Ruhnke, 2017). Feed pelleting can also contribute to a reduction ($P < 0.05$) in the number of fungi compared to loose feed (Ghaemmaghami et al., 2018).

The Role of Water in the Immunological Safety of Poultry

Regular water sanitation is one of the essential elements affecting the rearing of birds while maintaining a high health status and, at the same time, better production results and increased welfare (Jacobs et al., 2020). Poor quality water can be contaminated with pathogenic bacteria *Salmonella* spp., *Escherichia coli, Campylobacter* (Maharjan et al., 2017), and *Pseudomonas* spp. (Maes et al., 2019). Measures limiting the growth of bacteria in water include the addition of chlorine, hydrogen peroxide (Maharjan et al., 2017), chlorhexidine (de Oliveira Branco et al., 2016), sodium bisulfate (Pineda et al., 2021), or calcium hypochlorite (Mohammed et al., 2020). *Salmonella* and *Campylobacter* are also characterized by the ability to be highly organized and adhere to various types of surfaces in livestock buildings, defined as biofilm (Schonewille et al., 2012). It may be one of the main reasons for the emergence of disease in the flocks due to the increased virulence and resistance of pathogens to antimicrobial agents (Bobinienė et al., 2012; Czyżewska-Dors et al., 2018).

The main factors influencing biofilm formation include the substrate's chemical composition, temperature, oxygen (**O_2**) content, and interactions between microbes (García-Gonzalo and Pagán, 2015). In addition to pathogenic microorganisms, water can also be contaminated with harmful xenobiotics that can cause an increase in macrophages, decrease the number of CD8+ lymphocytes, and initiate inflammatory reactions in the body (More-Bayona et al., 2020). Heavy metals such as copper (**Cu**) and lead (**Pb**) are other pollutants. They harm the immune system, causing a decrease in the antibody titers to Newcastle disease (**ND**) and inflammatory bowel disease (**IBD**) (Haggag et al., 2016). Watering birds with alkaline water (pH at level 8.05) can support the immune system of birds and improve production indicators (BWG, FCR) compared to water with a lower pH (Chung et al., 2020).

The Role of Light in the Immunological Safety of Poultry

The color of light, its intensity, and the length of the daylight (lightning program) is one of some critical factors in the microclimate of poultry buildings that affect the proper growth, development, and health of birds (Patel, 2016; Rault et al., 2017; Purswell et al., 2018; Mohammed, 2019). In previous studies with broiler chickens, the color of light had immunomodulatory properties. The use of green light increased antibody titer against ND (Firouzi et al., 2014), and light (LED), light blue (blue light), and pure blue (sky blue) had a positive effect on the proliferation of splenocytes (Seo et al., 2015). Changes in the level of B-lymphocyte proliferation in the bursa cloacae (*Fabricius bursa*) with a green light could also be associated with antioxidant processes and more intense melatonin secretion (Li et al., 2015).

On the other hand, the beneficial effect was achieved using blue light (5 W/m^2; 5.73 lux) at a stocking density of 10 birds/m^2 (Abdel-Azeem and Borham, 2019). In addition, bicolor light (green and blue) also increased antibody titer and lymphocyte proliferation index. Bicolor light may reduce the effects of stress reactions in broiler chickens (Zhang et al., 2014). White and green LED light with an intensity of 10 lux significantly affected the body's immune response through increased levels of interleukin-2 (**IL-2**) compared to blue light at 5 and 15 lux (Tan et al., 2022). Another issue related to lighting is the photoperiod, which is the length of day and night. Pekin ducks reared in a building with 20 h of uninterrupted light achieved improved FCR, lower stress hormone levels, and enhanced immune response against ND (House et al., 2021). One of the methods of reducing the negative impact of heat stress is intermittent lighting (from 1 h of light to 3 h of darkness). According to Alaqil et al. (2022), it positively affected production indicators, the immune system, and liver functions.

The Influence of Harmful Gases on the Immunological Safety of Poultry

The air in livestock buildings intended for the production of poultry meat or table eggs may be polluted with harmful and toxic gases, which include ammonia (**NH_3**), hydrogen sulfide (**H_2S**), and carbon dioxide (**CO_2**) (Kic et al., 2012; Brouček and Čermák, 2015; Nissa et al., 2018). Following Council Directive 2007/43/EC of 28 June 2007 laying down minimum rules for the protection of chickens kept for meat production (Council Directive, 2007), the permissible concentration of NH_3 should not exceed 25 ppm and CO_2—3,000 ppm.

Increasing the NH_3 concentration to 70 ppm can reduce spleen weight, lysozyme, and globulin concentrations and limit lymphocyte proliferation. At the same time, the increased relative humidity of the air (85%) decreased the weight of the thymus and bursa fabricii. Also, it increased the expression of IL-1B and OL-4 compared to chickens kept in a building with a humidity of 60% (Wei et al., 2015). The negative effect of NH_3 may result in a decrease in mRNA expression of genes affecting the appearance of oxidative stress (e.g., GPx) and inflammation in the thymus of birds (e.g., IL-1B, IL-6) (Chen et al., 2019). Impairment of the immune response due to the high concentration of NH_3 is also the result of the toxicity of this gas to the bursa fabricii. Damage and disintegration of bursa cells and impaired functioning of mitochondria have been demonstrated (Shah et al., 2020). Lower spleen weight was found in laying ducks, significantly correlated with intestinal microbiota composition (Tao et al., 2019). The appearance of NH_3 at a concentration of 15 ppm affects the microbiota of the chickens' trachea, increasing the possibility of upper respiratory tract infections (Zhou et al., 2021). NH_3 increased the number of *E. coli* and *Shigella* in the lung tissue and activated inflammation (Liu et al., 2020). In Hy-Line Brown laying hens, high NH_3 and high temperature combination increased IgG and decreased IgA. In addition, the increased cortisol level confirmed the stress-inducing effect of this gas on the birds' organisms (Li et al., 2020).

H_2S is a toxic gas that can cause oxidative stress, inhibits the appropriate functioning of energy metabolism, and stimulates inflammatory reactions in the spleen of chickens (Chi et al., 2019). Impairment of immune function by H_2S was also observed in the spleen, which caused inflammatory reactions and initiated cell apoptosis (Zheng et al., 2019). Similar changes were found in bursa fabricii at 20 ppm H_2S (Hu et al., 2018) and the thymus (Xueyuan et al., 2021; Wang et al., 2022). Considering the muscular system, the action of the above factor contributes to the breakdown of heart muscle cells due to mitochondrial fission (Wang et al., 2019).

The Role of Temperature in the Immunological Safety of Poultry

Global temperature rise is currently one of the main challenges poultry producers face. High temperatures lead to economic losses and affect birds' health through heat stress (Goel, 2021). As a result, higher stress hormone levels (corticosterone) were observed (Honda et al., 2015; Xu et al., 2018). Immunological changes in the spleen of birds manifest the negative effect of heat stress. These include an increase in cytokines (interleukin-4 and interleukin-12) and a decrease in interferon-γ (**IFN-γ**) and even atrophy (Ohtsu et al., 2015).

In other research, high temperature (34.5°C for 14 d of rearing) damages the thymus cortex and bursal follicles while disturbing the maturation of T and B lymphocytes (Hirakawa et al., 2020). Temperature increases the expression of heat shock proteins (**HSP**70, 60, and 47). It is related to the presence of cytokines in the small intestine, constituting an element of adaptation to the prevailing environmental conditions (Siddiqui et al., 2020). The housing system for laying hens also affects the immune function when exposed to heat stress (Abo Ghanima et al., 2020). Lower values of immune cells were found in hens from the barn system, for example, lymphocytes, basophils, eosinophils, and decreased phagocytic index. There is also an increased risk of infections with pathogenic bacteria (*Salmonella* spp.) due to intestinal damage and limiting the proper functioning of immune mechanisms, that is, an increase in the concentration of inflammatory cytokines TNF-α and IL-2 (Alhenaky et al., 2017). Already at the stage of embryonic development of poultry, an attempt can be made to adapt the birds to the unfavorable effects of temperature. Increasing the egg incubation temperature to 39°C allows for the higher adaptation of the birds' organism to the conditions of heat stress in the area of action of the immune response (Saleh and Al-Zghoul, 2019).

PATHWAYS OF IMMUNOSTIMULATION AND IMMUNOMODULATION

Immunomodulation is the regulatory adjustment of the immune system. This is homeostasis in the immune system whereby the system self-regulates to adjust the immune response to adaptive levels (using signaling molecules, etc.). The modulator, in this case, may be a gene or protein capable of changing the expression of an endogenous gene (Flores et al., 2013). Immunostimulation is defined as the overactivation of the immune system under the influence of exposure to pathogens or substances (immunostimulants) (Volger, 2014). The search for alternative solutions in poultry production for the health status while increasing production results and improving the quality of meat or eggs was subjected by many authors. The ban on antibiotic growth stimulants prompted producers and scientists to look for new ones. Following the trends prevailing in the agrifood and consumer markets, these substances should affect birds' growth and health. At the same time, it is required that these solutions will be natural and safe for the environment. In recent years, the use of bioactive additives has become popular. These include probiotics, prebiotics, synbiotics, phytobiotics, eubiotics, organic acids, and minerals. Most studies indicate their beneficial effect on production results, phenotypic features, and the health status of birds. Early stimulation of the intestinal microbiota in ovo is also a promising method (Dhama et al., 2014; Oladokun and Adewole, 2020; Abd El-Hack et al., 2022).

Probiotics

Probiotics most often belong to the genus *Lactobacillus, Bacillus, Lactococcus* (Park et al., 2016), *Enterococcus, Bifidobacterium*, and *Saccharomyces* (Adhikari and Kim, 2017). Many studies have confirmed the health-promoting effect of probiotics on the organism of birds in the aspect of the digestive tract (Biswas et al., 2019a), the immune system (Zhang et al., 2016; Fathi et al., 2018; Alaqil et al., 2020), intestinal microbiota (Khan et al., 2020) or by preventing bacterial infections (Smialek et al., 2018; Ahmed et al., 2019; Tabashsum et al., 2020), viral (Al-Khalidi et al., 2020), and protozoan (Erdoğmuş et al., 2019). The immunomodulatory properties of probiotics include changes in the levels of interleukins (IL-2, IL-10) and immunoglobulins (IgG, IgA) (Rajput et al., 2013), as well as an increase in the weight of the immune system organs (spleen, thymus, bursa fabricii), as demonstrated by the use of *Bacillus subtilis* in ducks (Guo et al., 2016).

Higher diversity of intestinal microbiota and changes in the secretion of some immunoglobulins and cytokines under *Clostridium butyricum* (Liu et al., 2021). Probiotics also had a positive effect on the immune system of laying hens by increasing immunoglobulin M (*Bacillus subtilis*) (Fathi et al., 2018), antibody titers against sheep red blood cells (**SRBC**), and proliferation of T and B lymphocytes (Alaqil et al., 2020), and antibodies against ND (*L. acidophilus*) (Forte et al., 2016). Probiotics may also affect birds' immunity by regulating the expression of immune genes during *Salmonella enteritidis* infections (Adhikari et al., 2019). The combination of a probiotic with chicory or coriander seed powder reduced the content of *E. coli* and *Salmonella* spp. in the small intestine of chickens (Gurram et al., 2022). Higher antibody titers against ND were found using a probiotic with garlic (Elbaz et al., 2021). The combination of mentioned mixture with the *Bidens pilosa* reduced the effective infection with *Eimeria* (Memon et al., 2021). The possibility of modulating the intestinal microbiota composition occurs without the appearance of inflammation in the intestines of birds (Yu et al., 2021).

Prebiotics

Prebiotics are substances that support the functioning of beneficial bacteria (probiotics) in the host organism (Bikric et al., 2022) and have a positive effect on the immune system (Madej et al., 2015a; Mahmoud et al., 2018; Rehman et al., 2020) and have the ability to modulate the microbiome of the gastrointestinal tract (Ricke et al., 2020). In poultry nutrition, fructooligosaccharides (**FOS**), galactooligosaccharides (**GOS**), and mannooligosaccharides (**MOS**) are mainly used (Ricke, 2018).

The beneficial effect of prebiotics on immunity has been demonstrated by enhancing the humoral and cellular immune responses in birds (Biswas et al., 2019b) and the weight of thymus and bursa fabricii (Madej et al., 2015; Mahmoud et al., 2018). Health-promoting effects of these substances on the organism of birds occur during infections with *E. coli*, among others, increased lymphocytes and activity of phagocytes, as a consequence of which the number of pathogens in the intestinal contents decreased (Mohamed and Younis, 2018). FOS supplementation in poultry nutrition can effectively influence changes in the immune system, which are protective during potential infections with *Salmonella enteritidis*. They concern, for example, changes in cytokine gene expression and leukocyte and immunoglobulin levels (Shang et al., 2015; Adhikari et al., 2018).

Prebiotics have a positive impact on the health of broiler chickens (Froebel et al., 2019). The addition of a prebiotic reduced the spread of *Campylobacter* in the intestines (Abu-Akkada and Awad, 2015). The number of *Eimeria tanella* oocysts excreted was also reduced. The beneficial production results of chickens fed with the addition of prebiotics may result from elongating intestinal villi (Abudabos et al., 2015). Prebiotics also protect the birds' organisms during heat stress (Mahmoud et al., 2018).

Synbiotics

Another feed additive with bioactive properties is a synbiotic (combination of a probiotic and a prebiotic) (Yadav et al., 2016; Sharma et al., 2018). Since they can be treated as one of the alternatives to the use of antibiotics in poultry production, they affect the health of birds, biochemical blood indicators, and modulate the functioning of the immune system of birds (Żbikowski et al., 2020), and also limit the negative impact of high density in the building on the organism of birds (Kridtayopas et al., 2019).

Using a synbiotic with a water disinfectant increased the number of immune cells, such as B and T lymphocytes (Chechet et al., 2022). These substances can modify the intestinal microbiota by increasing the number of beneficial bacteria and the concentration of lactic acid in the intestines (Sliżewska et al., 2020). The study by Dibaji et al. (2014) has also demonstrated similar results. The effect of prohealth synbiotics is the ability to mitigate the adverse effects of heat stress, which was found by lowering the level of heat shock proteins in birds kept at higher temperatures (Jiang et al., 2020) and elongation of the intestinal villi (Ghasemi et al., 2020). At the same time, under similar conditions, the use of synbiotics increased the BWG and final BW of the birds (Mohammed et al., 2018). A positive effect was also found in reducing FCR (Mookiah et al., 2014; Abdel-Hafeez et al., 2016). Beneficial histological changes have been demonstrated in Ross 308 chickens infected with *Clostridium perfringens* (Al-Baadani et al., 2016). A significant effect on the immune system was confirmed by the increase in serum antibody titers in infectious bronchitis, infectious bursa fabricii (Naghi Shokri et al., 2017), and ND (Hassanpour et al., 2013).

Minerals

Aluminosilicates are a group of natural minerals. They include zeolite, halloysite, kaolin, or bentonite (Trckova et al., 2004; Korczyński et al., 2013). Zeolite is the most commonly used mineral in research. It is characterized by many sorption properties that bind water. This type of aluminosilicates, of volcanic origin, has found its application in medicine and other industries, including animal production (Lamprecht et al., 2022).

Previous studies on using aluminosilicates in poultry production confirmed their effect as a feed or bedding additive on production results, slaughter yield, meat quality, and intestinal morphology (Banaszak et al., 2020, 2021a, 2022b; Biesek et al., 2021a). Aluminosilicates also affect the expression of intestinal mucosa genes in the context of supporting health status (Biesek et al., 2021b; Dunislawska et al., 2022).

The addition of zeolite and halloysite to the feed at the level of 0.5 to 2% and bedding (800 g/m^2 surface, in various proportions) had a beneficial effect on BWG and FI, as well as on the qualitative characteristics of the breast muscles (water absorption, proteins) (Banaszak et al., 2022a). The authors suggested using aluminosilicates in production due to their beneficial effects (Banaszak et al., 2021a,b, 2022b). The cited studies focused on the production results of broiler chickens. However, each was performed using different proportions of aluminosilicates as an additive to feed and bedding (wheat, rye, pellet, and peat straw). The use of aluminosilicates may additionally have a beneficial effect on intestinal morphology. In the study where zeolite or halloysite was used for feed, the authors found a beneficial effect of the addition of halloysite on the histomorphometry features of the jejunum (Banaszak et al., 2020).

Using zeolite in the feed at the level of 0.5% increased the expression of interleukin and interferon genes in the intestinal mucosa. Studies have shown an improvement in the intestinal barrier and increased intestinal tightness. Zeolite might be an immunomodulatory agent of the immune system (Dunislawska et al., 2022). When using aluminosilicates in other proportions (0.650 kg/m^2 of halloysite or zeolite and 0.5−2% in the feed, in the ratio of zeolite and halloysite, 1:1), a beneficial effect on the immune status of chickens was found (immunostimulating and regulating properties) (Biesek et al., 2021b). The other authors studied the effect of zeolite in feed at the level of 2 and 3% on the immune system of poultry and production performance (Jarosz et al., 2017). Higher BWG and increase with CD4+ CD25+ T and B lymphocytes and higher level of IL-2 and IL-10 were demonstrated. Zeolite improves antigen presentation and leads to an increase in Th1 and Th2 responses. However, it was concluded that too much zeolite in the feed could damage the intestinal barrier by inducing a local inflammatory reaction in the body. An excessive supply of zeolite can also negatively affect production results. In a study where zeolite was added to loose feed for ducks at 4%, lower production efficiency was shown (Biesek et al., 2021a). The mechanism of action of zeolite on the immune system may consist of stimulating intracellular adhesion molecules of enterocytes, the adhesion of leukocytes to the epithelium, and their migration and activation. The result of these actions is the production of proinflammatory cytokines that trigger a systemic immune response (Jarosz et al., 2017). In addition, zeolite can modulate the intestinal microbiome and affect the maturation and development of the immune response associated with the mucosa. Similar conclusions have been reported in the study by Grądzki et al. (2020).

Organic Acids

Another feed additive with a health-promoting and immunostimulating effect is organic acids (Fathi et al., 2016; Sugiharto et al., 2019). They are classified as organic chemical compounds that contain the carboxyl group −COOH in their structure (Hajati, 2018). In poultry nutrition, formic, acetic, propionic, malic, fumaric, and citric acids are used primarily (Haq et al., 2017). These substances are an additive that has a positive effect on feed hygiene through their preservative impact (Feye et al., 2021) and inhibition of the development of pathogenic microorganisms as a result of lowering the pH of the environment (Pope et al., 2022). One of the basic mechanisms of the bacteriostatic function of organic acids is their ability to penetrate through the biological membranes of microorganisms. Then, the process of electrolytic dissociation takes place, resulting in the formation of molecules that disrupt the proper functioning of cells (Ragaa et al., 2016).

The beneficial effects of formic acids on the broiler chickens were demonstrated in the production indicators (BWG, FI, or FCR) (Venkatasubramani et al., 2014; Sohail et al., 2015), gastrointestinal tract (elongation of the intestinal villi) (Tawfeeq and Al_Mashhdani, 2020) and immunological functions (increase in the number of lymphocytes in the spleen, antibody titers against

Gumboro disease) (Sohail et al., 2015; Ragaa and Korany, 2016). Similarly, in laying hens, administration of formic acid at 1 or 1.5 mL/L of water increased the quality of eggs and the immunity of birds against ND (Abbas et al., 2013). Formic and propionic acids can be effective agents against the spread of *Salmonella*, potentially transmitted through the poultry products (Bourassa et al., 2018). Adhikari et al. (2020) confirmed the effect of a mixture of organic acids against the pathogens mentioned above. Selected immunological and biochemical indicators may also be improved (Mohamedy et al., 2022). The use of formic and propionic acids positively affected the digestibility of nutrients (Ndelekwute et al., 2015; Palupi et al., 2022). Also, the use of a combination of formic acid with the yeast *Saccharomyces cerevisiae* had a positive effect on the quality of chicken meat by increasing the protein content in the breast muscles (Ukhro et al., 2021), as well as with thyme, which increased the share of breast and leg muscles in the carcass (Ragaa et al., 2016). Combining formic acid with essential oil (cinnamaldehyde) effectively reduced the negative impact of *E. coli* infection in birds (improved BWG and FCR). It also reduced the number of *Clostridium* spp. in the small intestine (Pathak et al., 2016).

Herbs

Herbs have long been used in human medicine (Ekor, 2014) and for feeding livestock, including poultry (Radkowska, 2013). The main advantages of herbs are the high content of biologically active substances that affect the processes of digestion and absorption of nutrients and the immune system (Makała, 2022). As a herbal additive to feed for poultry, for example, thyme (Yalçin et al., 2020), oregano (Ri et al., 2017), rosemary (Alagawany and Abd El-Hack, 2015), mint, fenugreek (Abed and Kadhim, 2014), ginger (Salih and Gürbüz, 2015), or garlic (Sangilimadan et al., 2019) were used. Prohealth significance is also attributed to herbal extracts (Skomorucha and Sosnówka-Czajka, 2014; Omar et al., 2016; Habibi et al., 2016) and phytobiotics—additives whose main components are bioactive substances of plant origin (Rafeeq et al., 2022).

The beneficial properties of oregano essential oil (**OEO**) are mainly due to the high content of 2 main components—carvacrol and thymol (Zhang et al., 2021). Some studies have confirmed the beneficial effect of OEO on production results, such as BW, average daily BWG, and FCR (Peng et al., 2016; Hernández-Coronado et al., 2019). It could be due to the increase in the ratio of the height of the intestinal villi to the depth of the intestinal crypts (Peng et al., 2016). On the other hand, OEO can modify the intestinal microbiota of birds, which was found in the Cherry Valley ducks, where this additive was used at 150 and 300 mg/kg of feed (Abouelezz et al., 2019). The powder form of oregano improved bird growth and antioxidant properties in the blood serum (Ri et al., 2017). In addition, using OEO affects the humoral and cellular immune response (Galal et al., 2015) by increasing selected antibodies in chickens (Ruan et al., 2021).

Thyme, particularly its essential oils, contains the previously mentioned bioactive compounds (found in oregano). However, there are also substances from the group of flavonoids with antioxidant properties. The beneficial effect of thyme on the organism of birds was found after its use at the level of 2%, affecting the quality of eggs and the immune system of laying birds (Yalçin et al., 2020). The research on broiler chickens found a definite production improvement, indicating daily BWG, final BW, and FCR (Ali, 2014).

Biologically active substances in ginger affected the increased secretion of digestive enzymes, as a result of which the ingredients from the feed were better absorbed, and the birds characterized with the higher BWG (Abd El-Hack et al., 2020) and could modulate the intestinal microbiota (Adeyemo et al., 2016). The beneficial effect of adding ginger root and its extracts on poultry products, that is, meat and eggs (Abd El-Hack et al., 2020).

The use of rosemary in the amount of 9 g/kg of feed affected the concentration of IgA and IgM and the content of cholesterol and triglycerides in the serum of laying hens (Alagawany and Abd El-Hack, 2015). Yildirim et al. (2018) described where an ethanol extract of rosemary was used in feed for Ross 308 broiler chickens (200 mg/kg). In the case of the addition of rosemary in the form of a powder, other authors indicate an increased secretion of the thyrotropic and growth hormone (Tayeb et al., 2019).

Garlic and its substances (mainly allicin) are considered additives with prohealth effects due to their antibacterial, antifungal, and antioxidant properties (Ogbuewu et al., 2019). At the same time, it can be one of the natural alternatives to antibiotic growth stimulants with high biological activity. It stimulates body weight gain (Islam et al., 2018). In the study by Puvaca et al. (2015), the most favorable effect on production indicators was found using 0.5 g of garlic per 100 g of feed.

DNA Immunostimulators

The innate system in chickens can be stimulated using DNA immunostimulators. For this purpose, unmethylated CpG oligodeoxynucleotides (**CpG-ODN**) are used. They are molecules that activate the host's immune system. These short single strands act as antigen-associated molecular patterns (**PAMPs**). They initiate an immune response by binding to a specific pattern recognition receptor (**PRR**) in dendritic cells, macrophages, and B lymphocytes responsible for antigen presentation (Klinman et al., 1996). Chicken TLR21 and its human TLR9 homolog recognize CpG-ODN containing the GTCGTT motif (Keestra et al., 2010). Already at the beginning of the 21st century, their immunoprotective effect on Eimeria infection (Dalloul et al., 2004), *Escherichia coli* (Gomis et al., 2003, 2004) and *Typhimurium septicemia* (Taghavi et al., 2008) were demonstrated. The administration of CpG-ODN to neonatal chickens via the mucosa accelerates the development of immunity by enriching the immune niches in the chicks. It was reported that intrapulmonary aerosol administration of CpG-ODN provided protective immunity against *E. coli* sepsis, enhancing local mucosal immunity and systemic immune response (Goonewardene et al., 2020). A commercial poultry DNA immunomodulator has been available for several years. Victrio (Elanco Canada Limited, Mississauga, Canada) is a bacterial plasmid DNA rich in unmethylated CpG motifs in a liposomal envelope. It is administered in ovo in the perinatal period (according to the manufacturer's recommendations, the 18th day of egg incubation) and effectively prevents posthatch mortality in chickens associated with *Escherichia coli* infection. Comparative studies on in vitro models (HEK293-NFκB-SEAP, HD11) have shown that Vicrio stimulation compared to ODNs (2006-PTO, 2006-PDE, 2007-PTO, 2007-PDE) on TLR21 activity is not higher than the indicated ODNs. The study's author showed that, most likely, the specific liposomal formula of Victrio provides a clear advantage in the in ovo application (due to a much lower dose compared to the ODNs in the in ovo application, about 1,000-fold less). Another possibility is that Victrio has a second mode of operation that PTOODNs do not. It may be related to the cGAS/STING pathway (Ilg, 2020). Recently, the activation of this pathway was confirmed in studies using another commercial formulation approved for cattle, which contains the same liposome-loaded plasmid as Victrio (Ilg, 2017).

SUMMARY

The awareness of production safety is constantly increasing. The safety of poultry production is defined as biosecurity and the health status of birds. Hence the constant pursuit of developing new strategies in this area is necessary. Biosecurity is an element of good production practices that ensures adequate hygiene of poultry production.

DISCLOSURES

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in the present study.

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