# Immunomodulatory Properties of Bioactive Products

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Bioactive products have an effect on the molecular and biochemical functions of a living organism, causing a physiological response of the given tissue. Such a products are biologically active. Depending on the active component and amount, the effects of such products can be positive or negative. Bioactive products can be food ingredients or dietary supplements, and while they are not required for survival, they are responsible for changes in the body's health.

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## 1. Introduction

Poultry production in Poland develops dynamically, especially in the broiler sector. Due to the large scale of the poultry production, the use of antibiotics is often required to reduce disease outbreaks [1]. Since 2009, the European Union has implemented legislation that aims to reduce the number of veterinary antibiotics in the poultry production. The use of antibiotic growth promoters in the chicken industry has been also reduced due to rising bacterial resistance to synthetic antibiotics and greater public awareness of health and food safety issues. This issue prompted researchers, the poultry industry, and the sector at large to look for safe alternatives to antibiotic growth promoters and focus on creating better long-term feed management solutions to boost chicken intestinal health and growth [2]. The trend to reduce antibiotics is correlated with the increased use of bioactive products that can have a positive effect on poultry growth, immune system, and health [3]. It is also worth noting that better animal health may lead to better food safety and quality, which benefits the consumers [4].

Bioactive products have an effort on the molecular and biochemical functions of living organisms, causing the physiological response of a given tissue. Such products are biologically active. Depending on the active component and dosage, the effects of such products can be positive or negative. Bioactive products consist of molecules that can have therapeutic effects such as reducing proinflammatory states, oxidative stress, and metabolic disorders [5]. Bioactive products can be food ingredients or dietary supplements, and while they are not required for survival, they are responsible for changes in the body's health [6]. Sources of bioactive products are plants (herbs and spices) and certain foods (fruits, vegetables, nuts, oils, and whole grains), but are also found in living organisms and microorganisms such as bacteria or fungi [6].

Immunomodulation refers to any process that modifies the immune system or immune responses triggered by an immunomodulator [7]. Immune responses can be enhanced with immunostimulants or natural compounds, synthetic chemicals, and microorganisms that are capable of modulating the function of the immune system [8]. Many immunomodulators are synthetic or semi-synthetic, and there is growing interest in natural compounds. Consumers consider natural products with pharmacological properties and therapeutic effects as being safer than manufactured chemicals. Natural compounds originating from plants and microbes have long been recognized as useful in drug discovery and development [9].

# 2. Immunomodulatory Properties of Bioactive Products

## 2.1. Plant Extracts

Plant extracts, such as thyme, oregano, or cinnamon, are widely used in poultry production [3][10]. Plant extracts supplemented in animal feed contain bioactive compounds that improve appetite, digestion, and prevent certain pathological conditions [11]. Bioactive compounds are plant chemicals, so-called phytochemicals, that have a positive effect on the various physiological functions of their consumer, including immune responses and health [12][13][14][15]. The influence of the phytogenic feed additives, such as herbs, spices, essential oils, or various mixtures on the health traits of different animal species is well documented. These products have been used as natural growth promoters in pigs and poultry [10][11][13][16]. Plant extracts (oregano, laurel, sage, anise, and citrus essential oils) have a positive effect on slaughter performance and the health of broiler chickens [17][18]. Some herbs and spices, including turmeric, cumin, black, and red peppers, nutmeg, mint, ginger, as well as chamomile or anise, also have immunostimulating properties [10]. The mechanisms of action of many phytochemicals have been established using avian cell lines and cultured lymphocytes [19]. Cinnamon has been tested for its immunomodulatory properties and was found to have antibacterial, antioxidant, and anti-cancer properties. Lee et al. (2011) stimulated chicken spleen lymphocytes with 25 mg/mL cinnamaldehyde (a component of cinnamon) and found increased cell proliferation when compared to the control [20]. Lower concentrations of cinamoldehydeneotheli caused the activation of macrophage growth or the inhibition of tumor cell growth [20]. Based on studies performed on in vitro and in vivo models, it is believed that plants such as rosemary or thyme may serve as alternatives to coccidiostatics [21]. Such testing is typically performed using *Eimeria* spp. challenged with different bioactive products, which directly indicates the coccidias' sensitivity to a given compound. Studies have shown that the addition of plant extract from Bidens pilosa inhibited the penetration of parasites into intestinal cells in chickens [22]. Numerous studies show the ability of phytochemicals to prevent diseases or strengthen the immunity of chickens, but there is still a lack of information about the underlying mechanisms [8][23][24][13][14][25][26].

## 2.2. Prebiotics, Probiotics, and Synbiotics

Many bioactive compounds have immunomodulatory properties, and can affect the intestinal microbiota, as well as the host's immune system. Some of them are described below. Prebiotics, probiotics, and synbiotics affect the development of a healthy intestinal microbiota and inhibit the development of intestinal pathogens [27].

Prebiotics are oligosaccharides that are not fermented by the host, but only by the intestinal microbiota. This way, they support the growth of the intestinal microbiota [28]. Commonly used prebiotics in poultry include inulin, fructooligosaccharides (FOS), galactooligosaccharides (GOS), soybeans-oligosaccharides (SOS), xylo-oligosaccharides (XOS), pyrodektrins, isomacaccharides (IMO), and lactulose [29]. Prebiotics are tested in vivo on livestock to determine their effects on gut microbiota, host immunomodulation, and the inhibition of microbial infections [29]. Bednarczyk et al. (2016) used three different prebiotics administered in different ways (injected in ovo, in water, or combined methods) to stimulate the intestinal microflora populations of broiler chickens. All of the methods and the three prebiotics increased feed intake and the feed conversion ratio compared to the control. Such results suggest a balanced consumption of energy and nutrients by healthy intestinal microflora, which is directly related to the better immune status of the animals [30].

Probiotics are “living microorganisms that, when given in the right amount, bring health benefits to the host” [31]. Supplemented in the right amount, they exert a positive effect on the microbial ecosystem of the host intestine, primarily ensuring a balance between commensal and pathogenic microbiota [32]. The use of probiotic supplements improves bowel function and protects the digestive tract from pathogenic organisms [33]. Some probiotics have shown protective properties against *Salmonella* [34]. Brisbin et al. (2010) investigated the effect of bacteria normally living in the digestive tract of chickens on the expression of cytokine genes in lymphoid cells [35]. These bacteria were *Lactobacillus acidophilus*, *Lactobacillus reuteri,* and *Lactobacillus salivarius*. Mononuclear cells isolated from cecal tonsils and the spleens of chickens were used in this experiment. The results indicated that mRNA expression of IL-1 was higher in spleen cells than in caecal tonsil cells. In the caecal tonsil cells, there were similarities and differences between the probiotic strains in inducing the mRNA levels of the tested cytokines IL-12p40, IL-10, IL-18, TGF-β4, and IFN-γ. *L. acidophilus* induced higher levels of IFN-γ, IL-12, and IL-1 expression than *L. reuteri* and *L. salivarius*, indicating that it has a greater ability to induce a putative Th1 response. *L. salivarius* inhibited the expression of proinflammatory cytokines and had the unique ability to generate TGF-β, suggesting that these bacteria may trigger an immune response. This experiment provides evidence that *Lactobacillus* spp. are capable of stimulating spleen and cecal tonsil cells in vitro [35].

Synbiotics are defined as synergistic combinations of probiotics and prebiotics that enhance the positive effects of these products administered alone. One of the functions of synbiotics is to improve the viability of microorganisms in the digestive tract [27]. Sunu et al. (2021) examined a synbiotic of garlic combined with *Lactobacillus acidophilus* for broilers [36]. After administration of the synbiotic, the intestinal morphology was assessed based on the height of the villi in the duodenum, jejunum, and ileum. The effect of the synbiotic on the immune organs was also assessed and an increased weight of the bursa of Fabricius, thymus, spleen, and caecal tonsil was found. Effects on pH, the number of *E. coli,* and the number of coliforms were also noted. Giving synbiotics T2 (T2 = basal feed + 4 mL synbiotic) reduced the coliform bacteria. The number of lactic acid bacteria was increased, which is beneficial for its host. The pH of the duodenum, jejunum, and ileum were significantly reduced by the synbiotics. The results showed that this treatment improved many aspects in broiler chickens such as performance, nutrient digestibility, blood profile, and intestinal health [36].

## 2.3. Immunomodulatory Effects of Bioactive Compounds

Plant extracts as well as prebiotics, probiotics, and synbiotics may have immunomodulatory properties. **Table 1** summarises the bioactive products and compounds tested in chicken in vitro and in vivo models. Al-Kassie (2009) used thyme and cinnamon to test their effects on broiler performance and biochemical results [37]. This experiment showed that herbal extracts of vegetable oil can affect both performance and the immune system in broiler chickens. The H/L ratio was lowered, and the number of white blood cells increased using only small amounts of this supplement [37]. Other studies have used aqueous and ethanol extracts of *Ficus religiosa* to test the anti-coccidiosis effects in broiler chickens [38]. Brisbin et al. (2015) investigated the effects of three different *Lactobacillus* spp. on chicken macrophages in vitro and determined that lactobacilli stimulated the immune response of the macrophage-like cell line MQ-NCSU [39]. The immunostimulating potency of acemannan from *Aloe vera* was determined in spleen-derived macrophages collected from vaccinated chickens [40]. The effect of probiotic bacteria on immune cells has also been studied using in vivo models. An example of this type of research may be the dietary supplementation of lactobacilli in broiler chickens, which increased cytokine levels and T cell counts [39][40]. The probiotic also triggered an increase in antibody production and intestinal immune responses [41]. Jung et al. (2010) studied a combination of probiotics and fermented herbs and confirmed that the mixture increased the activity of the immune system and helped overcome *Salmonella gallinarum* infection in chicken [34]. Extracts from herbs and spices contain molecules (flavonoids and terpenoids) that inhibit the metabolism of inflammatory prostaglandins [34]. Supplementation of *Aloe secundiflora* in chickens increased antibody titres and concentrations of IL6 [42].

**Table 1.** Examples of bioactive products and compounds with immunomodulatory properties in chicken.

| Bioactive Compound | Amount | Bird Models | Results | Reference |
|---|---|---|---|---|
| Arabinoxylan wheat bran (AXs) | Group A: AXs 100 mg/kg body weight/day<br>Group B: AXs 200 mg/kg body weight/day<br>Group C: AXs 300 mg/kg body weight/day | Industrial broiler chicks (Hubbard) | The results indicated a higher amount of anti-SRBC IgM in chickens in the experimental group compared to the control group. In the case of the amount of anti-SRBC IgG, it was also significantly higher in the experimental group than in the control group. | Adapted from Akhtar et al., 2012 [43] |
| Acemannan (ACM 1), a complex carbohydrate extracted from *Aloe vera* | 500 μg ACM vaccinated intramuscularly (6 chickens) and seemingly vaccinated (6 chickens) 3 days and 9 days before experimental analysis | 2-month-old White Leghorn chickens homozygous for the main | ACM 1 permanently and effectively increased the activation capacity of macrophages | Adapted from Djerba et al., 2000 [40] |

| Bioactive Compound | Amount | Bird Models | Results | Reference |
|---|---|---|---|---|
| | | histocompatibility haplotype B13 | from the systemic immune compartment (especially from the blood and spleen after intramuscular injection) in chickens, especially for the production of NO. | |
| Thyme oil extract | 100 and 200 ppm (parts per milion) in the diet | 1 day-old broiler chicks of mixed-sex Arbor-Acres | Thyme improved weight gain, feed intake, and feed conversion rate, improving the digestive system. Chickens fed thyme oil extract had lower cholesterol levels and higher red blood cells, packed cell volume, hemoglobin, and white blood cells. | Adapted from Al-Kassie. 2009 [37] |
| *Ficus religiosa* | I. Aqueous extract—100, 200, 300 mg/kg body weightII. Ethanol extract—100, 200, 300 mg/kg body weight | 1-day broiler chicks–Cobb | Both types of extracts affected the immune system by improving cellular immune performance. The researchers also noted growth-promoting effects. | Adapted from Mumtaz et al., 2021 [38] |
| Combination of herbs fermented with probiotics: *Curcuma longa*, *Houttuynia cordata*, *Prunus mume*, and *Rubus coreanus* | Chickens in the experimental groups received the same feed containing 1% or 2% of a combination of fermented probiotics | 20-day-old Ross broiler chicks from one healthy Salmonella-free parent herd | The combination of probiotic-fermented herbs increased immune activity in broiler chicks such as antibody production level in serum and increased survival against *Salomenlla* | Adapted from Jung et al., 2010 [34] |

| Bioactive Compound | Amount | Bird Models | Results | Reference |
|---|---|---|---|---|
| | | | *gallinarum* in experimentally infected broiler chickens due to stimulation of a nonspecific immune response. | |
| *Sacharomyces boulardii* and *Bacillus subtilis* | $1 \times 10^6$ cfu/mL for 3-, 6- and 12-h *S. boulardii, B. subtilis* and coculture *S. boulardii* and *B. subtilis*, 1 µg/mL lipopolysaccharide, saline phosphate buffer added to the control group | Chinese crossed chickens—dendritic cells derived from chicken bone marrow | The treatment groups modulated the phenotype and biological functions of chi-BMDC. Upstream levels of MHC-II, CD40, CD80, and CD86 gene expression in the stimulated groups, toll-like receptors TLR1, TLR2, TLR4, and chicken-specific TLR15 expressions improved, and the accompanying factors myD88, TRAF6, TAB1, and NFk-B increased in all treatment groups compared to control. The NFk-B response was significantly higher in the treatment of LPS in all groups. In addition, IL-1β, IL-17, IL-4, TGF-β, and IL-10 contrast, the LPS groups showed a marked increase in IL-12, INF-γ, and IL-8 concentration levels compared to the control group. | Adapted from Rajput et al., 2014 [44] |
| *Lactobacillus acidophilus, Lactobacillus reuteri, Lactobacillus salivarius* | $1 \times 10^6$ CFU thermally killed *S. typhimurium*, live *L.* | 22 commercial broiler chicks of mixed-sex at the | The three lactobacilli induced a much higher | Adapted from Brisbin et |

| Bioactive Compound | Amount | Bird Models | Results | Reference |
|---|---|---|---|---|
| | *acidophilus*, live *L. reuteri*, and live *L. salivarius* | age of 5 or 6 weeks. The mononuclear cells of the spleen and the tonsils of the spleen were isolated and cultured | expression of interleukin 1β in spleen cells than in cecal tonsil cells—more inflammatory response in the spleen than in the cecal tonsil cells. *L. acidophilus* was more effective in inducing T-helper-1 cytokines, while *L. salivarius* induced a more anti-inflammatory response. | al., 2010 [35] |
| *E. faecium* AL41, *E. faecium* 31, *L. fermentum* AD1 and infected *Salmonella enterica* serovar *Enteritidis* (SE147) | 200 µg *E. faecium* AL41, *E. faecium* H31, *L. fermentum* AD1 and Salmonella *enterica* infected serovar *Enteritidis* (SE147) 1 × $10^9$ cfu/ml | Healthy poultry reared under standard conditions—peripheral mononuclear blood cells (PMBC) | The results showed that *E. faecium* AL41 exhibited the highest immunostimulating effect on the expression of selected cytokines by PMBC from chickens after Salmonella infection. | Adapted from Husáková et al., 2015 [45] |
| Probiotic based on *Lactobacillus* | Probiotic added in the amount of 1 g/kg of feed | 100-day broiler chicks Ross 308 | The results indicate that probiotic bacteria influenced the local immune response characterized by altered subpopulations of gut intraepithelial lymphocytes and increased birds' resistance to *E. acervulina*, reflecting reduced oocyst shedding. | Adapted from Dalloul et al., 2013 [46] |

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