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Emine Baydan
Ankara University, baydan@veterinary.ankara.edu.tr, Ankara-Turkey
Emre Arslanbaş
Cumhuriyet University, earslanbas@cumhuriyet.edu.tr, Sivas-Turkey

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ORCID ID	0000-0001-5459-8616	0000-0003-0030-7195
CORRESPONDING AUTHOR	Emre Arslanbaş	

THE IMPORTANCE OF IMMUNOSTIMULANTS IN THE TREATMENT AND PREVENTION OF POULTRY DISEASES

ABSTRACT

Improvement of consumer consciousness and the increasing tendency towards consumption of natural products, and increasing resistance to antibiotics and antiparasitic medicines, have increasingly limited utilization of medicines for protection from diseases. It has also become impossible to use antibiotics and similar medicines for animals in order for preventive purposes except medical treatments as a result of recent legal arrangements and this situation caused new approaches for fighting with diseases. People have now focused on using as natural as possible products for treatment and prevention purposes. Immunostimulants are natural or synthetic components that are used at pets and poultries for various purposes, such as health, growth and performance increase, and they stimulate humoral and non-specific cellular immune system against pathogens. Studies showed that immunostimulants provide immunity against various disease factors, such as bacterial, viral and parasitic diseases, increase the survival rate and productivity, increase the effect of vaccines and antibiotics. They are preferred also because they are safer than chemotherapeutics. Taking necessary actions to protect hencoop from viral, bacterial and parasitic diseases and to prevent economic losses is important in poultry farming. It seems more suitable to use immunostimulants for prevention purposes before the disease occurs. However, since they have effectiveness increasing properties as adjuvants, it is also possible to state that they will be more effective for treatment if they can be used in combination. Therefore it is expected that therapeutically effective components can be developed in recent future with single or combined immunostimulant trials, which are not harmful to animals, humans and environment.

Keywords: Immunostimulants, Prevention of Diseases, Poultry, Treatment, Immunomodulators

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1. INTRODUCTION

There are various studies on controlling immune system disorders and/or preventing the diseases of host in human medicine and veterinary medicine. The concept of immunomodulation has emerged for the first time in 1796. Many substances, such as endotoxin, Mycobacterium adjuvant (BCG), zymosan, interferon, liposomes, maya glucan, levamisole, muramil dipeptide, etc., which are defined as an immunomodulators has a long history (respectively, 1865, 1937, 1941, 1957, 1964, 1970, 1971, 1975). Immunomodulation means manipulation of immune system and it develops specifically or non-specifically. Augmentation of immune responses are called as immunostimulation or immunopotentiation. On the other hand suppression of immune responses is known as immunosuppression and it is preferred in case of allergy, autoimmune diseases, organ transplantation, etc. Immunomodulators are biological or synthetic substances that do not directly affect the microorganism, do stimulate or suppress the immune system [1]. Today, diseases in humans and animals are usually taken under control by using broad spectrum antibiotics or vaccines. However the resistance that is rapidly developed in microorganisms against antibiotics and veterinary medicine residue risk in animal products forced researchers to develop alternative protection and treatment strategies [1]. According to WHO, antibiotics would be useless after 2020 due to the resistance of bacteria [2 and 3].

2. RESEARCH SIGNIFICANCE

It is very important to take precautions to protect poultry from viral, bacterial and parasitic diseases and to prevent economic losses. Factors such as the inadequate care and feeding conditions, stress, especially at places where intensive poultry farming are done, cause poultry to break down in the immunity system and to be sensitive to diseases. The history of the use of immunostimulants, which are natural or synthetic compounds that stimulate the immune system against pathogens, is based on very ancient. Immunostimulants can be used in almost all areas of husbandry, such as animal health and welfare, production [1 and 3].

3. CLASSIFICATION OF IMMUNOSTIMULATORS

Immunostimulants can be classified in various ways, depending on their origins, chemical structures, effect models and their application areas in veterinary medicine.

3.1. Natural Immunostimulators (Biological Substances)

3.1.1. Microbial Derivatives

β-glucan, peptidoglycans, lipopolisaccharides, bacteria, Freund's complete adjuvan (FCA) and EF 203 are examples of this group [4]. There are 200-300 natural immunoactive products, most of which are derived from herbs and fungi. These immunoactive ingredients in herbs and fungi are polysaccharides, glycosides, alkaloids, volatile fatty acids and organic acids [5 and 6]. Various glucans isolated from yeasts, fungi, cereals and algae have immunological and other biological affects. Glucans are the oldest and most common immunomodulators. Recent studies showed that β-glucans, which were initially thought only to increase cellular immunity, have also pleiotropic biological effects [7]. β-glucans are effective in the systems of mammals through toll-like receptors and dectine-1 [8]. Prohibition of utilization of antibiotics as growth factor by governments has caused focusing on utilization of glucan in animal farming [7]. Probiotics (*Lactobacillus casei*, *L. acidophilus*, *L. plantarum* DK119, *Lactococcus lactis* BFE920, *Peptostreptococcus*,

Bifidobacterium bifidus, *Bacillus subtilis natto*) are immune system supporting live microorganisms that suppress pathogen microorganisms living in intestines and they are capable to increase useful organisms and absorb microorganism originated toxins [1].

3.1.2. Animal and Herbal (Medical) Extracts

Many herbal preparation is used because of their immunomodulator effects. *Tinospora cordifolia* (Gudichi), *Ocimum sanctum* (tulsi), *Withania somnifera*, *Asparagus racemosus* (Satavar), Taishan *Robinia pseudoacacia* are some of these [9]. Ete, Hide, Fireflysquid, Quillajasaponin (scaptree) and glycyrrhizin (licorice) as well as some hormones (lactoferrin, interferon, growth hormone, and prolactin) do also have immunostimulator effects [4].

3.1.3. Foods (Vitamins, Minerals, Fatty Acids)

Nutrition is necessary for overall cell growth, including the cells of immune system, for energy metabolism and for production of proteins and antioxidants and it has a significant role in immunomodulation. Therefore amino acids and essential fatty acids are effective on immune system functions. Arginine, one of these amino acids, is significant in phagocytic cells for its capability to kill depending on oxygen. Glutamine is necessary for activation of immune system during inflammation and for suitable functions of macrophage and lymphocytes [1 and 10]. Two important classes of polyunsaturated fatty acids (PUFA) in diet are n-6 and n-3 fatty acids. Linoleic acid is a precursor of n-6 and it can be found in vegetable oils, corn and soybean. Since linoleic acid transforms into arachidonic acid, n-6 has an inflammating effect, unlikely n-3. n-3, one of unsaturated fatty acids (docosahexaenoic acid, eicosapentaenoic acid, and linolenic acid), have an effect to reduce inflammation and correct autoimmune disorders [1, 11 and 12]. When fish oil, flax seed oil and whole flax seed (contains n-3 fatty acid) is added to the diet of one day old chicks, it was found that it has a protective effect against *E. tenella* but it couldn't show the same effect against *E. maxima* [12]. Vitamins and minerals do also have an important role for immune system functions. Sufficient amounts of vitamin A, C, D, E and B complexes, copper, folate, iron, iodine, selenium, magnesium and zinc in diet are important for immune functions [1 and 10].

3.2. Synthetic Immunostimulants

Levamisole, FK-565, muramyl dipeptide (MDP) are examples of this group [4].

4. UTILIZATION OF IMMUNOMODULATORS IN POULTRY FARMING

Infectious poultry anemia, poultry tuberculosis, avian influenza, adenoviral infections, Marek's disease, etc. are diseases that cause serious economic threat for poultry industry [10]. Respiration and intestine diseases are considered among the reasons of significant economic losses in broiler farming and therefore correct strategies must be identified in order to minimize losses. Preventive medicine forms the basis of these strategies. Vaccines and preventive medicine practices, genetic breeding, increasing the quality of shelters and equipment is effective practices in preventing diseases [13]. Coccidiosis in poultry is an infection occurs in intestines due to intracellular protozoa of *Eimeria* genus (*Eimeria tenella*, *Eimeria necatrix*, *Eimeria acervulina*, *Eimeria maxima*, *Eimeria brunetti*, *Eimeria mitis*, and *Eimeria praecox*) it causes significant damages. The medicines to be used for treatment of coccidiosis have a history of

50-60 years. Recombinant vaccine practices with vaccines tolerating to live virulents, attenues and ionophores against *Eimeria* parasites are also an option. High costs of live vaccines was the reason to choose recombinant vaccines. Vaccines are sometimes used together with expression plasmid that code IL-1, IL-2, IL-6, IL-8, IL-15, IL-16, IL-17, IL-18, or IFN-γ genes [14].

It is reported that application of β(1-3)(1-6)-D-Glucan to chickens and strengthening of immune system would be useful in increasing the productivity of commercial farms. Studies showed that glucan supplements decrease cholesterol in animals and increase phagocytosis of macrophages and growth performance after a bacterial infection and reduces the effect of *Eimeria* infections [7]. It is also found that β-glucan, extracted from edible mushrooms (*Pleuratus florida*) initiates the immune response in broilers and provides a protective effect from diseases [15]. Natstim® (*E. coli* 29, *E. coli* J5, *Staphylococcus aureus* 27/58 derivative lyophilised dead bacteria cells), an immunomodulator, significantly affects serum lysozyme concentrations (200% decrease) and ensures to control chicken diseases [16].

It is seen in experimental studies that usage of propolis, a product of bees, together with vaccines (Newcastle-ND and *Bordetella avium*) in chicks increases the potency of vaccines [17 and 18].

Artemisinin is an endoperoxide with antimalaria features, isolated in China from *Artemisia annua*. Including 8.5-17 ppm to initial feeds reduces oocyte output from *E. acervulina* and *E. tenella*. It is also reported that including the extracts of *Sophora flavescens* Aiton to the feed with 8 ppm γ-tocopherol (abundant in seed oils, such as wheat, corn, soybean) and turmeric spice (1%) or curcumin (0.05%) does also have similar effects [19]. It has been scientifically proven that *Phyllanthus emblica*, *Withania somnifera*, *Magnifera indica*, *Ocimum sanctum* and other herbs, which compose Stresroak, have antistress, immunomodulator and performance increasing effects. It was also found that this mixture has hematinic, hepatoprotective and immunomodulator effects on chickens [20].

First recorded in Japan in 1979, chicken infectious anemia (CIA) is a viral disease that causes significant economic losses in poultry industry throughout the world. This disease is characterized with decrease in weight gain, anemia, bone marrow aplasia and lymphoid atrophy. Chicks are vulnerable to infection related strong immune suppressions and secondary infections (viral, bacterial, fungal). It was reported that hematinic (composed of elemental iron, vitamin B_{12}, vitamin B_6, folic acid, potassium chloride, sodium chloride, vitamin K3, copper sulphate, and copper chloride) + immunomodulator (composed of vitamin E, vitamin C, amino acid, omega oils, sodium chloride, potassium chloride, selenium, manganese sulphate, *Withania somnifera*) combination can be protective against the disease [21].

Morinda citrifolia is a medical herb with broad therapeutic effect and nutritional value, known as Noni. It contains some amino acids, vitamins, minerals, coenzymes, carbohydrates and alkaloids. It was found effective in performance of poultries [22]. Taishan *Robinia pseudoacacia* has various effects in chickens, such as reinforcing the defense against microbes, correcting elasticity of capillary vessels, decreasing blood lipids and antitumor effects [23]. It was also reported that pollen polysaccharide of Taishan *Pinus massoniana* causes a synergic affect on chicks when it is used together with *Bordetella avium* vaccine [18]. Extracts of *Eugenia jambolana* (contains menthol, eucalyptole and ormocyn) and *Hypericum perforatum* L. were used effectively to control avian influenza [24]. It was found that

saponins derived from leaves and body of ginseng increases adjuvant effect of Newcastle (ND) vaccine in chicks and therefore it can be given to chicks with their drinking water and its effect is increased as the duration extends [25]. It was found that volatile oil of rosemary (*Rosmarinus officinalis* L.) is more effective in white layer chickens than antibiotics against infection when it is given with a dosage of 300 mg/kg (90 days) [26]. It is recorded that extract of sugar cane (*Saccharum officinarum* L.) has positive effects, such as adjuvant over antibody activation, increasing the immune response through cells, protective against *Eimeria tenella* and radioprotective for immune functions and intestine damages in x-rayed chickens [27]. It was found that *Lentinus edodes* (LenE) and *Tremella fuciformis* (TreE), which are extracts of polysaccharides and derived from mushrooms, and polysaccharides in *Astragalus membranaceus* (AstE) herb protect chicks from *E. tenella* with their humoral and cellular immunity [28]. When polysaccharide gel (3g/100 g diet, 42 days) is applied to broilers as a nutritional supplement, it has also stimulated humoral immune responses in addition to its other positive effects [29].

Newcastle disease is an important viral disease in poultries in terms of public health. Vaccine is still the most important practice in controlling the disease. However death can still be encountered despite of vaccine. There are various efforts to increase the potency of vaccine. The effect of levamisole, a synthetic immunomodulator, was experimented on cockerels before the vaccine. But no positive result was achieved [30]. Mycotoxins are metabolic products of toxigenic mushrooms and aflatoxin is the most common mycotoxin. These toxins cause adverse effects, such as host sensitivity, immunosupression and hepatoxicity. Applying vitamin E (200mg/kg feed) and selenium (salt with sodium, 1mg/kg) combination in aflatoxicosis findings in broilers may cause immunomodulation [31].

5. POSITIVE AND NEGATIVE ASPECTS OF IMMUNOSTIMULATORS

Although immunostimulators are increasingly used for protection and fighting against diseases, they have some positive and negative aspects. For example, while antimicrobials are addressing more specific factors, immunomodulators have some superiorities, such as affecting various factors, e.g. viruses, fungi, helminth, etc [1]. But this doesn’t mean that all diseases can be treated [4]. While the resistance against antibacterials is developing rapidly, there is not any such effect for immunostimulants [1]. Vaccines are used with an antigen, but immunomodulators do not need them. However they can be used in combination with vaccines in order to increase the vaccine’s potency. Use of synthetic chemicals particularly in culture fishing causes contamination of environment and has an effect on natural species, but use of immunostimulators decreases this effect. But, the price of immunostimulators is quite high and when they are used parenterally, their effects are limited. Also their high dosages may cause immunosuppression [4].

6. CONCLUSION

Infectious diseases are economically important for poultry industry. Vaccination is one of the most effective methods for protection from diseases. But the disease must be treated with medicines, which are powerful for treatment. However, it is increasingly prohibited to use medicines, which are mostly synthetic, in animals for protection and treatment purposes, which caused farmers and veterinary physicians to follow good farming programs and choose

practices that reinforce immune system against diseases. As a result of these challenges, use of immunostimulators or, generally, immunomodulators has become widespread. But it must be noted that current immunostimulators are not as effective as medicines in case the disease begins. On the other hand, their high prices is another significant factor in limiting the use of immunostimulants. However it can be easily predicted that the significance of immunostimulants would be noticed more in future as public health has become more important as well as eating.

NOTICE

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