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## Immunomodulation in poultry

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### Abstract

Immunity plays a key role in disease susceptibility. Immunomodulators are agents which specifically modulate immune system regulating immunity and disease resistance. In poultry it is specifically important as the growth, disease resistance, FCR, body weight gain production output mainly depends on the health and immunity of the chickens. Different types of immunomodulators are prebiotics, probiotics, vitamins, adjuvants, polysaccharides, herbs etc. Immunology has great potentials in prevention and treatment of various range of disorders for instance the various inflammatory diseases of skin, respiratory tract, gut, central organs and joints. The preliminary objective of immunomodulation is to improve host resistance to external and internal attacks by the microbes or other infectious agents. Immunomodulators can substitute many agents like antibiotics, antimicrobials etc. for the improvement of the immune system. They also enhance the qualities of feed and immune molecules enhancing all possibilities to fight diseases and maintain health homeostasis. Since, they are not popular and not included in the poultry feed on routine basis, more efforts should be made to popularize it.

**Keywords:** Immunomodulators, immunity, chicken, phytochemicals, probiotics, prebiotics

### 1. Introduction

Poultry sector of India ranks 1<sup>st</sup> in the world. It has been a major source of income for rural farmers along with people making it a business. A major part of India's GDP is contributed by poultry industry. Around 70-80% of Indian people consume chicken, hence the health and growth of poultry (chicken) plays a major role in health of humans.

Immunomodulators are agents which modulate and regulate immune system affecting the immunity of the body. They are either natural or man induced. Immunity plays a crucial role in poultry farming. The growth, disease resistance, FCR, body weight gain etc everything depends directly and indirectly on the immunity of the bird. It also hence affects the profit of the farmer and the health of the consumer.

Immunomodulators modify and optimumly control immune responses of the body, modifying disease resistance, vaccine and antibiotic efficacy, improving digestive tract microflora. Nowadays, microbes are increasing resistance against antibiotics, hence immunomodulation can be a virtuous alternative prophylactic and therapy. Different types of immunomodulators are prebiotics, probiotics, vitamins, adjuvants, polysaccharides, herbs etc.

Immunomodulators have upper hand against antimicrobials. They act on the immune system and its molecules and not on the microbes directly, along with broad spectrum ability. Immunomodulators can come closer to the idea of one health one medicine concept. (Dhama *et al.*, 2013) [7].

### 2. Immunity system of chicken

Immunology has great potentials in prevention and treatment of various range of disorders for instance the various inflammatory diseases of skin, respiratory tract, gut, central organs and joints. Moreover, infectious diseases are being primarily considered as immunological disorders. Neoplastic diseases along with numerous autoimmune diseases causes immunosuppression. (Patil *et al.*, 2012)

Immunomodulators are either natural or synthetic substances which regulate and normalize the immune system. (Patil *et al.*, 2012) Immunomodulators moderate immune response to help restore immunity towards treatment of diseases. (John Hadden, Immunomodulators) Hence, immunomodulators are also called as *biological response modifiers* (BRMs).

immunomodulators rectify instable immune system. (Patil *et al.* 2012, John Hadden, Immunomodulators) They include microbial products, drugs, and proteins derived from the immune system (cytokine and antibodies) are currently used agents. (John Hadden, Immunomodulators). The cytokines (*lymphokines* and *interleukins*) are produced commonly by recombinant genetic methods in diverse vectors while the antibodies are produced by monoclonal antibody-producing cell cultures. most of these have anticancer activity directly. (John Hadden, Immunomodulators)

### 3. Objectives of Immunomodulation

The preliminary objective of immunomodulation is to improve host resistance to external as well as internal attacks by the microbes or other infectious agents. The basic objectives of immunomodulation in domestic animals include (Kuldeep Dhama *et al.* 2015) <sup>[31]</sup>:

- To trigger disease powerful and sustained immune response against disease causing microorganism
- To improve maturation of specific and non specific immunity throughout neonatal period besides in susceptible young animals.
- To augment local protective immune reactions at susceptible sites or gastro intestinal tract.
- To overcome the immunosuppressive effects of stress and environmental pollution
- To enhance duration and level of immune response following vaccination
- To maintain immune surveillance

### 4. Types of Immunomodulators

Treatment immunomodulators are more potent and possibly cause aggravated side effects than Natural immunomodulators. synthetic immunomodulator suppositories, for example azathioprine, methotrexate, 6-mercaptopurine, and mycophenolate mofetil, function by the immune system suppression. The benefits of immunomodulators branch from their proficiency to accelerate defense mechanisms of natural and adaptive types, for instance cytokines, which empowers the body to assist itself.

Generally, two types of immunomodulators exist - immunostimulants and immunosuppressants.

Immunosuppressants subdue the immune system hence used for pathological immune response control in autoimmune disease, etc. Immunostimulants are the mediators which help enhance the body's resistance towards infections. Immunostimulants improve the basal levels of the immune response, and in individuals with impairment of immune response as an immunotherapeutic agent. immunodeficiency state, cancer, autoimmune disease, and viral infection can successfully be treated with immunostimulant drugs. (U.S Patil *et al.* 2012, John Hadden, Immunomodulators)

#### 4.1 Probiotics and Prebiotics

Some species of non-pathogenic intestinal microbiota also interlink with the epithelium and immune system, modulating tissue physiology and ability to respond to infection. (John Hadden, Immunomodulators) Probiotics and prebiotics modifies the intestinal microbiota and immune system to lower pathogens colonization in definite conditions. Growth promoting antibiotics, stress status and environmental conditions influence effectiveness of prebiotics and probiotics. (John Hadden, Immunomodulators) These are

spectacular alternatives for antibiotics used as growth promoters. (John Hadden, Immunomodulators)

#### 4.2 Phytochemicals

Improving animal health and the GIT tract health are priorities in animal production other than reproduction. These are potential feed additives possessing multiple functions, including anti-inflammatory, antifungal, antiviral, and antioxidative properties. On the molecular level, it has impact of inflammatory gene expression on underlying mechanisms, similar to the effects of environmental stimuli along with phytochemicals in initiating nuclear factor kappa B and mitogen activated protein kinases signaling pathways improving health conditions. The active constituents in phytochemicals, Phytochemicals, divided into two groups terpenes and terpenoids, or aromatic and aliphatic compounds, on the different synthetic pathways in plants: Phytochemicals can be used as alternative feed additives. Addition of phytochemicals had tremendous effects on the pancreatic and intestinal enzyme secretion in broilers and improved dry matter along with crude protein digestibility. immune response improved besides GIT protective capacity against exogenous stressors, when phytochemicals was introduced in diet. (John Hadden, Immunomodulators) Their major components regulates NFκB (nuclear factor enhancing kappa light chains of activated B cells) and MAPKs (mitogen-activated protein kinase) signaling pathways in rodents (John Hadden, Immunomodulators) Therefore, phytochemicals regulate the immune response and moderate the expression of inflammatory mediators in chickens (John Hadden, Immunomodulators). The stress response was alleviated as the NFκB and MAPKs signaling pathways were suppressed, also the expression of anti-inflammatory cytokines increased due to this, the blood levels of nonspecific immune cells like heterophils (neutrophils) reduced, and lymphocyte and antibody production increased to defend against invading pathogens. The lesser energy spent by chickens on the non-specific immunity, the more energy is available for production and growth. Phytochemicals modulate NFκB and/or MAPKs signaling pathways in chickens, but detailed mechanisms, expression of upstream molecules involving signalling of NFκB and MAPKs and the relationship between antioxidant and antiinflammation, are still unknown.

#### 4.3 Turmeric Rhizome Powder (TRP)

TRP in the diet significantly increased blood IgA, IgG, and IgM levels, and decreased the ratio of monocytes in 42dayold broilers given SRBCs (sheep red blood cells) (Emadi M, *et al.* 2007) <sup>[29]</sup>. 0.2% TRP supplementation increased the total secondary antibody titer against SRBCs in broilers and decreased the heterophils and lymphocytes ratio (H/L) under heat stress treatment (Akhavan-Salamat H2016) <sup>[27]</sup>. The H/L ratio denotes stress level Treatment of 0.33%, 0.66%, and 1.0% TRP reduced abdominal fat content and serum triglyceride concentration. (Nouzarian R2011) <sup>[28]</sup> hence, dietary curcumin regulates immune responses in poultry and it has the potential to enhance growth performance.

#### 4.4 Cinnamon

Dietary supplementation of cinnamon extracted oil or leaves has shown to decrease coliform bacteria in the jejunum and large intestine and improve growth performance in broilers. inclusion of 0.4% and 0.8% cinnamon in broiler diets improved the FCR and (C. M. Huang, 2018) <sup>[26]</sup> the

proportion of lymphocytes in the blood and increased the concentration of hemoglobin; Cinnamon essential oil has antioxidant properties (Case and his colleagues 1995; Lee and his colleagues 2001; Yu and his colleagues 2002; Lee and his colleagues 2007).

The response of cinnamon powder or oil on humor and innate immunity responses is significant. Phagocytosis and lysosomal activity, host resistances mortality (Balekar *et al.* 2014) suggested that PP-CZ (polyphenol cinnamon) treatments was effective immunostimulant in immune system in dose dependent manner. Peripheral PMN was increased by PP-CZ treatment along with increase in the number of resident peritoneal macrophages in mice, pp-CZ stimulates non-specific immunity as phagocytosis activity in mice improved by increasing the number of macrophages and phagocytic activity in mice on sub-acute treatment. A dose-dependent trend for increased numbers of peritoneal macrophages was observed and increased survival rate in mice. There are specialized phagocytic cells that cells attack foreign substances, infectious microbes through destruction and ingestion [Ovchinnikov DA., 2008] <sup>[9]</sup>. [Balekar *et al.* Journal of Applied Pharmaceutical Science 4(07); 2014:114-122] demonstrated sub-acute treatment of PP-CZ showed increased peritoneal macrophage and increased PMN observed in their study the potential PP-CZ in stimulating adaptive immunity against infectious pathogens. [A. Sivagurunathan *et al.* 2014] <sup>[3]</sup> demonstrated significant increase in TLC can be considered as indicator for improving general resistance, increase in neutrophil, non-specific immune response and increase in lymphocytes counts in cinnamon along with specific immune response. Cinnamon verum essential oil showed stimulator effect on macrophages, phagocytosis and killing of invading microorganisms by macrophage constitute the body's primary line of defense against infection Van furt R (1982) (Tamam S. M *et al.* 2017).

#### 4.5 Thyme

Thyme is the name for Thymus; thymol, carvacrol, p-cymene and  $\gamma$ -terpinene are the major active components in the essential oil. Supplementation is in the form of essential oil or leaf powder. This essential oil improved cutaneous basophil hypersensitivity to phytohaemagglutinin P (PHAP) along with reducing the H/L ratio. It produced more balanced intestinal microbiology, indicated by higher Lactobacillus and Bifidobacterium counts and lower Escherichia coli (E. coli) levels in the ileum. A reduced H/L ratio shows enhanced immunoregulatory capacity of the bird. Intestinal microbiota plays vital role in the immune system of chickens. Thyme improved body weight gain and FCR in broilers. Hence, thyme is a potent feed additive in poultry production.

#### 4.6 Essential oils and Carvacrol

Essential oils (EOs) are vital aromatic components, which are used as natural substitutes for antibiotic growth promoters (AGPs) in poultry feed. These have antimicrobial, antiviral, antifungal, antiparasitic properties. Other benefits are, it acts as appetite stimulant, improves enzyme secretion related to food digestion, and immune response activation.

Carvacrol, or cymophenol is monoterpenoid phenol having characteristic pungent, (16)

Carvacrol is found in the essential oil of *Origanum vulgare* (oregano), oil of thyme, oil of pepperwort, and wild bergamot. (Vladić, J. 2016) <sup>[24]</sup>. EOs are comprised of mainly two classes of compounds- terpenes and phenylpropenes.

The antimicrobial properties of the various chemical compounds of EOs has a cumulative effect on various targets in different cell parts (Burt, 2004) <sup>[19]</sup>. The effectiveness depends on pH, concentration, chemical structure, or the individual bioactive compound, along with the affected microorganisms types and population. The antimicrobial mechanisms comprise of different activities, like membrane disruption by phenolics and terpenoids, metal chelation by flavonoids and phenols, and effect on genetic material by coumarin and alkaloids due to inhibition of microorganisms growth (Cowan, 1999) <sup>[20]</sup>.

EOs are more effective against Gram-positive in comparison to Gram-negative pathogens (Burt, 2004) <sup>[19]</sup> as the outer membrane through its lipopolysaccharide structures limits the intrusion of hydrophobic compounds (Vaara, 1992) <sup>[21]</sup>. Many EOs increase beneficial microbe growth and control pathogenic bacteria population in poultry (Wenk, 2000) <sup>[11]</sup>. Cerisuelo *et al.* (2014) <sup>[12]</sup> showed a clear effectiveness of low doses of EOs and sodium butyrate in Salmonella control in broilers.

EOs enhance the growth of beneficial microbes and limit the number of pathogenic bacteria in poultry (Wenk, 2000) <sup>[11]</sup>. Cerisuelo *et al.* (2014) <sup>[12]</sup> showed clear effectiveness of low doses of EOs and sodium butyrate in Salmonella control in broilers. Thymol and Carvacrol, are the main ingredients in oregano oil, possessing anticoccidial actions against mixed *Eimeria* spp. and *E. tenella* infection (Oviedo-Rondón, 2003) (Giannenas *et al.*, 2003) <sup>[4]</sup>. Several *in vitro* and *in vivo* studies suggested that phenols can be used against *E. tenella* as oocysticides (Williams, 1997) <sup>[23]</sup>.

Several EOs are antiparasitic in function as well. EOs and seeds of onion (*Allium cepa*), garlic (*Allium sativum*), and mint (*Mentha spp.*) are effective against gastrointestinal parasitism. EO also suppress inflammatory prostaglandin metabolism. (Craig, 2001) <sup>[1]</sup>. Plants with anti-inflammatory potentials are licorice, chamomile, marigold, and anise (Srinivasan, 2005 (Gopal Krishan and Asmita Narang, 2014) <sup>[10]</sup>).

#### 4.7 Butyrate

Butyrate stimulates digestive secretions (bile and mucus) while enhancing enzymatic activity (Platel, 2004; Manzanilla *et al.*, 2004). In broilers, EO (essential oils) boost trypsin, amylase and jejunal chyme secretions (Jang *et al.*, 2007) <sup>[15]</sup>, as well as reduces the pathogens adherence (for example, *E. coli* and *C. perfringens*) to intestinal wall (Jamroz *et al.*, 2006). (Gopal Krishan and Asmita Narang, 2014) <sup>[10]</sup>

#### 4.8 Nutritional Strategies

Reduced feed intake is observed at high environmental temperature. It causes micronutrient deficiency like that of vitamins and minerals. Vitamin A, C and E in heat-stressed chicken has stress alleviation and immunomodulation role.

##### 4.8.1 Vitamin A

Fat soluble vitamin A has significant role in immunity. It reduces heat stress when layer supplemented @ 8000 IU/Kg. diet, along with increased egg production. In broilers, when supplemented @ 15000 IU/Kg. diet, significant improved weight gain with, feed efficiency and carcass quality is reported. In combination with zinc it is more effective to minimize heat stress.

##### 4.8.2 Vitamin C

Ascorbic acid is a water soluble vitamin and can be synthesized in poultry and not required as a supplement under normal condition. However, in heat stressed chicken, it is proven to be beneficial by reducing corticosterone production with simultaneous increase in insulin and thyroid levels. It also deprives protein derived glucose synthesis and increase fat degradation. In case of broiler breeders, it increases egg weight, fertility and hatchability. In heat stressed broilers, ascorbic acid requirement is more, as it also acts as antioxidant. It improves carcass yield and quality, feed efficiency, carcass protein content and reduces crude fat.

#### 4.8.3 Vitamin E

Vitamin E is a fat-soluble vitamin and its dietary intake reduces heat stress and improves egg production. It increases yolk and albumen content in the egg. It increases plasma concentration of yolk lipids by production and release from liver. It protects the liver and body cells from oxidative injuries also. Vitamin E supplementation @ 250 mg /Kg. diet is beneficial for egg production at high temperature. Vitamin E shall be supplemented before, during and after any stressful condition.

##### 4.8.3.1 Herbal plants and HSPs

Herbal plants and derivatives like secondary metabolites include saponins, polysaccharides, glycoproteins, and flavonoids etc are being used for therapeutic and immunomodulatory functions. Aloe vera, Panax ginseng, Agelcagiggas, Gingiber officinale, and Saussurealappacan are few other herbs. Many of these are used as the immunomodulators, tonics and adaptogens. These metabolites improve lymphocyte stimulation.

#### 4.8.4 Minerals and others

Chromium, being essential trace mineral improves feed intake, feed efficiency, body weight and carcass characteristics when supplemented @120ppb/Kg of diet. It substitutes for insulin levels and serum cortisol deprivation. Chromium reduces heat stress in birds. Chromium is in biological system one. Cr-Nano particles are comparatively effective than Cr-Macroparticles having greater absorption rate in the gut. Whereas Organic form is more active than inorganic form. It improves leucocytic activity and antibody response. Many feed additives like essential oil mixtures, polyherbal preparations, probiotics, betaine, acetic acid, aspirin, and prebiotics alleviates heat stress and potentiates chicken immunity and is very promising in enhancing heat tolerance of birds.

#### 5. Conclusion

Immunomodulators can substitute many agents like antibiotics, antimicrobials etc. for the improvement of the immune system. As immune system is directly related to the disease resistance, gut health, FCR, etc., hence they must be used in combination and/or alone according to the needs. They also improve the qualities of feed and immune molecules enhancing all possibilities to fight diseases and maintain health homeostasis. However, they are not popular and not included in the poultry feed on routine basis. Hence, more studies should be done and efforts should be made to popularise it.

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