Herbal Plants as New Immuno-stimulator in Poultry Industry: A Review

1S.R. Hashemi and 2H. Davoodi
1Faculty of Animal Science, Gorgan University of Agricultural Sciences and Natural Resources, Gorgan, Iran
2Department of Microbiology and Immunology, Golestan University of Medical Sciences, Golestan, Iran

Corresponding Author: S.R. Hashemi, Faculty of Animal Science, Gorgan University of Agricultural Sciences and Natural Resources, Golestan, Gorgan, Iran Tel: 00989111704427

ABSTRACT
The aim of this study was to review research currently being carried out on the herbal plants and phytogenics that have been shown to modulate the immune system and special attention is given to the use of herbal plants on poultry herbal feed supplement. The uses of herbal plants as health promoters are gaining increasing attention in both consumer and scientific circles. Although, there are few studies which have revealed the mechanism of action of the immunostimulatory compounds of herbal plants but the exact molecular mechanisms of some herbs are not already known. There are several possible explanations for immunomodulation mechanisms of herbal plants and their derivatives that have been put forward. Our attempt here would be to look more closely at the herbal plants mechanisms involved, including from the immunomodulation point of view, and relationships between structures and activities.

Key words: Feed additive, phytogenic, herbal plant, poultry, animal

INTRODUCTION
The immune system provides protection against infectious diseases that are caused by various microorganisms including viruses, bacteria genetic, pathogenic fungi and parasites. Unfortunately, over the years in poultry industry, most of the selection emphasis has been on the improvement of growth performance, and these changes have been shown to be negatively associated with immunological parameters of poultry and animals (Emmerson, 1997). Havenstein et al. (1994) showed that over a period of 35 years, a modern commercial broiler strain hatched in calendar year 1991 gained 3.9 times more body weight compared to a randonbred control line developed in 1957. While, control strain from 1957 performed significantly better in antibody response (total, IgM and IgG) against Sheep Red Blood Cells (SRBC) compared with the 1991 commercial broiler strain (Havenstein et al., 1994). It has also been showed that genotypes with higher body weight give poor antibody response to Sheep Red Blood Cells (SRBC) than lower body weight line of broilers (Miller et al., 1992; Qureshi and Havenstein, 1994; Rao et al., 1999). On the other hand, National Research Council (NRC) recommendation for feeding regimes are usually based on the needs of healthy birds under ideal management, but birds in commercial systems are normally exposed to different kinds of stresses and diseases. However, in many cases it is not known whether the requirement values that maximize productivity in healthy, unchallenged birds are optimal
for immunocompetence and disease resistance. Animal feeding studies indicate that changes in components of the immune system are sensitive to dietary amino acid intake (Dea et al., 1999).

It has been reported that chicks fed deficient amino acid had suboptimal interleukin production during immunologic stress (Klasing and Barnes, 1988). Rama-Rao et al. (2003) showed that methionine levels lower than 0.50% in broiler diet generates a poorer immune cell response as compared to higher concentrations. Bhargava et al. (1971) showed that increasing of threonine level more than NRC requirements increased serum antibody titres in chickens infected with the Newcastle disease virus. In poultry production, it is very important to improve immunity so as to prevent infectious diseases. Minimizing immunosuppression and its impact is also an important strategy for success in the broiler industry. However, strategies to control immunosuppression are largely based on vaccination programs for poultry and management to minimize stress during rearing (Fussell, 1998). Utilization of immunostimulants is one solution to improve the immunity of animals and to decrease their susceptibility to infectious diseases (Liu, 1999). Relationship between nutrition and the immune system has been the centre of attention in scientific communities in last decade. The use of plant products as immunostimulants has a traditional history. Modern herb research and new understanding of the immune system have explained many mechanisms by which these herbs work. Unfortunately, there are a small number of studies which have revealed the mechanism of action of the immunostimulatory compounds of herbal plants. An understanding of the mechanisms through which phytochemical influences the immune system is necessary to appreciate the use of herbal plant as immunostimulator and veterinary medicinal products.

**Immune system:** The primary role of the immune system is to recognize foreign or non-self organisms or substances that have managed to enter the body and to initiate and manage the appropriate physiological responses to neutralize or eliminate them. The immune system uses a variety of mechanisms to achieve this goal, including inactivation of biological agents, lysis (rupture) of foreign cells, agglutination (clumping) or precipitation of molecules or cells and phagocytosis (engulfing and inactivating) of foreign agents (Roitt, 1997). The immune response has two ways of dealing with foreign pathogens. The B-lymphocytes synthesize specific antibodies called immunoglobulins. This is known as humoral immunity (Sproul et al., 2000). The other system involves T-lymphocytes, which regulate the synthesis of antibodies as well as direct killer cell activity and the inflammatory response of delayed type hypersensitivity. This system is known as cell-mediated immunity (Radoja et al., 2006). The T-cells are further divided into helper lymphocytes (Th) and cytotoxic cells (Tc), also known as suppressor cells. When the T-cells encounter a foreign pathogen (antigen) they further secrete a number of communication molecules called lymphokines, cytokines, interleukins or interferons (Abbas et al., 1996; Abbas et al., 2007). These factors further elaborate and direct the immune response to a specific antigen. The whole process is a symphony of many co-factors, which are orchestrated into a sophisticated immune response.

**Plant immune system and secondary metabolites:** Herbal plants and their effects on immune system are shown in Table 1. Plants, unlike mammals, lack mobile defender cells and a somatic adaptive immune system. Instead, they rely on the innate immunity of each cell and on systemic signals emanating from infection sites (Dangl and Jones, 2001; Ausubel, 2005; Chisholm et al., 2006). This type of defense response is due to the presence of a large, diverse array of organic compounds that appear to have no direct function in growth and development (Jones and Dang, 2006). These substances are known as secondary metabolites, secondary products, or natural
products. Secondary metabolites have no generally recognized, direct roles in the processes of photosynthesis, respiration, solute transport, translocation, protein synthesis, nutrient assimilation, differentiation, or the formation of carbohydrates, proteins and lipids. Secondary metabolites also differ from primary metabolites (amino acids, nucleotides, sugars, acyl and lipids) in having a restricted distribution in the plant kingdom. That is, particular secondary metabolites are often found in only one plant species or related group of species, whereas primary metabolites are found throughout the plant kingdom. Also, they are often generated only during a specific developmental period of the plant. Many such compounds occur in nature as anti-feedant and anti-infectant chemicals, and are found effective against microbes. Flavonoids and hydroxylated phenols, for example, are naturally synthesized by plants in response to infection (Dixon et al., 1983). Flavones and flavanones, being bitter, also have natural anti-feedant effects. Alkaloids are the most common plant metabolites (Levin and York, 1978). An alkaloid derivative, nicotine, for example, has been shown to have insecticidal activities (George et al., 2000). Quinine, another alkaloid isolated from the bark of the South American Cinchona tree in, 1817 was the first effective anti-malarial drug (Mita et al., 2009). More recently, many secondary metabolites have been suggested to have Immuno-modulation properties in animals (Table 1) (Hashemi and Davoodi, 2011).

**Herbal plants as growth and health promoters:** Results of research on phytobiotics as growth and health promoters in poultry are not completely consistent (Hashemi and Davoodi, 2010). Some authors state significant positive effects on broiler performance (Ertas et al., 2005; Cross et al., 2007; Peric et al., 2008; Hashemi et al., 2009a, 2009b), whereas another group of researchers established no significant effects on performance (Cross et al., 2007; Ooak et al., 2008). Assumption is that differences in results are consequences of numerous factors such as: type and part of plant used and their physical properties, harvest time, phytoenic additive preparation method, herbal extraction methods and compatibility with other food components (Hashemi et al., 2008a: # Table 1: Herbal plants and their effects on immune system

<table>
<thead>
<tr>
<th>Species</th>
<th>Plant part</th>
<th>Chemical compound</th>
<th>Chemical identity</th>
<th>Biological activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aloe vera</td>
<td>Leaves</td>
<td>CARN750</td>
<td>Polysaccharide</td>
<td>Selectively stimulates cytokines, activates lymphocytes</td>
</tr>
<tr>
<td>Angelica gigas</td>
<td>Roots</td>
<td>Angelan</td>
<td>Polysaccharide</td>
<td>Selectively modulates cytokines</td>
</tr>
<tr>
<td>Astragalus membranaceus</td>
<td>Roots</td>
<td>-</td>
<td>Polysaccharide</td>
<td>Increase macrophage count</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Soluble extracts</td>
<td></td>
<td>Selectively stimulates cytokines</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Water-soluble extracts</td>
<td></td>
<td>Increase natural killer cell count</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Glycoproteins</td>
<td>Proteoglycan</td>
<td>Stimulate lymphocytes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Water- and ethanol-soluble extracts</td>
<td>Polysaccharide</td>
<td>Increase natural killer cell count</td>
</tr>
<tr>
<td></td>
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<td>GLIS</td>
<td></td>
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<tr>
<td>Panax ginseng</td>
<td>Roots</td>
<td>Panaxadiol, Panaxatriol</td>
<td>Saponins</td>
<td>Stimulate lymphocytes and cytokines</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ginsan</td>
<td>Acidic</td>
<td>Stimulat IL-1, IL-12, TNF-α and IFN-γ</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Polysaccharide</td>
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<tr>
<td></td>
<td></td>
<td>Rhamnogalacturonan II</td>
<td>Saponins</td>
<td>IL-6 stimulant</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Saponins</td>
<td>Enhance macrophage actions, Stimulate IL-6 activity</td>
</tr>
<tr>
<td>Panax ginseng</td>
<td>Leaves</td>
<td>Rhamnogalacturonan II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scutellaria baicalensis</td>
<td>Rhizome</td>
<td>Wogonin</td>
<td>Flavonoid</td>
<td>Stimulates TNF-α, activates iNOS</td>
</tr>
<tr>
<td>Zingiber officinale</td>
<td>Rhizome</td>
<td>Ethanol-soluble extracts</td>
<td></td>
<td>IL-1, IL-6 stimulant</td>
</tr>
</tbody>
</table>

Yang et al., 2009). Although, quality of chickens, health condition, environment management and production facility can also be considered as another parameters that positive effect of phytobiotics cannot always be confirmed. One of the Main mechanisms by which herbal plants exert helpful effects on animals’ growth and health is immunostimulatory properties (Yang et al., 2009; Hashemi and Davoodi, 2010, 2011).

**Herbal plants and their drivities effects on animal immune system:** Immuno-modulation can be defined as the changes in stimulating and suppressing of the indicators of cellular, humoral and non-specific defense mechanism. Typically, immune system is held in homeostatic balance between immunestimulation and immune suppression. Nutrition is a critical determinant of immune responses and malnutrition the most common cause of immunodeficiency worldwide (Kirk, 1997; Chandra, 1997). Of the micronutrients, zinc (Cardoso et al., 2006), selenium (Da Silva et al., 2010), copper (Hosseini et al., 2011) vitamin A (Dalloul et al., 2002), vitamin C (Kadam et al., 2010), vitamin E (Er et al., 1998; Cardoso et al., 2006; Abdukalykova and Ruiz-Feria, 2006) and B-6 (Bialock et al., 1984) have important influences on immune responses. Natural products and natural product derivatives has a traditional history as immunostimulants. Emerging evidence indicates that herbal plants exert their beneficial effects on animal immune system mostly by plant secondary metabolites (Hashemi et al., 2008b). The immunostimulating activities of many of these components have been most widely studied in mouse, chicken and human cell lines (Shan et al., 1999; Cao and Lin, 2003; Lin and Zhang, 2004). These pharmacological effects are extensive ranging. For example, Ginsing with its steroidal saponine, has immune-stimulating properties including cytokine production (IL-2, IL6, TNF-α and INF-γ), macrophage activation and lymphocyte activity (Tan and Vanitha, 2004). Conversely, flavonoids and terpenes from Ginkgo biloba can mediate production and inflammatory cytokines (Li, 2000). Saponins have ability to stimulate the cell-mediated immune system, as well as to enhance antibody production (Oda et al., 2000). Saponins reportedly induced production of cytokines such as interleukins and interferons (Jie et al., 1984; Kensil, 1996). Meyer saponins (Jie et al., 1984), Quillaja saponins (Maharaj et al. 1986) and the butanol extract of Lonicera japonica (Lee et al., 1998) and de-acylated saponin-1 administered on the nasal mucosa (Recchia et al., 1995), all stimulated the immune responses in vivo. The immunostimulants activity of saponins was thought to be associated to branched sugar chains or aldehyde groups (Bomford et al., 1992) or to an acyl residue bearing the aglycone (Kensil, 1996). As against the stimulatory effects on specific immunity components, saponins have also been shown to be capable to put a stop to some non-specic immune reactions such as inflammation (De Oliveira et al., 2001; Haridas et al., 2001) and monocyte proliferation (Delmas et al., 2000; Yui et al., 2001). Herbal plant polysaccharides, also has been extensively studied for immunomodulatory effects (Nair et al., 2004, 2006; Chen et al., 2010). Qiu and Cui (2008) reported that the polysaccharides obtained from four Chinese herbs, Astragalus root, Isatis root, Achyrantes root and Chinese Yam, considerably improved the antibody titer in vaccinated chicken. Beta-sitosterol and its glycoside are sterol molecules and a mixture of them showed that to have profound immune modulating activities. This phytosterol complex seems to target specific T-helper lymphocytes, the TH1 and TH2 cells, helping normalize their functioning, resulting in improved T-lymphocyte and natural killer cell activity (Boic and Lamprecht, 1999). Furthermore, it has also been reported that Chinese herbs can stimulate the development of immune organs, such as the thymus and spleen (Gao and Wu, 1994) as well as increase antibody production.

Although, there are a small number of studies which have revealed the mechanism of action of the immunostimulatory compounds of herbal plants but the exact molecular mechanisms of some
herbs are not already known. There are several possible explanations for immunomodulation mechanisms of herbal plants and their derivatives that have been put forward. Our attempt here would be to look more closely at the herbal plants mechanisms involved, including from the immunomodulation point of view and relationships between structures and activities. Although, more research on this topic needs to be undertaken before the association between herbal plant and immune systems is more clearly understood.

**Heat-shock proteins:** One recent area of research in immunity may explain the action of phylogenetics to protect against pathogens in production of Heat-Shock Proteins (HSPs) in cells. Heat-shock proteins are produced in abundance within the cell in response to various stressors. proteins are an evolutionary conserved family of proteins whose expression increases in response to a variety of different metabolic insults. Despite their designation, most of the HSPs are constitutively expressed and perform essential functions (Ellis, 1990; Lee and Tsai, 2005; Bukau et al., 2006).

Under stressful conditions such as heat shock, pH shift or hypoxia, increased expression of HSPs protect the cell by assists in protein transport into mitochondria and the endoplasmic reticulum, protects proteins under stress, stabilizes proteins prior to complete folding, giving the cell time to repair or re-synthesize damaged proteins and transports across membranes and proteolysis (Zulkifli et al., 2002; Zulkifli et al., 2003; Bukau and Horwich, 1998; Bergner, 2005). Cell stressors that induce heat shock proteins are shown in Table 2.

Heat shock proteins greatly enhance the efficiency of intracellular protein manufacture and transport and may enhance immunity against pathogens by improving immune surveillance of infected cells (Bergner, 2005). A number of herbs or their derivatives have been showed to induce or to facilitate HSP responses are listed below and such herbs may strengthen the systemic response to antigens. All have been traditionally use as tonics, adaptogens, or immuno-modulators. They include: *Allium sativum* (Sumioka et al., 2001) *Curcuma longa* (Dunsmore et al., 2001; Batth et al., 2001), *Schisandra chinensis* (Chiu et al., 2004) *Glycyrrhiza* spp. (Yan et al., 2004).

<table>
<thead>
<tr>
<th>Table 2: Cell stressors that induce heat shock proteins</th>
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<tbody>
<tr>
<td><strong>Stressor or stressor type</strong></td>
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<tr>
<td>-----------------------------</td>
</tr>
<tr>
<td>Physical</td>
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<tr>
<td>Oxygen</td>
</tr>
<tr>
<td>pH</td>
</tr>
<tr>
<td>Biologic</td>
</tr>
<tr>
<td>Psychological</td>
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<tr>
<td>Osmotic</td>
</tr>
<tr>
<td>Nutritional</td>
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<tr>
<td>Antibiotics</td>
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<tr>
<td>Alcohols</td>
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<tr>
<td>Metals</td>
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<tr>
<td>Other</td>
</tr>
</tbody>
</table>

Source: Macario and Macario (2005)
Paeonia spp. (Yan et al., 2004), and the Chinese medicinal herbs Panax notoginseng (Yao and Li, 2002), Platycodon grandiflorum (Lee et al., 2004) and Saussurea lappa (Matsuda et al., 2003), Zingiber zerumbet (Hashemi, 2010) and Zingiber officinale (Hashemi, 2010).

**Toll-like receptors:** Until recently it was assumed that the non-specific side of the immune system, characterized by tissue macrophages, dendritic cells and complement system has been viewed as the poor-cousin of the specific immunity produced by the humoral and cell-mediated systems. It was thought that non-specific immunity was primarily a local immune response and that the specific immunity, characterized by B-Cell and T-Cells must be directly activated to elicit a systemic response. Recent discoveries in the field of immunology showed that TLRs has main function in immune system. TLRs are a class of proteins that play a key role in the innate immune system. They are single, membrane-spanning, non-catalytic receptors that recognize structurally conserved molecules derived from microbes. Once these microbes have breached physical barriers such as the skin or intestinal tract mucosa, they are recognized by TLRs which activate immune cell responses. Recent discoveries in the area of TLRs in macrophages and dendritic cells has shown that different TLRs recognize different Pathogen-associated Molecular Patterns (PAMP’s) (Underhill and Ozinskiy, 2002) and those non-specific defense cells can also initiate a systemic response by previously unknown pathways (Bergner, 2005).

Research shows that some polysaccharides from medicinal plants can trigger the expression and activity of the some TLR and plants containing polysaccharides may assist in the initiation of system wide enhanced immune surveillance. Plants or plant-derived polysaccharides which have been shown to initiate or enhance TLR response and immune activation are: Ganoderma lucidum (Shao et al., 2004a), Astragalus membranaceus (Shao et al., 2004b), Panax ginseng (Nakaya et al., 2004; Pugh et al., 2005) Panax quinquefolius, Echinacea angustifolia and purpurea (Pugh et al., 2005), Acanthopanax senticosus (Han et al., 2003), Platycodon grandiflorum (Yoon et al., 2003), Tinospora cordifolia (Nair et al., 2006) and Cordyceps sinensis (Chen et al., 2010).

It should be noted that polysaccharides are insoluble in alcohol, and are not present in tinctures with greater than about 35% alcohol. These plants must be taken as powders, infusions, or decoctions for these effects on TLR to occur.

**TH-1/TH-2 Balance:** The T-Helper (TH) cells are like the “quarterbacks” of the specific immune system, and they coordinate the escalation of both the humoral (antibody) and cell-mediated responses (Bergner, 2005). Proliferating helper T cells that develop into effector T cells differentiate into two major subtypes of cells known as Th1 and Th2 cells. The major differences between Th1 and Th2 are shown in Table 3. Th1 cells producing INF-γ, IL-2 and TNF-β are involved in the regulation of cellular immunity. On the other hand, Th2 cells producing IL-4, IL-5 and IL-6 are important in humoral immunity. The composition of the TH pool of cells may become unbalanced,

<table>
<thead>
<tr>
<th>Table 3: Major differences between Th1 and Th2 function</th>
</tr>
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<tbody>
<tr>
<td><strong>Type 1 / T$_{1,1}$</strong></td>
</tr>
<tr>
<td>Main partner cell type</td>
</tr>
<tr>
<td>Cytokines produced</td>
</tr>
<tr>
<td>Immune stimulation promoted</td>
</tr>
</tbody>
</table>

INF-γ: interferon-gamma, TNF-β: Tumor necrosis factor-beta and IL: Interleukin

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favoring one side of the immune equation over the other. Several nutrients and hormones measurably influence Th1/Th2 balance, including plant sterols/sterolins, melatonin, probiotics, progesterone, minerals such as selenium, zinc and some long chain fatty acid like Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA) (Kidd, 2003). Herbal medicines may be used to help restore the TH1/TH2 balance, but evidence for consistent effects on either system is scarce and it is difficult to predict clinical effects from the suggestive in vitro and in vivo evidence that exists. The five herbal medicines with some evidence of being to restore balance in a TH-2 dominant system are Allium sativum, Astragalus membranaceus, Ganoderma lucidum, Grifola frondosa and Panax ginseng (Bergner, 2004).

CONCLUSIONS

The global for poultry production experienced leaps and bounces over the past fifty years to accommodate rising demand. On the other hand, popular demand and scientific interest for organic poultry production, particularly feeding with medicinal botanicals, has increased considerably in recent years. Previous studies have clearly established the fact that herbal plants and their derivatives have potential as immunomodulators. Both, the innate and adaptive components of the immune system are stimulated by phytogenics. However, the studies have overly relied on in vitro data and there is rare use of animal subjects in the research. Moreover, most studies have used herbal extracts rather than the purified compounds. Therefore, there is still suspicion concerning the efficacy and optimum dosage of herbal plants and their derivatives as immunostimulators. Hence, more research is required for scientific validation of herbal plants as potent animal immunostimulators.

REFERENCES


