aJava

Asian Journal of Animal and Veterinary Advances

Academic
Journals Inc.

www.academicjournals.com

Asian Journal of Animal and Veterinary Advances 7 (2): 105-116, 2012
ISSN 1683-9919 / DOI: 10.3923/ajava.2012.105.116

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

[1]S.R. Hashemi and [2]H. Davoodi

[1]Faculty of Animal Science, Gorgan University of Agricultural Sciences and Natural Resources, Gorgan, Iran

[2]Department 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 randombred control line developed in 1957. Whiles, 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 (Defa *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 recognise foreign or non-self organisms or substances that have managed to enter the body and to initiate and manage the appropriate physiological responses to neutralise 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 defence 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

Table 1: Herbal plants and their effects on immune system

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

Source: Tan and Vanitha (2004)

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; Ocak *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, phytogenic additive preparation method, herbal extraction methods and compatibility with other food components (Hashemi *et al*., 2008a:

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 difined 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 immunesuppression. 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 (Erf *et al*., 1998; Cardoso *et al*., 2006; Abdukalykova and Ruiz-Feria, 2006) and B-6 (Blalock *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 *Ginko 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, Achyranthes 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 (Bouic 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 phytogenics to protect against pathogens is 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 savitum* (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 2: Cell stressors that induce heat shock proteins

Stressor or stressor type	Name or description
Physical	Heat (including fever), cold, several types of irradiation, including ultraviolet light and magnetic fields
Oxygen	Oxygen-derived free radicals (reactive oxygen species), hydrogen peroxide, a shift from anaerobiosis to aerobiosis (e.g., reperfnsion), hypoxia-anoxia (ischemia)
pH	Alkalosis, acidosis, pH shift
Biologic	Infection, inflammation, fever
Psychological	Emotions, emotional conflicts, hormonal imbalance (hypothalamic-pituitary-adrenal axis and autonomic nervons system)
Osmotic	Changes in the concentrations of salt, sugars and other osmolytes (hyperosmotic or hypo-osmotic shock)
Nutritional	Starvation involving multiple nutritional components (carbon, glncose, phosphate, and nitrate) or any one of these
Antibiotics	Puromycin, tetracycline, nalidixic acid, doxorubicion
Alcohols	Ethanol, methanol, butanol, propanol, octanol
Metals	Cadmium, copper, chromium, zinc, tin, aluminum, mercury, lead, uickelMechanical Compression, shearing, stretching
Other	Desiccation, benzene and derivatives, phenol and derivatives, teratogens, carcinogens, mutagens, arseuite, arsenate, amino acid analogues, nicotine, anesthetics, insecticides, pesticides

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 recognizing different Pathogen-associated Molecular Patterns (PAMPs) (Underhill and Ozinskym, 2002) and these 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 3: Major differences between Th1 and Th2 function

	Type 1/ T_h1	Type 2/ T_h2
Main partner cell type	Macrophage	B-cell
Cytokines produced	INF-γ, TNF-β and IL-2	IL-4, IL -5, IL -6, IL -10, IL-13
Immune stimulation promoted	Cellular immune system	Humoral immune system

INF-γ: Iinterferon-gamma; TNF-β: Tumor necrosis factor-beta and IL: Interleukin 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

Abbas, A.K., K.M. Murphy and A. Sher, 1996. Functional diversity of helper T lymphocytes. Nature, 383: 787-793.

Abbas, A.K., A.H. Lichtman and S. Pillai, 2007. Cellular and Molecular Immunology. 6th Edn., Elsevier, Philadelphia, pp: 32-34.

Abdukalykova, S. and C.A. Ruiz-Feria, 2006. Arginine and vitamin E improve the cellular and humoral immune response of broiler chickens. Int. J. Poult. Sci., 5: 121-127.

Ausubel, F.M., 2005. Are innate immune signaling pathways in plants and animals conserved?. Nat. Immunol., 6: 973-979.

Batth, B.K., R. Tripathi and U.K. Srinivas, 2001. Curcumin-induced differentiation of mouse embryonal carcinoma PCC4 cells. Differentiation, 68: 133-140.

Bergner, P., 2004. Immunity: Herbal medicine and the TH1/TH2 balance Med. Herbalism, 14: 1-9.

Bergner, P., 2005. Antiviral botanicals in herbal medicine. Med. Herbalism, 14: 1-12.

Bhargava, K.K., R.P. Hanson and M.L. Sunde, 1971. Effects of threonine on growth and antibody production in chickens infected with Newcastle disease virus. Poult. Sci., 50: 710-713.

Blalock, T.L., J.P. Thaxton and J.D. Garlich, 1984. Humoral immunity in chicks experiencing marginal vitamin B-6 deficiency. J. Nutr., 114: 312-322.

Bomford, R., M. Stapleton, S. Winsor, J.E. Beesley, E.A. Jessup, K.R. Price and G.R. Fenwick, 1992. Adjuvanticity and ISCOM formation by structurally diverse saponins. Vaccine, 10: 572-577.

Bouic, P.J. and J.H. Lamprecht, 1999. Plant sterols and sterolins: A review of their immune-modulating properties. Altern Med. Rev., 4: 170-177.

Bukau, B. and A.L. Horwich, 1998. The Hsp70 and Hsp60 chaperone machines. Cell, 92: 351-366.

Bukau, B., J. Weissman and A. Horwich, 2006. Molecular chaperones and protein quality control. Cell, 125: 443-451.

Cao, L.Z. and Z.B. Lin, 2003. Regulatory effect of *Ganoderma lucidum* polysaccharides on cytotoxic T-lymphocytes induced by dendritic cells *in vitro*. Acta Pharmacol. Sin., 24: 312-326.

Cardoso, A.L.S.P., R. Albuquerque and E.N.C. Tessari, 2006. Humoral immunological response in broilers vaccinated against newcastle disease and supplemented with dietary zinc and vitamin E. Rev. Bras. Cienc. Avic., 8: 99-103.

Chandra, R.K., 1997. Nutrition and the immune system: An introduction. Am. J. Clin. Nutr., 66: 460S-463S.

Chen, W., W. Zhang, W. Shen and K. Wang, 2010. Effects of the acid polysaccharide fraction isolated from a cultivated *Cordyceps sinensis* on macrophages *in vitro*. Cell. Immunol., 262: 69-74.

Chisholm, S.T., G. Coaker, B. Day and B.J. Staskawicz, 2006. Host-microbe interactions: Shaping the evolution of the plant immune response. Cell, 124: 803-814.

Chiu, P.Y., K.M. Ko and B. Schisandrin, 2004. Protects myocardial ischemia-reperfusion injury partly by inducing Hsp25 and Hsp70 expression in rats. Mol. Cell. Biochem., 266: 139-144.

Cross, D.E., R.M. McDevitt, K. Hillman and T. Acamovic, 2007. The effect of herbs and their associated essential oils on performance, dietary digestibility and gut microflora in chickens from 7 to 28 days of age. Br. Poult. Sci., 48: 496-506.

Da Silva, I.C.M., A.M.L. Ribeiro, C.W. Canal, L. Trevizan and M. Macagnan *et al*., 2010. The impact of organic and inorganic selenium on the immune system of growing broiler submitted to immune stimulation and heat stress. Rev. Bras. Cienc. Avic., 12: 247-254.

Dalloul, R.A., H.S. Lillehoj, T.A. Shellem and J.A. Doerr, 2002. Effect of vitamin A deficiency on host intestinal immune response to *Eimeria acervulina*. in broiler chickens. Poult. Sci., 81: 1509-1515.

Dangl, J.L. and J.D.G. Jones, 2001. Plant pathogens and integrated defence responses to infection. Nature, 411: 826-833.

De Oliveira, C.A.C., A.C. Perez, G. Merino, J.G. Prieto and A.I. Alvarez, 2001. Protective effects of *Panax ginseng* on muscle injury and inflammation after eccentric exercise. Comp. Biochen Physiol. C. Toxicol. Pharmacol., 130: 369-377.

Defa, L., X. Changting, Q. Shiyan, Z. Jinhui, E.W. Johnson and P.A. Thacker, 1999. Effects of dietary threonine on performance, plasma parameters and immune function of growing pigs. Anim. Feed Sci. Technol., 78: 179-188.

Delmas, F., C. di Giorgio, R. Elias, M. Gasquet and N. Azas *et al*., 2000. Antileishmanial activity of three saponins isolated from ivy, alpha-hederin, beta-hederin and hederacolchiside A(1), as compared with their action on mammalian cells cultured *in vitro*. Planta. Med., 66: 343-347.

Dixon, R.A., P.M. Dey and C.J. Lamb, 1983. Phytoalexins: Enzymology and molecular biology. Adv. Enzymol., 55: 1-69.

Dunsmore, K.E., P.G. Chen and H.R. Wong 2001. Curcumin, a medicinal herbal compound capable of inducing the heat shock response. Crit. Care. Med., 292: 199-204.

Ellis, R.J., 1990. The molecular chaperone concept. Semin. Cell. Biol., 1: 1-9.

Emmerson, D.A., 1997. Commercial approaches to genetic selection for growth and feed conversion in domestic poultry. Poult. Sci., 76: 1121-1125.

Erf, G.F., W.G. Bottje, T.K. Bersi, M.D. Headrick and C.A. Fritts, 1998. Effects of dietary vitamin E on the immune system in broilers: Altered proportions of CD4 T cells in the thymus and spleen. Poult. Sci., 77: 529-537.

Ertas, O.N., T. Guler, M. Ciftci, B. Dalkiilc and U.G. Simsek, 2005. The effect of an essential oil mix derived from oregano, clove and anise on broiler performance. Int. J. Poult. Sci., 4: 879-884.

Fussell, L.W., 1998. Poultry industry strategies for control of *Immunosuppressive* diseases. Poult. Sci., 77: 1193-1196.

Gao, X. and W. Wu, 1994. The effect of dang-gui (*Angelica sinensis*) and ferulic acid on mice immune system. Chin. J. Biochem. Pharm., 15: 107-110.

George, J., H.P. Bais and G.A. Ravishankar, 2000. Biotechnological production of plant-based insecticides. Crit. Rev. Biotechnol., 20: 49-77.

Han, S.B., Y.D. Yoon, H.J. Ahn, H.S. Lee and C.W. Lee *et al*., 2003. Toll-like receptor-mediated activation of B cells and macrophages by polysaccharide isolated from cell culture of *Acanthopanax senticosus*. Int Immunopharmacol., 3: 1301-1312.

Haridas, V., C.J. Arntzen and J.U. Gutterman, 2001. Avicins, a family of triterpenoid saponins from *Acacia victoriae* (Bentham), inhibit activation of nuclear factor-kappa B by inhibiting both its nuclear localization and ability to bind DNA. Proc. Natl. Acad. Sci. USA., 98: 11557-11562.

Hashemi, S.R., I. Zulkifli, M. Hair-Bejo, A. Farida and M.N. Somchit, 2008a. Acute toxicity study and phytochemical screening of selected herbal aqueous extract in broiler chickens. Int. J. Pharmacol., 4: 352-360.

Hashemi, S.R., I. Zulkifli, Z. Zunita and M.N. Somchit, 2008b. The effect of selected sterilization methods on antibacterial activity of aqueous extract of herbal plants. J. Boil. Sci., 8: 1072-1076.

Hashemi, S.R., I. Zulkifli, M. Hair-Bejo, M. Karami and A.F. Soleimani, 2009a. The effects of *Euphorbia hirta* and acidifier supplementation on growth performance and antioxidant activity in broiler chickens. Proceedings of the 21st Veterinary Association Malaysia (VAM) Congress, August 7-9, 2009, Port Dickson, Malaysia, pp: 215-217.

Hashemi, S.R., I. Zulkifli, Z. Zunita, M. Hair-Bejo and T.C. Loh *et al*., 2009b. Effects of dietary supplementation with *Euphorbia hirta* and acidifier on performance and Salmonella colonization in broiler chickens. Proceedings of the 30th Malaysia Society of Animal Production Annual Conference, June 2-5, Kota Kinabalu, Malaysia, pp: 69-70.

Hashemi, S.R., 2010. Selected herbal plants as growth and health promoters in broiler chickens. Ph.D. Thesis, Universiti Putra Malaysia (UPM), Malaysia.

Hashemi, S.R. and H. Davoodi, 2010. Phytogenics as new class of feed additive in poultry industry. J. Anim. Vet. Adv., 9: 2295-2304.

Hashemi, S.R. and H. Davoodi, 2011. Herbal plants and their derivatives as growth and health promoters in animal nutrition. Vet. Res. Commun., 35: 169-180.

Havenstein, G.B., P.R. Ferket, S.E. Scheideler and B.T. Larson, 1994. Growth, livability and feed conversion of 1991 vs. 1957 broilers when fed typical 1957 and 1991 broiler diets. Poult. Sci., 73: 1785-1794.

Hosseini, S., J. Arshami and M.E. Torshizi, 2011. Viral antibody titer and leukocyte subset responses to graded copper and zinc in broiler chicks. Asian J. Anim. Vet. Adv., 6: 80-87.

Jie, Y.H., S. Cammisuli and M. Baggiolini, 1984. Immunomodulatory effects of *Panax ginseung* ca MEYER in the mouse. Agents Actions, 15: 386-391.

Jones, J.D.G. and J.L. Dang, 2006. The plant immune system. Nature , 444: 323-329.

Kadam, A.S., V.D. Lonkar, V.R. Patodkar, S.M. Kolangath and T.A. Bhosale, 2010. Comparative efficacy of supplementation of natural (*Citrous limon* Juice), herbal and synthetic vitamin c on the immune response of broiler chicken during summer stress. Asian J. Poult. Sci., 3: 57-62.

Kensil, C.R., 1996. Saponins as vaccine adjuvants. Crit. Rev. The. Drug. Carrier. Syst., 13: 1-55.

Kidd, P., 2003. Th1/Th2 Balance: The hypothesis, its limitations, and implications for health and disease. Altern. Med. Rev., 8: 223-246.

Kirk, C.K., 1997. Interaction Between Nutrition and Infections Disease Infectious Disease. In: Diseases of Poultry, Calnek, B.W. (Ed.). Iowa State University Press, Ames, IA., USA., pp: 73-74.

Klasing, K.C. and D.M. Barnes, 1988. Decreased amino acid requirements of grower chicks due to immunological stress. J. Nutr., 118: 1158-1164.

Lee, S.J., K.H. Son, H.W. Chang, S.S. Kang and H.P. Kim, 1998. Antiinflammatory activity of Lonicera japonica. Phytother Res., 12: 445-447.

Lee, J.H., Y.H. Choi, H.S. Kang and B.T. Choi, 2004. An aqueous extract of Platycodi radix inhibits LPS-induced NF-kappaB nuclear translocation in human cultured airway epithelial cells Int. J. Mol. Med., 13: 843-847.

Lee, S. and F.T. Tsai, 2005. Molecular chaperones in protein quality control J. Biochem. Mol. Biol., 38: 259-265.

Levin, D.A. and B.M. Jr York, 1978. The toxicity of plant alkaloids: An ecogeographic perspective. Biochem. Syst. Ecol., 6: 61-76.

Li, X.Y., 2001. Immuno-modulating components from Chinese medicines Pharm. Biol., 38: 33-40.

Lin, Z.B. and H.N. Zhang, 2004. Anti-tumor and immunoregulatory activities of *Ganoderma lucidum* and its possible mechanisms. Acta Pharmacol. Sin., 25: 1387-1395.

Liu, X.Y., 1999. Stress and Immunity. In: Poultry Immunology, Yin, T.B. (Ed.). China Agriculture Press, Beijing, China, pp: 230-252.

Macario, A.J. and E.C. de Macario, 2005. Sick chaperones, cellular stress and disease. N. Engl. J. Med., 353: 1489-1501.

Maharaj, I., K.J. Froh and J.B. Campbell, 1986. Immune responses of mice to inactivated rabies vaccine administered orally: Potentiation by Quillaja saponin. Can. J. Microbiol., 32: 414-420.

Matsuda, H., I. Toguchida, K. Ninomiya, S. Kageura, T. Morikawa and M. Yoshikawa 2003. Effects of sesquiterpenes and amino acid-sesquiterpene conjugates from the roots *Saussurea lappa* on inducible nitric oxide synthase and heat shock protein in lipopolysaccharide-activated macrophages Bioorg. Med. Chem., 11: 709-715.

Miller, L.L., P.B. Siegel and E.A. Dunnington, 1992. Inheritance of antibody response to sheep erythrocytes in lines of chickens divergently selected for fifty-six-day body weight and their crosses. Poult. Sci., 71: 47-52.

Mita, T., K. Tanabe and K. Kita, 2009. Spread and evolution of *Plasmodium falciparum* drug resistance. Parasitol. Int., 58: 201-209.

Nair, P.K.R., S. Rodriguez, R. Ramachandran, A. Alamo and S.J. Melnick *et al.*, 2004. Immune stimulating properties of a novel polysaccharide from the medicinal plant *Tinospora cordifolia*. Int. Immunopharmacol., 4: 1645-1659.

Nair, P.K.R., S.J. Melnick, R. Ramchandran, E. Escalon and C. Ramachandran, 2006. Mechanism of macrophage activation by (1,4)-α-D-glucan isolated from *Tinospora cordifolia*. Int. Immunopharmacol., 6: 1815-1824.

Nakaya, T.A., M. Kita, H. Kuriyama, Y. Iwakura and J. Imanishi, 2004. *Panax ginseng* induces production of proinflammatory cytokines via toll-like receptor. J. Interferon Cytokine Res., 24: 93-100.

Ocak, N., G. Erener, F. Burak Ak, M. Sungu, A. Altop and A. Ozmen, 2008. Performance of broilers fed diets supplemented with dry peppermint (*Mentha piperita* L.) or thyme (*Thymus vulgaris* L.) leaves as growth promoter source. Czech J. Anim. Sci., 53: 169-175.

Oda, K., H. Matsuda, T. Murakami, S. Katayama, T. Ohgitani and M. Yoshikawa, 2000. Adjuvant and haemolytic activities of 47 saponins derived from medicinal and food plants. Biol. Chem., 381: 67-74.

Peric, L., N. Milosevic, M. Dukic-Stojcic and S. Bjedov, 2008. Effect of phytogenic products on performance of broiler chicken. World Nutrition Forum, Nottingham University, Mayrhofen, Austria.

Pugh, N.D., P. Balachandran, H. Lata, F.E. Dayan and V. Joshi *et al.*, 2005. Melanin: Dietary mucosal immune modulator from *Echinacea* and other botanical supplements. Int. Immunopharmacol., 5: 637-647.

Qiu, Y. and B. Cui, 2008. Effects of four polysaccharides on antibody titer and T-lymphocyte in vaccinated chicken. J. Nanjing Agric. Univ., 31: 77-78.

Qureshi, M.A. and G.B. Havenstein, 1994. A comparison of the immune performance of a 1991 commercial broiler with a 1957 randombred strain when fed typical 1957 and 1991 boiler diets. Poult. Sci., 73: 1805-1812.

Radoja, S., A.B. Frey and S. Vukmanovic, 2006. T-cell receptor signaling events triggering granule exocytosis. Crit. Rev. Immunol., 26: 265-290.

Rama-Rao, S.V., N.K. Praharaj, R.V. Ramasubba and A.K. Panda, 2003. Interaction between genotype and dietary concentrations of methionine for immune function in commercial broilers. Br. Poult. Sci., 44: 104-112.

Rao, S.V.R., N.K. Praharaj, M.R. Reddy and B. Sridevi, 1999. Immune competence, resistance to *Escherichia coli* and growth in male broiler parent chicks fed different levels of crude protein. Vet. Res. Commun., 23: 323-336.

Recchia, J., M.H. Lurantos, J.A. Amsden, J. Storey and C.R. Kensil, 1995. A semisynthetic Quillaja saponin as a drug delivery agent for aminoglycoside antibiotics. Pharm. Res., 12: 1917-1923.

Roitt, I.M., 1997. Essential Immunology. 9th Edn., ELBS, Blackwell Scientific Publications, United Kingdom.

Shan, B.E., Y. Yoshida, T. Sugiura and U Yamashita, 1999. Stimulating activity of Chinese medicinal herbs on human lymphocytes *in vitro*. Int. J. Immunopharmacol., 21: 149-159.

Shao, B.M., H. Dai, W. Xu, Z.B. Lin and X.M. Gao, 2004a. Immune receptors for polysaccharides from *Ganoderma lucidum*. Biochem. Biophys. Res. Commun., 323: 133-141.

Shao, B.M., W. Xu, H. Dai, P. Tu, Z. Li and X.M. Gao, 2004b. A study on the immune receptors for polysaccharides from the roots of *Astragalus membranaceus*, a Chinese medicinal herb. Biochem. Biophys. Res. Commun., 320: 1103-1111.

Sproul, T.W., P.C. Cheng, M.L. Dykstra and S.K. Pierce, 2000. A role for MHC class II antigen processing in B cell development. Int. Rev. Immunol., 19: 139-155.

Sumioka, I., T. Matsura and K. Yamada, 2001. Therapeutic effect of S-allylmercaptocysteine on acetaminophen-induced liver injury in mice. Eur. J. Pharmacol., 433: 177-185.

Tan, B.K. and J. Vanitha, 2004. Immunomodulatory and antimicrobial effects of some traditional Chinese medicinal herbs: A review. Curr. Med. Chem., 11: 1423-1430.

Underhill, D. and A. Ozinsky, 2002. Toll-like receptors: Key mediators of microbe detection. Curr. Opin. Immunol., 14: 103-110.

Yan, D., K. Saito, Y. Ohmi, N. Fujie and K. Ohtsuka, 2004. Paeoniflorin, a novel heat shock protein-inducing compound. Cell Stress Chaperones, 9: 378-389.

Yang, Y., P.A. Iji and M. Choct, 2009. Dietary modulation of gut microflora in broiler chickens: A review of the role of six kinds of alternatives to in-feed antibiotics. Worlds Poult. Sci. J., 65: 97-114.

Yao, X.H. and X.J. Li, 2002. Protective effects and its mechanism of panaxatriol saponins isolated from *Panax notoginseng* on cerebral ischemia. Zhongguo Zhong Yao Za Zhi, 27: 371-373.

Yoon, Y.D., S.B. Han, J.S. Kang, C.W. Lee and S.K. Park *et al.*, 2003. Toll-like receptor 4-dependent activation of macrophages by polysaccharide isolated from the radix of *Platycodon grandiflorum*. Int. Immunopharmacol., 3: 1873-1882.

Yui, S., K. Ubukata, K. Hodono, M. Kitahara and Y. Mimaki *et al.*, 2001. Macrophage-oriented cytotoxic activity of novel triterpene saponins extracted from roots of *Securidaca inappendiculata*. Int. Immunopharmacol., 1: 1989-2000.

Zulkifli, I., M.T. Che Norma, D.A. Israf and A.R. Omar 2002. The effect of early-age food restriction on heat shock protein response in heat-stressed female broilers chickens. Br. Poult. Sci., 43: 141-145.

Zulkifli, I., P.K. Liew, D.A. Israf, A.R. Omar and M. Hair-Bejo, 2003. Effect of early age feed restriction and heat conditioning on heterophil/lymphocyte ratios, heat shock protein 70 expression and body temperature of heat-stressed broiler chickens. J. Ther. Biol., 28: 217-222.