International Journal of Pharmacology

ISSN 1811-7775

International Journal of Pharmacology 11 (4): 253-290, 2015
ISSN 1811-7775

ansinet
Asian Network for Scientific Information

REVIEW ARTICLE OPEN ACCESS

DOI: 10.3923/ijp.2015.253.290

Effect of Immunomodulation and Immunomodulatory Agents on Health with Some Bioactive Principles, Modes of Action and Potent Biomedical Applications

[1]Kuldeep Dhama, [1]Mani Saminathan, [2]Siju Susan Jacob, [3]Mithilesh Singh, [4]K. Karthik, [5]Amarpal, [6]Ruchi Tiwari, [7]Lakshmi Tulasi Sunkara, [8]Yashpal Singh Malik and [9]Raj Kumar Singh
[1]Division of Pathology,
[2]Division of Parasitology,
[3]Immunology Section,
[4]Division of Bacteriology and Mycology,
[5]Divsion of Surgery, Indian Veterinary Research Institute, Izatnagar (IVRI), Bareilly, Uttar Pradesh, 243122, India
[6]Department of Veterinary Microbiology and Immunology, College of Veterinary Sciences and Animal Husbandry, Uttar Pradesh Pandit Deen Dayal Upadhayay Pashu Chikitsa Vigyan Vishvidhyalaya Ewam Go-Anusandhan Sansthan (DUVASU), Mathura, Uttar Pradesh, 281001, India
[7]Department of Animal Science, Oklahoma State University, Stillwater, OK, 74078, USA
[8]Division of Biological Standardization, Indian Veterinary Research Institute, Izatnagar, Bareilly, Uttar Pradesh, 243122, India
[9]Indian Veterinary Research Institute, Izatnagar, Bareilly Uttar Pardesh, 243122, India

ARTICLE INFO
Article History:
Received: January 25, 2015
Accepted: April 03, 2015

Corresponding Author:
Kuldeep Dhama,
Division of Pathology,
Indian Veterinary Research Institute,
Izatnagar, Bareilly, Uttar Pradesh,
243122, India

ABSTRACT

In veterinary and medical sciences, immunomodulation is an area wherein extensive studies have been conducted to devise methods to improve disease resistance as well as to prevent or control immune disorders of host by optimum regulation of the immune system. Today, most infectious diseases of man and animals are treated and controlled mainly by using broad-spectrum antibiotics and vaccines. However, the antibacterial agents are becoming increasingly ineffective due to rapid emergence of resistant microbial strains. So, there is high requirement for novel and improved alternative therapeutic and prophylactic strategies to manage several diseases which are flaring at alarming pace because of the increase in international traffic, globalization and changing food habbits. Immunomodulation is focused on manipulation of immune system to control the infections and other adverse health effects with precise regulation to avoid any complications while suppressive or potentiating efforts are made to benefit the animal and human health. The main aim of this review is to give a closer insight into the potential immunomodulatory molecules, synthetic and natural, that are capable of modifying the immune responses including conventional and novel immunomodulators like adjuvants, cytokines, hormones, glucocorticoids, host defense peptides, microbial products, toll like receptors, synthetic compounds, probiotics, nutrients, vitamins, minerals, herbs, panchgavya, polysaccharides, helminths, vaccines and others. These immunomodulatory regimens could successfully offer the health industries with the most natural methods for enhancement of disease resistance, boosting vaccination immunity and prevention of various infections, disorders, cancer and stress related diseases. The updated information will be highly useful for scientists, veterinary/medical professionals, pharmaceutical industries, livestock and poultry industry to create a healthier future for people and their companion animals.

Key words: Immunomodulation, immunomodulators, adjuvant, cytokines, hormones, glucocorticoids, peptides, microbial products, probiotics, nutrients, vitamins, minerals, herbs, panchgavya, polysaccharides, helminths, vaccines, animals, humans, health

INTRODUCTION

At present chemotherapy is the most common and widely acceptable approach to control the microbial infections of veterinary and medical importance. According to the World Health Organization the antibiotics will not be effective beyond 2020 because of the rapid emergence of drug resistant strains (Hancock and Sahl, 2006; Hamill *et al*., 2008; Dhama *et al*., 2013a). Species evolution theory is so true that all the microorganisms try to evade antibiotics which are intended to kill them. This makes things worse for the animal and human community since only a handful of antibiotics are left with to protect from the dreadful pathogens (Karthik *et al*., 2012; Tiwari *et al*., 2013). Sooner these few antibiotics may also not act against those pathogens against which they are targeted. Antibiotic resistance is the hot topic of this decade and in order to survive there is need to search alternatives to counteract the pathogens and also to safeguard human and animal health. Novel treatments include phage therapy, cytokine therapy, herbal medicines, essential oils extracts and cowpathy (Dhama *et al*., 2013a-c, 2014; Karthik *et al*., 2014; Gopi *et al*., 2014; Verma *et al*., 2014). In that instance immunomodulation with an aim to increase the immune potential of the body remains the sole alternative to control the infection. During the course of time, so many immunomodulators are introduced and it was found that herbal immunomodulators based on ancient Indian ayurvedic system of medicine were most effective without any side effects (Tan and Vanitha, 2004; Spelman *et al*., 2006; Borsuk *et al*., 2011; Hashemi and Davoodi, 2012; Mahima *et al*., 2012a). In animals, immunomodulation is defined as the ability to regulate an immune response to enhance the production efficiency in food-producing animals and the substances that put forth this control are called immunomodulators (Chauhan, 2010; Fraile *et al*., 2012; Zhao *et al*., 2012). Immunomodulation refers to the manipulation of immune system and all therapeutic interruptions targeted for modulating the immune system (Mahima *et al*., 2013a). The augmentation of immune response, known as immunostimulation or immunopotentiation, can be utilized to prevent infection by vaccination through activation of humoral immunity, to fight against an already established infection by shifting the immune response to cell mediated type and to fight against cancer by the use of cytokines, tumour specific antibodies and tumour infiltrating lymphocytes. The suppression of immune responsiveness, known as immune suppression, is usually practiced in allergy, autoimmunity and organ transplantation. Immunomodulation can be either specific or non-specific. Specific immunomodulation is limited to a single antigen such as vaccination. Non-specific immunomodulation implies for a more generalized change in immune responsiveness both in innate and adaptive immunity, leading to altered host reactivity to many different antigens.

An immunomodulator may be defined as any biological or synthetic substance that can stimulate/suppress either innate or adaptive or both arms of the immune system (Agarwal and Singh, 1999). A potent immunomodulator have got many advantages over antimicrobials. Since immunomodulators do not affect directly microbes, they may avoid the problem of rapid emergence of resistance. Traditional antimicrobials in immuno compromised patients often work poorly and the importance of immunomodulators then can be realized. The antimicrobials are specific in nature whereas immunomodulators provide broad spectrum capability against bacterial, viral and fungal diseases and thereby provide non-specific emergency-therapeutic approaches in the event of emergence of a strange pathogen or biowarfare agents (Gallois and Oswald, 2008). In the era of one world one health one medicine concept, the potent applications of useful immunomodulators needs to be encouraged (Dhama *et al*., 2013d). Recently, immunomodulators like helminths and mesenchymal stem cells have been proposed to be promising therapeutics for autoimmune disorders including systemic sclerosis, systemic lupus erythematosus, Crohn's disease and allergic diseases (Reddy, 2010; Sanchez-Berna *et al*., 2014).

This review mainly aims at providing a close insight into the various kinds of potential immunomodulatory substances and regimens covering both synthetic and natural as well as conventional and novel immunomodulators including adjuvants, cytokines, thymic products, hormones, glucocorticoids, host defense peptides, microbial products, probiotics, synthetic chemical compounds, toll like receptors, nutrients, vitamins, minerals, herbs, panchgavya elements, polysaccharides, helminths, vaccines and others. The updated information will be highly useful for researchers, scientists, scholars, pharmacists, veterinary/medical professionals, pharmaceutical industries, animal producers/owners and livestock and poultry industry to create a healthier future for people and their companion animals.

HISTORY

The concept of immunomodulation was first emerged in 1796. It was introduced by Edward Jenner, who carried out the first "vaccination" against small pox. Thereafter, several efforts have been made to modulate the immune system to encounter the external as well as internal attacks by pathogens. A brief history of immunomodulators is summarized in Table 1.

Objectives of immunomodulation: The primary 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:

- To activate powerful and prolonged immune response against disease causing microorganism
- To speed up maturation of non specific and specific immunity during neonatal period and in young susceptible animals

Table 1: History of Immunomodulators

Contribution	References
Endotoxin (LPS)	Billroth (1865)
Erysipel toxins	Coley (1894)
Mycobacterium adjuvants (BCG)	Freund *et al*. (1937)
Zymosan	Pillemer and Eccker (1941)
FCA	Freund and McDermott (1942)
Interferon	Isaacs and Lindenmann (1957)
Liposomes	Bangham and Horne (1964)
Corynebacterium parvum	Prevot *et al*. (1963)
Thymic hormones	Maisin (1964)
Double stranded polynucleotides	Vilcek *et al*. (1968)
Yeast glucan	DiLuzio and Riggi (1970)
Lentinan	Chihara *et al*. (1969)
Levamisole	Renoux and Renoux (1971)
Muramyl dipeptide	Lederer *et al*. (1975)
IL-1 and IL-2	Robb *et al*. (1981)
Discovery of first chemokines (IL-8 or NAP 1)	Baggiolini *et al*. (1989) and Leonard and Yoshimura (1990)
CD25 as a marker of natural Treg cells	Sakaguchi *et al*. (1995)
Glucocorticoid induced TNF receptor (GITR)	McHugh *et al*. (2002)
Antibody-cytokine fusion protein	Ortiz-Sanchez *et al*. (2008)
Biogenic selenium nanoparticles	Yazdi *et al*. (2012)

- To enhance local protective immune reactions at vulnerable sites such as mammary gland in dairy cattle or gastro intestinal tract in neonatal ruminants
- To surmount the immunosuppressive effects of stress and environmental pollution
- To enhance level and duration of immune response following vaccination
- To maintain immune surveillance

Characteristics of an ideal immunomodulator:

- It must have short withdrawal period and low tissue residues
- It should stimulate both specific and non specific immune response
- It should exert an adjuvant effect when administered along with a vaccine
- It should be active by oral route after it enters into host system and should be stable both in its native state and upon incorporation into food and water
- It should be compatible with wide range of drugs including antibiotics and anthelmintics
- It should amplify primary and secondary immune response to infectious agents
- It should have a defined chemical composition and biological activity
- It should be inexpensive
- It should be nontoxic even at high dose rates for animals and humans
- It should neither be antigenic nor pyrogenic
- It should not be teratogenic, carcinogenic or have long-term side effects in animals
- It should not be excreted in milk or eggs

Purpose of immunomodulation: The modification of immune response in animals may be intended to the following:

- Immuno-stimulation of normal animals
- Immunosuppression of normal animals
- Immuno-restoration of immune suppressed animals

CLASSIFICATION AND APPLICATIONS OF IMMUNOMODULATORS

Physiological products

Neuroendocrine hormones: There exists a close interaction between the immune and nervous systems which has been extensively studied and documented (Ohira *et al*., 2013). The immuno competent cells not only express receptors to neuroendocrine mediators but also secrete many of them. The interaction between neuroendocrine and immune system is very essential to maintain the homeostasis of the body (Blalock, 1989; Dan and Lall, 1998). Any alteration in this interaction can lead to enhanced susceptibility of the body to various infectious, inflammatory or autoimmune diseases (Eskandari *et al*., 2003). High vagal tone may regulate immune and physiological activity of brain (Ohira *et al*., 2013). There are two main mechanisms by which the Central Nervous System (CNS) controls the immune system. The first mechanism is Hypothalamic-Pituitary-Adrenal (HPA) axis mediated hormonal response, the second is via the release of nor-epinephrine (nor-adrenaline) from sympathetic and acetylcholine from parasympathetic nerves supplied to most of the immune organs (bone marrow, thymus, lymph nodes, spleen, etc) (Shepherd *et al*., 2005). Furthermore, neuropeptides such as substance P, somatostatin etc., are released into tissues from the peripheral sensory nerves by the antidromic activation mechanisms, where these molecules also modulate lymphoid cell activities. In the regulation of immune response, the role of hypothalamic hormones such as Thyrotropin-releasing hormone (TRH), Corticotropin-releasing hormone (CRH) and Gonadotropin-releasing hormone (GnRH) and major stress hormones viz.,

Table 2: Neuroendocrine hormones having Immunomodulatory properties

Products and sub-products	Action on immune system
Autonomous nervous system action	
Sympathetic	↓ Mφ activity, ↑ B and T cell function
Parasympathetic	↑ B and T cell function
Hypothalamic Pituitary (H-P) hormones	
Oxytocin, vasopressin	↑ T cell growth
Growth hormone and prolactin	↑ T cell growth, Augment antibody synthesis, activity of cytotoxic T-lymphocytes and natural killer cells Maintains the size of thymus and induces production of super oxide anion
H-P-Thyroid (TRH and TSH)	↑ B and T cell function
H-P-Gonadal (Sex hormones)	Generally inhibitory to leukocytes action
H-P-Adrenal	
ACTH	↓ Mφ activity, ↑ B and T cell function, Immuno suppression, decrease blastogenic responses of lymphocytes, inhibits antibody synthesis
Glucocorticoid	Inhibitory action on leukocytes
Neuropeptides	
Substance P	Stimulatory action on leukocytes
Somatostatin	Inhibitory action
Endogenous opioid peptides	Mainly stimulatory
VIP*	Potent endogenous anti-inflammatory agent
NGF**	↑ T cell function
Melatonin	Increases antibody production, increase number of cells in the spleen

*VIP: Vasoactive intestinal peptide, **NGF: Nerve growth factor, ↑: Increase and ↓: Decrease

cortisol and dehydroepiandrosterone (DHEA) and growth hormone are important. All these hormones and specific neurotransmitters and neuropeptides are recognized by specific receptors of lymphoid cells resulting in production of intracellular signals which subsequently influence immune cell function (Quintanar and Guzman-Soto, 2013). Ghrelin, an orexigenic stomach hormone blocks the lipopolysaccharide (LPS)-induced secretion of pro-inflammatory cytokines (IL-6) from immune cells (Beynon *et al*., 2013). Conversely, the immune system can also control the CNS through cytokines and change the individual's behavior (Prieto-Moreno and Rosenstein, 2006; Uchakin *et al*., 2007). For both the immune and the neuroendocrine systems, cytokines are important endogenous modulators which along with their receptors are expressed in the neuroendocrine system thereby exerting effects both centrally as well as peripherally (Benveniste, 1998). To date, around 30 neuroendocrine mediators have been reported to be active upon the immune cells. The important neuroendocrine hormones, neurotransmitters and neuropeptides having immunomodulatory properties are summarized in Table 2.

Thymic products: Thymus plays a pivitol role in the formation of the lymphoid structures in the prenatal and early postnatal life and orchestrating the lymphoid system throughout the life. More than 20 thymic products have been discovered, of which thymosin-α 1, thymopoietin, thymulin, thymosin fraction 5, Thymic Humoral Factor (THF), THF-gamma 2, splenopentin and thymopentin are particularly important in regulation of immune system (Huang *et al*., 1981; Zatz *et al*., 1984; Singh *et al*., 1998). Among these major thymic hormones, thymopoietin (TP), was mainly isolated from the bovine thymus. It consists of 49 amino acids and has a molecular weight of 5 kDa. This protein mainly acts on neuromuscular system and has a role in T cell differentiation and its physiological function. It has two closely related polypeptides known as thymostimulin (TP-1) and TP-II. The thymopoietin shows cross reactivity with a protein found in lymph node and spleen known as splenin which differs from thymopoietin by aspartic acid at position 34. Interestingly, all these thymic products showed enhancement of immune efficiency in immunodeficient patients, cancer cases, bacterial and viral infections and can potentially be used for immunotherapy (Singh *et al*., 1998; Ben-Efraim *et al*., 1999). The immunomodulatory activity of each of them is summarized in Table 3.

Table 3: Thymic products and their Immunomodulatory activities

Products	Action on immune system
Thymosin α 1	Increases lymphocyte and interferon production
Thymopoietin	T cell differentiation
Thymulin	Key player during interaction of immune system to neuroendocrine system
Thymosin fraction 5	Increases cGMP, induces T-cell markers on bone marrow, enhances migration inhibitory factor, increases antibody production and interferon
Thymic humoral factor	Increases cytotoxic reactivity of lymphoid cells against synergic tumors
Splenopentin (SP-5, Arg Lys-Glu-Val-Tyr)	Affects the neuromuscular transmission and is subsequently observed to affect T cell differentiation and function
Thymopentin (TP-5, Arg-Lys-Asp-Val-Tyr)	-do-

Cytokines: Cytokines are hormone like low molecular weight glycoproteins which are essential for proper functioning of the immune system (Dhama *et al*., 2008b, 2013c). A variety of immune cells produce them to communicate and orchestrate immune attacks (Pollard and Earnshaw, 2004). There may be initiation and perpetuation of autoimmune and infectious diseases along with tumour growth due to imbalanced network or abnormal production of cytokines (Adorini, 2003). The role of cytokines as immunomodulators is considered important for cure in future. They are autocrine, paracrine or endocrine in action and may exert either synergistic or antagonistic effect on their own production. Cytokines interestingly represent an improved and alternative treatment strategy against emerging pathogens. Cytokines can be used to enhance immunity and treat diseased or immune compromised individuals and to augment or induce desired immune responses against vaccines (Schijns and Horzinek, 1997). Cytokine secretion, when modulated, may offer novel approaches to treat a wide variety of diseases (Spelman *et al.*, 2006). Modulation or intervention of immune response can essentially be affected by administering anti-inflammatory cytokines viz., interferon (IFN)-β; growth factors (transforming growth factor β, interleukin (IL)-4 and IL-10); or by neutralizing pro-inflammatory cytokines (IL-2, IFN-γ, IL-12, tumor necrosis factor (TNF)-α, IL-1β and IL-17) (Adorini, 2003). Daptomycin antibiotics have immunomodulatory properties and suppress the expression of inflammatory cytokines after host immune response stimulation by Methicillin Resistant *Staphylococcus aureus* (Tirilomis, 2014). Honey and its different components have the capacity to stimulate or inhibit the secretion of cytokines viz., TNF-α, IL-1β, IL-6 from monocytes and macrophages. It can also regulate the generation of reactive oxygen species from neutrophils (Majtan, 2014).

Cytokines as additional immunomodulators against infectious diseases: The concept that enhancement of the antimicrobial action of host immune mechanisms and/or antimicrobial agents is done by replacement or enhancement of natural mediators of host resistance, forms the basis of the rationale for using cytokines as adjunctive immunomodulators for infectious diseases. It is difficult to harness clinically the potential antimicrobial power of these agents despite the logical basis for this concept. A few examples are available, currently regarding the use of adjunctive immunomodulatory cytokines against infectious diseases. Examples are pegylated interferons and ribavirin for hepatitis C virus (HCV), use of recombinant nucleoside analogs and α-interferons for hepatitis B virus (HBV) (Forton and Karayiannis, 2006). Induction of Th1 immunity increases the efficacy of interferons against HCV (Trapero-Marugan *et al.*, 2006). Immunotherapy with adjuvants in combination of recombinant cytokines is helpful in case of candidiasis (Van de Veerdonk *et al.*, 2012). Depression is a common adverse effect of interferon-based therapies limiting their use in certain cases (Asnis and de la Garza, 2006). As an adjunctive agent for HIV-associated cryptococcal meningitis, adjunctive interferons hold promise in light of the confirmed benefits of interferon treatment for the prevention and cure of patients with chronic granulomatous disease associated bacterial infection (Gallin *et al.*, 1991). Adjunctive cytokines like interferon-gamma moreover, can be utilized against invasive fungal infections as it can exhibit a protective response against fungi through Th1 helper T-cell responses (Armstrong-James *et al.*, 2010; Jarvis *et al.*, 2012; Delsing *et al.*, 2014). IL-10 is effective against Leptospira infection (Rizvi *et al.*, 2012). The ability to alleviate neutropenia forms the basis of the rationale for using colony stimulating factors (CSFs) derived from macrophages (GM-CSF) or granulocytes (G-CSF) (Antachopoulos and Roilides, 2005).

Cytokines as novel immunomodulators for vaccines: Right formulation of an appropriate vaccine adjuvant or immunomodulator is required in order to achieve the protective immunity in host following immunization. This can be achieved by the correct selection of vaccine adjuvants like cytokines. The vaccine adjuvants cytokines can be administered by two basic methods as genes encoded by DNA vaccines or as soluble proteins. In cattle, sheep, pigs and poultry soluble cytokines have been successfully used to modulate the immune system. Since most of the cytokines have a very short half-life and so large doses are needed *in vivo* to alter the immune responses to the co-administered antigen which often leads to development of adverse effects. This problem can be avoided by use of slow and sustained release preparations that release the cytokine for a prolonged period (Nicholls *et al.*, 2010).

In order to ensure an appropriate immune response, new vaccines and their development necessitate production of new generation adjuvants (Nicholls *et al.*, 2010); e.g., use of cytokines viz., mucosal vaccine adjuvants such as IL-7 and IL-12 (Stevceva *et al.*, 2006). Cytokines and chemokines viz., monocyte chemotactic proteins (MCPs), granulocyte-macrophage colony-stimulating factor (GM-CSF) and macrophage inflammatory proteins (MIPs) have been incorporated into vaccines most recently. This can be done in lieu of their (cytokines') potential to enhance recruitment of dendritic cells and monocytes from blood into the interstitial sites of vaccine delivery (Klavinskis *et al.*, 2010). Killer cells, induced by cytokines like IL-2 and 15, can be used as vaccine against cancer (Lee and Margolin, 2011; Thanendrarajan *et al.*, 2011). The important cytokines with their source, function along with their therapeutic application are listed in Table 4.

In general, classification of cytokines has been arbitrary and it depends upon the individuals. But most often, cytokines have been classified on the basis of similarity in their functional properties in controlling immunity and inflammation i.e., colony stimulating factors, interferons and pro-inflammatory and anti-inflammatory cytokines (Kogut, 2000; Reefman *et al.*, 2010) (Table 5).

Importance of cytokines in veterinary practice: In the past, the usage of cytokines was restricted due to the problem of production of the protein in bulk. But recent developments in recombinant DNA technologies have solved this problem (Tossing, 2001). Different cytokines like interferons, interleukins etc., have been used successfully for treating various diseases. Minagawa *et al.* (1999) reported successful treatment of canine parvovirus in Europe by using alpha type 1 interferon of feline origin. In the poultry industry interferons

Table 4: Cytokines having Immunomodulatory activities

Cytokines	Source	Function	Therapeutic application
IL-1	Monocyte, lymphocyte, endothelium	Haematopoiesis, co-stimulation of T cell, fibroblast proliferation, acute phase response	Blockage of IL-1 activity
IL-2	Activated T cell and dendritic cells	T cell proliferation and differentiation, B cell proliferation and Ig secretion, proliferation and cytolytic activity	Treatment of cancer and infectious diseases, bone marrow transplantation
IL-3	Activated T cell, mast cell, NK cell	Proliferation and differentiation of myeloid progenitor stem cell, prevention of apoptosis induction in macrophages	Bone marrow transplantation
IL-4	T cell, mast cell, eosinophil, basophil	B cell proliferation and differentiation, Ig switching,	Antitumor agent, immune stimulator
IL-6	T cell, monocyte, endothelial cells, mast cells	Stimulate B cell for antibody production and T cell growth and CTL differentiation	Antitumor
IL-8	Monocyte, lymphocyte, endothelial cells	Neutrophil chemotaxis and activation, chemokine function	None
IL-10	Monocyte, lymphocyte, endothelial cells	Inhibition of proinflammatory cytokines by monocyte, granulocytes, inhibition of IL-2 production by T cell, inhibition of antigen specific T cell activation	Antiinflammatory and immunosupressive. Used in autoimmune disease
IL-12	Monocyte, B cells	Proliferation of T and NK cell, CTL response to tumor cell, ↑ IFN γ production by T and NK cell, inhibit Ig E production	Antimetastatic, antitumor, vaccine adjuvant
IL-13	Activated T, B cells	B cell growth and differentiation factor, stimulate chemotaxis	Antitumor, anti inflammatory agent
IL-15	Mononuclear cells, Natural Killer (NK) cells	Stimulation of activated B, T and NK cell, chemoattractant	Antitumor, in rheumatoid arthritis
IL-16	T cell, eosinophil	Chemotaxis for CD4 cells	Anti-HIV
IL-17	Th17 T-cells	Regulation of inflammation	Systemic lupus erythematosus; psoriasis, systemic sclerosis, multiple sclerosis as well as type-1 diabetes
IFN-α	Leucocyte	Antiproliferative action, immunoregulatory action	Cancers, hepatitis B, hepatitis C, AIDS, Kaposi sarcoma, multiple sclerosis
IFN-β	Fibroblast, epithelial cell, endothelial cell	Antiviral, MHC antigen upregulation, NK cell enhanced cytotoxicity, antimicrobial	Cancer, multiple sclerosis
IFN-γ	Monocyte, macrophage, dendritic cell, T cell, B cell	MHC class II expression, macrophage and NK cell activation, Ig isotype selection	Used as adjuvant
G-CSF	Stromal cell, endothelial cell,	Proliferation and differentiation of macrophage progenitor cell	After bone marrow transplantation
M-CSF	Fibroblast, endothelial cell, T cell, monocyte, neutrophil	Monocyte proliferation, differentiation and activation	Antitumor, anti-infection, myelo-supression
GM-CSF	T cell, macrophage, endothelial cell, B cell	Inhibit apoptosis of target, proliferation, differentiation and activation of granulocyte, macrophage lineage	Recruitment of peripheral blood stem cell, stimulation of APC for immunotherapy
A chemokines	Monocyte, neutrophil, endothelial cell, epithelial cell	Neutrophil chemotaxis and adherence, IL-6 secretion	None yet
B chemokines	Monocyte, fibroblast, epithelial cells, melanocytes	Monocyte activation, basophil activation, T cell chemotaxis, NK cell cytolysis	None yet
RANTES	T cell monocyte, NK cell, Fibroblast, epithelial cell, Endothelial cell	T cell chemotaxis and proliferation, monocytic chemotaxis and activation, NK cell chemotaxis, modulation of macrophages, eosinophils, T cells	Supression of HIV replication
TNF-α	Macrophages, T cell	Cytotoxic for tumor cell, antiviral, antibacterial, antiparasitic activity,	Cancer and autoimmune disease
TNF-β	Mast cell, platelet, fibroblast	Wound repair, cell growth regulation, tissue remodelling, immunosupression,	Inhibition of inflammatory cell, treatment of breast cancer

Table 5: List of important immunomodulatory cytokines

Interferons (IFN)	Colony Stimulating Factors (CSF)	Proinflammatory cytokines	Anti-inflammatory cytokines
Type I (IFN α/IFN-β)	IL-3/Multi-CSF	IL-1, IL-17	IL-4
Type II (IFN γ)	Macrophage-CSF (M-CSF)	IL-6	IL-10
	Granulocyte-CSF (G-CSF)	IL-12	TGF-β
	Granulocyte Macrophage-CSF (GM CSF)	TNF-α	

and other cytokines have been significantly used to reduce the use of vaccines and antibiotics in-feed (Lowenthal *et al*., 1998, 1999; Bedford, 2000). IFN-γ of poultry origin appears to have a significant role in the treatment of circovirus infection in young grey parrots (Stanford, 2004).

In *Staphylococcus aureus* mastitis, recombinant bovine interleukin-1 beta and interleukin-2 are found to be effective immunomodulators to augment natural resistant mechanisms similar to the normal response to pathogens. These may prove to be suitable alternatives to antibiotics or may be used along with them as effective therapeutic agents for mastitis

(Daley *et al*., 1991). It is found that IL-11 is useful in treating *Pseudomonas aeruginosa* induced sepsis in immunocompromised animals (Opal *et al*., 1998). IL-2, IFN-gamma and TNF-alpha are recombinant bovine cytokines and all of them can be used as adjuvants in normal mammary gland to mobilize innate and acquired immunity (Alluwaimi, 2004). Immunostimulant cytokines have therapeutic potential against recurrent canine pyoderma which is a major problem for veterinarians. The helper T cell (Th1) cytokines (TNF α, IFN-γ and IL-1β) have profound effect on cell-mediated responses against bacterial infections (DeBoer *et al*., 2009).

For invasive fungal infections, adjunctive cytokines can be administered along with antifungal agents resulting in T-cell immune responses mainly of Th1 type in protection against fungi in experimental models. This has given rise to the rationale for using Colony Stimulating Factors (CSFs) which was derived from granulocytes (G-CSF) and macrophages (GM-CSF); partly based on their property to mitigate neutropenia (Antachopoulos and Roilides, 2005). It is assumed that adjunctive interferon holds promise as an adjunctive agent for HIV associated cryptococcal meningitis in the light of the established benefits of interferon therapy in preventing further bacterial complications in chronic granulomatous diseases (Datta and Pirofski, 2006; Pirofski and Casadevall, 2006). The recombinant cytokines such as GM-CSF, TNF, IL-1 and IFN-γ are used as adjunctive immunotherapy for the cure of disseminated candidiasis. These cytokines cause increased expression of dectin-1 receptors on phagocytic cell macrophages. It also enhances the activity of chitotriosidase which causes degradation of the chitin from the internal cell wall of *C. albicans* (Van de Veerdonk *et al*., 2012). IL-17 has got a major role to play for treating diseases like systemic lupus erythematosus, rheumatoid arthritis, psoriasis, multiple sclerosis, systemic sclerosis and type-1 diabetes (Kunz and Ibrahim, 2009). The extensive drug-resistant tuberculosis (XDR-TB) emergence has rendered chemotherapy futile due to which cytokine therapy may become one of the possible useful alternative. The efficacy of therapeutic strategies employing a single cytokine has not been reported adequately; thus basic research would be necessary to attain a better understanding of the mechanisms and interactions of cyokines involved in successful promotion of immune response in order to generate efficient cytokine-based XDR TB therapies. New research projects concerning cytokines based treatment for XDR TB should be appreciated and liberally funded. Chemokines may increase both mycobacterial killing activity of the effector cells as well as defense against intracellular multiplication of the bacteria and thus their role must also be explored (Rivero-Lezcano, 2008). Tumor necrosis factor-α and interleukin-6 have enormous roles to play in conditions like obesity (German *et al*., 2010; Zoran, 2010).

Glucocorticoids: Most frequently glucocorticoids are used for treating chronic inflammatory diseases that involve lymphocytes but in diseases mediated by macrophages, they are effective to a lesser extent (Kugelberg, 2014). The effect of glucocorticoids on immune system is biphasic as there is an initial inhibition during initial release of corticosterone but prolonged release of glucocorticoids cause neutrophilia which results in increased phagocytosis and stimulation of immune system (Hall and Goldstein, 1984; Wilckens and de Rijk, 1997). The suppression of immune function and feedback repression of the Hypothalamo-Pituitary-Adrenal axis (HPA axis) by glucocorticoids are mediated through repression of gene transcription (Philips *et al*., 1997) results in inhibition of synthesis of various cytokines such as IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8 and IFN-γ, significantly the IL-2 and their receptors enhance the production of other molecules such as lipocortin-1 and type II IL-1 receptor (Nelson *et al*., 2003). In addition, glucocorticoids exert their anti-inflammatory mechanism by synthesizing lipocortin-1. Lipocortin-1 blocks phospholipase-A2. This blocks eicosanoid synthesis and suppresses many leukocyte inflammatory events (e.g., epithelial adhesion, emigration and chemotaxis, followed by phagocytosis and respiratory burst) (Van de Garde *et al*., 2014). Apart from suppressing immune response, glucocorticoids inhibit prostaglandins and leukotrienes (the two main products of inflammation).

Glucocorticoids primarily influence the cellular immunity but also suppress the humoral immunity. At physiological concentrations, glucocorticoids favor the Th2 type immunity (Franchimont *et al*., 2000). Glucocorticoids regulate transcription factors, characteristic of a steroid. Another important feature of glucocorticoids is that they down-regulate the Fc receptors expression on macrophages resulting in reduced phagocytosis of opsonised cells. Glucocorticoids show bi-directional positive and negative actions on the immune system. They act positively on the innate immune response by priming and modulating the genes and by promoting the humoral (Th2) immune response. Glucocorticoids can also act negatively by suppressing the cellular (Th1) immunity on the adaptive immune response. In addition, glucocorticoids provoke the tolerance to specific antigens by controlling maturation of dendritic cells and their function; and cause up regulation of activity of regulatory T cells which is main source of IL-10. Glucocorticoids can be used as an adjuvant in cell therapy for the treatment of autoimmune diseases (Franchimont, 2004). Inhalation of glucocorticoids may be better to dampen eosinophil induced inflammation (especially in cats) thereby normalizing the dysregulated immune system (Chang *et al*., 2013).

Host defense peptides: Antimicrobial peptides or Host Defense Peptides (HDPs) are considered in the recent times for their immunomodulating properties owing to their both anti-inflammatory and immunostimulatory activities. The HDPs are an evolutionarily conserved molecule of the innate immune system and short cationic peptides of most multicellular organisms. These host defense peptides are produced by all mammals and are mainly produced from their lymph nodes (Hancock and Sahl, 2006; Hamill *et al*., 2008). Cathelicidins, defensins and histatins are the classical example of the peptides produced by mammals during infection. The antimicrobial actions of HDPs are owing to their amphipathic nature which enables the peptides to act on the lipid bilayers of pathogens and cause their membrane damage, translocate the membrane and inhibit nuclear and protein synthesis machinery of pathogens. As the interactions between the HDPs and the anionic lipids of membranes of microbes are relatively nonspecific, many peptides have showed broad spectrum of antimicrobial activities, targeting both Gram-negative and Gram-positive bacteria, some viruses, protozoa and fungi (Zasloff, 2002; Powers and Hancock, 2003; Nijnik and Hancock, 2009; Sunkara *et al*., 2012). Furthermore, these peptides have antimicrobial activity by either damaging the membrane of the microbe or by entering the microbes and act inside especially in phagosomes of the host (Powers and Hancock, 2003). The HDPs are greatly effective against multidrug-resistant (MDR) bacterial strains by acting as immunomodulators. The HDPs have capability to modify gene expression of the host, enhance the chemokine production by acting like chemokines, prevent LPS induced pro inflammatory cytokine secretion, alter the dendritic cell responses and cells of the adaptive immune system and induce wound healing (Hunter *et al*., 2002; Nijnik and Hancock, 2009). Host defense peptides have been synthesized and research has been conducted for their efficacy to possess immuno-modulatory actions. Innate defense regulator 1 (IDR-1), is the first synthesized peptide that boosted host disease resistance against bacterial challenge. The correct mechanism by which this activity is accomplished is not clear, though it has been postulated that it increases cytokine production and also modulate cytokines like TNFα (Scott *et al*., 2007). RDP58, another peptide that was obtained from Human leukocyte antigen (HLA) 1 molecule, has activity similar to IDR-1 peptide, like decreasing the synthesis of pro-inflammatory cytokines (Easton *et al*., 2009). The postulated mechanism is that these peptides affect the signaling pathways but the exact picture remains unclear (Travis *et al*., 2005). There is a list of peptides which are available in the market as immunostimulatory agents and the list include pexiganan (MSI-78), HB-1345, hLF1-11, XOMA-629, iseganan (IB-367) and omiganan (MX-226). Glutoxim a tripeptide which holds anti-infective properties, is used along with traditional medicine for the treatment of *Mycobacterium tuberculosis* infection (Fimiani *et al*., 2002). Fowlicidin-3 has the property of inhibiting lipopolysaccharide-induced expression of pro-inflammatory genes in mouse macrophage RAW264.7 cells (Bommineni *et al*., 2007). In addition, chicken fowlicidin 1 analog showed strong Immunomodulatory activities and protected mice against methicillin-resistant *Staphylococcus aureus* infections (Bommineni *et al*., 2014), suggesting development of chicken fowlicidins as a unique antisepsis and antimicrobial agent, especially against antibiotic-resistant microbes. In recent years, proteins isolated from *Bacillus cereus* have been found to have antifungal activity and are immunomodulatory in nature (Salmen *et al*., 2013).

MICROBIAL PRODUCTS

Louis Pasteur first suggested in 1885, that the human immune system can be affected by microorganisms. Bacterial immunomodulators are a heterogeneous group of drugs usually composed of standardized lysates or extracts of different bacterial strains used for a non-specific activation of the immune system. They are administrated to increase mucosal immunity and to prevent recurrent infection of the respiratory tract (Spisek *et al*., 2004). Following exposure to Gram-positive and Gram-negative bacteria (or to the biologically active components of these microorganisms), the functioning of lymphocytes and macrophages may be significantly altered. There is either enhancement or inhibition of the functioning of immune cells by immmunomodulating substances related to bacteria. This increases probability of influencing specific immune resistance of host to infection. Substances derived from such bacteria may exert a continuing influence on the immune response by both specific and non-specific mechanisms due to continual exposure and colonization by bacteria (Friedman *et al*., 1984).

The microbial products are known for their potential for non-specific activation of macrophages and stimulation of NK cell activity. A wide variety of bacteria have been employed as immunostimulants as most of their cellular components act as ligands for different Toll-Like Receptors (TLRs). As a result, they activate macrophages and dendritic cells which in turn stimulate the release of a mixture of cytokines. The most potent cytokine synthesis enhancer is Bacillus Calmette-Guerin (BCG) which is derived from *Mycobacterium bovis* the attenuated and live vaccine strain. BCG generally enhances B and T cell mediated responses, phagocytosis, graft rejection and resistance to infection (Barakat *et al*., 1981; Vetskova *et al*., 2013). Muramyl dipeptide (MDP) (adjuvant active) is a simple glycopeptide and minimal active structure of whole *Mycobacteria* endowed with numerous biological activities. By activation of macrophages and enhancement of humoral immunity, MDP increases non-specific resistance against infectious challenges and increases resistance against tumor grafts under certain conditions. The biological activity of MDP is greatly enhanced by incorporation into the lysosomes because of its rapid rate of excretion in urine (Souvannavong *et al*., 1988). Phosphoglycolipids (PGLs) viz., PGL1 and PGL2 are new class of glycolipids (first isolated in 2006) from the thermophilic bacteria: *Thermus oshimai* and *T. thermophilus*, *Meiothermus ruber* and *M. taiwanensis*. PGL1 from *M. taiwanensis* and *T. oshimai* process the activity to induce proIL-1 in human THP-1 monocytes and blood-isolated primary monocytes but the same is not true in case of *T. thermophilus* and *M. rubber* (Yang *et al*., 2006, 2008).

It is well reported that bacteria can modulate the immune response to non-related antigens; classical example being *Propionibacteria* which are amongst the most potent immunomodulators stimulating cell populations involved in non-specific resistance. Through mechanisms of recognition and elimination, the activated immune system generally provides protection from infectious pathogens and prevents spread/growth of malignant cells. In experimental and clinical settings, *Propionibacteria* and its defined low molecular weight substances could be effective in the treatment of infections and neoplastic diseases (Pulverer *et al*., 1985). Heat killed or formaldehyde treated anaerobic suspension of corynebacteria, such as *Propionibacterium acnes* is used for immunotherapy. It activates macrophages and clears particulate material from the circulation and presumably stimulates cytokine synthesis through TLRs. It can enhance humoral and cell mediated immune responses and can cause tumor regression. It enhances defense to bacterial, viral and protozoan infections. These organisms have a general immunostimulatory action, leading to enhanced antibacterial and antitumor activity (Becker *et al*., 1989). *Propionibacterium avidum* KP-40 is preferably introduced for clinical evaluation on practical ground although its immuno-active capacity is absolutely identical to *P. granulosum* KP-45. The efficiency of propionibacterial immunomodulation is related not only to the type of tumour involved but also to the bacterial strain used along with route and timing of administration (Szmigielski *et al*., 1982). Treatment with propionibacteria proves to be of considerable clinical benefit, inducing potent immunostimulation and is essential in colorectal carcinoma wherein *Propionibacterium avidum* KP-40 (having stimulatory effect on non-specific immunity (Pulverer *et al*., 1985; Isenberg *et al*., 1995). *Propionibacterium avidum* KP-40 also enhances thymus weight and at the same time accelerates maturation of thymocytes. It also enhances significantly absolute counts of peripheral blood lymphocytes and monocytes by inducing expression of activation markers on monocytes viz., interleukin (IL)-2 receptors (on lymphocytes) and macrophage 3 antigen (MAC-3) (Lefrancois and Puddington, 1995).

Staphylococcal cell walls (especially staphylococcal phage lysates), some Streptococcal components and components of *Bordetella pertussis*, *Brucella abortus*, *Bacillus subtilis* and *Klebsiella pneumoniae* all have immunostimulative activity (Bessler *et al*., 1991).

Bacterial derived unmethylated cytosine-guanosine nucleotide is the specific ligand to the pattern recognition receptor TLR9 present over the antigen-presenting cells and thereby triggers a potent Th1 cytokine response. If given alone, the nucleotides can act as immunostimulant and can greatly enhance the innate immunity while if given with an antigen these nucleotides act as potent adjuvants (Wang *et al*., 2006). Certain complex carbohydrates obtained from yeasts viz., zymosan, glucans, aminated polyglucose and lentinans can also activate the macrophages. These may function as adjuvants and potentiate resistance to infectious agents. Acemannan is obtained from the *Aloe vera* plant which is a complex carbohydrate and is a potent cytokine synthesis enhancer with antitumor and antiviral activities. Lentinan is a neutral polysaccharide isolated from mycelia of an edible mushroom *Lentinus edodes*. It can augment antigen specific cellular immune response and also has antitumor action (Scaringi *et al*., 1988). For various *in vitro* assays as standards, synthetic lipopeptide analogues derived from bacterial lipoprotein can be used as potent mitogens for lymphocyte activation and also as polyclonal activators to induce immunoglobulin synthesis. They moreover induce tumor cytotoxicity apart from stimulating the secretion of IL-1, IL-6 as well as Tumor Necrosis Factor (TNF) and Nitric Oxide (NO) in monocytes and macrophages; constitute potent immuno-adjuvants *in vitro* and *in vivo*. Added advantage is their non-toxicity and long time storage capability even at room temperature thereby making them to meet the requirements for effective standards used in various biological assays (Bessler, 1992). Gram-negative bacterial cell wall primarily consists of lipopolysaccharide made up of Monophosphoryl Lipid A (MLA) which is proved to be a safe and effective compound in inducing immune responses to heterologous proteins in animal and human vaccines (Persing *et al*., 2002; Bohannon *et al*., 2013). As TLR4 agonist, it has strong immunomodulatory effects when used both as stand-alone products and vaccine adjuvants and importantly, unique approaches to vaccine manufacturing could be benefitted by both innate and adaptive responses.

Probiotics: Microorganisms serve as an important functioning constituent of the mammalian gastro-intestinal tract. The antibiotic and immunosuppressive therapy can alter the normal flora of the gastrointestinal tract. The introduction of beneficial flora into the system will not only help to reestablish the normal flora but also help to prevent the disease. The word "probiotic" was first introduced by Lilly and Stillwell (1965) in order to define substances produced by one organism which enhance the growth of the other organism. The word "probiotics" was obtained from the Greek word meaning "for life". According to the definition by FAO/WHO probiotics are defined as "Live microorganisms which when supplemented in adequate amounts provide a health benefit on the host".

Probiotics or Direct Feed Microbials (DFM) are naturally existing live microorganisms that provide a positive effect on the physiological status of the host (Behnsen *et al*., 2013; Hormannsperger *et al*., 2013; Rask *et al*., 2013). This is often accomplished by their ability to alter the intestinal microbial balance in a beneficial manner which in turn will improve the health and well being of animals, birds or human beings (Fuller, 2001; Dhama *et al*., 2008a; Behnsen *et al*., 2013). Probiotics include bacteria, fungi and yeast. Commonly, apathogenic live bacterial strains consisting of the genus *Enterococcus*, *Streptococcus* and *Lactobacillus* are mainly utilized in poultry and livestock. As growth promoters, probiotics have been found to increase feed conversion efficiency, improve growth performance and improve immune responses in poultry and livestock (Balevi *et al*., 2001;

Dhama *et al*., 2008a). They are capable of stimulating the immune system of human, animals and birds to fight against infectious agents, tumors and other stress factors (Fuller, 2001; Dalloul *et al*., 2005; Lee *et al*., 2007a; Ohashi and Ushida, 2009; Corcionivoschi *et al*., 2010; Dhama *et al*., 2011; Behnsen *et al*., 2013; Jacquet, 2013; Rask *et al*., 2013; Serban, 2014).

Probiotics play a crucial role in the induction of immune competence in neonates (Balevi *et al*., 2001). They exert immunostimulatory action by stimulating cell mediated immunity, increasing immunoglobulin and interferon production, activating macrophages, lymphocytes and Natural Killer (NK) cells and by regulating oxidative burst and degranulation of heterophils (Koenen *et al*., 2004; Dhama *et al*., 2008a). These probiotic bacteria stimulate the immune response in a strain-specific manner (Rask *et al*., 2013; Ho *et al*., 2013). Thus, a combination of strains should be used to provide all the beneficial effect of probiotics (Hsieh *et al*., 2013). *Lactobacillus* species have been reported to increase the intra-epithelial lymphocytes of intestinal lymphoid tissue which responds to microbes by secreting immunoglobulin A (IgA) and thereby providing local immunity (Balevi *et al*., 2001; Haghighi *et al*., 2006).

Various strains of probiotic bacteria such as *Lactobacillus casei, Lactobacillus delbrueckii* subsp. *bulgaricus*, *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus paracasei*, *L. fermentum*, *L. rhamnosus*, *L. brevis*, *L. helveticus, L. reuteri* and *Bifidobacterium* animals vary in their mechanisms of action for immunomodulation (Ho *et al*., 2013; Hsieh *et al*., 2013; Rask *et al*., 2013; Lahteinen *et al*., 2014). The immunomodulation for these probiotics is reflected in increased secretion of antibodies; induction of cell mediated immunity; increased phagocytic activity of granulocytes, increased expression of activation marker (CD25 and CD45RO) on T cells and natural killer cells and cytokine production etc (Kosaka *et al*., 2012; Lamprecht *et al*., 2012; Mokrozub *et al*., 2012; Tsai *et al*., 2012; Behnsen *et al*., 2013; Deng *et al*., 2013; Dongarra *et al*., 2013; Lahteinen *et al*., 2014; Hsieh *et al*., 2013; Rask *et al*., 2013). Strains of *Leukonostoc* and *Streptococcus* are known potent enhancers of Th1 cytokine. *Propionibacterium* and *Bifidobacterium* genera are the potent anti-inflammatory probiotics that induce IL-10 secretion. Lactocepin produced by *Lactobacillus casei* and *Lactobacillus paracasei* selectively degrade pro-inflammatory chemokines thus may have therapeutic application in control and treatment of inflammatory diseases like IBD, allergic skin inflammation and psoriasis (Hormannsperger *et al*., 2013). *Bacillus subtilis natto* (Sun *et al*., 2010) or other probiotics have shown to stimulate immune system. *Lactococcus lactis* activated human plasmacytoid dendritic cells and induced production of interferon thus can play a crucial role in anti-viral immunity (Sugimura *et al*., 2013).

Dietary oligosaccharide such as galacto-oligosaccharides, fructo-oligosaccharides and pectin-derived acidic oligosaccharides may be helpful in prevention of atopic dermatitis, food allergy and allergic asthma by alteration of the intestinal microbiota or by direct interaction on immune cells or both (Jeurink *et al*., 2013). Lactoferrin which is an iron binding protein in milk has immune modulating properties and can help in modifying the course of methicillin Resistant *Staphylococcus aureus* infection in udder (Hwang *et al*., 2014). Microbes with high CpG motif-rich DNA could better support mucosal functions of intestine in healthy individuals and improve the T-helper 1 (Th1)/Th2 imbalance in allergic diseases (Kant *et al*., 2014). Interaction of prebiotic like Agave fructans (*Agave salmiana*) with probiotics *Lactobacillus casei* and *Bifidobacterium lactis* are helpful in activation and selective differentiation of immune cells (Moreno-Vilet *et al*., 2014). Fructans can bind to TLR 2 and also TLR 4 hence can modulate the immunity (Peshev and van den Ende, 2014).

Irrespective of their origin and structure, the common mechanisms involved in probiotic action include: Increased production of immunoglobulins (IgG, IgM and IgA); absorption of antigens released from dead microbes; stimulation of cell mediated immunity; elevated production of vital immune factors (interferons etc.). Further, probiotics can increase macrophage as well as lymphocyte and NK cells activity and up regulate oxidative burst and degranulation of heterophils (Isolauri *et al.,* 2001; Trebichavsky and Splichal, 2006). *Saccharomyces boulardii* has stimulatory effect on secretory IgA and other secretory components of immunoglobulins in small intestine of rats (Buts *et al*., 1990). Kaila *et al*. (1992) reported that human *Lactobacillus* strain has potentiating effect on the circulating antibody producing cell response against diarrhea cases in humans. Park *et al*. (2002) reported that encapsulated *Bifidobacterium bifidum* enhances intestinal IgA secretion. Modulation of humoral immunity by probiotics and its effects on cytokine production are depicted in Table 6 and 7.

Table 6: Probiotic modulation of humoral immunity

Probiotic bacteria	Species	Assessment	Effect
Lactobacillus casei, Oral (Heat killed)	Rodent	Systemic antibody response to ovalbumin	Inhibited splenocyte immunoglobulin IgE *in vitro* and serum IgE
Lactobacillus casei, Oral (Live)	Rodent	Infection and antibody production in malnourished animals	Increased serum IgA and reduced enteric infections caused by *Salmonella*
L. acidophilus and *Peptostreptococcu* Oral (Live)	Rodent	Translocation of *Escherichia coli* and serum total anti *E. coli* IgG, IgE and IgM	Decreased translocation and increased anti *E. coli* IgM and IgE
Bifidobacterium bifidus. Oral (Live)	Human	Total IgA and response to polio virus	Increased serum IgA
Bacillus subtilis natto	Calf	Stimulate humoral immunity	Increases the production of IgG, IgM and IgA
Lactobacillus plantarum DK119	Rodent	Stimulate host innate immunity	Increase in dendritic cells, macrophages and cytokine production
Lactococcus lactis BFE920	Olive flounder	Stimulate host innate immunity	Increased lysosomal activities and production of IL-12 and IFN-γ

Table 7: Probiotic effect on cytokine production

Probiotic bacteria	Species	Assessment	Effect
Lactobacillus casei, Oral (dry)	Human	Serum Interferon γ	Increased
Lactobacillus GG, Oral (Live)	Human	TNFa in patients with food allergy	Decreased fecal TNFa
Lactobacillus, Bifidobacterium and *Streptococcus* (several strains), Oral (Live)	Rodent	Mitogen induced IL-6, IL-12, IFN-γ and TNFa production by intestinal lymphoid cells	Enhanced IL-6 and IL-12 (*Lactobacillus casei* and *L. acidophilus*), enhanced IFN-γ and nitric oxide (*L. cidophilus*)
Bacillus subtilis natto	Calf	Stimulate overall CMI response by helping in absorption of antigens by dead microbes	Elevation in the level of vital immune factors (interferons etc.) increase in macrophage, lymphocyte and NK cells activity and up regulation of oxidative burst and degranulation of heterophils
Lactococcus lactis BFE920	Olive flounder	Stimulate host innate immunity	Increased production of IL-12 and IFN-γ

SYNTHETIC CHEMICAL COMPOUNDS

Various chemicals having immunomodulatory properties have been reported in literature (Sultana and Saify, 2012). These compounds offer the advantage of oral administration. It is important, in this regard, to note that cell surface carbohydrates such as glycoconjugates and oligosaccharides are responsible for several vital life processes. These include; immune response, cell-cell interactions, cell growth and proliferation and combating numerous bacterial and viral infections. Recognition of structurally well-characterized and chemically pure carbohydrate antigens is necessary to understand the molecular mechanisms and to study the carbohydrate recognition and subsequent immunomodulation in various diseases. Lipid A analogues, such as monophosphoryl lipid A, have been developed as an immunomodulatory compound with reduced pro-inflammatory activities, thus can be used as an adjuvant in vaccine preparation (Bohannon *et al*., 2013). Chemically synthesized glycoconjugates are thus valuable to understand the role of cell surface carbohydrates in the pathogenesis of a disease. The important immunomodulatory chemicals which are being used widely are summarized in Table 8.

Various drugs which are chemically synthesized have immunomodulatory actions. The important drugs in this group of chemical agents include thalidomide and its versions namely lenalidomide and pomalidomide which are commonly used in the field of oncology (Zimmerman, 2009). These immunomodulatory agents are usually given orally. They act on cytokines involved in inflammation, molecules involved in expression and modulation of immune cells and finally in angiogenesis (Anderson, 2005). Thalidomide is the first among this group which was available in the market early in 1960s as a sedative and anti emetic but was soon withdrawn because of its side effects like teratogenicity (Eisen *et al*., 2000; Kumar and Anderson, 2005). Its usefulness as an immunomodulatory agent was understood late in 1990s and hence it was brought back into the market not as an anti emetic or sedative drug but as a drug against erythema nodosum leprosum. Thalidomide is the parent compound derivative of glutamic acid. Lenalidomide and pomalidomide are the derivatives of thalidomide but have higher activity as compared to the parent compound (Chanan-Khan *et al*., 2013). Thalidomide became a promising drug for the treatment of multiple myeloma condition after a series of clinical trials.

Table 8: Synthetic chemical compounds having Immunomodulatory activities

Compounds	Immunomodulatory action
Levamisole	Increases T cell and macrophage activity
Thiabendazole	Enhances blastogenic responsiveness to mitogens
Imuthiol	Increases lymphocyte blastogenesis, IL-2 production
Avridine	Increases bactericidal activity of neutrophils
Isoprinosine	Increases T-helper cells, Increases NK cell cytotoxicity
Glucan	Enhances chemotaxis for neutrophils
Indomethacin	Increases blastogenic responses to T-cells
Ascorbic acid	T lymphocyte proliferation, lymphokine production, Increases antibody production
Biostim	Improves DTH reaction
Dihydroheptaptenol	Increases number of neutrophils
Thalidomide	Decrease cytokine production (TNFα, IL6 and IL8) during tumour
Glatiramer acetate	Altering Th1 response to Th2 response during multiple sclerosis
Ciclosporin	Inhibition of calcineurin
Dapsone	Inhibition of folic acid

Several studies have also been conducted for its effect on other tumorous conditions like breast cancer, renal carcinoma, Kaposi's sarcoma, malignant melanoma, CNS malignancies and prostrate carcinoma (Fife *et al*., 1998; Escudier *et al*., 2002). But its activity was found to be more against multiple melanoma as compared to the other conditions (Garcia-Sanz, 2006). Mechanism of action of thalidomide and its derivatives is of two modes, one by directly acting on the tumor cells and another by down regulating their functions (Figg *et al*., 2001; Short *et al*., 2001). The first mode of action of thalidomide is done by decreasing the production of various cytokines which are involved in survival of the tumor cells like TNF-α, IL6 and IL8. TNF-α production is decreased by two ways, one by degradation of the mRNA which is intended to produce TNF-α. Alpha-1-acid glycoproteins are produced in excess which has anti TNF-α activity and hence it also helps to reduce the production TNF-α (Baidas *et al*., 2000). The second mode by which thalidomide helps to keep tumor under control is an indirect way where it makes the interaction possible between the tumor cells and the nearby micro environment. Thalidomide group of drugs can also activate Caspase 8 which can cause destruction of myeloma cells through Fas mediated pathway (Latif *et al*., 2012).

Multiple sclerosis is a common demyelinating condition of the central nervous system (CNS) which occurs throughout the globe. Various drugs have been used against this condition and only a few drugs including immunomodulatory agents have yielded good results. Glatiramer acetate is a chemical having structural similarity with the myelin basic protein and it is formed by alanine, lysine, glutamate and tyrosine amino acids arranged randomly. Mode of action of this chemical is by altering Th1 response to Th2 response during multiple sclerosis condition (Duda *et al*., 2000). Natalizumab is another chemical which is synthesized to α4 portion of the α4β1 integrin and its mechanism of action is preventing the migration of lymphocytes during inflammation along the Blood Brain Barrier (BBB) to the CNS (Steinman, 2005). Fingolimod is a drug intended for oral use acting on the sphingosine 1-phosphate (S1P) receptors preventing the movement of lymphocytes (Hanel *et al*., 2007). Teriflunomide, Laquinimod and Cladribine are the other drugs that can be used against multiple sclerosis owing to their immunomodulatory action (Nicholas *et al*., 2011).

Certain chemicals and drugs that are either naturally obtained or synthesized artificially have been found to have immunosuppressive property that are used in various conditions including organ transplantation (Georgakopoulou and Scully, 2013). Cyclosporin obtained from the fungus *Tolypocladium inflatum* has immunosuppressive properties which changed the course of transplantation biology. Mechanism of action is by inhibition of calcineurin which occur by binding of cyclosporin to immunophilin, an intracytoplasmic protein (Tedesco and Haragsim, 2012). Tacrolimus, a macrolide obtained from *Streptomyces tsukubaensis*, has similar mode of action to cyclosporin and has no antibiotic activities (Jacobson *et al*., 1998). Tacrolimus is more potent immunosuppressive agent compared to cyclosporin but the bioavailability is less, hence dosing of tacrolimus is 4 fold higher than cyclosporin (Hoorn *et al*., 2012). There are some adverse effects of these two drugs like hepatotoxicity, nephrotoxicity and hypertension, so patients need complete monitoring. Azathioprine is a purine derivative anti proliferative cytotoxic drug having action on purine synthesis thereby causing severe damage to the DNA (Saroj *et al*., 2012). Several steroid drugs are used to suppress immunity hence preventing graft rejection and Prednisolone is one such important drug (Saroj *et al*., 2012). Dapsone a well known drug used for the treatment of leprosy has immunomodulatory action and hence it is used for conditions like dermatitis herpetiformis (Cardones and Hall, 2012). Its mode of action is by inhibition of folic acid synthesis. Colchicine, an alkaloid derived from *Colchicum autumnaleit* blocks mitosis by binding tubulin in the microtubules (Molad, 2002). It is commonly used in auto immune disorders, gout, Behcet's disease and recurrent aphthous stomatitis (Brocklehurst *et al*., 2012). Cyclophosphamide is another agent which also has immunosuppressive action and used mostly in neoplastic conditions that are malignant in nature (Mukhtyar *et al*., 2009). An antiparasitic drug, Levamisole has been mostly studied for its immune stimulant properties. It has various potential immune stimulating properties and to name some; it activates macrophages and monocytes thereby increasing the phagocytosis in the body, T cells are activated, proliferated and also enhances antibody production to various antigens (Hegde *et al*., 2012). Levamisole can show its action in diseased as well as normal immune system hence it has both immune stimulant and immune regulatory actions. Its action on T cells is comparatively higher than on B cells. Levamisole has been used to stimulate immune cells in various cancers in human patients (Stevenson *et al*., 1991; Friis *et al*., 2005).

HERBAL PRODUCTS

Since long time, modulation of immune response to alleviate diseases using herbal medicines has been a form of therapy for livestock, particularly among the resource poor marginal farmers and in this aspect the traditional medicinal plants are especially important (Hasani-Ranjbar *et al*., 2012; Mahima *et al*., 2012a; Mirzaei-Aghsaghali, 2012; Tiwari *et al*., 2014a, b). In different parts of the world, plant extracts have been widely investigated for their possible immunomodulatory properties (Alamgir and Uddin, 2010). In Indian traditional medicine, several medicinal plants called 'Rasayanas' are known to increase the resistance of the body against a variety of infections and thus have attracted the attention of many scientists. Macrophages facilitating generation of an immune response are the main target of the immunomodulatory plant products. The activated macrophages cause increased phagocytosis and generate effector molecules like free radicals, nitric oxide and cytokines that facilitate intracellular killing of pathogens. These cytokines may have direct function or may affect the function of other immune cell population such as induction of natural killer cell mediated cytotoxicity or production of cytotoxic T lymphocytes. The plant derived immunomodulators have tremendous potential for generation of new pharmaceutical products (Tan and Vanitha, 2004; Chen *et al*., 2014; Mahima *et al*., 2013b). Extract of fresh ajoene (*Allium sativum*) protects CD8+cells from attack by HIV at low concentrations early in the viral life and has little toxicity with 45 times more powerful effect than dextran sulfate. *A. sativum* causes impairment of the activity of the liver enzymes (that process protease inhibitors) raising their level. *Allium sativum* extract (GE) has dose-dependent inhibitory effect on human cytomegalovirus (HCMV) *in vitro* (Guo *et al*., 1993).

Progress on the use of ethnomedicinal plants as immunomodulatory agents has been more pronounced recently as plant extracts have widely been explored during last few decades in various parts of the world for their possible immunomodulatory properties. Many studies have demonstrated the isolation of potential bioactive molecules which have been patented and have been tested as herbal formulations (Carrio *et al*., 2012). Sunila and Kuttan (2004) reported immunomodulatory and anti-tumour activity of *Piper longum* Linn and piperine. Botanicals like *C. versicolor* etc., are rich in glucans, having potent immunomodulatory action. Polysaccharides isolated from *Artemisia apiacea* can inhibit growth of hepatoma cells by stimulating apoptosis and immuno-defense (Chen *et al*., 2013). *Morinda citrifolia* (Noni) fruit juice contains a polysaccharide-rich substance which enhances the IFN-γ production from thymocytes. Noni (*M. citrifolia*) potentiates the immune system by activating the macrophages to secrete TNF-α, IFN-γ, IL-1β, IL-10, IL-12 and nitric oxide but it suppresses the release of IL-4. Hence, Noni reduces the tumour growth by potentiating the host immune system (Hirazumi and Furusawa, 1999). Noni juice potentiates the immune system by increasing the weight of the thymus resulting in protection from degenerative disease and aging (Pansuebchue *et al*., 2002). Feeding of Noni fruit juice to neonatal Holstein calves potentiates the immune system by increasing the expression of CD25 on $CD4^+$, $CD8^+$ and γδ T cells. Noni also increases the secretion of IL-1β, TNF-α and IFN-γ in bovine colostrums and results in enhancement of natural innate cell-mediated immunity (Brooks *et al*., 2009). The fermented Noni Exudate (fNE) treated dendritic cells cause immunoglobulin class switching to produce IgG and IgM, proliferation of splenocytes and B cells and promotes their differentiation (Zhang *et al*., 2009). The extract of *M. citrifolia* fruits enhances the activity of T and B lymphocytes which potentiates the both arms of the adaptive immune system such as humoral and cell mediated responses (Nayak and Mengi, 2010). Aqueous extracts of *Withania somnifera* show potent immunomodulatory properties (AbdEIslam *et al*., 2013). Mostly secondary metabolites of plants exert beneficial immunomodulatory effects many of which have been widely studied in mouse as well as chicken and human cell lines. Ginseng and steroidal saponin present in it, for instance, has immune-stimulating properties that include; Cytokine production (IL-2, IL-6,TNF-α and IFN-α); macrophage activation and lymphocyte stimulation (Lee *et al*., 2007b). Flavonoids and terpenes from *Ginko biloba* (Ginseng) conversely can mediate production of inflammatory cytokines. For stimulating cell-mediated immunity and to enhance antibody production, saponins are useful and can induce production of cytokines viz., interleukins and interferons. Meyer saponins and Quillaja saponins; butanol extract of *Lonicera japonica* and de-acetylated saponin-1 can be administered to the nasal mucosa to stimulate the immune response *in vivo*. Considerable improvement in antibody titre is caused by herbal plant polysaccharides obtained from four Chinese herbs viz., roots of *Astragalus*, *Isatis* and *Achyranthes*; and Chinese Yam (Hashemi and Davoodi, 2012; Chakraborty and Pal, 2012). Aquous extract of *C. nuda* (an edible mushroom) induces dendritic cell maturation through TLR-4 and/or TLR-2 suggesting its role in cancer vaccine immunotherapy (Chen *et al*., 2014). *Eupatorium adenophorum* polysaccharide increases the production of IL-6, TNF-α and IFN-γ suggesting its immunomodulatory properties for prophylaxis of H5N1 influenza infection (Jin *et al*., 2013). Naringenin and flavones are certain flavonoids which are found to be effective against filarial worms like *Brugia malayi* (Lakshmi *et al*., 2010). *Nigella sativa* has anti inflammatory effects and its active principle thymoquinone limits production of 5-lipooxygenase and 5-hydroxyeicosatetraenoic acid (Hajhashemi *et al*., 2004; Elkamel and Mosaad, 2012). Herbs have been found useful in amelioration of the immunosuppressive effects of chicken infectious anaemia virus in poultry (Bhatt *et al*., 2013). Various herbal products which can be used as immunomodulators and herbal preparations containing them are depicted in Table 9 and 10.

Table 9: Herbal products and their immunomodulatory activities

Plant	Immunomodulatory action	Clinical application	References
Acorus calamus	Ethanolic extract inhibits proliferation of phytohaemagglutinin and purified protein derivative stimulated human peripheral blood mononuclear cells (PBMCs), inhibition of growth of several cell lines of mouse and human origin, inhibition of production of nitric oxide (NO), IL-2 and TNF-a, down-regulates CD25 expression.	Immunosuppressant	Mehrotra *et al*. (2003)
Azadiracta indica (Neem)	Stimulate phagocytic and antigen presenting ability of macrophages	Effective in allergic disorders, enhances DTH in psoriasis patients, possess anti-leprotic activity	Bhowmik *et al*. (2010)
Allium sativum	Augment NK cells, stimulates T cells and IL-2 production, boosts IL-10 and IL-4	Inhibit tumour development, useful in treating psoriasis	Clement *et al*. (2010)
Aloe vera	Carboxypeptidase and salicylate	Anti inflammatory effect Improves wound healing	Davis *et al*. (1994) Chithra *et al*. (1998)
	Acemannan	Enhance production of IL 1 and TNF a from macrophages; beneficial effect in anti-retroviral therapy	Saeed *et al*. (2003) and Awodele *et al*. (2012)
Ocimum sanctum (Tulsi) (Queen of plants % The mother medicine of nature)	Tulsi leaves are regarded as an 'adaptogen' or anti stress agent, inhibit tumour development in mice	Aqueous extract of *O. sanctum* showed immunotherapeutic potential in bovine sub clinical mastitis, enhances survival of viral encephalitis patients	Singh *et al*. (2010)
Emblica officinalis (Amla)	Fruit is considered as an adaptogenic that improves immunity, improve both cell mediated and humoral responses	Potent immune suppressant in arthritis; help to reduce inflammation and oedema	Alamgir and Uddin (2010)
Evolvulus alsinoides	Mild synovial hyperplasia, decrease in nitric oxide synthase activity of mononuclear Phagocytes and immunosuppression	Anti-inflammatory and immunosuppressant like corticosteroids	Ganju *et al*. (2003)

Table 9: Continue

Plant	Immunomodulatory action	Clinical application	References
Panax ginseng	Saponins and glycosides	Macrophage migration, antibody plaque forming cells; stimulate lymphocytes and cytokines	Cho *et al*. (2002) and Lee *et al*. (2007b)
Tinospora cordifolia	Increases the number of macrophages and its phagocytic activity, inhibits myelo suppression induced by cyclophosphamide	Hepatoprotectant, show anti neoplastic and anti tuberculosis activity	Aher and Wahi (2010)
Withania somnifera (Ashwagandha)	Anti-carcinogenic effects in animal and cell cultures by decreasing the expression of nuclear factor-kappaB, suppressing intercellular tumor necrosis factor and potentiating apoptotic signalling in cancerous cell lines	Adaptogen or vitalizer	Ichikawa *et al*. (2006)

Table 10: Herbal preparation for immunomodulation

Name of preparation	Plants used	Clinical application
Immuplus	*Tinospora cordifolia*, *Ocimum sanctum*, *Emblica officinalis* and *Withnia somnifera*	It stimulates blastogenic capacity of B and T lymphocytes and increases antibody titre in dog, poultry and mice
ImmuplusR	*Tinospora cordifolia*, *Ocimum sanctum*, *Emblica officinalis* and *Withnia somnifera*	Similar to Immuplus but with a greater degree. Widely studied for having immunomodulatory activities in treating diseases of domestic animals and poultry
Immu-21	*Ocimum sanctum*, *Emblica officinalis*, *Withnia somnifera*	Increase phagocytic activity of peritoneal macrophages
Immusarc	*Withania somnifera* and *Embilica officinalis*	Helps to achieve optimum immune effectiveness
Septilin	*Balsamodendron mukul*, *Tinospora cordifolia*, *Rubia cordifolia*, *Glycyrrhiza glabra* and *Emblica officinalis*	Stimulates phagocytosis by macrophages, and polymorphonuclear cells. Also stimulates humoral immunity and antibody production

Essential oils from various herbal extracts possess the unique property to modulate immunity (Gopi *et al*., 2014). Carvacrol and thymol are the two main such extracts obtained from oregano and thyme. These oils in equal composition together have shown to protect pigs from pathogenic diseases (Walter and Bilkei, 2004). There was increase in CD4 and CD8 cells after giving these oils to the pigs which indicates its immune modulating potential. Thymol has anti inflammatory properties locally which are evident by the reduction of TNFα and it also increases the immunoglobulins like IgA and IgM (Trevisi *et al*., 2007). Cinnamon when extracted produces cinnamaldehyde which do have immune modulatory properties like other essential oils. *Echinacea purpurea* extract from plants of *Echinacea* shows to improve feed efficacy in animals (Maass *et al*., 2005). Immunity of animal was increased in pigs which were vaccinated against *Erysipelothrix rhusiopathiae* after administering extracts of *Echinacea purpurea*. Several Chinese herbs were also studied for their immune modulatory properties and one such *Astragalus membranaceus* showed to increase leucocyte count especially CD4 cells (Yuan *et al*., 2006). Soyabean extracts has two isoflavones namely genistein and daidzein have immune modulatory activities (Greiner *et al*., 2001). Auraptene extracted from a citrus fruit peel has property of enhancing macrophage and lymphocyte activities. Ethanolic extract of *Allium hirtifolium* Boiss has shown to reduce acquired immunity in a concentration dependent manner (Sharma *et al*., 2011). Extracts of *Randia dumetorum* Lamk increases both humoral and cell mediated immunity in mice model. Extract of *Cleome gynandra* Linn. has immune suppressive activity (Gaur *et al*., 2009). Apart from oils from herbs, fish oil with emulsion of lipids also has anti inflammatory properties (Hecker *et al*., 2014).

An illustration depicting an overview of immunomodulation, immune mechanisms and modes of action of various immunomodulatory agents is presented as Fig. 1.

ADJUVANTS

Adjuvant is a term derived from the Latin word Adjuvare, meaning to help or to aid or to enhance (Kumar *et al*., 2013) which was coined by Ramon (1926), who reported that horses that developed abscesses following injection of diphtheria toxoid produced higher antitoxin titers than animals without abscesses (Ramon, 1926). Jolles and Paraff (1973) defined adjuvants as any substances which act on a hapten or antigen enhancing its antigenic properties or which act on the cells involved in the immune response. Vaccine adjuvants are a group of structurally heterogeneous compounds that may stimulate or modulate the immune system thereby enhance specific immune responses against co-administered antigens without having any specific antigenic effect itself (Petrovsky and Aguilar, 2004; Singh and O'Hagan, 2003). Enhancing host defenses is a highly efficient approach to counteract infectious diseases either through vaccination as a means of prevention or therapeutically by the use of immunomodulators. Different vaccines currently in use are effective partly due to molecules that possess low immunogenicity by themselves but which may help to increase and modulate the immune response to an antigen which is

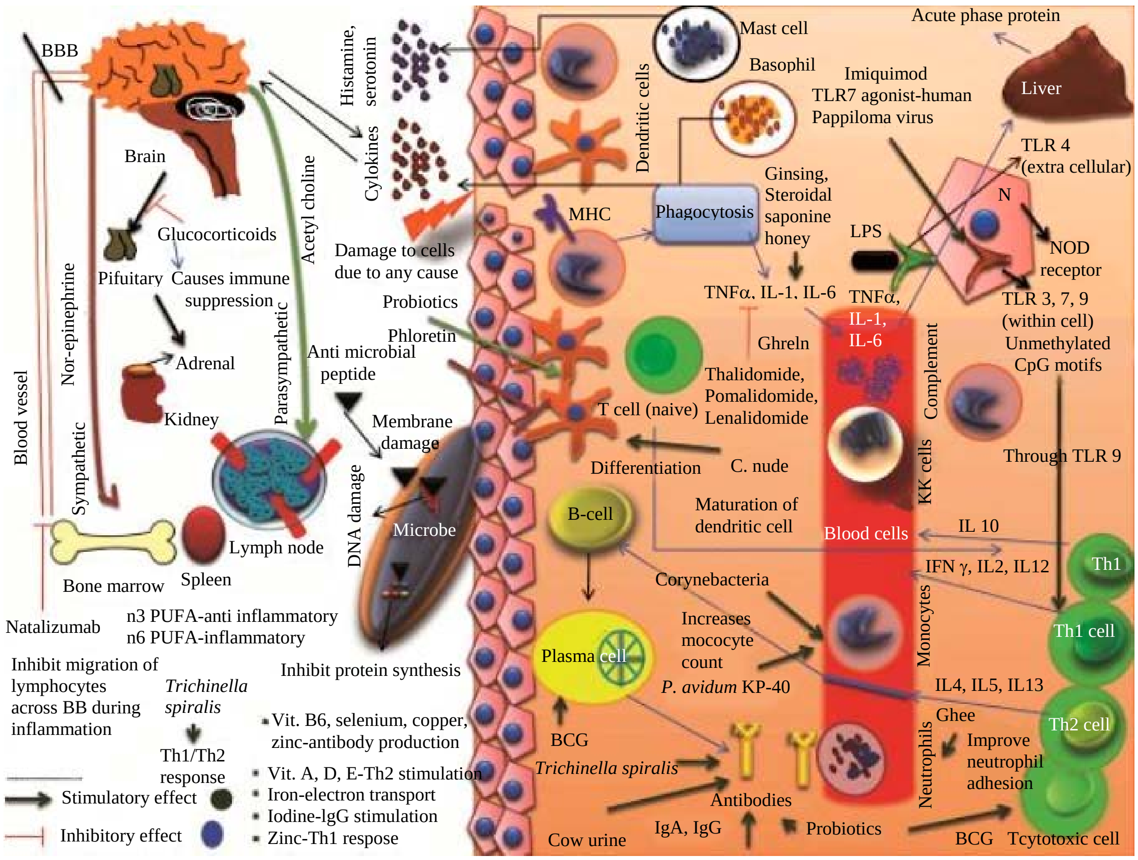

Fig. 1: An overview of immunomodulation and modes of action of various immunomodulatory agents

characteristic feature of adjuvants. There is a wide array of adjuvants that are being developed and used, from a variety of sources (Sun *et al.*, 2009). Despite a plethora of options, only aluminium salts have gained wide acceptance as human and veterinary vaccine adjuvants (Edelman, 2002). Adjuvants increase the humoral as well as T cell mediated immune responses by enhancing antigen presentation, activating dendritic cells, increasing the inflammatory cytokine production etc (McElhaney *et al.*, 2013).

The immunostimulatory property of aluminium salts is dendritic cell (DC)-dependent (Kool *et al.*, 2008a); whereas the T-cell response partially depends on Nalp3 inflammasome activation (Eisenbarth *et al.*, 2008). Nalp3 is an intracellular recognition receptor and is a member of the NOD-like receptor (NLRs) family. Nalp3 can recognize stimuli from microbial entry and origin and endogenous molecules produced during the cellular damage. Along with Apoptosis-associated Speck-like Protein (ASC) and caspase-1, it forms the inflammasome and controls the cleavage and secretion of the strong pro-inflammatory cytokines like interleukin (IL)-1b, IL-18 and IL-33 (Sutterwala *et al.*, 2006, 2007). Induction of Nalp3 inflammasome is done by alum thereby inducing the secretion of pro-inflammatory cytokines IL-1b and IL-18 leading to strong production of uric acid. Crystals of monosodium urate and aluminium containing adjuvants activate the differentiation and recruitment of inflammatory monocytes (F4/80^{int} CD11b+Ly6G^{-}Ly6C^{+}) that differentiate into inflammatory dendritic cells and induce CD4+T-cell activation and multiplication results in antibody secretion (Kool *et al.*, 2008b). Saponin-based adjuvants are obtained from the bark of the quillaja tree and possess immunomodulatory properties of activation of a balanced TH1/TH2 response with antibody (Maloy *et al.*, 1995) and cytotoxic CD8+lymphocytes production (Lipford *et al.*, 1994). Cationic liposome formulations (CAF) having positive surface charge with lipid bilayer vesicles cannot be adequately immunostimulatory thus can be administered along with immunostimulators viz., α, α-trehalose 6, 6'-dibehenate (TDB). TDB (adjuvant CAF01) is a synthetic mycobacterial cord factor analogue and act as a stabilizing agent on liposomes and prevents precipitation and aggregation in suspension (Agger *et al.*, 2008). It also has potential adjuvant action in animal model in tuberculosis (TB) vaccine. The CAF01 adjuvant is considered to be safe and possesses short immunogenicity in Phase I studies. The experimental studies showed that the CAF01 adjuvanted TB vaccine enhances depot formation and prolonging antigen release while targeting the antigens and immunomodulator to the same activated antigen presenting cells (APCs) (Kamath *et al*., 2009). Along with efficient polyfunctional memory T cells both humoral and cellular immune responses are stimulated by such preparation (Lindenstrom *et al*., 2009). In order to obtain well-defined non-toxic adjuvants and antigens which can be used for human vaccination and immunostimulation, efforts have been made for several years. One of the most studied family of compounds is Muramyl dipeptide (MDP) (synthetic adjuvant) that has got other pharmacological properties viz., pyrogenic and somnogenic activities. Several hundreds of MDP derivatives have been synthetized and some of the biological activities have been dissociated. One MDP derivative presently under clinical trials has been shown to be active adjuvant but devoid of pyrogenicity (Leclerc and Vogel, 1985).

A widely used vector is adenovirus serotype (Ad) 5 as an adjuvant and has been investigated for the potential to deliver human immunodeficiency virus (HIV-1) gene products and stimulating HIV-specific immune responses in human clinical trials (Cheng *et al*., 2010). In some instances, vector immunity can lead to reduction in CD4 and CD8 immunity and decrease in vaccine efficacy. To avoid pre-existing immunity due to Ad5 vaccination, diverse vaccination strategies are used such as prime-boost approaches and increased vaccine doses. An encouraging approach is the use of replication-defective recombinant lymphocytic choriomeningitis virus (rLCMV) vectors wherein vaccine gene replaces the LCMV glycoprotein gene to generate replication-defective vaccine vectors. For producing tetramer specific CD8+T-cells response in mice rLCMV is 1000-fold more potent than rAd5 (Flatz *et al*., 2010).

F3, a high molecular weight polysaccharide extract of *Ganoderma lucidum,* has been comprehensively analysed for adjuvant and immunomodulatory activities both *in vitro* and *in vivo* studies. F3-treated mice have shown more number of dendritic cells and other cells of the immune system during *in vivo* experiments. These cells viz., CD4+ and CD8+ cells, regulatory lymphocytes and plasma cells, NK and NKT cells elevate the quantity of multiple chemokines and cytokines in the spleen and blood of mice. F3, in addition, possesses strong adjuvant activity in tetanus toxoid in the lack of alum and enhances antibody responses to alum-formulated tetanus toxoid in mice and boost Th1 and Th2 response. F3 *in vitro* can induce dendritic cell maturation derived from human monocytes by up regulating CD40, CD54, CD80, CD83, CD86 and HLA-DR; enhance mixed lymphocyte reaction and stimulate cytokine and chemokine production (Lai *et al*., 2010). Appreciable success has been possible by using many peptide antigen based formulations. Nowadays peptide-based vaccines are arising as the next generation of prophylactic and corrective immunotherapy. But the major disadvantage is that peptide-based vaccines are poorly immunogenic and require strong immunostimulatory adjuvants which can make active both innate and adaptive immune systems. Studies have thus been conducted to create ideal peptide antigen delivery systems by incorporating multiple pattern-recognition receptor (PRR) agonists. Nowadays peptide antigen delivery systems are designed to stimulate Toll-like receptors (TLRs) on dendritic cells (DCs) and evaluation of the profiles of various cytokines (viz., IL-4, IL-6, IL-10, IL-12, IL-23 etc. of DCs) induced by individual TLR agonists. TLR agonists are commonly used as immunostimulatory agents, for example imiquimod an agonist of TLR 7 is approved for use against Human pappiloma virus topically (Romagne, 2007; Kanzler *et al*., 2007; Malik *et al*., 2013). In predicting the influence of specific TLR agonists on a particular T helper cell (Th) response such studies are helpful (Mitchell *et al*., 2011). Innate immunity also known as non-specific or semi specific immunity because it differentiates self from microbes through toll-like receptors (TLRs) which are evolutionarily conserved receptors. Recent research evidences have shown that TLRs can act as adjuvant receptors that act as bridge between innate and adaptive immunity, resulting in stimulation of adaptive immunity (Mutwiri *et al*., 2007; Akira, 2011). TLR 7 agaonist Imiquimod, has been approved by FAO for use against Herpes sarcoma virus-2 (HSV-2) (Prins *et al*., 2006). Similarly LPS which act against agonist of TLR 4 are also used against glioblastoma multiforme tumours in mice models (Chicoine *et al*., 2007; Deng *et al*., 2014). TLR 9 agonist has been used in mice models against brain tumours which resulted in apoptosis of glioblastoma cell (El Andaloussi *et al*., 2006; Rookhuizen, 2012). Stils (2005) described adjuvants and antibody production that has dispelled the myths in relation to Freund's complete as well as other adjuvants. Conjugation of monophosphoryl lipid A and oligodeoxynucleotides to nanolipoprotein significantly increased/activated the production of cytokine, cell surface expression of activation markers and upregulation of immunoregulatory genes (Weilhammer *et al*., 2013). Curdlan sulfates i.e., synthetic product of curdlan with sulfur trioxide-pyridine complex was found effective in increasing the Nitric Oxide (NO) release and the cytokines TNF-α, IL-6 and IL-1β production by macrophages in mice model and can be developed as a new immunotherapy agent and anti-viral vaccine adjuvant (Li *et al*., 2014). Recently, high mobility group box 1 (HMGB1) protein has been found to act as a novel immunoadjuvant generating highly protective immune responses during DNA vaccine trial of chicken infectious anemia virus in poultry. The most common adjuvants which are used for veterinary vaccine production are depicted in Table 11.

Role of adjuvants in immunomodulation/ veterinary vaccine development: Adjuvants enhance the host immune response against vaccine antigens in many different mechanisms as mentioned below:

- Enhance the immunogenicity of weak antigens
- Increase the duration and speed of the immune response

Table 11: Adjuvants for veterinary vaccine production

Vaccine	Strain	Adjuvant
Raksha ovac	FMD (O, A, C and Asia 1)	Mineral oil
Raksha biovac	FMD (O, A and Asia 1)+HS	Double emulsion oil adjuvant (Mineral oil)
Raksha monovalent	FMD O strain	Aluminium hydroxide and saponin
Raksha bivalent	FMD (O and A)	Aluminium hydroxide and saponin
HS vaccine	Inactivated *Pasteurella multocida* organism	Aluminium hydroxide
Raksha HS+BQ vaccine	Inactivated culture of *Pasteurella multocida* and *Clostridium chauvoei*	Aluminium hydroxide
ET vaccine	Clostridium perfringens type D and Epsilon toxoid	Aluminium hydroxide
Botulinum vaccine	Toxoid of *Clostridium* type C and D	Aluminium hydroxide
Raksharab	Inactivated rabies virus	Aluminium hydroxide
Botuthrax	Inactivated alum precipitated toxoids of *Clostridium botulinum* types C and D	Aluminium hydroxide
Rotavec corona	Inactivated bovine rotavirus, coronavirus and *E. coli* K99 antigens	Aluminium hydroxide and mineral oil
Equilis prequenza	Purified haemagglutinin/neuraminidase subunits from equine influenza viruses	Purified saponin
Pulpyvax	*Clostridium perfringens* type D toxoids	Aluminium hydroxide

- Modulate avidity as well as specificity and isotype or subclass distribution of antibodies
- Enhance strong Cell Mediated Immunity (CMI)
- Stimulates the mucosal immunity
- Augment immune responses in immunologically immature (newborn) or senescent and compromised individuals
- Reduce the antigen dose or the number of immunizations needed for protective immunity to reduce the vaccine costs
- Help to avoid antigen competition in combination vaccines
- Increase the overall antibody titer or functional titers
- Induce broader immune response (cross-protection) (Vogel and Hem, 2004)

Mode of action of adjuvants: The identification of adjuvants has largely been factual for decades but a series of new adjuvants and novel formulations are upcoming nowadays that can act through immunomodulatory mechanisms. They direct immune responses against disease causing organisms and enhance memory responses. It is thus beneficial for vaccine design and to build new model to assess adjuvant safety at regulatory level and at development stages (Mastelic *et al*., 2010). Adjuvants enhance the immune response by various mechanisms that include antigen presentation and targeting, "depot" effect, immunomodulation as well as cytotoxic lymphocyte induction (Cox and Coulter, 1997). "Depot" effect is a classical mechanism of action of adjuvant that helps the adjuvant to protect the antigen from rapid degradation and removal by the host due to slow release of intact antigen, thereby, permitting a prolonged and slow exposure of the cells of the immune system to a low level of antigen. Furthermore, adjuvants protect the antigen from proteolytic destruction by carrying the vaccinal antigens. Adjuvant can also preserve and maintain the conformational integrity of antigen and enables to present the antigen to professional antigen-presenting cells such as dendritic cells and macrophages (Stils, 2005; Leroux-Roels, 2010; Noe *et al*., 2010; De Gregorio *et al*., 2013). For designing vaccine, it is necessary to understand mechanism of action of adjuvant which helps in immune responses directly towards effector mechanisms which should be efficacious as well as disease-specific in nature and could provide appropriate memory (Mastelic *et al*., 2010).

Risk of adjuvants: From the past 70 years various kinds of adjuvants have been made but they were not used in routine vaccination programmes due to their immediate toxicity and delayed effects which include the following:

- Localized acute or chronic inflammation that may lead to painful abscess formation
- Formation of persistent ulcers, nodules and draining lymphadenopathy
- Fever with influenza like illness
- Anaphylaxis and immediate IgE type hypersensitivity against vaccine antigen
- Toxicity to organs and tissues due to chemicals of adjuvants
- Hypersensitivity reactions to host tissue that produces anterior uveitis, amyloidosis and autoimmune arthritis
- Cross reaction with host tissue antigens results in meningoencephalitis and glomerulonephritis in humans
- Oral tolerance and immune depression
- Carcinogenic potential
- Teratogenic potential

These adverse effects can be reduced by imparting regulatory control over use of adjuvant, developing relatively non-toxic synthetic immunoregulators and by standardizing safety and potency tests (Edelman, 2002).

NUTRIENTS

It is well known that nutrition plays a significant role in immunomodulation and malnutrition is the most common cause of immunodeficiency worldwide. Thus, for the proper functioning of the immune system, adequate supply of nutrients is must and both deficiencies and excesses of nutrients adversely affect the various components of the immune system. This is because of the fact that optimal functioning of immune system involves a variety of biological activities which include cell growth, energy metabolism, production of proteins and antioxidants (El-Gamal *et al*., 2011; Mahima *et al*., 2013a; Rahal *et al*., 2014a, b). Apart from normal nutrition, various proteins and peptides derived from hen's egg have biological properties like antimicrobial, antioxidant and immunomodulatory that regulate different functional systems of the body (Yu *et al*., 2014). Regarding the amino acids role for the oxygen dependant killing of microbes in the phagocytic cells, arginine (a direct precursor of nitric oxide and a effective killer) is important (Duff and Daly, 2002). Glutamine is essential for appropriate functioning of the lymphocytes and macrophages and induction of the immune system during the inflammation. It has also been reported that the utilization of glutamine by macrophages and lymphocytes during inflammation is high. Glutamine is also necessary for secretion of cytokines and antibodies as well as for the cell division (Calder and Field, 2002). In the pregnant animals both low and high protein: carbohydrate ratios in the diet had significant effect on the immune system of the offsprings (Tuchscherer *et al*., 2012).

Essential fatty acids in the food may enhance the immune system and maintains health (Pond, 2005). In the diet n-6 and n-3 are two major classes of polyunsaturated fatty acids (PUFA). Linoleic acid is precursor of n-6 and present in the vegetable oils, corn and soybean. In the plasma membrane of immune cells linoleic acid is converted into arachidonic acid. So, the n-6 PUFA is inflammatory in action which is opposite to n-3. These findings denote that diet more in n-3 PUFA reduces inflammation by enhancing the docosahexanoic acid and eicosapentanoic acid levels in the plasma membrane by inhibiting arachidonic acid (Mantzioris *et al*., 2000; Calder, 2001). n-3 PUFA reduces inflammatory and autoimmune disorders (Miles and Calder, 2012; Pae *et al*., 2012). Fatty acids and amino acids along with other secondary plant substances viz., carotenoids, flavonoids and spices inhibit the release of prestored mast cell mediators like histamine or de novo expression of mast cell mediators such as cytokines and eicosanoids thus can be used in prevention of allergic diseases (Hagenlocher and Lorentz, 2015). Micronutrient deficiency inhibits immune functions by affecting the innate and adaptive immunity which finally leads to dysregulation of the optimal host responses. This increases the susceptibility to various microbial infections, with increased morbidity and mortality (Wintergerst *et al*., 2007). The micronutrients which are important for immune function comprise of vitamins A, C, E and B_6, copper, folate, iron, selenium and zinc. Other nutrients such as beta-carotene which is precursor of vitamin A, vitamin B_{12} and vitamin D play a significant role in immune function. Generally, they contribute to the body's natural defenses on three levels by influencing physical barriers (skin/mucosa) and other innate immune cells, cell mediated immunity and humoral immunity. To enhance skin barrier function nutrients like vitamins A, C, E and the trace element zinc are essential. Vitamins A, C, D, E, B_6, B_{12}, folic acid and trace elements like copper, iron, selenium and zinc act synergistically to maintain the defensive activities of the immune cells. For antibody production all these micronutrients (except iron and vitamin C) are necessary. Copper, selenium, zinc and vitamin B_6, have significant role in B-cell proliferation and antibody production. Vitamins A, D and E potentiates Th2 response which leads to augmentation of humoral immunity and other micronutrients indirectly involved in protein synthesis and cell growth (Chandra, 2002; Maggini *et al*., 2007). In addition, several studies have shown that a four carbon short chain fatty acid, butyrate and its analog phenylbutyrate enhance disease resistance against shigellosis in humans and rabbits, respectively, by enhancing host defense peptide synthesis (Raqib *et al*., 2006; Sarker *et al*., 2011). Moreover, vitamin D and phenylbutyrate are effective in controlling *Mycobacterium tuberculosis* in human studies by enhancing host defense peptide, cathelicidin expression in macropahges (Mily *et al*., 2013). Furthermore, butyrate and other fatty acids enhance disease resistance of chicken against *Salmonella* Enteritidis by enhancing host defense peptide synthesis (Sunkara *et al*., 2011, 2012). Recently, short chain fatty acids have also shown their ability in enhancing host defense peptide synthesis in porcine intestinal epithelial cells and alveolar macrophages, suggesting the importance of fatty acids as immunostimulators both in human and animals (Zeng *et al*., 2013).

As a matter of fact, these micronutrients also act as antioxidants and cofactors in the cytokine production and regulation. Micronutrient deficiency and chronic under nutrition nevertheless can suppresses cytokine production and disturb immune cell trafficking and in association with infection further impairs the immune response. Malnutrition at an early age might have long-term effects on health and results in modified immune cell populations and a generalized production of more inflammatory mediators as the immune system is immature at birth. Zinc deficiency and protein calorie malnutrition stimulates the hypothalamic-pituitary-adrenal axis resulting in increased production of glucocorticoids. Increased levels of circulating glucocorticoids result in thymic atrophy which inturn affects hematopoiesis. Leptin is a potent cytokine-like immune regulator that exerts complex effects like inflammatory response in both malnutrition and over nutrition (Cunningham-Rundles *et al*., 2005). A water-soluble polysaccharide (JS-MP-1) obtained from Korean mulberry fruits Oddi (*Morus alba*) has immunomodulation property by stimulating macrophage to release chemokines and proinflammatory cytokines (TNF-α and IL-6), thus can be used as immunotherapeutic adjuvant (Lee *et al*., 2013). Phloretin, a natural dihydrochalcone found in many fruits has ability to suppress the activation and function of dendritic cells in mice thus may be useful in inflammatory and autoimmune disorders (Lin *et al*., 2014).

Vitamins and immune function: Vitamins are vital amines and have crucial role as nutrients. Apart from this, these play important role in regulation of the host immune defense and balancing the physiologic and pathologic conditions (Kunisawa and Kiyono, 2013). Vitamin A plays an important role in maintaining the integrity of mucosal surfaces in the respiratory and gastrointestinal tracts and in the regulation of innate and adaptive immune response (Villamor and Fawzi, 2005). Vitamin A and its metabolites like trans retinoic acid and retinol; retinal and retinoic acid play essential roles in both cellular and humoral immunity. They also enhance phagocytic activity and regulate immune homeostasis via the peripheral induction of regulatory T-cells. Further, they can control CD4 T-cell differentiation; mucosal immunity and immune tolerance and induces regulatory and inflammatory responses (Prabhala *et al*., 1991; DePaolo *et al*., 2011; Cassani *et al*., 2012). Vitamin A deficiency results in decreased phagocytic activity and diminished oxidative burst activity of activated macrophages during inflammation (Ramakrishnan *et al*., 2004) and a decreased number of natural killer (NK) cells and their activity (Dawson *et al*., 1999). Vitamin A deficiency strongly impairs the humoral immunity (Long and Santos, 1999) and provokes an inflammatory state in the body due to enhanced secretion of TNF-α and IL-12. But Vitamin A supplementation can restore these actions (Aukrust *et al*., 2000).

Vitamin D, especially 1,25-dihydroxycholecalciferol (1,25(OH) 2D3)) is biologically active and is considered to be an important immunoregulator besides its role in calcium metabolism. Most cells of the immune system like T lymphocytes and macrophages (except B cells) express vitamin D receptors in significant concentrations (Veldman *et al*., 2000; Mocanu *et al*., 2013). Vitamin D performs its immunomodulatory action by inhibiting excessive production of inflammatory cytokines and enhancing the oxidative burst activity of macrophages. Additionally, it also induces the secretion of potent anti-microbial peptides in most of the immune competent cells (Cannell *et al*., 2006). Deficiency of vitamin D leads to development of autoimmune diseases and other inflammatory diseases like multiple sclerosis (MS), chronic rhinitis, tonsillar hypertrophy due to increase in inflammatory substances (tumor necrosis factor alpha, IL-1 and prostaglandin D2) (McCarty *et al*., 2013; Mocanu *et al*., 2013). Vitamin D also has got significant effect on immune as well as neural cells (Fernandes de Abreu *et al*., 2009). It also plays an important anti-neoplastic role and is used for anticancer immunotherapy. Vitamin D binding protein (DBP) is an essential precursor for macrophage activation and is crucial for providing innate defense against cancer (Karbasi and Saburi, 2012; Vuolo *et al*., 2012).

Vitamin E has a strong lipid soluble antioxidant activity that scavenges free radicals and can enhance both the cell division and cytokine secretion from naive T cells but not by memory T cell. Vitamin E can also suppress a variety of inflammatory processes by blocking the activity of transcription factor NFkB which is essential for transcription of many proteins, especially pro-inflammatory cytokines. Vitamin E favors the immune response which is biased towards Th1 immunity (Meydani *et al*., 2005).

Leukocytes are enriched in Vitamin C which is a major water-soluble antioxidant in cells and plasma. Vitamin C performs its antioxidant activity by scavenging Reactive Oxygen Species (ROS) generated during the process of phagocytosis by activated immune cells (Puertollano *et al*., 2011). Supplementation of vitamin C results in enhancement of various components of immune response and therefore besides its metabolic functions, its significant role in immune homeostasis cannot be overlooked (Jacob *et al*., 1991; Hartel *et al*., 2004). Vitamin C is essential in order to safeguard the host cell from free radicals produced during the respiratory burst from phagocytes. Lack of sufficient quantity of this vitamin in diet results in altered phagocytosis and more free radical mediated injury to the host cells. After the administration of the ascorbic acid the condition changes as there are enhanced sensitivity of B cells to the mitogen as well as it is responsible for DTH and prevention of T cell apoptosis. An improvement in the immune function of juvenile cobia, *Rachycentron canadum* has been recorded after dietary supplementation of vitamin C (Hartel *et al*., 2007; Zhou *et al*., 2012). Vitamin C has also got significant impact as an immunomodulator in case of infection caused by *Pasteurella monodon* (Kanagu *et al*., 2010).

Induction of vitamin B complex deficiency in pregnant rats resulted in defect in the formation of lymphoid organs especially thymus and spleen in their progeny. The study indicates a role of vitamin B in the development of these vital organs and thus on the level of circulating lymphocyte (Dhur *et al*., 1991). Further, vitamin B complex deficiency leads to reduced number of plasma cells; suppressed lymphocyte proliferation and diminished CT cell activity etc., resulting in lowered DTH response (Fawzi *et al*., 1999; Liu *et al*., 2011b). Vitamin B_6 is essentially required as a cofactor in the biosynthesis of nucleic acids and proteins and hence its role in immune function can be appreciated, since most of the immune key performers like antibodies and cytokines built up from these biomolecules (Leklem, 2001). The deficiency of vitamin B_6 favors the Th2 mediated immunity (Long and Santos, 1999) and thus affects cellular immunity. Deficiency of biotinase may lead to cellular immunity abnormalities in mice (Pindolia *et al*., 2014). Similar to Vitamin B_6, folate also plays a significant role in protein and nucleic acid synthesis and therefore folate deficiency significantly impairs the immune response. Folate deficiency also alters immune competence and protection against microbes and impairs cell-mediated immunity by decreasing the proportion of circulating T lymphocytes and their multiplication in response to mitogen activation (Dhur *et al*., 1991). Folate, moreover, increases biochemical constituents and enhances total IgG generation; in poultry it exhibits pleiotropic effects in inflammatory responses (Munyaka *et al*., 2012). In *Helicobacter*-associated gastric cancer in mice, folic acid supplementation can be chemo-preventive as it prevents global loss of methylation and suppresses inflammation (Gonda *et al*., 2012). Vitamin B_{12} may have an immunomodulatory influence on cellular immunity (Tamura *et al*., 1999). Vitamin B_{12} deficiency may influence the purine and thymidine synthesis and ultimately RNA and DNA synthesis that may lead to alterations in immunological secretions (Bailey and Gregory, 2006).

Trace elements and immune function: Essentially trace elements are nutrients which are required in small quantities for supporting an organism's cellular functions (McClung and Peterson, 2010). The immune system is a sensitive indicator of the nutritional state with regard to trace elements (Girish, 2011). The list of micronutrients that have significant influence on immune function is ever increasing. It essentially includes zinc, copper, iron, selenium etc. Deficiency of the trace elements would increase one's susceptibility to various infections (Goswami *et al*., 2005).

Selenium is crucial for maximal immune response and modulates both arms of immunity as it is a potent nutritional antioxidant. Selenium is required as a trace mineral even in individuals who are not suffering from overt deficiency of the mineral (Moeini *et al*., 2011; Zhang *et al*., 2012; Safaralizadeh *et al*., 2013). It carries out biological effects through Selenium-dependent enzyme or selenoproteins (Hoffmann and Berry, 2008) and glutathione peroxidase (Chaudhary *et al*., 2010). It further protects cellular membranes and organelles from peroxidative damage (Mahima *et al*., 2012b) and oxidative stress generated by the microbial effect of macrophages that could contribute to its anti-inflammatory effects (Huang *et al*., 2012). It plays an important role in balancing the redox state and help to protect the host from oxidative stress through glutathione peroxidases. The thioredoxin reductase which is a selenoenzyme, impairs the redox regulation of various key enzymes, transcription receptors and factors, including glucocorticoid receptors, ribonucleotide reductase, nuclear factor-kappa B (NFκB) and anti-inflammatory protein AP-1 which binds to DNA and potentiates the expression of genes responsible for coding of proteins involved in immune response such as cytokines and adhesion molecules (Wintergerst *et al*., 2007; Arthur *et al*., 2003; Ryan-Harshman and Aldoori, 2005). Selenium in addition also promotes TR1 expression and enhances antioxidative capacity in porcine splenocytes causing TCR or ConA-induced T-cell activation enhancement (Ren *et al*., 2012). Deficiency of Selenium causes poor development of immune organs due to oxidative stress (Zhang *et al*., 2012). It ultimately influences the innate and non-adaptive; acquired and adaptive immune responses (Beckett *et al*., 2003; Carlson *et al*., 2010).

Zinc is a trace mineral that is required as a cofactor for the activities of more than 300 enzymes besides its involvement in various metabolic processes (Cuevas and Koyanagi, 2005). Zinc is crucial for highly multiplying cells of the immune system and potentiates both arms of the immunity. Its superoxide dismutase activity results in protective action against oxidative stress and it is a crucial cofactor for thymulin production which regulates cytokine secretion and enhances proliferation. Sufficient amount of zinc intake favors the Th1 type immunity and enables to manage skin and mucosal membrane integrity (Wintergerst *et al*., 2006; Prasad, 2000; Fraker and King, 2004; Haase and Rink, 2009).

Copper plays a significant role in the formation and maintenance of the immune system and a very small quantity of it is required for individual's well being (Josko, 2011). Catalase and glutathione peroxidase are important cytosolic antioxidant agents and have synergistic defense activity against ROS. Copper is necessary for the dismutation of superoxide anion into H_2O_2 and oxygen. Moreover, it minimizes damage to lipids as well as proteins and DNA. Both deficiency and chronic excessive intakes of copper can alter various components of the immune response (Minatel and Carfagnini, 2000; Bonham *et al*., 2002; Klotz *et al*., 2003). Copper deficiency leads to decrease in thymus weight and ceruloplasmin activity; T-helper cells and immunoglobulins; responsiveness of lymphocytes to mitogens (T and B-cell mitogens); antibody response with increased susceptibility to infection and cytokine production (Solaiman *et al*., 2007). Natural Killer (NK) cells and antimicrobial activity of phagocytes are also decreased in copper deficiency (Klurfeld, 1993).

Iron plays a crucial role in gene regulation and electron transfer reactions and is an important component of nitric oxide and peroxide producing enzymes. Iron is also important in the control of cytokine production. It activates protein kinase C which is necessary for phosphorylation of factors responsible for regulating cell proliferation. Furthermore, iron is essential for myeloperoxidase activity which is responsible for the killing of bacteria by neutrophils via the generation of highly toxic hydroxyl radicals (Food and Nutrition Board, 2001; Weiss, 2004). Any disturbance in the homeostasis of cellular iron such as either deficiency or excess has detrimental effects on the immune system. Because pathogens need iron and other micronutrients for their replication and survival, it is essential to prevent the access of iron to the infecting microorganism. It is also necessary to maintain an appropriate concentration of iron so that the host can maintain optimal immune response and avoid the overload of iron which may cause free radical mediated injury to the host cells (Openheimer, 2001; Schaible and Kaufmann, 2004; Weiss, 2002). Iron deficiency leads to anemia making individuals susceptible to infection. Iron deficiency also causes lymphopenia due to decrease in IgM-positive lymphocyte counts (in piglets); impairment or delay in the development of cell mediated immunity; decrease in myeloperoxidase and phagocytic activity of neutrophils. Eosinophil counts and immunoglobulin concentration become low; there may be delay in cutaneous hypersensitivity and Natural Killer (NK) cell activity (Svoboda *et al*., 2007; Nairz *et al*., 2010; Cherayil, 2011).

Iodine acts with the myeloperoxidase *in vitro* in the phagocytic cells to destroy the bacteria; increases production of IgG by the humans B lymphocytes. Iodine has antioxidant activity in stomach, breast and thyroid and immunodeficiency results in increased risk for cancers (Venturi *et al*., 2000). Overload of iodine is responsible for hypo or hyperthyroidism characterized by impairment of natural killer cell activity (Wenzel *et al*., 1998). Iodine acts as an inducing factor in autoimmunity of thyroid gland as with the increase in iodine concentration in rats, the antigen presentation activity of macrophages is increased (Zhao *et al*., 2008).

Polysaccharides: Polysaccharides and oligosaccharides from various plants mimic pathogen associated molecular patterns

(PAMPs) and bind to Toll Like Receptor (TLR) so these modulates immunity. TLRs are thus gaining importance as targets to modulate immunity (Liu *et al*., 2011a). Polysaccharides namely β-D-glucans and α-D-mannans are the two components found in the cell wall of yeast. Yeast extracts are mostly used in poultry and swine industry as growth promoters. These two polysaccharides act on macrophages and other immune cells thereby modulating the immunity of these animals (Tzianabos, 2000). Other polysaccharides from different sources can also have similar immunomodulatory functions. Anti inflammatory properties are possessed by one of the polysaccharide component present in the yeast which is β-D-glucan. Yeast fed to pigs and challenged with lipopolysaccharide (LPS) of bacterial origin has shown that β-D-glucans has reduced the production of pro inflammatory cytokines and increased the production of anti inflammatory cytokines (Li *et al*., 2005, 2006). Due to the reduction in proinflammatory cytokines like IL 1, IL 6 and Tumor necrosis factor α (TNF α) it controls the release of acute phase proteins (Baumann and Gauldie, 1994). β-glucans can bind with many receptors of the immune system which include scavenging receptors, complement receptor 3, TLR 4 and also TLR 7 (Tsoni and Brown, 2008). β-glucans from *Candida albicans* when administered to laboratory animal model showed increase in neutrophils, macrophages, eosinophils and CD80+ and CD86+ activated leukocytes in the alveolar tissues (Suzuki *et al*., 2001). Studies in pigs with β-glucans showed that there is reduction in the heptaglobulin content of blood which usually increases post weaning in piglets. There is increase of both pro-and anti-inflammatory response in pigs that are challenged with LPS after giving β-glucans (Eicher *et al*., 2006). These β-glucans also have different activity against different class of antibodies in a dose dependent manner. At higher concentration they suppress IgG class of antibodies and at lower concentration they increase IgA class antibody release. β-glucans at times act on different pathways in the cells like NF-kappa B pathway and this is dependent on the concentration of the glucan.

Another polysaccharide mannan has the fascinating property to adsorb the pathogens in the intestinal tract there by protecting the animals from infection (Sohn *et al*., 2000). Mannan fed through diet to animals has shown increased phagocytic activity of macrophages especially in the lamina propria of the intestine (Davis *et al*., 2004). Systemically there is a shift towards B cells than T cells after animals are fed with mannans (Davis *et al*., 2004). There is no alteration in the proliferation of blood lymphocytes in vitro after administrating mannan. Mannan from *C. albicans* possesses immune suppressive activities which are evident after administering this agent. Mannan of *C. albicans* also raises pro inflammatory cytokines like TNFα, IL 1 and IL 6 (Garner *et al*., 1990). This increase of pro inflammatory cytokines is in the control of the dose of the mannan being administered and this increase can be blocked by using antibodies specific to the mannan. This phenomenon also reflects the pathogenesis of *C. albicans* (Garner and Hudson, 1996). Similarly, mannan from *Cryptococcus neoformans* has immune suppressive action which is regulated by T suppressor cells (Blackstock and Casadevall, 1997).

HELMINTHS

During helminth infection, there would be a mutual interaction between the helminth and host immune system which favors survival of both the host and the parasite (Gause *et al*., 2013). In this process helminth can control the development of autoimmune disease in the host (Maizels *et al*., 2009; Ashour, 2013; Shor *et al*., 2013; Dalton *et al*., 2013; Osada *et al*., 2013). There has been an increased demand for the development of novel therapy for treating as well as preventing a range of debilitating and life threatening conditions. Identification of parasite mediated key pathways involved in regulation of immune system is helpful for further development of novel therapies (Zaccone and Cooke, 2013). Th2 events which are evoked by helminths have been found to improve Th1 mediated immune disorders (El-Malky *et al*., 2011). Nutman and Kumaraswami (2001) reported that during filarial infection there will be decreased multiplication of lymphocytes which leads to reduced secretion of IFN-γ and enhanced production of IL-4, IL-10 and antibody isotype IgG4. As Th2 cells secretes important cytokine IL-4 and anti-inflammatory cytokine IL-10, so an immune response is predominantly of Th2 type. Thus autoimmune diseases considered as Th1 mediated disease would not be able to flourish with helminth infection in the same host. Host Defense Peptides (HDPs) are produced by various helminth worms such as *Clonorchis*, *Fasciola*, *Opisthorcis*, *Paragonimus* and *Schistosoma* species have potential immunomodulating property through action of molecular mimicry resulting in anti-inflammatory effect against helminth diseases (Cotton *et al*., 2012). Infections of schistosomes and filariae have immunomodulatory capacity that is activated by different stages of life-cycle of parasites (Hubner *et al*., 2013). *Heligmosomoides polygyrus*, a gastrointestinal nematode prevents the decrease in pancreatic islet cells via Th2 polarization-independent mechanisms (Osada *et al*., 2013). Helminths exhibit the anti-inflammatory activities in various diseases like rheumatoid arthritis, type-1 diabetes, inflammatory bowel disease etc., through inhibition of IL-17 and IFN-γ secretion, promotion of IL-4, IL-10 and TGF-β production, induction of FoxP3(+) expression, CD4(+) T cell and generation of regulatory macrophages, dendritic cells and B cells (Shor *et al*., 2013). *Trichinella spiralis* can have the immunomodulatory activity through Th1/Th2 phenotype with predominance of Th2 response, macrophage activation, regulation of B cells (Ashour, 2013). By establishing the mechanism in which helminths regulate the immune response and inhibit autoimmune disease, it is feasible to formulate modern therapeutic options that may not need infection with live worms. To achieve this, molecules are prepared that mimic the activity of modulators derived from helminths to develop worm based drugs (Reddy, 2010).

Table 12: Vitamins and trace minerals as immunomodulator for livestock health

Vitamins and trace elements	Animal	Use	References
Vitamin E and selenium	Broiler chicken	Act as immunomodulator in afflotoxicosis	Mubarak *et al*. (2009)
Vitamin D_3	Turkey	Help in stress immunomodulation	Huff *et al*. (2009)
Vitamin C	Pigs	Act as growth enhancer in newborn pigs, immunomodulator after weaning	Eicher *et al*. (2006)
Vitamin A	Chicken	Increased innate immunity to enteric parasites	Dalloul *et al*. (2003)
Vitamin E	Chicken	Role in modulating mucosal immunity in chicken	Muir *et al*. (2002)
Vitamin C	Cattle	Increased neutrophils oxidative metabolism, neutrophils mediated, antibody dependent cellular cytotoxicity	Roth and Kaeberle (1985)
Folic acid	Poultry	Increased biochemical constituents, enhanced generation of total IgG, as well as exhibition of pleiotropic effects in inflammatory responses	Munyaka *et al*. (2012)
Selenium	Pigs	Increased humoral immune response	Blodgett *et al*. (1986)

Helminthic parasites also help to prevent allergies like asthma. *Ascaris suum* adult worm antigen and products of *Toxascaris leonina* prevents allergy during challenge studies (McSorley *et al*., 2012). *Litomosoides sigmodontis* and *Schistosoma mansoni* can prevent auto immune disorders (McSorley *et al*., 2013). *Trichuris suis* can be used in treatment of multiple sclerosis. Parasitic products suppress Th1 response while induce Th2 response thereby reduce inflammation (Fleming, 2011). Based on this concept various therapeutic trials have been conducted which are summarized in Table 12.

NON-SPECIFIC IMMUNOMODULATION BY VACCINES

Apart from all the above mentioned immunomodulators, researches have proved that vaccination of an individual against some infectious diseases could increase the host defense to counter other infectious agent. For example, tuberculosis and measles vaccine are linked with decrease in overall child mortality. The probable reason of this phenomenon might be the cross-reactivity of host immune system with some other infectious agent (Benn *et al*., 2013). Vaccination against vaccinia virus showed para-immune effects such as more than 40% reduction in adult mortality in low income countries (Aaby *et al*., 2006), whereas it reduces risk of asthma, malignant melanoma and infectious disease hospitalizations in high income countries (Pfahlberg *et al*., 2002; Sorup *et al*., 2011). The cancer vaccination or immunotherapy enhances the host body's immune system nonspecifically and provides innate resistance to cancer. This method of immunomodulation in cancer therapies offers specific cytotoxicity to cancer cells and negligible cytotoxicity to the rest of the cells of the body (Kuhn and Hanke, 1997). It has been found in recent years that certain vaccines (viz., sipuleucel-T against prostate cancer in advanced stage) that provides non-specific immunity against cancer have got approval in the market (Winter *et al*., 2011). One of the most commonly administered vaccines against tuberculosis (TB) is Bacille Calmette-Guerin (BCG). Apart from TB, it can also reduce overall mortality of children which is attributed to non-specific effects (Ritz *et al*., 2013). Vaccine against *Streptococcus pneumoniae* also provides non-specific immunity (Flasche *et al*., 2013). Protection against orthopox diseases can also be provided non-specifically by vaccinia based vaccines (Rice *et al*., 2014).

Monoclonal antibodies can also have immunomodulation. Muromonab-CD3, a monoclonal antibody targeted against CD 3, led to decrease of T lymphocyte population in the blood circulation, this helps to prevent graft rejection (Patil *et al*., 2012).

PANCHGAVYA (COW THERAPY)

Cow therapy or cowpathy is made up of five constituents derived from Indian Zebu cow (panchagavya), namely milk, curd, ghee, urine and dung extract. Panchagavya has significant role in Ayurveda system of medicine and it has been mentioned in ancient Indian literature that the panchagavya increases body's resistance and makes body refractory to infections (Dhama *et al*., 2005; Mathivanan *et al*., 2006a, b; Joseph and Sankarganesh, 2011; Mathivanan and Edwin, 2012). By enhancement of both cellular as well as humoral immune responses cowpathy upregulates the lymphocyte proliferation activity; secretion of cytokines and macrophage activity; decreases apoptosis of lymphocytes thereby helping them to survive and fight infection; acts as anti-aging factor by preventing formation of the free radicals and efficiently repairing the damaged DNA (Dhama *et al*., 2005). Ameliorative effect on certain viral diseases (e.g., New Castle disease in layer chicken) is an additional benefit of panchgavya (Sumithra *et al*., 2013). Recently, cow urine has been patented (U.S. Patents No. 6896907 and 6,410,059) for its medicinal properties especially fight against cancers and in controlling bacterial infection (Randhawa, 2010). Cow urine was found to potentiate the humoral and cell mediated immune response in mice, to increase B and T lymphocyte blastogenesis and to increase IgG and IgA antibody titers in mice. Based on these findings a preparation called Kamadhenu Ark was manufactured by Govigyan Anusandhan Kendra, Nagpur from the urine of Indian cows and was tested for its immunomodulatory properties in mice. There was an increase in T and B lymphocyte blastogenesis and IgG, IgM and IgA antibody titers in mice. The therapy also protected the DNA from oxidative damage, responsible for ageing, cancer etc. Cow ghee is traditionally believed to improve resistance of body to infections. It possesses immunostimulant activity that has been indicated by increase in neutrophil adhesion as well as haemagglutination (HA) titre and delayed type hypersensitivity (DTH) responses in rats (Fulzele *et al*., 2001).

Both Panchagavya and Ark can help to reduce multiplication of the viruses such as the one causing swine flu (Chauhan *et al*., 2001; Dhama *et al*., 2013b). Anticonvulsant as well as hypoglycemic effects are exerted by Cow Urine Concoction (CUC) and has been found to be useful against liver disorders as well as fever; inflammation and anemia (Dhama *et al*., 2013b). Gauloka Peya which translates as 'drink from the land of cow' is another beverage prepared by incorporation of distilled and sterile cow urine with water and traditional Indian herbs and medicinal plants viz., Brahmi and basil (1: 7 ratio) and thus has medicinal properties (Rahman, 2010; Kulkarni, 2009; Ganguly and Prasad, 2011).

CONCLUSION

Nowadays, in natural health industry, immunomodulators are becoming very popular due to realization of people about the significance of a healthy immune system in the preservation of health as well as prevention and recovery from diseases. The issue of helping the body to help itself by optimizing the immune system is of vital significance. In this context immunomodulation holds great value in veterinary and medical sciences and needs to be explored extensively for the development of compounds that can increase the immunity in rapid changing environmental scenario. An ideal immunomodulator is yet to be discovered, developed and validated. Depending upon the situation, an immunomodulator can be used either to stimulate the immunity or to suppress the immunity to help the individual patient to maintain homeostasis. Lots of invalidated natural compounds, claimed to possess immunostimulating effects, circulate in the market that may mislead many physicians about the action and use of these compounds. Many of them are put out by companies for mere financial gain, it is therefore essential for a physician to have a thorough knowledge of their effects and side effects and idea regarding the techniques involved in comparing them. In the context of the affected individual's immune response a good understanding of pathogenesis of microbes and the relative need for immune modulation and immune activation is required. This will be essential for the future use of adjunctive immunomodulators for infectious diseases. Moreover, it needs utmost care while testing the immunomodulatory properties of herbs or the materials from cow for their stability, effectiveness, duration of action and effect of temperature or moisture and pesticide and heavy metal residues present in them. Efforts should also be directed towards patenting effective plant products or preparations so that we can utilize our rich resources for the benefit of mankind and animal welfare. Due emphasis need to be given for exploring fully the mechanisms and modes of actions of potent and novel immunomodulatory molecules like cytokines, hormones, host defense peptides, TLRs, probiotics, nutrients, herbs, panchgavya, polysaccharides and others which would help in developing effective immunoadjuvants and prophylactics, boosting vaccinal and general immunity, enhancement of disease resistance ability and safeguarding health of humans and their companion animals from various diseases, disorders and stressful conditions. Strengthening of the field of immunomodulatory substances could equip the health industries with the powerful pharmaceuticals, biologicals and medicines for nurturing a healthier future in the era of one world, one health and one medicine concept.

ACKNOWLEDGMENT

All the authors of the manuscript thank and acknowledge their respective Universities and Institutes.

REFERENCES

Aaby, P., P. Gustafson, A. Roth, A. Rodrigues and M. Fernandes *et al*., 2006. Vaccinia scars associated with better survival for adults: An observational study from Guinea-Bissau. Vaccine, 24: 5718-5725.

AbdEIslam, N.M., S. Ahmad, R. Ullah, A. Bibi, I. Ahmad, M.S. Mostafa and J.A. Khader, 2013. Antibacterial assay of *Withania somnifera*. J. Pure Applied Microbiol., 7: 791-794.

Adorini, L., 2003. Cytokine-based immunointervention in the treatment of autoimmune diseases. Clin. Exp. Immunol., 132: 185-192.

Agarwal, S.S. and V.K. Singh, 1999. Immunomodulators: A review of studies on Indian medicinal plants and synthetic peptides. Part 1: Medicinal plants. Proc. Indian Natl. Sci. Acad. Part B: Biol. Sci., B65: 179-204.

Agger, E.M., I. Rosenkrands, J. Hansen, K. Brahimi and B.S. Vandahl *et al*., 2008. Cationic liposomes formulated with synthetic mycobacterial cordfactor (CAF01): A versatile adjuvant for vaccines with different immunological requirements. PloS ONE, Vol. 3. 10.1371/journal.pone.0003116

Aher, V.D. and A. Wahi, 2010. Pharmacological study of *Tinospora cordifolia* as an immunomodulator. Int. J. Curr. Pharmaceut. Res., 2: 52-54.

Akira, S., 2011. Innate immunity and adjuvants. Philos. Trans. R. Soc. Lond. B: Biol. Sci., 366: 2748-2755.

Alamgir, M. and S.J. Uddin, 2010. Recent Advances on the Ethnomedicinal Plants as Immunomodulatory Agents. In: Ethnomedicine: A Source of Complementary Therapeutics, Chattopadhyay, D. (Ed.). Research Signpost, Kerala, India, ISBN-13: 9788130803906, pp: 227-244.

Alluwaimi, A.M., 2004. The cytokines of bovine mammary gland: Prospects for diagnosis and therapy. Res. Vet. Sci., 77: 211-222.

Anderson, K.C., 2005. Lenalidomide and thalidomide: Mechanisms of action-similarities and differences. Semin. Hematol., 42: S3-S8.

Antachopoulos, C. and E. Roilides, 2005. Cytokines and fungal infections. Br. J. Haematol., 129: 583-596.

Armstrong-James, D., I.A. Teo, S. Shrivastava, M.A. Petrou, D. Taube, A. Dorling and S. Shaunak, 2010. Exogenous interferon-γ immunotherapy for invasive fungal infections in kidney transplant patients. Am. J. Transplantation, 10: 1796-1803.

Arthur, J.R., R.C. McKenzie and G.J. Beckett, 2003. Selenium in the immune system. J. Nutr., 133: 1457S-1459S.

Ashour, D.S., 2013. *Trichinella spiralis* immunomodulation: An interactive multifactorial process. Expert Rev. Clin. Immunol., 9: 669-675.

Asnis, G.M. and G.R. de la Garza, 2006. Interferon-induced depression in chronic hepatitis C: A review of its prevalence, risk factors, biology and treatment approaches. J. Clin. Gastroenterol., 40: 322-335.

Aukrust, P., F. Mueller, T. Ueland, A. Svardal, R. Berge and S.S. Froland, 2000. Decreased vitamin A levels in common variable immunodeficiency: Vitamin A supplementation *in vivo* enhances immunoglobulin production and downregulates inflammatory responses. Eur. J. Clin. Invest., 30: 252-259.

Awodele, O., S.O. Olayemi, T.A. Adeyemo, T.A. Sanya and D.C. Dolapo, 2012. Use of complementary medicine amongst patients on antiretroviral drugs in an HIV treatment centre in Lagos, Nigeria. Curr. Drug Saf., 7: 120-125.

Baggiolini, M., A. Walz and S.L. Kunkel, 1989. Neutrophil-activating peptide-1/interleukin 8, a novel cytokine that activates neutrophils. J. Clin. Invest., 84: 1045-1049.

Baidas, S.M., E.P. Winer, G.F. Fleming, L. Harris and J.M. Pluda *et al*., 2000. Phase II evaluation of thalidomide in patients with metastatic breast cancer. J. Clin. Oncol., 18: 2710-2717.

Bailey, L.B. and J.F. Gregory, 2006. Folate. In: Present Knowledge in Nutrition, Bowman, B.A. and R.M. Russel (Eds). 9th Edn., Chapter 22, ILSI Press, Washington, DC., pp: 278-301.

Balevi, T., U.S. Ucan, B. Cokun, V. Kurtolu and I.S. Cetingul, 2001. Effect of dietary probiotic on performance and humoral immune response in layer hens. Br. Poult. Sci., 42: 456-461.

Bangham, A.D. and R.W. Horne, 1964. Negative staining of phospholipids and their structural modification by Surface-active agents as observed in the electron microscope. J. Mol. Biol., 8: 660-668.

Barakat, B.A., M.S. Saber and N. Emad, 1981. Preliminary studies on the use of BCG immunopotentiating agent against Rift Valley Fever among sheep as in Egypt. Bull. Off. Int. Epizoot., 93: 1387-1393.

Baumann, H. and J. Gauldie, 1994. The acute phase response. Immunol. Today, 15: 74-80.

Becker, A.M., T.A. Janik, E.K. Smith, C.A. Sousa and B.A. Peters, 1989. *Propionibacterium acnes* immunotherapy in chronic recurrent canine pyoderma. An adjunct to antibiotic therapy. J. Vet. Internal Med., 3: 26-30.

Beckett, G.J., J.R. Arthur, S.M. Miller and R.C. McKenzie, 2003. Selenium, Immunity and Disease. In: Dietary Enhancement of Human Immune Function, Hughes, D.A., A. Bendich and G. Darlington (Eds.). Humana Press, Totowa, New Jersey.

Bedford, M., 2000. Removal of antibiotic growth promoters from poultry diets: Implications and strategies to minimise subsequent problems. World's Poult. Sci. J., 56: 347-365.

Behnsen, J., E. Deriu, M. Sassone-Corsi and M. Raffatellu, 2013. Probiotics: Properties, examples and specific applications. Cold Spring Harbor Perspect. Med., Vol. 3. 10.1101/cshperspect.a010074

Ben-Efraim, S., Y. Burstein, Y. Keisari, R. Ophir, M. Pecht and N. Trainin, 1999. Immunopotentiating and immunotherapeutic effects of thymic hormones and factors with special emphasis on thymic humoral factor THF-γ2. Crit. Rev. Immunol., 19: 261-284.

Benn, C.S., M.G. Netea, L.K. Selin and P. Aaby, 2013. A small jab-a big effect: Nonspecific immunomodulation by vaccines. Trends Immunol., 34: 431-439.

Benveniste, E.N., 1998. Cytokine actions in the central nervous system. Cytokine Growth Factor Rev., 9: 259-275.

Bessler, W.G., 1992. Synthetic lipopeptide immunomodulators derived from bacterial lipoprotein: Tools for the standardization of *in vitro* assays. Dev. Biol. Stand., 77: 49-56.

Bessler, W.G., P. Beck, U. Konetznick, M. Loleit and E. Sedelmeier *et al*., 1991. Biological activity of bacterial surface components. Immunogenicity and immunomodulatory properties of a bacterial extract from *Escherichia coli*. Arzneimittelforschung., 41: 274-279.

Beynon, A.L., M.R. Brown, R. Wright, M.I. Rees, I.M. Sheldon and J.S. Davies, 2013. Ghrelin inhibits LPS-induced release of IL-6 from mouse dopaminergic neurones. J. Neuroinflammation, Vol. 10. 10.1186/1742-2094-10-40

Bhatt, P., S.K. Shukla, M.Y. Wani, R. Tiwari and K. Dhama, 2013. Amelioration of chicken infectious anaemia virus induced immunosuppression by immunomodulator and haematinic supplementation in chicks. Veterinarski Arhiv, 83: 639-652.

Bhowmik, D., Chiranjib, J. Yadav, K.K. Tripathi and K.P.S. Kumar, 2010. Herbal remedies of *Azadirachta indica* and its medicinal application. J. Chem. Pharm. Res., 2: 62-72.

Billroth, T., 1865. Beobachtung-studien uber wundfieber und accidentelle wundkrankheiter. Arch. klin. Chir., 6: 372-399.

Blackstock, R. and A. Casadevall, 1997. Presentation of cryptococcal capsular polysaccharide (GXM) on activated antigen-presenting cells inhibits the T-suppressor response and enhances delayed-type hypersensitivity and survival. Immunology, 92: 334-339.

Blalock, J.E., 1989. A molecular basis for bidirectional communication between the immune and neuroendocrine systems. Physiol. Rev., 69: 1-32.

Blodgett, D.J., G.G. Schuring and E.T. Kornegay, 1986. Immunomodulation in weanling swine with dietary selenium. Am. J. Vet. Res., 47: 1517-1519.

Bohannon, J.K., A. Hernandez, P. Enkhbaatar, W.L. Adams and E.R. Sherwood, 2013. The immunobiology of Toll-like receptor 4 agonists: From endotoxin tolerance to immunoadjuvants. Shock, 40: 451-462.

Bommineni, Y.R., H. Dai, Y.X. Gong, J.L. Soulages and S.C. Fernando *et al.*, 2007. Fowlicidin-3 is an α-helical cationic host defense peptide with potent antibacterial and lipopolysaccharide-neutralizing activities. FEBS J., 274: 418-428.

Bommineni, Y.R., G.H. Pham, L.T. Sunkara, M. Achanta and G. Zhang, 2014. Immune regulatory activities of fowlicidin-1, a cathelicidin host defense peptide. Mol. Immunol., 59: 55-63.

Bonham, M., J.M. O'Connor, B.M. Hannigan and J.J. Strain, 2002. The immune system as a physiological indicator of marginal copper status? Br. J. Nutr., 87: 393-403.

Borsuk, O.S., N.V. Masnaya, E.Y. Sherstoboev, N.V. Isaykina, G.I. Kalinkina and D.V. Reihart, 2011. Effects of drugs of plant origin on the development of the immune response. Bull. Exp. Biol. Med., 151: 194-196.

Brocklehurst, P., M. Tickle, A.M. Glenny, M.A. Lewis and M.N. Pemberton *et al.*, 2012. Systemic interventions for recurrent aphthous stomatitis (mouth ulcers). Cochrane Database Syst. Rev. 10.1002/14651858.CD005411.pub2

Brooks, V.J., M. Schafer, P. Sharp, J. Xu and J. Cai *et al.*, 2009. Effects of *Morinda citrifolia* (noni) on $CD4^+$ and $CD8^+$ T-cell activation in neonatal calves. Prof. Anim. Scientist, 25: 262-265.

Buts, J.P., P. Bernasconi, J.P. Vaerman and C. Dive, 1990. Stimulation of secretory iga and secretory component of immunoglobulins in small intestine of rats treated with *Saccharomyces boulardi*. Dig. Dis. Sci., 35: 251-256.

Calder, P.C., 2001. Polyunsaturated fatty acids, inflammation and immunity. Lipids, 36: 1007-1024.

Calder, P.C. and C.J. Field, 2002. Fatty Acids, Inflammation and Immunity. In: Nutrition and Immune Function, Calder, P.C., C.J. Field and H.S. Gill (Eds.). 1st Edn., CAPI Publishing, New York, pp: 57-92.

Cannell, J.J., R. Vieth, J.C. Umhau, M.F. Holick and W.B. Grant *et al.*, 2006. Epidemic influenza and vitamin D. Epidemiol. Infect., 134: 1129-1140.

Cardones, A.R.G. and R.P. Hall, 2012. Management of dermatitis herpetiformis. Immunol. Allergy Clin. North Am., 32: 275-281.

Carlson, B.A., M.H. Yoo, R.K. Shrimali, R. Irons, V.N. Gladyshev, D.L. Hatfield and J.M. Park, 2010. Role of selenium-containing proteins in T-cell and macrophage function. Proc. Nutr. Soc., 69: 300-310.

Carrio, E., M. Rigat, T. Garnatje, M. Mayans, M. Parada and J. Valles, 2012. Plant ethnoveterinary practices in two pyrenean territories of Catalonia (Iberian Peninsula) and in two areas of the Balearic Islands and comparison with ethno-botanical uses in human medicine. Evidence-Based Complem. Altern. Med. 10.1155/2012/896295

Cassani, B., E.J. Villablanca, J. de Calisto, S. Wang and J.R. Mora, 2012. Vitamin A and immune regulation: Role of retinoic acid in gut-associated dendritic cell education, immune protection and tolerance. Mol. Aspects Med., 33: 63-76.

Chakraborty, S. and S.K. Pal, 2012. Plants for cattle health: A review of ethno-veterinary herbs in veterinary health care. Ann. Ayurvedic Med., 1: 144-152.

Chanan-Khan, A.A., A. Swaika, A. Paulus, S.K. Kumar and J.R. Mikhael *et al.*, 2013. Pomalidomide: The new immunomodulatory agent for the treatment of multiple myeloma. Blood Cancer J., Vol. 3. 10.1038/bcj.2013.38

Chandra, R.K., 2002. Nutrition and the immune system from birth to old age. Eur. J. Clin. Nutr., 56: S73-S76.

Chang, C.H., L.A. Cohn, A.E. DeClue, H. Liu and C.R. Reinero, 2013. Oral glucocorticoids diminish the efficacy of allergen-specific immunotherapy in experimental feline asthma. Vet. J., 197: 268-272.

Chaudhary, M., A.K. Garg, G.K. Mittal and V. Mudgal, 2010. Effect of organic selenium supplementation on growth, se uptake and nutrient utilization in guinea pigs. Biol. Trace Elem. Res., 133: 217-226.

Chauhan, R.S., 2010. Nutrition, immunity and livestock health. Indian Cow: Scient. Econ. J., 7: 2-13.

Chauhan, R.S., B.P. Singh and L.K. Singhal, 2001. Immunomodulation with kamdhenu ark in mice. J. Immunol. Immunopathol., 3: 74-77.

Chen, J., X. Wang and C. Liu, 2014. Anti-tumour effects of polysaccharides isolated from *Artemisia annua* L by inducing cell apoptosis and immunomodulatory anti-hepatoma effects of polysaccharides. Afr. J. Tradit. Complem. Altern. Med., 11: 15-22.

Chen, M.H., W.S. Li, Y.S. Lue, C.L. Chu and I. Pan *et al.*, 2013. Clitocybe nuda activates dendritic cells and acts as a DNA vaccine adjuvant. Evidence-Based Complem. Altern. Med. 10.1155/2013/761454

Cheng, C., J.G. Gall, M. Nason, C.R. King and R.A. Koup *et al.*, 2010. Differential specificity and immunogenicity of adenovirus type 5 neutralizing antibodies elicited by natural infection or immunization. J. Virol., 84: 630-638.

Cherayil, B.J., 2011. The role of iron in the immune response to bacterial infection. Immun. Res., 50: 1-9.

Chicoine, M.R., M. Zahner, E.K. Won, R.R. Kalra, T. Kitamura, A. Perry and R. Higashikubo, 2007. The *in vivo* antitumoral effects of lipopolysaccharide against glioblastoma multiforme are mediated in part by Toll-like receptor 4. Neurosurgery, 60: 372-380.

Chihara, G., Y. Maeda, J. Hamuro, T. Sasakia and F. Fukuoka, 1969. Inhibition of mouse sarcoma 180 by polysaccharides from *Lentinus edodes* (Berk.) sing. Nature, 222: 687-688.

Chithra, P., G.B. Sajithlal and G. Chandrakasan, 1998. Influence of *Aloe vera* on the glycosaminoglycans in the matrix of healing dermal wounds in rats. J. Ethnopharmacol., 59: 179-186.

Cho, J.Y., A.R. Kim, E.S. Yoo, K.U. Baik and M.H. Park, 2002. Ginsenosides from Panax ginseng differentially regulate lymphocyte proliferation. Planta Med., 68: 497-500.

Clement, F., S.N. Pramod and Y.P. Venkatesh, 2010. Identity of the immunomodulatory proteins from garlic (Allium sativum) with the major garlic lectins or agglutinins. Int. Immunopharmacol., 10: 316-324.

Coley, W.B., 1894. Treatment of inoperable malignant tumors with the toxines of erysipelas and the *Bacillus prodigiosus*. Am. J. Med. Sci., 108: 50-66.

Corcionivoschi, N., D. Drinceanu, I.M. Pop, D. Stack, L. Stef, C. Julean and B. Bourke, 2010. The effect of probiotics on animal health. Anim. Sci. Biotechnol., 43: 35-41.

Cotton, S., S. Donnelly, M.W. Robinson, J.P. Dalton and K. Thivierge, 2012. Defense peptides secreted by helminth pathogens: Antimicrobial and/or immunomodulator molecules? Front. Immunol., Vol. 3. 10.3389/fimmu.2012.00269

Cox, J.C. and A.R. Coulter, 1997. Adjuvants-a classification and review of their modes of action. Vaccine, 15: 248-256.

Cuevas, L.E. and A. Koyanagi, 2005. Zinc and infection: A review. Ann. Trop. Paediatr., 25: 149-160.

Cunningham-Rundles, S., D.F. McNeeley and A. Moon, 2005. Mechanisms of nutrient modulation of the immune response. J. Allergy Clin. Immunol., 115: 1119-1128.

Daley, M.J., P.A. Coyle, T.J. Williams, G. Furda, R. Dougherty and P.W. Hayes, 1991. *Staphylococcus aureus* mastitis: Pathogenesis and treatment with bovine interleukin-1 β and interleukin-2. J. Dairy Sci., 74: 4413-4424.

Dalloul, R.A., H.S. Lillehoj, T.A. Shellem and J.A. Doerr, 2003. Intestinal immunomodulation by vitamin a deficiency and *Lactobacillus*-based probiotic in *Eimeria acervulina*-infected broiler chickens. Avian Dis., 47: 1313-1320.

Dalloul, R.A., H.S. Lillehoj, N.M. Tamim, T.A. Shellem and J.A. Doerr, 2005. Induction of local protective immunity to *Eimeria acervulina* by a Lactobacillus-based probiotic. Comp. Immunol. Microbiol. Infect. Dis., 28: 351-361.

Dalton, J.P., M.W. Robinson, G. Mulcahy, S.M. O'Neill and S. Donnelly, 2013. Immunomodulatory molecules of *Fasciola hepatica*: Candidates for both vaccine and immunotherapeutic development. Vet. Parasitol., 195: 272-285.

Dan, G. and S.B. Lall, 1998. Neuroendocrine modulation of immune system. Indian J. Phamacol., 30: 129-140.

Datta, K. and L. Pirofski, 2006. Towards a vaccine for *Cryptococcus neoformans*: Principles and caveats. FEM Yeast Res., 6: 525-536.

Davis, R.H., J.J. Donato, G.M. Hartman and R.C. Haas, 1994. Anti-inflammatory and wound healing activity of a growth substance in *Aloe vera*. J. Am. Podiatr. Med. Assoc., 84: 77-81.

Davis, M.E., C.V. Maxwell, G.F. Erf, D.C. Brown and T.J. Wistuba, 2004. Dietary supplementation with phosphorylated mannans improves growth response and modulates immune function of weanling pigs. J. Anim. Sci., 82: 1882-1891.

Dawson, H.D., N.Q. Li, K.L. DeCicco, J.A. Nibert and A.C. Ross, 1999. Chronic marginal vitamin A status reduces natural killer cell number and function in aging Lewis rats. J. Nutr., 129: 1510-1517.

De Gregorio, E., E. Caproni and J.B. Ulmer, 2013. Vaccine adjuvants: Mode of action. Front. Immunol., Vol. 4. 10.3389/fimmu.2013.00214

DeBoer, D.J., S.S. Bondurant and A. Diesel, 2009. Gene expression analysis of canine peripheral blood mononuclear cells exposed to *Staphylococcus* phage lysates. Proceedings of the 12th Annual Congress of the ESVD-ECVD on Veterinary Dermatology, September 2009, Bled, Slovenia, pp: 135.

DePaolo, R.W., V. Abadie, F. Tang, H. Fehlner-Peach and J.A. Hall *et al*., 2011. Co-adjuvant effects of retinoic acid and IL-15 induce inflammatory immunity to dietary antigens. Nature, 471: 220-224.

Delsing, C.E., M.S. Gresnigt, J. Leentjens, F. Preijers and F.A. Frager *et al*., 2014. Interferon-gamma as adjunctive immunotherapy for invasive fungal infections: A case series. BMC Infect. Dis., Vol. 14. 10.1186/1471-2334-14-166

Deng, J., Y. Li, J. Zhang and Q. Yang, 2013. Co-administration of *Bacillus subtilis* RJGP16 and *Lactobacillus salivarius* B1 strongly enhances the intestinal mucosal immunity of piglets. Res. Vet. Sci., 94: 62-68.

Deng, S., S. Zhu, Y. Qiao, Y.J. Liu, W. Chen, G. Zhao and J. Chen, 2014. Recent advances in the role of toll-like receptors and TLR agonists in immunotherapy for human glioma. Protein Cell, 5: 899-911.

Dhama, K., R. Rathore, R.S. Chauhan and T. Simmi, 2005. Panchgavya: An overview. Int. J. Cow Sci., 1: 1-15.

Dhama, K., M. Mahendran, R.S. Chauhan and S. Tomar, 2008a. Cytokines-Their functional roles and prospective applications in Veterinary practice: A review. J. Immunol. Immunopathol., 10: 79-89.

Dhama, K., M. Mahendran, S. Tomar and R.S. Chauhan, 2008b. Beneficial effects of probiotics and prebiotics in livestock and poultry: The current perspectives. Intas Polivet, 9: 1-12.

Dhama, K., V. Verma, P.M. Sawant, R. Tiwari, R.K. Vaid and R.S. Chauhan, 2011. Applications of probiotics in poultry: Enhancing immunity and beneficial effects on production performances and health: A review. J. Immunol. Immunopathol., 13: 1-19.

Dhama, K., S. Chakraborty and R. Tiwari, 2013a. Panchgavya therapy (Cowpathy) in safeguarding health of animals and humans: A review. Res. Opin. Anim. Vet. Sci., 3: 170-178.

Dhama, K., S. Chakraborty, M.Y. Wani, R. Tiwari and R. Barathidasan, 2013b. Cytokine therapy for combating animal and human diseases: A review. Res. Opin. Anim. Vet. Sci., 3: 195-208.

Dhama, K., S. Chakraborty, Mahima, M.Y. Wani and A.K. Verma *et al*., 2013c. Novel and emerging therapies safeguarding health of humans and their companion animals: A review. Pak. J. Biol. Sci., 16: 101-111.

Dhama, K., S. Chakraborty, S. Kapoor, R. Tiwari and A. Kumar *et al*., 2013d. One world, one health-veterinary perspectives. Adv. Anim. Vet. Sci., 1: 5-13.

Dhama, K., S. Chakraborty, R. Tiwari, A.K. Verma and M. Saminathan *et al*., 2014. A concept paper on novel technologies boosting production and safeguarding health of humans and animals. Res. Opin. Anim. Vet. Sci., 4: 353-370.

Dhur, A., P. Galan and S. Hercberg, 1991. Folate status and the immune system. Prog. Food Nutr. Sci., 15: 43-60.

DiLuzio, N.R. and S.J. Riggi, 1970. The effects of laminarin, sulfated glucans and oligosaccharides of glucan on reticuloendothelial activity. J. Reticuloendothel. Soc., 8: 465-473.

Dongarra, M.L., V. Rizzello, L. Muccio, W. Fries, A. Cascio, I. Bonaccorsi and G. Ferlazzo, 2013. Mucosal immunology and probiotics. Curr. Allergy Asthma Rep., 13: 19-26.

Duda, P.W., M.C. Schmied, S.L. Cook, J.I. Krieger and D.A. Hafler, 2000. Glatiramer acetate (Copaxone®) induces degenerate, Th2-polarized immune responses in patients with multiple sclerosis. J. Clin. Invest., 105: 967-976.

Duff, M.D. and J.M. Daly, 2002. Arginine and Immune Function. In: Nutrition and Immune Function, Calder, P.C., C.J. Field and H.S. Gill (Eds.). 1st Edn. CAPI Publishing, New York, USA., pp: 93-108.

Easton, D.M., A. Nijnik, M.L. Mayer and R.E. Hancock, 2009. Potential of immunomodulatory host defense peptides as novel anti-infectives. Trends Biotechnol., 27: 582-590.

Edelman, R., 2002. The development and use of vaccine adjuvants. Mol. Biotechnol., 21: 129-148.

Eicher, S.D., C.A. McKee, J.A. Carroll and E.A. Pajor, 2006. Supplemental vitamin C and yeast cell wall beta-glucan as growth enhancers in newborn pigs and as immunomodulators after an endotoxin challenge after weaning. J. Anim. Sci., 84: 2352-2360.

Eisen, T., C. Boshoff, I. Mak, F. Sapunar and M.M. Vaughan *et al*., 2000. Continuous low dose thalidomide: A phase II study in advanced melanoma, renal cell, ovarian and breast cancer. Br. J. Cancer, 82: 812-817.

Eisenbarth, S.C., O.R. Colegio, W. O'Connor, F.S. Sutterwala and R.A. Flavell, 2008. Crucial role for the Nalp3 inflammasome in the immunostimulatory properties of aluminium adjuvants. Nature, 453: 1122-1126.

El Andaloussi, A., A.M. Sonabend, Y. Han and M.S. Lesniak, 2006. Stimulation of TLR9 with CpG ODN enhances apoptosis of glioma and prolongs the survival of mice with experimental brain tumors. Glia, 54: 526-535.

El-Gamal, Y.M., O.A. Elmasry, D.H. El-Ghoneimy and I.M. Soliman, 2011. Immunomodulatory effects of food: A Review. Egypt J. Pediatr. Allergy Immunol., 9: 3-13.

El-Malky, M., N. Nabih, M. Heder, N. Saudy and M. El-Mahdy, 2011. Helminth infections: Therapeutic potential in autoimmune disorders. Parasite Immunol., 33: 589-593.

Elkamel, A.A. and G.M. Mosaad, 2012. Immunomodulation of Nile Tilapia, *Oreochromis niloticus*, by *Nigella sativa* and *Bacillus subtilis*. J. Aquacult. Res. Dev., Vol. 3. 10.4172/2155-9546.1000147

Escudier, B., N. Lassau, D. Couanet, E. Angevin and F. Mesrati *et al*., 2002. Phase II trial of thalidomide in renal-cell carcinoma. Ann. Oncol., 13: 1029-1035.

Eskandari, F., J.I. Webster and E.M. Sternberg, 2003. Neural immune pathways and their connection to inflammatory diseases. Arthritis Res. Ther., 5: 251-265.

Fawzi, W.W., R.L. Mbise, E. Hertzmark, M.R. Fataki, M.G. Herrera, G. Ndossi and D. Spiegelman, 1999. A randomized trial of vitamin A supplements in relation to mortality among human immunodeficiency virus-infected and uninfected children in Tanzania. Pediatr. Infect. Dis. J., 18: 127-133.

Fernandes de Abreu, D.A., D. Eyles and F. Feron, 2009. Vitamin D, a neuro-immunomodulator: Implications for neurodegenerative and autoimmune diseases. Psychoneuroendocrinology, 34: S265-S277.

Fife, K., R.H. Phillips, M.R. Howard, M. Bower and F. Gracie, 1998. Activity of thalidomide in AIDS-related Kaposi's sarcoma and correlation with HHV8 titre. Int. J. STD AIDS, 9: 751-755.

Figg, W.D., W. Dahut, P. Duray, M. Hamilton and A. Tompkins *et al*., 2001. A randomized phase II trial of thalidomide, an angiogenesis inhibitor, in patients with androgen-independent prostate cancer. Clin. Cancer Res., 7: 1888-1893.

Fimiani, V., A. Cavallaro, T. Ainis, G. Baranovskaia, O. Ketlinskaya and L. Kozhemyakin, 2002. Immunomodulatory effect of glutoxim on some activities of isolated human neutrophils and in whole blood. Immunopharmacol. Immunotoxicol., 24: 627-638.

Flasche, S., W.J. Edmunds, E. Miller, D. Goldblatt, C. Robertson and Y.H. Choi, 2013. The impact of specific and non-specific immunity on the ecology of *Streptococcus pneumonia* and the implications for vaccination. Proc. R. Soc. Biol. Sci., Vol. 280. 10.1098/rspb.2013.1939

Flatz, L., A.N. Hegazy, A. Bergthaler, A. Verschoor and C. Claus *et al*., 2010. Development of replication-defective lymphocytic choriomeningitis virus vectors for the induction of potent $CD8^+$T cell immunity. Nat. Med., 16: 339-345.

Fleming, J.O., 2011. Helminths and multiple sclerosis: Will old friends give us new treatments for MS? J. Neuroimmunol., 233: 3-5.

Food and Nutrition Board, 2001. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium and Zinc. National Academy Press, Washington, DC., ISBN-13: 9780309072908, Pages: 800.

Forton, D. and P. Karayiannis, 2006. Established and emerging therapies for the treatment of viral hepatitis. Dig. Dis., 24: 160-173.

Fraile, L., E. Crisci, L. Cordoba, M.A. Navarro, J. Osada and M. Ontoya, 2012. Immunomodulatory properties of β-sitosterol in pig immune responses. Int. Immunopharmacol., 13: 316-321.

Fraker, P.J. and L.E. King, 2004. Reprogramming of the immune system during zinc deficiency. Annu. Rev. Nutr., 24: 277-298.

Franchimont, D., 2004. Overview of the actions of glucocorticoids on the immune response: A good model to characterize new pathways of immunosuppression for new treatment strategies. Ann. N. Y. Acad. Sci., 1024: 124-137.

Franchimont, D., J. Galon, M. Gadina, R. Visconti and Y.J. Zhou *et al*., 2000. Inhibition of Th1 immune response by glucocorticoids: Dexamethasone selectively inhibits IL-12-induced Stat4 phosphorylation in T lymphocytes. J. Immunol., 164: 1768-1774.

Freund, J. and K. McDermott, 1942. Sensitization to horse serum by means of adjuvants. Exp. Biol. Med., 49: 548-553.

Freund, J., J. Casals and E.P. Hosmer, 1937. Sensitization and antibody formation after injection of tubercle bacilli and paraffin oil. Exp. Biol. Med., 37: 509-513.

Friedman, H., T. Klein and R.C. Butler, 1984. Bacterial Antigens as Immunomodulators. In: Immunomodulation: New Frontiers and Advances, Fudenberg, H.H., H.D. Whitten and F. Ambrogi (Eds.). Springer, USA., ISBN: 978-1-4615-9360-7, pp: 209-228.

Friis, T., A.M. Engel, B.M. Klein, J. Rygaard and G. Houen, 2005. Levamisole inhibits angiogenesis *in vitro* and tumor growth *in vivo*. Angiogenesis, 8: 25-34.

Fuller, R., 2001. The chicken gut micro flora and probiotic supplements. J. Poult. Sci., 38: 189-196.

Fulzele, S.V., P.M. Satturwar and A.K. Dorle, 2001. Immunostimulant activity of cow's ghee. J. Immunol. Immunopathol., 3: 87-88.

Gallin, J.I., H.L. Malech, W. Curnutte, P. Quie, H. Jaffe and R. Ezkowitz, 1991. A controlled trial of interferon gamma to prevent infection in chronic granulomatous disease. N. Engl. J. Med., 324: 509-516.

Gallois, M. and I.P. Oswald, 2008. Immunomodulatoes as efficient alternatives to in-feed antimicrobials in pig production. Archiva Zootechnica, 11: 15-32.

Ganguly, S. and A. Prasad, 2011. Role of plant extracts and cow urine distillate as immunomodulators: A review. J. Med. Plant Res., 5: 649-651.

Ganju, L., D. Karan, S. Chanda, K.K. Srivastava, R.C. Sawhney and W. Selvamurthy, 2003. Immunomodulatory effects of agents of plant origin. Biomed. Pharmacother., 57: 296-300.

Garcia-Sanz, R., 2006. Thalidomide in multiple myeloma. Expert Opin. Pharmacother., 7: 195-213.

Garner, R.E. and J.A. Hudson, 1996. Intravenous injection of *Candida*-derived mannan results in elevated tumor necrosis factor alpha levels in serum. Infect. Immun., 64: 4561-4566.

Garner, R.E., A.M. Childress, L.G. Human and J.E. Domer, 1990. Characterization of *Candida albicans* mannan-induced, mannan-specific delayed hypersensitivity suppressor cells. Infect. Immun., 58: 2613-2620.

Gaur, K., M.L. Kori and R.K. Nema, 2009. Comparative screening of immunomodulatory activity of hydro-alcoholic extract of *Hibiscus rosa sinensis* Linn. and ethanolic extract of *Cleome gynandra* Linn. Global J. Pharmacol., 3: 85-89.

Gause, W.C., T.A. Wynn and J.E. Allen, 2013. Type 2 immunity and wound healing: Evolutionary refinement of adaptive immunity by helminths. Nat. Rev. Immunol., 13: 607-614.

Georgakopoulou, E.A. and C. Scully, 2013. Systemic use of non-biologic agents in orofacial diseases: Other immunomodulatory agents. Oral Dis. 10.1111/odi.12172

German, A.J., V.H. Ryan, A.C. German, I.S. Wood and P. Trayhurn, 2010. Obesity, its associated disorders and the role of inflammatory adipokines in companion animals. Vet. J., 185: 4-9.

Girish, S., 2011. Role of antioxidant vitamins in immune function in leprosy. Pharmacie Globale, 2: 1-3.

Gonda, T.A., Y.I. Kim, M.C. Salas, M.V. Gamble and W. Shibata *et al*., 2012. Folic acid increases global DNA methylation and reduces inflammation to prevent Helicobacter-associated gastric cancer in mice. Gastroenterology, 142: 824-833.

Gopi, M., K. Karthik, H.V. Manjunathachar, P. Tamilmahan and M. Kesavan *et al*., 2014. Essential oils as a feed additive in poultry nutrition. Adv. Anim. Vet. Sci., 2: 1-7.

Goswami, T.K., R. Bhar, S.E. Jadhav, S.N. Joardar and G.C. Ram, 2005. Role of dietary zinc as a nutritional immunomodulator. Asian-Aust. J. Anim. Sci., 18: 439-452.

Greiner, L.L., T.S. Stahly and T.J. Stabel, 2001. The effect of dietary soy daidzein on pig growth and viral replication during a viral challenge. J. Anim. Sci., 79: 3113-3119.

Guo, N.L., D.P. Lu, G.L. Woods, E. Reed, G.Z. Zhou, L.B. Zhang and R.H. Waldman, 1993. Demonstration of the anti-viral activity of garlic extract against human cytomegalovirus *in vitro*. Chinese Med. J., 106: 93-96.

Haase, H. and L. Rink, 2009. The immune system and the impact of zinc during aging. Immunity Ageing, Vol. 6. 10.1186/1742-4933-6-9

Hagenlocher, Y. and A. Lorentz, 2015. Immunomodulation of mast cells by nutrients. Mol. Immunol., 63: 25-31.

Haghighi, H.R., J. Gong, C.L. Gyles, M.A. Hayes and H. Zhou *et al*., 2006. Probiotics stimulate production of natural antibodies in chickens. Clin. Vaccine Immunol., 13: 975-980.

Hajhashemi, V., A. Ghannadi and H. Jafarabadi, 2004. Black cumin seed essential oil as a potent analgesic and antiinflammatory drug. Phytother. Res., 18: 195-199.

Hall, N.R. and A.L. Goldstein, 1984. Endocrine Regulation of Host Immunity. In: Immune Modulation Agents and their Mechanisms, Fenichel, R.L. and M.A. Chirigos (Eds.). Dekker, New York, pp: 533-563.

Hamill, P., K. Brown, H. Jenssen and R.E.W. Hancock, 2008. Novel anti-infectives: Is host defence the answer? Curr. Opin. Biotechnol., 19: 628-636.

Hancock, R.E.W. and H.G. Sahl, 2006. Antimicrobial and host-defense peptides as new anti-infective therapeutic strategies. Nat. Biotechnol., 24: 1551-1557.

Hanel, P., P. Andreani and M.H. Graler, 2007. Erythrocytes store and release sphingosine 1-phosphate in blood. Federat. Am. Soc. Exp. Biol. J., 21: 1202-1209.

Hartel, C., T. Strunk, P. Bucsky and C. Schultz, 2004. Effects of vitamin C on intracytoplasmic cytokine production in human whole blood monocytes and lymphocytes. Cytokine, 27: 101-106.

Hartel, C., A. Puzik, W. Gopel, P. Temming, P. Bucsky and C. Schultz, 2007. Immunomodulatory effect of vitamin C on intracytoplasmic cytokine production in neonatal cord blood cells. Neonatology, 91: 54-60.

Hasani-Ranjbar, S., S. Khosravi, N. Nayebi, B. Larijani and M. Abdollahi, 2012. Systematic review of the efficacy and safety of anti-aging herbs in animals and human. Asian J. Anim. Vet. Adv., 7: 621-640.

Hashemi, S.R. and H. Davoodi, 2012. Herbal plants as new immuno-stimulator in poultry industry: A review. Asian J. Anim. Vet. Adv., 7: 105-116.

Hecker, M., J. Ott, C. Sondermann, M.B. Schaefer and M. Obert *et al*., 2014. Immunomodulation by fish-oil containing lipid emulsions in murine acute respiratory distress syndrome. Crit. Care, Vol. 18. 10.1186/cc13850

Hegde, M., S.S. Karki, E. Thomas, S. Kumar and K. Panjamurthy *et al*., 2012. Novel levamisole derivative induces extrinsic pathway of apoptosis in cancer cells and inhibits tumor progression in mice. PLoS ONE, Vol. 7. 10.1371/journal.pone.0043632

Hirazumi, A. and E. Furusawa, 1999. An immunomodulatory polysaccharide-rich substance from the fruit juice of *Morinda citrifolia* (Noni) with antitumour activity. Phytother. Res., 13: 380-387.

Ho, N.K., S.P. Hawley, J.C. Ossa, O. Mathieu, T.A. Tompkins, K.C. Johnson-Henry and P.M. Sherman, 2013. Immune signalling responses in intestinal epithelial cells exposed to pathogenic *Escherichia coli* and lactic acid-producing probiotics. Benef. Microbes, 4: 195-209.

Hoffmann, P.R. and M.J. Berry, 2008. The influence of selenium on immune responses. Mol. Nutr. Food Res., 52: 1273-1280.

Hoorn, E.J., S.B. Walsh, J.A. McCormick, R. Zietse, R.J. Unwin and D.H. Ellison, 2012. Pathogenesis of calcineurin inhibitor-induced hypertension. J. Nephrol., 25: 269-275.

Hormannsperger, G., M.A. von Schillde and D. Haller, 2013. Lactocepin as a protective microbial structure in the context of IBD. Gut Microbes, 4: 152-157.

Hsieh, P.S., Y. An, Y.C. Tsai, Y.C. Chen and C.J. Chuang *et al*., 2013. Potential of probiotic strains to modulate the inflammatory responses of epithelial and immune cells *in vitro* New Microbiol., 36: 167-179.

Huang, K.Y., P.D. Kind, E.J. Jagoda and A.L. Goldstein, 1981. Thymosin treatment modulates production of interferons. J. Interferon Res., 1: 411-420.

Huang, Z., A.H. Rose and P.R. Hoffmann, 2012. The role of selenium in inflammation and immunity: From molecular mechanisms to therapeutic opportunities. Antioxid. Redox Signaling, 16: 705-743.

Hubner, M.P., L.E. Layland and A. Hoerauf, 2013. Helminths and their implication in sepsis: A new branch of their immunomodulatory behaviour? Pathog. Dis., 69: 127-141.

Huff, G.R., W.E. Huff and N.C. Rath, 2009. Nutritional immunomodulation as an approach to decreasing then effects of stress in poultry production. J. Arkansas Acad. Sci., 63: 87-92.

Hunter, H.N., D.B. Fulton, T. Ganz and H.J. Vogel, 2002. The solution structure of human hepcidin, a peptide hormone with antimicrobial activity that is involved in iron uptake and hereditary hemochromatosis. J. Biol. Chem., 277: 37597-37603.

Hwang, S.A., M.L. Kruzel and J.K. Actor, 2014. Immunomodulatory effects of recombinant lactoferrin during MRSA infection. Int. Immunopharmacol., 20: 157-163.

Ichikawa, H., Y. Takada, S. Shishodia, B. Jayaprakasam, M.G. Nair and B.B. Aggarwal, 2006. Withanolides potentiate apoptosis, inhibit invasion and abolish osteoclastogenesis through suppression of nuclear factor-κB (NF-κB) activation and NF-κB-regulated gene expression. Mol. Cancer Ther., 5: 1434-1445.

Isaacs, A. and J. Lindenmann, 1957. Virus interference. I. The interferon. Proc. R. Soc. Lond., B, Biol. Sci., 147: 258-267.

Isenberg, J., B. Stoffel, U. Wolters, J. Beuth, H. Stuetzer, H.L. Ko and H. Pichimaier, 1995. Immunostimulation by propionibacteria: Effects on immune status and antineoplastic treatment. Anticancer Res., 15: 2363-2368.

Isolauri, E., Y. Sutas, P. Kankaanpaa, H. Arvilommi and S. Salminen, 2001. Probiotics: Effects on immunity. Am. J. Clin. Nutr., 73: 444S-450S.

Jacob, R.A., D.S. Kelley, F.S. Pianalto, M.E. Swendseid and S.M. Henning *et al*., 1991. Immunocompetence and oxidant defense during ascorbate depletion of healthy men. Am. J. Clin. Nutr., 54: 1302-1309.

Jacobson, P., J. Uberti, W. Davis and V. Ratanatharathorn, 1998. Tacrolimus: A new agent for the prevention of graft-versus-host disease in hematopoietic stem cell transplantation. Bone Marrow Transplant., 22: 217-225.

Jacquet, A., 2013. Probiotic-derived factors: Efficient treatment for allergic asthma? Clin. Exp. Allergy, 43: 268-270.

Jarvis, J.N., G. Meintjes, K. Rebe, G.N. Williams and T. Bicanic *et al*., 2012. Adjunctive interferon-gamma immunotherapy for the treatment of HIV-associated cryptococcal meningitis: A randomized controlled trial. Aids, 26: 1105-1113.

Jeurink, P.V., B.C. van Esch, A. Rijnierse, J. Garssen and L.M. Knippels, 2013. Mechanisms underlying immune effects of dietary oligosaccharides. Am. J. Clin. Nutr., 98: 572S-577S.

Jin, Y., Y. Zhang, C. Wan, H. Wang and L. Hou *et al*., 2013. Immunomodulatory activity and protective effects of polysaccharide from *Eupatorium adenophorum* leaf extract on highly pathogenic H5N1 influenza infection. Evid Based Complement Alternat. Med., Vol. 2013. 10.1155/2013/194976

Jolles, P. and A. Paraf, 1973. Biological Activity of Adjuvants. In: Chemical and Biological Basis of Adjuvants, Jolles, P. and A. Paraf (Eds.). Springer, California, ISBN: 9780387063089, pp: 53-77.

Joseph, B. and P. Sankarganesh, 2011. Antifungal efficacy of panchagavya. Int. J. PharmTech Res., 3: 585-588.

Josko, O., 2011. Copper and zinc, biological role and significance of copper/zinc imbalance. J. Clin. Toxicol., 10.4172/2161-0495.S3-001

Kaila, M., E. Isolauri, E. Soppi, E. Virtanen, S. Laine and H. Arvilommi, 1992. Enhancement of the circulating antibody secreting cell response in human diarrhea by a human *Lactobacillus* strain. Pediatr. Res., 32: 141-144.

Kamath, A.T., A.F. Rochat, D. Christensen, E.M. Agger, P. Andersen and P.H. Lambert, 2009. A liposome-based mycobacterial vaccine induces potent adult and neonatal multifunctional T cells through the exquisite targeting of dendriticcells. PLoS One, Vol. 4. 10.1371/journal.pone.0005771

Kanagu, L., P. Senthilkumar, C. Stella and M. Jaikumar, 2010. Effect of vitamin C and E and B-1, 3 Glucan as immunomodulators in *P. monodon* disease management. Middle-East J. Sci. Res., 6: 537-543.

Kant, R., W.M. de Vos, A. Palva and R. Satokari, 2014. Immunostimulatory CpG motifs in the genomes of gut bacteria and their role in human health and disease. J. Med. Microbiol., 63: 293-308.

Kanzler, H., F.J. Barrat, E.M. Hessel and R.L. Coffman, 2007. Therapeutic targeting of innate immunity with Toll-like receptor agonists and antagonists. Nat. Med., 13: 552-559.

Karbasi, A. and A. Saburi, 2012. Role of vitamin D on cancer immunotherapy. Front. Endocrinol., Vol. 3.

Karthik, K., I. Sophia, V. Rekha, M. Bhardwaj, N. Singh and A. Jain, 2012. Antibiotic resistance-counter attack by *Salmonella*. Int. J. Livestock Res., 2: 42-47.

Karthik, K., N.S. Muneeswaran, H.V. Manjunathachar, M. Gopi, A. Elamurugan and S. Kalaiyarasu, 2014. Bacteriophages: Effective alternative to antibiotics. Adv. Anim. Vet. Sci., Vol. 2.

Klavinskis, L.S., P. Hobson and A. Woods, 2010. Incorporation of Immunomodulators into Plasmid DNA Vaccines. In: Vaccine Protocols, Robinson, A., M.J. Hudson and M.P. Cranage (Eds.). Springer, New York, ISBN: 9781592593996, pp: 46-61.

Klotz, L.O., K.D. Kroncke, D.P. Buchczyk and H. Sies, 2003. Role of copper, zinc, selenium and tellurium in the cellular defense against oxidative and nitrosative stress. J. Nutr., 133: 1448-1451.

Klurfeld, D.M., 1993. Human Nutrition: A Comprehensive Treatise. Vol. 8, Plenum Press, Lewiston, New York, USA., ISBN-13: 9780306443664, pp: 309-332.

Koenen, M.E., J. Kramer, R. van der Hulst, L. Heres, S.H.M. Jeurissen and W.J.A. Boersma, 2004. Immunomodulation by probiotic lactobacilli in layer- and meat-type chickens. Br. Poult. Sci., 45: 355-366.

Kogut, M.H., 2000. Cytokines and prevention of infectious diseases in poultry: A review. Avian Pathol., 29: 395-404.

Kool, M., T. Soullie, M. van Nimwegen, M.A. Willart and F. Muskens *et al*., 2008a. Alum adjuvant boosts adaptive immunity by inducing uric acid and activating inflammatory dendritic cells. J. Exp. Med., 205: 869-882.

Kool, M., V. Petrilli, T. de Smedt, A. Rolaz and H. Hammad *et al*., 2008b. Cutting edge: Alum adjuvant stimulates inflammatory dendritic cells through activation of the NALP3 inflammasome. J. Immunol., 181: 3755-3759.

Kosaka, A., H. Yan, S. Ohashi, Y. Gotoh and A. Sato *et al*., 2012. *Lactococcus lactis* subsp. cremoris FC triggers IFN-γ production from N K and T cells via IL-12 and IL-18. Int. Immunopharmacol., 14: 729-733.

Kugelberg, E., 2014. Glucocorticoids shift response in macrophages. Nat. Rev. Immunol., Vol. 14. 10.1038/nri3615

Kuhn, C.A. and C.W. Hanke, 1997. Current status of melanoma vaccines. Dermatol. Surg., 23: 649-654.

Kulkarni, S.K., 2009. Hand Book of Experimental Pharmacology. 3rd Edn., Vallabh Prakashan, New Delhi.

Kumar, A., A.K. Verma, A. Rahal, P.K. Panwar and K. Dhama, 2013. Recent trends in development of adjuvant of vaccine. Trends Med. Res., 8: 32-35.

Kumar, S. and K.C. Anderson, 2005. Drug insight: Thalidomide as a treatment for multiple myeloma. Nat. Clin. Pract. Oncol., 2: 262-270.

Kunisawa, J. and H. Kiyono, 2013. Vitamin-mediated regulation of intestinal immunity. Frontiers Immunol., 4: 189-189.

Kunz, M. and S.M. Ibrahim, 2009. Cytokines and cytokine profiles in human autoimmune diseases and animal models of autoimmunity. Mediators Inflammation. 10.1155/2009/979258

Lahteinen, T., A. Lindholm, T. Rinttila, S. Junnikkala and R. Kant *et al*., 2014. Effect of *Lactobacillus brevis* ATCC 8287 as a feeding supplement on the performance and immune function of piglets. Vet. Immunol. Immunopathol., 158: 14-25.

Lai, C.Y., J.T. Hung, H.H. Lin, A.L. Yu and S.H. Chen *et al*., 2010. Immunomodulatory and adjuvant activities of a polysaccharide extract of *Ganoderma lucidum in vivo* and *in vitro*. Vaccine, 28: 4945-4954.

Lakshmi, V., S.K. Joseph, S. Srivastava, S.K. Verma and M.K. Sahoo *et al*., 2010. Antifilarial activity *in vitro* and *in vivo* of some flavonoids tested against *Brugia malayi*. Acta Trop., 116: 127-133.

Lamprecht, M., S. Bogner, G. Schippinger, K. Steinbauer and F. Fankhauser *et al*., 2012. Probiotic supplementation affects markers of intestinal barrier, oxidation and inflammation in trained men: A randomized, double-blinded, placebo-controlled trial. J. Int. Soc. Sports Nutr., Vol. 9. 10.1186/1550-2783-9-45

Latif, T., N. Chauhan, R. Khan, A. Moran and S.Z. Usmani, 2012. Thalidomide and its analogues in the treatment of Multiple Myeloma. Exp. Hematol. Oncol., Vol. 1.

Leclerc, C. and F.R. Vogel, 1985. Synthetic immunomodulators and synthetic vaccines. Crit. Rev. Therapeutic Drug Carrier Syst., 2: 353-406.

Lederer, E., A. Adam, R. Ciorbaru, J.F. Petit and J. Wietzerbin, 1975. Cell walls of mycobacteria and related organisms: Chemistry and immunostimulant properties. Mol. Cell. Biochem., 7: 87-104.

Lee, J.H., S.H. Choi, O.S. Kwon, T.J. Shin and J.H. Lee *et al*., 2007a. Effects of ginsenosides, active ingredients of Panax ginseng, on development, growth and life span of Caenorhabditis elegans. Biol. Pharm. Bull., 30: 2126-2134.

Lee, S., H.S. Lillehoj, D.W. Park, Y.H. Hong and J.J. Lin, 2007b. Effects of *Pediococcus*-and *Saccharomyces*-based probiotic (MitoMax®) on coccidiosis in broiler chickens. Comp. Immunol. Microbiol. Infect. Dis., 30: 261-268.

Lee, S. and K. Margolin, 2011. Cytokines in cancer immunotherapy. Cancers, 3: 3856-3893.

Lee, J.S., A. Synytsya, H.B. Kim, D.J. Choi and S. Lee *et al*., 2013. Purification, characterization and immunomodulating activity of a pectic polysaccharide isolated from Korean mulberry fruit Oddi (*Morus alba* L.). Int. Immunopharmacol., 17: 858-866.

Lefrancois, L. and L. Puddington, 1995. Extrathymic intestinal T-cell development: Virtual reality? Immunol. Today, 16: 16-21.

Leklem, J.E., 2001. Vitamin B6. In: Handbook of Vitamins, Rucker, R.B., J.W. Suttie and D.B. McCormick (Eds.). Chapter 10, 3rd Edn., CRC Press, New York, ISBN: 9781420029666, pp: 339-396.

Leonard, E.J. and T. Yoshimura, 1990. Neutrophil attractant/activation protein-1 (NAP-1 [interleukin-8]). Am. J. Respir Cell. Mol. Biol., 2: 479-486.

Leroux-Roels, G., 2010. Unmet needs in modern vaccinology: Adjuvants to improve the immune response. Vaccine, 28: C25-C36.

Li, J., J. Xing, D. Li, X. Wang, L. Zhao, S. Lv and D. Huang, 2005. Effects of β-glucan extracted from *Saccharomyces cerevisiae* on humoral and cellular immunity in weaned piglets. Arch. Anim. Nutr., 59: 303-312.

Li, J., D.F. Li, J.J. Xing, Z.B. Cheng and C.H. Lai, 2006. Efects of β-glucan extracted from *Saccharomyces cerevisiae* on growth performance and immunological and somatotropic responses of pigs challenged with *Escherichia coli* lipopolysaccharide. J. Anim. Sci., 84: 2374-2381.

Li, P., X. Zhang, Y. Cheng, J. Li and Y. Xiao *et al*., 2014. Preparation and *in vitro* immunomodulatory effect of curdlan sulfate. Carbohydr. Polymers, 102: 852-861.

Lilly, D.M. and R.H. Stillwell, 1965. Probiotics: Growth-promoting factors produced by microorganisms. Science, 147: 747-748.

Lin, C.C., C.L. Chu, C.S. Ng, C.Y. Lin, D.Y. Chen, I.H. Pan and K.J. Huang, 2014. Immunomodulation of phloretin by impairing dendritic cell activation and function. Food Funct., 5: 997-1006.

Lindenstrom, T., E.M. Agger, K.S. Korsholm, P.A. Darrah and C. Aagaard *et al*., 2009. Tuberculosis subunit vaccination provides long-term protective immunity characterized by multifunctional CD4 memory T cells. J. Immunol., 182: 8047-8055.

Lipford, G.B., H. Wagner and K. Heeg, 1994. Vaccination with immunodominant peptides encapsulated in Quil A-containing liposomes induces peptide-specific primary CD8+ cytotoxic T cells. Vaccine, 12: 73-80.

Liu, X., J. Zheng and H. Zhou, 2011a. TLRs as pharmacological targets for plant-derived compounds in infectious and inflammatory diseases. Int. Immunopharmacol., 11: 1451-1456.

Liu, Y., H. Jing, J. Wang, R. Zhang and Y. Zhang *et al*., 2011b. Micronutrients decrease incidence of common infections in type 2 diabetic outpatients. Asia Pac. J. Clin. Nutr., 20: 375-382.

Long, K.Z. and J.I. Santos, 1999. Vitamins and the regulation of the immune response. Pediatric Infect. Dis. J., 18: 283-290.

Lowenthal, J.W., T.E. O'Neil, M. Broadway, A.D.G. Strom, M.R. Digby, M. Andrew and J.J. York, 1998. Coadministration of IFN-γ enhances antibody responses in chickens. J. Interferon Cytokine Res., 18: 617-622.

Lowenthal, J.W., T.E. O'Neil, A. David, G. Strom and M.E. Andrew, 1999. Cytokine therapy: A natural alternative for disease control. Vet. Immunol. Immunopathol., 72: 183-188.

Maass, N., J. Bauer, B.R. Paulicks, B.M. Bohmer and D.A. Roth-Maier, 2005. Efficiency of *Echinacea purpurea* on performance and immune status in pigs. J. Anim. Physiol. Anim. Nutr., 89: 244-252.

Maggini, S., E.S. Wintergerst, S. Beveridge and D.H. Hornig, 2007. Selected vitamins and trace elements support immune function by strengthening epithelial barriers and cellular and humoral immune responses. Br. J. Nutr., 98: 29-35.

Mahima, A. Rahal, R. Deb, S.K. Latheef and H.A. Samad *et al*., 2012a. Immunomodulatory and therapeutic potentials of herbal, traditional/indigenous and ethnoveterinary medicines. Pak. J. Biol. Sci., 15: 754-774.

Mahima, A.K. Garg and V. Mudgal, 2012b. Influence of sodium selenite on growth, nutrient utilization and selenium uptake in *Cavia porcellus*. Pak. J. Biol. Sci., 15: 448-453.

Mahima, A.K. Verma, R. Tiwari, K. Karthik, S. Chakraborty, R. Deb and K. Dhama, 2013a. Nutraceuticals from fruits and vegetables at a glance: A review. J. Biol. Sci., 13: 38-47.

Mahima, A.M. Ingle, A.K. Verma, R. Tiwari and K. Karthik *et al*., 2013b. Immunomodulators in day to day life: A review. Pak. J. Biol. Sci., 16: 826-843.

Maisin, J., 1964. Existence in the thymus of a factor protecting the skin of the mouse against the induction of skin cancers induced by 20-methylcholanthrene. Nature, 204: 1211-1215.

Maizels, R.M., E.J. Pearce, D. Artis, M. Yazdanbakhsh and T.A. Wynn, 2009. Regulation of pathogenesis and immunity in helminth infections. J. Exp. Med., 206: 2059-2066.

Majtan, J., 2014. Honey: An immunomodulator in wound healing. Wound Repair Regener., 22: 187-192.

Malik, Y.S., K. Sharma, L.M. Jeena, N. Kumar, S. Sircar, K.K. Rajak and K. Dhama, 2013. Toll-like receptors: The innate immune receptors with ingenious anti-viral paradigm. South Asian J. Exp. Biol., 3: 207-213.

Maloy, K.J., A.M. Donachie and A.M. Mowat, 1995. Induction of Th1 and Th2 $CD4^+$ T cell responses by oral or parenteral immunization with ISCOMS. Eur. J. Immunol., 25: 2835-2841.

Mantzioris, E., L.G. Cleland, R.A. Gibson, M.A. Neumann, M. Demasi and M.J. James, 2000. Biochemical effects of a diet containing foods enriched with n-3 fatty acids. Am. J. Clin. Nutr., 72: 42-48.

Mastelic, B., S. Ahmed, W.M. Egan, G. del Giudice and H. Golding *et al*., 2010. Mode of action of adjuvants: Implications for vaccine safety and design. Biologicals, 38: 594-601.

Mathivanan, R., S.C. Edwin, K. Viswanathan and D. Chandrasekaran, 2006a. Chemical, microbial composition and antibacterial activity of modified panchagavya. Int. J. Cow Sci., 2: 23-26.

Mathivanan, R., S.C. Edwin, R. Amutha and K. Viswanathan, 2006b. Panchagavya and *Andrographis paniculata* as alternatives to antibiotic growth promoter on broiler production and carcass characteristics. Int. J. Poult. Sci., 5: 1144-1150.

Mathivanan, R. and S.C. Edwin, 2012. Effects of alternatives to antibiotic growth promoters on intestinal content characteristics, intestinal morphology and gut flora in broilers. Wudpecker J. Agric. Res., 1: 244-249.

McCarty, D.E., A.L. Chesson Jr., S.K. Jain and A.A. Marino, 2013. The link between vitamin D metabolism and sleep medicine. Sleep Med. Rev., 18: 311-319.

McClung, J.P. and D.G. Peterson, 2010. Trace Elements and Immune Function. In: Dietary Components and Immune Function, Watson, R.R., S. Zibadi and V.R. Preedy (Eds.). Humana Press, New York, ISBN: 978-1-60761-060-1, pp: 253-262.

McElhaney, J.E., R.N. Coler and S.L. Baldwin, 2013. Immunologic correlates of protection and potential role for adjuvants to improve influenza vaccines in older adults. Exp. Rev. Vaccines, 12: 759-766.

McHugh, R.S., M.J. Whitters, C.A. Piccirillo, D.A. Young, E.M. Shevach, M. Collins and M.C. Byrne, 2002. $CD4^+CD25^+$ immunoregulatory T cells: Gene expression analysis reveals a functional role for the glucocorticoid-induced TNF receptor. Immunity, 16: 311-323.

McSorley, H.J., M.T. O'Gorman, N. Blair, T.E. Sutherland, K.J. Filbey and R.M. Maizels, 2012. Suppression of type 2 immunity and allergic airway inflammation by secreted products of the helminth Heligmosomoides polygyrus. Eur. J. Immunol., 42: 2667-2682.

McSorley, H.J., J.P. Hewitson and R.M. Maizels, 2013. Immunomodulation by helminth parasites: Defining mechanisms and mediators. Int. J. Parasitol., 43: 301-310.

Mehrotra, S., K.P. Mishra, R. Maurya, R.C. Srimal, V.S. Yadav, R. Pandey and V.K. Singh, 2003. Anticellular and immunosuppressive properties of ethanolic extract of *Acorus calamus* rhizome. Int. Immunopharmacol., 3: 53-61.

Meydani, S.N., S.N. Han and D. Wu, 2005. Vitamin E and immune response in the aged: Molecular mechanisms and clinical implications. Immunol. Rev., 205: 269-284.

Miles, E.A. and P.C. Calder, 2012. Influence of marine n-3 polyunsaturated fatty acids on immune function and a systematic review of their effects on clinical outcomes in rheumatoid arthritis. Br. J. Nutr., 107: S171-S184.

Mily, A., R.S. Rekha, S.M. Kamal, E. Akhtar and P. Sarker *et al*., 2013. Oral intake of phenylbutyrate with or without vitamin D3 upregulates the cathelicidin LL-37 in human macrophages: A dose finding study for treatment of tuberculosis. BMC Pulm. Med., Vol. 13. 10.1186/1471-2466-13-23

Minagawa, T., K. Ishiwata and T. Kajimoto, 1999. Feline interferon-ω treatment on canine parvovirus infection. Vet. Microbiol., 69: 51-53.

Minatel, L. and J.C. Carfagnini, 2000. Copper deficiency and immune response in ruminants. Nutr. Res., 20: 1519-1529.

Mirzaei-Aghsaghali, A., 2012. Importance of medical herbs in animal feeding: A review. Ann. Biol. Res., 3: 918-923.

Mitchell, D., M. Yong, J. Raju, N. Willemsen and M. Black *et al*., 2011. Toll-like receptor-mediated adjuvanticity and immunomodulation in dendritic cells: Implications for peptide vaccines. Hum. Vaccines, 7: 85-93.

Mocanu, V., T. Oboroceanu and F. Zugun-Eloae, 2013. Current status in vitamin D and regulatory T cells-immunological implications. Revista Medico-Chirurgicala Societatii Medici Naturalisti Iasi, 117: 965-973.

Moeini, M.M., A. Kiani, E. Mikaeili and H.K. Shabankareh, 2011. Effect of prepartum supplementation of selenium and Vitamin E on serum Se, IgG concentrations and colostrum of heifers and on hematology, passive immunity and Se status of their offspring. Biol. Trace Element Res., 144: 529-537.

Mokrozub, V.V., L.M. Lazarenko, L.P. Babenko, L.M. Shynkarenko-Sichel and Z.M. Olevinska *et al*., 2012. Effect of probiotic strains of lacto and bifidobacteria on the activity of macrophages and other parameters of immunity in cases of staphylococcosis. Mikrobiolohichnyi Zhurnal, 74: 90-98.

Molad, Y., 2002. Update on colchicine and its mechanism of action. Curr. Rheumatol. Rep., 4: 252-256.

Moreno-Vilet, L., M.H. Garcia-Hernandez, R.E. Delgado-Portales, N.E. Corral-Fernandez, N. Cortez-Espinosa, M.A. Ruiz-Cabrera and D.P. Portales-Perez, 2014. *In vitro* assessment of agave fructans (*Agave salmiana*) as prebiotics and immune system activators. Int. J. Biol. Macromol., 63: 181-187.

Mubarak, A., A. Rashid, I.A. Khan and A. Hussain, 2009. Effect of vitamin E and selenium as immunomodulators on induced aflatoxicosis in broiler birds. Pak. J. Life Soc. Sci., 7: 31-34.

Muir, W.I., A.J. Husband and W.L. Bryden, 2002. Dietary supplementation with vitamin E modulates avian intestinal immunity. Br. J. Nutr., 87: 579-585.

Mukhtyar, C., L. Guillevin, M.C. Cid, B. Dasgupta and K. de Groot *et al*., 2009. EULAR recommendations for the management of primary small and medium vessel vasculitis. Ann. Rheumatic Dis., 68: 310-317.

Munyaka, P.M., G. Tactacan, M. Jing, J.D. House and J.C. Rodriguez-Lecompte, 2012. Immunomodulation in young laying hens by dietary folic acid and acute immune responses after challenge with Escherichia coli lipopolysaccharide. Poult. Sci., 91: 2454-2463.

Mutwiri, G., V. Gerdts, M. Lopez and L.A. Babiuk, 2007. Innate immunity and new adjuvants. Rev. Sci. Tech. Off. Epiz., 26: 147-156.

Nairz, M., A. Schroll, T. Sonnweber and G. Weiss, 2010. The struggle for iron-a metal at the host-pathogen interface. Cell. Microbiol., 12: 1691-1702.

Nayak, S. and S. Mengi, 2010. Immunostimulant activity of noni (*Morinda citrifolia*) on T and B lymphocytes. Pharm. Biol., 48: 724-731.

Nelson, H.S., D.Y. Leung and J.W. Bloom, 2003. Update on glucocorticoid action and resistance. J. Allergy Clin. Immunol., 111: 3-22.

Nicholas, R., P. Giannetti, A. Alsanousi, T. Friede and P.A. Muraro, 2011. Development of oral immunomodulatory agents in the management of multiple sclerosis. Drug Des. Dev. Ther., 5: 255-274.

Nicholls, E.F., L. Madera and R.E.W. Hancock, 2010. Immunomodulators as adjuvants for vaccines and antimicrobial therapy. Ann. N. Y. Acad. Sci., 1213: 46-61.

Nijnik, A. and R.E.W. Hancock, 2009. Host defence peptides: Antimicrobial and immunomodulatory activity and potential applications for tackling antibiotic-resistant infections. Emerg. Health Threats J., Vol. 2. 10.3134/ehtj.09.001

Noe, S.M., M.A. Green, H. HogenEsch and S.L. Hem, 2010. Mechanism of immunopotentiation by aluminum-containing adjuvants elucidated by the relationship between antigen retention at the inoculation site and the immune response. Vaccine, 28: 3588-3594.

Nutman, T.B. and V. Kumaraswami, 2001. Regulation of the immune response in lymphatic filariasis: Perspectives on acute and chronic infection with *Wuchereria bancrofti* in South India. Parasite Immunol., 28: 389-399.

Ohashi, Y. and U. Ushida, 2009. Health-beneficial effects of probiotics: Its mode of action. Anim. Sci. J., 80: 361-371.

Ohira, H., M. Matsunaga, T. Osumi, S. Fukuyama, J. Shinoda, J. Yamada and Y. Gidron, 2013. Vagal nerve activity as a moderator of brain-immune relationships. J. Neuroimmunol., 260: 28-36.

Opal, S.M., J.W. Jhung, J.C. Keith, J.E. Palardy, N.A. Parejo, L.D. Young and A. Bhattacharjee, 1998. Recombinant human interleukin-11 in experimental *Pseudomonas aeruginosa* sepsis in immunocompromised animals. J. Infect. Dis., 178: 1205-1208.

Openheimer, S.J., 2001. Iron and its relation to immunity and infectious disease. J. Nutr., 131: 616S-633S.

Ortiz-Sanchez, E., G. Helguera, T.R. Daniels and M.L. Penichet, 2008. Antibody-cytokine fusion proteins: Applications in cancer therapy. Exp. Opin. Biol. Ther., 8: 609-632.

Osada, Y., S. Yamada, A. Nabeshima, Y. Yamagishi and K. Ishiwata *et al*., 2013. *Heligmosomoides polygyrus* infection reduces severity of type 1 diabetes induced by multiple low-dose streptozotocin in mice via STAT6-and IL-10-independent mechanisms. Exp. Parasitol., 135: 388-396.

Pae, M., S.N. Meydani and D. Wu, 2012. The role of nutrition in enhancing immunity in aging. Aging Dis., 3: 91-129.

Pansuebchue, N., N. Soonthornchareonnon and K. Pattanapanyasat, 2002. Chemical study and immunostimulating activity of *Morinda citrifolia*. Thai J. Pharm. Sci., Vol. 26.

Park, J.H., J.I. Um, B.J. Lee, J.S. Goh, S.Y. Park, W.S. Kim and P.H. Kim, 2002. Encapsulated *Bifidobacterium bifidum* potentiates intestinal IgA production. Cell Immunol., 219: 22-27.

Patil, U.S., A.V. Jaydeokar and D.D. Bandawane, 2012. Immunomodulators: A pharmacological review. Int. J. Pharm. Pharm. Sci., 4: 30-36.

Persing, D.H., R.N. Coler, M.J. Lacy, D.A. Johnson, J.R. Baldridge, R.M. Hershberg and S.G. Reed, 2002. Taking toll: Lipid a mimetics as adjuvants and immunomodulators. Trends Microbiol., 10: 32-37.

Peshev, D. and W. van den Ende, 2014. Fructans: Prebiotics and immunomodulators. J. Funct. Foods, 8: 348-357.

Petrovsky, N. and J.C. Aguilar, 2004. Vaccine adjuvants: Current state and future trends. Immunol. Cell Biol., 82: 488-496.

Pfahlberg, A., K.F. Kolmel, J.M. Grange, G. Mastrangelo and B. Krone *et al.*, 2002. Inverse association between melanoma and previous vaccinations against tuberculosis and smallpox: Results of the FEBIM study. J. Invest. Dermatol., 119: 570-575.

Philips, A., M. Maira, A. Mullick, M. Chamberland, S. Lesage, P. Hugo and J. Drouin, 1997. Antagonism between Nur77 and glucocorticoid receptor for control of transcription. Mol. Cell. Biol., 17: 5952-5959.

Pillemer, L.A. and E.E. Ecker, 1941. Anticomplementary factor in fresh yeast. J. Biol. Chem., 137: 139-142.

Pindolia, K., H. Li, C. Cardwell and B. Wolf, 2014. Characterization and functional analysis of cellular immunity in mice with biotinidase deficiency. Mol. Gen. Metabol., 112: 49-56.

Pirofski, L.A. and A. Casadevall, 2006. Immunomodulators as an antimicrobial tool. Curr. Opin. Microbial., 9: 489-495.

Pollard, T.D. and W.C. Earnshaw, 2004. Signalling Mechanisms: Plasma Membrane Receptors. In: Cell Biology, Schmitt, W. and J. Mahon (Eds.). Saunders-Elsevier, Philadelphia, pp: 427-442.

Pond, C.M., 2005. Adipose tissue and the immune system. Prostaglandins, Leukotrienes Essent. Fatty Acids, 73: 17-30.

Powers, J.P.S. and R.E. Hancock, 2003. The relationship between peptide structure and antibacterial activity. Peptides, 24: 1681-1691.

Prabhala, R.H., H.S. Garewal, M.J. Hicks, R.E. Sampliner and R.R. Watson, 1991. The effects of 13-cis-retinoic acid and beta-carotene on cellular immunity in humans. Cancer, 67: 1556-1560.

Prasad, A.S., 2000. Effects of zinc deficiency on immune functions. J. Trace Elem. Exp. Med., 13: 1-20.

Prevot, A.R., B. Halpern, G. Biozzi, C. Stiffel and D. Mouton *et al.*, 1963. [Stimulation of the reticuloendothelial system (RES) by killed microbial substances from *Corynebacterium parvum*]. Hebd Seances Acad. Sci., 257: 13-17, (In French)..

Prieto-Moreno, G.A. and Y. Rosenstein, 2006. The Links between the Neuroendocrine and the Immune Systems: Views of an Immunologist. In: Molecular Endocrinology, Joseph-Bravo, P. (Ed.). 1st Edn., Chapter 9, Research Signpost, Kerala, India, pp: 171-192.

Prins, R.M., N. Craft, K.W. Bruhn, H. Khan-Farooqi and R.C. Koya *et al.*, 2006. The TLR-7 agonist, imiquimod, enhances dendritic cell survival and promotes tumor antigen-specific T cell priming: Relation to central nervous system antitumor immunity. J. Immunol., 176: 157-164.

Puertollano, M.A., E. Puertollano, G.A. de Cienfuegos and M.A. de Pablo, 2011. Dietary antioxidants: Immunity and host defense. Curr. Top. Med. Chem., 11: 1752-1766.

Pulverer, G., H.L. Ko, K. Roszkowski, W. Roszkowski and J. Jeljaszewicz, 1985. Immunomodulation by propionibacteria. Clin. Immunol. Newslett., 6: 51-54.

Quintanar, J.L. and I. Guzman-Soto, 2013. Hypothalamic neurohormones and immune responses. Front. Integr. Neurosci., Vol. 7. 10.3389/fnint.2013.00056

Rahal, A., A. Kumar, V. Singh, B. Yadav, R. Tiwari, S. Chakraborty and K. Dhama, 2014a. Oxidative stress, prooxidants and antioxidants: The interplay. BioMed Res. Int. 10.1155/2014/761264

Rahal, A., Mahima, A.K. Verma, A. Kumar and R. Tiwari *et al.*, 2014b. Phytonutrients and nutraceuticals in vegetables and their multi-dimensional medicinal and health benefits for humans and their companion animals: A review. J. Biol. Sci., 14: 1-19.

Rahman, S.A., 2010. Doctors scoff at hindu health drink containing cow urine. The National, (Abu Dhabi).

Ramakrishnan, U., A.L. Web and K. Ologoudou, 2004. Infection, Immunity and Vitamins. In: Handbook of Nutrition and Immunity, Gershwin, N.E., P. Nestel and C.L. Keen (Eds.). Humana Press, New Jersey, ISBN-13: 9781588293084, pp: 93-115.

Ramon, G., 1926. Procedes pour accroitre la production des antitoxines. Ann. Inst. Pasteur Paris, 40: 1-10.

Randhawa, G.K., 2010. Cow urine distillate as bioenhancer. J. Ayurveda Integr. Med., 1: 240-241.

Raqib, R., P. Sarker, P. Bergman, G. Ara and M. Lindh *et al.*, 2006. Improved outcome in shigellosis associated with butyrate induction of an endogenous peptide antibiotic. Proc. Nat. Acad. Sci. USA., 103: 9178-9183.

Rask, C., I. Adlerberth, A. Berggren, I.L. Ahren and A.E. Wold, 2013. Differential effect on cell-mediated immunity in human volunteers after intake of different lactobacilli. Clin. Exp. Immunol., 172: 321-332.

Reddy, M.V., 2010. Immunomodulators of helminthes: Promising therapeutics for autoimmune disorders and allergic diseases x. Indian J. Clin. Biochem., 25: 109-110.

Reefman, E., J.G. Kay, S.M. Wood, C. Offenhauser and D.L. Brown *et al.*, 2010. Cytokine secretion is distinct from secretion of cytotoxic granules in NK cells. J. Immunol., 184: 4852-4862.

Ren, F., X. Chen, J. Hesketh, F. Gan and K. Huang, 2012. Selenium promotes T-cell response to TCR-stimulation and ConA but not PHA in primary porcine splenocytes. PloS One, Vol. 7. 10.1371/journal.pone.0035375

Renoux, G. and M. Renoux, 1971. [Immunostimulating effect of an imidotiiazole in the immunization of mice against *Brucella abortus* infection]. C. R. Acad. Sci. Hebd. Seances Acad. Sci. D, 272: 349-350, (In French).

Rice, A.D., M.M. Adams, S.F. Lindsey, D.M. Swetnam and B.R. Manning *et al.*, 2014. Protective properties of vaccinia virus-based vaccines: Skin scarification promotes a nonspecific immune response that protects against orthopoxvirus disease. J. Virol., 88: 7753-7763.

Ritz, N., M. Mui, A. Balloch and N. Curtis, 2013. Non-specific effect of bacille calmette-guerin vaccine on the immune response to routine immunisations. Vaccine, 31: 3098-3103.

Rivero-Lezcano, O.M., 2008. Cytokines as immunomodulators in tuberculosis therapy. Recent Patents Anti-Infect. Drug Discov., 3: 168-176.

Rizvi, M., M. Azam, A. Sultan, F. Khan, I. Shukla, A. Malik and M.R. Ajmal, 2012. Assessment of interleukin-10 in *Leptospira* associated acute hepatic syndrome. J. Pure Applied Microbiol., 6: 1-7.

Robb, R.J., A. Munck and K.A. Smith, 1981. T cell growth factor receptors. Quantitation, specificity and biological relevance. J. Exp. Med., 154: 1455-1474.

Romagne, F., 2007. Current and future drugs targeting one class of innate immunity receptors: The Toll-like receptors. Drug Discovery Today, 12: 80-87.

Rookhuizen D.C., 2012. Regulation of germinal center antibody responses by TLR signaling in dendritic cells and B cells. Master's Thesis, University of California, Berkeley.

Roth, J.A. and M.L. Kaeberle, 1985. *In vivo* effect of ascorbic acid on neutrophil function in healthy and dexamethasone-treated cattle. Am. J. Vet. Res., 46: 2434-2436.

Ryan-Harshman, M. and W. Aldoori, 2005. The relevance of selenium to immunity, cancer and infectious/inflammatory diseases. Can. J. Diet. Pract. Res., 66: 98-102.

Saeed, M.A., I. Ahmad, U. Yaqub, S. Akbar, A. Waheed, M. Saleem and Nasir-ud-Din, 2003. *Aloe vera*: A plant of vital significance. Sci. Vision, 9: 1-13.

Safaralizadeh, R., M. Nourizadeh, A. Zare, G.A. Kardar and Z. Pourpak, 2013. Influence of selenium on mast cell mediator release. Biol. Trace Element Res., 154: 299-303.

Sakaguchi, S., N. Sakaguchi, M. Asano, M. Itoh and M. Toda, 1995. Immunologic self-tolerance maintained by activated T cells expressing IL-2 receptor alpha-chains (CD25). Breakdown of a single mechanism of self-tolerance causes various autoimmune diseases. J. Immunol., 155: 1151-1164.

Salmen, S.H., S.A. Alharbi, H.M. Yehia, M.A. Khiyami, M. Wainwright, N.S. Alharbi and A. Chinnathambi, 2013. Antifungal protein 35kDa produced by *Bacillus cereus* inhibits the growth of some molds and yeasts. J. Pure Applied Microbiol., 7: 401-406.

Sanchez-Berna, I., C. Santiago-Diaz and J. Jimenez-Alonso, 2014. [Immunomodulatory properties of stem mesenchymal cells in autoimmune diseases]. Med. Clin., 144: 88-91, (In Spanish).

Sarker, P., S. Ahmed, S. Tiash, R.S. Rekha and R. Stromberg *et al*., 2011. Phenylbutyrate counteracts *Shigella mediated* downregulation of cathelicidin in rabbit lung and intestinal epithelia: A potential therapeutic strategy. PLoS One, Vol. 6. 10.1371/journal.pone.0020637

Saroj, P., M. Verma and K.K. Jha, 2012. An overview on immunomodulation. J. Adv. Sci. Res., 3: 7-12.

Scaringi, L., P. Marconi, M. Boccanera, L. Tissi, F. Bistoni and A. Cassone, 1988. Cell wall components of *Candida albicans* as immunomodulators: Induction of natural killer and macrophage-mediated peritoneal cell cytotoxicity in mice by mannoprotein and glucan Fractions. Microbiology, 134: 1265-1274.

Schaible, U.E. and S.H.E. Kaufmann, 2004. Iron and microbial infection. Nat. Rev. Microbiol., 2: 946-953.

Schijns, V.E.C.J. and M.C. Horzinek, 1997. Cytokines in Veterinary Medicine. 1st Edn., CABI International, UK., ISBN-13: 978-0851992099, Pages: 352.

Scott, M.G., E. Dullaghan, N. Mookherjee, N. Glavas and M. Waldbrook *et al*., 2007. An anti-infective peptide that selectively modulates the innate immune response. Nat. Biotechnol., 25: 465-472.

Serban, D.E., 2014. Gastrointestinal cancers: Influence of gut microbiota, probiotics and prebiotics. Cancer Lett., 345: 258-270.

Sharma, R., A. Rohilla and V. Arya, 2011. A short review on pharmacology of plant immunomodulators. Int. J. Pharmaceut. Sci. Rev. Res., 9: 126-131.

Shepherd, A.J., J.E.G. Downing and J.A. Miyan, 2005. Without nerves, immunology remains incomplete-*in vivo* veritas. Immunology, 116: 145-163.

Shor, D.B.A., M. Harel, R. Eliakim and Y. Shoenfeld, 2013. The hygiene theory harnessing helminths and their ova to treat autoimmunity. Clin. Rev. Allergy Immunol., 45: 211-216.

Short, S.C., D. Traish, A. Dowe, F. Hines, M. Gore and M. Brada, 2001. Thalidomide as an anti-angiogenic agent in relapsed gliomas. J. Neurooncol., 51: 41-45.

Singh, V.K., S. Biswas, K.B. Mathur, W. Haq, S.K. Garg and S.S. Agarwal, 1998. Thymopentin and splenopentin as immunomodulators. Immunol. Res., 17: 345-368.

Singh, M. and D.T. O'Hagan, 2003. Recent advances in veterinary vaccine adjuvants. Int. J. Parasitol., 33: 469-478.

Singh, V., S. Amdekar and O. Verma, 2010. *Ocimum sanctum* (Tulsi): Bio-pharmacological activities. Pharmacology, Vol. 1, No. 10. 10.9754/journal.wmc.2010.001046

Sohn, K.S., M.K. Kim, J.D. Kim and I.K. Han, 2000. The role of immunostimulants in monogastric animal and fish-review. Asian Austr. J. Anim. Sci., 13: 1178-1187.

Solaiman, S.G., T.J. Craig Jr., G. Reddy and C.E. Shoemaker, 2007. Effect of high levels of Cu supplement on growth performance, rumen fermentation and immune responses in goat kids. Small Rumin. Res., 69: 115-123.

Sorup, S., M. Villumsen, H. Ravn, C.S. Benn and T.I. Sorensen *et al*., 2011. Smallpox vaccination and all-cause infectious disease hospitalization: A Danish register-based cohort study. Int. J. Epidemiol., 40: 955-963.

Souvannavong, V., S. Brown and A. Adam, 1988. The synthetic immunomodulator muramyl dipeptide (MDP) can stimulate activated B cells. Mol. Immunol., 25: 385-391.

Spelman, K., J. Burns, D. Nichols, N. Winters, S. Ottersberg and M. Tenborg, 2006. Modulation of cytokine expression by traditional medicines: A review of herbal immunomodulators. Altern. Med. Rev., 11: 128-150.

Spisek, R., J. Brazova, D. Rozkova, K. Zapletalova, A. Sediva and J. Bartunkova, 2004. Maturation of dendritic cells by bacterial immunomodulators. Vaccine, 22: 2761-2768.

Stanford, M., 2004. Interferon treatment of circovirus infection in grey parrots (*Psittacuse erithacus*). Vet. Rec., 154: 435-436.

Steinman, L., 2005. Blocking adhesion molecules as therapy for multiple sclerosis: Natalizumab. Nat. Rev. Drug Discovery, 4: 510-518.

Stevceva, L., M. Moniuszko and M.G. Ferrari, 2006. Utilizing IL-12, IL-15 and IL-7 as mucosal vaccine adjuvants. Lett. Drug Des. Discovery, 3: 586-592.

Stevenson, H.C., I. Green, J.M. Hamilton, B.A. Calabro and D.R. Parkinson, 1991. Levamisole: Known effects on the immune system, clinical results and future applications to the treatment of cancer. J. Clin. Oncol., 9: 2052-2066.

Stils, H.F., 2005. Adjuvants and antibody production: Dispelling the myths associated with Freund's complete and other adjuvants. ILAR J., 46: 280-293.

Sugimura, T., K. Jounai, K. Ohshio, T. Tanaka, M. Suwa and D. Fujiwara, 2013. Immunomodulatory effect of *Lactococcus lactis* JCM5805 on human plasmacytoid dendritic cells. Clin. Immunol., 149: 509-518.

Sultana, N. and Z.S. Saify, 2012. Naturally occurring and synthetic agents as potential anti-inflammatory and immunomodulants. Antiinflamm Antiallergy Agents Med. Chem., 11: 3-19.

Sumithra, A., P. Srinivasan, G.A. Balasubramaniam, T.R.G. Murthy and P. Balachandran, 2013. Ameliorative effect of panchagavya on newcastle disease in layer chicken. Int. J. Agric. Biosci., 2: 60-63.

Sun, H.X., Y. Xie and Y.P. Ye, 2009. Advances in saponin-based adjuvants. Vaccine, 27: 1787-1796.

Sun, P., J.Q. Wang and H.T. Zhang, 2010. Effects of *Bacillus subtilis* natto on performance and immune function of preweaning calves. J. Dairy Sci., 93: 5851-5855.

Sunila, E.S. and G. Kuttan, 2004. Immunomodulatory and antitumor activity of *Piper longum* Linn. and piperine. J. Ethno. Pharmacol., 90: 339-346.

Sunkara, L.T., M. Achanta, N.B. Schreiber, Y.R. Bommineni and G. Dai *et al*., 2011. Butyrate enhances disease resistance of chickens by inducing antimicrobial host defense peptide gene expression. PLoS One, Vol. 6. 10.1371/journal.pone.0027225

Sunkara, L.T., W. Jiang and G. Zhang, 2012. Modulation of antimicrobial host defense peptide gene expression by free fatty acids. PLoS One, Vol. 7. 10.1371/journal.pone.0049558

Sutterwala, F.S., Y. Ogura, M. Szczepanik, M. Lara-Tejero and G.S. Lichtenberger *et al*., 2006. Critical role for NALP3/CIAS1/Cryopyrin in innate and adaptive immunity through its regulation of caspase-1. Immunity, 24: 317-327.

Sutterwala, F.S., Y. Ogura and R.A. Flavell, 2007. The inflammasome in pathogen recognition and inflammation. J. Leukocyte Biol., 82: 259-264.

Suzuki, Y., Y. Adachi, N. Ohno and T. Yadomae, 2001. Th1/Th2-balancing immunomodulating activity of gel-forming (1→3)-β-glucans from Fungi. Biol. Pharmaceut. Bull., 24: 811-819.

Svoboda, M., K. Nechvatalova, J. Krejci, J. Drabek, R. Ficek and M. Faldyna, 2007. The absence of iron deficiency effect on the humoral immune response of piglets to tetanus toxoid. Vet. Med., 52: 179-185.

Szmigielski, S., J. Gil, K. Roszkowski, H.L. Ko, G. Pulverer and J. Jeljaszewicz, 1982. Antineoplastic and antiviral properties of *Propionibacterium granulosum*. Drugs Exp. Clin. Res., 4: 387-401.

Tamura, J., K. Kubota, H. Murakami, M. Sawamura and T. Matsushima *et al*., 1999. Immunomodulation by vitamin B12: Augmentation of $CD8^+$ T lymphocytes and Natural Killer (NK) cell activity in vitamin B12-deficient patients by methyl-B12 treatment. Clin. Exp. Immunol., 116: 28-32.

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

Tedesco, D. and L. Haragsim, 2012. Cyclosporine: A review. J. Transplant. 10.1155/2012/230386

Thanendrarajan, S., M. Nowak, H. Abken and I.G.H. Schmidt-Wolf, 2011. Combining cytokine-induced killer cells with vaccination in cancer immunotherapy: More than one plus one? Leukemia Res., 35: 1136-1142.

Tirilomis, T., 2014. Daptomycin and its immunomodulatory effect: Consequences for antibiotic treatment of methicillin-resistant staphylococcus aureus wound infections after heart surgery. Front Immunol., Vol. 5. 10.3389/fimmu.2014.00097

Tiwari, R., S. Chakraborty, K. Dhama, S. Rajagunalan and S.V. Singh, 2013. Antibiotic resistance-an emerging health problem: Causes, worries, challenges and solutions: A review. Int. J. Curr. Res., 5: 1880-1892.

Tiwari, R., A.K. Verma, S. Chakraborty, K. Dhama and S.V. Singh, 2014a. Neem (*Azadirachta indica*) and its potential for safeguarding health of animals and humans: A review. J. Biol. Sci., 14: 110-123.

Tiwari, R., S. Chakraborty, M. Saminathan, K. Dhama and S.V. Singh, 2014b. Ashwagandha (*Withania somnifera*): Role in safeguarding health, immunomodulatory effects, combating infections and therapeutic applications: A review. J. Biol. Sci., 14: 77-94.

Tossing, G., 2001. New developments in interferon therapy. Eur. J. Med. Res., 6: 47-65.

Trapero-Marugan, M., L. Garcia-Buey, C. Munoz, N.E. Quintana and J.A. Moreno-Monteagudo *et al*., 2006. Sustained virological response to peginterferon plus ribavirin in chronic hepatitis C genotype 1 patients is associated with a persistent Th1 immune response. Aliment. Pharmacol. Ther., 24: 117-128.

Travis, S., L.M. Yap, C. Hawkey, B. Warren, M. Lazarov, T. Fong and R.J. Tesi, 2005. RDP58 is a novel and potentially effective oral therapy for ulcerative colitis. Inflammatory Bowel Dis., 11: 713-719.

Trebichavsky, I. and I. Splichal, 2006. Probiotics manipulate host cytokine response and induce antimicrobial peptides. Folia Microbiol., 51: 507-510.

Trevisi, P., G. Merialdi, M. Mazzoni, L. Casini and C. Tittarelli *et al*., 2007. Effect of dietary addition of thymol on growth, salivary and gastric function, immune response and excretion of *Salmonella enterica* serovar typhimurium, in weaning pigs challenged with this microbe strain. Italy J. Anim. Sci., 6: 374-376.

Tsai, Y.T., P.C. Cheng and T.M. Pan, 2012. The immunomodulatory effects of lactic acid bacteria for improving immune functions and benefits. Applied Microbiol. Biotechnol., 96: 853-862.

Tsoni, S.V. and G.D. Brown, 2008. β-glucans and dectin-1. Ann. New York Acad. Sci., 1143: 45-60.

Tuchscherer, M., W. Otten, E. Kanitz, M. Grabner and A. Tuchscherer *et al*., 2012. Effects of inadequate maternal dietary protein: Carbohydrate ratios during pregnancy on offspring immunity in pigs. BMC Vet. Res., Vol. 8. 10.1186/1746-6148-8-232

Tzianabos, A.O., 2000. Polysaccharide immunomodulators as therapeutic agents: Structural aspects and biologic function. Clin. Microbiol. Rev., 13: 523-533.

Uchakin, P.N., O.N. Uchakina, B.V. Tobin and F.I. Ershov, 2007. Neuroendocrine immunomodulation. Vestn. Ross Akad. Med. Nauk., 9: 26-32.

Van de Garde, M.D.B., F.O. Martinez, B.N. Melgert, M.N. Hylkema, R.E. Jonkers and J. Hamann, 2014. Chronic exposure to glucocorticoids shapes gene expression and modulates innate and adaptive activation pathways in macrophages with distinct changes in leukocyte attraction. J. Immunol., 192: 1196-1208.

Van de Veerdonk, F.L., B.J. Kullberg and M.G. Netea, 2012. Adjunctive immunotherapy with recombinant cytokines for the treatment of disseminated candidiasis. Clin. Microbiol. Infect., 18: 112-119.

Veldman, C.M., M.T. Cantorna and H.F. DeLuca, 2000. Expression of 1,25-dihydroxyvitamin D_3 receptor in the immune system. Arch. Biochem. Biophys., 374: 334-338.

Venturi, S., F.M. Donati, A. Venturi, M. Venturi, L. Grossi and A. Guidi, 2000. Role of iodine in evolution and carcinogenesis of thyroid, breast and stomach. Adv. Clin. Pathol., 4: 11-17.

Verma, A.K., K. Dhama, S. Chakraborty, A. Kumar and R. Tiwari *et al*., 2014. Strategies for combating and eradicating important infectious diseases of animals with particular reference to India: Present and future perspectives. Asian J. Anim. Vet. Adv., 9: 77-106.

Vetskova, E.K., M.N. Muhtarova, T.I. Avramov, T.R. Stefanova, I.J. Chalakov and M.H. Nikolova, 2013. Immunomodulatory effects of BCG in patients with recurrent respiratory papillomatosis. Folia Medica, 55: 49-54.

Vilcek, J., M.H. Ng, A.E. Friedman-Kien and T. Krawciw, 1968. Induction of interferon synthesis by synthetic double-stranded polynucleotides. J. Virol., 2: 648-650.

Villamor, E. and W.W. Fawzi, 2005. Effects of vitamin A supplementation on immune responses and correlation with clinical outcomes. Clin. Microbiol. Rev., 18: 446-464.

Vogel, F.R. and S.L. Hem, 2004. Immunologic Adjuvants. In: Vaccines, Plotkin, S.A. and W.A. Orenstein (Eds.). 4th Edn., W.B. Saunders Company, Philadelphia, PA., pp: 69-79.

Vuolo, L., C. di Somma, A. Faggiano and A. Colao, 2012. Vitamin D and cancer. Front. Endocrin., Vol. 3.

Walter, B.M. and G. Bilkei, 2004. Immunostimulatory effect of dietary oregano etheric oils on lymphocytes from growth-retarded, low-weight growing-finishing pigs and productivity. Tijdschrift Voor Diergeneeskunde, 129: 178-181.

Wang, H., E.R. Rayburn, W. Wang, E.R. Kandimalla, S. Agrawal and R. Zhang, 2006. Immunomodulatory oligonucleotides as novel therapy for breast cancer: Pharmacokinetics, *in vitro* and *in vivo* anticancer activity and potentiation of antibody therapy. Mol. Cancer Ther., 5: 2106-2114.

Weilhammer, D.R., C.D. Blanchette, N.O. Fischer, S. Alam and G.G. Loots *et al*., 2013. The use of nanolipoprotein particles to enhance the immunostimulatory properties of innate immune agonists against lethal influenza challenge. Biomaterials, 34: 10305-10318.

Weiss, G., 2002. Iron and immunity: A double-edged sword. Eur. J. Clin. Investigat, 32: 70-78.

Weiss, G., 2004. Iron. In: Diet and Human Immune Function, Hughes, D.A., L.G. Darlington and A. Bendich (Eds.). Humana Press, Totowa, USA., pp: 203-215.

Wenzel, B.E., A. Chow, R. Baur, H. Schleusener and J.R. Wall, 1998. Natural killer cell activity in patients with Grave's disease and Hashimoto's thyroiditis. Thyroid, 8: 1019-1022.

Wilckens, T. and R. de Rijk, 1997. Glucocorticoids and immune function: Unknown dimensions and new frontiers. Immunol. Today, 18: 418-424.

Winter, H., N.K. van den Engel, M. Rusan, N. Schupp and C.H. Poehlein *et al*., 2011. Active-specific immunotherapy for non-small cell lung cancer. J. Thoracic Dis., 3: 105-114.

Wintergerst, E.S., S. Maggini and D.H. Hornig, 2006. Immune-enhancing role of vitamin C and zinc and effect on clinical conditions. Ann. Nutr. Metab., 50: 85-94.

Wintergerst, E.S., S. Maggini and D.H. Hornig, 2007. Contribution of selected vitamins and trace elements to immune function. Ann. Nutr. Metab., 51: 301-323.

Yang, F.L., K.F. Hua, Y.L. Yang, W. Zou and Y.P. Chen *et al*., 2008. TLR-independent induction of human monocyte IL-1 by phosphoglycolipids from thermophilic bacteria. Glycoconjugate J., 25: 427-439.

Yang, Y.L., Yang, F.L., S.C. Jao, M.Y. Chen, S.S. Tsay, W. Zou and S.H. Wu, 2006. Structural elucidation of phosphoglycolipids from strains of the bacterial thermophiles *Thermus* and *Meiothermus*. J. Lipid Res., 47: 1823-1832.

Yazdi, M.H., M. Mahdavi, B. Varastehmoradi, M.A. Faramarzi and A.R. Shahverdi, 2012. The immunostimulatory effect of biogenic selenium nanoparticles on the 4T1 breast cancer model: An *in vivo* study. Biol. Trace Element Res., 149: 22-28.

Yu, Z., Y. Yin, W. Zhao, F. Chen and J. Liu, 2014. Application and bioactive properties of proteins and peptides derived from hen eggs: Opportunities and challenges. J. Sci. Food Agric., 94: 2839-2845.

Yuan, S.L., X.S. Piao, D.F. Li, S.W. Kim, H.S. Lee and P.F. Guo, 2006. Effects of dietary *Astragalus* polysaccharide on growth performance and immune function in weaned pigs. Anim. Sci., 62: 501-507.

Zaccone, P. and A. Cooke, 2013. Vaccine against autoimmune disease: Can helminths or their products provide a therapy? Curr. Opin. Immunol., 25: 418-423.

Zasloff, M., 2002. Antimicrobial peptides of multicellular organisms. Nature, 415: 389-395.

Zatz, M.M., J. Oliver, C. Samuels, A.B. Skotnicki, M.B. Sztein and A.L. Goldstein, 1984. Thymosin increases production of T-cell growth factor by normal human peripheral blood lymphocytes. Proc. Natl. Acad. Sci. USA., 81: 2882-2885.

Zeng, X., L.T. Sunkara, W. Jiang, M. Bible and S. Carter *et al*., 2013. Induction of porcine host defense peptide gene expression by short-chain fatty acids and their analogs. PLoS ONE, Vol. 8. 10.1371/ journal pone.0072922

Zhang, X., J. Li, D.K.W. Wong, T.E. Wagner and Y. Wei, 2009. Fermented noni exudate-treated dendritic cells directly stimulate B lymphocyte proliferation and differentiation. Oncol. Rep., 21: 1147-1152.

Zhang, Z.W., Q.H. Wang, J.L. Zhang, S. Li, X.L. Wang and S.W. Xu, 2012. Effects of oxidative stress on immunosuppression induced by selenium deficiency in chickens. Biol. Trace Element Res., 149: 352-361.

Zhao, S.J., F.J. Sun, E.J. Tian and Z.P. Chen, 2008. [The effects of iodine/selenium on the function of antigen presentation of peritoneal macrophages in rats]. Zhonghua Yu Fang Yi Xue Za Zhi, 42: 485-488, (In Chinese).

Zhao, X., R. Li, J. Huang, J. Li, M. Hou and J. Zhong, 2012. Association of some physiological factors and milk performance in Chinese holstein. Asian J. Anim. Vet. Adv., 7: 1356-1363.

Zhou, Q., L. Wang, H. Wang, F. Xie and T. Wang, 2012. Effect of dietary vitamin C on the growth performance and innate immunity of juvenile cobia (*Rachycentron canadum*). Fish Shellfish Immunol., 32: 969-975.

Zimmerman, T., 2009. Immunomodulatory agents in oncology. Update Cancer Therapeut., 3: 170-181.

Zoran, D.L., 2010. Obesity in dogs and cats: A metabolic and endocrine disorder. Vet. Clin. North Am.: Small Anim. Pract., 40: 221-239.