Review Article

[Patel, 3(3): Mar., 2012]

ISSN: 0976-7126

INTERNATIONAL JOURNAL OF PHARMACY & LIFE SCIENCES

A review on herbal immunoadjuvant

Khyati Patel

Sardar Patel College of Pharmacy, Vidhyanagar, (Gujrat) - India

Abstract

The world population relies upon traditional remedies (mainly herbs) for the health care of its people. In fact, herbs and/or plants are the oldest friends of mankind. There are biological or synthetic substances that can stimulate suppress or modulate any aspect of the immune system including both adaptive and innate arms of the immune system. The present paper enumerates the herbal immunoadjuvant.

Key-Words: Herbs, Immunity, Immunoadjuvants

Introduction

According to the World Health Organization (WHO), about three-quarters of the world population relies upon traditional remedies (mainly herbs) for the health care of its people. In fact, herbs and/or plants are the oldest friends of mankind. They not only provided food and shelter but also served to cure different ailments. Herbal medicine, sometimes called traditional or natural medicine, has always existed in one way or another in different cultures and civilizations, such as Ayurvedic (India), Egyptian, Western, Chinese, Kampo (Japan) and Greco-Arab or Unani-Tibb (south Asia).

In the early nineteenth century, the advent of modern medicine saw a rapid decline in botanical medicinal use. Vaccination, the discovery of antibiotics and improvements in medical technology all contributed to this demise. Today, plant-derived medicines are classified as complementary and alternative medicines (CAM) and are regulated by the Therapeutic Goods Administration (TGA) in Australia and by the Dietary Health and Supplement Education Act (DHSEA) under the Federal Drug Administration (FDA) in the USA[1-3]

Vaccines are one of the most successful interventions for infectious diseases.However,major challenges remain in vaccine design, including improving their efficacy significantly and developing new vaccines for emerging diseases. Current vaccines typically include an antigen or live attenuated microorganism, an adjuvant to enhance the immune response, and a delivery system to target delivery to the right location.

*** Corresponding Author**

E-Mail: Pkhyati28@yahoo.com

Mob.: +919510357712

An adjuvant is an agent that stimulates the immune system, increasing the response to a vaccine, while not having any specific antigenic effect. Adjuvants perform one or more of three main functions. (i) They provide a "depot" for the antigen for slow release; (ii) they facilitate targeting of the antigen to immune cells and enhance phagocytosis, and (iii) they modulate and enhance the type of immune response induced by the antigen alone[5-8] Adjuvants may also provide the danger signal the immune system needs in order to respond to the antigen as it would to an active infection[9]. Thus, adjuvants play a significant role on every aspect of the immune response.

Immunity

This may be defined as the body's ability to identify and resist large numbers of infectious and potentially harmful microorganisms, enabling the body to prevent or resist diseases and inhibit organ and tissue damage. The immune system is not confined to any one part of the body. Immune stem cells, formed in the bone marrow, may remain in the bone marrow until maturation or migrate to different body sites for maturation. Subsequently, most immune cells circulate throughout the body, exerting specific effects. The immune system has two distinct but overlapping mechanisms with which to fight invading organisms, the antibody-mediated defense system (humoral immunity) and the cell-mediated defense system (cellular immunity).[10]

Immune systems

The basic architecture of the immune system is multilayered, with defenses on several levels. Most obvious and primary is the skin: the first barrier against infection.

Another is physiological, where conditions like the temperature and pH of the body provide inappropriate living conditions for foreign organisms. Once

pathogens have successfully entered the body, they are addressed by the innate and/or the acquired or adaptive immune system. Both systems consist of a multitude of cells and molecules that interact in a complex manner to detect and eliminate pathogens. Detection and elimination depend upon chemical bonding: surfaces of immune system cells are covered with various receptors, some of which chemically bind to pathogens, while others bind to other immune system cells or molecules to enable the complex signaling system that mediates the immune response.[11]

Immunomodulators

These are biological or synthetic substances that can stimulate, suppress or modulate any aspect of the immune system including both adaptive and innate arms of the immune system.

Classification of immunomodulators

Clinically, immunomodulators can be classified into the following three categories: **Immunoadjuvants** are used to enhance the efficacy of vaccines and therefore could be considered specific immune stimulants. Immunoadjuvants hold the promise of being the true modulators of the immune response. It has been proposed that they be exploited as selectors between cellular and humoral helper T1 (Th1) and helper T2 cells (Th2), immunoprotective, immunodestructive, and reagenic [immunoglobulin E (IgE)] versus IgG type immune responsesdposing a real challenge to vaccine designers.[12]

Immunostimulants are inherently non-specific as they are envisaged as enhancements to a body's resistance to infection. They can act through innate as well as adaptive

immune responses. In healthy individuals, the immunostimulants are expected to serve as prophylactic and promoter agents, i.e., as immunopotentiators, by enhancing the basic level of immune response. In the individual with impairment of immune response, they are expected to act as immunotherapeutic agents.[13]

Immunosuppressants are a structurally and functionally heterogeneous group of drugs, which are often concomitantly administered in combination regimens to treat various types of organ transplant rejection and autoimmune diseases.[14]

Immune response mechanisms[15-23]

A physiological immune response begins with the antigen presenting cell (APC). This is the crucial step of the activation of the immune system. The best APCs responsible for activation of helper T cells, killer T cells and B cells are dendritic cells (DCs). Immature DCs are found under the skin and mucous membranes where they sample surrounding for possible pathogens

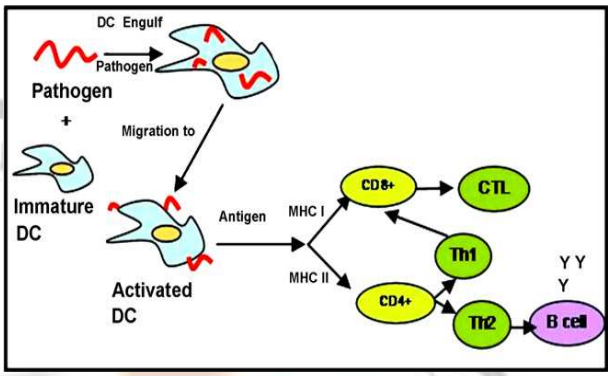

Fig. 1: Mechanism of immune responce

through pattern recognition receptors. After detecting pathogen, these cells engulf it via phagocytosis and pinocytosis and migrate to lymph nodes where

they become mature. Once inside the DC, pathogens are degraded into small fragments that are further expressed at their surface where they can be presented to T cells and B cells (Fig. 1). After the T cells and B cells become activated, they generate a cascade of events that lead to attack the disease. There are two antigen presenting pathways within DCs that lead to the major histocompatibility complex (MHC) olecules. These molecules bind peptide fragments from pathogens and display them on the DC surface for recognition by T cells. One of these pathways is endogenous, which involves presentation of MHC I molecules to CD8+ T cells. The CD8+ T cells activated by DCs presenting antigens can kill infected cells directly by activating cytotoxic T lymphocytes (CTLs). On the other hand, the exogenous pathway involves presentation of MHC II molecules to CD4+ T cells. A subset of the activated CD4+ T cells, known as helper T cells, Th1 and Th2, are responsible for cellmediated immunity (CMI) and humoral immunity, respectively. T cells of the immune system which generate CMI or a Th1 response require the antigen to be processed and presented on the surface of an antigen presenting cell to stimulate T cells. B cells are responsible for the humoral or Th2 response, and they recognize antigens through B cell receptors and can secrete antibodies in response. Most current vaccine designs generate an acquired immune response but do not stimulate the Th1 pathway. An immune response of the Th2-type is characterized by the production of cytokines such as IL-4, IL-5, IL-10 and IL-13 producing elevated IgG1 and IgE antibody isotypes. Th1-type responses are characterized by the production of the cytokines IFN-_ and TNF-_, antibodies of the IgG2 isotype and are usually associated with CMI including activated macrophages and delayed-type hypersensitivity.. Immune responses of the Th1 type are directed more

towards intracellular pathogens and are necessary for clearance of many viruses, some bacteria (e.g., *Mycobacterium tuberculosis*) and anti-tumor effects, whereas a Th2 response is generally sufficient for the neutralization of toxins, viruses, and bacterial adhesion. Further, CD4+ cells can be classified as Th17 or Treg. For efficacious vaccines, it is essential to induce the appropriate immune response is essential for vaccine efficacy. For example, in the BALB/c model of leishmaniasis, a Th2-biased immune response does not afford protection and the mice are unable to clear the infection. In another example, the currently used Bacille Calmette Guerin (BCG) vaccine for tuberculosis is ineffective in preventing disease because it is unable to redirect a pre-existing immune response (due to previous infection) to a protective, Th1 dominant immune response. Similarly, current vaccines against feline infectious peritonitis viruses are ineffective because they are biased towards enhancing humoral immunity, which has been shown to exacerbate the disease, whereas a CMI or regulatory response would be protective. As mentioned before, DCs are critical components of innate immunity that affect the acquired immune response (and their activation is a powerful tool to manipulate the immune system. DCs are present in an immature state where they cannot stimulate T cells, but the presence of an antigen causes the DCs to mature and mobilize. Therefore vaccines that can stimulate DC maturation are promising in order to obtain a more balanced immune response and to increase the efficacy of vaccines. Harnessing both immune system pathways and facilitating immunomodulation to obtain an unbiased immune response (i.e., Th0, which is a balance between Th1 and Th2) is key to effective vaccine treatments against infectious agents

Limitations of current vaccines[24-30]

Current vaccine designs do not target the DC system. DCs can readily stimulate T cells and can operate at mucosal surfaces,where early protection is needed in many infections, while existing vaccines are weak stimulators of T cells. T-cell activation is only guaranteed by repeated encounters with persistent low levels of antigens Therefore therapeutic strategies based on modulating the immune response may significantly expand treatment options and circumvent the problem of rapid emergence of resistance. The major advantage of infectious disease therapies based on immunomodulation is that it harnesses a systemthat has evolved and is continuously evolving to protect against microorganism-related diseases. While both the innate immune system and antimicrobial agents show rapid onset of action, modulators of innate immunity are not likely to develop resistance because they do not disable a specific microbial target and their mechanisms of action involve multiple effector cells. Vaccinology, including adjuvant design, has focused mainly on parenteral routes of administration. However, most pathogens enter through mucosal routes such as oral, nasal or genital and parenteral vaccines alone do not typically produce mucosal immune responses. The difference between the mucosal mode of entry of most pathogens versus the parenteral route of administration of most vaccines leads to stimulation of production of different isotype antibodies. Current vaccines elicit mainly IgG isotype antibodies, in contrast to natural infections that elicit a wide range of antibody isotypes. Therefore the protection afforded by the vaccines is not as long-lasting. Immunization of one mucosal surface also sensitizes other remote mucosal surfaces because of a common mucosal immune system. However, mucosal delivery of vaccines poses several challenges. Most protein antigens are poor immunogens when administered mucosally and may induce immunological tolerance instead There have been several intranasal vac cines that have been developed to counter infectious diseases such as diphtheria and pneumonic plague . These vaccines are more effective when adjuvanted with either microbially derived components or synthetic polymers and are usually inhaled in particulate form. Some of these intranasal vaccines induce cellmediated immunity, leading to protection. On the other hand, oral administration provides access to the largest immunological organ of the body, the intestine. Digestive degradation following oral administration causes large and repeated doses of killed microbe or peptide antigens to be required. Therefore potentially new solutions to this problem are imperative, and a U.S. National Research Council (NRC) panel recently addressed grand challenges in this area. The panel's main recommendations. to improve vaccine design include: (1) Research to identify good delivery mechanisms and (2) identification of potential molecular targets for targeting DCs and modulating innate immunity without undesired side effects. The NRC report identified the determination of how to elicit protective non-IgG responses and simulate the mucosal response, and devising strategies to target DCs and optimize antigen delivery to DCs as the most likely approaches to improve vaccinations and combat infectious diseases.

Immunomodulation by plant-derived medicines

Experimental evidence has shown that the development of immune responses following infection or vaccination can be influenced by plant-derived

medicines. The ability to modulate immune function offers many advantages from maintaining health through immunity to stimulating or suppressing beneficial or deleterious immune responses. Plant medicines could mediate such effects through targeted modulation of key cellular and molecular interactions of antigen-presenting cells (e.g. dendritic cells), T-lymphocytes and B-lymphocytes as illustrated by the paradigm in Fig. 1. Identification of such immunomodulatory properties will be crucial in the discovery of novel, clinically-relevant compounds for augmenting existing immunotherapy or vaccination practices. Perhaps more importantly, immunomodulatory plant-derived medicines may be critical in developing regions of the world – where burden of disease is high and access to medical care limited – as a low cost alternative to achieve a better health status through enhanced protective immunity. It is imperative therefore to elucidate the mechanism(s) by which plant-derived medicines modulate immune responses. In this context, the important functions of dendritic cells (DCs), B-lymphocytes and Tlymphocytes are discussed.

Modulation of dendritic cell activity

Dendritic cells (DCs) are recognised as specialised 'professional' antigen-presenting cells capable of initiating and directing immune responses following infection. Dependent on the pathogenic 'signals' received by DCs, the immune system can be triggered to respond in a TH1or TH2 restrictedmanner30-31. As such, DCs are often described as critical regulators of immunity that operate at the interface between the innate and adaptive immune systems. Dendritic cells that reside in peripheral lymphoid tissues become activated following encounter and phagocytosis of antigen through engagement of cell-surface receptors (e.g. Toll-like receptors [TLRs] and CD14) with pathogenic molecules such as bacterial lipopolysaccharide (LPS)[32-33]. Activated DCs interact with antigen-specific CD4+ T-lymphocytes and migrate to the infected site where the expression of co-stimulatory molecules on the cell surface is upregulated (e.g. CD80, CD40, CD86, and CTLA-4) to stimulate appropriate effector T-lymphocyte function[34-35]. Given the integral role for DCs in the initiation of immune responses, experimental approaches based on the design of novel therapeutics that exploit DC function may provide effective alternatives to current immunotherapies. Indeed, emerging vaccine candidates that modulate the activity of DCs are of particular interest where certain types of immune responses have proven difficult to generate with existing vaccines[31].

The biological activities of plant-derivedmedicines are therefore dependent on the species, purified components and experimental conditions used. The identification of immunosuppressive drugs is becoming increasingly important in the context of the rising incidence of chronic diseases such as autoimmunity, allergy and cancer. Plant compounds that are able to down-regulate DC-specific immune parameters may provide an alternate new class of pharmaceuticals. Treatment of human DCs with Tripterygium wilfordii saponins in vitro resulted in 75% lower CD80 expression that was postulated to be IL-10 dependent, suggesting a mechanism of action for this preparation . Furthermore, the suppression of LPS-induced MHC Class II, CD80 and CD86 expression on DCs by the polyacetylene compound, falcarindiol (from Notopterygium incisum) was due to inhibition of the transcription factor, NF-κB [44]. Differential effects on human DC maturation in vitro was observed for various Echinacea purpurea extracts,with increased expression of CD83 by the root and flower extracts whereas whole plant and stem/leaf extracts reduced this expression[36-43].

Herbal component	Interact with specific-antigen	Action
Polysaccharides from Astragalusmongholicus	CD11c and MHC Class II molecules in vitro	enhanced DC antigen presentation capacity
flavonoid-rich fraction of Alchornea cordifolia	increased HLA-DR, CD40, CD80 and CD86 expression	Maturation of human and murine DCs
volatile oil rich extracts of Amomi semen	activation of CD86 but not CD80	murine bone marrow-derived DCs
steroidal Ginseng saponin M4	higher T-cell stimulatory capacity in a mixed lymphocyte reaction	to immature DCs in vitro
saponin-rich Panax notoginseng extract	TLR ligands such as LPS, CpG and poly (I:C	to attenuate the activation of murine DCs

Modulation of B-lymphocyte function

B-lymphocytes are critical for the induction of effective antibodybased immunity following pathogen

challenge. Current vaccines have been developed to exploit the exquisite specificity of antibody secreted by B-lymphocytes to confer protection from diseases such as diphtheria, tetanus, pertussis, hepatitis, measles, Haemophilus influenzae type b(Hib), and pneumococcal and meningococcal infections [47–49]. Plantderived medicines that modulate B-lymphocyte effector functions may be a useful tool in the maintenance of protective immunity in resource-poor settings where access to vaccines is limited. Moreover, the demonstrated activity of plant drugs delivered mucosally offers significant advantages over the conventional parenteral routes of immunisation in these regions.[44-46]

Parenteral administration

The parenteral administration of plant-derived medicines has been a convenient method to identify bioactive properties on host specific immune responses. Even in the absence of antigen, plant drugs are able to modulate adaptive immune responses.

Plant-derived medicines	Administration	Immune responses[51-59]
fruit-derived monoterpenes, limonene, perillic acid and carvone	intraperitoneally (ip) to mice	enhance the anti-sheep red blood cell (SRBC) antibody response up to 10-fold above untreated mice
vegetable-derived isothiocyanates or a Tridax procumbens extract,	immunisation (ip)	increased B-cell proliferation by an elevated SRBC plaque-forming cell (PFC) response
total (T)-ginseng preparation	guinea pigs immunised with a porcine parvovirus (PPV) vaccine	serum haemagglutination inhibition (HI) antibody titres six times higher than guinea pigs immunised with PPV alone
purified Astragalus polysaccharides	rabbit HI antibody titre	inactivated rabbit hemorrhagic disease (RHD) vaccine up to 49 days post-immunisation compared to a non-adjuvanted vaccine
Polygala senega vaccine	mice immunised subcutaneously with a combined ovalbumin (OVA)-	producing a four-fold rise in serumanti- OVA IgG compared to control mice
Bupleurum chinense or Glycyrrhiza uralensis	mice immunised with OVA	stimulating serumOVA-specific IgG, IgG1 and IgG2b titres up to 16-fold equivalent to the human vaccine adjuvant, alum and was attributed to its saponin content
Saponins isolated from Anemone raddeana (ARS)	mice	enhanced the OVA-specific IgG, IgG1 and IgG2b levels in mice

Mucosal administration

The adjuvant activity of plant-derived medicines is particularly important in the context of mucosal vaccines. Since infections occur predominately through the mucosal surface, new-generation vaccines that elicit protective immunity following mucosal administration will be critical. Using this approach, the oral administration of a phenolic-rich extract of Mangifera indica to mice augmented the serum anti-SRBC HA titre almost 20-fold above control mice. More recently, these authors reported that the serum anti-influenza titres of mice were substantially elevated following immunisation with a combined intranasal influenza vaccine containing saponins derived from P. tenuifolia. The effects of P. tenuifolia in this study was attributed to enhanced APC activity and that the combined vaccine preparation may protect from antigen degradation events, allowing a slow and sustained exposure to the immune system. It could be proposed that such activity might ultimately provide heightened and prolonged T and/or B-lymphocyte activation resulting in the reported increased antibody response detected. Similarly, the anti-influenza IgG response of mice orally administered with Pinellia ternata-derived Pinelliae tuber for 16 days was elevated above control mice.[47-49]

Modulation of T-lymphocyte function

Pathogenic molecules are presented to T-lymphocytes by dendritic cells in peripheral lymphoid tissues and, depending on the nature of the signals received via T-cell receptor (TCR) engagement, co-stimulation and

the cytokine milieu, produce TH 1 or TH2-based immune responses. Although critical to the success of vaccination, these responses can also be deleterious when unregulated in the context of allergy and autoimmune diseases. The presence and function of CD4+ T-lymphocyte populations such as regulatory T cells (Treg), TH17 and TH9 cells all contribute to the balance between health and disease. Equally important is the development of CD8+ T-lymphocytes that act to destroy and remove virally-infected cells and tumours. The discovery of plant-derived medicines that modulate CD4+ and CD8+ T-lymphocyte function will therefore be an important class of novel therapeutic agents.[50]

Plant-derived medicines that modulate CD4+ T-lymphocytes

Data from in vitro studies have documented the effects of plant derived medicines on CD4+ T-lymphocyte function.

Plant-derived medicines	**CD4+ T-lymphocytes**[60-65]
Bupleurum falcatum-derived saikosaponin-d	enhance the proliferative response of concanavalin A (ConA)-stimulated mouse spleen cells associated with higher IL-2 production
Sho-seiryu-to following incubation with ConAtreated mouse splenocytes	reduction in IL-4 mRNA
alkylamides derived from E. angustifolia and E. purpurea	increased the level of the NF-κB in LPS and PMA-stimulated human Jurk at T-lymphocytes had no such effect on unstimulated cells
C. sinensis & alkaloid containing extracts of Tylophora indica	treatment of ConA stimulated mouse splenic CD4+ T-lymphocytes resulted in abrogated IL-2 levels.
T. wilfordii hook F, triptolide	elicit this activity, and could inhibit peripheral CD4+ T-lymphocytes but increased CD8+ T-lymphocyte numbers in Peyer's patches of mice in a collagen-induced mouse arthritis model of inflammation

Plant-derived medicines that modulate CD8+T-lymphocyte function

The cytotoxic CD8+ T-lymphocyte response is particularly important for the protection against virally-infected cells and tumour cells.

Plant-derived medicines	**Modulate CD8+T-lymphocyte**[66-68]
Oral administration of mice with S. cerevisiae-derived β-glucan	increased the levels of CD8+ and CD4+ intraepithelial lymphocytes (IELs) compared with control mice with increased IFNγ mRNA in IELs
Lentinan, the β-glucan purified from Lentinus edodes	antigen-specific CTL production in vivo and in vitro through increased IL-2 responsiveness of CD8+ T-lymphocytes
oral treatment of mice with a water-extract of Dok Din Daeng	increased the T cell proliferative response by 31% compared to control cells in vitro, supporting earlier results using the related A. indica seed extracts

Conclusion

Evidence from the scientific literature supports the use of plantderived medicines to stimulate immune function. Characterisation of these preparations in terms of biological activity and bioactive componentswill promote the utility of such preparations in the future. While the potential for use of plant-derived medicines should not be underestimated, the cellular and molecular mechanisms of action need to be clearly defined. Onemajor limitation appears to be the lack of congruence in research strategy and experimental design,with numerous approaches implemented in examination of the biological effects. The choice of plantderived medicine, whether this is a whole formula, extract or purified component, the level of endotoxin and method of administration are all key questions that influence biological activity. In addition, the dose and timing of administration also needs to be evaluated extensively. In summary, the biological properties of plant-derived are increasingly being appreciated by the scientific community. The immune modulating activity of these preparations has provided the impetus for further characterisation and in some cases, potential mainstream utilisation as part of an integrated healthcare system.

References

1. Matthews HB, Lucier GW, Fisher KD. Medicinal herbs in the United States: research needs. Environ Health Perspect 1999;107:773–8.
2. Talalay P. The importance of using scientific principles in the development of medicinal agents from plants. Acad Med 2001;76:238–47.
3. Wohlmuth H, Oliver C, Nathan PJ. A review of the status of Western herbal medicine in Australia. J Herb Pharmacother 2002;2:33–46.
4. Pashine, A., Valiante, N.M., Ulmer, J.B., 2005. Targeting the innate immune response with improved vaccine adjuvants. Nat. Med. 11, S63–S68.
5. Cox, E., Verdonck, F., Vanrompay, D., Goddeeris, B., 2006. Adjuvants modulating mucosal immune responses or directing systemic responses towards the mucosa. Vet. Res. 37, 511–539.
6. Trujillo-Vargas, C.M., Mayer, K.D., Bickert, T., Palmetshofer, A., Grunewald, S., Ramirez-Pineda, J.R., et al., 2005. Vaccinations with T-helper type 1 directing adjuvants have different suppressive effects on the development of allergeninduced T-helper type 2 responses. Clin. Exp. Allergy 35, 1003–1013.
7. Lutsiak, M.E., Kwon, G.S., Samuel, J., 2006. Biodegradable nanoparticle delivery of a Th2-biasedpeptide for induction ofTh1immuneresponses. J. Pharm. Pharmacol. 58, 739–747.
8. Petrovsky, N., 2006. Novel human polysaccharide adjuvants with dual Th1 and Th2 potentiating activity. Vaccine 24, S2-26-9.
9. Janeway, C.A., Travers, P.,Walport, M., Shlomchik, M.J. (Eds.), 2001. Immunobiology
10. The Immune System in Health and Disease, 5th ed. Garland Publishing, New York, NY.
11. Ford MS, Roach SS. Introductory clinical pharmacology. 27th ed. USA: Lippincott Williams and Wilkins; 2009. 567e568.
12. Hofmeyr SA. An interpretative introduction to the immune system. In: Cohen I, Segel L, editors. Design principles for the immune system and other distributed autonomous systems. NY, USA: Oxford University Press, Inc; 2001. p. 3e24.
13. Alfons B, Patrick M. Modes of action of Freund's adjuvants in experimental models of autoimmune diseases. J Leukoc Biol 2001; 70:849e60.
14. El-Sheikh ALK. Renal transport and drug interactions ofimmunosuppressants [thesis]. Nijmegen, Netherlands: Radbound University; 2008:62.
15. O'Neill, L.A.J., 2005. Immunity's early warning system. Sci. Am. 292, 38–45.
16. McNeela, E.A., Mills, K.H., 2001. Manipulating the immune system: humoral versus cell-mediated immunity. Adv. Drug Deliv. Rev. 51, 43–54.
17. Brewer, J.M., Pollock, K.G.J., 2004. Adjuvant-induced Th2 and Th-1 dominated immune responses. In: Kaufmann, S.H.E. (Ed.), Novel Vaccination Strategies. WILEY-VCH Verlag GmbH & Co. KGaA,Weinheim, pp. 147–163.
18. Finkelman, F.D., Urban, J.F.J., 1992. Cytokines: making the right choice. Parasitol. Today 8, 311–314.
19. Annunziato, F., Cosmi, L., Santarlasci, V., Maggi, L., Liotta, F., Mazzinghi, B., et al., 2007. Phenotypic and functional features of human Th17 cells. J. Exp. Med. 204 1849–1861.
20. Villadangos, J.A., Schnorrer, P., 2007. Intrinsic and cooperative antigen-presenting functions of dendritic-cell subsets in vivo. Nat. Rev. Immunol. 7, 543–555.
21. Woodland, D.L., 2004. Jump-starting the immune system: prime-boosting comes of age. Trends Immunol. 25, 98–104.
22. Sedlik, C., Dériaud, E., Leclerc, C., 1997. Lack of Th1 or Th2 polarization of CD4+ T cell response induced by particulate antigen targeted to phagocytic cells. Int. Immunol. 9, 91–103
23. Chatelain, R.,Mauze, S., Coffman, R.L., 1999. Experimental leishmaniamajor infection in mice: role of IL-10. Parasite Immunol. 21, 211–218.
24. Alpar, H.O., Eyles, J.E., Williamson, E.D., Somavarapu, S., 2001. Intranasal vaccination against plague, tetanus, and diphtheria. Adv. Drug Deliv. Rev. 51, 173–201.
25. Bielinksa, A.U., Janczak, K.W., Landers, J.J., Markovitz, D.M., Montefiori, D.C., Baker, J.R., 2008. Nasal immunization with a recombinant HIV gp120 and nanoemulsion adjuvant produces Th1 polarized responses and neutralizing antibodies to primary HIV type 1 isolates. AIDS Res. Hum. Retroviruses 24, 271–281.
26. Bielinska, A.U., Chepurnov, A.A., Landers, J.J., Janczak, K.W., Chepurnova, T.S., Luker, G.D., et al., 2008. A novel killed-virus nasal vaccinia vaccine. Clin. Vaccine Immunol. 15, 348–358.
27. Jones, T., Adamovicz, J.J., Cyr, S.L., Bolt, C.R., Bellerose, N., Pitt, L.M., et al., 2006. Intranasal Protollin/F1-V vaccine elicits respiratory and serum antibody responses and protectsmice

against lethal aerosolized plague infection. Vaccine 24, 1625–1632.
28. Immunomodulation, 2006. Treating Infectious Diseases in a MicrobialWorld: Report of Two Workshops on Novel Antimicrobial Therapeutics. National Research Council of the National Academies,Washington DC.
29. Immunomodulation, 2006. Treating Infectious Diseases in a MicrobialWorld: Report of Two Workshops on Novel Antimicrobial Therapeutics. National Research Council of the National Academies,Washington DC.
30. Bendelac A, Medzhitov R. Adjuvants of immunity: harnessing innate immunity to promote adaptive immunity. J Exp Med 2002;195:F19–23.
31. Hu H, Moller G. Lipopolysaccharide-stimulated events in B cell activation. Scand J Immunol 1994;40:221–7.
32. van Duin D, Medzhitov R, Shaw AC. Triggering TLR signaling in vaccination. Trends Immunol 2006;27:49–55.
33. Datta SK, Raz E. Induction of antigen cross-presentation by Toll-like receptors. Springer Semin Immunopathol 2005;26:247–55.
34. Banchereau J, Briere F, Caux C, Davoust J, Lebecque S, Liu YJ, et al. Immunobiology of dendritic cells. Annu Rev Immunol 2000;18:767–811.
35. Steinman RM. The dendritic cell system and its role in immunogenicity. Annu Rev Immunol 1991;9:271–96.
36. Shao P, Zhao LH, Zhi C, Pan JP. Regulation on maturation and function of dendritic cells by Astragalus mongholicus polysaccharides. Int Immunopharmacol 2006;6: 1161–6.
37. Nworu CS, Esimone CO, Tenbusch M, Nabi G, Proksch P, Uberla K, et al. Adjuvant properties of AcF1, an immunostimulant fraction of Alchornea cordifolia extract. Immunol Invest 2010;39:132–58.
38. Fukui H, Mitsui S, Harima N, Nose M, Tsujimura K, Mizukami H, et al. Novel functions of herbal medicines in dendritic cells: role of Amomi Semen in tumor immunity. Microbiol Immunol 2007;51:1121–33.
39. Takei M, Tachikawa E, Hasegawa H, Lee JJ. Dendritic cells maturation promoted by M1 and M4, end products of steroidal ginseng saponins metabolized in digestive tracts, drive a potent Th1 polarization. Biochem Pharmacol 2004;68: 441–52.
40. Rhule A, Rase B, Smith JR, Shepherd DM. Toll-like receptor ligand-induced activation of murine DC2.4 cells is attenuated by Panax notoginseng. J Ethnopharmacol 2008;116:179–86.
41. Wang SJ, Yao K, Xie FD, Ji XH. Effects of Tripterygium wilfordii saponins and interleukin-10 on dendritic cells from human peripheral blood. Acta Pharmacol Sin 2001;22:721–4.
42. Mitsui S, Torii K, Fukui H, Tsujimura K,Maeda A, Nose M, et al. The herbalmedicine compound falcarindiol from Notopterygii Rhizoma suppresses dendritic cell maturation. J Pharmacol Exp Ther 2010 Epub ahead of print.
43. Wang CY, ChiaoMT, Yen PJ,HuangWC,Hou CC, Chien SC, et al.Modulatory effects of Echinacea purpurea extracts on human dendritic cells: a cell- and gene-based study. Genomics 2006;88:801–8.
44. Brenzel L, Wolfson LJ, Fox-Rushby J, Miller M, Halsey NA. Vaccine-preventable diseases. Disease Control Priorities in Developing Countries. 2nd ed. IBRD/The World Bank and Oxford University Press; 2006.
45. Makela PH. Vaccines, coming of age after 200 years. FEMS Microbiol Rev 2000;24:9–20.
46. Zimmerman RK, Burns IT. Child vaccination, part 2: childhood vaccination procedures. J Fam Pract 2000;49:S34–9 quiz S40.
47. Makare N, Bodhankar S, Rangari V. Immunomodulatory activity of alcoholic extract of Mangifera indica L. in mice. J Ethnopharmacol 2001;78:133–7.
48. Nagai T, Suzuki Y, Kiyohara H, Susa E, Kato T, Nagamine T, et al. Onjisaponins, from the root of Polygala tenuifolia Willdenow, as effective adjuvants for nasal influenza and diphtheria–pertussis–tetanus vaccines. Vaccine 2001;19:4824–34.
49. Nagai T, Kiyohara H, Munakata K, Shirahata T, Sunazuka T, Harigaya Y, et al. Pinellic acid from the tuber of Pinellia ternata Breitenbach as an effective oral adjuvant for nasal influenza vaccine. Int Immunopharmacol 2002;2:1183–93.
50. Akdis CA, Akdis M. Mechanisms and treatment of allergic disease in the big picture of regulatory T cells. J Allergy Clin Immunol 2009;123:735–46 quiz 47–8.
51. Raphael TJ, Kuttan G. Immunomodulatory activity of naturally occurring monoterpenes carvone, limonene, and perillic acid. Immunopharmacol Immunotoxicol 2003;25:285–94.

52. Manesh C, Kuttan G. Effect of naturally occurring isothiocyanates on the immune system. Immunopharmacol Immunotoxicol 2003;25:451–9.
53. Tiwari U, Rastogi B, Singh P, Saraf DK, Vyas SP. Immunomodulatory effects of aqueous extract of Tridax procumbens in experimental animals. J Ethnopharmacol 2004;92:113–9.
54. Yang L, Hu Y, Xue J, Wang F, Wang D, Kong X, et al. Compound Chinese herbal`1 medicinal ingredients can enhance immune response and efficacy of RHD vaccine in rabbit. Vaccine 2008;26:4451–5.
55. Estrada A, Katselis GS, Laarveld B, Barl B. Isolation and evaluation of immunological adjuvant activities of saponins from Polygala senega L. Comp Immunol Microbiol Infect Dis 2000;23:27–43.
56. Sun HX. Haemolytic activities and adjuvant effect of Bupleurum chinense saponins on the immune responses to ovalbumin in mice. Vaccine 2006;24:1324–31.
57. Sun HX, Pan HJ. Immunological adjuvant effect of Glycyrrhiza uralensis saponins on the immune responses to ovalbumin in mice. Vaccine 2006;24:1914–20.
58. Sun Y, Li M, Liu J. Haemolytic activities and adjuvant effect of Anemone raddeana saponins (ARS) on the immune responses to ovalbumin in mice. Int Immunopharmacol 2008;8:1095–102
59. Rivera E, Hu S, Concha C. Ginseng and aluminium hydroxide act synergistically as vaccine adjuvants. Vaccine 2003;21:1149–57.
60. Yamaguchi N, Kohno H, Tawara M, Odashima S, Abe H. Effect of saikosaponin derivatives upon the immune response against T-dependent and T-independent antigens in mice. Int J Immunopharmacol 1985;7:827–32.
61. Kato M, Pu MY, Isobe K, Iwamoto T, Nagase F, Lwin T, et al. Characterization of the immunoregulatory action of saikosaponin-d. Cell Immunol 1994;159:15–25.
62. Ikeda Y, Kaneko A, Yamamoto M, Ishige A, Sasaki H. Possible involvement of suppression of Th2 differentiation in the anti-allergic effect of Sho-seiryu-to in mice. Jpn J Pharmacol 2002;90:328–36.
63. Matthias A, Banbury L, Bone KM, Leach DN, Lehmann RP. Echinacea alkylamides modulate induced immune responses in T-cells. Fitoterapia 2008;79:53–8.
64. Tomita M, Irwin KI, Xie ZJ, Santoro TJ. Tea pigments inhibit the production of type 1 (T(H1)) and type 2 (T(H2)) helper T cell cytokines in CD4(+) T cells. Phytother Res 2002;16:36–42.
65. Ganguly T, Badheka LP, Sainis KB. Immunomodulatory effect of Tylophora indica on Con A induced lymphoproliferation. Phytomedicine 2001;8:431–7.
66. Tzianabos AO. Polysaccharide immunomodulators as therapeutic agents: structural aspects and biologic function. Clin Microbiol Rev 2000;13: 523–33.
67. Hamuro J, Rollinghoff M, Wagner H, Seitz M, Grimm W, Gemsa D. Depressed prostaglandin release from peritoneal cells induced by a T cell adjuvant, lentinan. Z Immunitatsforsch Immunobiol 1979;155:248–54.
68. Chai JG, Bando T, Nagasawa H, Himeno K, Sato M, Ohkubo S. Seed extract of Aeginetia indica L induces cytokine production and lymphocyte proliferation in vitro. Immunopharmacology 1994;27:13–21.