www.sphinxsai.com

PharmTech

International Journal of PharmTech Research
CODEN (USA): IJPRIF ISSN : 0974-4304
Vol.3, No.3, pp 1837-1842, July-Sept 2011

Phytosaponin Adjuvants : A Better Option for Vaccines

Prashant Bagherwal

Institute of Pharmacy,Vikram University,Ujjain (M.P.),India.

Corres.author: prashant_bagherwal@rediffmail.com
Mob.- 09685024006

Abstract: In the present study the importance of adjuvant, their role & effect of saponin in immune system is reviewed. Phytosaponins adjuvant have the advantage that only a low dose of vaccine is needed when combined use of immunostimulant adjuvant. Herbal drugs have preferential effect on Th1 & Th2 immunity. It regulate the immune response & strengthen the primary as well as secondary adaptive immune response by increasing the efficacy of vaccine. Saponins induces strong cytotoxic CD8+ lymphocytic response & have the ability to modulate cell mediated immune response to enhance the antibody production. In the present study we reviewed that phyto saponins i.e. ISCOM, Astragalus saponin & Ginseng has been reported to enhance specific antibody response against antigens. They increases IgG & IgM antibody response, & interferon that might mediate their immunostimulant effect.

An adjuvant can be used for increasing the immunogenicity of a poor antigen, improving the efficacy of vaccine in new born & reducing the amount required of antigen in antigenic vaccine or by reducing the number of immunizations. So, it might be successful to controlling the mortality rate in the growing world.

Key words – Phyto immuno-adjuvants, Saponin adjuvants, ISCOM, Astragalus, Ginseng.

INTRODUCTION

Vaccines are successful in controlling a substantial portion of the morbidity and mortality in the developing world & great toll as a prophylactic agent to improve the quality of human life. Saponin based adjuvants have the ability to stimulate the cell mediated immune system as well as to enhance antibody production and have the advantage that only a low dose is needed for adjuvant activity. In the present study the importance of adjuvants, their role and the effect of saponin in immune system is reviewed.

Herbal modulators can be administered along with the vaccine to elicit a faster and stronger immune response. Rationally designed adjuvants, in order to improve immune responses, are challenging to develop. Further, these adjuvants are also challenging to get approval because adjuvants frequently induce toxicity.

Most common adjuvants mainly aluminum or oil adjuvants are used in vaccine, but these chemical adjuvants have many disadvantages, such as side effects, strong local stimulation and carcinogenesis, together with complicated preparations or failure to increase immunogenicity of weak antigen and so on[1,2,3]. Comparative studies in humans and animals showed that aluminum is a weak adjuvant for antibody induction to recombinant protein vaccines and induces a Th2, rather than a Th1 response[4].

Phytocomponents and mammalian proteins have been used to novel vaccine strategies are required to make the vaccine sufficiently immunogenic to initiate a potent immune response. Herbal immuno-modulators are paving its way as a safe alternative[5-10].

Selection of herbal drugs for such bioprospecting herbal drugs for increasing body resistance to fight external threats such as infection. Evidence-based studies shown their potential to modulate immune targets such as dendritic cells, Th1/Th2, NK cells[11]. Use of herbal immuno-modulators perhaps might be helpful in overcoming the initial lag. For, e.g., Angelica sinensus polysaccharide (ASP) increased the production of IL-2and IFNγ, while that of IL-4 was decreased[12]. Some experiments also established oral adjuvant activity of selected Rasayana botanicals with DPT vaccine[13]. In bacterial & viral infections which need IL-4 for its clearance should be combined with herbal modulators favoring Th2 responses, like ginseng[14]. Herbal adjuvants with thorough experimental data will be an ideal candidate to down regulate the inflammatory response and strengthen the primary and the memory adaptive responses thereby increasing the efficacy of the vaccine. Combined use of vaccines and immunostimulants is emerging as one of innovative approaches in adjuvant development[15]. We found that herbal drugs have preferential effects on Th1/Th2 immunity, which is one of emerging targets for adjuvant discovery[16,17].

Immunomodulatory adjuvants are one of approaches currently being considered for improving protective efficacy of existing vaccine formulations[18]. Importance of Saponin based adjuvants have the unique ability to These are a group of structurally heterogeneous compounds that enhance or modulate the genicity of the poorly immunogenic vaccine proteins or peptides[19,20]. Most immunostimulants enhance immunity compared to injection of antigen alone, injection of antigen plus an adjuvant generally permits use of a much smaller quantity of the antigen and greatly enhances the antibody titer[21].

An adjuvant can be used for increasing the immunogenicity of poor antigen, improving the efficacy of vaccine in new born and reducing the amount of antigen or the number of immunizations[22].

SAPONINS

Saponins are steroid or triterpenoid glycosides found in wild or cultivated plants, lower marine animals and some bacteria[23,24].

There is significant demand for saponins, particularly due to their presence in phytomedicines and as modern immune-adjuvants in commercial vaccines. The annual global market for herbal medicines was over US$ 63 billion in 2003[25] and the ever growing vaccine market is approaching US$ 15 billions[26].

Experiments demonstrating the physiological, immunological and the pharmacological properties of saponins have aroused considerable clinical interest in phytoadjuvants. Triterpenoid saponins have been detected in many legumes such as soybeans, beans, peas, lucerne, etc., and also in alliums, tea, spinach, sugar beet, quinoa, liquorices, sunflower, horse asparagus, yam, fenugreek, yucca and ginseng. Saponins are a class of high molecular weight secondary metabolites widely distributed in plants. Their relevance is a consequence of their industrial use and potential pharmacological activity as immunoadjuvant[27,28].

Various studies have shown the effect of saponins on the immune system. Saponins induce a strong adjuvant effect to T-dependent as well as T-independent antigens & it also induces strong cytotoxic CD8+ lymphocyte responses and potentiate the response to mucosal antigens[29]. Saponin based adjuvants have the ability to modulate the cell mediated immune system as well as to enhance antibody production and have the advantage that only a low dose is needed for adjuvant activity[30].

However, saponins are surface active agents and cause haemolysis of red blood cells in vitro, although haemolysis does not appear to be correlated with adjuvant activity[29]. Saponins have been widely used as adjuvants for many years and have been included in several veterinary vaccines. The adjuvant action of saponins was, however, not so pronounced in some of the non-mammalian species tested[31,32]. Saponin not only has stimulatory effects on the components of specific immunity, but also presents some non-specific immune reactions such as inflammation[33,34] and monocyte proliferation[35,36].

The mechanisms of immune-stimulating action of saponins have not been clearly understood, Saponins reportedly induce production of cytokines such as interleukins and interferons that might mediate their immunostimulant effects,[37,29] saponins have been shown to intercalate into cell membranes, through interaction with cholesterol, forming ‘holes’ or pores. It is currently unknown if the adjuvant effect of saponins is related to pore formation, which may allow antigens to gain access to the endogenous pathway of antigens presentation, promoting cytotoxic T-lymphocyte (CTL) response[38].

It was believed that the adjuvant activity of saponins could be related to branched sugar chains or aldehyde groups or to an acyl residue bearing the aglycone[29]. Latter, soyasaponins and lablabosides were found to show strong adjuvant activity despite lacking acyl

residues and possessing only un-branched sugar chains[30].

Oda et al. concluded that not only the functional groups themselves, but the overall conformation of such functional groups, affected adjuvant activity of saponins. Soyasaponins, It s a natural product composed of more than 23 different saponins and is generally considered too toxic for human use. However, ascribed to high toxicity, haemolytic effect and instability Quillaja saponins have been restricted for human vaccination[39,40].

In addition to severe local reactions and granulomas, toxicity includes severe haemolysis reflecting the affinity of saponins for cholesterol present in erythrocyte membranes, resulting in membrane solubilization and haemolysis[41,42,43].

IMMUNOSTIMULATING COMPLEX (ISCOM)

These are comprised of antigen, cholesterol, phospholipid and saponin. ISCOM-based vaccines have been shown to promote both antibody and cellular immune responses in a variety of experimental animal models[44], resulting in greatly augmented immunogenicity of the antigen. The combined vector was a highly effective enhancer of a broad range of immune responses, including specific serum Abs and balanced Th1 and Th2, CD4(+) T cell priming as well as a strong mucosal IgA response[45].

ASTRAGALUS SAPONIN

Astragalus a Chinese traditional herb, is thought to strengthen and boost the immune system by improving the ability of the macrophages. It contains numerous triterpene saponins (astragalosides I~X, isoastragalosides I~IV and soyasaponin I). Most of the modern research on astragalus has focused on its immune-enhancing effects. Laboratory studies have found astragalus to increase macrophages, T-cell transformation, NK cell activity, interferon production, and phagocytosis. The study also documented increased levels of IgA and IgG antibodies in nasal secretions after two months of treatment[46]. Astragalus saponin is believed to induce the cellular and humoral immune responses with slight hemolytic activity.

Peripheral lymphocyte proliferation and serum antibody titer increased in chicken vaccinated with New castle disease have also been found[47]. Astragalus herbal mixture stimulated macrophages to produce interleukin-6 and tumor necrosis factor[48]. Achyranthes bidentata saponins (ABS) modulated immune responses and the haemolytic activities have been observed in mice. ABS significantly enhanced the OVA-specific IgG, IgG1, IgG2b antibody titers with slight haemolysis in mice[49], Saponins from soybean have been separated into six[50] or eight[51] fractions of soyasapogenol and soyasaponins groups. Oda et al[51] found that the soyasaponins exhibited high adjuvant with low hemolytic activity while the soyasapogenol group exhibited low activity.

GINSENG

Ginseng is the best traditional Chinese medicine known containing saponin which is the major constituents of ginseng[52] Sapogenins have been identified from the ginseng plant and have been extracted from its root. The oral administration of ginseng extract. Wu et al.(1991) reported that ginseng extract enhanced the proliferative response of human blood lymphocytes to phytohemagglutin in (PHA) at lower concentrations, but inhibited the response at higher concentration. Ginseng extract has been reported to have modulatory effects on phagocytic cells, lymphocytes and antibody production in humans and animals. Increase in the human immune responses was reported by Scaglione et al[53], Oral administration of ginseng extract has been found to enhance the antibody response and blood lymphocyte proliferation in human[53,54].

Ginseng extract has also been reported to enhance, specific antibody response against diphtheric toxoids in mice[55] increase IgG and IgM antibody responses in mice immunized with sheep red blood cells and oral administration of ginseng extract at the same time[55]. The Rb1 fraction of ginseng elicits a balanced Th1 and Th2 immune response. In a study conducted by Rivera et al[56], porcine parvovirus (PPV) vaccines containing Rb1 was evaluated for inducing Th1 or Th2 type of immunity in mice. Study revealed the production of large amounts of cytokines including IFN-gamma, IL-2, IL-4, IL-10 and TNF-alpha and stimulated titers of antigen specific IgG1, IgG(2a) and IgG(2b). saponin could reduce leukocyte adhesion in venules under the inhibitory effect on the expression of adhesion molecules (CD11b and CD18) on neutrophils.

CONCLUSION

The development of new vaccines has highlighted the need for new strategies to enhance and guide the immune response for effective and long lasting protection. In particular, vaccines based on soluble recombinant antigens typically require adjuvant in order to enhance an antigen specific

adaptive immune response, i.e. a T cell and antibody response. Recent advances in immunology and the better understanding of the innate and adaptive immune system interactions has provided new insights on how to design new vaccines using appropriate selection of antigens and new adjuvant adapted to the desired immune response. Antigen Presenting Cells (APCs) play a key role towards a specific adaptive immune response, and phytosaponin adjuvants such as ISCOM, ginseng, soyasaponins and astragalus adjuvant based vaccines interact with APCs through specific receptors. On the basis of improved understanding of the immune system, it is now possible to design vaccines containing the appropriate match of antigens and adjuvant to respond to the needs of challenging diseases, as shown here for viral disease. This approach will allow in the future, the development of effective vaccines against other remaining challenges in immunization.

REFERENCES

1. Bowersock T.L., & Martin S., Vaccine delivery to animals, Adv. Drug Deliv. Rev., 1999, 38(2):167-194.
2. Gupta R.K., Rost B.E., Relyveld E., Siber G.R., Adjuvant properties of aluminum and calcium compounds. Pharm. Biotechnol.,1995, 6:229-248.
3. Gong X.M., Wu Y.Z., Research actuality and tendency of immune adjuvant. Chin. J. Vet. Drug,1996, 1:41-44.
4. Gupta R.K., Aluminum compounds as a vaccine adjuvants. Adv. Drug Deliv. Rev.,1998, 32(3):155-172.
5. Sun J.L, Hu Y.L., Wang D.Y., Zhang B.K., Liu J.G., Immunologic enhancement of compound Chinese herbal medicinal ingredients and their efficacy comparison with compound Chinese herbal medicines. Vaccine, 2006, 24:2343–8.
6. Quan F.S., Compans R.W., Cho Y.K., Kang S.M., Ginseng and Salviae herbs play a role as immune activators and modulate immune responses during influenza virus infection. Vaccine, 2007, 25:272–82.
7. Kuroiwaa A., Lioua S., Yana H., Eshita A., Naitoh S., Nagayama A., Effect of a traditional Japanese herbal medicine, Hochu-ekki-to(Bu-Zhong-Yi-Qi Tang), on immunity in elderly persons. Int Immunopharmacol, 2004, 4:317–24.
8. Wang D., Li X., Xu L., Hu Y., Zhang B., Liu J., Immunologic synergism with IL-2 and effects of cCHMIs on mRNA expression of IL-2 and IFNγ in chicken peripheral T lymphocyte. Vaccine, 2006, 24:7109–14.
9. Yang T., Jia M., Meng J., Wu H., Mei Q., Immunomodulatory activity of polysaccharide isolated from Angelica sinensis. Int J Biol Macromol, 2006, 39:179–84.
10. Mitra S.K., Gupta M., Sarma D.N., Immunomodulatory effect of IM-133. Phytother Res, 1999, 13:341–3.
11. Patwardhan B., Gautam M., Botanical immunodrugs: scope and opportunities. Drug Discovery Today, 2005, 10(7):495–502.
12. Yang T., Jia M., Meng J., Wu H., Mei Q., Immunomodulatory activity of polysaccharide isolated from Angelica sinensis. Int J Biol Macromol, 2006, 39: 179–84.
13. Gautam M., Diwanay S., Gairola S., Shinde Y., Patki P., Patwardhan B., Immunoadjuvant potential of Asparagus racemosus aqueous extract in experimental system. Journal of Ethnopharmacology, 2004, 91(2–3):251–5.
14. Quan F.S., Compans R.W., Cho Y.K., Kang S.M., Ginseng and Salviae herbs play a role as immune activators and modulate immune responses during influenza virus infection. Vaccine, 2007, 25:272–82.
15. Sakure S., Negi V.D., Mitra S.K., Nandakumar K.S., Chakravortty D., Vaccine with herbal adjuvant—a better cocktail to combat the infection. Vaccine, 2008, 26(27–28):3387–8.
16. Bani S., Gautam M., Sheikh F.A., Khan B., Satti N.K., Suri K.A., Selective Th1 up-regulating activity of Withania somnifera aqueous extract in an experimental system using flow cytometry. Journal of Ethnopharmacology, 2006, 107(1):107–15.
17. Gautam M., Diwanay S.S., Gairola S., Shinde Y.S., Jadhav S.S., Patwardhan B.K., Immune response modulation to DPT vaccine by aqueous extract of Withania somnifera in experimental system. International Immunopharmacology, 2004, 4(6):841–9.
18. Podda A., The adjuvanted influenza vaccines with novel adjuvants: experience with the MF59-adjuvanted vaccine. Vaccine, 2001, 19(17–19):2673–801.
19. Gupta R.K., Relyveld E.H., Lindblad E.B., Bizzini B., Ben-Efraim S., Gupta C.K.,

Adjuvants—a balance between toxicity and adjuvanticity. Vaccine, 1993, 11(3): 293-306.
20. Vogel F.R., Immunologic adjuvants for modern vaccine formulations. Ann. N.Y. Acad. Sci., 1995, 754(1 combined vacc):153-160.
21. Kaeberle M.L., Functions of Current Adjuvants in Induction of Immune Response. In: Nervig, R.M., Gough, P.M., Kaeberle, M.L., Whetstone, C.A. (Eds.), Advances in Carriers and Adjuvants for Veterinary Biologics, Iowa State University Press, Ames, IA, 1986, p.11-24
22. McElrath M.J., Selection of potent immunological adjuvants for vaccine construction. Semin. Cancer Biol., 1995, 6(6):375-385.
23. Riguera R., Isolating bioactive compounds from marine organisms. J. Marine Biotechnol., 1997, 5:187-193.
24. Yoshiki Y., Kudou S., Okubo K., Relationship between chemical structures and biological activities of triterpenoid saponins from soybean (review). Biosci. Biotechnol. Biochem., 1998, 62(12):2291-2299.
25. Higson A.P. & Hamer A., Specialty non-food crops. In A. E. Osbourn & V. Lanzotti (Eds.), Plant-derived natural products, 2009, (pp. 569–584). New York, NY: Springer.
26. Taylor K., Nguyen A. & Ste´phenne J., The need for new vaccines. Vaccine, 2009, 27 S, G3–G8.
27. Fleck J.D., Kauffmann C., Spilki F., Lencina C.L., Roehe P.M.. & Gosmann G., Adjuvant activity of Quillaja brasiliensis saponins on the immune responses to bovine herpesvirus type 1 in mice. Vaccine, 2006, 24, 7129–7134.
28. Sun H.X., Ye Y.P., Pan H.J. & Pan Y.J., Adjuvant effect of Panax notoginseng saponins on the immune responses to ovalbumin in mice. Vaccine, 2004, 22, 3882–3889.
29. Kensil C.R., Saponins as vaccine adjuvants. Crit. Rev. Ther. Drug Carrier Syst.,1996, 13(1-2):1-55.
30. Oda K., Matsuda H., Murakami T., Katayama S., Ohgitani T., Yoshikawa M., Adjuvant and haemolytic activities of 47 saponins derived from medicinal and food plants. Biol. Chem., 2000, 381(1):67-74.
31. Cossarini-Dunier M., Effect of different adjuvants on the humoral immune response of rainbow trout. Dev. Comp. Immunol., 1985, 9(1):141-146.
32. Grayson T.H., Williams R.J., Wrathmell A.B., Munn C.B., Harris J.E., Effects of immunopotentiating agents on the immune response of rainbow trout, Salmo gairdneri Richardson, to ERM vaccine. J. Fish Biol.,1987, 31(sa):195-202.
33. de Oliveira C.A.C., Perez A.C., Merino G., Prieto J.G., Alvarez A.I., Protective effects of Panax ginseng on muscle injury and inflammation after eccentric exercise. Comp. Biochem. Physiol., 2001, 130(3):369-377.
34. Haridas V., Arntzen C.J., Gutterman J.U., Avicins, a family of triterpenoid saponins from Acacia victoriae (Bentham), inhibit activation of nuclear factor-kappa B by inhibiting both its nuclear localization and ability to bind DNA. Proc. Natl. Acad. Sci. USA, 2001, 98(20): 11557-11562.
35. Delmas F., Di Giorgio C., Elias R., Gasquet M., Azas N., Mshvildadze V., Dekanosidze G., Kemertelidze E., Timon-David P., Antileishmanial activity of three saponins isolated from ivy, alpha-hederin, beta-hederin and hederacolchiside A(1), as compared with their action on mammalian cells cultured in vitro. Planta Medica, 2000, 66(4):343-347.
36. Yui S., Ubukata K., Hodono K., Kitahara M., Mimaki Y., Kuroda M., Sashida Y., Yamazaki M., Macrophage-oriented cytotoxic activity of novel triterpene saponins extracted from roots of Securidaca inappendiculata. Int. Immunopharmacol., 2001, 1(11):1989-2000.
37. Jie Y.H., Cammisuli S., Baggliolini M., Immuno- modulatory effects of Panax ginseng CA Meyer in the mouse. Agents Actions, 1984, 15(3-4):386-391.
38. Sjölander A., Drane D., Maraskovsky E., Scheerlinck J., Suhrbier A., Tennent J., Pearse M., Immune responses to ISCOM formulations in animal and primate models. Vaccine, 2001, 19(17-19):2661-2665.
39. Marciani D.J., Press J.B., Reynolds R.C., Development of semisynthetic triterpenoid saponin derivatives with immune stimulating activity. Vaccine, 2000, 18(27):3141-3151.
40. Liu G. Anderson C., Scaltreto H., Barbon J., Kensil C.R., QS-21 structure/function studies: effect of acylation on adjuvant activity. Vaccine, 2002, 20(21-22):2808-2815.
41. Kensil C.R., Patel U., Lennick M., Marciani D., Separation and characterization of saponins with adjuvant activity from Quillaja-saponaria molina cortex. J. Immunol., 1991, 146(2):431-437.
42. Warren H.S., Chedid L.A., Future prospects for vaccine adjuvants. Crit. Rev. Immunol., 1988, 8(2):83-101.
43. Dalsgaard K., Adjuvants. Vet. Immunol. Immunopathol., 1987, 17(1-4):145-152.

44. Sanders M.T., Brown L.E., Deliyannis G., Pearse M.J., ISCOM-based vaccines: the second decade. Immunol. Cell Biol., 2005, 83(2):119-128.
45. Helgeby A., Robson N.C., Donachie A.M., Beackock-Sharp H., Lovgren K., Schon K., Mowat A., Lycke N.Y., The combined CTA1-DD/ISCOM adjuvant vector promotes priming of mucosal and systemic immunity to incorporated antigens by specific targeting of B cells. J. Immunol., 2006, 176(6):3697-3706.
46. Chang H.M., But P.P., Pharmacology and Applications of Chinese Materia Medica, Vol. 1. Singapore, World Scientific, 1986, p.1041.
47. Kong X., Hu Y., Rui R., Wang D., Li X., Effects of Chinese herbal medicinal ingredients on peripheral lymphocyte proliferation and serum antibody titer after vaccination in chicken. Int. Immunopharmacol., 2004, 4(7): 975-982.
48. Yoshida Y., Wang M.Q., Shan B.E., Yamashita U., Immunomodulating activity of Chinese medical herbs and Oldenlandia diffusa in particular. Int. J. Immunopharmacol., 1997, 19(7):359-370.
49. Sun H.X., Adjuvant effect of Achyranthes bidentata saponins on specific antibody and cellular response to ovalbumin in mice. Vaccine, 2006, 24(17):3432-3439.
50. Khalil A.H., El-Adawy T.A., Isolation, identification and toxicity of saponin from different legumes. Food Chem., 1994, 50(2):197-201.
51. Oda K., Matsuda H., Murakami T., Katayama S., Ohgitani T., Yoshikawa M., Relationship between adjuvant activity and amphipathic structure of soyasaponins. Vaccine, 2003, 21(17-18):2145-2151.
52. Wang M.Z., Gao F.Y., Zhang G.D., Zhang S.R., Analysis of ginseng. Acta Pharm. Sin., 1979, 14(5):309-315.
53. Scaglione F., Ferrara F., Dugnani S., Falchi M., Santoro G., Fraschini F., Immunomodulatory effects of two extracts of Panax ginseng C.A. Meyer. Drugs Exp. Clin. Res., 1990, 16(10):537-542.
54. Wu S., Hua Z.J., Xio Y.L., Wang Y., Effect of Ginsengopolypeptide on the 3H-TdR integration of human blood lymphocyte. Chin. Med. J., 1991, 104(5):399-401.
55. Yang G.Z., Bao T., Fu N., Gen P.L., A preliminary study on the immunomodulatory effects of ginseng saponins in vitro and in vivo. J. Norman. Bethune Univ. Med. Sci., 1983, 9:7.
56. Rivera E., Ekholm P.F., Inganas M., Paulie S., Gronvik K.O., The Rb1 fraction of ginseng elicits a balanced Th1 and Th2 immune response. Vaccine, 2005, 23(46-47): 5411-5419.

*****