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Review

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Immunomodulatory Indian medicinal plants

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Abstract

The traditional Indian system of medicine (Ayurveda) describes different modalities involved in the prevention and treatment of disease and stresses upon the role of diet, life style and drugs as cornerstones of therapy. Medicinal plant products are known to modify different aspects of human physiology and exert an alleviating influence on several pathophysiological states, and concepts of immunity and immunomodulation can be traced back several hundred years to the history of medicine. However, it is only in recent years that the scientific concept of immunomodulation has been forwarded, and it now appears that some of the beneficial effects of Indian medicinal plants, proposed in Ayurveda by Charaka and Sushruta Samhita, may be due to these "immunomodulatory" effects. Several research groups have worked on the scientific basis of such immunomodulatory effects of plant products, and as a result, considerable data has accrued. The present review summarizes some of these experimental data in an attempt to justify some of their beneficial effects in health and disease, and also to provide insights into the future research in this area.

Keywords: Immunomodulation, Indian medicinal plants.

1. Introduction

The prime objective of Ayurveda, the ancient Indian system of medicine is the prevention of the disease process. To achieve this, it advocates a vast range of health care practices. These measures include systematized daily routine to govern the life style of the individuals, and a seasonal routine to harmonize the physiology with the circadian rhythm that govern the nature [l]. Thus complete harmonization both at systemic and cellular levels is involved. The system also explores various natural resources, both pharmacological and non-pharmalogical, to optimize the inherent physiological abilities of living systems, to modify the overall quality of life.

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The different health care measures to be adopted by an individual are grouped together under the heading of "Rasayana." The word Rasayana in Sanskrit, literally implies to the circulation of Rasa, the nutrient.

Rasayana aims at optimizing the circulation of nutrients to all components of the physiology, whether in a system, in any tissue or even within a cell. In the words of Charaka [2], with a Rasayana "One obtains longevity, regains youth, gets a sharp memory and intellect and freedom from disease, gets a lustrous complexion and the strength of a horse". Sushruta [3] was more specific, describing a Rasayana as one, which is antiaging, increases the life-span, promotes intelligence and memory, and increases resistance to diseases (indicating immunostimulant effect).

Rasayana plants are particularly recommended for the treatment of epidemic diseases [4]. Apart from immunostimulant activity, they have also been evaluated for their anabolic, anti-stress / adaptogenic, nootropic, antioxidant and antiaging effects [5].

The modern system of medicine had always been enthusiastic to evoke nonspecific defence mechanisms of human physiology, which led to the discovery of active immunization using microbial preparation to enhance the host defence against infection. Recently, the same enthusiasm has taken an important leap towards exploring a novel group of substances from natural resources that modulate the immune response of living systems and influence the disease process.

An immunomodulator can be defined as a substance, which can influence any constituent or function of the immune system in a specific or nonspecific manner including both innate or adaptive arms of the immune response [7]. It can cause immunostimulation by stimulating effector cells or production of their metabolic inducers or by inhibiting the immunity limiting factors.

Immunosuppression can be achieved by stimulating the inhibitor cells and humoral factors, or inhibition of effector cells. In clinical practice, both aspects of immunomodulation, *viz*. immunostimulation and immuno-suppression are equally important. Immuno-stimulation may be required during conventional chemotherapy when the host defence mechanisms are to be activated under conditions of impaired immune responsiveness. In addition, it may help in prophylaxis of opportunistic infections in risk-prone, sensitive patients. On the other hand, immunosuppression may be of choice in treatment of autoimmune disorders such as rheumatoid arthritis, multiple sclerosis etc. [5].

Investigations on Indian medicinal plants having immunomodulatory activity are scattered and sometimes repetition of the same work has also been noted. In majority of cases these studies have been preliminary in nature. But the important fact is that the importance of Indian medicinal plants has been realized in the modern medicine and there is hope for a bright future. But, to fully utilize the potential of such drugs and systematize the future response on this topic, there is a need for a comprehensive review on the work done in this area.

2. Indian medicinal plants classified as Rasayana

Plants and other natural products have been in use for ages for health and maintenance of life. The Vedic literature, the most authentic, ancient Indian scripture, gives the reference of many plants for different diseases and their prevention. Rig and Sama Veda describe 67 plants, Yajour Veda 81, Atharva Veda 289, Brahamana 129, while in Upanishads 31 plants are referred [8].

A significant part of Ayurvedic therapeutics aims at prevention of disease. This is the concept of 'Vyadhirodhak Chamatav' i.e. capacity of the body to resist disease [5]. The immune system, a part of Modern system of medicine of Western origin, which provides protection against microbes, appears to be part of it.

An entire section of Materia Medica of Ayurveda termed 'Rasayana' is devoted to enhancement of body's resistance [9]. It aims at fulfilling two important aspect of the life process – maintenance of health and therapeutic management of disease state either as an adjuvant, or as drug. Emphasis is laid down on its action and uses only on physical health, but recent research had shown that it improves both mental, as well as physical health.

Thirty four plants have been identified as Rasayanas in the Ayurvedic system of medicine. These plants possess various pharmacological properties e.g. immunostimulant, antibacterial, antiviral, anti-inflammatory, anticancer, antirheumatic etc. Besides these, several, other medicinal plants, which are not included as Rasayana in Ayurveda have also been found to possess immunomodulatory properties. These are enlisted in Table 1.

3. Indian medicinal plants and immunomodulation

Out of these two groups, Rasayana and Non-Rasayana several plants have been investigated in experimental animals and humans for their immunomodulatory properties. The results of some of these studies are summarized in Table 2.

Besides rasayana, there is another concept in Ayurveda which may reveal an immunostimulant potential of the plants. 'Ama' are immunologically active complexes generated in the intestine due to improper digestion of food [6] which is the cause of pathogenesis of several diseases like rheumatoid arthritis, ulcerative colitis and liver disease, all of which have a immunological background.

Drugs can influence 'ama' in two ways : (a) those which increase digestion capacity and prevent formation of 'ama' (deepak) e.g. *Ferula narthex, Garcinia pedunculata, Piper longum, Piper retrofractum, Plumbago zeylanica, Semicarpus anacardium, Trachyspremum ammi, Zingiber officinalis,* and (b) those which digest 'ama' (pachak), e.g. *Aconitum heterophyllum, Berberis aristata, Cissampelos pareira, Curcuma longa, Cyperus rotundus, Aleatory cardomonium, Emblica officinalis, Picrorrhiza kurroa, Plumbago zeylanica, Saussurea lappa, Semicarpus anacardium, Terminalia bellerica, Terminalia chebula.*

Several other plants have anti-allergic properties and this can also be categorized as 'immunomodulators'. This activity could be explained on the basis of stimulation of T-suppressor cells, e.g. *Picrorrhiza kurroa* has been shown to blunt the sensitivity of guinea pigs to histamine and sympatho-mimetic amines, and prevent allergen and PAF - induced bronchial obstruction [74, 75]. *Piper longum* is another example of anti-allergens used often for the therapy of bronchial asthma [76].

Besides, recommending, individual plants for specific disease or vitalizing the specific organs polyherbal 'Rasayan' formulations have also been described in Charaka Samhita [77]. Chywanprash Awaleha has been in use for more than 4000 years. *Emblica Officinalis* is the prime ingredient along with the powders and extracts of several other herbs. It has been shown to confer a non-specific immunity in the experimental animals [78].

It has also been shown to block the development of fibrosarcoma induced by chloranthrene in albino mice [79]. In a brief clinical evaluation

Table 1
Indian medicinal plants (Rasayana and Non rasayana) with suggested immunomodulatory properties

Rasayana	**Non rasayana**	
Acorus calamus (Bach)	*Abrus precatorius* (Gunja)	*Hibiscus esculentus* (Bhindi)
Allium sativum (Lahsuna)	*Aconitum heterophyllum* (Atis)	*Holarrhena antidysenterica* (Kurchi)
Aloe vera (Ghrit-kumari)	*Albizzia lebbeck* (Shrisha)	*Hoppea dichotoma* (Kuki)
Argyreia speciosa (Samandar ka pat)	*Amoora rohituka* (Harin-hara)	*Hyoscyamus niger* (Parsikaya)
Asparagus racemosus (Satawar)	*Andrographis paniculata* (Kalmegh)	*Jasminum sambac* (Motia)
Azadirachta indica (Nimba, Neem)	*Aristolochia indica* (Isharmul)	*Lawsonia inermis* (Mehndi)
Bacopa monnieri (Brahmi)	*Artocarpus lakoocha* (Dahua)	*Luffa acutangula* (Torai)
Boerhavia diffusa (Sant)	*Astragalus multiceps* (Sarmul)	*Luffa cylindrica* (Ghiatarui)
Cissampelos pareira (Akanadi)	*Bauhania variegata* (Kachnar)	*Mallotus philippinensis* (Kamala)
Commiphora mukul (Guggul)	*Berberis aristata* (Dar-hald)	*Mangifera indica* (Am)
Convolvulus pluricaulis (Shankhapushp)	*Blechnum orientale* (Rajhans)	*Manilkara kauki* (Khirni)
Curculigo orchioides (Krishna Musali)	*Bombax malabaricum* (Simul)	*Melia azadirachta* (Bakain)
Curcuma longa (Haldi)	*Bupleurum falcatum* (Sipil)	*Mentha spicata* (Pudina)
Desmodium gangeticum (Shalaparni)	*Butea monosperma* (Dhak)	*Mucuna pruriens* (Kaunch)
Dioscorea bulbifera (Ratalu)	*Butea superba* (Palas)	*Nardostachys jatamansi* (Jatamansi)
Emblica officinalis (Amla)	*Calotropis procera* (Madar)	*Nelsonia campestris* (Patta Kamraj)
Embelia ribes (Vidanga)	*Carissa carandus* (Karaunda)	*Ocimum canum* (Mamiri tulsi)
Glycerrhiza glabra (Yashtimadhu)	*Catharanthus roseus* (Sada Bahar)	*Ocimum sanctum* (Tulsi)
Gmelina arborea (Gamari)	*Celastrus paniculatus* (Malkangni)	*Ougeinia oojeinensis* (Sandan)
Hemidesmus indicus (Ananta mul)	*Centella asiatica* (Madukaparni)	*Picrorrhiza kurroa* (Kutaki)
Ipomoea digitata (Ajvayan)	*Cicer arietinum* (Chana)	*Piper aurantiacum* (Shambhatuka)
Leptadenia reticulata (Dori)	*Citrullus colocynthis* (Indrayan)	*Piper betel* (Paan)
Piper longum (Piplamul)	*Clerodendrum infortunatum* (Bhant)	*Pluchea lanceolata* (Sorahi)
Plumbago zeylanica (Chita)	*Clitoria ternatea* (Aparajita)	*Prosopis spicigera* (Jhand)
Psoralea corylifolia (Babchi)	*Costus speciosus* (Keu)	*Randia dumetorum* (Maniphal)
Pterocarpus marsupium (Bijasar)	*Cucumis sativus* (Khira)	*Saraca indica* (Ashoka)
Semecarpus anacardium (Bhilawa)	*Cuminum cyminum* (Jira)	*Selaginella bryopteris* (Amarbooti)
Sida spinosa (Gulsakari)	*Cymbopogon martinii* (Gandh)	*Solanum trilobatum* (Agnidamini)
Solanum nigrum (Makoi)	*Dryopteris cochleata* (Jatashankar)	*Syzygium cumini* (Jamun)
Sphaeranthus indicus (Mundi)	*Elephantopus scaber* (Gobhi)	*Valeriana wallichi* (Tagar)
Terminalia belirica (Bahera)	*Elytraria acaulis* (Sahustra muli)	*Viscum album* (Banda)
Terminalia chebula (Haritaki/ Panhara)	*Eupatorium cannabinum* (Tongollati)	*Vitex negundo* (Nirgandi)
Tinospora cordifolia (Guduchi)	*Flacourtia indica* (Bilangra)	*Woodfordia fruticosa* (Dhal)
Withania somnifera (Ashwagandha)	*Gymnema sylvestre* (Medhasingi)	*Zingiber officinalis* (Adrak)

Table 2
Some of the indigenous plants investigated for immunomodulatory effects

Plants with (common name)	Primary Ayurvedic Use	Immunomodulatory Effects
1. *Allium sativum* (Lahsuna)	– Antibacterial – Antiviral	– Stimulates humoral immune response [10] – Inhibits growth of cancer cell lines [11] – Enhances macrophage (oxidative burst) and T lymphocytes (blastogenesis) [12] – Inhibits growth of tumors [13, 14] – Modulates activity of chemical carcinogens [15, 16] – Protects from UV induced suppression of contact hypersensitivity [17] – Cytoprotective effect on heart, liver and pancreas against isoproterenol induced damage [18] – Enhances capillary skin perfusion [19] – Augments NK-cells, stimulates T-cells and IL-2 production [20]
2. *Aloe vera* (Ghrit-kumari)	Antiseptic	– Polysaccharides from it show adjuvant activity for antibody production and DTH [21] – Enhances IL-6, TNF-α and NO release [22] – Inhibits inflammation [23] – Improves wound healing [24] – Serves as oxygen radical scavenger, acts synergistically with NO [25] – Causes regression of tumor [26] – Prevents UV-induced suppression of DTH [27]
3. *Andrographis paniculata* (Kalmegh)	Immunostimulant	– Stimulates macrophage migration, phagocytosis of *E.coli;* Induces stimulation of antibody and DTH response to SRBC in mice [28] – Proliferation of splenic lymphocytes [28] – Inhibits NO synthase [29]
4. *Asparagus racemosus* (Satawar)	– Antistress – Anticancer – Antiseptic – Immunostimulant – Antiageing	– Stimulates RE System and PMN cell [30] – Induces lag in tumor development [31] – Prevents leucopenia induced by cyclophosphamide [32] – Inhibits ochratoxin A induced suppression of IL-1, TNF-α and marcophage chemotaxis [33]
5. *Azadirachta indica* (Neem)	– Antiseptic – Anti-eczema	– Stimulates IL-1, INF-γ, TNF-α production, enhances proliferative response of spleen cells to Con A and tetanus toxoid [34] – Inhibits both complement pathways as well as activates PMN cells [35] – Enhances macrophage phagocytosis and expression of MHC II antigen [36] – Enhances anti-ovalbumin antibody response, DTH response, macrophage migration inhibition [37] – Attenuation of stress and xenobiotic induced suppression of humoral and cell-mediated immunity [38, 39] – Enhances PMN leucocytes and cell-mediated immunity [40] – Induces production of interferons [41] – Reduces mortality induced by Tacaribe viral encephalitis [42] – Inhibits intracellular multiplication of Chlamydia and cytopathic effects of herpes [43] – In a clinical study reduced erythema desquamation and infiltration of psoriatic lesions [5]

6. *Curcuma longa* (Haldi)	– Antiseptic – Antiinflammatory – Tonic	– Increases mitogenic response of lymphocytes [44] – Inhibits NO production and scavenges reactive oxygen species [45] – Enhanced IgG level but did not affect DTH and NK cell activity [46] – Helps in rheumatoid arthritis [47] – Chemoprotective agent against cancer [48]
7. *Emblica officinalis* (Amla)	– Antibacterial – Rejuvenant – Improves vitality	– Stimulates PMN cells and RE system [30] – Inhibits PMN activity induced by leukotriene B4 and FMLP [49] – Protects against parcreatitis [50] – Induces positive nitrogen balance [51] – Protects against toxic effects of metals [52] – Enhances NK cell and antibody dependent cellular cytotoxicity against Dalton's lymphoma ascites tumor [53]
8. *Nyctanthes arbor-stristis* (Har-singhar)	– Hepatoprotective – Antileishmanial – Antiviral – Antifungal	– Stimulates macrophage migration. Stimulates humoral and DTH response to SRBC in mice [54] – Protects mice against Candida albicans as a result of enhanced humoral, DTH and macrophage activity [55]
9. *Ocimum sanctum* (Tulsi)	– Antitubercular – Antiviral – Antifungal – Antiasthmalic – Antiinflammatory	– Induces lag in tumor development in mice [31] – Increases colony forming unit in spleen and protects mice after irradiation [56] – Enhances survival of viral encephalitis patients [57] – Enahances humoral immunity; inhibits histamine release from sensitized mast cells and antagonizes tissue responses to histamine [58]
10. *Panax pseudoginseng* (Ginseng)	– General health tonic – Adaptogen	– Stimulates macrophage migration; Enhances circulating antibody and antibody forming cells to SRBC in mice [59]
11. *Picrorrhiza kurroa* (Kutaki)	– Immunostimulant – Antioxidant	– Enhances phagocytosis, stimulates PHA, ConA and LPS induced lymphocyte proliferation, macrophage migration, enhances antibody response against SRBC [60] – Enhances antibody and DTH response to SRBC in mice [61] – Inhibits ochratoxin A induced suppression of IL-1, TNF-α and macrophage chemotaxis [33] – Protects animals against leishmania and filarial infections [62]
12. *Tinospora cordifolia* (Guduchi)	– Antibacterial – Antiaging – Anti-allergic – Anti-rheumatic – Immunostimulant – Antidiabetic – Diuretic	– Shows anticancer activity against D11 and Ehrlich ascites carcinoma cells [31] – Enhances humoral immune response to SRBC but the response to Con A was suppressed [63] – Mitogenic to splenocytes and lymph-node cells [63] – Protects against gastric mucosal damage [64] – Inhibits myelosuppression induced by cyclophosphamide [64] – Enhances peritoneal macrophage number and their phagocytic activity in cholestatic animals [65] – Induces resistance to infection, reduces mortality in mice with *E. coli* [66, 67] – Enhances MHC class II expression and antigen presenting ability of macrophage; Enhances antigen specific antibody, inhibits ochratoxin A induced suppression of IL-1, TNF-α and macrophage chemotaxis, enhances IgG antibody and macrophage activation [66, 67]. – Increases granulocyte macrophage colony forming units in mice serum, improves Kupffer cell function in chronic liver disease in rats [68]

Plants with (common name)	Primary Ayurvedic Use	Immunomodulatory Effects
		– Anticomplement activity, Increases IgG, Stimulates PMN cells [69]
		– Induces lag in tumor development [31]
13.*Withania somnifera* (Ashwagandha)	– Immunostimulant – Antistress – Anti-rheumatic – Antiinflammatory	– Stimulates RE system and PMN cells [4] – Inhibits tumor development [31] – Increases WBC counts in irradiated mice [70] – Prevents myelosuppression induced by azathioprine, cyclophosphamide and prednisolone [71] – Inhibits Ochratoxin A induced suppression of IL-I, TNF-α and macrophage chemotaxis [33] – Enhances spleen colony forming units [72] – Enhances Radiosensitization for V97 Chinese hamster cell [73].

it showed a marked improvement in hematological status, protein metabolism, albumin globulin ratio, improved adrenal and testicular functions [80].

This review of pharmacological explorative studies on some 'Rasayana' and 'Non rasayana' plants substantiates their immunomodulatory property as mentioned in the Ayurveda. As visualized from the ancient concepts and analysed in the light of modern scientific investigations, it appears that immunomodulation is an integral part of multifaceted effects of 'Rasayana' and is closely linked to adaptogenic, anabolic, nootropic, antioxidant and anti-ageing effects. Rege *et al* [50] mentioned that only Rasayana with 'madhur vipaka' enhanced the clearance of colloidal carbon, indicating the stimulation of the reticulo-endothelial system. The other Rasayana with 'katu vipaka' were devoid of this immunostimulant property.

4. Future Prospects

Inspite of the availability of such vast data, it is not yet possible to allow their use in clinical practice and develop marketable drugs with modern standards of safety. Many research publications on plants show marginal or insufficient pharmacological activities or on less number of experimental animals or performed with different types of extracts of plants from varying ecotypes.

Further, sometimes a medicinal plant is screened for innumerable pharmacological activities without focusing on practical therapy benefits. There is a need of integrated systematic research on standardized products of a large number of plants (listed in Table 2) with the aim of developing commercially viable phytomedicines.

As discussed by Subramoniam [81], two approaches can be followed for developing successful drugs from medicinal plants. One is the phytochemical approach, which depends on identifying the active principle and developing pure phytochemicals as drugs.

However, this type of drug discovery is very expensive and also time consuming. The second approach is a phytotherapeutic approach wherein standardized crude drug preparations (extracts or active fractions) can be used as drugs with modern standards of safety & efficacy. As far as the Indian medicinal plants are concerned, the second approach could be followed. The Ayurvedic medicinal formulations prepared according to materia and medica incorporating the Rasayana therapy could be put to careful clinical trials.

However, care should be taken to ensure the ethical validity of such trials and to monitor the concentrations of active components in different preparations of extract. Once the clinical utility is established, the active phytochemical, and mechanism of action can be investigated.

However, the planning and conduct of such clinical trials is not an easy job as they have to be conducted on a large number of individuals at risk, and following them up adequately to monitor the outcome, compliance, sensitive as well as specific end points of efficacy, and most importantly the availability of standardized plants from the same ecotype are factors which require considerable attention.

Therapeutic value of medicinal plants could differ depending on soil conditions, nutritional status, climatic conditions, seasonal and diurnal variations. The variations in active principle of a medicinal plant in different ecotypes cannot be determined by phytochemical analysis, as mostly it is not established.

But pharmacological and toxicological evaluations on experimental animals could limit this variational aspect and determine the efficacy and safety of these agents. These studies can be simplified only by bringing together professionals from the Ayurvedic and modern systems of medicine interested in development of standardized herbal medicines for clinical use.

Formation of a single authority for supplying standardized medicinal plants could also be considered. Inspite of these problems, research on medicinal plants has recently assumed great importance. Rasayanas prove to be a rich source of immunostimulants and vitalizers and exploring them in the context of modern science appears to be the need for optimum and proper utilization of herbal drugs.

References

1. Sharma PV. (1981) Translation : *Charka Samhita,* Chikitsasthana, I Edn., Vol. 2, Chaukhamba Orientalia: Varanasi.

2. Sharma P. (1983) Chikitsasthana. In : *Charka Samhita,* Chaukhamba Orientalia: Varanasi.

3. Shastri AK. (1993) Sutrasthana. In : *Sushrut Samhita,* Chaukhamba Orientalia: Varanasi.

4. Dhanukar SA, Thatte UM, Rege NM. (1999) In: Wagner H. (Eds.) *Immunomodulatory agents from plants.* Birkhauser Verlag: Basel, Switzerland; 289-323.

5. Katiyar CK, Brindavanam NB, Tiwari P, Narayana DBA. (1997) In : Upadhyaya SN. (Ed.) *Immunomodulation*. Narosa Publishing House: New Delhi; 163-187.

6. Thatte UM, Dahanukar SA. (1986) *Trends Pharmacol. Sci.* 7 : 247-251.

7. Agarwal SS, Singh VK. (1999) *PINSA.* 65 (3 & 4): 179-204.

8. Datta GK, Debnath PK. (1999) In : *Proceedings of National Seminar on Rasayan,* CCRS: New Delhi; 62-75.

9. Thatte UM, Dahaukar SA. (1997) In : Upadhyaya SN. (Ed.) *Immunomodulation* Narosa Publishing House: New Delhi; 141-148.

10. Sutarjadi S, Bendryman MH, Dyataiko W. (1991) *Planta Med.* 52 (2) : 136.

11. Svendsen S, Ratan SIS, Clark BFC. (1994) *J. Ethnopharmacol.* 43 (2): 125.

12. Lan BH, Yamasaki T, Gridley DS. (1991) *Mol.. Biother* . 3 : 103-107.

13. Aboul EAM. (1986) *Nahrung* 30 : 161-169.

14. Corsi ZMM, Bertelli AA, Gaja G, Fulgenzi A, Ferrero ME. (1998) *Int J. Tissue React.* 20 : 115-118.

15. Chopra RN, Chopra IC, Handa KL, Kapur ID. (1958) *Indigenous Drugs of India,* UN Dhar and Sons Pvt. Ltd.: Calcutta.

16. Jain SK. (1994) *Ciba Found. Symp.* 185 : 153 - 164.

17. Reeve UE, Bosnic M, Rozinova E, Boehm-Wilcox C. (1993) *Photochem. Photobiol.* 58 : 813 - 817.

18. Ciplea AG, Ritcher KD. (1988) *Arzeim. Forsch.* 38 : 1592.

19. Jung EM, Jung F, Morweitz C, Kieswetter H, Wenzel E. (1991) *Arzneim. Forsch.* 41 : 626.

20. Tang Z, Sheng, Z, Liu S, Jian X, Sun K, Yan M. (1997) *Human Iko to Hsueh Hsueh Pao* 22 : 246 - 248.

21. t' Hart LT, Van-den Berg AJ, Kuis L, Van-Dijk H, Labadic RP. (1989) *Planta Med.* 55 : 509 - 512.

22. Karaca K, Sharma JM, Nordgren R. (1995) *Int. J. Immunopharmacol.* 17 : 183 - 188.

23. Davis RH, Donato JJ, Hartman GM, Haas RC. (1994) *J. Am. Pediatr. Med. Assoc.* 84 : 77-81.

24. Chithra P, Sajithlal GB, Chandrakasan, G. (1998) *Mol. Cell Biochem.* 181 : 71-76.

25. Heggers JP, Elzaim H, Garfield R, Goodheart R, Listengarten D, Zhao J, Philipps LG. (1997) *J. Altern. Complement. Med.* 3:149-153.

26. Peng SY, Norman, J, Curtin G, Corrier D, McDaniel HR, Bushee D. (1991) *Mol. Biother,* 3:79 - 87.

27. Bycon SW, Pelley RP, Ullrich SE, Waller TA, Bucana CD, Strickland FM. (1998) *J. Invest. Dermatol,* 110 : 811 - 817.

28. Puri A, Saxena R, Saxena RP, Saxena KC, Srivastava V, Tandon JS. (1993) *J. Nat. Prod.* 56 : 995 - 999.

29. Chiou WF, Lin JJ, Chen CF. (1998) *Br. J. Pharmacol.* 125 : 327 - 334.

30. Dahanukar SA, Thatte UM. (1997) *Phytomed.* 4(3) : 297 - 306.

31. Seena K, Kuttan G, Kuttan R. (1993) *Amla Res. Bull.* 13 : 41 - 45.

32. Thatte UM, Dahanukar SA. (1998) *Meth. Find. Expt. Clin. Pharmacol.* 10 : 639 - 644.

33. Dhuley JN. (1997) *J. Ethnopharmacol.* 58 : 15 - 20.

34. Upadhyaya SN. (1997) *Immunomodulation,* Narosa Publishing House: New Delhi; 149 - 297.

35. Labadie RP. (1990) *Actes du let Colloque European d' Ethnopharmacologie;* Metz : 291 - 297.

36. Upadhyay SN. (1992) *Int. J. Immunopharmacol.* 14 : 1187 - 1193.

37. Ray A, Banerjee BD, Sen P. (1996) *Indian J. Exp. Biol.* 34 : 698 - 701.

38. Sen P, Mediratta, Ray A. (1992) *Indian J. Exp. Biol.* 30 : 1170-1175.

39. Ray A, Banerjee BD, Koner BC, Sen P. (1997) *Indian J. Pharmacol.* 29 : 38 - 39.

40. Sai Ram M, Sharma SK, Ilvazhagan G, Kumar D, Selvamurthy L. (1997) *J. Ethnopharmacol.* 55 : 133 - 139.

41. Fujuwara T, Takeda T, Ogihara Y, Shimizu M, Nomura T, Tomita Y. (1982) *Chem. Pharm. Bull.* 30 : 4025-4030.

42. Columbie FC, Andrie GM, Laguens RP, de Torres RN, Coto CE. (1992) *Phytother. Res.* 6 : 15.

43. Upadhyay SN, Dhawan S. (1994) In : *"Neem (A.I.) : Immunomolulator properties and*

therapeutic potential", Abstract Book of Update Aryuveda, (Feb.): Bombay; PR 2.

44. Yasni S, Yashiie K, Oda H, Sugano M, Lniazumi, K. (1993) *J. Nutri, Sci. Vitaminol.* 39 : 345 - 354.

45. Brouet I, Ohshima H. (1995) *Biochem. Biophy. Res. Com.* 206 : 533 - 540.

46. South EH, Exon JH, Hendrix K. (1997) *Immunopharmacol. Immunotoxicol.* 19 : 105-119.

47. Deodhar SD, Seth R, Srimal RC. (1980) *Int. J. Med. Res.* 71 : 632 - 634.

48. Rao CV, Rivenson, A, Simi B, Reddy BS. (1995) *Cancer Res.* 55 : 259 - 266.

49. Ihantola-Vormisto A, Summanen J, Kanakaranta H, Vuorela H, Asmawi ZM, Moilanen E. (1997) *Planta Med.* 63 : 518 - 524.

50. Rege NN, Thatte UM, Dahanukar SA. (1999) *Phytother. Res.* 13 : 275 - 291

51. Singh IP, Guru LV. (1975) *J. Res. Indian Med.* (3) : 141

52. Roy AK, Dhir H, Sharma A, Talukder G. (1991) *Int. J. Pharmacog.* 29(2) : 117.

53. Suresh K, Vasudevan DM. (1994) *J. Ethnopharmacol.* 44 : 55 - 60.

54. Puri A, Saxena KC, Srivastava V, Tandon JS. (1994) *J. Ethnopharmacol.* 42 : 31-37.

55. Khan ZK, Manglani A, Shukla PK, Puri A, Saxena RP, Tandon J. (1995) *Int. J. Pharmacog.* 33 : 297-304.

56. Ganasoundari A, Devi P, Rao BS. (1998) *Mutat. Res.* 397 : 303 - 312.

57. Das SK, Chandra A, Agarwal SS, Singh N. (1983) *Aniseptic* July: 1 - 5.

58. Mediratta PK, Dewan V, Bhattacharya SK, Gupta VS, Maiti PC, Sen P (1998) *Indian J. Med. Res.* 87 : 384 - 386.

59. Dua PR, Shankar G, Srimal, RC, Saxena RP, Puri A, Dhawan BN. (1989) *Indian J. Exp. Biol.* 27 : 631 - 634.

60. Sharma ML, Rao CS, Duda PL. (1994) *J. Ethnopharmaol.* 41 : 185 - 192.

61. Atal CK, Sharma ML, Kaul A, Kajuria A. (1986) *J. Ethnopharmacol.* 18 : 133 - 141.

62. Puri A, Saxena RP, Sumati Guru PY, Kulshreshtha DK, Saxena KC, Dhawan BN. (1992) *Planta Med.* 58 : 528 - 532.

63. Sainis KB, Sumariwala PF, Goel A, Chintalwar GJ, Sipahimalani AT, Banerji A. (1997). In : Upadhyay SN. (Ed.) *Immunomodulation*. Narosa Publishing House: New Delhi; 115 - 162.

64. Thatte UM, Dahanukar SA. (1989) *Phytother. Res.* 3 : 43 - 49.

65. Rege NN, Abraham P, Bapat RD, Ray V, Thatte UM, Dahanukar SA. (1999) In : Upadhayay SN. (Ed.) *Immuno-pharmacology : Strategies for Immuno-therapy.* Narosa Publishing House: New Delhi; 105 - 116.

66. Thatte UM, Kulkarni MR, Dahanukar SA. (1992) *J. Postgrad. Med.* 38 : 13 - 15.

67. Thatte UM, Rao SG, Dahanukar SA. (1994) *J. Postgrad. Med.* 40 : 202 - 203.

68. Nagarkatti DS, Rege NN, Desai NK, Dahanukar SA. (1994) *J. Postgrad. Med.* 40 : 65 - 67.

69. Kapil A, Sharma S. (1997) *J. Ethnopharmacol.* 58 : 89 - 95.

70. Kuttan G. (1996) *Indian J. Exp. Biol.* 34 : 854 - 856.

71. Ziauddin M, Phansaikar N, Patki P, Diwanay S, Patwardhan B. (1996) *J. Ethnopharmacol.* 50 : 69 - 76.

72. Ganasoundari A, Zare SM, Devi P M. (1997) *Br. J. Radiol.* 70 : 599 - 602.

73. Devi PV. (1996) *Indian J. Exp. Biol.* 34 : 927 - 932.

74. Mahajani SS, Kukarani RD. (1977) *Int. Archs Allergy Appl. Immunol.* 53 : 137 - 144.

75. Dorsch W, Stuppner H, Wagner H, Gropp M, Demoulin S, Ring J. (1991) *Int. Arch. Allergy Appl. Immunol*. 95 : 128 - 133.

76. Gogtay VK. (1982) *Dravyagunavigyan*, Continental Prakashan: Pune.

77. Sharma PV. (1981) *Charaka Samhita*. Chikitsasthana, Vol. II, I edn., Chaukhambha Orientalia, Varanasi, 62 - 74.

78. Ghosal S, Bhattacharya SK. (1992) *Experimental studies on Chyawonprash Awaleha,* Data on DRF files.

79. Alam M, Joy S, Desan KKS, Bhimarao R. (1989) *J. Res. Ayu. Siddha.* XI (1.4) : 43.

80. Verma MD, Singh RH, Udupa KN. (1973) *J. Res. Indian Med.* 8(2) : 1.

81. Subramoniam A. (2001) *Indian J. Pharmacol.* 33 (3) : 145 - 146.