



E-ISSN: 2321-2187
P-ISSN: 2394-0514
IJHM 2018; 6(6): 10-14
Received: 05-09-2018
Accepted: 07-10-2018

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Immunomodulatory action of traditional herbs for the management of acquired immunodeficiency syndrome: A review

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Abstract

Immunomodulatory treatment is usually needed under the conditions of impaired immune responsiveness and when the defense mechanisms of host have to be activated. Though conventional immunomodulatory chemotherapy is available it costs a huge expense and is not usually affordable to ordinary people with low socio economic status. Therefore the modulation of immune system by traditional medicinal plant products has become a subject matter for current scientific investigations worldwide. A wide number of medicinal plants have been indicated in Siddha classical literature towards the management of several diseases that results in immune deficiency. Hence the present literature analysis was performed to have a scientific perspective on some of the selected traditional herbs with immunomodulatory action.

Keywords: Traditional herbs, immunomodulation, medicinal plants, HIV, rheumatoid arthritis

1. Introduction

Traditional medicinal plants have been virtually used since ancient times as immunomodulators for the treatment of many ailments. Immunity provides protection to the individual and has the ability to neutralize and eliminate pathogenic micro-organism and their toxic products [1]. Presently immunomodulation of immune response could provide as a substitute for a variety of disease conditions with immunodeficiency. Immunity is a complex, multicellular homeostatic process that allow an individual to recognize foreign material and eliminate the foreign matter [2]. Herbal drugs are known to stimulate both specific and nonspecific immunity and thereby possess immunomodulatory property [3]. The term immunostimulation implies primarily the non antigen dependent stimulation of the function and efficiency of granulocytes, macrophages, complement and natural killer (NK) cells and comprise a prophylactic or therapeutic concept [4].

Expansion in clinical and experimental immunology sturdily suggests that stressful environmental conditions provoke many infectious diseases and are associated with suppression of immune system. The ability to modify the immune response in humans confer better protection against infectious agents through a more complete understanding of the functioning of the immune system. Naturally occurring or synthetic compounds capable of altering those mechanisms offered further possibilities for modulating immune responses [5]. Mechanisms of immunomodulation activity occur mainly via stimulation of phagocytes, macrophages, lymphoid cells, increasing circulating total white cell counts and interleukin-2 levels [6]. Immunological defense is a constant interplay between nonspecific and specific, cellular and humoral immune responses, stimulation and suppression of immunocompetent cells, and the influence of endocrine and other mechanisms. Primary targets of the Immunostimulant are T or B lymphocytes and play a central role in immunostimulation [7]. Activation of macrophages is the second most important role in the stimulation of T lymphocytes, which can be achieved either directly or indirectly, via macrophages [8]. This review article involved various data collected from various Siddha classical texts, manuscripts and research details from several books and research journals to get adequate information of traditional herbs as immunomodulators so that it can be used as a complement therapy for Acquired immune deficiency syndrome and also for other immune deficiency disorders.

2. Siddha system and Immunomodulation

The great Tamil saint 'Thiruvalluvar' has insisted the significance of diet as the cause of disease in his chapter called *Marunthu* (Medicine). According to *Siddha* system, the phrase "Food is medicine and medicine is food" denotes that proper diet and healthy lifestyle containing medicinal herbs has intrinsic elements allowing the body to remain healthy.

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The ultimate essence of our consumed food acts as an essential component to strengthen the seven *Udal kattugal* Saaram (Plasma), Seneer (Blood), Oon (Muscles), Kozhuppu, Enbu, Moolai, Sukkilam, Suronitham thereby stimulating immunomodulation.

3. Immunomodulatory action of Traditional herbs

3.1. *Cedrus deodara* (Tamil Name-*Devadaru*)

Cedrus deodara is an evergreen tree (conifer) belonging to genus Pinacea that grows in tropical as well as subtropical region. It grows to a height of 85 m with needle like sharp pointed leaves, flowers are monoecious and unisexual [9]. The various phytochemicals such as wickstromal, taxifolin, cedeodarin, cedrinol, deodardione, diosphenol, limonene, carboxylic acid, (-)-matairesinol, (-)-nortrachelogenin, A new dihydroflavonol named deodarin (3, 4, 5, 6-tetrahydroxy-8-methyl dihydroflavonol) has been isolated from the stem bark it also contains beta-sitosterol, shikimic acid, methylconiferin and ferulic acid beta-glucoside. The essential oil of wood contain a sesquiterpenes-L II: Isohemacholone and sesquiterpenes L III: deodarone, atlantone, α -himacholone, β himacholone, α -pinene, β -pinene, myrcene, himachalene, cis-atlantone, α -atlantone [10]. The volatile oil of *Cedrus deodara* wood, administered orally at doses of 50 and 100 mg/kg, significantly inhibited neutrophil adhesion to nylon fibers and inhibited Type III hypersensitivity Arthus reaction induced by methylated bovine serum albumin as well as Type IV, delayed type hypersensitivity reaction induced by sheep erythrocytes and oxazolone, indicating an inhibitory effect on humoral and cell-mediated immune responses [11].

3.2. *Cinnamomum tamala* (Tamil Name-*Lavanga pathiri*)

Cinnamomum tamala belongs to the family Lauraceae and is found in tropical and sub-tropical Himalayas and in eastern Bengal, India, and. The leaf extract is being used for various ailments like anorexia, dryness of mouth, bladder disorders etc. The leaf extract of this plant is found to have antidiarrheal property and hypoglycemic activity [12]. Cinnamaldehyde (CM) is the Pale yellow, viscous organic compound that gives cinnamon its flavour that occurs naturally in the bark of cinnamon trees. The essential oil of cinnamon bark contains about 90% CM. The major constituents of the leaf essential oils of these species contain furanosesquiterpenoids as principal constituents. Furanogermene (59.5%) was found to be the major compound in the leaf essential oil is β -caryophyllene, sabinene, germacrene D and curcumenol. Apart from that, Leaf oil mainly contains α -linalool, α -pinene, β -pinene, limonene and camphene. The volatile oil of the buds contains more monoterpene and sesquiterpene compounds than oils from the flowers and fruits [13]. Chen, L. *et al.* reported procyanidin oligomer compounds, cinnamtannin B1, cinnamtannin D1, para meri tannin A1, procyanidin B2 and procyanidin C1 from *C. tamala* showed immune-suppressive effects mediated through significant reduction of IFN- γ and IL-2 in LPS induced splenocytes proliferation model [14].

In another study conducted by Chaurasia *et al.*, the hexane extract *tamala* and solvent free extract (CTH) of *Cinnamomum* was fed orally to rats in various doses for 10 days, and was compared with ascorbic acid (1,000 mg/kg, immune-stimulant) and cyclophosphamide (10 mg/kg, immune-suppressant) for its effect on peritoneal macrophage functions,. CTH significantly suppressed phagocytosis activity, reduced production of superoxide and cellular NADPH content in concentration dependent manner. Thus, it

could be suggested that the leaves of *C. tamala* possesses immunosuppressive property, which is mediated through modulation of innate immunity [15].

According to one more study authors disclosed the study results of immunomodulation activity of different solvent extracts of *C. tamala* which revealed the butanol extracts had greater inhibition against tested pathogens in the host Swiss albino mice by increasing its immune power [16].

3.3. *Alpinia galangal* (Tamil Name-*Sitrarathai*)

Alpinia galanga Linn. (Zingiberaceae) is a perennial, aromatic and rhizomatous herb which is widely distributed in India. It is traditionally used as a carminative, stomachic, disinfectant, aphrodisiac and for the treatment of inflammation. *Alpinia galangal* contains essential oil pinene, b-pinene, limonene, α -terpineol, linalool, methyl eugenol, eugenol and 1, 8-cineol. It contains phytoconstituents such as quercetin, kaempferol, isorhamnetin, kaempferide, quercetin, galangin, galangal A, B and galanolactone [17].

The effect of different extract fraction was tested on cell-mediated immunity by measuring T cell proliferation, at two different dose levels 100 and 200 mg/kg body weight on animals for spleenocyte proliferation and DTH response. DTH is antigen specific and causes erythema and induction at the site of antigen infection in immunized animals. T-cells are required to initiate the reaction [18]. Results obtained during present investigation showed significant ($P < 0.001$) increase in reaction index (RI). The study results revealed that *Alpinia galanga* was an effective modulator of T cell mediated immune response and DTH response [19]. In another study by Jain *et al.*, it was concluded that *A. galanga* may have immunomodulatory potential due to presence of quercetin, the flavonoid fraction. Jain, Alok & Pawar, Rajesh & Lodhi, Santram & Singhai, A.K. (2012) [20]. Also, methanolic extract of *A. galanga* and 1'S-1'- Acetoxychavicol acetate showed potent inhibitory activity against human immunodeficiency virus type-1 (HIV-1) and against human cytomegalovirus (HCMV) [21, 22].

3.4. *Withania somnifera* (Tamil Name-*Amukkara*)

Withania somnifera (WS), has been a significant herb in traditional Siddha and Ayurvedic medical systems for over 3000 years. It is also known as Ashwagandha, Indian ginseng, and winter cherry. Among the various alkaloids present in *Withania*, withanine is the main constituent. The other active chemical constituents are alkaloids (isopelletierine, anferine), steroidal lactones (withanolides, withaferins), saponins containing an additional acyl group (sitoindoside VII and VIII), and withanolides, somniferine, somnine, pseudo-withanine, tropine, pseudo-tropine, 3-a-glyoxytropine, choline, cuscohygrine, isopelletierine, anaferine and anahydrine [23].

Several studies confirm the immunomodulatory action of *Withania somnifera*. The The root powder extract of *Withania somnifera* was found to stimulate the immunological activity in Babl/c mice and was found to enhance the total WBC count on 10th day. Bone marrow cellularity (27×10^6 cells/femur) as well as alpha-esterase positive cell number also increased significantly ($P < 0.001$) after the administration of *Withania* extract. Further *Withania* extract along with the antigen (SRBC) produced an enhancement in the circulating antibody titre and the number of plaque forming cells (PFC) in the spleen and also enhancement in phagocytic activity. Studies also show that *Withania* extract inhibited delayed type hypersensitivity reaction in mice (Mantoux test). These results

confirm the immunomodulatory activity of *W. somnifera* extract, which is a known immunomodulator *Withania somnifera* (L.) Dunal (Solanaceae), namely WST and WS2, were studied in mice for immune inflammation and showed positive results on active paw anaphylaxis and delayed type hypersensitivity (DTH) on comparing with the standard drug disodium chromoglycate. A significant boost in white blood cell counts and platelet counts was observed in animals treated with WST [24].

3.5. *Tinospora cordifolia* (Tamil Name-*Seenthil*)

Tinospora cordifolia (Willd.) Hook. f. belonging to the family Menispermaceae is a large, glabrous, deciduous climbing shrub. It is distributed throughout the tropical Indian subcontinent and China, ascending to an altitude of 300m [25-27]. The plant mainly contains alkaloids, glycosides, steroids, sesquiterpenoid, aliphatic compound, essential oils, mixture of fatty acids and polysaccharides, Aporphine alkaloids, clerodane diterpenes, berberine, palmatine, tembetarine, magniflorine, choline, and Tinosporin etc. It also contains the Alkaloids like Berberine, Palmatine, Tembetarine, Magnoflorine Choline, Tinosporin [28].

It also stimulated proliferation of spleenocytes in a dose-dependent manner. Administration of *Tinospora cordifolia* (Tc) before irradiation also increased levels of IL-1beta and GM-CSF from 56 pg/mL and 53 pg/mL in irradiated group to 59 pg/mL and 63 pg/mL, respectively. Similarly, radiation-induced decrease of antioxidant potential of plasma [32 Fe (2+) equiv.] as compared to control. RTc treatment thus suggesting its radio-protective mechanism. Ten days of treatment with *T. cordifolia* (100 mg/kg/d) induced a significant ($P < 0.01$) increase in the number of (Colony Forming Units of granulocyte-macrophage series. This suggests that activation of macrophages by *T. cordifolia* leads to increase in GM-CSF, which leads to leukocytosis and improved neutrophil function [29]. A combination of *Tinospora* herb (100mg/kg body wt. For 15 days) and cisplatin reduce the organ's alteration effectively, through a prominent increase in proliferation and differentiation of lymphocytes [30]. *Tinospora* also modulates the IL level and strengthens its antiscabies activity [31]. The aqueous stem extract of TC enhances secretion of macrophagic NO in dose-dependent manner in the presence of LPS that help in destroying tumor cell and immunomodulation with the secretion of IL-6 which plays a vital role in the stimulation of B-cell proliferation [32]. This induced proliferation activity of B-cell and degradation of IκB-α by G1-4A as well as LPS are blocked by TLR4-MD2 antibody which indicates that G1-4A attached to the TLR-4 receptor on the surface of B cell, activate the NF-κB and regulate gene expression, cytokine production and proliferation of B cell [33, 34]. TC extract has the ability to modify the activity of macrophages which regulate the secretion of lysozyme and NO at the sight of bacterial infection (bactericidal property) and improves the immunity of the organism [35].

3.6 *Cynodon dactylon* (Tamil Name-*Arugampul*)

Cynodon dactylon belongs to the family Poaceae. It contains phenolic phytotoxins viz. ferulic, syringic, p araucoumaric, vanillic, para hydroxyl benzoic and orthohydroxy phenyl acetic acid [36, 37]. Flavonoids and glycosides were found to be present in the aqueous extract of *C. dactylon* while alkaloids, glycosides and flavonoids were reported to be present in ethanol extract of the plant [38]. Other compounds like vitamin

C, β carotene, fats, palmitic acid etc. have also been reported [39]. Immunomodulatory activity of the protein fraction of *Cynodon dactylon* was evaluated in healthy swiss albino mice by testing humoral and cellular immune responses to the antigenic challenges with sheep RBCs and by neutrophil adhesion test. A significant increase in the test parameters viz., neutrophil test, haemagglutinating antibody titre and delayed type hypersensitivity response was observed [40]. Mangathayaru and co-workers implicated that, *C. dactylon* possesses immunomodulatory activity which was tested by, using its freshly prepared juice. The test was conducted on BALB/c mice by the humoral antibody response (determined by haemagglutination antibody titre and spleen cell assay). It was found that, oral administration of the juice at 250 and 500 mg/kg in BALB/c mice increased humoral antibody response upon antigen challenge, as evidenced by a dose-dependent, statistically significant increase in antibody titre in the haemagglutination antibody assay and plaque forming cell assay [41]. The daily treatment of 70 μl of ethyl acetate fraction of *dactylon* polyphenols significantly prevented the immunosuppression caused by pyrogallol in Balb/c mice which was observed [42]. *C. dactylon* protein fraction promises strong utility for effective immunostimulant in swine albino mice [43]. Humoral antibody response upon antigen challenge and it was evidenced by a dose-dependent, significant level increase in antibody titer in the haemagglutination antibody and plaque forming cell assay oral administration of *Cynodon* juice at 250 and 500 mg/kg in Balb/c mice were. Furthermore, the fresh juice of *C. dactylon* doses equivalent to 50, 100 and 200 mg total phenols/kg body weight. The juice protected human DNA against doxorubicin-induced DNA damage [44].

3.7 *Curcuma longa* (Tamil Name-*Manjal*)

Turmeric (*Curcuma longa* Linn) is extensively used as a spice and grown widely throughout Indian subcontinent. Belonging to family Scitaminae are very important for their therapeutic potentials [45, 46]. The most important chemical components of turmeric are a group of compounds called curcuminoids, which include curcumin (diferuloylmethane), demethoxycurcumin, and bisdemethoxycurcumin [47]. One study showed curcumin to be an effective compound to inhibit the HIV-1 LTR-directed gene expression without any major effects on cell viability [48].

Turmeric has been reported to increase mitogenic responses of splenic lymphocytes [49]. Japanese investigators have isolated a polysaccharide (Ukonan A-D) which stimulates carbon clearance [50]. They have also isolated a lipopolysaccharide from the root of *C. longa* which is immunostimulant [51]. Dietary curcumin (40 mg/kg) in rats for 5 weeks enhanced IgG levels but did not affect delayed type hypersensitivity and NK cell activity. Curcumin inhibits NO production in activated macrophages [52]. The anticancer properties of curcumin may be mediated atleast in part by inhibition of inducible form of NO synthase [53].

4. Conclusion

Through this review the Immunomodulatory action of selected traditional herbs have been evaluated and discussed. These herbs can be used as complement to the HIV affected patients to boost their immunity and a few of them also possess anti-HIV activity besides having immunomodulatory action. However preclinical and clinical studies of these herbs may be warranted to provide more evidence scientifically.

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