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Immun., Endoc. & Metab. Agents in Med. Chem., **2016**, *16*, **1-22**

RESEARCH ARTICLE

Immunological Effects of Medicinal Plants: A Review (Part 2)

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ARTICLE HISTORY

Received: August 19, 2016
Revised: October 02, 2016
Accepted: October 06, 2016

DOI: 10.2174/1871522216666161014155814

Abstract: Many studies showed that medicinal plants possessed immunological effects. The plants with immunological effects were included: *Agrimonia eupatoria, Alpinia galanga, Althaea officinalis, Althaea officinalis, Althaea rosea, Avena sativa, Bauhinia variegata, Betula alba, Brassica rapa, Bryophyllum pinnatum, Caesalpinia cristaCalendula officinalis, Calotropis procera, Canna indica, Capsicum annuum, Capsicum frutescens, Carthamus tinctorius, Carum carvi, Cassia occidentalis, Cichorium intybus, Cistanche tubulosa*, Citrus species, *Clerodendrum inerme, Clitoria ternatea, Convolvulus arvensis, Cordia myxa, Crocus sativus, Cuminum cyminum, Cydonia oblonga, Cynodon dactylon, Cyperus rotuntdus, Eupatorium cannabinum* and *Euphorbia hirta*. This review will highlight the immunological effects of these medicinal plants.

Keywords: Medicinal plant, pharmacology, Immunological, herbs, experimental.

INTRODUCTION

The immune system is one of most complex biological systems in the body. The human immune system has the essential function of protecting the body against the damaging effects of pathogenic microbial agents. Innate and adaptive immunity depends on the activity of white blood cells. Innate immunity largely depends upon granulocytes and macrophages, while adaptive immune response depends upon lymphocytes, which provide long term immunity. Modulation of the immune system denotes any change in the immune response that can involve induction, expression, amplification or inhibition of any part or phase of the immune response, therefore, immunemodulator may be defined as a biological or synthetic substance, which can stimulate, suppress or modulate any of the components of the immune system including both innate and adaptive arms of the immune response. Plants are a valuable source of a wide range of secondary metabolites, which are beside their use in medicine, they are also used as agrochemicals, flavours, fragrances, colours, biopesticides and food additives. Recent studies showed that many medicinal plants possessed immunological effects, included *Agrimonia eupatoria, Alpinia galanga, Althaea officinalis, Althaea officinalis, Althaea rosea, Avena sativa, Bauhinia variegata, Betula alba, Brassica rapa, Bryophyllum pinnatum, Caesalpinia cristaCalendula officinalis, Calotropis procera, Canna indica, Capsicum annuum, Capsicum frutescens, Carthamus tinctorius, Carum carvi, Cassia occidentalis, Cichorium intybus, Cistanche tubulosa*, Citrus species, *Clerodendrum inerme, Clitoria ternatea, Convolvulus arvensis, Cordia myxa, Crocus sativus, Cuminum cyminum, Cydonia oblonga, Cynodon dactylon, Cyperus rotuntdus, Eupatorium cannabinum* and *Euphorbia hirta*. This study will highlight the immunological effects of the medicinal plants.

Agrimonia eupatoria

An aqueous ethanol extract of the herb was tested for immunomodulative activity in the peri-

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Table 1. Immuno-modulating effects of medicinal plants.

Medicinal Plants	Effects on Immune System	Ref.
Agrimonia eupatoria	Increase in phagocytic activity and increase in the activities of lysozyme and peroxidase	[1-3]
Alpinia galangal	significantly stimulated T cell proliferation and splenocyte proliferation in mice spleen at a dose of 100 mg/kg bw.	[4]
	Inhibited the release of hexosaminidase and the antigen-IgE-mediated TNF-alpha and IL-4 production in passive cutaneous anaphylaxis reactions in mice	[5]
	decreased cytokine production by T helper cells	[6-11]
Althaea officinalis	Showed an anti-complement activity on normal human serum in concentrations of 100 – 1000 ug/ml	[12-13]
	Inhibited intracellular calcium mobilisation in normal human melanocytes activated by endothelin-1, and strongly inhibited endothelin-1-induced proliferation of melanocytes.	[14]
Althaea rosea	Induced a transient non-specific polyclonal response indicated by the production of IL-4 in treated, non-immunized mice initially boosted the production of anti-EA antibodies and IL-4, a T- helper 2 cytokine suppress production of gamma-interferon	[13, 15-16]
Avena sativa	β- glucan helped neutrophils to reach the site of infection more rapidly and enhanced their ability to eliminate the bacteria	[17-18]
	β-glucan mildly up-regulated the inflammation-related genes with differential gene expression patterns. Similar gene expression kinetics, but different fold induction values, was found for the crude β-glucan extracts and their corresponding commercial forms. Pre-incubation of THP-1 macrophages with β-glucans prior to lipopolysaccharide (LPS) exposure decreased the induction of inflammation-related genes compared to LPS treatment. No production of nitric oxide (NO) and hydrogen peroxide was detected in β-glucan stimulated THP-1 macrophages. Phagocytic activity not differ after stimulation by β-glucan samples	[19]
Bauhinia variegata	Showed immunomodulatory activity on the primary and secondary antibody responses. Phagocytic index and percentage neutrophil adhesion have also increased.	[20-21]
Betula alba	Betulinic acid isolated from the plant increased the total number of thymocytes, splenocytes, lymphocytes of mesenteric lymph node cells, and the weight ratio of the spleen and mesenteric lymph nodes in non-immunized mice. It also changed the percentage of T cell subsets in the thymus and T and B lymphocytes in peripheral lymphatic organs. Five exposures to betulinic acid (0.5 mg/kg) decreased the percentage of immature CD4+ CD8+ thymic cells with corresponding increases in the percentage and absolute count of mature, single-positive CD4+ thymocytes and decreased the percentage and total count of CD3+ splenocytes and mesenteric lymph node cells with corresponding decreases in the percentage and absolute count of CD4+ and CD8+ cells. Multiple administration of betulinic acid at the investigated doses augmented the percentage and absolute count of CD19+ cells in the peripheral lymphatic organs. It also increased the number of plaque forming cells (PFC) but decreased the production of anti-SRBC antibodies in red blood cells (SRBC)-immunized mice on day 4 after priming	[22-23]

Table 1. Contd…

Medicinal Plants	Effects on Immune System	Ref.
Brassica rapa	In both innate and acquired immunity models, chloroform, ethyl acetate and methanolic extracts significantly and dose-dependently reduced paw thickness. Ethyl acetate extract showed better effect	[24-25]
Bryophyllum pinnatum	Reduced production of OVA-specific IgE antibodies, reduced eosinophilia, and impaired production of the IL-5, IL-10 and TNF- α cytokines	[26-27]
	Induced significant inhibition of cell-mediated and humoral immune responses in mice .The spleen cells of animals pretreated with plant extract showed a decreased ability to proliferate in response to both mitogen and antigen in vitro as well as, the specific antibody responses to ovalbumin were also significantly reduced by treatment	[28]
Caesalpinia crista	Produced an increase of 93.03 ± 4 mean hemagglutinating antibody titer and a change of 0.56 ±0.058 mm in delayed type hypersensitivity as compared to control at a dose of 400 mg/kg bw	[29-30]
	Evoked a significant increase in percent neutrophil adhesion to nylon fibers, as well as a dose-dependent increase in antibody titer values, and potentiated the delayed-type hypersensitivity reaction induced by sheep red blood cells. Also it prevented myelosuppression in cyclophosphamide treated rats with a good response towards phagocytosis in carbon clearance assay	[31]
Calendula officinalis	Polysaccharides isolated from an aqueous extract of Flos enhanced phagocytosis in human granulocytes *in vitro* in the colloidal carbon clearance test polysaccharides isolated from flowers aqueous extract also enhanced phagocytosis when administered (10 mg/kg bw) intraperitoneally to mice intraperitoneal administration of unsaponifiable fraction (0.5 ml) of a hydroalcoholic extract of the flowers also stimulated phagocytosis in mice inoculated with *Escherichia coli*	[32-35]
Calotropis procera	Latex fractions induced production of antibodies significantly ($p<0.05$) in response to sheep red blood cells. Immunostimulation was counteracted by up regulating macrophage phagocytosis in response to carbon particles. DTH reaction was found to be augmented significantly ($p<0.05$) by increasing the mean foot pad thickness after 48h. It reduced mortality in rats injected with 1 x 108 *E. coli* intraperitoneally from 0.0% - 16.6%. Water-soluble extract in mice (2 mg/mouse) induced migration of macrophages to the intraperitoneal cavity. Adding water-soluble extract (1-10 microg/ml) to the culture medium of the murine monocyte/macrophage cell line RAW264.7 caused an increase in NO production and expression of iNOS mRNA.	[36-38]
Canna indica	Ethanolic extract inhibited the production of inflammatory mediators including NO, IL-1β, and PGE2 from LPS-induced RAW 264.7 macrophages. The increases in HG-induced mRNA expressions of IL-8 and MCP-1 were also significantly inhibited by ethanolic extract. Stimulation of HG in U937 monocytes resulted in activation of p38 MAPK, ERK1/2, and JNK. However, ethanolic extract treatment significantly decreased phosphorylation of p38 MAPK, ERK1/2, and JNK	[39-40]

Table 1. Contd…

Medicinal Plants	Effects on Immune System	Ref.
Capsicum annuum ***Capsicum frutescens***	Suppressed interleukin (IL)-2, interferon (IFN)-gamma, IL-4 and IL-5 production. The population of CD3(+) cells in the PP cells was significantly reduced while CD19(+) cells increased after oral administration of capsicum extract (1 and 10 mg/kg/day) and capsaicin in mice.	[41-42]
	The intratumoral administration of capsaicin into a preexisting tumor results in retarded progression of the injected tumor. Capsaicin-elicited immunity is shown to be T cell-mediated and tumor-specific	[43]
	Capsaicin attenuated the proliferation and activation of autoreactive T cells in pancreatic lymph nodes. Engagement of vanilloid receptor 1 enhanced a discreet population of CD11b(+)/F4/80(+) macrophages in PLN, which express anti-inflammatory factors interleukin (IL)-10 and PD-L1. This population is essential for CP-mediated attenuation of T-cell proliferation in an IL-10-dependent manner.	[44]
	Significantly reduced ovalbumin-induced allergic airway inflammation, including increased inflammatory cell recruitment to the airways, airway hyper-responsiveness, and increased levels of T-helper type 2 cytokines. It also attenuated ovalbumin-induced increases in NF-κB activity in lungs.	[45]
	Increased the relative proportion of lymphocytes. It also increased the proportion of total CD4(+) cells and total CD4(+) cells that co-expressed the activation status signal and CD25 in blood.	[46]
	Showed potent anti-complementary activity. Capsicum oleoresin reduces the adverse effects of respiratory syndrome virus by improving the immune responses of pigs.	[47-48]
Carthamus tinctorius	Modulated immune function in mice, produced declines in both nonspecific and specific immune functions, showed inhibitory effects on [3H]TdR incorporation during human peripheral T- and B-lymphocyte proliferation and inhibited the production of proinflammatory cytokines (IL-1α, IL-1β, IL-6, IL-8 and TNF- α) from lipopolysaccharide-stimulated human monocytes.	[49-52]
Carum carvi	Hydroalcoholic extract and essential oil were investigated in an immunological model of colitis in rats, they reduced colon tissue lesions and colitis.	[53-54]
Cassia occidentalis	Protected mice against cyclophosphamide-induced immune-suppression, stabilized membrane, inhibited inflammatory mediators and reduced lymphoid organ weights and decreased diameter of the follicles of bursa of Fabricius in chicken	[55-59]
Cichorium intybus	Increased the circulating leukocytes and the relative weights of liver, spleen and thymus, increased phagocytic activity, natural killer cell activity and proliferation as well as interferon (IFN-gamma) secretion and inhibited local anaphylactic reaction activated by anti-dinitrophenyl (DNP) IgE,	[60-62]

Table 1. Contd…

Medicinal Plants	Effects on Immune System	Ref.
Cistanche tubulosa	Decreased lymphocyte proliferation, phagocytosis of peritoneal macrophages and blood IL-2 content	[63]
Citrus species	Reduced the degranulation and histamine release of IgE-activated basophilic cells and mast cells and inhibited the IgE- and PMA/A23187-induced increases in IL-8, TNF-α and GM-CSF production in mast cells.	[64]
	Reduced allergen-specific chronic inflammatory	[65]
	Diminished degranulation of basophilic and inhibited the production of IL-8 and TNF-α from human mast cells.	[66]
	Demonstrated therapeutic immunological and clinical effects in allergic rhinitis	[67]
Clerodendrum inerme	Moderated the release of histamine, IL1α and IL8	[68-69]
Clitoria ternatea	Decreased milk induced leucocytosis and eosinophilia, protected against egg albumin induced degranulations of mast cells, possessed antihistaminic effect, and significant decreased primary and secondary antibody titers in SRBCs-sensitized rats, paw thickness in response, neutrophil adhesion and *in vitro* phagocytosis	[70-73]
Convolvulus arvensis	Increased total leukocytes and percentage lymphocyte, enhanced the phagocytic function of reticular endothelial system and blocked immunosuppressive effect produced by dexamethasone.	[74-75]
Cordia myxa	Caused marked hyperplasia of lymphoid tissues, inhibited percentage of PMNLs forming Formazan granules and elevated leucocyte count with insignificant elevation of lymphocyte.	[76-79]
Crocus sativus	Inhibited viability of lymphocytes, inhibited secretion of IFN-γ in stimulated cells and IL-10 secretion in both stimulated and nonstimulated cells and potentiated the Th2 response of humoral immunity, causing significant increases in agglutinating antibody titre	[80-84]
Cuminum cyminum	Increased T cells (CD4 and CD8) count and Th1 predominant immune response in a dose dependent manner	[85-[86]
Cydonia oblonga	Affected the induction of the allergen-specific Th1 pathway, inhibited the production of IL-8 and TNF- α from human mast cells, reduced the mRNA expression of the high-affinity IgE receptor (FcepsilonRI) gamma subunit and suppressed cytokine expressions of mouse bone marrow-derived mast cells (BMMCs). Leukotriene C_4 and prostaglandin D_2 production in BMMCs were also reduced	[87-93]
Cynodon dactylon	Inhibited compound 48/80 induced anaphylactic reaction, nitric oxide production and mast cell activation. It also increased humoral antibody response upon antigen challenge	[94-96]
Cyperus rotuntdus	Enhanced the lymphocyte proliferation in the absence and presence of mitogens.	[97-98]

Table 1. Contd…

Medicinal Plants	Effects on Immune System	Ref.
Eupatorium cannabinum	Its polysaccharides showed a phagocytosis enhancing effect and significant immunostimulating activities as determined by granulocytes- and carbon clearance tests.	[99-100]
	Increased the phagocytic index and stimulated the specific immune response by increasing the antibody titer in fish infected with *Aeromonas hydrophila*.	[101-102]

toneal cavities of mice. Immunostimulant activity resulted in an increase in phagocytic activity and increases in the activities of lysozyme and peroxidase [1]. The antioxidative properties of aqueous plant extracts were evaluated using common methods such as the Rancimat and 2,2'-diphenyl-1-picrylhydrazyl (DPPH) free radical method. Moreover, a voltammetric procedure based on the protective effect of antioxidants against the oxidative DNA damage was employed using a disposable DNA biosensor fabricated as a screen-printed electrode chemically modified by calf thymus double stranded (ds) DNA [2-3].

Alpinia galangal

The flavonoid fraction of *Alpinia galanga* Linn. extract significantly stimulated ($P < 0.001$) T cell proliferation and splenocyte proliferation in mice spleen at a dose of 100 mg/kg body weight of mice. The aqueous fraction had a lower stimulatory effect than the flavonoid fraction. The antioxidant level of the spleen cells also increased following treatment with the flavonoid fraction. Hot water soluble polysaccharide extract of *A. galanga* rhizome possesses a marked stimulating effect on the reticulo endothelial system (RES) and increased the number of peritoneal exudates cells and spleen cells of mice [4]. 1'S-1'- acetoxychavicol acetate and 1'S-1'-acetoxyeugenol acetate from aqueous extract of rhizome inhibited the release of hexosaminidase and the antigen-IgE-mediated TNF-alpha and IL-4 production in passive cutaneous anaphylaxis reactions in mice [5]. 1'-acetoxychavicol acetate and the related compounds in the rhizomes of *Alpinia galanga* exerted antioxidative activity [6]. The antioxidant activity of *Alpinia galanga* extracts and essential oil *was* determined using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) and oxygen radical absorbance capacity (ORAC) methods. The ethanolic extract showed the highest DPPH free radical scavenging ability as well as the highest ORAC value when compared to the water extract and the essential oil [7]. Ethanolic extract of *Alpinia galanga* showed a potent scavenging activity by DPPH method with the IC 50 value of 69.5±1.375 μg/ml, by lipid peroxidation method with the IC_{50} value of 77±1.876 μg/ml, hydrogen peroxide radical scavenging activity with the IC_{50} value 55±1.59 μg/ml, and ABTS radical scavenging method with the IC_{50} value 0.086±1.10 μg/ml [8]. Acetoxychavicol acetate of *Alpinia galanga* exhibited potent antioxidant activity, increased cell apoptosis and decreased cytokine production by T helper cells [9-11].

Althaea officinalis

Althaea-mucilage O, an acidic polysaccharide isolated from marshmallow root, has been demonstrated to have an anti-complement activity on normal human serum in concentrations of 100 – 1000 ug/ml [12-13]. An extract (extraction medium 45 % 1,3-butylene glycol solution) of marshmallow root was found to inhibit intracellular calcium mobilisation in normal human melanocytes activated by endothelin-1, and to strongly inhibit endothelin-1-induced proliferation of melanocytes. The extract can diminish the physiological effect of endothelin-1 on normal human melanocytes following UVB irradiation [14]**.** Scopoletin produced dual action on tumoral lymphocytes exhibiting both a cytostatic and a cytotoxic effect on the cell, and also exert apoptosis. Proliferation of normal T lymphocytes was found due to the interaction with kinase C (PKC) protein. It indicates that scopoletin may be a potential antitumoral compound [15].

Althaea rosea

Water extract of *Althaea rosea* produced the following effects on immune system [13,16]

1- Induced a transient non-specific polyclonal response indicated by the production of IL-4 in treated, non-immunized mice.

2- Initially boosted the production of anti-EA antibodies and IL-4, a T- helper 2 cytokine.

3- Suppressed the production of gamma-interferon, a T- helper 1 cytokine.

Avena sativa

β- glucan helped neutrophils to reach the site of infection more rapidly and enhanced their ability to eliminate the bacteria [17-18]. The different immunological aspects of β-glucans derived from different food sources (oat, barley and shiitake) were examined on phorbol myristate acetate (PMA)-differentiated THP-1 macrophages. Inflammation-related gene expression kinetics (IL-1β, IL-8, nuclear factor kappa B [NF-κB] and IL-10) were evaluated after 3, 6 and 24 h of stimulation with 100 μg/ml β-glucan. All tested β-glucans mildly up-regulated the observed inflammation-related genes with differential gene expression patterns. Similar gene expression kinetics, but different fold induction values, was found for the crude β-glucan extracts and their corresponding commercial forms. Pre-incubation of THP-1 macrophages with β-glucans prior to lipopolysaccharide (LPS) exposure decreased the induction of inflammation-related genes compared to LPS treatment. No production of nitric oxide (NO) and hydrogen peroxide was detected in β-glucan stimulated THP-1 macrophages. Phagocytic activity did not differ after the stimulation by β-glucan samples. Based on these in vitro analyses, β-glucans have varying levels of immunomodulating properties, which are likely related to structure, molecular weight and compositional characteristic of β-glucan [19].

Bauhinia variegata

The ethanolic extract of the stem bark of *B. variegata* showed immunomodulatory activity on the primary and secondary antibody responses. Phagocytic index and percentage neutrophil adhesion have also increased [20-21].

Betula alba

Betulinic acid, a pentacyclic triterpene isolated from the bark of white birch *Betula alba* exerted many immunological effects. It was found that betulinic acid administered orally five times at the dose of 0.5 mg/kg increased the total number of thymocytes, splenocytes, lymphocytes of mesenteric lymph node cells, and the weight ratio of the spleen and mesenteric lymph nodes in non-immunized mice. Betulinic acid also changed the percentage of T cell subsets in the thymus and T and B lymphocytes in peripheral lymphatic organs. The effects of betulinic acid on T and B cell subpopulations depended on the dose applied. The strongest stimulating effect of betulinic acid was observed when the drug was administered at the dose of 0.5 mg/kg. Five exposures to betulinic acid (0.5 mg/kg) decreased the percentage of immature CD4+ CD8+ thymic cells with corresponding increases in the percentage and absolute count of mature, single-positive CD4+ thymocytes and decreased the percentage and total count of CD3+ splenocytes and mesenteric lymph node cells with corresponding decreases in the percentage and absolute count of CD4+ and CD8+ cells. Multiple administration of betulinic acid at the investigated doses augmented the percentage and absolute count of CD19+ cells in the peripheral lymphatic organs. Moreover, betulinic acid at the dose of 5 mg/kg administered prior to SRBC immunization increased the number of plaque forming cells (PFC) but decreased the production of anti-SRBC antibodies in red blood cells (SRBC)-immunized mice on day 4 after priming [22-23].

Brassica rapa

The effects of chloroform, ethyl acetate and methanolic extracts of *Brassica rapa* were investigated on cell-mediated immune response in mice. Chloroform, ethyl acetate and methanolic extracts of *Brassica rapa* glands were prepared by maceration method. Sheep red blood cell (SRBC) was injected (sc, 1×108cells/ml, 0.02 ml) and 5 days later, different extracts (10, 100 and 500 mg/kg), betamethasone (4 mg/kg) and Levamisol (4 mg/kg) as a positive control and normal saline as a negative control were given ip. After 1 h SRBC was injected to footpad (sc, 1×108 cells/ml, 0.02 ml) and footpad swelling was measured up to 72 h. To investigate the effects of *B. rapa* on innate im-

munity the same procedure was used, but animals only received one injection of SRBC 1 h after ip injection of test compounds. The results showed that SRBC induced an increase in paw swelling with maximum response at 6-8 and 2-4 h for innate and acquired immunity, respectively. Betamethasone inhibited and levamisol increased paw thickness in both models. In both innate and acquired immunity models, chloroform, ethyl acetate and methanolic extracts of *B. rapa* glands significantly and dose-dependently reduced paw thickness. Ethyl acetate extract showed better effect [24-25].

Bryophyllum pinnatum

Mice treated daily with oral *B. pinnatum* during hypersensitization with ovalbumin were protected against death. Oral protection was accompanied by a reduced production of OVA-specific IgE antibodies, reduced eosinophilia, and impaired production of the IL-5, IL-10 and TNF- α cytokines. Oral treatment with the quercitrin flavonoid isolated from plant extract prevented fatal anaphylaxis in 75% of the animals. These findings indicated that oral treatment with *Bryophyllum pinnatum* effectively downmodulates pro-anaphylactic reactions inducing immune responses [26-27]. The aqueous extract of leaves causes significant inhibition of cell-mediated and humoral immune responses in mice .The spleen cells of animals pretreated with plant extract showed a decreased ability to proliferate in response to both mitogen and antigen in vitro as well as, the specific antibody responses to ovalbumin were also significantly reduced by treatment [28].

Caesalpinia crista

The aqueous extract of *Caesalpinia crista* seeds was tested for its effect on cell mediated and humoral components of the immune system in rats. Administration of *Caesalpinia crista* seed extract produced an increase of 93.03 ± 4 mean hemagglutinating antibody titer and a change of 0.56 ±0.058 mm in delayed type hypersensitivity as compared to control at a dose of 400 mg/kg bw [29-30]. The immunomodulatory activities of ethanolic extract of *Caesalpinia crista* seeds were tested via neutrophil adhesion test, haemagglutinating antibody titer, delayed-type hypersensitivity response, phagocytic activity and cyclophosphamide-induced myelosuppression. Oral administration of ethanolic seed extract of *Caesalpinia crista* (200-500 mg/kg) evoked a significant increase in percent neutrophil adhesion to nylon fibers, as well as a dose-dependent increase in antibody titer values, and potentiated the delayed-type hypersensitivity reaction induced by sheep red blood cells. Also it prevented myelosuppression in cyclophosphamide treated rats with a good response towards phagocytosis in carbon clearance assay [31].

Calendula officinalis

The polysaccharides isolated from an aqueous extract of Flos Calendulae enhanced phagocytosis in human granulocytes *in vitro* in the colloidal carbon clearance test. The polysaccharides isolated from flowers aqueous extract also enhanced phagocytosis when administered (10 mg/kg bw) intraperitoneally to mice. On the other hand, intraperitoneal administration of unsaponifiable fraction (0.5 ml) of a hydroalcoholic extract of the flowers also stimulated phagocytosis in mice inoculated with *Escherichia coli* [32-35].

Calotropis procera

The immunological potential of the latex of *Calotropis procera* against sheep red blood cells (SRBC) as antigen was investigated in Wistar albino rats by studying cell-mediated, delayed type hypersensitivity reaction (DTH), humoral immune response, macrophage phagocytosis and *E. coli* induced bacteremia sepsis. The latex was fractionated according to water solubility and molecular size of its components. The fractions were named as non-dialyzable latex (NDL) which corresponding to the major latex proteins, dialyzable latex (DL) corresponding to low molecular size substances and rubber latex (RL) which was highly insoluble in water. The HA titer levels were quantified by primary and secondary humoral immune response in rats. The fractions induced production of antibodies titer level significantly ($p<0.05$) in response to SRBC. In addition immunostimulation was counteracted by up regulating macrophage phagocytosis in response to carbon particles. Rats received NDL fractions by oral route displayed considerable immunological response. Oral administration of NDL fractions, dose dependently increased immunostimlatory responses. DTH reac-

tion was found to be augmented significantly ($p<0.05$) by increasing the mean foot pad thickness after 48h. In the survival study, control group I and negative control group II in *E. coli* induced peritonitis has shown 50% and 66.6% mortality, while pretreated groups with NDL has reduced mortality in rats injected with 1 x 108 *E. coli* intraperitoneally from 0.0% - 16.6% [36-37]. The immunomodulatory functions of the water-soluble *C. procera* extract (CPE) was investigated via determination of its ability to activate macrophages-effector cells in inflammatory and immune responses. Intraperitoneal injection of CPE in mice (2 mg/mouse) induced migration of macrophages to the intraperitoneal cavity. The direct effects of CPE on macrophages were then assessed by measuring the production of nitric oxide (NO) as an indicator for macrophage activation. Addition of CPE (1-10 microg/ml) to the culture medium of the murine monocyte/macrophage cell line RAW264.7 caused an increase in NO production in a time- and dose-dependent manner. CPE-elicited NO production was blocked by application of an inhibitor of inducible nitric oxide synthase (iNOS). Expression of iNOS mRNA was induced by treatment of cultured macrophages with CPE. Injection of CPE in mice also resulted in an increase in plasma NO level. The hexane, ethyl acetate, and dichloromethane crude extracts of *C. procera* (250 and 500μg/mL), showed toxicity to human macrophages (U-937). However, methanol and aqueous extracts were less toxic up to >2000μg/ml. The lower concentrations (100-12.5μg/ml) were devoid of toxic effects and morphological changes of cells. However, various toxic effects were observed in the *C. procera* crude extracts in a dose-dependent manner compared to control cells [38].

Canna indica

The effect of *Canna indica* ethanolic extract (CIE) on productions of nitric oxide (NO), prostaglandin E2 (PGE2), and interleukin-1β (IL-1β) in lipopolysaccharide (LPS)-induced RAW 264.7 macrophages was investigated. In addition, the effects of CIE in high glucose (HG)-induced U937 monocytes on mRNA expressions of IL-8 and monocyte chemoattractant protein-1 (MCP-1), and regulation of mitogen-activated protein kinase (MAPK) pathways were also identified. CIE was found to inhibit the production of inflammatory mediators including NO, IL-1β, and PGE2 from LPS-induced RAW 264.7 macrophages. The increases in HG-induced mRNA expressions of IL-8 and MCP-1 were also significantly inhibited by CIE. Stimulation of HG in U937 monocytes resulted in activation of p38 MAPK, ERK1/2, and JNK. However, CIE treatment significantly decreased phosphorylation of p38 MAPK, ERK1/2, and JNK [39-40].

Capsicum annuum and Capsicum frutescens

The immunological effects of red pepper (*Capsicum annuum* Lin.) extracts (capsicum extract) and its main pungent capsaicin was investigated on T helper 1 (Th1) and 2 (Th2) cytokine production in cultured murine Peyer's patch (PP) cells *in vitro* and *ex vivo*. Direct administration of capsicum extract (1 and 10 mug/ml) and capsaicin (3 and 30 muM) resulted in suppression of interleukin (IL)-2, interferon (IFN)-gamma, IL-4 and IL-5 production. In an *ex vivo* experiment using PP cells removed from the mice after oral administration of capsicum extract (10 mg/kg/day for 4 consecutive days), IL-2, IFN-gamma and IL-5 increased in response to concanavalin A (Con A). Oral administration of 3 mg/kg/day capsaicin, also enhanced IL-2, INF-gamma and IL-4 production in response to Con A stimulation but did not influence the production of IL-5. Orally administered capsazepine (3 mg/kg/day), a selective transient receptor potential vanilloid 1 (TRPV1) antagonist, slightly enhanced IL-2 production also irrespective of Con A stimulation. The capsaicin-induced enhancement of both IL-2 and IFN-gamma production was not reduced by oral administration of capsazepine (3 mg/kg/day), suggesting a TRPV1 receptor-independent mechanism. Flow cytometric analysis revealed that the population of CD3(+) cells in the PP cells was significantly reduced while CD19(+) cells increased after oral administration of capsicum extract (1 and 10 mg/kg/day) and capsaicin (0.3 and 3 mg/kg/day). Capsazepine (3 mg/kg/day) weakly but significantly reversed these effects. Orally administered capsicum extract and capsaicin did not change the T cell subset (CD4(+) and CD8(+), Th1 (IFN-gamma(+) and T2 (IL-4(+) ratio [41-42]. It appeared that dendritic cells, a key cell type in immune responses, have the receptor for capsaicin, and engagement of this receptor has powerful immune consequences. The intratumoral administration of capsaicin into a

preexisting tumor results in retarded progression of the injected tumor regardless of whether the tumor is at its early or late stage. Furthermore, it leads to significant inhibition of growth of other, uninjected tumors in the same animal. Capsaicin-elicited immunity is shown to be T cell-mediated and tumor-specific [43]. Vanilloid receptor 1 (VR1) is expressed on immune cells. VR1 can regulate immunological events in the gut in response to its ligand Capsaicin (CP). Oral administration of CP attenuates the proliferation and activation of autoreactive T cells in pancreatic lymph nodes (PLNs) but not other lymph nodes. Engagement of VR1 enhances a discreet population of CD11b(+)/F4/80(+) macrophages in PLN, which express anti-inflammatory factors interleukin (IL)-10 and PD-L1. This population is essential for CP-mediated attenuation of T-cell proliferation in an IL-10-dependent manner [44]. The effect of a methanolic *C. annuum* L. extract (CAE) was investigated in mice model of ovalbumin-induced allergic airway inflammation. Animals were treated with CAE by oral gavage before ovalbumin challenge. Oral treatment with CAE significantly reduced the pathophysiological signs of allergic airway disease, including increased inflammatory cell recruitment to the airways, airway hyper-responsiveness, and increased levels of T-helper type 2 cytokines. Reactive oxygen species were also decreased in cells from broncho-alveolar lavage fluid. In addition, the administration of CAE attenuated ovalbumin-induced increases in NF-κB activity in lungs [45]. Treatment with capsicum oleoresin of lactating dairy cows increased the relative proportion of lymphocytes compared with the control. It also increased the proportion of total CD4(+) cells and total CD4(+) cells that co-expressed the activation status signal and CD25 in blood. The percentage of peripheral blood mononuclear cells (PBMC) that proliferated in response to concanavalin A and viability of PBMC was not affected by treatment. Cytokine production by PBMC was not different between control and capsicum oleoresin treated cows. Expression of mRNA in liver for key enzymes in gluconeogenesis, fatty acid oxidation, and response to reactive oxygen species was not affected by the treatment. No difference was observed due to the treatment in the oxygen radical absorbance capacity of blood plasma [46]. The effects of 10 mg/kg Capsicum oleoresinon on growth performance and immune responses were studied in weaned pigs experimentally infected with porcine reproductive and respiratory syndrome virus (PRRSV). The results indicate that supplementation with capsicum oleoresin reduces the adverse effects of PRRSV by improving the immune responses of pigs [47]. Hot water-soluble crude polysaccharide (HCAP-0) that was obtained from the fruits of *Capsicum annuum* showed potent anti-complementary activity. The activity was unchanged by pronase digestion, but decreased by periodate oxidation. The HCAP-0 was fractionated by DEAE ion-exchange chromatography to give two major fractions, HCAP-II and III. These two fractions were finally purified by gel filtration to give HCAP-IIa, HCAPIIIa1, and IIIa2 fractions that had high anticomplementary activities. The HCAP-IIIa1 and IIIa2 consisted of homogeneous polysaccharides. The anticomplementary activities were unaffected by treatment with polymyxin B, indicating that the modes of complement activation were not due to preexisting lipopolysaccharide [48].

Carthamus tinctorius

The polysaccharide of *Carthamus tinctorius* modulated immune function in mice [49-50]. Safflower yellow (SY) produced declines in both nonspecific and specific immune functions. Administration of safflower yellow (SY) ip 50-450 mg/kg/day for 6-8 days in mice decreased serum lysozyme concentration and phagocytosing functions of both peritoneal macrophages and peripheral leukocytes; diminished the production of plaque forming cells, specific rosette forming cells, and antibody production; inhibited delayed type hypersensitivity reaction and the activation of T suppressor cells elicited by supraoptimal immunization. *In vitro* experiments showed inhibitory effects on [3H]TdR incorporation during human peripheral T- and B-lymphocyte proliferation by SY 0.03-3.0, 0.1-2.0 mg/ml respectively, murine mixed lymphocyte culture response and the production of interleukin-2 by SY 0.1-2.5 mg/ml. In conclusion, SY produced declines in both nonspecific and specific immune functions [51]. *N*-(*p*-coumaroyl) serotonin and *N*-(*p*-coumaroyl) tryptamine, active ingredients in CT, were shown to strongly inhibit the production of proinflammatory cytokines (IL-1α, IL-1β, IL-6, IL-8 and TNF- α) from lipopolysaccharide-stimulated human monocytes. HSYA treatment increased adhesion potency (HSYA dose 1.01 x 10-4 mol x L-1), free

calcium concentration (HSYA dose 3.1 x 10-5 mol x L-1), TNF-alpha and IL-6 mRNA expression elevation (HSYA dose 5.2 x 10-5 mol x L-1) induced by LPS. HSYA also inhibited NF-kappaB p65 subgroup nuclear translocation (HSYA dose 5.2 x 10-5 mol x L-1) [52].

Carum carvi

The effects of caraway hydroalcoholic extract (CHE) and its essential oil (CEO) were investigated in an immunological model of colitis in rats induced by trinitrobenzene sulfonic acid (TNBS). Different doses of CHE (100, 200, 400 mg/kg) and CEO (100, 200, 400 µl/kg) were administered orally and also doses of CHE (100, 400 mg/kg) and CEO (100, 400 µl/kg) were given intraperitoneally. Administration of the doses started 6 h after induction of colitis and continued daily for 5 consecutive days. CHE and CEO at all tested doses were effective in reducing colon tissue lesions and colitis indices and the efficacy was nearly the same when different doses of plant fractions were administered orally or intraperitoneally [53-54].

Cassia occidentalis

The protective effect of *Cassia occidentalis* against cyclophosphamide (CP)-induced immunosuppression was evaluated in animal models. Swiss albino male mice were treated orally with the aqueous extract of *C. occidentalis*, 100 mg/kg, body weight, for 14 days. Cyclophosphamide was given intraperitoneally in a single dose of 50 mg/kg bw. Body weight, relative organ weight, lymphoid organ cellularity, hemagglutination titre (HT), plaque forming cell (PFC) assay and quantitative hemolysis of SRBC (QHS) were studied in these animals. CP showed suppressive effects on lymphoid organ weight and cellularity and other parameters of humoral immunity. Plant extract treatment itself produced no toxicity. The administration of plant extract to CP-exposed animals resulted in improved humoral responses. *C. occidentalis* treatment significantly ($P<0.01$) enhanced PFC response in CP-treated animals. In QHS assay, *C. occidentalis* also showed protection in CP-treated animals. Bone marrow cell counts, which were reduced in CP-treated animals, were reversed significantly ($p<0.01$) to normal levels in CP + plant extract group animals [55-56]. The effects of *Cassia occidentalis* (CO) on rat mast cell degranulation inhibition and human red blood cell (HRBC) membrane stabilization were studied *in vitro*. The anti lipid peroxidant effects of CO were also studied *in vitro*. Effect of CO on carrageenan-induced mouse paw oedema inhibition was also assessed. CO significantly decreased maximum protection of 80.8% at 15 microg/ml. The extract also caused significant reduction in malondialdehyde (MDA) levels of murine hepatic microsomes at 100 microg/ml (56%) and significantly reduced carrageenan induced inflammation in mice at a dose of 250 mg/kg [57]. The effects of the treatment with seeds of *C. occidentalis* and its external tegument fraction (TE) on the development of chicks and their lymphoid organs bursa of Fabricius and spleen were studied. Chicks that received a commercial ration with 1% TE had reduced body and lymphoid organ weights. The bursa of Fabricius presented reduction in the diameters of the follicles, and in the thickness of the cortical and medullary regions. The spleen presented depleted lymphoid tissue in the white pulp. These results indicate that the active principle of *C. occidentalis* is more concentrated on its TE fraction, and that it can cause weight loss as well as alterations in the lymphoid organs in chicks [58]. The possible immunotoxic effects of *Cassia occidentalis* (Co) seeds were studied through incorporation of seeds in broiler chicken rations at different concentrations (0.0%, 0.25%, 0.50% and 0.75%), for 28 or 42 days. The innate immune function (macrophage activities of spreading, phagocytosis, peroxide and nitric oxide production) and acquired immune function (humoral and cellular immune responses), as well as lymphoid organ weights and pathology were evaluated. There was enhanced macrophage activity, increased hydrogen peroxide production ($P<0.05$) in cells of birds given 0.75% Co, but there were no other pro-inflammatory effects. Birds receiving 0.75% of Co in ration for 42 days gained less weight ($P<0.01$), and showed a decrease in relative weight of the bursa of Fabricius ($P<0.05$) and spleen ($P<0.01$). In addition, morphological changes were also noted in these lymphoid organs, with depletion of lymphoid cells on the spleen and bursa of Fabricius, resulting in lower relative weight of both lymphoid organs. No impairment of humoral immune response against Newcastle disease and in cellular immune response after a phyto-haemagglutinin challenge was recorded. The authors postulated that mitochon-

drial damage and related apoptosis may be responsible for the enhanced peroxide production and the reduced relative weight of the bursa of Fabricius and spleen [59].

Cichorium intybus

The effects of the ethanol extract of *Cichorium intybus* (CIEE) on the immunotoxicity of ethanol (EtOH) were investigated in mice. CIEE at dose of 300 mg/kg was orally administered to mice daily for 28 consecutive days. The combination of CIEE and EtOH showed significant increases in circulating leukocytes and the relative weights of liver, spleen and thymus, as compared with those in mice treated with EtOH alone. However, the body weight gain was not affected. Splenic plaque forming cells (PFC) and hemagglutination (HA) titers to sheep red blood cells (SRBC), and the secondary IgG antibody response to bovine serum albumin (BSA) were markedly enhanced by CIEE plus EtOH treatment as compared with EtOH alone. In mice receiving the combination of CIEE and EtOH when compared with EtOH alone-treated mice. There were also significant increases in delayed-type hypersensitivity (DTH) reaction, phagocytic activity, natural killer (NK) cell activity and cell proliferation as well as interferon (IFN-gamma) secretion. Interleukin-4 (IL-4) content showed insignificant induction by CIEE plus EtOH treatment. Accordingly, findings indicate that the immunotoxicity induced by EtOH is significantly restored or prevented by CIEE treatment [60-61].

The effect of an aqueous extract of *Cichorium intybus* (CIAE) on mast cell-mediated immediate type allergic reactions was studied. CIAE (0.1-1000 mg/kg) dose-dependently inhibited systemic anaphylactic reaction induced by compound 48/80 in mice. CIAE inhibited compound 48/80-induced anaphylactic reaction 100% with the dose of 1000 mg/kg. CIAE 1000 mg/kg, also significantly inhibited local anaphylactic reaction activated by anti-dinitrophenyl (DNP) IgE. When mice were pretreated with CIAE at a concentration ranging from 0.1 to 1000 mg/kg, the plasma histamine levels were reduced in a dose-dependent manner. CIAE (1-1000 microg/ml) dose-dependently inhibited histamine release from the rat peritoneal mast cells (RPMC) activated by compound 48/80 or anti-DNP IgE. When CIAE (1000 microg/ml) was added to RPMC, the level of cAMP in RPMC, increased significantly compared with that of control cells. The results indicate that CIAE inhibits mast cell-mediated immediate-type allergic reactions *in vivo* and *in vitro* [62].

Cistanche tubulosa

The effect of **Cistanche tubulosa** (Scheuk) Whight acteoside (CTWA) was studied on malondialdehyde (MDA) content, telomerase activity in heart, liver and brain tissues and immune function of experimentally aging model mice. Mice were given sc 10% **D**-galactose 10 ml/kg, once daily for 8 weeks to establish model of aging mice. CTWA 10, 20 and 40 m/kg were given ig, respectively, from the ninth week once daily for 2 weeks. In model untreated group, MDA content was significantly increased in heart, liver and brain, telomerase activity was significantly decreased in heart and liver, and lymphocyte proliferation, phagocytosis of peritoneal macrophages and blood IL-2 content were obviously decreased. After treatment with CTWA for 2 weeks, MDA content in heart, liver and brain was significantly decreased. In CTWA 40 mg/kg group telomerase activity in heart and brain was significantly increased, lymphocyte proliferation, phagocytosis of peritoneal macrophages and peripheral blood IL-2 content were enhanced. Accordingly, the authors concluded that CTWA may delay aging, which may be attributed to antagonizing free radical injury and enhancing immunity of aging mice [63].

Citrus species

Gencydo®, a combination of *Citrus limon* juice and aqueous quince (*Cydonia oblonga*) extract has been used traditionally in anthroposophical medicine for treating patients with allergic rhinitis or asthma. The anti-allergic effects of this preparation were investigated *in vitro* by using cell lines and primary cells in various biological and immunological endpoints. The release of soluble mediators from basophilic cells, mast cells and lung epithelial cells, which were essential for the initiation of early- and late-phase allergic reactions, was analyzed in relation to the synthetic anti-allergic drugs azelastine and dexamethasone. In addition, the impact of Gencydo® on the viability and activation of GM-CSF-activated eosinophil granulocytes was investigated. Gencydo® reduced the degranulation and histamine release of IgE-activated

basophilic cells and mast cells and inhibited the IgE- and PMA/A23187-induced increases in IL-8, TNF-α and GM-CSF production in mast cells. The effects were comparable to that of azelastine and dexamethasone. Furthermore, Gencydo® partially blocked eotaxin release from human bronchial epithelial cells, but has no impact on the viability and activation of GM-CSF-activated eosinophil granulocytes. The results gave a rational base for the topical use of Gencydo® in the treatment of allergic disorders through the down regulation of soluble mediators, which were essential for the initiation and maintenance of allergic reactions [64].

The effects of the combined *Citrus medica* ssp. *limonum /Cydonia oblonga* (0.01 g/ml of each one), separate products of *Citrus medica* ssp. *limonum* (0.01 g/ml) and *Cydonia oblonga* (0.01 g/ml) were investigated on the immunological pathways involved in seasonal allergic rhinitis (SAR). Peripheral blood mononuclear cells (PBMCs) from five healthy and five grass pollen allergic donors were isolated and analyzed *in vitro* after polyclonal and allergen-specific stimulation of T cells in the presence of the three extracts. The analyses demonstrated acceptable cell survival with no signs of toxicity. Citrus mainly had a selective effect on reducing allergen-specific chronic inflammatory (TNF-*α*; Citrus compared to Cydonia and Citrus/Cydonia: −87.4 ($P < 0.001$) and −68.0 ($P < 0.05$), resp.) and Th2 pathway activity (IL-5; Citrus compared to Cydonia: −217.8 ($P<0.01$); while, both Cydonia and Citrus/Cydonia mainly affected the induction of the allergen-specific Th1 pathway (IFN-*γ*; Cydonia and Citrus/Cydonia compared to Citrus: 3.8 ($P<0.01$) and 3.0 ($P<0.01$), respectively). Citrus and Cydonia demonstrated different working mechanisms in the treatment of SAR and the combination product did not demonstrate larger effects than the separate preparations [65].

The immunomodulatory and antiallergic properties of preparations from lemon, *Citrus medica* L. (citrus), and *Cydonia oblonga*, which were used in pharmaceutical products to treat patients suffering from allergic disorders, were investigated. Preparations were analyzed with respect to their impact on the degranulation capacity from basophilic cells as well as mediator release from activated human mast cells *in vitro*, including IL-8 and TNF- α secretion. The results showed that the degranulation of basophilic cells was diminished only in the presence of Citrus. Furthermore, Citrus and Cydonia both inhibited the production of IL-8 and TNF- α from human mast cells, and at low concentrations additive effects were observed [66].

To compare the efficacy and safety of two routes of administration (nasal spray versus subcutaneous injections) of Citrus/Cydonia in seasonal allergic rhinitis, a randomised, comparative clinical trial with two parallel groups was carried out. After a one- or two-week wash-out period, 23 patients were randomized, to a 6-week treatment period and the immunological and symptom severity changes and safety were evaluated. Both routes of administration were safe, they demonstrated therapeutic immunological and clinical effects [67].

Clerodendrum inerme

The G7, a Siddha medicine [herbal mixture (500mg capsule) contained 100 mg *Clerodendrum inerme*] moderated the release of histamine, IL1α and IL8 *in vitro* and therefore it is a promising alternative for the management of allergic disorders [68-69].

Clitoria ternatea

Ethanol extract of *Clitoria ternatea* root (ECTR) was evaluated for antiasthmatic activity using milk induced leucocytosis and eosinophilia in mice, egg albumin induced mast cell degranulations in rats and passive cutaneous anaphylaxis in rats at doses (100-150 mg/kg ip). The results showed that ECTR significantly decreases milk induced leucocytosis and eosinophilia, protected against egg albumin induced degranulations of mast cells in mice and inhibited area of blue dye leakage in passive cutaneous anaphylaxis in rats [70-71].

The antiasthmatic activity of ethanol extract of *Clitoria ternatea* roots was evaluated in histamine aerosol induced bronchospasm in Wister rats. The ethanolic extract of *Clitoria ternatea* (400 mg/kg, po) showed 47.45 % protection against histamine induced bronchoconstriction in rats. The results showed that aqueous extract of *C. tenatea* has not only bronchodilating activity but also decreases bronchial hyperreactivity by decreasing the infiltration of inflammatory cells in the airway and in-

hibition of release of histamine like mediators from the mast cell by stabilizing it [72].

The immunomodulatory activity of *Clitoria ternatea* seed and root extracts was investigated, the effects on humoral immune response were investigated in SRBCs-sensitized rats, while, the effects on cell medicated immunity were studied by measuring delayed type hypersensitivity (DTH) response in SRBC-sensitized rats. Neutrophil recruiting and phagocytosis were measured by studying neutrophil adhesion and carbon clearance method respectively. Furthermore the effects on hematological parameters were also studied. *Clitoria ternatea* seed and root extracts showed significant immunosupressive effects as evident from significant decrease in primary and secondary antibody titers in SRBCs-sensitized rats, paw thickness in DTH response, and neutrophil adhesion and *in vitro* phagocytosis. The immunomodulatory effects of *Clitoria ternatea* on humoral, cell mediated and non-specific immune response could be attributed to decreased immune cell sensitization, immune cell presentation and phagocytosis. The authors concluded that the anti-inflammatory and antioxidant properties of plant might be playing a major role in immunomodulatory activity [73].

Convolvulus arvensis

Intraperitoneal injection of 1/10 LD_{50} of aqueous extract of *Convolvulus arvensis* to rats significantly increased total leukocytes and percentage lymphocyte, enhanced the phagocytic function of reticular endothelial system and blocked immunosuppressive effect produced by dexamethasone. Furthermore, the aqueous extract significantly increased the concentration of some immunomodulators such as leptin, neopterin, immunoglobulins and lysosmal enzyme activity. These results showed that the *Convolvulus arvensis* leaves contain water soluble fraction that was immunostimulant [74-75].

Cordia myxa

The immune-modulatory activity of aqueous extract of *Cordia myxa* fruit was studied in mice immunized by hydatid cyst fluid antigen HCFAg. Delayed type hypersensitivity (DTH), Mitotic index (MI) and histopathological change in spleen were studied. A higher increase in thickness of the spleen was shown in immunized mice treated with aqueous extract of *Cordia myxa* fruit after 10 days of the treatment. The MI of bone marrow and spleen cells was significantly increased as a post immunized and treated mice in comparison with the other groups. Histopathological examination of spleen showed marked hyperplasia of lymphoid corpuscles and some times formed large follicle. Accordingly, aqueous extract was found to stimulate cell mediated and immune responses in mice [76-77].

The immune-modulating effect of ethanolic extract of *Cordia myxa* fruits was investigated by *in vitro* activated mouse (males type BALB/c) lymphoid & phagocyte, and tested by lymphoproliferation and reduction of NBT stain. The results indicated that concentration of (750, 1000) μg/ml inhibited the proliferation in comparison with negative and positive control. The results of NBT indicated the significant inhibition (without cytotoxicity) in the percentage of PMNLs forming Formazan granules in comparison with control. The percentage of cytotoxicity of the extract on lymphocytes and phagocytes was inhibited significantly ($P<0.05$) with increased concentration of extract [78].

The ethyl alcohol (70%) extracts of the fruits of *Cordia myxa* caused elevation in some of blood parameters particularly total count of leucocyte with insignificant elevation of lymphocyte [79].

Crocus sativus

The effects of three concentrations of macerated extract of *Crocus sativus*, dexamethasone, and saline were evaluated on cell viability and production of cytokines, including interleukin (IL)-4, IL-10, and interferon-γ (IFN-γ) were evaluated. In cells stimulated with phytohemagglutinin (PHA), different concentrations of the extract significantly inhibited cell viability of lymphocytes ($P<.001$ for all concentrations). High concentrations of the extract (500 μg/ml) also inhibited secretion of IFN-γ in stimulated cells and IL-10 secretion in both stimulated and nonstimulated cells ($p<0.05$ for all cases). The effects of high and low concentrations of the extract (500 and 50 μg/ml, respectively) on IL-4 secretion were lower than that of dexamethasone ($P<.05$ to $P<.001$). The extract showed a stimulatory effect on IFN-γ and IL-4 secretion in nonstimulated cells. The ratios of IFN-γ to IL-4 in the presence of

all concentrations of saffron on stimulated cells were significantly higher than for the control group (P<.05 to P<.01)[80-81].

The effect of the extract of *Crocus sativus* and one of its constituents (safranal) on the inflammatory changes was exaimined in sensitized guinea pig. Treatment of animals with dexamethasone, all concentrations of the extract and safranal significantly improved most types of WBCs but total WBC number was only decreased in treated groups with dexamethasone and high concentration of the extract compared to control group ($p<0.05$ to $p<0.001$). Safranal was more effective in the improvement of eosinophil and lymphocyte compared to the extracts ($P<0.001$ for both cases). However, the preventive effect of the extract of *Crocus sativus* on total WBC count was more prominent than that of the safranal ($P<0.01$) [82].

The effects of *Crocus sativus* extract on total and differential white blood cells (WBC) count in lung lavage fluid (LLF) were studied in ovalbumin-sensitized rats. Total WBC count, neutrophil, and eosinophil percentage in LLF were significantly increased in sensitized animals compared with the control group ($p<0.001$). Treatment of sensitized animals with all doses of the extract significantly reduced WBC number and the percentage of neutrophil and eosinophil compared with the sensitized animals ($p<0.01$-0.001) [83].

The immunomodulatory activity of *Crocus sativus* was studied on Th1 and Th2 limbs of the immune system. Oral administration of alcoholic extract of *Crocus sativus* (ACS) at graded dose levels (1.56-50 mg/kg, po), potentiated the Th2 response of humoral immunity, causing significant increases in agglutinating antibody titre in mice at a dose of 6.25 mg/kg and an elevation of CD19(+) B cells and IL-4 cytokine, a signature cytokine of Th2 pathway. Appreciable elevation in levels of IgG-1 and IgM antibodies of the primary and secondary immune response was also observed. However, ACS showed no appreciable expression of the Th1 cytokines IL-2 (growth factor for CD4(+) T cells) and IFN-γ (signature cytokine of Th1 response). A significant modulation of immune reactivity was observed in all the animal models [84].

Cuminum cyminum

The health modulating effects and immunomodulatory properties of *Cuminum cyminum* were evaluated using flowcytometry and ELISA in normal and immune-suppressed animals. *Cuminum cyminum* stimulated the T cells and Th1 cytokines expression in normal animals. Swiss albino mice subjected to Cyclosporine-A induced immune-suppression were dosed orally with *Cuminum cyminum* (25, 50, 100 and 200 mg/kg) on consecutive days. The results showed that administration significantly increased T cells (CD4 and CD8) count and Th1 predominant immune response in a dose dependent manner, suggesting immunomodulatory activity through modulation of T lymphocytes expression. In restraint stress induced immune-suppressed animals, *Cuminum cyminum* countered the depleted T lymphocytes, decreased the elevated corticosterone levels and size of adrenal glands and increased the weight of thymus and spleen [85-86].

Cydonia oblonga

The effects of the combined *Citrus medica* ssp. limonum *efructibus/ Cydonia oblonga efructibus* (*Citrus medica* ssp limonum and *Cydonia oblonga*: each 0.01 g/ml), and separate products of citrus (0.01 g/ml) and cydonia (0.01 g/ml) were investigated on the immunological pathways involved in seasonal allergic rhinitis (SAR). Peripheral blood mononuclear cells (PBMCs) from five healthy and five grass pollen allergic donors were isolated and analyzed *in vitro* after polyclonal and allergen-specific stimulation of T cells in the presence of the three extracts. The analyses demonstrated acceptable cell survival with no signs of toxicity. Citrus mainly had a selective effect on reducing allergen-specific chronic inflammatory (TNF-α; Citrus compared to Cydonia and Citrus/Cydonia: -87.4 ($p<0.001$) and -68.0 ($p<0.05$), respectively) and Th2 pathway activity (IL-5; Citrus compared to cydonia: -217.8 ($p<0.01$); while, both cydonia and citrus/cydonia mainly affected the induction of the allergen-specific Th1 pathway (IFN-γ; Cydonia and citrus/cydonia compared to citrus: 3.8 ($p< 0.01$) and 3.0 ($p<0.01$), respectively). Citrus and cydonia demonstrated different working mechanisms in the treatment of SAR and the combination product did not demonstrate

larger effects than the separate preparations [87-88].

The immunomodulatory and antiallergic properties of preparations from lemon, *Citrus medica*, and *Cydonia oblonga*, which were used in pharmaceutical products to treat patients suffering from allergic disorders, were investigated. Preparations were analyzed with respect to their impact on the degranulation capacity from basophilic cells as well as mediator release from activated human mast cells *in vitro*, including IL-8 and TNF- α secretion. The results showed that the degranulation of basophilic cells was diminished only in the presence of Citrus, and this effect was compared to the synthetic drug azelastine. Furthermore, Citrus and Cydonia both inhibited the production of IL-8 and TNF- α from human mast cells, and at low concentrations additive effects were observed [89].

The effect of a crude hot-water extract (HW) of *Cydonia oblonga* fruit was studied in type I allergy *in vivo* and *in vitro*. The oral administration of the quince HW-added diet to NC/Nga mice for 63 day showed a significant decrease in the development of atopic dermatitis-like skin lesions under conventional conditions. The concentration of IgE in the serum collected from mice fed with quince HW was also lowered in a dose-dependent manner. Moreover, quince HW inhibited the release of beta-hexosaminidase from rat basophilic leukemia cell line RBL-2H3 after a 24-hr treatment. The quince HW fraction of less than 3 kDa reduced the mRNA expression of the high-affinity IgE receptor (FcepsilonRI) gamma subunit [90].

To compare the efficacy and safety of two routes of administration (nasal spray versus subcutaneous injections) of Citrus/Cydonia in seasonal allergic rhinitis, a randomised, comparative clinical trial with two parallel groups was carried out. After a one- or two-week wash-out period, 23 patients were randomized, to a 6-week treatment period and the immunological and symptom severity changes and safety were evaluated. Both routes of administration were safe, they demonstrated immunological and clinical effects, with larger inflammatory and innate immunological effects of the nasal spray route and larger allergen-specific clinical effects of the subcutaneous route [91].

In a three-way-crossover study in 18 healthy male and female subjects aged from 20 to 49 years the influence of a 1% and 3% solution of a standardized composition of *Citrus limon*, succus, and extract from *Cydonia oblonga*, fructus (Gencydo) on the intranasal mucociliar clearance was investigated after multiple administration. Neither after intranasal administration of the 1% and 3% Citrus/Cydonia solution nor after placebo solution, a prolongation of the perception time was found. It could be concluded that there was no measurable influence of the test products on the intranasal ciliar function [92].

The effect of a crude hot-water extract (HW) of quince (*Cydonia oblonga* Miller) fruit on immunoglobulin E (IgE)-dependent late-phase immune reactions of mast cells was evaluated using *in vitro* system. Mast cell-like RBL-2H3 cells were treated with quince HW and late-phase reaction was then induced by stimulation with IgE + Antigen. Quince HW reduced the elevation of interleukin-13 and tumor necrosis factor-α expression level. Furthermore, quince HW suppressed these cytokine expressions of mouse bone marrow-derived mast cells (BMMCs). Leukotriene C_4 and prostaglandin D_2 production in BMMCs were also reduced by treating the cells with quince HW after 1 and 6 h of stimulation. The induction of intracellular cyclooxygenase (COX)-2 expression but not COX-1 expression in BMMCs was also reduced by quince HW [93].

Cynodon dactylon

The possible antianaphylactic and mast cell stabilization mechanism of *Cynodon dactylon* was evaluated by using compound 48/80 induced mast cell activation and level of nitric oxide in serum, rat peritoneal mast cells. The results showed that a *Cynodon dactylon* compound (CDC) isolated by bio-assay guided fractionation, produced significant ($p<0.01$) inhibitory effect on compound 48/80 induced anaphylactic reaction and ($p<0.001$) mast cell activation. This CDC also inhibited significantly, compound 48/80 induced increased level of nitric oxide in rat serum and rat peritoneal mast cells [94-95].

The immunomodulatory activity of *Cynodon dactylon* was carried out in mice using the humoral antibody response. Oral administration of the juice at 250 and 500 mg/kg in mice increased humoral antibody response upon antigen challenge as evidenced by a dose-dependent, significant in-

crease in antibody titre in the haemagglutination antibody assay and plaque forming cell assay [96].

Cyperus rotuntdus

The proliferation of lymphocytes in the absence and presence of mitogens was assessed at a concentration range 1-1000 μg/ml of *Cyperus rotundus* extract. The tested extracts significantly enhanced the lymphocyte proliferation at 1 mg/ml [97-98].

Eupatorium cannabinum

The polysaccharides isolated from the alkaline aqueous extract of *Eupatorium cannabinum* showed a phagocytosis enhancing effect as determined in three immunological test systems (carbon clearance, granulocyte- and chemiluminescence test) [99].

Polysaccharide fractions were isolated from the water or alcaline-water extracts of *Eupatorium cannabinum*. They showed significant immunostimulating activities according to the granulocytes- and carbon clearance tests [100].

Euphorbia hirta

The immunomodulatory activity of the ethanol extract of aerial parts of *Euphorbia hirta* was investigated using macrophage activity testing, carbon clearance test and mast cell de-granulation assay. The ethanol extract of *E. hirta* was found to be increasing the phagocytic index at a concentration of 80 mg/ml and 160 mg/ml. However, the ethanol extract of *Euphorbia hirta* was found to be cytotoxic at a concentration of 1000 μg/ ml. Maximum phagocytic activity was evident at 62.5 μg/ml [101].

The immunostimulatory effect of *Euphorbia hirta* was studied in *Cyprinus carpio*. The hematological, immunological and enzymatic studies were conducted on the *Euphorbia hirta* medicated fish infected with *Aeromonas hydrophila* pathogen. The results obtained from the hematological studies show that the RBC count, WBC count and hemoglobin content were increased in the infected fish at higher concentration of leaf extract. The feeds with leaf extract of *Euphorbia hirta* were able to stimulate the specific immune response by increasing the titer value of antibody. It was able to stimulate the antibody production only up to the 5^{th} day, when fed with higher concentrations of (25 g and 50 g) plant leaf extract. At higher concentration, the leaf extract of *Euphorbia hirta* significantly eliminated the pathogen in blood and kidney. It was observed that fish have survival percentage significantly at higher concentration of *Euphorbia hirta*, when compared with the control [102].

CONCLUSION

The immune system is one of most complex biological systems in the body. The human immune system has the essential function of protecting the body against the damaging effects of pathogenic microbial agents. Innate and adaptive immunity depends on the activity of white blood cells. Innate immunity largely depends upon granulocytes and macrophages, while adaptive immune response depends upon lymphocytes, which provide long term immunity. Modulation of the immune system denotes to any change in the immune response that can involve induction, expression, amplification or inhibition of any part or phase of the immune response, therefore, immune-modulator may be defined as a biological or synthetic substance, which can stimulate, suppress or modulate any of the components of the immune system including both innate and adaptive arms of the immune response. There are a number of plants that have been reported to have immune modulation activity. The current paper review the plants which have shown experimental and clinical immune modulatory activity.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

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