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Medicinal Plants as Immunosuppressive Agents in Traditional Iranian Medicine

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ABSTRACT

Immunomodulation using medicinal plants provides an alternative to conventional chemotherapy for several diseases, especially when suppression of inflammation is desired. The "Canon of Medicine", the epochal work of Avicenna, the great Persian scientist of the middle ages, provides comprehensive information about medicinal plants which used to cure inflammatory illnesses in traditional Iranian medicine. Taking into consideration that the mechanisms of damage in these illnesses are mediated by immune responses, it is reasonable to assume that the plants used for such diseases may suppress the immune responses and the resultant inflammation. In Iran, because of great diversity of climate and geographical conditions, numerous varieties of plants grow and at least 1000 species are recorded as medicinal plants. Many of these plants such as *Punica granatum*, *Glycyrrhiza glabra*, *Foeniculum vulgare* and *Polygonum species* prescribed by ancient Iranian physicians have been shown to possess anti-inflammatory and immunomodulatory effects. In recent literature, different species of native medicinal plants such as *Stachys obtusirena*, *Salvia mirzayanii*, *Echium amoenum*, *Dracocephalum kotschy* and *Linum persicum* have been shown to have appreciable anti-inflammatory and immunomodulatory effects including inhibitory effects on lymphocyte activation, suppression of cellular and humoral immunity and induction of apoptosis. This review focuses on plants that are used in Iranian traditional medicine and have been reported to act as immunoinhibitory agents.

Keywords: Immunomodulation, Iran, Traditional Medicine

INTRODUCTION

In recent years, the use of medicinal plants as an alternative to conventional medicine for treatment of various diseases has increased. This is mainly due to their safety and lower side effects, and in some cases, their more effectiveness. A number of medicinal plants have shown inhibitory potentials in immune responses and some of them have been used traditionally to treat inflammatory diseases. This review describes plants that have immunosuppressive effects and are used in Iranian traditional medicine.

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This information was obtained upon searching the Canon of Medicine and the recent literature.

THE HISTORY OF TRADITIONAL MEDICINE IN IRAN

Traditional medicine is deeply rooted in the history and culture of Iran. The origin of traditional medicine in Iran dates back to 9150 years ago when the Maad dynasty began to compile knowledge on medicinal herbal plants. In the fourth century AD, a great center of medical learning was founded at Gondi Shapur University, and the hospital that was built was active for many years. After the emergence of Islam, a brilliant age of creativity in the field of medicine and pharmacy appeared from 900-1100 AD. In this period, Iranian scientists, like Razes, Avicenna, Birouni and Jorjani, made great advances in the treatment of various diseases. These well-known physicians and philosophers left invaluable legacy of textbooks on traditional medicines titled Al-Havi, Canon of Medicine, Al-Sydney and Zakhireh, respectively. The Canon of Medicine by the great medieval physician and philosopher Avicenna (980–1037) and the Al-Havi of Razes (864-930) were among the central texts in Western medical education from the thirteenth to the eighteenth centuries (1-4)

IMMUNOMODULATORY PLANTS IN IRANIAN TRADITIONAL MEDICINE

Medicinal plants have been widely used to prevent and treat illnesses in the traditional medicine. The great scientists Avicenna and Razes developed many pharmaceutical preparations and dosages based on medicinal plants. These physicians used herbal medicine to treat many conditions including cancer, infections and inflammatory diseases. Avicenna developed a number of plant preparations to treat arthritis, inflammation and fever, and used *Polygonum* species (Polygonaceae), *Punica granatum* (Punicaceae), *Satureja hortensis* (Lamiaceae), *Euphorbia* species (Euphorbiaceae), *Trigonella foenum graecum* (Fabaceae), *Aristolochia bottae* (Aristolochiaceae), *Foeniculum vulgare* (Apiaceae), *Glycyrrhiza glabra* (Leguminosae), *Mentha longifolia* (Labiatae), *Lawsonia inermis* (Lythraceae), *Quercus* species (Fagaceae) and *Robina pseudocacia* (Fabaceae) and many other species. These plants were mainly used separately or in combination with others in preparations for topical use. Interestingly, the anti-inflammatory and immunomodulatory effects of some of these medicinal plants have been documented in recent studies (Table1) strengthening the rationale for their use by Avicenna.

Several studies, for example, have reported the immunomodulatory activity of *Polygonum* species. Tryptanthrin, a biologically active compound found in the medicinal plant *Polygonum tinctorium*, has shown a dose-dependent inhibitory effect on the production of IFN- γ and IL-2 cytokines by mouse spleen cells and Peyer's patch lymphocytes in vitro, indicating that this compound may be effective in the treatment of disorders that are associated with activated lymphocytes (5). Other researchers have documented the ability of emodin from *Polygonum hypoleucum* Ohwi to regulate cell proliferation, inflammatory cytokine production and calcium mobilization in primary human T lymphocytes (6). The aqueous extract of *Trigonella foenum graecum* L, a widely-used medicinal and dietary herb, led to a significant increase in relative organ weight of the

thymus in mice (7). Protodioscin purified from this plant displayed a strong inhibitory effect on HL-60 myeloid cells. (8). A compound known as punicalagin isolated from the fruit of *Punica granatum* has shown potent immunosuppressant effects. This compound induced a marked decrease in IL-2 production from CD4⁺ T cells and significantly suppressed the mixed leukocyte reaction in allogenic cells, and also inhibited phorbol myristate acetate-induced chronic ear edema in mice in vivo (9).

Table 1. Anti-inflammatory and immunosuppressive effects of the extracts or compounds isolated from some medicinal plants used in Iranian traditional medicine.

Plants	Common name/ Persian name	Use in folk medicine	Compound/s or extract	Immunosuppressive effects	Ref.
<i>Polygonum species</i>					5, 6
<i>P. tinctorium</i>	Knotweed / Alaf Haft band	Asthma, cold, eczema, intestinal edema, blisters, burns	Tryptanthrin	- Inhibits interferon-gamma and interleukin-2 (IL-2) production	
<i>P. hypoleucum</i>			Emodin	- Suppresses IL-2 production, and Ca mobilization in T cells.	
<i>Trigonella foenum graecum</i>	Fenugreek / Shanbelileh	Cough, arthritis, inflammation,	Protodioscin	- Inhibits growth of HL-60 myeloid cells	8
<i>Punica granatum</i>	Pomogranate / Anar	Sore throat, burns, inflammation, pain	Punicalagin	- Inhibits activation of the nuclear factor of activated T cells (NFAT). - Suppresses chronic ear edema in mice - Decreases CD3 ⁺ T cell infiltration of the inflamed tissue.	9
<i>Foeniculum vulgare</i>	Sweet fennel/ Razianeh	Asthma, cough, bronchitis, joint pain, arthritis	Methanolic extract	-Inhibits acute and sub acute inflammations - Suppresses type IV allergic reactions	10
<i>Glycyrrhiza glabra</i>	Licorice / Shirin byan	Wound and ulcers, oral inflammation, rheumatitis, cough, stomach edema,	Glycyrrhizin Liquiritigenin beta-Glycyrrhetic acid	- Suppresses allergic reaction - Down-regulates IgE production - Inhibits the classical pathway of complement system	13-15
<i>Lawsonia inermis L.</i>	Henna / Hana	Oral ulcers, burns, edema, healing wounds	Various compounds, e.g. lawsone, apigenin, luteolin, cosmo.	- Inhibits the release of histamine - Inhibits the release of leukotrienes	16
<i>Euphorbia species</i>					17
<i>E. royleana</i>	Churee / Farfiun	allergy, blisters,	Ethyl acetate extract	- Inhibits delayed-type hypersensitivity reaction - Inhibits antibody synthesis - Reduces CD4 ⁺ expression on T cells - Inhibits the process of phagocytosis - Suppresses ear edema in the mouse model	
<i>E. lactea</i>			Tirucallol	- Suppresses the influx of neutrophils - Inhibits nitric oxide production - Inhibits inducible nitric oxide synthase expression - Inhibits prostaglandin E(2) generation	20, 21

The methanolic extract of *Foeniculum vulgare* has been effective in relieving inflammation (10). The immunomodulatory effects of members of the genus *Glycyrrhiza* have been reported in several studies. This medicinal plant has shown proven effects on the T cell activation, CD69 expression on T cells, and phagocytosis (11-12). Medicarpin derived from *Glycyrrhiza glabra*, inhibited lymphocyte blastogenesis in a dose-dependent fashion, with IC₅₀ values 20 to 100 times lower than the IC₅₀ of prednisolone (13). Anti-allergic effects and inhibition of human complements have been reported for various compounds isolated from this plant (14-15). A variety of compounds with immunomodulatory and antioxidant activities have been isolated from henna (*Lawsonia inermis L.*) leaves (16). A variety of components including jatrophone, ingenol, and myrsinane diterpenoids with PGE₂-inhibitory and immunosuppressive activity have also recently been isolated from different *Euphorbia* species (17-20). Anti-inflammatory effect of tirucallol, a triterpene isolated from *Euphorbia lactea* latex and the aqueous extract of *Euphorbia hirta* on the ear edema in the mouse model and on early and late phase allergic reactions have been shown (21-22). Tirucallol affects the influx of polymorphonuclear cells and reduces NO production and PGE₂ generation (21).

IMMUNOMODULATORY PLANTS RECENTLY REPORTED FROM IRAN

Iran is one of the most geographically diverse countries in the world. This diversity in climate and ecological conditions offers great potentials for growing numerous varieties of flora in different regions. More than 7,000 species of plants grow in the Iranian plateau, out of which 1,000 have medicinal effects. Indeed, with the large number of botanical species present, identification of those valued for their immunomodulatory effects is very difficult. As a result of an extensive literature search, we identified several species of medicinal plants with immunomodulatory effects grown in Iran. A summary of these plants is presented in Table 2. The following is a comprehensive report on individual species:

Table 2. Recent experimental data on immunomodulatory plants reported from Iran.

Medicinal Plants (Ref)	Immunoinhibitory effects	
	<i>In vivo</i>	<i>In vitro</i>
<i>Stachys obtusirena</i> (42)	- Inhibits delayed-type hypersensitivity reaction	- Inhibits proliferation of human lymphocytes
<i>Salvia mirzayanii</i> (39-41)	- Suppresses antibody synthesis	- Inhibits IL-2 production
	- Inhibits both primary and secondary antibody synthesis at low concentrations.	- Induces apoptosis in activated lymphocytes
<i>Salvia macrosiphon</i> (24)		- Inhibits proliferation of human lymphocytes
<i>Haussknechtia elymatica</i> (34)	- Inhibits delayed-type hypersensitivity reaction	- Inhibits IL-2 production
	- Suppresses antibody synthesis	- Inhibits proliferation of human lymphocytes
<i>Dracocephalum kotschy</i> (27- 28)		- Inhibits IL-2 production
<i>Dionysia termeana</i>		- Inhibits both allogenic and mitogenic lymphocyte proliferation
<i>Linum persicum</i> (24)		- Induces apoptosis in activated lymphocytes
<i>Echinophora cinerea</i>		- Inhibits mitogenic lymphocyte proliferation
<i>Cirsium bracteosum</i>		- Induces apoptosis in activated lymphocytes
<i>Ferulago angulata</i> (24)		- Inhibits mitogenic lymphocyte proliferation
<i>Echium amoenum</i> (30)	- Suppresses antibody synthesis	
<i>Achillea talagonica</i> (47)		
<i>Artemisia annua</i> (48)	- Suppresses delayed type hypersensitivity reaction	- inhibitory effect on calmodulin
<i>Sambucus ebulus</i> (49)	- Anti-inflammatory effect on rats (carrageenan induced edema or paw inflammation models)	
<i>Biebersteinia multifida</i> (50)		
<i>Elaeagnus angustifolia</i> (51)		

***Dionysia termeana* (Primulaceae family).** *D. termeana* is an endemic species that grows in different parts of Iran and has been used against ulcers, insect bites, as well as diarrhea in folk medicine (23). This plant has caused a dose related inhibitory effect on human lymphocyte activation. It has been reported that the inhibitory activity observed for this extract on the lymphocytes might have been due to its apoptosis inducing properties (24).

***Dracocephalum kotschy* Boiss (Labiateae family).** This plant known as "badaranjboye" in Persian is indigenous to Iran and grows wild in Isfahan and in some parts of northern Iran (25). The aerial parts of *D. kotschy* are traditionally used to treat rheumatoid arthritis. Several compounds isolated from this plant include monoterpene glycosides and trypanocidal terpenoids (26). Various concentrations of the methanolic extract of this herb have shown inhibitory effects on both allogenic and mitogenic lymphocyte proliferation (27-28). This inhibitory effect was possibly due to its apoptosis inducing properties (28). Investigation on the active components of *D. kotschy* resulted in the isolation of a compound known as calycopterin. This compound was responsible for the inhibitory effect of the plant observed on stimulated lymphocytes (28).

***Echium amoenum* (Boraginaceae family).** *E. amoenum* known as "Gol-e-gavzaban" in Persian is a plant that has not been reported to grow in Europe or other parts of the world and is found exclusively in Iran (29). It is for centuries that the flower heads of this herb is traditionally used as an important tonic and tranquilizer in Iran. Avicenna in his invaluable work "Cannon of Medicine" has elaborated on the use of the ash as well as other preparations of the plant for treatment of mouth ulcer and oral inflammations. *E. amoenum* has been described as a remedy for cough, sore throat, grippe, pneumonia and dyspnea in Makhzan-al-Adviya written by Khorasani, an ancient Iranian physician. Results of the study on the immunomodulatory effects of this herb have shown that the anti-inflammatory and anti-infectious properties of *E. amoenum* are associated with stimulation of cellular immune response and suppression of humoral antibody synthesis (30). Its stimulatory effect could demonstrate its therapeutic potential for the treatment of infections and the inhibitory action could partly be considered for its anti-inflammatory effect.

***Ferulago angulata* (Apiaceae family).** *F. angulata* is a perennial, herbaceous plant that grows in different areas of Iran including the southern parts and is used as a traditional medicine for the treatment of infectious diseases (31). Previous phytochemical studies on *Ferulago* species have revealed the presence of coumarins as the most frequent metabolites (32). In a study performed on the immunomodulatory effects of *F. angulata*, an inhibitory effect was demonstrated (24).

***Hausknechtia elymatica* (Apiaceae family).** This plant is represented by one species in the flora of Iran growing in Zagros Mountains in the southwest of Iran (33). A recent study showed that *H. elymatica* methanolic extract reduces the immune reaction to sheep red blood cell (SRBC) as a T cell dependent antigen. The extract had the capacity to inhibit both delayed hypersensitivity and antibody production in both primary and secondary immune responses in mice (34). The inhibition of humoral response to SRBC could be due to the suppression of antigen processing and presentation

or might have been influenced by the relative amounts of different cytokines produced at the site of T and B cell stimulation (34).

***Linum persicum* (Linaceae family).** *L. persicum* is an endemic plant, growing wild in Dena Mountain, and is used in folk medicine for its antimicrobial and anti-inflammatory effects. *L. persicum* appeared to have the inhibitory effects on the activation of lymphocytes. This inhibitory activity on lymphocytes might be partly due to apoptosis inducing properties (24). Previous reports regarding the health benefits associated with the consumption of another species of *Linum* genera, *L. usitatissimum* commonly known as flaxseed have shown its anticancer, antiviral, antibacterial and anti-inflammatory effects (35). Cytotoxic activity and induction of apoptosis in tumor cell lines and isolation of three podophyllotoxin-related lignans from *L. persicum* have been reported recently (36).

***Salvia macrosiphon* (Lamiaceae family).** The plant *S. macrosiphon* is used in folk medicine as an antiseptic, an anti-inflammatory and a spasmolytic herb (37). Methanolic extract of the aerial parts of this plant has shown significant inhibitory effects on the proliferation of mitogen-treated lymphocytes (24).

***Salvia mirzayanii* (Labiatae family).** The genus *Salvia* (Labiatae) includes a large number of plants growing in temperate and subtropical regions throughout the world (38). *S. mirzayanii* known as "maryam goli" in Persian is a native plant that is widely distributed in Iran. This plant is used for the treatment of inflammatory diseases and also as a tonic in folk medicine. *S. mirzayanii* has shown inhibitory effects on both lymphocyte proliferation and the release of IL-2 in mitogen-treated cell cultures (39). Improvement of both primary and secondary humoral immune responses in mice after exposure to antigen using a low concentration of the extract, and a dose-related decrease in the effect at higher concentrations have also been demonstrated (40). *S. mirzayanii* has been shown to induce apoptosis in lymphocytes (41). This event could result in a decrease in cell proliferation and therefore cause an inhibition of immune responses.

***Stachys obtusirena* (Lamiaceae family).** *S. obtusirena* is one of the endemic species which grows in the western and southern parts of Iran (42). The methanolic extract of *S. obtusirena* has been shown to inhibit proliferation of human lymphocytes and reduce the secretion of IL-2: demonstrating the inhibitory action of this plant on both lymphocyte activation and cytokine production (42). The extract has also reduced the cellular reaction to SRBC in mice and has diminished the humoral immune response to this antigen. Increase in the sub-G1 accumulation of lymphocytes in flow cytometric analysis has indicated its capacity to induce apoptosis in activated lymphocytes. Induction of apoptosis in activated T cells might be due to two important mechanisms of extrinsic and mitochondrial pathways in which modulation of CD95 expression and caspases activation could result in a decrease of cell proliferation after antigen priming and therefore inhibit immune responses (43-44). Induction of apoptosis could diminish the number of alloreactive T cells after organ transplantation or eliminate autoreactive T cells in the treatment of autoimmune diseases (45). Components having this capacity may be useful for clinical design of immunosuppressive regimens. Anti-inflammatory

activity of hydroalcoholic extract from aerial parts of another species of *Stachys*, *S. inflata* in rats has also been reported (46).

The immunoinhibitory effects of several other plants have also been reported in various studies. *Echinophora cinerea* (Umbelliferae family) and *Cirsium bracteosum* (Compositae family) that are among endemic species and are found in some central and western provinces of Iran have demonstrated strong inhibitory effects on activated lymphocytes (24). *Achillea talagonica* Boiss (Asteraceae), which has long been used in traditional medicine for treatment of fever, asthma, bronchitis, cough, skin inflammation, jaundice, and other liver ailments have inhibitory effects on humoral antibody synthesis in immunized mice (47). Immunosuppressive effects of artemisinin, a compound purified from *Artemisia annua* (Compositae family), on the delayed type hypersensitivity against sheep blood capsule in Balb/c mice has been demonstrated (48). *Sambucus ebulus* rhizome (49), *Biebersteinia multifida* root extract (50) and *Elaeagnus angustifolia* fruit extract (51) have revealed anti-inflammatory effects in rats. Benefits of *Zataria multiflora* Boiss in an experimental model of mouse inflammatory bowel disease (52) and the suppression of nitric oxide production in activated murine peritoneal macrophages in vitro and ex vivo by *Scrophularia striata* ethanolic extract have also been reported (53).

In conclusion, the great diversity in medicinal plants growing in Iran on one hand, and the invaluable contributions of famous scientists involved in this field, have remarkably increased the application of traditional medicine in Iran. Various medicinal plants have been used for centuries in the treatment of different diseases including those related to the immune system. Some of these plants have been used by Iranian pioneers in folk medicine, and in recent years their immunomodulatory activities have been documented. Recent studies on the immunoinhibitory effects of various medicinal plants indicate the existence of a tremendous potential for future studies in identifying effective plants and studying their mechanisms of action. Identification and study of these plants not only will show the potential use of traditional medicine but will also lead to the improvement and discovery of new immunomodulatory drugs.

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