

REVIEW ARTICLE

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Herbal Medicines for Immunosuppression

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ABSTRACT

Herbal medicines have been used for centuries to treat different illnesses. Among more than 20,000 herbal medicines available for humans, a limited number have sufficiently been studied and numerous remained to be investigated for their efficacy in treating human diseases.

A number of herbal products are in use for their immunosuppressive effects. This capacity of herbs may have useful applications in immune-mediated disorders including autoimmune diseases and organ transplant rejection. Plants such as *Salvia miltiorrhiza* and *Tripterygium wilfordii* has been shown to reduce inflammatory cytokines and mediators, indicating their value in the treatment of acute graft rejections and autoimmunity. *Tanacetum parthenium* inhibits the release of pro-inflammatory mediators from macrophages and lymphocytes and *Curcuma longa* down regulates the expression of cytokines and chemokines as well as the transcription factor NF-kappaB. There has been growing interest to investigate novel anti-inflammatory or immunosuppressive activities from various sources particularly herbal medicines.

This review focuses on the plants that have recently received more attention regarding their influence on the immune system, being reported as immunosuppressive and anti-inflammatory agents and promising protective effects for immune-mediated diseases.

Keywords: Herbal medicines; Immunosuppression

INTRODUCTION

A number of herbal medicines have shown useful biological and pharmacological activity, including immunosuppressive effects. Immunosuppression using herbal products can provide an alternative to conventional chemotherapy, particularly since some chemical immunosuppressive drugs have shown various adverse

effects, and there is an increasing need to find new drugs with fewer side effects.

In reviewing the recent literature, this article discusses the immunosuppressive potentials of several plants. Before our discussion of the herbal medicines, we provide a brief review of the immune system and current synthetic immunosuppressive drugs.

The Immune System

The human immune system has a fundamental role in protecting the body against the pathogenic microbial agents. This system is mediated by leukocytes that derive from precursors in the bone marrow and develop

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under the influence of cytokines and growth factors. The immune-committed cells recognize antigens trapped in the peripheral lymphoid tissues and are then activated. B cells produce antibodies that serve as receptors for antigens and can bind to pathogens to prevent or neutralize infection. T cells recognize antigen on the surface of antigen-presenting cells (APCs) e.g., dendritic cells (DCs) and secrete cytokines which determine the differentiation of T helper (TH) and B lymphocytes.¹ The TH response involves the activation of macrophages and cell-mediated immunity and also affects immunoglobulin differentiation and antibody secretion and therefore humoral immunity.² TH cells after recognizing the antigen proliferate and differentiate to specific lineages according to the local cytokine environment, either TH1 or TH2 cells, each of which secretes certain cytokines. TH1 cells secrete cytokines interleukin (IL)-2, interferon (IFN)- γ and tumor necrosis factor (TNF)- α , whereas TH2 lymphocytes secrete IL-4, IL-5 and IL-10. Recently two novel subsets of CD4+ T cells including TH17 and regulatory T cell (Treg) were also identified. "Each phenotype of T cells is characterized by unique signaling pathways and expression of specific transcription factors, notably T-bet for TH1, GATA-3 for TH2, forkhead box P3 (FoxP3) for Tregs and receptor-related orphan receptor (ROR) α and ROR γ for TH17 cells".³ Altered T cell responses and impaired regulatory function of the immune system play a major role in development of inflammatory and autoimmune diseases, such as multiple sclerosis and rheumatoid arthritis.⁴ A number of anti-inflammatory drugs including various traditional medicines and natural products are being under study for the treatment of various disorders. The effects of drugs on the immune system can be assessed by in vitro testing T cell-mediated immunity in the presence of an antigen or mitogen. T cell stimulation by these molecules initiates a cascade of events and gene expression, which induce the resting T cells to enter the cell cycle, then proliferate and differentiate.⁵ This process trigger proliferation signals which in turn lead to the activation of certain transcription factors, synthesis of proteins and secretion of cytokines. General functioning of the T cells in various inflammatory diseases can be examined in different animal models, e.g. experimental autoimmune encephalomyelitis (EAE) as a model of multiple sclerosis and collagen-induced arthritis as a model of rheumatoid arthritis.⁶

Synthetic Immunosuppressive Drugs

Immunosuppressive drugs comprise a large number of drugs that by different mechanisms of action can modulate the immune system. Glucocorticoids are the most common of these drugs, and are widely used for the management of inflammatory diseases. These drugs inhibit various immune functions by affecting gene transcription events.^{7,8} They mediate their actions by binding to intracellular receptors, resulting in altered protein-protein interactions and consequently regulation of gene expression.⁹ Cyclophosphamide is another immunosuppressive drug, which affects mainly B cells. This alkylating agent is currently used to treat diseases in which autoantibodies play a pathogenic role, such as rheumatoid diseases.¹⁰ Depending on the dosage and timing of administration, cyclophosphamide can also affect T cells.¹¹ Cyclosporin A and FK-506 belong to the group of kinase and phosphatase inhibitors. These drugs, after binding to a specific immunophilin inhibit calcineurine which play a key role in the transcription of cytokines (particularly IL-2) and T cell activation.¹² They also inhibit the JNK and p38 cascades linked to the T cell receptor.¹³ Various other immunosuppressive drugs have been developed with inhibitory effects on de novo purine synthesis, including 6-mercaptopurine, azathioprine, mizoribine and mycophenolate mofetil (MMF). Azathioprine acts on the S-phase of the cellular cycle and MMF acts specifically on inosine monophosphate dehydrogenase.¹⁴ Leflunomide is an example of drugs with inhibitory effects on pyrimidine nucleotide synthesis. The main mechanism of action of these drugs is inhibition of dihydroorotate dehydrogenase and subsequent suppression of lymphocyte proliferation. These synthetic drugs can be distinguished from the large number of reagents (including monoclonal antibodies) that have been produced for immunosuppressive applications.¹⁵ Despite the effectiveness of these various immunomodulating drugs in reducing immune function, a major concern in recommending these drugs for therapeutic purposes is their side effects.¹⁶⁻¹⁸ Glucocorticoids have various side effects, particularly when used at high doses for prolong periods.¹⁹ Metabolic, gastrointestinal, cutaneous, neurological, musculoskeletal and ophthalmologic adverse effects have been associated with long-term glucocorticosteroid therapy.¹⁹ Among the side effects of cyclophosphamides are gonadal toxicity, leukopenia

as well as mutagenicity and increased risk of developing cancer.¹⁹ Due to these effects, the discovery and recognition of safer new drugs without severe adverse effects has become a major goal for experimental medicine.

Immunosuppressive Effects of Herbal Medicines

The capacity of herbal medicines to inhibit cellular and humoral immune responses can have useful applications in some immune-mediated disorders including autoimmune diseases.²⁰ Both activation of T and B lymphocytes and macrophages and defective apoptosis of immune effector cells play critical roles in the pathogenesis of these disorders.^{21,22} There is an ever-increasing interest in research on different plant species to document their therapeutic applications. Various studies have investigated the immunosuppressive effects of herbal medicines growing in different parts of the world. We review some of the herbs that have recently received more attention regarding their inhibitory influence on the immune system below.

Curcuma Longa

Curcuma longa (Zingiberace), a perennial plant native to tropical South Asia, has been extensively utilized in folk medicine for treatment of infections and inflammatory diseases. Turmeric, the bright yellow pigment extracted from the tuberous rhizome of this plant has been shown to inhibit the activation of human DCs in response to inflammatory cytokines. Treatment of DCs with turmeric also inhibited the ability of DCs to stimulate the mixed lymphocyte reaction (MLR).²³ The main biological effects of turmeric have been attributed to curcumin, a major curcumanoid found in turmeric. This naturally occurring polyphenolic phytochemical is a strong anti-inflammatory and antioxidant agent which can change the expression of various transcription factors, cell cycle proteins, and signal transducing kinases. Curcumin has been shown to be active on lymphocytes and affect on a series of immunological functions including antigen presentation, humoral and cell-mediated immunity, and cytokine production.²⁴ This compound can inactivate the transcription factor NF-kappaB and by this function down regulates the secretion of a variety of proinflammatory cytokines and chemokines.²⁵ Considering the strong anti-inflammatory effect of curcumin, its efficacy and mechanism of action against

EAE has been recently investigated. The treatment of Lewis rats with curcumin significantly reduced both the clinical severity of EAE, and leukocyte infiltration in the spinal cord. A decrease in the IL-17, TGF- β , IL-6, and IL-21 mRNA expression as well as STAT3 and ROR γ expression in curcumin-treated rats indicated that the usefulness of curcumin in EAE treatment was mainly due to inhibition of TH17 cells differentiation.²⁴ Several clinical trials indicate curcumin may have potential as a therapeutic agent in diseases such as inflammatory bowel disease, pancreatitis, arthritis, and chronic anterior uveitis.²⁵

The effect of this compound on B cell activation has also been studied. Curcumin at high doses reduced the proliferation of B cells stimulated with the Toll-like receptor (TLR) ligands LPS and CpG oligodeoxynucleotides²⁶ and at low doses enhanced antibody responses indicating that curcumin could be a strong modulator of B cell activation.²⁶

Tripterygium Wilfordii Hook F

The "thunder god" vine, *Tripterygium wilfordii* Hook F (TWHf) growing in southern China, has been extensively used to treat autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis. TWHf (Celastraceae) not only inhibits mitogen-stimulated lymphoproliferation, but its active derivatives have also been shown to inhibit production of proinflammatory cytokines by monocytes and lymphocytes, as well as PGE2 production via the cyclooxygenase pathway.²⁷ In a recent clinical trial, the clinical efficacy of this plant versus sulfasalazine for the treatment of patients with symptomatic rheumatoid arthritis was demonstrated.²⁸ There are both laboratory and clinical data showing significant beneficial immunosuppressive effects of the derivatives of this herb.²⁷ Triptolide, a diterpenoid component isolated from TWHf has been shown anti-inflammatory and immunosuppressive activities by its inhibitory effect on T-cells. The effect of triptolide on induction of oral tolerance in the Peyer's patch as important site of mucosal immune responses has also been studied. This compound by lowering CD4⁺ and CD8⁺ cells in the Peyer's patch and the CD4⁺ cells in periphery reduced arthritis severity in a model of experimental inflammatory polyarthritis.²⁹

The effect of triptolide on the TH17 cells that are involved in the immunopathogenesis of various autoimmune diseases has been investigated. This

compound significantly inhibited the generation of TH17 cells from murine splenocytes and purified CD4⁺ T cells in a dose-dependent manner and suppressed collagen-induced arthritis. The transcription of IL-17 mRNA and IL-6-induced phosphorylation of STAT3 signaling molecule was inhibited by triptolide.³⁰ Triptolide treatment in EAE caused a significant inhibition of the mRNA expression of both TH1/TH17 and TH2 cytokines in mononuclear cells as well as in spinal cord tissues, indicating the protective effect of triptolide in this model.³¹

The immunosuppressive activity of TWHf has also been shown in organ transplantation. In an *in vivo* rat kidney transplant model, demethylzeylasteral (T-96), isolated from this plant in combination with prednisone significantly prolonged the survival of kidney-transplanted rats,³² indicating the potential usefulness of TWHf bioactive compounds in the treatment of acute graft rejections and autoimmunity.

Glycyrrhiza Species

Glycyrrhiza (liquorice) belonging to Fabaceae family, has been grown for centuries in China, Africa, Europe, India and the Middle East. This plant is used for its antimicrobial, hepatoprotective, cardioprotective and immunomodulatory properties in folk medicine.³³ The inhibitory effect of flavonoids extracted from licorice on LPS-induced acute pulmonary inflammation in mice has been shown.³⁴ Liquorices (*Radix glycyrrhizae*) have been used for treatment of hepatitis. In this regard a component known as diammonium glycyrrhizinate (DG) was purified from liquorices that could prevent murine T-cell-mediated fulminant hepatitis.³⁵ DG inhibited the recruitment of lymphocytes into the liver and protected hepatocytes from apoptosis through an IL-6-dependent way.³⁵ In a pilot randomized open-label study, the effect of a new emollient cream containing milk proteins and *Glycyrrhiza glabra* extracts in patients with psoriasis was demonstrated.³⁶

Liquorice root contains glycyrrhizin and the major metabolite of glycyrrhizin is Glycyhrritinic acid,³⁷ which has shown antiinflammatory effects in different animal models.³⁸ The inhibition of calcineurin activity and T cell proliferation by glycyrol from *Glycyrrhiza uralensis* has also been reported.³⁹

Salvia Miltiorrhiza

Salvia miltiorrhiza (Labiateae) is a popular medicinal plant growing abundantly in China (locally called

Danshen), widely used to treat hepatitis, heart and brain diseases.^{40,41} This plant has been shown to inhibit IL-12 production in activated macrophages and IFN- γ production in lymph node cells.⁴² IFN- γ production may be a key therapeutic strategy for modulating immunological diseases dominated by TH1-derived cytokine responses. These results may explain some known biological activities of this plant including its anti-inflammatory effect, and suggest its possible use in the treatment of immunological diseases dominated by TH1-derived cytokine responses.⁴² In a clinical trial the usefulness of *S. miltiorrhiza* extract in treatment of patients with severe acute pancreatitis by reducing the proinflammatory cytokines has been shown.⁴³

The major active component of *Salvia miltiorrhiza* is Tanshione IIA (TSN). TSN have been shown to reduce inflammatory cytokines including IL-2, IL-4, IFN- γ and TNF- α , whereas increasing anti-inflammatory cytokine, IL-10. Considering the effect of this component on reducing plasma alanin aminotransferase and aspartate amino transferase levels observed in mice with concanavalin A-induced immune-mediated liver injury, TSN has been suggested to be useful for liver injury therapeutics.⁴⁴

Camellia Sinensis

Green tea, a product of the dried leaves of *Camellia sinensis* (Theaceae), growing throughout Asia, Middle East and Africa, is a commonly consumed beverage in the world. This products is used for many purposes in folk medicine including as analgesic, cardi tonic, carminative, CNS-stimulant, digestive and diuretic. The polyphenolic compounds from green tea possess antiinflammatory properties, in various experiments using animal models its immunosuppressive effect have been shown. Green tea reduced autoimmune symptoms in the rat adjuvant arthritis, a model of human rheumatoid arthritis⁴⁵ and in a murine model for human Sjogren's syndrome.⁴⁶

In recent years, the attentions have been made on epigallocatechin-3-gallate (EGCG), a component of green tea with anti-inflammatory and immunomodulatory activities.⁴⁷ This compound has shown inhibitory effects on human monocyte-derived DCs and, consequently, on the T-cell-mediated immune responses.⁴⁷ EGCG has considerably suppressed brain inflammation and neuronal damage in EAE induced by a proteolipid protein.⁴⁸

Tanacetum Parthenium

Tanacetum parthenium (Asteraceae) originally is native to Europe's Balkan mountains, and now grows in different parts of the world. This plant, known under the common name of feverfew, has been used as a folk remedy for rheumatoid arthritis and fever.⁴⁹ The crude feverfew extract and its purified parthenolide can modulate adhesion molecule expression in human synovial fibroblasts.⁵⁰ This species has shown the capacity to inhibit several pro-inflammatory enzymes including 5-lipoxygenase, phosphodiesterase-3 and phosphodiesterase-4. It also inhibits the release of pro-inflammatory mediators nitric oxide, prostaglandin (PG) E2 and TNF- α from macrophages and IFN- γ and IL-4 from human peripheral blood mononuclear cells.⁵⁰ The bioactive compounds of this plant have been suggested to safely support the immunotherapy of colon cancer.⁵¹

Berberis Species

Berberis species (Berberidaceae) are the plants with long history of application in traditional medicine. These

plants grow in subtropical regions of Europe, Asia, Africa and America. Iran is the largest producer of this plant in the world. Berbamine is a purified compound from *Berberis vulgaris* and other *Berberis* species with strong anti-inflammatory properties in EAE model. In early studies, the inhibitory effects of berbamine on the delayed type hypersensitivity reaction (DTH) and MLR was shown.⁵² This compound also prolonged allograft survival in skin-transplanted mice. Recently, study on the production of cytokines from CD4⁺ T cells treated with berbamine has shown the selective inhibitory effect of this compound on STAT4 expression and production of IFN- γ in the cells, indicating the immunosuppressive effects of this compound.⁵³

Other plants

In various other studies, the capacity of herbal medicines to suppress the immune response has been studied,⁵⁴⁻⁶³ e.g. garlic has shown to reduce the proinflammatory cytokines IL-1, TNF- α , and IL-8, and

Table 1. Various other medicinal plants with immunosuppressive effects

Plants	Family	Immunosuppressive effects	Ref.
<i>Campylotropis hirtella</i>	Leguminosa	-Inhibits mitogen-induced splenocyte proliferation	64
<i>Andrographis paniculata</i>	Acanthaceae	-Relief of rheumatoid arthritis symptoms -Inhibitory effects on NF- κ B trans-activation activity	65-67
<i>Bupleurum falcatum</i>	Umbelliferae	-Inhibits nitric oxide and prostaglandin E2 -Inhibits the proliferation and activation of T cells through cell cycle arrest and induction of apoptosis -Inhibits T cell activation through the modulation of NF-kappaB transcription factor	68-69
<i>Clerodendron trichotomum</i>	Verbenaceae	-Inhibits arachidonic acid release and prostaglandin E2 production -Inhibits NF- κ B dependent pathway in macrophages	70-71
<i>Periploca sepium</i>	Asclepiadaceae	-Suppresses IL-17 production and inhibits differentiation of Th17 cells -Inhibits NKT-derived inflammatory cytokine productions	72-73
<i>Artemisia vestita</i>	Compositae	-Inhibits IFN- γ signaling -Down-regulates the activation, adhesion and metalloproteinase production of T lymphocytes	74-75
<i>Salvia mirzayanii</i>	Labiatae	-Inhibits lymphocyte proliferation -Induce apoptosis in activated lymphocytes, -Inhibits humoral and DTH response to SRBC in mice, -Inhibits IL-2 production	76-77
<i>Dracocephalum kotschy</i>	Labiatae	-Inhibits lymphocyte proliferation -Induce apoptosis in lymphocytes	78-80
<i>Argyrolobium roseum</i>	Papilionaceae	- Down regulates Th1/Th2 cytokines release - Decreased T cells and B cells numbers	81

Other plants

In various other studies, the capacity of herbal medicines to suppress the immune response has been studied,⁵⁴⁻⁶³ e.g. garlic has shown to reduce the proinflammatory cytokines IL-1, TNF- α , and IL-8, and stimulate IL-10 secretion. IL-10 is an antagonist of proinflammatory cytokines, and therefore this effect may be a potential mechanism justifying the garlic's use in inflammatory diseases.⁵⁴ *Astragalus membranaceus*, a plant used as tonic in Chinese folk medicine, has shown to lower the secretion of IL-6 that is a cytokine involved in the inflammatory disorders.⁵⁵ Decrease in the secretion of different cytokines has also been reported for various other plants including *Zizyphus lotus* (IL-2), *Polygala tenuifolia* (IFN- γ), *Stachys obtusirena* (IL-2) and *Haussknechtia elymatica* (IL-2).⁵⁶⁻⁵⁹ Several other plants that have recently been studied for their immunosuppressive effects are presented in Table 1.⁶⁴⁻⁸¹

CONCLUSION

Various herbal medicines have been used for centuries in treatment of different diseases including those related to immune system. There are many evidences that a variety of substances derived from these plants could act as immunosuppressive agents. A number of studies have been conducted to confirm the pharmacological effectiveness of these agents. Plants such as *Salvia miltiorrhiza*, *Curcuma longa*, TWHF, green tea and garlic have been extensively studied for their active constituents and their mechanism of action, however there are many plants that their active ingredients have not yet been identified or studied. In this regard, future investigations both *in vivo* and *in vitro* are required.

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