Review

The Immunopharmaceutical Effects and Mechanisms of Herb Medicine

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In recent years, studies on evaluation of the therapeutic and toxic activity of herbal medicinal products became available and popular. The advances in modern biotechnology have led to discovery of many new active constituents. However, it is a constant challenge to establish the pharmacological basis for efficacy and safety of herbal medicinal products. A better understanding of the effects and bioavailability of phytopharmaceuticals can help in discovering suitable and rational therapies. In this review, we present the bioavailability studies in immune system that has been conducted for some of the more important or widely used phytopharmaceuticals. Furthermore, various new drug targets worthy of using for drug development in immunomodulating herbal medicine area and their regulatory mechanisms are also discussed. Adverse effects, drug interactions, and contraindications are also discussed which show that caution should be exercised when combining phytopharmaceuticals with chemically derived pharmaceutical components. *Cellular & Molecular Immunology*. 2008;5(1):23-31.

Key Words: phytomedicine, herbal medicine, alternative medicine, T-lymphocyte, autoimmune disease

Introduction

Herbs have been used not only for food but also for medicinal purposes for centuries. Research interest has been focused on various herbs that possess immunomodulating properties that may be useful in reducing the risk of various diseases and cancers. Although the working mechanisms of some of the herbs are unclear and remain to be elucidated, they are worth further studying as newly potential therapy agents for immunomodulation. Herein, the bioavailability and mechanism studies of the immunopharmaceuticals were summarized below and their interactions were schematic presented in Figure 1.

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Effects on T cells

Along the way of investigating the pathogenesis of immune diseases, the activated immune effector cells such as T cells, B cells, monocytes/macrophages, and dendritic cells have been consistently found in the peripheral blood and the involved organs. Among these immune effector cells, T cells have been considered to be the most important because the regulation of T cell activation requires antigen specificity and a great amount of cytokines released in immune responses are from T cells (1). It is clear that full activation of T cells requires the integration of two signals: one is from a T cell receptor signal and the other is from a co-stimulatory signal (2). T cells play an important role in the regulation of immune response and it is important to modulate the activation and inhibition of T cells in immune-related diseases.

Among the molecules possessing co-stimulatory activities on T cells, CD28 could in combination with the activation of T cell receptor induce detectable levels of interleukin (IL)-2 and prevent anergy, a status of unresponsiveness (3, 4). Moreover, the investigation of herbs-regulated T cell receptor downstream signaling pathways has clearly shown that tetrandrine, a purified traditional Chinese medicinal herb that acts as an immunosuppressant, inhibited T cell proliferation, IL-2 secretion and the expression of the T cell activation antigen,

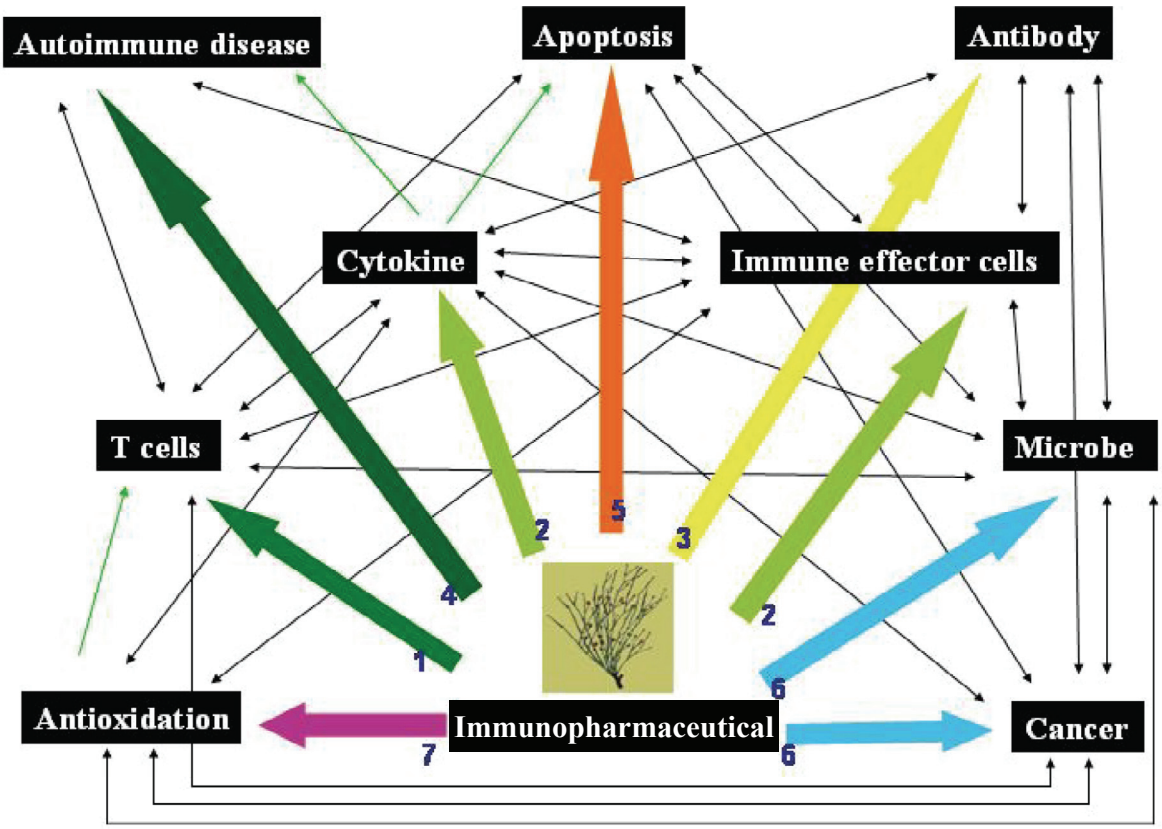

Figure 1. The effects on the mechanisms of immunopharmaceuticals interact with each other, directly or/and indirectly. The seven principal effects (1-7) discussed in the text were shown in different colors. (1) Effects on T cells; (2) Effects on cytokine production and other immune effector cells; (3) Effects on antibody production; (4) Herbs used in autoimmune disease; (5) Effects on programmed cell death (apoptosis); (6) Anti-microbe and anti-cancer effects; (7) Anti-oxidative effects. The arrow head symbol means the way of effects, either positive or negative.

CD71 (5). Dang-Gui-Bu-Xai-Tang (DGBXT), which includes Radix Angelicae Sinensis and Radix Astragali Membranaceus, is a traditional Chinese medicine used to modulate the lymphocyte activity of cancer patients after chemotherapy and radiotherapy (6). It has also been demonstrated that T cells activated by plant mitogens showed non-specific cytotoxicity providing phytohemagglutinin was present during the killing reaction (7).

Effects on cytokine production and other immune effector cells

A network of cytokines regulates the growth and function of the cells of the immune system. T cells possess a dominant role in this network since they are the main source of many cytokines. The production of different cytokines is specifically regulated by means of cell interactions and cytokine concentration and is dependent largely on the state of differentiation of the T cells. Two different types of differentiated T cells can be characterized according to the pattern of cytokine production of T cells: IL-2 and IFN-γ are typically produced by T helper 1 (Th1) cells, whereas predominantly T helper 2 (Th2) cells produce IL-4, IL-5 and IL-10. Th1 and Th2 cytokines exert a mutual cross-regulation on the precursors of Th1- or Th2-type effector cells which are important mediators in directing the immune system towards the appropriate response. The selective activation of either Th1 or Th2 type cells depends on the antigen and is influenced by cytokines produced partly by antigen-presenting cells and partly by T helper cells (8). Both Th1 and Th2 cytokines are possibly susceptible to the herb activation or suppression (9). Recently, it was suggested that NF-κB may be one of multiple factors in the immuno-suppressive effects mediated by tea pigments (10). In our lab, we demonstrated that increased secretion for both Th1- (IL-2 and IFN-γ) and Th2-pattern (IL-4 and IL-10) cytokines in mouse serum can be achieved with a diet of *Canavalia ensiformis* (L.) seeds (11, 12) and the effect on Th1- and Th2-pattern cytokine modulation *in vivo* is related to its dosage and the process of heat treatment (12).

Both fangchinoline and isotetrandrine, two tetrandrine analogues, active extract of radix Stephaniae tetrandrae used in rheumatoid arthritis, also inhibit IL-1 and TNF-α production from Cowan 1-stimulated human peripheral blood mononuclear cells (13, 14). Such an effect is suggested to

mediate through transcriptional regulation of mRNA expression of these cytokine genes (15). Some herbs, such as radix Stephaniae tetrandrae and Fissistigma oldhamii may directly block cytokine-mediated signaling pathways to function their immunomodulatory effects. Research reviews (16, 17) postulate that extracts of Panax ginseng affect the hypothalamus-pituitary-adrenal axis and the immune system, which could account for many of the documented effects. Animal models and *in vitro* studies indicate that Panax ginseng enhances phagocytosis, natural killer cell activity, and the production of interferon and may explain the treatment for weakness and fatigue. Licorice contains triterpenoids, such as glycyrrhizin and its aglycone glycyrrhizic acid, various polyphenols, and polysaccharides. It is known or suspected that licorice has a number of pharmaceutical effects, e.g., anti-inflammatory, anti-viral, anti-ulcer, and anti-carcinogenesis. Radix paeoniae alba is the root of a traditional Chinese herb named Paeonia lactiflora pallas. Earlier studies have indicated that Radix paeoniae has anti-cancer growth activity (18). Epicatechin derivatives, which are commonly called 'polyphenols' are the active ingredients in green tea and possess anti-oxidant, anti-inflammatory and anti-carcinogenic properties. Green tea polyphenol has potent anti-oxidative activity and anti-inflammatory effects by decreasing cytokine IL-2 production (19). Craig (20) found that natural anti-oxidants or phenolic compounds rich in plant foods such as fruits and herbs, and terpenoids would provide a milieu of phytochemicals, non-nutritive substances in plants that possess health-protective benefits. Pharmacological experiments have preliminarily demonstrated that the compound prescription is better than its individual components in the range and potency of pharmacological activities (21).

The immunomodulating effects of herbs could also be demonstrated in other immune effector cells, including macrophages, monocytes, B cells, neutrophils, and mast cells. Tetrandrine, a plant alkaloid, was reported to inhibit the production of TNF-α by monocytes (22). Previous studies demonstrated that Ginseng radix and Radix paeoniae alba in a phytopharmaceuticals that augmented monocyte and leucocyte counts in the peripheral blood (23). Moreover, Yi-fey Ruenn-hou (YR) Tea, as a pharmaceutical composition constituted by licorice root, American ginseng, Radix paeoniae alba and green tea, its effect on Th cytokine modulation *in vivo* has been investigated in our lab by analyzing the effect of combined herbs on the T-cell immune response by analysis of Th1-pattern cytokines, IL-2 and IFN-γ, and Th2-pattern cytokines, IL-4 and IL-10, concentrations in serum (24). We found that feeding with YR tea can elevate levels of both Th1- (IL-2 or IFN-γ) and Th2-(IL-4 or IL-10) pattern cytokines in mouse serum, and Th2-pattern cytokines respond earlier and higher than the Th1-pattern cytokines. Furthermore, the cytokine modulation effect is dependent on herb dosage. In addition, it was reported that Tanshinlactone A from Salvia miltiorrhiza Bunge (Tanshen) significantly decreased the IL-2 and IFN-γ gene expression in phytohemagglutinin-activated peripheral blood mononuclear cells (25). Gamcho-Sasim-Tang, a traditional Chinese medication which constituted by Glycyrrhiza uralensis radix, Scutellaria baikalensis radix, Zingiber officinale rhizoma, Pinellia ternata tuber, Panax giseng radix, Coptis japonica rhizoma, has been used to treat inflammatory diseases including Adamantiades-Behçet's disease and its action may be due to the inhibitory effects on proinflammatory cytokine production including TNF-α, IL-1β, and IFN-γ (26).

Effects on antibody production

Antibodies are used by the immune system to identify and neutralize foreign objects, such as bacteria and viruses. However, when a person has an autoimmune disease, the body's antibodies are attacking healthy and normal cells. Therefore, not only searching for herb preparations showing stimulating effects on antibody production is needed, but also is necessary for herb preparations showing inhibitory effects. For example, crude preparations of Fun-boi (Stephania tetrandra), a traditional anti-rheumatic herb, have been reported to have immunomodulatory effects on both cell-mediated and humoral immunities *in vitro*. Especially, Fun-boi therapy markedly reduced the severity of arthritis and tended to reduce the serum anti-type II collagen antibody level (27). Formosanin-C, a diosgenin saponin, was isolated from a perennial herb, Paris formosana Hayata (Liliaceae) which has been used as a folk remedy for snake bite and as an anti-inflammatory or anti-neoplastic agent. It was reported that this agent significantly inhibited the antibody production of S-antigen induced experimental autoimmune uveitis in guinea pigs (28). Aqueous extract of *Trigonella foenum graecum* (L.), a widely used medicinal and dietary herb, shows a significantly stimulatory humoral immune response in mice (29). The polysaccharide extracts from 2 mushrooms, *Lentinus edodes* and *Tremella fuciformis*, and an herb, Astragalus membranaceus, on cellular and humoral immune responses also show significantly higher production of specific IgA, IgM, and IgG in chickens (30). Pectic polysaccharide fraction (BR-2) containing pharmacologically active pectic polysaccharide, bupleuran 2IIc, which is prepared from a medicinal herb, the roots of *Bupleurum falcatum* (L.), is suggested to stimulate lymphocytes, deplete adherent cells and increase subpopulation of $CD25^+$ and surface IgM-positive lymphocytes (31). Artemisinin (Qinghaosu) is a potent antimalarial sesquiterpene lactone isolated from the Chinese herb Artemisia annua. Arteether, a potent semi-synthetic analogue of dihydroartemisinin is being developed by the World Health Organization as the artemisinin derivative of choice for the treatment of malaria. It is also found to exhibit marked suppression of humoral responses (32). Moreover, the chloroform extract of *Tripterygium wilfordii* Hook f., a traditional immunosuppressive Chinese herb, shows inhibition on cellular immune responses and antibody production on type II collagen-induced arthritis (33). It was also reported recently that an aqueous-ethanolic extract of the mixed herbal drugs Thujae summitates, Baptisiae tinctoriae radix, Echinaceae purpureae radix and

Echinaceae pallidae radix caused a significant enhancement of the antibody response against sheep red blood cells but there was no enhancement of the tested cytokine, i.e., IL-2, IFN-γ and GM-CSF, titers in the serum (21).

Herbs used in autoimmune disease

The immune system is a well-organized and well-regulated system and its dysregulation may lead to the development of immune deficiency, hypersensitivity, or autoimmune diseases. One prototype of autoimmune diseases is rheumatoid arthritis, a disease with progressive and massive destruction of joints accompanied with or without other organ involvement. Although many contributing factors were considered to play roles in causing rheumatoid arthritis, the etiology remains unclear. While no single agent was proven to be enough to control disease progression, current acceptable therapy for rheumatoid arthritis is aimed to attenuate disease activity with a combination of disease-modifying anti-rheumatic drugs such as methotrexate, sulfasalazine, leflunomide, hydroxychloroquine, cyclosporin, azathioprine, etc. (34-36). The purpose of a combination therapy is to obtain synergistically therapeutic effects of drugs with different immunomodulatory mechanisms and, in the meantime, to reduce side effects from each drug by decreasing their dosages. Periplocoside E (PSE), a pregnane glycoside with potent immunosuppressive activity used for treating rheumatoid arthritis, had been identified from a traditional Chinese herb medicine, Periploca sepium Bge. It has been shown that PSE in a dose-dependent manner significantly inhibited the proliferation of splenocytes induced by concanavalin A, and mixed lymphocyte culture reaction at no cytotoxic concentrations (37). Administration of PSE suppressed a delayed type hypersensitivity reaction, and ovalbumin induced antigen-specific immune responses in mice. *In vivo* treatment with PSE dose-dependently suppressed ovalbumin-induced proliferation and Th1 cytokine (IL-2 and IFN-γ) production from splenocytes *in vitro*. In the study of Zhu et al. (37), PSE was shown to dose-dependently inhibit anti-CD3 induced primary T cell proliferation, activation for IL-2R (CD25) expression, and IFN-γ and IL-2 production at the transcriptional level. PSE was highly specific, significantly inhibited the activation of ERK and JNK. These results demonstrated that Periploca sepium Bge can be used for treatment of T cell-mediated disorders, such as autoimmune diseases (37).

Radix Stephaniae tetrandrae (Han-Fang-Chi), the dried tuberous root of the creeper Stephania tetrandra S. Moore (Menispermaceae), has been demonstrated to have anti-allergic, anti-inflammatory and hypertensive effects in experimental animals (38). It has been used in China for several decades to treat patients with silicosis and autoimmune diseases that are associated with the activation and infiltration of immune effector cells at lesion sites. However, it was noted that such a therapeutic strategy caused limited side effects including abdominal distension, diarrhea, dry eye, itching, hyperpigmentation and mildly elevated liver enzymes (39).

Effects on programmed cell death (apoptosis)

Aside from the activation of immune effector cells, the defective apoptotic mechanism also plays a crucial role in disease progression (40). Apoptosis is a natural protective mechanism for embryogenesis, for thymic organ to eliminate inappropriate T cells and for immune privilege sites to protect from inflammatory cell invasion. Different from the necrotic process, the apoptotic process does not induce any inflammatory response because dead cells or their degraded products are rapidly phagocytosed before any leakage of cellular contents (41). Since the etiology of autoimmune diseases is largely unknown, the immune reaction towards the apoptotic bodies released or apoptotic antigens expressed from dead cells has been implied as one of the mechanisms leading to autoimmune diseases (42-44). After development of autoimmune diseases, the failure to execute the appropriate apoptotic program may result in sustention of inflammatory process (45-47).

In light of the significance of apoptotic process, the apoptosis-based therapy has been suggested as one of the approaches to control the progression of immune diseases (48). Altogether, both the inappropriate activation of immune effector cells and the ineffective deletion (through apoptosis) of these cells may lead to the development and progression of immune disorders. The therapeutic approaches for immune diseases may rely on both the inhibition of cell activation and the maintenance or enhancement of the apoptotic program of immune effector cells. For example, Shen-Mai, a Chinese medical herb, was reported that could protect the apoptosis of peritoneal macrophage induced by lipopolysaccharide in mice (49). However, it is noteworthy that curcumin, the major component of the spice turmeric, may inhibit chemotherapy-induced apoptosis in models of human breast cancer (50). The exposure to curcumin-containing foods for breast cancer patients should be limited.

Since the apoptotic process is defective in autoimmune diseases (45-47), any drug that could potentially induce the apoptosis of activated immune effector cells may have its additional advantage to control the inappropriate expansion of immune responses. Several western anti-rheumatic drugs such as corticosteroid, nonsteroidal anti-inflammatory drugs-dhydroxychloroquine, and a Chinese anti-rheumatic herb, *Tripterygium wilfordii* Hook f, have been shown to preserve the capacity of inducing cellular apoptosis by a class of compounds related to TNF (51). Furthermore, it was shown that plant alkaloid tetrandrine and its analogues within therapeutic concentrations could induce cellular apoptosis, which is defective in autoimmune diseases (5).

Anti-microbe and anti-cancer effects

The main pharmacological constituents of Chinese traditional medicine herb Cnidium monnieri are coumarin compounds and volatile oil. In addition, it contains monoterpene polyols, glucides, as well as recently discovered sesquiterpene components. In recent years, rather active investigations of

its anti-tumor actvity were performed and this effect was from the improving immune functions (52). More recently, Ching-Wei-San and its individual herbal components, Coptidis rhizoma, Angelicae sinensis radix, Rehmanniae radixet rhizom, Moutan radicis cortex, and Cimicifuga foetida, were tested in our lab for *in vitro* inhibitory effects on three well-known plaque-causing bacteria, *Porphyromonas gingivialis*, *Streptococcus sanguis*, and *Streptococcus mutans*, and two common pathogens, *Staphylococcus aureus* and *Escherichia coli* (53). The cytokine modulating effects were also evaluated in BALB/c mice. Our results suggested that Ching-Wei-San is comparable to tetracycline, and had similar inhibitory effects on the tested bacteria. Coptidis rhizoma was the only individual herbal component to show 100% inhibitory effects on the bacteria. Moreover, the results showed that Ching-Wei-San modulated the immunity of mice, up-regulated IL-2, IL-4 and TNF-α, but down-regulated IFN-γ. With anti-microbial activity it appears that Coptidis Rhizoma is the most potent. However, when cytokine modulating effects were taken into consideration, none of the individual herbal components alone could substitute for the cumulative (anti-microbial and cytokine modulating) effects of Ching-Wei-San. Based on these results, we suggested that none of the individual herbal components alone can substitute for the cumulative effects of Ching-Wei-San.

Caffeic acid phenethyl ester (CAPE) is an anti-oxidant component of the propolis and known to have anti-mitogenic, anticarcinogenic, anti-inflammatory and immunomodulatory properties (54-56). Moreover, CAPE can selectively inhibit virus-transformed and oncogene-transformed rodent cells and human tumour cells, including colon adenocarcinoma (HT-29 and HCT116), glioblastoma multiforme (GBM-18), melanoma (HU-1, SK-MEL-28 and SK-MEL-MO) (57), and human oral cancer cells (GNM and TSCCa) (58). The activation of NF-κB by TNF can be dose- and time-dependently blocked by CAPE (59). CAPE can also be used as a lipoxygenase inhibitor, performing anti-oxidation (60, 61) and anti-inflammatory activity (62). Recently, we have shown that CAPE-like compounds exhibited different effects on anti-HIV replication and cytokine modulation (63). It is therefore suggested that these compounds affect virologic and immunologic response *via* different mechanisms. Furthermore, we recently showed that daily dietary administration of Echinacea purpurea root extract to normal mice for as little as 1 week resulted in significant elevations of natural-killer cells which are immune cells that cytolytic to virus-containing cells and many tumor cells (unpublished data). Recently, Centaurea hubermorathii was shown to display prominent anti-bacterial activity against *Citrobacter freundii*, *Enterococcus faecalis* and *Salmonella goldcoast* (64). Such results suggested a prophylactic or remedial role for herbs in animals with microbial infections and cancers.

Anti-oxidative effects

One of the important effects of immune-related herbs that may explain many of its biological activities is the anti-oxidative property. In measuring both hypoxanthine/xanthine oxidase and erythrocytes auto-oxidation systems, Radix of Stephaniae tetrandrae S. Moore effectively scavenges the generated superoxide anions (65). Other evidence also shows that Radix inhibits freshly fractured quartz-induced lipid peroxidation (66). In addition, Radix inhibits hexose-monophosphate shunt activity and hydrogen peroxide production in neutrophils (67). Part of the effects is mediated through G protein modulation (13). It is suggested that significantly inhibiting the production of nitric oxide, a critical mediator of inflammation in lipopolysaccharide-stimulated macrophages may also explain the effects of these drugs on autoimmune diseases (68). Ginsenoside, the main constituent of American Ginseng, was shown to combat stress, enhance both the central nervous and immune systems and contribute toward maintaining optimal oxidative status against certain chronic disease states and aging (69). The hepatoprotective effect of licorice root has recently been explained as the inhibitory effects on immune-mediated cytotoxicity against hepatocytes and on NF-κB, which activates genes encoding inflammatory cytokines in the liver (70). Singh et al. (71) reported that epigallocatechin-3-gallate, a green tea polyphenol might be of potential benefit in inhibiting IL-1β-induced catabolic effects in osteoarthritis chondrocytes that are dependent on JNK activity. As licorice root and green tea, many herbs were found to contain potent anti-oxidant compounds that provide significant protection against chronic diseases or have anti-viral or anti-tumor activity (20). Kroes et al. (72) found that β-glycyrrhetinic acid is a potent inhibitor of the classical complement pathway, whereas no inhibitory activity was observed against the alternative pathway and β-glycyrrhetinic acid acts at the level of complement component C2. Tomada et al. (73) demonstrated that an acidic polysaccharide, which was isolated from the root of Paeonia lactiflora pallas exhibited reticuloendothelial system-potentiating activity in a carbon clearance test and anti-complementary activity. As nitric oxide plays an important role in immune function, Friedl et al. (74) revealed that Panax ginseng treatment could modulate several aspects of host immune defense mechanisms due to stimulation of inducible nitric oxide synthase.

Emerging new drug targets for immune-related herbal drug development

In recent years, there are many new drug targets discovered in the immune area and they exhibit strong potential in the development of herbal immunopharmaceuticals. The migration of lymphocytes into distinct microenvironments in secondary lymphoid tissues and maintenance of cells in these micro-domains are strictly structured and likely support the proper regulation of immune responses to both foreign and self-antigens. Chemokine and other chemoattactant signals serve as signposts to direct cell migration. They signal cells through heptahelical receptors, which couple to hetero-trimeric G proteins (G protein-coupled receptors, GPCRs) (75). The regulation of the signals transduced through these receptors ultimately determines the positioning of cells in

lymphoid tissues. A variety of mechanisms regulate GPCR signaling including a family of approximately 25 proteins termed regulators of G protein signaling (RGS). These proteins act as GTPase activating proteins for Gα subunits and can also function as effector antagonists of specific Gα subunits, thereby attenuating signaling through GPCRs such as chemokine receptors. In addition, physiologic modulators of G protein signaling, such as RGS and G protein receptor kinases (75, 76), represent potential new therapeutic targets in the treatment of atopy and other inflammatory conditions. Thus, the particular spectrum of GPCR proteins and their expression levels within a cell will determine the duration and magnitude of G protein signaling initiated by chemokines for immunomodulating drug targets.

Moreover, some other types of cellular receptors also possess the immune modulating effects. For example, genistein, the estrogen receptor agonist, induces thymic atrophy in mice, and decreases both humoral and cell-mediated immunity (77). The vitamin D receptor (VDR) agonists are expressed in many different target tissues including bone, blood, breast, activated B- and T-lymphocytes, monocytes and keratinocytes (78). Most dividing of these cell types, normal and malignant, can express VDR, respond to 1, 25(OH)2D3, and be regulated, including the cells in immune system. Another case is the chemokine receptor CCR4. CCR4 is broadly expressed on cells of the immune system and plays a central role in T cell migration to several sites of inflammation and T cell maturation. It is best known as a drug target for airway inflammation and atopic dermatitis, but cells expressing CCR4 are found in many inflammatory diseases (79).

Further, the toll-like receptors play an essential role in antigen presentation and latter development of immune response into pro-allergic (Th2), cellular (Th1) or regulatory (Tr1) responses. Since toll-like receptors govern decisive points in immune regulation, an extensive research focuses on agents interfering with their immunomodulatory activities (80). Other case is the histamine receptor. Histamine can selectively recruit the major effector cells into tissue sites and affect their maturation, activation, polarization, and other functions leading to chronic inflammation. Histamine also regulates dendritic cells, T cells and B cells, as well as related antibody isotype responses. Differences in affinities of these receptors for histamine are highly decisive for the biological effects of histamine and drugs that target histamine receptors. Recent findings in histamine immunobiology imply their relevance in allergic inflammation and application (81).

Finally, a large body of recent researches suggests that inhibition of NF-κB blocks inflammation, cancer development and progression, diabetes, and other diseases. The enormous potential for the treatment of disease by inhibiting NF-κB leads to the development of inhibitory drugs that specifically target this pathway in immune area (82).

Adverse effects, drug interactions, and contraindications

Interpretation of documented adverse effects and drug interactions can be difficult because of the variety of available herb formulations, and because the exact amount of herb in these products may not be identified. Generally, herbs are well tolerated, and their adverse effects are mild and reversible (83). However, some herbs may interact with some drugs used at present and have drug interactions with some unpredicted results. Associated adverse effects include nausea, diarrhea, euphoria, insomnia, headaches, hypertension, hypotension, mastalgia, and vaginal bleeding (83, 84). For example, Panax ginseng may interact with caffeine to cause hypertension, and it may lower blood alcohol concentrations (85). It may also decrease the effectiveness of warfarin (Coumadin) (86). Concomitant use of Panax ginseng and the monoamine oxidase inhibitor phenelzine (Nardil) may result in manic-like symptoms (87, 88).

Contraindications to the use of herbs appear to occur primarily with high dosages or prolonged use rather than the immune response induced by herbs themselves (89, 90). Herbs may also causes hypoglycemic activity, and caution should be exercised in using ginseng products in patients with diabetes because of possible interactions with oral hypoglycemic agents and insulin. Cautious use of herb products in children and in women who are pregnant or lactating is needed until more rigorous studies prove safety in these groups (89, 91).

Structural modification and compound prescription

A great potential for identifying the active ingredients is the advantage that there are several structurally similar analogues of the active ingredients. Importantly, the subtle structural difference among the active ingredient analogues appears to have great impact on their differential immunostimulating and immunosuppressive activities. Based upon their structural similarity and the difference in biological activity, structural modification of some groups of the active ingredients can lead to the discovery or development of more potent yet less toxic immunostimulating and immunosuppressive drugs (90, 92).

Conclusion

Nowadays the extensive use of herbal remedies in large doses has reached an all time high in the general public. Several herbs are reported and advertised as immune stimulants and may interfere with patients suffering from immune modification, autoimmune diseases, or transplant recipients. Drug interactions probably can occur in patients using dietary supplements in conjunction with traditional immunopharmaceuticals for healthy conditions. It is thus very important for patients with a new symptom if they are using herbs, or dietary supplements. On the other side, it is the responsibility for the manufacturers to ensure that herbs contain pure ingredients and list all the side effects and drug interactions. The results of well-designed studies on the molecular target(s) of herbs will be helpful to physicians and

patients for the treatments of immune diseases.

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