

Immune Stimulants and Antiviral Botanicals: Echinacea and Ginseng

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Preparations of echinacea and ginseng likely comprise the most popular and commercially successful combination of medicinal plant products in North America. Interestingly, the development of *Echinacea* species for medicinal purposes stems from use by indigenous American people, but research has been conducted predominantly in Germany (Bauer and Wagner 1991). On the other hand, the reputation of ginseng is firmly planted in China and has spread west in modern times, research in China, Japan, and Korea, being bolstered by European investigations of mainly extracts of the Asian species, *Panax ginseng*. Following its discovery outside present-day Montreal, Quebec, in 1716 (Foster 1992), the trade in North American ginseng, *Panax quinquefolius*, grew steadily and now constitutes a considerable market in the Orient, where roughly 90% of Canada- and US-grown root is sold. Only one of the additionally recognized *Panax* species, namely *Panax notoginseng* (Sanchi or Tienchi ginseng), is of commercial significance, primarily in Asia, where it finds application as a hemostatic, cardiogenic, and anti-infective agent (Gao et al. 1996).

The traditional use of echinacea by native Americans as a topical anti-infective and snake-bite remedy, and to assuage coughs associated with colds, was presumably the impetus for investigation of its anti-microbial potential. Anti-bacterial, anti-fungal and anti-viral activities were subsequently assessed for a variety of preparations, the identity of the particular *Echinacea* species being still somewhat equivocal (Bauer and Wagner 1991). Latterly, attention has concentrated on the plant's application to the treatment of symptoms of cold and other influenza-like infections, the basis for its economic success; any effectiveness in such conditions is widely attributed to effect on the immune system—potentiation or “stimulation” being generally regarded more particularly as “immunomodulation” (Bauer and Wagner 1991). Any benefit deriving from treatment with echinacea preparations is thought to be due to such stimulation of the immune system, rather than to any direct anti-viral effect.

Ginseng (*P. ginseng*) has a traditional reputation as a tonic and drug of longevity in Asia, where it has also long been used to treat a variety of diseases, including cancer and diabetes, as well as various infections; in modern times, it has been characterized as an ‘adaptogen’ or anti-stress agent, exerting a non-specific normalizing effect on bodily functions. Ginsenosides, also termed panaxosides, are triterpene saponins regarded as the main active constituents of *Panax* species; hydrophilic bioactive polysaccharides are held responsible for anti-complementary and anti-tumor activities (Gao et al. 1991). However, while the attention of the herbal industry has focused almost exclusively on ginsenosides, almost all investigations of the immunomodulatory effects of ginseng have involved crude extracts of *P. ginseng* (see later) and polysaccharide fractions of *Panax* species (Yun et al. 1993; Gao et al. 1996). The results of one human study with a proprietary *P. ginseng* extract, support the claim of enhancement of immune response against influenza and colds, *after vaccination* (Scaglione et al. 1996).

ECHINACEA

The German Commission E (Blumenthal et al. 1998) approves the use of *Echinacea purpurea* herb as follows: (1) “Internally, as supportive therapy for colds and chronic infections of the respiratory tract and lower urinary tract,” and (2) “Externally, on poorly healing wounds and chronic ulcerations.” *E. pallida* is recognized as “supportive therapy for influenza-like infections.”

Investigation towards identification of the principle(s) responsible for the claimed immunomodulatory effects of echinacea preparations, and related effort to establish effective standardized therapeutic formulations have focused on five classes of echinacea constituents, namely, caffeic acid derivatives, alkylamides, ‘polyacetylenes’ (ketoalkenes/ketoalkynes), glycoproteins, and polysaccharides (Bauer 1988).

Constituents/Species Variation/Activity

Echinacoside, a caffeoylic popular for “standardization” but absent in appreciable quantity from roots of *Echinacea purpurea*, “has low anti-bacterial and anti-viral activity, and does *not* show immunostimulatory effects” (Beuscher et al. 1989; Bodinet and Beuscher 1991). Echinacoside is present in the roots of *E. angustifolia* and *E. pallida* at levels between 0.3% and 1.7%, but the roots of the two species can be differentiated by the occurrence of 1,3-*O*-(cynarin) and 1,5-*O*-dicaffeoylquinic acids present only in *angustifolia*. Cichoric acid, which possesses phagocytosis stimulatory activity *in vitro* and *in vivo*, is present in *E. purpurea*, but in only trace amounts in *E. angustifolia* roots; it is also apparently subject to ready enzymatic degradation in the plant matrix and its content in commercial preparations has been observed to be extremely variable (Bauer 1998).

In echinacea, alkamides accumulate primarily in the roots and inflorescences. The highest alkamide content is found in *E. angustifolia* root, while *E. pallida* roots contain only trace amounts. Small quantities of alkamides also occur in the expressed juice of *E. purpurea*. Alkylamide content also has been reported to vary widely in commercial products (Bauer 1998). However, it is important to note that the alkylamides of *E. purpurea* and *E. angustifolia* differ in general chemical structure. All but one from *E. purpurea* have *two* double bonds in conjugation with the amide carbonyl group, whereas eight *E. angustifolia* alkamides have only *one* double bond in conjugation with the amide group; *E. angustifolia* and *E. purpurea* share five alkamides with the diene structure conjugated with the amide grouping, including the prominent isomeric tetraene pair, readily observable at 260 nm, whereas the three most prominent monene alkamides of *angustifolia* are most conveniently detected at 210 nm (Bauer and Wagner 1991).

The main *lipophilic* constituents of *E. pallida* roots are ketoalkenes and ketoalkynes, all with a carbonyl group at the C-2 position of the carbon chains. It is misleading to designate these prominent lipophilic constituents of *E. pallida* root as polyacetylenes, in differentiation from the corresponding alkamide constituents of *E. angustifolia* (15 identified) and *E. purpurea* (11 identified), since many of these latter compounds have conjugated diacetylenic (diyn-) functionality (8 so far identified). Only two ketodiynes have been identified in *E. pallida* roots (Bauer 1998).

The hydrophilic, highly polar constituents, notably polysaccharides and glycoproteins, are present most prominently in expressed juice of the plant, and in aqueous and hydroalcoholic extracts of the aerial parts. Two polysaccharides have been isolated from an aqueous extract of the aerial parts of *E. purpurea* and shown to stimulate phagocytosis *in vitro* and *in vivo* and to enhance production of oxygen radicals by macrophages in a dose-dependent way (Stimpel et al. 1984; Lohmann–Matthes and Wagner 1989). Other activities, such as anti-infective and antitumor, have also been noted (Bauer 1998). In a phase-I clinical trial, a polysaccharide fraction, isolated from *E. purpurea* tissue culture, caused an increased production of leukocytes, segmented granulocytes, and tumor necrosis factor *alpha* (TNF α). In addition, high-molecular weight proteins have been isolated from roots of *E. angustifolia* and *E. purpurea*; purified extracts of a glycoprotein-polysaccharide complex were found to exhibit B-cell stimulating activity and to induce release of interleukin I, TNF α and IFN α , β in macrophages. *E. angustifolia* and *E. purpurea* roots are reported to contain similar levels of glycoproteins, *E. pallida* less (Beuscher et al. 1995). It should be noted, however, that these activities of polysaccharide and glycoprotein-polysaccharide have been observed with *isolated fractions* of polar echinacea extracts: traditional ethanolic extracts likely contain insignificant amounts of polysaccharides, and Bauer and Wagner (1991) have stated that “...only low concentrations of polysaccharides are present in the expressed juice and they do not have the same composition as those in the extracts of aerial parts.” In addition, polysaccharides are expected, for reasons of stability, to be ineffective by oral administration.

While levels and profiles of caffeoylics (Beuscher et al. 1995) and alkylamides from *E. angustifolia* and *E. purpurea*, as well as ketoalkenes and ketoalkynes from *E. pallida*, may be obtained by HPLC procedures with excellent resolution and a high level of sensitivity (Maffei Facino et al. 1995), glycoproteins are most conveniently assessed by an ELISA method (Egert and Beuscher 1992) and polysaccharides by enzymatic hydrolysis and determination of total fructose (L.D. Lawson pers. commun.).

The stimulation of macrophage activity earlier noted for the polar glycoprotein-polysaccharide complement of echinacea preparations, is paralleled by apparently similar activity of their lipophilic component. In fact, the lipophilic fractions of alcoholic extracts from *E. angustifolia* and *E. purpurea* aerial parts and roots showed the greatest activity (Bauer et al. 1989; Jacobson 1967); such extracts of aerial parts exhibited an “immunomodulating effect on the phagocytotoxic, metabolic, and bactericidal activities of peritoneal macrophages in mice” (Bauer 1998).

Attempts to assess the therapeutic potential of echinacea preparations have mainly focused on measurement of phagocytotoxic capacity by the carbon-clearance-test; enhancement by a factor of 1.5 to 1.7 was found in purified alkamide fractions from *E. angustifolia* and *E. purpurea* roots (Bauer et al. 1989). However, overwhelmingly the major constituent of the alkamide fraction of *E. purpurea* root, namely the dodecatetraenoic acid isobutylamide 10 E/Z isomeric pair, exhibited only weak activity, and, in the language of Bauer (1998), “the most effective constituent remains to be found.” In consideration of all of the above, Bauer properly infers that immunostimulant activity of echinacea extracts resides in various classes of echinacea constituents. In acknowledgment of that reality, what remains to be appreciated is which of these constituents are responsible for the medicinal value observed in the limited number of clinical studies available to this point. Is measurement of phagocytotoxic activity a sensible, reliable indicator of immunostimulant potential in terms of effectiveness in the treatment of symptoms of cold and flu, and abatement of respiratory and urinary infections?

At an even further level of reduction, is there any real benefit—beyond identity and quality control considerations—in monitoring levels of *individual* echinacea constituents? And which ones would one select? As far as total tare of the five designated classes of compounds: caffeoylics, alkamides, ketoalkenes/ketoalkynes, glycoproteins, and polysaccharides, their relative importance regarding therapeutic effect yet remains to be properly assessed.

Clinical Testing

Cold. Treatment with the dose equivalent of 900 mg root per day of an alcoholic extract of *E. purpurea* stimulated a faster reduction of cold symptoms in patients compared to the placebo group, and to a group treated with the equivalent of 450 mg per day of root (Braunig et al. 1992). An *E. purpurea* root extract, combined with vitamin C, was also found effective in treating the common cold (Scaglione and Lund 1995). A double-blind, placebo-controlled study was conducted with freshly-expressed juice of *E. purpurea* 108 volunteers with chronic upper respiratory tract infections (Schoneberger 1992). Compared to the placebo, the echinacea preparation reduced the number of infections, lengthened the time between infections, shortened the duration of the illness and lessened the severity of symptoms; patients with diminished immune response seemed to benefit most from the treatment. (Curiously, the German Commission E does not recognize the usefulness of *E. purpurea* root in treating colds, while approving *E. purpurea* “fresh above-ground parts, harvested at flowering time” as a supportive treatment for colds and chronic infections of the respiratory tract and lower urinary tract).

Infections. *E. purpurea* expressed juice promoted faster healing in bronchitis, a viral infection, than an antibiotic (Baetgen 1988) and, as adjuvant, reduced the frequency of occurrence of *Candida* infection better than econazol nitrate (Coeugniet and Kuhnast 1986).

A hydroalcoholic tincture of *E. pallida* roots produced significantly faster recovery from upper respiratory tract infections than placebo (Braunig and Knick 1993). A placebo controlled, double-blind trial conducted on 160 adults (Dorn et al. 1997) indicated that a daily dose of 900 mg of the extract of *E. pallida* root was effective in shortening the duration of upper respiratory tract infections in infected adults, whether of bacterial or viral origin; however, the precise character of the preparation cannot be ascertained from the published information.

Clearly, there is a need for more and better studies to determine the most effective and condition-appropriate echinacea preparations, with respect to species, plant part, character of preparations, and recommended dosage. Given the present state of knowledge of the pharmacology of echinacea constituents, attempts at *therapeutic* standardization based on individual chemical constituents are unrealistic—pending identification

of the constituent(s) responsible for beneficial clinical effect. While such efforts continue, any meaningful standardization must rest with careful and extensive chemical profiling of proven efficacious medications, and/or *relevant* bioactivity correlation.

GINSENG

Undoubtedly because of the difficulty of confirming such diffuse and protracted actions as “tonic,” rejuvenating, and “adaptogenic” effects, most modern research on *Panax* has been conducted on more specific influences, with more easily determined end-points. Such experiments have invariably utilized either gross extracts of one sort or another, fractions of extracts, or individual ginseng constituents isolated from them.

Various Extracts, Fractions and Isolated Principles

In an attempt to resolve conflicting reports of ginseng’s effect on the immune system, a 70% ethanolic extract of *P. ginseng* was subjected to a comprehensive testing battery capable of detecting subtle immune changes in mice, whose immune function was suppressed by cyclophosphamide, a common chemotherapeutic agent (Kim et al. 1990). The observation that basal natural killer (NK) cell activity was stimulated, supports an immunomodulatory property for ginseng. However, while subchronic exposure helped stimulate recovery of NK function in cyclophosphamide—immunosuppressed mice, NK activity was not further stimulated in polyinosinic-polycytidilic treated mice—and other immunological parameters examined, such as T and B cell responses, were not affected.

Using a sensitive two-site enzyme immunoassay specific for human basic fibroblast growth factor (bFGF), “bFGF-like immunoreactivity” was detected in a *P. ginseng* extract prepared by methanol extraction, followed by aqueous buffer treatment which precipitated a water-insoluble fraction, centrifugation, and filtration. A bFGF-like molecule was identified (Takei et al. 1996).

The ethanol-insoluble fraction of an aqueous extract of *P. ginseng*, tested for immunomodulatory activity, was found to induce proliferation of splenocytes and to generate activated killer cells in vitro (Yun et al. 1993); the activated killer cells killed both NK cell sensitive and insensitive tumor target cells without MHC-restriction. Activation of splenocytes was mediated through endogenously produced interleukin-2. Treatment of young male mice with this ethanol-insoluble ginseng fraction significantly reduced lung tumor incidence, compared with a cohort treated only with tumor-inducing benzo [*a*] pyrene. Prior to treatment with 95% ethanol, the original aqueous extract was solubilized in methanol and the methanol-soluble fraction, which exhibited cytotoxicity to splenocytes in vitro, was excluded.

Stimulated by the observation that several polysaccharides from *P. ginseng* exhibit the immunological effects of increasing serum IgG level and activating the reticuloendothelial system (RES), Japanese researchers have isolated two acidic polysaccharides, named ginsenan PA and ginsenan PB, whose detailed structures were determined (Tomoda et al. 1993). Both polysaccharides displayed similar RES, anti-complementary, and alkaline-phosphatase-inducing activity. In this study, *P. ginseng* root was extracted, in the traditional Chinese manner, with hot water, the polysaccharides precipitated with cetyltrimethylammonium bromide, extracted with dilute sodium chloride solution and the free polysaccharides precipitated by the addition of ethanol; column chromatography, followed by dialysis and then gel filtration, yielded ginsenan PA and PB.

Immunostimulating activity of *Panax* has been observed also in polysaccharidic material extracted from the leaves of *P. ginseng* (Sum et al. 1994). In order to estimate the potential of ginseng leaves which can be harvested annually, as compared to ginseng roots which usually require at least four years of maturation, these researchers compared the immune complex binding enhancing activity of water and alkaline-soluble polysaccharide fractions of root and leaves of *P. ginseng*. Binding of glucose oxidase-anti-glucose oxidase complexes (GAG) to macrophages was enhanced by crude polysaccharide fractions GL-2 and GR-3, from leaves and root respectively, GL-2 being the most active of all four fractions; the alkaline-soluble leaf extract GLA-2 showed no activity. A pure active polysaccharide GL-4IIb2 containing 33% uronic acid, was isolated. GAG binding to macrophages by GLIIb2 increased in a dose-dependent fashion. The authors judge that their observations “... suggest that the carbohydrate moiety of GL-4IIb2 activated the mononuclear phagocytic system in vivo through an increase of Fc receptor expression mediated by de novo synthesis of the receptor protein and resulted in enhanced immune complexes clearance.”

Immunostimulating polysaccharides have also been isolated from *P. notoginseng*; (Sanchi or Tienchi ginseng). A RES-active polysaccharide, sanchinan A (Ohtani et al. 1987), and four distinct homogeneous active polysaccharide fractions (Gao et al. 1991), have been isolated from the roots of *P. notoginseng*; in the latter study, one fraction showed strong anti-complementary activity, two significantly induced the production of interferon- γ in the presence of concanavalin-A, and all induced the production of TNF α , using human serum and antibody-sensitized sheep red blood cells.

One study with an isolated saponin from *P. ginseng*, ginsenoside Rg1, assessed its stimulatory effect on immune function of lymphocytes in the elderly (Liu et al. 1995). A reduced responsiveness of lymphocytes has been associated with aging as well as a lower percentage of IL-2 receptor positive cells, compared with the younger population. Rg1 was found to stimulate proliferation of lymphocytes and to increase the fluidity of lymphocyte membrane in the aged.

G115 (Ginsana®)

In the past two decades, a considerable number of studies have been conducted on the proprietary *P. ginseng* extract, G115, from Pharmaton SA, Lugano-Bioggio, Switzerland. The immunomodulatory activity of G115 was assessed in mice (Singh et al. 1984). Pretreatment with the ginseng extract led to an increase in the number of antibody forming cells, as well as of the titers of circulating antibodies. Pretreatment with ginseng extract also modulated the cell mediated immune response in test animals. Ginseng extract significantly elevated NK cell activity in test animals, as compared to control animals, and enhanced production of interferon of both the pH stable and labile types, induced by 6-MFA, an interferon inducer of fungal origin.

Subsequently, three controlled human studies, with G115 conducted in Italy, examined the immunomodulatory effects of the extract, in one case was comparing G115 with an aqueous extract of *P. ginseng*. In a controlled single-blind study (Scaglione et al. 1994) placebo was compared to 100 mg of G115 administered every 12 hours for 8 weeks to patients suffering from chronic bronchitis. The functioning of alveolar macrophages, collected by bronchoalveolar lavage, was determined by measuring the phagocytic activity and killing power towards *Candida albicans*, which were “significantly ... *increased* at the eighth week of treatment.” The observed improvement in macrophage immune response was seen to indicate an important role for G115 in “the *prevention and therapy* of respiratory disorders (emphasis added).

A comparative double-blind study with healthy volunteers was conducted with G115 and an aqueous extract of *P. ginseng* root (PKC 167/79), using the same dosing regime followed in the previous study (Scaglione et al. 1990). No details are provided for preparation of the aqueous extract, as are the mode of preparation and the constituent profile of G115 not disclosed, except for a roughly 4% combined content in the seven major ginsenosides usually assayed for in ginseng materials. While both extracts demonstrated immunostimulatory activity, the two extracts differed in some parameters. A noticeable increase in phagocytosis was observed in the fourth week in the group treated with G115, whereas elevation in the PKC 167/79 group “appeared to be delayed to the end of the eighth week.” A similar difference was observed regarding increase in T helper lymphocytes (T4). These researchers interpreted “the earlier effective action of G115”—also evident in an enhancement of T4/T8 ratio—as due an earlier onset of immune response, as compared with PKC 167/79. The final sentence of the publication: “It can be suggested that on the basis of its different actions on the immune system, the G115 extract may have a different composition in comparison with the PKC 167/79 extract *in terms of ginsenoside content*” (emphasis added).

The third human trial with G115 involved 227 volunteers at 3 private practices (Scaglione et al. 1996). Subjects were given either placebo or 100 mg of G115 daily, for 12 weeks, an anti-influenza polyvalent vaccination being administered after the 4th week. The frequency of influenza or common cold between 4 and 12 weeks was 42 cases in the placebo group, and only 15 in the G115 group, the difference being highly significant ($p < 0.001$). NK cell activity was also significantly higher in the ginseng group after 8 weeks, as were specific antibody titers. The researchers concluded that G115 can improve the immune response in humans and can protect against influenza and the common cold.

As with echinacea, the results of studies assessing the immunostimulatory effect of ginseng preparations cannot be confidently interpreted in terms of particular plant constituents. The relative contribution of

ginsenoside, polysaccharide, or other ginseng components cannot be estimated and, therefore, inferences regarding relative effectiveness of different extracts of ginseng remain entirely speculative. Estimation of ginsenoside effect, for example, may depend not only on the total content of the most prominent 6–8 neutral ginsenosides, but also on their relative ratios and perhaps contributions from their more-than-20 other closely related triterpene saponins. As Scaglione et al. (1990) have posited, contradictory results from studies on the effect of ginseng extracts on the immune system “could arise from the difference in *dose levels, composition and duration of therapy*” (emphasis added).

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