

## REVIEW

# Medicinal properties of *Echinacea*: A critical review

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### Summary

Preparations from *Echinacea purpurea* are among the most widely used herbal medicines. Most uses of *E. purpurea* are based on the reported immunological properties.

A series of experiments have demonstrated that *E. purpurea* extracts do indeed demonstrate significant immunomodulatory activities. Among the many pharmacological properties reported, macrophage activation has been demonstrated most convincingly. Phagocytotic indices and macrophage-derived cytokine concentrations have been shown to be *Echinacea*-responsive in a variety of assays. Activation of polymorphonuclear leukocytes and natural killer cells has also been reasonably demonstrated. Changes in the numbers and activities of T- and B-cell leukocytes have been reported, but are less certain. Despite this cellular evidence of immunostimulation, pathways leading to enhanced resistance to infectious disease have not been described adequately. Several dozen human experiments – including a number of blind randomized trials – have reported health benefits. The most robust data come from trials testing *E. purpurea* extracts in the treatment for acute upper respiratory infection. Although suggestive of modest benefit, these trials are limited both in size and in methodological quality. Hence, while there is a great deal of moderately good-quality scientific data regarding *E. purpurea*, effectiveness in treating illness or in enhancing human health has not yet been proven beyond a reasonable doubt.

**Key words:** *echinacea*; coneflower; immunostimulation; immunomodulation, immunity; common cold; upper respiratory infection

### Introduction

*E. purpurea* is the best known of the dozen or so species of the genus *Echinacea*, a group of perennial prairie wildflowers native to the central grasslands of North America. *Echinacea*, once classified as *Rudbeckia*, is grouped within the Aster family (Compositae or Asteraceae) (Bauer and Foster, 1989; Flannery, 1999; Foster, 1996; Hurlbert, 1999; McGregor, 1968). Also known as common purple coneflower, *E. purpurea* is characterized by erect main stems up to 2 meters in height, alternate leaves on long stalks, coarse hairs, and solitary spiny, reddish-orange flowers surrounded by purplish bracts. *E. purpurea* is cultivated widely throughout the United States, Canada and Eu-

rope, especially in Germany, for its beauty as well as for its reported medicinal properties.

Prior to European colonization, a number of Native American nations, including the Blackfoot, Cheyenne, Choctaw, Comanche, Dakota, Delaware, Lakota, and Sioux, used various *Echinacea* preparations for a variety of purposes (Flannery, 1999; Foster, 1991). European settlers learned about native botanical species from their indigenous teachers, soon bringing *Echinacea* into the colonial pharmacopoeia. The first historical mentions of *Echinacea* were by Clayton in the *Flora Virginica* (1762) and by Schöpf in the *Materia Medica Americana* (1787) (Flannery, 1999; Foster, 1991). Euro-American

physicians – from Eclectics to Homeopaths to Naturpaths – kept various *Echinacea* potions in their medicinal kits, for use against snakebite, or to counter infectious disease. *Echinacea* was described in the *National Formulary of the United States* from 1916 to 1950. During the 20<sup>th</sup> century, the gradual dominance of allopathic “scientific” medicine was accompanied by a reduction in the use of herbals including *Echinacea* included. A 1909 *JAMA* editorial by American Medical Association Secretary W.A. Puckner titled “*Echinacea* considered valueless” said that its use was based on “the absurd claims of an evidently ignorant man”, and declared that *Echinacea* should be “deemed unworthy of further consideration” (Puckner, 1909).

Nevertheless, medicinal use of *Echinacea* preparations continued among certain sectors of North American society. In Europe, the most widespread use has occurred in Germany. Apparently, Gerard Madaus came to the United States seeking germplasm of *E. angustifolia*, but mistakingly returned with *E. purpurea* seeds, beginning a long line of German cultivation (Foster, 1991). Since that time, the German market – the largest in Europe – has been dominated by *E. purpurea*. German scientists were at the forefront of *Echinacea* research throughout the twentieth century, with most of the scientific research done on *E. purpurea*. Only in the last decade or so have U.S. markets and U.S. research efforts begun to catch up.

Currently, extracts and whole plant products made from *Echinacea purpurea*, *E. angustifolia*, and *E. pallida* comprise one of the largest sectors of the several billion dollar herbal medicine market, in North America as well as in Europe. Annual sales of *Echinacea* products have been estimated at \$300 million in the U.S. alone (Brevoort, 1998). Hundreds of commercial preparations, ranging from direct pressed juices to freeze-dried ethanolic or hydrophilic extracts to whole or powdered dried leaves and flowers are available in groceries, pharmacies and health food stores throughout the industrialized world. *Echinacea* is used most widely as prevention or treatment for the common cold, with the proposed mechanism of action relating to its reported ability to stimulate the immune system (Anonymous, 2001; Bone, 1997a; Foster, 1991; Mark et al. 2001).

## Pharmacology – Immunomodulating effects

*Echinacea purpurea* is best known for its effects on the immune system (Bauer and Wagner, 1991; Foster, 1991; Hobbs, 1995; Sun et al. 2001). Stimulation of various immune cells such as macrophages, other monocytes, and natural killer (NK) cells has been demonstrated repeatedly *in vitro* (Bauer, 1998; Bauer,

1999a; Burger et al. 1997; Rininger et al. 2000; Sun et al. 2001). However, if and how these “immunostimulating” effects translate into better human health is less well understood (Becker, 1996). One theory postulates that immunosuppression can result from exposure to allergens, illness, malnutrition, drugs, toxins or psychological or social stress. In that view, treatment with *Echinacea* could strengthen a weakened immune system, restoring balance and health (Schellenberg, 2001). However, “immunomodulation” may be a more appropriate term for *Echinacea*’s effects, as the “immune system” that *Echinacea* is reported to “stimulate” is a highly complex multi-component system with no clear “up” or “down” (Abbas et al. 2000; Janeway et al. 1999). Some immune activities are beneficial, others harmful. Beneficial immunomodulation would include the reduction of harmful host responses, such as inappropriate irritation or inflammation.

Inflammation appears to be the central event leading to symptoms of infectious rhinosinusitis (the common cold) and pharyngitis (sore throat), the primary illnesses for which *Echinacea* is currently used. Inflammation involves tissue swelling (resulting from vasodilation and capillary leakage) and infiltration of leukocytes. These processes appear to be triggered primarily by substances secreted by macrophages: toxic oxygen radicals, peroxide, nitric oxide, IL-1, IL-6, IL-8, IL-12, TNF- $\alpha$ , leukotienes, and platelet-activating factor (Garofalo et al. 1993; Igarashi et al. 1993; Noah et al. 1995; Roseler et al. 1995). C-reactive protein and various kinins are also involved in upper airway inflammation (Korppi and Kröger, 1992; Naclerio et al. 1988). In addition to this multitude of immunochemical influences, nasal and pharyngeal inflammation are modulated by neural pathways, primarily parasympathetic (Baraniuk, 1992; Kaliner, 1992). While *Echinacea* appears to activate macrophages and affect their cytokine secretions *in vitro*, the *in vivo* mechanisms and pathways have not yet been adequately investigated.

The concept of immunomodulation can be traced to Paul Ehrlich’s experiments in the latter nineteenth century. Enhancing “adaptive” immunity with immunization clearly works, as stimulation with vaccine leads to increased clonal proliferation of antibody-producing cells and hence to an enhanced resistance to the organisms from which the vaccines are derived. Stimulation of the “innate” immune system has not yet yielded such clear benefit. Although there have been a few reports of experimental “immunostimulatory” drugs, conventional medical science has not yet adopted any therapies based on nonspecific stimulation of immune response (Becker, 1996; Bergmann, 1995; Collet, 1992; Lersch et al. 1992; Riedl-Seifert et al. 1995; Valleron and Grimfeld, 1992; Wagner, 1995; Wagner et al. 1999). As the innate response involves potentially destructive

pathways and leads to symptomatic expression, broad stimulation may seem unlikely to lead to overall benefit. Selective stimulation of antiviral pathways, coupled with moderation of inflammatory pathways, is theoretically the goal of successful immunomodulation. Said differently, successful immunomodulation would decrease severity and duration of symptoms while increasing the rate of elimination of infective pathogens. Such biphasic or multiphasic pharmacological fine tuning has been termed "adaptogenic" by some authors (Panossian et al. 1999; Wagner, 1995).

### ■ Immunomodulating effects – In vitro and animal studies

Attempts to use *Echinacea* as an immune modulator date back to 1913, when von Unruh published his observations of increased phagocytosis of tuberculosis bacteria (von Unruh, 1913). In 1921 Couch and Giltner published a report of their experiments of *Echinacea* in guinea pigs (Couch and Giltner, 1921). Subsequently, in Germany, immunological investigations were carried out by a number of laboratory investigators from 1923 until the present day. Early studies confirmed phagocyte-stimulating, hyaluronidase-inhibiting and properdin-generating activities (Bauer and Wagner, 1991; Bauer, 1998). Many of the early experiments were performed using extracts of *Echinacea angustifolia* and *E. pallida*, which at that time could not be reliably distinguished from each other. Most of the early studies were done in various *in vitro* assays or in live rats or mice, many with parenteral (injected) dosing (Bauer et al. 1988; Becker, 1982; Stimpel, 1984).

Activation of macrophage and PMN immune cells is the most widely reported of *Echinacea*'s many claimed pharmacological activities (Schellenberg, 2001). Experiments using all 3 medicinal species of *Echinacea* (*purpurea*, *angustifolia* and *pallida*) have demonstrated macrophage-activating properties using yeast-particle ingestion, carbon-clearance, and macrophage-product (cytokine) measurement methods (Bauer et al. 1988; Bauer et al. 1989; Bauer, 1999a; Rininger et al. 2000). One experiment reported a 3-fold higher carbon clearance in mice fed *E. purpurea* extract as compared to controls (Bauer et al. 1988). In this experiment, *E. purpurea* extract (dosed orally at 10 ml/kg/day of a solution made from 0.5 ml of ethanolic extract in 30 ml saline) performed slightly better than comparable *E. angustifolia* or *E. pallida* extracts. Orally-administered ethanolic extract of dried *E. purpurea* herb (5 mg/kg) led to a 40% increase in carbon clearance in a mouse model, with the lipophilic portion more stimulatory than the polar fraction (Bauer, 1999a). Spleen cell monocyte proliferation, enhanced antibody re-

sponse, and increased levels of IL-1, IL-6, TNF and IFN were reported following oral dosing of a patented mixture (Esberitox<sup>®</sup>) of *E. purpurea*, *E. pallida*, *Thuja occidentalis* (white cedar), and *Baptisia tinctoria* (wild indigo) (Bodinet and Freudenstein, 1999). Exposure to an extract of *E. purpurea* root led to higher levels of "induction of IL-1, IL-6, TNF and IFN *in vivo* and *in vitro* and antibody production" than did extracts of *E. angustifolia* and *E. pallida*. In another set of experiments, a 30% ethanolic *E. purpurea* extract was reported to induce IFN in viral-infected animal cell cultures (Skwarek et al. 1996). Several experiments have reported increased activity of macrophages from mouse liver and spleen following oral dosing with *E. purpurea* extract (Bauer et al. 1989; Carr et al. 1999; Rininger et al. 2000). In one experiment, increased activity of mouse peritoneal macrophage was reported following 5 days' exposure to an ethanolic extract of *E. purpurea* herb (Bukovsky et al. 1995).

Activation of human macrophages was reported in one early experiment in which 12 young men were injected with 2 ml Echinacin<sup>®</sup> daily for 4 days, after which their blood was collected, fractionated, and immune cells exposed to *Candida albicans* (Möse, 1983). Increased rates of macrophage phagocytosis of *Candida* were judged to be statistically significant as compared to controls. No effect on NK cells activity was noted. More recent work has reported activation of NK cell as well as macrophage phagocytosis following exposure of *ex vivo* human immune cells to *E. purpurea* extracts (See et al. 1997). Reports of increased macrophage phagocytic activity have been accompanied by several reports of enhanced cytokine production (Bauer, 1999a; Burger et al. 1997; Rininger et al. 2000). Increases in IL-1, IL-6, and TNF were first reported in experiments using a rat model. However, significant effects on cytokines were not observed following exposure of 23 tumor patients to oral doses of 3 ml per day of "Echinacea Complex".

Rininger and colleagues performed a series of experiments in which mouse macrophages and their cytokine products (TNF- $\alpha$ , IL-1 $\alpha$ , IL-1 $\beta$ , IL-6, IL-10 and NO) were measured following exposure to various *Echinacea* products (Rininger et al. 2000). Effects on the viability of *ex vivo* human peripheral blood mononuclear cells (PBMCs) were assessed. Anti-inflammatory and antioxidant activities were also measured, with results reported below. Methods included positive (lipopolysaccharide = LPS) and negative controls, variable dosing to assess dose-response, and "simulated digestion methodology" (in which the *Echinacea* products were subjected to gastric fluid preparation before the assays). Concentrations of *E. purpurea* extracts varying from 1.25 to 1280  $\mu$ g/ml, processed with "simulated digestion", yielded reproducible and

characteristic dose-response curves of the macrophage products TNF- $\alpha$ , NO, IL-1 $\alpha$ , IL-1 $\beta$ , and IL-6. While TNF- $\alpha$  levels peaked at 30 h, the other macrophage products continued to increase over several days. While solutions made from both herb and root *E. purpurea* powders produced definite reproducible macrophage activity, "extracts chemically standardized to phenolic acid or echinocaside content and fresh pressed juice preparations were found to be inactive as immunostimulatory agents but did display, to varying degrees, anti-inflammatory and antioxidant properties" (Rininger et al. 2000). Testing a dozen different products, Rininger et al. noted that 2 of 7 *E. purpurea* herb powders and 1 of 5 *E. purpurea* root powders "had activity similar to the original test material". Several products standardized to 4% phenolics were found to be inactive, as were a few fresh pressed juice powders and liquids. In summary, certain *E. purpurea* products stimulated macrophages in dose-dependent, reproducible manners that differed dramatically from placebo controls, while others did not. Noting the "high degree of variability found amongst similarly standardized extracts", Rininger and colleagues did not hazard an opinion as to the active phytochemicals, but did note that the variability "may reflect growth conditions, time of harvest, milling, and storage conditions".

In addition to well-demonstrated macrophage activation, increased activity of polymorphonuclear (PMN) granulocytes has been reported from a number of animal experiments using carbon-clearance, bioluminescence, *Candida* ingestion, and modified Brandt granulocyte assays (Bauer et al. 1999; Jurcic et al. 1989; Bauer, 1999a; Stotzem et al. 1992; Wildfeuer and Mayerhofer, 1994; Wolf et al. 1998). Polysaccharide-rich fractions from pressed juice extracts have been reported to increase carbon clearance in live mice and in *in vitro* human PMNs (Bauer et al. 1999; Lohmann-Matthes and Wagner, 1989; Wagner et al. 1984; Wagner et al. 1988; Emmendorffer et al. 1999). Phagocytic uptake of fluorescein-labelled *E. coli* bacteria was reported to be enhanced following *E. purpurea* juice exposure in *ex vivo* tests using human PMN and monocytes (Wolf et al. 1998). Dose-dependent increases in PMN-reactivity have been reported (Bauer et al. 1999; Stotzem et al. 1992). Most of these experiments used Echinacin<sup>®</sup> (aka. Echinagaard<sup>®</sup>), a fresh-pressed *E. purpurea* juice product made by Madaus AG, Cologne, Germany.

Enhancement of viability and clonal proliferation of immune cells has been reported. Rininger et al. (2000) reported that viability of PBMCs was enhanced by the same *Echinacea* preparations that induced macrophages to secrete TNF- $\alpha$ , but not by the inactive preparations or the controls. These authors note that "*Echinacea*-induced enhancement of PBMC viability was found to be

dose-dependent with optimal stimulation by *Echinacea* at concentrations of 1  $\mu$ g/ml and was effective with different donors" Sun and co-workers at McGill carried out a study in which mice fed 0.45 mg/day of *E. purpurea* root extract for 1–2 weeks were assayed for immune cells. Compared to controls, mice fed *E. purpurea* root extract had significantly higher numbers of NK cells and monocytes, but not granulocytes, lymphocytes or their precursors (Sun et al. 2001).

Other indices of immune stimulation have also been reported. In one study, cultured cells infected with virus and exposed to *E. purpurea* juice demonstrated an increased rate of presentation of viral antigen (Eichler and Krüger, 1994). In another, an extract of *E. purpurea* increased both antibody-dependent and innate NK-mediated activities against herpes virus infections in *ex vivo* cells from both normal and immune-depressed individuals (See et al. 1997). Changes in the numbers and activities of T and B cell leukocytes in response to *Echinacea* exposure have been reported, but are controversial. In general, increased white cell counts in peripheral blood have been noted following intramuscular or intravenous injection of *E. purpurea* extracts, but not following oral dosing (Lorenz et al. 1972). However, oral dosing of a mixture of *E. purpurea*, *E. pallida*, *Thuja occidentalis*, and *Baptisia tinctoria* was in one study reported to increase antibody levels to inoculated sheep red blood cells in mice (Bodinet and Freudenstein, 1999).

In addition to classification of studies using extracts from different *Echinacea* species, investigations can be grouped into those using root or herb products, and those comparing lipophilic (fat-soluble) or hydrophilic (water-soluble) preparations. Not too surprisingly, there is little consensus as to which species, plant part, or extraction method yields the product with the greatest "immune-stimulating" properties. Extracts soluble in water, ethanol and chloroform have all demonstrated phagocyte-stimulating activity (Bauer et al. 1989; Bauer and Wagner, 1991; Bauer, 1999a). In a series of controlled experiments using mice, oral ingestion of *E. purpurea* root extract led to increased carbon clearance (Bauer, 1999a). In one of these studies, the lipophilic fraction increased activity by 70%, while the hydrophilic fraction increased carbon clearance by 90% (Bauer, 1999a). Hydrophilic polysaccharide fractions from *E. purpurea* have induced mouse macrophage secretion of TNF, interferon- $\beta$ 2, and oxygen radicals (Lohmann-Matthes and Wagner, 1989). Fractions high in glycoproteins have also been shown to enhance murine macrophage activity and levels of cytokine by-products (Bauer, 1999a). Purified glycoproteins were reported to have macrophage-activating, cytokine-generating, and antiviral activities (Bodinet and Beuscher, 1991). Other authors have argued that lipophilic ex-

**Table 1.** *Echinacea purpurea* Trials – Methods and Results.

Author	Purpose	Number of Participants*	Random	Blind**	Benefit	Limitations
Schulten 2001	Treat URI	N = 80 (E = 41; P = 39) ITT = 70	Yes	Double	Yes	No evidence of blinding; Unclear data analysis; Unvalidated measures
Lindenmuth 2000	Treat URI	N = 95 (E = 48; P = 47) ITT = 95	Quasi	Double	Yes	Alternate allocation; No evidence of blinding; Poor outcome measures (retrospective global assessment)
Turner 2000	Prevent URI	117 (E = 63; P = 54) ITT = 92	No	Double	No (Trend)	No evidence of blinding; Induced rhinovirus exposure. Unvalidated measures; Product may not be <i>E. purpurea</i>
Henneicke-von Zepelin 1999	Treat URI	263 (E = 131; P = 132) ITT = 259	Yes	Double	Yes	No evidence of blinding; Multi-species product. Unvalidated measures
Brinkeborn 1999	Treat URI	N = 180 (E1 = 41; E2 = 49; E3 = 44; P = 46) ITT = 246	Yes	Double	Yes	No evidence of blinding; Unvalidated measures
Melchart 1998	Prevent URI	302 (E1 = 103; E2 = 103; P = 96) ITT = 289	Yes	Single	Trend	Placebo distinguishable from active treatment; Unvalidated measures
Berg 1998	Immunoassay	N = 42 (E = 14; P = 13; Mg = 13) ITT = 42	Unclear	No	Trend	Unclear randomization; Blinding not possible since Echinacea as liquid and placebo and magnesium as tablet
Hoheisel 1997	Treat URI	120 (E = 60; P = 60) ITT = 120	Yes	Double	Yes	No evidence of blinding; Unvalidated measures; Selective reporting of outcomes; Outcomes defined retrospectively
Scaglione 1995	Treat URI	32 (E = 16; P = 16) ITT = 32	Yes	Single	Yes	No evidence of (single) blinding; Small sample size; Unvalidated measures; Poor symptom measures
Melchart 1995 (1988 trial) (also reported in Jurcic 1989)	Immunoassay	24	Yes	Double	Trend	No evidence of blinding; Unclear randomization; Unvalidated measures; Small sample size
Melchart 1995 (1989 trial)	Immunoassay	36	Yes	Double	No	No evidence of blinding; Unclear randomization; Unvalidated measures; Small sample size
Melchart 1995 (1990 trial)	Immunoassay	24	Yes	Double	No	No evidence of blinding; Unclear randomization; Unvalidated measures; Small sample size
Bräunig 1992	Treat URI	180 (E1 = 60; E2 = 60; P = 60) ITT = 180	Yes	Double (Single)	Yes	Unvalidated measures; High dose group not blinded; No evidence of blinding of low dose group

Table 1. (Continued).

Author	Purpose	Number of Participants*	Random	Blind**	Benefit	Limitations
Schöneberger 1992 (Grimm 1999)	Prevent URI	N = 108 (E = 54; P = 54) ITT = 109	Yes	Double	Trend	No evidence of blinding; Unvalidated measures; Selective reporting of outcomes
Reitz 1990	Treat URI	150	Yes	Double	Trend	No evidence of blinding; Unvalidated measures; Multi-species product
Jurcic 1989 (Melchart 1995)	Immunoassay	27	Yes	Single	Trend	No evidence of blinding; Unclear randomization; Unvalidated measures; Small sample size
Coegniet 1986	Candida	203	No	No	Yes	Not randomized or blinded; Unvalidated measures
Vorberg 1984	Treat URI	100	Yes	Double	Trend	No evidence of blinding; Unclear randomization; Unvalidated measures; Multi-species product
Calabres (Unpublished)	Prevent URI	164	Yes	Double	No	Unpublished (methods not reported)

\*N – Number of participants included in analysis; E – Number of participants in Echinacea group (When more than one type of preparation, E1, E2, E3 are used); P – Number of participants in placebo group; ITT – Intention to treat (number of participants originally included)

\*\* No trials adequately demonstrated intact concealment (blinding). Blinding of liquid products particularly suspect.

tracts demonstrate more activity (Bone, 1997a). Alkylamides, especially isobutylamides, have been studied, and appear to be important in phagocyte-stimulating effects (Bauer, 1998).

Wagner and co-workers have worked extensively to investigate the immunostimulant effects of polysaccharides (heteroglycans) from *Echinacea* species (Emmendorffer et al. 1999; Schöllhorn et al. 1993; Wagner, 1999). A number of polysaccharide structures, including a variety of arabinogalactans, are reported active in macrophage-stimulating and other immunological assays (Scaglione et al. 2001; Wagner et al. 1984; Wagner et al. 1988). Investigators in other laboratories have also reported a wide variety of antigen-specific *E. purpurea* polysaccharides and proteoglycans (Scaglione et al. 2001; Egert and Beuscher, 1992). Using a variety of models, *E. purpurea*-derived polysaccharides were reported to increase mouse, rat and human macrophage activity (Bauer, 1999a; Lohmann-Matthes and Wagner, 1989; Emmendorffer et al. 1999). For example, following experiments using an *ex vivo* mouse model, it was reported that “highly purified polysaccharides from plant cell cultures of *Echinacea purpurea* [were] effective in activating macrophage to cytotoxicity against

tumor cells and ... Leishmania” (Luettig et al. 1989). However, B and T-cell activation was not observed (Luettig et al. 1989). In another experiment, pretreatment with *E. purpurea*-derived polysaccharides was reported to enhance resistance and decrease mortality of immunosuppressed mice infected with *Candida albicans* and *Listeria* sp. (Steinmuller et al. 1993). One problem with the polysaccharide hypothesis is that these carbohydrate structures are either digested into simple, pharmacologically, inactive sugars, or are not absorbed through the gut wall. Hence, it appears that polysaccharide-induced activities would have to result from interactions with immune cells in the gastrointestinal epithelium, which in turn would have to regulate the body's response through as-yet-unknown endocrine, neurological, or immunological mechanisms. Another problem rests with the fact that polysaccharides are ubiquitous in the plant kingdom, and are generally not pharmacologically active. Nevertheless, Wagner et al. have shown that several *Echinacea*-derived polysaccharides – including arabinogalactans, fructofuranosides and heteroxylans – are indeed active in certain immunological models (Emmendorffer et al. 1999).

## ■ Immunomodulating effects – Human clinical trials

The early twentieth century conventional medical literature contained scattered references to *Echinacea*, including mention in the *Journal of the American Medical Association* (Puckner, 1909) and the *American Journal of Pharmacy* (Beringer, 1911; Couch and Giltner, 1921). Undoubtedly, there was a great deal of observational study during these years. However, no systematic investigations were reported until after Gerhard Madaus brought *E. purpurea* to Germany in the 1920s. Unfortunately, most of the foundational *Echinacea* work in Germany remains untranslated, and cannot be reviewed here. Bauer provides the most comprehensive English-language reviews (Bauer and Wagner, 1991; Bauer, 1998; Bauer, 1999a). It appears that the first controlled human trial measuring immunological parameters was reported by Möse, a translation of which was reviewed for this report. Möse injected “12 healthy male subjects” with 2 ml of *E. purpurea* juice (Echinacin®) for 4 consecutive days (Möse, 1983). Using *ex vivo* cell uptake methods, he reported “a definite increase in phagocytic efficiency” of *Candida albicans* by macrophages, but “no definite evidence of effect” on lymphocytes and NK cells. Physical examination and various urine and blood tests demonstrated “no adverse reactions”.

A few years later, Jurcic and colleagues (including Bauer, Melchart and Wagner) reported two randomized placebo-controlled human trials in a single publication (Jurcic et al. 1989). The first, a single-blind study of 27 volunteers, reported a 20% increase in phagocytotic activity at day 4 in the *Echinacea* group (injected intravenously with an undescribed *E. purpurea* preparation). The second study, reported as double-blinded and randomized, subjected 24 men to oral dosing, with 30 drops 3 times daily for 5 days, with either an ethanolic extract of *E. purpurea* root or a similar-appearing placebo (Jurcic et al. 1989). Increases in PMN phagocytic activity were reported, reaching peak levels at day 5. No changes in white cell counts or other blood measurements were noted. No tests of blinding or randomization were reported, nor were appropriate statistical tests of claimed effects presented.

Melchart and colleagues (including Jurcic and Wagner) reported the results of five separate studies in a single 1995 report (Melchart et al. 1995). Although described as randomized and blinded, the even numbers in treatment and placebo groups and the lack of descriptions of allocation and concealment procedures limit interpretation somewhat. The first of the three studies using *E. purpurea* was conducted in 1988, and appears to be the same study on 24 men as reported

above (Jurcic et al. 1989). The active solution was made using 20 grams of dried *E. purpurea* root steeped in 100 ml of an ethanol-water solution. Volunteers took 30 drops 3 times daily for 5 days. Phagocytic activity was significantly higher in the *Echinacea* group than in the placebo group, especially at days 3, 4, 5 and 6. The second Melchart-reported study using *E. purpurea* extract was carried out in 1989, and compared capsulized ethanolic extracts of *E. purpurea* and *E. pallida* roots with placebo. The capsules, containing 380 mg of dried extract, were taken 3 times daily for 5 days. No differences were noted among the 3 treatment groups in phagocytic activity or other measured outcomes. The third *E. purpurea* study, carried out in 1990, compared a liquid 70% ethanolic extract of 95% herb and 5% root of *E. purpurea* with placebo, again using 30 drops 3 times daily. No significant differences in phagocytic indices or white-cell counts were noted. All three studies monitored adverse effects using self-report and a small array of blood tests. No adverse effects were noted. Finding mostly negative results, this team suggested using sick or immunocompromised “patients” rather than “healthy volunteers” for future studies. One criticism of these studies is that the doses used were relatively low, much lower than those used by many practicing herbalists and naturopaths.

In 1998, Berg et al. reported a trial in which 42 triathletes were randomly administered magnesium, similar appearing placebo tablets, or *E. purpurea* juice (Echinacin®), 8 ml daily during 28 days of training and directly before and after a competition (Berg et al. 1998). “Blood and urine samples were collected (7–9 h) before (day 0) and at the end (day 28) of the treatment period.” Outcomes assessed were “changes in T-cell populations and serum concentrations of IL-6 and sIL-2R.” Although the authors claimed in the abstract that changes in urinary sIL-2R, IL-6 and cortisol were attributable to Echinacin®, a close reading of the results shows that differences noted between the placebo and *Echinacea* groups were neither consistent nor significant. T-lymphocyte and NK cell populations did not differ among the groups. While three of 13 in the magnesium group and four of 13 in the placebo group got colds, none of the athletes taking *Echinacea* developed respiratory infections. This trend toward benefit was not statistically significant; hence the observed 25% reduction in incidence of upper respiratory infection could be caused by *Echinacea*, or could be due to chance alone.

It seems logical to conclude from the evidence outlined above that *Echinacea* can indeed stimulate certain immunological activities. Whether these effects are associated with desired health outcomes – such as reduced incidence, severity or duration of illness – is perhaps a more important question. Although macro-

phage and PMN-derived production of peroxides and oxygen radicals may be necessary for the destruction of virus-invaded host cells, the oxidative process has been linked with cellular and organ damage, and with premature aging. In the case of upper respiratory infection, it could be argued that a down-regulation of macrophage activity might be preferable to stimulation, as the inflammatory response leading to symptoms could be attenuated. In fact, it could be argued that it is the host's symptomatic inflammatory response that is the problem, and that a dampening of pro-inflammatory mechanisms would be the primary aim of immunomodulation. However, it could also be argued that, as in the case of *Echinacea*, stimulating the immune system boosts anti-viral activity, leading to an early decrease in viral replication, and therefore to reduced symptoms. Unfortunately, these competing hypotheses have not yet been tested under adequate study designs. Evidence from randomized trials using steroids and nonsteroidal anti-inflammatories (eg. aspirin, ibuprofen, naproxen) for experimental colds has so far failed to provide clear evidence on the role of anti-inflammatory immunomodulation (Farr et al. 1990; Gustafson et al. 1996; Sperber et al. 1992; Sperber et al. 2000).

### Anti-inflammatory and antioxidant effects – *In vitro* and animal studies

*Echinacea*'s claims as an anti-inflammatory rest on both theoretical and observed inhibition of inflammatory mechanisms. Inhibition of hyaluronidase was among the earliest pharmacological properties attributed to *Echinacea* (Bauer, 1999a). Hyaluronidase hydrolyzes hyaluronic acid and chondroitin, allowing penetration of the ground substance by fluids containing pro-inflammatory cytokines. Inhibition of fibroblast activity and collagen-building has been reported from a number of laboratories (Bauer 1999a; Tunnerhoff and Schwabe, 2001). One experiment reported that both herb and root extracts from *E. purpurea* inhibited fibroblast-mediated collagen contraction (Zoutewelle, 1990). According to Bauer, cichoric acid has been implicated as the most potent of *Echinacea*-derived substances in terms of anti-hyaluronidase inhibition (Bauer, 1996). Wagner has reported lipoxygenase-inhibiting anti-inflammatory activity attributable to one of *E. purpurea*'s isobutylamides, dodecatrienoic acid (Wagner, 1989). Reported inhibition of cyclooxygenase and 5-lipoxygenase by alkamide-rich *Echinacea* extracts lends mechanistic credibility to reported anti-inflammatory effects (Müller-Jakic et al. 1994). Arachidonic acid metabolism and prostaglandin E<sub>2</sub> production were reduced by several *E. purpurea*

products in Rininger's laboratory (Rininger et al. 2000). Looking at inflammatory endpoints, an *E. purpurea* preparation was reported to have shown anti-inflammatory effects in experiments measuring rat paw edema responses to formalin, hyaluronidase, serotonin, and trypsin (Voitenko et al. 1996). Similar experiments using extracts from *E. angustifolia* have reported anti-inflammatory activity (Tragni et al. 1985; Tubaro et al. 1987; Tragni et al. 1988). Enhancement of free-radical scavenging activity has been reported by laboratories in the U.S. and Canada (Hu and Kitts, 2000; Rininger et al. 2000). Hu and Kitts reported anti-oxidant and free-radical scavenging activity, including suppression of oxidation of human low-density lipoprotein (Hu and Kitts, 2000). Despite these encouraging results, we are unaware of any randomized, blinded trials that have demonstrated clinically useful health-enhancing, anti-inflammatory or wound-healing properties.

### Anti-fungal effects – *In vitro* and animal studies

Extracts from *E. purpurea* have been attributed significant antifungal activities in a series of *in vitro* experiments testing activity against various *Saccharomyces cerevisiae* and various *Candida* species, including *Candida albicans*, the most common fungal cause of human skin disease (Binns et al. 2000). Ultraviolet-mediated and light-independent antimicrobial actions were observed following exposure to various *E. purpurea* root and herb extracts, including a number of commercial products. Other laboratories have also reported anti-*Candida* activity (Stotzen et al. 1992; Wildfeuer and Mayerhofer, 1994). For example, phagocytosis of *Candida* by *ex vivo* human macrophages and natural killer cells was reported to be enhanced following exposure to extracts of both *E. purpurea* and ginseng (See et al. 1997). Mouse macrophage activity against *Candida* has also been reported to be stimulated by *E. purpurea* polysaccharide exposure (Lohmann-Matthes and Wagner, 1989). Pretreatment with a polysaccharide-rich *E. purpurea* extract was reported to decrease the infection and death rates of immunosuppressed mice infected with *Candida* (Steinmüller et al. 1993).

### Anti-fungal effects – Human clinical trials

Coeugniet and Kühnast reported a trial testing an expressed juice of *E. purpurea* (Echinacin<sup>®</sup>) for ability to effect recurrent vaginal yeast infections. Women with laboratory-confirmed *Candida* infections were treated



**Table 2.** *Echinacea purpurea* Trials – Materials and Dosing.

Author	Species/Product*	Plant part	Daily Dosing**
Lindenmuth 2000	<i>E. purpurea</i> & <i>E. angustifolia</i>	herb & root	5 to 6 cups of tea qd initially
Turner 2000	Unknown	unknown	300 mg tid
Henneicke-von Zepelin 1999	<i>E. purpurea pallida</i> /Esberitox-N®	root	3 tablets tid
Brinkeborn 1999	<i>E. purpurea</i> /Echinaforce®	herb, root	2 tablets tid
Melchart 1998	<i>E. purpurea</i> & <i>E. angustifolia</i>	root	50 drops bid
Berg 1998	<i>E. purpurea</i> /Echinacin EC31	herb	8 cc qd
Höheisel 1997	<i>E. purpurea</i> /Echinagard®	herb	20 drops q2h 1st day, tid on subsequent days
Scaglione 1995	<i>E. purpurea</i> , rosemary, eucalyptus, fennel, vitamin C	root	4 tablets daily
Melchart 1995 (1988 trial) (also reported in Jurcic 1989)	<i>E. purpurea</i>	root	30 drops tid
Melchart 1995 (1989 trial)	<i>E. purpurea</i>	root	3 capsules daily
Melchart 1995 (1990 trial)	<i>E. purpurea</i>	herb, root	30 drops tid
Bräunig 1992	<i>E. purpurea</i> (2 doses)	root	90 drops qd; 180 drops qd
Schöneberger 1992 (Grimm 1999)	<i>E. purpurea</i> /Echinacin®	herb	4 cc bid
Reitz 1990	<i>E. purpurea pallida</i> /Esberitox-N®	root	3 tablets qd
Jurcic 1989 (Melchart 1995)	<i>E. purpurea</i>	herb?	intravenous
Coeugniet 1986	<i>E. purpurea</i> /Echinacin®	herb	injections (SC, IM, IV)
Vorberg 1984	<i>E. purpurea pallida</i> /Esberitox®	root	3 tablets qd
Calabrese (Unpublished)	<i>E. purpurea</i> /Echinagard®	herb	8 cc qd

\*Echinaforce® contains a direct extract from the above-ground parts (95%) and roots (5%) of *E. purpurea* Echinagard® (aka Echinacin®) contains a direct pressed extract from the above-ground parts of *E. purpurea* Resistan® contains extracts of *E. angustifolia*, *Eupatorium*, *Baptisia* and *Arnica* Esberitox-N® contains extracts from the roots of *E. purpurea*, *E. pallida* and *Baptisia tinctoriae*, and *Thuja occidentalis* Esberitox® contained *E. purpurea*, *E. angustifolia*, *Baptisia*, and *Thuja* & homeopathic dilutions of *Apis*, *Crotal*, *Silicea* and *Lachesis*

\*\*qd – Once a day; bid – Two times each day; tid – Three times each day; qid – Four times each day

with topical econazole, then administered either oral (N = 60) or injected Echinacin® (subcutaneous N = 20; intramuscular N = 60; intravenous N = 20), with 43 reserved as controls. Treatments continued for 10 weeks, and recurrence of yeast infection and response to the Meriux Multitest™ (antigenic skin test) were measured. Echinacin®-treated groups demonstrated increased skin reactivity and decreased recurrence of vaginal candidiasis over the 6-month monitoring period. While 60% of controls got new infections, only 5–17% of women in the treatment groups were diagnosed with recurrent vaginal infections (P < 0.05). Unfortunately, randomization and blinding methods were not described. Hence, we can only assume that allocation was non-random and blinding was not attempted.

### ■ Anti-cancer effects – Human clinical trials

Specific and nonspecific immune targeting of cancer cells forms the basis of successful mammalian re-

sponse to transformation of normal cells into cancerous ones. Although immune-stimulation makes good theoretical sense, few if any immune-stimulating therapies have proven effective in combating human cancer. A few modest attempts at using *Echinacea*'s immune-stimulating properties have been attempted. Lersch and colleagues treated patients with advanced liver cancer (N = 5) and advanced colorectal cancer (N = 15) with intramuscular *E. purpurea* juice, cyclophosphamide, and thymostimulin (Lersch et al. 1990; Lersch et al. 1992). Although increases in activities of natural killer cells, lymphokine activated T-cells and PMNs were claimed, no dramatic health benefits were noted. Survival rates similar to those expected without treatments were reported among *Echinacea*-treated patients. In another open trial, 23 patients with cancers (breast (N = 8), colorectal (N = 8), renal (N = 1), lung (N = 1), prostate (N = 2), uterus (N = 1) and melanoma (N = 1)) were treated with 3 ml per day of "Echinacea complex". No changes in measured cytokines were noted; disease progression and survival rates have not been reported. Isolation and synthesis of a diene olefin found

in *Echinacea* root oils and thought to have antitumor activity in a 1972 publication seems to have followed thousands of other early leads in the "war against cancer" into the dustbins of history (Voaden and Jacobson, 1972). We are not aware of any current trials testing *Echinacea* for cancer prevention or treatment.

### Bronchitis and pertussis – Human clinical trials

Clinically, bronchitis is distinguished from upper respiratory infection (URI) by the lack of nasal and throat symptoms, and by the prominence of cough, production of sputum, and fever (Oeffinger et al. 1997). Many experts consider URI and bronchitis to be different ends of the same spectrum, usually caused by viral infection and usually unresponsive to antibiotics (Becker et al. 1999; Bent et al. 2000). In 1988 Baetgen reported a retrospective analysis of 1280 children who had received either *E. purpurea* juice (Echinacin<sup>®</sup>) as an intramuscular injection (N = 468), antibiotics alone (N = 482) or a combination of the two (N = 330) (Baetgen, 1988; Melchart et al. 1994). The duration of illness in the *Echinacea*-only group was reported as shorter than that in the *Echinacea*-plus-antibiotics group, which was shorter than in the antibiotics-only group. As neither randomization nor blinding were attempted, and as data were collected and assessed retrospectively, any inference on effectiveness is highly suspect. However, the fact that 798 children were injected with juice from *E. purpurea* without major adverse consequences provides at least a modicum of safety data.

In 1984 Baetgen reported a retrospective analysis of 170 people with clinically-defined pertussis (whooping cough) who again received either *E. purpurea* juice (Echinacin<sup>®</sup>) as an intramuscular injection (N = 77), antibiotics alone (N = 30) or a combination of the two (N = 63) (Baetgen, 1984; Melchart et al. 1994). Again, the author claimed a duration benefit for the Echinacin<sup>®</sup> groups. Unfortunately, the open-labelled, non-randomized, retrospective methodology limits interpretation of these claims.

### Anti-viral effects – *In vitro* studies

Although the hypothesis that *Echinacea* works directly as an antibacterial or antiviral has been advocated, there is little direct evidence to substantiate or refute this claim. Eichler and Krüger reported that cultured cells infected with virus and exposed to *E. purpurea* juice demonstrated an increased rate of presentation of viral antigen (Eichler and Krüger, 1994). However, no changes in replication or viral load were noted. Ex-

tracts of *E. purpurea* were reported to inhibit viral replication in animal cell viral culture models (Skwarek et al. 1996). Eilmes reported that complex hydrophilic and lipophilic extracts demonstrated more viral-infection-inhibition than did concentrated single-band fractions (Becker, 1982). Viracea<sup>®</sup>, a "blend of benzalkonium chloride and phytochemicals derived from *Echinacea purpurea*" was reported to have antiviral activity against herpes virus in a human cell model (Thompson, 1998). Activity against influenza virus has also been reported (Parnham, 1996b). Although Berman et al. reported a "dramatic increase in immune-mediated HIV killing activity induced by *Echinacea angustifolia*" in a conference abstract (Berman et al. 1998), no article has yet been forthcoming, and no HIV studies specific to *E. purpurea* have yet been published.

### Anti-viral effects – An induced-cold human trial

Turner and colleagues have recently reported a trial testing the efficacy of *Echinacea* in preventing or ameliorating the effects of experimental colds induced by a cultured rhinovirus (Turner et al. 2000). Using an induced-cold model, participants were treated with an unknown type of *Echinacea* extract for 2 weeks, then challenged with rhinovirus and monitored for infection (ability to re-culture virus) and clinical colds (defined by symptoms). Rhinovirus infection developed in 22 of 50 *Echinacea*-treated participants (44%) and in 24 of 42 in the placebo group (57%). Of those infected, 11 (50%) of *Echinacea*-treated participants and 14 (59%) of placebo-treated participants developed clinical colds. These apparent absolute risk reductions of 13% and 9% were not statistically significant. The authors claim that their experiment demonstrates the "ineffectiveness of *Echinacea* for prevention of experimental colds". However, if the observed trends were real and generalizable to naturally acquired colds, a 13% effect is arguable clinically significant, similar to the benefits expected with many standard treatments, such as antibiotics for middle-ear or sinus infection (Glasziou et al. 1999; van Buchem et al. 1997). The product used in this trial is known imperfectly. Independent analysis was reported to find "0.16% cichoric acid and almost no echinacosides or alkamides." Although this phytochemical profile may indicate a fresh *E. purpurea* steam-extract, the lack of data on species, plant part, extraction method and dose make interpretation problematic (Dennehy, 2001). In any case, as induced single-strain viral infections are not representative of naturally-acquired colds, these results are not generalizable.

## ■ Prevention of upper respiratory infection – Human clinical trials

In 1992, Schöneberger reported a trial testing the preventive efficacy of *E. purpurea* juice (Echinacin) among 108 patients attending a clinical practice in Detelbach, Germany. Inclusion criteria required a history of 3 or more infections in the year prior to study. Participants were randomized to either Echinacin or a similar alcohol content, brown-colored placebo liquid prepared by the manufacturer (Madaus). Participants were asked to take 4 ml twice each day for 8 weeks, and were evaluated at baseline and again at 4 and 8 weeks with history, physical exam, and blood analyses. New infections during the study period were investigated in-person, and were graded mild, moderate or severe and also assessed for duration. Schöneberger reported a significant preventive efficacy, with 32.5% of the *Echinacea* group versus 25.9% of the placebo group remaining healthy, alongside severity and duration benefits of similar magnitude. According to Schöneberger, participants with a T4/T8 ratio of less than 1.5 prior to the study benefited the most. Interestingly, seven years later Grimm and Muller published an English-language write-up of this trial, providing a distinctly less favorable interpretation (Grimm and Müller, 1999). Without referencing the Schöneberger report, these authors describe the trial in great detail, concluding that “fluid extract of *Echinacea purpurea* did not significantly decrease the incidence, duration or severity of colds and respiratory infections (Grimm and Müller, 1999). However, they do note a non-significant trend toward benefit, with a relative risk reduction (RR) of 12% in the odds of catching a cold while taking Echinacin<sup>®</sup> (RR 0.88, 95% CI 0.60, 1.22).

In 1998 Melchart, Linde and colleagues reported a 3-armed preventive double-blind, randomized, controlled trial comparing extracts of *E. purpurea* root and *E. angustifolia* root with placebo (Melchart et al. 1998). Some 302 healthy volunteers were recruited and 289 were randomized to 1 of these 3 groups. Extracts were produced using a 30% ethanol solution and a 1:11 plant extract ratio. Participants took 50 drops (about 1 ml) twice daily Mondays through Fridays for the 12-week trial. A total of 244 actually finished the trial. Similar numbers withdrew among the 3 groups. No clear pattern of adverse effects was noted. In the *E. purpurea* group, 29% experienced at least one cold, compared with 32% in the *E. angustifolia* group and 37% in the placebo group. The trends toward benefit – a 20% relative risk reduction in the *E. purpurea* group and a 13% relative risk reduction in the *E. angustifolia* group – were not statistically significant. Blinding was tested by asking participants whether they believed that

they had taken *Echinacea* or placebo, with 53% guessing correctly, 22% incorrectly, and 25% refusing to guess ( $p < 0.01$ ). Although this is one of the very best trials to date, the demonstrated lack of concealment and the lack of power (the trial was “massively under-sized” according to the authors), render interpretation of these results problematic.

## ■ Treatment of upper respiratory infection – Human clinical trials

In 1992, Bräunig et al. reported a randomized controlled trial that tested two doses of an ethanol-water extract of *E. purpurea* root among 180 patients with upper respiratory infection. While “high dose” participants took 180 drops (900 mg) daily, participants randomized to “low dose” ingested 90 drops (450 mg) of the extract. Compared to placebo, statistically significant reductions in self-reported symptom severity were reported in the “high dose” group, with effect sizes ranging from 10% to 50%. Trends to benefit were noted in the “low dose” *Echinacea* group. However, although randomization and double-blinding were claimed, all participants taking placebo were assigned the low dose-regimen (90 drops daily) (Melchart and Linde, 1999). This means that true concealment of allocation (blinding) was not possible. Also, although duration of illness was apparently an *a priori* primary outcome, duration results were not reported.

In 1995 Scaglione and Lund reported a single-blind randomized trial of a combination product containing *E. purpurea* extract, rosemary, eucalyptus, fennel and vitamin C. Thirty-two adults were randomized to four tablets of the active treatment or placebo (glucose) and followed for severity (number of facial tissues used each day) and duration. Participants in the *Echinacea* group showed a mean duration of 3.37 days (SD = 1.25) compared with 4.37 days (SD = 1.57) in the placebo group ( $p < 0.01$ ). The number of tissues used in the *Echinacea* group was 882, compared with 1,168 in the placebo group. Limitations of this study include lack of evaluator blinding, lack of testing for participant blinding, lack of symptomatic severity measures, poorly defined measures of duration, and small sample size.

Hoheisel and colleagues in 1997 reported a trial of standardized *E. purpurea* juice versus placebo among 120 participants with new onset common cold in a furniture factory work setting in Falköping, Sweden. The active product was liquid Echinagard (aka. Echinacin), produced by the study’s sponsor, Madaus AG, Köln, Germany. Participants with a history of at least 3 colds in the prior 6 months were enrolled “at first sign of a cold”, then “randomized” to either active treatment or a placebo (a liquid “identical in colour and ethanol con-

centration"). Although self-reported symptoms recorded daily in diaries "did not differ between the groups", the authors claim a 20% absolute and 50% relative reduction in the number of active group participants who went on to develop "a real cold". The definition of "a real cold" is not provided, but appears to have been created and applied retrospectively, after unblinding. Of those who developed a "real cold", a median duration of 8 days is reported for the placebo group versus 4 days for the *Echinacea* group. There are at least 3 significant problems here: 1) undefined, retrospectively – created measures, 2) the authors claim major reductions in chances of developing a "real cold," but also report that self-reported symptom severities "did not differ" between active and placebo groups, and 3) there is no report of testing for participants' ability to discern whether they were taking placebo or active treatment.

Brinkeborn et al. (1999) reported a double-blind, randomized trial comparing three formulations of *E. purpurea* tablets with a similar-appearing placebo. A total of 246 adults with new onset URI were randomized to placebo or to 1 of 3 active preparations: 1) Echinaforce (95% herb, 5% root), 2) a 7:1 Echinaforce concentrate, and 3) a "special" *E. purpurea* root extract. Twelve symptoms were assessed (using a 4-point severity scale) every day by participants and on days 1 and 8 by a physician-examiner. Per protocol and intention-to-treat analyses favored all 3 preparations over placebo, with trends toward greater benefit noted in the Echinaforce concentrate group. Randomized allocation and concealment methods were adequately described, but some question of concealment was left open with the authors' statement that the treatments "could almost not be distinguished from one another by their smell or taste", and by the fact that no report was made as to whether the participants thought they were taking placebo or active treatment. Reported benefits were greater for physician-assessed than for patient-assessed symptoms. Although statistical significance was reached, clinical significance remains in doubt, as day-by-day symptom scores were not reported, and as no duration benefits were noted.

Also in 1999, Henneicke-von Zepelin and co-authors reported a multi-center, double-blind, randomized controlled trial comparing Esberitox-N<sup>®</sup> to placebo in the early treatment of upper respiratory infection. Esberitox-N<sup>®</sup> is a standardized combination of 3.75 mg each of ethanol-water extracts of the roots of *E. purpurea* and *E. pallida*, along with extracts of *Thuja occidentalis* herb (2mg) and *Baptisia tinctoria* root (10mg). In this trial, some 263 participants "with an acute common cold" attending 15 family practice clinics were randomized to Esberitox-N<sup>®</sup> or to placebo. Dosing was 3 tablets 3 times per day for 7 to 9 days. Placebo and Esberitox-N<sup>®</sup> tablets "were similar in taste, smell and ap-

pearance, and blistered using opaque foil". Monitoring was accomplished by daily self-report, assessing 18 symptoms using 10-point Likert severity scales. Clinician assessments were made at days 1, 4, and 8. General well-being was assessed by Welzel-Kohnen color scales. "Patients and investigators remained blinded throughout the whole study ... until database lock". An intention-to-treat analysis yielded statistically significant benefit to Esberitox-N<sup>®</sup> for all symptom-based outcome variables (rhinitis score, bronchitis score, overall severity, general well-being), with effect sizes ranging from 20% to 33%. Analysis of physicians' "clinical global impressions" failed to show benefit to Esberitox-N<sup>®</sup> over placebo, and were not reported in detail. It was also not reported whether the participants thought they were taking placebo or *Echinacea*, hence evidence of adequate concealment is only moderate.

Recently, Lindenmuth and Lindenmuth a trial in which 95 employees of a nursing and rehabilitation center were treated with an *Echinacea* tea beginning "at the earliest sign of cold or flu symptoms (runny nose, scratchy throat, fever)". Each presenting participant was alternately given either a packet of 21 Echinacea Plus<sup>®</sup> tea bags or a packet of similar-appearing placebo tea bags (Eater's Digest<sup>®</sup>), and instructed to brew and drink "5 or 6 cups of tea on the first day of symptoms and titrating down 1 per day for the next 5 days". Outcomes were measured by "a simple three question questionnaire" which was "given to subjects 14 days after they started the program". These three questions asked the participants to use 5-point Likert scales to retrospectively judge: 1) overall effectiveness, 2) length of illness, and 3) "number of days it took to notice a difference". T-test comparison of means yielded significant ( $p < 0.01$ ) differences favoring the *Echinacea* group. No mention was made of whether the participants thought they took *Echinacea* or placebo, hence evidence of blinding was either not assessed or not reported. With alternate allocation and distinctly different tasting preparations likely influencing concealment, the results of this trial are suspect.

Most recently, Schulten and colleagues (2001) published an account of a "double blinded" randomized trial of 5mL of Echinacin, "pressed juice from fresh flowering purple coneflower [1.7–2.5 : 1], stabilized by ethanol ... twice daily for 10 days". The trial was sponsored by Madaus AG and was carried out among employees of the Madaus plant in Cologne, Germany. Inclusion criteria were defined as "an incipient infection of upper respiratory tract" with at least one of the Jackson criteria in the 24 h prior to study entry (Jackson et al. 1958; Jackson et al. 1960; Jackson et al. 1962). Using a predefined randomization code, 80 consecutive participants were assigned to the *Echinacea* product or to a placebo reported as "indistinguishable in

terms of appearance, taste, smell, colour and packaging." Severities were assessed using Jackson's 4 point (absent-mild-moderate-severe) system. The primary outcomes were prospectively defined as 1) duration (defined as the number of days from study entry to "the last day on which the cumulative score was greater than 1") and 2) full-blown-cold severity (reaching 5 Jackson points "and/or the patient reported the subjective sensation of having a cold"). As the major finding, the authors claim a 6.0-day median duration in the *Echinacea* group versus 9.0 days in the placebo group, "assigning a zero time for patients without a complete picture." Unfortunately, duration data are not adequately reported (no measures of variability), and the survival curve figure purporting to demonstrate *Echinacea* superiority gives *Echinacea* a 13% advantage at day zero, before any treatment effect could have occurred. Three patients dropped out (2 *Echinacea*, 1 placebo) and 7 were excluded from the per protocol analysis because they took non-protocol doses or "because no cold symptom started within the last 24 h before Visit 1" (5 placebo, 2 *Echinacea*). The authors state that results of the intention-to-treat and per-protocol analyses "did not differ", but do not provide adequate evidence of that claim. Areas under the Jackson symptom severity curves tended to favor *Echinacea*, and reached statistical significance for nasal congestion and drainage. No evidence of successful blinding is reported.

## ■ Safety

*Echinacea* appears to be a relatively safe herbal medicine (Barrett et al. 1999a; Blumenthal et al. 2000; Bone, 1997b; Cupp, 1999; De Smet et al. 1997; Ernst, 1998; Fugh-Berman, 2000; Melchart and Linde, 1999; Melchart et al. 2000; Mills and Bone, 2000; Percival, 2000; Rotblatt, 1999). Although there have been several reports of allergic reactions to *Echinacea*, no deaths have been reported (Donohue, 2000). No dose-dependent adverse effects have been characterized, and no overdoses have been reported. Contraindications are theoretical. Interactions are unknown.

Perhaps the most convincing argument for safety comes from the ratio of reported serious adverse effects (less than 100) to the estimated number of courses of treatment (more than 10 million). In the United States, *Echinacea* is one of the most commonly used herbal medicines. *E. purpurea* is the predominant *Echinacea* species used. Herbal medicines are estimated to be taken by between 15% and 40% of American adults in a given year (Astin, 1998; Eisenberg et al. 1998; Landmark Healthcare, 1998). According to Brevoort, *Echinacea* accounted for about 10% of the U.S. herbal mar-

ket in 1998 (Brevoort, 1998). Using these numbers, we can estimate that 1–4% of the general population uses *Echinacea* in a given year. Using these numbers and a U.S. population of approximately 200 million U.S. adults and self-treating adolescents, we can estimate that 2–8 million Americans use an *Echinacea* product at least once in a given year. With no deaths and few significant adverse effects reported, the overall risk ratio appears quite favorable, especially when compared with the thousands of deaths attributed to over-the-counter, non-steroidal, anti-inflammatory drugs (aspirin, ibuprofen, naproxen) and decongestants (phenylpropanolamine, pseudoephedrine) (Bates et al. 1995; Brewer and Colditz, 1999; Cetaruk and Aaron, 1994).

## ■ Contraindications

The German Commission E has approved oral preparations of *E. purpurea*, with a suggested time limit of 6 weeks (Blumenthal et al. 1998; Blumenthal et al. 2000). Chronic progressive immuno-mediated diseases such as tuberculosis and multiple sclerosis are listed as contraindications. These theoretical contraindications are based on the harm that could result if the immune-mediated inflammatory components of these diseases were exacerbated by *Echinacea*'s immunostimulating properties. Although there is no convincing empirical evidence to support these contraindications, they are reasonable from a theoretical pathophysiological perspective. More evidence is clearly needed.

## ■ Risks of adverse effects

In Germany, during the years 1989 to 1995, a total of 13 adverse events possibly associated with the use of Echinacin<sup>®</sup> (pressed juice from *E. purpurea* herb) were reported to the Germany BGA authority (Parnham, 1996a). Only 4 of these, all allergic skin reactions, were judged causally related to *Echinacea* exposure. During the same time period, several million people were thought to treat themselves or to receive a doctor's prescription for an *Echinacea* product. One study of 1,032 people patch-tested for skin sensitivity to *Echinacea* found 2 positive inflammatory reactions (De Smet et al. 1997).

In 1998, Mullins reported a case in which a woman with atopy ingested a liquid formulation combining *E. purpurea* and *E. angustifolia* root extracts immediately before experiencing "burning of the mouth and throat ... tightness in the chest, generalized urticaria, and diarrhoea" (Mullins, 1998). The incident precipitated a 2 hour visit to the emergency department, during which "her symptoms resolved completely". Ap-

parently Dr. Mullins' interest was piqued, as he later reported the results of a systematic search revealing 23 possible cases of *Echinacea*-related allergy in Australia (American Academy of Allergy, 2000; Donohue, 2000; Mullins and Heddle, 2002). Another report, by Dr's Soon and Crawford, detailed a single case of erythema nodosum – an acute inflammatory/immunological skin reaction – which they felt was “temporally and perhaps causally associated with the use of *Echinacea*” (Soon and Crawford, 2001). Together, these reports suggest that allergy to *Echinacea* exists, but is rare.

Parnham has reviewed the literature on the “benefit and risks of the squeezed sap of the purple coneflower (*Echinacea purpurea*)”, much of it in German, untranslated, and available only with manufacturer permission (Parnham, 1996a; Parnham, 1999). For example, an unblinded study of 1,231 children aged 2 to 20 treated with Echinacin<sup>®</sup> lozenges found a 5% overall rate of reported adverse effects. Of the 62 reported problems, unpleasant taste was the most frequent, with 21 reports (1.7%). Nausea, vomiting, sore throat, abdominal pain, diarrhea, and difficulty swallowing were reported by 6 or less (<0.5%) persons each. A number of smaller open trials and case series have provided similarly reassuring results. Parnham reports case series by Röseler (226 women) and Moell (120 women) of patients with post-partum infection who were injected intravenously with 0.1 ml to 1.2 ml of *E. purpurea* herb juice (Echinacin<sup>®</sup>) without observed ill effects (Parnham, 1999).

As detailed above, dose-response and dose-risk data are sparse, hence dosing recommendations must be made with caution. There are no good data to guide us in recommending duration of use, other than the general conclusion that treatment studies (short-term dosing) appear more positive than do prevention (extended-dose) studies.

### Pregnancy and reproductive toxicity

As with nearly all medicines, safety of *Echinacea* in pregnancy has not been determined (Gallo and Koren, 2001). Very little relevant data is available. In one study, a cohort of 206 women who used *Echinacea* during pregnancy were risk-matched with 206 controls and assessed for adverse effects (Gallo et al. 2000). Similar numbers of stillbirths, chromosome abnormalities and malformations were found in the 2 groups. *Echinacea* species and plant part were not detailed in this study. The authors concluded that “gestational use of *Echinacea* during organogenesis is not associated with an increased risk for major malformations”. It would perhaps have been more appropriate to conclude that the study supports the low likelihood of major or frequent adverse outcomes. Although no evidence of

increased risk was noted, the study lacked the statistical power and methodological rigor to determine pregnancy-associated risks with confidence.

### Toxicology

Animal experiments have failed to demonstrate significant risks. According to Mengs, in oral doses greater than 15 g/kg body wt. and intravenous doses greater than 5 g/kg body wt., it was impossible to kill either rat or mouse. This group concluded that a lethal dose could not be found, hence the LD<sub>50</sub> value was incalculable (Menges et al. 1991). In a different series of experiments, Lenk reported that injection of varying doses of concentrated polysaccharide fractions in 18 mice led to an estimated lethal dose (LD<sub>50</sub> value) of 2500 mg/kg body wt. (Lenk, 1989). Because of the small sample size, type of *Echinacea* product and mode of administration, these results are not generalizable to human use. However, the wide therapeutic window of safety between the typical doses consumed orally (200 to 2,000 mg in 50–80 kg adults = 2.5–40 mg/kg body wt.) and the estimated intravenous lethal dose of 2,500 mg/kg body wt. is reassuring, especially when compared with much less favorable therapeutic windows for common over-the-counter medications such as analgesics and decongestants.

Laboratory analysis of blood, urine, and organ specimens from animals treated with *Echinacea* products provides further evidence of safety. Extended (4 week) dosing of rat and mouse up to 8 g/kg body wt./day has similarly failed to cause measurable adverse effects, with RBC, WBC, platelets, liver enzymes, creatinine, urea, cholesterol, triglycerides, blood glucose and body weight as measured endpoints (Menges et al. 1991; Mengs et al. 2000). Studies looking for chromosome aberration and sister chromatid exchange in bacteria and cultured animal cells have also found no evidence of mutagenicity (Menges et al. 1991). One polysaccharide isolated from *E. purpurea* showed no evidence of mutagenicity in a genotoxicity human lymphocyte assay (Schimmer et al. 1989). Maximum feasible oral and intravenous doses of ethanol-stabilized fresh pressed juice of *E. purpurea* have similarly failed to cause measurable damage in mice or rats (Menges et al. 2000).

### Phytochemistry and Standardization

From the reports of laboratory assays of *Echinacea*'s immunomodulatory activities noted above, it is clear that no single agent or class of agents is solely responsible for all of the observed effects. Instead,

*Echinacea*-derived alkylamides, caffeic acid derivatives (cichoric, chlorogenic and cafeoyltartaric acids) and other phenol containing compounds, glycoproteins (many diverse forms), and polysaccharides (arabino-galactans, fructofuranosides and heteroxylans) all appear to be active and contributory to immunostimulatory (phagocyte-enhancing) effects (Bauer, 1998; Bauer, 1999b; Bodinet et al. 1993; Bone, 1997a; Emmendorfer et al. 1999; Perry et al. 1997; Willigmann et al. 1993). The concentration of the suspected active agents varies by species, plant part, season, and growing conditions (Li, 1998; Mazza and Cottrell, 1999; Perry et al. 1997; Shalaby et al. 1998; Sloley et al. 2001). Active constituents also vary in concentration depending on the method of extraction employed (Bauer, 1999a; Binns et al. 2001; Ganzera et al. 2001). Unfortunately, as there is no consensus as to which phytochemical constituents are active, there is as yet no consensus as to which should serve as standardization markers (Bauer, 1999b; Bauer, 2000; Perry et al. 2001; Schug and Blume, 2000).

## Conclusions

Although *Echinacea purpurea* is a relatively well-studied medicinal plant, there are still many gaps in the knowledge base. The most widely reported pharmacological activity – immunomodulation – is only partially understood. *In vitro*, animal, and human studies have demonstrated the ability of various *E. purpurea* extracts to enhance the activities of various immune cells. Stimulation of *ex vivo* macrophages to engulf particles and to secrete cytokines has been reported by a number of reputable laboratories (Bauer, 1999a; Burger et al. 1997; Rininger et al. 2000). Stimulation of lymphocytes and natural killer cells has also been reported (See et al. 1997; Sun et al. 2001). Human studies testing oral ingestion have yielded mixed results (Bauer 1999a; Melchart et al. 1995). Active constituents, bioavailability, pharmacokinetics, physiologic pathways, and importance to human health are not known with sufficient detail or confidence. Risks appear to be minor, with no known dose-dependent adverse effects or drug interactions.

The most widespread use, treatment of acute upper respiratory infection, is tentatively supported by the available literature (Barrett et al. 1999b; Barrett, 2000; Giles et al. 2000; Gunning, 1999; Melchart and Linde, 1999; Melchart et al. 2000; Messerschmidt, 2001). Reduction of symptoms with early treatment has been reported in several moderate quality randomized controlled trials (Bräunig et al. 1992; Hoheisel et al. 1997; Brinkeborn et al. 1999; Henneicke-von Zepelin et al. 1999; Schulten et al. 2001). Benefits appear to be a

modest, with a 10–40% reduction of symptoms as the most widely reported outcome. Benefit as a cold preventative appears marginal, at best, with an estimated 5–15% effect size in the best trial to date (Melchart et al. 1998). However, if *Echinacea*'s reported minor-to-moderate benefits as a cold treatment are real, the implications at a population level are significant, as the common cold is humanity's most universal illness. In addition to the discomfort and loss of productivity due to colds and flu-like syndromes, deaths among high-risk persons are not uncommon (Abdullah, 2000; Evans and Kaslow, 1997; Gwaltney, 1985; Monto, 1995; Temte, 2000). Although the published evidence to date supports the safety and perhaps the effectiveness of *E. purpurea* preparations as early treatment for the common cold, the quality of the evidence is limited; hence more and better research is needed before more definitive recommendations can be made.

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