The Longwood Herbal Task Force

(http://www.mcp.edu/herbal/default.htm) and

The Center for Holistic Pediatric Education and Research

Echinacea (*E. angustifolia, E. pallida, and E. purpurea*)

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Primary use: Prevention and treatment of upper respiratory tract infections (URTI).

Other purported benefits: Prevention and treatment of viral, bacterial and fungal infections such as otitis media, pharyngitis, sinusitis, Candidiasis, cystitis; complementary therapy for cancer chemotherapy to support the immune system; chronic fatigue syndrome; acquired immunodeficiency diseases (AIDs); snake bites[1,2,3].

Overview

Data from *in vitro* studies, animal studies and randomized, controlled trials in adults support the use of echinacea in preventing and treating the common cold. Data are conflicting regarding the best formulations (products), dosages and duration of therapy. There are no studies reporting the effectiveness or safety of using echinacea to prevent or treat URTI in children or to prevent or treat serious bacterial or fungal infections in adults or children. Use of echinacea to support the immune system in treating cancer, chronic fatigue or immunodeficiency states remains experimental. Despite its long historical use as a wound healing agent, there are no controlled trials suggesting benefits in treating specific dermatologic conditions. Echinacea appears to be safe for oral and topical use, except for patients allergic to it. Widespread recommendations to limit oral use to less than eight weeks or to avoid it in patients with hepatic disease or immune disorders appear to be based on hypothetical concerns, but have not been supported by scientific data.

Historical and Popular Uses

A perennial plant native to North American, echinacea was used by the Plains Indians to treat fever and respiratory infections and by the Delaware Indians to treat venereal disease[4]. A paste made of the entire mashed plant was used topically to treat snake bites, stings, burns, and swelling of the lymph glands ("mumps"). The roots were chewed or the juice ingested to treat sore gums, toothaches, and sore throats[5]. European colonists soon began to use echinacea and to send the valued plant back to European markets.

In the 1800's *Echinacea angustifolia* was used as an all-purpose "blood purifier" and an anti-infective agent[5]. Echinacea was used to treat diphtheria, small pox, scarlet fever, and meningitis. In the late 1800's, *E. angustifolia* was the most commonly used plant remedy in the United States. Although American use of echinacea began declining in the 1920's, European demand for the herb had grown significantly, outstripping the unsteady American supply. In Germany, the Madaus Company imported echinacea seeds (mistakenly receiving *E. purpurea* instead of *E. angustifolia*) from the United States to grow their own plants and make the now-popular product Echinacin®. Most subsequent clinical research has used *E. purpurea* in the form of Echinacin®.

Recently, its anecdotal successes and a few scientific studies have propelled echinacea back to the top ranks of American herbal sales. Nowadays it is used primarily as a non-specific immunostimulant and to prevent and treat upper respiratory infections (URTI), but occasionally also as a primary or complementary therapy to prevent or treat ear infections, yeast infections, urinary tract infections, furuncles, carbuncles, pharyngitis, tonsillitis, and prostatitis[6]. It is used less commonly as a topical preparation to enhance healing for minor wounds, eczema, burns, psoriasis, herpes, and other dermatologic conditions. Echinacea is also included in a number of dental and cosmetic preparations.

Botany

Medicinal species: *Echinacea angustifolia* (Narrow-leafed Purple Coneflower), *E. pallida* (Pale Purple Coneflower), *and E. purpurea* (Purple Coneflower) are the species most often used medicinally, but six other species of Echinacea have been identified[7,8]; two are on

the endangered species list[1]. The various species are often misidentified. As recently as 1955 *E. angustifolia* was classified as a variety of *E. pallida*[9]. Much of the early research on *E. angustifolia* and *E. purpurea* was probably actually conducted on *E. pallida* , and studies published prior to 1987 must be viewed with suspicion in terms of the actual species being evaluated[10],[11],[12]. Echinacea products have also been frequently adulterated with another similar appearing plant, Missouri snakeroot (*Parthenium integrifolium)*, which has none of the same pharmacologic actions. In products made from *E. pallida* and *E. angustifolia*, the roots are typically used, whereas *for E. purpurea*, juices from the fresh leaves, stems and flowers are most often used, though roots are sometimes included[13].

Common names: "Echinacea" comes from the Greek *echinos*, meaning hedgehog or sea-urchin, because of its conical spiny seed heads. Its common names include: Black Sampson, Cock Up Hat, Comb Flower, Indian comb, Indian Head, Kansas Snakeroot, Kansas Coneflower, Purple Coneflower, Red Sunflower, Rudbeckia, Scurvy root, Snakeroot, and "Sonnenhutkraut" (Ger)[11],[14]. Missouri Snakeroot (*Parthenium integrifolium*) which has often been a contaminant (intentional and unintentional) in products sold as echinacea[15].

Botanical Family: Asteraceae/Compositae, which also includes calendula, chamomile and feverfew

Plant description: Echinacea plants are herbaceous perennials reaching 10–60 cm in height. The stem ascends either from a vertical taproot (*Echinacea angustifolia*) or branched, fibrous roots (*Echinacea purpurea*). As members of the Compositae family, each "flower" or daisy-like head unit is actually a conglomeration of many tiny flowers. The inner (disc) flowers end in spines, and are surrounded by droopy outer (ray) flowers with teeth at their ends. Echinacea is characterized by spiny flowering heads, with an elevated receptacle which forms the "cone". Colors of the disc flowers range from green to red-brown, and the ray flower petals may be white, pink, or purple. Echinacea plants are resilient and drought resistant, but grow slowly.

Where it's grown : Indigenous to United States and Canada. It has been grown commercially in Germany since the1930s.

Biochemistry

Echinacea: Chemical Constituents

- Carbohydrates: polysaccharides (arabinogalactan, xyloglycan, echinacin), inulin
- Glycosides: caffeic acids and derivatives (cichoric acid, echinacoside); cynarin, a quinic acid in *E. angustifolia*[16]
- Alkaloids: isotussilagine, tussilagine in *E. angustifolia* and *E. purpurea*
- Alkylamides (alkamides), e.g., echinacein
- Polyacetylenes[17]; germacrene sesquiterpene alcohol[18]
- Others: fatty acids, essential oil, phytosterols, and others

The various echinacea species contain numerous chemical constituents. There is still no consensus on exactly which of these is the most active immunomodulator.

Some experts believe that the polysaccharides are the primary active ingredients for immune modulating effects[19,20,6]. *Arabinogalactan* is a 75,000 dalton, acidic polysaccharide which generates an oxidative burst and induces selective cytokine production (TNF- α, IL-1, interferon-B) in mouse macrophages, and causes specific toxicity to certain tumor cell lines, to *Leishmania* intracellular parasites, and *Candida albicans* [21,22]. There is a slight proliferative effect on B lymphocytes, but no direct stimulation of T lymphocytes. The molecular site of action remains unknown, and it is unclear whether or not the same mechanism is responsible for both macrophage and neutrophil stimulation. The polysacccharide level may be severely reduced or lost during processing and storage.

Echinacin is credited with wound healing effects, presumably by inhibiting hyaluronidase and stimulating the growth of fibroblasts[6].

Cichoric acid is a polar *caffeic acid* derivative, concentrated in the roots and flowers of *E. purpurea,* and to lesser degrees of the other species[5,23,24]. Many products are standardized for *echinacoside* content (found primarily in *E. pallida*), which was once thought to be a major active ingredient, but is now believed to be minor, aside from its role in species identification[25].

The pyrrolizidine *alkaloids*, isotussilagine and tussilagine, are found only in trace amounts in *E. angustifolia* and *E. purpurea*; due to their unique chemical structure, they are not believed to be hepatotoxic like the pyrrolizidine alkaloids in other plants[6].

Amides are the principle lipophilic constituents of *E. purpurea* and *E. angustifolia* roots[26,27]. The *isobutylamides* found in high concentrations in the roots of *E. angustifolia* and *E. purpurea* are thought to cause echinacea's topical effect, which is often described as tingling or tongue numbing[26,28]. Isobutylamides from *E. purpurea* and *E. angustifolia* roots also inhibit arachidonic acid metabolism to inflammatory prostaglandins and may account for some of echinacea's anti-inflammatory effects[29]. The alkylamide content varies over *E. purpurea's* life cycle, gradually decreasing in the aerial parts and increasing in the roots as the plant matures[30]. The alkylamides from the roots of *E. purpurea* and *E. angustifolia* contain different structures, but the aerial portions contain similar compounds[28]. *Echinacein* is an unsaturated amide found in the roots of *E. pallida* and *E. angustifolia*; it is toxic to house flies[31].

Polyacetylenes and *polyenes* are the major lipophilic constituents of *E. pallida* roots, which contain very low concentrations of amides[32]; the polyacetylenes are very susceptible to auto-oxidation, making the chemical composition of the roots highly dependent on processing and storage conditions[12]. *E. angustifolia* is typically devoid of these polyacetylenes[12].

Terpenoids previously isolated from *E. purpurea* (e.g. germacrene) have been attributed more recently to the similar appearing plant, *Parthenium integrifolium*, which is a frequent contaminant of echinacea products[6].

Given the multiple chemical constituents in echinacea and the different compounds present in different parts of the plant and in different species, the actual active ingredient for its immunomodulating effects is not known. Many herbalists simply conclude that the effects are due to a complex interaction among the ingredients, but this assertion has not been formally evaluated.

Experimental Studies

Echinacea: Potential Clinical Benefits

1. Cardiovascular: none
2. Pulmonary: Prevention and treatment of upper respiratory tract infections (URTI): see Immune modulation and Antimicrobial
3. Renal and electrolyte balance: none
4. Gastrointestinal/hepatic: none
5. Neuro-psychiatric: none
6. Endocrine: none
7. Hematologic: none
8. Rheumatologic: none
9. Reproductive: none
10. Immune modulation: Immunostimulant; anti-inflammatory; also see Antimicrobial: antiviral
11. Antimicrobial: Antibacterial, antiviral, antifungal
12. Antineoplastic: Complementary immune support for chemotherapy
13. Antioxidant: none
14. Skin and mucus membranes: Vulnerary (wound healing)
15. Other/miscellaneous: none

1. **Cardiovascular:** none
2. **Pulmonary:** Prevention and treatment of upper respiratory tract infections: see Immune modulation and Antimicrobial
3. **Renal and electrolyte balance:** none
4. **Gastrointestinal/hepatic:** none
5. **Neuro-psychiatric:** none
6. **Endocrine function:** none
7. **Hematologic:** none
8. **Rheumatologic:** none
9. **Reproductive:** none

10. **Immune modulation:** Immunostimulant; anti-inflammatory

a. Immunostimulant

i. *In vitro data*: In one study in mice treated with water soluble extracts of *E. angustifolia* (Echinacosid), no effects on phagocytosis were noted[10]. In other studies, incubating mouse serum with polysaccharides from Echinacea's (*E. purpurea, E. angustifolia and E. pallida*) roots stimulated the proliferation of bone marrow cells and promoted phagocytosis by macrophages; there was no effect on T lymphocytes[21,33,34,35]. In isolated, perfused rat livers, echinacea extracts (Esberitox) enhanced phagocytosis[36].

In human polymorphonuclear (PMN) cells, echinacea's polysaccharides and the fresh juice enhanced spontaneous motility and phagocytosis[37]. In a dose-dependent fashion, the polysaccharides and fresh juice of *E. purpurea* induced human macrophages to produce TNF–α, IL-1, IL-6 and IL-10 cytokines, enhanced leukocyte mobility and increased killing of *Staphylococci*[38,21,22,39,40]. Echinacea extracts appear to induce non-specific T cell activation *in vitro*[41,33].

When *E. purpurea* extract was added to blood from normal, AIDS, and CFS patients in concentrations of at least 1 μg/ml, there was a significant dose-response in both the antibody-dependent cellular cytotoxicity (ADCC) and natural killer (NK) cell activity for all three groups[2]. Echinacea extracts also appeared to enhance interferon levels[42,43].

ii. *Animal data*: Giving mice an ethanolic extract of echinacea roots led to increased phagocytosis by macrophages and neutrophils. The rate was tripled by *E. purpurea*, and doubled by *E. pallida* or *E. angustifolia*[35]. Giving mice *E. angustifolia* extracts orally for five to seven days induced general immunostimulatory effects including enhanced phagocytosis and metabolic activity in peritoneal macrophages[44,45].

In immunosuppressed mice, prophylactic treatment with echinacea polysaccharides prior to infection with *Candida albicans* reduced renal Candida load by 80%, compared to controls. Similarly, echinacea treatment prior to infection with a

lethal dose of *Listeria monocytogenes* reduced the bacterial counts in both liver and spleen by 95% compared to the levels in control mice. By between days 4 and 6 following infection, all untreated mice died, while 68% of those that received polysaccharides lived[46]. In a similar study in immunodeficient mice, treatment with *E. purpurea* polysaccharide led to enhanced production of TNF-α and enhanced cytotoxicity against *Leishmania enrietti*, and protected the mice against lethal infections with *Listeria monocytogenes* and *Candida albicans*[46].

iii. *Human data*: A 1994 systematic review of 26 controlled clinical trials concluded that most studies were not methodologically rigorous, but that echinacea was an effective immunomodulator; however, the specific clinical indications, most efficacious product and dosing schedule had not been established[47]. For example, in a double-blind study, 24 healthy men were given oral Echinacin® (*E. purpurea*) administered as 30 drops, 3 times a day. After five days, isolated neutrophils from the Echinacin®-treated group showed significantly increased phagocytic activity (+120%) compared to the placebo group[48],[42].

Several European studies have evaluated the immunologic effects of parenteral administration of echinacea. Injecting five healthy adults with 5 mg of *E. purpurea*-derived polysaccharides induced adherence of polymorphonuclear cells (PMN) to blood vessels, migration of both PMNs and monocytes from bone marrow into peripheral blood, and enhanced serum levels of C-reactive protein (CRP); there were no significant increases in TNF–α, neopterin, IL-1B, C3, or IL-6[38]. In 12 healthy men who were given Echinacin® by intramuscular injection daily for four days, there was a statistically significant rapid increase in granulocyte phagocytosis against *C. albicans*, with phagocytosis decreasing slowly after Echinacea was discontinued[42].

Repetitive parenteral dosing may have different effects than a one time admnistration. In adults given a single 2 mL injection of echinacea, cell mediated immunity was enhanced; however, when the injections were given daily for two weeks, cell mediated immunity was depressed[49]. Similarly in another study, repeated

parenteral administration led to blunting of the immune response; it recovered completely after one week without injections[40]. Based on the results of these studies on parenteral administration, many herbalists have concluded that chronic daily use of any type of echinacea may depress the immune response. This has led to widespread recommendations that echinacea should not be taken for prolonged periods to avoid inhibiting immune function. Also see below in the antimicrobial: antiviral section.

b. Anti-inflammatory

i. *In vitro data*: In assays of sheep and porcine tissues, the isobutylamides from *E. angustifolia* roots inhibited the activity of cyclooxygenase and lipoxygenase[50].

ii. *Animal data*: In the rat paw and rat ear model of inflammation, rats that received prophylactic parenteral treatment with Echinacea Polysaccharidic Fraction (EPF) (from *E. angustifolia*) had significantly less edema and inflammation, in a dose-dependent manner, than their controls[19]. In similar studies, oral pre-treatment with an *E. angustifolia* extract from either leaves or roots protected against experimentally induced inflammation[51,52].

iii. *Human data*: There are no controlled trials evaluating the clinical anti-inflammatory effects of echinacea in adults or children.

11. **Antimicrobial:** Antibacterial, antiviral (URTI prophylaxis; URTI treatment), antifungal

a. Antibacterial

i. *In vitro data*: A multi-herb formula including echinacea had *in vitro* activity against several bacteria including *E. coli, P mirabilis, Pseudomonas aeruginosa*, and *Staphylococcus aureus*[53].

ii. *Animal data*: none

iii. *Human data*: There are no controlled trials evaluating the effectiveness of any echinacea product in treating bacterial infections such as otitis media, sinusitis, pharyngitis, cystitis or pneumonia.

b. Antiviral

i. *In vitro data*: In cultures of mouse cells, treatment with aqueous *E. purpurea* extracts (Echinacin®) for four to six hours prior to exposure to Influenza and Herpes viruses

caused 50-80% resistance to infection for 24 hours after exposure; by 48 hours, the cells were again sensitive to infection[54,55,56].

ii. *Animal data*: none

iii. *Human data*: URTI prophylaxis; URTI treatment

a. **URTI (upper respiratory tract infection) prophylaxis**: Evidence from randomized controlled trials on prophylaxis has been conflicting, and studies have been of mixed quality. No studies have been published on the effectiveness of any echinacea product in preventing childhood upper respiratory tract infections.

Two trials reported no significant benefits of using echinacea for URTI prophylaxis. In one double-blind, placebo controlled, randomized controlled trial of 302 healthy adults, neither *E. angustifolia* nor *E. purpurea* root extracts (50 drops of ethanolic extract twice daily for 12 weeks) had a statistically significant effect in preventing upper respiratory tract infections; the authors stated that their sample size was too small to reliably detect an improvement as small as 10% - 20%, and urged that additional studies be done[57]. In a second randomized, double-blind controlled trial of 109 patients with a history of recurrent URTI's, those randomized to 4 mL of *E. purpurea* fluid extract twice daily had fewer colds; the illnesses that did develop were two days shorter than in the control group. However, none of these differences were statistically significant[58].

Three trials did report statistically significant prophylactic effects. In a double-blind, placebo-controlled clinical trial in 108 patients, the 54 assigned to Echinacin (2-4 mL daily) had significantly fewer colds over the eight week follow-up; the colds they did get were less severe than in the placebo-treated group[59]. In another double-blind, placebo controlled trial testing echinacea (Resistan) as prophylaxis for upper respiratory infection in 363 German college students with a history of recurrent colds and flu-like illnesses, those randomized to eight weeks of active treatment had significantly fewer recurrences than those assigned to placebo[13]. Finally, in a randomized, placebo-controlled trial among 42 male triathletes to assess treatment with echinacea during the 28 days prior to

competition, those given echinacea had decreased serum and urine levels of soluble interleukin 2 receptors (sIL-2R) and significantly fewer respiratory infections than the control group[60].

b. **URTI (upper respiratory tract infection) treatment**: Randomized controlled trials have consistently supported the use of echinacea as a treatment at the first sign of a URTI in adults.

In a randomized, double-blind, placebo-controlled trial of 180 adults suffering from flu-like symptoms, those who received 900 mg of *E. purpurea* root ethanol tincture daily had a statistically significant improvement in symptoms (weakness, chills, sweating, sore throat, muscle/joint aches, and headaches); the improvement for those taking only 450 mg daily was not statistically better than in the control group[61].

In a randomized, single-blind, placebo-controlled trial of 32 adults suffering from the common cold, treatment with a preparation including *E. purpurea* root extract, as well as vitamin C, rosemary leaf, eucalyptus leaf, and fennel seed, significantly reduced illness duration (by one day) and reduced the number of tissues used[62].

In a 1989 randomized, placebo controlled trial, 100 adults suffering from an acute flu-like illness took 30 mL of echinacea extract (Resistan) daily for two days, followed by 15 mL daily for 4 days; significantly more symptoms resolved within 8 days for patients taking echinacea than for those taking the placebo[13].

In a double-blind, randomized controlled trial of 160 adults suffering from a new URTI, treatment with 900 mg of *E. pallida* root extract significantly shortened the average length of infection and decreased symptom scores ($P<0.01$)[63].

In a randomized, double-blind, placebo controlled trial of 120 patients with a history of at least three URTI's in the past year, those assigned to Echinagard treatment at the first sign of a cold (doses of 20 drops every two hours the first day, followed by 20 drops po TID thereafter), developed significantly fewer cold

symptoms and had a significant reduction in duration of symptoms; no adverse effects were reported[64].

These five randomized controlled trials published between 1992 and 1997 all support the use of echinacea treatment at the first sign of a URTI in adults.

c. Antifungal

i. *In vitro data*: Human granulocytes and monocytes treated with *E. purpurea* extracts demonstrated enhanced mobility and increased phagocytosis of *Candida albicans* by 30% - 45%[65]. Purified polysaccharides from *E. purpurea* inhibited *Candida albicans* growth *in vitro*[52].

ii. *Animal data*: Pre-treatment with polysaccharides from *E. purpurea* provided significant protection against injections of lethal doses of *C. albicans* in mice[66].

iii. *Human data*: In a German study, 203 women suffering from recurrent vaginal infections with *Candida albicans* were all treated with topical econazole cream; over ten weeks, 90 also received Echinacin parenterally, 60 received Echinacin topically and 43 served as controls. Recurrence rates were 60% in the control group vs. only 16% in those receiving Echinacea by any route ($P<0.01$)[67]. There are no controlled trials evaluating the effectiveness of echinacea in treating systemic fungal infections or fungal/yeast infections in childhood, or for using echinacea alone as a therapeutic strategy in adults suffering from yeast infections.

12. **Antineoplastic:** Complementary immune support for chemotherapy

i. *In vitro data*: Purified polysaccharides from *E. purpurea* strongly activated murine macrophages and stimulated a cytotoxic response of macrophages against tumor targets[22]. Echinacea had no direct effect on T lymphocytes and only weakly stimulated B lymphocytes. The polysaccharide solution had to be stored at -20 degrees Celsius to retain optimal activity[21]. Echinacea's polysaccharides also activated macrophages from mice previously treated with cyclophosphamide or cyclosporin A. The resulting cytotoxic activity was 80% of that observed with interferon-gamma and Lipopolysaccharide (LPS), and more than four times that observed for control macrophages[46].

ii. *Animal data*: Intravenous administration of *E. purpurea*-derived polysaccharides to mice, once a day for three days directly following injection of cyclophosphamide, dramatically increased the number of PMNs as well as the total white blood cell count, compared to controls, for the nine days following treatment[46]. Among rats undergoing experimental irradiation, dietary supplements with *E. purpurea* enhanced the mobilization of vitamin E mediated oxidation/reduction pathways, potentially protecting against radiation damage[68].

In rats with Walker carcinosarcoma and mice with lymphocytic leukemia, a long-chain alkene from the root oil of *E angustifolia* and *E. pallida* inhibited tumor growth[53].

iii. *Human data*: In 35 adults with brain tumors, oral treatment with 3 mL/day of an herbal complex (which was 40% *E. angustifolia)* for four weeks had no statistically significant impact on white blood cell counts or on cytokine production[69].

Fifteen adults with advanced, metastatic colorectal cancer, who had already undergone surgery and/or chemotherapy, were treated with a combination of low-dose cyclophosphamide, thymostimulin, and Echinacin®; the mean survival time was four months[70]. In a case series of five patients with inoperable hepatocellular carcinoma treated with combination therapies including *E. purpurea* (Echinacin), the median survival time was 2.5 months[71]. No significant adverse effects were attributed to echinacea in either of these Phase I trials.

Although echinacea had no significant toxicity, these data appear inadequate to recommend the routine use of echinacea as an adjunct to standard cancer therapies.

13. **Antioxidant:** none

14. **Skin and mucus membranes:** Vulnerary (wound healing)

i. *In vitro data*: Chicoric acid, cynarine and other compounds from *E. angustifolia* have antihyaluronidase activity, which may reduce inflammatory changes in damaged tissues[72]. Several Echinacea constituents have protected collagen from degradation during exposure to free radicals, leading to suggestions that echinacea may be helpful in protecting against sun damage to skin[73].

ii. *Animal data*: Guinea pig skin wounds healed significantly more quickly when treated with Echinacin® ointment than when treated with control ointment[74]. Echinacin® also reduced the incidence of necrosis in skin flaps in animal models[75].

iii. *Human data*: In a German case series of 626 adults with minor burn injuries, all of whom were treated with an echinacea-containing ointment, complete healing was noted in an average of 7 days; of 628 patients with eczema, complete healing was noted within 7 days for 517 (82%)[76]. Despite its long historical use as a vulnerary, there are no randomized, controlled clinical trials evaluating the effects of echinacea products on human skin injuries, nor any comparing it with standard medical therapies.

15. **Other/miscellaneous:** none

Toxicity and Contraindications

All herbal products carry the potential for contamination with other herbal products, pesticides, herbicides, heavy metals and pharmaceuticals.
Allergic reactions can occur to any natural product in sensitive persons.

Allergic reactions to echinacea have been reported[77]. Of 1032 subjects who were patch tested with different plant ointments, two had a reaction to *E. angustifolia* ointment[78].

Potentially toxic compounds in echinacea: None. Unlike the unsaturated compounds found in comfrey, the trace amounts of pyrrolizidine alkaloids found in echinacea have a saturated pyrrolizidine nucleus and are thought to be non-toxic[79,6,80]. No serious side effects (aside from extremely rare allergic reactions) have been reported in over 2.5 million prescriptions per year in Germany and over a century of use in the United States[81].

Acute toxicity: Even with a four week course of therapy that greatly exceeded typical human doses, rats and mice showed no evidence of mutagenic or carcinogenic effects[81,80]. Aside from rare allergic reactions, acute toxicity from echinacea in humans has only been reported with parenteral, not oral administration[48]. Symptoms after parenteral administration include shivering, fever, and muscle weakness. An unpleasant taste and brief tingling or numbing of the tongue is often reported after oral administration[82,48].

Very high concentrations (corresponding to orders of magnitude above any recommended dose) of *E. purpurea* extract inhibited T cell proliferation *in vitro*[48,40]. In mice, LD50 values of >2500 mg/kg were found for polysaccharide mixtures from the aerial parts of *E. purpurea*, indicating non-toxicity . The mice that died had signs of acute circulatory failure, indicating that they were probably killed by excess hyperosmolarity of blood caused by the polysaccharide solutions, as opposed to any direct toxic effect of the polysaccharides.

Washed sperm that were incubated directly in low concentration *E. purpurea* (0.81 mg/ml) showed no difference in sperm motility compared to the control, even after 48

hours. Sperm incubated directly in high concentration *E. purpurea* had decreased sperm motility after 24 hours of incubation[83].

Chronic toxicity. *In vitro* experiments involving *Echinacea purpurea* administration to both bacteria and mammalian cells, as well as in vivo experiments in mice and rats spanning four weeks of daily gastric tube administration, all showed no evidence of mutagenic action nor of any toxic effects, even at doses and concentrations that far exceed those recommended for humans[81].

However, German guidelines recommend that echinacea not be used chronically for more than eight weeks, because of possible hepatotoxicity or immunosuppression and loss of beneficial immunostimulation; these guidelines appear to be based on extremely small samples of adults given echinacea by injection rather than the more common oral administration[84,85]. In fact, when *E. purpurea* juice was taken orally for 10 -12 weeks by healthy adults in two different studies, there were no adverse effects either subjectively or in terms of leukocyte counts[86]. In a Phase I trial of 14 HIV+ adults taking standard anti-retroviral therapy who then added *E. purpurea* extracts (1000 mg po TID for 12 weeks), no adverse symptoms were noted, and there were no toxic effects on any immune parameter. Viral load levels actually fell during the 12 week trial[87]. There were no reported toxic effects to hepatic enzymes or renal function.

Limitations during other illnesses or in patients with specific organ dysfunction: Echinacea is typically not used for patients with progressive systemic diseases (e.g. multiple sclerosis, tuberculosis, systemic lupus erythematosus (SLE), autoimmune diseases, and AIDS or HIV infection) or for patients with autoimmune disease, because of concerns that it might exacerbate dysfunctions in the immune system[88,6,86]; however, these concerns have not been formally evaluated, and there are no convincing data indicating any adverse clinical effects with prolonged use even in these populations[1,89].

Interactions with other herbs or pharmaceuticals: Little is known. Echinacea theoretically could interfere with immunosuppressive therapy, based on its immunomodulating effects, and therefore is not typically recommended for organ-recipients or people with other conditions in which immuno-suppression is necessary[6]. Many herbalists caution that

echinacea may cause hepatotoxicity and avoid using it in patients who require other potentially hepatotoxic medications (e.g., anabolic steroids, amiodarone, methotrexate, or ketoconazole). However, it is not clear that Echinacea causes significant hepatotoxicity; it lacks the 1,2 unsaturated necrine ring system that makes pyrrolizidine alkaloids hepatotoxic[82].

Safety during pregnancy and/or childhood: Unknown. No studies have systematically addressed its safety in these contexts[6,84].

Typical dosages

Provision of dosage information dose NOT constitute a recommendation or endorsement, but rather indicates the range of doses commonly used in herbal practice.

Doses are given for single herb use and must be adjusted when using herbs in combinations.

Doses may also vary according to the type and severity of the condition treated and individual patient conditions.

Availability of standardized preparations: Various brands and clinical studies use different species of Echinacea, different parts of the plant, different growing conditions, and different preparations (pressed juice, tincture, alcoholic extraction or powdered capsules), all of which can affect the amounts and/or activities of active ingredients[90]. Different species may be difficult to distinguish from one another and are frequently substituted for one another.

Typical doses used in adults: No dosages have been universally standardized. The pressed juice of the above-ground parts of *E. purpurea*, in alcohol tincture, is the preferred form, according to several experts, because some of the active constituents are not water soluble. Recommended doses vary widely.

Powdered root extract:

500 mg - 1 gm initially, then 500 mg – 1 gram q 4 hours to TID[6,9,91]

900 mg/day recommended by German Commission E[84,91]

Freeze-dried capsules/tablets: 1 – 2 capsules or tablets TID [91]

Pressed fresh juice:

½- 1 tsp. initially, then ¼ - ½tsp every 2 hours to TID[91]

6-9 ml daily of E. purpurea aerial parts[84]

Pressed juice in alcohol tincture: (1:5 in 45% alcohol)

1.5 - 7.5 ml daily dose or 1-4ml TID[9,91,6]

60 drops po TID consumed in one ounce of water or juice[6,1]

Liquid (fluid) extract (1:1 in 45% alcohol): 0.25 – 2.0 mL TID[6,91]

Teas: not recommended because active constituents may not be extracted with hot water

Injections: not available in US; available, but uncommonly used in Germany

Continuous prophylactic use: Most herbalists recommend a maximum duration of continuous use not to exceed eight weeks at a time; this recommendation appears to be based on data from parenteral injections of echinacea rather than daily oral use[84].

Dosages used in herbal combinations: Variable and not well studied

Pediatric dosages: Unknown

Single ingredient products: Echiherb, Echinacin, Echina Pro, Resplant

Multi-ingredient preparations: Allergenid, Antifect, Cold-eeze, Echinacea ACE Plus Zinc, Echine, Enertonic, Esberitox, Herbal Booster, Herbal Cold & Flu Relief, Nasalgon, Sambucus powder, Uralyt, Urgenin, Vitaglow

NOTE: The German Commission E recommends *E. purpurea* aerial parts expressed juice, but not *E. purpurea* root; conversely, it recommends *E. pallida* alcohol root extracts. Neither the roots nor aerial portions of *E. angustifolia* are recommended[84,92,93].

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