Echinacea

Echinacea purpurea (L.) Moench, *E. pallida* (Nutt.) Nutt.,
E. angustifolia DC.

[Fam. *Asteraceae*]

Overview

The native American medicinal plant, echinacea, is one of the most popular herbs in the U.S. marketplace. Preparations made from several plant species and plant parts of the genus *Echinacea* constituted the top-selling herbal medicine in all channels of sales (mass market, multilevel, and natural food stores) in 1997, capturing 9% of the total market based on $3.6 billion of total sales. Echinacea preparations ranked fourth with retail sales of over $58 million in the mainstream market in 2000. While the main constituents in the different species and plant parts have pharmacological activity, the exact compounds responsible for the therapeutic value are unclear. For this reason it is important to note the taxonomic source and type of preparation for each clinical study.

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Primary Uses

- Upper respiratory tract infections (URTIs) — Treatment

Other Potential Uses

Internal

- Immune system stimulant
- Adjunct therapy in chronic candidiasis in women
- URTIs — Prevention

External

- Wound healing

Pharmacological Actions

Internal

Promotes immunomodulatory activity. In animal studies: demonstrates antitumor activity in combination with *Thuja occidentalis* tips and *Baptisia tinctoria* rhizome; increases phagocytosis; increases serum leukocytes; stimulates granulocyte migration; stimulates cytokine production; protective effects on influenza A-virus infection in mice.

External

Protects against photodamage; promotes wound healing; increases total lymphocyte count with a decreased percentage of T-helper cells.

Dosage and Administration

The German Commission E recommends limiting the use of internal and external echinacea preparations to 8 weeks because the conditions for which echinacea preparations are used are usually relatively minor and transient. If symptoms still persist after 8 weeks of echinacea therapy, more aggressive treatment is presumably needed.

Internal

***E. purpurea* herb**

EXPRESSED JUICE FROM FRESH AERIAL PARTS: (2.5:1), stabilized in 22% alcohol: 6–9 ml daily.

INFUSION: For upper respiratory and flu symptoms, 150–240 ml boiling water poured over about 1 g dried herb and steeped, covered, for 10–15 minutes, 5–6 times daily.

TINCTURE: 1:10 (*w/v*), in 65% (*v/v*) alcohol: 5 drops, 1–3 times daily. For acute conditions, 5 drops every 1/2–1 hr.

***E. purpurea, E. pallida, E. angustifolia* root**

DRIED ROOT: 0.9–1 g, approximately 900 mg cut root 3 times daily.

INFUSION: 0.9 g root in 150 ml boiled water steeped for 10 min., several times daily between meals.

DECOCTION: 1 g in 150 ml water boiled for 10 min., 3 times daily.

FLUID EXTRACT: 1:1 in 45% alcohol: 0.5–1.0 ml 3 times daily.

TINCTURE: 1:5 (*g/ml*), ethanol 55% (*v/v*): 30–60 drops, approximately 1.5–5 ml, 3 times daily.

External

OINTMENT: Semisolid preparation containing at least 15% pressed juice in a base of petroleum jelly, or anhydrous lanolin, and vegetable oil applied locally.

POULTICE: Semisolid paste or plaster containing at least 15% pressed juice applied locally.

Contraindications

Caution may be advised with internal echinacea preparations in cases of increased tendency for allergies, especially to members of the family *Asteraceae,* including arnica (*Arnica* spp.*)*, chamomile (*Matricaria* spp.), marigold (*Calendula officinalis*), yarrow (*Achillea* spp.), ragweed (*Ambrosia* spp.), asters (*Aster tataricus*), and chrysanthemums (*Chrysanthemum* spp.). Based on theoretical considerations, the Commission E also advises using echinacea with caution in progressive systemic diseases such as tuberculosis, leukosis, collagenosis, multiple sclerosis, AIDS, HIV infection, and other autoimmune diseases. No contraindications are known for external echinacea preparations.

Pregnancy and Lactation: No known restrictions. In a recent controlled trial, echinacea consumption by pregnant women showed no evidence of risk.

Adverse Effects

Few adverse effects have been reported for internal and external echinacea preparations. Ingestion of an echinacea preparation made of *E. angustifolia* (whole plant) and *E. purpurea* root has been associated with anaphylaxis. It is possible that pollens might be present in echinacea preparations made with aerial parts and not in those preparations containing root material only.

Drug Interactions

None known.

Clinical Review

Of 21 studies on echinacea that included a total of 3,508 participants, all but three demonstrated positive effects for indications including cold, flu, upper respiratory tract infections (URTIs), candidiasis, and gestational safety. Five positive randomized, double-blind, placebo-controlled (R, DB, PC) studies, involving a total of 825 subjects, supported the use of specific and unique echinacea monopreparations for the treatment (incidence, severity, and/or duration) of acute upper respiratory or flu-like infections. The acute treatment was further supported by six additional R, DB, PC studies using combination preparations containing echinacea and other herbs. One R, DB, PC study on an echinacea monopreparation did not find measurable benefit for treatment of URTI symptoms, though this may be due to the low dose and lack of severity of the symptoms.

The prevention of URTIs was studied in five R, PC studies with a total of 1,209 subjects focused on the use of distinct monopreparations and unique combination products. Two of these studies did not find a significant effect. Non-continuous administration of the treatment in one study may have been a factor, though the authors attributed the results to a sample size smaller than desired. In another study, the authors reported that the "treatment with fluid extract of *Echinacea purpurea* did not significantly decrease the incidence, duration or severity of colds and respiratory infections compared to placebo."

Other trials included a study on genital herpes that found no demonstrated effect. One R, PC study on immunology in athletes concluded that the echinacea group had no URTIs compared to placebo. Women using echinacea drops as an adjunct therapy in the treatment of chronic candidiasis showed a reduced recurrence rate. A study on the safety of echinacea during pregnancy found no statistical difference between echinacea and control groups.

A review of 13 R, DB, PC trials studying the treatment and prevention of URTIs evaluated the effectiveness of orally ingested echinacea preparations. The authors concluded that the published trials suggest echinacea may be beneficial for *treatment*, but the variation of preparations and compositions (including combination products containing other botanicals) makes recommending specific doses problematic. They claimed that there was very little evidence supporting the prolonged use of echinacea for *prevention* of URTIs. An assessment of the methodology of 26 controlled clinical trials concluded that the published clinical studies suggest that some preparations containing echinacea can be efficacious as immunomodulators. However, the evidence is insufficient to recommend an exact dosage or specific preparation for use. A review observed that despite contraindications in autoimmune diseases based on theoretical considerations (e.g., those suggested by Commission E), current clinical use and scientific evidence do not support limitations on long-term use of echinacea with particular auto-immune diseases. The author suggested echinacea should be considered an immunomodulator rather than an immunostimulant.

Echinacea

Echinacea purpurea (L.) Moench, *E. pallida* (Nutt.) Nutt., *E. angustifolia* DC.
[Fam. *Asteraceae*]

Overview

The native American medicinal plant echinacea is one of the most popular herbs in the U.S. marketplace. Preparations made from several plant species and parts of echinacea are used, including the above-ground parts, or the roots, stems or leaves from *Echinacea purpurea*, *E. pallida*, and/or *E. angustifolia*. While all of these species variations can be effective for treating different ailments, the exact chemical compounds responsible for the therapeutic effects are not yet known.

Uses

Supportive care to treat colds and chronic infections of the upper respiratory tract.

Dosage

Consult your healthcare practitioner if symptoms have not improved within eight weeks.

***E. purpurea* herb**
TINCTURE: 5 ml, 3 times daily.

***E. purpurea, E. pallida, E. angustifolia* root**
DRIED ROOT: 900 mg, 3 times daily.

FLUID EXTRACT: 0.5–1.0 ml, 3 times daily.

TINCTURE: 30–60 drops, 3 times daily.

Echinacea preparations are also available as teas, capsules, and tablets.

Contraindications

Consult your healthcare provider before ingesting echinacea preparations in cases of an increased tendency toward allergies to plants in the daisy family (*Asteraceae*), including arnica, chamomile, chrysanthemum, marigold, ragweed, and yarrow.

PREGNANCY AND LACTATION: There are no known restrictions for use during pregnancy or while breast-feeding.

Adverse Effects

Rare cases of allergic reactions to plants in the family *Asteraceae* are the only known adverse effects of echinacea.

Drug Interactions

There are no known drug interactions.

Comments

When using a dietary supplement, purchase it from a reliable source. For best results, use the same brand of product throughout the period of use. As with all medications and dietary supplements, please inform your healthcare provider of all herbs and medications you are taking. Interactions may occur between medications and herbs or even among different herbs when taken at the same time. Treat your herbal supplement with care by taking it as directed, storing it as advised on the label, and keeping it out of the reach of children and pets. Consult your healthcare provider with any questions.

AMERICAN BOTANICAL COUNCIL

Echinacea

Echinacea spp.

Echinacea purpurea (L.) Moench, *E. pallida* (Nutt.) Nutt., *E. angustifolia* DC.

[Fam. *Asteraceae*]

Overview

The medicinal plant echinacea, indigenous to the U.S., is one of the most popular herbs in the U.S. marketplace. The roots of several species were the most widely used medicines of Native Americans of the Great Plains. Ethnobotanist M.R. Gilmore noted, "Echinacea seems to have been used as a remedy for more ailments than any other plant" (Gilmore, 1911). Foster (1991) and Moerman (1998) have reviewed the ethnobotany of both the roots and leaves of various species of *Echinacea*. They were used by Native Americans for toothache, enlarged glands (mumps), sore throat, snakebite, coughs, burns, and as an analgesic. Eclectic medical physicians of the late 19th century employed *E. angustifolia* root for a variety of indications, both internally and externally, including sepsis (e.g., gangrene, boils, septicemia), foul mucous discharges, cancerous growths, typhoid, various types of fevers, and locally applied for chronic skin sores (Felter and Lloyd, 1898). They also used it for mitigation of the pain of gonorrhea and syphilis, as a local anesthetic, for snakebite and other venomous stings (Foster, 1991).

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Preparations made from several plant species and plant parts of the genus *Echinacea* constituted the top-selling herbal supplement sold in all U.S. channels of sales (mass market, multilevel, and natural food stores) in 1997, consisting of 9% of the total market based on $3.6 billion in total sales (Brevoort, 1998). In 2000, echinacea preparations ranked fourth in the mainstream market with retail sales of $58,422,932 (Blumenthal, 2001). While the main constituents of the different species and plant parts have pharmacological activity, the exact compounds responsible for echinacea's therapeutic value are unclear. For this reason, it is important to note the taxonomic source, plant part, and type of preparation for each clinical study (Parnham, 1999; Bauer 1999; Melchart and Linde, 1999).

Description

Nine species of the genus *Echinacea* have been classified taxonomically (Hobbs, 1994) although recent chemical and genetic research suggests possible reclassification of the genus to four species (Binns *et al.*, 2002). Echinacea preparations consist of any one or more of the plant parts from three *Echinacea* species [Fam. *Asteraceae*], including the fresh, above-ground parts (harvested at the time of flowering), the fresh or dried root of *E. purpurea* (L.) Moench, and the fresh or dried root of *E. pallida* (Nutt.) Nutt., and/or *E. angustifolia* D.C., and their preparations in effective dosage. Occasionally, the fresh or dried above-ground parts of *E. pallida*, collected at the time of flowering, are used but are often labeled incorrectly as "*E. angustifolia*" in the marketplace (Blumenthal *et al.,* 2000).

Primary Uses

Respiratory

- Treatment of symptoms and duration in upper respiratory tract infections (URTIs)

  E. purpurea herb and root (Brinkeborn, 1998; Hoheisel *et al.,* 1997; Bräunig *et al*, 1992)

  E. pallida root (Dorn *et al.,* 1997)

  E. angustifolia root (Galea *et al*., 1996)

  E. purpurea and *E. angustifolia* stems and *E. purpurea* root (Lindenmuth and Lindenmuth, 2000)

  E. purpurea and *E. pallida* roots (Henneicke-von Zepelin *et al.,* 1999; Reitz *et al.*, 1990; Vorberg, 1984)

Other Potential Uses

Internal

- Immune system stimulant

  E. purpurea (Berg *et al.*, 1998; Brinkeborn, 1999; Hoheisel *et al.*, 1997; Braunig *et al.*, 1992)

  E pallida (Dorn *et al.*, 1997)

- Adjunct therapy in chronic candidiasis in women

  E. pupurea (Coeugniet and Kuhnast *et al.,* 1986)

- Prevention of URTIs:

  E. purpurea (Grimm and Müller, 1999; Schöneberger *et al.*, 1992)

  E. angustifolia (Melchart *et al*, 1998)

  E. purpurea and *E. pallida* (Forth *et al.*, 1981)

  E. angustifolia herb and root combination (Schmidt *et al.,* 1990)

External

- Wound healing

  E. purpurea (Blumenthal *et al.,* 1998; WHO, 1999)

  E. pallida root (Speroni *et al.,* 1998)

  E. angustifolia root (Bradley, 1992)

Dosage

Internal

Crude Preparations

E. purpurea herb

Juice: 6–9 ml daily expressed juice from fresh *E. purpurea* aerial parts 2.5:1, stabilized in 22% alcohol, (Bauer and Liersch, 1993; Blumenthal *et al.*, 1998).

Infusion: For upper respiratory and flu symptoms, 150–240 ml boiling water poured over about 1 g dried herb and steeped covered, for 10–15 minutes, 5–6 times daily (Lindenmuth and Lindenmuth, 2000).

Tincture: 5 drops, 1–3 times daily 1:10 (*w/v*), in 65% (*v/v*) alcohol. For acute conditions, 5 drops every 1/2–1 hour (Bauer and Liersch, 1993).

E. purpurea, E. pallida, E. angustifolia root

Dried root: 0.9–1 g (approximately 900 mg) cut root, 3 times daily.

Infusion: 0.9 g root in 150 ml boiled water steeped for 10 minutes, several times daily between meals (Bauer and Liersch, 1993; Wichtl and Bisset, 1994).

Decoction: 1 g in 150 ml water boiled for 10 minutes, 3 times daily (Bradley, 1992).

Fluid extract: 1:1 in 45% alcohol, 0.5–1.0 ml 3 times daily (Newall *et al.*, 1996; Bradley, 1992).

Tincture: 1:5 (*g/ml*), ethanol 55% (*v/v*) 30–60 drops, approximately 1.5–5 ml (Bradley, 1992), three times daily (Bauer and Liersch, 1993; ESCOP, 1999).

External

Crude Preparations

Ointment: Semisolid preparation containing at least 15% pressed juice in a base of petroleum jelly or anhydrous lanolin, and vegetable oil applied locally (Blumenthal *et al.*, 1998; Blumenthal *et al.*, 2000).

Poultice: Semisolid paste or plaster containing at least 15% pressed juice, applied locally (Blumenthal *et al.,* 2000).

Duration of Administration

Internal and External

The German Commission E recommended use for no longer than eight weeks (Blumenthal *et al.,* 1998). Note: This duration limit has been misinterpreted as meaning that echinacea preparations may not be safe for use for longer than eight weeks, but this is not the case. This restriction was adopted by the Commission E due to its opinion that most conditions for which echinacea preparations are to be used are usually relatively minor and transient. Therefore, if therapy with echinacea has not succeeded within eight weeks, and symptoms still persist, more aggressive treatment is presumably needed.

Chemistry

The constituents of echinacea preparations vary depending on the particular species and plant part used.

E. purpurea herb (i.e., aerial parts) and root both contain caffeic acid derivatives (0.6–2.1% in roots), including mainly cichoric acid (1.2–3.1% in the flowers), caffeic acid, caftaric acid, chlorogenic acid and 0.001–0.04% alkamides. *E. purpurea* herb also contains water-soluble polysaccharides (arabinoxylan and arabinogalactan types); fructans; 0.48% flavonoids of quercetin and kaempferol type; and 0.08–0.32% essential oil (Bauer, 1999; Bauer and Liersch, 1993). *E. purpurea* root differs in containing polyacetylene derivatives; polysaccharides (fructosans, arabinogalactans); glycoproteins comprised of approximately 3% protein, of which the dominant sugars are 64–84% arabinose, 1.9–5.3% galactose, and 6% glucosamine, and up to 0.2% essential oil (Bauer 1999; Bauer and Liersch, 1993; ESCOP, 1999; Pietta *et al.*, 1998).

E. pallida herb contains caffeic acid derivatives including cichoric acid, caftaric acid, echinacoside, verbascoside, chlorogenic acid, and isochlorogenic acid; flavonoids (mainly rutoside); alkamides; and <0.1% essential oil (Bauer, 1998; Bauer and Liersch, 1993; Leung and Foster, 1996; Pietta *et al.*, 1998).

E. pallida root contains caffeic acid derivatives, mainly 0.7–1.0% echinacoside, followed by isochlorogenic acid, 6–*O*-caffeoylechinacoside, and chlorogenic acid; 0.2–2.0% essential oil comprised mainly of ketoalkynes and ketoalkenes, polyacetylenes, polysaccharides, and glycoproteins (Bauer, 1999; Bauer and Liersch, 1993; ESCOP, 1999; Pietta *et al.*, 1998). Methyl jasmonate, a naturally-occurring cellular signal molecule, increased content of alkamides and ketoalene/ynes (Binns, 2001).

E. angustifolia herb contains caffeic acid derivatives such as cichoric acid, echinacoside, verbascoside, chlorogenic acid, and isochlorogenic acid; flavonoids (mostly quercetin); alkamides; polysaccharides; and less than 0.1% essential oil (Bauer, 1998; Bauer and Liersch, 1993; Leung and Foster, 1996; Pietta *et al.*, 1998).

E. angustifolia root contains caffeic acid derivatives, mainly 0.3–1.7% echinacoside, followed by chlorogenic acid; an isochlorogenic acid and its characteristic constituent, cynarin; polysaccharides, including 5.9% inulin; glycoproteins comprised of approximately 3% protein, of which the dominant sugars are 64–84% arabinose, 1.9–5.3% galactose, and 6% glucosamines; 0.01–0.15% alkamides; and less than 0.1% essential oil (Bauer, 1998; Bauer, 1999; Bauer and Liersch, 1993; Pietta *et al.*, 1998).

Pharmacological Actions

Echinacea's pharmacological activity is believed to result from the combined effect of several of its chemical constituents, found within the different species and parts of echinacea.

Internal

Human

E. angustifolia

Promotes immunomodulatory activity (Melchart *et al.*, 1994).

E. pallida

Exhibits immunomodulatory (Melchart *et al.*, 1994) and immunostimulant activity (Dorn *et al.*, 1997).

E. purpurea

Demonstrates immunomodulatory (Melchart *et al.*, 1994); immunostimulant (Berg *et al.*, 1998; Braunig *et al.*, 1992; Brinkeborn, 1999; Hoheisel *et al.*, 1997; Parnham, 1996); and antimycotic activity (Coeugniet and Kuhnast, 1986).

Animal

E. angustifolia and E. pallida

Demonstrate antitumor activity (Voaden *et al.*, 1972) in combination with *Thuja occidentalis* tips and *Baptisia tinctoria* rhizome (per oral application).

E. purpurea

Increases phagocytosis (Bauer, 1999; Roesler *et al.*, 1991; Wagner *et al.*, 1988; Mose, 1983); increases serum leukocytes (Bauer,

1999); stimulates granulocyte migration (Roesler *et al.*, 1991; Wildfeuer and Mayerhofer, 1994); stimulates cytokine production (Bauer, 1999; Burger *et al.*, 1997; Wagner *et al.*, 1985); protective effects on influenza A-virus infection in mice (Bodinet, 1999).

In vitro

E. purpurea

Enhances phagocytosis (Bauer, 1999); increases NO-production of macrophages (Bodinet, 1999); demonstrates natural killer cell action (See *et al.*, 1997); and enhances the cytotoxicity of macrophages against tumor cells (Stimpel *et al.*, 1984).

E. purpurea, E. angustifolia, E. pallida

Enhances antibody production (IgM, number of antibody-producing cells) (Beuscher *et al.*, 1995; Bodinet, 1999); induces cytokine production (IL-1, IL-6, TNFa, IFNab) (Beuscher *et al.*, 1995).

External

Human

E. angustifolia

Promotes wound-healing for skin inflammation and abrasions (Boon and Smith, 1999).

E. purpurea

Increases total lymphocyte count with a decreased percentage of T-helper cells in patients with eczema, neurodermatitis, candida, and herpes simplex (Boon and Smith, 1999).

E. purpurea, E. angustifolia, E. pallida

Protect against photodamage (Facino *et al.*, 1995).

Animal

E. pallida and *E. angustifolia*

Inhibit inflammation (Speroni *et al.*, 1998; Tubaro *et al.*, 1987; Tragni *et al.*, 1985).

E. pallida

Demonstrates cicatrizing and vulnerary activity (Speroni *et al.*, 1998).

Mechanism of Action

Although the mechanism of action for *Echinacea* spp. is not fully understood, the following are proposed:

- Binds polysaccharides to carbohydrate receptors on the cell surface of T-cell lymphocytes and macrophages (Wagner *et al.*, 1984; Mose *et al.,* 1983).
- Promotes tissue regeneration and reduces inflammation by inhibiting hyaluronidase production (Tragni *et al.*, 1985).
- Generates oxidative burst and selective cytokine production in macrophages, leading to specific toxicity to tumor cell lines (Luettig *et al.,* 1989; Stimpel *et al.*, 1984).
- A combination of three polysaccharides from *E. purpurea* cell cultures produced a substantial increase in the number of peripheral blood leukocytes, due to an increase in polymorphanuclear cells (PMNs) in mice (Roesler, 1991).
- Enhances phagocytosis by human neutrophils *in vitro* and in human studies (Mose, 1983; Parnham, 1996).

Contraindications

Internal

Individuals with an increased tendency to have allergies, especially allergies to members of the family *Asteraceae* including arnica (*Arnica* spp.) flower, chamomile (*Matricaria* spp.) flower, marigold (*Calendula officinalis* L.) flower, yarrow (*Achillea* spp.) flower (Braun *et al.*, 1996); ragweed (*Ambrosia* spp.); asters (*Aster tataricus*); and chrysanthemum (*Chrysanthemum* spp.) (Blumenthal *et al.*, 2000). The Commission E noted that progressive systemic diseases such as tuberculosis, leukosis, collagenosis, multiple sclerosis, Acquired Immune Deficiency Syndrome (AIDS), Human Immunodeficiency Virus (HIV) infection, and other autoimmune diseases are contraindicated (Blumenthal *et al.*, 1998), though these cautions were made based on theoretical considerations and not on reports of adverse findings (Bone, 1997–98).

External

None known (Blumenthal *et al.* 1998).

PREGNANCY AND LACTATION: The Commission E found no known restrictions (Blumenthal *et al.*, 1998). Although consumption of most medications and herbs is contraindicated during the first trimester, one recent controlled trial showed no evidence of increased risk for pregnant women who consumed echinacea (*E. angustifolia* and *E. purpurea*) (Gallo *et al.*, 2000).

Adverse Effects

There are few reported adverse effects for internal and external applications. Aanaphylaxis has been reported with ingestion of an echinacea preparation made of *E. angustifolia* (whole plant) and *E. purpurea* root (Mullins, 1998; Mullins and Heddle, 2002). It is possible that pollens might be present in echinacea preparations made with aerial parts and not in those preparations containing root material only. NOTE: One source suggests that hepatotoxic effects have been reported with the persistent use of echinacea, causing one source to caution against the simultaneous use of echinacea with known hepatotoxic agents (e.g., anabolic steroids, amiodarone, methotrexate, or ketoconazole) (Miller, 1998). However, the significance of this purported hepatotoxicity is questionable, since echinacea lacks the 1, 2 unsaturated necine ring system associated with hepatotoxic pyrrolizidine alkaloids (PAs) (Roeder *et al.*, 1984). PAs do not constitute a significant part of echinacea chemistry, and those PAs found in echinacea species are not of the saturated type. No known documentation of hepatotoxicity is associated with ingestion of echinacea.

Drug Interactions

The Commission E stated that there are no known interactions (Blumenthal *et al.*, 1998). Several sources raise the issue of potential interactions with immunosuppressive drugs (e.g., cyclosporine and corticosteroids), but to date these concerns are speculative and lack clinical documentation (Brinker, 2001).

American Herbal Products Association (AHPA) Safety Rating

CLASS 1: Herbs that can be consumed safely when used appropriately (McGuffin *et al.*, 1997).

Regulatory Status

AUSTRIA: The combination *E. purpurea* and *E. pallida* root, *Thuja occidentalis* herb, and *Baptisia tinctoria* root is approved as a nonprescription drug.

CANADA: When labeled as a Traditional Herbal Medicine (THM) or as a homeopathic drug, echinacea root (*E. angustifolia, E. pallida, E. purpurea*) is regulated as a nonprescription drug, requiring premarket registration and assignment of a Drug Identification Number (DIN) (Health Canada, 1990, 1997, 2000; WHO, 1998).

FRANCE: The homeopathic mother tincture of the whole fresh plant, 1:10 (*w/v*) in 55% alcohol, is official in the *French Pharmacopoeia* (Ph.Fr.X) (Bauer and Liersch, 1993).

GERMANY: Approved by Commission E as a nonprescription drug (*E. purpurea* herb and *E. pallida* root) (Blumenthal *et al.*, 1998). The combination of *E. purpurea* and *E. pallida* root, *Thuja occidentalis* herb, and *Baptisia tinctoria* root has not yet been approved as a nonprescription drug. The homeopathic mother tincture of the whole fresh plant (*E. angustifolia* or *E. pallida*) or aerial parts (*E. purpurea*) and dilutions are official in the *German Homeopathic Pharmacopoeia* (HAB, 2000).

SWEDEN: Classified as a natural remedy, intended for self-medication, requiring advance application for marketing authorization (MPA, 2001; Tunón, 1999; WHO, 1998). A monograph for Echinagard® (Echinacin®), is published in the Medical Products Agency (MPA) "Authorised Natural Remedies" (MPA, 1997).

SWITZERLAND: Echinacea anthroposophical, homeopathic, and phytomedicines have positive classification (List D) by the *Interkantonale Konstrollstelle für Heilmittel* (IKS) and corresponding sales category D, with sale limited to pharmacies and drugstores, without prescription (Morant and Ruppanner, 2001; *Codex*, 2000/01; WHO, 1998).

U.K.: Herbal medicine in *General Sale List*, Schedule 1 (medicinal products requiring a full Product License), Table A (for internal or external use) (Bradley, 1992).

U.S.: Dietary supplement (USC, 1994). Homeopathic mother tincture, 1:10 (*w/v*) in 55% alcohol (*v/v*), is a Class C over-the-counter (OTC) drug official in the *Homeopathic Pharmacopoeia of the United States* (1991), Official Compendium (1992). Rhizome with roots, powdered root and powdered extract are subjects of botanical monographs in development for the USP-NF. Previews of the standards development were published in *Pharmacopeial Forum* (USP, 2002).

Clinical Review

Twenty-one studies are outlined in the following table "Clinical Studies on Echinacea," including a total of 3,508 participants. All but three of these studies (Galea and Thacker, 1996; Melchart *et al.*, 1998; Vonau *et al.*, 2001), demonstrated positive effects for indications including cold, flu, upper respiratory tract infections (URTIs), candidiasis, and gestational safety. Five positive randomized, double-blind, placebo-controlled (R, DB, PC) studies, involving a total of 825 subjects, supported the use of echinacea monopreparations for the treatment (incidence, severity, and/or duration) of acute upper respiratory or flu-like infections (Brinkeborn *et al.*, 1998, 1999; Dorn *et al.*, 1997; Hoheisel *et al.*, 1997; Bräunig *et al.*, 1992). The acute treatment was further supported by six additional R, DB, PC studies using combination preparations of echinacea and other herbs (Lindenmuth and Lindenmuth, 2000; Henneicke-von Zepelin *et al.*, 1999; Reitz *et al.*, 1990; Dorn 1989; Vorberg and Schneider, 1989; Vorberg, 1984). One R, DB, PC study on an echinacea monopreparation did not find measurable benefit for treatment of URTI symptoms, though this may be due to the low dose and lack of severity of the symptoms (Galea and Thacker, 1996).

The prevention of URTIs was studied in a total of five R, PC studies with a total of 1,209 subjects, focused on the use of distinct monopreparations (Grimm and Müller, 1999; Melchart *et al.*, 1998; Schöneberger, 1992) and unique combination products (Schmidt *et al.*, 1990; Forth and Beuscher, 1981). Two of these studies concluded that echinacea did not significantly prevent URTIs. In the Melchart (1998) study, the treatment was administered noncontinuously, which may have been a factor in the lack of positive results, although the authors attributed the results to a subject group that was smaller than desired. Grimm and Muller (1999) reported that the "treatment with fluid extract of *Echinacea purpurea* did not significantly decrease the incidence, duration or severity of colds and respiratory infections compared to placebo."

Other trials included a study on genital herpes that found no demonstrated effect (Vonau *et al.,* 2001). One R, PC study on immunology in athletes, concluded that the echinacea group had no URTIs compared to placebo (Berg *et al.*, 1998). Women using echinacea drops as an adjunct therapy in the treatment of chronic candidiasis showed a reduced recurrence rate (Coeugniet and Kuhnast *et al.*, 1986). A prospective, controlled study on the safety of echinacea during pregnancy found no statistical difference between the groups (Gallo *et al.*, 2000).

A review of 13 R, DB, PC trials studying the treatment and prevention of URTIs, evaluated the effectiveness of orally ingested echinacea preparations (Barrett *et al.*, 1999). The authors concluded that the published trials suggest echinacea may be beneficial for *treatment*, but the variation of preparations and compositions (including combination products containing other botanicals) makes recommending specific doses problematic. They claimed that there was little evidence supporting the prolonged use of echinacea for *prevention* of URTIs (Barrett *et al.*, 1999). An assessment of the methodology of 26 controlled clinical trials concluded that the published clinical studies suggest that some preparations containing echinacea can be efficacious as immunomodulators. However, the evidence is insufficient to recommend an exact dosage or specific preparation for use (Melchart *et al.*, 1994). A review by Bone (1997-1998) observed that despite contraindications in auto-immune diseases based on theoretical considerations (e.g., those suggested by Commission E), current clinical use and scientific evidence do not support limitations on long-term use of echinacea with particular autoimmune diseases. Bone suggested echinacea should be considered an immunomodulator rather than an immunostimulant.

Branded Products*

Echinacea Plus®: Traditional Medicinals®, Inc. / 4515 Ross Road / Sebastopol, CA 95472 U.S.A. / Tel: (707) 823-8911 / Fax: (800) 886-4349 / www.traditionalmedicinals.com. Each tea bag 1,095 mg of the flowering aerial parts of *E. purpurea* and *E. angustifolia*, 30 mg of Echinacea purpurea extract (6:1) and flavor components lemongrass leaf and spearmint leaf.

Echinacin®: Madaus AG / Ostermerheimer Strausse 198 / Köln, Germany / Tel: +49-22-18-9984-76 / Fax: +49-22-18-9987-21 / Email: b.londener@madaus.de. Expressed juice of the aerial parts of *Echinacea purpurea*, stabilized with 22% ethanol, by volume.

Echinaforce®: Bioforce AG / CH-9325 Roggwil TG/ Switzerland / Tel: +41 71 454 61 61 / Fax: +41 71 454 61 62 / E-mail: Info@bioforce.ch / www.bioforce.com. Each tablet contains 400 mg dried extract, concentrated from a hydroalcoholic mother tincture (1:10) of *E. purpurea* herb fresh-flowering tops (380 mg) and E. purpurea root (20 mg), plus inert excipients materials.

EchinaGuard®: Nature's Way Products, Inc. / 10 Mountain Spring Parkway / Springville, Utah 84663 / U.S.A. / Tel: (801) 489-1500 / www.naturesway.com. Expressed juice of the aerial parts of *Echinacea purpurea*, stabilized with 22% ethanol, by volume.

Esberitox® (prior to 1985): Schaper and Brümmer GmbH & Co. KG / Bahnhofstrasse 35 / 38259 Salzgitter / Ringelheim / Germany / Tel: +49-5341-30-70 / Fax: +49-5341-30-71-24 / Email: info@schaperbruemmer.de / www.schaper-bruemmer.com. Ethanolic extract of 7.5 mg of extracts of E. purpurea and E. pallida root (1:1), 2 mg of *Thuja occidentalis* herb, and 10 mg *Baptisia tinctoria* root and homeopathic dilutions of Apis mell. (D4), Crotalus (D6), Lachesis (D4), and Silicea (D4).

Esberitox® N1 Tablets (1985 formulation based on Esberitox®): Schaper and Brümmer GmbH & Co. KG. 7.5 mg of extracts of E. purpurea and *E. pallida* root (1:1), 2 mg of *Thuja occidentalis* herb, and 10 mg Baptisia tinctoria.

Esberitox® N2 Tablets (1990 formulation based on Esberitox® N1): Schaper and Brümmer GmbH & Co. KG. 7.5 mg of *E. purpurea* and *E. pallida* root (1:1), 2 mg of Thuja occidentalis herb, and 10 mg *Baptisia tinctoria* root. Subsequently changed sources of echinacea.

Resistan®: TRUW Arzneimittel Vertriebs GmbH / Ziethenstrasse 8 / 33330 Gutersloh / Germany / Tel: +49-52-41-3007-40 / www.truw.de. Each 100 mg of Resistan® contains: 12 g *Echinacea angustifolia*; 2.9 g *Eupatorium perfoliatum*; 2 g *Baptista tinctoria*; 2 g *Arnica montana* D2. Contains 13 vol. percent. (NOTE: this product is being reformulated and may change names.)

* American equivalents, if any, are found in the Product Table beginning on page 398.

REFERENCES

Barrett B, Vohmann V, Calabrese C. *Echinacea* for upper respiratory tract infection. *J Fam Pract* 1999;48(8):628–35.

Bauer R, Liersch R. *Echinacea*. In: Hänsel R, Keller H, Rimpler G. Schneider (eds.). *Hagers Handbuch der Pharmazeutischen Praxis,* 5th ed. Vol. 5. Drogen E–O. New York: Springer Verlag; 1993:1–34.

Bauer R. Chemistry, analysis and immunological investigations of *Echinacea* phytopharmaceuticals. In: Wagner, H. (ed.) *Immunomodulatory Agents from Plants*, Basel; Boston; Berlin: Birkhäuser Verlag; 1999:41–88.

Bauer R, Wagner H. *Echinacea* species as potential immunostimulatory drugs. In: Wagner H, Farnsworth N (eds.). *Economic and Medicinal Plants Research,* Vol. 5. New York: Academic Press; 1991;5:253–321.

Berg A, Northoff H, König D, *et al.* Influence of Echinacin (EC31) treatment on the exercise-induced immune response in athletes. *J Clin Res* 1998;1:367–80.

Beuscher N, Bodinet C, Willigmann I, Egert D. Immune-stimulating effect of several echinacea root extracts. [in German]. *Z Phytother* 1995;16:157–66.

Binns SE, Livesey JF, Arnason JT, Baum BR. Phytochemical variation in echinacea from roots and flowerheads of wild and cultivated populations. *J Agric Food Chem* 2002;50(13):3673–87.

Binns SE, Inparajah I, Baum BR, Arnason JT. Methyl jasmonate increases reported alkamides and ketoalkene/ynes in *Echinacea pallida* (*Asteraceae*). *Phytochemistry* 2001;57:417–20.

Blumenthal M, Busse WR, Goldberg A, Gruenwald J, Hall T, Riggins CW, Rister RS (eds.). Klein S, Rister RS (trans.). *The Complete German Commission E Monographs—Therapeutic Guide to Herbal Medicines*. Austin, TX: American Botanical Council; Boston: Integrative Medicine Communication; 1998;122–3.

Blumenthal M, Goldberg A, Brinckmann J. *Herbal Medicine: Expanded Commission E Monographs*. Newton, MA: Integrative Medicine Communications; 2000; 88–102.

Blumenthal M. Herb sales down 15 percent in mainstream market. *HerbalGram* 2001;51:69.

Bodinet K. Immune-pharmacological assessment of a plant derived immune-stimulator [dissertation]. [in German]. Ernst-Moritz-Arndt-Universitat Greifswald. 1999.

Bone K. Echinacea: When should it be used? *Eur J Herb Med* 1997–1998;3(3):13–7.

Boon H, Smith M. *The Botanical Pharmacy: The Pharmacology of 47 Common Herbs*. Kingston, Ontario: Quarry Health Books; 1999;103–13.

Bradley P (ed.). *Echinacea angustifolia radix*. In: *British Herbal Compendium*, Vol. 1. Dorset, England: British Herbal Medicine Association; 1992:81–91.

Bratman S, Kroll D. *The Natural Pharmacist: Clinical Evaluation of Medicinal Herbs and Other Therapeutic Natural Products*. Rocklin, CA: Prima Publishing; 1999:1–8.

Bräunig B, Knick E. Therapeutical experiences with *Echinacea pallida* for influenza-like infections. [in German]. *Naturheilpraxis* 1993;1:72–5.

Bräunig B, Dorn M, Limburg E, *et al. Echinacea purpurea radix* for strengthening the immune response in flu-like infections. [in German]. *Z Phytother* 1992;13:7–13.

Brevoort P. The booming US botanical market. *HerbalGram* 1998;44:33–40.

Brinkeborn R, Shah D, Degenring F. Echinaforce® and other *Echinacea* fresh plant preparations in the treatment of the common cold. A randomized, placebo controlled, double-blind clinical trial. *Phytomedicine* 1999;6(1):1–6.

Brinkeborn R, Shah D, Geissbuhler S, Degenring F. Echinaforce® in the treatment of acute colds: Results of a placebo-controlled, double-blind study carried out in Sweden. [in German] *Schweizensche Z Ganz Med* 1998;10(1):16-9.

Brinker F. *Herb Contraindications and Drug Interactions*, 3rd ed. Sandy, OR: Eclectic Medical Publications; 2001:84–5.

Bruneton J. *Pharmacognosy, Phytochemistry, Medicinal Plants.* Paris: Lavoisier Publishing; 1995:151.

Burger R, Torres A, Warren R, *et al*. *Echinacea*-induced cytokine production by human macrophages. *Int J Immunopharmacol* 1997;19(7):371–9.

Codex 2000/01. (Monographs): Floraceae *Echinacea* Kautabletten und Saft; Echinacin Salbe; Echinaforce Tabletten und Tropfen; Echinamed Tabletten; Similasan *Echinacea* Homöopathische Globuli; Wala *Echinacea* Anthroposophisches Mundspray; Esberitox N Tabletten. Schönbühl, Switzerland: Galenical Informations Systems; 2000.

Coeugniet E. Kühnast R. Recurrent candidiasis: adjutant immunotherapy with different formulations of Echinacin®. *Therapiewoche* 1986;36:3352–8.

Dorn M, Knick E, Lewith G. Placebo-controlled, double-blind study of *Echinacea pallida* radix in upper respiratory tract infections. *Complement Ther Med* 1997;5:40–2.

Dorn, M. Mitigation of flu-like effects by means of a plant immunostimulant. *Natur und Ganzheitsmedizin* 1989;2:314–9.

ESCOP. Echinacea—Proposal for the Summary of Product Characteristics. *Monographs on the Medicinal Uses of Plant Drugs.* Exeter, U.K.: European Scientific Cooperative on Phytotherapy; 1999.

Facino R, Carini M, Aldini G, *et al*. Echinacoside and caffeoyl conjugates protect collagen from free radical-induced degradation: a potential use of *Echinacea* extracts in the prevention of skin photo damage. *Planta Med* 1995;61(6):510–4.

Felter HW, Lloyd JU. *King's American Dispensatory*. Cincinnati, OH: The Ohio Valley Co.; 1898:673–77.

Forth H and Beuscher N. Influence of Esberitox on the frequency of the common cold. [in German]. *Z Allgemeinmed* 1981;57:2272–5.

Foster S. *Echinacea: Nature's Immune Enhancer*. Rochester, VT: Healing Arts Press; 1991:20–24.

Galea S, Thacker K. Double-blind prospective trial investigating the effectiveness of a commonly prescribed herbal remedy in altering the duration, severity and symptoms of the common cold. Unpublished. 1996.

Gallo M, Sarkar M, Au W, *et al*. Pregnancy outcome following gestational exposure to *Echinacea*: a prospective controlled study. *Arch Intern Med* 2000;160:3141–3.

General Sale List 1984–1994. Statutory Instrument (S.I.). The Medicines (Products other than Veterinary Drugs). London, UK: Her Majesty's Stationery Office; 1984; S.I. No. 769, as amended 1985; S.I. No. 1540, 1990; S.I. No. 1129, 1994; S.I. No. 2410.

Gilmore MR. Bureau of American Ethnological Association's Annual Report; 1911;33:368.

Grimm W, Muller H. A randomized controlled trial of the effect of fluid extract of *Echinacea purpurea* on the incidence and severity of colds and respiratory infections [see comments]. *Am J Med* 1999;106(2):138–43.

GSL. See: *General Sale List*.

HAB. See: *Homöopathisches Arzneibuch*.

Health Canada. *Drug Product Database (DPD).* Ottawa, Ontario: Health Canada Therapeutic Products Programme; 2000.

Health Canada. *Drugs Directorate Guidelines: Traditional Herbal Medicines*. Ottawa, Ontario Canada: Minister of National Health and Welfare; Canada. 1990.

Health Canada. *Labeling Standard* Echinacea *Root*. Ottawa, Ontario: Health Canada Therapeutic Products Directorate; 1997 June 1;1–4.

Henneicke-von Zepelin H, Hentschel C, Schnitker J, Kohnen R, Kohler G, Wustenberg P. Efficacy and safety of a fixed combination phytomedicine in the treatment of the common cold (acute viral respiratory tract infection): results of a randomized, double blind, placebo controlled, multicenter study. *Curr Med Res Opin* 1999;15(3):214–27.

Hobbs C. Echinacea: A Literature Review. *HerbalGram* 1994;30:33–48.

Hoheisel O, Sandberg M, Bertram S, *et al*. Echinagard® treatment shortens the course of the common cold: a double-blind, placebo-controlled clinical trial. *Eur J Clin Res* 1997;9:261–8.

Homeopathic Pharmacopoeia of the United States — Revision Service Official Compendium from July 1, 1992. Falls Church, VA: American Institute of Homeopathy; 1991 June;3212-ECHN.

Homopathisches Arzneibuch. Echinacea. In: HAB 2000. Stuttgart, Germany: Deutscher Apotheker Verlag; 2000.
HPUS. See: *Homeopathic Pharmacopoeia of the United States*.
Leung A, Foster S. *Encyclopedia of Common Natural Ingredients Used in Food, Drugs, and Cosmetics*, 2nd ed. New York: John Wiley & Sons; 1996;216–9.
Lindenmuth G, Lindenmuth E. The efficacy of *Echinacea* compound herbal tea preparation on the severity and duration of upper respiratory and flu symptoms: a randomized, double-blind placebo-controlled study. *J Altern Comp Med* 2000;6(4):327–34.
Luettig B, Steinmuller C, Gifford G, *et al*. Macrophage activation by the polysaccharide arabinogalactan isolated from plant cell cultures of *Echinacea purpurea*. *J Natl Cancer Inst* 1989;81(9):669–75.
McGuffin M, Hobbs C, Upton R, Goldberg A (eds.). *American Herbal Products Association Botanical Safety Handbook*. Boca Raton, FL: CRC Press; 1997.
Medical Products Agency (MPA). *Naturläkemedel: Authorised Natural Remedies* (as of January 24, 2001). Uppsala, Sweden: Medical Products Agency; 2001.
Medical Products Agency (MPA). *Naturläkemedelsmonografi: Echinagard*. Uppsala, Sweden: Medical Products Agency; 1997.
Melchart D, Linde K, Worku F, *et al*. Immunomodulation with *Echinacea*—A systematic review of controlled clinical trials. *Phytomedicine* 1994;1:245–54.
Melchart D, Walther E, Linde K, *et al*. *Echinacea* root extracts for the prevention of upper respiratory tract infections: a double-blind, placebo-controlled randomized trial. *Arch Fam Med* 1998;7(6):541–5.
Melchart D, *et al*. Results of five randomized studies on the immunomodulatory activity of preparations of *Echinacea. J Altern Comp Med* 1995;1(2):145–60.
Melchart D, Linde K. Clinical investigations of *Echinacea* phytopharmaceuticals. In:. *Immunomodulatory Agents from Plants.* Wagner, H (ed.). Basel: Birkhauser Verlag; 1999:105–18.
Mengs U, Clare C, Poiley J. Toxicity of *Echinacea purpurea*. *Arzneimittelforschung* 1991;41(10):1076–81.
Miller L. Herbal medicinals: selected clinical considerations focusing on known or potential drug-herb interactions. *Arch Intern Med* 1998 Nov 9;158(20):2200–11.
Moerman D. *Native American Ethnobotany.* Portland, OR: Timber Press; 1998; 205-6.
Morant J, Ruppanner H (eds.). *Arzneimittel-Kompendium der Schweiz 2001*. Basel, Switzerland: Documed AG. 2001.
Mose JR. Effect of Echinacin on phagocytosis and natural killer cells. [in German]. *Med Welt* 1983;34(51–2):1463–7.
MPA. See: Medical Products Agency.
Mullins R. Echinacea–associated anaphylaxis. *Med J Aust* 1998;168(4):170–2.
Mullins RJ, Heddle R. Adverse reactions associated with echinacea: the Australian experience. *Ann Allergy Asthma Immunol* 2002 Jan;88(1):7–9.
Newall C, Anderson L, Phillipson J. *Herbal Medicines: A Guide for Health-Care Professionals.* London: The Pharmaceutical Press; 1996:101–3.
Parnham M. Benefit-risk assessment of the squeezed sap of the purple coneflower (*Echinacea purpurea*) for long-term oral immunostimulation. *Phytomedicine* 1996;3(1):95–102.
Parnham, M. Benefits and risks of the squeezed sap of the purple coneflower (*Echinacea purpurea*) for long-term oral immunistimulant therapy. In: Wagner H (ed.). *Immunomodulatory agents from plants*. Basel; Boston; Berlin: Birkhäuser Verlag; 1999:119-35.
Ph.Fr. See: *Pharmacopée Française*.
Pharmacopée Française (Ph.Fr.X). Moulins-lès-Metz, France: Maisonneuve SA; 1982–96.
Pietta P, Mauri P, Bauer R. MEKC analysis of different *Echinacea* species. *Planta Med* 1998; 64:649–52.
Pizzorno JE, Murray MT (eds.). *Textbook of Natural Medicine*, Vol. 1, 2nd ed. New York: Churchill Livingston; 1999: 703–11.
Reitz, HD. Immunomodulation with phytotherapeutic agents: a scientific study on the example of Esberitox®. [in German]. *Notebene Medici* 1990;20:362–6.
Richman A. Witkowski J. A wonderful year for herbs. *Whole Foods* 1996; Oct:52–60.
Richman A. Herb sales still strong. *Whole Foods* 1998; Oct:19–26.
Richman A. Herbs…by the numbers. *Whole Foods* 1997; Oct:20–28.
Roeder E, Wiedenfeld H, Hille Th, Britz-Kirstgen R. Pyrrolizidines in *Echinacea angustifolia* and *Echinacea purpurea*. *Deut Apoth Ztg*. 1984;124(45):2316–8.
Roesler J, Emmendorffer A, Steinmuller C, *et al*. Application of purified polysaccharides from cell cultures of the plant *Echinacea purpurea* to test subjects mediates activation of the phagocyte system. *Int J Immunopharmacol* 1991;13(7):931–41.
Scaglione F, Lund B. Efficacy in the treatment of the common cold of a preparation containing an echinacea extract. *Int J Immunother* 1995;21(4):163–6.
Schmidt U, Albrecht M, Schenk N. Botanical immunostimulant lowers frequency of influenzal infections [in German]. *Natur- und Ganzheitsmedizin* 1990;3:277–81.
Schöneberger D. The influences of immune-stimulating effects of pressed juice from *Echinacea purpurea* on the course and severity of colds: results of a double-blind study. [in German]. *Forum Immunol* 1992;8:2–12.
Schultz V, Hänsel R, Tyler V. *Rational Phytotherapy: A Physicians' Guide to Herbal Medicine*. New York: Springer-Verlag; 1997:259–60, 273–8.
See D, Berman S, Justis J, *et al*. A Phase I study on the safety of *Echinacea angustifolia* and its effect on viral load in HIV infected individuals. *JAMA* 1998;1(1):14–7.
See D, Broumand L, Sahl L, Tilles J. *In vitro* effects of echinacea and ginseng on natural killer and antibody-dependent cell cytotoxicity in healthy subjects and chronic fatigue syndrome or acquired immunodeficiency syndrome patients. *Immunopharmacol* 1997;35(3):229–35.
Speroni E, Crespi-Perellino, Guerra M, Mearelli F, Minghetti A. Skin effects of *Echinacea pallida* Nutt. root extract [oral presentation abstract]. *Fitoterapia* 1998;64(Suppl 5):36.
Stimpel M, Proksch A, Wagner H, Lohmann-Matthes M. Macrophage activation and induction of macrophage cytotoxicity by purified polysaccharide fractions from the plant *Echinacea purpurea*. *Infect Immun* 1984;46(3):845–9.
Stoll A, Renz J, Brack A. Antibacterial substances II. Isolation and constitution of echinacoside, a glycoside from the roots of *Echinacea angustifolia*. *Helv Chim Acta* 1950;33:1877–93.
Tragni E, Tubaro A, Melis S, Galli C. Evidence from two classic irritation tests for an anti–inflammatory action of a natural extract, Echinacea B. *Food Chem Toxicol* 1985;23(2):317–9.
Tubaro A, Tragni E, Del Negro P, *et al*. Anti-inflammatory activity of a polysaccharidic fraction of *Echinacea angustifolia*. *J Pharm Pharmacol* 1987;39(7):567–9.
Tunón H. Phytotherapie in Schweden. [in German]. *Z Phytother* 1999;20:269–77.
United States Congress. Public Law 103–417: *Dietary Supplement Health and Education Act of 1994* (S 7840). Washington, DC: 103rd Congress of the United States; October 25, 1994.
United States Pharmacopeia (USP 25th Revision) - The National Formulary (NF 20th Edition). Rockville, MD: United States Pharmacopeial Convention, Inc. 2002.
USC. See: United States Congress.
USP. See: United States Pharmacopeial.
Voaden D, Jacobson M. Tumor inhibitors. 3. Identification and synthesis of an oncolytic hydrocarbon form American coneflower roots. *J Med Chem* 1972;15:619–23.
Vonau B, Chard S, Mandalia S, *et al.* Does the extract of the plant *Echinacea purpurea* influence the clinical course of recurrent genital herpes? *International Journal of STD & AIDS* 2001;12:154–8.
Vorberg G. A double-blind study shows: The proven phytotherapeutic Esberitox® shortens the duration of symptoms. *Arztliche Praxis* 1984;36(6):97–8.
Vorberg G, Schneider B. Phythotherapeutic immunostimulator decreases the duration of influenza-like syndrome. Double-blind trial proves the enhancement of unspecific immune defense. [in German]. *Ärztliche Forschung* 1989;36:3–8.
Wacker A, Hilbig W. Virus-inhibition by *Echinacea purpurea.* [in German]. *Planta Med* 1978;33(1):89–102.
Wagner H, Jurcic K. Immunologic studies of plant combination preparations. *In vitro* and *in vivo* studies on the stimulation of phagocytosis. [in German]. *Arzneimittelforschung* 1991;41(10):1072–6.
Wagner H, Proksch A, Riess-Maurer I, *et al.* Immunostimulating action of polysaccharides (heteroglycans) from higher plants. [in German]. *Arzneimittelforschung* 1985;35(7):1069–75.
Wagner H, Proksch A, Riess-Maurer I, *et al*. Immunostimulant action of polysaccharides (heteroglycans) from higher plants. Preliminary communication. [in German]. *Arzneimittelforschung* 1984;34(6):659–61.
Wagner H, Breau W, Willer F, *et al*. *In vitro* inhibition of arachidonate metabolism by some alkamides and phenylated phenols. *Planta Med* 1989;55:566–7.
Wagner H. Search for potent immunostimulating agents from plants and other natural sources. In: Wagner H (ed.). *Immunomodulatory Agents from Plants*. Basel; Boston; Berlin: Birkhäuser Verlag; 1999:1–39.
Wagner H. Herbal immunostimulants for the prophylaxis and therapy of colds and influenza. *Eur J Herbal Med* 1997;3(1).
Wagner H, *et al*. Immunologically active polysaccharides of *Echinacea purpurea* cell cultures. *Phytochemistry* 1988;(27)1:119–26.
Weiss RF, Fintelmann V. *Herbal Medicine* 2nd ed. New York: Thieme; 2000:216–217.
WHO. See: World Health Organization.
Wichtl M, Bisset N (eds.). *Herbal Drugs and Phytopharmaceuticals.* Stuttgart: Medpharm Scientific Publishers; 1994:182–4.
Wildfeuer AT, Mayerhofer D. The effects of plant preparations on cellular functions in body defense. [in German]. *Arzneimittelforschung* 1994;44(3):361–6.
World Health Organization (WHO). 1999. *Herba Echinacea Purpureae Radix Echinacea* and *Radix Echinacea*. *WHO Monographs on Selected Medicinal Plants,* Vol. 1. Geneva: World Health Organization; 136–44; 125–35.
World Health Organization. *Regulatory Status of Herbal Medicines: A Worldwide Review.* Geneva, Switzerland: World Health Organization Traditional Medicine Programme; 1998:25–7.
Wüstenberg P, Henneicke von Zepelin H, Köhler G, Stammwitz U. Efficacy and mode of action of an immunomodulator herbal preparation containing echinacea, wild indigo, and white cedar. *Advs Ther* 1999;16(1):51–70.

Clinical Studies on Echinacea (*Echinacea* spp.)

Cold/Flu/Upper Respiratory Tract Infection (URTI) Treatment

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Brinkeborn *et al*., 1999	URTI symptoms	R, DB, PC (4 arm) n=246 subjects with colds	7 days from the start of acute URTI (1–2 days of symptoms)	2 tablets, 3x/day	Echinaforce® concentrate, special *E. purpurea* root preparation	Relative reduction in complaint index for 12 symptoms in the 4 groups differed significantly (p=0.015). Echinacea patients reductions in complaint index were significantly higher than in the placebo group (p=0.003 and p=0.020). Echinacea was concluded to be a low-risk, effective alternative for symptomatic acute treatment of the common cold.
Brinkeborn *et al*., 1998	URTI symptoms	R, DB, PC n=119	8 days from the start of acute URTI (1–2 days of symptoms)	Two, 400 mg tablets 3x/day	Echinaforce® tablet	Based on 12 symptoms, the "overall clinical picture" for the intention-to-treat was reduced in the treatment group from 9.0 to 4.1 (p=0.045), while the placebo group decreased from 8.8 to 5.3. Echinacea was concluded to be a low-risk, effective alternative for symptomatic acute treatment of the common cold.
Dorn *et al*., 1997	URTI symptoms	R, DB, PC n=160 (ages >18 years)	8–10 days from onset of flu-like respiratory symptoms	45 drops extract 2x/day (equivalent to 900 mg/day)	Brand not stated	The length of the illness decreased from 13 to 9.8 days (bacterial infections) and to 9.1 days (viral infections) compared to placebo (p=0.0001). The infection type was determined by lymphocyte and neutrophil counts in the blood. Echinacea appears to shorten the duration of URTIs.
Hoheisel *et al*., 1997	URTI symptoms	R, DB, PC n=120 with at least 3 infections in the past 6 months	10 days from the first sign of URTI, before full development	20 drops, every 2 hours on day 1, 20 drops, 3x/day thereafter	Echinaguard® extract	Of the echinacea group, 40% developed a "real cold" compared to 60% in the placebo group (p=0.044), while in 4 days symptoms improved for echinacea group compared to 8 days for the placebo group. Echinacea showed more rapid recovery in the intention-to-treat population (p<0.0001).
Galea and Thacker, 1996	URTI symptoms	R, DB, PC, P n=190	From the first sign of URTI through 10 days	250 mg capsule	*E. angustifolia* root dried (brand not stated)	8 symptoms were assessed and no measurable benefits were reported, attributed to the relatively low dose and lack of severity of the symptoms being measured.
Bräunig *et al*., 1992	Flu-like symptoms	R, DB, PC n=180 one group of 60 per preparation	From onset of flu-like respiratory symptoms until symptoms subsided	90 drops (450 mg)/day or 180 drops (900 mg)/day	*E. purpurea* root extract (1:5, 55% ethanol) (brand not stated)	Echinacea patients receiving 180 drops (900 mg) dose displayed statistically significant improvement (p<0.05) compared with placebo group in relieving symptoms and decreasing the duration of symptoms. The study suggests that dosage influences effectiveness.

Combination Preparations (Treatment)

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Lindenmuth and Lindenmuth, 2000	Cold, flu-like, URTI symptoms	R, DB, PC n=95 with early symptoms of cold or flu, primarily females (mean age 39.7 years)	From first sign of flu-like symptoms through 6 days	5–6 cups tea first day of symptoms and titrating down 1 cup of tea/day for next 5 days (equivalent of 1,275 mg dried herb and root per tea bag serving)	Echinacea Plus® tea vs. Traditional Medicinals Eater's Digest® herbal tea (placebo)	Based on questionnaire on effectiveness of echinacea, duration of symptoms, and time taken for subjects to notice any changes in symptoms, echinacea group was shown to be statistically significant in effectiveness (p<0.001); duration (p<0.001); and in noticeable change in symptoms (p<0.001). Authors concluded that treatment with echinacea compound tea, given at early onset of symptoms was effective in relieving cold or flu symptoms in noticeably fewer days compared to placebo.
Henneicke-von Zepelin *et al*., 1999	Common cold (acute viral URTI)	R, DB, PC, MC (15 centers) n=238 patients (ages 18–70 years)	7–9 days once identified as having a common cold	3 tablets 3x/day	Esberitox® N2 tablet vs. placebo	The echinacea combination product was significantly better than placebo (p=0.0497), with highly statistically significant results in overall well-being (p=0.0048), rhinitis, and bronchitis scores. This study suggests this is a safe and effective treatment and notes the greatest benefits would be experienced if treatment is started as soon as possible after onset of the cold.

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Clinical Studies on Echinacea (*Echinacea* spp.) (cont.)

Combination Preparations (Treatment) (cont.)

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Reitz,1990	URTI symptoms and signs	R, DB, PC n=150	8 weeks initially, with monitoring for an additional year	One, 22.5 mg tablet 3x/day or placebo (vitamin C)	Esberitox® N1 tablet vs. placebo	Majority of symptoms and signs at 7 and 14 days were significantly better than placebo; nasal symptoms were most affected. No difference in result from blood work was reported.
Dorn, 1989	URTI symptoms and signs	R, DB, PC n=100	From 2 days of URTI onset	Day 1–2: 30 ml/day Day 3–6: 15 ml/day	Resistan® vs. placebo	Echinacea patients experienced a decrease in the length of illness and severity in 7 of 7 self-assessed symptoms compared to 4 of 7 in placebo group (p=0.001). The study suggests that taking the preparation as soon as symptoms first appear shortens duration of URTI.
Vorberg and Schneider, 1989	URTI symptoms and signs	R, DB, PC n=100	10 days beginning 2 days after onset of URTI	15–30 ml/day	Resistan® vs. placebo	Most symptoms were significantly better in the echinacea group compared to placebo at both 2 to 3 days and at 8 to 10 days. The results indicate echinacea has efficacy for the prevention and treatment of URTIs.
Vorberg, 1984	URTI symptoms and signs in patients suffering from common cold	R, DB, PC n=100	10 days	15 mg tablet 3x/day	Esberitox® tablet vs. placebo	Echinacea group reported significant superiority compared to placebo group in all examined parameters of common cold (p<0.001) including fatigue, reduced performance, runny nose, and sore throat.

Cold/Flu/URTI Prevention

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Grimm and Müller, 1999	URTI occurrence	R, PC n=108 with history of 3 colds or respiratory infections in the preceding year (mean age echinacea group 42 years; mean age placebo group 38 years)	2 months	4 ml expressed juice 2x/day	*E. purpurea* fluid (expressed juice of aerial parts, brand not stated, though test material was provided by Madaus AG and it presumably is Echinacin®)	During 8-week treatment period, 35 (65%) of 54 patients in echinacea group and 40 (74%) of 54 patients in placebo group had at least one cold or respiratory infection (relative risk [RR]=0.88; 95% confidence interval [CI] [0.60, 1.22]). Average number of colds and respiratory infections per patient was 0.78 in echinacea group, and 0.93 in placebo group (difference=0.15; 95% CI [-0.12, 0.41], p=0.33). Median duration of colds and respiratory infections was 4.5 days in echinacea group and 6.5 days in placebo group (95% CI [-1, +3 days]; p=0.45). There were no significant differences between treatment groups in number of, duration, or severity of colds. Side effects were observed in 11 patients (20%) of echinacea group and in 7 patients (13%) of placebo group (p=0.44).
Melchart *et al*., 1998	URTI occurrence	R, DB, PC n=289 (ages 18–65 years)	12 weeks (M-F only)	50 drops *E. angustifolia* 2x/day or 50 drops *E. purpurea* 2x/day or placebo	*E. angustifolia* and *E. purpurea* roots extracts (1:11 in 30% ethanol) (brand not stated)	Participants in treatment group believed they had more benefit than placebo group (p=0.04). URTIs (at least one) were experienced by 32%, 29%, and 37% of *E. angustifolia*, *E. purpurea*, and placebo groups respectively, and onset was at 66, 69, and 65 days, respectively, with no significant differences in duration, incidence, or severity of URTIs. Noncontinuous administration of treatment was not addressed in the conclusion.
Schöneberger, 1992	URTI occurrence	R, DB, PC, MC n=108 patients with increased susceptibility to colds (suffered at least 3 colds in previous year) (ages 13–84 years)	2 months	4 ml 2x/day	Echinacin®	Echinacea group experienced decreased in URTI incidence in 35% (vs. 26%), decrease in duration of 5.34 days (vs. 7.54 days), increase in interval between infections of 40 days (vs. 25 days), and decreased severity of symptoms calculated as 78% (vs. 68%) compared with placebo. Patients with weakened defense (calculated as a T4/T8-ratio of less than 1.5) benefited most.

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Clinical Studies on Echinacea (*Echinacea* spp.) (cont.)

Combination Preparations (Prevention)

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Schmidt *et al.*, 1990	URTI occurrence	R, DB, PC n=609 college students	2 months	12 ml/day	Resistan® vs. placebo	Echinacea patients experienced 15% fewer primary infections, and relapses decreased by 27%, or relative risk reduction of 12%. Due to potential immuno-stimulant activity of other botanicals, the results could not be attributed to echinacea alone.
Forth and Beuscher, 1981	URTI occurrence	R, PC (not fully double-blind) n=95	16 weeks (November through February)	25 drops 3x/day or 1 mg tablet or placebo	Esberitox®	Patients had relative risk reduction of 49% overall, even though no apparent difference for other 7 symptoms was observed in all groups compared to placebo. However, improvement of nasal symptoms was significant.

Other

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Vonau *et al.*, 2001	Effect on clinical course of genital herpes	SC, P, DB, PC, CO n=50 (mean age 36.5 years)	1 year (6 months placebo, 6 months echinacea)	800 mg 2x/day	Echinaforce® tablet	No statistically significant benefit was shown for use of echinacea to treat frequently recurring genital herpes.
Gallo *et al.*, 2000	Safety of gestational exposure to echinacea	P, C n=206 patients who used echinacea during pregnancy	Until birth or termination of the pregnancy n=112 (echinacea used during first trimester)	Range of 250–1,000 mg/day capsule or tablets taken by 114 females or range of 5–10 to 30 drops maximum/day taken by 76 females continuously for 5–7 days	Primarily *E. angustifolia* and *E. purpurea*; only one reported using *E. pallida* (brand not stated)	Of 206 subjects who used echinacea during pregnancy, there were 195 live births, 13 spontaneous abortions, and one therapeutic abortion, compared to the control group giving 198 live births, 7 spontaneous abortions, and 1 therapeutic abortion. These results indicated no statistical differences between the 2 groups in terms of pregnancy outcome, delivery method, maternal weight gain, gestational age, birth weight, or fetal distress. Rates of major malformation between study and control groups were not statistically different.
Berg *et al.*, 1998	Exercise-induced immunological effects	R, PC, PG n=42 male athletes, 3 groups (mean age 27.5 years)	28 days (prior to triathlon)	40 drops 3x/day (8 ml/day) (n=14) or magnesium (n=13) or placebo (n=13)	Echinacin®	Echinacea facilitated IL-6 release and reduced SIL-2R release in serum and urine, significantly increased serum cortisol (one hour after the event), and may exert slight effects on natural killer cells and T-cells. Echinacea group did not report any URTIs compared to 7 total from 2 other groups, along with 6 reporting other infections.
Coeugniet and Kuhnast, 1986	Chronic candidiasis in females	OL, Cm (5-arm) n=203	10 weeks	30 drops 3x/day with cream for 6 days (n=60) or cream alone (6 days only) (n=43)	Echinacin® and econazole nitrate cream (antimycotic treatment)	Use of echinacea as adjunct therapy reduced recurrence rate 5–16% compared to women using only cream, who experienced a recurrence rate of 60.5%.

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