



ECHINILIN[®]

Echinacea purpurea

Phytopharmaceutical Name:

Echinacea purpurea

Description: *ECHINILIN* is the only patented triple-standardized phytopharmaceutical that is certified organic and has completed two Phase II clinical trials with statistically significant and reproducible evidence of effectiveness as an immune system stimulant. *ECHINILIN* is the first phytopharmaceutical that is unconditionally guaranteed for pharmaceutical purity in labeled potency of standardized levels of *Echinacea purpurea*'s three key active compounds.

Pharmacological Properties: In vitro and in vivo studies demonstrate that *ECHINILIN* stimulates the immune system via standardized levels of three key active compounds found in *Echinacea purpurea*, which are alkylamides, polysaccharides and cichoric acid. The randomized, double-blinded, placebo-controlled Phase II trials clearly indicate that *ECHINILIN* possesses viral fighting ability, with patients reporting statistically significant reductions in the severity of the common cold.

Indicated Use: *ECHINILIN* is indicated for the treatment of upper respiratory viral infections, to reduce infection severity and duration. When taken for acute immune support at the first sign of a viral infection, (chills, fever, muscle ache, headache, sore throat, cough or congestion), *ECHINILIN* can be expected to prevent upper respiratory viral infections from developing, such as the common cold.

ECHINILIN may also be indicated in upper respiratory viral infections to reduce the risk of acquiring a secondary bacterial infection, and/or the establishment of exaggerated mucus membrane inflammation.

Prophylactic use of *ECHINILIN* may also be useful for those particularly at risk of upper respiratory infections due to age or risk exposure conditions, such as teachers, physicians, healthcare workers, airline passengers, and others.

***ECHINILIN* Enhances Immunomodulation:** *ECHINILIN* demonstrated its ability to stimulate the innate (non-specific) immune system in two Phase II clinical trials. These randomized, double-blinded and placebo-controlled studies clearly showed that *ECHINILIN* reduces the duration and severity of the common cold.

The results of these clinical trials are further supported through in vitro studies with *Echinacea purpurea*, which demonstrated its ability to induce immunomodulation of the innate immune system.^{1,2} *Echinacea* has been shown to stimulate phagocytic activity of macrophages,^{3,4,5} the production of macrophage cytokines which are crucial proteins for mediating the immune system, such as interleukin-1 (IL-1), interleukin-6 (IL-6), tumour necrosis factor-A(TNF-A),^{1,6,7,8} and enhance natural killer cell function of human peripheral blood mononuclear cells.^{9,10}

Bioactive Constituents: Of the many botanical constituents that have been investigated in *Echinacea purpurea*, cichoric acid, polysaccharides, and alkylamides are considered to be the most important botanical bioactives for modulating the innate immune system.¹¹ *ECHINILIN* incorporates all three of these key bioactives in order to capture each of their unique immunomodulatory nuances.

Botanical Background: *Echinacea* is a member of the daisy or Asteraceae family, and the genus name for a perennial flowering herb called the purple coneflower. *Echinacea* is native to North America, with *Echinacea purpurea* being the most commonly used and extensively studied species.^{12,13,14}

Traditional Use of *Echinacea purpurea*: The herb *Echinacea purpurea* has a long history of traditional use for fighting off colds, influenza and infections, especially upper respiratory track infections, as attested to by a number of authorities.^{11,15,16,17,18}

***ECHINILIN* Provides Product Standardization:** *ECHINILIN* successfully addresses product standardization requirements through its proprietary formulation. In addition, full spectrum extraction methodology ensures precise isolation and concentration of the key bioactive constituents. *ECHINILIN* is the only commercial extract of any *Echinacea* species to provide standardized concentrations of the three immunomodulating botanical bioactives, which gives *ECHINILIN* its pharmacological consistency and effect.

***ECHINILIN* Dosing Scientifically Defined:** *ECHINILIN* research is the first to provide defined efficacious phytopharmaceutical dosing of any *Echinacea* species. This was accomplished by researching effective dosing options through in vivo, quantitative and dose-related animal studies.^{19,20} *ECHINILIN* dosing for humans is based on pharmacological information derived from effective animal dosing, which has been confirmed in two Phase II clinical trials.

***ECHINILIN* Research:** *ECHINILIN* research conformed to the high standards of pharmaceutical investigations, in which its bioactive constituents were evaluated via in vitro, in vivo animal studies, and through randomized, double-blinded, placebo-controlled clinical trials.

Animal Studies: In vivo dose-related animal research with *ECHINILIN* demonstrates statistically significant linear increases in the alveolar macrophage phagocytic response, compared to the response associated with the placebo agent.^{19,20} Phagocytosis is the central biological feature of the innate immune response against foreign particles like bacteria and viruses. The dose-related and statistically significant increase in phagocytosis in the in vivo mammalian model is evidence that the bioactive components in *ECHINILIN* induce immunomodulation and provide biological plausibility for similar effects in human alveolar macrophages.^{19,20}

The *in vivo* dose-related animal research with *ECHINILIN* also demonstrates a statistically significant increase in alveolar macrophage production of tumor necrosis factor-A (TNF-A) and nitric oxide.^{19,20} Since the release of nitric oxide is known to be the predominant mechanism by which alveolar macrophages chemically destroy foreign particles in the lungs,^{21,22} the ability of *ECHINILIN* to induce nitric oxide release demonstrates another important mechanism of its efficacy in mammalian lung tissue. As well, the increased release of TNF- by *ECHINILIN* is thought to relate to its antiviral effects and may explain why it appears to have both a preventative and a therapeutic effect.^{19,20}

Phase II Clinical Trial No.1:²³ The objective of this randomized, double-blinded, placebo-controlled clinical trial was to test the efficacy of *ECHINILIN* in reducing both the severity and the duration of the symptoms of a naturally acquired common cold. Participants were recruited, with 282 meeting inclusion criteria and assigned by randomization to the treatment and placebo groups. Of these 282 participants, 128 developed a naturally acquired common cold, and of these 128 participants, 17 failed to meet trial completion criteria, or discontinued treatment. The remaining qualified participants were 111, with 54 in the *ECHINILIN* group and 57 in the placebo group.

Trial results were based on a 7-day treatment period in which the participants would take the *ECHINILIN* or placebo treatments at the first sign of a common cold. Self-assessed daily symptom severity scores, based on a trial provided scale, were used to assess the severity of cold symptoms between the *ECHINILIN* and placebo treatments. Participants entered their symptom severity scores in a daily log at the same approximate time each evening. A physician trained trial nurse also performed visual and physical examinations on the mornings of day-3 and day-8 to assess participants' severity of symptoms.

The nurse also examined participants for possible secondary complications such as sinusitis, bronchitis, conjunctivitis, otitis media, and pneumonia. The symptoms reported on in the trial data analysis were the seven "most annoying symptoms" of previous colds identified by the majority of participants, which included: runny nose, sore throat, stuffy nose, cough, fatigue, headache, and sneezing. A Total Daily Symptom Score (TDSS) was determined for each of the 7 trial days by adding the seven individual symptom scores for the respective days.

Results: At the end of the 7-day trial, the average TDSS (mean of 7 days) was found to be 23.1 percent lower in the *ECHINILIN* group than in the placebo group ($P < 0.01$). Throughout the 7 days of treatment, the response rate to treatment was greater in the *ECHINILIN* group, illustrated in Figure 1.

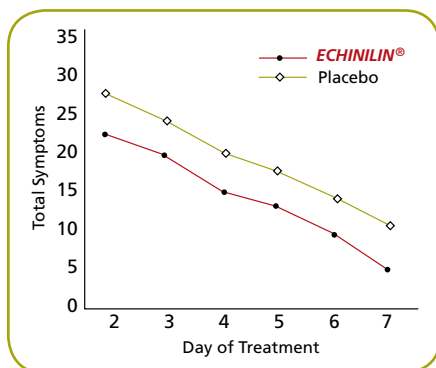


Figure 1 Total Daily Symptom Scores (TDSS) during treatment with *ECHINILIN* or placebo

Figure 2 illustrates the overall mean self-assessed symptom severity score differences between the *ECHINILIN* and placebo treatments for the 7-day treatment period.

The 7-day mean severity scores for runny nose, sore throat, stuffy nose, fatigue, headache and chills were respectively found to be 27, 25, 22, 31, 39, and 44 percent ($P < 0.05$) lower in the *ECHINILIN* group than in the placebo group. Only cough was higher in the *ECHINILIN* group than in the placebo group.

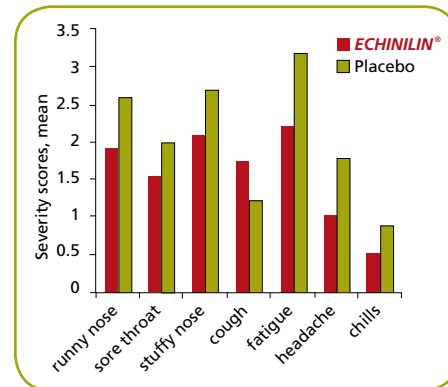


Figure 2. The mean symptom severity scores during treatment with *ECHINILIN* and placebo.

Similar results were also obtained from assessments made by the trial nurse. In fact, the nurse's scores and the self-assessed symptom severity scores showed significantly high

Pearson correlation coefficients. This verification of the participants self-assessment scores by the physician trained trial nurse also validates the effectiveness and superiority of the highly standardized *ECHINILIN* over the placebo in reducing the severity of cold symptoms and the duration of the common cold. It is of interest to note that nurse-obtained evidence for the development of secondary complications, such as bronchitis, was found in two cases treated with *ECHINILIN* and five cases treated with placebo. This evidence may indicate that *ECHINILIN* has a preventive role in secondary infections.

In regards to the duration of symptoms, the treatment response rate was greater with *ECHINILIN* than with the placebo. By day-4, 50 percent of the participants in the *ECHINILIN* group showed at least a 50 percent reduction of their maximum TDSS, illustrated in Figure 3. This measure of symptom reduction was not evident in the placebo group until approximately 5.5 days. This represents a shortening of the cold duration by approximately 1.5 days or 27 percent and the potential for a more rapid return to normal activity and productivity. Furthermore, the response rate by day-7 increased to 95 percent in the *ECHINILIN* group, but to 63 percent in the placebo group. Thus, in terms of the overall response rate, by day-7 *ECHINILIN* demonstrated a 51 percent greater efficacy in treatment outcome compared to placebo.

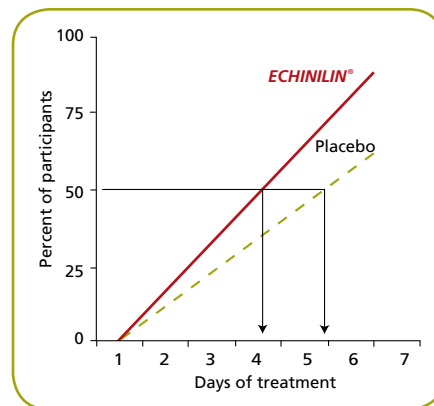


Figure 3. Treatment response rate: Percent of participants demonstrating at least a 50% reduction in their maximum TDSS.

Of interest is the observation that neuraminidase inhibitors as a class generally do not provide a greater reduction in course duration of influenza viral infections than approximately 1.3

days.²⁴ Thus, the *ECHINILIN* intervention outcome for upper respiratory infection of the common cold is comparable to that of neuraminidase inhibitors for treating acute influenza infections,^{25,26} but without the adverse side effect profile and costs associated with neuraminidase inhibitors. In addition, neuraminidase inhibitors only work for specific strains of influenza, whereas *ECHINILIN* does not appear to have that limitation.

Summary: The foregoing animal and clinical research information concerning *ECHINILIN*, manufactured from freshly harvested Echinacea purpurea plants and triple standardized on the basis of the three most

productive bioactive plant components, demonstrates that early use of *ECHINILIN* for the common cold results in reducing the cold symptoms and duration, and that these results are attributed to enhanced alveolar macrophage phagocytosis with timely viral destruction and thereby reduced propensity for symptom-driven inflammation. These results also indicate that *ECHINILIN* performance presents a rationale for preventative use for the common cold, or other viral upper respiratory infections.

Directions and Dosages: *ECHINILIN* is intended for therapeutic and preventative use. The recommended daily dosages are given below.

Therapeutic Use: At the first sign of a viral infection (including the common cold), take 1 softgel 5 times per day for the first two days. Take 1 softgel 3 times per day on subsequent days until symptoms resolve, or as directed by a physician.

Preventative Use: Throughout the year take 1 softgel daily when immune system needs support.

Adverse Effects: In the *ECHINILIN* clinical trials, gastrointestinal adverse effects, (nausea, heartburn and constipation), were reported by 13 percent of the *ECHINILIN* treatment group, compared with 9 percent of the group who were given a placebo. Other adverse effects included itching, burning sensation, and numbness of the tongue were reported by 13 percent of the *ECHINILIN* treatment group, compared with 11 percent of the placebo group. However, no participants withdrew as a result of these events.²³

Historically, the incidence of adverse effects with *Echinacea purpurea* has been extraordinarily low. However, in rare cases some people may experience fever, nausea, vomiting, unpleasant taste, abdominal pain, diarrhoea, sore throat, dizziness, and allergy.²⁷

Reports by Parnham of the potential for adverse effects thought to be possibly associated with *Echinacea purpurea*, indicated that there were only 13 adverse events reported to the German Federal Health Authority between 1989 and 1995, of which four were judged to be clearly caused by *Echinacea* exposure. All four were allergic skin rashes.^{28,29} Barrett comments on this very low incidence rate, noting that in the same time period several millions of people in Germany used *Echinacea purpurea* by self-selection or by physician prescription without reported adverse effects, suggesting that *Echinacea purpurea* has a similar incidence of adverse effects associated with wheat, milk, or peanuts.³⁰

Yang et al. note that reports of *Echinacea* adverse effects in California fit into a category of mild, manageable at home, and rarely resulting in severe outcomes or sequelae.³¹

Allergic Reactions: There were no reports of allergic reactions or anaphylaxis associated with *ECHINILIN* or the placebo groups during the clinical trials.²³

A measure of the risk for allergic reaction with *Echinacea* is indicated by De Smet et al. who patch-tested 1,032 people with *Echinacea*, but found that only 2 subjects showed positive inflammatory reactions.³²

Barrett observes that there have been rare reports of allergic reactions, but most reactions occurred in situations where a causal relationship could not be established. He further notes that the most convincing rationale for the safety of *Echinacea* comes from the epidemiological evidence, in which the ratio of reported serious adverse effects, compared to the estimated number of courses of *Echinacea* treatment, is respectively 100 to more than 10 million, yielding a risk estimate of 1 in 100,000.³⁰

Australian researchers have noted that individuals with atopy may be more likely to encounter an allergic reaction.³³ Mullins et al. reviewed 51 reports of adverse drug effects in which *Echinacea* was implicated, 26 of which were suggestive of possible IgE mediated hypersensitivity (4 anaphylaxis, 12 acute asthma, and 10 urticaria/angioedema).³⁴

Echinacea is used in Australia to a similar extent to that of Canada, the United States, and Europe,^{35,36} implying that hundreds of thousands of

courses of *Echinacea* are used each year, so that the actual incidence of serious allergic reaction is very small, and the data implies relative safety rather than risk.³⁰

People allergic to the Asteraceae family of plants, (ragweed, chrysanthemums, marigolds, and daisies), may also be more likely to experience an allergic reaction to *Echinacea*.

Toxicology: There were no reports of toxic effects associated with *ECHINILIN* during the Phase II clinical trials.²³

Standard toxicological assessment methods have not demonstrated any *Echinacea purpurea* related toxicity in animals.³⁰

Mengs et al. report that a single oral dose of 15 grams/kg or single intravenous dose of 5 grams/kg produced no abnormalities from the *Echinacea purpurea* and that no LD50 calculation could be made.³⁷ Mengs et al. also found that after 4 weeks of oral dosing of male and female rats at 800, 2400, and 8000 mg/kg per day of *Echinacea purpurea*, amounts that are exceedingly greater than human therapeutic doses, laboratory tests and necropsy findings gave no evidence of any toxic effects in rats.³⁷

Tests for mutagenicity carried out on microorganisms and mammalian cells in vitro and in mice all gave negative results. In vitro carcinogenicity testing using *Echinacea purpurea* did not produce malignant transformations in hamster embryo cells.³⁷ Mengs et al. conclude that in view of the favourable toxicology results and several decades of experience in human use, *Echinacea purpurea* can be classified as non-toxic, and particularly in reference to genotoxic risk.³⁷

Drug Interactions: There were no reported incidences of drug interactions associated with *ECHINILIN* during the Phase II clinical trial.²³

Because *Echinacea purpurea* has immunostimulating action, there is theoretical concern that it could interfere with immunosuppressant therapy.³⁸

Although Gorski et al.³⁹ found some indication of potential for *Echinacea purpurea* to affect the cytochrome P450 system, in clinical terms there has been no practical body of evidence indicating *Echinacea purpurea* has significant adverse cytochrome P450 interactions as reported in humans. It should be noted that inhibition of the cytochrome P450 system is actually quite common and is in fact affected by numerous foods.^{27,40}

Concern has also been expressed that pyrrolizidine alkaloids found in *Echinacea purpurea* might exert hepatotoxic effects when it is taken on a long-term basis, exacerbating the harmful effects of concurrently used hepatotoxic drugs. However, Miller questions the magnitude of any hepatotoxic effect of *Echinacea purpurea* since it lacks the specific class of pyrrolizidine alkaloids that contain the 1, 2-unsaturated ring system responsible for hepatotoxicity.^{40,41}

Use In Pregnancy: *Echinacea purpurea* has a long history of safe use, with no documented cases of birth defects. Gallo et al.⁴² studied a cohort of 206 women with 112 using *Echinacea* during the first trimester with cases risk-matched with controls. Similar numbers of stillbirths, chromosome abnormalities, and malformations were found in the two groups. Gallo et al. reached the conclusion that gestational use of *Echinacea* during organogenesis is not associated with an increased risk for major malformations. The study's statistical power to conclude that *Echinacea* is safe to use during pregnancy has been questioned by others, however.⁴³

Contraindications: There are no contraindications established for *ECHINILIN*. Furthermore, *Echinacea purpurea* products in general have not been associated with contraindications in North American experience given its safety record and low incidence of serious adverse effects.

However, the German Commission E has suggested that its use be restricted to 6 weeks, but provides no evidence that harm could arise if used indefinitely as a preventative.^{18,43} The German Commission E has also indicated that use of *Echinacea* is contraindicated in those

with chronic progressive diseases that are mediated by the immune system, including tuberculosis, rheumatoid arthritis, collagen vascular disease, and multiple sclerosis.⁴⁴ Barrett states that such restrictions have been considered theoretical because there is no empirical evidence to support or refute them, nevertheless he views them as precautions to be aware of since harm could arise from unexpected immune-mediated inflammation induced by Echinacea.³⁰

Supplied: *ECHINILIN* is available in softgel capsules, tinctures and in cough syrup formulas. The non-medicinal constituents of *ECHINILIN* are required to stabilize its bioactives, and include vegetable oil shortening, vegetable oil, starch, lecithin, carob, silicon dioxide, gelatin, glycerin and water.

This Monograph is based on currently available scientific information and therefore is subject to updating and is not intended for general distribution.

References

- Stimpel, H., et al., "Macrophage activation and induction of macrophage cytotoxicity by purified polysaccharide fractions from the plant *Echinacea purpurea*," *Infect Immun*, 46:845-849, 1984
- Leuttig, C., et al., "Macrophage activation by the polysaccharide arabinogalactin isolated from plant cell cultures of *Echinacea purpurea*," *J Natl Cancer Inst* 81:669-675, 1989
- Wagner, H., et al., "Immunologic studies of plant combination preparations. in vitro and in vivo studies on the stimulation of phagocytosis," *Arzneimittel Forschung*, 41:1072-1076, 1991
- Stotzem, C.D., et al., "Influence of *Echinacea purpurea* on the phagocytosis of human granulocytes," *Med Sci Res*, 20:719-720, 1992
- Bukovsky, M., et al., "Testing for immunomodulating effects of ethanol-water extracts of the above ground parts of plant *Echinacea* (Moench) and *Rudbeckia L.*," *Ceskoslovenska Farmacia*, 42:228-231, 1993
- Burger, R.A., et al., "Echinacea induced cytokine production by human macrophages," *Int J Immunopharmacol*, 19:371-379, 1997
- Roesler, A., et al., "Application of purified polysaccharides from cell cultures of the plant *Echinacea purpurea* to test subjects mediates activation of the phagocyte system," *Intl J Immunopharmacol*, 13: 931-941, 1991
- Steinmuller, C., et al., "Polysaccharides isolated from plant cell cultures of *Echinacea purpurea* enhance the resistance of immunosuppressed mice against systemic infections with *Candida albicans* and *Listeria monocytogenes*," *Intl J Immunopharmacol*, 15:605-614, 1993
- See, D.M., et al., "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," *J Immunopharmacol*, 35:229-235, 1997
- Currier, N.L., et al., "Natural killer cells from aging mice treated with extracts from *Echinacea purpurea* are quantitatively and functionally rejuvenated," *Exp Gerontol*, 35:627-639, 2000
- Bauer, R., et al., "Echinacea species as potential in immunostimulatory drugs," In Wagner H., Farnsworth, N.R., editors, *Economic and Medicinal Plants Research*, Vol 5, London (UK), Academic Press, 1991
- Bauer, R., et al., "HPLC analysis of *Echinacea* simulate and *E. paradoxa* roots," *Planta Medica*, 55:637, 1989
- O'Hara, M.A., et al., "A Review of 12 commonly used medicinal herbs," *Arch Family Med*, 7(6):523-536, 1998
- Murray, Michael T., *The Healing Power of Herbs*, Prima Publishing, Rocklin, CA, 1995
- Awang, D.V.C., et al., "Herbal Medicine, Echinacea," *Canadian Pharmaceutical Journal*, 124: 512-516, 1991
- Barnes, J., et al., *Herbal Medicines: A guide for healthcare professionals*, 2nd edition, London (UK), Pharmaceutical Press, 2002
- Blumenthal, M., et al., editors, *Herbal Medicine: Expanded Commission E Monographs*, Boston, MA, Integrative Medicine Communications, 2000
- Boon, H., et al., *The Botanical Pharmacy: The Pharmacology of 47 Common Herbs*, Kingston, ON, Quarry Press Inc. 1999
- Goel, V., et al., "Alkylamides of *Echinacea purpurea* stimulate alveolar macrophage function in normal rats," *International Immunopharmacology*, 2:382-387, 2002
- Goel, V., et al., "Echinacea stimulates macrophage function in lung and spleen of normal rats," *J Nutr Biochem*, 13:487-492, 2002
- Ding, A., et al., "Release of reactive nitrogen intermediates and reactive oxygen intermediates from mouse peritoneal macrophages. Comparison of activating cytokines and evidence for independent production," *J Immunol*, 141:2407-2412, 1988
- Kaplan, J.R., et al., "Effect of nitric oxide on staphylococcal killing and interactive effect with superoxide," *Infect Immun*, 64:69-76, 1996
- Goel, V., et al., "Efficacy of a standardized Echinacea preparation (Echinilin™) for the treatment of the common cold: a randomized, double-blind, placebo-controlled trial," *Journal of Clinical Pharmacy and Therapeutics*, 29: 75-83, 2004
- Canadian Pharmacists Association, "Tamiflu™ Monograph," *Compendium of Pharmaceuticals and Specialties*, 1653-1654, 2003
- Makela, M.J., et al., "Clinical efficacy and safety of the orally inhaled neuraminidase inhibitor zanamivir in the treatment of influenza: a randomized, double-blinded, placebo-controlled European study," *Journal of Infection*, 40: 42-48, 2000
- Management of Influenza in the Southern Hemisphere Trialists Study Group, "Randomized trial of efficacy and safety of inhaled zanamivir in treatment of influenza A and B virus infections," *Lancet*, 352: 1877-1881, 1998
- Jellin, J.M., et al., "Pharmacist's Letter/Prescriber's Letter," *Natural Medicines Comprehensive Database*, 4th edition, Stockton, CA: Therapeutic Research Faculty, 2002
- Parnham, M.J., "Benefit-risk assessment of the squeezed sap of the purple coneflower (*Echinacea purpurea*) for long-term oral immunostimulation," *Phytomedicine*, 3:95-102, 1996
- Parnham, M.J., "Benefit and risk of the squeezed sap of the purple coneflower (*Echinacea purpurea*) for long-term oral immunostimulation," *Immunomodulatory Agents from Plants*, Wagner, H., editor, Basel, Boston, Berlin, Birkhauser Verlag, pp 119-136, 1999
- Barrett, B., "Echinacea: A Safety Review," *Herbal-Gram*, 57:36-39, 2003
- Yang, S. et al., "Characterizing Adverse events Reported to the California Control System on Herbal Remedies and Dietary Supplements: A pilot Study," *Herbal Pharmacotherapy*, 2(3):1-11, 2002
- De Smet, P.A.G.M., et al., *Adverse Effects of Herbal Drugs*, Vol 3, Berlin, Heidelberg, New York, Springer-Verlag, 1997
- Mullins, R.J., "Allergic reactions to Echinacea," *J Allergy Clin Immunol*, 104 (1 of part 2):s340-s341 (Abstract 1003)
- Mullins, R.J., et al., "Adverse reactions associated with echinacea: The Australian Experience," *Annals of Allergy, Asthma & Immunology*, 88 (1):42-51, 2002
- MacLennan, A.H., et al., "Prevalence and cost of alternative medicine in Australia," *Lancet*, 347:569-573, 1996
- Drew, A.K., et al., "Safety issues in herbal medicine: Implications for the health professions," *Med J Aust*, 166:538-541, 1997
- Mengs, U., et al., "Toxicity of *Echinacea purpurea*. Acute, subacute and genotoxicity studies," *Arzneimittel Forschung (Drug Research)*, 41(II):1076-81, 1991
- Newall, C.A., et al., *Herbal Medicine: A Guide for Healthcare Professionals*, The Pharmaceutical Press, London, UK, 1996
- Gorski, J.C., et al., "The effect of echinacea (*Echinacea purpurea* root) on cytochrome P450 activity in vivo," *Clin Pharmacol Ther*, Jan;75(1):89-100, 2004
- Miller, L., "Herbal medicinals: selected clinical considerations focusing on known or potential drug-herb interactions," *Archives of Internal Medicine*, 159(9):2200-2211, 1998
- Bauer, R., "Chemistry, analysis and immunological investigations of *Echinacea* phytopharmaceuticals," *Immunomodulatory Agents from Plants*, Wagner, H., Editor, Birkhauser Verlag, Basel, Switzerland, 1999
- Gallo, M., et al., "Pregnancy outcome following gestational exposure to echinacea: a prospective controlled study," *Annals of Internal Medicine*, 160:3141-3143, 2000
- Blumenthal, M., et al., *The Complete German Commission E Monographs: Therapeutic Guide to Herbal Medicines*, Austin, TX, American Botanical Council, Boston, MA: Integrative Medicine Communications, 1998
- Blumenthal, M., et al., "Echinacea: *Echinacea purpurea* (L) Moench, *E. pallida* (Nutt) Nutt, *E. angustifolia* D.C. [Family Asteraceae]," *The ABC Clinical Guide to Herbs*, Austin, TX, American Botanical Council, 2000

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