The benefits and risks of Echinacea in treatment of common cold and influenza

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ABSTRACT

The common cold is one of the world’s most prevalent illnesses in adults and children. This upper respiratory tract infection is caused by different kinds of agents. Effects on health, well-being, and productivity are significant. Preparations made from plants of the genus Echinacea are widely used for the prevention and treatment of colds. Three species of Echinacea used for medicinal purposes are Echinacea purpurea, Echinacea angustifolia, and Echinacea pallida. The beneficial effects of Echinacea are thought to be due to its immunomodulatory activity, most notably activation of macrophages, polymorphonuclear leukocytes and natural killer cells. Many clinical trials, including a number of blind randomized trials, have reported health benefits. Although these studies show beneficial effects, recommendations on Echinacea use cannot be made due to lack of product standardization and variability in dosage, sample size and methodological quality used in the trials. Therefore, well-designed studies with consistent standardized measures are required for assessment of the efficacy of Echinacea in treatment of common cold and influenza.

Keywords: Echinacea, immunomodulation, common cold, influenza

INTRODUCTION

The common cold is one of the most prevalent illnesses in the United States. The infection is self-limited, usually resolving within a week, but a number of viruses may persist more than three weeks, because of the large number of viral strains involved. The infection causes considerable economic loss, due to loss of 40% of work time and 30% of school time. Adults experience an average of 2-4 infections annually, whereas children experience 6-10 infections a year. A study conducted in the United States in 2003 showed that Americans spend 3 billion dollars annually on medical visits and over-the-counter (OTC) drugs. At least one third of patients are prescribed antibiotics, although these drugs are not effective in viral infections. This not only adds to the costs, but also contributes to the emergence of bacterial antibiotic resistance.
The use of herbal supplements has increased by more than 100% in the last decade.\textsuperscript{(3)} One of the factors accounting for this situation is the high cost of prescription drugs and the increased awareness of people of the side effects of these drugs. In addition, there is a widely held belief in the community that herbal preparations are natural and consequently safer to consume. In reality there is evidence that the increased usage of herbal preparations are accompanied by an increase in side effects, drug interactions, and deaths. This is due to the fact that many of the commercially available herbal preparations have not been tested in respect with efficacy, safety, and purity of their contents. The Food and Drug Administration (FDA), which issues licenses for the use of OTC drugs, does not evaluate and license preparations of plant origin.

Echinacea is one of the herbal preparations that is increasingly being used, and for years has been the second most sold medication in the United States. To the 300 million US dollars spent on herbal preparations in the United States, Echinacea contributes 40 million US dollars.\textsuperscript{(4)} One of the reasons why people consume Echinacea preparations is for the prevention of common cold and influenza, and for enhancing the immune system.\textsuperscript{(5)}

The common cold and influenza

The common cold is an acute nasopharyngitis caused by more than 100 kinds of viruses. More than 50% of colds is caused by rhinoviruses, 15% by coronaviruses and 5% by adenoviruses.\textsuperscript{(6)}

Infection with rhinoviruses is characteristically limited to the nasopharynx, but may also affect the middle ear and the paranasal sinuses. The rhinovirus grows in the narrow temperature range (33-35°C) that is associated with the upper respiratory tract. The lower respiratory tract has a higher temperature and consequently is less conducive to viral growth. The virus is transmitted by direct contact from one individual to another, by contact with contaminated surfaces of objects (eg. telephone receiver handles, staircase railings), and by inhalation of large-sized aerosol particles.\textsuperscript{(6)}

The rhinovirus binds to receptors for intracellular adhesion molecules 1 (ICAM-1) on the surface of nasopharyngeal epithelial cells. The infected cells release interleukin-8 (IL-8), a strong chemoattractant that is capable of stimulating the release of proinflammatory mediators, such as kinins and prostaglandins. The presence of these mediators may lead to increased vasodilation, vascular permeability, and secretion of exocrine glands, which ultimately give rise to the classic symptoms of the common cold, such as nasal congestion, rhinorrhea, and sneezing. The severity of cold symptoms is correlated with the concentration of IL-8.\textsuperscript{(6)}

Rhinoviral infections are generally self-limited. The symptoms commonly appear within 1-2 days after inoculation, and reach a peak within 2-4 days, although some reports state that symptoms may appear within less than 24 hours after exposure. The symptoms are frequently heralded by itching or pain in the throat, followed by sneezing, nasal drip, nasal congestion, and general malaise. The body temperature is usually normal. Initially, the nasal secretions are clear, thin and copious, then become more mucoid and purulent. If cough is present, it is usually mild and may persist for more than two weeks. Uncomplicated colds usually resolve within 10 days.\textsuperscript{(1)}

Complications may be secondary, as a result of other disorders accompanying upper respiratory infections, such as asthma, cystic fibrosis, chronic bronchitis, or infections of the lower respiratory tract in infants, the elderly, and immunocompromized patients. Purulent
sputum or lower respiratory tract infections may indicate something more serious than rhinoviral infections alone. Viral pneumonia is another potential complication; it is commonly mild and may resolve within a few weeks without treatment, but in a number of cases it may worsen and require hospitalization.

The rhinoviral infection may also spread to the sinuses or the ear, and cause excessive secretion of mucus. The ostium of the sinus or the auditory meatus may become blocked by accumulated mucus and provide a substrate for the multiplication of bacteria and other microorganisms. It has been reported that 80% of children with otitis media recovers even without the use of antibiotics. Excessive use of systemic antibiotics (particularly penicillin derivatives) induce significant antibiotic resistance in the two pathogenic bacteria most commonly isolated from the nasopharynx of children with otitis media, namely Streptococcus pneumoniae and Haemophilus influenzae. 

Influenza is caused by a virus that comprises three serotypes (A, B, and C), but only types A and B are associated with the human disease that is called flu. The virus is divided into a number of subgroups on the basis of their characteristic antigens. Mutation occurring in types A and B give rise to new viral strains, due to transfer of antigens from one virus to another (antigenic drift). As a result of mutation, antibody formed against previous strains have limited protective effect against newer strains of the virus.

Influenza epidemics are generally associated with certain serotypes. However, it is still possible for multiple viral strains to simultaneously cause infection in the same location. The United States experiences influenza epidemics every 2-3 years, mostly caused by influenza virus type A. Influenza type B commonly causes a milder illness and does not experience antigenic drift as readily as does influenza virus type A.

The incubation period of influenza is 1-4 days. In mild cases of flu, the symptoms resemble those of the common cold (eg. sore throat, runny nose); conjunctivitis may also occur, but in general the individual rapidly has a high fever and chills, cough, body aches, headache, and photophobia. The respiratory symptoms include sore throat, rhinitis, and productive or dry cough. Children may also suffer from nausea, vomiting, or abdominal pain; in infants the symptoms of influenza may resemble a sepsis-like syndrome. Acute symptoms of influenza commonly resolve within 2-3 days, but the fever may persist for more than five days. In uncomplicated cases, the patient commonly recovers after 3-7 days; however, cough and general malaise may persist for weeks.

All of the complications occurring in the common cold may also be found in influenza. Although rarely encountered in influenza, encephalitis may also develop. The virus enters the blood stream, then relocates to the brain, causing inflammation of the brain tissues and meninges. In an attempt to combat the infection, the leukocytes invade the tissues of the brain, causing edema and tissue destruction. The symptoms that develop are fever, severe headache, drowsiness, nuchal rigidity, muscle weakness, or convulsions. A comparison of the characteristics of the common cold and influenza may be seen in Table 1.

Table 2 lists the population groups identified as being at high risk for suffering from influenza. These groups should have first priority in receiving influenza prophylaxis or therapy.
Characteristics | Common cold | Influenza
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Etiologic agent | >100 viral strains; most commonly rhinovirus | 3 strains of influenza virus: influenza virus A, B, and C
Site of infection | Upper respiratory tract | Upper and lower respiratory tract
Onset of symptoms | Insidious: 1-3 days | Acute: within hours
Fever and chills | Rare, temperature <38.3°C | Typical, temperature >38.3°C, lasting 2-4 days
Headache | Frequent, usually mild | Typical, more severe
Body aches | Mild, if any | Typical, frequently severe and affecting whole body
Cough, congestion of chest | Mild to severe | Common, may become severe
Sore throat | Common, usually mild | Occasionally found
Nasal drip & obstruction | Very frequent, with sneezing | Occasionally found
Tiredness, weakness | Mild, if any | Common, may be severe and last >2-3 weeks
Exhaustion | Never | Frequent, usually at onset of illness
Season | Throughout the year, peaks in winter | Most cases in November through February
Effect of antibiotics | None, except in secondary bacterial infection | None, except in secondary bacterial infection

Table 2. Populations at high risk for complications of influenza(1)

- Adults ≥ 65 years
- Children < 2 years
- Pregnant women
- Individuals treated for extended periods in health care facilities
- Individuals with cardiovascular disease
- Individuals requiring regular medical visits or extended periods of hospitalization due to chronic metabolic diseases (eg. diabetes mellitus), renal dysfunction, hemoglobinopathies or immunosuppression (eg. HIV)
- Individuals suffering from various conditions capable of impairing respiratory function or secretion or increasing risk of aspiration
- Children and adults receiving long-term aspirin therapy (due to risk of Reye’s syndrome)

**Echinacea (Echinacea spp.)**

Echinacea is a plant species that has since long been utilized as a medication by the indigenous peoples of North America and the settlers. Echinacea was used for wounds, insect bites, infections, toothache, joint pains, and as an antidote against rattlesnake bites. In 1916-1950 Echinacea was included in the National Formulary of the United States. Although the popularity of this medication has been waning since 1920, Echinacea continues to be utilized and investigated in Europe, especially Germany. In 1980 Echinacea was again widely used when consumers were beginning to be interested in...
medications capable of enhancing the immune system in conditions of decreased immune function, such as in Acquired Immunodeficiency Syndrome (AIDS) and cancer. Since then Echinacea was again being widely used for viral infections, because of its immunostimulant properties. Currently Echinacea is being promoted for prevention and treatment of respiratory tract infections, including the common cold and influenza.

Echinacea is also known under the name of purple coneflower. The plant is an herbaceous perennial (a plant capable of living more than two years) that grows in the western and central parts of the United States, Southern Canada, and Europe, especially Germany. Echinacea is a member of the family Compositae/Asteraceae. Its maximal height is 50-180 cm, depending on the species. Up to date nine Echinacea species have been found. The three species used medicinally are E. angustifolia, the narrow-leafed purple coneflower; E. purpurea, the Eastern purple coneflower; and E. pallida, the pale purple coneflower. Of the three, E. purpurea is the one most extensively cultivated and utilized, because all parts of the plant (roots, leaves, flowers, seeds) may be utilized and also because this species is easy to cultivate. The parts of E. angustifolia and E. pallida that are used as medicine are the roots and the rhizomes.

Echinacea preparations and their indications

In Germany, herbal medicines are widely used, and a commission, the German Commission E, has been assigned the task of studying the data on herbals. For internal use, the aerial parts of E. purpurea (the parts of the plant above the ground, thus excluding the roots) have been approved for treating the common cold, flu-like symptoms, fever, chronic respiratory tract infections (e.g. bronchitis), urinary tract infections, inflammation of the mouth and pharynx, and recurrent infections. The plant is used externally for superficial wounds and burns. In addition, the root of E. pallida is used in supportive therapy of fever and the common cold. The German Commission E has not yet approved E. angustifolia for medicinal use. Currently there are more than 800 phytopharmacological products containing Echinacea. A large variety of Echinacea preparations are available commercially, involving different species of Echinacea, various parts of the plant, with a number of added products, such as vitamin C and propolis. Echinacea is mostly sold in the form of powders, extracts, tinctures, and teas. The phenolic components contained in Echinacea are active constituents exhibiting immunostimulant, antihyaluronidase, antiviral, antioxidant, and antiinflammatory effects. There is no agreement on the dosage of Echinacea, and each company gives a different dosage on the label. There is also no agreement on when to start consumption of Echinacea, and the duration of the course. The duration of treatment of the common cold varies from 7 to 10 days. The Physicians’ Desk Reference (PDR) states that a course for prevention of recurrent infections should not exceed eight weeks and should be about 1-2 weeks for acute infections. The oral dose for short-term treatment should be 3-4 times daily, whilst for long-term treatment it should be 2 times daily.

Up to now Echinacea was regarded as a fairly safe medication to consume. The majority of reported side effects are allergic reactions, usually skin rashes. The study conducted by Parnham et al. on 1,231 children treated with Echinacea showed that the most frequently reported side effect of the herbal preparations is bad taste of the medication, and less frequently nausea, vomiting, sore throat, abdominal pain, diarrhea, and difficulty in swallowing. Taylor et al.
performed a study on children between 2-11 years of age and found an increase in the occurrence of skin rashes in children receiving Echinacea, compared with those not receiving the medication. Another study reported on 51 cases of allergy possibly associated with Echinacea, among which 26 were thought to be due to immunoglobulin E mediated hypersensitivity reactions.\(^{16}\)

In view of the immunostimulant effects of Echinacea, the German Commission E states that Echinacea should not be used in individuals with immune-related chronic progressive diseases, such as autoimmune diseases, tuberculosis, multiple sclerosis, and AIDS. This warning was issued not on the basis of clinical evidence, but only on the theory that the mechanisms of inflammation in these diseases may be exacerbated by the immunostimulatory properties of Echinacea.\(^{12}\) More concrete evidence is needed on this issue.

As is the case with nearly all medicines, the safety of Echinacea usage in pregnancy has not been determined. There are very few relevant data available. A prospective controlled study was conducted on 206 pregnant women consuming Echinacea, compared to 206 pregnant women used as controls. Stillbirths, chromosomal abnormalities, and malformations were found in comparable numbers in both groups. The results of the study indicated that the use of Echinacea during organogenesis was not associated with an increased risk of major malformations.\(^{17}\) However, the study still has limitations in statistical power and methodology. The systemic review by Perri et al.\(^{18}\) showed that Echinacea is not teratogenic when used in pregnancy. The use of Echinacea during lactation needs further investigation.

**Mechanism of action**

The precise mechanism of action of Echinacea is not fully understood. The main constituents of Echinacea are (i) alkylamides and polyacetylenes, (ii) derivatives of caffeic acid, (iii) polysaccharides, and (iv) glycoproteins. Most of the alkylamides are isobutylamides that are capable of causing a burning sensation in the mouth. The derivatives of caffeic acid give rise to several components, such as caftaric acid, chlorogenic acid, cyanarin, echinacoside, and chicoric acid. Chicoric acid is the main phenolic component found in *E. purpurea*, whereas echinacoside is the main phenolic component found in *E. angustifolia* and *E. pallida*. Chicoric acid reportedly has immunostimulant and phagocytic properties, is an antihyaluronidase, and has a protective effect against antioxidants that induce destruction of collagen, and exerts an anti-inflammatory action. Echinacea also protects collagen against damage-inducing reactive oxygen species. Chicoric acid and echinacoside are the constituents most frequently encountered in varying concentrations, depending on the species of Echinacea.\(^{19}\) The roots of *E. purpurea* contain chicoric acid in high concentrations, but do not contain echinacoside. In contrast, the roots of *E. pallida* and *E. angustifolia* contain echinacoside in large amounts. The immunomodulatory mechanisms of Echinacea may assist in reducing the symptoms of upper respiratory tract infections through activation of macrophages, leukocytes, and granulocytes.

**Immunomodulatory effects**

*E. purpurea* is well-known for its effects on the immune system. Stimulation of various components of the immune system, such as macrophages, other monocytic cells, and natural killer (NK) cells, and modulation of cytokines have also been repeatedly demonstrated *in vitro*.\(^{20,21}\) The mechanisms of its *in vivo* immunomodulatory effects are not yet fully understood. One theory states that immunosuppressive effects occur on exposure to
allergens, diseases, malnutrition, drugs, toxins, or psychological or social stresses. Administration of Echinacea may bolster a weakened immune system and restore health. The term immunomodulation appears to be more appropriate for the effects of Echinacea, because in the immune system Echinacea reportedly stimulates a large number of complex components without clearly enhancing or impairing the functions of the immune system. Several of the immune activities are beneficial, whilst others are detrimental. The term immunomodulation conveys the meaning of a reduction in dangerous host responses such as irritation or inflammation.\(^{(22)}\)

Many studies have been performed to investigate the effects of Echinacea on human leukocytes, either by adding Echinacea to a leukocyte extract, or by administering Echinacea to human subjects and subsequently preparing a leukocyte extract. These studies demonstrate increased neutrophil chemotaxis and enhanced bactericidal activities against Staphylococcus; there were also raised levels of tumor necrosis factor (TNF) α, interleukin-1 (IL-1), and IL-6. Addition of a polysaccharide extract of an Echinacea plant cell culture to immune cells will result in enhanced phagocytosis, chemotaxis, and oxidative bursts in neutrophils and macrophages. The polysaccharide constituents of Echinacea do not activate B cells and do not stimulate antibody production. Chicoric acid is a constituent with immunomodulatory effects that is capable of enhancing in vitro and in vivo phagocytosis. This substance also protects cells against free radicals capable of inducing degradation of collagen. Echinacoside does not have immunomodulatory properties, but has a protective effect against destruction of collagen by reactive oxygen. Constituents of Echinacea such as echinacoside and chicoric acid have the highest free radical scavenging activity. The caffeoyl derivatives commonly found in Echinacea protect cells against superoxide and hydroxyl radicals. Polyunsaturated alkylamides found in E. angustifolia act as antiinflammatory substances by inhibiting microsomal cyclooxygenase and 5-lipoxygenase activities.\(^{(22)}\)

**Clinical trials of Echinacea in respiratory infections**

Many studies have been conducted with variable results on the effects of Echinacea in reducing the symptoms and duration of illness of acute respiratory infections. The following studies revealed positive results of Echinacea on upper respiratory tract infections.

One study that was undertaken for assessing the duration of the common cold, recruited 80 adults, who received E. purpurea extract or placebo from the onset of cold symptoms until their resolution. The mean duration of illness was 6 days in the group receiving Echinacea and 9 days in the placebo group (p = 0.0112).\(^{(23)}\)

In a randomized double-blind controlled study involving 282 adults, the effects of an *Echinacea purpurea* formulation (1 unit = 0.25 mg/mL alkamide, 2.5 mg/mL chicoric acid, and 25 mg/ml polysaccharide) were compared to those of a placebo. The proportions in the preparation had been extrapolated on body weight from studies in rats that demonstrated an enhancement in alveolar macrophage functions. This study was conducted for a period of seven days after the onset of cold symptoms. On the day of onset 10 units were administered, which was followed by 4 units daily for the following seven days. The severity of symptoms was measured using a 10-point scale (0 = minimal; 9 = maximal). The Echinacea group showed a 23.1% lower reduction in severity of symptoms than that in the placebo group (p<0.01).\(^{(24)}\)
In a follow-up study conducted by the same investigators on 150 adults, using the same Echinacea preparation, 8 units (5 ml/unit) were administered on the first day, followed by 3 units daily for seven days. Fasting blood glucose samples were collected before and during the illness. The results of the study showed a reduction in total symptoms of illness and an increase in the numbers of red cells, monocytes, neutrophils, and NK cells in the group receiving Echinacea compared with the placebo group. (25)

A randomized double-blind controlled clinical trial on 430 children aged 1-5 years used a Chizukit preparation containing 50 mg/mL Echinacea, 50 mg/mL vitamin C, or placebo, in a dosage of 5.0 mL in children aged 1-3 years and 7.5 mL in children aged 4-5 years, twice daily for 12 weeks. In the group receiving the herbal preparation there was a reduction of 36.2% in the number of episodes of respiratory infection, compared with the group receiving placebo. The weakness of this study is that the preparation used was unrefined and contained other substances that may have influenced the results of the study. (26)

Schoop et al. (27) performed a meta-analysis of studies investigating the efficacy of Echinacea extracts in preventing the development of cold symptoms, experimentally induced using rhinovirus. From a total of 234 papers that were identified, 231 were dropped from the analysis because in those studies the common cold occurred spontaneously. The results of the meta-analysis indicated that standardized Echinacea extracts were effective in preventing cold symptoms when compared with placebo.

Conversely there were several studies reporting that Echinacea had not been proven to be effective. A randomized double-blind controlled study, with alfalfa as placebo, was undertaken by Barrett et al. (28) on 148 school children with recently acquired common cold. They were given capsules containing a mixture of unrefined E. purpura herbs (25%) and roots (25%) and the roots of E. angustifolia (50%) in a dosage of 1 gram 6 times daily on the first day of illness, and three times daily on the following days, for a maximal period of 10 days. There were no significant differences in severity and duration of symptoms between the Echinacea group and the placebo group. A limitation of this study was the use of unrefined Echinacea and young healthy subjects. Another limitation was that the placebo used was in reality not an inert substance, because it contained the active substances of alfalfa. This bias may have reduced the difference in efficacy between the group on Echinacea and the group on placebo, such that the advantages of Echinacea could not be made evident in this study.

Another placebo-controlled clinical trial used a total of 148 students, who were given 100 mg E. purpurea (as the freeze-dried pressed juice from the aerial parts of the plant) or a placebo, three times daily until the symptoms of illness resolved or until the fourteenth day. No statistical difference was apparent between both groups. The study performed by Yale et al., (29) using the pressed juice from the aerial parts of the plant, indicated that there were no beneficial effects in the use of E. purpurea within 24 hours of onset of the common cold for reducing the symptoms or severity of the illness.

To compensate for the variability of the cold virus, Sperber et al. (30) administered rhinovirus type 39 in advance, before randomly assigning the subjects to the Echinacea or placebo group. The pressed juice of the aerial parts of E. purpurea was given for seven days before and after the subjects had been infected with rhinovirus. The results of the study revealed that the use of Echinacea before and
after exposure to rhinovirus type 39 did not reduce the rate of rhinovirus infection. There was a tendency for reduction of symptoms on days 2-7 in subjects receiving Echinacea, when compared with those receiving placebo, but this was statistically not significant. The limitation of this study lies in its statistical power, which was too low to detect differences.

The randomized study by Turner et al. (31) on 437 volunteers, who received extracts of E. angustifolia roots or a placebo, showed no significant differences in rate of viral infection or severity of symptoms. Upper respiratory infections also constitute a health problem in children. To reduce the symptoms of illness, these children are given decongestants, antihistamines, and cough medicines. Unfortunately, however, there is scant evidence demonstrating the efficacy of the drugs in children under the age of 12 years. This fact prompted a study by Taylor et al. (15) on the efficacy and safety of E. purpurea in combating infection in children. The results of the study showed that use of the pressed dried juice from the aerial parts of E. purpurea did not cure respiratory tract infections in children aged 2-11 years, and revealed an increased incidence of skin rashes in the group receiving Echinacea. Although this study failed to show a reduction in symptoms of respiratory tract infections, there was a statistically significant reduction in the frequency of attacks of infection.

Linda et al. (32) performed a systemic review of the Cochrane database, under the title “Echinacea for preventing and treating the common cold”. A total of 16 trials were selected according to existing criteria, from 40 previous studies. The sixteen studies were divided into three categories: five placebo-controlled prevention trials, three controlled prevention trials without treatment, and eight placebo-controlled treatment trials. The total number of participants in the sixteen trials was 3,396. The large heterogeneity in the products used and the poor quality of reports caused difficulties in assessing the limitations in methodologies of the studies. However, there was some evidence that E. purpurea preparations derived from the aerial parts may be effective for initial treatment of the common cold in adults, but the results were not always consistent. There was no clear evidence that other Echinacea preparations were effective, and the effects of Echinacea on respiratory tract infections in children were not proven. The side effects of Echinacea were infrequently found, but one study reported the occurrence of skin rashes in children.

A summary of several studies on the benefits of Echinacea in the common cold and influenza is listed in Table 3.

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CONCLUSIONS

Extracts of Echinacea plants are widely used in the United States for prevention and treatment of respiratory tract infections. However, the available evidence from clinical trials on its efficacy is inconsistent. Assessment of the efficacy of Echinacea preparations is difficult to perform due to limited resources for comparing the available preparations. Data on the use of Echinacea in pregnancy and lactation are still limited, thus its use should be avoided. The use of Echinacea for the prevention of the common cold is not yet supported by adequate data, so that it is not recommended.

REFERENCES


