The Pharmacodynamics, Pharmacokinetics and Clinical Use of *Echinacea purpurea*

By Kevin Spelman, PhD

Upon successful completion of this article, the pharmacist should be able to:

1. List the main Echinacea species in use today.
2. Identify four active constituents in E. purpurea extracts.
3. Contrast doses used for acute infections versus doses used for chronic conditions.
4. Identify a strategy for converting adult doses to children's doses.

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2. Identify four active constituents in E. purpurea extracts.
3. Contrast doses used for acute infections vs. doses used for chronic conditions.
4. Identify at point-of-sale when a pharmacist should be consulted to calculate a child's dose.

BOTANY

Depending on how this Asteraceae family member is classified, there are up to 12 different species of *Echinacea*. The most commonly used species for medicinal purposes is *Echinacea purpurea*, which is easy to cultivate and therefore, product demand does not put a stress on native populations of *Echinacea* species that are difficult to cultivate. Most preparations found in the market are derived from the above ground, or aerial, parts of *E. purpurea* and/or underground parts of *E. purpurea*; these preparations account for 80 percent of commercial production. In addition, *E. angustifolia* and *E. pallida* are also utilized in commerce but much less than *E. purpurea*.

CHEMISTRY

All three species of *Echinacea* seen in commercial preparations have undergone chemical and pharmacological studies. However, there are several other species of *Echinacea* that have little to no research on their chemistry and pharmacology. Due to the confusion between *Echinacea* species the current body of scientific literature on *Echinacea* can be confusing due to the three species in use – namely *E. purpurea*, *E. pallida* and *E. angustifolia.* These three have phytochemical similarities but have notable differences, particularly around the identity and concentration of key constituents. A number of German studies in the 1980s were called into question when it was discovered that the species they intended to study was the wrong *Echinacea* species. Because of multiple species, plant parts, and preparations used, there are different constituent profiles for various products. *"Echinacea"* may refer to the roots, aerial parts, whole plant or a combination of the above; *Echinacea* products can be made from fresh or dried plant parts, and may be prepared by juicing, alcohol extraction, infusion, decoction, or consumed as tablets or capsules. Most preparations are derived from the aerial parts of *E. purpurea* and/or underground parts of *E. purpurea*, *E. angustifolia*, or *E. pallida*.

In spite of the prolific research done on *Echinacea* spp, there is still uncertainty as to which constituents *primarily* contribute to the purported immunomodulatory action of *Echinacea* species, although many believe it to be the alkylamides. Importantly, it appears that multiple constituent groups are responsible for *Echinacea's* activity. Since *E.*

purpurea makes up most of the *Echinacea* material available this discussion will be limited to that species.

To date more than 216 different phytochemicals have been identified in the literature based on *E. purpurea*. These compounds cover a diverse number of constituent families with varying polarities. Besides the alkylamides, three other constituent groups may have activity; the hydroxycinnamates (such as caffeic acid derivatives), the polysaccharides and the glycoproteins. More divergent research points at generally unrecognized, but active, lipopolysaccharides and/or lipoproteins present in *Echinacea* root capsule and extracts occurring from the endophytes of the roots, although this is not yet well established.

In regard to tincture extractions with ethanol concentrations above 40 percent, only very low levels of polysaccharides are left in suspension, and denaturing of proteins is expected. Thus, the major constituents of ethanolic *Echinacea* extracts are caffeic acid derivatives and alkylamides (and possibly the before mentioned lipopolysaccharides and/or lipoproteins). The capsule or powder of *Echinacea* spp. root would have all four constituents available including the important polysaccharides and glycoproteins, provided the starting material is of good quality.

PHARMACOKINETICS

Absorption of Hydroxycinnamic Acids

In order to fully discuss the absorption of hydroxycinnamates in *Echinacea*, it is necessary to first examine the research from other plant species. Hydroxycinnamic acids are one of the major classes of phenolic acids. Members of this group are ubiquitous in food stuffs, herbal medicines and beverages such as coffee. This group includes cinnamic acid, cichoric acid, coumaric acid, ferulic acid, rosmarinic acid, cynarin, caftaric acid, caffeic acid, and chlorogenic acid.

Gut absorption of caffeic acid is well characterized in both humans and animal models. However, the absorption of chlorogenic acid is more controversial. Some groups have failed to detect chlorogenic acid in the plasma of humans or rats after ingestion as either a pure compound or coffee, a rich source of chlorogenic acid. However, metabolites of chlorogenic acid, caffeic acid derivatives and its O-methylated metabolites (such as ferulic acid) are commonly found in plasma and urine after ingestion of chlorogenic acid in humans and rats. This research shows that chlorogenic acid is absorbed and quickly metabolized, particularly into its methylated derivate, ferulic acid, by catechol-O-methyltransferase which is present in the intestines. Others have shown metabolites of chlorogenic acid, such as ferulic acid, isoferulic acid, vanillic acid, dihydroferulic acid, hippuric acid and 3-hydroxyhippuric acid, are detected in human urine samples after ingestion of multiple cups of coffee. However, caffeic acid is better absorbed than chlorogenic acid. In human studies with volunteers who had undergone colonic resection, chlorogenic acid absorption was a third of caffeic acid absorption. Other studies concur, Lafay *et al*. utilizing a murine model, reported that while 19.5 percent of caffeic acid is absorbed in small intestines only, 8 percent of chlorogenic acid is absorbed in small intestines. The time frame for maximum concentration in human plasma for caffeic acid has been reported to be one hour.

In the case of *Echinacea*, we are particularly interested in caftaric acid, cynarin, caffeic acid, chlorogenic acid, cinnamic acid and echinacoside. The occurrence of these compounds differs depending on the particular *Echinacea* species. While one in *vitro* study done on an *Echinacea* product showed absorption of only about 3 percent of ingested cichoric acid and 1 percent of caftaric acid over 90 minutes, there was a substantial absorption of cinnamic acid (83 percent) over the same time frame. However, this research was on a specific Echinacea product and the results differ significantly from other research that examined hydroxycinnamate pharmacokinetics. For example, in a murine model, caftaric acid was detected in plasma at 10 minute (293 ng/mL) and 20 minute (334 ng/mL) time points. By 20 minutes a derivative of caftaric acid, fertaric acid, was detected in plasma as well. Caftaric acid was detected in kidney, and in some animals, in the brain. In general, hydroxycinnamates are eliminated rapidly from the circulatory system with T1/2 values ranging from 0.3 to 1.9 h.

Alkylamide Absorption

The alkylamides have also been studied for absorptive capacity. Thus far, it has been reported

that the higher the unsaturation of the alkylamide, the higher the absorbability. For example, the 2,4-diene alkylamides have been reported to cross Caco cells more readily than 2-ene alkylamides (see table 1). Incidentally, *E. purpurea* has a higher concentration of 2,4-dienes than *E. angustifolia*, which has a higher concentration of 2-ene alkylamides (table 1.9).

The concentrations of alkylamides reported in serum have been between 10.88 - 336 ng/mL. The $T_{1/2}$ of the predominant alkylamide dodeca-2,4,8,1 0-tetraenoic acid isobutylamide in a murine model has been reported to be 71.9 minutes, while in another study a $T_{1/2}$ of 0.4 -1.03 hr. was observed for the same compound. Of particular interest, two independent studies have reported that there is no difference between alkylamide absorption between liquid extracts (tinctures) and tablets except for a delay in T_{max} which would be expected due to the necessary digestion of the tablet. One group reported alkylamides being detectable in serum for up to 12 hours. $T_{1/2}$ values range from 1.8 – 5.0 depending on the molecular structure of the alkylamide.

Murine models investigating alkylamide absorption have shown that the alkylamides cross the blood brain barrier with an elimination half-life of 253 minutes with a mean residence of 323 minutes. Others have reported a rapid passage across the blood brain barrier. This may be related to *Echinacea's* recently reported anxiolytic activity.

TRADITIONAL USE

Native Americans utilized *Echinacea* for a number of uses including as an anesthetic, analgesic, for coughs and sore throats and as an antidote for poisons such as snake venom. The physicians of the early 20th century learned many of these uses from the native Americans and utilized *Echinacea* for many indications, including sepsis, as well as less severe infections. At this point in time, *Echinacea* spp. have been documented in therapeutic use for more than a century by physicians for a variety of infections (Couch and Giltner, 1920). Even though 80 percent of the *Echinacea* products sold to consumers are made from *purpurea*, all three species are often used interchangeably for the treatment of cold, flu, respiratory infection, and inflammation. However, this crossover between species and plant parts for the same indications should be examined more closely for further refinement in indications. With further evolution of the understanding of the clinical effects of various extractions and constituents of *Echinacea*, an enhanced understanding of species and products will develop.

MODERN USE

Echinacea is one of the most frequently used medicinal plants in clinical settings. There are more than 800 *Echinacea* products on the market. For example, of the most prescribed drugs in Germany, *Echinacea* preparations have been in the top 200 for many years. Despite the hesitancy to use *Echinacea* products clinically in the United States, German physicians have written more than three million prescriptions annually for *Echinacea* products for the treatment of upper respiratory tract infections for well over a decade.

Medical doctors, naturopathic physicians and professional clinical herbalists in the United States have utilized *E. purpurea* as an acute remedy for upper respiratory tract infections. In addition, for clinicians comfortable with *Echinacea* as an immune enhancer, it is used as an addition to antibiotics to improve the therapeutic outcome. For example, *Echinacea* added to an antifungal regime of topical econazole nitrate reduced fungal reoccurrence rates from 60.5 percent to 16.7 percent. Those clinicians with more in depth understanding of *Echinacea* may also use it to accelerate wound healing both topically and internally.

In Russia, *E. purpurea* tops are mixed with animal feeds to improve the natural resistance of cattle to diseases, and improve milk production and quality. A study in horses showed that *Echinacea* is effective in strengthening immune response and acts as a hematinic agent, increasing hemoglobin levels, the number of red blood cells, and improves exercise physiology parameters and performance. A study in humans athletes demonstrated a significant increase in erythropoietin and IL-3. A recent experiment in aquaculture showed that *Echinacea* improved weight gain, resistance against infection, resistance to cold stress during the winter season, and survival in fish. Echinacea is proving to be so useful that numerous attempts have been underway in some non-traditional *Echinacea* growing countries, in Africa, Asia, Latin America,

and the Middle East to introduce cultivation, processing, and marketing.

INDICATIONS

Indications given are for *E. purpurea* root.

1. Treating the common cold, flu, and upper respiratory tract infections.
2. To increase general immune system function.
3. Treating vaginal candidiasis.
4. Non-healing wounds (topical or oral formulation)
5. Prophylaxis of common cold, flu, and upper respiratory tract infections. (weak evidence)

WHERE DOES THE RESEARCH POINT?

The bottom line: The most consistent results identified by the majority of the studies previous to the year 2000 indicate that *Echinacea* has nonspecific immunostimulating properties through the triggering of the innate immune system. However, more recent work indicates that *Echinacea* is a true immunomodulator and in some cases may be useful for conditions exhibiting an autoimmune response.

Research suggest that *Echinacea* species have immunological effects, as well as anti-viral, antibacterial, antifungal, insecticidal and anti-inflammatory properties. Although there is ongoing controversy in the literature as to whether the immunomodulating properties of Echinacea are attributable to the alkylamides, caffeic acid derivatives or the polysaccharides/glycoproteins, the in *vitro* and in *vivo* investigations previously performed demonstrate that there are multiple compounds that are active. Full spectrum extracts are, based on research, clinical experience and this author's opinion, the wisest choice of therapeutic application for *Echinacea* products.

A great deal of excitement has been generated due to the recent elucidation of the alkylamides activity on cannabinoid 2 receptors (CB2R; see section below entitled Cannabinoid activity). Some in the natural products industry now think that the basis of *Echinacea's* activity has finally been established. This may be short-sighted as CB2R activation comes up short as an explanation as to the various observations clinicians and researchers have made. If the alkylamide activation of CB2R was the primary basis of activity for *Echinacea*, it would suggest that *Echinacea* is essentially a complex antiinflammatory. Both research and clinical experience strongly suggest otherwise. Most of the Echinacea preparations that have shown an effect in clinical trials are not impressively high in alkylamides and contain the caffeic acid derivatives and often the polysaccharide/glycoproteins as well. Extracts that contain a wide spectrum of constituents currently appear to be the most reasonable direction for clinical use since it is not clear what compounds are the most important.

However, the CB2 activity strongly does suggest that *Echinacea* may also be used for a broader array of immune dysregulation than its current indications. For, example CB2R activation is therapeutic in autoimmune diseases. This challenges the Commission E's contraindication of autoimmune diseases for *Echinacea*.

Interesting new directions in *Echinacea* research investigate a much wider application than immune issues. Recent research suggests the possibility that *Echinacea* may be useful in type II diabetes and metabolic syndrome, although this still needs further work. The CB2 activity alone would potentially be useful in these conditions. However alkylamides have been shown in two independent models to activate PPAR-γ, the site of action of the thiazolidines commonly used to treat insulin resistance. Investigations on gene response show that *E. purpurea* root extract upregulates PPAR-γ expression in cells infected by human rhinovirus and the polysaccharides of *E. purpurea* extracts upregulate PPAR expression in non-infected cells. Provided that the PPAR activity can be shown in *vivo*, Echinacea may have an intriguing new indication on the horizon.

IN VITRO AND EX VIVO ACTIVITY IMMUNOMODULATION

Immunomodulators are defined as agents that modulate the dynamic regulation of immunologically relevant informational molecules such as cytokines, hormones, neurotransmitters, and other proteins and peptides. Physiological effects of *Echinacea* include immunomodulatory activities, such as stimulation of phagocytosis and induction/inhibition of cytokines from various leukocytes depending on the research model utilized. In addition, investigators report antioxidant activity. Immunostimulating activity of extracts from

Echinacea appear to be well established as well. Studies have reported that *Echinacea* extracts have the ability to activate human phagocytic function both in *vitro* and in *vivo*.

Other researchers have noted up-regulation of immune function in ex vivo models including in human immunodeficiency disorders. Conversely, down regulation of TNF-α and IL-8 have been demonstrated by *E. purpurea* extracts in ex vivo models of healthy individuals. While this appears contradictory, keep in mind that the 'physiological context' appears to be crucial as to *Echinacea's* direction of the pharmacological effect. One of these studies examined individuals with immunodeficiency disorders, the other examined healthy individuals. Intriguingly, *E. purpurea* extracts appear to function differently in a healthy individual's system than in an ill individual's system.

In human cells lines that are infected by a pathogen, a normal response is the upregulation of proinflammatory cytokines to counteract the infection. Recall that during upper respiratory tract infections (URIs) upregulation of inflammatory cytokines is responsible for the majority of clinical symptoms. A number of studies demonstrate that *E. purpurea* extracts will counteract this proinflammatory response due to infection from virus or bacteria. This has been suggested to be the main effect of *Echinacea* by many in the natural products industry whom have suggested that Echinacea is a simple CB2R agonist. Furthermore, interviews with experts on *Echinacea* from the natural products industry are quick to point out that *Echinacea* is not an antibiotic, rather the majority of its action is due to immunomodulatory activity. While there is quite a significant body of research on the immunomodulatory activity of *Echinacea*, there is also a body of research on specific antimicrobial activity.

E. purpurea has been shown to have "potent virucidal activity against viruses with membranes" including specific rhinoviruses, influenza virus, respiratory syncytial virus, adenovirus types 3 and 11, and herpes simplex virus type 1. In addition, antibacterial activity has been found against pathogenic bacteria such as *Streptococcus pyogenes*, *Hemophilus influenza*, *Legionella pneumophila, Propionibacterium acne and Clostridium difficile.* In recent studies that received very little attention, investigators showed that the virus known as H5N1 HPAIV was inhibited from replication and entry into cells by an E. purpurea extract. Moreover, while oseltamivir (Tamiflu®) induced resistance after multiple passages, *E. purpurea* extract did not induce resistance. These researchers also found that oseltamivir resistant virus were sensitive to *E. purpurea*. Other in *vitro* experiments show that *E. purpurea* extracts have the potential for use in alleviating the symptoms and pathology associated with infections with H1N1 influenza A virus by attenuating the production of TNF-α, G-CSF, CCL2/MCP-1, CCL3/MIP-1alpha and CCL5/RANTES from infected cells. In monocytes exposed to aerial or root extracts of E. purpurea, upregulation of IL-1α, TNF-α , ICAM, IL-8, and IL-10 was observed consistent with an activated antiviral physiological response. In these studies, the aerial versus root extracts did not differ significantly in their effects. Recall that both aerial parts of the plant and the root contain the hydroxycinnamates and the alkylamides, although in different concentrations.

Cyclooxygenase (COX) and COX-2 inhibition, as well as minor lipoxygenase inhibition, have also been noted for *Echinacea* extracts and specific alkylamides. This would potentially have an additive, or possibly synergic, effect in the anti-inflammatory activity that the CB2R activation has demonstrated.

While the inhibition of proinflammatory cytokines and chemokines in infection will make a significant difference in symptoms of upper respiratory tract infections, the anti-inflammatory activity and the direct antibacterial/antiviral activity will also be important. Add to these actions the inhibition of mucin secretion by goblet cells in the respiratory tract when infected by rhinovirus and the direct upregulation of phagocytosis and it is obvious that *E. purpurea* has multiple activities that should not be attributed to one class of constituents or one pharmacological target.

CANNABINOID ACTIVITY

The alkylamides (examples shown in Table 1, compounds 3, 4, 5, 9 and 10) found in *Echinacea* species and other medicinal plants, have been of pharmacological interest since humans first noted the tingling and numbing effect from chewing plants rich in these compounds. This

anesthetizing tingling of these compounds is associated with activation of tactile and thermal trigeminal neurons. This property was utilized by native Americans and eventually by physicians in the early 20th century for a variety of purposes including toothache and infections. Alkylamides were later recognized as insecticidal by a number of researchers, but eventually interest in these compounds waned. Recently, however, these fatty acid derivatives have become a subject of renewed interest due to their recent identification as cannabinoid ligands. The endogenous cannabinoid ligands are specific fatty acid metabolites, known as eicosanoids. It should be explicitly stated that the alkylamides do not interface with the cannabinoid 1 receptor, which is responsible for the psychotropic effects of the cannabinoids from *Cannabis* spp.

The CB2R is located on T & B lymphocytes, natural killer cells, macrophages, neutrophils, and mast cells and provides immunomodulatory responses. The CB2R has been found to play a significant role in immune dynamics including the resolution of inflammation, cancer, atherosclerosis, osteoporosis and chronic pain. This is a particularly attractive site for cannabinoid agonists selective for CB2R because of a paucity of psychomimetic activity. Nonetheless, in the face of remarkable volumes of preclinical data, only one CB2 drug molecule (cannabinor) has made it to phase II clinical trials. Data from marijuana smokers provide leading clues as to the effects of CB2 ligands on immune function. Lung alveolar macrophages removed from marijuana smokers have diminished capacity for the generation of TNF, gmCSF and IL-6 (inflammatory cytokines). Moreover, marijuana smokers that are matched with tobacco smokers for the frequency of smoking, have significantly lower rates of lung cancer that tobacco smokers or non-smokers. Further data suggest that CB2 ligands can inhibit the production of TNF and other cytokines by several different pathways, some independent of cannabinoid receptors. Conversely, cannabinoids have also been shown to increase the production of cytokines (including TNF, IL-1, IL-6, and IL-10) if administered with appropriate immune stimulation (bacteria or antigens) or, in some cases, without immune stimulation. These data strongly suggest true immunomodulation and not simple immunosuppression by Echinacea. Again, it should be stated that *Echinacea* has no psychotropic effects as the alkylamides of *Echinacea* do not bind to the CB1 receptor found in the central nervous system.

Induction of tumor necrosis factor (TNF) mRNA by alkylamides is greatest (12 fold) with alkylamides known as the tetraene isomers at a concentration of 5 μM. Another alkylamide common to both *E. purpurea* and *E. angustifolia* is dodeca-2E,4E-dienoic acid isobutylamide, which also upregulated TNF mRNA nine-fold. Dodeca-2E,4E,8Z-trienoic acid isobutylamide, also common to *purpurea* and *angustifolia* up regulates TNF mRNA five-fold. The effect of these alkylamides on TNF is blocked by the CB2R antagonist WR144528. In another study on CB2R binding, investigators demonstrated that the isobutylamides dodeca-2E,4E,8Z,10Z-tetraenoic acid (Table 1.3) and dodeca-2E,4E-dienoic acid (not shown) inhibited the binding of a CB2 ligand.

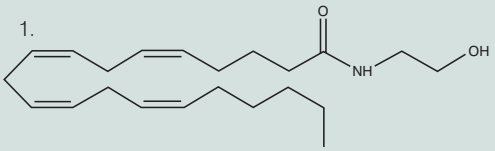
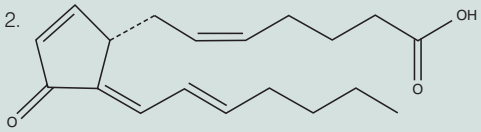
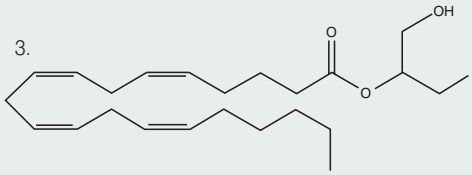
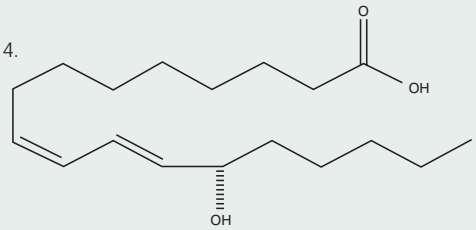
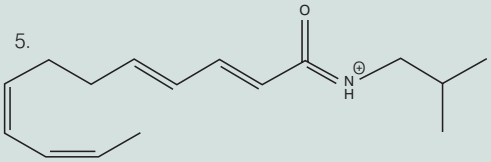
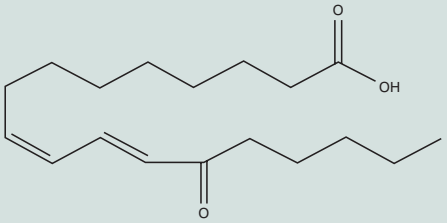
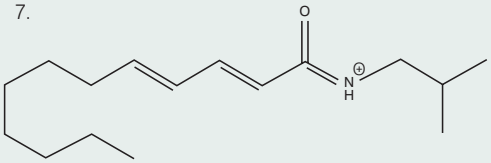
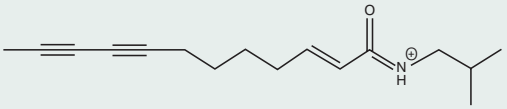
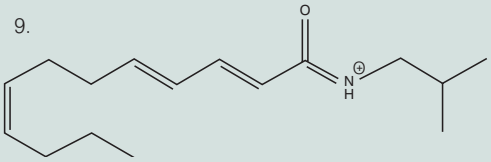
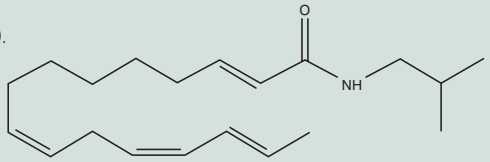
As previously mentioned, extracts with a wide array of constituents, not focused primarily on alkylamides appear to be important. For example, while TNF-α induction has been induced by the alkylamides, one of the caffeic acid derivatives, cichoric acid (also known as, chichoric acid), as well as extracts of *E. purpurea* and *E. angustifolia* roots have demonstrated counteraction of increases in TNF-α levels. Again these data suggest that the effects of Echinacea may be dependent on the immunological "tone" of the system as well as the type of extract.

HUMAN RESEARCH *IN VIVO/EX VIVO*

While a number of clinical trials have shown a beneficial effect for *Echinacea* spp. on colds and flus, a number of trials have failed to show a reduction of the symptoms of colds and flus. For example, Turner *et al* demonstrated no effect of *E. angustifolia* on the reduction of symptoms or duration of an experimentally induced cold.

Further research with an *E. purpurea* extract that was dosed with a loading dose (5 mL for 8 doses) for the first day and subsequently 5 mL three times daily for six days, in volunteers with URIs demonstrated a reduction in cold symptoms compared to placebo from days 2–7 of treatment (constituent doses 0.25/2.5/25.5 mg/mL alkylamides, cichoric acid, polysaccharides respectively). In *ex vivo* analysis of these sub-

Table 1: Ligands of CB2 and PPARγ

CB2 ligands	PPARγ ligands
1.  Anandamide MW 347.3 (PPARγ)	2.  15-deoxy-Δ-prostaglandin J2 MW 316.4 (fibroblasts activity 7 μM)
3.  2-arachidonylglycerol MW 378.3 (PPARγ)	4.  13-hydroxyoctadecadienoic acid MW 296.4
5.  Dodeca-2E,4E,8Z,10Z-tetraenoic acid isobutylamide MW 247.3 from Echinacea spp.	6.  13- oxooctadecadienoic acid MW 294.4
7.  Dodeca-2E, 4E-ene-dienoic acid isobutylamide MW 251.3 from Echinacea spp.	8.  Undeca-2E-ene-8,10-diynoic acid isobutylamide MW 231.3 from Echinacea spp.
9.  Dodeca-2E,4E,8Z-trienoic acid isobutylamide MW 249.3 from Echinacea spp.	10.  Hexadeca-2E,9Z,12Z,14E-tetraenoic acid isobutylamide MW 303.3 from Echinacea spp.

a. When information was available concentrations found to be active are stated.
b. Compounds 3 & 4 are also PPARγ activators. From with Ki of 57 nM and 60 nM. Other studies confirm similar affinities for these alkylamides. Notably, these affinities are within range of serum concentrations previously observed (10.88 - 336 ng/mL). Other observations in these studies include the activation of MEK 1/2 as well as JNK1/2 and NF-κB.

jects' blood, the number of circulating total white blood cells, monocytes, neutrophils and NK cells was significantly increased by the seventh day of treatment. In the later stages of the cold, the *Echinacea* treatment normalized the increase in neutrophilic superoxide production by day eight while the placebo group continued to show increases in superoxide production up to day eight.

The most recent clinical trial to date studied *E. purpurea* mixed with *E. angustifolia* and weighted heavily with alkylamide concentrations in 1,422 subjects, showed a non-statistical effect on shortening colds and flus. In addition, the researchers reported an increase in neutrophils and IL-8. However, due to high inter-individual variability this was not statistically significant.

Despite the negative outcomes, there are enough positive data in the human trials to offset the negative results. As a result, the meta-analyses that have been performed suggest that *Echinacea* products are effective. A Cochrane review reports some *Echinacea* preparations may be better than placebo and that the majority of the Echinacea studies demonstrate positive results. A meta-analysis by Schoop *et al*., reports that standardized extracts of *Echinacea* were effective in the prevention of symptoms of the common cold as compared with placebo. Islam and Carter conclude that there is a beneficial effect from *Echinacea*, but also suggest that differences in products and doses make evaluation challenging. Linde *et al*. suggest that there is evidence, although inconsistent, that *Echinacea* is effective in treating URIs. A meta-analysis of studies with children (under the age of 18) found that *Echinacea* reduces the incidence of URIs by 40 percent. Finally, the most recent meta-analysis finds that the evidence supports *Echinacea's* benefit in decreasing the incidence and duration of the common cold in adults.

Recent data on 995 patients with chronic recurrent respiratory disease shows that treatment with an *E. purpurea* extract reduces the incidence of illness by 2.3 times and saves 1.4 days with each illness. These researchers calculated the average daily cost per patient and reported that there is an economic benefit to the use of *Echinacea*.

In a study of URI prevention, subjects were dosed with 2.5 mL three times daily of *E. purpurea* extract or placebo, for seven days. After the initial seven days of dosing the subjects were inoculated with rhinovirus and dosed with another seven days of *E. purpurea* extract or placebo. URIs developed in 58 percent of the *Echinacea* group, as compared to 82 percent of placebo recipients. A recent trial which failed to show a positive outcome for treating URIs in children (ages 2 and 11) with *E. purpurea* did find that there was a prophylactic effect reducing the incidence of a second acute respiratory tract infection over a four month period. In a study of athletes, an *E. purpurea* tablet was rated as "good" or above by 75 percent of patients and investigators and prevented colds in 71 percent of the subjects. *Echinacea* products to date have never resulted in a false positive for banned substances used by athletes. A meta-analysis of the prevention studies suggest that there is a 55 percent reduction in the occurrence in URIs when using *Echinacea* as compared to placebo.

In another human *ex vivo* study researchers gave 1,500 mg three times daily of capsule of *E. purpurea* aerial parts and roots and *E. angustifolia* root to human subjects for two days plus one additional morning. After the dosing period a downregulation of a number of inflammatory genes was observed in most subjects; IL-1β (4 of 6 subjects); TNF-α (5 of 6 subjects); IL-8 (3 of 6 subjects); COX-2 (4 of 6 subjects); and ICAM-1 (4 of 6 subjects). These results achieved statistical significance on day five, despite dosing having ceased two days earlier. Cownversely, the relative expression of IFN-α2, an endogenous antiviral cytokine found to decrease symptoms and duration of colds, increased steadily in all subjects reaching statistical significance by day 12. Another study found that after seven days of dosing with *E. purpurea* extract, immune function, measured by CD69 expression on CD4 and CD8 cells, was upregulated.

Other research has shown that a lozenge of *E. purpurea* root in a range of doses (0.07–0.9 mg alkylamides) downregulates the production of IL-12p70, IL-8, IL-6, IL-10, and TNF within 24 hours of the dose. These researchers also showed that the alkylamides in the *E. purpurea* product were absorbed in 10 minutes, suggesting that absorption is taking place through the oral mucosa.

Brinker has done an excellent analysis of *Echinacea* clinical trials and pointed out that of the studies that have shown an effect on URIs,

the products used were all liquid extracts. Further analysis by Brinker has suggested that of the studies that failed, none used liquid extracts. Thus, Brinker speculates that liquid extracts may be a more efficacious dosing strategy, especially using the small doses that have been used in the clinical trials. An important factor when treating URIs may be oral mucosal exposure to the extract. However, both small and large infrequent doses of whole fresh plant extract tablets have produced benefit. In studies of the liquid juice (above ground parts of the plant) using frequent and early but small doses or larger infrequent doses of the juice positive effects have been achieved, but not with regular moderate doses of the dried juice.

A recent review of the *Echinacea* clinical trials showed that less than 9 percent of studies that had a "high-quality" rating incorporated phytochemical testing as an investigational criteria. As Cooper points out, clarity and consistency on identity and dosing are essential for validating and comparing outcomes when carrying out research. Researchers who study specific product formulations administered in appropriate doses will vastly improve the quality of available data.

CLINICAL OBSERVATIONS

While *Echinacea* preparations, properly dosed, are generally associated with the treatment of URIs, they can be potentially effective for the treatment of many different types of infections. Keep in mind that the eclectic physicians of the late 19th century and early 20th century used *Echinacea* spp. for sepsis. In the case of infections, proper dosing is crucial. (See Dosage section.) Additionally, topical *Echinacea* can be useful for non-healing and spreading wounds. For instance, in combination with turmeric (*Curcuma longa*), both internally and topically, *E. purpurea* root has been useful for the particularly difficult-to-heal bites of brown recluse spiders (*Loxosceles reclusa*). A clinical observation of a brown recluse bite that occurred two years before herbal treatment makes an interesting case study. The bite had progressed into severe dermonecrotic lesions migrating up the left arm and down the right arm. The lesions were resolved over about 16 weeks' time with topical and internal use of *E. purpurea radix* and *Curcuma longa rhizoma*. This is likely due to *Echinacea's* stimulation of fibroblast activity, its hylaronidase inhibition and its wound healing properties. Native Americans also used *Echinacea* for rattlesnake bites. It is quite likely that the anti- hyaluronidase effect is the basis of this anti-venom activity, since viper venom contains hyaluronidase, allowing it to break down connective tissue.

One of the most intriguing uses of Echinacea in 1:1 combination with dandelion root have been the reports of attenuating IgE mediated allergic responses to food and other substances. However, until conclusive evidence is available, life threatening allergic responses should be treated with proper medical care.

DOSAGE

The suggested dose varies widely on various *Echinacea* products. Moreover, clinician's opinions on what dose is effective for the treatment of URIs vary extensively. But one thing appears to be obvious to most clinicians: The dosages suggested on most *Echinacea* products are subclinical and ineffective for most acute infections. Based on the above discussion of the pharmacokinetics of hydroxycinnamates and alkylamides which show half-lives of a few hours, as well as clinical experience, the efficacious dose of *E. purpurea* root extract for treating URIs is one teaspoon (of a liquid extract) as a loading dose (or 1,500 mg capsule), followed by a half a teaspoon (or 500–750 mg capsule) every one-two hours for the first day (sleep should not be interrupted). While this may sound like a high dose, there is support for this dosing regimen. The following two days one teaspoon (1,500 mg capsule) should be used three times a day to make sure the virus doesn't regain a foothold. For preventing an impending URI, this dosing regimen must be started *at the first signs of illness*. This dosing protocol is based on the most common extract available 1:2 fresh root extracts. Clarks rule should be used for dosing children age 2–17 based on the above dosing. Clark's rule looks like this (Child's weight in pounds/150)(Adult dose) = Child's dose.

If consumer use is to support general immune function, a lower dose is used. In this case half a teaspoon is used once daily of the liquid extract (or 750–1,000 mg capsule).

SAFETY AND HERB DRUG INTERACTIONS

The search for and appraisal of information relating to the metabolism of phytochemicals and the phytochemical influence on drug metabolism has thus far been a challenge for researchers and educators, and readily accessible information among the scientific and medical community is lacking. Metabolic studies on phytochemicals have only recently been published in the scientific literature. Unfortunately, it appears that in regard to phytochemical influence on the metabolism of pharmaceuticals, much of the literature does not evaluate the quality of evidence from which conclusions are drawn.

Of particular concern for healthcare providers, Freeman and Spelman report that drug-herb interactions related to *Echinacea* products were cited in some 49 articles, only 16 percent (eight) of these 49 papers contained primary data relevant to interactions between *Echinacea* products and pharmaceuticals. Two studies were clinical trials and the remaining were in *vitro* assays, three of which did not contain complete information about the concentration of extract used; only half of the studies verified the authenticity of the *Echinacea*.

The most clinically relevant study done to date on the potential of *Echinacea* spp. to interact with pharmaceuticals was a study done on HIV patients (n = 15) who were receiving antiretroviral therapy including darunavir-ritonavir (600/100 mg twice daily) for at least four weeks. *E. purpurea* root capsules (500 mg every six hours) for 14 days were used by patients. Darunavir-ritonavir plasma concentrations were determined before, during and after the *E. purpurea* dosing. Although patients did show a decrease in darunavir concentrations, this did not affect the overall darunavir or ritonavir pharmacokinetics. Coadministration of *E. purpurea* with darunavir-ritonavir was safe and well tolerated.

The available data on the metabolic influence of *Echinacea* spp. and the alkylamides mainly focuses on the predominant alkylamides known to be responsible for drug interactions such as the CYP1, CYP2 and CYP3 families. Three different reviews conclude that *Echinacea* supplements pose minimal risks for interacting with most conventional medications.

Regarding concentrations of alkylamides used in in vitro research; recall that the highest serum concentration documented for alkylamides is 336 ng/mL, and this was 10 fold higher than the majority of pharmacokinetic studies investigating these concentrations. This should provide information for realistic analysis of future drug-herb interaction literature.

Cytochrome P450 Isoenzymes

Studies show *E. purpurea* herb and root may minimally inhibit CYP1A2. Patients taking drugs with a narrow therapeutic index metabolized by CYP1A2 (such as theophylline and clozapine) should avoid taking them with *E. purpurea*. However, studies conclude that no clinically significant interactions were expected between *E. purpurea* and substrates of CYP2D6, CYP2C19 and CYP2E1. There is no reliable research on *E. purpurea's* interaction with CYP2C9.

CYP3A4

There are a number of investigations done with real world dosing with humans on *E. purpurea* root extracts influence on CYP3A4. Human investigations by Gorski *et al*., (2004), found no changes in the metabolism of midazolam, a 3A4 substrate, after participants ingested 1,600 mg of *E. purpurea* root daily for eight days. While the authors observed an 85 percent increase in intestinal availability of midazolam, a 15 percent reduction of hepatic availability ($p < 0.003$) was also noted. The authors postulated that the induction of hepatic 3A4 counteracted inhibition of intestinal 3A4, leading to little to no effect in midazolam metabolism overall. Using *E. purpurea* whole plant extract (aerial and root combined) in a human trial Gurley *et al*. (2004) found no statistically significant differences in 3A4 phenotypic ratios. CYP 450 phenotypic ratios have been shown to provide a practical method for predicting CYP mediated drug interactions. Finally, in another human trial with healthy volunteers (n = 13) given lopinavir (400 mg-ritonavir 100 mg twice/day) with meals for 29.5 days, found that *E. purpurea* (500 mg three times a day for 28 days) induced CYP3A activity but did not alter lopinavir concentrations. The authors concluded that *E. purpurea* is unlikely to alter the pharmacokinetics of ritonavir-boosted protease inhibitors.

Organic Anion-Transporting Polypeptide (OATP-B)

Fuchikami et al., found inhibition of OATP-B by the aerial parts of *E. purpurea* in vitro. The clinical significance of this finding is unclear, as few

drugs are metabolized via this pathway and the findings have not been demonstrated in *vivo*.

P-Glycoprotein

Romiti *et al*., report that the hexane root extracts of all three *Echinacea* species inhibited P-glycoprotein, with *E. pallida*, a little used species, having an effect at 3 μg/mL. The *E. angustifolia* and *E. purpurea* extracts were inhibitory at 30 μg/mL. Considering the concentrations of the extracts used in this study, these data appear to have no relevance to real world use of *Echinacea* spp., especially since the percentage of *E. pallida* extracts in the market place is less than 5 percent.

Although drug-herb interactions are generally thought to be negative, there are potentially positive drug-herb interactions due to the potential of immune enhancement by *Echinacea*. For example, *Echinacea* may protect white blood cell counts in chemotherapy induced myelosuppression from myelosuppressive antineoplastic chemotherapies. In therapies exploiting TNF-α antagonists and other immunosuppressive drugs, *Echinacea* may theoretically be used to protect against opportunistic infection by enhancing cellular immunity during temporary drug withdrawals.

Echinacea is considered to be one of the safest herbal medicines, with few reported adverse effects. Given that Echinacea generally ranks in the top five in herbal sales in the United States from year to year, this is particularly notable. Barrett notes that less than 100 serious adverse events have been reported for over 10 million courses of treatment, leaving the risk estimate of less than one in 100,000. Echinacea products consisting of roots and aerial parts do not appear to be a risk to consumers provided that the preparations are authenticated.

ADVERSE EVENTS AND TOXICOLOGY

Short-term use of *Echinacea* is associated with a relatively good safety profile, with a slight risk of transient, reversible, adverse events. In clinical trials the most common complaint was gastrointestinal side effects. Adverse events are rarely reported with *Echinacea*, though in rare cases *Echinacea* has been associated with severe allergic reactions. The severe allergic responses are predominantly with the use of intravenous or intramuscular injection. Mild reported allergies, though rare, suggest that those with tendencies towards atopic dermatitis or asthma should use caution. People are more likely to experience allergic reactions to *Echinacea* if they are allergic to related plants in the daisy family, which includes ragweed, chrysanthemums, marigolds, and daisies. In ethanol extracts, as the proteins are denatured, allergic response to the ethanol extracts should not occur.

It should be noted that a good quality liquid extract (made with ethanol) of *Echinacea*, due to the alkylamide content, will induce a sensation of numbness and tingling on the tongue, mouth and throat. It is possible if the user is not expecting this sensation, it could be mistaken as an allergic reaction.

There appears to be no in vivo toxic level (overdose level), as defined by several assays and criteria of *Echinacea* spp. Research shows the toxic dose of *E. purpurea* is extremely high; chronic administration of hundreds of times the therapeutic dose has shown no toxicity. Furthermore, inducing toxic effects on cell cultures by *E. purpurea* extracts are possible with only with very high concentrations of *Echinacea* extracts that would not be possible to attain in even high dose use by humans.

TIPS FOR THE PHARMACIST

While *Echinacea* products are ubiquitous in the market place, it can be challenging to distinguish between these products in regard to quality of product, proper part of plant used and, importantly, ease of use for the consumer. Most American generated products are made with root and/or flower and seed. These parts provide the highest availability of alkylamides and will have reasonable levels of caffeic acid derivatives. Polysaccharides will be present if these plant parts are put into capsule, but if extracted with ethanol, polysaccharides are present only in substantial concentrations if the ethanol concentration is below 40 percent. Conversely, most European-based products (primarily German) are juiced above ground parts of the plant. These products will be rich in caffeic acid derivatives and polysaccharides, but low in alkylamides (notice the lack of numbing and tingling from one of these products – a sure sign of very low alkylamide content).

Clinicians in the United States prefer products richer in alkylamides since these are CB2R agonists. However, alkylamides are not the only active constituent in *Echina-*

cea. Since a primary active constituent in *Echinacea* has yet to be identified, a full spectrum phytochemical extract is a prudent choice.

For consumer use, the easiest approach is probably in liquid extract form. The taste of *Echinacea* can be (mostly) hidden in juice or teas. However, the capsule is easier if consumers are sensitive to the taste. For both capsules and liquid extracts, proper dosing is important if attempting to shorten the discomfort of an URI.

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Editor's Note: For the list of references used in this article, please contact *America's Pharmacist* Managing Editor Chris Linville at 703-838-2680, or at chris.linville@ncpanet.org.

CONTINUING EDUCATION QUIZ

Select the correct answer.

1. What is the primary *Echinacea* species used in products?
a. *E. purpurea*
b. *E. angustifolia*
c. *E. pallida*
d. All of the above

2. Which is a list of three active constituents in *E. purpurea* extracts
a. Alkylamides, caffeic acid derivatives and polysaccharides
b. Eicosanoids, Alykylamides, glycoproteins
c. Alkylamides, polysaccharides, cannabinoids
d. Alkylammines, polysaccharides and the glycoproteins

3. What is the $T_{1/2}$ of caffeic acid derivatives?
a. 253–323 minutes
b. 0.4 to 1.9 h
c. 2–3 hours
d. 1.8–5 hours

4. What is the $T_{1/2}$ of alkylamides of *E. purpurea*?
a. 253–323 minutes
b. 0.4 to 1.9 h
c. 23 hours
d. 1.8–5 hours

5. What is the serum Cmax for the alkylamides of *E.purpurea*?
a. between 10.88–336 ng/mL
b. between 293–520 ng/ mL
c. 20–30 μg/mL
d. Cmax has not been studied for alkylamides of *E. purpurea*

6. State three basis of activity for *Echinacea purpurea's* immunomodulatory activity.
a. CB2 activation, downregulation of inflammatory cytokines, Antioxidant activity
b. CB1 activation, downregulation of inflammatory cytokines, antioxidant activity
c. CB1 activation, upregulation of inflammatory cytokines, antioxidant activity

d. CB2 activation, upregulation of inflammatory cytokines, PPARγ activity

7. List a traditional use by the Native Americans for *Echinacea* spp.
a. Snakebites
b. Coughs and sore throats
c. Toothaches
d. All of the above

8. Which answer below best defines: immunomodulator?
a. Agent that inhibits the production of inflammatory cytokines
b. Agent that catalyzes the activity of hyaluronidase
c. Agents that modulate the dynamic regulation of informational molecules such as cytokines, hormones, neurotransmitters and other proteins and peptides
d. Agent that stimulates the production of prostaglandins

9. Which cannabinoid receptor are the alkylamides known to activate? Name a tissue (or cell type) where this receptor is found.
a. CB2R in the brain
b. CB1R in the brain
c. CB2R in immune cells
d. CB1R in immune cells

10. Identify clinical indications for *Echinacea*.
i. Lowering glycosylated hemoglobin A1C
ii. Treating the common cold, flu, and upper respiratory tract infections.
iii. To increase general immune system function.
iv. Other uses may include treating non-healing wounds (topically and internally)

a. i, ii and iii
b. i, iii and iv
c. ii, iii and iv
d. All of the above

11. N. S. is a 38-year-old female with no significant past medical history, allergy to penicillin and current medication is a multivitamin with iron. Which of the following doses might you recommend to her to treat what she suspects is a cold that began bothering her this morning?
a. One teaspoon as a loading dose, followed by a half a teaspoon every two hours for the first day. Then one teaspoon three times daily for two days.
b. A single dose of 1,500 mg at the earliest onset of symptons
c. One teaspoon or a 1,500 mg capsules once daily for seven days.
d. *Echinacea* is not recommended for patients with allergy to penicillins.

12. Describe the current conclusion on drug-*Echinacea* interactions.
a. *In vitro* research shows a mild inhibition of CYP3A4.
b. Studies show CYP1A2 inhibition.
c. Inhibition of *P-glycoprotein* is problematic and *E. pallida* should be avoided.
d. A. and B. only

13. Which of the following is a major safety concerns for the use of *Echinacea* products?
a. Toxicity at doses 10 times recommended
b. Common cross-allergenicity with penicillins
c. Irreversible numbing of oral mucosa
d. No serious adverse events are commonly reported

14. What are the rare adverse events that could occur with *Echinacea* products?
a. Allergic reaction to active constituents
b. Guillain-Barre Syndrome
c. Angioedema
d. Maxillofacial neuropathy

15. What indication might the pharmacist have to predict an allergy to *Echinacea* products?
a. Asthma
b. Atopic dermatitis
c. Seasonal allergy to ragweed, chrysanthemums, marigolds, and daisies
d. All of the above

16. What warning should consumers be given about liquid extracts of *Echinacea*?
a. Alcohol concentrations may impair driving.
b. Athletes may test positive for banned substances.
c. It is common for liquid extracts to cause tingling or numbness.
d. All of the above

17. What is the toxic dose of *Echinacea* spp. products?
a. 10 times the recommended dose (15,000 mg)
b. 25 times the recommended dose (37,500 mg)
c. 50 times the recommended dose (75,000 mg)
d. Studies have not identified a toxic dose, even at 100 times the recommended dose.

18. Which formulation of *Echinacea* will have the highest alkylamide content?
a. Alcohol extract
b. Capsule of whole, dried plant
c. Juiced aerial plant

19. Which formulation will have the highest polysaccharide content?
a. Alcohol extract
b. Capsule of whole, dried plant
c. Juiced aerial plant

20. N.S. returns to the pharmacy the next day with her son. She asks the pharmacist what dose her 11-year old, 39-kilogram, son, who is otherwise healthy, can take to keep from catching her cold; how do you reply?
a. 390 mg daily
b. 858 mg daily
c. 1,500 mg daily
d. Echinacea is not recommended for children 12 and under

The Pharmacodynamics, Pharmacokinetics and Clinical Use of Echinacea Purpurea

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Quiz: Shade in your choice

	a	b	c	d	e		a	b	c	d	e
1.	❑	❑	❑	❑	❑	11.	❑	❑	❑	❑	❑
2.	❑	❑	❑	❑	❑	12.	❑	❑	❑	❑	❑
3.	❑	❑	❑	❑	❑	13.	❑	❑	❑	❑	❑
4.	❑	❑	❑	❑	❑	14.	❑	❑	❑	❑	❑
5.	❑	❑	❑	❑	❑	15.	❑	❑	❑	❑	❑
6.	❑	❑	❑	❑	❑	16.	❑	❑	❑	❑	❑
7.	❑	❑	❑	❑	❑	17.	❑	❑	❑	❑	❑
8.	❑	❑	❑	❑	❑	18.	❑	❑	❑	❑	❑
9.	❑	❑	❑	❑	❑	19.	❑	❑	❑	❑	❑
10.	❑	❑	❑	❑	❑	20.	❑	❑	❑	❑	❑

Quiz: Circle your choice

21. Is this program used to meet your mandatory C.E. requirements?
a. yes **b.** no

22. Type of pharmacist: **a.** owner **b.** manager **c.** employee

23. Age group: **a.** 21–30 **b.** 31–40 **c.** 41–50 **d.** 51–60 **e.** Over 60

24. Did this article achieve its stated objectives? **a.** yes **b.** no

25. How much of this program can you apply in practice?
a. all **b.** some **c.** very little **d.** none

How long did it take you to complete both the reading and the quiz? _____ minutes

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