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COMMENTARY

Use of Echinacea in Medicine

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ABSTRACT. Echinacea, also known as the purple coneflower, is an herbal medicine that has been used for centuries, customarily as a treatment for the common cold, coughs, bronchitis, upper respiratory infections, and some inflammatory conditions. Research on echinacea, including clinical trials, is limited and largely in German. More information is needed before a definitive statement about the efficacy of echinacea can be made. Future work needs to clearly identify the species of echinacea and distinguish between the efficacy of the different plant parts (roots versus upper plant parts). Although many of the active compounds of echinacea have been identified, the mechanism of action is not known, nor is the bioavailability, relative potency, or synergistic effects of the active compounds known. Interpretation of existing literature suggests that echinacea should be used as a treatment for illness, not as a means for prevention of illness. The consensus of the studies reviewed in this article is that echinacea is indeed effective in reducing the duration and severity of symptoms, but that this effect is noted only with certain preparations of echinacea. Studies show that the plant and its active components affect the phagocytic immune system, but not the specifically acquired immune system. BIOCHEM PHARMACOL **60**;2:155–158, 2000. © 2000 Elsevier Science Inc.

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Consumer interest in herbs and botanicals is growing; sales of herbal products have grown by about 10–15% per year since the passage of the Dietary Supplements Health and Education Act (DSHEA) in 1994. Barrett *et al.* [1] report several estimates (10, 15, and 32%) of Americans who use medicinal botanicals in a given year. The law defines a dietary supplement as a vitamin, mineral, amino acid, herb, or other botanical or combination [2]. Alternatively, a dietary supplement is a dietary substance that is to be used to supplement the diet. It may be a concentrate, metabolite, constituent, or an extract, *and* it must be intended for ingestion in the form of a capsule, powder, softgel, or gelcap and not represented as a conventional food or as a sole item of a meal or the diet.

Dietary supplements do not require premarket approval and, therefore, are sold without undergoing extensive testing for safety and efficacy. The manufacturer must make sure that the ingredient list is accurate and that the ingredients are safe. The label must be truthful and not misleading, and follow specific regulations implemented in March 1999. Obviously, then, dietary supplements are regulated very differently than are food additives or drugs. By law, dietary supplements are not meant to "diagnose, prevent, mitigate, treat, or cure disease" [2]. Only certain FDA-approved disease-related claims are allowed, such as the claim relating calcium to osteoporosis. The law requires the supplement to contain a certain level of the nutrient. Structure/function claims may be made relating the supplement to some structure or function of the body, including overall well-being.

Although not explicitly stated, dietary supplements are, by default, treated as preparations that maintain health. In a perfect world, DSHEA would benefit the consumer by allowing free access to potentially useful preparations without the long delay and research necessary to prove efficacy and safety. However, it is not a perfect world; many preparations are not standardized to any active component, and, oftentimes, the amount of the ingredient is not listed. Many supplements that are on the market have not been rigorously and scientifically tested for efficacy. The subject of this review is echinacea, an herb purported to have immunomodulating capabilities. The scientific literature regarding efficacy and safety will be reviewed.

HISTORY

Echinacea has been used for centuries. This is not an argument for efficacy, but it does indicate some degree of safety. The longevity of its use suggests that it is not just an ancient fad, but perhaps has a true benefit. The plant is grown in the central and eastern United States and is cultivated in Europe. In general, the herb is used for treating the common cold, coughs, bronchitis, and inflammation of the mouth and pharynx [3].

PHARMACOLOGY

Three species of echinacea are used medicinally. Each is purported to have different medicinal properties; however,

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little has been done to compare the effectiveness of each species. The composition of each species of herb is similar, with slight variations in the amount of each active component. Variation between and among the herb species also exists due to geographical location, stage of development, time of harvest, and growth conditions. The roots, the leaves, or the whole plant may be used in the dietary supplement preparation. The composition of the root when compared with the upper plant is very different. Root parts have more volatile oils and pyrrolizidene alkaloids, such as tussilagine and isotussilagine, than the above-ground parts. The active components of the upper plant are thought to be caffeic and ferulic acid derivatives (such as cichoric acid and echinacoside) and complex polysaccharides (such as acidic arabinogalactan, rhamnoarabinogalactans, and 4-*O*-methylglucuronylarabinoxylans). Many other active components in echinacea have been identified. As with any botanical, we do not know the relative potency of each of these compounds, whether they act additively or synergistically, or their bioavailability when consumed. Earlier studies found active components in the water-soluble, ethanol-soluble, alkaline, lipophilic, and polar fractions. A German article (abstract in English) discussed the importance of the dose and the method of administration in evaluating the efficacy of the herb [4].

The German Commission E ([5] translated by the American Botanical Society) has approved the oral use of *Echinacea purpurea* herb, i.e. the above-ground parts, for colds, respiratory tract infections, and urinary tract infections, and its topical use for poorly healing wounds. The *E. pallida* root (fresh or dried) has been approved for use in the treatment of influenza-like infections.

Four preparations of echinacea are unapproved by the German Commission E. These preparations are the *E. angustifolia* and *E. pallida* herbs and the *E. angustifolia* and *E. purpurea* roots. These preparations are unapproved for one of two reasons: either the research that was performed cannot be substantiated because of a lack of information, or the research may have been done with preparations that were not identified adequately. Some early pharmacological studies claimed to have been done with *E. angustifolia* were actually done with *E. pallida*. The fact that these preparations are currently unapproved does not mean that they are not efficacious.

STUDIES OF EFFICACY IN ANIMALS AND *IN VITRO*

In vitro, active components of echinacea have been found to have protective effects on skin connective tissue. Caffeoyl derivatives, typical constituents of echinacea, protected collagen from damage caused by the superoxide and hydroxyl radicals generated in a xanthine/xanthine oxidase system [6]. The polyunsaturated alkamides from *E. angustifolia* were found to inhibit microsomal cyclooxygenase activity and leukocyte 5-lipoxygenase activity, suggesting an anti-inflammatory effect [7]. Animal studies in the late 1980s also showed an anti-inflammatory effect from topical application of the polysaccharide fraction derived from *E. angustifolia* root [8–10]. Both carrageenan paw edema and the inflammation associated with the croton oil ear test were reduced significantly in animals treated topically with echinacea.

Echinacea may be best known as an immunostimulant. A series of studies in mice using purified polysaccharides from echinacea plant cell cultures showed a stimulatory effect when applied to immune cells in culture or injected intraperitoneally into mice. These effects include an increase in phagocytosis, chemotaxis, and oxidative burst of either neutrophils [4, 11] or macrophages [12, 13]. Peritoneal macrophages produced more TNF,* IL-1, IL-6, and IL-10 [14] and were able to kill tumor cells (WEHI 164 cells) and cells infected either with the parasite *Leishmania enriettii*, or with yeast cells, *Candida albicans* [15, 16]. Mice with suppressed immunity due to treatment with cyclophosphamide or cyclosporin also had an increase in these immune functions when given purified polysaccharides from echinacea [16]. These studies suggest that echinacea stimulates immune functions in healthy or in immunosuppressed animals.

These immunologically active polysaccharides did not stimulate all immune cells. B cells were not activated, nor did the B cells produce more antibodies to sheep red blood cells [12]. Although in one study T-cell proliferation was increased slightly, the T-cells did not produce more IL-2, IFN-β2, or IFN-γ. A common T-cell response, delayed type hypersensitivity, was not affected by echinacea treatment [15]. Apparently, then, purified polysaccharides from *E. purpurea* act on the nonspecific branch of immunity, the phagocytic cells, rather than the specifically acquired branch.

EFFICACY AND SAFETY STUDIES IN HUMANS

Although animal studies can give an idea as to the efficacy of the herb and perhaps insight into the mechanism, only human clinical trials provide the necessary information about efficacy, dosage, and length of time needed for results. Trials with humans have generally taken two formats: (i) leukocytes are isolated from the periphery and then treated with echinacea extract *ex vivo*, or (ii) the subject takes the extract, and the leukocytes are isolated to measure a specific function. Roesler *et al.* [17] studied the effect of echinacea on humans using both of these designs. *Ex vivo*, echinacea increased neutrophil chemotaxis and bactericidal activity against staphylococcus. Monocytes produced more TNF, IL-6, and IL-1, but not TH_2 cytokines. When echinacea was injected intravenously, there was a reduction in the number of neutrophils in the blood, which the authors interpreted as an increase in adherence of the cells to the endothelium. They also observed the appearance of juve-

*Abbreviations: TNF, tumor necrosis factor; IL, interleukin; IFN, interferon; and URI, upper respiratory infection(s).

nile forms of cells in the periphery, an increase in C-reactive protein, and an increase in erythrocyte sedimentation rate. This suggested that echinacea enhanced the acute phase response.

In another *ex vivo* study, peripheral blood macrophages that were isolated from healthy humans were incubated with freshly pressed *E. purpurea* juice [14]. This preparation used the above-ground parts, which were harvested and pressed immediately in 20% ethanol. The macrophages had an increased production of TNF, IL-10, IL-6, and IL-1.

In another study, peripheral blood mononuclear cells were isolated from healthy adults and from adults with chronic fatigue syndrome or AIDS [18]. Dried and ground *E. purpurea* was homogenized in cell culture medium and incubated with the peripheral blood mononuclear cells. Natural killer cells had an increased ability to kill K562 human leukemic cells. An increased antibody-dependent cytotoxicity against H9 cells infected with Herpes 6 virus was also found. Whereas these studies show that echinacea can activate human immune cells, they do not tell us if the extract can be effective when consumed orally. Many phytochemicals are absorbed poorly and thus may not be available for direct stimulation of immune cells. On the other hand, communication by the gut-associated lymphoid tissue to other immune systems is well documented. Evidence exists to show that arabinogalactan [19] and fucogalactoxyloglucan [20] are absorbed and are able to stimulate immune function.

In the early 1990s, *E. purpurea* extracts were given to seriously ill patients having advanced, metastatic colorectal cancer [21] or inoperable hepatocellular cancer [22]. In addition to the echinacea therapy, the regimen was also combined with cyclophosphamide and thymostimulin and was well tolerated. This was a prospective cohort with no controls; therefore, the outcome is difficult to assess. Partial tumor regression was noted in one colorectal cancer patient and stable disease in six other patients. Mean survival time was 4 months. Median survival time in the hepatocellular carcinoma patients was 2.5 months.

Several human clinical trials have been done by Melchart *et al.* Five randomized, placebo-controlled studies involving a total of 134 subjects were summarized [23]. These studies measured the phagocytic activity of peripheral neutrophils as the primary outcome. The first study was a single-blind placebo-controlled trial using *E. angustifolia* in a complex preparation (two other herbs were also in the preparation). This was taken as an injection for 5 days. Study 2 was a double-blind placebo-controlled trial using *E. purpurea* root in an ethanol extract taken orally for 5 days. The third study used an ethanol extract of *E. purpurea* and *E. pallida* roots taken in the form of an acid-resistant capsule. Study 4 used an ethanol extract of *E. purpurea* herb and root prepared for oral ingestion. The final study was done with *E. angustifolia* in a complex preparation for injection. The first two studies measured phagocytosis by the Brandt-Test method in which cells were incubated with bacteria and then enumerated under light microscopy. The last three studies measured phagocytosis by flow cytometry. Only the first two studies showed an increase in phagocytic activity of peripheral blood neutrophils. These results underscore the importance of knowing the species of echinacea, the method of extraction, and the route of administration. Each study was prepared with different amounts of echinacea from different plant parts. Studies should only be undertaken with standardized, chemically defined preparations of echinacea. Melchart comments in this paper that, although his studies have shortcomings, echinacea may have no effect in young, healthy volunteers. He suggested that future studies be conducted primarily on patients with immune disorders.

A larger study by Melchart looked at the ability of echinacea to prevent URI using either *E. purpurea* root or *E. angustifolia* root that had been prepared as an ethanol extract [24]. 'Time to event' was the primary outcome measure on 302 subjects who were healthy at the start of the study. Twelve weeks of oral ingestion of the herb preparations or a placebo did not result in a significant prevention of URI. Grimm and Müller completed a study with 109 healthy subjects using fresh juice of *E. purpurea* or placebo juice. The number of subjects having a URI, the number of URI per subject, and the duration of any colds were measured. There was no significant difference in these measures between the echinacea group and the placebo [25]. A study, not yet published in a scientific journal, was reported on the Internet suggesting that those people who consumed an echinacea supplement had more severe symptoms than those taking a placebo [26].

Many other studies have been done on echinacea, but are published largely in the German language, and therefore this author can only obtain limited information from the abstracts. Fortunately, Barrett *et al.* [1] recently reviewed seven German studies published between 1984 and 1997. All studies were classified as double-blind, randomized clinical trials with a total of 910 subjects. The outcome measure for two studies was flu-like symptoms, and the outcome measure for five studies was URI symptoms. Outcome was determined by self-reporting as well as by physical examination. All seven studies showed a significant benefit due to echinacea. Barrett notes that the quality of these published trials is moderate, but in general it appears that these studies support the use of echinacea to modify the severity and duration of cold symptoms.

Studies that examine the ability of echinacea to prevent illness show little to no significant benefit. Echinacea was never meant to prevent colds or flu; rather, it is a treatment and, therefore, meant to be consumed at the onset of symptoms. As Melchart *et al.* [23] suggested, echinacea may be beneficial to those already having immune disorders and therefore may show little to no effect on a healthy immune system. Because of the evidence, limited as it is, that echinacea affects the phagocytes, chronic ingestion of echinacea may potentially do more harm than good. Increased reactivity of the phagocytic system may result in the potential generation of free radicals. Free radicals, in turn,

then may cause damage to the host. The German studies reviewed by Barrett *et al*. show that the benefit of echinacea lies in its ability to shorten the duration and lessen the symptoms of an illness.

To summarize, echinacea has the potential to boost the phagocytic immune cell response. It appears that only certain preparations are able to do so, such as the fresh pressed juice or isolated polysaccharides. More research is needed in this area. Exploration of the efficacy of the different species of echinacea as well as different modes of preparation would be beneficial. The need for standardized, chemically defined preparations is considerable. Echinacea is meant to be therapeutic, not prophylactic. More randomized, double-blind placebo-controlled trials that are designed to show the efficacy towards treating cold and flu-like symptoms are needed to support the existing data.

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