Echinacea: What Makes It Work?

Kerry Bone, B.Sc. (Hons), Dip. Phyto.

Abstract

Extrapolations from pharmacological research have led some authors to suggest restrictions or contraindications for the use of Echinacea. This article examines the known chemistry and pharmacology of the various Echinacea species and products, and challenges some of these popular concepts. In particular, the hypotheses that Echinacea is a T cell activator and that it will accelerate pathology in HIV/AIDS, are found to be unsupported by careful analysis of known data. These misunderstandings have arisen mainly from enthusiastic extrapolations of *in vitro* data on polysaccharide components. The low levels of polysaccharides in most Echinacea products, particularly traditional extracts and tinctures, and their poor bioavailability suggest in most cases the therapeutic activity of Echinacea is due to other component fractions, including the alkylamides. The suggestion that Echinacea should not be prescribed for extended periods of time will be examined in a second article.
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Echinacea is probably the most widely used herbal medicine in the English-speaking world. Despite its popularity, however, the scientific understanding of how Echinacea works on the immune system is incomplete. The existing scientific information has often been over-enthusiastically applied or even misinterpreted. Unfortunately, this has led some writers to suggest restrictions and contraindications for the use of Echinacea which are premature at best, and probably ill-advised. The purpose of this article is to examine the possible pharmacological activities of Echinacea on the immune system, specifically in respect to the suspected active compounds of the herb. Through this process, some of the recently-suggested restrictions of how and when to use Echinacea will be challenged.

The first complicating factor is that the term "Echinacea" describes many different preparations currently in use around the world. They include:

1. The stabilized juice of *Echinacea purpurea* tops, which is often sold under the trade name "Echinacin."
2. Fresh or dried whole plant or aerial preparations of *Echinacea purpurea*, *E. angustifolia* or *E. pallida*.
3. Fresh or dried preparations from the roots of *E. purpurea*, *E. angustifolia* or *E. pallida*.
4. Mixtures of any of the above.

Preparations of either 2, 3, or 4 above are given in various dosage forms including tablets, liquids (in ethanol-water mixtures or other), capsules, and spray-dried powders (in tablets or capsules). Some preparations, especially category 1 above, are often administered by intramuscular injection. It would be unreasonable to expect these diverse preparations and dosage forms to contain the same chemical profile and have the same pharmacological effects in the human body.

Echinacea Purpurea

Excluding physicians in Germany, most practitioners do not use stabilized *E. purpurea* juice administered by injection, and yet research on this product and dosage form comprises the bulk of the clinical work on Echinacea. In short, most research on Echinacea is probably irrelevant to Echinacea's common use in the English-speaking world, i. e., oral preparations from the root of *E. angustifolia* and/or *E. purpurea*. Because of the different nature of the preparation and mode of administration, it is arguably flawed science to assume the research on injected Echinacea necessarily applies to other uses of Echinacea.

Active Components

The active components which occur in the various Echinacea preparations can be divided into three major groups: caffeic acid derivatives, polysaccharides, and lipophilic components.

Caffeic Acid Derivatives: Originally echinacoside was isolated from the roots of *E. angustifolia*,[1] but it also was later found in *E. pallida*.[2] *E. angustifolia* root additionally contains cynarin,[2] whereas cichoric (chicoric) acid and some derivatives are the predominant caffeic-acid-based compounds in *E. purpurea*.[3] Interestingly, the cichoric acid in *E. purpurea* is a different optical isomer than the cichoric acid found in chicory (*Cichorium intybus*) and lettuce (*Lactuca sativa*).[3] Therefore, this compound might be expected to confer different pharmacological properties to *E. purpurea* compared to these other plants. Cichoric acid is also found in the aerial parts of *E. pallida*.[3] Other caffeic acid derivatives are found in the three main Echinacea species, especially in the aerial parts.[3]

Polysaccharides: Two immunostimulatory polysaccharides (PSI and PSII) were isolated from the aerial parts of *E. purpurea*.[3] Studies showed PSI to be a 4-O-methyl glucurono-arabinoxylan (i. e., composed mainly of glucuronic acid and the sugars arabinose and xylose), while PSII was shown to be an acidic arabinorhamnogalactan (mainly composed of the sugars arabinose, rhamnose and galactose).[3] A xyloglucan (xylose and glucose polymer) was also isolated from the leaves and stems of *E. purpurea*.[4]

Most studies on Echinacea polysaccharides have been on those derived from tissue cultures of *E. purpurea* which yielded two fucogalactoxyloglucans and an arabinogalactan (AG).[3] Tissue cultures are artificially cultured plant cells. As expected, the structure of the tissue culture polysaccharides differ from those of the aerial parts of the naturally grown plant, since cells in culture possess only primary cell wall components.[3] Glycoproteins, which are polysaccharides bonded to proteins also have been detected in Echinacea.[3]

The chemical components of plants can be divided into two categories: primary and secondary metabolites. Primary metabolites are essential for life processes or provide important structural elements for the plant. The utility to the plant of many secondary metabolites is unknown, although some are thought to have a defensive or

adaptive role for the plant in its natural environment. Most of the active components found in medicinal plants fall into the category of secondary metabolites. However, polysaccharides are generally primary metabolites. Their functions include structural elements beneath the cell wall and carbohydrate storage molecules. Because of their important role in primary metabolism, all plants contain polysaccharides. Moreover, the levels found in Echinacea preparations are not high when compared to mushrooms and other accumulators of polysaccharides, such as *Althaea officinalis* and Aloe species. It is possible Echinacea polysaccharides possess some unique and potent pharmacological actions on the immune system, but this argument is not helped by research which indicates many polysaccharides have immunological activity.[5-7]

Lipophilic Components: The lipophilic components of Echinacea species comprise two main groups, the polyacetylenes and the alkylamides. The occurrence of polyacetylenes (polyenes) is typical of the Asteraceae family, in which the highest levels are usually found in the roots. *E. pallida* root contains significant levels of some unique polyacetylenes, namely the ketoalkynes and ketoalkenes, which do not occur in the other Echinacea species.[3] These compounds give *E. pallida* root a unique earthy-metallic taste which makes it easy to differentiate.

Alkylamides are not common plant constituents. Most compounds have been found to occur in two tribes of the Asteraceae.[3] Many alkylamides (particularly isobutylamides) have been isolated from the roots and aerial parts of *E. angustifolia* and *E. purpurea* , but they are largely absent from *E. pallida*.[3] Since the alkylamides cause the characteristic tingling sensation on the tongue, it is therefore not surprising that *E. pallida* lacks this property. The alkylamides in Echinacea are composed of a highly unsaturated carboxylic acid (often with triple carbon-carbon bonds) and an amine compound, either isobutylamine or 2-methylbutylamine.[3] It is possible this bond between the acid and the amine is broken during digestion, and the true active entity from these compounds is the carboxylic acid.

Being highly unsaturated, both the polyacetylenes and the alkylamides are prone to oxidation, although they are probably somewhat protected in the natural plant matrix.[8] Nonetheless, Echinacea roots should not be stored in powdered form for prolonged periods.

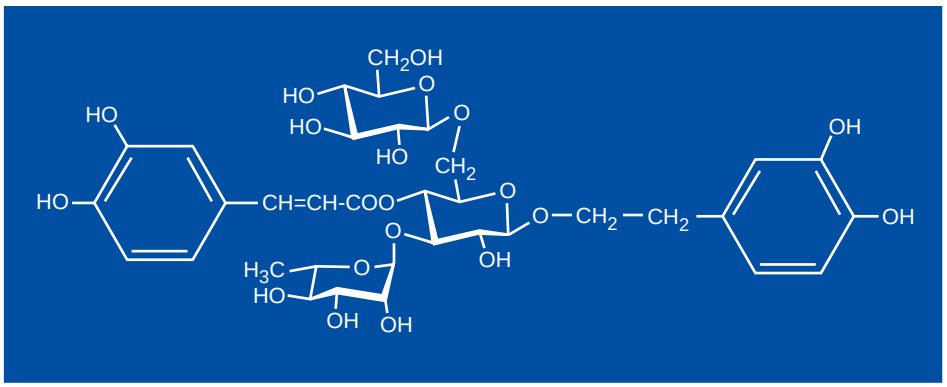
Pharmacological Studies

A. Caffeic Acid Derivatives: Echinacoside (see Figure 1) has weak antibacterial activity which is probably insignificant for the normal use of *E. angustifolia* and *E. pallida*.[1] What is more significant is echinacoside has no immunological activity in any test applied to date.[3] Therefore, companies producing extracts standardized to echinacoside are choosing this entity merely as a marker compound, rather than as an indicator of therapeutic activity. Since echinacoside is not unique to a single Echinacea species, and since there is an incentive to optimize extraction to give the highest yield of what is essentially an inactive compound, it is suggested that other markers of identity and/or activity should be chosen.

In contrast to the lack of activity of echinacoside, cichoric acid (see Figure 2)from Echinacea caused a marked stimulation of phagocytosis in the *in vitro* granulocyte test, which was confirmed in the *in vivo* carbon-clearance test.[9] This suggests cichoric acid may be an important active component, mainly in *E. purpurea*.

Bauer found considerable variation of cichoric acid levels in different commercial preparations of the expressed juice of *E. purpurea* .[8] He concluded this finding was caused by the persistence of enzymatic activity in some fresh plant products, which catalyzed the breakdown of cichoric acid.

Figure 1. Chemical Structure of Echinacoside



Bauer stressed that cichoric acid is stable in preparations from dried *E. purpurea*.[8] However, his research has been misinterpreted by some writers who have concluded cichoric acid is particularly unstable and only found at significant levels in the stabilized juice of *E. purpurea* tops. This is clearly not the case. Cichoric acid is a stable compound, provided the enzymes which have the potential to degrade it are inactivated, as is the case for preparations from the dried plant.

B. Polysaccharides: Much of the confusion about Echinacea has arisen from misinterpretation or overemphasis of the polysaccharide research. Statements such as: "Echinacea will not be immunologically active if given as an ethanolic extract," or "Echinacea is a T cell activator," or "Echinacea is contraindicated in AIDS," have all arisen from an overly enthusiastic interpretation of the pharmacological literature pertaining to Echinacea polysaccharides. It is worthwhile to examine what pharmacological studies on Echinacea polysaccharides do say and consider the relevance, if any, of these to the normal use of Echinacea in the English-speaking world.

Early studies on a crude polysaccharide mixture from the aerial parts of *E. purpurea* showed this mixture stimulated T-lymphocyte numbers and activity *in vitro*.[10] This mitogenic action on T-lymphocytes was probably due to nitrogenous impurities in the polysaccharide mixture, since this activity was found to be extremely low in later investigations with purified polysaccharides.[3] These nitrogenous (protein) impurities are unlikely to survive normal human digestion. Nonetheless, the herbal literature abounds with statements that Echinacea enhances T-cell function, often with elaborate pharmacological theories based on polysaccharide activity. This is despite the fact that this finding has never been demonstrated for Echinacea itself in any pharmacological test, much less an *in vivo* or clinical test following oral doses (the most useful tests for oral therapy with herbal extracts).

A protein-free, highly enriched polysaccharide mixture from the aerial parts of *E. purpurea* (EPS) seems to preferentially stimulate the mononuclear immune system *in vitro*.[3] EPS stimulated both peritoneal and bone marrow macrophages to behave cytotoxically *in vitro*.[3] In a second experiment it was shown that EPS stimulated bone marrow macrophages to release interleukin 1 (IL-1), although it was much less potent than endotoxin in this respect.[3]

Subsequent research was mainly on either an acid arabinogalactan (AG) or an industrially prepared polysaccharide mixture (EPAG), which differs markedly from those found in *E. purpurea*, both isolated from tissue cultures of E. purpurea.[3] AG induces a dose-dependent release of tumor necrosis factor α (TNFα) from peritoneal macrophages *in vitro*.[3] When bone marrow macrophages were used *in vitro*, a dose-dependent release of interferon B2 (IL-6) was also found.[3] There is also indirect evidence that EPAG stimulates TNFα from peritoneal macrophages *in vitro*.[3] The effect of Echinacea arabinogalactan from tissue cultures (AG or EPAG) is strikingly selective for macrophages *in vitro*.[3]

EPAG given by intravenous injection to mice at the very high dose (relative to levels in Echinacea) of 10 mg/kg caused a protective effect against *Candida albicans* infection.[11] Other similar tests have been performed with positive results.

At this point, some of the erroneous conclusions about the use of Echinacea drawn from research on polysaccharides will be examined.

1. "Echinacea is a T-cell activator." As has been stated previously, this is an inappropriate conclusion from *in vitro* research on polysaccharide isolates contaminated with nitrogenous impurities. The relevance of this research to normal clinical use of Echinacea ethanolic extracts is minimal. (See below for further elaboration on this assertion.)

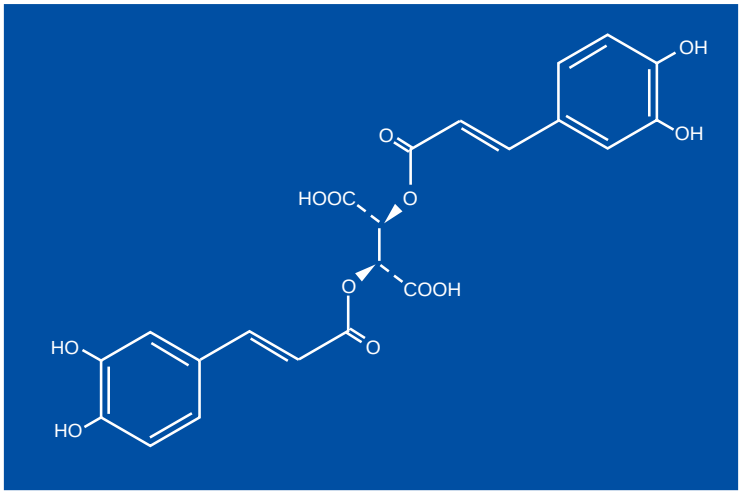
2. "Echinacea stimulates TNFα, IL-1 and IL-6 production and therefore will accelerate pathology in HIV/AIDS." This conclusion suggests there is a strong contraindication for Echinacea in HIV/AIDS. However, for this concern to have a rational basis for oral doses of Echinacea, the following unsupported assumptions are required:

a. The polysaccharides in question are present in significant quantities in all preparations used. This is not valid, since root preparations contain different polysaccharides and in much lower quantities than preparations of tops. If the Echinacea preparation contains 50% ethanol or more, the quantities of polysaccharides present are likely to be negligible (in phytochemistry, a standard technique to precipitate, i.e. remove, polysaccharides is to use a 50% ethanol solution).

b. *Echinacea purpurea* polysaccharides isolated from tissue culture are pharmacologically equivalent to those found naturally in Echinacea preparations. Since they differ chemically,[3] this is not necessarily the case.

c. Polysaccharides are absorbed in significant quantities after oral doses. Polysaccharides are very large molecules which are destroyed in the colon by bacterial activity.[12] Research on acemannan from Aloe vera juice shows that polysaccharide absorption through the gut is about 1%.[13] In order to achieve an immunologically active dose, a daily dose of 600 ml of Aloe vera juice, which is rich in polysaccharides, must be consumed.[13] This implies the quantity of polysaccharides in *E. purpurea* tops (let alone root preparations) will not be absorbed in levels sufficient to achieve the concentrations used in the *in vitro* studies.[3] Perhaps polysaccharides act directly on gut tissue, e.g., Peyer's patches, but it is doubtful they would be present in pharmacologically significant quantities in most Echinacea preparations.

Figure 2. Chemical Structure of Cichoric Acid



d. Polysaccharides are the primary immunologically active components in Echinacea. The research on various root extracts suggest otherwise (see below). Moreover, polysaccharides are a component of the cell wall found in every plant and are not unique to Echinacea.

e. Other components in Echinacea would not modify or change any polysaccharide effect (if such effects exist at

all after oral doses of Echinacea). Phytotherapy is concerned with therapy using plants, not isolated compounds.

f. *In vitro* effects observed on isolated cells can be translated to whole organisms. In other words, there are no biological mechanisms in the whole organism which would modify the effects observed in *in vitro* models. In particular, gastrointestinal breakdown, poor absorption and poor tissue mobility of polysaccharides suggest many significant unknowns in the translation of *in vitro* findings to effects in living organisms after oral dosage.

3. "Arabinogalactan isolated from the Larch is therapeutically equivalent to Echinacea." While there is no doubt arabinogalactan from Larix species has therapeutic activity, even after oral intake if doses are sufficiently high, all of points "a" through "f" above lead to the conclusion that this comparison with Echinacea is not scientifically supported.

C. Extracts of Echinacea: In landmark research on Echinacea, Bauer, with Wagner and co-workers, demonstrated considerable immunological activity for the lipophilic components of the three major species of Echinacea.[14] As with other research on Echinacea, this work has been misunderstood. Roots were first extracted with pure ethanol (which would exclude polysaccharides). A lipophilic fraction (chloroform fraction) and a polar fraction (water-soluble fraction) were separated from the original ethanolic extract. The three solutions were tested for each species using two pharmacological tests – the carbon-clearance test after oral administration and the granulocyte smear test, which is an *in vitro* test.

Results showed significant enhancement of phagocytosis for the following:

In the carbon-clearance test, for ethanolic extracts of *E. purpurea*, *E. angustifolia* and *E. pallida*.; for *E. pallida* the chloroform and water-soluble fractions were also tested, but only the chloroform fraction was active; and for *E. purpurea* only the water-soluble fraction was tested, and it was found to be active, although this activity was less than the ethanol extract. Fractions of *E. angustifolia* were not tested.

In the granulocyte smear test, all ethanolic root extracts caused *in vitro* a 20 - 30% increase in phagocytosis. Chloroform fractions of *E. pallida* and *E. angustifolia* were considerably more active than their water-soluble fractions, which showed negligible activity. In contrast, high activity was found in the chloroform and water-soluble fractions of the ethanolic extract of *E. purpurea*.

Bauer's team analyzed various fractions tested in the study. The chloroform fractions contained essential oils and largely alkylamides for *E. purpurea* and *E. angustifolia* and polyenes for *E. pallida*. The water-soluble fractions respectively contained the characteristic caffeic acid derivatives of each root.

Misunderstanding has arisen because this work has been misinterpreted as implying the water-soluble fractions of Echinacea roots have significant immunological activity. This has led to an argument for low-ethanol extracts of Echinacea root. But what Bauer and co-workers tested was the water-soluble fraction of a pure ethanol extract. Their work, in fact, supports the value of high percentage ethanol extracts of the root. (The Eclectic Physicians used an 80% ethanol extract of *E. angustifolia* root.)

In follow-up work, ethanolic extracts of the aerial parts of the three Echinacea species were found to be active in the carbon-clearance test, but activity was lower than the corresponding root extracts.[9] In every case the lipophilic fraction was more active.

Conclusions

The importance of polysaccharides to the activity of most Echinacea preparations has been misinterpreted and over-emphasized. Traditional ethanolic extracts of Echinacea do not rely on polysaccharides for their activity (in fact, these extracts probably contain insignificant amounts of polysaccharides). Therefore, conclusions regarding the appropriate use of such extracts should not be based on arguably incorrect interpretations of the polysaccharide research.

In particular, the several hypotheses that: 1. Echinacea is a T-cell activator; 2. Echinacea will accelerate pathology in HIV/AIDS; and 3. Arabinogalactan isolated from the Larch is therapeutically equivalent to Echinacea, are not supported by careful analysis of known data.

It is probably appropriate to include a quote from Bauer and Wagner,[3] since most of this article is based on their research.

"The immunological investigations conducted to date permit the following conclusions. Lipophilic alkylamides as well as the polar caffeic acid derivative, cichoric acid, probably make a considerable contribution to the immunostimulatory action or activity of alcoholic Echinacea extracts. Apart from these two compounds, polysaccharides are also implicated in the activity of expressed Echinacea juice (Echinacin) and aqueous extracts, and in the response to the oral administration of powdered whole drug (herb). However, only low concentrations of polysaccharides are present in the expressed juice, and they do not have the same composition as those in the extract of aerial parts."

There are only a few solid pharmacological and clinical studies to support Echinacea's obvious popularity. As a result, several authors have attempted to fill the Echinacea information gap by interpreting *in vitro* data. The fact is, we do not yet fully understand how this herb works on the immune system, and well-intentioned misinterpretations of *in vitro* research have added to the confusion. We live in a time of information overload. As practitioners using medicinal plants, we must become more discerning about the quality of information upon which our clinical decisions are based.

References

1. Stoll A, Renz J, Brack A. Isolation and constitution of echinacoside, a glycoside from the roots of Echinacea angustifolia D.C. *Helv Chim Acta* 1950;33:1877-1893.
2. Bauer R, Wagner H. New results in the analysis of Echinacea roots. *Sci Pharm* 1987;55:159-161.
3. Bauer R, Wagner H. Echinacea species as potential immunostimulatory drugs. In: Wagner H, Farnsworth NR, eds. *Economic and Medicinal Plant Research*. Vol 5. London: Academic Press Limited; 1991:253-321.
4. Stuppner H. Dissertation. Munich; 1985. Cited in Reference 3 above.
5. Egert D, Beuschner N. Studies on antigen specificity of immunoreactive arabinogalactan proteins extracted from Baptisia tinctoria and Echinacea purpurea. *Planta Medica* 1992;58(2):163-165.
6. Gonda R, Tomoda M, Ohara N, Takada K. Arabinogalactan core structure and immunological activities of ukonan C, an acidic polysaccharide from the rhizome of Curcuma longa. *Biol Pharm Bull* 1993;16(3):235-238.
7. Shimizu N, Tomoda M, Gonda R, et al. The major pectic arabinogalactan having activity on the reticuloendothelial system from the roots and rhizomes of Saposhnikovia divaricata. *Chem Pharm Bull* (Tokyo) 1989;37(5):1329-1332.
8. Bauer R. Lecture presented at Plants for Food and Medicine Conference, London, 1996.
9. Bauer R, Remiger P, Jurcic K, Wagner H. Influence of Echinacea extracts on phagocytotic activity. *Z Phytother* 1989;10:43-48.
10. Wagner H, Proksch A. An immunostimulating active constituent from Echinacea purpurea. *Z Phytother* 1981;2:166-171.
11. Lohmann-Matthes M-L, Wagner H. Macrophage activation by plant polysaccharides. *Z Phytother* 1989;10(2): 52-59.
12. Vince AJ, McNeil NI, Wager JD, Wrong OM. The effect of lactulose, pectin, arabinogalactan and cellulose on the production of organic acids and metabolism of ammonia by intestinal bacteria in a faecal incubation system. *Br J Nutr* 1990;63(1):17-26.
13. McAnalley BH, Carpenter RH, McDaniel HR. Uses of Acemannan or other Aloe products in the treatment of diseases requiring intervention of the immune system for cure. International Patent 1993: 08810.
14. Bauer R, Jurcic K, Puhlmann J, Wagner H. Immunological in vivo and in vitro examinations of Echinacea extracts. *Arzneim Forsch* 1988;38:276-281.