

The MediHerb Echinacea Research Story

by Kerry Bone

Introduction

The most well-known herbal support for the immune system is Echinacea. But many patients and practitioners are confused as to the best way to use this herb. There are many Echinacea products available which differ according to plant species (*E. angustifolia*, *E. purpurea* or *E. pallida* or combinations of these), plant part (root, leaves or seeds or combination of these), quality markers (alkylamides, polysaccharides or caffeic acid conjugates such as cichoric acid) and dosage.

Underlying this diversity of preparations was a lack of consensus over what phytochemicals are responsible for Echinacea's immune activity and only a rudimentary understanding of the exact mode of action of this herb on immune function. However, recent research, in which the MediHerb scientific team has played a key role, has provided some answers to these key questions. In particular the alkylamides, the unique and characteristic phytochemicals found mostly in the roots of *E. angustifolia* and *E. purpurea* have been shown to be the best choice as markers of immune activity.

Historical Context

Before discussing the exciting new research developments for Echinacea, its use as an immune herb needs to be understood in its historical context. Information about the therapeutic value of Echinacea first came from Native American tribes. Their use of Echinacea was then adopted by the Eclectics, a group of doctors who were prominent around the late 19th and early 20th centuries in the United States. By 1921 Echinacea (specifically the root of *E. angustifolia*) was by far the most popular treatment prescribed by Eclectic physicians.¹ The Eclectics used Echinacea for about 50 years and accumulated extensive clinical experience in its use. The best sources of such uses are King's American Dispensatory² and Ellingwood.³

What is also important to note is that Echinacea's reputation as an immune herb came from the solid traditional data generated by the Eclectics on only one form of Echinacea: a fluid extract of the dried root of *Echinacea angustifolia* extracted in a high percentage of alcohol. We can call this a "traditional Echinacea extract" and, because it was extracted in a high percentage of alcohol, the term "lipophilic extract" (fat loving) is also relevant. In particular, the Eclectics defined good quality Echinacea root "as imparting a persistent tingling sensation" which is a clear reference to alkylamide levels as a quality indicator.²

In Europe during the 1930s the German herbalist Madaus used *E. purpurea* as he was more successful at growing this species. His interest in homoeopathy led him to use the stabilised juice of fresh *E. purpurea* tops. This remains the most popular form of Echinacea in Germany today (and contains very low levels of alkylamides). We can call this style of product a "hydrophilic extract" (water loving) of Echinacea.

Naturally German scientists were interested to investigate how these new hydrophilic extracts of Echinacea might work in the body and undertook a search for active components. Polysaccharides possessing immunological activity were isolated from the aerial parts of *E. purpurea*.⁴ Some clinicians and scientists then mistakenly applied this research to the very different lipophilic or traditional Echinacea preparations, and came to the conclusion that they were therapeutically inferior because of their low or absent content of polysaccharides. (The low levels of polysaccharides in traditional Echinacea extracts are due to the low starting levels in the root and the fact that high levels of alcohol do not effectively extract these water-loving molecules.)

However, many herbal clinicians remained unconvinced. A key aspect of modern phytotherapy is a respect for traditionally-generated knowledge and this suggested that a lipophilic extract of *E. angustifolia* root was the preferred form. Some felt that the concept of polysaccharides failed to explain what was unique about Echinacea and expressed concerns about the low oral bioavailability of these large, polar compounds.⁵ So what was clearly needed was a different understanding of Echinacea,

especially of the phytochemicals important for the activity of traditional Echinacea products and their mode of action on the immune system.

What is Active Must First Be Absorbed

It can be concluded from both traditional use and clinical studies that Echinacea acts on the immune system at various sites in the body. Hence for Echinacea to exert this influence, the active phytochemicals must be absorbed in significant quantities in the bloodstream. Accordingly MediHerb undertook both test tube (*in vitro*) and clinical (pharmacokinetic) research to understand which of the key phytochemicals in Echinacea were absorbed.

The Caco-2 Intestinal Absorption Model

A particular strain of human colon cells (Caco-2) can be grown in a test tube to form a tight layer of single cells (a monolayer). This can serve as a model of absorption by the human digestive tract. The test components are placed on one side of the monolayer and after a period of time anything that has been transported across to the other side of the monolayer is sampled and measured. When the MediHerb scientists carried out this research using the Echinacea Premium extract (made from the roots of *E. angustifolia* and *E. purpurea*) they found that:

- all the alkylamides were transported across the Caco-2 monolayer
- the caffeic acid derivatives were not transported

Results from this model indicate that only the alkylamides in Echinacea Premium are likely to be absorbed (and hence bioavailable to the immune system).

This Caco-2 work by MediHerb and collaborators has recently been published as: Matthias A et al in the Journal of Clinical Pharmacy and Therapeutics 2004; 29:7-13. Another paper entitled "Bioavailability of Echinacea constituents: Caco-2 monolayers and pharmacokinetics of the alkylamides and caffeic acid conjugates" was published as: Matthias A et al in *Molecules* 2005; 10:1242-1251.

Absorption in Human Volunteers

These results from the Caco-2 model were confirmed in a human pharmacokinetic study. Basically, volunteers took 4 tablets of Echinacea Premium with a meal and the levels of any detectable Echinacea phytochemicals were measured in their blood. Only alkylamides could be detected in the blood after taking the Echinacea Premium. There were no caffeic acid conjugates found and no degradation products of these or the alkylamides. This work was published in August 2005 by MediHerb and collaborators as: Matthias A et al in *Life Sciences* 2005; 77:2018-2029.

The Importance of Liver Metabolism

Only alkylamides were found in human plasma after ingestion of Echinacea Premium tablets, but the levels were quite variable and first pass liver metabolism was suspected as influencing this observation. (First pass metabolism is the rapid degradation by the liver as the products from digestion first pass through the liver on their way to the general circulation). The alkylamides mainly found in *E. purpurea* were found to be rapidly degraded by human liver microsomes. In contrast the alkylamides mainly found in *E. angustifolia* were much more slowly degraded. Interestingly, it was discovered that the latter type of alkylamide actually slowed down the rate of degradation of the former type of alkylamide. This protective effect of the *E. angustifolia* alkylamide is a highly novel finding and it was deduced that the presence of only relatively small proportions of this compound will result in a product with enhanced bioavailability. This is a strong justification for the combination of *E. angustifolia* root with *E. purpurea* root, as in the Echinacea Premium. A patent has been applied for to protect this very important finding. This work has been published as: Matthias A et al. in *Chemico-Biological Interactions* 2005, 155: 62-70.

Echinacea Premium: Liquid Extracts versus Tablets

One question that is often asked is whether herbs work better as liquid extracts or tablets. MediHerb tablets are likely to work just as well as liquids because they are made using extracts (not the powdered herb) and are formulated to pharmaceutical standards to ensure rapid disintegration. This was verified in a clinical study which compared equivalent doses of Echinacea Premium in liquid or in tablet form. The total amount of alkylamides absorbed into the bloodstream was essentially the same for both products. This work has been published as: Matthias A et al. Comparison of Echinacea alkylamide pharmacokinetics between liquid and tablet preparations. *Phytomedicine* 2006; In Press. To our knowledge it is the first study of this kind (comparing the bioavailability of equivalent doses of a herbal liquid extract against a tablet) ever undertaken.

What is Absorbed Must Be Active

The research undertaken by the MediHerb team has established that alkylamides are the only phytochemicals which are bioavailable from traditional lipophilic extracts of Echinacea root. In addition combining *E. angustifolia* with *E. purpurea* will enhance the alkylamide bioavailability of the latter and there is no difference (in terms of alkylamide bioavailability) between the tablet and liquid extract forms of Echinacea Premium.

The next question to be answered was whether the alkylamides do have an effect on the immune system. The MediHerb research team in collaboration with other scientists undertook test tube research to investigate such activity. The key findings of these studies were that:

- Echinacea did not activate the immune system in the absence of any immunological challenge
- The Echinacea alkylamides tended to modulate the immune responses of macrophages and T cells, toning the response down in the face of a strong stimulus, hence helping the immune system to operate more efficiently

This macrophage work was published as Stevenson LM et al in *Molecules* 2005; **10**:1279-1285 and the T cell study is currently awaiting submission for publication.

A recent significant discovery, first presented at a major international conference, was the observation by two separate research teams that the immune effects of Echinacea may be mediated by the interaction of Echinacea alkylamides with cannabinoid receptors. A Swiss research team found that an *in vitro* immune-modulating effect of a lipophilic Echinacea extract (and individual alkylamides) on monocytes/macrophages could be neutralised by the presence of agents which block CB2 cannabinoid receptors.⁶ Bauer, in collaboration with US scientists, found that alkylamides from Echinacea bound to both CB1 and CB2 cannabinoid receptors.⁷ In particular, certain alkylamides exhibited selectivity for CB2 receptors.

Taken together, these developments first presented at the conference suggest the hypothesis that the alkylamides are largely responsible for the systemic immune effects of Echinacea lipophilic extracts and that this immune modulating activity is (at least in part) due to the interaction of alkylamides with cannabinoid receptors, specifically CB2.

CB1 receptors are highly localised in the central nervous system (CNS) and are believed to primarily modulate behaviour, while CB2 receptors predominate in immune tissues outside the CNS, especially the spleen, and are believed to modulate immune function.⁸ Cannabinoid receptors are remarkably preserved across the animal kingdom which suggests they play an important developmental and physiological role.^{9,10} Much of the immune activity of the cannabinoid system appears to be mediated by the cytokine network. Cytokines include the interleukins (IL-3, IL-6, etc), tumour necrosis factor alpha (TNF α) and the interferons (IFN).

The Swiss team mentioned above has followed on from this ground-breaking research and shown that certain Echinacea alkylamides bind strongly to CB2 receptors.¹¹ In addition they have shown that alkylamides also exert additional effects on immune cells which are independent of CB2.¹¹ Their research has been particularly insightful into one aspect of the mode of action of Echinacea alkylamides.¹² A lipophilic extract of *Echinacea purpurea* strongly stimulated TNF α mRNA synthesis in peripheral monocytes, but not TNF α protein production. In other words, the Echinacea-induced new TNF α transcripts (mRNA) were not translated into TNF α itself. When monocytes are treated with LPS (lipopolysaccharide or endotoxin, a powerful stimulator of the immune system) TNF α protein production is substantially increased. However, co-incubation of monocytes with LPS and Echinacea extract resulted in a strong inhibition of this effect of LPS. This is consistent with the findings of the MediHerb research team.

Investigation over a longer time-span revealed that the lipophilic Echinacea extract, via interaction with CB2 receptors, modulated and prolonged TNF α production following immune stimulation. The results of this study suggest that Echinacea works more as a modulator or facilitator of the immune response, rather than as an immune stimulant. In resting monocytes it prepares them for a quicker immune response by inducing TNF α mRNA. However, in overstimulated monocytes (as in the case of LPS) it first reduces and then extends their response in terms of TNF α production. In particular, these key findings challenge the mythology that traditional Echinacea extracts will “overstimulate and wear out” the immune system if taken continuously.

Clinical Effects on Immune Function

To further understand the effects of Echinacea Premium at a clinical level, a small study was undertaken to investigate its effects on heat shock proteins and whole blood parameters. Healthy volunteers were dosed with two Echinacea Premium tablets per day for two weeks, with assessment at the beginning and the end of the trial. Positive results were evident, with increased heat shock protein levels (hsp70) and increased white cell counts. (Heat shock proteins are molecular chaperones which modulate the immune response). This work was published in August 2005 as: Agnew LL et al in *Journal of Clinical Pharmacy and Therapeutics* 2005; **30**:363-369. Further work is planned to further evaluate these effects in a much larger study.

This increase in white cell count for Echinacea Premium ties in well with research from the team of Dr Miller in Canada, which has shown (in experimental models) that *E. purpurea* root boosts the number and function of natural killer (NK) cells (a class of white blood cell).¹³

A New Understanding of Echinacea

The research on Echinacea Premium by the MediHerb scientists has made a substantial contribution to a new understanding of lipophilic extracts of Echinacea. It can be concluded from this research that:

- Alkylamides must be used as the markers of quality and activity
- The root of Echinacea is the preferred plant part, since it is highest in alkylamides
- The preferred species of Echinacea are *E. angustifolia* and *E. purpurea* since they contain high levels of alkylamides (compared to *E. pallida*)
- Echinacea must be extracted using an alcohol percentage sufficiently high to efficiently extract the alkylamides
- Echinacea modulates the immune response by the interaction of the bioavailable alkylamides with CB2 receptors
- Echinacea root (rich in alkylamides) additionally boosts the white cell count, especially NK cells
- The traditional way Echinacea was used has been validated by scientific research at the cutting edge of modern immunology

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