New Developments at the Frontier of Echinacea Research

There have been some exciting new developments in the field of Echinacea research (my favorite herb) in the past few years. Some of this research has been featured in several of my previous columns, but recently I took the opportunity to interview three prominent scientists who are working and publishing in this field. I believe that it is important to know the perspectives of the actual scientists, as nonscientists often misinterpret their work. The very latest insights from these acknowledged experts are provided below.

Dr Jürg Gertsch

Your research has focused on the alkylamide (isobutyramide) components of Echinacea angustifolia and purpurea and their mechanism of action on the immune system. What have you discovered?

We found that some of these compounds have a very strong effect on the regulation of tumour necrosis factor, which is a key substance in the cellular immune system. Later we managed to find a mechanism of action for alkylamides, namely that they bind to the type-2 (CB2) cannabinoid receptors, which are known to modulate different aspects of immune function.

Are these effects specific to the alkylamides in Echinacea? What about other plants that also contain this phytochemical class?

To date, we know that the alkylamides from Echinacea possess the most potent compounds with regard to their interaction with the CB2 receptor. There are at least 20 other plant species from different families that produce this class of natural products, but so far we have not found more potent compounds than those found in Echinacea.

What are cannabinoid receptors, and what effects do they mediate in the body?

There are two types of cannabinoid receptors, the so-called CB1 receptor and the CB2 receptor. CB1 receptors are strongly expressed on neurons in the central nervous system, and CB2 receptors are mainly found in the periphery and on immune cells. Both receptors have been shown to mediate analgesic effects. The CB1 receptor mediates the psychotropic effect of THC in marijuana. The CB2 receptor has no such function but appears to be involved in a series of pathophysiological processes, such as acute infection, atherosclerosis, and osteoporosis. This makes the CB2 receptor an interesting target for the development of new medicines. Overall, one could say that most CB2-specific compounds are anti-inflammatory.

Do all alkylamides in Echinacea have an equal affinity for CB2 receptors?

No, there are striking differences, which depend on the chemical structure of the molecule. So far, we know that the flexibility of the alkyl tail in the alkylamide molecule plays a role and that the isobutyl head group seems to be an ideal moiety for the receptor interaction. There are also alkylamides that have no affinity for the CB2 receptor at all.

Does this mean that the Echinacea alkylamides merely act as anti-inflammatory agents during acute infections, or are there immune-enhancing effects?

It is very difficult to study immunological process in vitro, and it is also dangerous to draw conclusions from such experiments. But we have clearly seen that alkylamides exert potent anti-inflammatory effects. We have also observed that in whole blood assays these compounds induce IL-6, which can be either pro-inflammatory or anti-inflammatory, depending on the molecular context.

Is interaction with CB2 receptors the only mechanism of action for Echinacea alkylamides?

During our work, we proved that there are CB2-independent effects, which are also anti-inflammatory. Moreover, the strong tingling of these compounds in the mouth is independent of CB2 interaction. Thus, there may well be one or two other mechanisms. We have screened the alkylamides on more than 50 receptors with the result that only CB2 was positive, which also shows that these compounds are much more specific than other classes of natural products, such as, for example, flavonoids.
What are the implications of this research for the best way to use Echinacea?

We think that Echinacea preparations rich in alkylamides should be effective at the onset of an inflammatory condition, such as a sore throat, beginning of a common cold, or even an infection of the mouth or gastrointestinal tract.

It has been suggested that Echinacea is contraindicated in diseases that have a TH1 dominance such as many autoimmune diseases. Is your research consistent with this hypothesis?

From our research, we see a clear effect on the T-cell response, which is a TH1 to TH2 shift typically observed for CB2 agonists. This means that the acute response is resolved and replaced by TH2 cytokines, such as interleukin 4 and 10. To my knowledge, there is no scientific data that would show that Echinacea is problematic for autoimmune diseases. On the contrary, CB2 agonists have been proposed to be of interest in the treatment of rheumatoid arthritis.

Dr Anita Matthias

Can you comment on your test tube research on Echinacea and its clinical relevance?

We have shown that ethanolic Echinacea preparations are able to ameliorate the effects induced by an immune stimulus in both macrophages and T-lymphocytes. On examination of the different components found in Echinacea, it was found that both the alkylamide fraction, isolated alkylamides, and cichoric acid affected the induced immune response. This is in agreement with the literature. The difficulty with this type of research, however, is that all of the components investigated were able to have an effect on the cells under investigation. This is not necessarily true in a whole body situation. Some of or even all of the compounds present in the extract examined are not necessarily going to encounter these cells, as they may not be absorbed into the blood stream. Even if they are absorbed, they may not remain in the form found in the herbal extract. This means that the compounds that are effective must first be shown to be bioavailable before any in vitro data has any relevance to a clinical situation when oral dosing is the method of delivery. Also, the in vitro test looks at just one specific mechanism of action in a narrow context. What happens in whole body systems is generally more complex. There is also the likelihood that an agent could exert other effects not tested by the specific in vitro models used.


Given that determining the bioavailable compounds is so important, can you comment on your research on the bioavailability of Echinacea phytochemicals?

We examined the bioavailability of Echinacea phytochemicals on two levels: in cell culture using a cell monolayer made from human colon cancer cells, where the alkylamides were found to readily cross the monolayer, suggesting that they will be able to cross the intestinal barrier and be found in blood, hence gaining access to immune cells and therefore able to modulate their actions. The caffeic acid derivatives (cichoric acid and echinacoside) did not cross the cell monolayer. This was an indication that they would not cross the intestinal barrier when taken orally. These results were then confirmed in a clinical trial. Alkylamides, but not caffeic acid derivatives, have been found in blood samples after ingestion of Echinacea preparations.


What about Echinacea as a liquid extract versus the same product in tablet form?

Traditionally, Echinacea preparations are ethanolic liquids. It is reasonable to assume that if the bioavailable compounds are present, then they should be able to cross the intestinal barrier no matter their starting form – tablet or liquid. As expected, we found that the alkylamides were present in blood after ingestion of both liquid and tablet preparations of Echinacea. From ingestion of equivalent doses, blood concentrations were found to be the same in the three individuals examined. The only real difference is the speed with which the alkylamides are able to be detected in blood. Alkylamides were detectable after five minutes for a liquid dose and 20 minutes for a tablet dose. These time differences are not unexpected, as the tablet needs time to dissolve before the alkylamides are free and available for absorption.


Is there value from a pharmacokinetic perspective in combining E. angustifolia with E. purpurea?

There certainly is. When doing the pharmacokinetic studies, we found that we were not getting the plasma levels that we expected after seeing how easily the alkylamides diffused across the Caco-2 cell monolayers. This suggested to us that there was a high probability that the liver was degrading the alkylamides before they reached the general circulation. In studies with liver microsomes containing cytochrome P450 enzymes (these are the enzymes responsible for most of the first pass liver metabolism), we found that some of the alkylamides were rapidly degraded. Monoene alkylamides, which are only found in Echinacea angustifolia, are not degraded by the liver P450s and are able to prevent the degradation of the diene alkylamides found in both Echinacea angustifolia and Echinacea purpurea. Hence, combining E. angustifolia with E. purpurea improves the bioavailability of the alkylamides in E. purpurea. We patented this finding.


Do you see a disease-preventative role for an Echinacea preparation rich in alkylamides?

We know from animal models that Echinacea purpurea root (which has significantly higher levels of alkylamides than the leaf) powerfully stimulates natural killer (NK) cell and monocyte production. (Whether this effect is also mediated by CB2 receptors has not yet been established.) These cells are the main part of innate immunity that is our
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frontline defense against an invading pathogen. We also know from these animal models that it takes two weeks of continuous use to fully stimulate the higher levels of these cells. (Our research group has seen a similar effect in humans, but we are still actively researching this.) Hence, it is quite likely that the continuous use of Echinacea will prime the innate immunity and thereby act to prevent common infections. We certainly saw this effect clinically for a combination of E. angustifolia and E. purpurea roots rich in alkylamides. In a clinical trial conducted at the National College of Naturopathic Medicine, Portland, Oregon, the rate of winter infections was significantly reduced by this protocol. Hence, it is quite erroneous to suggest that Echinacea root preparations high in alkylamides will not act to prevent infections.

Associate Professor Reg Lehmann

Are Echinacea alkylamides stable in pure form or in the dried herb?

Over the past six years, we have worked to synthesise pure alkylamides for use as reference standards to enable us to accurately quantify the levels of alkylamides in our raw materials and finished products. We have found that these pure compounds, particularly the tetraenes, are quite unstable, even when stored at -20°C (-4°F). This is similar to what we have found when working with dried Echinacea root, where at 40°C and below, we found that the alkylamides were quite unstable in the herbs. We presumed this to be due to enzyme activity.

So what about their stability in Echinacea products?

MediHerb has been doing stability studies on the finished tablets and liquids since we introduced the alkylamides target level on the label over five years ago – the first company to do so in the US. During this time, we have shown that stability of alkylamides is not an issue for these preparations. Under Good Manufacturing Practice (GMP), products that claim a level of active or marker compound must have this level at the end of its shelf life, not just at the beginning. We have shown that the alkylamides are stable throughout the recommended lifetime of the products. This is a testimony to an inherent strength of herbal medicine: that an unstable compound is rendered stable in a complex plant extract. We understand, however, that not all products sold in the US market are made under pharmaceutical GMP and therefore may not have stability data for the expected lifetime of the product.

What clinical effects have you discovered for a combination of E. purpurea/angustifolia roots?

We have been manufacturing a blend of E. purpurea and E. angustifolia roots for over ten years, and over this period, we have gain immeasurable amounts of compelling feedback from our customers. We have also been fortunate to have had the opportunity to have this product clinically tested as well in two trials to date and another one underway. The first trial was with the research group of Dr. Anna Macintosh at the National College of Naturopathic Medicine in Oregon and showed a reduction in the incidence of winter infections in a group of highly stressed and therefore susceptible students over those on placebo. We have also recently published a clinical study looking at the effect of supplementation of this combination upon the human immune response. Specifically, it was found that supplementation for two weeks caused an increase in white cell counts, an increase in the expression of leucocyte heat shock proteins, and an improvement of erythrocyte antioxidant defenses.

About the Scientists

Dr. Jürg Gertsch, PhD

Dr. Gertsch is currently senior scientist and group leader in the group of Prof. Dr. Karl-Heinz Altmann at the Department of Chemistry and Applied Biosciences (D-CHAB), ETH Zürich, Switzerland. Before that, he held a postdoctoral position at the Department of Chemistry and Applied Biosciences (D-CHAB), ETH Zürich, Switzerland. He has also been extraordinary supervisor for the Venezuelan government for the census of indigenous peoples (Yanomani area), Amazon State, Venezuela and conducted ethnobotanical fieldwork among the Yanomani Amerindians. His research interests include cannabinomimetics, signal transduction (cellular immune response), and Amazonian ethnobotany.

A/Professor Reg Lehmann, PhD

Since 1996, Prof. Lehmann has worked with MediHerb in quality assurance, production, technical, and research areas. His present position is Research Manager, where he is responsible for the group's research activities, clinical trial management, phytochemical research, and agronomic research. Prof. Lehmann is regarded as a leading phytochemist around the world and has been invited to present at numerous international scientific conferences. He is also an adjunct Associate Professor in the School of Molecular and Microbial Sciences at the University of Queensland.

Dr. Anita Matthias, PhD

Dr. Matthias gained her BSc (Hons) from the University of Tasmania, majoring in Biochemistry and Microbiology, and PhD from the University of Tasmania (1995) in Biochemistry. Her first post doctorate was in Sweden at the Department of Zoophysiology, Wenner-Gren Institute, University of Stockholm from 1996-1999. The second post-doctorate was at the Biochemistry Department at the University of Cambridge, UK 1999-2000. Dr Matthias investigated the pharmacology and pharmacokinetics of Echinacea preparations, providing greater scientific clarity to the quality and efficacy issues of Echinacea products funded by MediHerb's BIF grant.

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