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Echinacea: Modern Research Confirms Traditional Use

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Defining Echinacea

Not all Echinacea is equal. The term "Echinacea" in fact describes many different preparations in use around the world. One of the difficulties with published research is that often the Echinacea used is not the best available, therefore the results can be misrepresentative of the efficacy of a good quality preparation of high grade Echinacea.

Echinacea preparations include:

- The stabilised juice of *E. purpurea* tops.
- Fresh or dried plant preparations of whole plant or aerial parts or roots of *E. purpurea*, *E. angustifolia*, or *E. pallida*.
- Mixtures of any of the above.

The above preparations can be given in various dosage forms including liquids (ethanol/water or glycetract), tablet or capsules. Tablets and capsules can contain either dried extract, powdered dried herb or mixtures.

Traditional Use of Echinacea

Echinacea angustifolia is a traditional medicine of the Native Americans and it continues to be an important part of their medicine today. It was used as a "remedy for more ailments than any other plant" to treat a wide variety of disorders including snake bites and other venomous bites and stings; enlarged glands; sore throat; septic conditions; rabies and toothache (also used topically for toothache).[1]

The Lakota Native Americans, indigenous to South Dakota, still use the roots of *Echinacea angustifolia* more extensively than any other plant. This usage is reflected in the Lakota name for the plant "ica'hpe hu" which means something used to knock something down, which is reference to its use in chronic immune deficiencies.[2] The Lakota people are in the heart of *E. angustifolia* territory and neighbouring tribes, many of who had ready access to *E. purpurea*, traded with the Lakota to obtain the much valued *E. angustifolia* root.

The quality of the root was determined by chewing a small amount – the greater the tingling sensation the better the quality was considered to be. It is clear from this historical information that the original users of Echinacea valued *E. angustifolia* above *E. purpurea* and only used the roots.

After observation of its use by the Native Americans, Echinacea became a popular herb with the Eclectic Medical Movement, which was at its peak in the late 19th and early 20th centuries. The Eclectics wrote extensively about Echinacea and were adamant that *E. angustifolia* was the most active species. In accordance with the Native Americans, they believed that the best quality root came from the prairie lands and that plants growing in the marshes and lowlands were of inferior quality. They stressed that, "when chewed the root, if of good quality, imparts a persistent tingling sensation".[3] We now know that this tingling sensation is caused by the presence of alkylamides.

The clinical experience of the Eclectics is particularly valuable since it occurred at a time before the use of antibiotics. The Eclectics found frequent and high doses of *E. angustifolia* to be very effective for the treatment of life-threatening disorders such as snake bite, septicaemia, bacterial meningitis, cholera, dysentery and even rabies and gangrene. Echinacea was effective for viral and bacterial infections as well as for venomous bites.[4]

Problems with Herbal Research Interpretation

When assessing published research there are a number of things to consider in order to understand how the results may impact on the clinical use of the herb. For example:

- What was being assessed by the research and is this relevant to the accepted clinical use of the herb?
- What part of the plant and what type of preparation was used?
- What was the duration of the research?
- Was the research clinical, *in vivo* or *in vitro*?
- If an *in vivo* model was used, how was the herb administered, what dosage was used and how does this relate to oral dosage in humans?

- In clinical trials what style of study was performed eg open trial; single-blind?, placebo- controlled; randomised double-blind placebo controlled, cross-over trial.
- How was the herb administered and at what dosage?

It would be unreasonable to expect that all of the Echinacea preparations and dosage forms listed above are likely to contain the same phytochemical profile and have the same pharmacological effects in the human body. Much of the research has centered on the use of *E. purpurea* stabilised juice administered by injection. With the exception of Germany, most practitioners do not use Echinacea in this way. In the English-speaking world, practitioners commonly use preparations from the root of *E. angustifolia* and/or *E. purpurea*. Because of the different nature of the preparation and the different mode of administration, it is flawed science to assume that the research on injected Echinacea necessarily applies to other uses of Echinacea. (It is interesting to note that the administration of Echinacea by injection is now illegal in Germany on the recommendation of BfArM.[5,6] BfArM is the German equivalent of the Australian Therapeutic Goods Administration.)

In order to interpret research using isolated constituents, the pharmacokinetics of Echinacea following oral administration need to be understood. For example, *in vitro* research using isolated polysaccharides has to be interpreted carefully.[7]

- Most of the studies on Echinacea polysaccharides have been on those derived from tissue cultures of *E. purpurea*. Tissue cultures are artificially cultured plant cells and as expected, the structure of the tissue culture polysaccharides differed from those of the aerial parts of the naturally grown plant.[8]
- Polysaccharides are large molecules and are not readily absorbed across the gut mucosa. However, it is likely that they have a local immune effect on the Peye's patches in the gut.
- Polysaccharides are not well extracted from plant material in an aqueous/alcoholic preparation.
- The effect on isolated cells during *in vitro* research is likely to be very different to that which occurs in a person taking the herb orally.

Likewise research into the activity of isolated caffeic acid derivatives such as echinacoside and cichoric acid can be misleading. Pharmacokinetic research conducted in 2004 has demonstrated that caffeic acid conjugates (cichoric acid and echinacoside) or degradation products of caffeic acid conjugates were not absorbed in humans after oral dosing of MediHerb Echinacea Premium tablets.[9] Therefore the pharmacological activity of these isolated constituents cannot be extrapolated to the oral use of Echinacea root preparations.

What makes Echinacea Work?

Although research has demonstrated immune activity for Echinacea polysaccharides and cichoric acid, for the reasons stated above these constituents have little, if any, relevance to the activity of traditional Echinacea root preparations (extracted in alcohol) when taken orally. The alkylamides appear to be the most important constituents as they have been demonstrated *in vitro* to exert an immune modulating effect, which allows the body's natural immune system to operate more efficiently than is possible in a dysfunctional system. *In vitro* research by Bauer[10] and Gertsch[11] suggests that the cannabinoid receptors play a role in this immune modulating effect. Most importantly, human pharmacokinetic studies demonstrate that the alkylamides are absorbed.[12]

There are two cannabinoid receptors, CB1 and CB2, which were originally found because they were activated by the major psychoactive component of marijuana. CB1 receptors are highly localised in the central nervous system and are believed to primarily modulate behaviour, while CB2 receptors predominate in immune tissues outside the central nervous system, especially the spleen, and are believed to modulate immune function.

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

The most important point is that the alkylamides **are** absorbed across the gut mucosa. This was initially demonstrated using the Caco-2 intestinal absorption model[13] and then in a human phase 1 trial[9] using MediHerb Echinacea Premium tablets. (The Caco-2 model is widely used in the pharmaceutical industry to predict which compounds are likely to be absorbed in the gut.) Alkylamides were the only phytochemicals from Echinacea which were identified in the human plasma samples. After approximately 6 hours most of the alkylamides had been metabolised or excreted. This is consistent with the recommended dosing of one tablet 3 times per day. These findings are supported by research carried out by Professor Dr Rudolph Bauer of Karl Franzens University in Austria.[10] His team investigated the bioavailability of a 60% ethanolic extract of *E. angustifolia* root in 12 healthy volunteers. The alkylamides were shown to be rapidly absorbed after oral ingestion of the liquid. Preliminary pharmacokinetic work conducted earlier also demonstrated that the alkylamides were absorbed.[14]

Another important finding of the 2004 research initiated by MediHerb[12] demonstrated differences in degradation of the two major alkylamides. The 2, 4-diene alkylamides (found in both *E. angustifolia* and *E. purpurea*) were found

to be rapidly degraded by human liver microsomes. In contrast, the 2-ene alkylamides (found only in *E. angustifolia*) were degraded much more slowly. More interestingly, it was discovered that one of the 2-ene alkylamides actually slowed down the rate of degradation of 2,4-diene alkylamides. This finding supports the traditional use of *E. angustifolia* root preparations. (As previously stated, it was *E. angustifolia* root that was used by the Native Americans and the Eclectics while *E. purpurea*, which was also readily available, was largely ignored.)

Unfortunately today, the high cost of *E. angustifolia* can mitigate against its long-term use. For this reason it is often combined with *E. purpurea* root, giving a more affordable product, while maintaining efficacy. We can see from the above research that using *E. purpurea* alone may not yield the best clinical outcomes due to the rapid degradation of alkylamides. If *E. purpurea* is used it should be combined with *E. angustifolia* root in order to slow degradation of alkylamides and enhance alkylamide bioavailability.

When should Echinacea be Used?

Based on its traditional use and our current scientific understanding Echinacea can be used in the treatment of a wide variety of conditions:

- Long-term for the treatment of chronic immune deficiency.
- For the treatment of acute infections.
- For the prevention of infections (long-term if necessary in some individuals).
- For the treatment of allergies due to the immune modulating effect.
- For the treatment of autoimmune diseases due to the immune modulating and anti-inflammatory effects.
- For the treatment of skin conditions due to effects on immunity and its depurative activity.
- For the treatment of lymphatic congestion due to immune and lymphatic effects.
- For the treatment of spider and other venomous bites (not to the exclusion of medical treatments where applicable).
- For immune support in individuals receiving conventional cancer treatments.

Myths and Fallacies surrounding the Use of Echinacea

Much of the confusion about Echinacea has arisen in part from the misinterpretation or overemphasis of the polysaccharide research. The potential problems with this research have already been discussed. Some of the fallacies surrounding the use of Echinacea are listed below.

1. *Echinacea should not be used to treat patients who suffer from asthma* because it stimulates TNF-alpha (tumor necrosis factor-alpha), an inflammatory cytokine. This assumption is based on *in vitro* research in which isolated polysaccharides stimulated TNF-alpha production. In contrast, later research (2004) demonstrated that a mixture of alkylamides (which are known to be absorbed) actually decreased TNF-alpha production.[9]

In addition to this latest scientific information there is a large body of clinical experience among many leading herbalists to suggest that not only are Echinacea root preparations safe but can be extremely beneficial in reducing the incidence of infections that often precipitate an asthma attack. However, the use of Echinacea tops, especially in a hydrophilic preparation such as a tea or stabilised juice, should be avoided by asthmatic patients (due to the risk of an allergic reaction).

2. *Echinacea should not be used in many chronic conditions.* The German Commission E monograph states "that in principle, Echinacea should not be used in progressive conditions such as tuberculosis, leukaemia, collagen disorders, AIDS, HIV infection, multiple sclerosis and other autoimmune disease".[15]

However:

- The key words in the above statement are "in principle". There are no clinical studies which document an adverse effect resulting from Echinacea use in any of these conditions.
- The assumption that Echinacea is contraindicated in autoimmune disease assumes that any enhancement of the immune system is detrimental. This is naive since the immune system is very complex.
- Although there is still much to learn about Echinacea, rather than being a straight out immune stimulant, it appears to act more as an immune modulator.
- Research published in 2004[16] demonstrates that Echinacea does not stimulate the immune system in the absence of other immunological stimuli. This means that the immune system will not be stimulated unless there is an infective organism present at the time.
- Infectious microorganisms are thought to play a role in the aetiology of autoimmune diseases. If this is the case, Echinacea may be a valuable herb for reducing the presence of chronic infections.[17,18]
- Clinical observations by many Australian practitioners indicate that Echinacea is not harmful and is probably beneficial as part of the treatment of autoimmune diseases.
- Likewise there is no evidence to suggest that the use of Echinacea in leukaemia is harmful. There is one recorded case study of long-term Echinacea use in chronic lymphocytic leukaemia which did not reveal adverse effects and may have contributed to a favourable outcome.[19]

3. *The duration of Echinacea use should be limited* because it will deplete the immune system if used continuously for more than a few days. This misunderstanding appears to have come from the misinterpretation of research published in 1989.[20] The research tested the effect of *E. purpurea* tincture on the phagocytic activity of human granulocytes following intravenous or oral administration for 5 days (see Figures 1 and 2 below). A cursory examination of the figures might lead to the conclusion that use of Echinacea for more than a few days does deplete the phagocytic response. The misinterpretation may have resulted from extrapolation of results obtained following intravenous administration of the herb. However, closer examination of the results shows quite clearly that oral dosing with Echinacea does not deplete immunity. It is interesting that a comment by the authors on an atypical use of Echinacea ie injection should have caused such a widespread misunderstanding about the oral use of Echinacea, a misunderstanding that continues to be perpetuated.

- The results of the above study clearly show that following intravenous administration, phagocytic activity increased up to day four after which time it began to decline (see Figure 1). However, because Echinacea use was stopped on day five it is unknown whether this trend would have continued with the extended use of the herb. The authors comment that, "The observation that a consistent decrease in activity occurred after the last injection may indicate that operation of a tiring or exhaustive effect after a short period of stimulation". A more likely explanation is that the decline in phagocytic activity was within experimental variation, followed by a normal washout effect.
- More importantly, after oral administration, phagocytic activity continued to increase significantly until the Echinacea was stopped after day five (see Figure 2). Upon the cessation of Echinacea administration, as expected, phagocytic activity began to decrease. Testing continued until day eleven at which time phagocytic activity was still higher than at the beginning of the study. It did not ever decrease phagocytic activity below normal (baseline) levels.
- These results clearly indicate that far from causing depletion, oral use resulted in a residual stimulating effect after Echinacea was stopped.

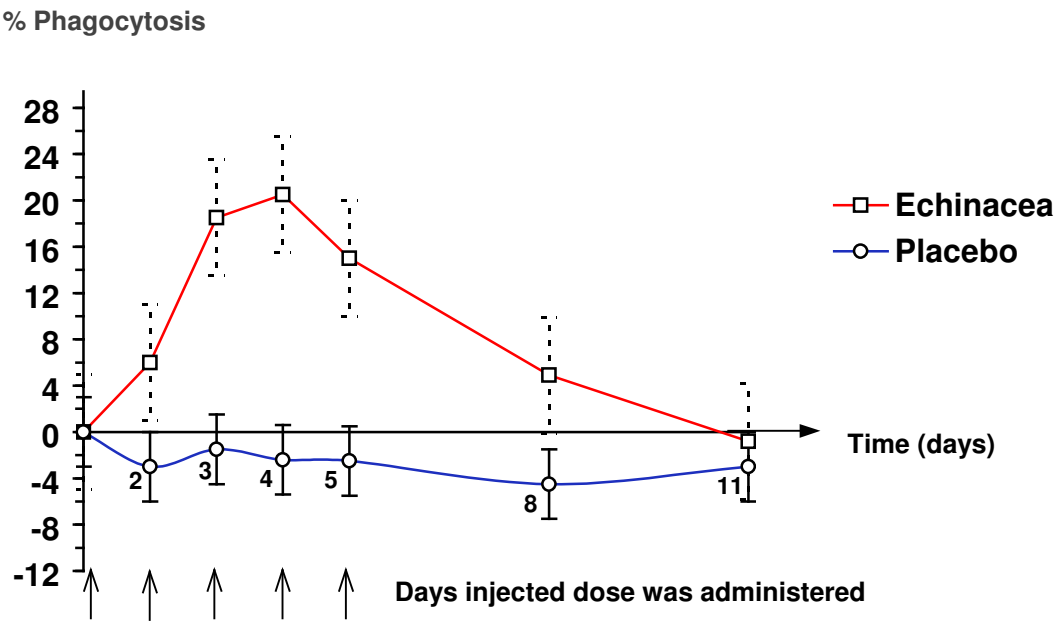

Figure 1. Single-blind study with injectable Echinacea versus placebo.

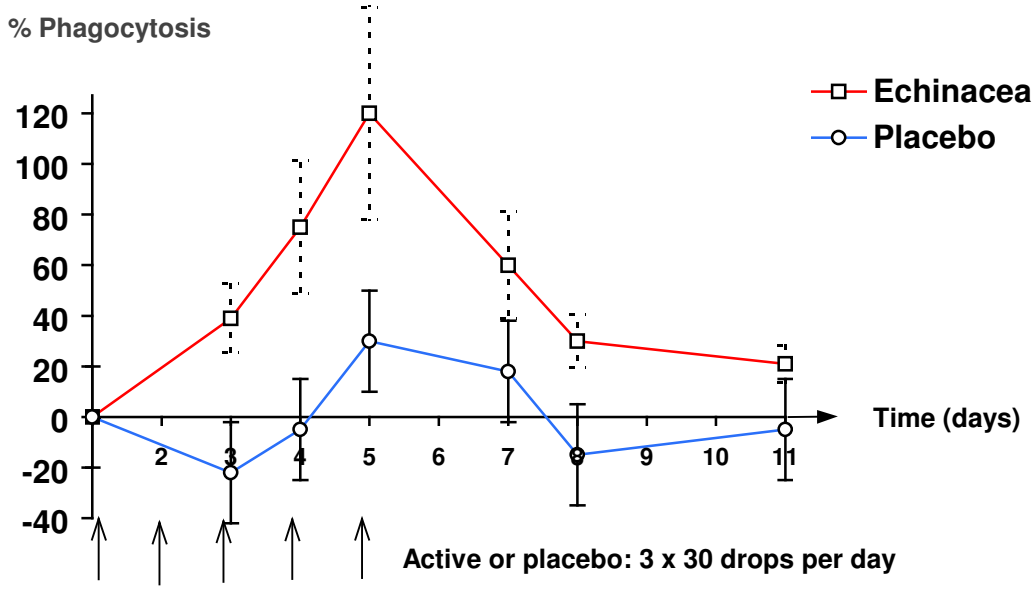

Figure 2. Oral double-blind study with *Echinacea purpurea* versus placebo.

The assumption by the authors of the above study is not supported by other research.

- A review[21] of published Echinacea studies found that adverse events on oral administration for up to 12 weeks are infrequent and consist mainly of digestive symptoms.
- Another study[22] found that immune reactivity (in response to applied antigen) after 10 weeks of continuous oral doses of Echinacea was considerably greater than after 2 weeks, which in turn was significantly greater than before therapy. (normalisation of cell-mediated immunity)

Clinical Trials

Over the years there has been a number of clinical trials designed to assess the efficacy of Echinacea. The majority of these have concentrated on the treatment of upper respiratory tract infections (URTIs). Many of these studies have demonstrated that Echinacea is superior to placebo in treating symptoms of URTIs. However, one of the biggest problems in assessing this research is that many different Echinacea preparations have been used and in most cases levels of active constituents are not stated.

As already discussed, it is clear that the efficacy or otherwise of Echinacea will depend entirely on the quality of the preparation used and the dosage administered. If we are to be guided by the most recent research (as well as the traditional understanding), we would accept the fact that the alkylamides are probably the most important constituents contributing to the immune modulating effect of traditional alcoholic preparations of Echinacea. We would also accept that *E. angustifolia* is the preferred species.

The first three clinical trials listed below are good examples of clinical trials which yield unfavourable results probably due to the fact that ethanolic root preparations of Echinacea high in alkylamides were not used?

A randomised, double-blind placebo controlled trial[23] involving 117 participants was carried out in order to evaluate the efficacy of an Echinacea preparation with a defined chemical profile for the prevention of rhinovirus colds. Participants were given either 300 mg of Echinacea (species and part used not defined) or a placebo three times each day for 14 days prior to virus challenge and continued for 5 days after virus challenge.

The particular Echinacea preparation used in the trial did not exert a significant effect on either the occurrence of infection or the severity of illness. For example infection occurred in 44 and 57% and illness occurred in 36 and 43% of the Echinacea- and placebo-treated subjects, respectively.

These results are hardly surprising given the chemical profile of the preparation, which indicates it was of poor quality. It contained some cichoric acid but almost no

echinacosides, and most importantly, **no alkylamides**, and as discussed previously, it appears to be the alkylamides that are the most important constituents for exerting a systemic immune effect.

The results of two individual randomised, double-blind, placebo-controlled clinical trials were published in mid-2004. The first of these was published in the May 15th edition of the journal of the Infectious Diseases Society of America[24] and was reviewed in the MediHerb e-Newsletter Issue 6, August 2004. The second appeared in the June 2004 issue of *Archives of Internal Medicine*.[25] In both trials the pressed juice of *E. purpurea* was used.

Forty-eight previously healthy adults took part in the first trial (24 in the treatment group and 24 in the placebo group), which was designed to determine the ability of *Echinacea purpurea* to prevent infection with rhinovirus type 39 (RV-39).[24] They were given either 2.5 mL of an *E. purpurea* pressed juice extract (in a 22% alcohol base) or placebo for 7 days before and 7 days after intranasal inoculation with rhinovirus. Not all participants became infected after inoculation with the virus. Of those who did became infected colds developed in 59% in the Echinacea group and 86% in the placebo group ($p = 0.088$). Those in the Echinacea group experienced a lesser degree of symptoms than those in the placebo group.

In scientific terms, although the results are not statistically significant ($p = 0.088$), they do show a strong tendency towards Echinacea preventing the occurrence of cold symptoms in individuals infected with rhinovirus. Clinically there is a big difference between 59% and 86% of patients developing symptoms. Echinacea also appears to have reduced the severity of symptoms. A p value of 0.088 means that there is an 8.8% probability that the results happened by chance. In order for a result to be considered statistically significant, the probability of chance must be 5% or less ($p = 0.05$, or $p < 0.05$). The method of calculating this figure is quite complex and is determined by a number of factors particularly trial size (number of trial participants) and size of effect. The smaller the number of participants in a trial the more difficult it is to determine the statistical significance of the results.

In the second trial[25] the authors sought to determine the efficacy of a standardised preparation of *E. purpurea.* One hundred and twenty-eight patients were enrolled within 24 hours of cold symptom onset. The were administered either placebo or 100 mg of *E. purpurea* freeze-dried pressed juice (from aerial parts), which was standardised for β-1,2-D-fructofuranosides (polysaccharides), three times per day. No statistically significant difference was observed between the two groups in total symptom scores, mean individual symptom scores or time to resolution of symptoms. The authors concluded, "Some studies have found that Echinacea effectively reduces the symptoms and duration of the common cold. We were unable to replicate such findings. Further studies using different preparations and dosages of *E. purpurea* are necessary to validate previous claims".

In contrast, two clinical trials (sponsored by MediHerb) using a root preparation rich in alkylamides have yielded positive results. A randomised, single-blind trial was conducted among students at the Duval College, University of New England (in New South Wales, Australia) from June to September 1994, to assess the effectiveness of a liquid Echinacea preparation in the prevention and treatment of colds and influenza.[26] The Echinacea preparation consisted of *E. purpurea* root 1:2 extract (50%), *E. angustifolia* root 1:2 extract (35%), both standardised for alkylamides, and a small amount of flavouring mixture. The placebo was a similar tasting preparation consisting of flavouring mixture and prickly ash (*Zanthoxylum clava-herculis* – to mimic the tingling effect of Echinacea).

Eighty students volunteered to take part in the 12-week trial, however compliance dropped off during the trial. This was possibly due to the occurrence of University holidays and only forty-three participants completed the trial. The volunteers were assigned either to the test group or the control group. The co-ordinator of the trial was aware of which preparation was being given to each individual. The participants were not. A General Health Report was filled out prior to the commencement of the trial and a Weekly Health Report was filled out during the trial. Analysis of the General Health Report indicated that no statistically significant difference existed between the two groups prior to treatment in terms of general health status, current medications taken, chronic health problems and several other health parameters.

The analysis of results began in the second week to allow the medicine to take effect. The general health and well-being of the Echinacea group was better than the control group during the study ($p = 0.04$ and $p = 0.08$). In weeks 7 and 9, the incidence of colds appeared to be lower in the Echinacea group (27–33%) than the control group (56–78%). In week 8 the symptoms of illness seemed to be more severe in the control group than the Echinacea group. Bed rest was required more often in the control group (43%) than in the Echinacea group (5%), and 14% of participants in the control group were prescribed antibiotics while nobody in the test group was.

Although not conclusive due to the small number of subjects completing the trial, Echinacea demonstrated a tendency towards preventing colds and influenza. The results demonstrate that the Echinacea preparation used in the trial is probably efficacious in the prophylaxis and treatment of colds and influenza. Further clinical trials of sufficient sample size and response rate are required to bear this out statistically.

A randomised, double-blind, placebo-controlled trial[27] carried out by Dr. Anna MacIntosh (National College of Naturopathic Medicine, Portland, USA) and co-workers in 1999 demonstrated that an Echinacea root liquid and a liquid formula made from three tonic herbs both significantly reduced the incidence of winter colds in students. The Echinacea liquid consisted of a flavoured blend of *E. angustifolia* and *E. purpurea* roots (in equal quantities) standardised to contain at least 1 mg/mL of alkylamides. The trial was conducted on 265 medical students because this group tends to be highly stressed and susceptible to winter infections. The students were assigned to receive either one of the two active formulas or the placebo in late autumn and were followed for 105 days. Three dosage protocols were tested over the length of the trial: high (4 mL twice/day) followed by medium (3 mL twice/day) followed by low (2 mL twice/day). Whereas the incidence of colds remained at about 10% of the test population for the placebo group, the incidences for the Echinacea and the tonic formula fell to between 2% and 3% at both 42 and 70 days, winding back to between 4% and 8% at 105 days. This reduction in effect at 105 days probably reflects a reduction of effect resulting from the low dose protocol. The differences between the active liquids and placebo were both at the borderline of statistical significance at 42 days (p = 0.06–0.07), and achieved statistical significance at 70 days (p = 0.03). Results at 105 days were not significantly different from placebo (reflecting the low dose protocol).

There was no significant difference between side effects for the three groups, although there was a slightly greater incidence of digestive upset for the Echinacea group. In particular, the Echinacea treatment did not increase or aggravate allergies.

The authors suggested that their study demonstrated that the effective dose for the Echinacea root combination as a preventative treatment was approximately 4 mL to 5 mL per day. Such a dose range is considerably higher than previously used in Echinacea clinical trials, which may explain some of their negative findings. They also stressed the importance of using high quality herbal preparations with active or marker compounds quantified by HPLC to meet suitable minimum levels of activity.

Conclusion

After considering the relevant research, traditional use and clinical experience of many herbal practitioners, there is no doubt that Echinacea is an effective herb for the prevention and treatment of infections. The clinical experience of practitioners also supports its use as an immune modulating herb in the treatment of allergic conditions and autoimmune diseases. This immune modulating effect has also been scientifically demonstrated in recent research initiated by MediHerb.[16]

It is critical however, that appropriate Echinacea products be used. It is becoming clear from research carried out by different research groups around the world that the alkylamides are the most important constituents for the immune effects of Echinacea when taken orally by humans. It has also emerged that, in accordance with the traditional understanding, that *E. angustifolia* is the most therapeutic species.

Although more research is needed to further enhance our understanding of how Echinacea works, research carried out in the last few years has given us new insights into the workings of this herb. Particularly exciting is the finding that the immune modulating effect is potentially mediated by the ability of alkylamides to interact with the cannabinoid CB2 receptors.

Practitioners can confidently use *E. angustifolia* root either alone or in combination with *E. purpurea* root (for cost effectiveness) for the treatment of many acute and chronic conditions as outlined in this article.

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