CONFERENCE REPORT

Echinacea in today's world

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A.Vogel Research

Introduction

Respiratory tract infections are the most frequently encountered illnesses in the Western world. These infections encompass common colds and flu, both of which may be manifested by a wide variety of symptoms – from slight nasal stuffiness, an itching throat, to pulsating headaches, chesty cough and fever[1].

Even with mild episodes of colds or flu, patients seek relief from acute symptoms and the general discomfort experienced. Data from the National Institute of Allergy and Infectious Diseases of the National Institutes of Health estimate that up to 1 billion colds are experienced in the United States every year[2,3]. A total of 100 million visits to the doctor, approximately 42 million days of absence from school, as well as 148 million days of restricted activity are attributed to colds and flu[2,3]. The overall cost of these illnesses amounts to 39.5 billion US dollars and in terms of economic burden, colds and flu rank in the same league as hypertension, stroke and COPD[5].

Colds and flu are caused by a wide variety of viruses such as the Rhinovirus, Coronavirus, Respiratory Syncytial Virus, Metapneumovirus, Bocca virus and finally, the Parainfluenza and Influenza viruses[2].

It is often difficult to differentiate between colds and flu clinically. In the absence of viral tests, it is impossible to identify the causative organism. Even during influenza epidemics, only about 15% of clinically identified flu-like illnesses are caused by Influenza viruses[6,7].

On the other hand, infections by the Parainfluenza and Respiratory Syncytial Viruses, and even the most common virus causing colds, the Rhinovirus, can produce substantial morbidity and mortality. Complications of respiratory tract infections include otitis media, sinusitis, bronchitis, bronchiolitis and pneumonia, and colds are known to exacerbate asthma, especially in children[8].

Vaccination provides an effective means of combating infections by the influenza virus but there are currently no pharmacological agents able to protect against other respiratory viruses. The development of a specific prophylactic against colds and flu is hampered by the multiplicity of viruses and their propensity to mutate.

An alternative approach is to support the body's own immune mechanism, falling back on the principle that the human organism is able to defend itself naturally against viruses and bacteria. It is here that *Echinacea purpurea* claims a unique therapeutic role. A few standardised Echinacea products carry the status of registered medicines with approved indications covering support of immune resistance and / or the prevention and acute treatment of cold and flu symptoms.

In the recent past, research on a special extract of *Echinacea purpurea* (Echinaforce®) has intensified, mainly as a consequence of our experience with newly occurring respiratory viruses (Influenza or Coronaviruses), the novel understanding of pharmacological mechanisms of respiratory infections and the known weaknesses of available therapies.

In September 2012, a scientific conference on Echinaforce® was held in London, where experts in the fields of respiratory infections, immunology and virology reported their experience of the extract in the context of colds and flu. The event saw the presentation of new data from the largest prevention study using Echinacea.

The antiviral activity of Echinaforce®

Prof. Pleschka, University Giessen, Germany

The predominance of viruses in cold and flu infections has repeatedly been outlined. They are involved in 90 to 95% of episodes.

From 2009 to 2011 three major scientific articles reported the potency of Echinacea to broadly inhibit a series of respiratory viruses *in vitro*[9-11]. Antiviral activity was found against Influenza A/B (H3N2, H1N1, H5N1, H7N7 and S-OIV), Respiratory Syncytial Virus (RSV) and Herpes simplex (HSV).

Very recent, yet unpublished research data indicate that Coronaviruses and Parainfluenza viruses are sensitive to the extract as well, reinforcing the theory that Echinaforce® broadly blocks membranous viruses.

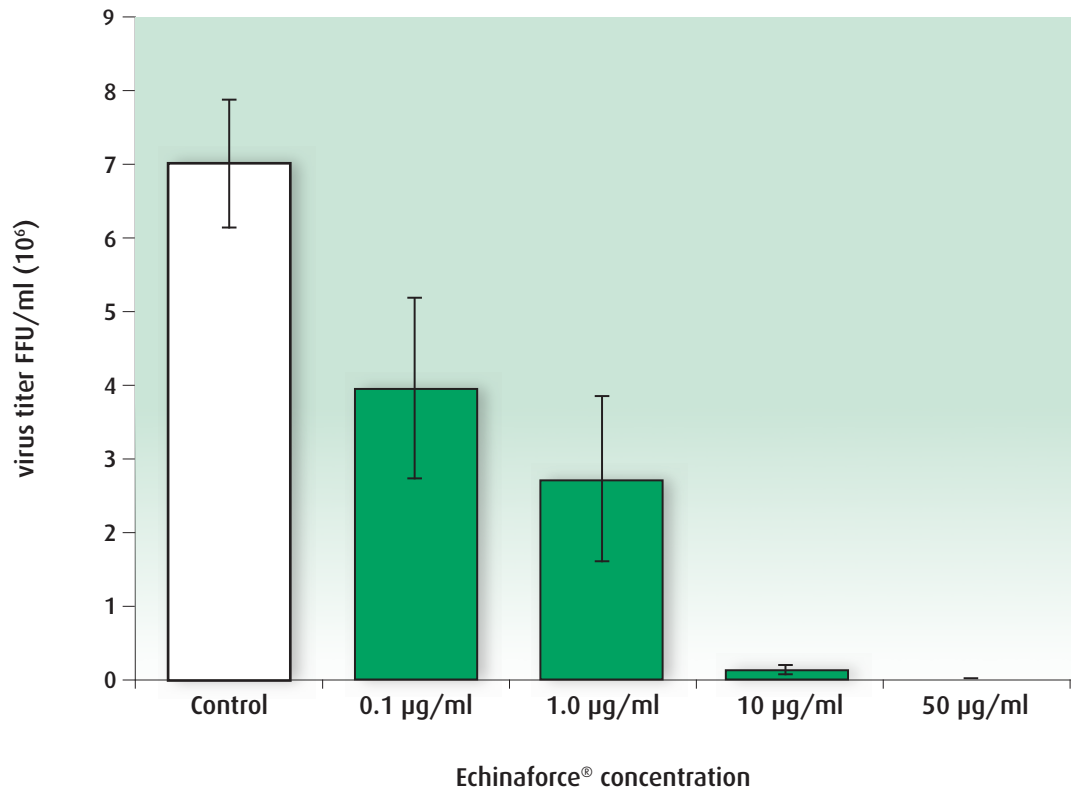

Figure 1: Echinaforce® dose-dependently inhibits influenza virus H5N1. At physiologically relevant concentrations a significant reduction of replication was observed[7]. Similar inhibitory activity was seen for other respiratory viruses with membranes.

We found that the extract modified the structure of surface receptors of Influenza viruses (Haemagglutinin) required for entry into the cell. The data suggested that Echinaforce® interfered with the virus replication process at the earliest possible step (cellular infection) thereby preventing infection (Figures 2a & b). Intracellular replication was however not affected by the extract, or only at higher concentrations.

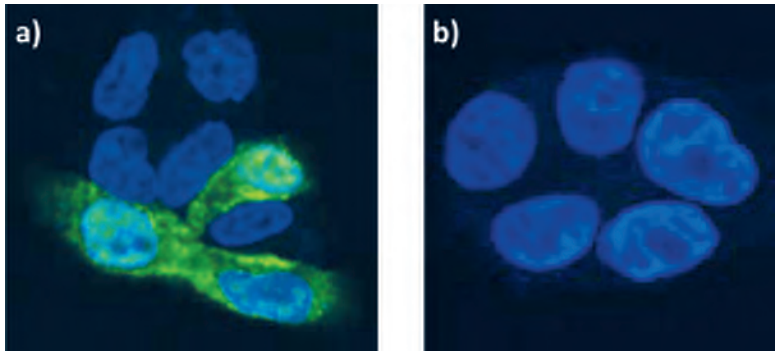

Figure 2a) Intracellular virus replication can be visualised by histological staining of nucleocapsid protein (NP, green; nucleus, blue). **b)** In the presence of Echinaforce® both infection and therefore, replication, is inhibited *in vitro*.

Even continuous passaging of influenza viruses in the presence of Echinaforce® did not result in the emergence of resistant influenza strains, whereas culturing of viruses in the presence of a neuraminidase inhibitor (Tamilflu®) rapidly generated drug-resistant strains (Figure 3, white bars). Intriguingly, Tamiflu®-resistant influenza viruses remained susceptible to Echinaforce® (data not shown).

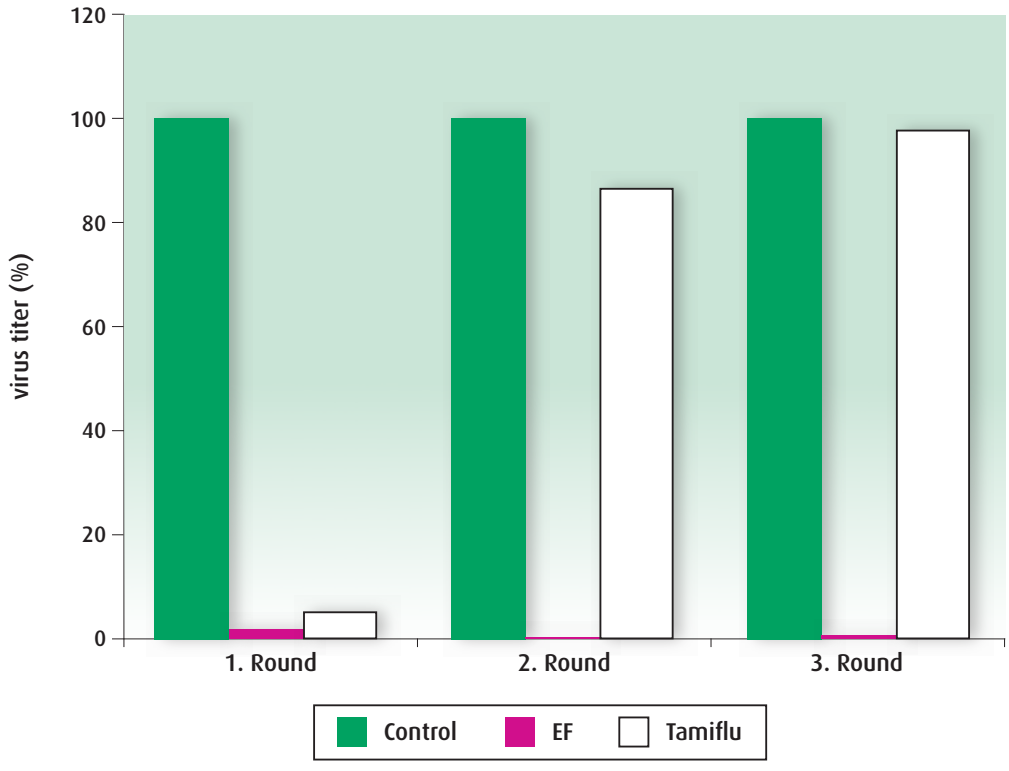

Figure 3: Even repeated cycles of Echinaforce® (EF) treatment did not select for resistant H5N1 strains, as seen with the neuraminidase inhibitor Tamiflu®.

The immunological effects of Echinaforce®

Dr. M. Ritchie, University of London, United Kingdom

An intact immune system is a pre-requisite for successful immune defence as seen in patients with AIDS, where even opportunistic infections can lead to death[12]. However in colds and flu it was recently argued that simply boosting the immune system might be the last thing you want to do[4].

In this context our group in Scotland aimed to explore the immunological effects of a prophylactic treatment with Echinaforce®. After a run-in phase of two days (baseline), subjects began to take oral doses of Echinaforce® over eight days[13]. On every day blood was collected and immunological parameters were measured after *ex vivo* stimulation using SEB/LPS. Even after a few days of treatment, the extract reduced inflammatory proteins (TNF-α and IL-1β) in the total population.

Interestingly, effects on anti-viral Interferon-gamma (IFN-γ) or on chemotactic molecules (IL-8 or MCP-1) depended on the respective constitutions at the run-in phase (baseline). In subjects with a low initial production of IFN-γ, IL-8 and MCP-1 at baseline, Echinacea treatment induced an additional formation of these signal substances (from +18% to +49% in comparison to baseline representing 100%). In contrast, there was no further increase in subjects with a high initial formation of these factors at baseline (Figure 4, blue bar).

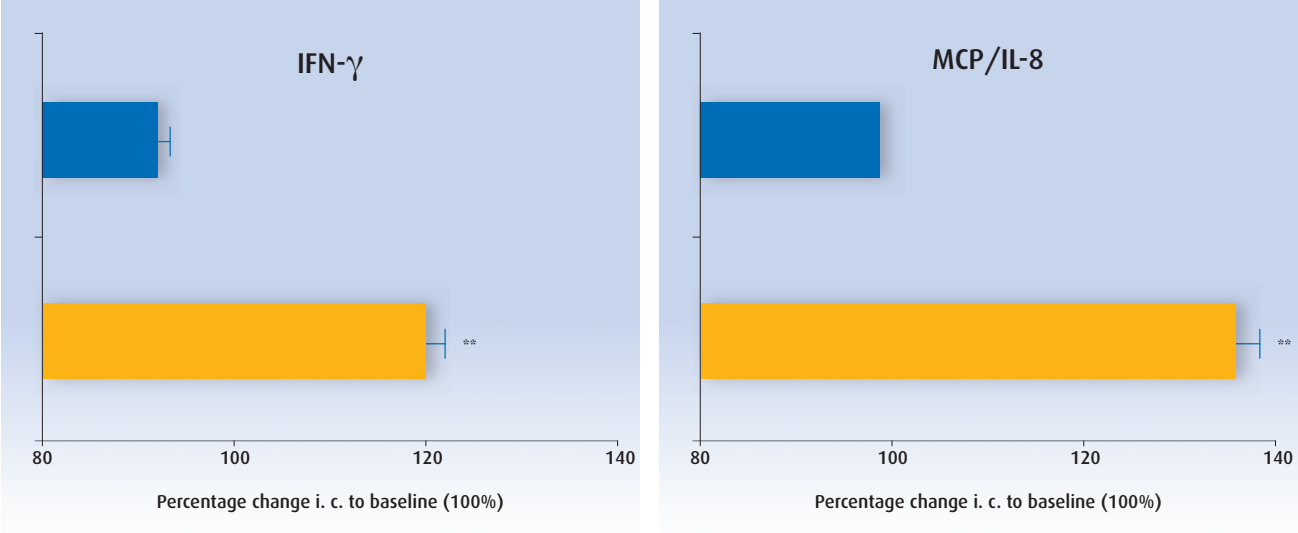

Figure 4: Effects of Echinaforce® on the production of immune mediators (cytokines and chemokines) appear to depend on the initial constitution of the user. Anti-viral IFN-γ and chemotactic proteins (e.g. MCP/IL-8) were significantly induced only in subjects with initial low production of these substances pre-treatment (yellow bar).

This selective support of the immune reaction was also observed in subjects reported to have increased stress or with a higher susceptibility to cold infections in the past.

This clinical trial indicates that Echinacea supports low-running immune systems, and in phases of increased stress or susceptibility to cold infections. It also shows that well-performing immune systems are not over-stimulated by Echinacea.

Safety and Efficacy of Echinaforce in long-term prevention of colds and flu

Prof. R. Eccles, Cardiff University, United Kingdom

Respiratory viruses and diseases such as colds and flu are common from October until April and any preventive treatment should be effective and safe to take throughout the whole winter season.

The very latest randomised, double blind, placebo-controlled clinical trial investigated the safety and efficacy of Echinaforce® prophylaxis over 4 months. Nasal secretions from participants with acute colds were taken and analysed for respiratory viruses. With 755 included subjects this clinical trial represents the largest study ever with Echinacea. It was carried out at the Common Cold Centre at Cardiff University, UK[14].

With regard to adverse events, adverse drug reactions, laboratory blood parameters and finally the physician's and participant's assessment of tolerability, Echinaforce® was found to be non-inferior to placebo. Previously reported safety concerns such as induction of allergic reactions, leucopenia or autoimmune diseases were not observed under Echinacea treatment.

As seen in Figure 5, considerably more cold episodes and episode days (with colds) occurred under placebo and 52% more episodes required pain-medication ($p<0.05$). Virally-confirmed infections were reduced by Echinaforce®, especially Influenza, Respiratory Syncytial Virus, Parainfluenza and Coronavirus infections (Figure 6).

Maximal prevention was seen in subjects with recurring cold infections and 100 episodes observed in 43 subjects with placebo were reduced to 63 episodes in 28 subjects with Echinaforce®. This corresponds to a ratio of frequencies of recurring infection of 1.59. With $p=0.017$ the difference reached statistical significance. Recurring episodes with positive virus nasal samples went down from 34 to 14 infections.

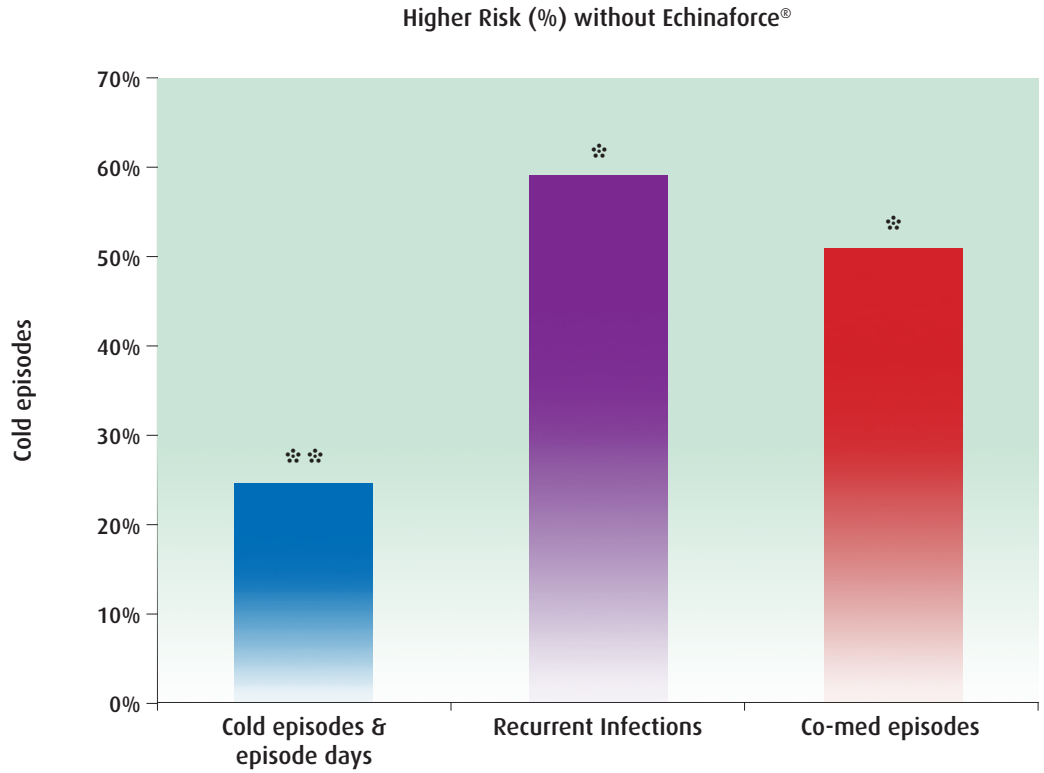

Figure 5: Prophylactic Echinaforce® treatment was associated with a reduced number of recurrent cold episodes, episode days and episodes requiring pain-medication (*$p<0.05$; **$p<0.01$).

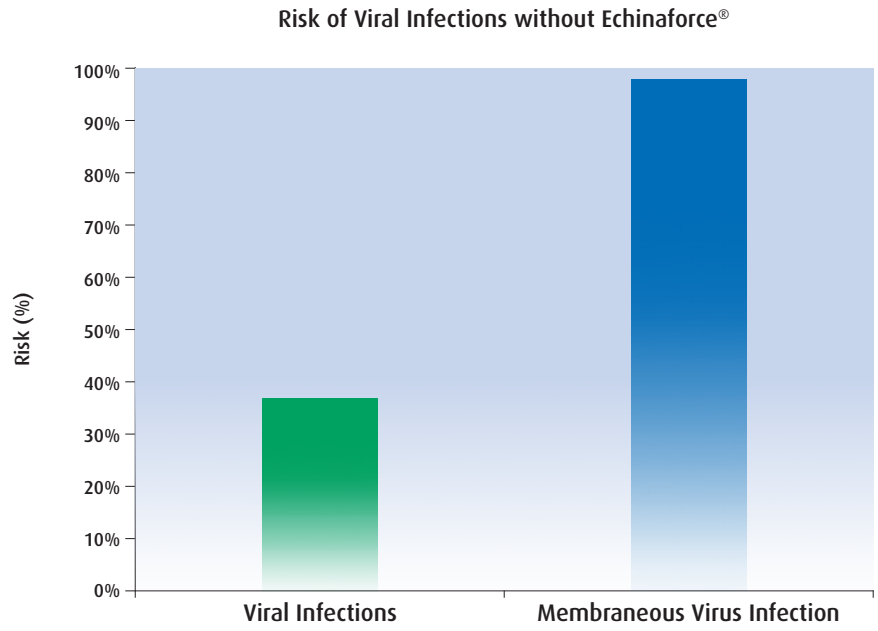

Figure 6: Throughout the study period, 54 viral infections were detected in the Echinaforce® group and 74 in the placebo group (+37%, p>0.05). Intriguingly, the strongest effect was seen with membranous viruses such as Coronavirus, Influenza, Parainfluenza or RS-virus with 24 and 47 detected infections in the two groups (p<0.05).

A sub-group (N=187) who had taken at least 100% of the recommended dosing reported a total of 58 cold episodes with 268 episode days when taking placebo, in comparison to only 36 cold episodes with 155 episode days with Echinaforce®[15]. This corresponded to a highly significant difference in both cold episodes and episode days of 61.1% and 72.9% respectively (p<0.0001).

The preventive effect was further studied in a group who reported stress. Stressed individuals were selected when they had a score exceeding 14 points on the perceived stress scale developed by Cohen (PSS-10)[16]. Cold episodes and episode days in the placebo treated group were significantly higher by 66.6% and 40.7% (p<0.05). Similar results were seen in more susceptible individuals (>2 colds/year), those with poor sleep (<8 hours sleep) and finally those who smoked, although the last population was very small at 43 subjects (Figure 7).

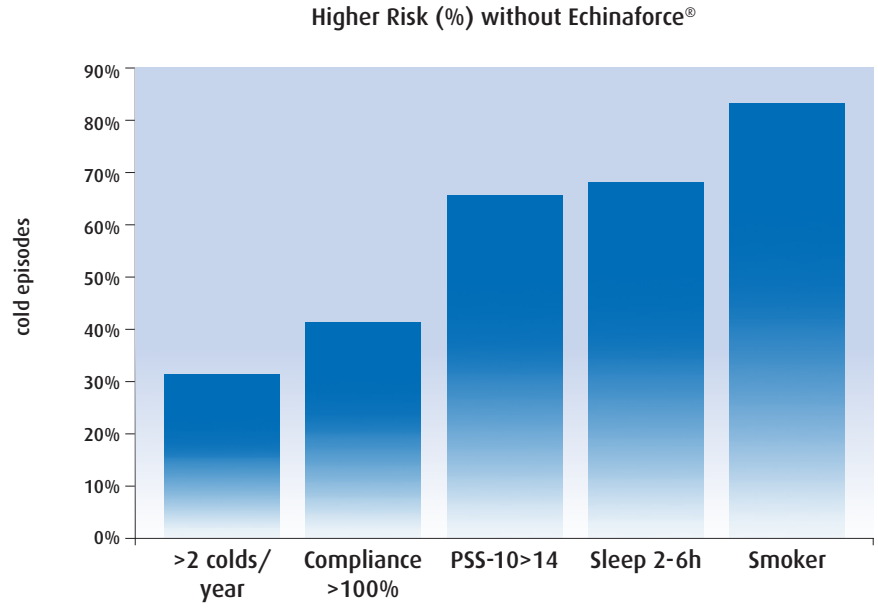

Figure 7: The prophylactic benefits in subgroups with suspected impaired immune response and susceptibility to respiratory infections were more pronounced than for the overall population.

The newly reported results confirm that Echinaforce® supports the immune resistance, and in parallel acts directly against a series of viruses. This appears to be an effective therapeutic approach, which not only works at the level of the human host but also acts on the infectious organisms – all of this with highly acceptable tolerability.

The importance of Echinaforce® in today's world

Prof. A. Schapowal, Landquart, Switzerland

Colds and flu present a significant interference to an individual's productivity, physical fitness, wellbeing and vitality, and they are also burdens to the whole health care system. These infections have the potential to lead to complications such as pneumonia, bronchitis or sinusitis, exacerbate existing asthma and COPD, and are associated with substantial morbidity and mortality.

From a therapeutic point of view, colds and flu remain a mystery and a real challenge. The efficacy of dietary supplements (including vitamins and zinc) is uncertain; neuraminidase inhibitors and vaccines are ineffective against infections outside influenza epidemics.

In light of the frequent 'off-label-use' of medicines, inappropriate use of antibiotics and increasing antibiotic drug resistance rates worldwide, the need for an alternative, clinically proven and effective remedy for the prevention of respiratory tract infections is urgently needed.

The research evidence we have on Echinaforce® is relevant to clinical practice in the following ways:

- ✓ **It represents one solution for prevention and acute treatment of colds and flu**
- ✓ **It has a broad spectrum of antiviral activity**
- ✓ **It supports and modulates immune activity especially during stress**
- ✓ **It has been shown to be a safe medicinal product**

The combination of immune-modulatory and antiviral effects opens novel therapeutic possibilities and areas for the use of Echinacea, and especially of Echinaforce®. Recommendations on use can be divided into three therapeutic scenarios:

Long-term Prevention (throughout the winter season)

From a clinical perspective, long-term preventative use is advisable in individuals susceptible to colds and flu with a history of more than 3 infections per year. Echinaforce® can also be recommended for long-term use in children, the elderly as well as those suffering from COPD, asthma patients or smokers – people in whom the consequences of colds and flu can be severe.

Short-term Prevention (weeks to months)

During times of increased stress and poor sleep, it is beneficial to support the immune resistance with Echinacea to balance the negative effects on the immune system. It is in these situations where short-term preventative use of Echinacea (over a few weeks) can apply.

During peaks of viral outbreaks one is surrounded by people with cold infections (in public places or the office) as well as a higher level of active viruses on public surfaces (hand-rails, public telephones, etc). This probably represents the most important scenario for short-term preventative use of Echinacea, with its proven anti-viral effects.

Acute Treatment (at the first symptoms)

Whereas prevention might be of interest to a select group of people, acute treatment of colds and flu is advantageous to everyone. Here, it is crucial to administer Echinacea at the earliest possible opportunity, and best at the first signs of symptoms (usually an itchy throat or sneezing). By blocking inflammation and viral replication at this stage, the development of further cold symptoms can be limited, leading to a reduced need for nasal decongestants, pain medication, cough medicines and unnecessary prescriptions of antibiotics.

Figure 8: Recommendation on the use of Echinaforce® from a clinical perspective

Conclusion

From the point of view of clinical practice, it is clear that Echinacea is able to fill a therapeutic gap in the treatment of colds and flu in a unique way. The science presented at this conference increases our confidence that Echinaforce® is effective for all three indications (long-term prevention, short-term prevention and acute treatment), and as an overall solution for the management of colds and flu.

There is a strong argument for clinicians and other healthcare professionals to recommend that Echinacea, and especially Echinaforce®, should be one of the remedies present in every home and readily available so that one can take early action when colds and flu viruses strike.

Expert Panel

Prof. Ronald Eccles

Director of Common Cold Centre, Cardiff School of Biosciences, Cardiff University (UK)

Professor Ronald Eccles established the Common Cold Centre at Cardiff University in 1988, which today is known worldwide as a centre of excellence for clinical trials on new treatments for common colds and flu. He has acted as a principal investigator on over 100 clinical trials. His research focuses on the understanding and measuring the symptoms of upper airway diseases—cough, blocked nose, sore throat, runny nose and sneezing.

As primary or co-author of more than 250 scientific publications, he has exceptional expertise on the scientific background of conventional and also of alternative cold therapies.

Prof. Dr. Stephan Pleschka

Institute for Medical Virology, Justus-Liebig University Giessen (Germany)

Professor Pleschka's research focuses on virus/host interactions that regulate the replication of influenza viruses, including experiments with highly pathogenic strains. In his biological safety laboratory, mechanisms of pathogenicity and transmission, in particular, of new influenza viruses are studied and new therapeutic approaches against influenza viruses are tested.

He has been the coordinator of the former European funded international research project EUROFLU and is currently involved in national and international funded research programs on the investigation of influenza viruses. He is a faculty member of the German Centre for Infection Research (DZIF) and of the University Giessen and Marburg Lung Centre (UGMLC).

Dr. Margaret Ritchie

Institute for Optimum Nutrition and University of London (UK)

Dr. Ritchie has experience in identifying biomarkers of phytochemical intake and performing clinical studies testing the pharmacological activity of herbal medicinal drugs and nutraceuticals. She is a Registered Nutritionist (Nutrition Science) and member of the Royal Society of Chemistry. She is currently a national adviser and inspector in Science and member of the editorial board for the Journal of Nutrition and Food Science.

Prof. Andreas Schapowal MD, PhD, DSc (hon)

ENT specialist, Landquart (Switzerland)

Professor Andreas Schapowal passed the medical state examination at the University Heidelberg (GE) in 1982. Since 1988 he has been an active medical practitioner and a specialist in ENT, allergies and clinical immunology. As medical consultant to the World Economic Forum and with his experience as former head of the ENT department in Davos (Switzerland) and ENT lecturer at Hannover Medical College (GE), he has a vast amount of experience in treating colds and flu.

Prof. Michael Heinrich

Centre for Pharmacognosy and Phytotherapy, UCL School of Pharmacy, University of London (UK)

The conference was chaired by Professor Michael Heinrich, Head of Centre for Pharmacognosy and Phytotherapy at the School of Pharmacy (University of London). His expertise covers the areas of pharmacognosy, phytochemistry, ethnopharmacology and ethnopharmacy. Recent research has explored value chains of herbal medicines, the safety of herbal medical products and the use of medicinal plants in immigrant communities. Prof. Heinrich serves as professional member of the Herbal Medicine Advisory Committee (MHRA) and as Council member and member of Scientific Advisory Board, IMDEA Alimentación. Among other editorial roles, he is the Reviews Editor of the Journal of Ethnopharmacology and the Editor in Chief of Frontiers in Ethnopharmacology.

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Echinaforce®

- ✓ Extract of freshly harvested *Echinacea purpurea*
- ✓ Combination of 95% herba and 5% radix
- ✓ Standardised ethanolic extract
- ✓ Grown from own (recycled) seeds
- ✓ Organically (biologically) cultivated