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The Triple Action of the Herbal Medicine Echinaforce® in the Treatment of Colds and Flu-Like Infections

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Keywords

Echinacea · Antiviral · Antibacterial · Anti-inflammatory · Colds and flu

Summary

The symptoms of colds and flu are generally caused by specific respiratory viruses and bacteria, acting either as primary agents or secondary agents following a virus infection. These infections can induce the secretion of pro-inflammatory cytokines by various cell types and, in conjunction with other inflammatory mediators, thereby produce the familiar symptoms. Echinaforce®, a standardized ethanol extract of the aerial parts and roots of *Echinacea purpurea*, can inactivate many viruses, such as rhinoviruses and influenza viruses (including Tamiflu®-resistant strains), as well as certain respiratory bacteria, including *Streptococcus pyogenes* and *Haemophilus influenzae*. In addition, the infection-induced secretion of pro-inflammatory cytokines, such as IL-6, IL-8, and TNF-α, is inhibited by Echinaforce administered before or after the infection of airway cells or tissues. Thus, Echinaforce can potentially provide a triple benefit: inactivation of cold and flu viruses, inactivation of certain pathogenic respiratory bacteria, and inhibition of the pro-inflammatory response induced by cold and flu agents.

Schlüsselwörter

Echinacea · Antiviral · Antibakteriell · Antiinflammatorisch · Erkältungen und Influenza

Zusammenfassung

Dreifache Wirkung des pflanzlichen Arzneimittels Echinaforce® in der Therapie von Erkältungen und grippalen Infekten

Die Symptome von Erkältungen und Influenza werden durch spezifische, respiratorische Viren oder Bakterien entweder als primäre Auslöser oder als sekundäre Erreger als Folge einer Virusinfektion verursacht. Diese Infektionen können die Sekretion proinflammatorischer Zytokine aus verschiedenen Zellen bewirken und so zusammen mit anderen Entzündungsmediatoren die Infektsymptome hervorrufen. Echinaforce®, ein standardisierter, ethanolischer Extrakt aus frischem, blühendem Kraut und frischen Wurzeln von *Echinacea purpurea*, kann sowohl viele Viren, wie z.B. Rhinoviren und Influenzaviren (inklusive Tamiflu®-resistente Stämme), als auch bestimmte respiratorische Bakterien, inklusive *Streptococcus pyogenes* und *Haemophilus influenzae*, inaktivieren. Zusätzlich wird die durch die Infektion induzierte Sekretion proinflammatorischer Zytokine, wie z.B. IL-6, IL-8 und TNF-α, durch Echinaforce vor oder nach Infektion von Respirationszellen oder -gewebe gehemmt. So kann Echinaforce potenziell eine dreifache Wirkung entfalten: Inaktivierung von Erkältungen und Influenza auslösenden Viren, Inaktivierung bestimmter pathogener, respiratorischer Bakterien und Hemmung der proinflammatorischen Antwort, die durch die Auslöser von Erkältung und Influenza induziert wird.

Mots-clés

Echinacée · Antiviral · Antibactérien · Anti-inflammatoire · Refroidissements et grippe

Résumé

Triple effet du médicament phytothérapeutique Echinaforce® dans le traitement des refroidissements et des infections grippales

Les symptômes des refroidissements et de la grippe sont causés par des virus ou des bactéries respiratoires spécifiques qui agissent comme déclencheurs primaires ou comme agents pathogènes secondaires suite à une infection virale. Ces infections peuvent induire la sécrétion de cytokines pro-inflammatoires par différents types de cellules et, combinées à d'autres médiateurs de l'inflammation, peuvent ainsi provoquer les symptômes infectieux. Extrait alcoolique standardisé de plantes fraîches en fleurs et de racines fraîches d'*Echinacea purpurea*, Echinaforce® peut aussi bien inactiver de nombreux virus, comme les rhinovirus et les virus grippaux (y compris les souches résistant au Tamiflu®), que certaines bactéries respiratoires, y compris *Streptococcus pyogenes* et *Haemophilus influenzae*. De plus, la sécrétion de cytokines pro-inflammatoires (p. ex. IL-6, IL-8 et TNF-α) induite par l'infection est inhibée par Echinaforce pris avant ou après l'infection de cellules ou de

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tissus des voies respiratoires. Ainsi, Echinaforce peut potentiellement déployer un triple effet: inactivation des virus provoquant les refroidissements et la grippe, inactivation de certaines bactéries respiratoires pathogènes et inhibition de la réponse pro-inflammatoire induite par les agents déclencheurs de refroidissement et de grippe.

Introduction

Colds and flu are generally attributed to certain viruses, such as rhinovirus (RV), of which there are more than 100 serotypes, and influenza virus A or B, although other respiratory viruses and bacteria have often been implicated as causative agents, either as primary infecting agents or as secondary agents following a primary virus infection [1–3]. Because of this multitude of possible etiological agents, it has been difficult to conceive of successful direct virucidal or bactericidal activities by means of synthetic compounds. In addition, there are many cases of so-called influenza-like illnesses (ILI) for which causative agents have not been determined [1, 3]. Furthermore, since the well-described symptoms of colds and flu-like diseases are common and are often due to or exacerbated by the induction of cytokines and other inflammatory mediators, it is usually not feasible to attempt specific antiviral or antibacterial therapy.

For these reasons, alternative therapeutic strategies have been considered, including herbal extracts derived from known medicinal plants, i.e. phytotherapy [3–6]. Many of these well-known herbal extracts have been shown to contain antiviral, antimicrobial, antioxidant, and anti-inflammatory activities according to established laboratory and animal tests, although the active components have seldom been identified. Thus, a combination of such beneficial activities could play a role in counteracting the agents and the symptoms of colds and flu [5].

Several herbal extracts have recently been shown to possess activities that could be potentially useful in the control of colds and flu [3, 4, 6]. Among the more attractive candidates are extracts of various species of *Echinacea*, especially *Echinacea purpurea* and *Echinacea angustifolia* [7]. However, a problem with *Echinacea* extracts in general (in common with most herbal products) has presented a difficulty in identifying the active ingredients, due to inadequate characterization and standardization. Consequently, different commercial sources, derived from different species and plant parts, and with resulting distinctive chemical compositions, may show different combinations of bioactivities or in some cases relatively little bioactivity [7–9]. The more recent studies have focused on a consistent chemically characterized preparation derived by ethanol extraction from freshly harvested *E. purpurea* aerial parts and roots. The composition of the traditional chemical markers in this preparation (Echinaforce®, EF) is shown in table 1. EF was shown in our laboratory to possess potent antiviral activity, selective antibacterial activity, and potent anti-inflammatory activity in human cell culture and tissue models relevant to natural infections.

Table 1. Composition of EF [12][a]

Ethanol content, v/v	65%
Dry weight, mg/ml	160
Caffeic acid	0
Caftaric acid	264.4
Chlorogenic acid	40.2
Cichoric acid	313.8
Cynarin	0
Echinacoside	6.9
Alkylamides	36.3
Polysaccharide	not detected

[a]Concentrations of marker components expressed as mg/ml.

Antiviral Activities

Earlier studies showed that not all *Echinacea* extracts possessed antiviral activity. *E. purpurea* aerial parts and roots contained anti-influenza and anti-HSV (herpes simplex virus) activities, which were distributed among more than one solvent fraction, and *E. angustifolia* root extracts were also active, but in contrast corresponding extracts of *Echinacea pallida* were devoid of activity. There was no correlation, however, between antiviral activity and composition of caffeic acid derivatives or polysaccharides. Furthermore, none of the extracts appeared to contain activity against RV, at least under the assay conditions used [10, 11].

More recent studies with EF have confirmed that this preparation is very active as a virucidal agent against viruses with membranes, as indicated in table 2. In addition to HSV-1 and respiratory syncytial virus (RSV), all tested human and avian strains of influenza A virus, as well as influenza B virus, were susceptible [12, 13]. In addition, RV was also equally susceptible at the relatively high concentrations of EF recommended for oral consumption (table 1). Thus, EF at a dilution of 1:10 (equivalent to 1.6 mg/ml dry weight/volume) is capable of killing at least 10^5 infectious viruses by direct contact.

In further studies, EF was found to be relatively ineffective against intracellular viruses; direct contact with the virus was required [13]. Consequently, a virus already present within a cell would be refractory to the inhibitory effect of EF, but virus particles shed into the extracellular fluids should be vulnerable [12, 13]. Therefore, the actions of EF should be manifest during initial contact with the virus, i.e. at the inception of infection, and also by inhibiting transmission of the virus from the infected subject.

Table 2. Antiviral activities of EF: Inhibition of viral infectivity is expressed either as minimal concentration of EF to inhibit 100% virus growth (MIC_{100}), given by the absence of cytopathic effects, or by focus assay [12, 13]

Virus	MIC_{100}, µg/ml
Influenza A (human and avian strains) and Influenza B	0.58–50
RSV	2.5
HSV type 1	0.39
RV 1A and 14	800
Adenovirus 3 and 11	>800
Poliovirus	800
Feline calicivirus	800

Table 3. Bactericidal activities of EF against respiratory microbes: Different bacteria at concentrations of 6×10^8 cfu/ml PBS were incubated with EF at a dilution of 1:100 (160 mg/ml) for 30 min at 20 °C. Growth was observed on the respective agar plates under aerobic and anaerobic conditions [14]

Bacterial species	Susceptible to EF (log10 killed)
S. pyogenes	+ (> 3 log)
S. aureus (MRSA/MSSA)	+/– (~1 log)
H. influenzae	+ (> 3 log)
L. pneumophila	+ (> 3 log)
M. smegmatis	+/– (~1 log)
Candida albicans (yeast form)	–

Hemagglutination assays showed that the extract inhibited the receptor-binding activity of influenza A viruses, suggesting that EF interfered with viral entry into the cells, thus effectively rendering the virus non-infectious [13].

Additional experiments showed that continuous passage of influenza A virus in cell cultures in the presence of EF did not result in the emergence of resistant strains, whereas a passaging of the virus in the presence of Tamiflu® rapidly generated Tamiflu-resistance. Furthermore, Tamiflu-resistant viruses remained fully susceptible to EF [13]. Therefore, continuous usage of EF in the population would be less likely to generate resistant strains of a virus than in the case of Tamiflu.

Antibacterial Activities

The acute episode of a cold or flu is often accompanied by, and may even be enhanced by, a significant bacterial infection, which may lead to more severe pulmonary and other diseases, as well as inflammatory activity. The commonest bacterial isolates from people with cold syndromes include normal naso-pharyngeal flora, such as *Streptococcus pyogenes,* a group A Streptococcus (GAS) responsible for pharyngitis or 'strep throat'; *Staphylococcus aureus*, which may be highly antibiotic-resistant, e.g. MRSA (methicillin-resistant *S. aureus*); as well as *Haemophilus influenzae* and *Legionella pneumophila*, the agent of 'Legionnaires' disease'. In addition, *Candida* yeasts are often present and may colonize respiratory tissues. Any of these organisms can lead to serious complications [14].

Previous studies with various commercial *Echinacea* preparations indicated a wide variety of responses by different human pathogenic bacteria [8]. In more recent studies, EF showed potent bactericidal activity against the typical respiratory pathogens *S. pyogenes, H. influenzae*, and *L. pneumophila*, moderate activity against *S. aureus* and a *Mycobacterial* strain, but no or less activity against other untypical respiratory pathogens and *Candida* (table 3) [14]. This selectivity should be considered an advantage, however, since only certain organisms associated with colds and flu would be killed or controlled, while other normal flora would be spared. The mechanisms of the antibacterial activities have not been evaluated and could conceivably be different for each species, as suggested by the results of Sharma et al. [8].

Anti-Inflammatory Activity

Studies on RV-infected human bronchial and lung epithelial cell lines showed that the virus could stimulate the secretion of more than 30 different cytokines, including the pro-inflammatory IL-1, IL-6, IL-8, and TNF-α, which are known to be collectively involved in many of the symptoms common to colds and flu, such as sneezing, fever, sore throat, nasal discharges, and inflammation in various respiratory tissues. However, certain *Echinacea* preparations, especially EF, were able to completely or partly reverse this stimulation [15]. At concentrations of 20–160 µg/ml, EF dose-dependently inhibited cytokine secretions (IL-6 and IL-8) as induced by all investigated viruses (e.g. H3N2, RSV, or RV). In some cases, these stimulations and inhibitions were a reflection of corresponding alterations in specific gene transcription, but this was not always the case, indicating that transcriptional changes and secretion of mature cytokine proteins were not necessarily linked [15–17].

In more detailed studies, it was shown that EF could be added before or after virus infection, and the results were not affected by virus dose or the time of exposure to EF [15].

A similar result was obtained with other viruses and cell types. Thus, HSV-1, influenza A virus, adenovirus type 3 and 11, and RSV all stimulated the secretion of cytokines, although only live infectious viruses were able to do this. In each case the stimulation was reversed by EF while using identical experimental protocols for investigated viruses and their respective target cells [12].

Several human pathogenic bacteria, including *S. pyogenes*, *S. aureus* (MRSA and MSSA (methicillin-sensitive *S. aureus*)), *H. influenzae, L. pneumophila*, and *Mycobacterium smegmatis*, also stimulated the secretion of IL-6, IL-8, and other cytokines in cell cultures, but in all of these

Table 4. Anti-inflammatory activities in epithelial cell cultures: BEAS-2B, A549 cells, and primary human skin fibroblasts were growth to confluent monolayers. EF at concentrations of 160 µg/ml and less was added 1 h after viral (1 pfu/cell) or bacterial (about 6×10^8 cfu/ml) inoculation. Cytokines were analyzed 24 or 48 h after viral challenge by ELISA and by Raybiotech fluorescent antibody array system [14, 15]

Cytokine-inducing agent	Inhibition in IL6 and IL8 secretion by EF
RV 1A and 14	+
Influenza A (H3N2)	+
RSV	+
HSV type 1	+
Adenovirus type 3 and 11	+
S. pyogenes	+
S. aureus (MRSA and MSSA)	+
H. influenzae	+
L. pneumophila	+
M. smegmatis	+

cases the stimulation was reversed by EF, even for those bacteria that were relatively resistant to the bactericidal effect of EF, such as *S. aureus* (table 4) [14].

Thus, EF evidently reversed the stimulation of pro-inflammatory cytokines regardless of the inducing microbe or virus. This indicates that EF is effectively a general anti-inflammatory agent and should be capable of ameliorating many of the symptoms of colds and flu.

3-D Tissues of Human Airway Epithelium

Not only is it important to carry out research on *Echinacea* preparations that have been standardized and chemically characterized, but in addition it is also important that the cell culture models used to evaluate anti-infectious agents reflect conditions in vivo as far as possible [18]. This condition was evaluated by means of a commercial source of normal human airway epithelial tissue (EpiAirway™ tissue, a 3-D organotypic model; MatTek Corporation, Ashland, MA, USA), which can be propagated in vitro under defined conditions so that tissue architecture and differentiation patterns are preserved [19]. Such a system more closely resembles in vivo tissue and might be more appropriate than cell lines for the analysis of *Echinacea* and RV infection. The objective was to assess the effects of RV infection as well as EF on various parameters of tissue integrity and cytokine induction.

Individual replicate tissue samples, maintained as inserts in culture for 3 days or 3 weeks, were infected with RV type 1A (RV1A), EF alone, a combination of the two, or medium only. None of the treatments affected the histological appearance or integrity of the tissues, all of which maintained a high level of cell viability and preservation of cilia. RV infection resulted in increased mucopolysaccharide inclusions in the goblet cells, but this feature was reversed by EF treatment. This result was confirmed by measurements of mucin secretion, which was stimulated by RV but reversed by EF, suggesting that mucus production during colds could be ameliorated by EF [20]. There was no evidence of virus replication, although the RV-infected tissues secreted substantial amounts of the pro-inflammatory cytokines IL-6 and IL-8 (CXCL8), and this response was reversed by EF treatment. These results confirmed previous findings derived from studies of bronchial and lung epithelial cell lines, namely, that RV infection results in a substantial inflammatory response in the absence of virus replication.

Conclusions

These studies on EF indicate a triple action of the herbal preparation: (i) a direct virucidal activity against several viruses involved in colds and flu; (ii) a direct bactericidal action against certain potentially pathogenic respiratory bacteria; (iii) a reversal of the pro-inflammatory response of epithelial cells and tissues to different viruses and bacteria. Thus, a combination of these beneficial activities could reduce the amount of prevailing viable viruses and bacteria, and their transmission, and could also lead to an amelioration of the cold and flu symptoms.

Disclosure Statement

The author declares that no conflict of interest exists.

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