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Review

The multiple actions of the phytomedicine *Echinacea* in the treatment of colds and flu

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The symptoms of cold and flu are generally attributed to specific respiratory viruses and bacteria acting either as primary agents, or as secondary agents following a viral infection. These infections can induce the secretion of pro-inflammatory cytokines by various airway epithelial cells and in conjunction with other inflammatory mediators, thereby producing the familiar symptoms of a cold or flu. Certain types of *Echinacea* (family Asteraceae) extract, but not all, were found to inactivate different viruses, such as rhinoviruses and influenza viruses (including Tamiflu-resistant strains) and herpes simplex virus ("cold sores"), as well as certain respiratory bacteria, including *Streptococcus pyogenes* (sore throat) and *Hemophilus influenzae*. In addition, infection of cultured epithelial cells and tissues by viruses and bacteria, induced the secretion of pro-inflammatory cytokines such as IL-6, IL-8, TNFα and excessive mucin secretion. These cellular responses were reversed by exposure to the active *Echinacea* extracts. Thus certain *Echinacea* extracts could provide multiple benefits to cold and flu sufferers, such as inactivation of the viruses themselves, inactivation of certain pathogenic respiratory bacteria and reversal of the pro-inflammatory responses induced by cold and flu agents. These extracts did not produce cytopathic effects in cultured epithelial cells and tissues.

Key words: *Echinacea*, antiviral, antibacterial, anti-inflammatory, influenza, colds.

INTRODUCTION

The nature and causes of symptoms

"Colds" and "flu" are terms that have been coined to describe a combination of common symptoms, brought about by the actions of specific viral or sometimes bacterial infections of the upper respiratory tract. These symptoms may include such familiar discomforts as sneezing, stuffy nose, irritation of mucous membranes, excess mucus production, sinusitis, cough, sore throat, malaise and fever, as well as exacerbation of asthma and COPD (chronic obstructive pulmonary disease). In the case of flu, the symptoms may be more severe and may spread to include the lower respiratory tract and lungs, resulting in bronchitis or pneumonia (Gwaltney, 2002; Roxas and Jurenka, 2007; See and Wark, 2008).

The majority of "common colds" are initiated by one of more than a hundred rhinoviruses, while 'flu' symptoms are usually ascribed to influenza viruses, the current prevailing strains being Influenza A virus H3N2 or H1N1, and influenza virus B (See and Wark, 2008). However, many other respiratory viruses and bacteria have also been incriminated. In addition, herpes simplex virus,which is frequently associated with cold sores and other infections of the oral mucosa are also relevant to this discussion.

How do all these multiple microbes bring about these common symptoms? The invading pathogens, such as respiratory viruses and bacteria, initially encounter epithelial tissues of the nose, oral mucosa and airway linings. These are composed primarily of epithelial cells (ciliated or not), which are covered by a "soup" of macromolecules such as proteins, glycoproteins, muco-polysaccharides, some of which possess intrinsic anti-microbial properties (LeClair, 2003; Diamond et al., 2008). Interspersed among these epithelial cells are occasional phagocytes and various types of leukocytes. The epithelial and other cells, possess a variety of pattern recognition receptors (PRRs), on and within the cells, which serve as molecular sensors. In response to the recognition of a pathogen, various signaling pathways may be activated, resulting in the production and/or secretion of many pro-inflammatory cytokines and chemokines, as well as anti-microbial peptides and other inflammatory mediators (Diamond et al., 2008; See and Wark, 2008; Evans et al., 2010). Further signaling among cells of the tissues and migrating leukocytes attracted to the site of invasion, causes amplification of the output of inflammatory molecules.

However, it has become clear from recent studies that direct cytopathic damage by the pathogen is not a prerequisite for the induction of inflammatory mediators. For example, rhinoviruses and respiratory syncytial virus generally show limited replication and cause little or no cellular damage, yet they can induce large amounts of inflammatory cytokines (Mosser et al., 2005; Sharma et al., 2009a). Thus, the epithelium has a two-fold function in response to potential pathogens; it has a barrier function and also serves as a sensor that signals an efficient anti-microbial response. However, incomplete elimination of the pathogen or over-stimulation of the responses, can lead to an excessive or chronic inflammatory condition. Such a heterogeneous collection of causative agents presents a formidable obstacle to the design of therapeutic strategies, which have in the past focused on curbing the reproductive potential of a specific virus or bacterium (Fedson, 2009; Ludwig, 2009). However, since the majority of the symptoms may simply reflect this common non-specific host response to infecting agents rather than to the cytopathic effects of the agents themselves, then a more rational therapeutic approach could be the application of anti-inflammatory agents. Since many herbal extracts have been shown to contain antiviral and antimicrobial activities as well as anti-inflammatory properties (Hudson and Towers, 1999; Hudson, 2009; Burns et al., 2010), then consequently it would seem worthwhile pursuing this multi-functional approach, as a generic treatment for the symptoms of “colds and flu”. If the treatment can also control the spread and transmission of the pathogen as well, then it would be so much better.

Among the more attractive candidates are extracts of various species of *Echinacea*, especially *E. purpurea*, *E. angustifolia*, and *E. pallida* (Barnes et al., 2005). However, a problem with *Echinacea* extracts in general (in common with many other herbal products) has been the difficulty in identifying active ingredients and 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 bio-activities or in some cases relatively little bioactivity (Binns et al., 2002a; 2002b; Vohra et al., 2009). Recent studies in our laboratory have attempted to circumvent these limitations by focusing on chemically characterized preparations, some of which have been shown to possess potent antiviral activity, selective antibacterial activity and potent anti-inflammatory activity in human cell cultures and tissue models relevant to natural infections.

BOTANICAL NOMENCLATURE

In this review, the three most commonly used species of *Echinacea* for research are simply designated by their traditional botanical names which still prevail in the literature, although recent revisions of these names have been described (Binns et al., 2002a; Barnes et al., 2005). The corresponding equivalents are as follows: *E. purpurea* = *E. purpurea (L.) Moench*; *E. angustifolia* = *E. pallida var angustifolia (DC.) Cronq*; *E. pallida* = *E. pallida var pallida (Nutt.) Cronq*.

ANTIVIRAL ACTIVITIES

Earlier studies showed that not all *Echinacea* extracts possessed antiviral activity. *E. purpurea* aerial parts and roots contained potent anti-influenza virus and anti-HSV activities, which were distributed among more than one solvent fraction, probably reflecting the presence of more than one antiviral compound (Vimalanathan et al., 2005). However, there was no obvious correlation between antiviral activity and composition of caffeic acids, polysaccharides and alkylamides.

In a recent study, a series of aqueous and ethanol extracts of *E. pallida* aerial parts showed significant virucidal activity against HSV-1 and HSV-2 (Schneider et al., 2010) and some of the extracts also appeared to inhibit virus replication within infected cells. The different extracts had distinct chemical profiles, as expected but the authors concluded that combinations of components, rather than individual compounds, were responsible for these different activities. Root extracts of three species were compared for antiviral activity in a similar manner to the aerial parts (Hudson et al., 2005). Aqueous extracts of *E. purpurea* roots contained relatively potent activity against influenza virus and HSV, although their contents of caffeic acid and alkylamides was low. In contrast, the antiviral activities of *E. angustifolia* roots were found in the ethanol and ethyl acetate fractions and included anti-rhinovirus activity, whereas the aqueous fractions were devoid of activity. *E. pallida* root extracts showed no antiviral activity whatsoever in any of the solvent fractions, in spite of the presence of caffeic acid and in some fractions, alkylamides. Thus, in addition to the variation in activity among different species and extracts, there was clearly no correlation between antiviral activity and relative content of caffeic acid, polysaccharides and alkylamides (Table 1), suggesting that these compounds are not the active ingredients, although certain individual compounds do possess weak or moderate activity e.g. cichoric acid (Binns et al., 2002b). The presence of multiple antiviral activities among different extracts and

Table 1. Antimicrobial activities of *Echinacea* extracts-summary.

Species	Plant parts	Susceptible micro-organisms	Anti-cytokine activity in epithelial cells	References
*E. purpurea*1	Aerial parts	Influenza viruses (A & B); RSV; HSV-1; RV; [not adenovirus or poliovirus]; *S. pyogenes*(G+); *H. influenzae*(G-); *L. pneumophila*(G-)	+	Vimalanathan et al., 2005; Sharma et al., 2008a, 2009a; Pleschka et al., 2009
	Roots	Influenza A; HSV-1; *L. pneumophila*	+	Hudson et al., 2005; Sharma et al., 2008a
E. pallida	Aerial parts	HSV-1/2	_	Schneider et al., 2010
	Roots	HSV-1 (weak);	_	Hudson et al., 2005
E. angustifolia	Aerial parts	HSV-1; influenza A; RV	+ (weak)	Vimalanathan et al., 2005; 2009
	Roots	HSV-1 (weak); *S. pyogenes*; *L. pneumophila*	_	Hudson et al., 2005; Sharma et al., 2008a
E. sanguinea	inflorescence	HSV-1, influenza A	nt	Binns et al., 2002b
E. atrorubens *E. teneseensis* *E. laevigata*	roots	HSV-1 (weak activity)	nt	Binns et al., 2002b

1-not all extracts of a given species were active (varied according to source, type of extract, solvent etc); nt = not tested; Viruses: HSV = herpes simplex virus; RSV = respiratory syncytial virus; RV=rhinovirus; G+, Gram positive; G-, Gram negative.

fractions suggests that different kinds of preparations such as tinctures, sprays, tablets, etc. could all be beneficial; although not all commercial preparations are likely to be effective. Detailed studies with the standardized preparation Echinaforce® (EF, comprising ethanol extracts of *E. purpurea*, 95% aerial parts plus 5% roots) showed that this preparation was very active as a virucidal agent against several viruses with membranes, as indicated in Table 1. In addition to HSV-1 and respiratory syncytial virus, all tested human and avian strains of influenza A virus, as well as influenza B virus, were susceptible (Sharma et al., 2009a; Pleschka et al., 2009). In addition, rhinoviruses were also equally susceptible at the relatively high concentrations of EF recommended for oral consumption (Table 1). Thus, EF at 1:10 dilution (equivalent to 1.6 mg/ml dry weight/volume) was capable of killing at least 10^5 infectious viruses by direct contact.

In contrast, EF was found to be less effective against intracellular viruses. Consequently, viruses already present within a cell could be refractory to the inhibitory effect of EF but virus particles shed into the extracellular fluids should be vulnerable. Therefore, the actions of the Echinaforce® should be manifest during initial contact with the virus, that is at the inception of infection and also during transmission of virus from infected cells. 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 in contrast, passing the virus through successive cultures in the presence of Tamiflu rapidly generated Tamiflu-resistance. Furthermore, Tamiflu-resistant virus remained fully susceptible to EF. Therefore, continuous usage of Echinaforce® in the population would be less likely to generate resistant strains of viruses than Tamiflu or other anti-influenza compounds currently in the market. Recent studies have illustrated the relative ease with which resistant strains of influenza virus can arise (Cheng et al., 2009).

It was shown by hemagglutination assays that EF inhibited the receptor binding activity of influenza A viruses, over a range of EF concentrations including the recommended oral dose, suggesting that EF interfered with viral entry into the cells, thus effectively rendering the virus non-infectious (Pleschka et al., 2009).

ANTIBACTERIAL ACTIVITIES

The acute episode of a cold or flu is often accompanied

Table 2. Bactericidal activities of EF against respiratory microbes.

Bacterial species	Gram +/-	Susceptible to EF (log_{10} killed)
S. pyogenes	+	+ (> 3 log)
S. aureus (MRSA/MSSA)	+	+/- (~ 1 log)
H. influenzae	-	+ (> 3 log)
L. pneumophila	-	+ (> 3 log)
M. smegmatis		+/- (~1 log)
C. albicans (yeast form)		~ 0

Data from Sharma et al. (2008a).

by and may even enhance a significant bacterial infection, which may lead to more severe pulmonary and other diseases, as well as increased inflammatory activity (Gwaltney, 2002; Roxas and Jurenka, 2007). The commonest bacterial isolates from people with cold syndromes include normal naso-pharyngeal flora, such as *S. pyogenes*, a group A *Streptococcus* (GAS) responsible for pharyngitis or “strep throat”; *Staphylococcus aureus* which may be highly antibiotic resistant, e.g MRSA, as well as *H. influenzae* and *Legionella pneumophila*, the agent of “Legionnaires disease”. In addition, Candida yeasts and bacterial opportunists are often present and may colonize respiratory tissues. Any of these organisms could lead to serious complications.

Studies with various commercial *Echinacea* preparations indicated a wide variety of responses by different human pathogenic bacteria (Sharma et al., 2008a). Among the respiratory bacteria tested, three of them, *S. pyogenes, H. influenza* and *L. pneumophila*, were very sensitive to one or more of the extracts particularly ethanol extracts (Table 2). Two others, *S. aureus* and *Mycobacterium smegmatis*, were slightly sensitive to some extracts while other bacteria tested were essentially resistant. Since the composition of the extracts varied considerably with respect to caffeic acids, alkylamides and polysaccharides, it was not possible to relate any of these to antibacterial activity. Furthermore, the distinct patterns of activity suggested that there was no common mechanism of antibacterial activity. Since *Echinacea* is part of the Asteraceae family, which is known to contain many plants rich in antibacterial polyynes and thiophenes, such compounds might also have contributed to the activities observed. This antibacterial selectivity should be considered an advantage, since only certain organisms associated with colds and flu would be killed or controlled, while other normal flora might be spared.

ANTI-INFLAMMATORY ACTIVITY

In some cases, the inflammatory responses due to pro-inflammatory cytokines/chemokines and other mediators (eicosanoids, kinins, nitric oxide), may be excessive or chronic and consequently a dampening down or suppression could be beneficial. Many extracts derived from medicinal plants have been shown to possess anti-inflammatory activities in a variety of animal and cellular models, although these have not usually involved infectious agents (Burns et al., 2009).

A series of recent studies by Sharma and colleagues focused on the application of standardized *E. purpurea* extract (Echinaforce®) to epithelial cells and tissues infected by viruses or bacteria. In rhinovirus infected human bronchial and lung epithelial cell lines, the virus stimulated the secretion of numerous cytokines including the pro-inflammatory IL-1, IL-6, IL-8 and TNFα, which are known to be collectively involved in many of the symptoms common to colds and flu. Certain *Echinacea* preparations, especially Echinaforce®, were able to completely or partly reverse this stimulation (Sharma et al., 2008b; 2009a). It was shown that EF could be added before or after virus infection, with similar success and also the results were not affected by virus dose or the time of exposure to EF (Sharma et al., 2008b).

A similar result was obtained with other viruses and cell types. Thus HSV-1, influenza A virus, adenovirus type 3 and 11, and respiratory syncytial virus, all stimulated the secretion of pro-inflammatory cytokines and in each case the stimulation was reversed by EF (Table 3). However, only live infectious viruses were able to do this, for infection by equivalent doses of ultraviolet-inactivated viruses, failed to elicit the responses. This suggests that the virus has to enter the cells and undergo some degree of gene expression in order to stimulate the cytokine expression or secretion. It is also interesting that viruses such as adenoviruses, which are not vulnerable to direct attack by *Echinacea* but could nevertheless stimulate cytokine secretion, were still susceptible to cytokine inhibition (Sharma et al., 2009a).

In an attempt to correlate immune modulation effects with specific classes of *Echinacea* components, various chemically characterized extracts and fractions, derived from three species of *Echinacea,* were evaluated for their possible inhibitory effects on the secretion of pro-inflammatory cytokines IL-6 and IL-8 by human bronchial epithelial cells infected with rhinovirus type 14. All of the

Table 3. Cytokine/chemokine induction in bronchial epithelial cells.

Virus/bacterium	Cytokines/chemokines induced	Reversed by EF
Influenza	IL-1α, IL-6, IL-8, TNFα, GROα	+
Rhinovirus 1A/14	IL-1α, IL-6, IL-8, TNFα, GROα (RV 1A only)	+
Respiratory syncytial virus	IL-1α, IL-6,IL-8, TNFα, GROα, MCP-1, RANTES (CCL-5)	+
Adenovirus 3	IL-1a, IL-5, IL-6, IL-8, TNFα, MIP-1α(CCL-3), MIP-1β (CCL-4)	+
S. pyogenes	IL-4, IL-6, IL-8, GROα, MIP-1a, GMCSF, MCP-1	+
S. aureus	IL-4, IL-6, IL-8, GROα, MIP-1α, MCP-1, VEGF	+
H. influenzae	IL-6, IL-8	+
L. pneumophila	IL-6, IL-8	+

Data from Sharma et al. (2009a: viruses; 2010: bacteria).

E. purpurea fractions, comprising aqueous or ethanol extracts of roots, leaves and stems, but to a lesser degree flowers, strongly inhibited the secretion of both cytokines. In contrast, corresponding fractions derived from *E. angustifolia* and *E. pallida* showed relatively weak cytokine-inhibitory activity, whereas their aqueous fractions significantly enhanced cytokine secretion, both in virus-infected and in uninfected cells (Vimalanathan et al., 2009). These properties did not correlate with the presence or absence of alkylamides or specific caffeic acid derivatives; although there was some correlation between anti-cytokine effects and the previously reported anti-viral activities with the same extracts.

Several human pathogenic bacteria, including *S. pyogenes*, *S. aureus*, *H. influenzae*, *L. pneumophila* and *M. smegmatis,* also stimulated the secretion of IL-6, IL-8 and other cytokines in cell cultures but in all these 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 3). Thus, Echinaforce® 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.

MUCIN SECRETION

Most sufferers of colds would agree that secretion of excessive mucus is one of the most annoying symptoms and accordingly, many pharmaceuticals have been designed to relieve this feature of a cold or flu, usually with the accompaniment of undesirable side effects.

Rhinoviruses induced the secretion of excess MUC5A, the dominant respiratory mucin in bronchial epithelial cells in culture and in cultured airway tissues and EF reversed this secretion in both systems (Sharma et al., 2009b), suggesting that this could be an additional benefit of *Echinacea* treatment. This result was supported by histochemical examination of cultured airway tissues, which revealed the conspicuous presence of mucopolysaccharide-filled goblet cells resulting from rhinovirus infection, whereas EF treated/infected tissues appeared normal.

3-D TISSUES OF HUMAN AIRWAY EPITHELIUM

It is important to focus on standardized *Echinacea* preparations and it is also important that the cell culture models used to evaluate anti-infectious agents reflect conditions *in vivo* as far as possible (Nickerson et al., 2007). This condition was evaluated by means of a commercial source of normal human airway epithelial tissue (EpiAirwayTM tissue, a 3-D organotypic model), which could be propagated *in vitro* under defined conditions such that tissue architecture and differentiation patterns were preserved. 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 rhinovirus infection and EF, on various parameters of tissue integrity and cytokine induction (Sharma et al., 2009b). Individual replicate tissue samples, maintained as inserts in culture for three days or three weeks, were infected with rhinovirus 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. 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 and this response was reversed by EF treatment. These results confirmed the previous findings derived from studies of bronchial and lung epithelial cell lines (above), namely, that RV infection resulted in a substantial inflammatory response in the absence of virus replication. In a preliminary study, similar results were obtained for influenza-infected tissues.

MECHANISMS OF ACTION

The results described have indicated that some *Echinacea* extracts, evidently contain compounds or combinations of compounds, with ability to interact specifically with viral and bacterial targets. In addition, these extracts can affect various signalling pathways of epithelial cells and inhibit the virus/bacterium-induced secretion of cytokines/chemokines and other inflammatory mediators that were responsible for the cold/flu symptoms. Since many signalling pathways seem to be involved (Altamirano-Dimas et al., 2007; 2009; Wang et al., 2008), it is conceivable that the overall beneficial effects are due to a particular combination of compounds acting synergistically. Examples of synergism in herbal medicine have been described and in some cases validated experimentally (Spelman, 2006) and it is likely that certain *Echinacea* preparations also display synergism.

RELEVANCE TO NORMAL CONSUMPTION

Echinacea intended for treatment of colds and flu is normally marketed in the form of tinctures, sprays, lozenges, etc. for oral consumption. The ingredients therefore acquire immediate but brief exposure to the mucosal epithelia. According to our studies (as described above), the recommended doses ensure that physiologically appropriate amounts, that is adequate antiviral, antibacterial and anti-inflammatory concentrations, are achieved. Subsequent absorption and metabolism of the various components are less relevant, since the sites of infection and inflammation are at the level of airway epithelial tissues.

CONCLUSIONS

Studies on selected *Echinacea* extracts have indicated multiple beneficial actions in the treatment of colds and flu: (i) a direct virucidal activity against several respiratory viruses; (ii) a direct bactericidal action against certain potentially pathogenic respiratory bacteria; (iii) reversal of the pro-inflammatory response of epithelial cells and tissues to different viruses and bacteria; (iv) reduction in the excessive secretion of mucin by airway cells and tissues. However, there was no evidence of cytopathic effects or disruption of tissue integrity by *Echinacea* in airway cell cultures or tissues. Thus, a combination of these beneficial activities could reduce the amount of prevailing viable virus and bacteria and their transmission and also lead to amelioration of the cold and flu symptoms.

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