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Potential of the Phytomedicine *Echinacea* in the Treatment of Pulmonary Infections and Bronchitis

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1. Introduction

Acute bronchitis is generally attributed to certain respiratory viruses, such as influenza virus A or B, respiratory syncytial virus, coronavirus, rhinoviruses, or others, although various bacteria have often been implicated in some cases, either as causative agents or as secondary agents following the initial virus infection (Gwaltney, 2002; Roxas & Jurenka, 2007; See & Wark, 2008). Chronic bronchitis may also be exacerbated by the same agents.

These viruses and bacteria initially encounter epithelial tissues of the nose, oral mucosa, bronchi and airway linings, which are composed primarily of epithelial cells covered by a "soup" of proteins, glycoproteins, muco-polysaccharides, some of which possess intrinsic antimicrobial properties (Diamond et al., 2008; Evans et al., 2010). Interspersed among these epithelial cells are occasional phagocytes and various types of leukocyte. 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 antimicrobial peptides and other inflammatory mediators. Further signaling among resident cells of the tissues, and migrating leukocytes attracted to the site of invasion, causes amplification of the output of inflammatory molecules. This situation may become chronic and lead to prolonged bronchitis. However, recent virological studies have shown 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 antimicrobial response. This is the primary component of the innate "immune" or "non-specific" host response (Diamond et al., 2008; Evans et al., 2010). However, incomplete elimination of the pathogen, or over-stimulation of the responses, can lead to an excessive or chronic inflammatory condition. Since the pathogens comprise such a heterogeneous collection of causative agents, this presents a formidable obstacle to the design of therapeutic strategies, which have in the past focused on curbing the growth of a specific virus or bacterium (Fedson, 2009; Ludwig, 2009).

But because 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 antiinflammatory agents, especially if such agents also possess antimicrobial activities (Fedson, 2009).

Many herbal extracts have been shown to contain antiviral and antimicrobial activities as well as antiinflammatory properties (Roxas & Jurenka, 2007; Vimalanathan & Hudson, 2009; Hudson, 2009; Burns et al., 2009). Consequently it seems worthwhile pursuing a multi-functional approach, as a generic treatment for the symptoms of bronchitis and other pulmonary infections, especially if the agent can also control the spread and transmission of the pathogen.

Among the more attractive candidates are extracts of certain species of *Echinacea* (Barnes et al., 2005; Hudson, 2009). However, a problem with commercial *Echinacea* extracts, and for that matter many other herbal formulations, is inadequate characterization and standardization. Consequently, different commercial sources derived from different species and plant parts may have variable chemical composition and hence variable or even insignificant bio-activities (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 and standardized preparations, some of which have been shown to possess potent antiviral activity, selective antibacterial activity and potent antiinflammatory activity, in human cell cultures and tissue models relevant to natural infections.

2. Antiviral activities

Earlier studies showed that only a few *Echinacea* extracts possessed significant antiviral activity (Binns et al., 2002; Table 1). *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; Hudson et al., 2005). However, there was no apparent correlation between antiviral activity and composition of the customary chemical markers (see section on Mechanisms).

Echinacea sp. and plant part	Susceptible viruses	Anti-inflammatory	references
E. purpurea aerial parts	Influenza viruses A & B; HSV-1; respiratory syncytial virus; rhinoviruses	+	Vimalanathan et al., 2005; Sharma et al, 2008a; Pleschka et al., 2009; Vimalanathan et al., 2009
E. purpurea roots	Influenza A, HSV-1	+	Hudson et al., 2005; Sharma et al., 2008a; Vimalanathan et al., 2009
E. angustifolia aerial parts	Influenza A, HSV-1, rhinovirus	+ (weak)	Vimalanathan et al., 2005, 2009
E. angustifolia roots	HSV-1	-	Hudson et al., 2005
E. pallida, aerial parts & roots	HSV-1/2	-	Schneider et al., 2010
E. sanguinea, inflorescence	HSV-1, influenza A	nt	Binns et al., 2002
Other species	Weak or no activity	nt	Binns et al., 2002

nt, not tested

Table 1. Antiviral activities of *Echinacea* species.

In a more 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. In contrast, the antiviral activities of *E. angustifolia* roots were found in the ethanol and ethyl acetate fractions and included antirhinovirus activity, which was not detected in the aqueous fractions. *E. pallida* root extracts showed no antiviral activity whatsoever in any of the solvent fractions, in spite of the presence of the usual chemical markers for *Echinacea* species. Thus, in addition to the variation in activity among different species and extracts, there was no correlation between antiviral activity and relative content of caffeic acid derivatives, polysaccharides and alkylamides, suggesting that these compounds are not individually the active ingredients.

Recent detailed studies with the standardized preparation Echinaforce® (EF, comprising ethanol extracts of *E. purpurea*, 95% aerial parts plus 5% roots) revealed 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 of all these infectious viruses by direct contact. In contrast, EF was found to be less effective intracellularly. 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 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 produced Tamiflu-resistance (Pleschka et al., 2009). Furthermore, Tamiflu-resistant virus remained fully susceptible to EF. Therefore, continuous usage of Echinaforce in the population would be less likely to yield resistant strains of viruses than Tamiflu or other anti-influenza compounds currently in the market (Cheng et al., 2009).

In mechanistic studies it was shown that EF, at concentrations recommended for oral consumption, was able to inhibit the influenza virus hemagglutinin and viral neuraminidase, both of which are necessary for influenza virus entry and dissemination (Pleschka et al., 2009; and unpublished observations).

3. Antibacterial activities

Upper respiratory infections (URI) are often accompanied by and may even enhance a significant bacterial infection, which may lead to more severe pulmonary infection and

bronchitis (Gwaltney, 2002; Roxas and Jurenka, 2007). Bacterial isolates from people with URI include normal naso-pharyngeal flora, such as *Streptococcus pyogenes*, a group A *Streptococcus* (GAS) responsible for pharyngitis or "strep throat"; *Streptococcus pneumoniae*; *Staphylococcus aureus* which may be highly antibiotic resistant, (e.g MRSA, methicillin-resistant *S.aureus*), as well as *Hemophilus 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.

Echinacea sp. and plant part	Susceptible bacteria	Anti-inflammatory	references
E. purpurea aerial parts	*S. pyogenes*(G+); *H. influenzae*(G-); *L. pneumophila*(G-) *S. aureus* (G+), weak *M. smegmatis*, weak	+	Sharma et al., 2008a; Vimalanathan et al., 2009
E. purpurea roots	*L. pneumophila*	+	Sharma et al., 2008a; Vimalanathan et al., 2009
E. angustifolia roots	*S. pyogenes*; *L. pneumophila*	-	Sharma et al., 2008a; Vimalanathan et al., 2009
Other species	nt	nt	

G+, Gram-positive organisms; G-, Gram-negative organisms; nt, not tested

Table 2. Antibacterial activities of *Echinacea* species

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 a member of the Asteraceae family, which is known to contain many plants rich in antibacterial polyynes and thiophenes (Hudson & Towers, 1999), such compounds might also have contributed to the activities observed. This selective antibacterial activity should be considered an advantage, since it suggests that only certain organisms associated with pulmonary infections would be killed or controlled, while other normal flora might be spared.

4. Antiinflammatory activity

In some cases, the inflammatory responses due to proinflammatory 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, at non-toxic concentrations, in a variety of animal and cellular models, although these have not usually involved infectious agents (Burns et al., 2009).

Studies on rhinovirus infected human bronchial and lung epithelial cell lines showed that the virus could stimulate the secretion of more than 30 different cytokines, including the proinflammatory 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. However, certain *Echinacea* preparations were able to completely or partly reverse this stimulation (Sharma et al., 2008a). 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 (Altamirano-Dimas et al., 2007; 2009).

More 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 proinflammatory IL-1, IL-6, IL-8 and TNFα, which are known to be collectively involved in many of the symptoms common to pulmonary infections. Echinaforce was able to completely or partly reverse this stimulation (Sharma et al., 2008b; 2009a). It was also shown that EF could be added before or after virus infection, with similar success, and furthermore the results were not affected by virus dose or time of exposure to EF (Sharma et al., 2008b).

cytokine	RV	flu	RSV	Ad 3	S.pyog	S.aureus	L.pneum	H.infl
IL-1a	+	+	+	+				
IL-4					+	+		
IL-5				+				
IL-6	+	+	+	+	+	+	+	+
IL8 (CXCL-8)	+	+	+	+	+	+	+	+
TNFα	+	+	+	+				
GROα	+	+	+		+	+		
VEGF						+		
CCL-3			+	+	+	+		
CCL-4			+	+				
CCL-5			+					
MCP-1					+	+		

RV, rhinovirus; flu, influenza virus; RSV, respiratory syncytial virus; Ad 3, adenovirus type 3; S.pyog, *Streptococcus pyogenes*; S.aureus, *Staphylococcus aureus;* L.pneum, *Legionella pneumophila;* H.infl, *Hemophilus influenzae.*

Table 3. Cytokines/chemokines induced by viruses/bacteria and reversed by EF

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 proinflammatory cytokines, although the pattern and relative amounts of stimulation differed; but in each case the stimulation was reversed by EF (Sharma et al., 2009a; 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 and secretion. It is also interesting that adenoviruses, which are not

vulnerable to direct attack by *Echinacea,* could nevertheless stimulate cytokine secretion, and were susceptible to cytokine inhibition (Sharma et al., 2009a).

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

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, as well as 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* (Sharma et al., 2010; Table 3). Thus, Echinaforce evidently reversed the stimulation of proinflammatory cytokines regardless of the inducing bacterium or virus. This indicates that EF is effectively a general anti-inflammatory agent and should be capable of ameliorating many of the symptoms of URI.

5. Mucin secretion

The secretion of excessive mucus is a common feature of bronchitis, and accordingly many pharmaceuticals have been designed to relieve this symptom, usually with the accompaniment of undesirable side effects.

In our studies, 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, Table 4), 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 in virus-infected tissues, and their relative scarcity in EF treated tissues, which appeared normal (Sharma et al., 2009b).

Treatment	In cells (ratio)	In tissue (ratio)
None-control	1.00	1.00
Echinacea (EF) only	0.76	0.82
Virus only (RV)	2.18	2.00
Echinacea (EF) + RV	0.64	0.76

Table 4. Mucin (MUC 5A) secretion in cells (BEAS-2B) and tissues

6. 3-D tissues of human airway epithelium

It is 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 (EpiAirway™

tissue, a 3-D organotypic model), which could be propagated *in vitro* under defined conditions such that tissue architecture and differentiation patterns were preserved. 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, with the exception of the virus-induced muco-polysaccharide inclusions in the goblet cells (as mentioned above). There was no evidence of virus replication, although the RV infected tissues secreted substantial amounts of the proinflammatory 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 virus-infected tissues.

7. Mechanisms of action

The results described have indicated that some *Echinacea* extracts evidently contain compounds, or combinations of compounds, with the ability to interact specifically with viral and bacterial targets (Pleschka et al., 2009; Hudson, 2009; Schneider et al., 2010; Sharma et al., 2010). In addition, these extracts can affect various signaling pathways of epithelial cells and inhibit the virus/bacterium-induced secretion of cytokines/chemokines and other inflammatory mediators that were responsible for the pulmonary symptoms. Since many signaling pathways can be affected by *Echinacea* in different cell types (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; Burns et al., 2009) and it is likely that certain *Echinacea* preparations also display synergism. However, in spite of our attempts to correlate bioactivities of Echinacea preparations with recognized chemical markers, ie. polysaccharides, caffeic acid derivatives, and alkylamides (Binns et al., 2002; Barnes et al., 2005), we have not succeeded in doing so. In contrast, preliminary evidence in our laboratory has implicated other classes of compounds (unpublished data).

8. Relevance of bioactivities to normal consumption

Echinacea extracts intended for treatment of colds and flu, and sore throats, are normally marketed in the form of tinctures, sprays, lozenges, etc. for oral consumption. The active ingredients therefore acquire immediate exposure to the mucosal epithelia. According to our studies with standardized preparations (as described above), the recommended applications ensure that physiologically relevant amounts, that is to say, adequate local antiviral, antibacterial and antiinflammatory concentrations, are achieved under normal conditions of consumption. Subsequent absorption and metabolism of the various components, however, are less relevant to this discussion, since the sites of infection and inflammation are at the level of airway epithelial tissues.

9. Conclusions

These studies on *Echinacea*, especially the standardised formulations such as Echinaforce, indicate multiple actions of the herbal preparation, resulting either from the individual activities of several compounds, or the synergistic effect of different compounds. The resulting benefits are: (i) direct virucidal activity/activities against several viruses involved in colds, 'flu and bronchitis, at concentrations which are not cytotoxic; (ii) direct bactericidal actions against certain potentially pathogenic respiratory bacteria; (iii) reversal of the proinflammatory response of epithelial cells and tissues to various viruses and bacteria; (iv) reversal of the excessive mucin secretion induced by virus. 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 symptoms of bronchitis.

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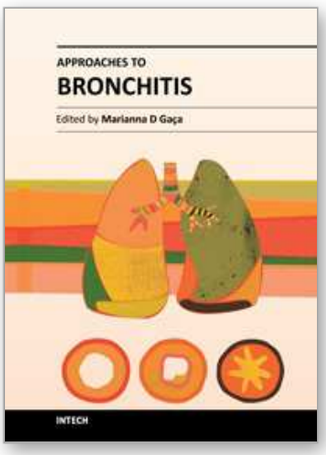

Approaches to Bronchitis

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The aim of this book is to present some recent and interesting findings in the field of bronchitis, which will serve as a supplement to the book Bronchitis. In particular, this volume focuses on the successful use and development of novel tools in the diagnostics and treatment of bronchitis. Contributions include clinical case studies, the impact of air pollution on bronchitis, the presentation and diagnosis of the respiratory disease eosinophilic bronchiolitis, primary ciliary dyskinesia, the development of a method for the swift detection of the infectious bronchitis virus and studies investigating the successful use of alternative medicines in the treatment of bronchitis. The editor would like to thank the authors of the chapters who have contributed to this book and hopes that this will book not only supplement the book on Bronchitis, but may increase interest in the subject.

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