Application of *Echinacea purpurea* in general practice – a clinical synopsis of the evidence

**Section 1 - Introduction**

The common or broad-leaved purple cone flower is the most cultivated and widely used species of *Echinacea*, as the whole plant can be used for medicinal purposes, and because it is the most easily cultivated species [1]. Echinacea was first traditionally used by the Native American tribes and later adopted by the Eclectic physicians who practiced in North America in the late 19th and early 20th Centuries. Echinacea was one of the most common medicines used by the Eclectics over a 50-year period, largely prescribed for infections and envenomations most probably due to its noticeable effect on the immune system. Echinacea was traditionally prescribed for conditions including – snake bite, syphilis, typhus, septic wounds, diphtheria, scarlet fever and dysentery [1].

**Section 2 - Quality and Quantity**

When producing herbal medicines, standardisation is imperative, as seasonal and environmental factors may influence the quantity and quality of active ingredients in plants and ultimately the quality of the product. A holistic standardisation method ensures that the primary active ingredients as well as secondary substances are retained and accounted for and a product has high degree of consistency [2].

Ideally selected farming sites, biological cultivation methods, careful choice of seeds and soil conditions as well as harvesting at the correct times contribute to a consistent concentration of ingredients. Production facilities which are closely located to farms allow for processing of freshly harvested plant material which has higher levels of active ingredients and does not require disinfection.

Tobler et al. (1994) [2] demonstrated that Echinacea extracts produced from fresh and dried raw material of the same origin differed significantly in terms of their active ingredients. The fresh group had three times the quantity of the dried group. This was attributed to the volatility of the active ingredient and its loss during the drying process, confirming that a fresh plant *echinacea extract* is superior. Such findings were confirmed by Vimalanathan et al. (2013) who determined that extracts from freshly harvested material had significantly superior anti-viral properties than those from dried plant [3]. Fresh plant extracts of *Echinacea purpurea* have demonstrated efficacy and been extensively tested in both the pre-clinical and clinical environment in a number of studies, culminating in a variety of high quality publications [3-11].
In addition to using fresh plant material, an additional measure which ensures a consistent profile of active ingredients despite seasonal and batch variations, is the process of **batch blending** to produce homogenous annual batches [2].

Due to the variety of species of Echinacea, and differing manufacture techniques with respect to methodology and quality, not all Echinacea products are the same. Various studies have objectively demonstrated phytochemical variation amongst Echinacea products [1]. In clinical practice, it is essential to be discerning in the choice of Echinacea prescribed, based on empirical scientific evidence.
Section 3 – Active ingredients and mechanism of action

Extensive research into *Echinacea* [12, 13] has identified and isolated the main active ingredients as being a group of bioactive lipidic compounds known as *alkylamides* which have an important range of biological activities [14].

Research has shown that, after an oral dose of *Echinacea purpurea* fresh plant extract, the active alkylamides reach peak concentration in the blood ($C_{max}$) within **28-45 minutes** ($T_{max}$) depending on the dosage format [15, 16] but are detectable as early as 15min post administration and they remain in measurable concentrations for up to 180 min post administration [16].

*Echinacea purpurea* has demonstrated the ability to **inhibit the production of proinflammatory cytokines IL-6 (interleukin-6), IL-8 (chemokine CXCL-8)** which are produced in various inflammatory and infections scenarios [5, 6, 8].

**Tumour necrosis factor alpha (TNF-α)** a pro-inflammatory cytokine is modulated by the alkylamides of *Echinacea purpurea* [5, 15]. This is achieved also by interacting with CB$_2$ receptors and **upregulation of TNF-α mRNA** and also **inhibition of TNF-α protein expression** [17, 18].

A unique combination of alkylamides from the roots and herba (aerial parts) of *Echinacea purpurea* are able to synergistically **activate type 2 cannabinoid receptors (CB$_2$)** which results in **stimulation of IL-10** (a major anti-inflammatory cytokine) [18, 19]. IL-10 is known to strongly inhibit IL-1, IL-6 and IL-8, all of which are associated with the inflammatory process in upper respiratory tract infections [20].
incorporating aerial parts and roots are suited for this purpose [3] and have proved efficacious accordingly [3-11].
Section 4 – Biological activity of *Echinacea purpurea*

Fresh plant extracts of *Echinacea purpurea* (derived from roots and aerial parts) in a series of studies have demonstrated the following effects:

<table>
<thead>
<tr>
<th>Biological effect</th>
<th>Mechanism of action explained</th>
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<tbody>
<tr>
<td><strong>Anti-inflammatory effect</strong></td>
<td>Modulation [17] and/or down regulation of TNF- α protein [5, 15, 17, 18, 22]</td>
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<tr>
<td></td>
<td>Inhibition of IL-6 and IL-8 [4-6, 8, 22]</td>
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<td></td>
<td>Stimulation of IL-10 (which inhibits IL-1, IL-6, IL-8) [18, 22]</td>
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<tr>
<td><strong>Anti-viral effect</strong></td>
<td>Direct viricidal effect on membrane containing viruses (Influenza, HSV, RSV) [10]</td>
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<td></td>
<td>Anti-cytokine activity against viral induced cytokines (IL-6, IL-8, TNF- α) [8, 10]</td>
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<td>Impairment of influenza virus propagation of strains of seasonal, avian, and swine origin (H3N2, H1N1, H5N1, H7N7) [11]</td>
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<td></td>
<td>Prevents viral/host receptor binding by inhibiting haemagglutination activity and preventing viral entry into cells [11]</td>
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<tr>
<td><strong>Anti-bacterial effect</strong></td>
<td>Anti-inflammatory (Anti-cytokine) activity against bacterial induced cytokines (IL-6, IL-8, MCP-1, GMCSF, GROα - S. pyogenes, S. aureus [MRSA]) (IL-6 &amp; IL-8 - S. pyogenes, S. aureus, H. influenzae, L. pneumophila) [4]</td>
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<td></td>
<td>Strong bactericidal effect (S. pyogenes, H. influenzae, L. pneumophila)</td>
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<td></td>
<td>Partial bactericidal effect (S. aureus [MRSA &amp; MSSA], Mycobacterium smegmatis) [4]</td>
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<table>
<thead>
<tr>
<th>Virus</th>
<th>MIC&lt;sub&gt;100ug/ml&lt;/sub&gt;</th>
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</thead>
<tbody>
<tr>
<td>Influenza A (human &amp; avian) &amp; Influenza B</td>
<td>0.58-50</td>
</tr>
<tr>
<td>RSV</td>
<td>2.5</td>
</tr>
<tr>
<td>HSV type 1</td>
<td>0.39</td>
</tr>
<tr>
<td>RV 1A &amp; 14</td>
<td>800</td>
</tr>
<tr>
<td>Adenovirus 3 &amp; 11</td>
<td>&gt;800</td>
</tr>
<tr>
<td>Poliovirus</td>
<td>800</td>
</tr>
<tr>
<td>Feline calicivirus</td>
<td>800</td>
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</tbody>
</table>

**Antiviral activity of *E. purpurea* demonstrating specific effect against enveloped viruses**

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### Table: Bacteria Susceptible to *E. purpurea* (log10 killed)

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Susceptible to <em>E. purpurea</em> (log10 killed)</th>
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</thead>
<tbody>
<tr>
<td><em>S. pyogenes</em></td>
<td>+ (&gt; 3 log)</td>
</tr>
<tr>
<td><em>S. aureus</em> (MRSA/MSSA)</td>
<td>+/- (~ 1 log)</td>
</tr>
<tr>
<td><em>H. influenzae</em></td>
<td>+ (&gt; 3 log)</td>
</tr>
<tr>
<td><em>L. pneumophila</em></td>
<td>+ (&gt; 3 log)</td>
</tr>
<tr>
<td><em>M. smegmatis</em></td>
<td>+/- (~ 1 log)</td>
</tr>
<tr>
<td><em>Candida albicans</em></td>
<td>-</td>
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</tbody>
</table>

Bactericidal effects of *E. purpurea* 160mg/ml against respiratory microbes

### Table: Cytokine-inducing agent Inhibition of IL6 and IL8 by *E. purpurea*

<table>
<thead>
<tr>
<th>Cytokine-inducing agent</th>
<th>Inhibition of IL6 and IL8 by <em>E. purpurea</em></th>
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<tbody>
<tr>
<td>RV 1A &amp; 14</td>
<td>+</td>
</tr>
<tr>
<td>Influenza A (H3N2)</td>
<td>+</td>
</tr>
<tr>
<td>RSV</td>
<td>+</td>
</tr>
<tr>
<td>HSV Type 1</td>
<td>+</td>
</tr>
<tr>
<td>Adenovirus type 3 &amp; 11</td>
<td>+</td>
</tr>
<tr>
<td><em>S. pyogenes</em></td>
<td>+</td>
</tr>
<tr>
<td><em>S. aureus</em> (MRSA &amp; MSSA)</td>
<td>+</td>
</tr>
<tr>
<td><em>H. influenzae</em></td>
<td>+</td>
</tr>
<tr>
<td><em>L. pneumophila</em></td>
<td>+</td>
</tr>
<tr>
<td><em>M. smegmatis</em></td>
<td>+</td>
</tr>
</tbody>
</table>

Anti-inflammatory effect of *E purpura* in Viral/bacterial induced epithelial cell inflammation

### Section 5 – Clinical application

#### 5.1 Treatment of the Common cold

**Human rhinovirus** with its 150 subtypes account for more than 50% of recurrent upper RTIs [23]. They are responsible for the common cold, but new evidence suggests their significant role in paediatric upper and lower RTI where they cause wheezing, exacerbation of asthma and pneumonia [24].

Studies have shown that rhinovirus (RV) infection results in the production of pro-inflammatory cytokines and chemokines which contribute to disease pathogenesis [25, 26]. This has been shown in the absence of significant rhinovirus replication [8, 27], suggesting that the clinical presentation of RV infection could be attributed to the inflammatory response and not necessarily to virus itself [8, 26-29]. Using a 3D tissue model of human airway epithelium infected with RV, *Echinacea purpurea* was shown to reverse production of mucopolysaccharides in goblet cells and mucin secretion and...
reverse the production of inflammatory cytokines IL-6 and IL-8. The study concluded that Echinacea purpurea not only reduces levels of inflammatory cytokines produced by RV but also reduces excessive mucus production in vitro [8].

246 healthy volunteers who caught common colds were recruited in a randomised double-blind placebo controlled study [9], and treated for a maximum of 7 days with various preparations of Echinacea purpurea or placebo. Data was collected using a 12-point complaint index (doctor and patient rated) and doctor and patient assessments of efficacy. Patients receiving active interventions of Echinacea purpurea improved significantly compared to placebo in terms of doctor & patient reported complaint indices and confirmed by doctor and patient assessments of efficacy, further active interventions were well tolerated by 95% of participants [9].

A 2007 meta-analysis on prevention and treatment of the common cold further concluded that Echinacea significantly reduced incidence and duration of common colds compared with placebo[30]. A Cochrane Review on the use of various species and extracts of various parts of the Echinacea plant in the treatment and prevention of the common cold, determined that preparations derived from the herb (aerial parts) of Echinacea purpurea were effective in this regard [21].

5.2 Influenza

Using cell culture assays researchers have demonstrated the ability of Echinacea purpurea fresh plant extract to inhibit influenza virus (IV) propagation of various strains of influenza virus including those of seasonal origin, avian & swine origin (human Victoria H3N2, human H1N1-type IV, Avian IV [HPAIV] H5 & H7 types, pandemic swine IV [S-OIV & H1N1]) it appears to do by interfering with viral entry into cells. The study demonstrated further that the emergence of viral resistance does not occur in response to Echinacea purpurea treatment as it did in those treated with oseltamivir. Interestingly the oseltamivir resistant virus remained was as sensitive to Echinacea purpurea as wild, untreated virus [11]. Anti-influenza activity of Echinacea purpurea was further confirmed in vitro (against IV Type A H3N2) with the aerial parts of the fresh plant appearing to have the most potent antiviral activity [3].
In a randomised, double-blind, controlled clinical trial (n=473) an *Echinacea purpurea* hot drink extract was shown to be as effective as gold standard oseltamivir in the early treatment of confirmed IV. In addition, it was associated with less risk of complications (p=0.076) and fewer adverse events [31].
5.3 Limiting duration and risk of complication of RTI

A meta-analysis of randomised placebo controlled studies applying Echinacea in prevention and treatment of common colds, based on seven studies, confirmed that the use of Echinacea reduces the duration of colds [32].

Use of Echinacea in RTI’s has also been shown to reduce the risk of common complications of RTI’s overall by up to 50% [33], and most specifically risk of pneumonia (64.9% decrease [p=0.0001]) otitis (media and externa) and tonsillitis/pharyngitis (p=0.0001 and p=0.021 respectively) are reduced. In addition to being associated with fewer complications, use of Echinacea in RTI’s is also associated with a decreased need for antibiotics [33]. A reduced risk of complication was confirmed in influenza cases treated with an Echinacea purpurea hot drink compared with those receiving gold standard Oseltamivir; 2.5% incidence and 6.5% incidence respectively [31].

In vitro studies have confirmed that when human bronchial epithelial cells are infected with Influenza virus A (H3N2), bacterial ligands such as ICAM-1 (intracellular adhesion molecule 1), fibronectin and platelet activating factor receptors (PAFr) are stimulated allowing for subsequent attachment of bacteria such as Haemophilus influenzae and Staphylococcus aureus and the onset of secondary bacterial infection. In this context Echinacea purpurea has demonstrated the ability to reverse the expression of these bacterial ligands, thus preventing the likelihood of secondary bacterial attachment. Further, in the same context, the significant Influenza A driven inflammatory cytokine expression (cytokine storm) was prevented by Echinacea purpurea by supressing expression of Toll like receptor 4 (TLR-4) and NF-κB (nuclear factor kappa)[34]. The study concluded that Echinacea purpurea has the potential to reduce respiratory complications by inhibiting virus induced bacterial attachment, and the inflammatory cytokine storm caused by influenza A [34].
5.4 Prevention and reduced risk of common cold & RTI [7, 33, 35, 36]

Significant evidence exists confirming that *Echinacea* reduces the incidence of colds in comparison to placebo [30]. Such has been further explored in various contexts - *Echinacea purpurea* was given prophylactically for 8 weeks in an open, phase 4 multicentre study of 80 athletes against colds, (athletes being a population known to be susceptible to URTI) [35]. Both investigators and participants rated the prophylactic efficacy as ‘very good’ (55%, 53% respectively) or ‘good’ (19% & 24% respectively). *Most participants (71%) reported no cold episodes*, and only 3% had two colds during the treatment period which is considered to be significantly below the average of 2-4 colds per winter [37]. Further, those that did experience cold episodes, had very low symptom scores. A four-month prevention study determined that in addition to a reduced number of cold episodes, *Echinacea* also inhibited specifically enveloped viral infections. Further in the group receiving *Echinacea*, there were **fewer cold episode days and less pain-killer use** [7].

Data pooled from three studies testing prophylactic effects of *Echinacea* against induced Rhinovirus colds, found that there was a 55% higher chance of developing cold symptoms in those who received placebo compared to those who received *Echinacea* concluding that *Echinacea* was effective in preventing symptoms of common cold [36].

A meta-analysis concluded that *Echinacea* reduces the risk of recurrent RTI (p<0.0001). This was based on an analysis of six studies, which included 2458 participants. Further, it concluded that **complications from RTI were also reduced** including pneumonia, otitis, tonsillitis and pharyngitis. The prophylactic benefit also appears particularly beneficial to those with higher susceptibility in which incidence of RTI was halved [33].

Section 6 – Safety & Tolerability

*Echinacea purpurea* has an **impressive safety and tolerability record** [33, 35] which has been confirmed in a number of RCT’s [7, 9, 31, 35, 38] and meta-analyses [33]. A 2009 Cochrane review [21] confirmed this in both short term treatment scenarios as well as short and long-term prevention use [7].

A large RCT determining the safety and efficacy profile *Echinacea purpurea* as prophylaxis for common colds, concluded that the safety of *Echinacea purpurea* was non-inferior to placebo, and prophylactic use for 4 months provided a positive risk to benefit ratio [7].

The majority of participants in RCTs using *Echinacea purpurea* generally rate **tolerability of treatment as ‘good’ or ‘very good’** [7, 31, 33, 35]. Furthermore, in most studies, haematological and metabolic parameters did not exhibit any clinically relevant changes in response to *Echinacea purpurea* [31, 33, 35] including long term prophylactic treatment [7].

Adverse events reported in *Echinacea* studies were infrequent and the majority mild or transient only and mostly significantly different to placebo [9, 21, 33].

**Echinacea use in pregnancy** was reported to pose no increased risk of malformations or adverse pregnancy outcomes based on data obtained from a large cohort of 68522 women and their babies, 363 women used *Echinacea* during their pregnancies (mainly for colds and flu). Those who used *Echinacea* in pregnancy did not have any increased risk of preterm births, low birth weight or small
for gestational age, and no increased risk of malformations in women who used Echinacea during early pregnancy i.e. conception to 17 weeks [39].

In terms of drug interactions, the literature does suggest potential negative interactions with immunosuppressant drugs [1]. This is most likely due to the potential for Echinacea to inhibit the action of such drugs, believed to be possibly due to the immune enhancing effects of Echinacea (not due to any reported adverse events) and as a result thereof Echinacea is currently ‘theoretically’ contraindicated [1, 40].

Currently there is no reliable evidence which contraindicates the use of Echinacea in HIV positive patients [1]. Various studies have evaluated the potential herb-drug interactions between Echinacea purpurea and anti-retroviral drugs [41-43]. Since concurrent use of complementary and alternative medicines (CAM) is common in patients with HIV infection [43-45]. More specifically Echinacea may be used by HIV patients for its antiviral and immune modulation effects [45, 46]. A common concern with co-administration of herbal medicines with ARV therapy is the potential for interaction with CYP3A4 activity [46] (Cytochrome P450 3A). In the case of Echinacea, it is believed that CYP3A activity is induced [43]. ARV protease inhibitor drugs e.g. Lopinavir and Darunavir, combined with CYP3A inhibitors such as ritonavir (boosted protease inhibitors), appear not to be negatively affected by concomitant use of Echinacea purpurea [41-43]. However, in one study, Darunavir concentrations did decrease in some patients, but without the need for dose adjustment and without affecting Darunavir or Ritonavir pharmacokinetics. Co-administration with Etravirin (a nonnucleoside reverse transcriptase inhibitor) without the assistance of a boosted protease inhibitor however is also considered to be safe and well tolerated with no need for dose adjustments [42]. The studies reviewed seem to conclude that concomitant Echinacea use does not warrant the need for dose adjustment and does not significantly alter pharmacokinetics [41-43] however these patients should disclose the use of Echinacea [46] and be monitored individually [41-43].

Echinacea should be used with caution with concurrent IV Midazolam. In one study, IV Midazolam clearance was increased by co-administration of Echinacea purpurea root, oral Midazolam was not affected [47]. A Human study has confirmed that co-administration of Echinacea with Warfarin did not significantly alter Warfarin pharmacodynamics [1, 48]

Section 7 – Conclusion

Echinacea purpurea appears unique in its ability to treat and prevent RTIs holistically due to its apparent anti-inflammatory, anti-viral and anti-bacterial ability [5]. Whether viral or bacterial in origin, RTI is characterised by an inflammatory response, this is caused by pro-inflammatory cytokines which are believed to trigger the actual symptoms experienced; Echinacea has clearly demonstrated the ability to inhibit (IL-6, IL-8, TNF-α) these according [4, 5, 8, 10]. In addition, direct anti-viral and anti-bacterial effects of Echinacea purpurea against common RT pathogens, including but not limited to rhinovirus, influenza virus, S.pyogenes, H.influenzae have been demonstrated in vitro [4, 5, 10, 11]. The findings of In vitro studies in this context have been confirmed by a number of human trials confirming efficacy in the treatment [9, 21, 30, 31] and prevention of RTI [7, 30, 33, 35, 36]. Common complications of RTI are reduced by 50% [33] and secondary bacterial infections are prevented by inhibiting viral induced expression of bacterial receptors.[34]
List of references

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