R e search into herbs used to treat or prevent the common cold, a viral upper respiratory tract infection (URT), has focused mainly on the effects of echinacea, also known as the purple coneflower. Several other herbs, such as ephedra (Ephedra sinica and other Ephedra species) and elder (Sambucus nigra) have been used traditionally for treating the common cold, but have been subject to little scientific investigation (although the effects of the ephedra alkaloids ephedrine and pseudoephedrine are well-documented). Many other herbal ingredients, particularly essential oils (eg, peppermint, eucalyptus and pine oils) and herbal constituents (eg, menthol, thymol) are ingredients of several over-the-counter (OTC) cold products intended for use as steam inhalations or salves. Such products can lead to subjective improvements in cold symptoms (eg, nasal congestion), but there is no objective evidence of this.

A recent article provided guidance on the OTC treatment of coughs and colds (PJ, 26 October, pp612—4). Pharmacists are encouraged to probe discreetly, where possible, individuals’ reasons for purchasing herbal products used to treat or prevent URTIs and to apply usual protocols to establish who the product is for, treatments already tried or being used, other action taken, and so on.

BACKGROUND

Three Echinacea species are used medicinally: E angustifolia, E pallida and E purpurea. E purpurea is easily cultivated and is the most widely used of the three species. Usually, the aerial (above ground) parts of E purpurea and the roots of E angustifolia and E pallida are the parts used pharmaceutically, although sometimes roots of E purpurea are also used. Some commercial echinacea raw material may contain more than one of these three species, possibly through accidental or intentional contamination with E pallida; in the past, E pallida was often confused with E angustifolia. Some marketed echinacea products contain more than one echinacea species as part of the formulation, sometimes in combination with other plant species.

MAJOR CONSTITUENTS

There are differences in the constituents of each species of Echinacea (see Table 11—3). E angustifolia and E purpurea contain alkalylamides as their major lipophilic constituents, but the structural types of these compounds differ between the two species. E pallida contains only low concentrations of alkylamides. All three species contain a polysaccharide component and other carbohydrates. Polysacetylenes, initially thought to be specific to E pallida, have since been documented for E purpurea and E angustifolia. The polysaccharide and polyacetylene components of echinacea are thought to be important for immunostimulant activity.

EVIDENCE OF EFFICACY

As with other plants, there can be variation in the profile and concentration of constituents found in echinacea material. The issue of variation between manufactured products, and the suggestion that evidence for efficacy and safety should be considered to be extract- or product-specific, were raised in the first article in this series (PJ, 8 June, pp804—6). This is particularly relevant for echinacea since, as stated earlier, marketed products may contain chemically different species of echinacea. Certain constituents, such as echinacoside, are sometimes used as markers for quality control purposes. Users and potential users of echinacea products should be made aware of the possible differences between products and the implications of this for efficacy and safety.

Analysis of north American commercial samples of raw echinacea material has shown that in some cases Echinacea species were incorrectly assigned to the sample. Further, analysis of echinacea products marketed in the United States has shown that the quality and labelling of some products are inadequate. One study of 25 marketed echinacea products found that six were inadequately labelled, eg, the label did not state the species or plant part used. Of the remaining 19 products, four did not contain labelled or minimum expected quantities of marker compounds, and one contained unacceptable concentrations of microbes.

Numerous studies have explored the effects of echinacea preparations in preventing or treating the common cold and other URTIs. Collectively, the findings are difficult to interpret because different studies have assessed different preparations and dose regimens, some have involved healthy volunteers, whereas others have involved individuals diagnosed with non-specific viral URTIs (including influenza-like syndrome and others), and several trials have methodological limitations. Overall several, but not all, studies have reported beneficial effects with echinacea for preventing and treating URTIs compared with placebo. However, for the reasons listed above, current consensus is that there is insufficient evidence to recommend any specific echinacea preparation, or to advise on optimal dose and treatment duration.

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This article considers evidence for the efficacy and safety of echinacea in the prevention and treatment of symptoms of the common cold.
Systematic reviews A recent systematic review included 16 randomised and quasi-randomised controlled trials (involving almost 3,400 participants) of extracts of echinacea for preventing (n = 8) or treating (n = 8) URTIs. Five of the “prevention” trials were placebo-controlled and tested combination echinacea preparations or monopreparations of E. purpurea herb or root, or E. angustifolia root administered orally typically for eight to 12 weeks. Two of these studies reported a statistically significant reduction in the incidence of URTIs in echinacea recipients compared with placebo recipients (odds ratios, 95 per cent confidence interval (CI): 0.45, 0.22–0.92 and 0.27, 0.11–0.66, respectively), and one also found that the duration of infections was significantly shorter with echinacea than with placebo, although two other studies reported no difference in this outcome. Three other prevention trials compared a preparation containing extracts of E. angustifolia and E. pallida root, Baptisia tinctoria root and Thuya occidentalis herb, as well as several homeopathic dilutions, with no treatment. All three reported that the frequency of infection was significantly lower in the group receiving the preparation (odds ratio 0.36; 95 per cent CI 0.28–0.46).6

The eight randomised, placebo-controlled “treatment” trials tested three different combinations of echinacea extracts and two monopreparations, taken orally typically for six to 10 days.6 Six studies reported statistically significant beneficial effects for echinacea recipients, compared with placebo, on outcome measures such as duration of illness and symptoms (eg, “running nose”). However, heterogeneity of the studies precluded any further summary of the results. The authors of the review concluded that although many of the studies reported positive results for echinacea, it was not possible to recommend any specific product for the prevention or treatment of the common cold. Further research was deemed necessary.6

New trials New prevention trials have not shown beneficial effects for echinacea preparations, compared with placebo, on main outcome measures.7 By contrast, new studies of echinacea preparations for the treatment of the common cold generally have reported positive effects.8,9 Details of some of these studies are given below.

Prophylaxis One randomised, double-blind, placebo-controlled trial involved 302 healthy volunteers recruited from military institutions and an industrial site who received either an ethanolic extract of E. purpurea or E angustifolia root (drug:extract ratio, 1:1 in 30 per cent alcohol), or placebo, 50 drops twice daily (Monday to Friday) for 12 weeks.7 In an intention-to-treat analysis, the proportion of participants who experienced at least one URTI was 32 per cent for E angustifolia recipients, 29 per cent for E. purpurea, and 37 per cent for placebo; these differences were not statistically significant (P=0.55). Similarly, there were no statistically significant differences between groups in time to occurrence of the first URTI (P=0.49), or in the duration of infections (P=0.29). However, a greater proportion of echinacea recipients believed they had benefited from the study medication than did placebo recipients (78, 70 and 56 per cent for E angustifolia, E. purpurea and placebo, respectively; P=0.04).7

Treatment Three different preparations and doses of E. purpurea were tested in a randomised, double-blind, placebo-controlled trial in healthy adults.8 The four arms of the study were:

<table>
<thead>
<tr>
<th></th>
<th>6.78mg (per tablet) E. purpurea crude extract, based on 95 per cent herb and 5 per cent root (Echinaforce)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>48.27mg (per tablet) E. purpurea crude extract, based on 95 per cent herb and 5 per cent root</td>
<td></td>
</tr>
</tbody>
</table>

In total, 246 participants experienced symptoms typical of the onset of a common cold and, accordingly, took their allocated study medication (two tablets three times daily) until they felt better or for up to seven days. According to an intention-to-treat analysis, the two extracts prepared from both E. purpurea herb and root were significantly more effective than the root extract alone and placebo in reducing symptoms as assessed by the investigator (the primary outcome measure).8

Statistically significant effects for an extract of E. purpurea herb (Echinacin), compared with placebo, on median duration of illness (six and nine days, respectively; P=0.0112) were reported in another randomised, double-blind trial involving 80 adults who experienced onset of a cold.9 Participants started taking their allocated medication on first experiencing symptoms and continued treatment until symptoms resolved.

A further placebo-controlled study involving adults with early symptoms of a cold (n = 95) explored the effects of a preparation containing E. purpurea and E. angustifolia herb and extract of E purpurea root formulated as a tea.10 It was reported that there was a statistically significant difference between the treatment and placebo groups in effectiveness and duration of symptoms. However, the study had several methodological limitations: it did not involve true randomisation, the “placebo” tea contained low doses of several herbs (peppermint leaf, sweet fennel seed, ginger rhizome, papaya leaf, alfalfa leaf and cinnamon bark), and outcomes were self-assessed.

Mechanism of action

The immunomodulatory activity of extracts and fractions of echinacea has been documented following numerous in vitro and in vivo studies. In particular, studies have shown immunostimulatory effects of echinacea preparations on the non-specific cell-mediated immune response, for example:

- In vitro studies have documented enhanced phagocytic activity of human granulocytes following application of echinacea extracts
- Immunostimulant activity has been shown in mice, indicated by enhanced phagocytosis and increased elimination of carbon particles in serum (carbon-clearance test)
- In vitro stimulation by E. purpurea of cytokine production, such as interleukin-1 (IL-1) and tumour necrosis factor-alpha (TNF-a), by macrophages has been documented11-3

Recent studies investigating the immunomodulating activity of echinacea administered to healthy volunteers have drawn different conclusions. In a randomised, double-blind, placebo-controlled trial, compared with a placebo group, volunteers who received extracts of E. purpurea and E. angustifolia with or without the addition of an arabinogalactan extracted from Larix occidentalis (larch) for four weeks were found to have increased concentrations of complement properdin (factor P, a non-immunoglobulin gamma globulin).11 By contrast, a double-blind, placebo-controlled crossover study involving 40 healthy volunteers found that oral administration of freshly expressed juice of E. purpurea herb, or placebo, for two weeks did not enhance phagocytic activity of polymorphonuclear leucocytes or monocytes, or affect TNF-a and IL-1 production.12

<table>
<thead>
<tr>
<th>Species</th>
<th>Plant part</th>
<th>Constituents</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. purpurea</td>
<td>Aerial parts</td>
<td>Alkylamides; caffeic acid esters, mainly chicoric acid; polysaccharides; polyacetylenes; traces of the saturated pyrrolizidine alkaloids</td>
<td>Echinacoside (a caffeic acid ester) is not present</td>
</tr>
<tr>
<td>E. angustifolia</td>
<td>Roots</td>
<td>Alkylamides; caffeic acid esters, particularly echinacoside; cynarin, polysaccharides; polyacetylenes; traces of the saturated pyrrolizidine alkaloids</td>
<td>Cynarin is characteristic of E. angustifolia</td>
</tr>
<tr>
<td>E. pallida</td>
<td>Roots</td>
<td>Caffeic acid esters, particularly echinacoside; polysaccharides; polyacetylenes (distinctive series)</td>
<td>Alkylamides largely absent</td>
</tr>
</tbody>
</table>

**TABLE 1: MAJOR CONSTITUENTS OF ECHINACEA SPECIES USED PHARMACEUTICALLY**

1. Statistical analysis
2. Treatment of the common cold
3. Prophylaxis
4. New trials
5. Conclusion
6. Systematic review
7. Evidence synthesis
8. Previous research
9. Study design
10. Outcome measures
Pregnancy and lactation There is a lack of data on the safety of echinacea taken during pregnancy and lactation and, given that the benefits of specific echinacea preparations have not been established definitively, excessive use during these periods should be avoided as a general precaution.6 A prospective study compared numbers of live births, and spontaneous and therapeutic abortions occurring among women who had taken echinacea preparations during pregnancy (n = 206, 112 of whom took echinacea during the first trimester) with those occurring among a control group of 206 women matched for maternal age and alcohol and cigarette use.17 There were no statistically significant differences in assessed outcomes between the two groups.

REFERENCES