JPP Journal of Pharmacy and Pharmacology

JPP 2005, 57: 929–954

Received December 3, 2004
Accepted February 7, 2005
DOI 10.1211/0022357056127
ISSN 0022-3573

Review Article

Echinacea species (*Echinacea angustifolia* (DC.) Hell., *Echinacea pallida* (Nutt.) Nutt., *Echinacea purpurea* (L.) Moench): a review of their chemistry, pharmacology and clinical properties

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Abstract

This paper reviews the chemistry, pharmacology and clinical properties of *Echinacea* species used medicinally. The *Echinacea* species *Echinacea angustifolia*, *Echinacea pallida* and *Echinacea purpurea* have a long history of medicinal use for a variety of conditions, particularly infections, and today echinacea products are among the best-selling herbal preparations in several developed countries. Modern interest in echinacea is focused on its immunomodulatory effects, particularly in the prevention and treatment of upper respiratory tract infections. The chemistry of *Echinacea* species is well documented, and several groups of constituents, including alkamides and caffeic acid derivatives, are considered important for activity. There are, however, differences in the constituent profile of the three species. Commercial echinacea samples and marketed echinacea products may contain one or more of the three species, and analysis of samples of raw material and products has shown that some do not meet recognized standards for pharmaceutical quality. Evidence from preclinical studies supports some of the traditional and modern uses for echinacea, particularly the reputed immunostimulant (or immunomodulatory) properties. Several, but not all, clinical trials of echinacea preparations have reported effects superior to those of placebo in the prevention and treatment of upper respiratory tract infections. However, evidence of efficacy is not definitive as studies have included different patient groups and tested various different preparations and dosage regimens of echinacea. On the basis of the available limited safety data, echinacea appears to be well tolerated. However, further investigation and surveillance are required to establish the safety profiles of different echinacea preparations. Safety issues include the possibility of allergic reactions, the use of echinacea by patients with autoimmune diseases and the potential for echinacea preparations to interact with conventional medicines.

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Note: The views expressed in this paper are those of the authors and do not represent those of the Medicines and Healthcare products Regulatory Agency.

Introduction

The genus *Echinacea* (Asteraceae) comprises a small number of species that are hardy, herbaceous perennial plants, native to parts of North America (Wichtl 2004). Three of the species, *Echinacea angustifolia* (DC.) Hell., *Echinacea pallida* (Nutt.) Nutt. and *Echinacea purpurea* (L.) Moench, are used medicinally. Before 1968, *E. angustifolia* and *E. pallida* were considered to be different varieties of the same species until a revision of the genus described them as two separate species (World Health Organization 1999). There is now a view that the name *E. purpurea* (L.) Moench has widely been used inappropriately, and a taxonomic revision of the genus has been proposed that comprises two subgenera and four species: *E. purpurea*, *E pallida*, *E. atrorubens* and *E. laevigata*, with *E. angustifolia* and *E. pallida* revised as *E. pallida* var *angustifolia* (DC.) Cronq. and *E. pallida* var *pallida* (Nutt.) Cronq. (Binns et al 2002a, 2004). This review summarizes the literature up to (and partly including) 2004 and therefore describes species as *E. angustifolia*, *E. pallida* and *E. purpurea*.

Vernacular names for *Echinacea* species include black Sampson, coneflower, pale/pale purple coneflower (*E. pallida*), purple coneflower (*E. purpurea*, *E. angustifolia*), narrow-leaf purple coneflower (*E. angustifolia*) and Kansas snakeroot (*E. angustifolia*) (Wichtl 2004).

The fresh or dried underground parts (roots, rhizomes) of all three species are used medicinally; in addition, the fresh or dried flowering tops and the fresh pressed juice from

the flowering tops of *E. purpurea* are used (European Scientific Co-operative on Phytotherapy 2003; Wichtl 2004). Commercial echinacea products may contain one or more of these crude drugs, obtained from different geographical areas, and are available in a range of dosage forms, including tinctures, tablets, teas, capsules and preparations for parenteral use. The phytochemical diversity across different echinacea products makes interpretation of pharmacological and clinical research findings difficult.

Echinacea has a long history of medicinal use for a wide variety of conditions, mainly infections, such as syphilis and septic wounds, but also as an "anti-toxin" for snakebites and blood poisoning (Hobbs 1994; Mills & Bone 2000). Traditionally, echinacea was described as an "anti-infective" agent, and was indicated in bacterial and viral infections, mild septicaemia, furunculosis (persistent recurring episodes of painful nodules in the skin) and other skin conditions, including boils, carbuncles and abscesses (British Herbal Medicine Association 1990; Bradley 1992; Tyler 1993; Williamson 2003). Other traditional uses listed include nasopharyngeal catarrh, pyorrhoea (periodontitis) and tonsillitis, as a supportive treatment for influenza-like infections and recurrent infections of the respiratory tract and lower urinary tract, and, externally, for poorly healing superficial wounds (British Herbal Medicine Association 2003).

Current interest in the medicinal use of echinacea is focused on its immunostimulant (increasingly described as immunomodulatory) effects, particularly in the treatment and prevention of the common cold, influenza and other upper respiratory tract infections (URTIs). Reliable data on the utilization of echinacea products in the UK for these and other conditions are lacking. In Germany, the largest European market for echinacea, products containing echinacea root or herb were among the top 20 most commonly prescribed monopreparation (containing only a single herbal ingredient) herbal medicines in 1997 (487 000 prescriptions), representing sales (based on pharmacy prices) of over DM8 million (Schulz et al 2000). Data from several sources indicate that crude echinacea material and echinacea extracts are listed among the 12 top-sellers in their respective categories and that echinacea-containing products are among the best-selling herbal preparations in the USA (Yu 2004).

The popularity of echinacea can also be gauged by exploring the growth in research and information concerning echinacea. Bibliometric studies for the period 1970 to 2002 have revealed that the number of scientific publications on echinacea is increasing year on year (Yu 2004). Several pharmacopoeial and other monographs relating to the medicinal species of *Echinacea* have been produced (World Health Organization 1999; European Scientific Co-operative on Phytotherapy 2003; Barnes et al 2004; Upton 2004; Wichtl 2004) and monographs for the European Pharmacopoeia are in development (Council of Europe 2004a, b).

Phytochemistry

There are some differences in the constituents of echinacea across the species and their respective plant parts (Table 1). It is generally thought that no single constituent or group of constituents is responsible for the activities of echinacea. Rather, several groups of constituents (the alkamides, caffeic acid derivatives, polysaccharides and alkenes (such as polyenes)) appear to contribute to activity. However, it has been reported that following oral administration in man, alkamides are bioavailable, whereas caffeic acid derivatives are not and, therefore, cannot contribute to activity (see Clinical Studies: Pharmacokinetics) (Matthias et al 2004b). A summary of the constituents of *Echinacea* species, compiled from several sources, is presented below, and structural formulae for several constituents are provided in Figure 1.

Alkamides

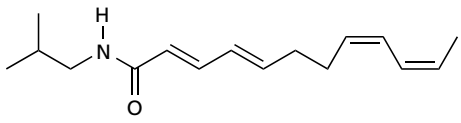
At least 20 alkamides are present, mainly isobutylamides of straight-chain fatty acids with olefinic and/or acetylenic bonds (Bauer & Wagner 1988, 1990; Bauer & Remiger 1989; Bauer et al 1989; Lienert et al 1998), for example isomeric dodeca-2*E*,4*E*,8*Z*,10*E*/*Z*-tetraenoic acid isobutylamide (Sloley et al 2001), present in the roots and aerial parts of *E. angustifolia* and *E. purpurea*, but mainly absent from *E. pallida*. Isobutylamides from the roots of *E. purpurea* contain mainly 2,4-dienoic units, while those of *E. angustifolia* contain mainly 2-monoene units (Bauer & Remiger 1989). The synthesis of the acetylenic amide *N*-(2-methylpropyl)-2*E*-undecene-8,10-diynamide, a constituent of *E. angustifolia* root, has been reported (Kraus & Bae 2003). *E. purpurea* root reportedly contains 0.01–0.04% alkamides (European Scientific Co-operative on Phytotherapy 2003).

Phenylpropanoids

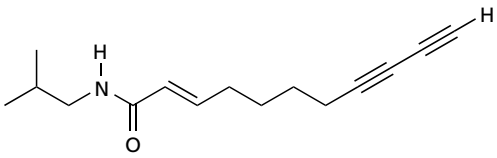
Caffeic acid glycosides (e.g. echinacoside, verbascoside, caffeoylechinacoside), caffeic acid esters of quinic acid (e.g. chlorogenic acid = 5-caffeoylquinic acid, isochlorogenic

Table 1 Major constituents of *Echinacea* species used medicinally (adapted from Barnes 2002)

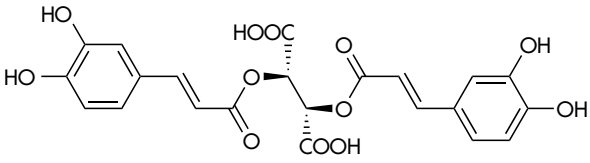
Species	Plant part	Constituents	Comment
Echinacea purpurea	Aerial parts	Alkamides; caffeic acid esters, mainly cichoric acid; polysaccharides; polyacetylenes	Echinacoside is not present
Echinacea angustifolia	Roots	Alkamides; caffeic acid esters, particularly echinacoside; cynarin; polysaccharides; polyacetylenes	Cynarin is characteristic of *E. angustifolia*
Echinacea pallida	Roots	Caffeic acid esters, particularly echinacoside; polysaccharides; polyacetylenes (distinctive series)	Alkamides largely absent



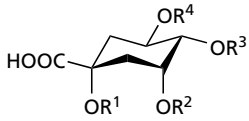
dodeca-2*E*,4*E*,8*Z*,10*Z*-tetraenoic acid isobutylamide



undeca-2*E*-enoic-8,10-diyne acid isobutylamide



cichoric acid (2,3-dicaffeoyltartaric acid)
(caftaric acid = 2-caffeoyltartaric acid)

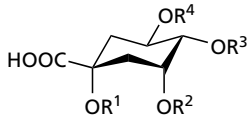


R^1	R^2	R^3	R^4
H	H	H	caffeoyl

chlorogenic acid (5-caffeoylquinic acid)

R^1	R^2	R^3	R^4
caffeoyl	caffeoyl	H	H

cynarin (1,3-dicaffeoylquinic acid)

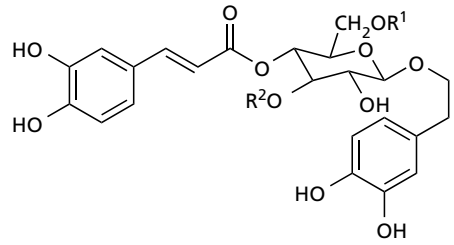


R^1	R^2	R^3	R^4
H	caffeoyl	caffeoyl	H

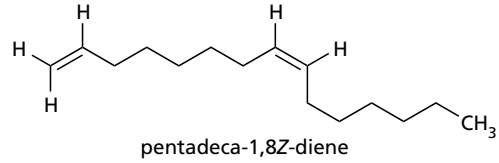
isochlorogenic acid (3,4-dicaffeoylquinic acid)

R^1	R^2	R^3	R^4
H	caffeoyl	H	caffeoyl

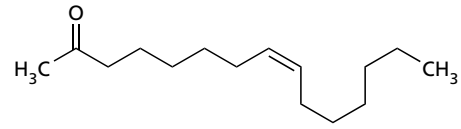
isochlorogenic acid (3,5-dicaffeoylquinic acid)



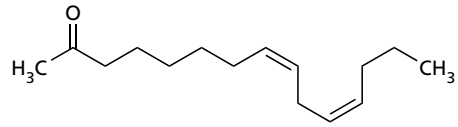
	R^1	R^2
echinacoside	glucosyl (1➞6)	rhamnosyl
verbascoside	H	rhamnosyl
caffeoyl-echinacoside	6-caffeoylglucosyl (1➞6)	rhamnosyl (1➞6)



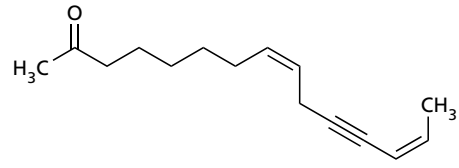
pentadeca-1,8*Z*-diene



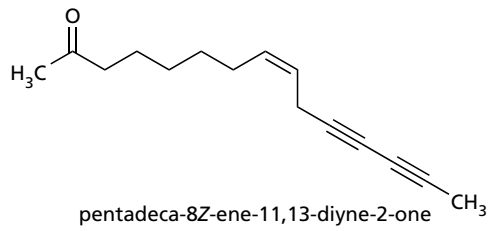
pentadeca-8*Z*-ene-2-one



pentadeca-8*Z*,11*Z*-diene-2-one



pentadeca-8*Z*,13*Z*-diene-11-yne-2-one



pentadeca-8*Z*-ene-11,13-diyne-2-one

Figure 1 Structural formulae for constituents of *Echinacea* species.

acid = 3,4- and 3,5-dicaffeoylquinic acid, cynarin = 1,3-dicaffeoylquinic acid) and of tartaric acid (e.g. caftaric acid = 2-caffeoyltartaric acid, cichoric acid = 2,3-dicaffeoyltartaric acid) (Pietta et al 1998). Varying mixtures of caffeic acid derivatives are present in the three species with echinacoside being the major component of the roots of *E. angustifolia* and *E. pallida* (Pietta et al 1998) (0.5–1.0%) (European Scientific Co-operative on Phytotherapy 2003), and cichoric acid being a major component of *E. purpurea* roots (0.14–2.05%) (Wills & Stuart 1999) and aerial parts (1.2–3.1%) (Nüsslein et al 2000; European Scientific Co-operative on Phytotherapy 2003). Cynarin is reportedly present in *E. angustifolia* root (Pietta et al 1998; Sloley et al 2001), but not in the roots of the other two species.

Polysaccharides

Polysaccharides PS1 (a methylglucuronoarabinoxylan, mol. wt. 35 kD), PS2 (an acidic rhamnoarabinogalactan, mol. wt. 450 kD) and a xyloglucan (mol. wt. 79 kD) have been isolated from *E. purpurea* herb (Bauer 1997; European Scientific Co-operative on Phytotherapy 2003). Polysaccharides and glycoproteins are present in *E. purpurea* herb and *E. pallida* root (European Scientific Co-operative on Phytotherapy 2003). The pressed juice from the aerial parts of *E. purpurea* (and the herbal medicinal product Echinacin prepared from the juice) contain heterogeneous polysaccharides (mol. wt. < 10 kD), inulin-type fractions (mol. wt. 6 kD) and an acidic highly branched arabinogalactan polysaccharide (mol. wt. 70 kD) (Blaschek et al 1998). The pressed juice of *E. purpurea* aerial parts has yielded an arabinogalactan-protein comprising 83% polysaccharide (galactose/arabinose 1.8:1), uronic acids (4–5%) and protein (7%) with high concentrations of serine, alanine and hydroxyproline (Classen et al 2000). The arabinogalactan-protein (mol. wt. 1.2×10^6 D) has a highly branched polysaccharide core of 3-, 6-, and 3,6-linked galactose residues with terminal arabinose and glucuronic acid units (Classen et al 2000).

Volatile oils

E. pallida root (0.2–2.0%) (European Scientific Co-operative on Phytotherapy 2003) mainly contains alkenes (such as polyenes) and alkynes (such as polyacetylenes), including pentadeca-1,8*Z*-diene and a range of ketoalkenes and ketoalkenynes (ketopolyacetylenes), principally pentadeca-8*Z*-ene-2-one, pentadeca-8*Z*,11*Z*-diene-2-one, pentadeca-8*Z*,13*Z*-diene-11-yne-2-one, tetradeca-8*Z*-ene-11,13-diyne-2-one and others (Bauer et al 1988b; European Scientific Co-operative on Phytotherapy 2003). These compounds are unstable and readily oxidize to 8-hydroxy derivatives (European Scientific Co-operative on Phytotherapy 2003). The alkenes of *E. pallida* and *E. purpurea* root are distinctly different from those of *E. angustifolia*, which are mainly alkylketones (Lienert et al 1998). The volatile oil from the aerial parts of the three species contains borneol, bornyl acetate, germacrene D, caryophyllene and other components (European Scientific Co-operative on Phytotherapy 2003; Wichtl 2004).

Other constituents

A series of other constituents has been reported, including the saturated pyrrolizidine-type alkaloids tussilagine and isotussilagine (0.006%) from *E. angustifolia* and *E. purpurea* (Röder et al 1984). Flavonoids, including quercetin, kaempferol, isorhamnetin and their glycosides (European Scientific Co-operative on Phytotherapy 2003), and also anthocyanins, are present in the aerial parts of *E. purpurea* (0.48%) (Wichtl 2004). The major flavonoid of the aerial parts of *E. angustifolia* has been identified as patuletin-3-rutinoside (Lin et al 2002), and not rutin as previously reported (Bauer 1998). Free phenolic acids, including *p*-coumaric, *p*-hydroxybenzoic and protocatechuic acids, have been isolated from the aerial parts of *E. angustifolia* and *E. purpurea* (Glowniak et al 1996). Other miscellaneous compounds reported include betaine, fatty acids, simple sugars, sterols and vanillin.

A conference abstract reported the presence of "melanin" in material from cultured *E. angustifolia* plants (Pugh et al 2004). Phytomelanin deposits are stated to be present in the roots of *E. pallida* and *E. angustifolia*, but absent from *E. purpurea* roots (Wichtl 2004).

Quality of plant material and commercial products

Alkamide concentrations vary between species and between different parts of the plant (Perry et al 1997). Commercial root samples of *E. purpurea* have been shown to vary in their alkamide content (0.12–1.2%) (Wills & Stuart 1999). In Germany, 25 commercial echinacea preparations were assayed for their alkamide (dodeca-2*E*,4*E*,8*Z*,10*E*/*Z*-tetraenoic acid isobutylamide) and cichoric acid contents (Osowski et al 2000). Some products were highly concentrated, whereas others had no detectable concentrations of alkamide or cichoric acid. Large differences were observed between comparable products from different manufacturers.

Several commercial echinacea products have performed poorly in examinations of their quality. Of 25 commercial echinacea products purchased in the USA, only 14 (56%) passed assessments for their quality (ConsumerLab 2003). Six were inadequately labelled, three of them not stating the species used, one not stating the plant part and two liquid preparations had no concentrations given for their echinacea content. The remaining 19 products were assessed for their stated content of a particular species and for claimed concentrations of phenols. Twelve of these products were labelled as containing only *E. purpurea* and two of them failed, as one contained only 54% of the expected concentration of phenols and the other had three times the accepted concentration of microbes as set out in World Health Organization guidelines. Two products were allegedly prepared from *E. angustifolia* and both failed, one having only one third of the stated phenolic content and the other having no detectable echinacoside. Five further products allegedly containing a mixture of species were also assessed and one failed because echinacoside could not be detected. Analysis of 59 commercial products

available in the USA revealed that 10% had no measurable echinacea content, 48% were not consistent with their labels in respect of the species present, and of 21 standardized preparations, 57% did not meet the standards stated on their labels; often products did not contain the species stated (Gilroy et al 2003).

A fresh plant product of *Echinacea* herb has been shown to possess three times the amount of alkamide than a product prepared from dried plants and this has been attributed to loss on drying (Tobler et al 1994). The alkamide and cichoric acid content of six commercial preparations of *E. purpurea* expressed juice have been shown to be variable (0.1 to 1.8 mg mL^{-1} and 0.0 to 0.4%, respectively) (Bauer 1999). Ten commercial preparations of echinacea were analysed for their betaine content and concentrations ranged from 0.04 to 0.64% (Ganzera et al 2001).

The concentrations of some constituents may be affected during growing, drying or storage of the plant material. The yields of some constituents are affected when plants are grown under conditions of drought stress (Gray et al 2003). Analysis of roots of *E. angustifolia* dried at a range of temperatures between 23°C and 60°C indicated that there were no significant changes in the alkamide content, whereas 25% and 45% of the echinacoside content was lost at 30°C and 60°C, respectively (Kabganian et al 2002). By contrast, roots of *E. purpurea* at −18°C in deep-freeze for 64 weeks were found to have lost 40% of their alkamide content (Perry 2000). An aqueous alcoholic extract of *E. purpurea* and its dried extract were stored at different temperatures for 7 months and then assayed for their alkamide and phenylpropanoid content (Livesey et al 1999). The amount of the major alkamide (dodeca-2*E*,4*E*,8*Z*,10*E*/*Z*-tetraenoic acid isobutylamide) in the liquid preparation was not significantly affected by storage at 25°C and 40°C, whereas the cichoric acid content declined. However, the reverse occurred for the dried extract where there was a significant loss of alkamide at storage temperatures of 25°C and 40°C but no significant loss of cichoric acid content.

The effects of drying temperatures on the constituents of all three *Echinacea* species have been investigated (Li & Wardle 2001). The results showed that there was an increase in cichoric acid content for *E. purpurea* and *E. pallida*. Furthermore, increased moisture content resulted in higher concentrations of echinacoside for *E. angustifolia* and *E. pallida* and of chlorogenic acid in *E. angustifolia*. The polysaccharide contents were significantly decreased by raised moisture levels in the roots of *E. angustifolia* and *E. pallida*.

The presence of colchicine in commercial echinacea products in the USA has been reported (Petty et al 2001), although subsequent analysis of 17 commercial echinacea products purchased in pharmacies in Chicago, USA, did not detect colchicine in any of the samples (Li et al 2002).

Detailed descriptions of *E. purpurea* root for use in botanical, microscopic and macroscopic identification have been published, along with qualitative and quantitative methods for the assessment of *E. purpurea* root raw material (Upton 2004).

Pharmacology

There is a vast scientific literature on the pharmacological activities of *Echinacea* species based on in-vitro and in-vivo (animal) studies. Research has focused on investigating the immunomodulatory activity of echinacea preparations, although other activities such as antiviral, antifungal, anti-inflammatory and antioxidant properties have also been explored. Effects on the immune system may play a role in some of these other activities. The activities of echinacea, particularly the immunomodulatory effects, have been reviewed in detail (Hobbs 1994; Bauer et al 1999; Barrett 2003; Miller 2004; Rininger et al 2004; Sestakova & Turek 2004), and a summary of some of the relevant scientific literature is given below.

Immunomodulatory activity

Currently, there is a view that immunomodulatory rather than immunostimulatory is the most appropriate term to describe the immunological effects of echinacea (Barrett 2003), although immunostimulatory is still used and is ubiquitous in the earlier scientific literature on echinacea. It has been suggested that broad stimulation of the various highly complex components of the immune system is unlikely to be beneficial, since some immune responses are harmful (Barrett 2003).

The immunological effects of a wide range of echinacea preparations, comprising different species, plant parts and types of extract, have been investigated extensively in-vitro and in-vivo. Collectively, the data indicate that echinacea preparations do have effects on certain indices of immune function, although at present there is no clear picture as to which specific preparations have the greatest activity. Enhancement of macrophage function has been documented for various preparations of echinacea in-vitro and in-vivo in studies using a range of methods, such as the carbon-clearance test and measurement of cytokine production, as indicators of macrophage activity (Schulte et al 1967; Vömel 1985; Bauer et al 1988a). In-vitro experiments with human macrophages found that fresh pressed juice and dried juice from the aerial parts of *E. purpurea* stimulated production of cytokines, including interleukin (IL)-1, IL-10, and tumour necrosis factor α (TNF-α) (Burger et al 1997).

Other studies have reported that purified polysaccharides from *E. purpurea* induced macrophage production of IL-1 (Stimpel et al 1984), and that a polysaccharide arabinogalactan isolated from plant cell cultures of *E. purpurea* induced TNF-α and interferon-β_2 production by murine macrophages (Luettig et al 1989). Polysaccharides obtained from plant cell cultures of *E. purpurea* have also been shown previously to have immunological activity in-vitro (Wagner et al 1988). In another series of in-vitro experiments, *E. purpurea* induced macrophage activation (as assessed by TNF-α production) following simulated digestion (incubation of echinacea with gastric fluid) in an attempt to mimic effects following oral administration (Rininger et al 2000). Other work has demonstrated that *E. purpurea* dry root powder (containing 1.5% total polyphenols, calculated as chlorogenic acid) increased the

resistance of splenic lymphocytes to apoptosis; splenic lymphocytes were obtained from mice administered the echinacea preparation orally at dosages of 30 or 100 mg kg^{-1} daily for 14 days (Di Carlo et al 2003).

In an in-vitro study, peripheral blood mononuclear cells from healthy individuals and from patients with chronic fatigue syndrome and AIDS incubated with increasing concentrations of extracts of *E. purpurea* led to enhanced natural-killer function of peripheral blood mononuclear cells (See et al 1997). In-vivo, oral administration of *E. purpurea* root extract has been reported to increase numbers of natural-killer cells in normal (Sun et al 1999), leukaemic (Currier & Miller 2001) and aging mice (Currier & Miller 2000).

A subsequent in-vivo study, conducted using a rigorous randomized, double-blind design, assessed the effects of an echinacea product (Nature's Resource; CVS Pharmacy, USA; capsules containing echinacea aerial parts 1.05 g and cichoric acid 10.5 mg) in 16 aging male rats (Cundell et al 2003). Animals received echinacea (species and method of preparation were not stated, although as aerial parts were used, the species may have been *E. purpurea*) 50 mg kg^{-1} bodyweight (equivalent to cichoric acid 0.5 mg kg^{-1}) or placebo orally as a bolus dose in peanut butter each morning for 8 weeks. Mean circulating total white cell counts were significantly higher in echinacea-treated rats than in the control group for the first 2 weeks ($P < 0.05$), although baseline counts for the two groups and a precise P value or confidence intervals (CI) were not given in a report of the study, and concentrations of IL-2 were significantly higher in echinacea-treated rats compared with the control group for the last 5 weeks of the study ($P < 0.05$). Differential white cell counts were significantly altered throughout the 8-week study period in the echinacea group compared with the control group: proportions of lymphocytes and monocytes increased while those of neutrophils and eosinophils decreased with echinacea compared with placebo (Cundell et al 2003). There were no changes in the phagocytic activity of circulating leucocytes, as assessed by ability to ingest latex particles, in either group during the study. Other in-vivo (rats) studies have shown that administration of water–ethanol extracts (100 μL twice daily by oral gavage for 4 days) of *E. purpurea* roots and aerial parts containing defined concentrations of cichoric acid, polysaccharides and alkamides stimulated phagocytic activity of macrophages: activity was increased with increasing concentrations of the three components (Goel et al 2002b). Subsequently, an increase in lipopolysaccharide-stimulated nitric oxide release was observed by macrophages obtained from the spleens of rats previously treated with the echinacea extracts. A similar set of experiments demonstrated stimulation of alveolar macrophage function by alkamides administered to healthy rats (Goel et al 2002a).

A proprietary preparation containing *E. purpurea* root extract and liquorice (*Glycyrrhiza glabra*) root extract stimulated phagocytosis in-vitro and in-vivo, as demonstrated by the carbon-clearance test, following oral administration to mice (Wagner & Jurcic 2002). The combination product produced a greater immunostimulatory effect in this test than did either extract tested alone. Another combination preparation, comprising aqueousethanol extracts of *E. purpurea* and *E. pallida* root, *Baptisia tinctoria* root and *Thuja occidentalis* herb, administered orally via the diet or drinking water to mice for 7 days enhanced the antibody response to sheep red blood cells (Bodinet & Freudenstein 1999).

In contrast with the extensive body of research supporting the immunostimulatory effects of echinacea preparations, some recent work has reported a lack of effect. No evidence of natural-killer cell activity or antibody formation was found in studies involving rats fed various preparations of echinacea, including an alcoholic extract of *E. purpurea* root and an alcoholic extract of the roots of *E. angustifolia*, *E. purpurea* and *E. pallida*, in their diet (South & Exon 2001).

A new study has described a concentration-dependent and cell-type specific de-novo synthesis of TNF-α mRNA in primary human CD14+ monocytes/macrophages in-vitro for an *E. purpurea* extract (Echinaforce; Bioforce) (Gertsch et al 2004). The alkamide constituents appeared to be responsible for this effect, at least in part, mediated via the cyclic AMP and other pathways, and involving activation of NF-κB. Further experiments using these cells and an anti-cannabinoid-2 polyclonal antibody and the cannabinoid-2 antagonist SR-144528 resulted in inhibition of the induction of TNF-α mRNA.

Antiviral activity

Antiviral activity has been described for various different preparations of echinacea following in-vitro studies. An "indirect" antiviral effect was documented in experiments involving addition of glycoprotein-containing fractions obtained from *E. purpurea* root to mouse spleen cell cultures (Bodinet & Beuscher 1991). Interferon-α and -β produced by the cells were then tested for activity against vesicular stomatitis virus. These glycoprotein-containing fractions were also tested directly against herpes simplex virus (HSV) and were reported to reduce the number of plaques by up to 80%, although raw data were lacking and statistical tests do not appear to have been carried out.

In other in-vitro studies, the antiviral activity of an aqueous solution of *E. purpurea* herb was tested using aciclovir-susceptible and aciclovir-resistant strains of HSV-1 and HSV-2 (Thompson 1998). In aciclovir-susceptible strains of HSV-1 and HSV-2, median ED50 (effective dose) values for the echinacea preparation were 1:100 (range 1:25 to 1:400) and 1:200 (range 1:50 to 1:1600), respectively. Similarly, for aciclovir-resistant HSV-1 and HSV-2, median ED50 values (range) were 1:100 (1:50 to 1:400) and 1:200 (1:50 to 1:3200), respectively.

An *n*-hexane extract of *E. purpurea* root, an ethanolic extract of *E. pallida* var *sanguinea* herb and the isolated constituent cichoric acid were the most potent inhibitors of HSV-1 in in-vitro studies designed to assess light-activated antiviral activity (Binns et al 2002b). The minimum inhibitory concentrations for these preparations were 0.12, 0.026 and 0.045 mg mL^{-1}, respectively.

Other in-vitro studies using mouse fibroblasts found that pre-incubation with *E. purpurea* herb juice and

methanolic and aqueous extracts of *E. purpurea* root resulted in resistance to influenza A_2, herpes and vesicular stomatitis virus infection for 24 h (Wacker & Hilbig 1978).

Antifungal and antibacterial activities

Activity against several yeast strains, including *Saccharomyces cerevisiae* and *Candida albicans*, has been described for *n*-hexane extracts of *E. purpurea* roots (Binns et al 2000). Antifungal activity was observed under near UV light irradiation and, in some cases, was also light independent. The pure polyacetylenic compound trideca-1-ene-3,5,7,9,11-pentayne, isolated from *E. purpurea* root extracts, demonstrated marked light-mediated inhibition of growth of *S. cerevisiae* (Binns et al 2000). Anti-candida activity for *E. purpurea* extracts has also been described previously (Barrett 2003). In contrast, *n*-hexane extracts of the fresh roots of *E. pallida* var *pallida* and *E. pallida* var *angustifolia* (identified according to a revised taxonomy after Binns et al 2002a) showed no measurable inhibition of *C. albicans*, but an amphotericin-B-resistant strain (D10) of *C. albicans* and *Tricophyton mentagrophytes* were susceptible to *E. pallida* var *pallida* root extract in the presence of UV light (Merali et al 2003).

Studies in mice have described a dose-dependent protective effect for polysaccharide fractions from *E. purpurea* plant cell cultures against lethal-dose infection with *C. albicans* and *Listeria monocytogenes* when administered intravenously within less than 18 h of the infection dose (Roesler et al 1991b). A similar finding was reported when such polysaccharide fractions were administered to immunosuppressed mice both before and after lethal-dose infection with *C. albicans* and *L. monocytogenes* (Steinmüller et al 1993).

Antibacterial activity against *Escherichia coli*, *Proteus mirabilis*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* has been demonstrated for a multi-herbal preparation containing *E. purpurea* root extract, although it was stated that the observed antibacterial effects were most likely attributable to one of the ingredients, extract of onion (Westendorf 1982).

Anti-inflammatory activity

In-vivo anti-inflammatory activity has been reported for a polysaccharide fraction obtained from *E. angustifolia* roots in the carrageenan-induced rat paw oedema test and in the croton oil mouse ear test, with the polysaccharide fraction administered intravenously and topically, respectively (Tubaro et al 1987). The isolated polysaccharide fraction was twice as active as the total aqueous extract in the carrageenan-induced oedema test, and about half as active as indometacin in the croton oil test. An aqueous extract of *E. angustifolia* roots was also reported to be more effective than benzydamine (a topical non-steroidal anti-inflammatory drug) in the croton oil test (Tragni et al 1985). Further work using fractions of an aqueous extract of *E. angustifolia* roots administered topically to mice in the croton oil test attributed the observed anti-inflammatory activity mainly to intermediate and high molecular weight fractions (Tragni et al 1988).

Oral administration of higher ($100\,mg\,kg^{-1}$) but not lower ($30\,mg\,kg^{-1}$) doses of *E. purpurea* dry root powder (containing 1.5% total polyphenols, calculated as chlorogenic acid) inhibited carrageenan-induced paw oedema in mice; the effect was stated to be similar to that of indometacin $0.25\,mg\,kg^{-1}$ (Mattace Raso et al 2002), although this was not tested statistically. Further exploration suggested that the observed effect may be due to down-regulation of cyclooxygenase-2 expression by the echinacea preparation. In-vitro inhibition of cyclooxygenase-1 and, to a lesser extent, cyclooxygenase-2, has been described for alkamides isolated from *E. purpurea* roots (Clifford et al 2002), and in-vitro inhibition of 5-lipoxygenase and cyclooxygenase (from sheep seminal microsomes) has been reported for polyunsaturated alkamides from *E. angustifolia* roots (Müller-Jakic et al 1994). Inhibition of 5-lipoxygenase has also been described for extracts of roots of *E. purpurea*, *E. pallida* var *pallida* and *E. pallida* var *angustifolia* (identified according to a revised taxonomy after Binns et al 2002a). IC50 (inhibitory concentration) values (μg root mL^{-1} assay volume) were 0.642, 1.08 and 0.444, respectively, and corresponding alkamide concentrations in the root of each species were 0.05%, trace and 0.2%, respectively (Merali et al 2003).

Anti-inflammatory and cicatrizing activities have been reported for gel preparations containing echinacoside 0.4 mg and *E. pallida* root extract 100 mg following studies in rats with experimental skin abrasions and excision wounds (Speroni 2002). These effects were observed 48 and 72 h after topical administration, and were stated to be greater than those observed for *E. purpurea* root extract and the control. However, no statistical analysis was reported.

The wound-healing properties documented for echinacea have been attributed in part to a polysaccharide fraction, which is thought to inhibit the action of hyaluronidase (Busing 1952). Ethanol extracts of *E. purpurea* roots and aerial parts have been reported to inhibit fibroblast-induced collagen contraction, although the significance of this activity for wound healing needs to be investigated (Zoutewelle & van Wijk 1990). Other studies have documented a protective effect for echinacoside, isolated from *E. angustifolia* root, and other caffeoyl esters against free radical induced degradation of collagen, an experimental model for skin damage caused by exposure to UV light (Facino et al 1995).

Other activities

A long-chain alkene from *E. angustifolia* is stated to possess antitumour activity in-vivo, inhibiting the growth of Walker tumours in rats and lymphocytic leukaemia (P388) in mice (Voaden & Jacobson 1972).

In an assay of the mosquitocidal activity of alkamides isolated from dried *E. purpurea* roots, a mixture of dodeca-2*E*,4*E*,8*Z*,10*E*-tetraenoic acid isobutylamide and dodeca-2*E*,4*Z*,8*Z*,10*Z*-tetraenoic acid isobutylamide at a concentration of $100\,\mu g\,mL^{-1}$ achieved 87.5% mortality of *Aedes aegyptii* L. mosquito larvae within 15 min. Several other alkamides assayed also demonstrated

mosquitocidal activity, but required longer incubation periods and were less effective (Clifford et al 2002).

Free radical scavenging activity has been documented for alcoholic extracts of the roots and leaves of *E. purpurea*, *E. angustifolia* and *E. pallida* in-vitro (Sloley et al 2001).

Dodeca-2*E*,4*E*,8*Z*,10*E*/*Z*-tetraenoic acid isobutylamides found in *Echinacea* species (but isolated in this experiment from *E. atrorubens* root) were transported across Caco-2 monolayers, an in-vitro model for the intestinal epithelial barrier, over a 6-h period (Jager et al 2002). Transport kinetics did not differ significantly following modification of the model (by pre-incubation of Caco-2 cells with lipopolysaccharide and phorbol 12-myristate-13-acetate) to mimic inflammation. A similar study explored the transport of 12 alkamides and five caffeic acid conjugates from a proprietary preparation of echinacea (Echinacea Premium Liquid; MediHerb, Australia), which contains a 60% ethanol-water extract of *E. angustifolia* root (200 mg mL^{-1}) and *E. purpurea* root (300 mg mL^{-1}) (Matthias et al 2004a). Almost all of the caffeic acid conjugates permeated poorly through the Caco-2 monolayers: their uptake was no better than that of control (mannitol, which is poorly absorbed); only cinnamic acid diffused readily (apparent permeability coefficient = 1×10^{-4} cm s^{-1}). By contrast, both 2,4-diene and 2-ene alkamides readily diffused through the monolayers, although apparent permeability coefficient values varied (range 3×10^{-6} to 3×10^{-4} cm s^{-1}) depending on structure. Saturated compounds and those with N-terminal methylation had lower permeability coefficients. These findings suggest that alkamides, but not caffeic acid conjugates, are likely to cross the intestinal barrier and thus be bioavailable following oral administration (Matthias et al 2004a).

Clinical studies

Pharmacokinetics

There are only limited data on the clinical pharmacokinetics of echinacea preparations (see also Pharmacology: Other activities; Contraindications, warnings: Interactions). One study reported that dodeca-2*E*,4*E*,8*Z*,10*E*/*Z*-tetraenoic acid isobutylamide (alkamides) was detectable in blood 1 h after oral administration of 65 mL of a concentrated ethanolic extract of *E. purpurea* herb (containing 4.3 mg isobutylamides) on an empty stomach to a single healthy volunteer (Dietz et al 2001). In a study involving nine healthy volunteers who ingested four Echinacea Premium tablets (MediHerb, Australia; each tablet contains *E. angustifolia* root extract 150 mg, containing 2.0 mg alkamides, and *E. purpurea* root extract 112.5 mg, containing 2.1 mg alkamides) after a high-fat breakfast, alkamides were detected in plasma obtained from blood samples taken 20 min after ingestion and some alkamides were detectable for 12 h after echinacea ingestion (Matthias et al 2004c). The mean (s.e.m.) maximum plasma concentration (C_{max}) for total alkamides was 336 (131), time to C_{max} was 2.3 (0.5) h and the area under the plasma concentration–time curve was 714 (181) μg equivalent h^{-1} L^{-1}. Most alkamides found in echinacea were detected in plasma. In contrast, caffeic acid conjugates could not be detected and therefore were reported not to be bioavailable (Matthias et al 2004c).

In a randomized, open, crossover study, in which 11 healthy volunteers received a single oral dose of 2.5 mL of a 60% ethanolic extract of *E. angustifolia* roots (containing 2.0 mg tetraene per 2.5 mL) in the morning following an overnight fast, C_{max} for tetraene (a polyene) was reported to be approximately 11 ng mL^{-1} (Wölkart et al 2004).

Therapeutic effects

Clinical trials of preparations containing echinacea have focused on testing effects in preventing and treating the common cold and other URTIs; some preliminary studies have explored the effects of echinacea in other infections, such as genital herpes, and as an adjunctive treatment in cancer chemotherapy. The rationale for the use of echinacea in these conditions is based on its immunomodulatory activity. Collectively, the findings of studies of echinacea are difficult to interpret as studies have assessed preparations containing different species of echinacea and/or different plant parts of echinacea, administered as monopreparations or in combination with other herbal ingredients, and products manufactured by different processes and with different dosage forms. Hence, the different preparations tested will vary quantitatively and qualitatively in their chemical composition (i.e. will contain different profiles and concentrations of chemical constituents).

Dosage regimens. Echinacea preparations (i.e. containing different *Echinacea* species and plant parts) and, therefore, dosage regimens tested in clinical trials have varied widely (Table 2). Trials of echinacea preparations for the prevention of URTIs have typically involved administration over an 8- or 12-week period; trials of echinacea preparations for the treatment of URTIs typically involve administration of the study medication for 6 to 10 days. Dosages given in older and more modern standard herbal reference texts are given in Table 3.

Immunomodulatory activity. One of the first systematic reviews of studies of echinacea-containing preparations assessed evidence of their immunomodulatory effects (Melchart et al 1994). The review included 26 controlled clinical trials, of which six investigated the treatment of URTIs and influenza-like syndromes, seven explored the treatment of other infections, such as sinusitis, bronchitis and candida, six studied the prophylaxis of URTIs and influenza-like syndromes, four tested the reduction by echinacea of adverse effects of antineoplastic treatment, and three explored the effects on immunological parameters in patients with infections or malignancies (Melchart et al 1994).

Most studies reported that echinacea-containing preparations were superior to placebo in the indications tested. However, trials included in the review tested different species, parts and preparations (e.g. pressed juice, extract) of echinacea administered via different routes

Table 2 Summary of recent placebo-controlled trials of echinacea preparations in (A) the prevention of the common cold and other upper respiratory tract infections (URTIs), and (B) the treatment of the common cold and other URTIs

Reference	Study design	Participants; n	Treatment group(s) regimen; n (ITT analysis)	Control group; n (ITT analysis)	Primary outcome measure(s)	Results (primary outcome measure)
A						
Melchart et al (1998)	R, DB, PC	Healthy adults from military/industrial organizations in Germany; n = 302 enrolled, n = 289 ITT analysis	Ethanolic extract (DER 1:11 in 30% alcohol) of Ep root (n = 99) or Ea root (n = 100); 50 drops bd on 5 days per week for 12 weeks	Placebo (coloured ethanolic solution); n = 90	Time to first URTI	No statistically significant difference between groups: mean time (95% CI) in days to first URTI 69 (64–74), 66 (61–72) and 65 (59–70) for Ep, Ea and placebo, respectively; $P = 0.49$
Grimm & Müller (1999)	R, DB, PC	Adults from a large general practice in Germany who had > three colds/URTIs in the previous year; n = 109 enrolled, n = 108 treated, ITT analysis	Fluid extract of Ep herb 4 mL bd for 8 weeks; n = 55	Placebo (coloured ethanolic solution); n = 54	Investigator assessed incidence, severity of colds/URTI	No statistically significant differences between groups: mean number colds/URTI per subject 0.78 and 0.93 for Ep and placebo, respectively (difference = 0.15; 95% CI −0.12, 0.41, $P = 0.33$); severity of infections ($P = 0.15$)
Turner et al (2000)	DB, PC	Healthy adults from university community in USA; n = 117 enrolled, n = 92 treated, analysed	Echinacea (0.16% cichoric acid; species, plant part not stated) 300 mg tds for 14 days before rhinovirus challenge and for 5 days after; n = 50	Placebo; n = 42	Incidence of colds	No statistically significant differences between groups: proportions with rhinovirus infection = 44% and 57% for E and placebo, respectively ($P = 0.3$); proportions with clinical colds = 50% and 59% for E and placebo, respectively ($P = 0.77$)

(cont.)

Table 2 *(Cont.)*

Reference	Study design	Participants; n	Treatment group(s) regimen; n (ITT analysis)	Control group; n (ITT analysis)	Primary outcome measure(s)	Results (primary outcome measure)
Sperber et al (2004)	R, DB, PC	Healthy adults; n = 48 enrolled	Pressed juice of aerial parts of Ep in 22% alcohol, 2.5 mL tds for 7 days before rhinovirus inoculation and for 7 days afterwards; n = 24	Placebo; n = 24	Frequency of rhinovirus infection as assessed by laboratory evidence; incidence of colds	No statistically significant differences between groups: proportions (95% CI) with laboratory evidence of rhinovirus infection = 92% (73–99) and 96% (77–100) for Ep and placebo, respectively (*P* value not reported); proportions (95% CI) with clinical colds = 58 (37–78) and 82 (60–94) for Ep and placebo, respectively ($P = 0.114$)
Cohen et al (2004)	R, DB, PC	Children aged 1 to 5 years; n = 430 enrolled, n = 328 efficacy analysis	Combination preparation containing extracts of aerial parts of Ep and roots of Ea, 5 mL (7.5 mL for 4 to 5 year olds) bd for 12 weeks; n = 160	Placebo; n = 168	Several stated, including total number of episodes of illness, mean number of episodes per child, proportion of children with one or more episodes of illness	Total number of episodes of illness, mean number of episodes per child, proportion of children with one or more episodes of illness were significantly lower (reductions of 55%, 50% and 43%, respectively) in the Ep/Ea group compared with the placebo group ($P < 0.001$)
B						
Barrett et al (2002)	R, DB, PC	University students in USA with colds of recent onset; n = 148 enrolled, n = 142 analysed (no post-enrollment data available for 6 participants)	Capsules containing dried Ea root 123 mg, Ep root 62 mg and Ep herb 62 mg plus flavourings, 4 Capsules 6 times during first 24 hours of cold onset, then 4 capsules tds until symptoms resolved (max 10 days); n = 69	Placebo (alfalfa 333 mg); n = 73	Self-reported duration, severity of colds	No statistically significant differences between groups: difference (95% CI) in duration = −0.52 days (−1.09 to 0.22); global severity (numerical data not shown)

Brinkeborn et al (1999)	R, DB, PC	Healthy adults 'prone' to common cold in Sweden; n = 559 enrolled, n = 246 who took study medication ITT analysis	Tablets containing crude extract of: (a) Ep 6.78 mg herb (95%), root (5%), n = 55; (b) Ep 48.27 mg herb (95%), root (5%), n = 64; (c) Ep 29.6 mg root (100%), n = 63; 2 tablets tds at cold onset until symptoms resolved (max 7 days)	Placebo; n = 64	Physician-assessed reduction in symptom index	Treatments a and b, but not treatment c, significantly more effective than placebo: mean (95% CI) relative reduction in sympoms = 58.7% (48.7, 68.7), 58.1% (47.7, 69.7), 46.1% (30.1, 62.1) and 33.6% (16.6, 50.6), for a, b, c and placebo, respectively ($P = 0.045$, 0.027 and 0.133 for a, b and c versus placebo, respectively)
Schulten et al (2001)	R, DB, PC	Adults with symptoms of a cold in Germany; n = 80 enrolled and analysed	EC31J0 (pressed juice of Ep herb) 5 mL bd for 10 days; n = 41	Placebo; n = 39	Duration of illness (full picture of common cold based on self-reported symptoms)	Duration significantly shorter in E group compared with placebo group (6 and 9 days, respectively; $P = 0.0112$)
Lindenmuth & Lindenmuth (2000)	QR, DB, PC	Adults with cold onset employed at nursing home in USA; n = 95	Tea comprising Ep and Ea herb and extract of Ep root (equivalent to 1275 mg dried herb and root per tea-bag); five to six cups of tea on Day 1, titrating down to one cup per day over the next 5 days; n = 48	Placebo: herbal tea containing seven herbal ingredients, including peppermint leaf and ginger rhizome; n = 47	No primary outcome stated; measures included self-reported symptoms and duration	Self-reported mean (s.d.) "effectiveness score" significantly higher for E compared with placebo (4.125 (0.959) and 2.787 (0.954), respectively; $P < 0.001$) but self-reported mean duration of symptoms significantly longer (4.33 (0.930) and 2.34 (1.09), respectively; $P < 0.001$)
Taylor (2003)	R, DB, PC	Children aged 2 to 11 years; n = 524 enrolled	Dried pressed juice of the aerial parts of Ep in syrup; n = 263	Placebo; n = 261	Duration and severity of symptoms	No statistically significant differences between groups for duration and severity of symptoms ($P = 0.89$ and 0.69, respectively)

(cont.)

Table 2 *(Cont.)*

Reference	Study design	Participants; n	Treatment group(s) regimen; n (ITT analysis)	Control group; n (ITT analysis)	Primary outcome measure(s)	Results (primary outcome measure)
Goel et al (2004)	R, DB, PC	Adults with history of colds in Canada; n = 282, of whom 128 contracted a cold	Echinilin (standardized Ep extract) 10 × 4 mL on Day 1 then 4 × 4 mL for the next 6 days; n = 59	Placebo; n = 69	Change in total daily symptom scores for the 7-day treatment period, duration of symptoms	Mean total daily symptom scores were significantly lower for E recipients, compared with placebo recipients ($P < 0.05$) but there was no statistically significant difference in duration of symptoms, according to ITT analysis (n = 128) ($P > 0.05$ for all symptoms)
Yale & Liu (2004)	R, DB, PC	Adults within 24 h of first symptoms of a cold in USA; n = 128	Capsules containing 100 mg freeze-dried pressed juice of Ep; one capsule tds until symptoms resolved or maximum of 14 days	Placebo	Modified Jackson method for severity of symptoms, time to resolution of symptoms	No statistically significant differences between groups for total symptom scores, mean individual symptom scores and duration of symptoms (P range 0.29 to 0.90; 0.09 to 0.93; $P = 0.73$, respectively)

DB, double-blind; bd, twice daily; DER, drug/extract ratio; E, Echinacea; Ep, *Echinacea purpurea*; Ea, *E. angustifolia*; ITT, intention-to-treat; QR, quasi-randomized; R, randomized; PC, placebo-controlled; tds, three times daily.

Table 3 Adult dosages for oral administration of *Echinacea* preparations provided in herbal reference texts

Older texts (British Herbal Medicine Association 1990; Bradley 1992)
Echinacea angustifolia root and/or *Echinacea pallida* root for various indications, including chronic viral and bacterial infections, skin complaints, prophylaxis of colds and influenza, mild septicaemia, furunculosis, nasopharyngeal catarrh, pyorrhoea and tonsillitis
Dried root/rhizome:1g by infusion or decoction three times daily
Liquid extract: 0.5–1.0 mL (1:5 in 45% alcohol) three times daily, or 0.25–1.0 mL (1:1 in 45% alcohol) three times daily
Tincture: 2–5 mL (1:5 in 45% alcohol) three times daily, or 1–2 mL (1:5 in 45% alcohol) three times daily
Modern texts (Blumenthal et al 1998; European Scientific Co-operative on Phytotherapy 2003)
As adjuvant therapy and for prophylaxis of recurrent infections of the upper respiratory tract (common colds); treatment should not exceed 8 weeks' duration
Echinacea pallida root: hydroethanolic extract corresponding to 900 mg crude drug daily, e.g. tincture (1:5 in 50% ethanol by volume) from dry extract (7–11:1 in 50% ethanol)
Echinacea purpurea herb: 6–9 mL expressed juice daily
Echinacea purpurea root: 3×60 drops of tincture (1:5 in 55% ethanol), equivalent to 3×300 mg crude drug daily
Echinacea angustifolia root: 1–3 g daily

(including oral and parenteral) and with different dosage regimens. In addition, many studies were of poor methodological quality (only eight achieved more than 50% of the maximum score in an assessment of quality), several preparations tested included other herbs in addition to echinacea, and the review included trials involving patients with a range of conditions. Evidence for the immunomodulatory activity of echinacea from this review can therefore only be considered tentative at best.

The same research group carried out another systematic review of five of its randomized, placebo-controlled studies (four were also conducted double-blind) that investigated the immunomodulatory activity of preparations of echinacea in healthy volunteers (Melchart et al 1995). Again, there were marked differences between the preparations tested in the studies included in the review: combination homoeopathic preparations containing *E. angustifolia* at potencies of D1 and D4 (which can be considered to contain reasonable quantities of starting material) for intravenous administration; ethanolic extracts of *E. purpurea* root and *E. pallida* root for oral administration; ethanolic extract of 95% *E. purpurea* herb and 5% *E. purpurea* root. In two of the five studies, phagocytic activity of polymorphonuclear neutrophil granulocytes (the primary outcome measure) was significantly increased in the echinacea groups compared with the placebo groups, although no such effects were noted in the other studies.

Recent studies investigating the immunomodulatory activity of *Echinacea* species administered to healthy volunteers have reported different findings. In a randomized, double-blind, placebo-controlled trial, volunteers who received extracts of *E. purpurea* and *E. angustifolia* with or without the addition of an arabinogalactan extracted from *Larix occidentalis* (larch) for 4 weeks were found to have increased concentrations of complement properdin (thought to be an indication of immune system stimulation) compared with a placebo group (Kim et al 2002). Other small placebo-controlled studies have reported stimulatory effects following 28 days of oral pre-treatment with pressed juice of *E. purpurea* on the exercise-induced immune response in athletes (Berg et al 1998), and of administration of purified polysaccharides from cell cultures of *E. purpurea* to healthy volunteers (Roesler et al 1991a). 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 2 weeks did not enhance phagocytic activity of polymorphonuclear leucocytes or monocytes, or affect TNF-α and IL-1 production (Schwarz et al 2002).

Preliminary studies have assessed the effects of a combination preparation containing extracts of *E. angustifolia*, *Eupatorium perfoliatum* (boneset) and *T. occidentalis* (thuja) on cytokine production in patients who have undergone curative surgery for various solid malignant tumours (Elsässer-Beile et al 1996), and the immunostimulatory effects of a regimen comprising intramuscular *E. purpurea* extract, low-dose intramuscular cyclophosphamide and intravenous thymostimulin in patients with advanced colorectal cancer (Lersch et al 1992). In another study, the effects of a polysaccharide fraction of *E. purpurea* herb obtained from cell cultures in reducing the adverse effects of cancer chemotherapy were explored in patients with advanced gastric cancer receiving palliative therapy with etoposide, leucovorin and 5-fluorouracil (Melchart et al 2002). Although these studies reported some positive findings with echinacea, no firm conclusions can be drawn because of the nature of the study designs and, therefore, further research in this area is required.

URTIs. Numerous studies have explored the effects of echinacea preparations in preventing or treating the common cold and other URTIs. Overall, several, but not all, studies have reported beneficial effects for certain echinacea preparations, compared with placebo, for the prevention and treatment of URTIs. However, for the reasons given above (see Therapeutic effects), current consensus is that there is insufficient evidence to recommend any specific echinacea preparations or to advise on optimal dose and treatment duration.

Prophylaxis. A Cochrane systematic review included 16 randomized and quasi-randomized controlled trials

(involving a total of almost 3400 participants) of extracts of echinacea for preventing (n = 8) or treating (n = 8) URTIs (Melchart et al 2004). The eight "prevention" trials comprised five that were placebo-controlled (n = 1272 participants) and largely considered to be of adequate methodological quality, and three (n = 1139 participants) in which the control group received no treatment. The five placebo-controlled trials tested combination echinacea preparations (n = 2) or monopreparations of *E. purpurea* herb or root, or *E. angustifolia* root (n = 3), administered orally typically for 8 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% CI: 0.45, 0.22–0.92 and 0.27, 0.11–0.66). One of these studies also found that in participants who did acquire infections, the duration was significantly shorter in those who had received echinacea compared with placebo recipients, although two other studies reported no difference in this outcome.

The three other "prevention" trials all involved children and compared a combination preparation containing extracts of *E. angustifolia* and *E. pallida* root, *B. tinctoria* root and *T. occidentalis* herb, as well as several homoeopathic dilutions, with no treatment. All three studies reported that the frequency of infection was significantly lower in the treatment group compared with the no treatment group (pooled odds ratio 0.36; 95% CI 0.28–0.46), although the methodological quality of all three studies was considered inadequate (Melchart et al 2004).

Several new trials of echinacea preparations in the prevention of the common cold have been completed since the Cochrane review, but most have not shown beneficial effects for echinacea preparations compared with placebo on main outcome measures (Melchart et al 1998; Grimm & Müller 1999; Turner et al 2000; Cohen et al 2004; Sperber et al 2004).

A randomized, double-blind, placebo-controlled trial involved 302 healthy adult volunteers, recruited from military institutions and an industrial plant, who received an ethanolic extract of *E. purpurea* root or *E. angustifolia* root (drug/extract ratio 1:11 in 30% alcohol), or placebo, 50 drops twice daily on 5 days per week (Monday to Friday) for 12 weeks (Melchart et al 1998). In an intention-to-treat analysis (n = 289), the proportion of participants who experienced at least one URTI was 32% (95% CI 23–41%) for *E. angustifolia* recipients, 29% (95% CI 20–38%) for *E. purpurea* recipients, and 37% (95% CI 27–47%) for placebo recipients; 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 ($P = 0.29$), although it is possible that the study was not large enough to detect differences. However, a greater proportion of echinacea recipients believed they had benefited from the study medication than did placebo recipients (78%, 70% and 56% for *E. angustifolia*, *E. purpurea* and placebo, respectively; $P = 0.04$) (Melchart et al 1998).

In another randomized, double-blind, placebo-controlled trial, involving 109 individuals who had experienced more than three colds or respiratory infections in the previous year, a fluid extract of *E. purpurea* prepared from the aerial parts of fresh flowering plants, administered at a dose of 4 mL twice daily for 8 weeks, had no statistically significant effect compared with placebo on the incidence of colds and URTIs (the rate ratio for number of participants in each group with at least one cold or URTI was 0.88, 95% CI 0.60–1.22) (Grimm & Müller 1999). Similarly, there was no statistically significant difference between groups in the duration and severity of occurring colds or URTIs.

Two further studies have tested the effects of echinacea preparations for the prevention of colds due to experimental rhinovirus infection (Turner et al 2000; Sperber et al 2004). In one study, adult volunteers (n = 117 enrolled) with a serum titre of neutralizing antibody to rhinovirus of $\leq$1:4 received echinacea (300 mg) or placebo three times daily for 14 days before and for 5 days after challenge with rhinovirus (n = 92 challenged due to study withdrawals). It is not stated in a report of the study (Turner et al 2000) whether random allocation to study group was undertaken or whether participants were masked (blind) to treatment allocation, although a blinding check before virus challenge found that 30 (60%) of the 50 echinacea recipients and 19 (45%) of the 42 placebo recipients thought they were receiving the "active" treatment ($P = 0.21$).

The study did not provide evidence to suggest that echinacea had effects over those of placebo. Rhinovirus infection occurred in 22 (44%) of echinacea recipients and in 24 (57%) of placebo recipients (rate ratio 0.77; $P = 0.3$), "clinical" colds developed in 50% and 59% of echinacea and placebo recipients, respectively ($P = 0.77$), and there was no difference in mean total symptom scores (11.4, 95% CI 3.9–18.9 and 13.6, 95% CI 7.5–19.7 for echinacea and placebo, respectively). However, the study involved small numbers of participants and a sample size calculation was not reported, hence it is possible that the study was not large enough to be able to detect a difference between the two groups if one existed. Additionally, information on the species of echinacea, plant part used, type of preparation (e.g. extract) and route of administration used was not provided in a report of this study (Turner et al 2000). It was stated that the preparation contained cichoric acid 0.16% and almost no echinacosides or alkamides; with this limited information, it is not possible to say with certainty which species is likely to have been used, although it may have been *E. purpurea*.

In a subsequent study (Sperber et al 2004), a randomized, double-blind trial, 48 healthy adults received a preparation containing the pressed juice of the aerial parts of *E. purpurea* in a 22% alcohol base (EchinaGuard) 2.5 mL three times daily, or placebo, for 7 days before and after inoculation with rhinovirus (RV-39) by intranasal administration in two inocula about 30 min apart (total dose 0.25 mL per nostril). The proportions (95% CI) of participants with laboratory evidence of infection (at least a 4-fold increase in RV-39 neutralizing antibody titre and/or recovery of rhinovirus on viral culture), the primary outcome measure, were 92% (95% CI 73–99) and 96% (95% CI 77–100) for echinacea recipients and placebo recipients, respectively, and with clinical

illness (presence of a cold defined as a 5-day total symptom score of 5 or more and 3 successive days of rhinorrhea or participant's positive self-report of a cold) 58% (95% CI 37–78) and 82% (95% CI 60–94) for the echinacea and placebo groups, respectively ($P = 0.114$). Thus, the results indicate that, in this study, echinacea was no more effective than placebo in preventing rhinovirus infection. However, it is possible that the study did not have sufficient statistical power to detect a difference between the two groups (Sperber et al 2004).

The lack of effect observed in these two studies raises the question as to whether the duration of administration (14 and 7 days in Turner et al 2000 and Sperber et al 2004, respectively) of echinacea before experimental rhinovirus infection was sufficient. On the other hand, the observed lack of effect may simply be because the studies were not large enough to be able to detect a difference between the treatment and placebo groups.

A further "prevention" trial assessed the effects of a combination preparation containing extracts of aerial parts of *E. purpurea* and roots of *E. angustifolia* (Chizukit; Hadas Corporation Limited, Israel) $50\,mg\,mL^{-1}$, propolis $50\,mg\,mL^{-1}$ and vitamin C $10\,mg\,mL^{-1}$ in children (Cohen et al 2004). In this randomized, double-blind study, 430 children, aged 1 to 5 years, received 5 mL of the preparation (7.5 mL for children aged 4 to 5 years), or placebo, twice daily for 12 weeks over a winter period. If a respiratory tract infection occurred, the dosage was increased to four times daily for the duration of the episode. In total, 328 children completed the study. According to an efficacy analysis, the total number of episodes of illness, the mean number of episodes per child and the proportion of children with one or more episodes of illness were all significantly lower in the echinacea group compared with the placebo group (reductions of 55%, 50% and 43%, respectively; $P < 0.001$ for each) (Cohen et al 2004).

The authors' justification for not carrying out an intention-to-treat analysis was that all dropouts occurred in the first week of the trial; however, this decision should have been made a-priori and not because of high dropout rates (Christakis & Lehmann 2004). Other methodological limitations of the study are that baseline data, other than mean age, for the two groups are lacking, so it is not possible to assess the success of randomization, and several, rather than one, primary outcomes were assessed (Christakis & Lehmann 2004). Additionally, there is a lack of detail regarding the preparation studied (e.g. types of extracts, content of active constituents).

Treatment. The Cochrane systematic review described above (see Prophylaxis) included eight randomized, placebo-controlled trials of echinacea preparations for the treatment of URTIs (Melchart et al 2004). These trials tested three different combinations of echinacea extracts and two monopreparations, taken orally typically for 6 to 10 days. Six studies reported statistically significant beneficial effects for echinacea recipients compared with placebo recipients on outcome measures such as duration of illness or symptoms (e.g. running nose). However, heterogeneity of the studies precluded any further summary of the results. In addition, several of the studies had methodological flaws or their methodological quality could not be determined due to a lack of detail about the study designs in published reports. For these reasons, although the majority of the studies described reported positive results for echinacea preparations, it was not possible to recommend any specific product for the treatment of the common cold and further research was considered necessary (Melchart et al 2004).

Several new trials of echinacea preparations in the treatment of URTIs have been completed since the Cochrane review (Table 2B) and have reported conflicting results (Brinkeborn et al 1999; Lindenmuth & Lindenmuth 2000; Schulten et al 2001; Barrett et al 2002; Taylor et al 2003; Goel et al 2004; Spasov et al 2004; Yale & Liu 2004).

The effects of capsules containing 100 mg freeze-dried pressed juice of the aerial parts of *E. purpurea*, standardized for 2.4% β-1,2-D-fructofuranosides, were explored in a randomized, double-blind, placebo-controlled trial involving 128 adults enrolled into the study within 24 h of their first symptoms of a cold (Yale & Liu 2004). Participants ingested one capsule three times daily until symptoms resolved, or for a maximum of 14 days. At the end of the study, there were no statistically significant differences between groups with respect to time to resolution of symptoms, daily self-recorded symptom scores, and frequency of adverse events. It is unclear why the preparation was standardized for content of β-1,2-D-fructofuranosides rather than, for example, alkamides, and why content of other constituents was not reported. Thus, it is difficult to interpret these results in the context of the findings of other studies.

In a larger randomized, double-blind, placebo-controlled trial, 282 adults with a history of two or more colds in the previous year received a standardized preparation of echinacea (Echinilin), or placebo, taken at the start of a cold (10 4-mL doses over Day 1, then four 4-mL doses daily for the next 6 days) (Goel et al 2004). The echinacea preparation contained concentrated water-ethanol extracts of alkamides, cichoric acid and polysaccharides, obtained from various parts (no further details provided) of freshly harvested *E. purpurea* plants, and combined in 40% ethanol to provide concentrations of 0.25, 2.5 and $25.5\,mg\,mL^{-1}$, respectively. At the end of the study, according to an intention-to-treat analysis for the 128 participants who contracted a cold, self-assessed mean total daily symptom scores (the primary efficacy parameter) were significantly lower for echinacea recipients than for placebo recipients (mean total daily symptom scores (95% CI) were 16.3 (13.6–19.0) and 19.9 (17.5–22.5) for the echinacea and placebo groups, respectively; $P < 0.05$).

A report of this study lacks several important details. Numbers of participants initially randomized to the echinacea and placebo groups, and demographic data (e.g. mean age, gender) are not provided for the 282 participants who entered the study, so it is not possible to judge whether the randomization process was successful in

balancing the two groups with respect to these variables. These data are reported for the intention-to-treat analysis, and the placebo group had a markedly higher proportion of females than did the echinacea group (75% vs 54%, respectively). However, it is not possible to establish whether the placebo group originally comprised a greater proportion of females simply by chance through randomization, or whether a markedly greater proportion of women in the placebo group perceived that they contracted a cold. This imbalance, and the implications it may have for the results, has not been considered adequately in the analysis.

A randomized, double-blind, placebo-controlled, community-based trial involving 148 students with common colds of recent onset assessed the effects of capsules containing unrefined *E. purpurea* herb (62 mg), root (62 mg) and *E. angustifolia* root (123 mg) (Barrett et al 2002). Analysis of samples of the preparation by independent laboratories found that they contained cichoric acid and alkamides (0.5 to $< 1.0\%$), and echinoside (sic), chlorogenic acid and caffeoyltartaric acid (all $> 0.1\%$ to $< 0.5\%$). Participants took four capsules six times during the first 24 h of the onset of a cold, followed by four capsules three times daily until symptoms resolved, or for up to 10 days. Among the 142 participants who completed the study, there was no difference in the mean duration of cold symptoms (6.27 and 5.75 days for the echinacea and placebo groups, respectively; difference: −0.52 days, 95% CI −1.09 to 0.22 days), even though the study had an adequate sample size; with a sample size of 150 participants, the study would have had 80% power to detect a benefit of 2 days' duration.

Three different preparations and doses of *E. purpurea* were tested in a randomized, double-blind, placebo-controlled trial in healthy adults (Brinkeborn et al 1999). The four arms of the study were: 6.78 mg *E. purpurea* crude extract, based on 95% herb and 5% root (Echinaforce); 48.27 mg *E. purpurea* crude extract, based on 95% herb and 5% root; 29.60 mg *E. purpurea* crude extract, based on root only; and placebo. In total, 246 participants experienced symptoms typical of the onset of a common cold and took their allocated study medication two tablets three times daily until they felt better, or for up to 7 days. According to an intention-to-treat analysis, the two echinacea extracts prepared from both *E. purpurea* herb and root were significantly more effective than *E. purpurea* root extract and placebo in reducing symptoms as assessed by the investigator (the primary outcome measure); the relative reductions in the mean complaint index for these preparations were 58.7% (95% CI 48.7, 68.7; $P = 0.045$ vs placebo) and 58.1% (95% CI 47.7, 69.7; $P = 0.027$ vs placebo) (Brinkeborn et al 1999).

Statistically significant effects for an extract of *E. purpurea* herb (Echinacin) on median duration of illness were reported in another randomized, double-blind, placebo-controlled trial involving 80 adults who experienced onset of a cold (median duration 6 and 9 days for echinacea and placebo, respectively; $P = 0.0112$) (Schulten et al 2001). Participants started taking their allocated medication on first experiencing symptoms and continued treatment (5 mL twice daily) until symptoms resolved.

A further placebo-controlled study involving adults with early symptoms of a cold ($n = 95$) explored the effects of a combination preparation containing *E. purpurea* and *E. angustifolia* herb and extract of *E. purpurea* root, as well as lemongrass leaf and spearmint leaf as flavourings, formulated as a tea (Lindenmuth & Lindenmuth 2000). When prepared as directed, tea prepared from one bag was stated to provide 31.5 mg of phenolic compounds, calculated as caftaric acid, cichoric acid, chlorogenic acid and echinacoside. The results suggested a statistically significant difference between the treatment and placebo groups in self-rated effectiveness (mean (s.d.) effectiveness score 4.13 (0.96) and 2.78 (0.95) for echinacea tea and placebo, respectively; $P < 0.001$), although the mean (s.d.) duration of symptoms was significantly longer in the echinacea group compared with the placebo group (4.33 (0.93) and 2.34 (1.09) for echinacea tea and placebo, respectively; $P < 0.001$). In addition, the study had several methodological limitations. For example, although stated to be randomized, the study did not involve true randomization (participants were allocated to groups alternately), 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 only.

Two further studies have assessed the effects of echinacea preparations in the treatment of URTIs in children. In a randomized, double-blind, placebo-controlled trial, 524 children, aged 2 to 11 years, received dried pressed juice of the aerial parts of *E. purpurea* (harvested at flowering) combined with syrup, or placebo (syrup only) 3.75 mL (5 mL for 6 to 11 year olds) twice daily during a URTI and until all symptoms had resolved up to a maximum of 10 days (Taylor et al 2003). Data were available for 707 of 759 (94%) URTIs that occurred during the study period; 370 and 337 of these occurred in the placebo and echinacea groups, respectively. A significantly greater proportion of children in the placebo group had more than one URTI when compared with the echinacea group (64.4% vs 52.3% for placebo and echinacea, respectively; $P = 0.015$). There were no statistically significant differences between groups for the primary outcome measures duration ($P = 0.89$) and severity of symptoms ($P = 0.69$), or for secondary outcome measures, including peak severity of symptoms, number of days of peak symptoms and number of days with fever ($P > 0.08$ for all). This study has been criticized because the preparation tested was not analysed to determine its chemical composition (Firenzuoli & Gori 2004). In response, the authors stated that the constituent(s) responsible for the putative clinical effects have not been definitively established (Taylor et al 2004). Although this is indeed the case, it is nevertheless important to describe the chemical composition of the product tested (e.g. its alkamide and polysaccharide content) so that the findings of the study can be considered in the context of other research.

The effects of a preparation containing expressed juice (80 mL/100 mL preparation) from freshly collected flowering *E. purpurea* plants (Immunal; SIA International, Volgograd, Russia) were compared with those of a preparation (SHA-10; Swedish Herbal Institute, Gothenburg, Sweden) containing a standardized extract of *Andrographis paniculata* (5.25 mg andrographolide and deoxyandrographolide per tablet) and extract of *Eleutherococcus senticosus* (9.7 mg per tablet) in a randomized, double-blind, placebo-controlled trial involving 133 children, aged 4 to 11 years, with uncomplicated URTI for whom treatment could begin within 24 h of the onset of symptoms (Spasov et al 2004). The dosage regimens were 10 drops three times daily for the echinacea preparation, and two tablets three times daily for the *A. paniculata* preparation; the duration of treatment was 10 days for both. The interventions were given in addition to standard treatment (warm drinks, throat gargles, nose drops and paracetamol 500 mg three times daily if required), and a control group received standard treatment alone.

At the end of the study, *A. paniculata* recipients had recovered more quickly than had participants in the other two groups ($P < 0.002$), and the amount of nasal secretion was significantly lower in the *A. paniculata* group compared with the echinacea group from Day 5 of the study ($P < 0.01$) (Spasov et al 2004). This study, however, has several methodological flaws: there was no pre-specified primary outcome measure, and a sample size calculation does not appear to have been carried out; the study was reported to be double-blind, although it is not stated that placebo drops and tablets were used; a doctor helped the children with their self-assessment of symptoms, and it is not clear if and how blinding was maintained throughout these interactions; the study was focused on *A. paniculata* and analyses comparing the echinacea and placebo groups were not carried out.

Several trials of echinacea preparations in the prevention of URTIs provide data on duration and severity of infections occurring in participants (see Prophylaxis). Although these data have some relevance to treatment, they should not be grouped together with those from "treatment" trials, since the dosage regimens are entirely different: in "prevention" trials, participants may have received study medication for several weeks or more before experiencing an infection, whereas in "treatment" trials, participants usually start study medication immediately after the onset of symptoms.

Other infections

A randomized, double-blind, placebo-controlled, cross-over trial assessed the effects of an extract of *E. purpurea* herb (95%) and root (5%) (Echinaforce) on the incidence and severity of recurrent genital herpes in 50 patients who had not been exposed to aciclovir or similar medicines within 14 days of enrolment into the study and who had had at least four recurrences of genital herpes within the previous 12 months (Vonau et al 2001). Study medication, or placebo, was taken orally (800 mg) twice daily for 6 months. The study did not show any significant difference between the two groups on the outcomes measured (frequency and duration of recurrences, pain score, CD4 cell count, neutrophil count), although there was a high drop-out rate during the study.

A systematic review of studies exploring the immunomodulatory effects of echinacea-containing preparations included seven controlled clinical trials in infections such as sinusitis, bronchitis and candida (see Immunomodulatory activity) (Melchart et al 1994).

Side-effects, toxicity

Frequency and type of adverse events

Data on numbers of participants experiencing adverse events were provided by several studies included in a Cochrane systematic review of 16 randomized and quasi-randomized controlled trials of extracts of echinacea for preventing or treating URTIs (see Clinical studies) (Melchart et al 2004). Four placebo-controlled "prevention" trials of echinacea reported these data: in three trials, involving a total of around 1000 participants, the frequency of adverse events in the echinacea group was similar to that in the corresponding placebo group, and in one trial, adverse events did not occur in either the echinacea or placebo groups. Three "treatment" trials provided adverse event data: in two studies, adverse events were not observed in either the echinacea or the placebo groups, and, in one study, numbers of patients experiencing adverse events in the echinacea and placebo groups were similar (four and five patients, respectively) (Melchart et al 2004).

New clinical trials published since the Cochrane review also report that there was no statistically significant difference in the frequency of adverse events noted for echinacea and placebo (Melchart et al 1998; Brinkeborn et al 1999; Grimm & Müller 1999; Barrett et al 2002; Taylor et al 2003; Cohen et al 2004), with the exception of one study that reported a significantly higher frequency of rash in the echinacea group compared with the placebo group (7.1% vs 2.7% for echinacea and placebo, respectively; $P = 0.008$) (Taylor et al 2003). Where adverse events were reported, most commonly these were mild gastrointestinal symptoms (Brinkeborn et al 1999; Grimm & Müller 1999; Barrett et al 2002; Taylor et al 2003; Cohen et al 2004; Goel et al 2004). Another review of clinical data, mostly from clinical trials, concluded that oral administration of the expressed juice of *E. purpurea* herb is well tolerated (Parnham 1996). The review included data from an unpublished post-marketing surveillance study involving over 1200 individuals, aged 2 to 20 years, who used oral *E. purpurea* lozenges for 4 to 6 weeks for URTIs, and which indicated that unpleasant taste was the most frequently reported adverse event.

On the basis of these limited data, it seems that the risk of acute adverse effects with echinacea is small. However, it is not possible to draw firm conclusions from these data for several reasons: different echinacea preparations and regimens were tested, different patient populations (adults, children) were involved, and echinacea preparations were administered for only a short time period, particularly in the "treatment" trials (Barnes 2002; Barnes et al 2004). In

addition, since clinical trials usually have the statistical power only to detect common, acute adverse effects and, as there is a lack of data on the safety of the longer-term use of echinacea preparations, there is a need for further evaluation of the safety of different echinacea preparations.

The low number of reports of suspected adverse reactions associated with echinacea preparations set against estimates of the high frequency of use of echinacea has been used as an argument for the safety of echinacea (Barrett 2003). However, this argument is flawed since it fails to consider that under-reporting of suspected adverse reactions associated with herbal medicines is likely at several levels (De Smet et al 1997; Barnes et al 1998) and that, in general, reporting systems for herbal medicines are not well established. The use of sales data to estimate the frequency of an adverse reaction can be misleading and, in addition, the argument takes no account of the differences in preparations of echinacea.

The UK Committee on Safety of Medicines and the Medicines and Healthcare products Regulatory Agency spontaneous reporting scheme (the "yellow card" scheme) for suspected adverse drug reactions received 34 reports describing 64 suspected adverse drug reactions associated with echinacea preparations for the period 1 July 1963 to 1 June 2004 (Table 4) (data from Adverse Drug Reactions On-line Information Tracking (ADROIT) system, Medicines and Healthcare products Regulatory Agency; accessed 1 June 2004). For the majority of these cases, echinacea had been administered orally; details of specific products, species of echinacea, type of extract and other details are not available.

The World Health Organization's Uppsala Monitoring Centre (WHO-UMC; Collaborating Centre for International Drug Monitoring) receives summary reports of suspected adverse drug reactions from national pharmacovigilance centres of over 70 countries worldwide, including the UK. To the end of the year 2004, the WHO-UMC had received a total of 259 reports, describing a total of 537 adverse reactions, for products containing a single species of *Echinacea*. The vast majority of these reports describes reactions associated with *E. purpurea*, most commonly (reaction listed 10 times or more): abdominal pain (n = 10); angioedema (10); dyspnoea (18); nausea (14); pruritus (17); rash (18); rash, erythematous (23); urticaria (23). (These data were obtained from the Vigisearch database held by the WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden. The information is not homogeneous at least with respect to origin or likelihood that the

Table 4 Spontaneous reports of suspected adverse drug reactions associated with echinacea preparations submitted to the UK Committee on Safety of Medicines and the Medicines and Healthcare products Regulatory Agency for the period 1 July 1963 to 1 June 2004 (Adverse Drug Reactions On-line Information Tracking (ADROIT) system; accessed 1 June 2004)

System organ class	Reactions	Total
Blood and lymphatic system disorders	Aplastic anaemia (1), coagulopathy (1), idiopathic thrombocytic purpura (1)	3
Cardiac disorders	Supraventricular tachycardia (1), ventricular arrhythmia NOS (1), palpitations (1)	3
Endocrine disorders	Basedow's disease (1)	1
Eye disorders	Blurred vision (1)	1
Gastrointestinal disorders	Faecal incontinence (1), irritable bowel syndrome (1), dysphagia (1), nausea (1), tongue oedema (1)	5
General disorders and administration site conditions	Rigors (1), drug interaction NOS (3), drug interaction potentiation (1), fatigue (1), malaise (1), feeling abnormal (1)	8
Hepatobiliary disorders	Sclerosing cholangitis (1)	1
Infections and infestations	Parotitis (1)	1
Investigations	Blood pressure increased (1), INR increased (2), liver function test abnormal (1), weight increased (1)	5
Metabolism and nutrition disorders	Hyponatraemia (1)	1
Musculoskeletal and connective tissue disorders	Arthralgia (2), myalgia (1), muscle twitching (1)	4
Nervous system disorders	Central pontine myelinolysis (1), memory impairment (1), ataxia (1), abnormal coordination NOS (1), loss of consciousness (1), burning sensation NOS (1), dysarthria (1), epilepsy NOS (1)	8
Psychiatric disorders	Agitation (1), panic reaction (1), confusional state (2), insomnia (1), sleep disorder NOS (1)	6
Renal and urinary disorders	Pollakiuria (1), urinary incontinence (1), haematuria (1)	3
Respiratory, thoracic and mediastinal disorders	Asthma NOS (1), dyspnoea (1), dry throat (1), pharyngolaryngeal pain (1)	4
Skin and subcutaneous tissue disorders	Face oedema (1), urticaria NOS (3), erythema multiforme (1), erythema (1), pruritus (1), rash NOS (1)	8
Vascular disorders	Flushing (1), hypertension NOS (1).	2
	Total number of reactions	64

INR, international normalized ratio; NOS, not otherwise stated.

pharmaceutical product caused the adverse reaction. Any information included in this report does not represent the opinion of the World Health Organization.)

When interpreting data relating to spontaneous reports, it is important to understand that these reports relate only to suspicions, and that causality has not been established.

Allergic reactions

Echinacea species belong to the Asteraceae (Compositae, daisy) family, members of which are known to cause allergic reactions. Individuals with allergic tendencies, particularly those with known allergy to other members of the Asteraceae family (e.g. chamomile) should be advised to avoid echinacea preparations containing aerial parts (Mills & Bone 2000).

Isolated spontaneous reports of suspected adverse drug reactions associated with the use of echinacea preparations include allergic skin reactions (Parnham 1996) (see also Frequency and type of adverse events). In Australia, detailed assessment of five cases of allergic reactions temporally associated with echinacea (anaphylaxis, 2; acute asthma attack in an echinacea-naive individual, 1; recurrent mild asthma, 1; macropapular rash, 1), three of which reported positive rechallenge, revealed that three patients had positive skin-prick test results for echinacea (Mullins & Heddle 2002). One case report described a 37-year-old woman with atopy who experienced anaphylaxis 30 min after ingesting several dietary supplements (vitamins B_{12} and E, an iron preparation, "folate", vitamin B complex, a multivitamin preparation, zinc, antioxidants, a garlic and onion preparation, evening primrose oil) and 15 min after taking 5 mL of an echinacea preparation, stated to be equivalent to *E. angustifolia* whole plant extract 3825 mg and *E. purpurea* dried root 150 mg (Mullins 1998). The woman took promethazine and was observed in an emergency department for 2 h; her symptoms resolved without further treatment. Two weeks later she gave a positive skin-prick test to the echinacea product, but not to "crude" extracts of the other supplements she had taken. She had been taking echinacea for 2 to 3 years and had previously taken the same product without experiencing any adverse effects. A causal association in this case has been questioned (Myers & Wohlmuth 1998).

Positive skin-prick test results for echinacea were also reported for 20% of 100 echinacea-naive atopic individuals, and over 50% of 26 Australian suspected adverse drug reaction reports of hypersensitivity associated with echinacea involved individuals with atopy (Mullins & Heddle 2002). Echinacea has previously been reported to have produced positive patch test reactions in four individuals with a previous history of plant dermatitis (Mitchell & Rook 1979). These reports raise hypotheses that require testing in formal studies.

An isolated report describes a 41-year-old man who experienced four episodes of erythema nodosum after using an echinacea preparation at each onset of an influenza-like illness (Soon & Crawford 2001). The man had been using echinacea intermittently for 18 months, as well as loratadine on an as required basis and St John's wort for the previous 6 months. Each episode of erythema nodosum responded to conventional treatment, including prednisone. The man was advised to discontinue treatment with echinacea and, after 1 year, had not experienced any further recurrences. However, the report does not provide any details (species, plant part, formulation, dosage regimen) of the echinacea (or the St John's wort) preparation involved and therefore is difficult to interpret. Causality has not been established.

Other reactions

A case of hypokalaemic renal tubular acidosis due to Sjögren's syndrome (a symptom complex of unknown aetiology, marked by keratoconjunctivitis sicca, xerostamia, with or without lacrymal and salivary gland enlargement, respectively, and presence of connective tissue disease, usually rheumatoid arthritis, but sometime systemic lupus erythematosus, scleroderma or polymyositis) has been reported in a 36-year-old woman (Logan & Ahmed 2003). She was stated to have begun taking echinacea, St John's wort and kava 2 weeks before becoming ill, but the report does not provide any further details of the echinacea species contained in the product(s), or of the types of preparations, formulations, dosages and routes of administration of any of the herbal medicines listed. The woman was hospitalized with severe generalized muscle weakness and tests revealed she had a serum potassium ion concentration of 1.3 mEq L^{-1}. She was given electrolyte replacement for 4 days after which the muscle weakness resolved, and was started on hydroxychloroquine 200 mg daily for probable Sjögren's syndrome. The authors suggested that ingestion of echinacea may have aggravated an autoimmune disorder, although rechallenge with echinacea was not undertaken, and causality has not been established (Logan & Ahmed 2003).

Another report describes a 49-year-old woman who presented with a 5-day history of numbness and weakness in her right arm (Schwarz et al 2000). For the previous 7 weeks she had received Echinacea Comp 2 mL mixed with 5 mL of her venous blood intramuscularly twice weekly to prevent infections and "boost" her immune system. The injection was stated to contain *E. angustifolia* D2 1.1 mL, Aconitum D4 0.3 mL and Lachesis (bushmaster snake venom) D8 0.3 mL (D nomenclature relates to a homoeopathic dilution step: D2 is equivalent to a 1 in 100 dilution, whereas D8 is equivalent to a 1 in 100 000 000 dilution; Kayne 1997). The woman was admitted to hospital with mild spastic paresis and fluctuating numbness of the right arm and was described as having acute disseminated encephalomyelitis. Symptoms resolved after treatment with methylprednisolone 500 mg daily by intravenous infusion. Causality has not been established.

There is an isolated report of exacerbation of pre-existing pemphigus vulgaris (a chronic, serious skin disorder characterized by the development of easily ruptured blisters on skin and mucous membranes) in a 55-year-old man who began taking an echinacea product orally after developing a URTI (Lee & Werth 2004). Within a week, he developed blisters on his trunk, head and oral mucosa; partial disease control was achieved after discontinuing the product. It is possible that this exacerbation was part

of the natural course of disease, and causality in this case has not been established. Furthermore, no further details of the product, including species of echinacea, plant part, type of preparation, and dosage were provided, and it is not stated whether a sample of the product was retained. Without verification that the product implicated did contain echinacea material and was free of other ingredients or adulterants, this report adds little to the debate on the safety of use of echinacea by individuals with autoimmune disorders.

Toxicology

In general, animal studies with different preparations and fractions of *Echinacea* species have indicated low toxicity (Barrett 2003). In acute toxicity studies involving polysaccharide fractions from *E. purpurea* administered by intraperitoneal injection to small numbers of mice, the LD50 (lethal dose) for female mice was 2500 mg kg^{-1} (Lenk 1989). Other acute toxicity studies using a preparation comprising pressed juice from *E. purpurea* herb have provided LD50 values in mice of > 30 000 mg kg^{-1} and > 10 000 mg kg^{-1} for oral and intravenous administration, respectively, and in rats of > 15 000 mg kg^{-1} and > 5000 mg kg^{-1} for oral and intravenous administration, respectively (Mengs et al 1991, 2000). Further experiments showed no evidence of mutagenic activity in bacteria and mammalian cells in-vitro and in-vivo in mice (Mengs et al 1991).

High concentrations of *E. purpurea* (8 mg mL^{-1}) have been reported to reduce sperm motility, sperm penetration of hamster oocytes and to be associated with sperm DNA denaturation in-vitro; no such effects were observed with low concentrations (Ondrizek et al 1999a, b). These findings are difficult to interpret since there is a lack of detail regarding the preparation of *E. purpurea* (the study reports simply state that the herbal material was "dissolved" in modified human tubal fluid and then filtered), and their clinical relevance is questionable.

The pyrrolizidine alkaloids isotussilagine and tussilagine have been documented for echinacea, although they possess a saturated pyrrolizidine nucleus and, unlike unsaturated pyrrolizidine alkaloids, are not thought to be toxic.

In-vivo antitumour activity and in-vitro stimulation of TNF-α secretion have been reported for echinacea. In addition to its antitumour effects, TNF is stated to be a mediator of cachexia and the manifestations of endotoxic shock. Concern has been expressed over the possible toxicity of TNF (Parfitt 2002).

Contraindications, warnings

It has been stated that echinacea is contraindicated in patients with progressive systemic diseases such as tuberculosis, leukaemia and leukaemia-like diseases, collagen disorders, multiple sclerosis and other autoimmune diseases (Schulz et al 2000). In the UK, some echinacea product labels also advise against use in AIDS and HIV infections. The basis for these statements appears to be a theoretical one, based on evidence that echinacea preparations have immunomodulatory activity; there is an opposing view that echinacea is not harmful in autoimmune diseases (Mills & Bone 2000). At present, there is a lack of reliable clinical evidence to support these views, although in view of the seriousness of the conditions listed, it is appropriate to avoid use in these disorders until further information is available.

Interactions

There are no reported drug interactions for echinacea, although on the basis of its documented immunomodulatory activity, as a general precaution, echinacea should only be used with caution in patients taking immunosuppressant drugs.

The effects of echinacea products available in Canada on inhibition of the human cytochrome P450 drug metabolizing enzyme CYP3A4 have been tested in-vitro using a fluorometric mitrotitre plate assay (Budzinski et al 2000). In the study, 10-mL samples of preparations of *E. angustifolia* roots, *E. purpurea* roots and herb, and a 1:1 blend of *E. angustifolia* and *E. purpurea* (plant parts not specified) were standardized to contain ethanol 55% and used as stock solutions. Samples of serial dilutions of these preparations, as well as different concentrations of the pure compounds echinacoside and cichoric acid, were assayed. The blend of *E. angustifolia* and *E. purpurea*, and *E. purpurea* herb showed "moderate" inhibition of CYP3A4: median (95% CI) IC50 values (% of full strength preparation) were 6.73 (4.75, 10.09) and 8.56 (5.95, 13.05), respectively. Echinacoside also showed moderate inhibitory activity (median IC50 values (95% CI) 6.29 (2.07, 71.56)), whereas cichoric acid showed low inhibitory activity (Budzinski et al 2000).

A study in mice fed both melatonin and an extract of *E. purpurea* root in their diet reported reduced numbers of proliferating myeloid cells in the spleen and bone marrow (Currier et al 2001). Further research is needed to determine whether these findings are clinically important.

A study involving 12 healthy non-smoking volunteers assessed the effects of *E. purpurea* root (Nature's Bounty, Bohemia, New York, USA) on the activity of the cytochrome P450 enzymes CYP1A2, CYP2C9, CYP2D6 and CYP3A using caffeine, tolbutamide, dextromethorphan and midazolam, respectively, as probe drugs (i.e. substrates for the respective CYP enzymes) (Gorski et al 2004). After a control phase in which volunteers received all of the probe drugs orally (with the exception of midazolam, which was given intravenously and, later, orally), participants took *E. purpurea* root 400 mg four times daily for 8 days; the product was stated to contain more than 1% phenols (caftaric acid, chlorogenic acid, echinacoside and cichoric acid). On the sixth day, the probe drugs were administered and blood and urine samples were collected as during the control phase.

The clearance of caffeine after oral administration was reduced significantly during echinacea administration compared with values obtained during the control phase (mean (s.d.): 6.6 (3.8) L h^{-1} and 4.9 (2.3) L h^{-1} for echinacea and control periods, respectively; $P = 0.049$), although the half-life of caffeine, area under the curve and C_{max} were not significantly altered. Time to maximum concentration was significantly increased for both caffeine and tolbutamide

during echinacea administration compared with baseline values ($P = 0.015$ and 0.004, respectively). Dextromethorphan pharmacokinetics were unaltered during echinacea administration in the 11 participants who were extensive metabolizers. The clearance of midazolam following intravenous, but not oral, administration was significantly increased during echinacea administration compared with baseline values (mean (s.d.): 43 (16) $L\,h^{-1}$ and 32 (7) $L\,h^{-1}$, respectively; $P = 0.003$).

These findings suggest that *E. purpurea* root inhibits CYP1A2, but not CYP2C9 and CYP2D6, and that CYP3A activity is selectively modulated: intestinal CYP3A activity is inhibited and hepatic CYP3A activity is induced. There are several possible explanations for the selective effects of *E. purpurea* root on CYP3A activity: (i) the constituent(s) of echinacea responsible for CYP3A inhibition may not be systemically available, thus avoiding hepatic CYP3A inhibition; (ii) the constituent(s) of echinacea responsible for CYP3A induction may be rapidly absorbed, thus intestinal CYP3A induction is avoided; (iii) hepatic CYP3A may be induced by a systemically formed metabolite of a constituent of echinacea; and (iv) CYP3A induction may involve tissue-specific activators that are differentially influenced by constituents of echinacea (Gorski et al 2004).

In a subsequent, similar study, 12 healthy volunteers received capsules containing a whole plant extract of *E. purpurea* (containing cichoric acid 13.7 mg; chlorogenic acid and echinacoside were not detected by high-performance liquid chromatography analysis) 800 mg twice daily for 28 days. Participants also received three other herbal products (*Citrus aurantium*, *Serenoa serrulata* and *Silybum marianum*), each administered separately for 28 days; the four herbal products were administered in random sequence, with a 30-day washout period between each, until each participant had received all four herbal products. It was stated that there were no statistically significant differences between serum ratios of probe drugs and their respective metabolites obtained before and after administration of *E. purpurea* extract and, therefore, that the extract had no significant effect on CYP1A2, CYP2D6, CYP2E1 or CYP3A4 activities. The authors' conclusions, however, included the caveat that the effects of *E. purpurea* extract on CYP enzyme activity, particularly that of CYP1A2 and CYP3A4, merit further study (Gurley et al 2004).

Pregnancy and lactation

There is a lack of data on the safety of echinacea preparations 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.

A cohort 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 disease (URTI), maternal age and alcohol and cigarette use (Gallo et al 2000). The exposed group of women had telephoned a hospital teratogen information service regarding the use of echinacea during pregnancy; the unexposed group had also telephoned the service for this reason, but subsequently did not use echinacea or used a non-teratogenic antibiotic instead.

There were no statistically significant differences between the two groups in assessed outcomes including number of live births, spontaneous and therapeutic abortions, gestational age, birth weight, and rates of malformations. In the exposed group, there were six major and six minor malformations compared with seven major and seven minor malformations in the control group (Gallo et al 2000). The study has several limitations, particularly the small sample size, meaning that the study would have the statistical power only to detect common malformations, and self-report of exposure, since it is possible that misclassification could have occurred (e.g. exposed women reported as unexposed). In addition, participants used a range of different preparations of echinacea at different dosage regimens, so the study does not provide adequate evidence for any specific preparation. Further study is required to establish the safety profile of echinacea during pregnancy.

Summary and conclusions

The chemistry of echinacea is well documented (see Phytochemistry). The three species are chemically dissimilar. *E. purpurea* and *E. angustifolia* both contain alkamides as their major lipophilic constituents, but of differing structural types. By contrast, the lipophilic fraction of *E. pallida* is characterized by polyacetylenes and contains only very low concentrations, if any, of alkamides. The alkene constituents are stated to be susceptible to auto-oxidation resulting in the formation of artefacts during storage (Wichtl 2004).

Commercial echinacea samples and marketed echinacea products may contain one or more of the three *Echinacea* species mentioned above. Analysis of commercial samples of raw echinacea material and marketed echinacea products has shown that in some cases the echinacea species assigned to the sample or product was incorrect, and that the pharmaceutical quality and labelling of some finished products was inadequate (see Quality of plant material and commercial products). 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.

Evidence from in-vitro and animal studies supports some of the uses for echinacea, particularly the reputed immunostimulant properties (Barrett 2003), although immunostimulant activity has been disputed following one series of studies (see Pharmacology: Immunomodulatory activity) (South & Exon 2001). Reported pharmacological activities have been documented for the alkene and high molecular weight polysaccharide constituents, as well as the alkamides and caffeic acid derivatives.

Several, but not all, clinical trials of echinacea preparations have reported effects superior to those of placebo in the prevention and treatment of URTIs. However,

evidence of efficacy is not definitive as studies have included different patient groups and tested various different preparations and dosage regimens of echinacea (Barnes et al 2004; Melchart et al 2004). As such, there is insufficient evidence to recommend any specific echinacea products, or to advise on optimal dose and treatment duration (see Clinical studies). Further well-designed clinical trials using well-defined, standardized preparations are necessary in order to establish efficacy.

There is a lack of clinical research on the anti-inflammatory and wound-healing properties of echinacea preparations documented in-vitro and in animal studies. Several other areas of interest, related to the immunostimulant effects of echinacea, such as prevention of recurrence of genital herpes and other infections, and reduction of adverse effects associated with antineoplastic treatment, also require further clinical investigation.

Another area that requires further study is whether certain groups of constituents, such as the polysaccharides, are active after oral administration and, if so, what is the mechanism of action since polysaccharides would usually be broken down into simple inactive sugars (Barrett 2003). There is a lack of data on the pharmacokinetics of echinacea preparations. Preliminary studies have reported transportation of isobutylamides across Caco-2 cells, an in-vitro model of intestinal absorption (Jager et al 2002), and detection of alkamides in blood taken from healthy volunteers who had ingested echinacea preparations (Dietz et al 2001; Matthias et al 2004c) (see Clinical studies: Pharmacokinetics).

On the basis of the available (limited) safety data, which come mostly from short-term clinical trials of echinacea preparations for the prevention and treatment of URTIs in otherwise generally healthy individuals, echinacea appears to be well-tolerated. However, firm conclusions cannot be drawn from these limited data, and further investigation is required to establish the safety profile of different echinacea preparations. At present, the main safety issues are the possibility of allergic reactions, and concern about the use of echinacea by patients with progressive systemic diseases, such as tuberculosis, leukaemia, collagen disorders, multiple sclerosis and other autoimmune diseases (see Side-effects, toxicity; Contraindications, warnings). In view of the lack of toxicity data, excessive use of echinacea should be avoided. In placebo-controlled trials of echinacea preparations for the prophylaxis of URTIs, treatment was taken typically for 8 to 12 weeks. As with other herbal medicines, the potential for echinacea preparations to interact with conventional (and other herbal) medicines should be considered. As *E. purpurea* root can inhibit CYP1A2 and selectively modulate CYP3A, echinacea should be used with caution in patients receiving therapeutic agents with a narrow therapeutic range and which are substrates for these CYP enzymes (Gorski et al 2004).

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