Review and Assessment of Medicinal Safety Data of Orally Used *Echinacea* Preparations

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Abstract

Echinacea purpurea, Echinacea angustifoli and *Echinacea pallida* are frequently used as medicinal plants. Besides asking for evidence on their efficacy, there is an increasing interest for safety data. This review systematically presents the available literature on drug interactions, contraindications, adverse events, duration of use, and safety of use in pregnant and nursing women, and assesses the safety profile of corresponding *Echinacea* preparations. It is noteworthy that all safety data reported are as product specific as the pharmacological or efficacy data are. In pharmacokinetic herb-drug interaction studies performed *in vivo*, no significant inhibitions of human CYP2D6 and CYP3A4 isoforms have been found after the administration of standardized *E. purpurea* preparations. However, contradictory results exist in studies using liver microsomes. Adverse events reported during clinical trials following administration of *Echinacea* spp. mono-preparations were generally mild and mostly without causality. Due to published long term studies with continuous ingestion of different *Echinacea* preparations up to 6 month with no reported toxicological concerns, *Echinacea* can be recommended also for long-term use. Moreover, the contraindications in cases of autoimmune diseases and immune-suppression are questionable, since lipophilic *Echinacea* preparations containing alkamides suppress cellular immune responses, and beneficial effects in autoimmunity were reported. The same applies for the use during pregnancy. Although there has been some impact reported on embryonic angiogenesis in mice, no association with an increased risk for major or minor malformations during organogenesis was found in a literature review. Altogether, the different evaluated *Echinacea* preparations are well-tolerated herbal medicines in the management in children and adults alike.

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Introduction

Echinacea purpurea (L.) Moench, *Echinacea angustifolia* DC., and *Echinacea pallida* (Nutt.) Nutt. (Asteraceae) are frequently used as medicinal plants for the prevention and treatment of the common cold, influenza, and upper respiratory tract infection. The aerial parts of *E. purpurea* are used, as well as the whole plant including the roots from all three species. Polysaccharides, glycoproteins, caffeic acid derivatives and alkamides have been considered as the constituents being most relevant for activity [1]. Polysaccharides, glycoproteins and caffeic acid derivatives have been shown to have immunomodulatory effects. However, the question of bioavailability is still not solved. Recent investigations have demonstrated that at least alkamides are detectable in human blood in reasonable concentrations after oral application of *Echinacea* preparations. Alkamides possess a structural similarity with anandamide, an endogenous ligand of cannabinoid receptors, and in fact it was shown that they also bind to cannabinoid receptors and trigger effects on cytokines [2]. Besides asking for evidence on their efficacy, there is an increasing interest for safety of these preparations. Therefore we have systematically reviewed the available literature for evidence on drug interactions, contraindications, adverse events, duration of safe use, and data on safety of use in pregnant and nursing women and have assessed the safety and tolerability profile of corresponding *Echinacea* preparations. Cautions from the Committee on Herbal Medicinal Products (HMPC) [3–7] have been critically evaluated, especially the use in children below 12 years of age, duration of use, contraindications like allergic diathesis or in case of immunosup-

pression and hematologic systemic diseases and special warnings that autoimmune diseases can be triggered. Many of these warnings are based only on the theoretical possibility that the immune-mediated inflammatory mechanism of diseases like autoimmune disease, tuberculosis, multiple sclerosis and human immunodeficiency virus infection, can be exacerbated by the immunostimulatory properties of *Echinacea* [3–8].

Therefore, this review shall help to make evidence based decisions about the advice safe use of *Echinacea* preparations.

Pharmacodynamic interactions

One study in healthy mice reported that a commercially prepared powder extract of the root of *E. purpurea* (0.45 mg/mouse/day) and melatonin (0.0142 mg/mouse/day) administered together, but not alone, had a detrimental effect on the levels of mature granulocytes in both, bone marrow and spleen [9,10]. A potentially positive interaction between *E purpurea* and the anticonvulsant medication phenytoin (Epanutin®, Phenhydan®, Zentropil®, Dilantin®) has been reported in mice. Phenytoin has a documented teratogenic activity. Most notably, phenytoin is known to increase the risk of cleft palate development if taken in pregnancy. Its use in pregnancy has also been reported to be associated with an increased risk of heart malformations. The increased incidence of cleft palate reportedly can be reduced by the stimulation of the maternal immune system. These led researchers to investigate the use of ethanolic (70%) extract of *E. purpurea* dried aerial parts with phenytoin in relationship to the incidence of cleft palate in mice. The incidence of cleft palate with phenytoin alone, phenytoin with the immune modulator levamisole, or phenytoin plus *E. purpurea* extract (360 mg i.p.) was 16%, 5.3% and 3.2%, respectively, showing that both levamisole and *Echinacea* decreased the incidence of cleft palate [11]. It is unknown whether the observed effects have any clinical relevance.

In a recently published clinical study by Abdul et al., the pharmacodynamic and pharmacokinetic interactions of either *Echinacea* (1275 mg four times daily containing a mixture of 600 mg of *E. angustifolia* roots and 675 mg of *E. purpurea* root; standardized to contain 5.75 mg of total alkamides per tablet) or policosanol (10 mg tablet twice daily) with warfarin in healthy subjects have been investigated. The apparent clearance of (S)-warfarin was significantly higher during a concomitant treatment with *Echinacea*, but this did not lead to a clinically significant change in an INR (International Normalised Ratio) measurement. No evidence of any apparent effect of CYP2C9 interaction has been found. Neither *Echinacea* nor policosanol significantly affected warafarin pharmacodynamics, platelet aggregation or baseline clotting status in healthy subjects [12].

Although details of drug administration, species, and type of extract are not stated, it is worth to mention a first report on a possible interaction between *Echinacea* and etoposide, a CYP3A4 substrate [13]. A 61-year-old man newly diagnosed with cell lung cancer began concurrent chemoradiation with cisplatin and etoposide. He was admitted to the hospital on day 8 of his first cycle and found to be thrombocytopenic. His platelet count reached a nadir of 16 × 10(3)/L, requiring platelet transfusion support. Upon admission, it was discovered that he was taking vitamin B12, vitamin E, vitamin D, vitamin C, *Echinacea* (not characterized) and "vitamin B17" (laetrile-apricots kernel), which were discontinued. He received his next cycle of chemotherapy without taking herbal products and vitamins and with the addition of pegfilgrastim. As the patient also stopped taking laetrile and his other vitamins after cycle 1, a potential interaction between laetrile and etoposide or cisplatin cannot be fully excluded. The authors of the report concluded that since the exact preparation of *Echinacea* and corresponding plant extract constituents was unkown, the interaction remains equivocal. However, it has been written that cautions should be exercised in patients receiving chemotherapy including CYP3A4 substrates (antracyclines, etoposide, vinca alcaloids, taxanes) while taking *Echinacea* [3,13].

Pharmacokinetic interactions

The vast majority of reported interactions are of pharmacokinetic nature, resulting in changes in biotransformation of the affected drug through inhibition or induction of drug metabolizing enzymes. A number of *in vitro* and *in vivo* studies suggest a potential for herb-drug interaction between different uncharacterized *Echinacea* extracts and the cytochrome P450 family of drug metabolizing enzymes (CYP 3A4, 2D6, 1 A2 and 2C9) [14–17]. But only the recently published pharmacokinetic drug interaction studies determined the influence of chemically characterized *Echinacea* preparations on CYP3A and CYP2D6, with four conducted in human [18–21] and seven *in vitro* studies [22–27].

In a recently performed clinical study on the activity of human CYP2D6, no significant inhibition was detected after the application of *E. purpurea* softgel capsules (Gaia Herbs, Inc., Brevard, NC, USA, 267 mg extract, three times daily) standardized to contain 2.2 mg alkamides per capsule [18]. Penzak et al. investigated the influence of standardized *E. purpurea* fresh plant liquid extract 8 : 1 (250 mg) softgel capsules with 500 mg (two 250 mg capsules) 3 times/day for 28 days on the pharmacokinetics of lopinavir (400 mg)/ritonavir (100 mg) twice/day and on CYP3A and p-glycoprotein activity by using the probe substrates midazolam (8 mg) and fexofenadine (120 mg) as single doses, respectively. The concentrated extract from freshly harvested *E. purpurea* plants contained standardized amounts of alkamides 0.25 mg/mL, polysaccharides 25.5 mg/mL and cichoric acid 2.5 mg/mL. The 13 volunteers received for 14 days *E. purpurea* in combination with lopinavir-ritonavir and for 14 days *E. purpurea* alone. Neither lopinavir nor ritonavir pharmacokinetics were significantly altered by 14 days of *E. purpurea* co-administration [21]. More recently, interactions between etravirine (a nonnucleoside reverse transcriptase inhibitor of HIV) and darunavir (protease inhibitor) with capsules containing *E. purpurea* root extract at a dosage of 500 mg every 6 h from days 1 to 14 has been investigated in HIV infected patients. Etravirine and darunavir undergo extensive metabolism by the hepatic CYP3A4 isoform. Similar to lopinavir studied by Penzak et al., no significant interaction has been found with darunavir [19]. Also no significant treatment effects were observed for any of the primary pharmacokinetic parameters after administration of etravirine with or without *E. purpurea* [20].

Already in 2007, Raner et al. evaluated the potential of 11 isolated alkamides and a 33% and 95% ethanolic *E. purpurea* root extract to inhibit cytochrome P450 2E1 in human liver microsomes and from an *in vitro* expression system. Extracts of *E. purpurea* root in 95% ethanol (2.0 µL of extract in 500 µL reaction) significantly inhibited the activity (30%) of cytochrome P450 2E1 in human liver microsomes. No inhibition was seen when 2 µL of the 33% ethanolic extract of the *E. purpurea* roots was used in a 500 µL reaction using human liver microsomes or expressed P450. The alkamides present in *E. purpurea* root preparations (undeca-2*E*/*Z*,4*E*-diene-8,10-diynoic acid isobutylamides and dodeca-2*E*,4*E*,8*Z*,10*E*/*Z*-tetraenoic acid isobutylamides) showed significant inhibition at concentrations as low as 25 µM, which corresponds to

roughly 6 µg/mL, whereas the caffeic acid derivatives had no effect [27]. Compared to the measured plasma levels in humans (~ 10 ng/mL) the concentration needed for *in vitro* CYP450 2E1 inhibition was about 600 times higher and therefore the relevance of these results for the *in vivo*-situation is questionable.

A standardized *E. purpurea* preparation (Echinaforce®) induced mild inhibition of CYP isoforms, with CYP3A4 being the most, and CYP2D6 the least sensitive enzyme. In further studies, the *Echinacea* alkamides were suspected to be responsible for CYP3A4 inhibitory activity [24]. In a more recent approach, a detailed analysis of six commercial *Echinacea* liquid preparations with emphasis on the metabolomics characterisation of the *Echinacea* compounds responsible for inhibiting CYP3A4 has been reported by Modarai et al. 2010. The used preparations were a pressed juice from the aerial parts of *E. purpurea* (Madaus AG), a tincture from the roots of *E. pallida* (Salus), and three different tinctures from *E. purpurea* (with 22% ethanol from Viridian, with 65% ethanol from Holland & Barrett, Echinagold® with 50% ethanol from a Health Food Shop in Denmark), and a herb/root preparation from *E. purpurea* (Echinaforce®, Bioforce). After the separation of each preparation into their ethanol and water-soluble components, the results directly confirmed the role of alkamides in the inhibition of CYP3A4. Levels of the alkamides (dodeca-2*E*,4*E*,8*Z*,10*E*/*Z*-tetraenoic acid isobutylamides and undeca-2*E*,4*E*/*Z*-diene-8,10-diynoic acid isobutylamides) correlated well with CYP3A4 inhibition [25]. Due to variable and conflicting results in CYP3A4 inhibition between laboratories, it is now suggested to use multiple CYP3A4 probes in the assessment of CYP3A4 interaction potentials. Hansen and colleagues compared the CYP3A4 inhibition profiles of *E. purpurea* (Echinagard®, with final concentrations between 0.24–6360 µg/mL) measured by three different CYP3A4 substrates and different methodologies. Testosterone metabolism showed a much lower CYP3A4 inhibition (IC_{50} 5394 µg/mL) compared to the fluorescent substrates BFC (7-benzyloxy-trifluoromethylcoumarin) and BQ (7-benzyloxyquinoline) (IC_{50} 354 and 452 µg/mL, respectively). The choice of substrate might thus be essential for the evaluation of the inhibition of CYP3A4 metabolism for some herbs when performing *in vitro* studies. The previously described inhibition potential of *E. purpurea* towards CYP3A4-mediated metabolism was confirmed by the use of three different substrates [28]. Aside from direct enzymatic inhibition also the transcriptional activity can be altered by different herbal medicinal products (e.g. induction or inhibition of CYP expression). Hellum and colleagues found that a commercial pressed juice from the aerial parts of *E. purpurea* (Echinagard® – Madaus AG) moderately suppressed CYP3A4 expression in primary human hepatocytes [22]. In addition, Gorski et al. found that an 8-day course of 400 mg of *E. purpurea* root preparation administered 4 times daily could cause an induction of CYP3A4 in intestinal cells, but suppressed hepatic CYP3A4 expression. However, the bioavailability of midazolam, a CYP3A4 substrate, increased by the same amount, leading to no overall change in AUC [15]. Kortenkamp et al. (2011) carried out an analysis of the CYP3A4 induction in human hepatocellular carcinoma HepG2 cells by an *E. purpurea* herb and root preparation (Echinaforce®, Bioforce), using real-time reverse transcription polymerase chain reaction (RT-PCR) to determine steady-state mRNA levels. HepG2 cells were exposed for 96 h to clinically relevant concentrations of the *E. purpurea* preparation (22, 11.6 and 1.16 µg/mL), or of four *Echinacea* alkamides (1.62 and 44 nM). Neither Echinaforce® nor the pure alkamides produced any significant change in the steady-state CYP3A4 mRNA levels [29]. A further study on the rat cytochrome P450 expression level has been carried out only recently by Mrozikiewicz and colleagues. The potential influence of a standardized *E. purpurea* 60% ethanolic extract of the aerial parts containing 3.7% m/m polyphenolic compounds expressed as caffeic acid on the mRNA expression level of major CYP450 enzymes using an animal model has been investigated. The male Wistar rats were randomly divided into four groups from A to D (n = 10). Group A was treated once a day with 50 mg/kg p.o. of *E. purpurea* ethanolic extract for 3 days, and group B received a standard diet. Group C was treated with the same extract like group A, 50 mg/kg p.o. once a day, but for 10 days, whereas group D was used as control for group C. Total RNA was isolated from the rat liver tissue sixteen hours after the last administration. The authors concluded that the obtained *in vivo* data indicated a potent inhibition of the expression of CYP3A1 (41%, $p < 0.05$) and CYP3A2 (25%, $p = 0.001$), and an induction of CYP1A1 (80%, $p = 0.01$) and CYP2D1 (40%, $p = 0.007$) after the administration of an *E. purpurea* ethanolic extract [26]. However, nothing has been reported about the important isoform CYP3A4.

In a pharmacokinetic herb-drug interaction study in rats, the effects of different phytochemically characterized preparations of *E. angustifolia, E. purpurea* and *E. pallida* were assessed for its cytochrome P450 (CYP) interaction potential. A total of 216 rats were assigned to the different experimental groups (n = 12) with various dosages, positive/negative controls (ketoconazole, quinidine, rifampicin) and dodeca-2*E*,4*E*,8*Z*,10*E*/*Z*-tetraenoic acid isobutylamides ("tetraenes"). *Echinacea* preparations were administered for two consecutive weeks. On the last day a CYP cocktail consisting of theophylline (CYP1A2), tolbutamide (CYP2C), dextromethorphan (CYP2D), and midazolam (CYP3A) was orally administered before blood sampling. Plasma levels of substrates and their metabolites were quantified using a validated LC-MS/MS method [30]. Pharmacokinetic parameters (C_{max} and AUC_{last}) were calculated and compared with the blank control group using geometric mean ratios (GMRs) and its 90% confidence interval (CI). *E. purpurea, E. angustifolia* and *E. pallida* preparations showed significant interactions mainly on CYP1A2 substrate activities. Co-administration of *E. purpurea* preparations (60% ethanolic root extract $p < 0.001$; CO_2-extract $p < 0.01$; Echinaforce® $p < 0.001$ and pressed juice $p < 0.01$) with theophylline led to a significant increase in the AUC_{last} of the metabolite, 1,3-dimethyluric acid. In addition, the main alkamides of *Echinacea* (tetraenes) inhibited CYP1A2 with a GMR of 8.65 (7.72–9.68) for the AUC_{last} and 2.96 (2.59–3.39) for C_{max}. The pharmacokinetics of dextrorphan (rat CYP2D2 metabolite) were moderately affected. However, *Echinacea* formulations showed no significant inhibition on CYP3A and CYP2C activities [3,31].

Preclinical studies conducted since 2004 indicate that *Echinacea* constituents modulate immune mechanisms and there is increasing evidence that lipophilic *Echinacea* preparations containing alkamides can suppress stress-related cellular immune responses [2,8,32–37], in contrast to older literature published, which described only "immunostimulatory" effects [38–43]. Therefore, the activity of *Echinacea* may better be described as "immunomodulatory" rather than immunostimulatory [44]. Warnings against the concomitant use of *Echinacea* spp. together with immunosuppressive drugs because of the theoretical possibility of diminished effectiveness and the ingestion in people with inflammatory conditions, such as asthma, and HIV, therefore remain questionable [45,46].

The Eclectics, a group of practitioners, who were prominent around the late 19th and early 20th centuries in the U.S., used *Echinacea* (especially the root of *E. angustifolia*) for an extensive range of conditions, including tuberculosis [47]. The use for tuberculosis and disorders related to autoimmunity such as diabetes, exophthalmic goiter, psoriasis, and renal haemorrhages contrasts with the contraindications suggested by some recent authors.

Although it is recommended by the authorities that "*Echinacea*" should be avoided in patients with autoimmune diseases, very few published case reports exist in this context, moreover they have a limited causal association [48,49]. The suggestion that *Echinacea* preparations are contraindicated in autoimmune diseases assumes that the modulation of any aspect of immune function is deleterious. However, immune function is extraordinarily complex and a substance that acts largely on phagocytic activity may be safe or even beneficial in autoimmunity [50–54]. There were no clinical or laboratory alterations (blood count, electrolytes, liver and kidney functions) reported after the ingestion of *E. angustifolia* whole plant dry extract (undefined extraction solvent) over 12 weeks by HIV positive subjects.

Special warnings and precautions for use

Since the possibility of immune-related adverse consequences has not been ruled out in atopic individuals, especially this group of patients should use *Echinacea* spp. with caution and under the supervision of a health care practitioner. The Community Herbal Monograph stated that atopic patients should consult their doctor before using *Echinacea* [4–6]. The potential allergenicity of *Echinacea* has received a fair amount of attention, although some may have not been definitively associated with the ingested *Echinacea* preparations [55].

Undesirable effects

Reports of adverse effects within clinical trials, comparing monopreparations of *Echinacea* with placebo since 1996 are summarized in **Table 1**. Most of the adverse events were specified as mild to moderate. However a causal relationship between *Echinacea* and the adverse events could not be established. Headache, one of the predominant mentioned adverse effects, may not accurately reflect adverse events because it is also a frequent symptom of the common cold.

Allergic reactions

E. angustifolia (3825 mg whole plant extract) and *E. purpurea* (150 mg dry root) have been associated with allergic reactions, including one reported case of anaphylaxis [56,57]. Skin allergy testing of 84 patients with asthma or allergic rhinitis demonstrated reactivity to those *Echinacea* extracts in 16 subjects (19%) [57].

Huntley et al. analysed a total of 8 case reports of allergic reactions to *Echinacea* with such typical signs as generalized urticaria, itchy and watery eyes, gastrointestinal upset, respiratory obstruction, asthma, and a positive reaction to skin prick test (skin allergy test, SPT), which may or may not resolve with time [45]. A 19-year-old female suffered an acute asthma attack and severely itchy and watery eyes and a runny nose within 10 minutes of her first ever exposure to an *Echinacea*-containing tea, with no further characterization of the species and the plant part. It is necessary to mention that combination products and homeopathic preparations were excluded from this safety reviwe.

Jeschke et al. [58] published the results of a prospective pharmacovigilance study of Asteraceae extracts, including *Echinacea*. The aim of this study was to analyze prescribing patterns and adverse drug reactions (ADRs) for Asteraceae-containing remedies in Germany. Altogether, 18 830 patients (58.0% female, 60.3% children) received 42 378 Asteraceae-containing remedies. This included 2672 patients receiving 4605 *Echinacea*-containing prescriptions with 69 different medications (30% phytotherapeutic, 60% < D4, 10% > D4). No serious adverse drug reactions were reported. In a subgroup analysis, considering also non severe adverse drug reactions in 6961 prescriptions for Asteraceae, 11 non-serious adverse reactions were detected (all for homeopathic preparations and none for phytotherapeutic preparations). This supports the observation that allergic reactions due to *Echinacea* products are rather rare and mostly not serious [3,58].

There is no literature available for the Stevens-Johnson Syndrome, which is mentioned in the HMPC Monograph as an hypersensitive reaction. But obviously there have been 4 cases reported in the Eudra vigilance database [3].

Thrombocytopenia

Only one adverse event report with thrombocytopenia was identified specifically for *E. pallida*. Liatsos et al. [59] reported a case of severe thrombotic thrombocytopenic purpura (TTP) in an otherwise healthy 32-year-old Caucasian man. Examination revealed hypotension, sinus tachycardia, mild elevation in temperature, and few diffused petechiae, anemia (Hb = 6.0 g/dL), severe thrombocytopenia (platelets = 20 000/µL), and microangiopathic-type haemolytic anemia with fragmented red blood cells, increased indirect bilirubin, and markedly elevated LDH levels. Bacterial and viral antibodies were negative. The patient was transfused with red blood cells and fresh frozen plasmas (FFPs) but had a syncope episode followed by seizures and finally entered *status epilepticus* which was controlled with general anesthesia and ventilator assistance. He was treated with large-volume plasmapheresis twice a day, and administration of FFPs. He finally had an uneventful outcome [59]. Causality has not been evidenced.

Leucopenia and eosinophilia

Kemp and Franco published a case report of leucopenia associated with the long-term use of an uncharacterized *Echinacea* product (450 mg tid). A 51-year old woman appeared healthy from all aspects with the exception that her white cell count had decreased from 5800/µL the preceding year to 3300/µL (normal range 4000 to 11 000). For the past 8 weeks she had been taking the undefined *Echinacea* product (1350 mg of *Echinacea* per day), *Ginkgo biloba* L. (Ginkgoaceae; dosage not given), bupropion for depression (300 mg daily), as well as vitamins-C, -E, -B, and calcium. She suffered from hayfever, but did not take medication for it. One month after the discontinuation of therapy with *Echinacea*, her white cell count had increased to 3700/µL. The next year she resumed taking *Echinacea* and after two months her white cell count was 2880/µL. Two months after discontinuing taking *Echinacea*, her white cell count was 3440/µL and 7 months later arose to 4320/µL. Due to the fact, that the authors could not find another reason for the leucopenia, they assumed a relationship to the intake of *Echinacea* [60]. Although it is known that the concomitant ingested product, bupropion (Wellbutrin SR®), releases changes in hematology. While in a study performed by Goel et al., no significant differences between groups taking *E. purpurea* (ethanol extraction of various freshly harvested parts) or a

Table 1 Adverse events reported during administration of *Echinacea* spp. to human subjects.

First author (reference)	N	Patient population and study design	Preparation	Adverse events experienced (cases or %)			
				Active treatment		Placebo	
Parnham; Schöneberger [88]	109	Patients with more than 3 colds during the previous winter. DB, PC	EP pressed juice twice daily for 8 weeks (Echinacin® Liquidum)	Gastrointestinal upsets, headache, dizziness and tiredness (11)		Gastrointestinal upsets, headache, dizziness and tiredness (7)	
Parnham; Madaus AG [88]	47	Marathon runners with at least 3 upper airway infections within 6 months. DB, PC	EP pressed juice four times a day for a total of 12 weeks (Echinacin® lozenges)	No adverse events reported		No adverse events reported	
Parnham; Madaus AG [88]	38 (n = 79 in total)	Prophylaxis of respiratory or urinary tract infections. O	EP pressed juice four times a day for 6 weeks (Echinacin® lozenges)	Various muscle aches, joint pain, gastrointestinal complaints (e.g. diarrhea, nausea, gastric discomfort), headache (1–3)		Various muscle aches, joint pain, gastrointestinal complaints (e.g. diarrhea, nausea, gastric discomfort), headache (1–3)	
Parnham; Madaus AG [88]	1231	Patients with relapsing respiratory and urinary infections. Multicenter study	EP pressed juice for 4–6 weeks (1 Echinacin® lozenges 3 times daily)	Unpleasant taste (21), nausea/vomiting (6), recurrent infection (5), sore throat (3), abdominal pain (3), diarrhea (3), difficulty in swallowing (2), other single reports (19) (not specified whether they received placebo or Echinacin®)			
Schapowal [104]	154	Patients with acute sore throat. Multicenter, R, DB, compared to chlorhexidine/lidocaine	*Echinacea*/Sage spray (863.3 mg/mL fresh plant extract EP [95% aerial parts and 5% roots] and 430 mg/mL leaves of *Salvia officinalis*) for 7 days	Rash on mucosa (1), burning sensation and dryness of the throat (1), joint pains (1); adverse event rate of 3.8%		Swelling of the tongue (1), bitter taste in the mouth (1)	
Hill [105]	47	Healthy volunteers (Effects of EP on aerobic and anaerobic bacteria in the GI tract has been determined). Comparison with baseline.	1000 mg total (two doses of two capsules each) of standardized EP tincture (Echinamide®) for 10 days	Flatulence (1), diarrhea (1), nausea (1)		No placebo group	
Vonau [87]	50	Patients with recurrent genital herpes. DB, PC, cross-over trial	Echinaforce® 800 mg of EP extract (95% aerial parts, 5% roots) twice daily for 6 month	Nausea without vomiting (4), diarrhea (5)		Nausea without vomiting (2)	
Melchart [86]	99 (EP) and 100 (EA) (n = 289 total)	Volunteers without acute illness at time of enrollment. R, DB, PC, three armed	Ethanolic EA root liquid extract *and* EP root extract for 12 weeks (50 drops twice daily, 5 days a week)	*E. angustifolia*	*E. purpurea*	Minor gastrointestinal symptoms (6), headache/dizziness (1), allergic symptoms (2), other symptoms (3)	
				Minor gastrointestinal symptoms (9), headache/dizziness (9), allergic symptoms (2), other symptoms (1)	Minor gastrointestinal symptoms (5), headache/dizziness (2), allergic symptoms (2), other symptoms (4)		
See [106]	14	HIV patients with or without antiretrovirals	EA whole plant dry extract (1000 mg three times daily, undefined type of solvent) for 12 weeks	No adverse events reported			
Grimm [107]	54 (n = 109 total in trial)	Patients with a history of more than 3 colds/respiratory infections in a year. DB, PC, R	EP pressed juice 4 mL twice daily for 8 weeks	11 patients with adverse events mainly GI upsets, dizziness and tiredness; 4 patients dropped out		7 patients with adverse events mainly GI upsets, dizziness and tiredness; 3 patients dropped out	
Brinkeborn [108]	181 (n = 246 total in trial)	Healthy adult volunteers. DB, PC, R	Echinaforce® EP extract (95% aerial parts, 5% roots), EP concentrate, EP radix special prep, two tablets three times daily for not longer than 7 days	Echinaforce	EP concentrate	EP radix special prep.	
				7 adverse events	8 adverse events	12 adverse events	6 adverse events
				The majority were GI in nature			

cont.

Table 1 *Continued*

First author (reference)	N	Patient population and study design	Preparation	Adverse events experienced (cases or %)	
				Active treatment	**Placebo**
Gallo [109]	112 women used *Echinacea* in the first trimester; 17 were exposed in all 3 trimester; (n = 206 total)	Pregnant women Prospective case control study	Capsules and/or tablets of undefined *Echinacea* with dosages between 250 to 1000 mg/day; tincture dose varied from 5 to 30 drops daily; Mostly EA or EP without detailed characterization. Duration 5 to 7 days	Comparison with control group suggested no increased risk of major malformations due to *Echinacea* ingestion during organogenesis	
Schulten [110]	41 (n = 81 total in trial)	Patients with the first signs of a cold. DB, PC, R	EP pressed juice 5 mL twice daily for 10 days	8 adverse events with GI upsets (6)	9 adverse events mostly with GI upsets (6)
Rostock [111]	128 (n = 187 total in trial)	Breast/colorectal cancer patients. Controlled, open pilot study	EP 8 mL or EP pressed juice 24 mL daily for 21 days	Number of adverse events were similar in 8 mL group to control and less in 24 mL group. 1 case each of elevated liver enzyme levels and leukopenia. 3 cases each of allergic skin reaction and vertigo. No other serious/potentially serious adverse events.	
Kim [112]	24 (n = 48)	Healthy female volunteers in each of the 3 groups. DB, PC, R	Standardized extract of EP, ultra-purified EP/EA or EA for 4 weeks	2 of 48 participants experienced adverse events Ultra-purified EP/EA: Self-reported anxiety, nervousness and heart palpitation	EP group: Bilateral arthritic symptoms in wrist, metacarpophalangeal and proximal interphalangeal joints. Both resolved on discontinuation.
Barrett [113]	69 (n = 142)	Students with common colds at least 2 of 15 cold symptoms for less than 36 hours. DB, PC, R	An encapsulated mixture of EP herb (25 %), root (25 %) and EA root (50 %), 1 g six times daily on the first day of illness and three times on each subsequent day of illness for up to 10 days	Sleeplessness (1), heartburn (1), nausea (1), stomach ache (1), upset stomach (1) and bad taste in mouth (3)	Stomach ache (3), nausea (1), belching (1), thirst (1) and abdominal pain with diarrhea (1)
Lindenmuth [114]	48 (n = 95)	Employees of a nursing and rehabilitation center with earliest symptoms of a cold. PC, DB	EP aerial parts, EP roots and EA roots in a tea preparation (Echinacea Plus®) with 2 flavoring components (lemon grass leaf and spearmint leaf) 5 to 6 cups on day 1, titration to 1 cup on day 5	There were no negative effects reported by any of the subjects in either group.	
Turner [115]	22 (n = 46)	Healthy goung adults with a titer of antibody of < 1 : 4 ro thinovirus type 23. R, PC; DB	4 % phenolic extract of a mixture of EP and EA formulated as powder, containing 0.16 % cichoric acid with almost no echinacoside or alkamides, 1 capsule (900 mg) once a day for 14 days prior to virus challenge and 5 days after virus challenge	One subject was removed due to an unspecified adverse event. No significant side effects of *Echinacea* were seen.	

cont.

Table 1 *Continued*

First author (reference)	N	Patient population and study design	Preparation	Adverse events experienced (cases or %)			
				Active treatment		Placebo	
Taylor [80]	200 (n = 407)	Treatment trial in children between 2 to 11 years. R, PC, DB	EP herb in syrup, 7.5 mL/day in children 2 to 5 years and 10 mL/day in those 6 to 11 years up to a max. of 10 days	Adverse events in 45.1 % with: stomach ache, diarrhea, drowsiness, headache, "hyper" behavior, rash and vomiting. Rash was the only side effect that was significantly more frequent in the *Echinacea* group compared to placebo (7.1 % versus 2.7 %; p = 0.008).		Adverse events in 39.5 % with: stomach ache, diarrhea, drowsiness, headache, "hyper" behavior, rash and vomiting.	
Sperber [116]	24 (n = 46)	Prevention trial (experimental virus inoculation with RV-39 after 7 days). R; PC, DB	EP pressed juice, 2.5 mL 3 times daily for 14 days	Two participants reported adverse events: Sleeplessness (1), severe oral aphthous ulcers (1)		4 participants in the placebo group reported 6 adverse events, which are not specified.	
Goel [61]	59 (n = 128)	Healthy adults with at least 2 colds last year. R, PC; DB	EP standardized extract (0.25 mg/mL alkamides, 2.5 mg/mL cichoric acid, 25.5 mg/mL polysaccharides); 10 × 4 mL the first day, then 4 × 4 mL for 6 days	Gastrointestinal side effects (nausea, constipation) and heartburn were reported by 13 % (8/59). Again itching, burning sensation and numbness of the tongue were reported by 13 % (8/59).		Gastrointestinal side effects (nausea, constipation) and heartburn were reported by 9 % (6/69). Again itching, burning sensation and numbness of the tongue were reported by 11 % (8/69).	
Yale [117]	63 (n = 128)	Adult patients presenting with acute sneezing and nasal discharge for 6 to 24 hours. R, PC, DB	Standardized freeze-dried pressed juice from EP herb, 3 capsules (100 mg) up to a max of 14 days	Nausea (9 %), abdominal pain (4 %), mouth irritation (2 %), bad taste (6 %), headache (14 %), dizziness (6 %), dry mouth (16 %)		Nausea (5 %), mouth irritation (3 %), bad taste (5 %), headache (11 %), dry mouth (9 %)	
Goel [118]	26 (n = 62)	Volunteers between 18 and 65 years with 2 or more colds previous year. R, PC, DB	EP standardized extract (0.25 mg/mL alkamides, 2.5 mg/mL cichoric acid, 25.5 mg/mL polysaccharides); 8 × 5 mL the first day, then 3 × 5 mL for 6 days	No adverse events reported		No adverse events reported	
Turner [119]	296 (n = 399)	Healthy young adults, serum-neutralizing antibody titer < 1 : 4 to rhinovirus type 39. R; PC; DB	60 % and 20 % ethanolic root extract of EA, and a CO_2 extract of the roots of EA; 1.5 mL tincture (300 mg *Echinacea* root) 3 times daily for 7 days before virus challenge and 5 days after challenge	5 % of the subjects receiving an *Echinacea* preparation reported an adverse event. Gastrointestinal side effects were reported by 12 subjects.		4 % of the placebo-treated subjects reported an adverse event. Gastrointestinal side effects were reported by 4 subjects.	
Hall [120]	18 (n = 32)	Active, non-smoking adults aged 19 to 46 years. R, PC, DB	EP herb 1.2 g in capsules, 8 capsules/day for 4 weeks	no adverse events reported		no adverse events reported	
O'Neill [121]	28 (n = 58)	Healthy adults recruited from hospital personnel	EP dried plant extract in capsules, 3 capsules 2 times daily for 8 weeks (300 mg per capsule)	Mild adverse effects were noted by 8 % of the *Echinacea* group.		Mild adverse effects were noted by 7 % of the placebo group.	
Barrett [122]	184 (n = 363)	Students with common cold symptoms since up to 36 hours. R, PC, DB	EP root (675 mg) and EA root (600 mg) standardized tablets, MediHerb (Australia), 2 tablets four times daily on the first day of illness and 1 tablet four times daily on each subsequent day for up to 4 days	Blinded to *Echinacea* Bad taste (12 %), diarrhea (10 %), headache (46 %), nausea (16 %), rash (1 %), stomach upset (15 %)	Open-Label *Echinacea* Bad taste (9 %), diarrhea (9 %), headache (48 %), nausea (7 %), rash (2 %), stomach upset (13 %)	No Pill Diarrhea (5 %), headache (62 %), nausea (10 %), rash (2 %), stomach upset (16 %)	Blinded to Placebo Bad taste (9 %), diarrhea (12 %), headache (49 %), nausea (13 %), rash (1 %), stomach upset (12 %)

cont.

Table 1 *Continued*

First author (reference)	N	Patient population and study design	Preparation	Adverse events experienced (cases or %)	
				Active treatment	Placebo
Jawad [89]	325 (n = 673)	Healthy adults with 2 or more colds per year. R, PC, DB	Alcoholic extraction from freshly harvested EP with 95 % herb and 5 % roots (Echinaforce®), 3 × 0.9 mL per day for illness prevention (2400 mg extract/day), during acute stages of cold dose was increased to 5 × 0.9 mL per day (4000 mg of extract/day) for 4 months.	25 subjects in the Echinaforce group (9 %) experienced 27 drug-related adverse events (causally related to the study medication). 293 adverse events were reported by 177 subjects treated with Echinaforce. Four adverse events led to discontinuation of treatment. No severe adverse event was observed with Echinaforce.	30 subjects in the placebo group (10 %) experienced 30 drug-related adverse events. 306 adverse events were reported by 172 subjects in the placebo group. Three adverse events led to discontinuation of treatment. One severe adverse event (glandular fever) occurred with placebo.
Tiralongo [123]	85 (n = 170)	Healthy adults, traveling on intercontinental flights. R, PC, DB	112. 5 mg EP root (675 mg dry root) and 150 mg EA root (600 mg dry root) standardized tablets, days – 14 to – 3 (1 tablet twice a day), days – 2 to + 7 (2 tablets twice a day), + 8 to + 32 (1 tablet twice a day), + 33 to + 42 (2 tablets twice a day), + 43 to + 49 (1 tablet twice a day)	Adverse events were reported by only 3 participants. Heartburn and diarrhoea. However, the participant who reported heartburn was also taking aspirin and several other medicines such as sleeping tablets. Tingling and burning of the tongue and mouth (2)	Vomiting and headache

EA = *Echinacea angustifolia*; EP = *Echinacea purpurea*; R = randomized; O = open; DB = double-blind; PC = placebo-controlled

placebo after white blood cell differential count were observed [61]. Furthermore, a case of a patient with eosinophilia of unclear aetiology whose condition resolved after the discontinuation of "*Echinacea*" has been reported. The authors felt that this represents an IgE-mediated allergic process to an uncharacterized used *Echinacea* preparation [62].

Erythema nodosum

One isolated report describes the case of a 41-year-old man who experienced four episodes of erythema nodosum after using an undefined *Echinacea* preparation at each onset of an influenza-like illness. The man had been using *Echinacea* intermittently for 18 months, as well as loratadine on a basis as required, 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 the treatment with *Echinacea* and, after 1 year, he 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 [63].

Sjögren syndrome

Logan and Ahmed reported on a 36 year old woman, who ingested St. John's wort, undefined *Echinacea*, and Kava for 2 weeks, a development of severe general muscle weakness, which resolved under supplementation of $NaHCO_3$ and KCl. The report did not provide any further details of the *Echinacea* species that was contained in the product, or of the types of preparations, formulations, dosages and routes of administration of any of the herbal medicines listed. Complaints of joint stiffness, fatigue, dry mouth and eyes surfaced 6 weeks later. Sjögren syndrome was diagnosed and a Plaquenil (hydroxychloroquine 200 mg daily) treatment begun. The abnormalities renal tubular function resulting in hypokalimea and acidification with muscle weakness, are reported because of the Sjögren syndrome. Problems resolved under therapy with prednisone and cyclophosphamide, which unterlines the autoimmunogenesis. This case may represent one example where an autoimmune disease was exacerbated. The connection between the *Echinacea* therapy and the undesirable effect has been estimated as possible, but is not conclusive [49].

Exanthema

An autoimmune disease supposedly triggered by an unspecified *Echinacea* supplement has been reported by Lee and Werth. A patient with pre-existing chronic inflammatory condition started taking *Echinacea* for the first time in his life at the onset of an upper respiratory tract infection. Within days the patient developed blisters on body, head and oral mucosa. The authors also mentioned that the temporal relationship of the patient disease flare with ingestion of *Echinacea* is strongly suggestive of a causal relationship. However, the practitioners could not rule out the possibility that the patient experienced an exacerbation as part of the natural course of his condition, nor could they dismiss the possibility that the upper respiratory tract infection contributed to his flare [48]. Furthermore, no further details of the product, including species of *Echinacea*, plant part, excipients, type of preparation, and dosage were provided. 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 [48].

Among a total of 64 493 reported adverse reactions submitted to the Swedish Medical Products Agency, only 778 reports concerned adverse reactions related to the use of complementary and alternative medicine (CAM) products. 63 (8.1%) reports concerned *E. purpurea*, among them mostly urticaria (11) and exanthema (13) were reported [64].

Acute cholestatic autoimmune hepatitis

In a case report by Kocaman et al. (2008) a 45-year old male patient complained of fatigue and jaundice of 1-week duration. He told that he had started taking "*Echinacea* root" (1500 mg/day) after catching a common cold. Physical examination revealed an icteric patient. Markers for viral hepatitis, ceruloplasmin, iron and ferritin levels, and alpha 1 antitrypsin level were not remarkable for acute hepatitis. Liver biopsy revealed an interface hepatitis, prominent cholestasis, and a portal lymphoplasmocytic and eosinophilic granulocyte infiltration. After admission, the patient stopped taking the "*Echinacea*". One month later, all laboratory values were normalized, except for the anti-smooth muscle antibody positivity. The authors concluded this first report of an *Echinacea*-induced acute cholestatic autoimmune hepatitis (ACAH) as a result in a breakdown of autoimmunity self-control in the liver. Due to the undefined *Echinacea* preparation used (species, formulation) it is difficult to interpret the connection between *Echinacea* and the severe acute hepatitis [65]. In the same year, a case communication reported a patient with autoimmune hepatitis and hypergammaglobulinemic purpura related to an uncharacterized herbal medicine including "*Echinacea*, Combucha, Chinese herbal mixtures, and Kava Kava". The 57 year old woman, a practitioner of alternative medicine, was hospitalized with jaundice and weakness. Viral serology for hepatitis B and C were negative. A liver biopsy demonstrated cirrhosis with severe piecemeal necrosis, severe intra-acinar necrosis, focal necrosis and cholestasis. The patient was started on prednisone 60 mg per day with a prompt laboratory improvement and complete normalization of her liver function. It remains speculative whether the association between the herbal preparation and the autoimmune hepatitis is causative or only coincidental. Above all, the connection between the uncharacterized "*Echinacea*" preparation and the autoimmune hepatitis is questionable [66].

Concerns of potential hepatotoxicity have been raised, although documented cases are lacking. Miller published that all *Echinacea* preparations, if used beyond 8 weeks, could cause hepatotoxicity and therefore should not be used with other known hepatotoxic drugs, such as anabolic steroids, amiodarone, methotrexate, and ketoconazole [46]. However, the magnitude of this hepatoxicity has been questioned since *Echinacea* lacks pyrrolizidine alkaloids with a 1,2 unsaturated necine ring associated with hepatotoxicity. There have also been hepatoprotective effects of *Echinacea* reported in male rats [67]. Therefore, there is no clear evidence for hepatotoxicity.

Autoimmune diseases like encephalitis disseminate and the Evans Syndrome are undesirable effects cited in the HMPC monographs with unclear background. There is no literature available in connection with *Echinacea*. In the recent update of the European Medicines Agency monograph on *E. purpurea*, herba recens [4] Evans Syndrome has already been deleted.

Effects on Reproduction and Development

Preclinical data indicate that *E. purpurea* aerial part or root preparations are unlikely to cause negative reproductive or developmental effects in laboratory animals. Oral doses up to 2700 mg/kg of Echinacin® did not cause embryotoxicity in rats or rabbits or affect postnatal development in rats. Studies looking for gene mutations, malignant transformation, or chromosome aberrations in bacteria, mouse lymphoma cells, cultured hamster cells, or human lymphocytes have found no evidence of mutagenicity of Echinacin® [68]. However, Ondrizek et al. reported that very high concentrations of *E. purpurea* (0.6 mg/mL, plant part undisclosed) applied directly to sperm impaired sperm motility and they suggested that this may have a negative effect on male fertility. Motility was inhibited at 24 and 48 h after incubation. They reported similar *in vitro* results using hamster sperm and oocytes [69, 70]. It is questionable whether these findings are relevant in an *in vivo* situation.

In 2007, the first study was conducted to evaluate whether pharmaceuticals containing alcoholic extracts of *E. purpurea* given to pregnant mice (n = 8) influence angiogenic activity and may then lead to severe developmental disturbances. They found an increase in the angiogenic activity of tissue homogenates in the Esberitox® group, containing 3.2 mg of a native dry extract (30% ethanol) from *Baptisia tinctoria* (L.) Vent. (Fabaceae) root, *E. purpurea* root, *E. pallida* root and *Thuja occidentalis* L. (Cupressaceae) herba, and a diminution in case of Immunal forte (1 tablet contains 80 mg dry *E. purpurea* pressed juice 31–60 : 1). The growth factor concentration was lower in all groups compared to the control. They concluded that there is some possibility that pharmaceuticals containing *E. purpurea* might influence the fetal development in humans also, because they may interfere with embryonic angiogenesis, and should not be recommended for pregnant women [71].

The vascular endothelial growth factor (VEGF) known as the most powerful angiogenesis promoter plays a crucial role in organogenesis, liver and pancreas induction, kidney glomerulus, bone and nervous system development. Moreover, VEGF contributes to the placentation and cytotrophoblast proliferation during pregnancy. Wasiutynski et al. (2009) evaluated the effect of the following *E. purpurea* containing drugs on the angiogenic activity and VEGF concentration of murine sarcoma L-1 tumors: Immunal forte tablets (1 tablet contains 80 mg dry *E. purpurea* pressed juice 31–60 : 1; LEK, Slovenia) and Echinapur tablets (no detailed characterization; Herbapol Poznan). They found that both drugs significantly diminished the VEGF concentration in L1 sarcoma tumor tissue and they speculated that therefore they may affect the placenta formation in pregnant women [72, 73].

Perri et al. (2006) conducted a literature review with no specification of *Echinacea* (species, plant part and extraction method used) of seven electronic databases from their inception through 2005 and compiled data according to the degree of evidence for the use, safety, and pharmacology of *Echinacea* pertaining to pregnancy and lactation [74]. No association with an increased risk for major or minor malformations with a reported gestational use of *Echinacea* during organogenesis was found [75–77]. Capsule and/or tablet formulations of undefined *Echinacea* were used by 114 (58%) of the 198 respondents, while 76 (38%) of the respondents used tinctures. The dosage of capsules and/or tablets used varied from 250 to 1000 mg/day. Tincture dose varied from a minimum of 5 to 10 to a maximum of 30 drops per day. Duration of use also varied but was normally continuous for 5 to 7

days. The different brands used covered the two species *E. angustifolia* and *E. purpurea* without detailed characterization. 112 women (54%) reported taking the herb in the first trimester of pregnancy, and 17 (8%) used *Echinacea* throughout their pregnancies. No significant differences were noted between the *Echinacea* and the control groups in the rate of major or minor birth defects, nor were there any differences in pregnancy outcome, delivery method, maternal weight gain, gestational age, infant birth weight, or foetal distress. Thirteen miscarriages were documented in the *Echinacea* group, compared with seven in the control group [76]. The study has several limitations. The most important is that participants used a range of different preparations of *Echinacea* at different dosage regimens. So the study does not provide adequate evidence for a specific preparation.

Use in children

Götte and Roschke [78] made an observation in children with recurring infections of the upper respiratory tract to assess the tolerability and efficacy of an alcohol free pressed juice from the aerial parts of *E. purpurea*. The children had to be at least 2 years of age, and the juice was administered over a period of 11 days with doses adjusted according to age. In more than 95% of cases (n = 1322), the physician and parents globally assessed the tolerability as good or very good [78]. It has been reported in a recently published study by Du et al. that the use of herbal medicinal products in general is closely associated with younger age between 0 and 17 years, and that two thirds of the preparations used are for the treatment of coughs and colds [79]. Taylor et al. found an increased risk of rash when children of 2 to 11 years (mean 5.5 years, standard deviation 2.7 years) received an alcohol-free preparation of dried pressed *E. purpurea* juice of the aerial parts, compared with those who received a placebo [80]. In this study adverse events were found in 45.1% of patients receiving *Echinacea* (and in 39.5% of patients receiving placebo). The most frequent adverse events were: stomach ache, diarrhoea, drowsiness, headache, "hyper" behaviour, rash and vomiting. Rash was the only side effect that was significantly more frequent in the *Echinacea* group compared to the placebo group (7.1% versus 2.7%, respectively). Therefore, caution is recommended when using this *E. purpurea* juice preparation in children who have atopy and asthma because they are likely to be at higher risk for a rash. In a subgroup analysis of the Taylor et al. data it has been found that children taking Echinacin® juice were significantly less likely to have another URI compared to children receiving placebo. Use of Echinacea was associated with a 28% decreased risk of subsequent URI (p = 0.01) [81]. Moreover, in a study performed by Saunders and colleagues, the safety and tolerability of an open-label *E. purpurea* product prepared from the dried, pressed juice of aerial parts (Echinagard®) has been examined in children. The dose was based on age (2.5 mL three times q day for children aged 2–5 years, and 5 mL two times per day for children aged 6–12 years) and administered for 10 days in an open-label trial. No allergic or adverse reaction occurred and no safety issues arose during this study [82].

Four observational studies regarding the safety of the oral administration of preparations of the aerial parts of *E. purpurea* in different dosages for children below the age of 18 were submitted by the German authority [3]. From the in total 1184 children, two cases of nausea and two generalized exanthema have been reported, which could be due to an infection as well. Three children dropped out due to the bad taste of the preparation. Otherwise there were no reports concerning adverse events even when used more than 10 days [3].

Duration of use

Several authoritative sources (e.g. EMA/HMPC/48 704/2014) have suggested that *Echinacea* should be used only for limited periods of time (not longer than one week or 10 days), without giving reasons and references to verify the scientific background. The World Health Organization (1999) and the European Scientific Cooperative on Phytotherapy (ESCOP) monographs [83], citing the German Commission E monographs on *Echinacea*, cautions that internal and external administration of *E. pallida* and *E. purpurea* should not exceed 8 weeks, again without rationale. There was no data found supporting a treatment duration limit for *Echinacea* [84]. When addressing the issue of a duration limit for *Echinacea* preparations, Bone (2004) emphasized the importance of reviewing the traditional use of *Echinacea* by the U.S. Eclectic physicians that were active in the late 19th and early 20th century. Authoritative works published by these physicians, based upon their extensive clinical experience, indicate that *Echinacea* was used over a long-term in chronic conditions without side effects [47].

Several studies of long-term (10–24 weeks) oral use of different *Echinacea* preparations without occurrence of serious adverse effects have been reported [85–87]. The longest intervention of *E. purpurea* whole plant dry extract (undefined extraction solvent) studied to date was 800 mg twice per day for 6 months. The only adverse events reported by these subjects were nausea without vomiting (n = 4) and diarrhoea (n = 5) [87]. Melchart et al. studied the oral use of an *E. purpurea* root liquid extract and *E. angustifolia* root extract for 12 weeks (100 drops daily of a 1 : 11, 30% ethanolic extract for 5 days a week). No toxicological concerns were reported [86]. Parnham published that no adverse reactions other than aversion to the taste have been reported after oral administration of Echinacin® (*E. purpurea* pressed juice) for up to 12 weeks [88]. Recently, Jawad et al. tested the safety and efficacy of *E. purpurea* (57.3% m/m alcoholic extraction from freshly harvested 95% herba and 5% roots, Echinaforce®) in a large clinical trial (755 healthy subjects) and investigated its risk/benefit in a long-term treatment (4 month). In the haematological or biochemical measures no significant or clinically relevant changes from before to after *Echinacea* treatment and in comparison to placebo were detected. No abnormalities were found after the 4-month exposure to *Echinacea* [89]. Schapowal reported that a standardized extract of *Echinacea purpurea* (Echinaforce®) can be recommended for long-term use, also in children, the elderly as well as those suffering from COPD, asthma patients or smokers, people in whom the consequences of cold and flu can be severe [90].

Discussion

After review of the available literature, all medicinal species of „*Echinacea*", including *E. purpurea, E. angustifolia,* and *E. pallida* appear to be quite safe. While the absence of severe drug-related adverse events does not conclusively prove safety, it is an indication that significant acute toxicological events are lacking. In a toxicity study by Mengs et al. it has been concluded that even a lethal dose could not be found [68]. Except for *in vitro* studies, which claim some cytotoxic effects [70,91], studies in humans and with experimental animals are reassuring and suggesting a

wide therapeutic window of safety. Oral treatment of rats for 4 weeks at doses up to 8 g/kg daily of the fresh juice of *E. purpurea* aerial parts failed to cause any toxicology. Moreover, oral doses up to 2700 mg/kg of the same preparation did not cause embryotoxicity in rats or rabbits or affect postnatal development in rats [68]. While *Echinacea* ingestion during human pregnancy is touted to be safe [74, 76, 77] others are more sceptical, indicating that other members of the family Asteraceae have distinctly negative effects on human pregnancy [56, 92]. However, the Asteraceae family is very big and plants are quite different in constituents. *Echinacea* for example is lacking sesquiterpene lactones. Some caution exists regarding the use of an *E. purpurea* extract (0.6 mg/day within Esberitox®, Immunal® or Echinapur®) in the first trimester of pregnancy based upon testing in mice. The growth factor concentration was lower in all *Echinacea* groups compared to the control. Based on animal studies, there is some suspicion that pharmaceuticals containing alcoholic extracts of *E. purpurea* and pressed juice of *E. purpurea* might influence fetal development in humans, because they may interfere with embryonic angiogenesis, and should therefore only be taken during pregnancy and lactation after consulting a physician [71–73, 93]. However, there is no evidence on the possibility that consuming *Echinacea* may promote spontaneous abortions. This hypothesis arose from only one report. Gallo et al. found a virtual doubling in the number of spontaneous abortions, i.e., in 13 women consuming two species, *E. angustifolia* and *E. purpurea* without a detailed characterization (total: 206), versus 7 in 206 women not consuming the herb [76]. It is known that, *in vivo, Echinacea*, given to either normal, healthy adult mice, or to adult leukemic mice, significantly increases the numbers of natural killer cells [94, 95]. Since, natural killer cells have been implicated in foetus rejection, manifesting in humans as spontaneous abortion [96–99] it was speculated that *Echinacea* may influence abortion. Actually, the results from the human and animal studies of *Echinacea* spp. are not sufficient to conclude on the safety in pregnancy [100]. No firm conclusions on the risk of spontaneous abortions and angiogenesis can be drawn from the animal studies [71, 93]. The small number of test animals and the dubious relation to human conditions make the results questionable. Furthermore, Perri et al. conducted a literature review and found no significant differences between the *Echinacea* group (*E. angustifolia* and *E. purpurea*, without detailed characterization) and the control groups in the rate of major or minor birth defects, nor were there any differences in pregnancy outcome, delivery method, maternal weight gain, gestational age, infant birth weight, or foetal distress. For clarification and rational evaluation more studies are needed, however, pregnancy is not necessarily a contraindication and application of *Echinacea* preparations during pregnancy should be subjected to medical supervision.

Cautions from several authoritative sources (Community Herbal Monographs) are available and concern especially hypersensitive persons like atopic or immunosuppressed patients, the duration of use, and children. However, many trademark products containing *Echinacea* sp. will be defined as dietary supplements and thus not be legally bound to follow the recommendations in the official plant monographs. E. g., in the latest Monographs stated from the official European Medicines Agency (EMEA) [3–7], it has been suggested that the medicinally used *Echinacea* species should not be used for more than 10 days, but there were no pharmacological, toxicological and clinical data found supporting a limit of treatment duration for any "*Echinacea*" species used in either modern or traditional medical literature. The primary concerns for these temporal limits appear to be theoretical, including over-stimulation of the immune system and possible immune depression and immune habituation following long-term use. However, up to now the limitations are not justified and no substance classes can be hold responsible for the temporal limits. Long-term use of the pressed juice of *Echinacea purpurea* has not shown evidence of a deleterious effect on immune cells. One study reported that the immune reactivity in mice was greater after 10 weeks of continuous oral doses of an expressed juice of the aerial parts of *Echinacea purpurea* than after 2 weeks [85]. Miller et al. reported in a study that the chronic administration of an *Echinacea purpurea* root extract (0.45 mg daily for 14 months) from puberty until old age in mice resulted in the preservation of NK cell activity. Natural killer cell activity normally decreases with age and contributes to an increased mortality. The use of *Echinacea purpurea* preparations increased the life span of most of the mice and no toxicological concerns were noted [52]. Moreover, three further long term studies (12–24 weeks) with continuous ingestion of ethanolic *Echinacea purpurea* root or whole plant extracts reported no toxicological concerns [86–89]. Moreover, no significant or clinically relevant changes from before to after the *Echinacea* treatment and in comparison to the placebo were detected in haematological or biochemical measures, after 4-month exposure to an *E. purpurea* preparation (alcoholic extraction from freshly harvested 95% herba and 5% roots) [89]. There is no firm evidence to conclude the debate on duration limits.

Application of "*Echinacea"* species and preparations in those taking immunosuppressive drugs has been assumed as with any immune stimulant. Similarly, those with allergic sensitivities to members of the plant family Asteraceae, as well as atopic individuals and patients with asthma, should use *Echinacea* species with cautions and after consulting a physician. Regardless, very few published reports exist in this context, and those have limited causal association [48, 49]. The cautions in taking "*Echinacea*" from atopic patients arise from the common known allergenicity to the pollen proteins from plants of the sunflower family (Asteraceae). *E. purpurea* aerial parts products have more potential to elicit allergic reactions in atopic individuals than do root products. Considering the fact that proteins are very poorly extracted in ethanol-water mixtures it is also unlikely that an allergy would result from the fluid extracts and tinctures of *Echinacea*, even if the aerial parts were used. Proteins that are potentially contained may be denaturized by alcohol and are unlikely to cause an allergic cross-reactivity [52]. This indicates that the general risk for an allergic reaction to *Echinacea* is low. However, atopic patients and those with asthma should be informed about such a possibility before intake of preparations containing *Echinacea*. The suggestion that "*Echinacea*" preparations are contraindicated in autoimmune disease assumes that the modulation of any aspect of immune function is deleterious. However, immune function is extraordinarily complex and a substance that acts largely on the phagocytic activity may be safe or even beneficial in autoimmunity [50–54]. It is known that a stimulation of cytokines may lead to an exacerbation of autoimmune related inflammation and a majority of autoimmune diseases are thought to be due to a loss of tolerance to self-antigens and a dysregulation of Th1T-helper cells. Th1 cells produce cytokines IL-2, TNF-α, and IFN-γ. There has been one report indicating that both Th1 cytokine and IFN-γ and T-cell proliferation can be stimulated by *E. angustifolia* [101]. Haemolytic anemia (thrombocytopenia, leucopenia and eosinophilia) have been published only in single cases, mostly with un-

characterized *Echinacea* preparations and concomitant intake of other drugs or herbal medicinal products, so that the relevance is not clear. The published data on leucopenia have to be considered as not relevant for the safety of *Echinacea* due to reports concerning the occurrence of changes in hematology, like anemia and pancytopenia after a concomitant ingestion of bupropion (product information Wellbutrin, PDR, USA). Moreover, the patient showed also low respectively borderline levels of the white cell counts without *Echinacea* [60].

A specific risk in children is not documented and adverse events are very rare, with no causality. Rash was the only side effect that occured significantly more frequent after the ingestion of an alcohol-free preparation of the dried pressed juice of the aerial parts of *E. purpurea* compared to a placebo (Taylor et al. 2003). Moreover, it has been found that those children taking the pressed juice from *E. purpurea* were significantly less likely to have another upper respiratory infection [81]. Risk/benefit results suggest that the use in children can be recommended, but an intake of any *Echinacea* preparation in children less than 1 year of age should be discussed with a physician, because their immune system is not fully developed.

Concerning pharmacokinetic herb-drug interactions, which can result in tremendous variability (over 10-fold changes) in pharmacokinetics of concomitantly administered drugs, only the studies published since 2007, present reasonable data. The studies before have been performed with different and phytochemically insufficient characterized *Echinacea* preparations. With the *in vivo* studies published no significant inhibitions of human CYP2D6 and CYP3A4 isoforms have been found after the application of standardized *E. purpurea* preparations (softgel capsules with 267 mg, 3 times daily or fresh plant liquid extract again in softgel capsules with 500 mg, 3 times daily) [18,21]. No significant interaction has been found with etravirine, darunavir, and lopinavir-ritonavir, which undergoes extensive metabolism by the hepatic CYP3A4 isoform [19–21]. Only a cautious conclusion can been drawn that *Echinacea* alkamides inhibit CYP2E1 and CYP3A4 in human liver microsomes or enzyme substrates (supersome assay) [27]. After separating each characterized *Echinacea* preparation (pressed juices or alcoholic tinctures from *E. purpurea* and *E. pallida*) into its ethanol- and water-soluble components, the results directly confirmed the role of alkamides in the inhibition of CYP3A4 [24,25]. Controversial results exist on the transcriptional/translational activities with, e.g., induction or inhibition of CYP3A4 expression. A pressed juice from the aerial parts of *E. purpurea* and an *E. purpurea* root preparation suppressed hepatic CYP3A4 expression [15,22]. Whereas, Kortenkamp et al. found no significant changes in the steady-state CYP3A4 mRNA levels neither for Echinaforce® nor the pure alkamides [29]. However, herbal products are often marketed as dietary supplements, which have fewer requirements for testing of pharmacokinetic interaction potential before marketing compared to registered drugs. Recently the U.S. Department of Health and Human Services, Food and Drug Administration (FDA) and the European Medicines Agency (EMA) released "Guidelines on the Investigation of Drug Interactions" [102,103]. Two pharmacodynamic interaction studies in mice exist about the administration of an *E. purpurea* root extract or an ethanolic extract of *E. purpurea* dried aerial parts. One study found a negative effect on levels of mature granulocytes after a concomitant ingestion of melatonin [9,10]. However, a positive interaction has been reported after taking phenytoin at the same time, with a decrease in the incidence of cleft palate [11]. No evidence of any apparent effect on warfarin pharmacodynamics with platelet aggregation or baseline clotting status in healthy subjects has been found after concomitant administration of *Echinacea* (600 mg *E. angustifolia* roots and 675 mg *E. purpurea* roots, four times a day) with (S)-warfarin [12].

A declaration of pharmacodynamic and pharmacokinetic interactions with homeopathic preparations is not needed.

In conclusion, these data suggest that medicinally used *Echinacea* spp. have a very good safety profile.

Conflict of Interest

The authors declare that they have performed consulting work and analytical investigations for companies producing *Echinacea* products.

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