Review

A critical evaluation of drug interactions with *Echinacea* spp.

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Accurate information concerning drug–herb interactions is vital for both healthcare providers and patients. Unfortunately, many of the reviews on drug–herb interactions contain overstated or inaccurate information. To provide accurate information on drug–herb interactions healthcare providers must account for product verification, dosage, medicinal plant species, and plant part used. This critical review assessed the occurrence of drug interactions with one of the top selling botanical remedies, echinacea including *Echinacea angustifolia*, *E. pallida*, and *E. purpurea*. Only eight papers containing primary data relating to drug interactions were identified. Herbal remedies made from *E. purpurea* appear to have a low potential to generate cytochrome P450 (CYP 450) drug–herb interactions including CYP 450 1A2 (CYP1A2) and CYP 450 3A4 (CYP3A4). Currently there are no verifiable reports of drug–herb interactions with any echinacea product. However, further pharmacokinetic testing is necessary before conclusive statements can be made about echinacea drug–herb interactions. Given our findings, the estimated risk of taking echinacea products (1 in 100 000), the number of echinacea doses consumed yearly (>10 million), the number of adverse events (<100) and that the majority of use is short term, *E. purpurea* products (roots and/or aerial parts) do not appear to be a risk to consumers.

1 Introduction

Medicinal plants, while necessarily part of healthcare in developing regions, are becoming increasingly popular in the industrial nations. Estimates suggest that up to 30% of the North American population use herbal supplements [1]. Given that nearly 3.6 billion prescriptions were purchased in 2005 [2] and 30% of Americans report using five or more drugs in the same week [3] it comes as no surprise that the incidence of consumers taking herbs in conjunction with prescription medications is quite high. Eisenberg *et al*.

[4] found that up to 15 million adults were concurrently using prescription medications and herbal supplements. A nationwide telephone survey by Kaufman *et al*. [5] supports this, finding that 16% of respondents had taken both prescribed medications and supplements in the week preceding the interview.

Echinacea is one of the most popular herbal supplements, with a sales ranking of #2 in the mass market [6] and total sales in 2006 (excluding Walmart sales), reaching more than $36 million in the US [7]. Native Americans introduced echinacea to European settlers, after which it became one of the most popular remedies used by the Eclectic physicians for a variety of conditions including septicemia, typhoid fever, and catarrhal conditions of the respiratory and reproductive tracts [8, 9]. Additionally, physicians practicing from the 19th century through the mid 20th century used echinacea to treat other infections and counteract venomous snakebites [10]. Echinacea was included in the National Formulary from 1906 until 1950, eventually falling out of favor as pharmaceuticals came to dominate clini-

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Abbreviations: CYP 450, cytochrome P450; **CYP1A2,** cytochrome P450 1A2; **CYP3A4,** cytochrome P450 3A4; **CYP2D6,** cytochrome P450 2D6; **OATP-B,** organic anion-transporting polypeptide; **ROS,** reactive oxygen species

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cal therapeutics. Currently, the aerial portion of *Echinacea purpurea* and the roots of *E. pallida* are approved for colds and infection of the respiratory and urinary tracts by the German Commission E [11].

The current body of scientific literature on echinacea can be confusing not only due to the multiple species in use – namely *E. purpurea*, *E. pallida*, and *E. angustifolia* – which have phytochemical similarities, but also have notable differences, particularly around the identity and concentration of alkylamides and other key constituents [12–14]. Even though 80% of the echinacea products sold to consumers are made from *purpurea* [15], all three species are often used interchangeably for the treatment of cold, flu, respiratory infection, and inflammation [16]. Multiple species, plant parts, and preparations are also used, each of which may have a different constituent profile [17]. "Echinacea" may refer to the roots, aerial parts, whole plant, or a combination of the above; echinacea products can be made from fresh or dried plant parts, and may be prepared by juicing, alcohol extraction, infusion, decoction, or consumed as tablets or capsules [18].

Many authors suggest that taking herbs such as echinacea is potentially unsafe for those taking prescription medications, and statements of warnings/cautions about drug–herb interactions are frequently found in the scientific and medical literature [19–21]. In discussing ranking schemes of medicinal plant efficacy and safety, Mills (Mills, S., submitted pers. comm.) points out that if safety statements were graded to the same rigor as efficacy statements, most of the papers citing poor safety records of herbal remedies would fail the burden of proof. For example, Messina [19], as well as Vickers and Zollman [21], citing an inaccurate report that echinacea is hepatotoxic due to pyrrolizidine alkaloid content [22], contend that echinacea should not be used with known hepatotoxic drugs. Other authors have noted that the echinacea poses no risk of hepatotoxicity [23–25]. The saturated pyrrolizidines found in echinacea lack any toxicity, unlike unsaturated pyrrolizidines which are highly susceptible to nucleophilic reactions [26].

To the detriment of the healthcare field, such misleading information appears to be common in the literature, misinforming healthcare providers and unnecessarily frightening patients. Brazier and Levine [27] found that of 240 articles that pertained to drug–herb interactions, the majority of the reports were anecdotal – less than 10% reported primary data. Coon [28] reported that of 165 possible drug–herb interactions, only 13% were supported by clinical data. Of the 352 papers we found as relevant to drug interactions with medicinal plant preparations in a MEDLINE search limited to 2006, only 4.2% were actual case reports and 4.0% were clinical trials. It appears that the vast majority of the data on drug–herb interactions are not based on primary reports. Hence, the aim of this review is to provide a critical evaluation of the primary literature on the evidence of drug interactions with *Echinacea* spp.

2 Methods

We searched the MEDLINE, SciFinder Scholar, Web of Science, Cochrane Library, CAPLUS, and EBSCO databases using the terms echinacea, and "drug interaction," "herb–drug interaction," or "P-glycoprotein" with a cutoff date of 12-15-2006. A manual search of bibliographies from published articles was also performed. Inclusion criteria included the following research models: clinical trials, *in vivo*, *ex vivo*, and *in vitro* investigations. The search was limited to English-language papers; otherwise no limits were placed on the search.

The authors independently assessed abstracts and titles of each publication for evidence pertaining to drug–herb interactions, and acquired full articles that made comments on any *Echinacea* species and drug–herb interactions. Publications that referenced an interaction but did not contain an original report were excluded; only primary literature was assessed. Each interaction reported in the primary literature was evaluated by both authors and later reconciled. Disagreements were resolved by discussion and consensus.

3 Results

Of the 49 articles located, only 8 contained primary evidence of potential interactions between echinacea products and drugs. All other articles either referenced these eight primary studies or were based upon hypothetical interactions (Table 1). Three of these primary articles did not contain complete information about the dosing used [29–31]; only four indicated that the product used was verified before the research was undertaken [31–34]. One of the eight papers tested echinacea in combination with other herbs [30], and therefore yielded little useful information concerning interactions due to echinacea alone and was eliminated from the review.

No documented case studies of echinacea–drug interactions were found. Of the eight primary papers, only two were conducted in a human model [32, 35]. No clinical pharmacokinetic studies that tested coadministration of echinacea products and pharmaceuticals were available. Table 2 summarizes the cytochrome P450 (CYP 450) modulation reported in the eight primary papers.

3.1 Cytochrome P450 interactions

3.1.1 CYP 450 1A2 (CYP1A2)

Both Gurley *et al*. [35] and Gorski *et al*. [32] report human pharmacokinetic results involving CYP1A2. In a study of 12 volunteers who took 1600 mg/day *E. purpurea* root for 8 day, Gorski *et al*. [32] found significant reduction in oral caffeine clearance by 27%. The authors postulated that inhibition at this level could affect CYP1A2 substrates with narrow therapeutic index such as theophylline and cloza-

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pine. Gurley *et al.* [35] found no significant inhibition of CYP1A2 in healthy volunteers after 28 day of 1600 mg/day of whole-plant extract of *E. purpurea*, although a 13% decrease in 6 h paraxanthine/caffeine values suggested a possible inhibitory effect of *E. purpurea* whole-plant extract on CYP1A2. This effect, however, was not statisti-cally significant and was not considered clinically signifi-cant by the authors.

3.1.2 CYP2C9

Yale and Glurich [31] using an unrevealed concentration of a remarkably concentrated 50:1 *E. purpurea* aerial extract,

Table 1. Primary research on drug interactions with *Echinacea* spp.

Author	System tested	Species and part used	Model	Comments
Budzinski *et al.*, 2000	CYP3A4	Tinctures of (ratio unknown), 55% EtOH of *E. angustifolia* + *E. purpurea* (1:1, part unknown); *E. angustifolia* roots; *E. purpurea* roots; *E. purpurea* tops	*In vitro* – fluorometric microtiter plate assay	Ratio of plant material: menstruum was not available. Thus dosing unclear the 1:1 ratio refers to proportion of *E. angustifolia* to *E. purpurea*. Products used were not au-thenticated.
Foster *et al.*, 2003	CYP3A4, CYP2C9, CYP2C19, CYP2D6	*Echinacea Plus* – blend including *E. purpurea* and *angustifolia (plant part not specified)*, extract of *E. purpurea* root, and assorted other herbs; *Echinacea* special – 210 mg \(triple Echinacea\) root *per* cup, 18 mg standardized *E. purpurea* root extract *per* cup	*In vitro* – aliquots screened for ability to affect *in vitro* metabolism of marker substances	Teas were mixtures, dosing of echinacea unclear, parts used unclear in some cases, mixed teas were not inspected visually or authenticated
Fuchikami *et al.*, 2006	OATP-B	*E. purpurea*, aerial parts	*In vitro* – uptake of estrone-3-sulfate (an OATP-B substrate) measured in human embryonic kidney 293 cells	No human studies contextualize clinical relevance of this info; paper does not indi-cate if product was verified to actually be *E. purpurea*
Gorski *et al.*, 2004	CYP1A2, CYP2C9, CYP2D6, CYP3A	*E. purpurea*, root	*In vivo* – 12 human volunteers underwent a control phase to test for metabolism of substrates of these 4 enzymes; then they took 400 mg *E. purpurea* root QID for 8 day. Substrates were readmi-nistered and blood/urine samples taken	Formulation used was previously tested by Consumer Labs and shown to have >1% phenols. No adverse events reported by volunteers or observed by researchers
Gurley, 2004	CYP3A4, CYP1A2, CYP2E1, CYP2D6	*Echinacea purpurea*, whole-plant extract	*In vivo* – 12 young adults partici-pated in an open-label study randomized for supplementation sequence (three other herbs were tested). Took 800 mg BID for 28 day. Phenotypic metabolic ratios were used to determine probe drug clearance before and after supplementation periods	While mean levels were not affected, there was interindividual varaion – some indi-viduals appear to have significant inhibi-tion or induction. One person had a minor rash while taking Ech. Product used was tested for marker compounds to confirm identity of *E. purpurea*
Moulick and Raner, 2003	CYP2E1, CYP1A	*E. purpurea*, root	*In vitro* – substrate *p*-nitrophenol concentration monitored using human liver microsomes and expressed CYP450 2E1 and 1A2	Only abstract available. Direct communi-cation with author provided information on species, plant part, dose, *etc.*
Raner *et al.*, 2007	CYP2E1	*E. purpurea*, root; isolated alkylamides; cichoric acid	*In vitro* – substrate *p*-nitrophenol concentration monitored using human liver microsomes and expressed CYP450 2E1	Extract characterized by MS, individual al-kylamides and cichoric acid also tested
Yale and Glurich, 2005	CYP2D6, 3A4, 2C9	*E. purpurea*, aerial portion, used cap with 50 mg of 50:1 extract, 15% pressed juice	*In vitro* – well plates with cDNA-derived enzymes in microsomes prepared from baculovirus-in-fected insect cells	Product tested by Consumer Lab to ensure identity of product and minimal lot-to-lot variation

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Table 2. The Effect of *Echinacea* spp. on CYP 450

CYP 450 isoform	Species	Plant part	Preparation	Concentration (dose)	Model	Results	Author
1A	*purpurea*	Root	95% EtOH, 1:2 fresh	0.2–2%	*In vitro*	No effect on ethoxycoumarin metabolism	(Moulick and Raner, 2003)
1A2	*purpurea*	Root	Capsule	1600 mg/day × 8 day	*In vivo*	27% ↓ in oral caffeine clearance	(Gorski *et al.*, 2004)
1A2	*purpurea*	Whole plant	Capsule	1600 mg/day × 28 day	Clinical trial	13% ↓ in paraxanthine/caffeine serum ratios, not statistically significant	(Gurley *et al.*, 2004)
2C9	*purpurea*	Aerial	50:1 extract (15% pressed juice)	Unspecified	*In vitro*	Inhibition of 7-methoxy-4-trifluoromethyl coumarin	[31] (Yale and Glurich, 2005)
2C9	*purpurea*	Root	Capsule	1600 mg/day × 8 day	*In vivo*	11% − in oral tolbutamide clearance	(Gorski *et al.*, 2004)
2D6	*purpurea*	Aerial	50 mg of 50:1 extract (15% pressed juice)	Unspecified	*In vitro*	No effect on AMMC metabolism	(Yale and Glurich, 2005)
2D6	*purpurea*	Root	Capsule	1600 mg/day × 8 day	*In vivo*	No effect on metabolism of dextromethorphan	(Gorski *et al.*, 2004)
2D6	*purpurea*	Whole plant	Capsule	1600 mg/day × 28 day	Clinical trial	No statistical significance in 4-hydroxydebrisoquin/[debrisoquin 4-hydroxydebrisoquin]) urinary ratios	(Gurley *et al.*, 2004)
2E1	*purpurea*	Root	95% EtOH 1:2 fresh	0.4%	*In vitro*	29% inhibition of *p*-nitrophenol metabolism	(Raner *et al.*, 2007)
2E1	*purpurea*	Whole plant	Capsule	1600 mg/day × 28 day	Clinical trial	No statistical significance in 6-hydroxychlorzoxazone/chlorzoxazone serum ratios	(Gurley *et al.*, 2004)
3A4	*angustifolia*	Root	55% EtOH ratio unspecified	Unspecified IC50 1–2%	*In vitro*	IC50 extrapolated, inhibition of 7-benzyloxyresorufin metabolism	(Budzinski *et al.*, 2000)
3A4	*angustifolia* + *purpurea* 1:1	Part unknown	55% EtOH ext, ratio unspecified	Unspecified IC50 >5% and <10%	*In vitro*	Inhibition of 7-benzyloxyresorufin metabolism	(Budzinski *et al.*, 2000)
3A4	*purpurea*	Aerial	55% EtOH ratio unspecified	Unspecified IC50 >5% and <10%	*In vitro*	\)Moderately inhibitory\) (IC50 >5% and <10%), concentration unlikely to be physiologically relevant	(Budzinski *et al.*, 2000)
3A4	*purpurea*	Aerial	50 mg of 50:1 extract, 15% pressed juice	Unspecified	*In vitro*	No inhibition of resorufin benzyl ether and \(mild inhibition\) of 7-benzyloxy-4-trifluoromethyl coumarin	(Yale and Glurich, 2005)
3A4	*purpurea*	Root	55% EtOH ratio unspecified	Unspecified IC50 >1% and <5%	*In vitro*	Inhibition of 7-benzyloxyresorufin metabolism	(Budzinski *et al.*, 2000)
3A4	*purpurea*	Root	Capsule	1600 mg/day × 8 day	Clinical trial	No change in oral clearance of midazolam; though F_H and F_G affected differently volume of distribution (AUC) not significantly affected 42% − systemic clearance; 18% ↓ F_H; F_G − two-fold; 50% − F_{oral} of midazolam	(Gorski *et al.*, 2004)
3A4	*purpurea*	Whole plant	Capsule	1600 mg/day × 28 day	Clinical trial	No statistical significant difference in 1-hydroxymidazolam/midazolam serum ratios	(Gurley *et al.*, 2004)
HLM	*purpurea*	Root	95% EtOH 1:2 fresh	0.4%	*In vitro*	27% inhibition of *p*-nitrophenol metabolism	(Raner *et al.*, 2007)

AMCC 3-[2-(*N*,*N*-diethyl-*N* methyl amino) ethyl]-7-methoxy-4-methylcoumarin; HLM, human liver microsomes; F_H, hepatic availability; F_G, GI availability.

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reported mild *in vitro* inhibition. Gorski *et al.* [32] reported an 11% reduction in clearance of tolbutamide, a substrate of CPY2C9, after 8 day of *E. purpurea* root supplementation. Gorski *et al.* [32] suggest this interaction is not clinically significant.

3.1.3 CYP 450 2D6 (CYP2D6)

Evidence from the Gurley *et al.* [35] and Gorski *et al.* [32] studies presented above, as well as *in vitro* evidence from Yale and Gurlich [31] have shown no interaction between *E. purpurea* (aerial parts or root) and CYP2D6. Both human studies concluded that no interactions were expected between *E. purpurea* and substrates of CYP2D6.

3.1.4 CYP2E1

Gurley *et al.* [35] found no significant effects on CYP2E1 after 28 day of 1600 mg/day *E. purpurea* whole-plant extract. *In vitro* data from Raner *et al.* [34], suggest inhibition of CYP2E1 by an ethanolic extract of *E. purpurea* root, reporting a concentration of 2 µL/mL of a 95% EtOH extract producing a 27–29% inhibition. Of particular interest was the finding that the same concentration of a 33% EtOH extract of *E. purpurea* root did not demonstrate CYP2E1 inhibition.

3.1.5 CYP3A4

Conflicting data were reported for CYP3A4; *in vitro* research, some at concentrations not obtainable with oral dosing, suggested mild to strong inhibition on CYP3A4 while human trials show no overall CYP3A4 activity. Budzinski *et al.*, using benzyloxyresorufin as a substrate and extract of (i) the *E. purpurea* aerial portion or (ii) a mixture of *E. purpurea* aerial portions and *E. angustifolia* root (1:1), observed moderate inhibition of CYP3A4 (unspecified extract ratio, IC50 >5% and <10%). Using solely the roots of both *angustifolia* and *purpurea* resulted in higher inhibition of CYP3A4 (unspecified extract ratio, IC50 >1% and <5%) [29]. The concentrations of extracts used in these assays, if typical of commercial extracts, are unobtainable by oral dosing.

Further *in vitro* research by Budzinski *et al.* [29] reported a significant difference in the effects of *E. purpurea versus E. angustifolia* roots on CYP3A4. While *E. angustifolia* demonstrated a strong inhibitory effect on CYP3A4 activity, *E. purpurea* was found to be a mild inhibitor of CYP3A4 for 7-benzyloxy-4-trifluoromethyl-coumarin metabolism and had no activity on resorufin benzyl ether metabolism, except at nonrelevant physiological concentrations (resulting in mild inhibition) [35]. Another *in vitro* investigation [29] demonstrated hydroethanolic extracts of *E. purpurea* aerial portion and a combination of *E. purpurea* and *E. angustifolia* (plant parts unspecified) moderately inhibited CYP3A4-mediated 7-benzyloxyresorufin metabolism while root extracts of *E. purpurea* and *E. angustifolia* demonstrated strong inhib-

ition. Unfortunately, not enough data were provided to calculate the concentration of plant material that generated these results.

Human investigations by Gorski *et al.* [32], found no changes in the metabolism of midazolam, a CYP3A4 substrate, after participants ingested 1600 mg of *E. purpurea* root daily for 8 day. While the authors observed an 85% increase in intestinal availability of midazolam, a 15% reduction of hepatic availability ($p < 0.003$) was also noted. The authors postulated that the induction of hepatic CYP3A4 counteracted inhibition of intestinal CYP3A4, leading to little to no effect in midazolam metabolism overall [32]. Using *E. purpurea* whole-plant extract (aerial and root combined) in a human trial Gurley *et al.* [35] found no statistically significant differences in CYP3A4 phenotypic ratios [35]. CYP 450 phenotypic ratios have been shown to provide a practical method for predicting CYP-mediated drug interactions [35].

3.2 Organic anion-transporting polypeptide (OATP-B)

Fuchikami *et al.* [36] found inhibition of OATP-B by the aerial parts of *E. purpurea in vitro*. The clinical significance of this finding is unclear, as few drugs are metabolized *via* this pathway and the findings have not been demonstrated *in vivo*.

3.3 P-glycoprotein

No primary reports involving the constituents of any *Echinacea* species could be found.

4 Discussion

The search for and appraisal of information relating to drug–herb interactions are a challenge for researchers and educators; accurate, readily accessible information for the medical community is lacking. Unfortunately, reports on drug–herb interactions have only recently been published in the scientific literature. Perhaps due to the void in primary data, it appears that the majority of authors make recommendations without evaluating the quality of evidence from which their conclusions are drawn.

A common shortcoming of many drug–herb interaction reports is that investigators fail to report species, plant part used, preparation type and concentrations assayed, and/or dose, each of which may affect the accuracy of reporting and the potential for drug–herb interactions. Additionally, a recent study of echinacea products found that the relationship between labeled milligrams and measured milligrams was poor, suggesting that clinical and research studies may be difficult to correlate with the products taken by consumers [37].

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Our results demonstrate that although drug–herb interactions related to echinacea products were cited in some 49 articles, only 16% (8) of these 49 papers contained primary data relevant to interactions between echinacea products and pharmaceuticals. Two studies were clinical trials [32, 35] and the remaining were *in vitro* assays, three of which did not contain complete information about the concentration of extract used [29–31]; only half of the studies verified the authenticity of the echinacea [31–34]. One paper was dropped because echinacea was used in combination with other herbs [30].

The bulk of the available data on possible drug–echinacea interactions concerns the CYP 450s, a large family of hepatic phase I detoxification enzymes that also are essential in a myriad of enzymatic reactions implicated in tissues other than the liver [38]. CYP 450 genes code for enzymes that play a role in the metabolism of drugs and foreign chemicals as well as arachidonic acid metabolism and formation of eicosanoids, cholesterol metabolism, bile acid synthesis, steroid metabolism, vitamin D and vitamin A metabolism [38]. CYP450s are crucial in understanding the clinical pharmacology of drug interactions in addition to interindividual variability in drug metabolism.

In vitro studies suggest that *E. purpurea* root may mildly reduce clearance of substrates of CYP1A2 and CYP3A4. Human trials by Gorski *et al.* [32] and Gurley *et al.* [35] demonstrate wide interindividual variability of metabolism of various echinacea preparations. Gurley *et al.* [35] concludes that there is a minimal risk of drug interaction from echinacea preparations. These data suggest that, as is the case with pharmaceutical drugs, while the general effect of echinacea products on consumers may be insignificant, rare individuals within the group could possibly experience a more significant induction or inhibition of these enzyme systems or drug transporters. In general, further study of interindividual variability is needed.

CYP1A2, which metabolizes theophylline and other pharmaceuticals, may be particularly relevant for asthma patients. It must be mentioned, however, that clinicians have observed an improvement of asthma and bronchitis with echinacea use, suggesting that echinacea may be useful to asthmatics [39]. Supporting these observations, Sharma *et al.* [40] found that preparations of root and aerial portions of echinacea reversed the inflammatory response of human bronchial epithelial cells to rhinovirus. Furthermore, particular alkylamides of *Echinacea* spp. are cyclooxygenase [41, 42] and lipoxygenase [41, 43] inhibitors, as well as antiviral [14, 44] and cannabinomimetic [45–49]. Considering that such activity may offer a significant reduction of spasm and the inflammatory processes of asthma [50–52], possibly protect against upper respiratory tract infections [53] and that echinacea inhibition of CYP1A2 is insignificant to mild as found in the human trials reviewed here, recommendations for individuals with asthma to halt echinacea should be reserved for exceptional circumstances.

Echinacea may mildly inhibit the CYP 450 3A4 enzyme system; this inhibition may be tissue specific. For example, Mouly *et al.* [54] report that selected substrates can increase hepatic CYP3A activity, yet have no effect on intestinal CYP3A4 or, conversely, substrates may generate CYP intestinal activity without inducing hepatic effects. Gorski *et al.* [32] also report tissue specific activity, finding that *E. purpurea* root extracts demonstrate inhibition of intestinal, and induction of hepatic, CYP3A activity. The molecular rationale behind these differential effects is still unclear. Gorski's group suggests that echinacea root preparations taken with high oral availability/low clearance drugs (*e.g.*, alprazolam) may induce hepatic CYP3A4 resulting in decreased serum concentrations. Conversely, they suggest that low oral clearance/first-pass metabolism drugs (*e.g.*, buspirone) taken with echinacea might result in increased drug serum concentrations. More data are needed to support this contention [32].

It has been suggested that CYP3A4 is the most important enzyme for the metabolism of antineoplastic drugs [55]. Thus the information that echinacea may modulate, even weakly, the activity of 3A4 may encourage healthcare providers to warn against the use of echinacea with patients undergoing chemotherapy. However, such warnings could be disadvantageous to the patient; *in vivo* studies of *E. purpurea* aerial parts demonstrate a reduction in chemotherapy induced leucopenia [12, 56–59], while *E. purpurea* root has demonstrated stimulation of natural killer cells [60–62] and prolongation of life in leukemic mice [63]. Additionally, a number of *Echinacea* species and constituents have demonstrated direct antineoplastic activity *in vitro* [64–66]. Thus again, case by case recommendations are needed for cancer patients rather than a generalized recommendation to halt echinacea use.

Another isoform of the CYP 450 system, CYP2D6, is known to play a primary role in the metabolism of pharmaceuticals used to treat psychiatric disorders (attention deficit/hyperactivity disorders, bipolar disorder, depression, schizophrenia) as well as cardiovascular disorders (β-blockers). *E. purpurea* products containing root or aerial parts in both human [35] and *in vitro* models [31] has shown no activity on CYP2D6. The current research suggests that no interactions are expected between *E. purpurea* products and substrates of CYP2D6.

The available data also suggest that extraction conditions, the various species and botanical part of echinacea have differing effects on the CYP 450 enzyme system [34]. For example, Raner *et al.* [34] found that the hydrophobic constituents of *E. purpurea* (*e.g.*, alkylamides) are much more inhibitory to CYP450 than its hydrophilic constituents (*e.g.*, phenylpropanoids) and this work is in agreement with other CYP 450 evaluations [67]. Recent work by Spelman *et al.* (Spelman, K., Wetschler, M. H., Cech, N. B., submitted.) demonstrated quantitative and qualitative differences in alkylamide concentrations, including the alkylamides

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reported to modulate CYP activity, depending on the extraction technique and the use of fresh or dry plant material in ethanolic preparations of *E. purpurea radix*. Thus, ethanolic extracts as well as other echinacea preparations may differ in their activity on the CYP 450 system and therefore generalizations about echinacea products and drug–herb interactions may be misleading (Spelman, K., Wetschler, M. H., Cech, N. B., submitted.).

Although there are two human trials in this collection of data, the remaining five studies attempt to extrapolate data from *in vitro* models. The fact that replicating relevant models of human physiology are difficult with *in vitro* methods is widely acknowledged. Researchers are globally aware that *in vitro* experimental models are often poorly representative of *in vivo* models, especially in regard to gene expression, enzyme levels and metabolism [68]. One constraint includes the absence of digestive and metabolic processing of compounds within an extract by *in vitro* models (although one study, Fuchikami *et al.* [36], attempted a "digestion" in their model). Cech *et al.* [69] has demonstrated that alkylamide metabolites of human liver microsomes have different immunological activity as compared to their nonmetabolized counterparts, yet such significant findings are frequently missed *in vitro*. Another limitation concerns the experimental concentrations of echinacea extracts utilized for *in vitro* models. Two of the studies appear to have used concentrations of extract that are impossible to achieve by oral dosing of echinacea extracts [29, 31]. Central to the evaluation of these studies are the previous investigations that have demonstrated that 0.4 ng/mL ($\pm$0.31 ng/mL) are the maximum serum levels reached by the dominant alkylamide, dodecatetraenoic acid isobutylamide, in echinacea [70]. This particular alkylamide has been previously shown, *in vitro*, to play a role in inhibition of CYP 450 3A4 [67]. A more recent study has suggested that the lowest obtainable IC50 for CYP 3A4 of dodecatetraenoic acid isobutylamide to be 1.96 mg/mL, almost 5000-fold higher than the predicted concentration within hepatocytes [71]. Thus, within the restraint of the available data, it seems unlikely, even with chemical potentiation by other echinacea constituents, that echinacea will generate drug interactions, *via* CYP 450, of any consequence.

A more obscure and less considered complication of *in vitro* research is the oxidative stress inherently generated by *in vitro* models. The increased exposure to oxygen due to *in vitro* conditions leads to significant reactive oxygen species (ROS) generation and may produce results that are not reflective of *in vivo* conditions [68]. Key to this issue is that many CYP 450 mechanisms are based in redox chemistry. In considering *in vitro* research on the CYP 450 system, increased ROS generation due to *in vitro* conditions may skew the results of these assays. In the case of echinacea extracts, increased ROS generation is particularly likely due to the ease of oxidation of the polyphenols of echinacea. Accordingly, there is an obligatory caution that must

be observed in extrapolating data derived from *in vitro* work to clinical realities, especially in regard to CYP 450 assays.

A missing yet, crucial point in much of the drug metabolism literature is that fruits, vegetables, grains, and legumes, with their inherent phytochemical content, modulate CYP450 enzyme expression, and activity [72]. Yet, except for grapefruit, and tyramine-containing foods, the majority of discussion on drug–herb interactions involves herbal medicine and neglects the more frequently consumed plant-based foods. Humans are routinely exposed to foods such as the cruciferious vegetables with their indole-3-carbinols that modulate phase I and phase II detoxification [38]. The ubiquitous flavonoids found in most plant-based foods are also known to modulate a number of isoforms of CYP 450 [73]. Other commonly consumed phytochemicals such as caffeine are known to modulate CYP 450 function [73]. Hence, it is crucial that pharmacokinetic studies investigating the possibility of drug–herb interactions control for diet. Fortunately, Gorski *et al.* [32], requested CYP 450 appropriate dietary restrictions of their subjects, as did Gurley *et al.* [35]. However, in both trials dietary restrictions depended on voluntary compliance as there is limited opportunity for such trials to impose dietary restrictions without significant burden. Nonetheless, to avoid ambiguity and to provide optimal evaluation of drug–herb interactions, it is crucial that clinical trials on drug–herb interactions include measures to rule out dietary effects on drug metabolism.

Ultimately, to generate clinically relevant data on the CYP 450 enzyme system, multiple substrate concentrations as well as multiple test inhibitor concentrations are required [27, 28, 74]. Unfortunately, this is commonly neglected in both *in vitro* and *in vivo* research and leaves much to the unknown. In the meantime, it appears that many warnings about the effects on *Echinacea* spp. on drug–herb interactions and the CYP 450 system have been based on inadequate evidence leading to inaccuracies in the literature.

We suggest more objective and detailed methods for reporting drug–herb interactions. Since many consumers do not realize that herbs qualify as supplements, investigators, and clinicians must enquire about both "supplement" and "herb" use when recording a proper medical history [29]. Additionally, product verification, dosage, species, and plant part used need to be documented. Occurrences of potential drug–herb interactions need to be investigated with greater accuracy and detail to identify what is clinically relevant and what is not. Currently, 68–90% of data on drug–herb interactions is based on unsubstantiated or poor quality information [28] resulting in anecdotal reporting.

Of the three *Echinacea* species typically used in herbal medicine, the available research predominantly focused on *E. purpurea*, which accounts for 80% of commercial production [15]. No case reports were found documenting an echinacea–drug interaction, a finding supported by other

reviewers [19, 74–77]. The fact that echinacea products rank second in sales of herbal remedies in the US [6] and the number of people using multiple pharmaceuticals (>75 million) [3], suggest that drug–herb interactions with echinacea products are uncommon events. Barrett [78] concludes that less than 100 serious adverse events have been reported involving echinacea for an estimated >10 million courses of treatment, leaving the risk estimate of less than 1 in 100 000.

5 Conclusion

Currently there are no verifiable reports of actual drug–herb interactions with any echinacea product. Both *E. purpurea* aerial parts and root appear to have a relatively low potential to produce CYP-mediated drug–herb interactions. However, further pharmacokinetic testing is required before conclusive statements can be made. Further research is also needed to confirm the potential for herb–drug interactions involving other species of *Echinacea*. In order to further clarify drug–herb interactions, healthcare providers and researchers must account for product verification, dosage, species, and part used. Additionally, data obtained from one product should not be extrapolated to other products, species, plant parts, or dosages.

Although there is not enough evidence to support the need for precautions at this time, a prudent clinical approach is to monitor patients taking echinacea products concurrently with substrates of CYP3A4 or CYP1A2. Given the data in this review, the number of echinacea doses consumed yearly and that the majority of use is short term for the treatment of upper respiratory tract infections, *E. purpurea* products, consisting of roots and aerial parts, do not appear to be a risk to consumers provided that the preparations are authentic. Lastly, for proper public safety measures, it is imperative that drug–herb reporting is done methodically.

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