# Effects on cytochrome P450 and P-glycoprotein

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26. Freeman and Spelman (2008) conducted a literature review and found no verifiable reports of drug–herb interactions involving Echinacea products. They noted that herbal remedies derived from E. purpurea appear to have a low

potential for cytochrome P450 (CYP450)-mediated interactions. The authors further estimated that, given the risk of adverse events (approximately 1 in 100,000), the annual consumption of Echinacea doses (around 10 million), and the fact that most use is short-term, products containing E. purpurea (roots and/or aerial parts) do not pose a significant risk to consumers. Nevertheless, they concluded that although current evidence does not support the need for specific precautions when Echinacea is co-administered with prescription medications, a prudent clinical approach would be to monitor patients taking Echinacea concurrently with substrates of CYP3A4 or CYP1A2.

27. The in vitro studies identified as part of the literature search performed by the Secretariat suggest that Echinacea has the potential to inhibit CYP3A4 (Yale and Glurich, 2005; Modarai et al. 2010; Hellum et al. 2007; Husain et al., 2023), CYP1A2 (Yale and Glurich, 2005; Hellum et al. 2007), CYP2E1 (Raner et al. (2007), CYP2C9 (Yale and Glurich, 2005), CYP2C19 (Modarai et al., 2010) and P-glycoprotein (Husain et al., 2023; Hansen and Nilsen, 2009). Some of the in vitro studies reported a positive association between the total alkylamide content of the Echinacea preparation and its ability to inhibit CYP3A4 (Modarai et al. 2010) and CYP1A2 (Raner et al. 2007).

28. A clinical study on human volunteers by Gorski (2004) found that E. purpurea root extract (Nature’s Bounty) taken orally at 1,600 mg/day for 8 days was capable of causing significant changes in drug disposition by inhibiting CYP1A2 and intestinal CYP3A activity and by inducing hepatic CYP3A activity. This preparation contained greater than 1% phenols (caftaric acid, chlorogenic acid, echinacoside and chicoric acid). Gorski (2004) concluded that the modest change in the clearance of compounds metabolised by CYP1A2 is considered clinically significant as this can lead to increased toxicity of narrow therapeutic window drugs such as theophylline, which is a substrate for CYP1A2. The authors also speculated that other drugs metabolised by CYP1A2 such as cyclobenzaprine, tacrine, and clozapine can be affected by Echinacea co-administration.

29. Another human study with 12 healthy volunteers (6 men, 6 women) investigated the effects of E. purpurea (800 mg, twice daily) for 28 days on CYP1A2, CYP2D6, CYP2E1 and CYP3A4 phenotypes (Gurley et al., 2004). The composition of the Echinacea preparation was analysed using HPLC and it was determined that it contained 13.7 mg chicoric acid per capsule, providing a daily dose of 43.8 mg chicoric acid. The administration of E. purpurea did not significantly change the activities of CYP3A4, CYP2E1, and CYP2D6 as estimated by comparing the phenotype ratios before and after treatment. Co-administration

of E. purpurea caused an approximately 13% decrease in the ratio of paraxanthine/caffeine, suggesting that there was a possible inhibitory effect on CYP1A2 enzyme. However, the difference was not statistically significant and the authors did not think it was clinically relevant (Gurley et al., 2004).

# Drug-herb interactions

30. Khaksary Mahabady *et al*. (2006) assessed whether *E. purpurea* extract or levamisole could reduce phenytoin-induced cleft palate in NMRI mice. Thirty-two pregnant NMRI mice were divided into four groups: saline control (10 mL/kg), phenytoin only (65 mg/kg), phenytoin (65 mg/kg) + levamisole (10 mg/kg), and phenytoin (65 mg/kg) + *E. purpurea* extract (360 mg/kg). All drugs were administered intraperitoneally from the first day of gestation, which was assumed to be upon the discovery of vaginal plug following mating. The study reported that phenytoin alone caused cleft palate in 16% of foetuses, while levamisole and *E. purpurea* reduced this to 5.3% and 3.2%, respectively. Foetal weight and length were significantly reduced in the phenytoin group but remained normal in the treatment groups. The authors concluded that the observed protective activity of levamisole and *Echinacea* against phenytoin-induced cleft palate was due to immunomodulating and anti-inflammatory effects of these agents.