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File: ■ *Echinacea* spp. (Asteraceae)
■ Drug Interactions
■ Adverse Effects

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RE: *Echinacea* spp. Extracts Are Well Tolerated with Few Adverse Effects

Ardjomand-Woelkart K, Bauer R. Review and assessment of medicinal safety data of orally used *Echinacea* preparations. *Planta Med*. 2016;82(1-2):17-31. doi: 10.1055/s-0035-1558096.

Several species of *Echinacea*, including *Echinacea purpurea*, *E. angustifolia*, and *E. pallida* (Asteraceae), are used as complementary medicines to reduce the severity and symptoms of the common cold and other upper respiratory infections. Ethanol or water extracts of the aerial portions of *E. purpurea*, as well as whole plant and root extracts of all three species, are used therapeutically. These extracts contain caffeic acid, alkamides, polysaccharides, and glycoproteins, which may help modulate immune response to infection. Both in vitro and in vivo evidence support this claim. Because plants contain compounds that are bioactive in humans, these compounds may cause side effects and interact with pharmaceutical medications. The focus of this review was to present current evidence on adverse effects, drug interactions, and overall safety of the consumption of echinacea extracts.

Several studies have measured the interaction of echinacea extracts and pharmaceutical drugs. In the developing fetuses of mice, the effect of phenytoin on birth defects was reduced with the simultaneous consumption of echinacea extract. In addition, echinacea extract was found to increase the clearance of warfarin, yet no clinically significant change in international normalized ratio (INR) measurement was noted. These effects are thought to be mediated through the cytochrome P450 family of oxidases, which are important in the metabolism of pharmaceutical drugs. No effect on drug metabolism has been found when probe drugs, including fexofenadine and several antiretroviral drugs metabolized by cytochrome oxidases, are consumed with echinacea extract. Yet, there is evidence that echinacea extracts, and in particular alkamides, can inhibit cytochrome oxidase activity. There is also evidence that echinacea extracts can affect transcription rates of some cytochrome oxidases, and this effect is dependent on the specific cytochrome oxidase. For instance, in rat livers, the expression of one cytochrome oxidase is increased, while that of another cytochrome oxidase is decreased. These effects may also be tissue dependent. The magnitude of change in

cytochrome oxidase activity and expression with echinacea consumption is not well characterized in humans.

Echinacea extracts can influence the immune response both positively and negatively, and thus, the authors characterize them as immunomodulatory rather than only immunostimulatory. Past recommendations have cautioned against the use of echinacea extracts by patients with autoimmune disorders, but the authors found no evidence to support this recommendation. In contrast, the authors caution the use of echinacea extracts in atopic patients, because these patients tend to have an excessively responsive immune system. Echinacea extracts may also lead to allergic reactions, including exacerbation of asthma symptoms and rash, though these reactions seem to be both mild and rare. Rash was the most common adverse effect seen in children who consumed echinacea extracts.

The consumption of echinacea extract has been associated with several cases of severe adverse effects. In some of these cases though, echinacea was consumed with other medicinal extracts, and the causal mechanism is unknown. For instance, when echinacea extract was consumed with St. John's wort (*Hypericum perforatum*, Hypericaceae), a subject developed erythema nodosum, and another subject experienced exacerbated symptoms of Sjögren's syndrome. In another case, a subject developed leucopenia with the consumption of echinacea, ginkgo (*Ginkgo biloba*, Ginkgoaceae), and bupropion. One healthy subject developed severe thrombocytopenia with the consumption of echinacea extract and another subject with chronic inflammation found this condition exacerbated with echinacea consumption. The symptoms of acute cholestatic autoimmune hepatitis resolved in one subject after the cessation of consumption of echinacea extract. These types of severe adverse reactions appear to be rare; mechanistic explanations are lacking; and causality has not been conclusively demonstrated.

The authors conclude from their review that consumption of echinacea extract is generally safe and that the relatively few serious adverse events repeatedly discussed in the medical literature are based on isolated or single anecdotal case reports with limited confirmatory details. Although several authoritative sources suggest limitations on the duration of therapy with echinacea, the authors could find no data to support such a warning. There is some evidence that echinacea extract can alter the activity and expression of cytochrome oxidases, which are important in the metabolism of pharmaceutical drugs and thereby alter the kinetics of drug metabolism. Despite isolated observed and postulated effects on cytochrome oxidases, there is limited evidence of any clinical significance for patients consuming echinacea concomitantly with pharmaceuticals. As with most botanicals containing complex constituents, allergic reactions are possible in sensitive individuals; those with known allergies or asthma should initiate therapy with caution and consult with their healthcare practitioner. In addition, the authors caution the use of echinacea extract by atopic individuals, individuals prone to asthma, and patients with very sensitive immune systems.

—Cheryl McCutchan, PhD

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