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NLM Citation: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Echinacea. [Updated 2019 Apr 10].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Echinacea

Updated: April 10, 2019.

OVERVIEW

Introduction

Echinacea is a popular herbal medication and extract derived from a flowering plant (Echinacea purpurea) that is native to the United States, East of the Rocky Mountains. Echinacea has been used mostly for treating and preventing the common cold and other upper respiratory illnesses. While echinacea is generally well tolerated with only few and minor adverse effects, there have been isolated reports of serum enzyme elevations and clinically apparent liver injury attributed to its use.

Background

Echinacea (ek" i nay' sha) is a widely used herb derived from the perennial plant, Echinacea purpurea, also known as American coneflower which is native to North America. The above ground parts and roots of the echinacea plant are used either fresh or dried to make teas, juice, extracts, capsules or tablets. The major use is treatment or prevention of upper respiratory infections, but it is also purported to improve immune function and protect against other viral, bacterial and fungal infections, as well as to alleviate anxiety, migraine headaches, dyspepsia, skin rashes and bee stings. There are at least 9 species of echinacea which may vary in therapeutic activities. Extracts of Echinacea purpurea, pallida and angustifolia are the most frequently used and are found in hundreds of commercial herbal and dietary products. The active ingredients of echinacea are not well defined, but plant extracts contain multiple polysaccharides, volatile oils, caffeic and ferulic acid derivatives, flavonoids, alkamides and polyenes. Controlled trials of echinacea in prevention and treatment of common upper respiratory illnesses have yielded mixed results and most systematic reviews have concluded that there is little evidence for its therapeutic effectiveness. On the other hand, echinacea extracts have been repeatedly found to be well tolerated and without major adverse events. The most common adverse events reported have been minor gastrointestinal upset and skin rashes. Rare instances of allergic reactions including urticaria, angioedema and anaphylaxis have been described.

Hepatotoxicity

In multiple controlled trials, echinacea by itself has not been linked to liver injury, either in the form of transient serum enzyme elevations or clinically apparent acute liver injury. Nevertheless, there have been isolated case reports of clinically apparent liver injury with jaundice, and summary reports from national registries of adverse reactions have reported elevated serum aminotransferase levels and toxic hepatitis attributed to echinacea. Few details of the liver injury were available but in two published reports, hepatitis with jaundice arose 1 to 3 weeks after starting echinacea extracts with mild jaundice, prominent ALT and AST elevations and rapid and complete recovery on stopping. Autoimmune features were present in one case, but neither case had features of

hypersensitivity (fever, rash, lymphadenopathy or eosinophilia). Because of the variability in the constituents of echinacea products, it is unclear whether the cases were due to a particular species or method of preparation or contamination of the product.

Likelihood score: D (possible rare cause of clinically apparent liver injury).

Mechanism of Injury

The mechanism by which some preparations of echinacea might cause liver injury is not known but may be due to a contaminant or mislabeling of the product. However, because echinacea has been linked to rare instances of severe allergic reactions, the isolated cases of hepatitis may represent hepatic manifestations of hypersensitivity. Echinacea-drug interactions have not been well defined. While some echinacea preparations demonstrate interference with CYP1A2 and 3A4 activity in vitro and in vivo, the clinical significance of these interactions has not been shown.

Outcome and Management

Patients on echinacea who develop unexplained symptoms such as fatigue, nausea, abdominal pain or dark urine should have routine liver tests drawn and discontinue the herb if there are any abnormalities.

Drug Class: Herbal and Dietary Supplements

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Echinacea – Generic

DRUG CLASS

Herbal and Dietary Supplements

SUMMARY INFORMATION

Fact Sheet at National Center for Complementary and Integrative Health, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Echinacea angustifolia, extract	84696-11-7	Herbal Extract	Not applicable

ANNOTATED BIBLIOGRAPHY

References updated: 10 April 2019

Abbreviations used: HDS, herbal and dietary supplements

Zimmerman HJ. Unconventional drugs. Miscellaneous drugs and diagnostic chemicals. In, Zimmerman, HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott,1999: pp. 731-4.

(Expert review of hepatotoxicity published in 1999; echinacea is not discussed).

Seeff L, Stickel F, Navarro VJ. Hepatotoxicity of herbals and dietary supplements. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 631-58.

(Review of hepatotoxicity of herbal and dietary supplements [HDS]; echinacea is not discussed).

Echinacea. In, PDR for herbal medicines. 4th ed. Montvale, New Jersey: Thomson Healthcare Inc. 2007: pp. 266-75.

(Compilation of short monographs on herbal medications and dietary supplements).

Melchart D, Walther E, Linde K, Brandmaier R, Lersch C. Echinacea root extracts for the prevention of upper respiratory tract infections: a double blind, placebo-controlled randomized trial. Arch Fam Med 1998; 7: 541-5. PubMed PMID: 9821828.

(Among 302 healthy adults treated with E. purpurae or E. angustifolia extracts or placebo twice daily for 12 weeks, the incidence and time to a respiratory tract infection was similar in the 3 groups and there were no serious adverse events).

Mullins RJ. Echinacea-associated anaphylaxis. Med J Aust 1998; 168: 170-1. PubMed PMID: 9507713.

(37 year old woman with a history of asthma and multiple allergies developed throat burning, chest tightness and urticaria within minutes of swallowing an echinacea preparation which resolved within a few hours, later showing positive skin reactions and RAST testing results with echinacea extract).

Brinkeborn RM, Shah DV, Degenring FH. Echinaforce and other Echinacea fresh plant preparations in the treatment of the common cold. A randomized, placebo controlled, double-blind clinical trial. Phytomedicine 1999; 6: 1-6. PubMed PMID: 10228604.

(Among 246 adults with a common cold treated with one of 3 echinacea preparations or placebo, symptom scores were less with two of the herbal preparations and the most frequent adverse event was transient and mild nausea).

Henneicke-von Zepelin H, Hentschel C, Schnitker J, Kohnen R, Köhler G, Wüstenberg P. Efficacy and safety of a fixed combination phytomedicine in the treatment of the common cold (acute viral respiratory tract infection): results of a randomised, double blind, placebo controlled, multicentre study. Curr Med Res Opin 1999; 15: 214-27. PubMed PMID: 10621929.

(Among 263 patients with a common cold treated with an herbal mixture containing echinacea or placebo for 7-9 days, total symptom scores improved faster with the herbal product, rates of adverse reactions were similar in the two groups and no serious adverse events were reported).

Mullins RJ, Heddle R. Adverse reactions associated with echinacea: the Australian experience. Ann Allergy Asthma Immunol 2002; 88: 42-51. PubMed PMID: 11814277.

(Report of 5 patients with allergic reactions to echinacea [2 anaphylaxis, 2 asthma, 1 rash], several with recurrence on rechallenge and review of Australian adverse drug reports identified 26 cases of suspected IgE mediated hypersensitivity reactions to echinacea; similar cases attributed to echinacea were also found in US, UK, Canadian and New Zealand registries).

Barrett BP, Brown RL, Locken K, Maberry R, Bobula JA, D'Alessio D. Treatment of the common cold with unrefined echinacea. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 2002; 137: 939-46. PubMed PMID: 12484708.

(Among 148 college students with early symptoms of a common cold treated with echinacea or placebo for up to 10 days, the severity and duration of symptoms were similar in the two groups and adverse events were mild and uncommon).

Ernst E. The risk-benefit profile of commonly used herbal therapies: Ginkgo, St. John's Wort, Ginseng, Echinacea, Saw Palmetto, and Kava. Ann Intern Med 2002; 136: 42-53. PubMed PMID: 11777363.

(Review of the efficacy and safety of common herbal therapies including echinacea mentions that data on its efficacy in preventing upper respiratory infections were inconclusive, and that adverse effects were rare but included allergic reactions which can be severe and include hepatitis).

Schiano TD. Hepatotoxicity and complementary and alternative medicines. Clin Liver Dis 2003; 7: 453-73. PubMed PMID: 12879994.

(Comprehensive review of herbal associated hepatotoxicity; echinacea is not listed as causing hepatotoxicity).

Taylor JA, Weber W, Standish L, Quinn H, Goesling J, McGann M, Calabrese C. Efficacy and safety of echinacea in treating upper respiratory tract infections in children: a randomized controlled trial. JAMA 2003; 290: 2824-30. PubMed PMID: 14657066.

(Among 407 children who developed an upper respiratory infection and were treated with echinacea or placebo for up to 10 days, the duration and severity of symptoms were not different in the two groups while rash was more frequent with echinacea [7.1% vs 2.7%]).

Yale SH, Liu K. Echinacea purpurea therapy for the treatment of the common cold: a randomized, double-blind, placebo-controlled clinical trial. Arch Intern Med 2004; 164: 1237-41. PubMed PMID: 15197051.

(Among 128 adults with an acute upper respiratory infection treated with echinacea [aerial portions of E. purpurea] or placebo for up to 14 days, symptom scores improved in both groups at a similar rate, and few adverse events were reported, mostly headache, dry mouth, nausea and abdominal pain, none considered severe).

Cohen HA, Varsano I, Kahan E, Sarrell EM, Uziel Y. Effectiveness of an herbal preparation containing echinacea, propolis, and vitamin C in preventing respiratory tract infections in children: a randomized, double-blind, placebo-controlled, multicenter study. Arch Pediatr Adolesc Med 2004; 158: 217-21. PubMed PMID: 14993078.

(Among 430 children [ages 1 to 5 years] treated with a commercial mixed echinacea product or placebo for 12 weeks, the number of upper respiratory infections and days of fever were less in the echinacea treated children, and adverse events were uncommon and mild and similar in rates between the two groups).

Russo MW, Galanko JA, Shrestha R, Fried MW, Watkins P. Liver transplantation for acute liver failure from drug-induced liver injury in the United States. Liver Transpl 2004; 10: 1018-23. PubMed PMID: 15390328.

(Among ~50,000 liver transplants reported to UNOS between 1990 and 2002, 270 [0.5%] were done for drug induced acute liver failure, including 7 [5%] for herbal medications, none attributed to echinacea).

Naser B, Lund B, Henneicke-von Zepelin HH, Köhler G, Lehmacher W, Scaglione F. A randomized, double-blind, placebo-controlled, clinical dose-response trial of an extract of Baptisia, Echinacea and Thuja for the treatment of patients with common cold. Phytomedicine 2005; 12: 715-22. PubMed PMID: 16323289.

(Among 91 adults with an upper respiratory infection treated with 1 of 2 doses of an herbal mixture containing echinacea or placebo for 3-12 days, facial tissue use was less on day 2 with the herbal product than placebo).

Turner RB, Bauer R, Woelkart K, Hulsey TC, Gangemi JD. An evaluation of Echinacea angustifolia in experimental rhinovirus infections. N Engl J Med 2005; 353: 341-8. PubMed PMID: 16049208.

(Amng 399 healthy adults treated with 1 of 3 preparations of E. angustifolia root extract or placebo and challenged with rhinovirus type 39, there were no differences in duration or severity of upper respiratory tract symptoms and adverse event rates were similar, the most common complaints being gastrointestinal).

Barnes J, Anderson LA, Gibbons S, Phillipson JD. Echinacea species (Echinacea angustifolia (DC.) Hell., Echinacea pallida (Nutt.) Nutt., Echinacea purpurea (L.) Moench): a review of their chemistry, pharmacology and clinical properties. J Pharm Pharmacol 2005; 57: 929-54. PubMed PMID: 16102249.

(Review of the chemistry, pharmacology and clinical efficacy of echinacea stresses the differences between different species in chemical constituents as well as in vitro and clinical effects and adverse events, which are generally mild but may include allergic reactions and herb-drug interactions).

Huntley AL, Thompson Coon J, Ernst E. The safety of herbal medicinal products derived from Echinacea species: a systematic review. Drug Saf 2005; 28: 387-400. PubMed PMID: 15853441.

(Systematic review of the literature on adverse events attributed to echinacea mentions that most studies did not report or reported no or only mild adverse events, largely gastrointestinal and frequently at a similar frequency as with placebo; mentions 8 case reports and data from 5 national registries that note serious allergic reactions including anaphylaxis, erythema nodosum and DRESS syndrome, but no mention of hepatotoxicity).

Kocaman O, Hulagu S, Senturk O. Echinacea-induced severe acute hepatitis with features of cholestatic autoimmune hepatitis. Eur J Intern Med 2008; 19: 148. PubMed PMID: 18249315.

(45 year old man developed jaundice within a month of starting an echinacea root extract [1500 mg daily] [bilirubin 2.8 mg/dL, ALT 1260 U/L, Alk P 984 U/L, INR 1.3, SMA 1:80], resolving within one month of stopping).

Freeman C, Spelman K. A critical evaluation of drug interactions with Echinacea spp. Mol Nutr Food Res 2008; 52: 789-98. PubMed PMID: 18618481.

(A systematic review of the literature found little evidence of clinically significant echinacea-drug interactions, but the number and quality of rigorous scientific studies were limited).

Wallace RB, Gryzlak BM, Zimmerman MB, Nisly NL. Application of FDA adverse event report data to the surveillance of dietary botanical supplements. Ann Pharmacother 2008; 42: 653-60. PubMed PMID: 18397972.

(Description of the FDA's Center for Food Safety and Applied Nutrition Adverse Event Reporting System [CAERS] reporting system and data from 1999 to 2003 for 6 commonly used herbal products including echinacea [68 of 362 reports], often in a multiingredient product [40:59%], most commonly gastrointestinal [23] and dermatologic symptoms [7], but one was "elevated liver function test results").

García-Cortés M, Borraz Y, Lucena MI, Peláez G, Salmerón J, Diago M, Martínez-Sierra MC, et al. [Liver injury induced by "natural remedies": an analysis of cases submitted to the Spanish Liver Toxicity Registry]. Rev Esp Enferm Dig 2008; 100: 688-95. Spanish. PubMed PMID: 19159172.

(Among 521 cases of drug induced liver injury submitted to a Spanish registry, 13 [2%] were due to herbals, but none were attributed to echinacea).

Jacobsson I, Jönsson AK, Gerdén B, Hägg S. Spontaneously reported adverse reactions in association with complementary and alternative medicine substances in Sweden. Pharmacoepidemiol Drug Saf 2009; 18: 1039-47. PubMed PMID: 19650152.

(Review of 778 spontaneous reports of adverse reactions to herbal medicines to a Swedish Registry between 1987 and 2006 found 63 reports of adverse reactions to echinacea [8%], including 5 to "increased hepatic enzymes", 2 to "elevated transaminase" and 2 for "liver necrosis", one of which was fatal in a 28 year old male who had taken "purple coneflower" for 6 months).

Maskatia ZK, Baker K. Hypereosinophilia associated with echinacea use. South Med J 2010; 103: 1173-4. PubMed PMID: 20890257.

(58 year old man with allergic rhinitis and multiple medical problems was found to have marked hypereosinophilia [17,800 per μL] that was unresponsive to medical therapies, but resolved spontaneously when echinacea supplements were stopped).

Barrett B, Brown R, Rakel D, Mundt M, Bone K, Barlow S, Ewers T. Echinacea for treating the common cold: a randomized trial. Ann Intern Med 2010; 153: 769-77. PubMed PMID: 21173411.

(Among 719 patients with early symptoms of a common cold treated with open-label echinacea, or blinded echinacea or placebo, or no pills for 5 days, there were no statistically significant differences in illness severity or duration in the four groups and adverse event rates were similar except that headache was more frequent in the no-pill group).

Teschke R, Wolff A, Frenzel C, Schulze J, Eickhoff A. Herbal hepatotoxicity: a tabular compilation of reported cases. Liver Int 2012 32: 1543-56. PubMed PMID: 22928722.

(A systematic compilation of all publications on the hepatotoxicity of specific herbals identified 185 publications on 60 different herbs and supplements; does not mention or discuss echinacea).

Jawad M, Schoop R, Suter A, Klein P, Eccles R. Safety and efficacy profile of Echinacea purpurea to prevent common cold episodes: a randomized, double-blind, placebo-controlled trial. Evid Based Complement Alternat Med 2012; 2012: 841315. PubMed PMID: 23024696.

(Among 755 healthy adults treated with an echinacea extract or placebo for 4 months, cold episodes were less with echinacea [42% vs 52%], while product related adverse event rates were similar [9.9% vs 9.7%] and there were no serious adverse events with echinacea).

Bunchorntavakul C, Reddy KR. Review article: herbal and dietary supplement hepatotoxicity. Aliment Pharmacol Ther 2013; 37: 3-17. PubMed PMID: 23121117.

(Systematic review of literature on HDS associated liver injury does not discuss echinacea).

Navarro VJ, Barnhart H, Bonkovsky HL, Davern T, Fontana RJ, Grant L, Reddy KR, et al. Liver injury from herbals and dietary supplements in the U.S. Drug-Induced Liver Injury Network. Hepatology 2014; 60:1399-408. PubMed PMID: 25043597.

(Among 85 cases of HDS associated liver injury [not due to anabolic steroids] enrolled in a US prospective study between 2004 and 2013, none were attributed to a known echinacea containing product).

Karsch-Völk M, Barrett B, Kiefer D, Bauer R, Ardjomand-Woelkart K, Linde K. Echinacea for preventing and treating the common cold. Cochrane Database Syst Rev 2014; (2): CD000530. PubMed PMID: 24554461.

(Systematic review of 24 controlled trials [with 4631 participants] of echinacea for preventing or treating the common cold concluded that the benefits of echinacea have not been proven, although many prophylaxis trials showed a trend towards a positive effect).

Seeff LB, Bonkovsky HL, Navarro VJ, Wang G. Herbal products and the liver: a review of adverse effects and mechanisms. Gastroenterology 2015; 148: 517-32. PubMed PMID: 25500423.

(Extensive review of possible beneficial as well as harmful effects of herbal products on the liver does not mention or discuss echinacea).

Gabranis I, Koufakis T, Papakrivos I, Batala S. Echinacea-associated acute cholestatic hepatitis. J Postgrad Med 2015; 61: 211-2. PubMed PMID: 26119446.

(44 year old man developed fatigue shortly after a 5 day course of an echinacea root extract [bilirubin 4.6 mg/dL, ALT 594 U/L, Alk P 269 U/L, GGT 442 U/L, INR 1.49], resolving within 3 months).

García-Cortés M, Robles-Díaz M, Ortega-Alonso A, Medina-Caliz I, Andrade RJ. Hepatotoxicity by dietary supplements: a tabular listing and clinical characteristics. Int J Mol Sci 2016; 17. pii: E537. PubMed PMID: 27070596.

(Listing of published cases of liver injury from HDS products does not mention or discuss echinacea in the listings).

Ardjomand-Woelkart K, Bauer R. Review and assessment of medicinal safety data of orally used echinacea preparations. Planta Med 2016; 82: 17-31. PubMed PMID: 26441065.

(Systematic review of the literature on the safety of oral echinacea concluded that adverse events during treatment are generally mild and not clearly attributable to the herb and that long term studies reported no toxicological concerns; discusses a case report of cholestatic hepatitis [Kocaman 2008]).

Asher GN, Corbett AH, Hawke RL. Common herbal dietary supplement-drug interactions. Am Fam Physician 2017; 96: 101-7. PubMed PMID: 28762712.

(Review of herbal-drug interactions of the commonly used herbal supplements including echinacea for which there are conflicting results of effects on CYP 1A2 and 3A4, for which reason "caution should be taken").

Brown AC. Liver toxicity related to herbs and dietary supplements: Online table of case reports. Part 2 of 5 series. Food Chem Toxicol 2017; 107 (Pt A): 472-501. PubMed PMID: 27402097.

(Description of an online compendium of cases of liver toxicity attributed to HDS products does not mention or discuss echinacea).

Wong LL, Lacar L, Roytman M, Orloff SL. Urgent liver transplantation for dietary supplements: an under-recognized problem. Transplant Proc 2017; 49: 322-5. PubMed PMID: 28219592.

(Among 2048 adult liver transplants recipients enrolled in the Scientific Registry of Transplant Recipients [SRTR] between 2003 and 2015, 625 were done for acute hepatic necrosis due to drug induced liver injury, half being due to acetaminophen and the 4th most frequent cause [n=21] being HDS products, but echinacea was not implicated in any case).