



## Butterbur

Updated: February 18, 2019.

## OVERVIEW

### Introduction

Butterbur is a popular herbal preparation that is used to treat migraine headaches, allergic rhinitis and respiratory illnesses. Butterbur is an extract of the roots of the butterbur bush and the extract has to be processed carefully to eliminate harmful pyrrolizidine alkaloids that occur naturally in the plant. Butterbur preparations processed to remove pyrrolizidine alkaloids do not appear to cause liver injury, either in the form of serum enzyme elevations during treatment or clinically apparent acute liver injury. However, recent cases of clinically apparent liver injury have been reported with use of several commercial preparations of butterbur, suspected to be due to residual pyrrolizidine alkaloid contamination.

### Background

Butterbur is a popular herbal product derived from the rhizomes and stems of the perennial butterbur bush (*Petasites hybridus*), a plant native to Europe. Butterbur is so named because its large leaves were used to wrap butter for storage. Butterbur extracts have been used for centuries in traditional medicine and purported uses were for plague, asthma, gastrointestinal and respiratory illnesses and cancer. Chemical components of butterbur extracts include sesquiterpene alcohol esters (petasitine, neopetasitine and isopetasitine), volatile oils, flavonoids and tannins. Extracts from butterbur leaves and stems can contain pyrrolizidine alkaloids (senecionine, integerrimine), which are toxic molecules capable of causing sinusoidal obstruction syndrome in animals as well as humans. Butterbur herbal products for oral use must be specially processed to remove any traces of pyrrolizidine alkaloids. Some evidence suggests that butterbur is effective in the treatment of migraine headaches and allergic rhinitis, but its long term efficacy and safety have not been established, and it is not specifically approved for these uses in the United States. Butterbur is available in a variety of formulations and the typical oral dosage is 100 to 150 mg per day in 2 to 3 divided doses. Side effects of butterbur are uncommon and mild, and include gastrointestinal upset, eructation, nausea, diarrhea, headache, dizziness, increased bleeding tendency and rash. In clinical trials, both serious and common side effects were often no more frequent with butterbur than placebo.

### Hepatotoxicity

Despite widespread use, butterbur extracts that are free of pyrrolizidine alkaloids have not been specifically linked to liver injury, either in the form of transient serum enzyme elevations or clinically apparent acute liver injury. However, because the processing of butterbur is critical to the safety of the herbal product, it has to be used with caution. After the European approval of a commercial butterbur product for use in migraine headache prevention, isolated reports of cholestatic hepatitis arose. Testing suggested that some preparations contained

detectable amounts of pyrrolizidine alkaloids and some of the products were withdrawn. The relationship of the liver injury to butterbur remains controversial. A single publication summarizing clinical features of 10 cases reported to the sponsor has suggested that the liver injury was not related to the butterbur product, but 8 of the 10 cases were reasonably convincing and described a consistent clinical phenotype of fatigue, nausea and jaundice usually arising within 2 to 12 weeks of starting the product and marked by a hepatocellular pattern of injury and moderate-to-severe jaundice. Two cases resulted in urgent liver transplants, while the others apparently recovered, usually within 2 to 12 weeks. The clinical features of cases did not resemble sinusoidal obstruction syndrome and liver biopsy showed an acute hepatitis with variable degrees of cholestasis, but minimal steatosis or fibrosis and no mention of sinusoidal obstruction. Similar cases have not been described from other butterbur products.

Likelihood score: C (probable cause of clinically apparent liver injury, possibly caused by contaminants).

## Mechanism of Injury

The mechanism by which some preparations of butterbur might cause liver injury is not known but is likely due to a contaminant or mislabeling of the product. Butterbur-drug interactions have not been defined. While pyrrolizidine alkaloids are mentioned as the possible cause of liver injury associated with butterbur use, the clinical features of cases occurring during treatment suggested idiosyncratic liver injury rather than direct sinusoidal cell damage.

## Outcome and Management

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

Other Names: Petasites Extract, Purple Butterbur

Drug Class: [Herbal and Dietary Supplements](#)

## PRODUCT INFORMATION

### REPRESENTATIVE TRADE NAMES

Butterbur – Generic

### DRUG CLASS

Herbal and Dietary Supplements

### COMPLETE LABELING

[Fact Sheet at National Center for Complementary and Integrative Health](#)

## CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Butterbur	90082-63-6	Herbal Extract	Not applicable

## ANNOTATED BIBLIOGRAPHY

References updated: 18 February 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; butterbur is not discussed).*

Liu LU, Schiano TD. Hepatotoxicity of herbal medicines, vitamins and natural hepatotoxins. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 2nd ed. New York: Informa Healthcare USA, 2007, pp. 733-54.

*(Review of hepatotoxicity of herbal and dietary supplements published in 2007; butterbur is not listed).*

Petasites. In, PDR for Herbal Medicines. 4th ed. Montvale, New Jersey: Thomson Healthcare Inc. 2007: pp. 646-8.

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

Grossman W, Schmidramsl H. An extract of Petasites hybridus is effective in the prophylaxis of migraine. Altern Med Rev 2001; 6: 303-10. PubMed PMID: 11410074.

*(Among 60 patients with migraine headaches enrolled in a 4 month controlled trial, monthly migraine frequency decreased more with butterbur [3.5 to 1.7] than placebo [2.9 to 2.6]) and “no adverse events were reported in the drug group”).*

Danesch U, Rittinghausen R. Safety of a patented special butterbur root extract for migraine prevention. Headache 2003; 43: 76-8. PubMed PMID: 12864764.

*(Summary of tolerability and safety results from pre- and postmarketing studies of a commercial butterbur product, found adverse event rates were similar in butterbur as placebo recipients, and surveillance identified only a low rate of complaints of eructation and skin rash; no mention of ALT levels but states that a single instance of reversible cholestatic hepatitis was attributed to a hypersensitivity reaction to butterbur in postmarketing surveillance studies; no details provided).*

Brattström A. A newly developed extract (Ze 339) from butterbur (Petasites hybridus L.) is clinically efficient in allergic rhinitis(hay fever). Phytomedicine 2003; 10 Suppl 4: 50-2. PubMed PMID: 12807342.

*(Among 317 patients with allergic rhinitis treated with butterbur, cetirizine or placebo for 2 weeks in 2 randomized controlled trials, “the incidence and type of adverse events were indistinguishable across the herbal treatment groups and placebo”).*

Lipton RB, Göbel H, Einhäupl KM, Wilks K, Mauskop A. Petasites hybridus root (butterbur) is an effective preventive treatment for migraine. Neurology 2004; 63: 2240-4. PubMed PMID: 15623680.

*(Among 245 adults with chronic migraines treated with butterbur [50 or 75 mg] or placebo twice daily for 4 months, migraine frequency rates decreased by 32% and 45% vs 28%, while adverse events that were more frequent with butterbur included mild gastrointestinal complaints identified in 26% and 22% vs 7%; no mention of ALT elevations or hepatotoxicity).*

Schapowal A; Petasites Study Group. Butterbur Ze339 for the treatment of intermittent allergic rhinitis: dose-dependent efficacy in a prospective, randomized, double-blind, placebo-controlled study. Arch Otolaryngol Head Neck Surg 2004; 130: 1381-6. PubMed PMID: 15611396.

*(Among 186 patients with allergic rhinitis treated with butterbur or placebo 2 or 3 times daily for 2 weeks, response rates were higher with butterbur [91% and 71% vs 46%] while adverse event rates were similar; no mention of ALT changes or hepatotoxicity).*

- Schapowal A; Study Group. Treating intermittent allergic rhinitis: a prospective, randomized, placebo and antihistamine-controlled study of Butterbur extract Ze 339. *Phytother Res* 2005; 19: 530-7. PubMed PMID: 16114089.
- (Among 330 patients with allergic rhinitis treated with a commercial butterbur product [Ze 339] vs fexofenadine vs placebo for 2 weeks, the response rates by day 14 were 32% vs 33% vs 5%, and there were no serious adverse events and no change in ALT, AST or GGT levels with treatment).*
- Pothmann R, Danesch U. Migraine prevention in children and adolescents: results of an open study with a special butterbur root extract. *Headache* 2005; 45: 196-203. PubMed PMID: 15836592.
- (Among 108 children [ages 6 to 17 years] with migraines treated in an open-label trial with a commercial preparation of butterbur [Petadolex] for 4 months, the frequency of migraines was reduced by 63% and side effects were uncommon and mild [eructation in 4%]; there were no severe adverse reactions and no mention of ALT elevations or hepatotoxicity).*
- Käufeler R, Polasek W, Brattström A, Koetter U. Efficacy and safety of butterbur herbal extract Ze 339 in seasonal allergic rhinitis: postmarketing surveillance study. *Adv Ther* 2006; 23: 373-84. PubMed PMID: 16751170.
- (Summary of two uncontrolled open-label trials of a commercial preparation of butterbur [Ze 339] in 580 patients with allergic rhinitis found that 90% of treated subjects reported improvements in symptoms).*
- 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 herbals to Swedish Registry, none of which were attributed to butterbur).*
- Navarro VJ. Herbal and dietary supplement hepatotoxicity. *Semin Liver Dis* 2009; 29: 373-82. PubMed PMID: 19826971.
- (Overview of the regulatory environment, clinical patterns, and future directions in research with HDS; butterbur is not listed as a potentially hepatotoxic botanical).*
- Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. *Hepatology* 2010; 52: 2065-76. PubMed PMID: 20949552.
- (Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 [11%] were attributed to drug induced liver injury of which 12 [9%] were due to HDS, but none incriminated butterbur).*
- Stickel F, Kessebohm K, Weimann R, Seitz HK. Review of liver injury associated with dietary supplements. *Liver Int* 2011; 31: 595-605. PubMed PMID: 21457433.
- (Review of liver injury from HDS focusing upon Herbalife and Hydroxycut products, green tea, usnic acid, Noni juice, and Chinese herbs; does not mention butterbur).*
- 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, none of which contained butterbur).*
- 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 butterbur).*

Prieto J. Update on the efficacy and safety of Petadolex, a butterbur extract for migraine prophylaxis. *Bot Target Ther* 2014; 4: 1-9. Not in PubMed

*(Review of the efficacy and safety of butterbur extract for migraine prophylaxis; mentions that the controlled trials of commercial preparations of butterbur reported low rates of mild adverse events, but that postmarketing studies from Europe have identified as many as 40 instances of clinically apparent liver injury [thought to be due to pyrrolizidine alkaloids in the products despite extraction methods thought to remove them]; these liver related adverse events led to the withdrawal of several butterbur products in Switzerland and Germany, but they are still available commercially in the US and via the internet).*

Teschke R, Eickhoff A, Schulze J, Wolff A, Frenzel C. Petadolex, a herbal extract for migraine prophylaxis with spontaneous case reports of disputed liver injury: robust causality evaluation by RUCAM. *Eur J Pharmaceut Med Res* 2016; 3 (12): 154-77. Not in PubMed

*(Clinical description of cases of liver injury attributed to butterbur [Petadolex] reported to the manufacturer from Germany and Austria; includes 8 reasonably convincing cases: 7 women, 1 man; ages 24 to 58 years; presenting with hepatocellular injury [bilirubin 5.7-14.0 mg/dL, ALT 220-4458 U/L, Alk P 107-252 U/L], resolving within 2-16 weeks in most but 2 requiring liver transplantation).*

Tepper SJ. Nutraceutical and other modalities for the treatment of headache. *Continuum (Minneap Minn)* 2015; 21 (4 Headache): 1018-31. PubMed PMID: 26252588.

*(Review of the mechanism of action, clinical efficacy and safety of herbal products used to treat or prevent migraine; mentions that butterbur may have some efficacy, but some commercial preparations have been found to be hepatotoxic).*

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: 537. PubMed PMID: 27070596.

*(Listing of published cases of liver injury from HDS products does not mention butterbur).*

Drugs for migraine. *Med Lett Drugs Ther* 2017; 59 (1514): 27-32. PubMed PMID: 28170366.

*(Concise review of the treatment and prevention of migraine headaches; mentions that butterbur has been reported to decrease rates of migraine headaches but may be hepatotoxic and is best avoided).*

Orr SL. The evidence for the role of nutraceuticals in the management of pediatric migraine: a review. *Curr Pain Headache Rep* 2018; 22: 37. PubMed PMID: 29619575.

*(Review of the efficacy and safety of nutraceuticals for migraine; mentions that butterbur extracts have shown efficacy in reducing the frequency of migraine in small clinical trials, but postmarketing surveillance revealed several cases of hepatotoxicity attributed to presence of pyrrolizidine alkaloids in some of commercial preparations).*

Sprenger T, Viana M, Tassorelli C. Current prophylactic medications for migraine and their potential mechanisms of action. *Neurotherapeutics* 2018; 15: 313-23. PubMed PMID: 29671241.

*(Review of the clinical efficacy and safety of drugs for prevention of migraine headaches discusses two herbal products, feverfew and butterbur for which only moderate evidence for effectiveness has been published).*