Chemical Information Review Document

for

Butterbur (*Petasites hybridus, ext.*) [CAS No. 90082-63-6]

Supporting Nomination for Toxicological Evaluation by the National Toxicology Program

November 2009

National Toxicology Program
National Institute of Environmental Health Sciences
National Institutes of Health
U.S Department of Health and Human Services
Research Triangle Park, NC
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Abstract

Butterbur, a perennial shrub found in Europe, Asia, and North America, has been marketed in the United States as a dietary supplement. It has been used to treat a variety of ailments including migraines and tension headaches, spasms of the urogenital and digestive tracts, asthma, allergic rhinitis, allergic skin disease, gastric ulcers, ocular allergy, and wounds. Overall, human studies suggest that there is good scientific evidence to support the use of butterbur for the prevention of allergic rhinitis and treatment of migraines and that there is unclear or conflicting evidence for its use for the treatment of allergic skin disease and asthma. There was insufficient evidence for a variety of other conditions including gastric ulcers, ocular allergy, and wound/skin healing. Numerous side effects have been reported in clinical studies (e.g., gastrointestinal upset, nausea, headache, drowsiness, and halitosis). Butterbur also may exacerbate the effects produced by anticholinergic drugs and herbs. In acute toxicity studies, butterbur had LD_{50}s of ≥2500 and 1000 mg/kg in rats by the oral and intraperitoneal routes, respectively. Butterbur extracts have been reported to have neuroprotective effects. Studies with butterbur components S-petasin and iso-S-petasin show that both modulate endocrine metabolism in rat testicular cells and Leydig cells, respectively. *In vivo*, S-petasin inhibited human chorionic gonadotropin-induced increases of plasma testosterone levels. Butterbur extracts were reported to be mutagenic in *Salmonella typhimurium* strains TA100 and TA98. Butterbur flower extracts inactivated the mutagenic effect of 3-amino-1,4-dimethyl-5H-pyrido[4,3β] indole but not tryptophan pyrolysates. Extracts also modulated cytochrome P450 side-chain cleavage enzyme, 11β-hydroxylase, cyclooxygenase-2, urokinase, and 5-lipoxygenase activity. S-petasin and iso-S-petasin displayed cardiovascular effects; for example, both antagonized calcium channel activity and decreased heart rates in male Sprague-Dawley rats after intravenous injection. Additionally, S-petasin was shown to have steroid effects *in vivo* and *in vitro*. It transiently inhibited basal and adrenocorticotropin-induced corticosterone concentrations in rats. In rat zona fasciculate-reticularis cells, it inhibited release of pregnenolone and 11β-hydroxylase activity induced by 25-hydroxycholesterol and release of corticosterone induced by adrenocorticotropin, forskolin, and 8-bromoadenosine 3,5-cyclic monophosphate.

Executive Summary

Basis for Nomination

Butterbur (*Petasites hybridus*) was nominated by the National Institute of Environmental Health Sciences for comprehensive toxicological characterization because of its widespread use and rapidly gaining popularity as a dietary supplement, lack of toxicological data, and suspicion of toxicity based on pharmacological activity of some butterbur constituents. An additional safety concern is the potential presence of hepatotoxic pyrrolizidine alkaloids in some butterbur products. It has numerous applications and expanding clinical interest in the treatment of migraines, allergic rhinitis, and asthma.

Nontoxicological Data

Butterbur is a perennial shrub found in wet, marshy soil, damp forests, and river banks or streams. It is found throughout Europe, Asia, and North America. Plant species other than *P. hybridus* may be referred to as butterbur or other synonyms. The extracts from butterbur are used to treat a variety of ailments including spasms of the urogenital and digestive tracts, asthma, migraines, and allergic rhinitis. It is typically processed by extraction of the leaves or rhizomes using carbon dioxide or propane under high pressure. The extracts include sesquiterpene esters, pyrrolizidine alkaloids (PAs) and essential oils. The PA levels are generally below the limit of detection. Butterbur is commercially available in a variety of forms (e.g., capsules, extracts, powders, tinctures, and softgels) and is marketed in the United States as a dietary supplement. Teas also can be prepared from the leaves, but consumption is not recommended due to the high PA content. Butterbur is regulated by the U.S. Food and Drug Administration under the Dietary Supplement Health and Education Act of 1994.

Human Data

Many human studies evaluating the beneficial effects of butterbur have been conducted to date; many focused on the treatment of migraines, asthma, and allergic rhinitis. Overall, the studies suggest that butterbur may be useful for the prevention of allergic rhinitis and treatment of migraines and that there is unclear or conflicting evidence for its use for the treatment of asthma Reported adverse effects include headaches, drowsiness, constipation, gastrointestinal upset, hair loss, reversible cholestatic hepatitis, depression, and skin discoloration. One report suggested that butterbur may increase liver enzyme levels. Several reports also describe the removal of a product in Switzerland due to the development of severe liver damage. Butterbur may exacerbate the therapeutic and adverse effects produced by anticholinergic drugs and herbs. Concomitant use of butterbur with agents containing PAs or those that induce cytochrome P450 3A4 should be avoided since there is potential for toxicity. Numerous contraindications to butterbur consumption have been noted.

Toxicological Data

The following sections predominantly pertain to toxicity associated with consumption or administration of *P. hybridus*. However, studies related to other *Petasites* species have been included when no additional information was identified.

No chronic, carcinogenicity, initiation/promotion, cogenotoxicity, or immunotoxicity studies were available for butterbur or its constituents.

Chemical Disposition, Metabolism, and Toxicokinetics

Petasins, a constituent in butterbur extracts, have been reported to have a half-life of 4-6 hours.

Acute Exposure

Acute exposure studies yielded LD_{50} values of ≥2500 and 1000 mg/kg body weight in Wistar rats after oral and intraperitoneal administration, respectively.

Subchronic Exposure

Wistar rats were evaluated for toxic effects after oral exposure for 26 weeks. A no observed adverse effect level could be determined; however, no further details or information were provided.

Synergistic/Antagonistic Effects

Butterbur has been reported to have a variety of synergistic and antagonistic effects. Giant butterbur (*Petasites japonicus* MAX) has neuroprotective properties *in vitro* and *in vivo*. *In vitro*, ethyl acetate and butanol fractions of butterbur blocked Fe^{+2}-induced lipid peroxidation of brain homogenates. *In vivo*, pre-treatment of male mice with butterbur extracts decreased the lethality of kainic acid, delayed onset of neurobehavioral effects associated with kainic acid, blocked the development of seizures, increased cytosolic brain glutathione levels, and reduced kainic acid-induced increases in thiobarbituric acid-reactive substances values. Butterbur extracts also blocked gastric damage induced by ethanol and reduced small intestinal ulcerations induced by indomethacin. Extracts containing different contents of petasin and isopetasin inhibited lipopolysaccharide-induced PGE2 release and p42/44 MAPK activation in primary rat microglial cells. Additionally, extracts inhibited β-hexosaminidase release, leukotriene synthesis, and tumor necrosis factor-α production from immunoglobulin E-sensitized RBL-2H3 mast cells and histamine- and leukotriene-induced contractions of guinea pig trachea strips. A single oral dose (1000 mg/kg) of Japanese butterbur suppressed development of passive cutaneous anaphylaxsis reaction in rats.

Extracts of the butterbur flower (*P. japonicas*) inactivated the mutagenic effect of 3-amino-1,4-dimethyl-5H-pyrido[4,3β] indole in *S. typhimurium* strain TA98. Comparatively, butterbur flower extracts (species not noted) did not inactivate the mutagenic effect of tryptophan pyrolysates.

Cytotoxicity

Bakkenolide A and selected eremophilanes, isolated from the buds and rhizomes of *P. hybridus* respectively, were shown to have cytotoxic activity.

Reproductive and Teratological Effects

S-Petasin inhibited testosterone release in rat testicular interstitial cells. Intravenous (i.v.) administration of S-petasin inhibited human chorionic gonadotropin (hCG)-induced increases of plasma testosterone in male Sprague-Dawley rats. Comparatively, iso-S-petasin reduced basal production of testosterone and/or pregnenolone, as well as that induced by compounds such as hCG and 25-hydroxycholesterol.

Genotoxicity

Butterbur methanol extract (species not noted) was mutagenic in *Salmonella typhimurium* strains TA100 and TA98. Specific activity was 2.7 revertants/mg wet weight.

Other Data

Enzyme Effects

Butterbur extracts and its components have been shown to modulate cytochrome P450 side-chain cleavage enzyme, 11β-hydroxylase, cyclooxygenase-2, urokinase, and 5-lipoxygenase activity.

Cardiovascular Effects

Butterbur constituents S-petasin and iso-S-petasin both antagonize calcium channel activity. Both decreased heart rates in male Sprague-Dawley rats after i.v. injection. Iso-S-petasin also decreased the mean arterial pressure in the treated rats. *In vitro* studies showed that S-petasin decreased the right atrial spontaneous firing rate, inhibited electrically stimulated contractions of the left atrium, and modulated L-type Ca^{+2} channels. Iso-S-petasin antagonized agonist-induced aortic ring contractions and modulated L-type Ca^{+2} channels.

Steroid Effects
S-Petasin transiently inhibited basal and adrenocorticotropin (ACTH)-induced corticosterone concentrations 30 minutes after i.v. administration to male Sprague-Dawley rats. *In vitro* studies showed that S-petasin inhibited ACTH-, forskolin-, and 8-bromoadenosine 3,5-cyclic monophosphate-induced release of corticosterone from rat cells and inhibited 25-hydroxycholesterol-induced release of pregnenolone and 11β-hydroxylase activity.

Structure-Activity Relationships
No data were available that were directly applicable.

Table of Contents

Chemical Information Review Document for Butterbur (*Petasites hybridus, ext.*) [CAS No. 90082-63-6]

1.0 Basis for Nomination

Butterbur (*Petasites hybridus*) was nominated by the National Institute of Environmental Health Sciences for comprehensive toxicological characterization because of its widespread use and rapidly gaining popularity as a dietary supplement, an almost complete lack of toxicological data, and suspicion of toxicity based on pharmacological activity of some butterbur constituents. An additional safety concern is the potential presence of hepatotoxic pyrrolizidine alkaloids in some butterbur products. It has numerous applications and expanding clinical interest in the treatment of migraines, allergic rhinitis, and asthma.

2.0 Introduction

Butterbur is a perennial shrub found in wet, marshy soil, damp forests, and in river banks or streams. It is found throughout Europe, Asia, and North America. The broad leaves, which open when flowering, can measure up to 60 cm in diameter and grows up to 3 feet in height. Runners, measuring a meter long, originate from the rhizome. The rhizomes (*Petasitidis rhizome*) and leaves (*Petasitidis folium*) are used for medicinal purposes (Giles et al., 2008; Kalin, 2002).

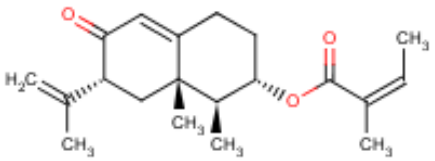
Butterbur (*Petasites hybridus, ext.*)
[CAS No. 90082-63-6]

Source: Wikipedia (2005)

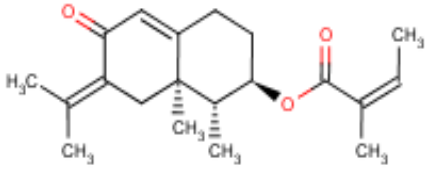
Butterbur extracts contain sesquiterpene esters, pyrrolizidine alkaloids (PAs) and essential oils. The pharmacological and toxicological properties of the sesquiterpene esters have been evaluated in experimental and clinical studies. At least 20 different sesquiterpene ester derivatives have been identified (Kalin, 2002). The main active constituents of butterbur are petasin and isopetasin (Anonymous, 2001 [PMID:11302783]). The major PAs (account for more than 90% of the total alkaloids in butterbur) are senecionine and integerrimine (Wildi et al., 1998 [PMID:17253240]).

Major Constituents

(+)-Petasin
[26577-85-5]



Isopetasin
[469-26-1]



Plant species other than *P. hybridus* may be referred to as butterbur or other synonyms [see list in **Section 2.1**]. Structural similarities in the leaf structure have been noted between *P. hybridus* and *Tussilago farfara* (coltsfoot). However, some differences have been noted. The length:basal diameter ratio of the marginal foliar teeth on both plants is different between the two (1.49 ± 0.26 vs. 0.76 ± 0.28, respectively). Furthermore, the marginal foliar teeth of coltsfoot leaves are stained reddish when sunlit (Gaffal, 2007).

2.1 Chemical Identification and Analysis

Butterbur synonyms and related substances include:

Blatterdock
Bog rhubarb
Boghorms
Butcher's rhubarb
Butter-dock
Butterbur coltsfoot
Butterfly dock
Capdockin
Coughwort
Donnhove
Exwort
European pestwort
Flapperdock
Fuki
Horsehoof
Japanese butterbur
Japonica petasites
Langwort
Pestwurz
Petadolex®
Petadolor H
Petaforce®
Petasites
Petasites hydbridus
Petasites officinalis
Petasites vulgaris folium
Petasitidis rhizome
Petasitidis hybridus
Plague root
Purple butterbur
Tesalin®
Tussilago hybrid
Tussilago petasites
Umbrella leaves
Western coltsfoot
Wild rhubarb
ZE339

Sources: Giles et al. (2008); Natural Medicines Comprehensive Database (2008); Sok et al., 2006 [PMID:15997340]

Constituents

(+)-Petasin ($C_{20}H_{28}O_3$) is also called:

2-Butanoic acid, 2-methyl-,1,2,3,4,6,7,8,8a-octahydro-1,8a-dimethyl-7-(1-methylethenyl)-6-oxo-2-naphthalenyl ester, (1R-(1alpha,2beta(Z),7beta,8aalpha))-

PubChem CID: 6450257
InChI: 1/C20H28O3/c1-7-13(4)19(22)23-18-9-8-15-10-17(21)16(12(2)3)11-20(15,6)14(18)5/h7,10,14,16,18H,2,8-9,11H2,1,3-6H3/b13-7-/t14-,16-,18+,20+/m1/s1
Smiles: CC=C(C)C(=O)OC1CCC2=CC(=O)C(=C(C)C)CC2(C1C)C

Isopetasin ($C_{20}H_{28}O_3$) is also called:
Eremophila-7(11),9-dien-8-one, 3alpha-hydroxy-, 2-methylcrotonate, (Z)-

PubChem CID: 5318627
InChI: 1/C20H28O3/c1-7-13(4)19(22)23-18-9-8-15-10-17(21)16(12(2)3)11-20(15,6)14(18)5/h7,10,14,18H,8-9,11H2,1-6H3/b13-7-/t14-,18+,20+/m0/s1
Smiles: C1[C@@]2([C@H]([C@@H](CCC2=CC(=O)\C1=C(/C)C)OC(=O)\C(=C/C)C)C)C

Sources: ChemIDplus (undated-a,b); PubChem (undated)

2.2 Physical-Chemical Properties

Property	Information	Reference(s)
	(+)-Petasin	
Physical State	Not available	
Odor	Not available	
Boiling Point (°C)	421.1 ± 45.0 (predicted)	Registry (2008a)
Melting Point (°C)	65-70	Registry (2008a)
Flash Point (°C)	181.6 ± 28.8 (predicted)	Registry (2008a)
Vapor Pressure (mm Hg)	2.68×10^{-7} @ 25 °C (predicted)	Registry (2008a)
Specific Gravity	Not available	
Water Solubility	Not available	
Octanol-water partition coefficient (log K_{OW})	Not available	
Bioconcentration factor	2558.97 (pH 1-10) @ 25 °C (predicted)	Registry (2008a)
Log P	4.78 ± 0.406 @ 25 °C (predicted)	Registry (2008a)
	Isopetasin	
Physical State	Not available	
Odor	Not available	
Boiling Point (°C)	428.4 ± 45.0 (predicted)	Registry (2008b)
Melting Point (°C)	96-98	Registry (2008b)
Flash Point (°C)	185.1 ± 28.8 (predicted)	Registry (2008b)
Vapor Pressure (mm Hg)	1.52×10^{-7} @ 25 °C (predicted)	Registry (2008b)
Specific Gravity	Not available	
Water Solubility	Not available	
Octanol-water partition coefficient (log K_{OW})	Not available	
Bioconcentration factor	9465.02 (pH 1-10) @ 25 °C (predicted)	Registry (2008b)
Log P	5.534 ± 0.413 @ 25 °C (predicted)	Registry (2008b)

Analysis

Several studies have evaluated the differences in butterbur constituent content based on a variety of factors (e.g., different parts of the plant and different sites). Below is provided a summary of some evaluated studies. Methods used for quantitative evaluation of the components of butterbur include high performance liquid chromatography (HPLC), gas chromatography, mass spectrometry, nuclear magnetic resonance, and enzyme immunoassays.

Qualitative analysis, using HPLC, of butterbur leaves and rhizomes found in different sites in Switzerland indicated varying levels of petasin and PAs. Petasin concentrations in rhizomes ranged from 7.4 to 15.3 mg/g dry weight. Similarly, petasin content in butterbur leaves ranged from 3.3 to 11.4 mg/g dry weight. In all samples, PA content was greater in the rhizomes (4.8 to 89.9 µg/g) than in the leaves (0.02 to 1.50 µg/g) (Wildi et al., 1998 [PMID:17253240]). Analysis of sesquiterpenes in butterbur plant parts (rhizome, roots, runners, buds, leaves, and stalks) was carried out by HPLC with photodiode array detection. Weight ratios for iso-, neo-, and petasin isomers were 1:17:14, 1:6:8, and 1:4:843 in roots, leaves, and stalks, respectively (Debrunner et al., 1995). Butterbur rhizomes, leaves, and buds were collected, washed, freeze-dried, ground to fine powder, centrifuged, and extracted with methylene chloride. Rhizomes extracts separated by medium pressure liquid chromatography and analyzed by HPLC with photodiode array detector identified furanoeremophilane, 9-hydroxy-furanoeremophilane (30-37%), furanopetasin (16-21%), 2-senecioyl-furanopetasol, 2-tigloyl-furanopetasol, and 2-methylthiocryloyl-furanopetasol (6-10%). Compounds found from flowers (9-oxo-furanoeremophilane and 9-oxo-furanopetasin) and leaves (furanopetasin and 9-oxo-furanopetassin) were not quantitated (Siegenthaler and Neuenschwander, 1997).

Essential oils of butterbur rhizomes obtained by hydrodistillation for 2.5 hours, collected in 1-mL *n*-hexane solvent, determined by gas chromatography, mass spectrometry, nuclear magnetic resonance, and chemical correlations identified two sesquiterpene hydrocarbons, petasitene and pethybrene (mass spectrum *m/z* 149) (Saritas et al., 2002 [PMID:11937157]). The alkaloid content of butterbur leaves determined by enzyme immunoassay was 3.86 ppm (calculated as senecionine) and 104.8 ppm in rhizomes (Langer et al., 1996 [PMID:8693043]).

2.3 Commercial Availability

The same extract as the one used in Germany since 1972 has been available in the United States since 1997 as a dietary supplement (Danesch, 2004 [PMID:15005644]).

Butterbur capsules, extracts, powders, tinctures, and softgels (e.g., Source Naturals, undated; The Vitamin Shoppe, 2008) are commercially available via the Internet (e.g., Amazon.com, 2008; Google.com, 2008; iHerb.com, 2008; Liveandfeel.com, 2008; Vitacost.com, 2008; Youbuy, 2008). Petadolex Butterbur Gelcaps are available throughout Europe and the Unites States from Weber and Weber (Migraineaid.com, undated). A Swiss company, Zeller, also markets a supplement known as Tesalin®, which is referred to as Ze 339 in most clinical studies (Anonymous, 2003). The Dietary Supplements Labels Database (2007), managed by the U.S. National Library of Medicine, did not show any supplements containing "Butterbur" as one of their ingredients.

Petadolex and Urovex are two popular commercial products that contain butterbur. Petadolex, a commercially available *P. hybridus* rhizome extract, is manufactured by Weber & Weber International GmbH & Co. The extract is obtained by using liquid carbon dioxide (CO_2) extraction and contains petasins at minimum concentration of 15% (Danesch, 2004 [PMID:15005644]). The commercially available gelcap currently comes in dosages of 50 and 75 mg (Migraineaid.com, undated). Urovex is an extract of the aerial parts of *P. hybridus* (Nutrition

Geeks.com, undated). One website noted that Urovex and Petadolex were not identical, but did contain similar amounts of petasins (Smartbodyz Nutrition, 2009).

3.0 Production Processes

Current processing methods of *P. hybridus* typically include extraction of the aerial parts or rhizomes. Extraction of butterbur rhizomes using liquid CO_2 under increased pressure yields extracts that contain PAs below the detection limit (0.1 ppm) (Danesch and Rittinghausen, 2003 [PMID:12864764]; Kalin, 2002). [For more information on PAs, see **Section 7.0**.] A CO_2 extraction of the aerial parts of the butterbur plant also removes PAs (Brown, 2003). High pressure propane also has been shown to produce butterbur extracts, while limiting PA levels (Knez et al., 1999; Koch and Rittinghausen, 2003 pat.). Most commercial products state that the preparations are "guaranteed to be pyrrolizidine alkaloid (PA) free" or "containing no detectable toxic pyrrolizidine alkaloids (PA)" (iHerb.com, 2008; Sahelian, undated); however, no additional information is typically provided. Blummenthal (1998) noted that the daily dose of butterbur must not exceed 1 µg of PAs containing a 1,2-necine structure.

Teas also can be prepared from the leaves. However, due to the high PA content, consumption is not recommended (Kalin, 2002).

4.0 Production and Import Volumes

No data were available.

5.0 Uses

Butterbur has been used since the 17th century to treat a variety of medical conditions. Its anti-inflammatory and spasmolytic effects have been traditionally used to treat spasms of the urogenital and digestive tracts, asthma, tension headaches, dysmenorrhoea, emmenagogue, back pain, and coughs (Kalin, 2002).

Currently, butterbur is used orally for treatment of migraines and tension headaches, spasms of the urogenital and digestive tracts, asthma, allergic rhinitis, gastric ulcers, and dysmenorrhoea (Anonymous, 2001 [PMID:11302783]; Kalin, 2002). Butterbur also is used to treat pain, upset stomach, chronic cough, chills, anxiety, plague, fever, insomnia, wounds, and whooping cough. Some of these uses are not supported by reliable scientific research (Natural Medicines Comprehensive Database, 2008). Arkko et al. (1980) reported the use of butterbur by Finnish cancer patients as an alternative treatment. Butterbur also is being evaluated for the treatment of inflammatory bowel disease (e.g., Crohn's disease and ulcerative colitis), chronic uticaria, and psoriasis (Kalin, 2002).

6.0 Environmental Occurrence and Persistence

No data were available.

7.0 Human Exposure

Exposure from Herbal Preparations

The recommended dosage of butterbur depends upon the manufacturer and the ailment for which it is being used to treat. Butterbur extract dosages range from 100-400 mg/day (Anonymous, 2001 [PMID:11302783]; Butterbur.co.uk, undated; National Supplement Center, undated;

Sahelian, undated). Typically, butterbur extracts have been standardized for at least 7.5 mg of petasin and isopetasin per 50 mg extract. Additional recommended dosages include 4.5-7 g drug/day. The recommended duration of administration ranges from 4-6 weeks per year up to 6 months (Blumenthal, 1998).

It has been noted that PAs are present in butterbur extracts. When metabolized by cytochrome P450, PA metabolites are shown to be toxic and carcinogenic. PA intoxication can lead to the development of Budd-Chiari syndrome. PAs have been associated with the development of benign and malignant epithelial hepatic tumors (e.g., hepatomas, hepatocellular carcinomas, and hemangiosarcomas) (Kalin et al., 2002; OEHHA, 1999). A case report described the death of an infant with lesions associated with veno-occlusive disease. It was shown that the mother consumed large amounts of herbal tea, which contained PAs, during pregnancy (Ernst, 2002).

Contamination by Heavy Metals

Heavy metal contamination of soils, water, and air may lead to absorption by growing herbs. Itoh et al. (1979) evaluated heavy metal contamination of butterbur from central Japan. Results indicated that cadmium and zinc levels ranged from 0.6-15.5 ppm and 37-767 ppm, respectively.

8.0 Regulatory Status

Butterbur is regulated by the U.S. Food and Drug Administration (FDA) under the Dietary Supplement Health and Education Act of 1994. Under this act, the responsibility for ensuring that a supplement is safe falls on the manufacturer. The FDA takes action against an unsafe supplement after it reaches the market (FDA, 2008a).

Under the Bioterrorism Act of 2002, facilities (domestic or foreign) that process, pack, or hold food (including dietary supplements) for consumption for the United States are required to register with the FDA (FDA, 2008b). Weber and Weber (manufacturers of Petadolex®) registered a facility in Germany under this act (Butterburresearch.org, undated).

9.0 Toxicological Data

The following sections predominantly pertain to toxicity associated with consumption or administration of *P. hybridus*. However, studies related to other *Petasites* species have been included when no additional information was identified.

9.1 General Toxicology

9.1.1 Human Data

Many human studies of the beneficial effects of butterbur are available. No attempt was made to retrieve all studies to identify side effects. The Natural Standard Monograph stated that there was good scientific evidence to support the use of butterbur for the prevention of allergic rhinitis and treatment of migraines and that there was unclear or conflicting evidence for its use for the treatment of allergic skin disease and asthma (Giles et al., 2008). There was insufficient evidence for a variety of other conditions including gastric ulcers, ocular allergy, and wound/skin healing.

Singh et al. (2007 [PMID:17994396]) conducted a systematic review of six databases to evaluate the quality of the available studies on ayurvedic/collateral herbs, including butterbur, for the

treatment of asthma. The authors identified four clinical trials on the effect of butterbur for the treatment of asthma; two clinical trials evaluated effects on seasonal allergic rhinitis while two other evaluated effects on asthma. Both studies that evaluated effectiveness on treating asthma showed that butterbur may be an effective in reducing the severity of asthmatic symptoms. The authors stated that the overall quality of the data and the studies was good, with some limitations.

Guo and Pittler (2007) conducted a systematic review of five databases to evaluate the quality of the available studies on butterbur, for the treatment of allergic rhinitis. Six clinical trials met the pre-determined study criteria and were included in the evaluation; three studies evaluated the effectiveness of Ze 399 (Zeller AG) and three studies evaluated Petaforce (Bioforce, Ltd.). Overall, the studies suggested that butterbur extracts were superior to placebos in treating the symptoms of allergic rhinitis. The authors stated that there were some limitations in the studies: (1) three trials were financially supported by the manufacturer, (2) inappropriate statistical analysis was used in one of the trials, and (3) small sample sizes.

Kaufeler et al. (2006 [PMID:16751170]) described the results of a postmarketing surveillance study which included 580 patients (age range 6-90 years) with symptoms of allergic rhinitis. Patients were treated with an average of two tablets of Ze 339 daily for two weeks. All evaluated symptoms (rhinorrhea, sneezing, nasal congestion, itchy eyes and nose, red eyes, and skin irritation) improved after two weeks of therapy. Administration of Ze 339 with another anti-allergenic medication did not lead to greater improvement in symptoms.

Adverse Effects

Side Effects

No reliable studies on the long-term safety (beyond 12-16 weeks) of butterbur are available. Below is a list of reported side effects after oral consumption:

headache	severe nausea	dermal/allergic symptoms
drowsiness	gastrointestinal upset	reversible cholestatic hepatitis
fatigue	difficulty breathing	halitosis
itchy eyes	skin discoloration	hair loss
eye discoloration	pruritis	severe depression
constipation	neurologic disorders	difficulty exhaling
stool discoloration	abdominal pain	

(Danesch, 2004 [PMID:15005644]; Giles et al., 2008; Lipton et al., 2004 [PMID:15623680]; Oelkers-Ax et al., 2008 [PMID:17659990]; Pothmann and Danesch, 2005 [PMID:15836592]).

It also has been noted that butterbur may increase liver enzyme levels (Giles et al., 2008). [Note: Review of the primary article (Schapowal, 2002) indicates that 10 adverse events were reported, one of which was identified as "raised liver enzyme activity." No additional information was provided.] Kaufeler et al. (2006 [PMID:16751170]) described the results of a postmarketing surveillance study which included 580 patients (age range 6-90 years) with symptoms of allergic rhinitis. A total of 28 adverse effects were reported by 22 individuals (3.8% of the study population). Gastric discomfort was the most often reported effect. While no clinical or laboratory parameters were evaluated, the authors reported that there was no evidence of liver

metabolism impairment. Commercial butterbur products were removed from the market in Switzerland due to reports of the development of severe liver damage (Anonymous, 2004; Schlenger, 2004a,b).

One case report in 1988 discussed the development of liver damage in a newborn whose mother consumed coltsfoot (*Tussilago farfara*) tea during pregnancy. Analysis of the tea indicated the presence of *P. hybridus*, which may be referred to as coltsfoot [see **Section 2.1**]. It was proposed that the presence of PAs in *P. hybridus* may have led to the liver damage and death of the child (Dharmananda, undated).

Human Drug/Herbal Interactions

Butterbur may exacerbate the therapeutic and adverse effects produced by anticholinergic drugs and herbs. Concomitant use of butterbur with agents containing PAs (e.g., borage, gravel root, and ragwort) should be avoided since there is potential for additive toxicity (Giles et al., 2008). Since herbs or drugs that induce cytochrome P450 3A4 could theoretically increase conversion of PAs to its toxic metabolites, concomitant use of these inducers and butterbur should be avoided (Natural Medicines Comprehensive Database, 2008).

Contraindications

Butterbur is not recommended for the following:

- pregnant or nursing mothers
- persons with known allergic sensitivity to plants in the *P. hybridus* or *Asteraceae/Compositae* family
- persons on anticoagulant therapy, barbiturates, or blood sugar lowering medications
- persons with liver disease

(Ernst, 2002; Giles et al., 2008; Hudson, 2007)

Drugs.com (undated) notes that the use of butterbur-containing preparations should be considered prior to administration to persons with congestive heart failure due to the negative chronotropic effects that have been seen. *P. formosanus* was reported to inhibit calcium channels (Tepper et al., 2006). [See **Section 9.10** for more information.]

It is not clear whether butterbur use would be unsafe in children (Giles et al., 2008).

9.1.2 Chemical Disposition, Metabolism, and Toxicokinetics

Petasins, a constituent in butterbur extracts, have been reported to have a half-life of 4-6 hours [no other details (e.g., species or route of administration) provided] (Giles et al., 2008).

9.1.3 Acute Exposure

In Wistar rats, an oral acute toxicity value (LD_{50}) of ≥2500 mg/kg body weight was reported for butterbur. The intraperitoneal LD_{50} value was 1000 mg/kg (Danesch and Rittinghausen, 2003 [PMID:12864764]).

9.1.4 Short-Term and Subchronic Exposure

An unpublished 26 week toxicity study in Wistar rats was briefly mentioned in a review article. The authors (employees of Weber & Weber, manufacturers of Petadolex®) stated a no-observed-

adverse-effect level could be determined; however, no further details or information were provided (Danesch and Rittinghausen, 2003 [PMID:12864764]).

9.1.5 Chronic Exposure

No data were available.

9.1.6 Synergistic/Antagonistic Effects

Giant butterbur (*Petasites japonicus* MAX [CAS No. 91845-41-9]) has been shown to possess neuroprotective properties in *in vitro* and *in vivo* animal models. *In vitro* studies showed that ethyl acetate and butanol fractions of butterbur blocked Fe^{+2}-induced lipid peroxidation (in the presence of ascorbic acid) of brain homogenates. *In vivo* studies showed that pretreatment of male ICR mice with methanol extracts of butterbur for 4-5 days decreased the lethality of kainic acid (from approximately 50% to 25%). Additionally, butterbur delayed onset of neurobehavioral effects associated with kainic acid, blocked the development of seizures, increased cytosolic brain glutathione levels, and reduced kainic acid-induced increases in thiobarbituric acid-reactive substances values (Oh et al., 2005 [PMID:16117608]; Sok et al., 2006 [PMID:15997340]). Comparison of sub-fractions of the extract evaluated indicated that the neuroprotective effects appeared to be concentrated within one of the evaluated fractions (Sok et al., 2006 [PMID:15997340]). [Noted: Butterbur extracts had no effect on body weight gain or brain weight.]

Alcoholic extracts of butterbur blocked gastric damage induced by ethanol and reduced small intestinal ulcerations induced by indomethacin (Brune et al., 1993 [PMID:8302945]). Butterbur extracts containing different contents of petasin and isopetasin inhibited lipopolysaccharide-induced PGE2 release and p42/44 MAPK activation in primary rat microglial cells (Fiebich et al., 2005 [PMID:15678367]). Extracts from the aerial parts of butterbur inhibited β-hexosaminidase release, leukotriene synthesis, and tumor necrosis factor-α production from immunoglobulin E-sensitized RBL-2H3 mast cells, and histamine- and leukotriene-induced contractions of guinea pig trachea strips. Additionally, a single oral dose (1 g/kg) of Japanese butterbur suppressed development of passive cutaneous anaphylaxsis reaction in rats (Shimoda et al., 2006 [PMID:16608208]).

Extracts of the butterbur flower (*P. japonicas*) inactivated the mutagenic effect of 3-amino-1,4-dimethyl-5H-pyrido[4,3β] indole in *S. typhimurium* strain TA98 (Ueda et al., 1991). Comparatively, butterbur flower extracts (species not noted) did not inactivate the mutagenic effect of tryptophan pyrolysates (Morita et al., 1978).

9.1.7 Cytotoxicity

Bakkenolide A and selected eremophilanes, isolated from the buds and rhizomes of *P. hybridus*, respectively, were shown to have cytotoxic activity (Bodensieck et al., 2007abstr., 2007; Jamieson et al., 1976).

Schmieder et al. (2007 [PMID:17141243]) evaluated whether plant extracts (including *P. hybridus* Folium extract) protected human umbilical vein endothelial cells from cigarette smoke extract mediated cell death and for direct cytotoxicity. Based on the available description, *P.*

hybridus Folium extract was not significantly protective. No information on cytotoxic effects was provided.

9.2 Reproductive and Teratological Effects

S-Petasin and iso-S-petasin were shown to modulate endocrine metabolism in rat testicular cells and Leydig cells, respectively. S-Petasin inhibited testosterone release in rat testicular interstitial cells. Comparatively, iso-S-petasin reduced basal production of testosterone and/or pregnenolone, as well as that induced by human chorionic gonadotropin (hCG), 8-bromoadenosine 3,5-cyclic monophosphate (8-Br-cAMP), A23187 (calcium ionophore), trilostaine, and 25-hydroxycholesterol (Fang et al., 2003 abstr.).

Intravenous (i.v.) administration of S-petasin (1 μg/mL/kg) inhibited hCG-induced increases of plasma testosterone levels in male Sprague-Dawley rats. *In vitro* studies in rat testicular interstitial cells further showed that S-petasin inhibited basal-, hCG-, forskolin-, and androstenedione-induced testosterone release (Lin et al., 2000 [PMID:11132091]).

9.3 Carcinogenicity

No data were available.

9.4 Initiation/Promotion Studies

No data were available.

9.5 Genotoxicity

Butterbur methanol extracts (species not noted) were mutagenic in *Salmonella typhimurium* strains TA98 and TA100. Specific activity and total activity were reported as 2.7 revertants/mg wet weight and 7 revertants $\times 10^{-2}$, respectively (Takahashi et al., 1979 [PMID:390386]). S-Petasin inhibited DNA synthesis in cardiomyocytes and vascular smooth muscle cells (Sheykhzade et al., 2008 [PMID:18655785]).

9.6 Cogenotoxicity

No data were available.

9.7 Immunotoxicity

No data were available.

9.8 Other Data

Enzyme Effects

Several studies have shown that butterbur and its components inhibit a variety of enzymes. In rat zona fasciculate-reticularis (ZFR) cells, S-petasin increased the Michaelis constants of cytochrome P450 side-chain cleavage enzyme and 11β-hydroxylase (Chang et al., 2004 [PMID:15063152]). In rat primary microglial cells, lipophilic extracts from *P. hybridus* rhizomes preferentially inhibited cyclooxygenase-2 compared to cyclooxygenase-1. Interestingly, the observed inhibitory effect was independent of petasin content (Fiebich et al., 2005 [PMID:15678367]). Japanese butterbur was shown to inhibit urokinase and 5-lipoxygenase activity (Fan et al., 2004 [PMID:15312585]; Sekiya, 1997).

Cardiovascular Effects

Studies with S-petasin and iso-S-petasin indicate that both butterbur constituents possess calcium-antagonizing activity. In anesthetized male Sprague-Dawley rats, i.v. injection (0.1-1.5 mg/kg) of S-petasin decreased heart rate up to 25%. *In vitro* studies further showed that S-petasin decreased the right atrial spontaneous firing rate, inhibited electrically stimulated contractions of the left atrium, and modulated L-type Ca^{+2} channels (Wang et al., 2004 [PMID:15010899]). S-Petasin also has been shown to have direct vasorelaxant effects in vascular smooth muscle cells (Wang et al., 2001; cited by Wang et al., 2004 [PMID:15010899]). Iso-S-petasin also decreased heart rates, as well as the mean arterial pressure, in anesthetized male rats after i.v. injection. Furthermore, iso-S-petasin antagonized agonist-induced aortic ring contractions and modulated L-type Ca^{+2} channels (Wang et al., 2002 [PMID:12079689]). Studies in adult ventricular myocytes showed that acute application of iso-S-petasin inhibited peak shortening and calcium-induced calcium release (Esberg et al., 2003 [PMID:12625873]). Vasodilatory effects of S-Petasinon on mesenteric arteries were proposed to occur through blockade of voltage gated calcium channels (Sheykhzade et al., 2008 [PMID:18655785]).

Steroid Effects

In vivo studies in anesthetized male Sprague-Dawley rats showed that S-petasin inhibited basal and adrenocorticotropin (ACTH)-induced corticosterone concentrations 30 minutes after i.v. administration. The effects were transient and not different from control and induced levels at time points greater than 60 minutes after drug administration. *In vitro* studies showed that S-petasin inhibited ACTH-, forskolin-, and 8-Br-cAMP-induced release of corticosterone from rat ZFR cells at concentrations ranging from 3-100 μM. S-Petasin also inhibited 25-hydroxycholesterol-induced release of pregnenolone and 11β-hydroxylase activity in rat ZFR cells (Chang et al., 2002 [PMID:12817704]).

10.0 Structure-Activity Relationships

No data were available that were directly applicable.

11.0 Online Databases and Secondary References Searched

11.1 Online Databases

National Library of Medicine Databases

PubMed

ChemIDplus – chemical information database that provides links to other databases such as CCRIS, DART, GENE-TOX, HSDB, IRIS, and TRI. A full list of databases and resources searched are available at http://www.nlm.nih.gov/databases/.

STN International Files

AGRICOLA	IPA
BIOSIS	MEDLINE
BIOTECHNO	PASCAL
CABA	Registry
EMBASE	TOXCENTER
ESBIOBASE	

Information on the content, sources, file data, and producer of each of the searched STN International Files is available at http://www.cas.org/support/stngen/dbss/index.html.

Government Printing Office
Code of Federal Regulations (CFR)

11.2 Secondary References

Blumenthal, M., Sr., Ed. 1998. Petasites root; Petasitidis rhizome; *Pestwurzelstock*. In: The Complete German Commission E Monographs: Therapeutic Guide to Herbal Medicines. American Botanical Council, Austin, TX, p. 183.

12.0 References

Amazon.com. 2008. Butterbur [search results]. Internet address: http://www.amazon.com/s/ref=nb_ss_gw/103-6406655-7774250?url=search-alias%3Daps&field-keywords=butterbur&x=18&y=15. Last accessed on July 23, 2008.

Anonymous. 2001. Monograph: *Petasites hybridus* (Butterbur). Altern Med Rev, 6(2):207-209. PubMed abstract Internet address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=11302783. Last accessed on July 29, 2008.

Anonymous. 2003. Petasites – Zeller – ZE 339. Drugs R D, 4:347-379. Abstract from TOXCENTER 2004:62753.

Anonymous. 2004. Revocation of the approval of certain medications containing petasites. Schweizer Apotheker Zeitung, 142:123,CP1. Abstract from IPA 2004:17266.

Arkko, P.J., Arkko, B.L., Kari-Koshinen, O., and Taskinen, P.J. 1980. A survey of unproven cancer remedies and their users in an outpatient clinic for cancer therapy in Finland. Soc Sci Med, 14(6):511-514. Abstract from EMBASE 1981083128.

Bodensieck, A., Gaunitz, F., Gebhardt, R., and Bauer, R. 2007 abstr. *In vitro* evaluation of the cytotoxicity of several eremophilane constituents of *Petasites hybridus* in rat hepatocytes. Planta Med, 73(9):996.

Bodensieck, A., Kunert, O., Haslinger, E., and Bauer, R. 2007. New eremophilane sesquiterpenes from a rhizome extract of *Petasites hybridus*. Helv Chim Acta, 90(1):183-195.

Brown, D. 2003. RE: Butterbur extracts may be effective for seasonal allergic rhinitis. HerbalGram, 56:26-27. Internet address: http://content.herbalgram.org/wholefoodsmarket/herbclip/review.asp?i=43616. Last accessed on August 6, 2008.

Brune, K., Bickel, D., and Peskar, B.A. 1993. Gastro-protective effects by extracts of *Petasites hybridus*: the role of inhibition of peptido-leukotriene synthesis. Planta Med, 59(6):494-496. Abstract from PubMed 8302945. PubMed abstract Internet address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=8302945. Last accessed on July 28, 2008.

Butterbur.co.uk. Undated. Herbal remedy information: medical applications of Butterbur. Internet address: http://www.butterbur.co.uk/medical-applications-of-butterbur.php. Last accessed on July 29, 2008.

Butterburresearch.org. Undated. FDA reviewed. Internet address: http://www.butterburresearch.org/fda.html. Last accessed on July 30, 2008.

Chang, L.L., Tseng, Y.C., Lin, Y.L., Wun, W.S., and Wang, P.S. 2002. Effects of S-petasin on corticosterone release in rats. Chin J Physiol, 45(4):137-142. PubMed abstract Internet address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=12817704. Last accessed on July 28, 2008.

Chang, L.L., Wun, W.S., A., Lin, Y.L., and Wang, P.S. 2004. Effects of S-petasin on cyclic AMP production and enzyme activity of P450scc in rat zona fasciculata-reticularis cells. Eur J Pharmacol, 489(1-2):29-37. Abstract from PubMed 15063152. PubMed abstract Internet address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=15063152. Last accessed on July 28, 2008.

ChemIDplus. Undated-a. (+)-Petasin; RN: 26577-85-5. Internet address: http://chem.sis.nlm.nih.gov/chemidplus/ [searched by CASRN]. Last accessed on June 19, 2008.

ChemIDplus. Undated-b. Isopetasin; RN: 469-26-1. Internet address: http://chem.sis.nlm.nih.gov/chemidplus/ [searched by CASRN]. Last accessed on June 19, 2008

Danesch, U.C. 2004. *Petasites hybridus* (butterbur root) extract in the treatment of asthma—an open trial. Altern Med Rev, 9(1):54-62. PubMed abstract Internet address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=15005644. Last accessed on July 29, 2008.

Danesch, U., and Rittinghausen, R. 2003. Safety of a patented special butterbur root extract for migraine prevention. Headache, 43(1):76-78. PubMed abstract Internet address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=12864764. Last accessed on July 28, 2008.

Debrunner, B., Neuenschwander, M., and Brenneisen, R. 1995. Sesquiterpenes of *Petasites hybridus* (L.) G.M. at Sch.: distribution of sesquiterpenes over plant organs. Pharm Acta Helv, 70(2):167-173.

Dharmananda, S. Undated. Safety issues affecting herbs: Pyrrolizidine alkaloids. Internet address: http://www.itmonline.org/arts/pas.htm. Last accessed on September 30, 2009.

Dietary Supplements Labels Database. 2007. Internet address: http://dietarysupplements.nlm.nih.gov/dietary/index.jsp. Last accessed on July 29, 2008.

Drugs.com. Undated. Butterbur. Internet address: http://www.drugs.com/npp/butterbur.html. Last accessed on July 29, 2008.

Ernst, E. 2002. Herbal medicinal products during pregnancy: Are they safe? BJOG, 109(3):227-235.

Esberg, L.B., Wang, G.J., Lin, Y.L., and Ren, J. 2003. Iso-S-petasin, a hypotensive sesquiterpene from *Petasites formosanus*, depresses cardiac contraction and intracellular Ca^{2+} transients in adult rat ventricular myocytes. J Pharm Pharmacol, 55(1):103-107. Abstract from PubMed 12625873. PubMed abstract Internet address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=12625873. Last accessed on July 28, 2008.

Fan, Y.-J., Ohara, A., and Matsuhisa, T. 2004. Test for urokinase-type plasminogen activator inhibitor of edible plants *in vitro*. Zhonghua Yu Fang Yi Xue Za Zhi [Chin J Prev Med], 38(4):252-256. Abstract from PubMed 15312585. PubMed abstract Internet address:

http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=15312585. Last accessed on July 28, 2008.

Fang, C.-F., Tseng, W.-M., Tseng, C.-I., Huang, W.-J., and Wang, P.S. 2003 abstr. Effect of iso-S-petasin on the production of testosterone in rat Leydig cells. Biol Reprod, 68(Suppl. 1):360.

FDA (U.S. Food and Drug Administration). 2008a. Dietary Supplements: Overview. Internet address: http://vm.cfsan.fda.gov/~dms/supplmnt.html. Last accessed on July 30, 2008.

FDA. 2008b. Registration of food facilities. Internet address: http://www.cfsan.fda.gov/~furls/ovffreg.html. Last accessed on July 30, 2008.

Fiebich, B.L., Grozdeva, M., Hess, S., Hull, M., Danesch, U., Bodensieck, A., and Bauer, R. 2005. *Petasites hybridus* extracts *in vitro* inhibit COX-2 and PGE2 release by direct interaction with the enzyme and by preventing p42/44 MAP kinase activation in rat primary microglial cells. Planta Med, 71(1):12-19. Abstract from PubMed 15678367. PubMed abstract Internet address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=15678367. Last accessed on July 28, 2008.

Gaffal, K.P. 2007. Fragments of the marginal teeth in pulverized drugs of coltsfoot leaves (*Tussilago farfara*) and butterbur leaves (*Petasites hybridus*) facilitate the proof of their identity. Z Arznei Gewurzpflanzen, 12(1):42-44. Abstract from CABA 2007:188080.

Giles, M., Park, C., Khalsa, K.P.S., Kirkwood, C. D.F., Ulbricht, C., and Basch, E. 2008. Butterbur (*Petasites hybridus*). Natural Standard Monograph. Internet address: http://naturalstandard.net/index-abstract.asp?create-abstract=/monographs/herbssupplements/butterbur.asp. Last accessed on August 6, 2008.

Google.com. 2008 Butterbur [search results]. Internet address: http://www.google.com/products?q=Butterbur&btnG=Search+Products&show=dd. Last accessed on July 22, 2008.

Guo, R., and Pittler, M.H. 2007. *Petasites hybridus* (butterbur) for treating allergic rhinitis. Focus Altern Complement Ther, 12(2):81-84.

Hudson, T. 2007. Relieving migraine headaches in women. Altern Complement Ther, 13(1):36-38.

iHerb.com. 2008. Butterbur [search results]. Internet address: http://www.iherb.com/ProductsList.aspx?c=1&cid=2214&gclid=CN_G4ObM1pQCFQpjnAodD0FMqQ. Last accessed on July 23, 2008.

Itoh, S., Tokunaga, Y., and Yumura, Y. 1979. Contamination of vegetable crops by excessive absorption of heavy metals. I. Concentration of heavy metals contained in the soil solution and contamination of vegetable crops by the excessive absorption of heavy metals. Yasai Shikenjo Hokoku, 5:145-66. Abstract from TOXCENTER 1979:109438.

Jamieson, G.R., Reid, E.H., Turner, B.P., and Jamieson, A.T. 1976. Bakkenolide A: its distribution in *Petasites*-spp and cytotoxic properties. Phytochemistry, 15(11):1713-1716. Abstract from BIOSIS 1977:166286.

Kalin, P. 2002. Bioforce Monograph: Common Butterbur. *Petasites hybridus* (L) Gaertner et al. Internet address: http://www.helhetsdoktorn.nu/MonographPetasites.pdf. Last accessed on August 6, 2008.

Kaufeler, R., Polasek, W., Brattstrom, A., and Koetter, U. 2006. Efficacy and safety of butterbur herbal extract Ze 339 in seasonal allergic rhinitis: postmarketing surveillance study. Adv Ther, 23(2):373-384. PubMed abstract Internet address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=16751170. Last accessed on July 29, 2008.

Knez, Z., Hadolin, M., and Debrunner, B. 1999. Separation of pyrrolizidine alkaloids from *Petasites hybridus* with high pressure n-propane extraction. Chemische Technik, 51(3):141-143. Abstract from Internet address: http://cat.inist.fr/?aModele=afficheN&cpsidt=1859264. Last accessed on August 6, 2008.

Koch, V., and Rittinghausen, R. [assignee: Weber & Weber GmbH & Co. KG]. 2003 pat. Composition containing pyrrolizidine-alkaloid-free petasites. U.S. Patent No. 6551626. Publication date: April 22, 2003. Internet address: http://www.freepatentsonline.com/6551626.html. Last accessed on August 6, 2008.

Langer, T., Mostl, E., Chizzola, R., and Gutleb, R. 1996. A competitive enzyme immunoassay for the pyrrolizidine alkaloids of the senecionine type. Planta Med, 62(3):267-271. Abstract from PubMed 8693043. PubMed abstract Internet address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=8693043. Last accessed on August 6, 2008.

Lin, H., Chien, C.H., Lin, Y.L., Chen, C.F., and Wang, P.S. 2000. Inhibition of testosterone secretion by S-petasin in rat testicular interstitial cells. Chin J Physiol, 43(3):99-103. PubMed abstract Internet address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=11132091. Last accessed on July 29, 2008.

Lipton, R.B., Gobel, H., Einhaupl, K.M., Wilks, K., and Mauskop, A. 2004. *Petasites hybridus* root (butterbur) is an effective preventive treatment for migraine. Neurology, 63(12):2240-2244. PubMed abstract Internet address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=15623680. Last accessed on July 28, 2008.

Liveandfeel.com. 2008. Health benefits of butterbur. Internet address: http://www.liveandfeel.com/medicinalplants/butterbur.html. Last accessed on July 29, 2008.

Migraineaid.com. Undated. Petadolex® migraine prevention – butterbur migraine treatment. Internet address: http://migraineaid.com/. Last accessed on July 22, 2008.

Morita, K., Hara, M., and Kada, T. 1978. Studies on natural desmutagens: screening for vegetable and fruit factors active in inactivation of mutagenic pyrolysis products from amino acids. Agric Biol Chem, 42:1235-1238.

Natural Medicines Comprehensive Database. 2008. Butterbur. Internet address: http://www.naturaldatabase.com/(S(dipgxb55byj0b2551oj0glnc))/nd/Search.aspx?cs=CE_NODEACT&s=ND&pt=100&id=649&ds. Last accessed on August 6, 2008.

National Supplement Center. Undated. KAL MigraDefense 60 Tablet. Internet address: http://www.nationalsupplementcenter.com/kal10633.html. Last accessed on July 29, 2008.

NutritionGeeks.com. Undated. Butterbur extract Urovex. Internet address: http://www.nutritiongeeks.com/butterbur-extract-urovex-20/butterbur-extract-urovex.html. Last accessed on September 30, 2009.

OEHHA (Office of Environmental Health Hazard Assessment). 1999. Final prioritized candidate chemicals under consideration for carcinogenicity evaluation: fifty-four chemicals within batch #3. Internet address: http: http://www.oehha.ca.gov/prop65/pdf/fbatch3.pdf. Last accessed on July 28, 2008.

Oelkers-Ax, R., Leins, A., Parzer, P., Hillecke, T., Hans, B.V., Fischer, J., Bender, S., Hermanns, U., and Resch, F. 2008. Butterbur root extract and music therapy in the prevention of childhood migraine: an explorative study. Eur J Pain, 12(3):301-313. PubMed abstract Internet address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=17659990. Last accessed on July 28, 2008.

Oh, S.H., Sok, D.-E., and Kim, M.R. 2005. Neuroprotective effects of butterbur and rough aster against kainic acid-induced oxidative stress in mice. J Med Food, 8(2):169-176. PubMed abstract Internet address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=16117608. Last accessed on July 29, 2008.

Pothmann, R., and Danesch, U. 2005. Migraine prevention in children and adolescents: Results of an open study with a special butterbur root extract. Headache, 45(3):196-203. PubMed abstract Internet address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=15836592. Last accessed on July 28, 2008.

PubChem. Undated. Compound Summary for

- (+)-Petasin; CID: 6450257. Internet address: http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=6450257&loc=ec_rcs.
- Isopetasin; CID: 5318627. Internet address: http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=5318627&loc=ec_rcs.

Last accessed on July 29, 2008.

Registry. 2008a. RN 26577-85-5. Record entered on November 16, 1984. Database available on STN International.

Registry. 2008b. RN 469-26-1. Record entered on November 16, 1984. Database available on STN International.

Sahelian, R. Undated. Butterbur and migraine research update. Internet address: http://www.raysahelian.com/butterbur.html. Last accessed on July 29, 2008.

Saritas, Y., Von Reuβ, S.H., and König, W.A. 2002. Sesquiterpene constituents in *Petasites hybridus*. Phytochemistry, 59(8):795-803. PubMed abstract Internet address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=11937157. Last accessed on July 29, 2008.

Schapowal, A. 2002. Randomised controlled trial of butterbur and cetirizine for treating seasonal allergic rhinitis. Br Med J, 324(7330):144-146. Internet address: http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=11799030. Last accessed on August 4, 2008.

Schlenger, R. 2004a. Liver damage due to butterbur extracts: preparations from the rhizome of *Petasites hybridus* have been removed from the market in Switzerland (German). Deutsche Apotheker Zeitung, 144(8):64-66. Abstract from EMBASE 2004107845.

Schlenger, R. 2004b. Liver damage through pestilence wort extracts: preparation from petasites rhizomes in Switzerland on the market (German). Deutsche Apotheker Zeitung, 144:64-66. Abstract from TOXCENTER 2004:230618.

Schmieder, A., Csordas, A., Backovic, A., Messner, B., Wick, G., Bernhard, D., Schwaiger, S., and Stuppner, H. 2007. Isogentisin—a novel compound for the prevention of smoking-caused endothelial injury. Atherosclerosis, 194(2):317-325. PubMed abstract Internet address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=17141243. Last accessed on August 6, 2008.

Sekiya, K. 1997. Inhibition of cyclooxygenase and lipoxygenase by foods. Bull Shikoku Natl Agric Exp Station, 61:31-37. Abstract from CABA 1998:54025.

Sheykhzade, M., Smajilovic, S., Issa, A., Haunso, S., Christensen, S.B., and Tfelt-Hansen, J. 2008. S-petasin and butterbur lactones dilate vessels through blockage of voltage gated calcium channels and block DNA synthesis. Eur J Pharmacol, 593(1-3):79-86. Abstract from PubMed 18655785. PubMed abstract Internet address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=18655785. Last accessed on October 2, 2009.

Shimoda, H., Tanaka, J., Yamada, E., Morikawa, T., Kasajima, N., and Yoshikawa, M. 2006. Anti type I allergic property of Japanese butterbur extract and its mast cell degranulation inhibitory ingredients. J Agric Food Chem, 54(8):2915-2920. Abstract from PubMed 16608208. PubMed abstract Internet address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=16608208. Last accessed on July 28, 3008.

Siegenthaler, P., and Neuenschwander, M. 1997. Sesquiterpenes from *Petasites hybridus* (Furanopetasin chemovar): separation, isolation and quantitation of compounds from fresh plant extracts. Pharm Acta Helv, 72(2):57-67.

Singh, B.B., Khorsan, R., Vinjamury, S.P., Der-Martirosian, C., Kizhakkeveettil, A., and Anderson, T.M. 2007. Herbal treatments of asthma: a systematic review. J Asthma, 44(9):685-698. PubMed abstract Internet address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=17994396. Last accessed on August 6, 2008.

Smartbodyz Nutrition. 2009. Urovex purple butterbur (*Petasites hybridus* extract) herb. Internet address: http://www.smartbodyz.com/Butterbur-urovex-petasites-hybridus-extract-herb-Dose.htm. Last accessed on September 30, 2009.

Sok, D.E., Oh, S.H., Kim, Y.B., Kang, H.G., and Kim, M.R. 2006. Neuroprotection by extract of *Petasites japonicus* leaves, a traditional vegetable, against oxidative stress in brain of mice challenged with kainic acid. Eur J Nutr, 45(2):61-69. PubMed abstract Internet address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=15997340. Last accessed on July 29, 2008.

Source Naturals. Undated. Butterbur [search results]. Internet address: http://www.sourcenaturals.com/search/?terms=butterbur. Last accessed on October 3, 2009.

Takahashi, Y., Nagao, M., Fujino, T., Yamaizumi, Z., and Sugimura, T. 1979. Mutagens in Japanese pickle identified as flavonoids. Mutat Res, 68:117-123. PubMed abstract Internet address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=390386. Last accessed on August 6, 2008.

Tepper, S.J., Bigal, M., Rapoport, A., and Sheftell, F. 2006. Alternative therapies: evidence-based evaluation in migraine. Headache Care, 3(2):57-64. Internet address: http://www.librapharm.com/headeradmin/upload/0139_3.pdf. Last accessed on August 6, 2008.

The Vitamin Shoppe. 2008. Butterbur [search results]. Internet address: http://www.vitaminshoppe.com/search/en/query.jsp?q=butterbur&intsource=main. Last accessed on July 23, 2008.

Ueda, S., Kuwabara, Y., Hirai, N., Sasaki, H., and Sugahara, T. 1991. Antimutagenic capacities of different kinds of vegetables and mushrooms. Nippon Shokuhin Kogyo Gakkaishi, 38(6):507-514. Abstract from CABA 92:116891.

Vitacost.com. 2008. Butterbur [search results]. Internet address: http://www.vitacost.com/productResults.aspx?ss=1&previousText=&Ntk=products&Ntt=butterbur. Last accessed on July 23, 2008.

Wang, G.J., Shum, A.Y.C., Lin, Y.L., Liao, J.Y., Wu, X.C., Ren, J., and Chen, C.F. 2001. Calcium channel blockade by S-petasin, a hypotensive sesquiterpene from *Petasites formosanus*, in vascular smooth muscle. J Pharmacol Exp Ther, 297:240-246. Cited by Wang et al. (2004).

Wang, G.J., Wu, X.C., Lin, Y.L., Ren, J., Shum, A.Y., Wu, Y.Y., and Chen, C.F. 2002. Ca^{2+} channel blocking effect of iso-S-petasin in rat aortic smooth muscle cells. Eur J Pharmacol, 445(3):239-245. PubMed abstract Internet address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=12079689. Last accessed on July 29, 2008.

Wang, G.J., Liao, J.F., Hintz, K.K., Chen, W.P., Su, M.J., Lin, Y.L., Shi, C.C., Chen, C.F., and Ren, J. 2004. Calcium-antagonizing activity of S-petasin, a hypotensive sesquiterpene from *Petasites formosanus*, on inotropic and chronotropic responses in isolated rat atria and cardiac myocytes. Naunyn Schmiedebergs Arch Pharmacol, 369(3):322-329. PubMed abstract Internet address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=15010899. Last accessed on July 29, 2008.

Wikipedia. 2005. Image: Butterbur.jpeg. Internet address: http://en.wikipedia.org/wiki/Image:Butterbur.jpg#filehistory. Last accessed on July 29, 2008.

Wildi, E., Langer, T., Schaffner, W., and Buter, K.B. 1998. Quantitative analysis of petasin and pyrrolizidine alkaloids in leaves and rhizomes of *in situ* grown *Petasites hybridus* plants. Planta Med, 64(3):264-267. PubMed abstract Internet address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=17253240. Last accessed on August 6, 2008.

Youbuy. 2008. Akita Butterbur Tea. Internet address: http://inaniwaudon.youbuy.jp/index/MbSyu0ABkofD8s9MM1i88QXZKr45uAAqn2j9903hQTXwMqlornYf6_btHAQ7-d7LIs9j4Xgvbjgn3MMiqavuxg../. Last accessed on July 29, 2008.

13.0 References Considered But Not Cited

Bielory, L.D., Resnick, E.S., and Bielory, B.P. 2008. Complementary therapy in allergic rhinitis. Curr Allergy Asthma Rep, 8(2):118-125. Abstract from EMBASE 2008182947.

Brattstrom, A. 2003. Ze 339 - a special extract from the leaves of butterbur (German). Z Phytother, 24(4):170-172. Abstract from CABA 2003:174719.

Cucu, V., Constantinescu, C., and Retezeanu, M. 1963. Criteria on the detection and prevention of adulteration in some of the drugs from native plants. II. *Tussilago farfara* L. (Romanian). Lucrarile Gradini Bot Bucuresti [Acta Bot Horti Bucurestiensis], 1961(1):543-553. Abstract from BIOSIS 1967:103700.

Guo, R., Pittler Max, H., and Ernst, E. 2007. Herbal medicines for the treatment of allergic rhinitis: A systematic review. Ann Allergy Asthma Immunol, 99(6):483-495. Abstract from PubMed 18219828.

Jeuch, J. 1941. Comparative pharmacognostic investigation of drugs from the genera arctium and petasites with special reference to their anatomy (German). Ber Schweiz Bot Ges, 51:5-76. Abstract from BIOSIS 1947:20510.

Kalin, P. 2003. The common butterbur (*Petasites hybridus*)—portrait of a medicinal herb (German). Forsch Komplementarmed Klass Naturheilkd, 10(1):41-44. Abstract from PubMed 12808361.

Lee, D.K.C., Haggart, K., Robb, F.M., and Lipworth, B.J. 2004. Butterbur, an herbal remedy, confers complementary anti-inflammatory activity in asthmatic patients receiving inhaled corticosteroids. Clin Exp Allergy, 34(1):110-114. Abstract from PubMed 14720270.

Schapowal, A. 2004. 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, 130(12):1381-1386.

Schapowal, A. 2006 slides. Efficacy and safety of Butterbur leaves extract Ze 339 in allergic rhinitis. Internet address: http://files.chuv.ch/internet-docs/ial/ial_schapowal_09_02_06.pdf. Last accessed on August 5, 2008.

Yarnell, E., and Abascal, K. 2007. Botanical medicines for headache. Altern Complement Ther, 13(3):148-152. Abstract from EMBASE 2007365346.

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Appendix A: Units and Abbreviations

ºC = degrees Celsius
8-Br-cAMP = 8-bromoadenosine 3,5-cyclic monophosphate
µg/g = microgram(s) per gram
µg/mL/kg = microgram(s) per milliliter per kilogram
µM = micromolar
ACTH = adrenocorticotropin
FDA = U.S. Food and Drug Administration
g/kg = gram(s) per kilogram
g/mL = gram(s) per milliliter
hCG = human chorionic gonadotropin
HPLC = high performance liquid chromatography
i.v. = intravenous(ly)
LD_{50} = lethal dose for 50% of test animals
mg = milligram
mg/g = milligram(s) per gram
mg/kg = milligram(s) per kilogram
mm = millimeter(s)
NTP = National Toxicology Program
PAs = pyrrolizidine alkaloids
PMID = PubMed identification
ppm = parts per million
ZFR = zona fasciculate-reticularis

Appendix B: Description of Search Strategy and Results

STN International files IN MEDLINE, AGRICOLA, CABA, EMBASE, BIOTECHNO, ESBIOBASE, IPA, BIOSIS, TOXCENTER, and PASCAL were searched simultaneously on June 20, 2008, after an initial search in the REGISTRY file (L1 below). The history of the search is reproduced below. On July 28, REGISTRY records were retrieved for petasin and isopetasin with the use of their CAS Registry Numbers.

```
L1             4  ("PETASITENINE (NEUTRAL)"/CN OR "PETASITES HYBRIDUS,
EXT."/CN
                  OR "PETASITES JAPONICUS, EXT."/CN OR PETASITIN/CN)
L2             782  BUTTERBUR OR PETASITES(W)(HYBRIDUS OR VULGARIS OR
OFFICINALE)
L3         403 DUP REM L2 (379 DUPLICATES REMOVED)
 57              ANSWERS '1-57' FROM FILE MEDLINE
 38              ANSWERS '58-95' FROM FILE AGRICOLA
 74              ANSWERS '96-169' FROM FILE CABA
 93              ANSWERS '170-262' FROM FILE EMBASE
 12              ANSWERS '263-274' FROM FILE BIOTECHNO
  3              ANSWERS '275-277' FROM FILE ESBIOBASE
 22              ANSWERS '278-299' FROM FILE IPA
 80              ANSWERS '300-379' FROM FILE BIOSIS
 18              ANSWERS '380-397' FROM FILE TOXCENTER
  6              ANSWERS '398-403' FROM FILE PASCAL
L4           403 SORT L3 1-403 TI
                 SAVE L4 X550BIO/A
```

A large number of publications on efficacy and growth in the environment were excluded during examination of the titles. A total of 249 records were selected for printing in full. The database tallies were MEDLINE, 55; AGRICOLA, 26; CABA, 31; EMBASE, 78; BIOTECHNO, 3; ESBIOBASE, 2; IPA, 15; BIOSIS, 26; and TOXCENTER, 13.

A review of the printed records indicated >70 were related to therapeutic uses and clinical trials assessing the efficacy of butterbur for the treatment of numerous indications including asthma, migraines, and allergic rhinitis. These records were reviewed and selected articles retrieved to evaluate potential adverse effects and contraindications of butterbur. The remaining records were filed and maintained for future use.

Of the printed records, approximately 45 additional references discussed isolation and identification of constituents of butterbur parts (e.g., leaves), differences in constituent concentration levels. These records were reviewed and selected articles were retrieved for evaluation and extraction. The remaining records were maintained for future use.

Google, Google Scholar, Google Images, and Google Products searches were done in June 2008 to find images of the plant, commercial products, clinical trials, efficacy and safety reviews, authoritative reviews (IPCS, OEHHA), and reports of side effects. HSDB profiles were found for some other pyrrolizidine alkaloids. Additional searches for products were conducted on variety of retail websites.

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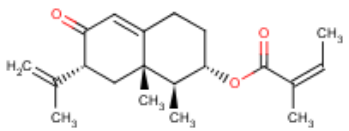
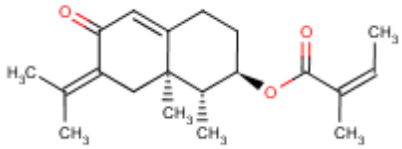
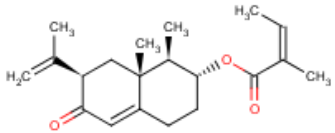
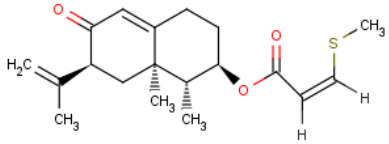
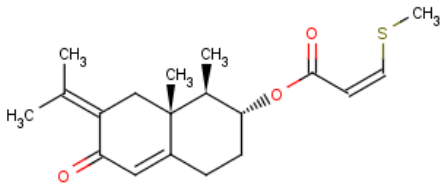
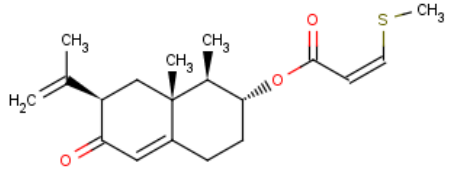
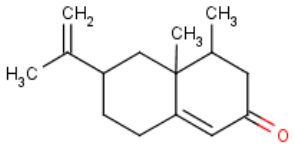
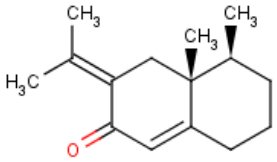
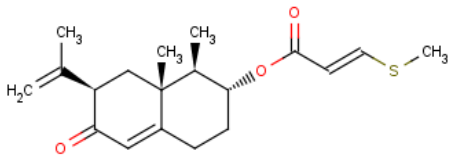
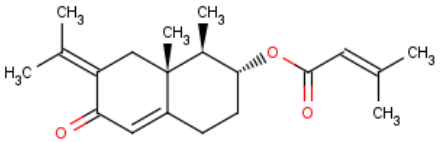
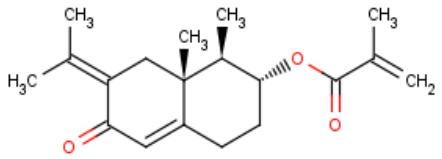
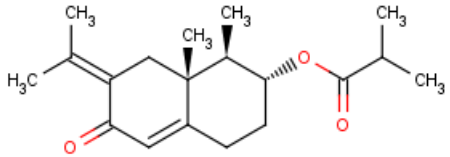
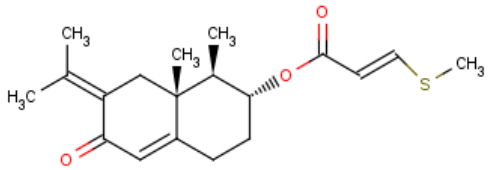
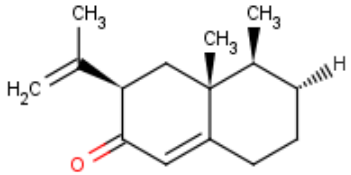
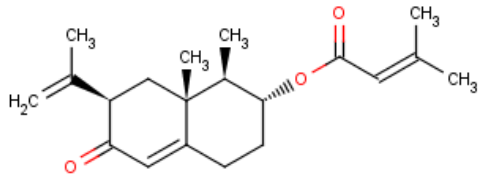
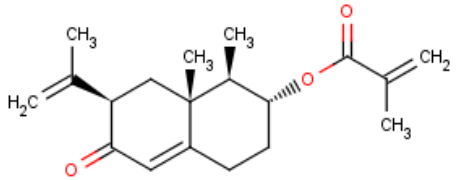
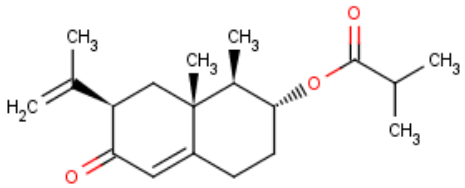
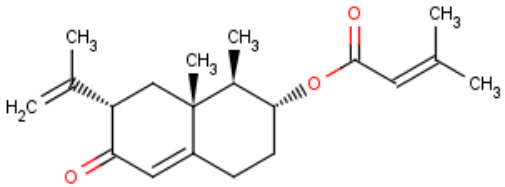
STN International files MEDLINE, AGRICOLA, CABA, EMBASE, BIOTECHNO, ESBIOBASE, IPA, BIOSIS, TOXCENTER, and PASCAL were searched simultaneously on September 16, 2009, for relevant publications published after the initial search on June 29, 2008. The search terms used were identical to the original search. A total of 78 titles were identified, 38 which were duplicates. Of the remaining 40 citations, nine had been identified in the original search. Two records were selected for further review; both were from MEDLINE.

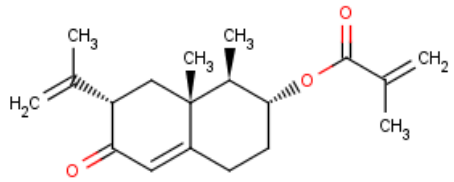
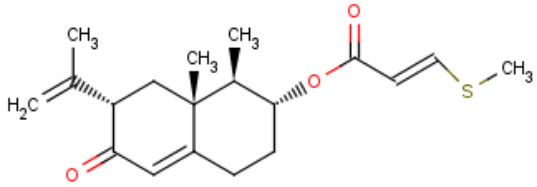
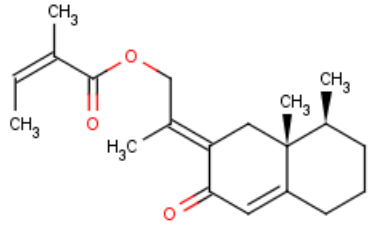
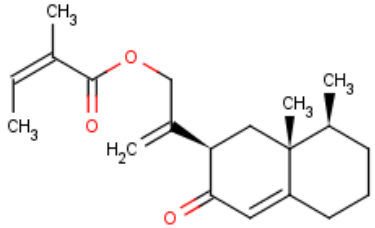
Appendix C: Selected Constituents of Extracts and Essential Oil of Butterbur*

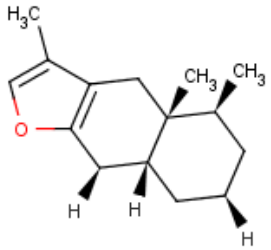
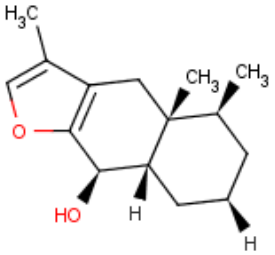
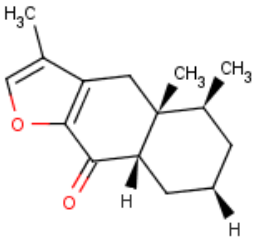
Constituent	CAS No.[a]	PubChem CID	Structure[b]	Comments and References
Sesquiterpene Esters				
(+)-Petasin	26577-85-5	6450257		Debrunner et al. (1995) Enantiomer of petasin structure (Chemical 3b) in Debrunner et al. (1995) and Debrunner (1998) is provided in ChemIDplus
Isopetasin	469-26-1	5318627		Chemical 1b; Debrunner et al. (1995); Debrunner (1998)
Neopetasin	70387-53-0	732903		Chemical 2b; Debrunner et al. (1995); Debrunner (1998)
S-petasin	Not available	16219858		Chemical 3f; Debrunner et al. (1995); Debrunner (1998)
Iso-S-petasin	Not available	Not available		Chemical 1f; Debrunner et al. (1995), Debrunner (1998)

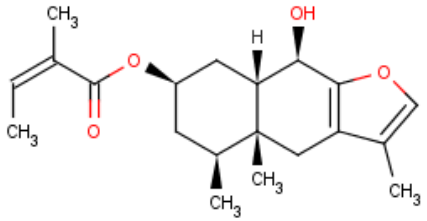
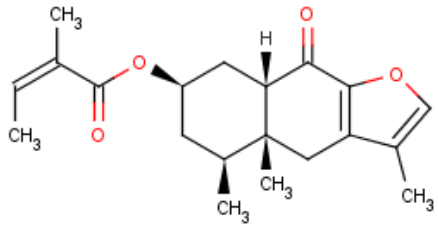
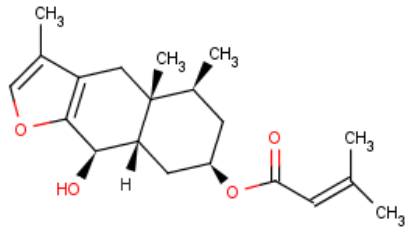
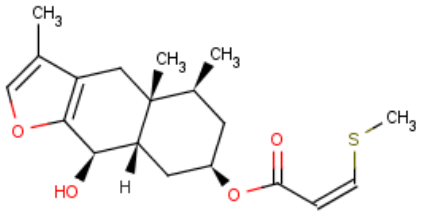
Constituent	CAS No.[a]	PubChem CID	Structure[b]	Comments and References
Neo-S-petasin	Not available	Not available		Chemical 2f; Debrunner et al. (1995); Debrunner (1998)
Nookatone	4674-50-4	29204442		Debrunner et al. (1995)
Dihydrokaranone	19598-45-9	177072		Chemical 1a; Debrunner et al. (1995)
(*E*)-3-Methylthio-acryoyl-neopetasol	Not available	Not available		Chemical 2g; Debrunner et al. (1995)
Chemical 1c	Not available	Not available		Debrunner et al. (1995)

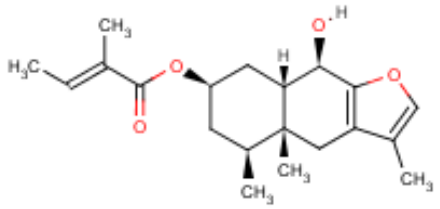
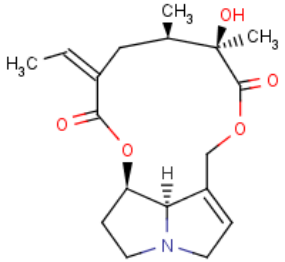
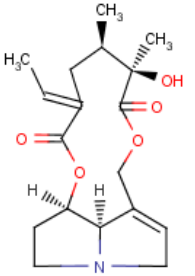
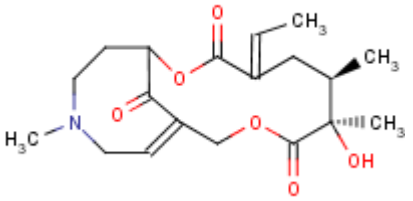
Constituent	CAS No.[a]	PubChem CID	Structure[b]	Comments and References
Chemical 1d	Not available	Not available		Debrunner et al. (1995)
Chemical 1e	Not available	Not available		Debrunner et al. (1995)
Chemical 1g	Not available	Not available		Debrunner et al. (1995)
Chemical 2a	Not available	Not available		Debrunner et al. (1995)

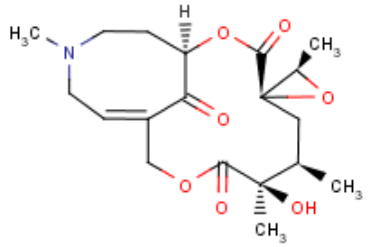
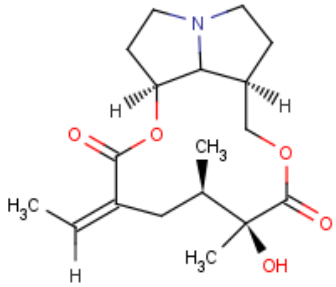
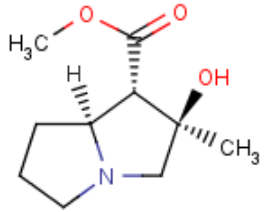
Constituent	CAS No.[a]	PubChem CID	Structure[b]	Comments and References
Chemical 2c	Not available	Not available		Debrunner et al. (1995)
Chemical 2d	Not available	Not available		Debrunner et al. (1995)
Chemical 2e	Not available	Not available		Debrunner et al. (1995)
Chemical 3c	Not available	Not available		Debrunner et al. (1995)

Constituent	CAS No.[a]	PubChem CID	Structure[b]	Comments and References
Chemical 3d	Not available	Not available		Debrunner et al. (1995)
Chemical 3g	Not available	Not available		Debrunner et al. (1995)
Chemical 4b	Not available	Not available		Debrunner et al. (1995)
Chemical 5b	Not available	Not available		Debrunner et al. (1995)

Constituent	CAS No.[a]	PubChem CID	Structure[b]	Comments and References
Furanoeremophilane	Not available	Not available		Siegenthaler and Neuenschwander (1997) - isolated from furanopetasin chemovar
9-Hydroxy-furanoeremophilane	Not available	Not available		Siegenthaler and Neuenschwander (1997) - isolated from furanopetasin chemovar
9-Oxo-furanoeremophilane	Not available	Not available		Siegenthaler and Neuenschwander (1997) - isolated from furanopetasin chemovar

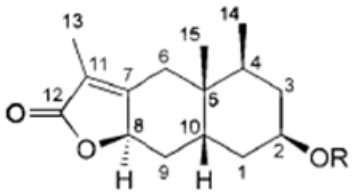
Constituent	CAS No.[a]	PubChem CID	Structure[b]	Comments and References
Furanopetasin	Not available	Not available		Siegenthaler and Neuenschwander (1997) - isolated from furanopetasin chemovar
9-Oxo-furanopetasin	Not available	Not available		Siegenthaler and Neuenschwander (1997) - isolated from *P. hybridus*(furanopetasin chemovar.) buds
2-Senecioyl-furanopetasol	Not available	Not available		Siegenthaler and Neuenschwander (1997) - isolated from furanopetasin chemovar
2-Methylthioacryloyl-furanopetasol	Not available	Not available		Siegenthaler and Neuenschwander (1997) - isolated from furanopetasin chemovar

Constituent	CAS No.[a]	PubChem CID	Structure[b]	Comments and References
2-Tigloyl-furanopetasol	6902-62-1	Not available		Langer et al. (1998); Siegenthaler and Neuenschwander (1997) - isolated from furanopetasin chemovar
Pyrrolizidine Alkaloids				
Senecionine	130-01-8	5280906		Wildi et al. (1998 [PMID:17253240])
Integerrimine	480-79-5	5281733		Wildi et al. (1998 [PMID:17253240])
Senkirkine	2318-18-5	6433332		Bartkowski and Röder (1998)

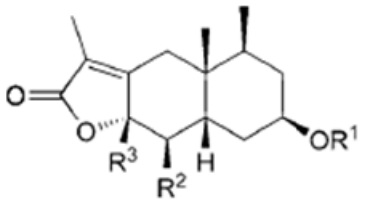
Constituent	CAS No.[a]	PubChem CID	Structure[b]	Comments and References
Petasitenine	60102-37-6	5281741		Wildi et al. (1998 [PMID:17253240])
Neopetasitenine	Not available	Not available	Not available	Wildi et al. (1998 [PMID:17253240])
Neoplatyphylline	480-78-4	6428025		Mroczek and Glowniak (2002)
Isotussilagine	Not available	Not available	Not available	Mroczek and Glowniak (2002)
Tussilagine	80151-77-5	185071		Mroczek and Glowniak (2002)

[a]CAS Registry Numbers were sought in ChemIDplus and PubChem records (including available links to other databases within the records [e.g., EMIC and GENETOX]). [b]Structures were obtained from ChemIDplus records or were drawn using the MarvinSketch available in ChemIDplus.

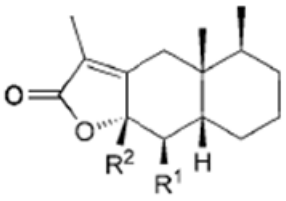
*An additional 18 chemicals were extracted from *P. hybridus* rhizomes (see figure below from Bodensieck et al, 2007). Chemicals 16, 20, and 21 represent 9-oxo-furanopetasin, iso-S-petasin, and neo-S-petasin, respectively, which are already included in the table above.



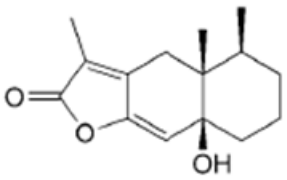
1 R = Ang
2 R = Sen
3 R = Tig
4 R = Met
5 R = Isobutanoyl



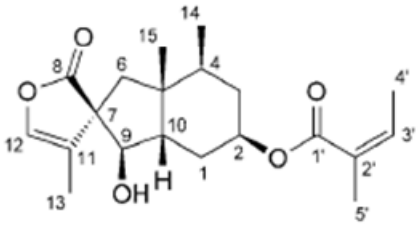
	R^1	R^2	R^3
6	Ang	H	H
7	Sen	H	H
8	Tig	H	H
9	Met	H	H
10	**A**	H	H
11	Ang	OH	H
12	Ang	OH	OH



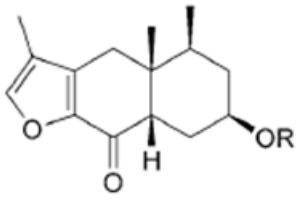
13 R^1 = H, R^2 = OH
14 R^1 = H, R^2 = H



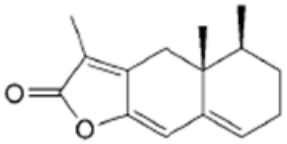
18



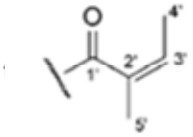
15



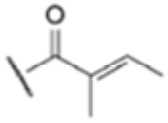
17 R = Sen



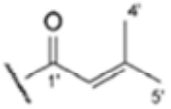
19



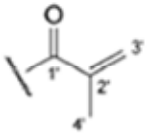
Angeloyl (Ang)



Tigloyl (Tig)



Senecioyl (Sen)



Methacroyl (Met)

Source: Bodensieck et al. (2007)

References

Bartkowski, B., and Röder, E. 1998. New color reaction for the qualitative and quantitative determination of otonecine alkaloids, especially senkirkine, pp. 368-369. In: Debrunner, B., and Meier, B. *Petasites hybridus*: a tool for interdisciplinary research in phytotherapy. Pharm Acta Helv. 72(6):359-380.

Bodensieck, A., Kunert, O., Haslinger, E., and Bauer, R. 2007. New eremophilane sesquiterpenes from a rhizome extract of *Petasites hybridus*. Helv Chim Acta, 90(1):183-195.

Debrunner, B. 1998. Influence of temperature and storage on the stability of some eremophilane esters in *Petasites hybridus* (L.) G.M. et Sch. (Petasin chemovar), pp. 364-365. In: Debrunner, B., and Meier, B. *Petasites hybridus*: a tool for interdisciplinary research in phytotherapy. Pharm Acta Helv. 72(6):359-380.

Debrunner, B., Neuenschwander, M., and Brenneisen, R. 1995. Sesquiterpenes of *Petasites hybridus* (L.) G.M. at Sch.: distribution of sesquiterpenes over plant organs. Pharm Acta Helv, 70(2):167-173.

Langer, T., Chizzola, R., and Vetter, S. 1998. A novel TLC system to discriminate sesquiterpenesters in *Petasites hybridus*, p. 366. In: Debrunner, B., and Meier, B. *Petasites hybridus*: a tool for interdisciplinary research in phytotherapy. Pharm Acta Helv. 72(6):359-380.

Mroczek, T, and Glowniak, K. 2002. Terrestrial natural products – Isolation, structure characterization, analytical methods, chemodifferentiation. Pyrrolizidine alkaloids. In. Rauter, A.P., Palma, F.B., Justino, J., Araujo, M.E., and dos Santos, S.P., Eds. Natural Products in the New Millenium: Prospects and Industrial Application. Kluwer Academic Publishers, Dordrecht, The Netherlands, pp. 1-46. Internet address: http://books.google.com/books?id=4rrC7c_6OUoC&pg=PA21&lpg=PA21&dq=Neopetasitenine&source=bl&ots=GVBMtwFYoN&sig=6XVTmjxJluTm7GtJOfCmJ6-AJD0&hl=en&ei=rT_KSvXhPIq4lAfnmeW5AQ&sa=X&oi=book_result&ct=result&resnum=10#v=onepage&q=Neopetasitenine&f=false. Last accessed on October 5, 2009.

Siegenthaler, P., and Neuenschwander, M. 1997. Sesquiterpenes from *Petasites hybridus* (Furanopetasin chemovar): separation, isolation and quantitation of compounds from fresh plant extracts. Pharm Acta Helv, 72(2):57-67.

Wildi, E., Langer, T., Schaffner, W., and Buter, K.B. 1998. Quantitative analysis of petasin and pyrrolizidine alkaloids in leaves and rhizomes of *in situ* grown *Petasites hybridus* plants. Planta Med, 64(3):264-267. PubMed abstract Internet address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=17253240. Last accessed on August 6, 2008.