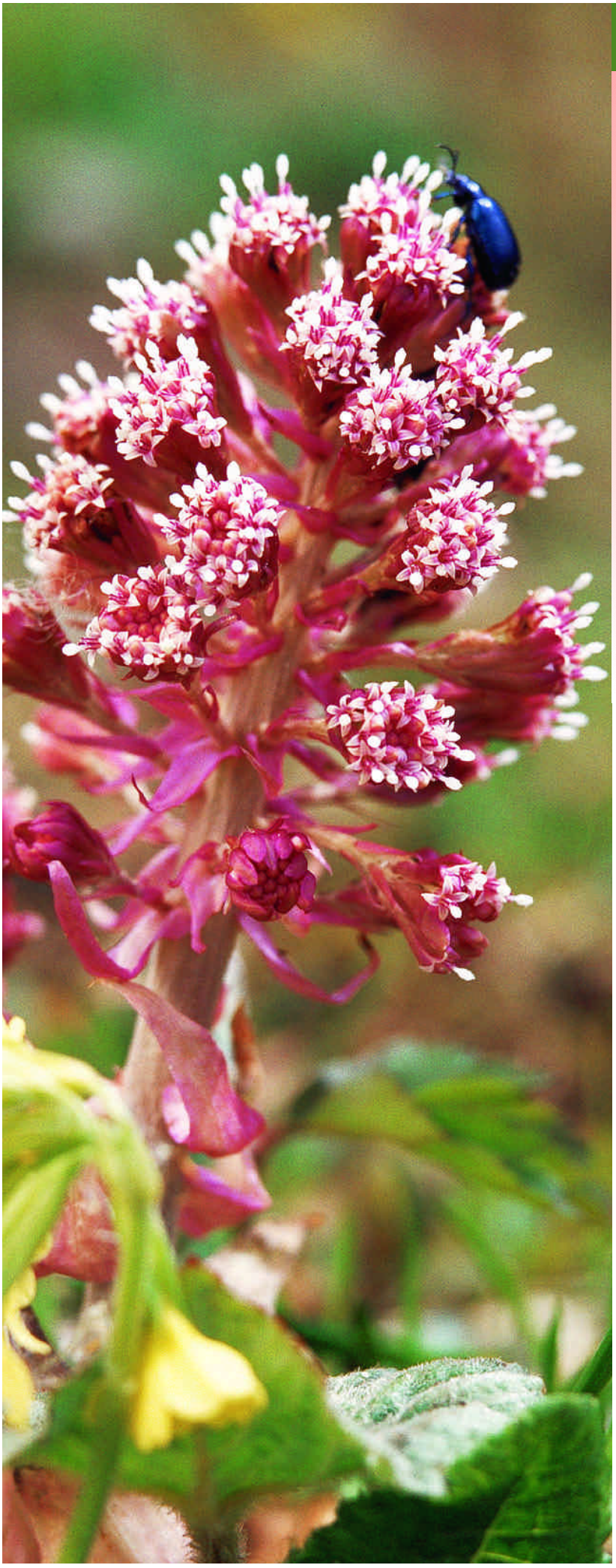


A.Vogel

Bioforce Monograph

Common butterbur

Petasites hybridus (L.) Gaertner et al.

Medicinal plant and drugs employed

Common butterbur (Petasites hybridus, syn. Petasites officinalis; Asteraceae family, Compositae) is native to all of Europe, northern and western Asia. It was introduced in North America.

Shortly after the snow thaws, often as early as the end of February in the lowlands, its reddish inflorescence appears on the still bare earth in wet ground that is rich in nutrients such as the banks of rivers and streams.

Fig. 1: Flower head of Petasites hybridus

The leaves, up to 60 cm in diameter, ***(Fig. 2)*** only unfold during flowering, which lasts until April; children still like to use them as hats today. The plant also owes its name to these large leaves. The Greek physician Dioscurides (c. 50 AD) compared the leaves to a broad-brimmed rain hat (petasos in Greek) and gave it the name Petasites [1].

Metre-long runners arise from the rootstock (rhizome), along which centimetre-thick nodules are formed repeatedly ***(Fig. 3)***. Thin roots run out from these. The rhizomes (Petasitidis rhizoma) and the leaves (Petasitidis folium) are used as a drug.

Historical

Dioscurides used the finely pounded leaves as a poultice for skin ulcers [2]. In his herbal of 1664, the German physician and botanist Tabernaemontanus recommended the root powder of the «Pestilentzwurz» or butterbur for internal use also in abdominal colic and asthma and as a mucolytic [3].

Because of the diuretic and sweat-producing effect, the root powder was also used in plague, hence the name «Pestwurz» or «plague-root». The English name is believed to have been given it because the large leaves were formerly used to wrap butter in hot weather.

In traditional European phytotherapy, coltsfoot (Tussilago farfara) for a long time displaced butterbur as a mucolytic cough medicine, until the marked spasmolytic characteristics of the root extract were confirmed experimentally recently [4]. These results, obtained with modern research methods, opened up whole new areas of indications for butterbur.

Pharmacology of the constituents

Plant extracts are mixtures of many substances, the components of which have been characterised only to a small extent. The effects must be attributed to the whole extract and not to individual constituents, even if the principal substances with their effects are known in many cases.

Fig. 2: Common butterbur in its natural location: the large leaves have opened after flowering. The white pappus hairs of the fruits typical of compositae (Asteraceae) are easily identified.

Butterbur extracts include sesquiterpene esters, pyrrolizidine alkaloids and essential oil [5]. This consists of compounds derived from fatty acid and terpene metabolism. Only the quantitatively predominating petasines (sesquiterpene esters), the effects of which have been studied in vitro and in clinical studies, and the potentially toxic and carcinogenic pyrrolizidine alkaloids will be discussed below. The structure of many other constituents has not yet been elucidated and their effects are thus unknown.

Sesquiterpene esters

Up to now, the structure of more than 20 derivatives of the isomeric sesquiterpene esters *petasine, isopetasine* and *neopetasine* has been elucidated ***(Fig. 4)***.

Their *anti-inflammatory* and *spasmolytic* actions have been well investigated: The marked *anti-inflammatory* effect of the petasines is due to the well- documented *inhibition of leukotriene synthesis* [6,7]: On the one hand, petasine inhibits the intracellular release of calcium from the endoplasmic reticulum, thus inhibiting the calcium-dependent 5-lipoxygenase ***(Fig. 5)*** of the leukocytes. On the other hand, 5-lipoxygenase is inhibited by petasine, neopetasine and isopetasine in a second, as yet unclarified way. The 5-lipoxygenase is thus inhibited at two stages.

In addition, the release of *ECP* (eosinophilic cationic protein) from eosinophilic granulocytes is reduced. The importance of leukotriene synthesis antagonism can be explained briefly by comparison with synthetic substances: The anti-inflammatory action of the leukotriene *receptor* antagonists (e.g. zafirlukast and montelukast) is due to antagonism of the Cys-LT_1 receptors for the leukotrienes LT C_4, LT D_4 and LT E_4 (=SRSA: slow reacting substances of anaphylaxis) [8].
Inhibitors of leukotriene *synthesis* such as butterbur rhizome extract reduce the synthesis of all leukotrienes, including LT B_4, the leukotactic effects of which are not blocked by the leukotriene receptor antagonists [6]. The superiority of the synthetic leukotriene synthesis inhibitor zileuton (licenced in the USA for the indication of asthma) over leukotriene receptor antagonists was documented in two studies in chronic urticaria [9,10].

Fig. 3: Butterbur rhizome

The mechanism of the *spasmolytic* effect of the Petasites extracts has not yet been conclusively elucidated:

Bucher in 1951 described the spasmolytic effect of an extract of Petasites root on the isolated guinea pig intestine, which was comparable to papaverine [4].

It was shown that S-petasine ***(Fig. 4)***, a sulphur-containing derivative of petasine, has an equally good relaxant effect on the smooth muscle of the isolated guinea pig trachea as the phosphodiesterase inhibitor aminophylline. This effect is probably produced by a reduction in the intracellular calcium concentration [11]. More recent investigations show that S-petasine has a vasodilator effect in vitro, which is probably due to direct inhibition of the calcium channels in the cell membranes of vascular smooth muscle [12].

It is apparent from these studies that butterbur extracts not only have a spasmolytic effect on the intestine but have a *relaxant effect on smooth muscle* generally.

For the sake of completeness, a further chemical feature of butterbur must be mentioned: there are two chemotypes of Petasites hybridus which cannot be distinguished externally, the petasine and the furanopetasine type [13].

The furanopetasine type contains potentially cytotoxic furanoeremophilans instead of petasines ***(Fig. 6)***;

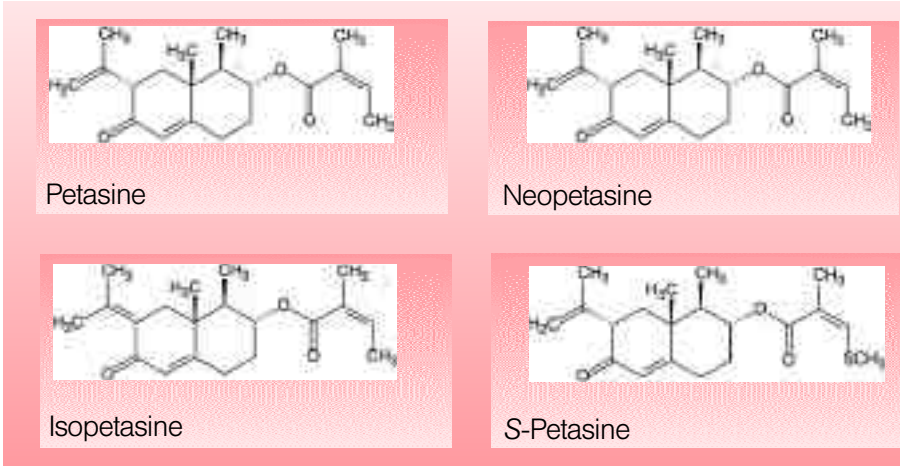


Fig. 4: Four of the over 20 known sesquiterpene esters of Petasites hybridus (petasine chemovariety)

however, these are converted during conventional drying processes into eremophilanlactones, which have a toxic effect only at higher concentrations.

Distinguishing the two chemotypes is of subordinate importance practically since finished preparations are standardised to a minimum petasine content.

Pyrrolizidine alkaloids (PA)

Pyrrolizidine alkaloids (PA) ***(Fig. 7)*** have so far been discovered in over 350 plant species from 13 families [13]. They taste bitter and protect the plants from being eaten by animals. PAs are widespread in the Astera-

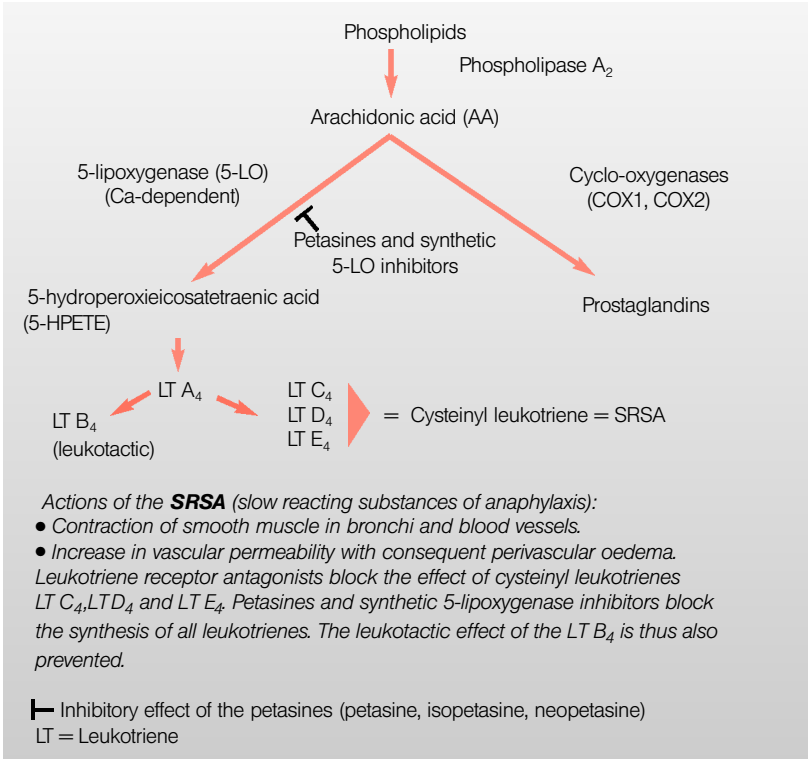


Fig. 5: Arachidonic acid cascade and site of action of the petasines

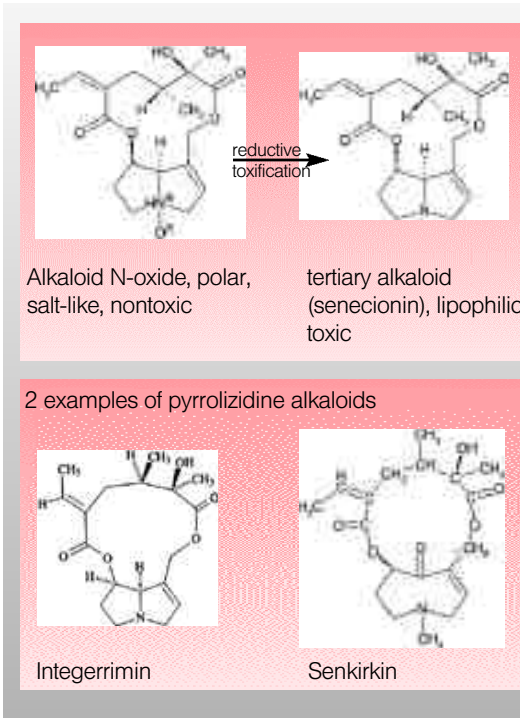
ceae (Compositae) and almost ubiquitous in the Boraginaceae (e.g. Symphytum officinale, comfrey). The PAs are present as hydrophilic nontoxic N-oxides in the rhizome of the butterbur. It is only after "reductive toxification" by bacteria of the bowel flora that the now lipophilic PAs are absorbed and oxidised in the liver by cytochrome P-450, and then metabolised to toxic or carcinogenic (alkylating) pyrrole derivatives. In the worst case, PA intoxication can manifest itself as Budd-Chiari syndrome (hepatic vein occlusion). The carcinogenicity leads to benign and malignant epithelial hepatic tumours (hepatomas, hepatocellular carcinomas, cholangiomas, haemangioendotheliomas etc.) [14].

Due to special extraction methods (see below), the concentrations of PAs in finished medicines are below the detection limit of 0.1 ppm [13] and are therefore safe toxicologically.

Extraction methods

Rhizomes, which currently are still obtained from collection in the wild, are used for the preparation of finished medicines. Large-scale culture of the petasine chemovariety will be available soon in order to ensure sustained use of the plant. A licence application for an extract of the leaves is in process while going to press. The constituents are today extracted with liquid CO_2 (lipophilic) under increased pressure. This process results in extracts that are practically pyrrolizidine-free (detection limit of 0.1 ppm), as the hydrophilic PA N-oxides are not extracted alongside. The PA had to be removed from ethanolic extracts subsequently by means of cation exchangers.

Tea (equivalent to an aqueous extract) made from leaves or rhizomes should no longer be used, as the PA content exceeds the permitted 0.1 g daily [13].



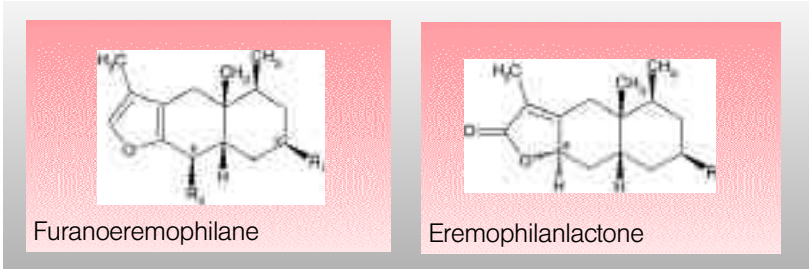


Fig. 6: Sesquiterpenes of the furanopetasine chemovariety

Indications

Only the indications confirmed by studies are discussed in this chapter. However, for the sake of completeness, ***Table 1*** lists the traditional uses of butterbur alongside the modern uses.

Migraine prophylaxis

Butterbur rhizome extract is effective in the prophylaxis of migraine; in a randomised, double-blind, placebo-controlled study of parallel groups of 60 patients (50 mg Petasites rhizome extract twice daily) for 12 weeks, the number of attacks per month ***(Fig. 8)*** fell from 3.3 1.5 at the start to 1.3 0.9 after 8 weeks ***(Tab. 2)***, which is equivalent to a maximum reduction of 60% (placebo 17.2%) compared to the baseline [15]. The number of migraine days per month also fell significantly ($p < 0.05$) from 3.4 1.6 days at the start to 1.7 0.9 days after 12 weeks. The intensity and duration of the attacks did not decrease significantly.

The tolerability was assessed by the patients as excellent. No adverse effects occurred. The extract employed is therefore comparable to the commonly used synthetic migraine prophylactic drugs propranolol (- 38.2%), timolol (- 43.9%)[16] and flunarizine (- 39%)[17] with regard to the percentage reduction in the number of attacks per month. The intensity and duration of the attacks were not influenced by these drugs either.

The leukotriene antagonism of the butterbur rhizome extract might be involved in this prophylactic effect on migraine: in an open study in 17 patients, the leukotriene receptor antagonist montelukast, which is employed in the treatment of asthma, was significantly effective in reducing the frequency of migraine attacks [18]. In addition, petasine inhibits a rise in the intracellular calcium concentration, just like the calcium antagonists (e.g. flunarizine) that have long been used in migraine prophylaxis.

Table 1: Butterbur indications

Indication	***traditional***	***modern***
Migraine	-	+
Tension headache	✔	*(+)*
Cramp-like pains in the urinary tract	✔	+
Cramp-like pains in the gastrointestinal and biliary area	✔	*(+)*
Dysmenorrhoea	✔	*(+)*
Emmenagogue	✔	-
Back pain	✔	-
Cough	✔	-
Asthma	✔	*(+)*
Allergic rhinitis	-	*+ [L]*
Wound healing, external	✔ *[L]*	-

Unless specially stated, rhizomes (extract or powder) were used.
✔ *traditional use*
+ indication confirmed by studies. – not used
(+) indication inadequately confirmed by studies
[L] leaf extract or pounded leaves used externally

As with all drugs used for migraine prophylaxis, the mechanism of action has still not been elucidated in detail.

Tension headaches

The efficacy in tension headaches (vasomotor headaches) was demonstrated in a multicentre prospective clinical study of 33 patients in general practices in Switzerland [19]. A general practice study by Gruia in 1986 of 22 patients for 4 weeks obtained similar results. However, the efficacy in migraine prophylaxis exceeded that in vasomotor headache [20].
The available studies indicate efficacy in tension headaches.

Spasm of the urogenital tract

The spasmolytic activity of butterbur extracts, similar to papaverine, was demonstrated in 1951 by Bucher in the isolated guinea pig intestine [4]. In 1955, Aebi et al. were the first to isolate and characterise two substances with a spasmolytic action from rhizomes of Petasites hybridus and named them petasine and isopetasine respectively [21].

In a controlled study with 20 patients in each of the 2 treatment groups, a butterbur extract in the subacute stage of ureteric colic (i.e. after treating the acute symptoms with papaverine i.v.) demonstrated a similar effect to N-butylscopolamine (Buscopan®): the 2 groups received either 1 Buscopan® tablet 5 times daily or 2 capsules of butterbur rhizome extract up to 2-hourly (max. 14 caps daily).

Despite this high dosage, no adverse side effects occurred [22].

A general practice clinical study in 40 patients showed a good effect in cystitis, renal/ureteric stones and pain in prostatitis [23].

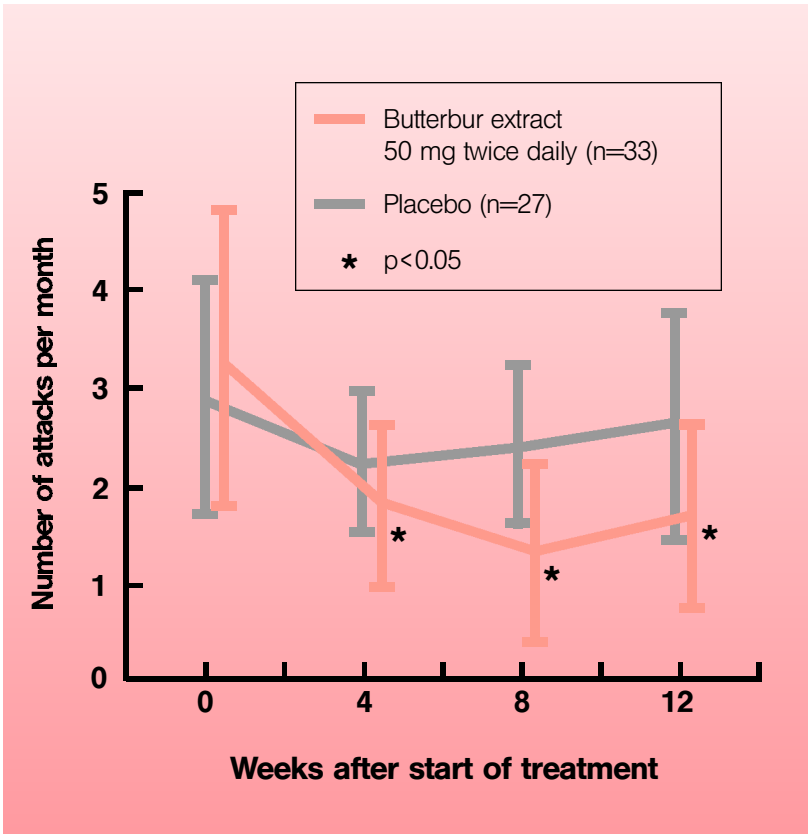


Fig. 8: Frequency of migraine attacks per month during treatment with butterbur extract or placebo:

After a preliminary period of 4 weeks to determine the baseline levels, 33 patients were treated with butterbur extract (50 mg twice daily) and 27 patients with placebo. From the 4th week until the end of the study, the number of migraine attacks had fallen significantly with treatment with butterbur extract compared to placebo (results with p < 0.05). A maximum reduction in the number of attacks of 60 % compared to the baseline levels (Tab.2) was recorded after 8 weeks.*

The use of butterbur extracts in mild to moderate colic-like pains of the excretory urinary tract thus appears justified.

In folk medicine, butterbur is also used in *dysmenorrhoea*.

Meier (1994) describes a placebo-controlled double-blind pilot study in 14 subjects with primary dysmenorrhoea using a preparation that included 90 mg of an alcoholic butterbur dried extract; 3 pills were taken daily for 3 months. There was a marked decrease in pain compared to placebo, especially on the 2nd day of menstruation, which indicates that butterbur extract is effective [24].

	Weeks after start of treatment			
	0	4	8	12
Butterbur extract	3.3±1.5	1.8±0.8	1.3±0.9	1.7±0.9
Placebo	2.9±1.2	2.2±0.7	2.4±0.8	2.6±1.1

Table 2: Number of migraine attacks per month (total SD)

Spasm of the digestive tract

Although butterbur is used in folk medicine in pain of the digestive tract and biliary tract, there are no studies in this regard that meet current standards.

However, a good effect can be expected from the mechanism of action discussed above and the results of investigations in animal models [4].

Asthma

The traditionl use of butterbur in asthma was investigated in recent studies:

In a clinical study of 22 patients with asthma or tracheobronchitis, Gruia (1986) assessed the result of treatment as good to very good in 94% of cases [20].

In an open clinical study (1998) Petasites hybridus (pulverised rhizome) was investigated for its efficacy and tolerability in 70 patients (3 groups) with chronic asthma or chronic obstructive bronchitis:

The authors found a significant improvement ($p<0.05$) in the FEV1 (forced expiratory volume in 1 sec.) 180 minutes after administration of 600 mg root powder in the first group (30 patients). In the second group (20 patients), the bronchial hyperreactivity in the metacholine test improved 120 minutes after the same single dose of root powder ($p<0.05$). The third group (20 patients) received 600 mg of drug 3 times a day for 14 days.
This resulted in an improvement in the metacholine test, but this was not significant [25].

Unfortunately, more precise figures cannot be found in the study. Thus,

neither of these studies meets present-day requirements. The efficacy in asthma must be confirmed by controlled clinical studies. A possible effect could be attributed to the inhibition of leukotriene synthesis described above, the inhibition of eosinophilic cationic protein (ECP) and the relaxant effect on the smooth muscle of the airways [11,26].

Allergic rhinitis

In a placebo-controlled, randomised double-blind study, 61 patients received 1 tablet of a CO_2 extract of butterbur leaves 4 times daily (standardised to 8 mg total petasines per tablet) and 64 patients received 1 tablet of cetirizine in the evening for two weeks. The results showed that the extract studied is equally effective as cetirizine in allergic rhinitis, but without its sedative side effect [27].
The good effect is explained by the inhibition of leukotriene synthesis by the petasines.

Prospects for further possible indications

Leukotrienes are important in the pathogenesis of many inflammatory diseases.

On the basis of analogy, new areas of indications could open up for butterbur extracts wherever leukotrienes play a part in pathogenesis:
Leukotriene synthesis inhibitors such as zileuton are currently being investigated in inflammatory bowel disease such as ***Crohn's disease and ulcerative colitis*** ; the results of investigations in animal models and clinical studies are promising [28,29].
Interestingly, sulphasalazine and 5-aminosalicylic acid, which are used as standard drugs in chronic inflammatory bowel diseases, also have an inhibitory effect on leukotriene synthesis in the mucosa of the small and large intestine besides their other effects [8].

A case study of 2 patients and an open clinical study of 12 patients with ***chronic urticaria*** suggest that the leukotriene receptor antagonists zafirlukast and montelukast are effective. In both studies, the better effect of the leukotriene synthesis inhibitor zileuton was found to be increased by inhibition of LT B_4 [9,10].

Various lipoxygenase inhibitors were successfully tested clinically topically or systemically in ***psoriasis*** also [30,31].

The future will show whether butterbur extract is also effective in these indications.

Dosage and duration of use

Only one CO2 root extract has been available on the market up till now; it is available as a spissated extract in capsule form and contains 4–11 mg total petasines per capsule of 25 mg extract. For migraine prophylaxis, 50 mg root extract are taken twice daily for at least 3-6 months (registered dosage).

In the first month, the dose can be increased to 75 mg twice daily in order to increase the effect [32].
A dosage of 25-50 mg 2-3 times a day is recommended for spastic pains.

When going to press, a licence application for CO2 leaf extract in tablet form (standardised to 8 mg total petasines per tablet) for the indication allergic rhinitis was in progress.

Restrictions on use

There have been no investigations of use during pregnancy and lactation and in children. Butterbur extracts should therefore not be taken by children under 12 years, pregnant women and breastfeeding mothers.

Adverse effects

There have been only rare reports of side effects. The numbers of side effects were recorded inadequately in the cited studies.
In most cases these were mild gastrointestinal complaints such as burping, nausea or a sensation of pressure in the stomach region. More severe gastrointestinal side effects are hardly to be expected, as butterbur extract was even found to have gastroprotective effects [33].
There have also been isolated reports of reversible allergic skin reactions.
Up to now there have been 3 cases of cholestatic hepatitis probably associated with the prolonged use of butterbur rhizome extract for migraine prophylaxis. In all 3 cases, the markedly raised liver parameters returned to normal in a short time after stopping the preparation. This suggests nonpredictable drug-induced hepatitis due to an allergic immunological reaction, which is familiar as a very rare side effect of innumerable widely used medications (e.g. including diazepam or paracetamol) [34]. Since the hepatitis in all cases only became apparent after more than 4 weeks of daily use of butterbur extract, it appears rational to measure liver function tests (transaminases, γ-GT, alkaline phosphatase and total bilirubin) and to stop the medication immediately if these parameters are increased.
Risk factors for the development of cholestatic hepatitis during prolonged

treatment with butterbur extract are alcohol abuse and additional long-term medication with potentially hepatotoxic medicines.

Butterbur extract overall is distinguished by a very goood side effect profile. The very rare cholestatic hepatitis can easily be prevented by appropriate precautions.

Interactions

No interactions have been identified so far.

Overdose

No adverse side effects were observed even with the highest dosage employed so far of 14 capsules of 25 mg daily in ureteric colic [22].

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