Petasites hybridus root (butterbur) is an effective preventive treatment for migraine

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Abstract—*Objective:* To evaluate the clinical efficacy of a standardized special root extract from the plant *Petasites hybridus* as a preventive therapy for migraine. *Methods:* This is a three-arm, parallel-group, randomized trial comparing *Petasites* extract 75 mg bid, *Petasites* extract 50 mg bid, or placebo bid in 245 patients with migraine. Eligible patients met International Headache Society criteria for migraine, were ages 18 to 65, and had at least two to six attacks per month over the preceding 3 months. The main outcome measure was the decrease in migraine attack frequency per month calculated as percentage change from baseline over a 4-month treatment period. *Results:* Over 4 months of treatment, in the per-protocol analysis, migraine attack frequency was reduced by 48% for *Petasites* extract 75 mg bid ($p = 0.0012$ vs placebo), 36% for *Petasites* extract 50 mg bid ($p = 0.127$ vs placebo), and 26% for the placebo group. The proportion of patients with a ≥50% reduction in attack frequency after 4 months was 68% for patients in the *Petasites* extract 75-mg arm and 49% for the placebo arm ($p < 0.05$). Results were also significant in favor of *Petasites* 75 mg at 1, 2, and 3 months based on this endpoint. The most frequently reported adverse reactions considered possibly related to treatment were mild gastrointestinal events, predominantly burping. *Conclusions: Petasites* extract 75 mg bid is more effective than placebo and is well tolerated as a preventive therapy for migraine. *Petasites* 50 mg PO bid was not significantly more effective than placebo on the primary study endpoints.

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Many persons with migraine use over-the-counter and complementary treatments to the exclusion of prescription drugs.[1,2] Complementary preventive treatments are often used in the absence of well-controlled trials, although feverfew, magnesium, and riboflavin have been studied specifically in migraine.[3-6] *Petasites hybridus* root (butterbur), a perennial shrub, was used for medicinal purposes in ancient times and has been rediscovered since the middle of the last century for clinical applications including migraine.[7-10]

An extract of *Petasites* root is an herbal or complementary medicine. From a regulatory perspective, it is considered a food product in the United States and the United Kingdom. (In the United States, *Petasites* extract is marketed as a food supplement [Petadolex]. In Germany, Petadolex is licensed as a pharmacy medicine under full regulatory supervision by the German Health Authority.) The *Petasites* plant has been used traditionally as a migraine preventive. In addition to anecdotal reports, one small study with 60 patients with migraine showed that an extract of the rhizome (root stock) from the *P. hybridus* plant 50 mg bid was more effective than placebo as a migraine-preventive therapy.[7,11] We further assessed the clinical effectiveness and tolerability of two different doses of *Petasites* extract vs placebo in the prevention of migraine in adults.

Additional material related to this article can be found on the *Neurology* Web site. Go to www.neurology.org and scroll down the Table of Contents for the December 28 issue to find the title link for this article.

Methods. *Study design.* This was a double-blind, randomized, three-arm, parallel-group, placebo-controlled study that compared *Petasites* extract 50 mg bid and 75 mg bid vs placebo. Participants enrolled in a 4-week baseline period where frequency and severity of migraine attacks were recorded using a daily headache diary. Eligible patients were then randomized to treatment groups for 16 weeks; headache frequency, duration, and intensity of attacks were recorded in diaries. Adverse reactions also were monitored and reviewed during office visits. Patients were seen at the clinic every 4 weeks following initiation of treatment.

Patients. Eligible patients were ages 18 to 65 and met International Headache Society criteria for migraine with or without aura.[12] Patients had a range of two to six attacks per month for the 3 months prior to treatment. The age at migraine onset was younger than 50. Patients also were required to have a minimum of two attacks during the 4-week baseline phase. Other prophylactic migraine medications had to be discontinued at least 3 months prior to study participation. Participants were excluded if they had nonmigraine headaches for >6 days per month during the previous 3 months prior to the start of the study. Women who were pregnant, breast feeding, or of child-bearing potential not using medically accepted birth control measures were excluded.

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Patients underwent a complete neurologic and physical examination prior to study entry, and routine laboratory studies were monitored (total blood cell count, serum glutamic–oxaloacetic [SGOT] and glutamic–pyruvic [SGPT] transaminases, gamma-glutamyl transferase [GGT], and bilirubin).

Ethics. Patients provided informed consent prior to study entry. This study was conducted in accordance with the ethical standards of good clinical practice and the regulations of the Declaration of Helsinki.

Treatment. *Petasites* root extract, standardized to contain a minimum of 15% petasins (Weber and Weber GmbH & Co, KG, Germany), or placebo was administered as a single capsule and given as a twice-a-day treatment regimen for a total of 16 weeks. Identical capsules contained either *Petasites* extract 50 mg or *Petasites* extract 75 mg or matching placebo. Compliance was assessed at 4-week intervals. Patients taking <80% of the appropriate medication were considered noncompliant.

The extraction method to produce active medication reduced the quantity of pyrrolizidine alkaloids below the limit of detection. This process meets the regulations of the German Health Authority (Bundesinstitut fuer Arzneimittel und Medizinprodukte).

Randomization and blinding. Double-blind study medication was individually assembled for each patient and identified by a patient number according to the randomization code prepared by an independent statistician. Enrollment was done by the study doctor. Following completion of screening procedures to confirm patient eligibility at visit 2, the patient entered the double-blind treatment period and was randomized to one of the three treatment groups. The randomization schedule was produced by a computer program. Each center had been allocated a block of patient numbers (and associated treatments).

Variables and endpoints. In this study, we tested the hypothesis that the prophylactic treatment with *Petasites* extract reduced headache attack number in persons with migraine and that the reduction was significantly higher than with placebo. The primary endpoint of the study was the change in the frequency of migraine attacks (number of migraine attacks per month) over the entire 4-month treatment period calculated as percentage change from baseline.

Secondary endpoints included the reduction in migraine attack frequency per month, number of therapy responders (reduction of at least 50% in attack frequency compared with baseline), patient's use of acute medications, adverse events, and safety laboratory parameters (SGOT, SGPT, GGT, bilirubin). All adverse events were reported during each clinic visit. At the final visit, patients gave a global assessment of efficacy and tolerability based on a 4-point scale (poor, moderate, good, excellent).

Sample size and statistical analysis. It was expected that the *Petasites*-induced reduction in monthly migraine attacks would be at least 55% for both active treatment groups (50 or 75 mg) and 35% under placebo. The assumed SD was 1.5.[7] Sixty-four patients per treatment group were required to detect significant differences with an experimental error $\alpha = 0.05$ and with a power of 80% ($\beta = 0.20$). To achieve a final sample of 192 patients (64 patients per arm $\times$ 3 arms), assuming that 80% of patients who entered the run-in phase would complete the study, we planned to enroll 240 patients.

Data management included data quality assurance and was performed according to international guidelines (Good Clinical Practice, International Conference on Harmonization E9 and E3) and internal standard operating procedures. No adjustment for covariates was made, as these factors revealed no significance. Analysis was done on the patients that followed the protocol (per-protocol population). In addition, the primary endpoint was also evaluated in all patients with available diaries to whom study medication was given at least once (intention-to-treat population). Endpoints were assessed using the two-sided Mann–Whitney *U* test. In addition to the *p* values, the corresponding effect sizes of the Wilcoxon–Mann–Whitney test (Mann–Whitney estimator) as measures of relevance were calculated with their 97.5% CIs. For proven superiority, the lower limit of the 97.5% CI of the Mann–Whitney estimator has to be above the benchmark for equality (0.5).

Results. *Subjects.* Two hundred forty-five participants were enrolled in the run-in phase; 233 completed the run-in and were randomized to one of three treatment groups (figure 1). Overall, 202 participants successfully completed the study according to the study protocol in the *Petasites* extract 50-mg arm (n = 71), the *Petasites* extract 75-mg arm (n = 68), and the placebo arm (n = 63). Fifteen patients did not receive study medication. During the treatment period, 27 participants were withdrawn or dropped out of the study. Reasons for withdrawal were mutually exclusive and included serious adverse event (n = 2 [1 patient had a planned elective hospitalization; the other patient was hospitalized due to epilepsy—neither patient should have been enrolled]), lack of compliance (n = 4), lack of efficacy (n = 3), patient request to discontinue (n = 12), investigator withdrew patient from study (n = 1), patient lost to follow-up (n = 11), and other miscellaneous reasons (n = 2; see figure 1).

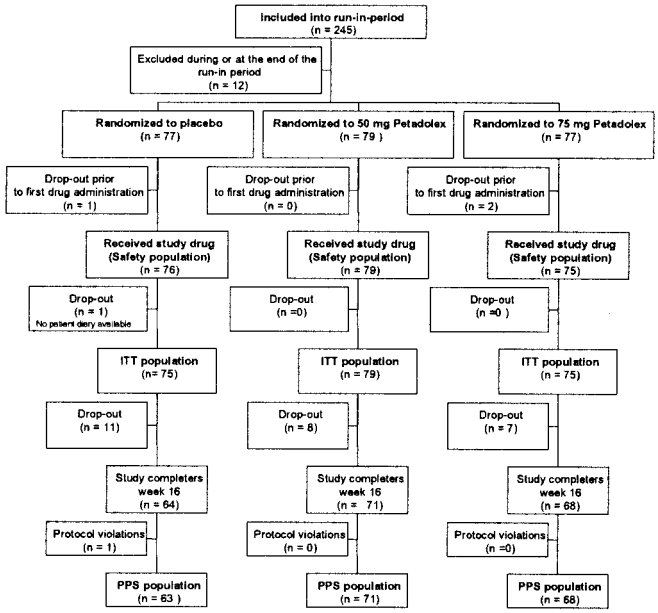

Figure 1. Study population. Overall, 245 patients were recruited into the study and enrolled in the 4-week run-in phase; 23 participants were excluded prior to randomization to treatment groups. Three participants dropped out of the study prior to receiving study medication, and one patient dropped out after receiving study medication, but no diary data were available. During the course of the 4-month treatment phase, 26 patients dropped out and 1 patient was excluded owing to protocol violation. Overall, 202 participants were included in the efficacy analysis. There were 229 participants in the ITT analysis. ITT = intention to treat; PP = per protocol.

There were no significant differences in demographic characteristics among the three treatment groups (table 1). All study participants were able to distinguish between migraine and nonmigraine headaches; all reported 24-hour pain-free intervals between migraine attacks. Medication compliance was not significantly different among the three treatment groups as measured using pill counts per bottle.

Clinical efficacy. The primary endpoint was a reduction in the mean number of migraine attacks measured as the percentage reduction from baseline in migraine attacks per month across the 4-month treatment period. The intention-to-treat population treated with *Petasites* extract 75 mg (n = 75) had an average reduction of 45% in the

Table 1 *Baseline characteristics (per protocol data set, n = 202) of patients randomized to one of three patient groups after end of run-in-period*

Baseline characteristic	Placebo, n = 63	50 mg Petadolex, n = 71	75 mg Petadolex, n = 68	Global difference between groups, *p*
Age, y	42 (22–58)	41 (22–60)	42 (22–60)	0.80
Height, cm	168 (158–189)	167 (158–181)	169 (157–185)	0.41
Weight, kg	69 (53–98)	66 (52–98)	66 (50–100)	0.38
Gender, % F	79	87	79	0.37
Type of migraine, %				
With aura	19 (n = 12)	23 (n = 16)	28 (n = 19)	0.16
Without aura	76 (n = 48)	77 (n = 55)	72 (n = 49)	
Both	5 (n = 3)	0 (n = 0)	0 (n = 0)	
Attack frequency	3 (2–7)	3 (2–6)	3 (2–7)	0.17
Attack days/mo	3 (2–8)	3 (2–7)	3 (2–7)	0.17
Attack duration, h	11 (2–46)	13 (4–61)	12 (4–45)	0.81
Attack intensity score	2 (1.7–2.7)	2 (1.5–3)	2 (1.5–3)	0.32

Values are medians (5th and 95th percentiles) and are rounded. Significance testing for continuous data: rank analysis of variance for frequencies: χ^2 test, exact if necessary.

number of attacks per month as compared with 28% for the placebo group (n = 75) ($p = 0.005$ vs *Petasites* extract 75 mg). The *Petasites* extract 50-mg group (n = 79) had a 32% decrease in attack number from baseline (figure 2; $p = 0.43$ vs placebo). *Petasites* extract 75 mg was significantly more effective than *Petasites* extract 50 mg ($p = 0.04$). Results were similar for the per-protocol analysis.

To describe the onset of action, we evaluated change in attack frequency for each individual month following start of treatment (figure 3). After 3 months of treatment, the reduction in the number of attacks per month in the per-protocol population was highest with the *Petasites* extract 75 mg (58%), followed by *Petasites* extract 50 mg (42%) and placebo (26%). Reduction in the attack frequency was significantly greater for *Petasites* extract 75 mg vs placebo at months 1, 3, and 4. There was no consistent pattern of treatment effect on attack duration or intensity.

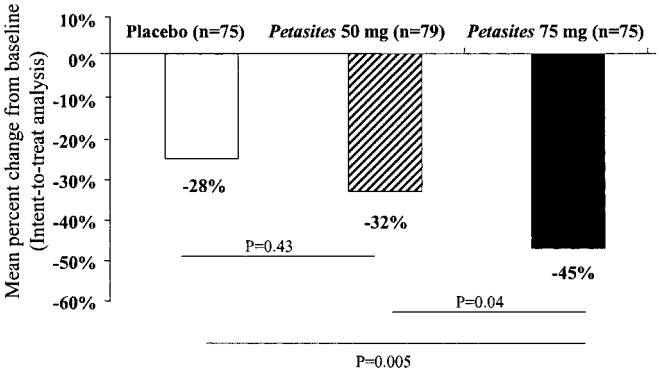

Figure 2. Reduction in headache frequency: intention-to-treat analysis over 4 months. Petasites *extract 75 mg was more effective (45%) than placebo (28%) in reducing migraine attack frequency over baseline (*p = *0.005).* Petasites *extract 75 mg was also more effective in reducing attack frequency over baseline as compared with* Petasites *extract 50 mg (32%;* p = *0.04).*

Patients who had a 50% reduction in mean attack frequency per month relative to baseline were considered "responders." Figure 4 shows that the mean percentage of responders in the *Petasites* extract 75-mg treatment group (per protocol) was significantly larger than for the placebo treatment for months 1 through 4 of the study. There were no statistically significant differences in the *Petasites* extract 50-mg treatment group as compared with either placebo or *Petasites* extract 75 mg.

Detailed results for other primary and secondary outcome variables with the corresponding effect sizes and their 95% CIs are available (see table E-1 on the *Neurology* Web site at www.neurology.org). Global assessment of effi-

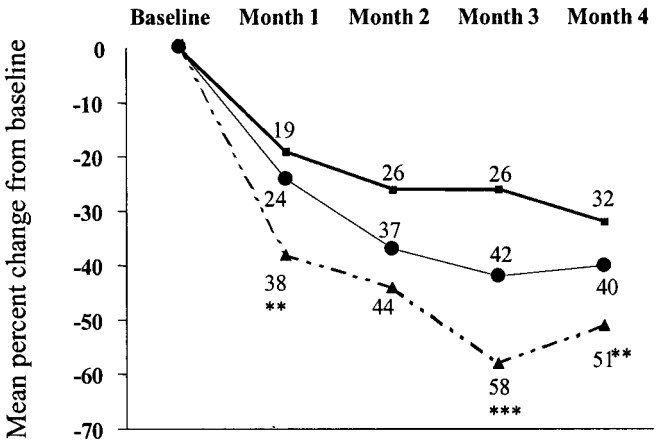

Figure 3. Mean percentage change in headache frequency by study month. Petasites *extract also was associated with a monthly improvement in headache frequency from baseline values, with significant differences observed as early as month 1 for patients treated with* Petasites *extract 75 mg bid.* **p = *0.02 vs placebo,* ***p = *0.001 vs placebo; all other comparisons,* p > *0.05. Squares = placebo; circles =* Petasites *50 mg; triangles =* Petasites *75 mg.*

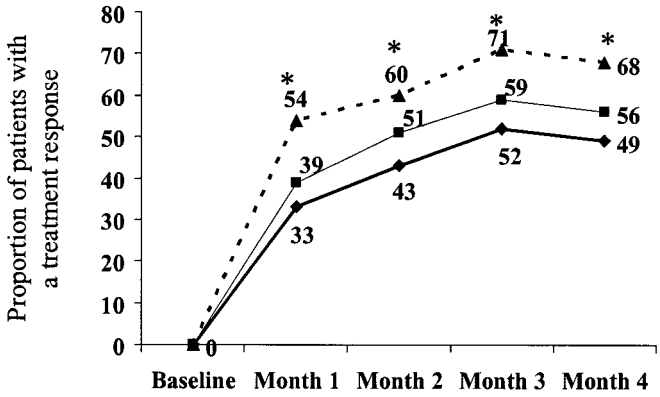

Figure 4. Treatment response. The percentage of patients who demonstrated a >50% reduction in attack count from baseline was highest in the group treated with Petasites *extract 75 mg bid, with differences from placebo achieved the first month following treatment.* *$p < 0.05$ *vs placebo; all other comparisons,* $p > 0.05$. *Diamonds = placebo; squares =* Petasites *50 mg; triangles =* Petasites *75 mg.*

cacy by the patients is shown in table E-2 (on the *Neurology* Web site).

Tolerability. Over the 4-month course of treatment, 131 adverse events were reported by 80 participants. Overall, there were five serious adverse events, which included one planned hospitalization for acupuncture and neural therapy (in the placebo treatment group), food poisoning (one patient in the placebo group), epilepsy (one patient in the *Petasites* extract 75-mg group), and basal cell carcinoma (*Petasites* extract 75 mg; two patients). None of these events was judged to be treatment related.

The majority of adverse events were either mild or moderate in intensity and occurred at comparable frequencies in all groups. The most common adverse events were gastrointestinal disorders and neurologic disorders (table 2). Significant differences in the incidence of adverse events between *Petasites* extract 75 mg or 50 mg vs placebo were observed only for burping. The patients' global assessment of tolerability is shown in table E-2 (on the *Neurology* Web site).

Other laboratory tests also show that *Petasites* extract was well tolerated. No changes were observed during the 5-month study for systolic blood pressure, diastolic blood pressure, heart rate, SGOT, SGPT, GGT, or bilirubin.

Discussion. The results from this study support the efficacy of *Petasites* extract (butterbur) extract as a preventive therapy for migraine. *Petasites* extract 75 mg bid was more effective than placebo on numerous endpoints. The 50-mg bid dose did not reach statistical significance in this study, although there is a suggestion of a dose–response curve; a previous single center study demonstrated that *Petasites* extract 50 mg bid was more effective than placebo in reducing headache frequency in patients with migraine.[7,11]

The magnitude of the treatment effect for the 75-mg dose of *Petasites* was substantial. Though cross-study comparisons may not be valid, this level of treatment effect is broadly comparable with results obtained with prescription preventive medications.[13-17] For example, the mean 4-week reduction in migraine headache frequency for *Petasites* extract 75 mg in the intention-to-treat analysis was 45% vs 28% for placebo. In clinical trials of prescription preventives, if 50% of patients achieve a 50% reduction in attack frequency, that is considered a good therapeutic response.[13-17]

The mechanism of action of *Petasites* extract in migraine is uncertain. Laboratory studies report that *Petasites* extract has anti-inflammatory properties including antileukotriene activity in in vitro studies.[18-21] Leukotrienes and other inflammatory mediators have been implicated in the inflammatory cascade associated with migraine.[22,23] Another possible site of action involves an effect on calcium chan-

Table 2 *Adverse events considered possibly related to study medication*

Adverse event	*Petasites* 75 mg, n = 75	*Petasites* 50 mg, n = 79	Placebo, n = 76
Cardiac disorders	1 (1.3%)	0	0
Disorders of ears and labyrinth	0	1 (1.3%)	1 (1.3%)
Gastrointestinal disorders	17 (22.4%)	20 (25.6%)	5 (6.7%)
General disorders	1 (1.3%)	0	1 (1.3%)
Infections and infestations	0	2	0
Neurologic disorders	1 (1.3%)	4 (5.1%)	1 (1.3%)
Neurologic disorders, general disorders	0	1 (1.3%)	0
Renal and urinary disorders	0	0	1 (1.3%)
Respiratory, thoracic, and mediastinal disorders	1 (1.3%)	0	0
Disorders of eye	0	0	1 (1.3%)
Skin and subcutaneous tissue disorders	2 (2.6%)	0	1 (1.3%)

All adverse events were classified according to the Medical Dictionary of Regulatory Affairs, and treatment groups were compared. No significant differences between treatment groups were observed in relation to incidence of adverse events, with the exception of an increase in burping observed in association with both doses of *Petasites* extract.

nels, as demonstrated in vascular smooth muscle and trachea.[24,25]

The higher than usual placebo rate may be a consequence of the medically naive study population that particularly benefits from education about trigger factor avoidance and disease self-management. These potential differences in study population also make comparisons across studies difficult.

Petasites extract 75 mg bid was associated with a significant improvement over placebo in mean monthly attack count and in the number of patients showing a ≥50% improvement in attacks. *Petasites* extract was well tolerated with only gastrointestinal upset (most commonly reported as burping) reported as the most common adverse event. Similar to other migraine studies, long-term studies need to be done that further explore the tolerability of *Petasites* extract of a ≥1-year period. However, the patented special *Petasites* extract has been marketed in Germany since 1988. More than a half-million individuals have been exposed to the product, and the overall frequency of adverse reactions from pharmacovigilance is very low. Most frequent organ-specific adverse effects are attributed to the gastrointestinal system and are of a mild and transient nature. Based on the volume of sales of a 100-mg daily dose regimen, it is estimated that approximately 500,000 individuals have been exposed to this specific product since 1992, with an estimated duration of intake for 3 months. From this postmarketing assessment, there have been 115 reports of suspected adverse events, representing an overall reported adverse event frequency of 0.02%, further supporting the published results from clinical studies that this specific formulation of *Petasites* extract is used as an alternative medicine and is well tolerated.[26] However, patients must be cautioned against consuming any part of the *Petasites* plant in any form other than the specific products prepared commercially (such as Petadolex), in which the plant carcinogens have been removed.

Appendix

Contributors: Dr. Lipton was the principal investigator for the United States, consulted on the design of the trial, and wrote the article. Dr. Göbel was the principal investigator for Germany, consulted on the design of the trial, and revised the manuscript. Drs. Einhäupl, Wilks, and Mauskop participated as site investigators and critically reviewed the manuscript. Data entry and statistical analysis were done in an independent statistical institute by Ulrich Stefenelli (Fachinstitut für Statistik, Würzburg, Germany) with support from Volker Rahlfs and Johannes Vester (IDV Datenanalyse und Versuchsplanung, Gauting, Germany) and Anette Knoll (BZT Clinical Research, Munich, Germany).

Participating centers: The study was conducted in nine primary care or specialty centers in the United States and Germany. European centers: H. Göbel (Kiel, Germany); R. Schellenber (Hüttenberg, Germany); W. Grossman (München, Germany); G. Müller-Schwefe (Göppingen, Germany); M. Einhäupl (Berlin, Germany). US centers: N. Mueller (Englewood Cliffs, NJ); K. Wilks and R.B. Lipton (Towson, MD); A. Mauskop (New York, NY).

References

1. Lipton RB, Scher AI, Steiner TJ, et al. Patterns of health care utilization for migraine in England and in the United States. Neurology 2003; 60:441–448.
2. Silberstein SD, Lipton RB, Dalessio DJ, ed. Wolff's headache and other head pain. 7th ed. Oxford, UK: Oxford University Press, 2001.
3. Murphy JJ, Heptinstall S, Mitchell JR. Randomised double-blind placebo controlled trial of feverfew in migraine prevention. Lancet 1988;2: 189–192.
4. Johnson ES, Kadam NP, Hylands DM, Huylands PJ. Efficacy of feverfew as prophylactic treatment of migraine. Br Med J 1985;291:569–573.
5. Peikert A, Wilimzig C, Kohne-Volland R. Prophylaxis of migraine with oral magnesium: results from a prospective, multi-center, placebo-controlled and double-blind randomized study. Cephalalgia 1996;16: 257–263.
6. Schoenen J, Jacquy J, Lenaerts M. Effectiveness of high-dose riboflavin in migraine prophylaxis. A randomized controlled trial. Neurology 1998; 50:466–470.
7. Grossman M, Schmidramsl H. An extract of *Petasites hybridus* is effective in the prophylaxis of migraine. Int J Clin Pharmacol Ther 2000;38: 430–435.
8. Ziolo G, Samochewiec L. Study on clinical properties and mechanism of action of *Petasites* in bronchial asthma and chronic obstructive bronchitis. Pharm Acta Helv 1998;72:359–380.
9. Barsom S. Behandlung von Koliken und Spasmen in der Urologie mit einem pflanzlichen Spasmolytikum. Erfahrungsheilkunde 1986;35:1–11.
10. Gruia FS. Pflanzliche Analgetika–Therapie bei WS-Syndrom. Biol Med 1987;3:454.
11. Diener HC, Rahlfs VW, Danesch U. The first placebo-controlled trial of a special butterbur root extract for the prevention of migraine: reanalysis of efficacy criteria. Eur Neurol 2004;51:89–97.
12. Headache Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Cephalalgia 1988;8(suppl 7):1–96.
13. Silberstein SD. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2000;55:754–762.
14. Gray RN, Goslin RE, McCrory DC, et al. Drug treatment for the prevention of migraine headache. Technical review 2.3, February 1999. Prepared for the Agency for Health Care Policy and Research under contract number 29009402025. Available from the National Technical Information Service; NTIS accession no. 127953.
15. Mathew NT, Saper JR, Silberstein SD, et al. Migraine prophylaxis with divalproex. Arch Neurol 1995;52:281–286.
16. Mathew NT, Rapoport A, Saper J, et al. Efficacy of gabapentin in migraine prophylaxis. Headache 2001;41:119–128.
17. Storey JR, Calder CS, Hart DE, Potter DL. Topiramate in migraine prevention: a double-blind, placebo-controlled study. Headache 2001;41: 968–975.
18. Thomet OA, Wiesmann UN, Blaser K, Simon HU. Differential inhibition of inflammatory effector functions by petasin, isopetasin and neopetasin in human eosinophils. Clin Exp Allergy 2001;31:1310–1320.
19. Brune K, Bickel D, Peskar BA. Gastro-protective effects by extracts of *Petasites hybridus*: the role of inhibition of peptido-leukotriene synthesis. Planta Med 1993;59:494–496.
20. Scheidegger C, Dahinden C, Wiesmann U. Effects of extracts of individual components from *Petasites* on prostaglandin synthesis in cultured skin fibroblasts and on leucotriene synthesis in isolated human peripheral leucocytes. Pharm Acta Helv 1998;72:359–380.
21. Thomet OA, Wiesmann UN, Schapowal A, Bizer C, Simon H. Role of petasin in the potential anti-inflammatory activity of a plant extract of *Petasites hybridus*. Biochem Pharmacol 2001;61:1041–1047.
22. Sheftell F, Rapoport A, Weeks R, Walker B, Gammerman I, Baskin S. Montelukast in the prophylaxis of migraine: a potential role for leukotriene modifiers. Headache 2000;40:158–163.
23. Pearlman EM, Fisher S. Preventive treatment for childhood and adolescent headache: role of once-daily montelukast sodium. Cephalalgia 2001;21:461.
24. Ko W, Lei C, Lin Y, Chen C. Mechanisms of relaxant action of S-petasine and S-Isopetasin, sesquiterpenes of *Petasites formosanus*, in isolated guinea pig trachea. Planta Med 2001;67:224–229.
25. Wang G-J, Shum AY-C, Lin Y-L, et al. Calcium channel blockade in vascular smooth muscle cells: major hypotensive mechanism of S-petasine, a hypotensive sesquiterpene from *Petasites formosanus*. J Pharmacol Exp Ther 2001;297:240–246.
26. Danesch U, Rittinghausen R. Safety of a patented special butterbur root extract for migraine prevention. Headache 2003;43:76–78.