



Petasites hybridus: evidence 1A on migraine prophylaxis

Carlos Alberto Bordini

Municipal Faculty of Medicine of Franca, Franca, Sao Paulo, Brazil



Carlos Alberto Bordini
cabord@com4.com.br

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Marcelo Moraes Valença

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Petasites hybridus extract is part of the therapeutic arsenal for migraine prophylaxis. In this commentary, we discuss the study by Lipton et al. (2004), published in *Neurology*, which presents a high-quality clinical trial demonstrating the efficacy of *Petasites hybridus* for migraine prevention. The study, conducted by renowned researchers, classifies *Petasites hybridus* as a Level A treatment (established efficacy based on >2 Class I trials). Despite this strong evidence, questions often arise regarding the appropriate clinical scenarios for prescribing this medication. In addition to analyzing the findings of this seminal study, this commentary explores potential indications for *Petasites hybridus* in clinical practice.

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Introduction

P*etasites hybridus* belongs to a genus of inflorescing plants in the sunflower family, the Asteraceae, also known as *butterburs*, or *coltsfoots*. They are perennials with thick, creeping underground rhizomes and large rhubarb-like leaves during the growing season (1).

The genus name is derived from the Greek word *πέτασος*, *petasos* due to the plant's broad leaves that resemble a wide-brimmed hat (2).

One of its species, *Petasites hybridus* is common in Europe and Mediterranean countries and has medicinal properties. Its butterbur designation is believed to have originated from the use of its leaves to wrap butter centuries ago. Other designations are - swamp rhubarb and devil's hat (1).

Medicinal uses of Petasites hybridus

Petasites hybridus has been used for more than 2,000 years to treat various ailments such as fever, pain, lung disease, and cramps. Currently, its extract is used for migraine prevention. *Petasites hybridus* extract contains several bioactive compounds, including sesquiterpenes, such as petasin and isopetasin. These compounds are considered to be primarily responsible for their therapeutic effects. Our emphasis will be on migraine prophylaxis (1).

The paper "Evidence-based guideline update: nonsteroidal anti-inflammatory drugs (NSAIDs) and other complementary treatments for prevention of episodic migraine in adults. The report of the Subcommittee on Quality Standards of the American Academy of Neurology and the American Headache Society" places *Petasites hybridus* in its "Level "A" RECOMMENDATIONS, meaning that the therapy is established as effective and should be offered for prevention of migraine (3).

In the same vein, the *Canadian Headache Society guideline* states that 11 prophylactics are highly recommended in migraine prophylaxis and *Petasites hybridus* is one of them (4).

This paper analyzes an article signed by luminaries of world cephaliatry, whose main author is Richard Lipton. The work is "*Petasites hybridus* root (*butterbur*) is an effective preventive treatment for migraine" (5). It was published in the prestigious "Neurology".

The lead author

Richard Lipton is one of the most important neuroepidemiologists in headache today. He has published more than 800 original articles, is a multi-award-winning author and director of the Montefiore

Headache Center. He is the lead author of the work that we will comment on: "The root of *Petasites hybridus* is effective in migraine prophylaxis", according to research published in the renowned journal *Neurology* (5).

The clinical trial

Petasites hybridus extract is an herbal medicine. In the United States it is marketed as a food supplement, but in Germany it is considered a drug and as such, under full supervision of the health service bodies (5). As already mentioned, *Petasites hybridus* has long been used in the treatment of migraine (5).

The study aimed to assess the efficacy and tolerability of two different doses of *Petasites hybridus* extract for migraine prophylaxis in adults (5). Given its methodological rigor and significant findings, this trial remains a key reference in the field. In this commentary, we analyze its implications and discuss potential clinical scenarios for prescribing *Petasites hybridus*.

Description of the method and sample

Lipton et al. (2004) conducted a double-blind, randomized, parallel-group, three-arm, placebo-controlled trial to compare the efficacy of *Petasites hybridus* extract at two different doses—50 mg twice daily (*Petasites hybridus* 50) and 75 mg twice daily (*Petasites hybridus* 75)—against placebo (5).

Participants had to be between 18 and 65 years old, diagnosed with migraine without and or with aura according to the ICHD-3 criteria of the International Headache Society (6). The disease should have started before the age of 50 years, patients should have had two to six migraine seizures per month in the three months prior to the start of treatment, had had at least 4 attacks during the baseline period, and had not used antimigraine prophylactics in the previous three months (5).

The main exclusion criteria were having had frequent non-migraine headaches in the last months, pregnant women, breastfeeding or women of childbearing age without effective contraception. The patients underwent detailed clinical and neurological examinations, hematological examinations, glutamic-oxaloacetic transaminases (SGOT), glutamic-pyruvic transaminases (SGPT), gamma-glutamyl transferase (GGT) and bilirubin were measured (5).

The sample size and the magnitude of the effect were properly calculated. It was estimated that in order to obtain 55% improvement in the active groups, 35% in the placebo group, and a dropout rate of 20%, 240



participants should be enrolled (5).

Results of the study

The primary outcome was the reduction in the monthly mean number of migraine attacks in the fourth month of treatment compared to baseline. The *Petasites hybridus* 75 mg group achieved a 45% decrease in the number of attacks per month, the placebo group, 28% ($p=0.005$). The *Petasites hybridus* 50 mg group achieved a 32% decrease compared to the placebo group, a non-significant difference, $p=0.43$. *Petasites hybridus* 75 mg group was also superior to *Petasites hybridus* 50 mg ($p=0.04$) (5).

Secondary outcome, percentage of responders. Patients who had a 50% reduction in the average frequency of attacks per month from baseline were considered "responders". The *Petasites hybridus* 75 group was significantly superior to placebo throughout all months of treatment. There was no statistically significant difference in the *Petasites hybridus* 50 mg treatment group compared to placebo.

Tolerability

No significant difference between the treatment groups was observed with respect to the incidence of adverse events, with the exception of an increase in belching in association with both doses of *Petasites hybridus* extract. No changes were observed during the study in blood pressure, heart rate, SGOT, SGPT, GGT, or bilirubin (5).

Comments on the discussion

This study proved the efficacy of *Petasites hybridus* extract in migraine prophylaxis.

Petasites hybridus 75 mg twice daily was more effective than placebo in both decreasing migraine days and percentage of responders. The 50 mg twice daily dose did not reach statistical significance in this study, although an earlier single-center study demonstrated that *butterbur hybridus* 50 mg twice daily was more effective than placebo in reducing the frequency of migraine seizures (7,8).

The authors emphasize that the magnitude of the treatment effect for the 75 mg dose of *Petasites hybridus* twice daily was substantial and that their results are similar to those of Diener et al. (8). They also emphasized that the average reduction of 45% in migraine attacks should be considered a good therapeutic response (8).

Although the exact mechanism of action of *Petasites*

hybridus is not yet completely understood, laboratory studies indicate that the extract has anti-inflammatory properties and antileukotriene activity in vitro. It has been suggested that the anti-inflammatory effects of *Petasites hybridus* are related to the ability to inhibit the biosynthesis of prostaglandins and leukotrienes. Given the importance of inflammation to migraine pain, such anti-inflammatory properties provide a rationale for the use of *butterbur* in the treatment of migraine (9).

Regarding tolerability, in this study, *Petasites hybridus* extract was well tolerated, the most common adverse events were gastrointestinal disorders (most commonly reported as belching) (5).

The authors caution that long-term studies are needed, hence, it is critical to further investigate the tolerability of *Petasites hybridus* extract over a one-year period. It should be mentioned, however, that the extract of *Petasites hybridus* has been marketed in Germany since 1988, used by more than half a million individuals and that the overall frequency of adverse reactions reported to pharmacovigilance is very low. In these 500,000 subjects, the estimated duration of ingestion was 3 months. There were 115 reports of suspected adverse events, representing an overall frequency of reported adverse events of 0.02%, strong evidence that such a formulation of *Petasites hybridus* extract is well tolerated (5).

Authors call attention to the fact that patients should be warned against the consumption of *Petasite hybridus* that they are not prepared as commercially available in Germany as Petadolex® and in Brazil as Petamig®.

Conclusion

This study clearly and objectively demonstrates that the extract of *Petasites hybridus*, classified as level A of evidence in the American guidelines, has proven efficacy in the prophylaxis of patients with episodic migraine (with or without aura). This finding corroborates the use of *Petasites hybridus* as a viable therapeutic option in the management of migraine.

In closing this work, it is pertinent to answer a question frequently raised by health professionals: When to prescribe *Petasites hybridus*? To offer an adequate answer to this question, it is essential to understand some key concepts, especially as they relate to the practice of neurology and evidence-based medicine.

1. Definition of Neurology and Medical Practice

Neurology (Greek: νεῦρον (neûron), "cord, nerve" and the suffix-logia, "study of") is the branch of medicine devoted to the diagnosis and treatment of diseases of the central



and peripheral nervous system. Neurological practice, as outlined by the American Academy of Neurology, seeks to advance both the art and science of neurology, with the goal of promoting the best possible care for patients (10).

2. Evidence-Based Medicine (EBM) and Patient-Centered Medicine (MCP)

In the last 30 years, there has been a growing trend in the use of Evidence-Based Medicine (EBM), which advocates the judicious use of the best scientific evidence to guide clinical decision-making. On the other hand, Patient-Centered Medicine (PCM) highlights the importance of tailoring treatment to each patient's individual needs, preferences, and values (11).

EBM, in seeking to standardize the treatment of clinical conditions, proposes that *Petasites hybridus* be offered to patients with episodic migraine, considering its proven efficacy. However, as neurology also involves an artistic dimension, it is up to neurologists to understand the individual needs and values of their patients. The personalization of treatment, based on communication and understanding of each patient's preferences (PCM), ensures more effective and humanized care. In this sense, *Petasites hybridus* may be the preferred choice for those patients whose needs and expectations align with the therapeutic properties of this substance (12).

In summary, the prescription of *Petasites hybridus* should be considered based on scientific evidence, but it should also be adjusted to the individual characteristics of each patient, ensuring both an effective and patient-centered approach. In this way, the use of *Petasites hybridus* in the prophylactic treatment of episodic migraine can be optimized, providing more targeted and personalized care (11,12).

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Carlos Alberto Bordini
<https://orcid.org/0000-0002-1249-5202>

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