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Review

Petasites hybridus in migraine prophylaxis: literature review

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Abstract

Introduction
Over the past 25 years, *Petasites hybridus* has been used effectively in migraine prophylaxis. It acts on its pathophysiological mechanisms, modulating nociception, reducing the release of CGRP, decreasing inflammatory mediators and blocking calcium channels.

Objective
To review clinical studies already published on *Petasites hybridus* in migraine prophylaxis, with emphasis on the initial study by Grossmann and Schmidramsl in 2000.

Methods
This study was an integrative and retrospective review of articles on the use of *Petasites hybridus* in the prophylactic treatment of migraine that were published in English in the last 25 years.

Results
Five clinical studies were found, all placebo-controlled, three of which were double-blind, involving 488 patients with migraine aged between 6 and 60 years. These studies showed that *Petasites hybridus* was superior to placebo, proving its effectiveness in the prophylactic treatment of migraine and with good tolerability, including by children and adolescents.

Conclusions
Clinical studies proved that *Petasites hybridus* was well tolerated by children and adults and effective in migraine prophylaxis, reducing the number of days with headache by ≥ 50% in the first three months.

Keywords:
Petasites hybridus
Butterbur
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Introduction

Migraine is a chronic neurological disease with a prevalence of 15.2% in Brazil. It is 2.2 times more prevalent in women, predominantly in the 18 to 50 age group (1). Regardless of the headache frequency, migraine interferes with patients' quality of life and is among the most disabling diseases in the world. According to the Global Burden of Disease, it is the second leading cause of disability among young adults aged between 18 and 50 years (2).

The pathophysiological mechanisms of migraine are not yet completely understood. There are multiple origins to explain headache attacks and associated symptoms, such as cortical spreading depression, trigeminovascular system, neurogenic inflammation, vasodilation and genetic vulnerability. Evidence suggests that the fundamental physiological disorder is central neuronal hyperexcitability, involving peripheral trigeminovascular or brainstem pathways, or both. Some factors can increase or decrease neuronal excitability, constituting the threshold for triggering headache attacks (3, 4).

Migraine treatment is based on patient education and abortive and prophylactic treatment of headache attacks (5). Prophylaxis is indicated for patients who have ≥ 3 headache attacks per month, interfering with functional capacity or who need to use symptomatic medications. Patients who have less than one headache day per month, but which interferes with their routine activities, should also begin prophylactic treatment (5-7).

The therapeutic classes of medications used in migraine prophylaxis are beta-blockers, tricyclic antidepressants, calcium channel blockers, anticonvulsant neuromodulators, biological therapies, such as onabotulinumtoxinA and monoclonal antibodies, and herbal medicines, such as *Petasites hybridus* (8).

Petasites hybridus has "level A" efficacy for the prophylactic treatment of migraine (9) because it acts on several of its pathophysiological mechanisms, modulating nociception, reducing the release of CGRP, reducing inflammatory mediators and blocking calcium channels (10-13).

Petasites hybridus has been used in the treatment of various diseases for several centuries, but in migraine, only after the clinical study published by Grossmann and Schmidramsl in 2000, which proved its effectiveness in the prophylactic treatment of migraine patients (14). However, following the commercialization of *Petasites hybridus* in Brazil, efficacy similar to the initial study has been observed. Therefore, our objective was to review the clinical studies already published on *Petasites hybridus* in migraine prophylaxis, highlighting the study by Grossmann and Schmidramsl, in 2000.

Methods

This study was an integrative and retrospective review of articles on the use of *Petasites hybridus* in the prophylactic treatment of migraine that were published in English from 1999 to 2024 (last 25 years). The search was carried out in the online databases LiLacs, SciELO and PubMed, using the descriptors "*Petasites hybridus* and migraine" and "butterbur and migraine". Editorials, comments, letters to the editor, monographs, review articles, and those that were not available in full or that did not contain accurate information were excluded.

Of the 117 articles found, repeated articles (49 articles) or those that did not describe *Petasites hybridus* as a prophylactic treatment for migraine (35 articles) were eliminated. Only 33 remained and were analyzed. After reading the abstracts and selecting those that met the inclusion criteria, five articles remained (clinical studies) that made up this review, involving 488 patients treated with Petasites hybridus. In these clinical studies, the study design, number of patients treated, age, interventions, results and conclusions were analyzed.

Results and Discussion

History, chemical composition and medicinal use

Butterbur is a plant in the *Asteraceae* family and the *Petasites* genus found in much of North America, throughout Europe and northern Asia. There are two known species, *P. hybridus* and *P. japonicus*, predominantly in Europe and Asia, respectively. It is a small plant, maximum 70 cm tall, but with large leaves that reach 120 cm. The name "butterbur" is attributed to the large leaves used to wrap butter in warmer periods in Europe. While the name "*Petasites*" is derived from the Greek word "pétaso" which means hat, due to the leaves having this shape (15).

Its use in traditional medicine has been known for many centuries. It is part of the herbal medicines used by healers to treat a variety of illnesses. In ancient Greece, it was used to treat asthma; in the Middle Age, it was used to treat fever; and in the Modern Age, it was used to treat coughs and skin wounds. Nowadays it is most commonly used in the prophylaxis of migraines, allergic rhinitis and urinary tract infections (antispasmodic effect) (12).

It is important to know the chemical composition of *Petasites hybridus* to understand its mechanisms of action. Its most important components are sesquiterpene lactones or esters of petasol and angelic acid, mainly petasins and isopetasins, which represent the active ingredient and have medicinal use (12, 16).

However, plants from the *Asteraceae* family produce pyrrolizidine alkaloids that have hepatotoxic, mutagenic and carcinogenic effects (12, 17), but the safety of *Petasites hybridus* in terms of the presence of this alkaloid has been proven through clinical studies. There is no evidence that *Petasites hybridus* extract (Petadolex®) poses a risk of liver injury to patients (18-20). The hepatotoxicity associated with the use of the herbal medicine Petadolex® was idiosyncratic and confused with the use of other medications (21). Likewise, the standardized extract of Petasites hybridus used in the production of Petamig®, and sold in Brazil, does not contain pyrrolizidine alkaloids. (22).

Mechanism of action

There are four known mechanisms of action of Petasites hybridus that arouse interest as a possible prophylactic treatment for migraine (11, 23, 24). They are: anti-nociceptive effect, anti-CGRP effect (calcitonin gene-related peptide), anti-inflammatory effect and effect on calcium channels.

1. Anti-nociceptive effect

In nociceptive sensory neurons, there is a group of ion channels, also called receptors, and among them are TRPA1 (transient receptor potential ankyrin 1) and TRPV1 (transient receptor potential vanilloid 1). When these receptors are activated, they provide nociception (the sensation of pain). There is a long list of activators, many of which we are exposed to on a daily basis, such as capsaicin and odors (25). They are non-selective, but are permeable to Ca^{2+}, Na^{+} and K^{+} ions. Therefore, these receptors are important targets for new drugs. Petasins and isopetasins act on TRPA1 and TRPV1 channels, providing anti-nociceptive modulation by desensitizing TRP calcium channels (10). Although efficacy data on migraine prophylaxis have been reported for almost 20 years, studies of the nociceptive effects of *Petasites hybridus* are recent (23).

2. Anti-CGRP effect

One study investigated the ability of isopetasins to inhibit TRP channels. The release of CGRP in rodent trigeminal neurons caused by TRPA1 and TRPV1 agonists was evaluated. The results showed that activation of TRPA1 channels by isopetasine resulted in the excitation of neuropeptide-containing nociceptors, followed by a marked heterologous neuronal desensitization, leading to possible attenuation in pain and neurogenic inflammation. This mechanism may be responsible for the anti-migraine action of *Petasites hybridus* (10).

Subsequently, another study demonstrated that activation of TRPA1 channels by mustard oil and TRPV1 channels by capsaicin induced the release of CGRP in the dura mater and trigeminal ganglion. Petasins and isopetasins act by inhibiting the TRPA1 and TRPV1 ion channels, causing a reduction in the release of CGRP in meningeal afferents during headache attacks in migraine patients (11).

These two studies found that *Petasites hybridus* extract desensitizes nociception by acting on both TRPA1 and TRPV1 channels. Therefore, *Petasites hybridus* works by modulating the TRPA1 and TRPV1 ion channels. This is important, because the current trend is ion channel modulation (23).

3. Anti-inflammatory effect

Petasins and isopetasins interact with inflammation. They reduce the production of inflammatory mediators by inhibiting the activity of phospholipase A2, lipoxygenase and cyclooxygenase 2. There is a decrease in the production of leukotrienes and prostaglandins, especially PGE2. Therefore, *Petasites hybridus* decreases inflammatory mediators that participate in migraine attacks (12).

4. Effect on calcium channels

Finally, the fourth mechanism of action. Petasins directly interact with L-type high-voltage calcium channels, which are crucial for anti-nociception (13).

Petasites hybridus has an anti-migraine action through these mechanisms that have been discussed. A recent study showed that Petasites hybridus is not only used to treat migraines, but appears to work in other diseases. It is used as an antispasmodic, antihypertensive, antiallergic, antiasthmatic and neuroprotective drug (15). However, the only indication on the package inserts for Petasites hybridus (Petamig®), which was recently approved and marketed in Brazil, is the prophylactic treatment of migraine.

Efficacy of Petasites hybridus in the migraine treatment

In this review, five clinical studies were found, all placebo-controlled, three of which were double-blind, involving 488 migraine patients aged between 6 and 60 years. These studies showed that *Petasites hybridus* was superior to placebo, proving its effectiveness in the prophylactic treatment of migraine and with good tolerability, including by children and adolescents, as shown in Table 1.

Table 1. Analysis of five clinical studies with Petasites hybridus (butterbur) used in migraine prophylaxis.

Variables	Published studies				
	Grossman and Schmidramsl, 2000[14]	Diener et al., 2004[26]	Lipton et al., 2004[22]	Pothmann and Danesch, 2005[27]	Oelkers-Ax et al., 2008[28]
Types of study	Double-blind, randomized, and placebo-controlled	Double-blind, randomized, and placebo-controlled	Randomized, parallel groups and placebo controlled	Open, multicenter and prospective	Double-blind, randomized, and placebo-controlled
Number of patients	60	60	202	108	58
Interventions	Petasites extract 25 mg twice a day vs. placebo for 12 weeks	Petasites extract 50 mg twice a day vs. placebo for 12 weeks	Petasites extract 75 mg twice a day vs. Petasites extract 50 mg twice a day vs. placebo twice a day for 16 weeks	Petasites extract 50 to 150 mg once a day for 16 weeks	Petasites extract 50 mg once a day (child aged 8 to 9 years) or 50 mg twice a day (child aged 10 to 12 years) vs. music therapy vs. placebo for 12 weeks
Results	The migraine group reduced the number of headache days from 3.3 to 1.7 ($p<0.05$), an improvement of 60%	The migraine group reduced the number of headache days from 3.4 to 1.8 ($p=0.002$); and in placebo, from 2.9 to 2.6 (ns)	Reduction in the number of headache days by 48% for Petasites extract 75 mg twice a day ($p=0.0012$); 36% for Petasites extract 50 mg twice a day ($p=0.127$); and 26% for placebo (ns)	In 77.2% of patients, there was a reduction of at least 50% in the number of headache days	Reduction in the number of headache days with both music therapy ($p=0.018$) and Petasites extract ($p=0.044$)
Conclusions	Migraine patients may benefit from prophylaxis with Petasites hybridus extract	Petasites hybridus was well tolerated and proved to be effective in migraine prophylaxis	Petasites hybridus 75 mg twice a day is more effective than placebo and is well tolerated in migraine prophylaxis	Petasites hybridus proved to be an effective migraine prophylactic and well tolerated by children and adolescents	Petasites hybridus e musicoterapia foram superiores ao placebo e podem representar um tratamento promissor na profilaxia da migrânea pediátrica

Of these five studies, the one published by Grossmann and Schmidramsl, in 2000, stands out as being the first to prove the effectiveness of *Petasites hybridus* in the prophylactic treatment of migraine patients. The authors carried out a double-blind, randomized, and placebo-controlled study involving 60 migraine patients, of which 33 used *Petasites hybridus* extract 25 mg twice a day; and 27, the placebo. At the beginning of the study, the group that used the medication had an average of 3.3±1.5 headache days per month and the control group had an average of 2.9±1.2 headache days per month. After 12 weeks of treatment, *Petasites hybridus* and placebo reduced the frequency of attacks, respectively to 1.7±0.9 and 2.6±1.1 headache days per month. Compared to baseline, *Petasites hybridus* reduced the number of headache days by 60% ($p < 0.05$) (Figure 1). It is important to highlight that of the 33 patients who used *Petasites hybridus*, five of them did not report headache attacks during eight weeks of treatment, and three of these patients remained pain free until the end of the study (14).

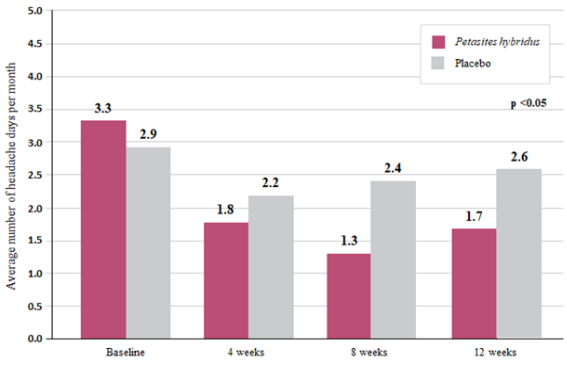

Figure 1. Reduction in the number of headache days in migraine patients treated with Petasites hybridus (Source: Grossmann and Schmidramsl, 2000).

These authors also observed that the group treated with Petasites hybridus, when compared to placebo, showed a reduction in the intensity and duration of headache attacks, in addition to a reduction in symptoms associated with headache ($p<0.005$) and in the intake of analgesics. Patients treated with *Petasites hybridus* reported no adverse events, but eight women noted marked improvement in dysmenorrhea (14).

The initial study carried out by Grossmann and Schmidramsl drew so much attention to reducing the frequency of migraine days (14), that a group of German researchers from the University of Essen decided to study *Petasites hybridus* as a migraine prophylactic. These authors performed an independent reanalysis of the previous study and confirmed the findings, showing that *Petasites hybridus* is effective and well tolerated (26).

Also because of the study by Grossmann and Schmidramsl (14), a new randomized, placebo-controlled study was carried out in 2004. In this study, the sample consisted of 202 migraine patients, divided into three groups: Group 1 used *Petasites hybridus* 75 mg twice a day; Group 2, *Petasites hybridus* 50 mg, twice a day; and Group 3, placebo twice a day. There was a reduction in the number of headache days in the groups that used *Petasites hybridus*, especially in the group that used 150 mg per day, after a 4-month follow-up. The study concluded that *Petasites hybridus* was significantly more effective than placebo and well tolerated as a prophylactic treatment for migraine (22).

All previous studies were carried out with patients aged between 18 and 60 years. In 2005, a study was carried out with children and adolescents, the difference between which was that *Petasites hybridus* was purified to remove all pyrrolizidine alkaloids. There were 108 migraine patients between 6 and 17 years old. They were treated

with doses of 50 to 150 mg of *Petasites hybridus* per day, depending on age, for a period of 4 months. There was a reduction in the frequency of migraine attacks ≥ 50% in 77% of all patients. Among the adverse effects, only eructation occurred (27).

Another clinical study was carried out with children and adolescents aged between 8 and 12 years. Of the 58 migraine patients, 19 used butterbur root extract at a dose of 50 mg per day (child aged 8 to 9 years) or 50 mg twice a day (child aged 10 to 12 years) versus music therapy versus placebo for 12 weeks. There was a reduction in the number of headache days with music therapy and butterbur root extract (p=0.018 and p=0.044, respectively) (28).

Due to these findings, the American Headache Society (AHS) and American Academy of Neurology (AAN) designated "level A" efficacy drugs for the prophylactic treatment of episodic migraine in their guidelines. Surprisingly, among the drugs that should be prescribed to patients who require migraine prophylaxis, *Petasites hybridus* was the only "level A" herbal medicine recommended for migraine prevention (9).

Conclusions

Clinical studies proved that Petasites hybridus was well tolerated by children and adults, and effective in migraine prophylaxis, reducing the number of days with headache by ≥ 50% in the first three months.

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