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Petasites hybridus: scientific evidence A

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Introduction

Migraine is the leading cause of years lived with disability worldwide among individuals aged 15 to 49, highlighting the urgent need for increasingly diversified and effective preventive treatments. In response to this demand, the national pharmaceutical industry launched highly purified *Petasites hybridus* in Brazil in 2023. This article comment the manuscript Loder and coworkers, 2012 one of the primary studies that positioned *Petasites hybridus* among the Level A evidence medications in the American Consensus of the episodic migraine preventive treatment in 2012.

Development

In the 1990s, a randomized, double-blind, placebo-controlled study involving 60 patients treated with a special *Petasites hybridus* root extract for migraine prophylaxis was conducted and published by researchers in Germany. The results suggested that the extract was an effective preventive treatment for migraine. However, the protocol, primary study report, and publication presented several significant shortcomings. To ensure the confirmatory nature of the study for regulatory purposes, an independent investigator and a third-party statistical institute were contracted to conduct a complete reassessment of the efficacy data, following the requirements of the International Conference on Harmonisation E9 Guideline and the advanced statistical principles of that time (2003 and 2004). At the end of the therapy, there were marked differences between the two groups, with at least a -50.0% reduction in migraine episodes (response rate) achieved by 45% of patients in the active treatment group and by 15% of patients in the placebo group (a 30% difference in therapeutic response rate). In the active treatment group, the mean percentage of migraine attacks requiring acute medication was reduced by more than half between the initial and final months (from 20.6% to 7.1%), whereas in the placebo group, the mean percentage changed only marginally (from 12.8% to 11.7%). The reanalysis, performed by the independent biometric institute, demonstrated that the active treatment group showed superiority over the placebo group for 12 primary efficacy variables (4 criteria at 3 time points) regarding percentage changes from baseline, as well as for absolute values and baseline changes.

Commentary

There are several studies supporting the efficacy of *Petasites hybridus* for migraine preventive treatment, including in both children and adults (such as the study reviewed in detail here). This reanalysis study, along with an American study, contributed to the classification of purified *Petasites hybridus* extracted through CO_2 as Level A evidence for migraine prevention. The mechanism of action of *Petasites hybridus* can be summarized as follows: 1) Antinociceptive effect; 2) Anti-CGRP effect; 3) Anti-inflammatory effect; 4) Antispasmodic effect.

Conclusion

The reanalysis study demonstrated the efficacy of *Petasites hybridus* in migraine prevention, originating from Grossman's study. The German group conducting the reanalysis took great care in using statistical methods to minimize bias and applied conservative statistics for primary outcomes. *Petasites hybridus* should be offered to migraine patients as a first-line preventive/prophylactic treatment, as well as in subsequent lines of therapy, and may be combined with other prophylactic medications based on the patient's profile and needs.

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Introduction

Migraine is the leading cause of years lived with disability worldwide among individuals aged 15 to 49, and the second leading cause across all ages(1), affecting 1.04 billion people globally (approximately 15% of the world population)(2). About 400 million people, or 40.4% of migraine sufferers worldwide, meet the criteria for preventive treatment (3).

For all these reasons and more, the need for increasingly diverse and effective preventive treatments is pressing. In recent years, the focus has shifted to antagonizing the calcitonin gene-related peptide (CGRP) pathway, whether through receptor antagonists, molecule antagonists, or antibodies (anti-CGRP monoclonal antibodies: erenumab, galcanezumab, fremanezumab, eptinezumab), as well as small molecule antagonists (gepants: atogepant, rimegepant, ubrogepant, zavegepant) (4).

Amidst these developments, the national industry launched a highly purified form of Petasites hybridus in Brazil in 2023, employing supercritical CO2 extraction technology to isolate petasins and isopetasins (the plant's active ingredients), freeing them from pyrrolizidine alkaloids, which are potentially hepatotoxic and carcinogenic (5).

The release of this medication highlights the need for knowledge regarding its efficacy, mechanism of action, and safety, despite it being well-established in other countries.
In this article, we discuss one of the key studies that led to Petasites hybridus being classified as a Level A evidence treatment in the 2012 American Consensus on the preventive treatment of episodic migraine (a status that remains current)(6), placing it among the most effective medications (propranolol, timolol, metoprolol, topiramate, divalproex, sodium valproate).

This Level A classification is granted to treatments supported by at least two high-quality, randomized, placebo-controlled clinical trials demonstrating efficacy. Such Level A medications are recommended for patients requiring migraine prophylaxis. In this context, we will comment on the article the first placebo-controlled trial of a special butterbur root extract for the prevention of migraine: reanalysis of efficacy criteria, published in 2004, which contributed to the classification of *P. hybridus* as a Level A treatment in the American guidelines (6).

Development

In the 1990s, a randomized, double-blind, placebo-controlled study was conducted and published by researchers in Germany, involving 60 patients treated with a special butterbur root extract for migraine prophylaxis (7). The results suggested that the extract was an effective preventive treatment for migraines.

However, the study's protocol, the primary study report, and the publication had significant deficiencies.

These included:

- Lack of appropriate information on baseline characteristics,
- Lack of appropriate information on acute migraine treatment medication,
- The primary sample for evaluation was the per-protocol population rather than the intention-to-treat (ITT) population (despite ITT being used for statistical analysis),
- Efficacy parameters were not precisely defined,
- The t-test used was not suitable for the data set,
- Apparent baseline differences were not accounted for as covariates in the primary efficacy analysis,
- No adjustments were made for multiple testing.

To confirm whether the study held confirmatory value for regulatory purposes, an independent investigator and a third-party statistical institute were hired to conduct a comprehensive reanalysis of the efficacy data, adhering to the International Conference on Harmonisation (ICH) E9 Guidelines and state-of-the-art statistical principles of the time (2003-2004) (8).

Both the initial and reanalysis studies adhered to ethical guidelines, following good clinical practice and the Declaration of Helsinki regulations (8). The study design was double-blind, randomized, and placebo-controlled, comparing the clinical effects of *Petasites hybridus* versus placebo at a German hospital.

The baseline period lasted 4 weeks, during which no experimental medication was administered. Afterward, participants received either 50 mg of *Petasites hybridus* twice daily or a placebo for 12 weeks. The patients were recruited from a neurology outpatient clinic, including both sexes, aged 18 to 60, with migraine with and without aura diagnoses according to the International Headache Society's criteria (the 1988 Classification at the time)(9).

Inclusion criteria:

- A history of migraines for at least 1 year,
- A minimum of 3 migraine attacks per month in the last 3 months, and
- A minimum of 2 attacks during the 4-week baseline period without study medication.
- Exclusion criteria:
- Treatment with agents known to affect migraines within 4 weeks before the baseline period, and
- Regular analgesic use for more than 12 days per month.
- It is important to note that the exclusion criterion

of not using analgesics for more than 12 days per month suggests that chronic migraine (15 or more days/month) was not included in this study. At the time, this was referred to as transformed migraine.

Patients were seen once every 4 weeks. At each visit, medication and a headache diary were provided for the next 4-week treatment period. The following were evaluated:

- Number of episodes,
- Pain intensity (measured using a visual analog scale from 1 to 10),
- Duration of migraine attacks,
- Associated symptoms, and
- Use of medication for acute attacks (as recorded in the pain diary).

A total of 60 patients (28 men and 32 women) were enrolled, with 33 allocated to the active treatment group and 27 to the placebo group. The data were analyzed based on the original forms. In the original analysis, the primary efficacy criteria and the timing of analysis were not predefined.

Since selecting efficacy criteria or time points post hoc for primary analysis is inappropriate, all four primary efficacy criteria from the patient diary (number of migraine attacks/month, number of migraine days/month, mean duration of migraine attacks/month, mean intensity of migraine attacks/month) and all three follow-up visits were evaluated equally using a multivariate technique to control for multiple testing at a significance level of α.

Many outcome measures were not continuous, so the authors chose to use the Wilcoxon-Mann-Whitney rank-sum test. All primary efficacy criteria were tested as a set for superiority of the medication using the non-parametric Wei-Lachin test. This method is a multivariate generalization of the Wilcoxon-Mann-Whitney test, accounting for the correlation between univariate Mann-Whitney tests for each outcome to provide an overall estimate of benefit and to test treatment differences.

If the combined global test yields a significant result, efficacy is confirmatively established. In addition to the p-values from the Wilcoxon-Mann-Whitney test, effect size measures and their confidence intervals were calculated, as required by the International Conference on Harmonisation E9 Guideline.

The Mann-Whitney test was used as a measure of the relevance of group differences, with the effect size measure associated with the Wilcoxon-Mann-Whitney test that is defined as the probability that a randomly selected patient from the test group has a better outcome than a randomly selected patient from the reference group. A robust estimator of this probability is implemented by comparing all pairs of patients, with one patient receiving the test treatment and one comparator.

A score of 1 is assigned if the actively treated patient has a better response; a score of 0.5 if both patients are tied; and a score of 0 if the comparator patient has a better response. The sum of these scores is then divided by the total number of pairs compared.

A Mann-Whitney estimator of 0.5 means patients fared equally well in both treatment conditions. Estimators greater than 0.5 suggest some benefit from the test treatment. The closer the Mann-Whitney estimator is to 1, the stronger the evidence.

The analysis of absolute values, as well as the analysis of changes from baseline, was conducted similarly (multivariate directional test) to the sensitivity analyses. These analyses also had to be statistically significant to maintain the near-confirmatory nature of the reanalyses and avoid bias from post hoc selection of baseline adjustment methods.

In reviewing the actual results, baseline characteristics were separated into demographic data, prior history, efficacy criteria, and criteria for medications used for acute migraine attacks (6).

Regarding the primary efficacy criteria, the reanalysis found that the number of migraine attacks per month decreased significantly in the verum group compared to the placebo group. The verum group refers to the group that received the active medication.

At the end of the therapy, there were notable differences between the two groups, with at least a 50.0% reduction in attack frequency (classified as responders) achieved by 45% of patients in the verum group and 15% in the placebo group, representing a 30% difference in response rate (therapeutic response).

The mean group difference in percentage change from baseline at the end of therapy for the variable "days with migraine attacks per month" was 24.3% in favor of the verum group. Responders (patients with at least a 50.0% reduction) comprised 48% of the verum group and 15% of the placebo group (6).
The duration and intensity of migraine attacks were also reduced by butterbur treatment compared to placebo. The mean group difference in percentage change from baseline after 3 months was 15.1% and 12.8%, respectively, favoring the verum group (6).

Regarding acute migraine medication use, the number of patients using acute medication was more than halved in the verum group between the initial and final months (from 44% to 18%), while it changed only marginally in the placebo group (from 27% to 26%). After 2 months

of treatment (visit 3), the number of patients using acute migraine medication was identical in both groups. By the end of the study, fewer patients in the verum group were using acute migraine medication compared to the placebo group. The mean percentage of migraine attacks treated with acute medication in the verum group was 20.6% at baseline; 16.7% after 4 weeks; 11.1% after 8 weeks; and 7.1% after 12 weeks of treatment.

In the placebo group, the percentages were 12.8% at baseline; 7.4% after 4 weeks; 6.2% after 8 weeks; and 11.7% after 12 weeks of treatment.

In the verum group, the mean percentage of migraine attacks treated with acute medication was reduced by more than half between the initial and final months (from 20.6% to 7.1%). However, in the placebo group, the mean percentage changed only marginally (from 12.8% to 11.7%).

Confirmatory Efficacy Analysis

The efficacy of the verum treatment was confirmed through a rigorous analysis. The combined result, measured by the Mann-Whitney estimator, demonstrates more than medium-sized superiority (significant) of the verum group (benchmark/reference 0.64). To avoid post hoc bias, this confirmatory analysis was based on a summarized evaluation of the four primary efficacy criteria from patients' headache diaries, with equal weighting given to all three follow-up visits. In Loder et al.(6), the table 3 presents the Mann-Whitney estimators and the confidence intervals for comparing the verum group with the placebo group.

The confirmatory test, controlling for multiple α levels, was statistically significant (one-sided Wei-Lachin $p < 0.0001$). The p-values were below the significance level ($\alpha = 0.025$ one-sided, corresponding to $\alpha = 0.05$ two-sided). Thus, the efficacy of the verum treatment is confirmed. The Mann-Whitney estimator for the combined result indicates more than medium-sized superiority (benchmark/reference 0.64).

The lower limit of the one-sided 97.5% confidence interval (worst-case scenario) is clearly above the reference parameter for small superiority (Mann-Whitney estimator $= 0.6159 > 0.56$). This confirms not only the superiority of verum but also a superiority greater than small for P. hybridus in patients suffering from migraine attacks. The results of the sensitivity analyses, including absolute values and changes from baseline, are also statistically significant (one-sided Wei-Lachin $p < 0.0001$) (6).

The combined result's Mann-Whitney estimator indicates greater than medium-sized superiority of the verum treatment (reference parameter 0.64). The lower limit of the one-sided 97.5% confidence interval (worst-case scenario) is above the reference parameter for small superiority (absolute values: Mann-Whitney estimator $= 0.5835 > 0.56$; changes from baseline: Mann-Whitney estimator $= 0.6080 > 0.56$).

All univariate effect sizes are above equality mark, demonstrating the superiority of *Petasites hybridus* for all efficacy criteria and at all time points. All 12 univariate effect sizes exceed the benchmark for small superiority (0.56).

Furthermore, 7 out of 12 effect sizes indicate more than medium-sized superiority (reference 0.64, relevant) or even large superiority (reference 0.71). For 7 out of 12 individual criteria, the lower limit of the one-sided 97.5% confidence interval (worst-case scenario) is above the equality benchmark, thus proving the superiority of *Petasites hybridus*.

Safety and Tolerability

Two patients in the verum group discontinued the study: one due to a suspected pregnancy, and the other chose not to complete the study without providing a reason. No significant changes were reported in vital signs or physical examination results compared to baseline.

Three patients treated with *P. hybridus* exhibited slight increases in transaminase levels (ALT and AST) above the normal range. In addition to ALT and AST, the mean changes from baseline were statistically significant for bilirubin levels and erythrocyte counts in the P. hybridus group. However, none of these changes were deemed clinically relevant.

In conclusion, the reanalysis of this study, conducted by an independent biometric institute, demonstrated that the active treatment group showed superiority over the placebo group for the set of 12 primary efficacy variables (4 criteria at 3 time points) in terms of percentage changes from baseline, as well as absolute values and changes from baseline.

Comments

Several studies have demonstrated the efficacy of *Petasites hybridus* for migraine preventive treatment, including in children(10,11) and adults (as highlighted in the study we developed for this detailed review) (8).

One notable study involved a randomized, placebo-controlled trial in adults with migraine. This three-arm, parallel-group study included 202 patients between the ages of 18 and 65 who experienced between two and six migraine attacks per month in the three months prior to the treatment phase (12).

Additionally, participants were required to have had at least two attacks during a four-week baseline phase. Patients were administered *P. hybridus* extract at 50 mg

twice daily (n = 71), 75 mg twice daily (n = 68), or placebo (n = 63) for 16 weeks (12)

Across the three groups, there was a 48% reduction in headache days for the group receiving 75 mg of *P. hybridus* twice daily (p = 0.0012 vs. placebo); a 36% reduction in the 50 mg group (p = 0.127 vs. placebo); and a 26% reduction in the placebo group (1).

In this study, *Petasites hybridus* was well tolerated. Over four months of treatment, 131 adverse events were reported by 80 participants, primarily gastrointestinal disturbances, particularly eructation. Most adverse events were mild to moderate in intensity and occurred at comparable frequencies across all groups. This study contributed to positioning *P. hybridus* among the major oral medications for migraine prevention, as reflected in the 2012 American Guidelines (12).

A multicenter, open-label, prospective clinical study involving 108 children and adolescents aged 6 to 17 years, diagnosed with migraine for over a year and experiencing ≥ 3 headache days per month in the last three months, treated these patients with 50 to 150 mg of butterbur root extract (depending on age) for a four-month period (13).

In 77.2% of the sample, there was at least a 50% reduction in the number of headache days per month during the treatment period compared to baseline, across both age groups (13).

The average number of headache days per month decreased from 9.4 and 9.7 to 4.0 and 5.8, respectively, in the 6 to 9-year-old and 10 to 17-year-old age groups (13).

Additionally, butterbur was well tolerated in children and adolescents, with adverse events (7.4%) primarily involving eructation (13) No serious adverse events occurred, nor did any cause treatment discontinuation (13)

This study was important as it demonstrated a high response rate in children, although it is important to note that *Petasites hybridus* is indicated for use in adults and children aged six years and older.

It is worth noting that *Petasites hybridus* also holds Level A evidence rating among nonsteroidal anti-inflammatory drugs and other complementary therapies for the preventive treatment of episodic migraine in the 2012 American Guidelines on complementary therapies (14).

In this guideline, medications are categorized as:

- Level B: Naproxen sodium, herbal therapies, vitamins, and minerals (riboflavin, magnesium, Tanacetum parthenium) (14)
- Level C: Flurbiprofen, mefenamic acid, herbal therapies, vitamins, and minerals (Coenzyme Q10, estrogen), cyproheptadine (14)

Butterbur has been used for medicinal purposes for many years, with clinical applications including the treatment of migraine and asthma, among other conditions (15)

From a regulatory perspective, the special root extract of Petasites hybridus is considered a food product in the United States and the United Kingdom (8).

In Germany, P. hybridus extract is regarded as a pharmacological agent, subject to full regulatory oversight by the German Health Authority (8)

In Brazil, it is a phytomedicine authorized and regulated by Anvisa for migraine prevention and is marketed by Herbarium (15)

It is a patented product supported by high-quality clinical trials and has a solid safety profile, making it an endorsed treatment option (15)

The leaves, rhizomes, and roots of *Petasites hybridus* contain a mixture of sesquiterpenes, eremophilane lactones, or petasins, such as petasin and isopetasin (16) .

The mechanism of action of Petasites hybridus can be summarized as follows:

1. Antinociceptive effect: Acts on TRPA1 and TRPV1 channels, modulating antinociception (17,18).

2. Anti-CGRP effect: Reduces CGRP release in the dura mater and trigeminal ganglion, indirectly by inhibiting its release at the presynapse (via TRPA1) (17,18).

3. Anti-inflammatory effect: Reduces inflammatory mediators involved in migraine attacks by acting on the inflammatory cascade through cyclooxygenase and lipoxygenase pathways (15).

4. Antispasmodic effect: Inhibits smooth muscle contraction through petasin antagonism (via L-type calcium channels) (19).

Due to these mechanisms of action, combined with its safety and tolerability (17,20,21), lack of significant drug interactions (including with contraceptives) (17), and low potential for adverse effects (with eructation being the most common at a rate of 22–25%)(12), *P. hybridus* is a therapeutic option that should be offered to migraine patients as a first-line preventive treatment, as well as in subsequent lines or in combination with other prophylactic medications.

Conclusions

The reanalysis study (originated from Grossman's work) demonstrated the efficacy of *Petasites hybridus* in migraine prevention. The German team that conducted the reanalysis took great care to apply statistical methods that minimized bias, using conservative statistical approaches for the primary outcomes.

This study, along with an American study, contributed to classifying purified *Petasites hybridus* extracted through CO2 as Level A evidence for the migraine preventive treatment. Therefore, P. hybridus should be offered to migraine patients as a first-line prophylactic treatment, as well as in subsequent lines and in combination with other preventive medications, depending on the patient's profile and needs.

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