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## REPORT

### What Europeans Are Doing to Limit Migraine Frequency

By Russell Martin



For more than three decades, migraine sufferers in Germany have been prescribed an extract derived from a perennial herb known as butterbur. Now medical practitioners in the United States are paying close attention to this herbal extract's remarkable ability to reduce the number of headaches that migraine sufferers experience each month by almost 50%.<sup>1</sup>

Butterbur's principal active constituent is petasin, which reduces smooth muscle spasms and appears to be particularly valuable in relaxing the constriction of cerebral blood vessels.<sup>2</sup> The petasin in butterbur also makes this herb useful in managing upper respiratory inflammation, asthma attacks, urinary disorders, menstrual cramps, kidney stones, and various gastrointestinal disorders associated with smooth muscle spasm.<sup>2</sup> However, it is butterbur's ability to markedly reduce the frequency of migraine headaches that has recently excited researchers and migraine sufferers alike.<sup>1</sup>

#### THE CHALLENGE OF MIGRAINE

More than 30 million Americans suffer regularly from migraine headaches.<sup>3,4</sup> Migraine's debilitating effects account for an estimated \$13-17 billion in lost work productivity each year. Prescription pain relievers, over-the-counter medications, and herbal supplements aimed at mitigating migraine make up a large percentage of the \$7.3 billion Americans spend each year on pain treatment.<sup>4,5</sup>

The exact causes of migraine are poorly understood, yet migraine headaches are fundamentally different from tension headaches that are caused by accumulated stress and constriction of muscles in the neck, head, and face. One theory of migraine holds that these headaches are caused by a cycle of dramatic constriction of the arteries that supply the brain with blood and nutrients. This constriction is followed by rapid dilation, then again by constriction, during which nerve pathway changes and brain chemistry imbalances cause blood vessels to become inflamed.

The so-called "classic" migraine is accompanied by an "aura," which is the appearance of spots, lines, or darkened vision that occurs just before the headache's onset. By contrast, a "common" migraine is one that is not preceded by an aura or other symptomatic warning. Following both kinds of migraine attacks, sufferers often feel exhausted, irritable, and confused, sometimes for days after the pain has subsided.<sup>6</sup>

Unlike the normally dull, pressing pain of tension headaches, migraine pain tends to pound and throb, and increases with physical activity. The intense pain of a migraine headache tends to occur on one side of the head, but can be bilateral as well. Migraine is often accompanied by nausea, vomiting, and acute sensitivity to light or sound. The word migraine originates from the Greek construction hemikranion, meaning pain on one side of the head.<sup>7</sup>



Migraine is widely considered a hereditary disease. If both parents of an individual suffer migraines, there is a 75% likelihood he or she will as well. If only one parent has migraine, the chance remains as high as 50% that the child will also suffer migraine, even quite early in life.<sup>7</sup> While 6% of American men endure regular migraines, fully 18% of American women are migraine sufferers. Together, male and female migraine sufferers average 1.5 attacks a month, ranging in duration from four to 72 hours, and lasting 24 hours on average. Ten percent of migraine patients have attacks once a week, and 20% suffer headaches that persist for 48 hours or longer. To frame these statistics more starkly, 5% of the US population has at least 18 migraine days a year, and more than 2.5 million Americans suffer at least one day of migraine every week.<sup>8</sup>

#### BUTTERBUR'S SUCCESS IN EUROPE

Migraine treatment in the United States has focused on pharmaceuticals. In Germany, however, where nutraceutical companies have long been recognized as world leaders in herbal medication research conducted under stringent government regulation, butterbur is a popular and proven prophylactic alternative to prescription drugs. Conventional migraine medications are expensive, can have serious side effects, and often are not effective in preventing migraine attacks.

In a study published in 2000 in the *International Journal of Clinical Pharmacology and Therapeutics*, German neurologist Dr. Werner Grossmann set out to determine whether a standardized butterbur extract could limit migraine attacks as successfully as conventional prescription medications, and whether it, too, posed a risk of dangerous side effects. Drugs most often prescribed to reduce migraine frequency include beta-blockers such as propranolol and metoprolol, whose common side effects are lowered blood pressure, muscle weakness, and depression. Also frequently prescribed are calcium antagonists such as flunarizine and serotonin antagonists such as methysergide and pizotifen, whose shared side effects include tiredness, weight increase, Parkinson-like symptoms, and concentration disturbances. In placebo-controlled, double-blind studies, these medications have reduced migraine frequency by 50-70%.<sup>9</sup>



Dr. Grossmann and his colleagues studied 60 migraine outpatients at the Munich-Harlaching Municipal Hospital. The 28 males and 32 females averaged 29 years of age. Each subject had experienced at least three migraine attacks a month for the previous three months and had taken no prophylactic migraine medication for four weeks before beginning the study. Thirty-three of the subjects took 50 mg of standardized butterbur extract twice a day, while 27 took placebo. Fifty-eight participants completed the study.<sup>10</sup>

Following one month of treatment, the butterbur-supplemented group's average of 3.3 migraine attacks a month before taking medication dropped to 1.8 attacks a month. After eight weeks on the supplement, they averaged 1.3 attacks a month. At the study's 12-week conclusion, the group averaged 1.7 attacks a month. Thus, the migraine sufferers experienced a 61% decrease in

headaches after eight weeks and a 49% decrease after 12 weeks while taking the butterbur extract. By contrast, the number of monthly headaches in the placebo group dropped from 2.9 attacks per month without medication to 2.2 attacks after four weeks, 2.4 attacks after eight weeks, and 2.6 attacks at the end of 12 weeks—a statistically insignificant reduction in total headaches.<sup>10</sup>

Among the butterbur group, the number of headache days per month fell from 3.4 to 1.7 by the end of the study period. The intensity of migraine pain and its duration (as reported by the study participants) did not decrease significantly for either the butterbur or placebo group. However, when asked whether they had benefited from the treatment, 23 subjects who received butterbur said yes, while eight responded no. By contrast, only seven people in the placebo group said they had benefited, while 20 said they had not.<sup>10</sup>

Moreover, not one participant in either the butterbur or placebo group reported any side effects during the three-month trial. According to Dr. Grossmann:

**“The results of this study demonstrate that the special extract of *Petasites hydrides* [butterbur] is effective in the prophylactic treatment of migraine. The significant reduction in the frequency of attacks and number of migraine days is comparable to other agents considered effective for migraine prophylaxis, such as beta-blockers, calcium antagonists, e.g. flunarizine, cyclandelate, as well as serotonin antagonists.”<sup>10</sup>**

### NEW STUDIES CONFIRM GERMAN FINDINGS

Four years after the German study was published, Dr. Richard Lipton, a neurologist at the Montefiore Medical Center in New York City, published the results of a similar study of 245 migraine sufferers. This trial likewise demonstrated that a standardized butterbur formulation significantly limited migraine frequency.

The participants averaged 42 years of age and had experienced two to six migraine headaches a month for the three months before the trial. Unlike the German study in which participants were evenly divided between males and females, females made up an average of 81% of the subjects in the three trial groups.<sup>1</sup> In Dr. Lipton's four-month study, approximately one third of the subjects were given placebo, one third received 50 mg of butterbur extract twice daily, and another third took 75 mg of butterbur twice daily.

After four months of treatment, those receiving placebo reported a 26% reduction in headache frequency. The group taking 50 mg of butterbur extract reported a 36% drop and the 75-mg group had a 48% reduction. In the 75-mg group, 68% of the subjects had a greater than 50% reduction in frequency of attacks after four months; in the placebo group, 49% reported a comparable reduction. Like the German researchers, Lipton and his colleagues found no reduction in the intensity of pain or duration of headaches that could be attributed to butterbur. The only statistically significant side effect was that roughly 10% of those taking both doses of butterbur experienced increased burping.<sup>1</sup>

Speaking with reporters following the study's publication in the journal *Neurology*, Dr. Lipton cautioned:

**“Before [they] take a medicine to prevent migraines, consumers should be pretty sure that they have migraines, and the best way to ensure that you have migraines is to get a diagnosis from a health care professional. Once migraine is diagnosed, [butterbur extract] is intended as a self-treatment. It is available over the counter without a prescription, and it’s a treatment that many people initiate on their own. For people who are taking prescription medications, it is worth checking with a doctor, though, before starting a natural product, and it’s important to remember that even though it is a natural product, it is a real drug, with real benefits but also the potential for real interactions with other medications.”<sup>11</sup>**

On the heels of the Lipton study, German researchers published the results of a trial conducted at five pediatric clinics and 13 medical practices in that country. The study's 108 participants included 29 children aged 6-9 years and 79 adolescents aged 10-17 years, each of whom had suffered from migraines for at least one year. Depending on their age and weight, the subjects were treated with 50-150 mg of standardized butterbur extract daily for four months. Treatment progression was recorded in migraine journals designed especially for children and adolescents.<sup>12</sup>



At the study's conclusion, the number of migraine attacks in both groups was substantially reduced: from 9.4 attacks during the three months preceding the study to 4.0 attacks over the four-month study in the younger group, and from 9.7 to 5.8 attacks among the adolescents. Seventy-seven percent of the participants reported a reduction of at least 50% in headache frequency, and 91% reported that they felt substantially or slightly improved after taking butterbur for the length of the study. The butterbur was well tolerated, with no serious adverse side effects reported. As in the Lipton study, a few participants reported experiencing belching in association with the butterbur extract.<sup>12</sup>

Study authors Raymond Pothmann and Ulrich Danesch cautioned that because of the trial's uncontrolled nature, its positive results could not be regarded as definitive proof of butterbur's effectiveness in children and adolescents suffering migraine. However, when combined with data from the Grossman and Lipton studies, the German researchers said their findings suggest that standardized butterbur extract is a safe, effective prophylactic migraine treatment in children and adolescents as well as adults. Furthermore, they noted that the results warranted a placebo-controlled trial to further document butterbur's efficacy in young migraine sufferers.<sup>12</sup>

Danesch also sought to determine the overall safety of the standardized German butterbur formulation, particularly because the plant is known to contain small quantities of pyrrolizidine alkaloids that are carcinogenic and potentially toxic to the liver. The German manufacturer of standardized butterbur extracts reports that these harmful substances are successfully removed using a high-pressure liquid carbon dioxide extraction process. This claim has been certified by the German government in its regulation of all nutraceuticals produced and distributed in that country. In repeated studies, Danesch and colleagues fed standardized butterbur extract to laboratory rats in dosages correlated to 333-1,250 times the recommended human daily dosage. They failed to detect any adverse effects on the animals, even after 26 weeks of study, a period representing roughly one quarter of the rats' average life span.<sup>13</sup>

## GINGER OFFERS COMPLEMENTARY MIGRAINE SUPPORT

Because migraine is a complex disorder with numerous symptoms, a synergistic combination of active ingredients may be the most effective strategy for achieving relief. Ginger's ability to help fight nausea, inflammation, pain, and anxiety makes it an ideal addition to formulas designed to prevent and manage migraine.

Nausea, vomiting, and other gastrointestinal symptoms commonly accompany migraine. Ginger is well recognized as a remedy for nausea and vomiting, with numerous trials demonstrating its efficacy. In fact, studies indicate that ginger can prevent or alleviate nausea and vomiting associated with such diverse causes as surgery, motion sickness, and early pregnancy.<sup>14-17</sup> Animal studies suggest that ginger's anti-emetic (i.e., anti-vomiting) activity is mediated through the peripheral nervous system rather than the central nervous system.<sup>18,19</sup> Ginger's anti-emetic action has been attributed to the combined action of constituents known as gingerols, zingerones, and shogaols.<sup>20</sup>

Many researchers believe that inflammation is related to the etiology of migraine.<sup>21</sup> Ginger acts through several mechanisms to quell chronic inflammation and pain. Ginger and its pungent constituents inhibit the metabolism of arachidonic acid through both the cyclooxygenase and lipoxygenase pathways, thus reducing the accumulation of prostaglandins and leukotrienes that contribute to pain and inflammation.<sup>22-24</sup> This is important because other compounds that are prophylactic against migraine attacks are postulated to work through the same pathways.<sup>25</sup>

Additionally, ginger extract inhibits the induction of several genes involved in the inflammatory response, including those that encode cytokines and chemokines.<sup>26</sup> Studies indicate that certain cytokines are overproduced in migraine sufferers.<sup>27</sup>

Animal studies suggest that ginger may help to relieve anxiety.<sup>28</sup> This is an important finding, since anxiety is frequently associated with migraine and is correlated with poorer responses to migraine treatment.<sup>29</sup> Anxiety and migraine appear to be so closely intertwined that some scientists believe that anxiety should be systematically checked and cared for in subjects reporting migraine.<sup>29</sup>

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### RELIEF FOR RESPIRATORY, GASTROINTESTINAL CONDITIONS

The ability of butterbur's active ingredient petasin to quell smooth muscle spasms in vascular walls (which may contribute to migraine) allows it to similarly benefit other parts of the body, thereby mitigating disorders unrelated to migraine.<sup>2,30</sup>

In Europe, butterbur extract is commonly used to battle allergic rhinitis (hay fever), and studies have confirmed its efficacy, both compared to a commonly used prescription medication and in a double-blind, placebo-controlled study. When butterbur extract was compared with Zyrtec®, the brand name of the anti-allergy prescription medication cetirizine, researchers determined that both compounds were equally effective in limiting sneezing, nasal congestion, runny nose, itchy nose, and itchy eyes. Among the 131 patients studied over two weeks, half took butterbur extract to relieve their symptoms and the other half took cetirizine. The researchers believe that petasin in butterbur extract proved efficacious by limiting histamine and leukotriene, which promote inflammation and mucous secretions, and by dilating constricted airways to ease breathing.<sup>30</sup>

Butterbur leaves and root have been used for centuries to manage bronchial asthma and whooping cough. A recent Scottish study showed that the anti-inflammatory action of 25 mg of butterbur extract taken twice daily significantly improved out-breath volume in asthma patients who regularly treat their symptoms with inhaled corticosteroids. The investigators noted that butterbur complemented the activity of the corticosteroids and showed a superior effect compared to placebo.<sup>31</sup>



Furthermore, in a German open trial, 80 asthma sufferers who took 50 mg of butterbur extract three times a day saw the number, duration, and severity of their asthma attacks decrease during an eight-week study period. The study authors speculated that butterbur extract may be effective both as a stand-alone asthma treatment and in combination with other asthma medications.<sup>32</sup>

Historically, butterbur has been used as a folk medicine for various gastrointestinal disorders, particularly digestive tract spasms associated with colic and bile flow obstruction. A contemporary German study found butterbur extract can block ethanol-induced damage to the stomach and reduce ulcerations in the small intestine.<sup>33</sup> German researchers are studying butterbur's potential applications in controlling spasms of the urogenital tract, which can contribute to urinary urgency and incontinence. They believe that butterbur may prove effective in managing these disorders.<sup>34</sup>

### RIBOFLAVIN THWARTS ONSET OF MIGRAINE

In recent years, researchers have found that riboflavin, or vitamin B2, shows promise in blocking the onset of migraine headaches. Like other B vitamins, riboflavin facilitates energy production in the body by aiding the metabolism of fats, carbohydrates, and proteins. It is also essential in the production of red blood cells and antibodies.

Although its mechanism of action in preventing migraine remains uncertain, riboflavin may help increase energy production in the cellular power plants known as mitochondria. Scientists speculate that low mitochondrial energy supplies may trigger migraines in many patients.<sup>35</sup>

In a 1994 open study at Belgium's University of Liege, 49 migraine sufferers took 400 mg of riboflavin with breakfast every day for three months. At the end of the study, the participants reported an average 68% reduction in the number of headaches they experienced each month, an impressive decrease that warranted a follow-up placebo-controlled study.<sup>35</sup>

Four years later, the Belgian scientists conducted a randomized trial of 55 migraine patients, half of whom consumed 400 mg of riboflavin daily while the other half received placebo. At the end of the three-month study, nearly 60% of the participants receiving riboflavin reported at least a 50% reduction in the number of monthly headaches, while only 15% of the placebo group reported decreased headache incidence of 50% or more. While two patients taking riboflavin reported diarrhea and increased urine volume as side effects, the high daily dose of riboflavin was otherwise well tolerated. Since the B vitamin cannot be stored in the body, the researchers postulated that the 400-mg daily dosage—250 times the FDA's recommended minimum daily intake—was required to achieve the therapeutic effect.<sup>36</sup>

In a 2004 open-label study at Humboldt University in Berlin, 23 people aged 20-65 were given 400 mg of riboflavin daily for six

months. At the study's onset, the participants averaged four headache days a month. By the end of three months, the group's average number of headache days had been reduced to two; after six months, their average number of monthly headaches remained at two. Patients reported that migraine duration and intensity did not decrease with the riboflavin treatment, yet they reported taking significantly less total pain-relieving medication over the course of each month compared to the amount they consumed at the beginning of the study. Minor diarrhea and abdominal pain were the only side effects reported.<sup>37</sup>

In a California study in 2004, researchers discovered that a much smaller daily dose of riboflavin similarly reduces the frequency of migraine headaches. In a three-month, controlled, double-blind study at an outpatient clinic, 48 people randomly received either a combination dosage of 400 mg of riboflavin, 300 mg of magnesium, and 100 mg of the herb feverfew (all three of which have been shown to have therapeutic benefits in managing migraine) or just 25 mg of riboflavin each day.

The clinical physicians who designed the study defined a positive response to treatment as a reduction of monthly migraine frequency by 50% or more. Forty-two percent of the patients taking the riboflavin-magnesium-feverfew combination successfully responded to the therapy at the end of three months—reducing their number of headaches by 50% or more—while 44% of those taking only the small dose of riboflavin responded successfully. The physicians were surprised by the efficacy of the low dose of riboflavin, and suggested further studies to determine what dosage of vitamin B2 provides the greatest possible reduction in headache incidence.<sup>38</sup>

Because it is inexpensive, essential to the body, and can be tolerated in high dosages with minimal side effects, riboflavin— together with butterbur, magnesium, and feverfew—will be the subject of much more research in coming years as to its effects and efficacy in preventing migraine.

## CONCLUSION

As more and more research documenting butterbur's ability to reduce migraine attacks comes to light, thousands of sufferers are turning to this herbal extract as a safe, effective, and natural way to limit the crippling effects of migraine headaches.

Since its clinical use began in Germany in 1985, nearly half a million people have been treated with standardized butterbur extract, with significant success and virtually no side effects.<sup>13</sup> Investigators in Europe and North America are testing butterbur's applications in managing various disorders like hay fever, gastrointestinal conditions, and urogenital disorders. Butterbur thus appears to be a promising natural remedy for many common health complaints.

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