

# Clinical Applications of Natural Medicine

## Migraine

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Migraine has been a well-known medical problem for over 5,000 years and represents one of the most investigated types of head pain. Epidemiological research has shown that in the United States, 18% of women and 6% of men suffer from migraine.<sup>1</sup> This extrapolates to approximately 18 million females and 5.6 million males over the age of 12 with this disorder.<sup>2</sup> The prevalence of migraine, according to the Center for Disease Control, has increased 60% from 1981 to 1989.<sup>3</sup> While migraine can occur at any age, 30% of migraine sufferers report their first attack before the age of 10, and the condition is most common in adolescents and young adults.<sup>4</sup> The economic impact of migraine is staggering, with annual cost of the disease estimated at 18 billion dollars.<sup>5</sup>

### Etiology

The basic cause of migraine is still unknown. Although genetics may play a role, with 50% to 70% of migraine sufferers reporting a familial occurrence, no consistent biochemical or physiological characteristic can be recognized in the relatives of those afflicted with the condition.<sup>6</sup>

### Pathophysiology

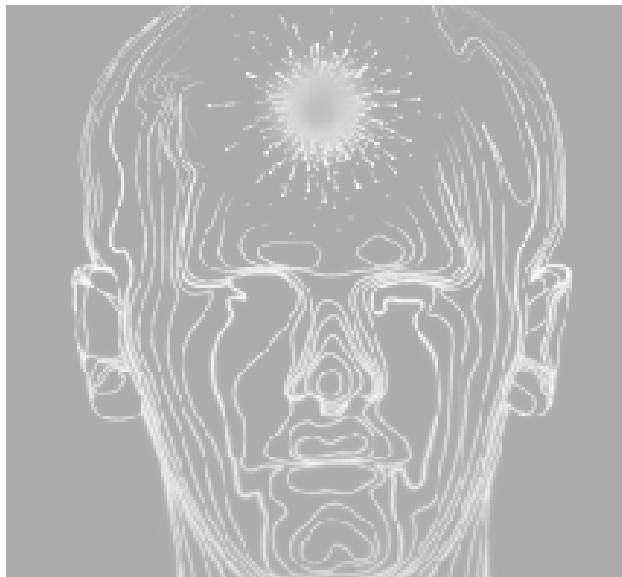
There are several pathophysiological theories on the origin of migraine. Not mutually exclusive, these theories include the vascular, central, platelet, and neurogenic inflammation hypotheses.

In 1938, Graham and Wolff, two of the period's most preeminent headache researchers, developed the vascular hypothesis of migraine. They suggested that contraction of the intra-cranial arteries caused

a reduction in blood flow to the visual cortex in the occipital lobe, resulting in the focal neurological symptoms ("aura") that accompany a migraine episode. They speculated that the head pain that followed was the result of extracranial vasodilation of the external carotid system, along with nerve compression in the carotid artery wall.<sup>7</sup> These conclusions were based on the observation that the vasoconstricting drug ergotamine tartrate dampened pulsation of the superficial temporal artery (and end branch of the external carotid artery), resulting in migraine pain relief.

Despite the fact that the vascular model has been a dominant concept in migraine pathophysiology, several difficulties arising from this theory have been noted. These include the fact that during a common migraine attack, only minor changes in cerebral blood flow have been noted. Furthermore, oligemia (phase of reduced blood flow) lasts for several hours longer than the aura. Lastly, the reduced blood flow is not sufficient to induce ischemia, alter neuronal function, and produce the aura phase.<sup>8</sup> As a consequence of these criticisms, the central theory of migraine has been proposed.

The central theory suggests that spreading oligemia is the consequence of spreading neuronal depression, which begins as a result of decreased neuronal function in the occipital poles of the brain. It progresses forward at a rate of two to three millimeters per minute.<sup>9</sup> Spreading depression involves the depolarization of neurons and has associated with it marked cellular ionic abnormalities. Lowered levels of cellular magnesium increase the likelihood of spreading neuronal depression occurring. This depression of neural



function results in a spreading oligemia that can last up to four to six hours. It progresses anterior, in a wave-like fashion, over the areas perfused by the middle and posterior cerebral arteries, temporarily impairing cortical vascular functioning. As a result, the aura of migraine may be the result of spreading depression, “a phenomenon originating within brain neurons and involving cerebral blood vessels only secondarily.”<sup>10,11</sup>

While the concept of spreading neuronal depression and oligemia may explain the migraine aura, it does not account for the ensuing headache. Migraine head pain may be the result of inflammation in the trigeminovascular system (TVS). This theory suggests that the trigeminal nerve fibers innervating cranial vessels are an important component of an elaborate defense network protecting the brain from an actual or perceived insult.<sup>11</sup> Inflammatory neurotransmitters such as substance P, calcitonin gene-related peptide and neurokinin A are released by the fifth cranial nerve signaling adjacent meningeal blood vessels to dilate.<sup>12</sup> The resulting neurogenic inflammation sensitizes the neurons and this induces head pain. It is interesting to note that stimulation of the presynaptic serotonin receptor (5HT-1) blocks the release of substance P, thus preventing inflammation and pain.

Many researchers have felt that serotonin (5HT) is the specific neurochemical fuel for migraine.<sup>13</sup> Platelets contain all of the 5HT normally present in blood, and, after they aggregate, 5HT is released, resulting in a potent vasoconstricting effect. During a migraine attack, platelet 5HT increases in the aura phase and diminishes in the headache phase. Following a migraine attack, this leads to an increase in urinary 5-hydroxyindolacetic acid (5-HIAA), the main metabolite of serotonin.<sup>14</sup> It is interesting to note that “serotonergic circuits are believed to be involved in modulation of sleep cycles, pain perception, and mood, all important factors in the pathogenesis of migraine.”<sup>15</sup> For example, “a decrease in the firing rate of serotonergic neurons of the midbrain dorsal raphe nucleus occurs with sleep, correlating with the observation that sleep often aborts a migraine attack.”<sup>16</sup> However, serotonin may not be the only vasoactive chemical involved in the pathogenesis of migraine. Histamine, tyramine, catecholamines (norepinephrine and dopamine), prostaglandin E, and free fatty acids may all have important roles to play in migraine pathogenesis.<sup>17</sup>

## Treatment

For the migraine sufferer, there is a wide variety of therapeutic approaches. Nonpharmacological prophylactic therapies may be highly effective. These include behavioral modification techniques such as stress management, biofeedback, exercise, acupuncture, trigger point injections, and numerous physical therapy techniques (e.g. massage, manipulation, and transcutaneous nerve stimulation).<sup>18</sup> Specific herbs may also help.

## Phytomedicine considerations

### • Feverfew

Feverfew (*Tanacetum parthenium*) is a member of the daisy family (*Asteraceae*) and is a short, bushy perennial that grows along fields and roadsides. Its yellow-green leaves and yellow flowers resemble those of chamomile, for which it is sometimes confused. The name “feverfew” is derived from the Latin for “chase away fevers.”

**Active constituents:** Feverfew is rich in compounds known as sesquiterpene lactones (STL). The most important of these compounds is parthenolide (see Figure 1). First identified in 1960, parthenolide represents about 85% of the STL content in feverfew and is the portion of the leaf believed to be responsible for feverfew’s anti-migraine activity.<sup>19</sup>

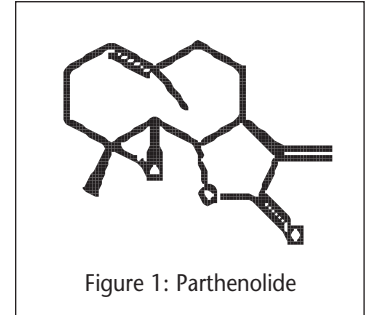


Figure 1: Parthenolide

A critical consideration in commercial feverfew products has been the highly variable content of parthenolide. An analysis of commercial feverfew products in Canada found about half to be virtually devoid of this compound.<sup>20</sup> As a minimal standard, the Health Protection Branch of the Health and Welfare Department of the Canadian government has proposed that feverfew preparations should contain at least 0.2% parthenolide content.

**Mechanism of action:** Feverfew, and specifically parthenolide, inhibits platelet aggregation and histamine release. It has also been shown to inhibit release of serotonin from platelets and polymorphonuclear leukocyte granules.<sup>21,22</sup> This is believed to reduce the severity, duration, and frequency of migraine headaches and lead to an improvement in blood vessel tone.

Feverfew also inhibits prostaglandin synthesis and the release of arachidonic acid.<sup>23,24</sup> This action may explain its historical use for inflammatory conditions such as arthritis.

**Clinical applications:** Clinical studies with feverfew have focused on the treatment and prevention of migraine and have primarily taken place in Great Britain. These studies indicate the efficacy of feverfew as a useful tool in the long-term management of migraines.

The initial clinical study enrolled migraine patients who had been using feverfew for several years.<sup>25</sup> Seventeen patients were enrolled and given either feverfew (50 mg daily) or placebo. Eight patients, who remained on feverfew, experienced continued relief of migraines over a six-month period. The nine receiving placebo had an almost three-fold increase in migraines. Many of these headaches were incapacitating, and anxiety, insomnia, and muscle and joint soreness were also reported.

**Recommended dosage:** Appropriate dosing of feverfew leaf for migraine prophylaxis is based on parthenolide

content. The Canadian Health Protection Branch has granted a Drug Identification Number (DIN) for feverfew.<sup>26</sup> They recommend a daily dosage of 125 mg of a dried feverfew leaf preparation from authentic *Tanacetum parthenium* containing a minimum of 0.2% parthenolide for migraine prevention. This translates to a daily parthenolide dosage of at least 250 mcg. This should be considered a minimum amount for efficacy. Whether considerably higher doses of parthenolide might offer greater results has yet to be proven. Continuous use for at least four to six weeks is recommended.

**Side effects/contraindications:** In addition to the adverse events listed in the clinical studies, the most common side effect reported with feverfew has been mouth ulceration.<sup>27</sup> This has predominantly been found in individuals chewing the leaves. Scattered reports of dermatitis have been reported with use of feverfew. To date, no long-term toxicity studies have been performed.

Feverfew is contraindicated for pregnant or lactating women and should not be used in children under the age of two years.

#### Other herbal considerations

##### • **Ginger**

The rhizome of ginger (*Zingiber officinale*) contains pungent constituents such as gingerols and shogaols that inhibit the formation of proinflammatory mediators and inhibit platelet aggregation.<sup>28,29</sup> Shogaols and gingerols are associated with the anti-nausea properties of ginger. Shogaols have also been shown to possess mild analgesic properties.<sup>30,31</sup>

While all of these actions point to the potential use of ginger with migraine, controlled clinical trials are lacking. One case study published in the *Journal of Ethnopharmacology* reported on a 42-year-old female migraine sufferer who found relief taking 500 to 600 mg of ginger powder mixed with water every four hours for four days.<sup>32</sup> The patient was instructed to begin ginger at the onset of visual aura. The authors report improvement within 30 minutes of beginning ginger. They also note that continued use of ginger by the woman led to decreased frequency and intensity of migraines.

##### • **Ginkgo biloba extract**

In addition to abnormal platelet aggregation in migraine patients, recent research also implicates platelet-activating factor (PAF) and proposes the use of PAF antagonists in the management of migraines.<sup>33</sup> The ginkgolides in Ginkgo biloba extract (GBE) have noted PAF antagonist actions.<sup>34</sup> GBE has been shown to offer some promise for the management of migraines in two small French clinical trials.<sup>35</sup> The daily dose ranged from 120 to 240 mg. Clearly, more research is needed on the potential use of GBE for migraine.

#### Nutritional supplement considerations

##### • **Magnesium**

Altura has pointed out that various factors known to trigger migraines (namely stress, pregnancy, menstruation, alcohol ingestion, and some diuretics) also promote magnesium wasting.<sup>36</sup> In addition, magnesium exerts many of the same effects as drugs that help prevent or treat migraines.<sup>37</sup> These effects include:

1. inhibition of vasospasm
2. inhibition of platelet aggregation
3. stabilization of cell membranes
4. interference with the synthesis, release, or action of inflammatory mediators
5. alterations in cerebral vascular tone.

In addition, brain magnesium concentrations (as measured by NMR spectroscopy) were significantly lower by 19% in patients during a migraine attack than in healthy controls. These observations suggest that magnesium may play a role in the prevention and/or treatment of migraine.

##### • **Riboflavin**

Riboflavin is the precursor of flavin adenine dinucleotide (FAD), a coenzyme involved in the electron-transport chain. A deficiency of mitochondrial energy reserve has been observed between attacks in patients with migraines. Theoretically, this defect might be ameliorated by compounds (such as riboflavin) that enhance the activity of the electron-transport chain.

To test that theory, 49 patients with recurrent migraines were given riboflavin, 400 mg/day with breakfast, for at least three months.<sup>38</sup> The mean number of migraine attacks fell by 67% and mean migraine severity improved by 68%. One patient stopped treatment because of gastric intolerance (that person was also taking small amounts of aspirin), but no other side effects were reported. This study suggests that riboflavin supplementation may reduce the recurrence rate of migraines. However, a placebo effect cannot be ruled out. A controlled trial is therefore needed to confirm these preliminary observations.

Although data on the effect of riboflavin remain preliminary, this vitamin is inexpensive and safe. A therapeutic trial therefore seems reasonable.

##### • **L-tryptophan**

It has been suggested that the pathogenesis of migraines is related in some way to the serotonergic system—possibly to a deficiency of serotonin in the brain.<sup>39</sup> As the precursor to serotonin, L-tryptophan might therefore play a role in migraine prophylaxis.

To test that hypothesis, eight migraine patients who had been refractory to therapy received 500 mg of L-tryptophan every six hours or a placebo (L-leucine), each for three months, in a double-blind, crossover trial.<sup>40</sup> The mean headache index (num-

ber of attacks multiplied by the intensity) was 32.8% lower with L-tryptophan than with placebo. Although that difference was not statistically significant, headache indices were markedly lower in four of the eight patients during L-tryptophan treatment, compared to placebo treatment.

These observations suggest that L-tryptophan may have prophylactic value for a subset of migraine patients. L-tryptophan has not been reported to cause any severe side effects. However, in 1989, a contaminated batch of L-tryptophan was implicated as the cause of a severe and sometimes fatal disorder known as eosinophilia myalgia syndrome. Uncontaminated L-tryptophan, on the other hand, has not been associated with this disorder. Currently, uncontaminated L-tryptophan is available by prescription from compounding pharmacists.

• **Fish oil**

Interest in the relationship between fish oil and migraines was triggered by the observation that migraine patients had significantly lower concentrations of omega-3 fatty acids in platelet and red blood cell membranes, compared with healthy individuals.<sup>41</sup> Omega-3 fatty acids (found primarily in fish oils, flaxseed oil, and some other vegetable and nut oils) are known to inhibit platelet aggregation. This effect would presumably decrease platelet serotonin release, with an accompanying reduction in cerebral vasospasm and migraine attacks.

Fifteen patients with migraines who had failed to respond to antimigraine drugs received (in random order) a fish-oil concentrate (5 g three times a day with meals) or placebo (vegetable oil) for six weeks, in a double-blind, crossover trial.<sup>42</sup> Compared with placebo, treatment with the fish oil concentrate resulted in a significant reduction in mean headache intensity.

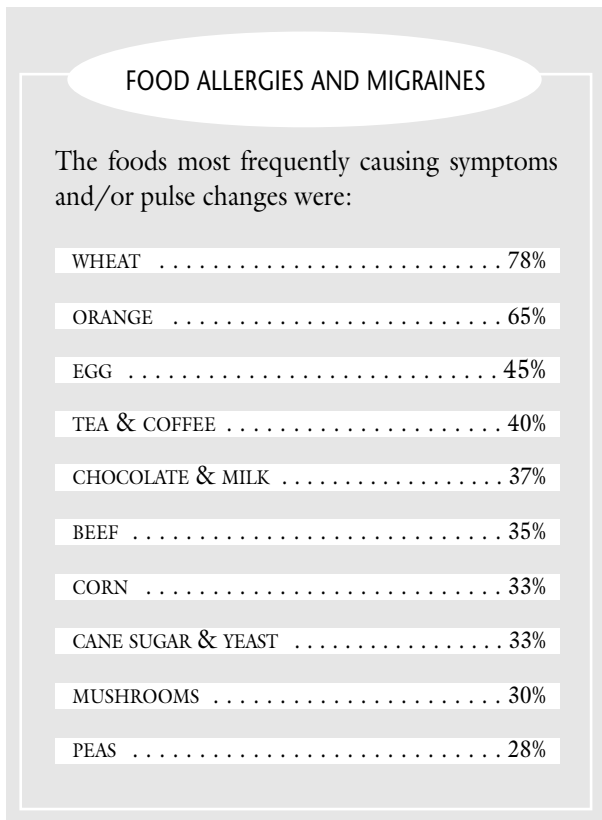
**Dietary considerations:** It is generally accepted that a small proportion of migraine patients will react to tyramine, a vasoactive amine found in aged cheese, yogurt, beer, wine, liver, yeast, and certain other foods. In these patients, avoidance of tyramine-containing foods will often prevent recurrences of migraine.

Abnormal glucose metabolism has been identified in some patients with migraines. In one study, a five-hour glucose tolerance test was performed on 74 patients who experienced migraines in the mid-morning or mid-afternoon.<sup>43</sup> Six patients (8%) were classified as diabetic and 56 (76%) had a pattern consistent with reactive hypoglycemia (i.e., serum glucose less than 65 mg/dl or a drop of 75 mg/dl within one hour). Following dietary therapy with a low-sucrose, six-meal regimen, all patients with a diabetic glucose curve and 56% of those with reactive hypoglycemia had an improvement of greater than 75% in the frequency and severity of migraines.

Food allergy has also been implicated as an important etiologic factor in migraine. In one study, 60 patients who had been suffering from frequent migraines for a mean duration of about 20 years followed an exclusion diet for five days.<sup>44</sup> During that time, only two low-risk foods (usually lamb and pears) and spring water were consumed. Migraines disappeared in most cases by the fifth day. Each patient then tested one to three common foods per day, looking for reactions. The mean number of foods causing symptoms was 10 per patient (range, 1 to 30). The foods most frequently causing symptoms and/or pulse changes were wheat

(78%), orange (65%), egg (45%), tea and coffee (40% each), chocolate and milk (37% each), beef (35%), corn, cane sugar and yeast (33% each), mushrooms (30%), and peas (28%).

Patients with recurrent migraines should be evaluated for possible blood-sugar abnormalities and food allergies. When either of these abnormalities is found, appropriate dietary modifications should be made. In addition, a trial of a low-tyramine diet should be considered.



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