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*The authors reported no
potential conflict of interest
relevant to this article.*

The evidence for herbal and botanical remedies, Part 1

While herbal supplements are popular among patients, few are supported by scientific evidence. A review of the literature suggests a few that are worth recommending.

PRACTICE RECOMMENDATIONS

- › *Consider capsaicin as an alternative to oral and topical nonsteroidal anti-inflammatory drugs to treat musculoskeletal pain in patients who don't respond to the latter.* **(B)**
- › *Consider ordering liver function monitoring for patients using butterbur because of the risk of toxicity.* **(C)**
- › *Recommend that patients consider drinking green tea as part of a healthy diet.* **(B)**
- › *Recommend peppermint to patients with irritable bowel syndrome.* **(B)**

Strength of recommendation (SOR)

- (A)** Good-quality patient-oriented evidence
- (B)** Inconsistent or limited-quality patient-oriented evidence
- (C)** Consensus, usual practice, opinion, disease-oriented evidence, case series

The National Center for Complementary and Integrative Health, a division of the National Institutes of Medicine, estimates that about 38% of American adults use complementary and alternative medicine.¹ That statistic includes 17.7% who say they use natural products. Despite their popularity, many physicians remain skeptical—and for good reason. Enthusiasts frequently offer dramatic anecdotes to “prove” their supplements' worth, but little scientific support is available for most herbal remedies. There are, however, exceptions. As this review of the medical literature will reveal, there is evidence to support the use of capsaicin to relieve osteoarthritis (OA) and postherpetic neuralgia (PHN) and support for green tea to serve as a lipid-lowering agent and help treat diabetes. Similarly, researchers have found that peppermint may be of value in the management of irritable bowel syndrome (IBS). (We also review the literature on butterbur for migraine headaches, but serious safety issues exist; **TABLE**.)

In the second part of this series, which is available online at jfponline.com, we explore what the evidence tells us about the use of turmeric, chamomile, rosemary, coffee, and cocoa.

Worth noting as you consider this—or any—review of herbals is that while there is limited scientific evidence to establish the safety and efficacy of most herbal products, they are nonetheless freely sold without US Food & Drug Administration (FDA) approval because under current regulations, they are considered dietary supplements. That legal designation means companies can manufacture, sell, and market herbs without first demonstrating safety and efficacy, as is required for pharmaceutical drugs. Because herbal medications do not require the same testing through the large randomized controlled trials (RCTs) required for pharmaceuticals, evidence is often based on smaller RCTs and other studies of lower overall quality. Despite these limitations, we believe it's worth keeping an open mind about the value of evidence-based herbal and botanical treatments.

Capsaicin

Overview

Capsaicin, an active compound in chili peppers, provokes a burning sensation, but also has a long history of use in pain treatment.² Qutenza, an FDA-approved chemically synthesized 8% capsaicin patch, is identical to the naturally occurring molecule.² Topically applied capsaicin exerts its therapeutic effect by rapidly depleting substance P, thus reducing the transmission of pain from C fibers to higher neurologic centers in the area of administration.³

Meta-analyses and systematic reviews have shown capsaicin is effective for various painful conditions, including peripheral diabetic neuropathy, OA, and PHN.

■ **Peripheral neuropathy.** A Cochrane review of 6 randomized, double-blind, placebo-controlled studies of at least 6 weeks' duration using topical 8% capsaicin to treat neuropathic pain concluded that high-concentration topical capsaicin used to treat PHN and human immunodeficiency virus (HIV)-associated neuropathy provided more relief in patients with high pain levels than control patients who received placebo, which was a subtherapeutic (0.04%) capsaicin cream. Number-needed-to-treat values were between 8 and 12. Local adverse events were common, but not consistently reported enough to calculate a number needed to harm.⁴

■ **OA.** Capsaicin provides mild to moderate efficacy in randomized trials for patients with hand and knee OA, when compared with placebo.⁵⁻⁷ A systematic review of capsaicin for all osteoarthritic conditions noted that there was consistent evidence that capsaicin gel was effective for OA.⁸ However, a 2013 Cochrane review of only knee OA noted that capsicum extract did not provide significant clinical improvement for pain or function in knee OA and resulted in a significant number of adverse events.⁹

■ **Low back pain (LBP).** Based on a 2014 Cochrane review of 3 trials (755 subjects) of moderate quality, capsicum frutescens cream or plaster appeared more efficacious than placebo in people with chronic LBP.¹⁰ Based on current (low-quality) evidence in one trial, however, it's not clear whether topical capsicum cream is more beneficial for acute LBP than a placebo.¹⁰

■ **PHN.** Topical 8% capsaicin is an FDA-approved treatment for PHN. A review and cost-effectiveness analysis demonstrated that 8% capsaicin had significantly higher effectiveness rates than the oral agents (tricyclic antidepressants, duloxetine, gabapentin, pregabalin) used to treat PHN.¹¹ In addition, the cost-effectiveness analysis found that the capsaicin patch was similar in cost to a topical lidocaine patch and oral products for PHN.¹¹

A meta-analysis of 7 RCTs indicated that 8% topical capsaicin was superior to the low-dose capsaicin patch for relieving pain associated with PHN.¹²

Adverse effects

Very few toxic effects have been reported during a half century of capsaicin use. Those that have been reported are mainly limited to mild local reactions.² The most common adverse effect of topical capsaicin is local irritation (burning, stinging, and erythema), which had been reported to occur in approximately 40% of patients.⁶ Nevertheless, more than 90% of the subjects in clinical studies were able to complete the studies, and pain rapidly resolved after patch removal.² Washing with soap and water may help prevent the compound from spreading to other parts of the body unintentionally.

The safety of the patch has been demonstrated with repeated dosing every 3 months for up to one year. However, the long-term risks of chronic capsaicin use and its effect on epidermal innervation are uncertain.⁵

The bottom line

Capsaicin appears to be an effective treatment for neuropathy and chronic LBP. It is FDA approved for the treatment of PHN. It may also benefit patients with OA and acute LBP. Serious adverse effects are uncommon with topical use. Common adverse effects include burning pain and irritation in the area of application, which can be intense and cause discontinuation.²

Butterbur

Overview

Petasites hybridus, also known as butterbur, is a member of the daisy family, Asteraceae,



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➤ **Butterbur appears to be effective in migraine prophylaxis, but there are serious concerns about liver toxicity.**

and is a perennial plant found throughout Europe and Asia.¹³ It was used as a remedy for ulcers, wounds, and inflammation in ancient Greece. Its calcium channel-blocking effects may counteract vasoconstriction and play a role in preventing hyper-excitation of neurons.¹⁴ Sesquiterpenes, the pharmacologically active compounds in butterbur, have strong anti-inflammatory and vasodilatory effects through lipoxygenase and leukotriene inhibition.¹⁴

■ **Migraine headache.** Butterbur appears to be effective in migraine prophylaxis. Several studies have shown butterbur to significantly reduce the number of migraine attacks per month when compared with placebo. In a small, randomized, placebo-controlled, parallel-group study on the efficacy and tolerability of a special butterbur root extract (Petadolex) for the prevention of migraine, response rate was 45% in the butterbur group vs 15% in the placebo group. Butterbur was well tolerated.¹⁵ Similar results were found in another RCT in which Petasites (butterbur) 75 mg bid significantly reduced migraine attack frequency by 48%, compared with 26% for the placebo group.¹⁶ Petadolex was well tolerated in this study, too, and no serious adverse events occurred. Findings suggest that 75 mg bid may be a good option for migraine prevention given the agent's safety profile.

Petadolex may also be a good option in pediatric migraine. A 2005 study in children and adolescents found that 77% of patients experienced a reduction in attacks by at least 50% with butterbur. Patients were treated with 50 mg to 150 mg over 4 months.¹⁷

In their guidelines for migraine prevention, the American Academy of Neurology (AAN) and American Headache Society gave butterbur a Level A recommendation and concluded that butterbur should be offered to patients with migraine to reduce the frequency and severity of migraine attacks.¹⁸ However, the AAN has since changed its position, stating that "The 2012 AAN guideline, 'Evidence-based guideline update: NSAIDs and other complementary treatments for episodic migraine prevention in adults' has been retired by the AAN Board of Directors on September 16, 2015, due to serious safety concerns with a preventative treatment, but-

TABLE

Conditions that may benefit from herbal and botanical supplements

Herbal, botanical/clinical indication	SOR
Capsaicin	
Neuropathic pain ^{4,11,12}	B
Chronic low back pain ¹⁰	B
Acute low back pain ¹⁰	C
Osteoarthritis pain ⁵⁻⁹	C
Butterbur*	
Migraine headache prophylaxis ¹⁵⁻¹⁸	A
Green tea	
Coronary artery disease prevention ²⁸⁻³⁰	B
Dementia prevention/improved cognition ²⁵⁻²⁷	C
Diabetes prevention or treatment ³⁴⁻³⁷	C
Cancer prevention or treatment ³¹⁻³³	C
Peppermint	
Irritable bowel syndrome ^{39,40,42-44}	B
Non-ulcerative dyspepsia ^{45,46}	B
Headache: Migraine and tension ⁵⁰⁻⁵³	B
Musculoskeletal pain ^{54,55}	B
Pain in carpal tunnel syndrome ⁵⁶	B

Strength of recommendation (SOR)

A Good-quality patient-oriented evidence; B Inconsistent or limited-quality patient-oriented evidence; C Consensus, usual practice, opinion, disease-oriented evidence, case series.

*Butterbur appears to be efficacious for migraine prophylaxis, but long-term safety is unknown and serious concerns exist for liver toxicity.

terbur, recommended by this guideline. The recommendations and conclusions in all retired guidelines are considered no longer valid and no longer supported by the AAN.¹⁹

■ **Allergic rhinitis.** Although the data is not convincing, some studies have shown that butterbur may be beneficial for the treatment of allergic rhinitis.^{20,21}

Adverse effects

While the butterbur plant itself contains pyrrolizidine alkaloids (PA), which are hepatotoxic and carcinogenic, extracts of butterbur root that are almost completely free from these alkaloids are available. (Patients who choose to use butterbur should be advised

to use only products that are certified and labeled pyrrolizidine alkaloids free.)

Petadolex, the medication used in migraine studies, was initially approved by the German health regulatory authority, but approval was later withdrawn due to concerns about liver toxicity.²² In 2012, the United Kingdom's Medicines and Health Care Products Regulatory Agency withdrew all butterbur products from the market due to associated cases of liver toxicity.²² Petasites (butterbur) products are still available in the US market, and the risks and benefits should be discussed with all patients considering this treatment. Liver function monitoring is recommended for all patients using butterbur.²²

The herb can also cause dyspepsia, headache, itchy eyes, gastrointestinal symptoms, asthma, fatigue, and drowsiness. Additionally, people who are allergic to ragweed and daisies may have allergic reactions to butterbur. Eructation (belching) occurred in 7% of patients in a pediatric study.¹⁷

The bottom line

Butterbur appears to be efficacious for migraine prophylaxis, but long-term safety is unknown and serious concerns exist for liver toxicity.

Green tea

Overview

Most tea leaves come from the *Camellia sinensis* bush, but green and black tea are processed differently to produce different end products.²³ It is estimated that green tea accounts for approximately a quarter of all tea consumption, and is most commonly consumed in Asian countries.²³ The health-promoting effects of green tea are mainly attributed to its polyphenol content.²⁴ While there are many types of tea due to how they are processed, green tea has the highest concentration of polyphenols, including catechins, which are powerful antioxidants.^{23,24} Green tea has been used in traditional Chinese and Indian medicine to control bleeding, improve digestion, and promote overall health.²³

■ **Dementia.** Green tea polyphenols may enhance cognition and may protect against the development of dementia. In-vitro studies have shown that green tea reduces hydrogen peroxide and beta-amyloid peptides,

which are significant in the development of Alzheimer's disease.²⁵ A 12-subject double-blind study found green tea increased working memory and had an impact on frontoparietal brain connections.²⁶ Furthermore, a cohort study with 13,645 Japanese participants over a 5-year period found that frequent green tea consumption (>5 cups per day) was associated with a lower risk of dementia.²⁷ Additional studies are needed, but green tea may be useful in the treatment or prevention of dementia in the future.

■ **Coronary artery disease.** In one study, green tea plasma and urinary concentrations were associated with plasma biomarkers of cardiovascular disease and diabetes.²⁸ In one review, the consumption of green tea was associated with a statistically significant reduction in low-density lipoprotein cholesterol.²⁹ Furthermore, a 2015 systematic review and meta-analysis of prospective observational studies concluded that increased tea consumption (of any type) is associated with a reduced risk of coronary heart disease, cardiac death, stroke, and total mortality.³⁰

■ **Cancer.** Many studies have shown that green tea may reduce the risk of cancer development, although epidemiologic evidence is inconsistent. Studies have shown that cancer rates tend to be lower in those who consume higher levels of green tea.^{31,32} Whether this can be attributed solely to green tea remains debatable. Several other studies have shown that polyphenols in green tea can inhibit the growth of cancer cells, but the exact mechanisms by which tea interacts with cancerous cells is unknown.²³

Several population-based studies have been performed, mostly in Japan, which showed green tea consumption reduced the risk of developing cancer. Fewer prostate cancer cases have been reported in men who consume green tea.³³ While studies have been performed to determine whether green tea has effects on pancreatic, esophageal, ovarian, breast, bladder, and colorectal cancer, the evidence remains inadequate.³²

■ **Diabetes.** Green tea has been shown in several studies to have a beneficial effect on diabetes. A retrospective Japanese cohort study showed that those who consumed green tea were one-third less likely to develop



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A meta-analysis that included 17 RCTs found that green tea improves glucose control and A1C values.

type 2 diabetes mellitus.³⁴ A 10-year study from Taiwan found lower body fat and smaller waist circumference in those who consumed green tea regularly.³⁵ A 2014 meta-analysis and systematic review of tea (any type) consumption and the risk of diabetes concluded that 3 cups or more of tea per day was associated with a lower risk of diabetes.³⁶ Another meta-analysis that included 17 RCTs and that focused on green tea concluded that green tea improves glucose control and A1C values.³⁷

Adverse effects

There have been concerns about potential hepatotoxicity induced by green tea intake.³⁸ However, a systematic review of 34 RCTs on liver-related adverse events from green tea showed only a slight elevation in liver function tests; no serious liver-related adverse events were reported.³⁸ This review suggested that liver-related adverse events after intake of green tea extracts are rare.³⁸

Consuming green tea in the diet may lower the risk of adverse effects since the concentration consumed is generally much lower than that found in extracts.

Contraindications to drinking green tea are few. Individuals with caffeine sensitivities could experience insomnia, anxiety, irritability, or upset stomach. Additionally, patients who are taking anticoagulation drugs, such as warfarin, should avoid green tea due to its vitamin K content, which can counter the effects of warfarin. Pregnant or breastfeeding women, those with heart problems or high blood pressure, kidney or liver problems, stomach ulcers, or anxiety disorders should use caution with green tea consumption.

The bottom line

Green tea consumption in the diet appears to be safe and may have beneficial effects on weight, diabetes mellitus risk, cancer risk, dementia, and cardiovascular risk. Patients may want to consider drinking green tea as part of a healthy diet, in combination with exercise.

Mint/peppermint/menthol

Overview

Mentha piperita, also known as peppermint, is a hybrid between water mint and spearmint.

It is found throughout Europe and North America and is commonly used in tea and toothpaste and as a flavoring for gum. It is used both orally and topically. Menthol and methyl salicylate are the main active ingredients in peppermint, and peppermint has calcium channel-blocker effects.³⁹ Menthol has been shown to help regulate cold and pain sensation through the TRPM8 receptor.⁴⁰ The peppermint herb has been studied in the treatment of multiple conditions.

■ **IBS.** It appears that peppermint inhibits spontaneous peristaltic activity, which reduces gastric emptying, decreases basal tone in the gastrointestinal tract, and slows down peristalsis in the gut.³⁹

The American College of Gastroenterology guidelines currently note that there is moderate-quality evidence for peppermint oil in the treatment of IBS.⁴¹ A Cochrane review concluded that peppermint appears to be beneficial for IBS-related symptoms and pain.⁴² In a systematic review of 9 studies from 2014, peppermint oil was found to be more effective than placebo for IBS symptoms such as pain, bloating, gas, and diarrhea.⁴³ The review also indicated that peppermint oil is safe, with heartburn being the most common complaint.⁴³ A 2016 study also found that triple-coated microspheres containing peppermint oil reduced the frequency and intensity of IBS symptoms.⁴⁴

■ **Non-ulcer dyspepsia.** In combination with caraway oil, peppermint oil can be used to reduce symptoms of non-ulcer dyspepsia.^{45,46} A multicenter, randomized, placebo-controlled, double-blind study found that 43.3% of subjects improved with a peppermint-caraway oil combination after 8 weeks, compared with 3.5% receiving placebo.⁴⁶

■ **Barium enema-related colonic spasm.** Peppermint can relax the lower esophageal sphincter, and it has been shown to be useful as an antispasmodic agent for barium enema-related colonic spasm.^{47,48}

■ **Itching/skin irritation.** Peppermint, when applied topically, has been used to calm pruritus and relieve irritation and inflammation. It has a soothing and cooling effect on the skin. At least one study found

it to be effective in the treatment of pruritus gravidarum, although the study population consisted of only 96 subjects.⁴⁹

■ **Migraine headache.** Initial small trials suggest that menthol is likely beneficial for migraine headaches. A pilot trial of 25 patients treated with topical menthol 6% gel for an acute migraine attack showed a significant improvement in headache intensity by 2 hours after gel application.⁵⁰ In a randomized, triple-blind, placebo-controlled, crossover study of 35 patients, a menthol 10% solution was shown to be more efficacious as abortive treatment of migraine headaches than placebo.⁵¹

■ **Tension headache.** A randomized, placebo-controlled double-blind crossover study of topical peppermint oil showed a significant clinical reduction in tension headache pain.⁵² Another small randomized, double-blind trial showed that tiger balm (containing menthol as the main ingredient) also produced statistically significant improvement in tension headache discomfort compared with placebo.⁵³

■ **Musculoskeletal pain.** A small study comparing topical menthol to ice for muscle soreness noted decreased perceived discomfort with menthol.⁵⁴ Menthol has also been shown to reduce pain in patients with knee OA.⁵⁵

■ **Carpal tunnel syndrome (CTS).** A triple-blind, randomized, placebo-controlled trial concluded that topical menthol acutely reduced pain intensity during the working day in slaughterhouse workers with CTS and should be considered as an effective non-systemic alternative to regular analgesics in the workplace management of chronic and neuropathic pain.⁵⁶

Adverse effects

Peppermint appears to be safe for most adults when used in small doses, and serious adverse effects are rare.^{43,57} While peppermint tea appears to be safe in moderate to large amounts, people allergic to plants in the peppermint family (eg, mint, thyme, sage, rosemary, marjoram, basil, lavender) may experience allergic reactions with swelling, wheals, or erythema. Peppermint may also cause heartburn due to relaxation of the cardiac sphincter.

Other symptoms may include nausea, vomiting, flushing, and headache.⁵⁸ The herb

may also be both hepatotoxic and nephrotoxic at extremely high doses.⁵⁹ Other considerations for women are that it can trigger menstruation and should be avoided during pregnancy. Due to uncertain efficacy in this population, peppermint oil should not be used on the face of infants, young children, or pregnant women.^{58,59}

The bottom line

Peppermint appears to be safe and well-tolerated. It is useful in alleviating IBS symptoms and may be effective in the treatment of non-ulcerative dyspepsia, musculoskeletal pain, headache, and carpal tunnel syndrome.^{54,55} **JFP**

Read part 2 online at jfponline.com.

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