



The evidence for herbal and botanical remedies, Part 2

In this second installment of our series, we explore what the evidence tells us about turmeric/curcumin, chamomile, rosemary, coffee, and cocoa.

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PRACTICE RECOMMENDATIONS

› Inform patients that curcumin appears to be a safe and effective adjunctive therapy for ulcerative colitis when used along with mesalamine or sulfasalazine. **(B)**

› Recommend chamomile extract to patients experiencing mild to moderate generalized anxiety disorder. **(B)**

› Tell patients that coffee is associated with a lower risk of mortality, reduced cardiovascular events, and a reduction in liver disease progression (in patients with end-stage liver disease). **(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

More than a third of American adults use complementary and alternative medicine.¹ Unfortunately, the public's enthusiasm for herbal products is not always consistent with the scientific evidence supporting their use. In part one of this series, we discussed the studies that have been done on capsaicin, butterbur, green tea, and peppermint. In this installment, we outline the research on 5 additional remedies: turmeric/curcumin, which may be of benefit in ulcerative colitis; chamomile, which appears to offer relief to patients with anxiety; rosemary, which may help treat alopecia; as well as coffee and cocoa, which may have some cardiovascular benefits (TABLE).

Turmeric/curcumin

Overview

Turmeric (*Curcuma longa*), a relative of ginger, has been used for 4000 years to treat a variety of conditions.^{2,3} Curcumin is the yellow pigment isolated from the rhizomes of *Curcuma longa*, commonly known as turmeric.³ Turmeric powder contains 5% curcumin, which is the main biologically active compound. Although it grows in many tropical locations, most turmeric is grown in India, where it is used as a main ingredient in curry. The roots and bulbs of turmeric that are used in medicine are generally boiled and dried, which results in a yellow powder.

Turmeric has been used in both Ayurvedic and Chinese medicine for its anti-inflammatory properties, in the treatment of digestive and liver problems, to fight infections, and to help heal skin diseases and wounds.³⁻⁷

■ **Functional GI disorders.** A recent review noted that curcumin has been shown in several preclinical studies and uncontrolled clinical trials to have effects on gut inflammation, gut permeability, and the brain-gut axis, especially in functional GI disorders.⁷ A double-blind, placebo-controlled study from 1989 found that turmeric reduced symptoms of bloating and gas in subjects suffering from undifferentiated dyspepsia.⁸

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A controlled clinical trial of chamomile extract suggested that it may have modest anxiolytic activity in patients with mild to moderate generalized anxiety disorder.

■ **Ulcerative colitis (UC).** A 2012 Cochrane review noted that curcumin appears to be a safe and effective therapy for maintenance of remission in quiescent UC when given as adjunctive therapy along with mesalamine or sulfasalazine.⁹ In a 2015 randomized controlled trial (RCT), the addition of curcumin to mesalamine therapy was superior to the combination of placebo and mesalamine in inducing clinical and endoscopic remission in patients with mild-to-moderate active UC, producing no apparent adverse effects.¹⁰

■ **Osteoarthritis (OA).** Because of turmeric's ability to reduce inflammation, it may help relieve OA pain.³ Clinical evidence is scant for the anti-arthritis efficacy of turmeric dietary supplements, although animal studies indicate that turmeric prevents inflammation through regulation of NF-kappaB-regulated genes that regulate the immune and inflammatory response.⁶ Inflammatory cell influx, joint levels of prostaglandin E2, and periarticular osteoclast formation were also inhibited by turmeric extract treatment.⁶

A 2013 review of turmeric for OA concluded that observational studies and in vitro results are promising for the use of curcumin for OA, but well-designed clinical studies were lacking and are needed to support the efficacy of curcumin in OA patients.¹¹ However, in a 2014 randomized trial of 367 patients, turmeric appeared to be similar in efficacy to ibuprofen for the treatment of pain and disability in adults with knee OA.¹² The curcumin (turmeric) group also had fewer adverse effects.¹²

■ **Cancer.** There has been a great deal of research on turmeric's anti-cancer properties, but clinical evidence is lacking. In vitro evidence, animal studies, and small clinical trials suggest that curcumin may help prevent or treat several types of cancers, but the overall evidence is poor. Nonetheless, curcumin and turmeric have been or are currently being evaluated for the treatment or prevention of prostate, liver, breast, skin, gynecologic, hematologic, pulmonary, thymic, bone, brain, and colon cancer.¹³⁻¹⁸

■ **Oral submucous fibrosis.** A small randomized trial found improvement in oral

function with curcumin lozenges, when compared to placebo, indicating that turmeric may hold promise as a treatment of oral submucous fibrosis.¹⁹

■ **Uveitis.** A small pilot study of 32 patients suggested that oral curcumin may be as effective as corticosteroids for uveitis.²⁰

■ **Heart disease.** Curcumin may have a cardiovascular protective role, as it has been shown to reduce atherosclerosis, but a reduction in myocardial infarction or stroke has not been documented.²¹

■ **Alzheimer's dementia.** Animal studies have shown a reduction in amyloid plaque formation with curcumin.²²

Adverse effects (and precautions)

Turmeric in food is considered safe. A variety of animal and human studies have also indicated that curcumin is safe and well tolerated, even at very high doses.¹³ However, taking large amounts of turmeric for long periods of time could cause stomach upset and gastric ulcers. In addition, patients with gallstones or bile obstruction should use it with caution due to increased bile production.⁷

Because turmeric may lower blood sugar levels, patients with diabetes should monitor for hypoglycemia when using turmeric in combination with diabetic medications. Similarly, those with bleeding disorders taking blood thinners should use turmeric and curcumin with caution, because it can inhibit platelet aggregation.²³

Although it is safe to eat foods with turmeric during pregnancy, pregnant and breastfeeding women should not take turmeric supplements, as the safety of large doses in pregnancy is unknown.

The bottom line

Turmeric/curcumin has anti-inflammatory properties and may be useful as an adjunct for ulcerative colitis and to improve the symptoms of OA. It may also have anticarcinogenic properties, although definitive data are lacking. Those with a history of gastrointestinal conditions such as gastric ulcer, patients taking blood thinners, and patients with diabetes who are prone to low blood sugar levels should use turmeric/curcumin with caution.

Chamomile

Overview

Chamomile, a member of the Asteraceae/Compositae family, is one of the oldest herbal medicines. It has been used for hay fever, inflammation, muscle spasms, menstrual disorders, insomnia, ulcers, wounds, gastrointestinal disorders, rheumatic pain, and hemorrhoids. Essential oils of chamomile are used extensively in cosmetics and aromatherapy. Many different preparations have been developed, the most popular being herbal tea.²⁴

Individuals with a hypersensitivity to plants of the Asteraceae (Compositae) family such as ragweed (*Ambrosia spp.*), marigold flower (*Calendula officinalis*), and chrysanthemum (*Chrysanthemum spp.*) may show a similar reaction to chamomile.²⁵

■ **Anxiety.** A controlled clinical trial of chamomile extract for generalized anxiety disorder (GAD) suggested that it may have modest anxiolytic activity in patients with mild to moderate GAD.²⁶ Another randomized, double-blind, placebo-controlled trial found oral chamomile extract was efficacious and well-tolerated in patients experiencing mild to moderate GAD and may provide an alternative therapeutic anxiolytic for patients with mild GAD.²⁵ In addition to its anxiolytic activity, chamomile may also provide clinically meaningful antidepressant activity.²⁶

■ **Insomnia.** Chamomile may have some impact on sleep diary measures (total sleep time, sleep efficiency, sleep latency, wake after sleep onset, sleep quality, and number of awakenings) relative to placebo in adults with chronic primary insomnia, according to a small randomized, double-blind, placebo-controlled pilot trial involving 34 patients.²⁷ However, a systematic review found no statistically significant difference between any herbal medicine (including chamomile) and placebo, for clinical efficacy in patients with insomnia. A similar, or smaller, number of adverse events per person were reported with chamomile compared with placebo, suggesting safe use.²⁸

■ **Infantile colic.** A small prospective double-blind study on the use of chamomile-containing tea on infantile colic showed statistically significant symptom improvement in tea-treated infants. The study did note,

however, that prolonged ingestion of herbal teas may lead to decreased milk intake.^{29,30}

Adverse effects

As noted earlier, a systematic review found that the number of adverse events per person reported with chamomile was comparable to the number associated with placebo, suggesting that it is safe.²⁸

The bottom line

Chamomile appears to be safe with minimal adverse effects and may be effective for the treatment of anxiety, insomnia, and infantile colic.

Rosemary

Overview

Rosemary, officially known as *Rosmarinus officinalis*, is a medicinal evergreen plant native to the Mediterranean area that appears to increase microcapillary perfusion.³¹

■ **Alopecia.** A randomized double-blind controlled trial found that essential oils including rosemary oil (as well as thyme, lavender, and cedarwood) massaged into the scalp improved hair growth in almost half of patients with alopecia areata after 7 months.³² Another randomized trial comparing rosemary oil to minoxidil 2% for androgenetic alopecia showed a significant increase in hair count at the 6-month endpoint compared with the baseline, but no significant difference was found between the study groups regarding hair count either at Month 3 or Month 6 ($P > .05$).³¹

Adverse effects

In the randomized trial described above comparing rosemary oil to minoxidil 2%, adverse effects appeared to be rare for topical rosemary oil. Scalp itching was more frequent in the minoxidil group.³¹

The bottom line

Topical rosemary oil may be useful in the treatment of alopecia with minimal adverse effects.

Coffee/caffeine

Overview

Coffee is one of the most widely used botanicals with approximately 3.5 billion cups



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A meta-analysis of 12 studies involving 832,956 participants found an inverse relationship between cutaneous melanoma and coffee consumption.

of coffee consumed per day worldwide. It is a popular beverage because of its unique aromatic taste and its use as a central nervous system stimulant. The coffee tree (genus *coffea*) is found throughout Latin America, Africa, and eastern Asia. Two of the most common commercially grown species are *Coffea arabica* (Arabicas) and *Coffea canephora* (Robusta). Processing and roasting methods may differ and produce variations in flavor and aroma. The degree of roasting also affects the caffeine content.

Coffee consumption leads to increased alertness and can boost mental performance. Based on the literature and US Food and Drug Administration recommendations, four 8-oz cups of coffee (about 400 mg of caffeine) daily is an acceptable average amount of caffeine. More than 500 mg/d is considered excessive use of coffee.^{33,34}

■ **Overall mortality.** A 2008 study showed that regular coffee was not associated with increased or decreased mortality in both men and women.³⁵ However, more recent studies show an inverse relationship between mortality and coffee consumption.

Specifically, a 2014 meta-analysis found an inverse relationship between coffee and mortality.³⁶ A large prospective cohort study from 2015 that included 79,234 women and 76,704 men found that drinking coffee was inversely associated with overall mortality.³⁷ In this cohort study, an inverse association were observed for deaths from heart disease, respiratory disease, diabetes, and self-harm.³⁷ While mechanisms were not analyzed, coffee may reduce mortality risk by affecting inflammation, lung function, insulin sensitivity, and depression.

■ **Cardiovascular disease.** Coffee consumption may modestly reduce the risk of stroke, according to a prospective cohort study of 83,076 women from the Nurses' Health Study who were followed for 24 years.³⁸ Reduced cardiovascular mortality was also found in a large prospective cohort study, as noted in the mortality discussion above.³⁷ A 2014 meta-analysis concluded that coffee consumption is inversely associated with cardiovascular mortality. Drinking 3 or 4 cups a day appears to be the

amount that may decrease one's risk of death when compared to those who do not drink coffee at all.³⁶

■ **Liver disease.** Friedrich et al performed a study involving 379 patients with end stage liver disease, and found that coffee consumption delayed the progression of disease in patients with both alcoholic liver disease and primary sclerosing cholangitis.³⁹ Coffee consumption also increased long-term survival after liver transplantation.³⁹ However, the study found that coffee did not have any effect on patients with chronic viral hepatitis.

In a 2016 meta-analysis, caffeinated coffee consumption reduced hepatic fibrosis of nonalcoholic fatty liver disease, although caffeine consumption did not reduce the prevalence of nonalcoholic fatty liver disease.⁴⁰ Another meta-analysis, including 16 studies, also found caffeine reduced the risk for hepatic fibrosis and cirrhosis.⁴¹

■ **Depression.** Based on 2 different systematic reviews and meta-analyses from 2016, coffee consumption appears to have a significant protective effect, decreasing the risk of developing depression.^{40,42}

■ **Alzheimer's disease/dementia.** Coffee, tea, and caffeine consumption show promise in reducing the risk of cognitive decline and dementia. Individuals who consume one to 2 cups of coffee per day had a decreased incidence of mild cognitive impairment compared to non-drinkers.⁴³ A 2015 Japanese study also found an inverse association between coffee consumption and dementia among women, nonsmokers, and those who do not drink alcohol.⁴⁴ Most recently, a 2016 study, the Women's Health Initiative Memory Study, looked at incident dementia rates in women >65 years of age with high vs low caffeine intake. Women with higher caffeine intake were less likely to develop dementia or any cognitive impairment compared with those consuming <64 mg/day.⁴⁵

■ **Type 2 diabetes.** A 2009 prospective cohort study, which included 40,011 participants followed for more than 10 years, found that drinking at least 3 cups of coffee or tea was associated with a lowered risk of type 2 diabetes.⁴⁶ A 2009 systematic review of 20 cohort studies showed that high intakes of

coffee, decaffeinated coffee, and tea are associated with a reduced risk of diabetes.⁴⁷

■ **Melanoma.** A meta-analysis of 12 studies involving 832,956 participants demonstrated an inverse relationship between cutaneous melanoma and coffee consumption.⁴⁷ The risk of melanoma decreased by 3% and 4% for one cup/day of total coffee and caffeinated coffee consumption, respectively. Furthermore, a 2016 meta-analysis found that caffeinated coffee may have greater chemopreventive effects against melanoma than decaffeinated coffee.⁴⁸

Adverse effects

Despite the many potential benefits of coffee, caffeine is a potent drug that should be used with caution.⁴⁹ People with underlying heart problems should avoid caffeine due to concern that it may cause palpitations from tachycardia. It may worsen anxiety problems or depression. Coffee may increase the production of stomach acids, which can worsen acid reflux or stomach ulcers.

Caffeine is a potent diuretic and may decrease absorption of calcium and cause OA. Caffeine may cause dependence and withdrawal symptoms. Some of the symptoms of withdrawal include drowsiness, headaches, irritability, nausea, and vomiting. It may disrupt sleeping patterns by causing jitters and sleeplessness.⁴⁹ Additionally, large amounts of caffeine may cause overdose and death.

The bottom line

Regular coffee intake is associated with a lower risk of mortality, reduced cardiovascular events, and a reduction in liver disease progression. Coffee may also have some utility for improving cognitive function and reducing the risk of type 2 diabetes. Caffeinated coffee should be limited to no more than 32 oz per day, due to the risk of insomnia, palpitations, anxiety, and gastritis.

Chocolate/cocoa

Overview

Few natural products have been claimed to successfully treat as many disorders as chocolate. The modern concept of chocolate as food has overshadowed its traditional medicinal use, although recent trials have

looked at evidence for some of its traditional uses. Chocolate is processed from the pod of the cacao plant. The earliest evidence for its medical use is in Mayan civilizations, and for most of its approximately 4000-year history, chocolate was consumed as a bitter drink referred to as the “drink of the Gods.” The traditional drink was mixed with water, vanilla, honey, chili peppers, and other spices. Important components in chocolate include flavonoids (antioxidants), cocoa butter, caffeine, theobromine, and phenylethylamine.

Chocolate has stimulating, anti-inflammatory, neuroprotective, and cardioprotective effects, and improves the bioavailability of nitric oxide, which can improve blood pressure and platelet function.⁵⁰ Epicatechin (an antioxidant) in cocoa is primarily responsible for its favorable impact on vascular endothelium via its effect on both acute and chronic upregulation of nitric oxide production. Other cardiovascular effects are mediated by the anti-inflammatory effects of cocoa polyphenols, and modulated through the activity of NF-kappaB.⁵¹

Dark chocolate appears to have the greatest benefit, as milk binds to antioxidants in chocolate, making them unavailable. Therefore, milk chocolate is not a good antioxidant source. There is no specific amount of chocolate that is known to be ideal, but an average of one to 2 ounces per day is often used in studies.

■ **Cardiovascular effects.** Chocolate does contain saturated fat, but a comparative, double-blind study found that short-term use of cocoa powder lowered plasma low-density lipoprotein (LDL) cholesterol, oxidized LDL, and apo B concentrations, and the plasma high-density lipoprotein (HDL) cholesterol concentration increased, relative to baseline in the low-, middle-, and high-cocoa groups.⁵² A small randomized crossover trial without clinical outcomes indicated that chocolate may increase HDL cholesterol without increasing weight.⁵³

A meta-analysis of short-term (2-12 weeks) treatment with dark chocolate/cocoa products showed reductions in LDL and total cholesterol, but no changes in HDL or triglycerides.⁵⁴ Another meta-analysis of RCTs, however, showed no short-term ef-



Regular coffee intake is associated with a lower risk of mortality, reduced CV events, and a reduction in liver disease progression.

Multiple studies have shown that chocolate is associated with a reduction in cardiovascular risk.

TABLE

Conditions that may benefit from herbal and botanical supplements

Herbal, botanical/clinical indication	SOR
Turmeric/curcumin	
Ulcerative colitis (as adjunct to standard treatment) ^{9,10}	B
Relieves osteoarthritic pain ³	B
Functional gastrointestinal conditions ^{7,8}	C
Treatment or prevention of cancer ¹³⁻¹⁸	C
Chamomile	
Anxiety ^{25,26}	B
Insomnia ^{27,28}	B
Infantile colic (as combination of chamomile, vervain, licorice, fennel, and balm-mint) ^{29,30}	B
Rosemary	
Alopecia ^{31,32}	B
Coffee/caffeine	
Cardiovascular disease ³⁶⁻³⁸	B
Reduction in overall mortality ^{36, 37}	B
Reduce the risk and progression of liver disease ^{39,41}	B
Decreases the risk of developing depression ^{40,42}	B
Dementia ⁴³⁻⁴⁵	B
Melanoma ^{47,48}	B
Reduced risk of type 2 diabetes ^{46,47}	C
Chocolate/cocoa	
Lowering blood pressure ⁶³⁻⁶⁵	C (good evidence, but no patient-oriented outcomes)
Lowers risk of stroke ^{57,60}	B
Lowers risk of diabetes ^{68,69}	C
Lowers risk of preeclampsia ^{66,67}	C
Improves lipid profile ^{52,53}	C
Improvement in mood/energy ⁷⁰⁻⁷²	C

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.

fect of cocoa/chocolate on lipid concentrations.⁵⁵ A randomized, placebo-controlled double-blind study of 62 patients with diabetes and hypertension showed that high polyphenol chocolate improved triglyceride levels.⁵⁶

Multiple studies have shown that chocolate is associated with a reduction in cardiovascular risk.⁵⁷⁻⁵⁹ A best case scenario analysis using a Markov model to predict the long-

term effectiveness and cost effectiveness of daily dark chocolate consumption in a population with metabolic syndrome at high risk of cardiovascular disease concluded that daily consumption of dark chocolate can reduce cardiovascular events by 85 per 10,000 population treated over 10 years. The study concluded that \$42 could be cost effectively spent per person per year on prevention strategies using dark chocolate.⁵⁹

In addition, a meta-analysis of 7 observational studies showed that high levels of chocolate consumption (any type) were associated with a 29% reduction in stroke compared with the lowest levels of chocolate intake.⁵⁷ Results of a similar meta-analysis from *Neurology* in 2012 also suggested that moderate chocolate consumption (any type) may lower the risk of stroke.⁶⁰

That said, 2 systematic reviews specifically relating to the risk of coronary heart disease and chocolate intake were inconclusive.⁶¹⁻⁶²

■ **Blood pressure (BP).** An RCT published in *JAMA* indicates that inclusion of small amounts of polyphenol-rich dark chocolate as part of a usual diet efficiently reduced BP and improved the formation of vasodilative nitric oxide.⁶³ A meta-analysis of 10 RCTs also showed mean BP change in the active cocoa treatment arms across all trials was -4.5 mm Hg (95% confidence interval (CI), -5.9 to -3.2; $P < .001$) for systolic BP and -2.5 mm Hg (95% CI, -3.9 to -1.2; $P < .001$) for diastolic BP.⁶⁴

A Cochrane Review meta-analysis of 20 studies revealed a statistically significant BP-reducing effect of flavanol-rich cocoa products compared with control in short-term trials of 2 to 18 weeks' duration.⁶⁵ Because studies have shown improvement in BP with chocolate intake, investigations into a role of chocolate in the prevention of preeclampsia have been undertaken. In some studies, chocolate intake was associated with reduced odds of preeclampsia and gestational hypertension.^{66,67}

■ **Diabetes.** Chocolate may exert significant vascular protection because of its antioxidant properties and possible increase of nitric oxide bioavailability, which can influence glucose uptake. A small trial comparing the effects of either dark or white chocolate bars (which do not contain the polyphenols) showed improved BP and glucose and insulin responses to an oral glucose tolerance test in healthy subjects on dark chocolate, but not white chocolate.⁶⁸ A comparison of chocolate consumption and risk of diabetes in the Physicians' Health Study showed an inverse relationship between chocolate intake with inci-

dent disease, but this association appeared only to apply in younger and normal-body weight men after controlling for comprehensive lifestyles, including total energy consumption.⁶⁹

■ **Fatigue.** The effect of chocolate on a person's energy level has been noted for centuries.⁷⁰ A small randomized trial showed improved energy levels in those treated with higher chocolate intakes. In a double-blind, randomized, clinical pilot crossover study, high cocoa liquor/polyphenol rich chocolate, reduced fatigue in subjects with chronic fatigue syndrome.⁷¹

■ **Anxiety.** A small randomized trial showed chocolate decreased anxiety in high-anxiety trait subjects and improved the anxiety level and the energy levels of low-anxiety trait participants.⁷²

■ **Eye effects.** The literature presents conflicting evidence regarding the effect of flavonoids on patients with glaucoma and ocular hypertension. However, a meta-analysis showed that flavonoids have a promising role in improving visual function in patients with glaucoma and ocular hypertension, and appear to play a part in both improving and slowing the progression of visual field loss.⁷³

■ **Cognitive decline.** Chocolate intake (any type) was associated with a lower risk of cognitive decline (RR=0.59; 95% CI, 0.38-0.92) with the greatest benefit noted in those who averaged more than one chocolate bar or one tablespoon of cocoa powder per week. This protective effect was observed only among subjects with an average daily consumption of caffeine <75 mg (69% of the participants; RR=0.50; 95% CI, 0.31-0.82).⁷⁴

The bottom line

Chocolate with high cocoa content (dark chocolate) appears to be safe and beneficial as part of a healthy diet and lifestyle that includes exercise and stress reduction to decrease cardiovascular risk and may improve energy levels. **JFP**

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Chocolate intake was associated with a lower risk of cognitive decline, with the greatest benefit noted in those who averaged more than one chocolate bar per week.

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