Analgesic Herbs

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Abstract

A wide range of herbs for pain conditions are discussed, with detailed information on their safe clinical application. *Aconitum* spp. (aconite, fū zǐ) and a formula featuring it, Gosha-jinki-gan (Niú Chē Shèn Qì Wán), are particularly good examples of powerful analgesics that are far too little used in North American prescribing. The global use of various species of aconite is particularly compelling. However, this herb should only be recommended by experienced clinicians (as with most of the other herbs discussed herein). Similarly, *Clematis* spp. (clematis, virgin's bower) and *Anemone* spp. (pasque flower) of various types are used for pain around the world. *Actaea racemosa* (black cohosh) is yet another analgesic from the Ranunculaceae family (along with aconite, clematis, and pasque flower). *Corydalis yanhusuo* (corydalis, yán hú suǒ) and its American cousin *Corydalis aurea* (golden smoke) are opium family plants discussed for pain relief. Other diverse analgesic herbs discussed include *Bryonia alba* (white bryony), *Bryonia cretica* ssp. *dioica* (Cretan or red bryony), capsaicin, and *Cannabis sativa* (cannabis, marijuana). Finally, herbs that both relax skeletal muscle and reduce pain are described, including *Piper methysticum* (kava), *Pedicularis bracteosa* (bracted lousewort), *Stachys officinalis* and *Stachys betonica* (wood betony), and *Lobelia inflata* (lobelia).

Keywords: pain, botanical medicine, aconite, cannabis, capsaicin, corydalis

Introduction

Arguably most pharmaceutical treatments for pain are derived ultimately, and often still directly, from herbs. Most obvious are the opioids, originally from the plant *Papaver somniferum* (opium poppy), used since prehistory to treat pain. Unfortunately, today there is an epidemic of death and dysfunction due to a perfect storm of corporate malfeasance, overprescription, and malprescription of opioid drugs.[1] The U.S. Food and Drug Administration's call for the development of non-opioid options for pain treatment ignores the rich therapeutic armamentarium in natural medicine already available, including herbs, acupuncture, physical medicine, hydrotherapy, bee venom, and many others.[2,3] The herbal portion of these options is reviewed here.

The full range of analgesic herbs is simply too extensive to discuss here, as the nature of various pain conditions varies widely. For instance, see my recent discussions of herbs for migraine and rheumatoid arthritis, two painful conditions mostly not addressed here, but which some of the herbs in this article could also help.[4,5]

Aconite

There are many species of aconite around the world used as medicine, most notably *Aconitum napellus* (monkshood) from Europe, *A. carmichaeli* (Sichuan aconite, fū zǐ in Mandarin Chinese, bushi in Japanese, buja in Korean) from Asia, and *A. columbianum* (western monkshood; Fig. 1) from western North America. While small doses of properly prepared aconite plant are very potent medicines, all these can be quite poisonous and even lethal when taken in excess or if they are not heat treated. Despite this concern, the unique efficacy of aconite for neuropathic pain in particular and its strong historical use warrants its continued prescription by trained practitioners. Sichuan aconite is often heralded as the "King of All Herbs" in Chinese herbal medicine and was introduced in the *Shén Nóng Běn Cǎo Jīng* (*Divine Husbandman's Classic of the Materia Medica*), one of the oldest herbals of Chinese medicine, sometime between 300 BCE and 200 CE.[6] Aconite is a member of the Ranunculaceae family.

Some of the most severe types of neuropathic pain can be effectively treated with aconite preparations, particularly trigeminal neuralgia, postherpetic neuralgia, sciatica, and pruritus ani.[7] Other types of severe pain, including acute gouty arthritis, rheumatoid arthritis, and osteoarthritis pain, and other less serious causes, including pharyngitis, otitis media, and sinusitis, are all susceptible to aconite's effects. Generally, this is a second- or third-line treatment for such types of pain, given aconite's risks.

Preliminary clinical trials support the efficacy of aconite. At least two open trials have shown that Sichuan aconite by itself, or combined with *Glycyrrhiza uralensis* (Asian licorice, gān cǎo) root, were helpful for osteoarthritis patients.[8,9] Powdered, heat-processed lateral roots of Sichuan aconite and the Japanese formula keishi-ka-jutsubu-tō (which is based on the Chinese formula guì zhī jiā shù fù tāng, Cinnamon Twig Decoction with Atractylodes and Aconite) featuring aconite were both reported to alleviate postherpetic neuralgia in a case series.[10] A combination of aconite root (species, preparation, and

Figure 1. ***Aconitum columbianum*** **herb and root (inset). Drawing by Meredith Hale and reprinted with permission.**

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dose unstated) and *Geranium* spp. (cranesbill, lǎo guàn cǎo) aerial parts relieved chemotherapy-induced neuropathy compared to no treatment.[11]

The aconite-containing Japanese formula gosha-jinki-gan (which is based on the Chinese formula niú chē shèn qì wán or Life Preserving Kidney Qi Pill, developed in 1253 CE by Yán Yòng-Hé in his book *Jì Shēng Fāng* [*Formulas to Aid the Living*]) bears closer scrutiny, as it has been studied fairly extensively. Its ingredients are outlined in Table 1. Despite the relatively low amount of aconite in the formula, it is a key component. In one randomized but open trial of 29 patients undergoing chemotherapy with paclitaxel and carboplatin, gosha-jinki-gan granules 2.5 g t.i.d. and methylcobalamin 500 μg t.i.d. were superior to methylcobalamin alone at preventing progression of peripheral neuropathy.[12] A similar trial involving 60 Japanese breast cancer patients treated with docetaxel found that neuropathy occurred in 40% of patients treated with gosha-jinki-gan and methylcobalamin compared to 89% of those taking methylcobalamin only.[13] A larger trial randomized 45 Japanese colon cancer patients to gosha-jinki-gan granules 2.5 g t.i.d. or no additional treatment while undergoing oxaliplatin, fluorouracil, and folinic acid (FOLFOX) chemotherapy.[14] No patient receiving gosha-jinki-gan developed grade 3 or higher neuropathy compared to 12% in the FOLFOX-only group after 10 courses. After 20 courses, 33% in the gosha-jinki-gan group versus 75% in the FOLFOX-only group had such severe neuropathy. There were no differences between the groups in terms of tumor response or other adverse effects, confirming that the formula does not work by interfering with the therapeutic effects of FOLFOX.

The first double-blind, randomized, placebo-controlled trial of gosha-jinki-gan granules 2.5 g t.i.d. involved 89 Japanese cancer patients undergoing oxaliplatin-containing chemotherapy.[15] Grade 2 and 3 peripheral neuropathy occurred significantly less often in the gosha-jinki-gan group compared to the placebo group. Given the positive results of so many prior trials, it was quite surprising that the largest double-blind, randomized clinical trial to date had a different outcome. In this, 142 Japanese colon cancer patients were randomized to gosha-jinki-gan granules 2.5 g t.i.d. or placebo along with FOLFOX chemotherapy.[16] An interim analysis found that neuropathy was actually significantly more common in the gosha-jinki-gan group compared to the placebo group, and the trial was halted (it was initially planned to enroll 310 patients in the trial). The authors speculate that gosha-jinki-gan was mostly effective at suppressing acute neuropathy induced by oxaliplatin, but either it did not affect chronic neuropathy from continuous use or it allowed for higher dose intensity, thus causing more chronic damage. They intend to do a five-year follow-up of treated patients to try to determine any long-term effects of the herbal formula. Based on these results, gosha-jinki-gan should only be used for patients with unremitting neuropathy that nothing else is helping. It should be closely monitored, and the formula should be stopped if there is worsening. Use of aconite by itself might also be considered in patients with chemotherapy-induced peripheral neuropathy.

Diabetic neuropathy is another indication for which gosha-jinki-gan appears helpful. In an open trial of the formula at a dose of 2.5 g t.i.d., neuropathic symptoms improved in 9/13 (69%) patients with diabetic neuropathy after three months.[17] After washout, 7/13 (54%) such patients worsened again within two months. There was a statistically significant improvement in vibratory sense during gosha-jinki-gan treatment compared to baseline. A group of 116 Japanese patients with diabetes mellitus type 2 taking standard therapies were randomized to take either gosha-jinki-gan granules 2.5 g t.i.d. or no additional treatment for five years.[18] In this open trial, there was a significant decrease in deterioriation of onset of neuropathy with gosha-jinki-gan compared to no additional treatment. A double-blind, randomized trial is needed to confirm whether these results are accurate.

Only lateral roots (not the central tap root) of aconite are recommended for use, and only after being cooked for one hour and then dried. This largely eliminates the C19-norditerpenoid

Table 1. Gosha-jinki-gan (Niú Chē Shèn Qì Wán) Ingredients

Latin binomial	Common names	Part used	Percent in formula
Rehmannia glutinosa	Rehmannia, shú dì huáng	Cooked root	10%
Dioscorea japonica	Chinese yam, shān yào	Rhizome	9%
Cornus officinalis	Cornelian cherry, shān zhū yú	Fruit	9%
Wolfiporia cocos	hoelen, fú líng	Sclerotium	9%
Alisma plantago-aquataica	water plantain, zé xiè	Rhizome	9%
Paeonia x *suffruticosa*	mountain peony, mǔ dān pí	Root bark	9%
Achyranthes bidentata	achyranthes, huái niú xī	Root	14%
Plantago asiatica	plantain, chē qián zǐ	Seed	9%
Cinnamomum cassia	cassia, ròu guì	Trunk bark	6%
Aconitum japonicum	aconite, fù zǐ	Processed lateral root	8%

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diester alkaloids* aconitine, mesaconitine, and hypaconitine that are largely responsible for the toxicity of aconite, converting them to far less toxic monoester and lipo-alkaloids.[19,20] The Chinese pharmacopoeia specifies that <0.02% of aconitine, hypaconitine, and mesaconitine be present in properly processed material.[21] *Glycyrrhiza* spp. (licorice) and *Paeonia lactiflora* (white or red peony) both reduce toxicity when either herb is taken simultaneously with aconite.[22,23] Aconite toxicity results largely from the norditerpenoid diester alkaloids, causing persistent activation of voltage-sensitive sodium channels, resulting in gastrointestinal, neuro-, and cardiotoxicity.[24] Norditerpenoid alkaloids such as aconitine can inhibit the inward-rectifying potassium channel (IRK), which is one mechanism of causing ventricular fibrillation.[25] Within two hours of overdose of aconite or its alkaloids, patients develop numbness of the mouth, lips, and limbs, weakness, nausea, vomiting, hypotension, and arrhythmias that can progress to lethal ventricular arrhythmia. Magnesium is a highly effective antidote for aconite-induced arrhythmias.[26] The precise toxic dose has not been established for humans because in case studies of accidental death, exact amounts are rarely available, and because it would of course be unethical to determine this experimentally. One text estimates that 2 mg of aconitine is a lethal dose.[27] In cases of overdose from medical use of decocted, cured Sichuan aconite, reported doses ranged from 3 to 20 g.[28] Aconite should not be given to patients with pre-existing uncontrolled arrhythmias except for atrial fibrillation, which it is not known to aggravate. Aconite should not be combined with drugs that prolong the QT interval, notably fluoroquinolone and macrolide antibiotics, class Ia and III anti-arrhythmic drugs, quinine, azole antifungals, pentamidine, various antipsychotics, loperamide, and methadone. Aconite should only be used topically on small areas during pregnancy and lactation.

The mechanisms of action of aconite are still being studied. However, several lines of preclinical research support that processed aconite extracts and its constituents are κ-opioid agonists.[29] While in the short term this can interfere with the analgesic properties of morphine and other opioids, it potentiates their effects in the long term.[30] The effects of aconite alkaloids on sodium channels and keeping neurons depolarized also seem to contribute to their analgesic effects.[31] Still other mechanisms of action are likely for this complex plant.[32]

The usual dose of an aconite cooked lateral root tincture is three to five drops up to several times a day for a few days, then decreasing to three times daily as pain is controlled. For granules, the dose is 1–2 g t.i.d. For crude aconite cooked lateral root in tea, the dose is 1–3 g t.i.d. In most cases, the low end of the dose should be used and slowly titrated up based on clinical pain relief and tolerance (primarily absence of palpitations). Aconite is also effective topically, but large areas of skin (such as the low back) should not be treated, and it should not be combined with topical heat due to reports of people developing systemic toxicity from absorption of excessive amounts of topical preparations.[33]

Other Ranunculaceae Analgesics

All members of the Ranunculaceae plant contain the glycoside ranunculoside (or ranunculin). Picking, chewing, or otherwise damaging the plant releases the aglycone of this compound, known as protoanemonin, from the glucose that was attached to it. Protoanemonin is a potent mucous membrane and skin irritant, and can even cause blistering with sufficiently extensive exposure in a sensitive person. The presence of protoanemonin is a herald of good-quality herb material, and all plants in the family can be tasted in tiny amounts to insure this during harvest. They should cause burning and numbness in the lips. With small exposures this causes no harm. Tincturing, drying, and heating all mostly destroy these compounds, rendering them safer for internal consumptions (in significant part by formation of its non-irritant dimerization product, anemonin, which is spasmolytic,

*Technically these are pseudoalkaloids, as they are derived from diterpenoids and not amino acids, unlike true alkaloids.

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analgesic, and mildly sedative[34]). However, all members of this family should be treated with great respect, as already seen with aconite.

Clematis spp. (clematis, virgin's bower) is a genus of vining plants in the Ranunculaceae family used for pain conditions in both Western and Chinese medicine. The flowering tops of *C. ligusticifolia*, *C. columbiana*, *C. drummondii*, *C. hirsutissima*, and other species native to western North America (sometimes called *barbo de chivo* or *yerba de chiva* in Spanish) have been recommended in particular for migraine and cluster headaches.[35] *C. hirsutissima* has been confirmed to yield anemonin when injured and is generally one of the strongest in the genus, so much so it may simply be too strong for general use.[36] Tincture made from the fresh plant of these species are also said to be useful counterirritants applied over joints affected by arthritis, reducing pain and inflammation deep inside while irritating the overlying skin.[30] The usual internal dose of all species mentioned, except *C. hirsutissima*, is 1 mL of fresh tincture three times daily in water.

Clematis chinensis, *C. manshurica*, and *C. hexapata* roots are used as the Chinese medicine wēi líng xiān or Chinese clematis. These and related species have shown inflammation modulating effects.[37] They are used traditionally for relieving pain. A combination of *C. manshurica* root, *Trichosanthes kirilowii* (trichosanthes, guā lóu gēn) root, and *Prunella vulgaris* (heal-all, xià kū cǎo) flowering tops in a ratio of 1:2:1 has been studied in several randomized, double-blind clinical trials. It has been shown helpful for osteoarthritis and rheumatoid arthritis at a dose of 200 mg t.i.d. in comparison to placebo, diclofenac, and celecoxib.[38–40] A typical dose of the root of Chinese clematis in decoction or as granules is 1–2 g t.i.d. Western and Chinese clematis are both contraindicated in pregnancy.

Actaea racemosa (black cohosh) root is another Ranunculaceae family analgesic, though it has become much more famous as a hormone-modulating medicine for menopausal symptoms and other women's health issues. However, it is traditionally a remedy for arthritis, rheumatism, and neuralgia, and clinically it is still helpful for these problems.[41] Indeed, a formula featuring black cohosh along with several other herbs (known by the trade name Phytodolor®) has been shown to relieve pain and inflammation in patients with rheumatoid arthritis, as previously reviewed in my article discussing herbs for rheumatoid arthritis.[4] Its mechanisms of actions are not well understood. A typical dose of black cohosh fresh root tincture is 1–2 mL t.i.d. It very occasionally causes headache, but black cohosh is otherwise very safe, including for short periods of use during pregnancy.

Anemone occidentalis (western pasque flower) and *A. tuberosa* (desert anemone) from North America, *A. pulsatilla* (European pasque flower) from Europe, and *A. chinensis* (bái tóu wēng, Chinese anemone) from Asia are all Ranunculaceae family plants that are used for pain. The aerial parts of American and European species are used, while the root of the Chinese species is used as medicine. European pasque flower is particularly traditionally known for treating pelvic pain. In vitro evidence supports that it is a smooth-muscle relaxant and could thus help cramping pain such as that caused by acute kidney stones, gallstones, dysmenorrhea, and spasmotic irritable bowel syndrome.[42] European pasque flower is also regarded traditionally as a treatment for eye pain, including topically (once processed; do not apply the fresh plant to the eyes or risk damaging them).[43] The author has found fresh plant tinctures of the American species to be significantly stronger than dried extracts of the European species, being active at doses as low as five drops (up to several times a day). Clinical trials are lacking but definitely indicated.

Corydalis

The root of *Corydalis yanhusuo* (corydalis, yán hú suǒ) in the Papaveraceae (opium poppy) family is a major pain reliever used in Chinese herbal medicine. The western North American species *C. aurea* (golden smoke) is used somewhat similarly, except the aerial parts are used. Substitution of other *Corydalis* species is not recommended, as they are too variable. The comparative potency of various analgesic members of the Papaveraceae family including corydalis is given in Table 2. As can be seen, most other members of the family are much less potent than opium, which also means they carry very little or no risk of tolerance, addiction, or lethal overdose. This

Table 2. Comparative Potency of Papaveraceae Analgesics

Latin binomial (Common names)	Part used	Relative potency
Papaver somniferum (opium poppy)	Latex	10
Corydalis yanhusuo (corydalis, yán hú suǒ)	Root	1[a]
Corydalis aurea (golden smoke)	Flowering tops	0.8
Argemone mexicana (Mexican poppy)	Flowering tops	0.7
Roemeria refracta (spotted Asian poppy, *kizgaldok*)	Flowering tops	0.5[b]
Eschscholzia californica (California poppy)	Flowering tops and roots	0.1

Opium is arbitrarily assigned a potency rank of 10. Ranked largely based on Dr. Yarnell's clinical experience, or on research as cited.
[a]Chang HM, But PPH, eds. Pharmacology and Applications of Chinese Materia Medica, vol. 1. Hackensack, NJ: World Scientific, 1986:479–487.
[b]Eisenman SW, Zaurov DE, Struwe L. Medicinal Plants of Central Asia: Uzbekistan and Kyrgyzstan. New York: Springer Science and Business Media, 2012.

comparison should be taken with reservations though, as analgesic herbs, even within the same family, can work in very different ways and still produce significant pain relief, thus subverting such simplistic models.

Several preliminary clinical trials support that corydalis has broad-ranging analgesic activity. A small trial found that a single dose of corydalis combined with *Angelica dahurica* (angelica, bái zhǐ) root significantly reduced pain severity and bothersomeness during cold-pressor testing in healthy American adults compared to untreated controls.[44] The effects were dose dependent. Animal research confirms that the coumarins and phenylpropanoids in angelica significantly increase absorption of the analgesic alkaloid tetrahydropalmatine from corydalis.[45] In a group of 76 Chinese patients with rheumatoid arthritis, a poorly characterized corydalis product combined with methotrexate was more effective than methotrexate alone at relieving rheumatoid arthritis symptoms after three months.[46]

A randomized trial of 58 Chinese patients with reflex sympathetic dystrophy (RSD; now often referred to as complex regional pain syndrome) compared a very complex Chinese herb formula including 10 g of prepared corydalis root taken internally (along with some Chinese herbs applied as a wash) to placebo for 10 days.[47] Whether the trial was blinded was unclear. Symptom severity declined significantly in the Chinese herb group compared to placebo. Given the large number of herbs involved, one cannot conclude that corydalis is proven in isolation to help RSD, but it likely contributed to the therapeutic benefit. A similar open trial randomized 93 Chinese patients with knee osteoarthritis to a very complex herbal formula containing corydalis as the lead and given as 600 mg t.i.d. compared to diclofenac 25 mg t.i.d.[48] After three months of treatment, the two were equally effective at reducing symptom severity, but the herbal formula caused significantly lower rates of adverse effects. Again, it cannot be said that corydalis alone accounted for these effects, only that it likely contributed.

Corydalis is also effective applied topically. In a double-blind trial, 130 Chinese patients with cancer-related pain were randomized to apply a formula known as tong kuai xiao, containing corydalis, *Lindera aggregata* (lindera, wū yào) root, *Curcuma longa* (turmeric) rhizome, pyrite, *Sinapis alba* (white mustard, bái jiè zǐ) seed, and synthetic borneol in ointment form or placebo daily for five days.[49] All subjects were also treated with oral morphine. Pain severity and morphine intake were significantly reduced in the treatment group compared to placebo. Other studies are needed on topical corydalis alone, but it is safe and effective clinically in this form.

A range of isoquinoline or protoberberine alkaloids in corydalis are believed to account for its analgesic effects. D-L-tetrahydropalmatine (THP), corydaline, protopine, canadine, and derivatives are some of the most commonly identified alkaloids in corydalis.[50] THP 0.3–0.6% and corydaline 0.2% have both been used succesfully and safely as injectable anesthetics during minor surgeries.[51] Various corydalis alkaloids, as well as crude extracts of its root, have been shown to be dopamine 2 receptor antagonists, which contributes directly to their analgesic activity.[52,53] They also inhibit inflammatory pain by mechanisms unrelated to dopamine receptors. Some compounds in corydalis have also been shown to be κ-opioid agonists, similar to aconite.[54] These are clearly quite distinctive from how standard opioids work.

Corydalis is particulaly suitable both as an adjunct to opioid analgesics and as a tool to help reduce their use and offset their adverse effects. A preliminary clinical trial in 120 Chinese patients with chronic withdrawal symptoms after heroin abstinence found that THP 60 mg b.i.d. for four weeks was more effective than placebo at reducing symptoms and at maintaining abstinence.[55] Unlike opioids, which commonly cause nausea and constipation due to decreased intestinal motility, corydalis stimulates motility.[56]

Several alkaloids in corydalis, most notably THP, have been reported to inhibit the IRK (similar to some alkaloids in aconite, as discussed above), which could theoretically lead to QT interval prolongation and potentially lethal ventricular fibrillation.[57] In three cases of accidental overdose on tetrahydropalmatine, rapid onset of transient bradycardia was reported.[58] Other cases of overdose on this alkaloid have not reported ventricular fibrillation or death.[59] Nevertheless, corydalis and its isolated alkaloids should not be combined with drugs that prolong the QT interval or in patients with known genetic problems with IRK predisposing to excessive QT prolongation until more information is available. Corydalis is not recommended for use during pregnancy.

Corydalis root is generally dried, cooked, and processed with vinegar before being used in Chinese medicine. Some studies suggest both alcohol and vinegar extract the alkaloids more effectively than water, and result in a more effective medicine.[60,61] A dose of 4.5–12 g of corydalis crude cooked root is used for making decoctions. A starting dose of 1 mL of tincture of corydalis cooked root at least three times daily is recommended for adults; this should be increased until efficacy is achieved or either gastrointestinal distress or sedation occurs. For topical use, the simplest preparation is to use any cream base and saturate it with corydalis tincture (usually about 40–50% of a tincture by volume can be added to a cream without changing its consistency), and this should be applied to the problem area twice daily.

Bryony

The roots of two Eurasian native species of bryony are generally used as medicine: *Bryonia alba* (white bryony) and *Bryonia cretica* ssp. *dioica* (Cretan or red bryony). Some sources separate *B. dioica* (red bryony) from *B. cretica*, while others consider them synonymous. The root of both (or all three) of these Cucurbitaceae family plants are used as medicine. Bryony is widely reported in older texts to be useful for pain and inflammation, particularly of serosal membranes such as the pleura, peritoneum, and pericardium.[62] The constituents responsible for these actions and their exact mechanisms remain unknown. Clinically, it does seem to help patients with pleurisy, rheumatoid arthritis, and inflammatory pericarditis.

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However, no controlled trials for such indications could be identified. Preclinical studies support the analgesic and inflammation-modulating effects of various species of bryony.[63,64]

This herb is prescribed in low doses only; it is toxic in high concentrations. A mild overdose will cause gastrointestinal upset, vomiting, or diarrhea. More severe overdoses can cause painful, bloody catharsis, vertigo, agitation, bradycardia, seizures, and ultimately death. The recommended dose of a full-strength (1:2–1:3 weight:volume ratio) tincture is three to five drops; for more dilute preparations (1:5 or 1:10), double this dose should be used. Bryony is contraindicated in pregnancy and lactation. Application of fresh material to the skin may cause blistering.

Capsaicin and Cayenne

Capsaicin (see Fig. 2) is the major spicy compound found in *Capsicum* spp. (cayenne) fruit of the Solanaceae family. Capsaicin, first discovered in 1846, binds to the transient receptor potential vanilloid 1 (TRPV1) that was identified in 1997 directly because of research investigating the mechanism of action of capsaicin.[65] TRPV1 is involved in both sensing heat and pain, as well as integrating information about pain in the central nervous system. It is also activated by the pungent isothiocyanates in Brassicaceae vegetables, as well as garlic and its relatives. Despite the burning sensation that these compounds cause, there is no actual tissue damage or chemical burn that occurs with their application.

Topical capsaicin has been fairly extensively studied for treating a wide range of pain conditions, reported as long ago as 1850.[66] The sheer number of trials for various conditions precludes any detailed review, but studies of various types have found benefit for low back pain,[67] chronic neck pain,[68] osteoarthritis,[69] pain due to Guillain–Barré syndrome,[70] post-amputation stump pain,[71] post-mastectomy pain,[72] postherpetic neuralgia,[73] cancer pain,[74] diabetic neuropathy,[75] and other neuropathic pain (including combined with topical doxepin).[76] Previously, I described the efficacy of intranasal capsaicin for various types of headache.[77] One study found capsaicin was not effective for human immunodeficiency virus–associated peripheral neuropathy in the 0.075% concentration. A newer 8% capsaicin patch has been shown effective for this and many other neuropathy pain conditions in multiple double-blind, randomized trials.[78,79]

Capsaicin was originally believed to work by overstimulating small-diameter pain fibers to the point that they were depleted of the pain neurotransmitter substance P. It is now known that repeated capsaicin application, or use of a high enough concentration, actually destroys sensory nerve endings and autonomic nerve fibers in the skin.[80] These do regenerate, as shown by the fact that with cessation of capsaicin therapy, sensation (and pain) returns. There is some concern that repeated use of the high-dose capsaicin patch might lead to irreversible nerve damage or paradoxical hyperalgesia.

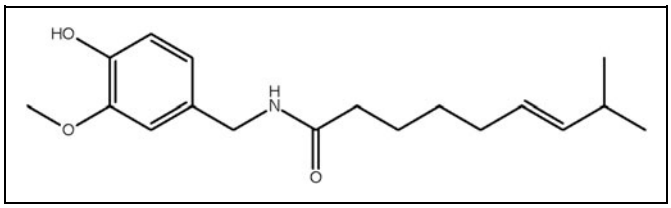

Figure 2. Capsaicin.

Capsaicin is a fat-soluble compound, and thus generally needs to be incorporated into either a cream or ointment form for topical use. Tinctures and plasters are another possible dose form, but tend to be messy and hard to dose. Commercial products typically contain 0.025% or 0.075% capsaicin. The 8% capsaicin patch mentioned before is available only by prescription (Qutenza®, Acorda Therapeutica, Ardsley, NY). Lower-dose forms require application two or three times a day, or pain sensation may return. The 8% patch has to be applied in a physician's office: topical anesthetic is placed, then the patch applied over it for one hour. It is then removed, and cleansing gel is used to move any residual capsaicin. This is applied once every three months. Except in the case of intranasal application of cayenne tincture to treat headaches, avoid touching mucous membranes with capsaicin to cause burning there. Have patients wash their hands with soap after handling capsaicin products to avoid inadvertent transfer to mucous membranes. Capsaicin is safe for use in pregnancy and lactation topically, as long as kept away from areas an infant might touch.

Cannabis

Cannabis sativa (cannabis, marijuana) in the Cannabaceae family has practically taken the world by storm of late. This well-known plant remains illegal in many jurisdictions (including at the federal level in the United States, though it is permitted in some states), but as these restrictions begin to be lifted in more and more locales, research is progressing. The flowering tops of female cannabis plants (the species is dioecious) are used as medicine. A combination of the unusual compounds known as cannabinoids along with terpenoids appear to be responsible for the analgesic activity of cannabis.

The two main cannabinoids in cannabis are present as inactive acids (Δ-9-tetrahydrocannabinol acid and cannabidiol acid) that require heat to decarboxylate to their more familiar active forms (Δ-9-tetrahydrocannabinol or THC and cannabidiol or CBD, respectively). Approximately 250˚F heat for one hour will convert almost all the THC from acid to active form. Research into the mechanism of action of cannabinoid receptors in the body is ongoing, but suggests that they play a role in *Cannabis*'s pain-mediating effects. These compounds act via two major types of receptors: CB1 (found primarily in the central and peripheral nervous systems) and CB2 (found primarily in non-nervous tissues, including on immune cells), which are involved in pain in complex and important ways.[81,82] Various strains of cannabis are differentiated by their terpenoids, not their cannabinoids, as it is these terpenoids that humans can taste and smell (while cannabinoids require

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chromatography or other advanced testing to characterize). All these components are needed for the full activity of cannabis, and likely to offset adverse effects, and so whole-plant extracts are strongly recommended.

Obviously, cannabis has a very long, complex history of use for pain. A meta-analysis of 18 clinical trials for pain due to brachial plexus avulsion, cancer, rheumatoid arthritis, multiple sclerosis, peripheral neuropathies, and fibromyalgia found various cannabis preparations moderately effective, but with significant risk of causing dysphoria, euphoria (arguably a benefit), blurry vision, and confusion.[83] Other studies have shown that it can be helpful for migraine.[84] THC 5 mg by itself was ineffective for postoperative pain in women who had undergone hysterectomy compared to placebo.[85] A separate dose-escalation study showed that 10 mg of cannabis extract (with defined THC and CBD content in a 1:0.5 ratio) after surgery provided effective rescue analgesia after opioid administration had been discontinued.[86]

Administration of cannabis is complicated. First, patients who have no experience of cannabis use must start with a low dose and increase it slowly, self-titrating based on symptomatic response and moderating adverse effects. For acute pain, vaporized cannabis is recommended, which involves heating it to just below the combustion point and inhaling the vapors. This is much safer than smoking (incinerating and inhaling the smoke), but it does require special equipment. This is different from using solvent extracts in electronic cigarette devices in that whole cannabis is used in vaporization. Onset of effects is rapid, within minutes, using inhaled cannabis. A starting dose uses material that is independently tested with a THC:CBD ratio of 1:1, and just a small pinch is vaporized. If tolerated, the amount is slowly increased each dose. For very sensitive or nervous patients (or those that have bad reactions to higher THC material), use CBD:THC 2:1 or higher CBD material. Give at least two weeks to decide if therapy works if the patient tolerates it. High CBD or CBD-only products are of unclear legal status, or are clearly illegal (in the view of the Drug Enforcement Agency in the United States). Total absence of THC almost certainly decreases the efficacy of cannabis and is not recommended.

Oral cannabis is used for chronic effects, but has a slow onset of action (after several hours, but can be maintained a day or more). Again, whole-plant material is recommended, not extracts or other poorly characterized materials. The starting dose orally should provide 2.5 mg each of THC and CBD, and this can be worked up to as high as 10 mg of each per day as tolerated. This should be dosed after vaporizing to sustain the benefits longer, and should be timed such that one to two hours after the oral dose, any opioid or other analgesic medication would be wearing off. With slow titration, there should be no paranoia or "bad trips" below 10 mg of THC. Again, all of this is predicated on following the rules locally as to whether cannabis can be legally recommended.

Cannabis should be avoided in pregnancy and lactation, and is also of concern for use in adolescents and people at risk for mental illness, as high intake has been associated with increased rates of psychosis.[87] Extremely high doses of cannabis are associated with hyperalgesia, and patients who have to take more and more to get the same effects should eventually stop.[88]

Skeletal Muscle Relaxants

A relatively limited number of botanicals relax skeletal muscle and thereby reduce pain related to hypertonicity. This is most obvious with chronic pelvic floor hypertonicity causing chronic pelvic pain syndrome, but also seems to apply to some cases of chronic low back or neck pain. There are four main skeletal muscle relaxant herbs of varying potency that will be reviewed here. These are largely based on clinical and historical use, as there has been very little study of the actual actions and effects of these herbs.

Piper methysticum (kava) root, Piperaceae, is the best attested for this purpose, though much more research is still needed. It likely works in part by increasing GABA activity in the central nervous system and by effects on sodium channels in nerves, and not via opioid receptors.[89–91] It does not act on the same part of the $GABA_A$ receptors as benzodiazepines, and not only does it not cause addiction or daytime sleepiness like those drugs, it actually improves sleep quality in both healthy people and those with anxiety disorders.[92,93] Sleep enhancement is another possible mechanism for pain reduction, and is shared with most herbs mentioned in this article, though this effect has not been emphasized here (reviewed in more depth in a previous article[94]). Traditionally it is regarded as most specific for chronic pelvic pain, very likely because of its ability to reduce pelvic floor hypertonicity in the fraction of pelvic pain patients who have this problem.[95]

Typical doses are 400–800 mg of kava extract in capsules b.i.d.–t.i.d. or 2–3 mL of tincture b.i.d.–t.i.d. Concerns about hepatotoxicity are greatly exaggerated and likely reflect only idiosyncratic liver damage, as opposed to some inherent problem kava has with harming hepatocytes, given the extreme rarity of such reports, despite very widespread kava use.[96] The disagreeable taste and fact that it always is coming from very far away (as kava is native to and grows only on the islands of Oceania) are the major clinical and ecological problems with this herb.

Pedicularis bracteosa (bracted lousewort) aerial parts, in the Orobanchaceae family, is a North American solution to the kava problems discussed here. This practically unresearched plant is nevertheless, based on traditional and clinical experience, very similar to kava's actions with a much superior flavor and coming from the Cascade, Sierra Nevada, and Rocky Mountains.[91] The dose is the same (though capsules are not available; tincture must be used). It can be taken as a rather delicious tea, but this tends to be diuretic and so is not recommended in patients who already have urinary frequency (such as many pelvic pain patients). *P. racemosa* (sickletop lousewort) and *P. groenlandica* (elephanthead) are two interchangeable species. Both kava and louseworts are safe for short-term use in pregnancy and lactation in the author's experience.

Stachys officinalis and *S. betonica* (wood betony) aerial parts from the Lamiaceae family and native to Europe are two other

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skeletal muscle relaxants. They have also not been assessed scientifically for this property, it has just been noted clinically that it helps. The potency of wood betony is significantly milder than that of kava or any species of *Pedicularis*. Therefore a significantly higher dose is needed, generally 3–5 mL of tincture three or more times a day. Wood betony is very safe, including in pregnancy and lactation, based on historical use and the author's experience.

Lobelia inflata (lobelia) flowering tops in fruit from the Campanulaceae family is a skeletal muscle relaxing herb with a range of other interesting properties. Unfortunately, the dose needed to achieve skeletal muscle relaxation is often very close to the dose that is nauseating or may cause vomiting. Again, it has not been systemically evaluated for these properties; they are what has been noted empirically. A usual starting adult dose of a 1:3 weight:volume fresh-herb tincture is five drops three times a day. If no nausea occurs, it can be increased by one drop per dose until either pain relief is achieved, sedation occurs, or nausea/vomiting is induced. Lobelia is not recommended for use in pregnancy or lactation until more information is available about its safety.

Conclusion

It is often stated that new options for pain need to be found to address the current epidemic of opioid overprescribing and resultant addiction and overdose. The reality is that the many existing options need to be exploited and not ignored almost completely by conventional practitioners, and need to be used more widely and more boldly by natural medicine practitioners. This article has addressed just a relatively small handful of potent (and some milder) analgesic herbs that could very much play a role in helping pain patients and reducing or eliminating opioid use by many of them. Research on these herbs should be made a top priority at the National Institute of Complementary and Integrative Health and other government and private funding agencies.

Many of the herbs discussed in this article can have significant adverse effects if used improperly, unlike many other herbs. Therefore, it is strongly recommended that anyone considering using these herbs first consult with a practitioner trained in their use for additional guidance before implementing them. At the very least, multiple sources of information besides just this article should be used to guide safe prescribing. However, these sources should be from people who have actually used the herbs and not just theoretical, for these tend to recommend excessively low doses, sacrificing efficacy in the name of safety. With that being said, they are very useful and worth the effort to improve the clinical approach to patients with chronic and acute pain. ■

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