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File: ■ Neuropathy
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RE: Review of Herbal Medicines for Neuropathic Pain

Forouzanfar F, Hosseinzadeh H. Medicinal herbs in the treatment of neuropathic pain: a review. *Iran J Basic Med Sci*. April 2018; 21(4):347-358. doi: 10.22038/IJBMS.2018.24026.6021.

Neuropathic pain is a common, difficult to treat cause of chronic suffering. Treatment is complicated by the fact that injuries and diseases of the somatosensory nerves causing neuropathic pain are so varied, and cause symptoms via so many mechanisms. The etiologies of neuropathic pain include "metabolic disease [notably, diabetes], viral, trauma, severe ischemic insults, and autoimmune diseases" as well as chemotherapy. Many of these injuries and diseases cause peripheral sensitization - i.e., oversensitivity of sensory nerves. Chronic pain can also be a result or cause of changes in the nociceptive neurons of the central nervous system (CNS), and can then be affected by agents that affect neuroplasticity. Existing pharmaceutical treatments are inadequate for or not tolerated by many sufferers.

Herbal medicine has been used to treat chronic pain in healing traditions around the world. The authors of this review searched Google Scholar, Medline, and Scopus search engines, using the search terms "neuropathic pain," "medicinal plants," "phytotherapy," and "natural products," to identify current research on the use of botanicals for neuropathy. Beyond these identifiers, the authors do not explain the inclusion or exclusion criteria they used to select the 18 medicinal plants, six isolated herbal constituents, and one herbal combination formula discussed in this review. In their summary of the medicinal agents, the reviewers explore the mechanisms they may affect, primarily focusing on in vivo animal model evidence.

This review contains two tables. Table 1 is entitled "Herbal medicines and their constituents tested for neuropathic pain in human studies." It lists substances, the neuropathic disorders they have been tested for, study type, results, and references. Table 2, entitled "Mechanisms of actions of herbal medicines against neuropathic pain in animal models," lists substances tested, animal models used, mechanisms of action, and references. Each of the substances in the two tables is elucidated further in the text.

Two studies described in this review give evidence for single whole herbs in human subjects. Colocynth (*Citrullus colocynthis,* Cucurbitaceae) fruit, an analgesic in Tunisian folk medicine, was found in a three-month long, double-blind, randomized, placebo-controlled, clinical trial to diminish pain caused by diabetic polyneuropathy. Oleaster (*Elaeagnus angustifolia*, Elaeagnaceae) fruit extract, used in Iranian traditional medicine against the pain of rheumatoid arthritis, was found in a randomized, controlled trial to be as effective as ibuprofen in reducing pain from osteoarthritis. [Note: Osteoarthritis pain is not usually classified as neuropathic, and a fair number of botanicals have reduced arthritis pain in human trials that are not mentioned here, so the rationale for including this trial is not explained.]

In vitro and in vivo animal models confirmed traditional use, clarifying pathways and specificity in calamus (*Acorus calamus,* Acoraceae), tarragon (*Artemisia dracunculus,* Asteraceae), flame-of-the-forest (*Butea monosperma,* Fabaceae), colocynth, turmeric (*Curcuma longa*, Zingiberaceae), saffron (*Crocus sativus*, Iridaceae), oleaster, ginkgo (*Ginkgo biloba*, Ginkgoaceae), kratom (*Mitragyna speciosa*, Rubiaceae), bitter melon (*Momordica charantia*, Cucurbitaceae), nigella (*Nigella sativa*, Ranunculaceae), holy basil (*Ocimum tenuiflorum* syn. *O. sanctum*, Lamiaceae), phyllanthus (*Phyllanthus amarus*, Phyllanthaceae), sucupira-branca (*Pterodon emarginatus* syn. *P. pubescens*, Fabaceae), Indian madder (*Rubia cordifolia*, Rubiaceae), and sage (*Salvia officinalis*, Lamiaceae). Parts used in cited studies are not specified.

Of the substances listed in this review, the one with the most evidence for its use as an analgesic medication is Δ9-tetrahydrocannabinol/cannabidiol (THC/CBD). Derived from cannabis (*Cannabis sativa*, Cannabaceae), THC/CBD has been shown to be effective in humans for a wide variety of neuropathic conditions. It is prescribed in Canada as an adjuvant medication for neuropathic pain in multiple sclerosis (MS). For MS and other CNS-derived pain, it has been shown to have minimal adverse effects and/or tolerance when taken for two years. It has also been found to be effective for peripheral neuropathic pain secondary to diabetes, cancer-related pain, and HIV-associated distal sensory predominant polyneuropathy.

Goshajinkigan is a traditional herbal formula in Kampo, Japanese traditional medicine. It is currently commercially available and prescribed in Japan as goshajinkigan TJ-107 (powdered water extracts of rehmannia [*Rehmannia* spp., Orobanchaceae] root, achyranthes [*Achyranthes* spp., Amaranthaceae] root, dogwood [*Cornus* spp., Cornaceae] fruit, yam [*Dioscorea* spp., Dioscoreaceae] rhizome, plantain [*Plantago* spp., Plantaginaceae] seed, water plantain [*Alisma* spp., Alismataceae] rhizome, poria [*Wolfiporia cocos*, Polyporaceae] sclerotium, tree peony [*Paeonia suffruticosa*, Paeoniaceae] bark, cinnamon [*Cinnamomum* spp., Lauraceae] bark, and processed aconite [*Aconitum* spp., Ranunculaceae] root, with magnesium stearate, lactose, and fructose fatty esters). It is commonly prescribed for diabetic neuropathy, though the only cited clinical trial was an open-label trial reporting benefit for a variety of complications of diabetes. A recent controlled trial demonstrated its effectiveness for pain from peripheral neurotoxicity due to oxaliplatin therapy for colorectal cancer.

Lappaconitine derived from aconite and DA-9801 derived from yam rhizome, both components of the goshajinkigan formula, have been shown to be effective in animals as monotherapies as well. Lappaconitine has been shown in animal models to attenuate pain signaling at the dorsal root ganglion, where the first-order neurons of pain sensing are located. DA-9801 has been demonstrated in animal models to improve damage

caused by diabetic neuropathy, increasing plasma nerve growth factor (NGF) levels and increasing nerve conduction velocity as well as protecting against nerve injury.

Other promising botanically-derived analgesic medicines discussed in this review are incarvillateine from incarvillea (hardy gloxinia; *Incarvillea sinensis*, Bignoniaceae), koumine from heartbreak grass (gou wen; *Gelsemium elegans*, Gelsemiaceae), naringin from grapefruit (*Citrus* × *paradisi*, Rutaceae) and related species, and quercetin, a phenolic compound found in many plants. While all have shown good results in animal models and have traditional use supporting them, these substances need more clinical research.

The authors note that herbally-derived therapies for neuropathic pain appear to be effective mainly due to their "antioxidant, anti-inflammatory, anti-apoptotic, neuroprotective and calcium inhibitory actions."

The authors make no statement regarding conflicts of interest.

–*Anne Louise Merrill*

Referenced article can be accessed at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5960749/.