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Review Article

Evidence Based Prescribing of Herbal Medicines for Medical Curricula

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Abstract

Despite considerable evidence for the efficacy of a growing number of herbal medicines, that evidence is rarely included in medical school curricula. This article provides a survey of plant-derived prescriptions supported by systematic reviews of controlled and randomized clinical outcome studies, also highlighting established biochemical mechanisms of action and known risks. Herbal medicines are presented according to standard drug classes used by the United States Pharmacopeia in order to promote inclusion in pharmacology curricula for medical students, who need an introduction to those plant medications available to patients and included in electronic prescribing formularies.

Introduction

Over the past twenty years evidence has mounted that some herbal medicines are as effective as pharmaceutical prescriptions. A surprising number of systematic reviews have supported longstanding empirical usage, biochemical analyses of plant constituents, and controlled studies of effectiveness. As evidence from these meta-analyses has grown, plant medicines have increasingly been included in electronic prescribing applications such as Medscape and epocrates. This expansion of medical pharmacology to include herbs has not been integrated into physician training.

In the most recent survey of complementary and alternative medicine (CAM) teaching in U.S. medical curricula, less than five percent of M.D. schools had a required course, and only 13.4% of the mostly elective courses included herbal medicine [1]. Percentages were higher in an earlier study of osteopathic medical schools with 64% of responding schools having a required course, but only 12% of instructors used an evidence-based approach to teaching CAM topics including botanicals and herbs [2].

Plant medicines with established effectiveness span the various drug classifications of the United States Pharmocopeia. This review provides a survey of herbal analgesics/anti-inflammatories, blood glucose regulators, cardiovascular agents, gastrointestinal agents, hormonal agents, immunological agents/antimicrobials, and sedative-hypnotics. Since these diverse actions cross medical specialties, the focus of this article will be on herbs suitable for inclusion in medical school pharmacology curricula.

Analgesics and Anti-inflammatories

Cayenne peppers (*Capsicum annuum*) are a colorful and spicy ingredient for many a cuisine, but they're also a significant addition to the analgesic formulary. Originally marketed as Zostrix cream for post-herpetic pain, an extract of cayenne applied topically is supported by systematic reviews of randomized controlled studies for neuralgia [3] and low back pain [4]. The most active phytochemical present in cayenne is believed to be capsaicin, a vanillylamide that inhibits the **neuropeptide substance P,** thereby blocking pain sensation [5]. Capsicum is also high in the antioxidant

vitamins A, C, and E, contributing to an anti-inflammatory effect. Used as a cream or transdermal patch, patients should be warned to avoid rubbing it in, contact with mucous membranes, or heat over the applied area, all of which can cause hyperemia and dysesthesia.

Feverfew (*Tanacetum parthenium*) is efficacious for prevention of migraine headache and with no major safety issues [6,7]. In one study cited in these reviews, there was a three-fold increase ($P < .02$) in headache frequency for feverfew users who switched to placebo [8]. The mechanism of action is multifactorial with prostaglandin inhibition, smooth muscle relaxation, and platelet granule blockage from sesqueterpine lactones, primarily parthenolide, contributing to effectiveness [9]. Feverfew is in the Asteraceae family and may initiate a hypersensitivity reaction for those allergic to other asters like ragweed and daisies.

Roses are a pleasant surprise in any circumstance, and their efficacy for osteoarthritis is no different. A recent meta-analysis of fifteen randomized controlled studies concluded that dried hips of the European wild rose (Rosa canina) had moderate quality evidence for improvements in pain and stiffness and low quality evidence for safety for patients with degenerative joint disease [10]. A review of the studies on rose hip pharmacological properties identified compounds with potent antioxidant and anti-inflammatory actions, including vitamin C, carotenoids, phenolics, and terpenoids [11]. This correlation between studies on outcome and mechanism along with minimal risks strongly supports the prescription of rose hips for osteoarthritis.

Turmeric (Curcuma longa) is even more widely used for osteoarthritis relief, and with good reason. Of the eight studies that met the selection criteria in a systematic review of turmeric for osteoarthritis, three reported a mean reduction of -2.04 on the pain visual analogue score compared to placebo [12]. Four additional studies showed a mean decrease of -15.36 on the Western Ontario and McMaster Universities Osteoarthritis Index. A separate meta-analysis of pharmacologic properties of turmeric identified decreases in interleukin-2, C-reactive protein, and malondialdehyde (MDA) concentration, biomarkers of oxidative stress and inflammation [13]. Dietary use of this Indian spice can be supplemented by a prescription of 500mg capsules four times a day. Turmeric capsules are often formulated with a small amount of black pepper, which aids in turmeric absorption and prevents side effects of bloating and loose yellow stool.

Blood Glucose Regulators

Holy basil (*Ocimum tenuiflorum, O.gratissimus*), also known as tulsi, is a revered medicinal plant in Ayurvedic medicine as an adaptogen affecting most organ systems. A systematic review of twenty-four randomized controlled studies supports tulsi for lowering blood sugar, blood pressure, and serum lipids and without adverse effects in patients with type 2 diabetes mellitus [14]. While the form and dosage used in these studies was diverse, several used 250-300mg dried leaf capsules daily, a dose easily formulated and standardized in western medicine.

Nettle (*Urtica species*) has a long history of use for improving digestion, circulation, and elimination. These observed metabolic effects are supported by a recent systematic review of eight randomized controlled studies indicating effectiveness at lowering fasting blood sugar in patients with type 2 diabetes mellitus [15]. This fast growing and ubiquitous plant is also nutritionally rich in vitamins, minerals, and amino acids, making it a potentially valuable food and feed source [16]. As human food, only the new leaves of a young plant can be eaten fresh. The stinging hairs of mature leaves contain formic acid that must first be neutralized by boiling before palatable consumption.

Cardiovascular Agents

Hawthorn (*Crataegus laevigata*) has been called a medicine chest in a tree because of differing uses of the leaves, berries, bark, and roots. One such application, relief of mild to moderate chronic congestive heart failure, is supported by a systematic review of nine randomized, placebo-controlled studies of dried hawthorn berries that also determined this use was safe with only minimal and mild adverse reactions [17]. This review noted likely mechanisms as antioxidant and hypotensive effects of procyanidins and flavonoids present in hawthorn berries. Like digitalis, hawthorn has positively ionotropic and negatively chronotropic actions, but with a more moderate effect and a much wider therapeutic window.

Horse chestnut (*Aesculus hippicastanum*) has a traditional use for reducing lower extremity swelling that is supported by a systematic review of seventeen controlled studies [18]. An extract of the nut was found to reduce pain and edema in chronic venous insufficiency and with only rare and mild side effects. The most active component is believed to be the saponin escin, a potent vasoconstrictor, but the seed extract also contains esculin, another saponin with antithrombin activity [19]. When prescribing horse chestnut, it's important to specify an extract standardized to 20-22% saponins to avoid potential hepatic and renal toxicity of higher doses.

Gastrointestinal Agents

Fennel (*Foeniculum vulgare*) is a familiar herb from the kitchen and checkout counter of Indian restaurants but is not so well known in the neonatal nursery. A systematic review of three randomized controlled studies indicated fennel is effective for infantile colic, with an average of seventy-two less minutes per day of irritability and crying [20]. Biochemical studies have identified antispasmodic, anxiolytic, and laxative properties that might account for fennel's effectiveness at relieving colic [21]. A cooled tea can be administered by bottle alone or mixed with milk or formula.

Peppermint (*Mentha piperita*) is probably the most widely used herbal medicine, although it isn't usually thought of as a

therapeutic agent. Mint's effects are utilized daily and with good reason in toothpaste, mouthwash, lip balm, tea, gum, candies, and topical analgesics. A meta-analysis of nine controlled studies found that peppermint oil was effective and safe for short term relief of abdominal pain and irritable bowel syndrome [22]. An additional review of two studies on tension headache found a reduction in severity compared to placebo and comparable to acetaminophen [23]. Menthol is believed to be the major active compound that, along with more than eighty other constituents, imparts smooth muscle relaxation, anti-microbial and anti-inflammatory activity, and stress reduction [24].

Hormonal Agents

Chasteberry (*Vitex agnus-castus*) is the fruit of a Mediterranean tree that was traditionally used for a range of female reproductive problems. Beneficial effects for premenstrual syndrome, premenstrual dysphoric disorder, and hyperprolactinemia were characterized as better than placebo and equivalent to prescription medications in a systematic review of twelve randomized controlled studies [25]. A more recent review of in-vitro and in-vivo studies posited that dopaminergic compounds present in vitex contribute to the beneficial effects for these conditions [26]. A dosage range of 20-240mg/d in divided doses is recommended, with lower amounts for premenstrual syndrome and higher for premenstrual dysphoric disorder hyperprolactinemia.

Red clover (*Trifolium pratense*) has a longstanding use for relieving menopausal symptoms that is supported by a systematic review of efficacy (Figure 1). In this meta-analysis of 17 studies, vaginal dryness and atrophy were both significantly improved with red clover compared to control groups [27]. This effectiveness is due at least in part to isoflavones that act as phytoestrogens. This raises a potential contraindication for women at risk for estrogen-sensitive breast cancers, though that risk has evidence of being less for red clover than for other estrogens [28]. Red clover can be prescribed as a capsule or tablet with standardized isoflavones at 40-160mg per day but should be used with caution with coagulation disorders due to coumarin and salicylate constituents.

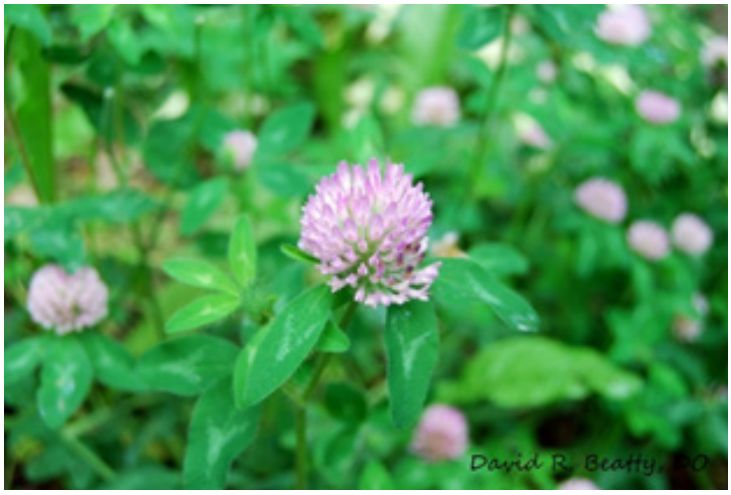

Figure 1: The flowering tops of red clover are high in isoflavones that help menopausal symptoms.

Immunological Agents and Antimicrobials

Elderberry (*Sambucus nigra, S.canadensis*) is an ancient remedy for colds and flu, and a recent systematic review supports this usage [29]. This meta-analysis of 180 patients found a large mean effect size that elderberry syrup reduced upper respiratory symptoms. A review of the pharmacological properties of this herbal extract identified substantial evidence for antiviral effects [30]. Recipes for elderberry syrup abound, but patients making their own should be warned to avoid red elderberries (S.rubra) that have a higher concentration of anthocyanins with potential toxicity (severe nausea and vomiting).

Goldenseal (*Hydrastis canadensis*) is an Appalachian plant that was historically overharvested because of observed effectiveness for gastroenteritis, bronchitis, and skin infections. One of its major constituents, berberine, has in-vitro and in-vivo inhibitory effects on proliferation and reproduction of hepatitis B virus and Helicobacter pylori, among other microorganisms [31]. Now cultivated for medicinal purposes, the dried root of goldenseal can be prescribed for gastroenteritis but should be avoided with pregnancy or lactation and in newborns due to risk of hyperbilirubinemia.

Reishi (*Ganoderma species*) is a shelf fungus often referred to as a medicinal mushroom. It's traditional Chinese use as an adaptogen is supported by a systematic review of five randomized controlled studies that cited low quality evidence that reishi stimulates host immunity in cancer chemotherapy [32]. A review of studies on bioactive components of reishi identified immunomodulatory proteins and polysaccharides [33]. Because it also inhibits platelet aggregation, reishi should be used with caution for patients taking other anticoagulants.

Sedative-Hypnotics

Gotu kola (*Centella asiatica*) is an Indian herb traditionally used for memory loss. A systematic review of five randomized controlled studies identified short-term improvements in mood as measured by increased alertness and decreased anger scores one hour after treatment [34]. These effects are postulated to be due to triterpenoid and glycoside constituents [35]. The findings of the meta-analysis plus minimal toxicity and no addiction potential support a prescription of gotu kola for anxiety with depressed mood.

Lavender (Lavandula angustifolia) essential oil has early evidence of helpfulness for insomnia [36]. In this systematic review, five of the eight studies meeting the inclusion criteria showed either increased deep sleep or reduced wake frequency compared to controls. The form used in these studies was diffused essential oil, making lavender a pleasant and safe option for the treatment of sleeplessness.

Valerian (*Valeriana officinalis*) is a bitter root with a longstanding use for insomnia supported by a meta-analysis of six controlled studies that asked subjects whether or not sleep was improved [37]. The most active ingredients, valerenic acid and valepotriates, have effects on GABA, serotonin, and adenosine receptors in the brain [38]. With the only risk being sedation and no evidence of dependence, valerian is a safe alternative to benzodiazepines for difficulty getting to sleep.

Prescribing Herbal Medicines

Since modern applications of plant medicines have evolved from millenia of traditional use, commercially available preparations are not always well standardized. Herbs are regulated as foods in the U.S. and are available as dried plants, teas, tinctures (*alcohol extractions*), essential oils, syrups, and pills. Of these forms, the latter can be standardized by weight of either the dried herb or the most active component. Capsules consist of the dried plant material in a dissolving gelatin or cellulose container, while tablets have additional contents for binding, compressibility, or solubility. Consumers make the choice of capsule or tablet based on availability, cost, and preference. Practitioners need only specify the dose, route, frequency, and quantity as with all prescriptions. A working knowledge of plant medicine risks and contraindications needs to be complemented by an interaction check between herbs and drugs as can be performed by most electronic health record formularies.

Another challenge to integration of herbal medicines into medical curricula is that some traditional systems of practice rely on multi-herb formulas. For example, temperature and moisture preferences for the patient, illness, or plant contribute to formulation in Chinese and Indian medicine. These observations about plant synergy, while sometimes appearing as unnecessary polypharmacy, present an opportunity for utilizing experimental design to test empirical hypotheses. Western prescribers need only assure that an herbal formula contains an effective dose of the desired plant medicine and that herb-herb interactions don't interfere with that effectiveness or introduce unnecessary risk.

The herbal medications described above and supported by systematic reviews of randomized controlled clinical outcome studies are summarized in Table 1. These and other emerging evidence-based plant medicines can and should be added to the appropriate section of pharmacology curricula at medical schools. Failure to do so will result in a generation of physicians with incomplete knowledge of the medications available to their patients and included in their prescribing formularies.

Table 1: Herbal medicines with evidence-based prescribing recommendations.

Herb	Use	Dose*	Risk
Cayenne	low back pain, neuralgia	topical cream 0.025-0.1% TID-QID transdermal patch BID with 1-hr between	localized dysesthesia, hyperemia
Chasteberry	premenstrual syndrome, premenstrual dysphoric disorder, hyperprolactinemia	10-40mg PO BID-TID 40-80mg PO BID-TID	estrogen sensitivity
Elderberry	cold, flu	syrup 15ml PO QID	nausea, vomiting
Fennel	colic	diluted tea 5oz PO TID	antibiotic interactions
Feverfew	migraine prophylaxis or treatment	50-100 mg PO QD	hypersensitivity, pregnancy, lactation
Goldenseal	gastroenteritis, bronchitis	0.5-1g PO TID	pregnancy, lactation, newborns
Gotu kola	anxiety with depressed mood	600mg PO TID	sedation
Hawthorne	congestive heart failure	300-1000mg PO TID	cardiovascular medications
Holy basil	type 2 diabetes mellitus	250-300mg PO QD (Jamshidi 2017)	none known
Horse chestnut	chronic venous insufficiency	125-250mg PO BID-TID standardized to 20-22% saponins	hepatic or renal impairment, inflammatory bowel disease
Lavender	insomnia	essential oil	none known
Nettle	type 2 diabetes mellitus	770mg PO BID	contraindicated with cardiac or renal impairment

Peppermint	irritable bowel syndrome, tension headache	0.2-0.4ml PO TID essential oil	achlorhydria, bronchospasm
Red clover	menopausal symptoms	40-160mg PO QD	estrogen sensitivity, anticoagulants
Reishi	immune stimulation	1-1.5 g/d PO	anticoagulants
Rose hips	osteoarthritis	500-750mg PO QD with food	tetracycline interaction
Turmeric	osteoarthritis	500mg PO QID	diarrhea prevented by black pepper
Valerian	insomnia	400-600mg PO HS	sedation

*Dose recommendations in capsule/tablet form from Medscape 2020[39] unless otherwise specified.

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Conflict of Interest

None.

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