Herbal Medicine in Canada
2008 Update

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This program has been approved for **2.5 CEUs**
by the Canadian Council on
Continuing Education in Pharmacy
CCCEP #829-1208UD
This lesson is valid until February 3, 2012

This lesson has been sponsored with
an unrestricted educational grant from

ratiopharm

Lesson description

This program is an update to the Herbal Medicine in Canada Part II continuing education lesson presented in 2000. Seven different herbal medicines are described and seven case studies are included. The herbal medicines that will be covered are:

- ginger
- milk thistle
- valerian
- German chamomile
- evening primrose
- wild yam
- licorice

This lesson includes detailed explanations of homeopathy, nutritional supplementation, and naturopathic medicine. This will allow community pharmacists to offer their clients appropriate advice regarding these different modalities. In addition, useful botanical medicine resources are identified and described and participants are provided with tips for critically evaluating both print and electronic information sources.

Learning objectives

Upon successful completion of this lesson, participants will be able to:

- distinguish the practice of herbal medicine from those of homeopathy and nutritional supplementation
- overcome challenges in obtaining information about herbal medicine
- facilitate critical evaluation of commercial claims
- understand the key features of current natural product legislation and learn the proposed regulatory changes
- advise a patient on seven common herbal products: ginger, milk thistle, valerian, German chamomile, evening primrose, wild yam, and licorice
- explain to a patient what to expect from these herbal products with regards to both intended action and adverse effects
- advise against the use of herbal products where contraindications exist

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1. Introduction

Herbal medicine (also known as botanical medicine) is considered by most to be a form of complementary/alternative medicine (CAM). It is currently estimated that approximately 54% of Canadians have used some form of CAM and that more than $5 billion is spent each year on CAM therapies and products.[1] According to A.C. Nielsen Canada, total sales of the top 6 herbal products in Canadian drug stores (echinacea, garlic, ginseng, ginkgo, evening primrose oil, St. John's wort) in 2001 were almost $57 million (*Pharmacy Post*, April 2002). A recent survey of a random sample of breast cancer survivors in Ontario found that almost 25% of those surveyed reported using herbal therapy.[2]

In addition, use of botanical medicine appears to be increasing dramatically, even faster than other forms of CAM. In general, use of CAM appears to be more common among women (who have also been reported to use more conventional health care services) and among individuals who have been diagnosed with a chronic disease. A variety of studies have found a correlation between the use of CAM and higher-than-average incomes and levels of education. Pharmacists are increasingly becoming primary sources of information about CAM generally and herbal medicine specifically, in part because of their accessibility to patients.

The motivation for patients to use CAM is complex. In general, it is important that patients seeking the use of CAM should assess the credibility as well as weigh the potential risks and benefits. Pharmacists may adopt a systematic approach developed to advise these patients on natural health products[3] and CAM in general.[4] This will be discussed in more details in a later section.

One important aspect of counselling patients interested in CAM is helping them distinguish herbal medicine from other CAM therapies such as homeopathy, naturopathic medicine, and the use of nutritional supplements. While some general advice may apply to all of these modalities, other safety and efficacy issues are specific to botanical medicine.

2. What exactly is herbal medicine?

Herbal medicine is the use of a plant, alga, or fungus or their extracts or isolates for a therapeutic reason. This could be in the prevention, the treatment, or the amelioration of a disease state or symptom. Other terms used to describe herbal medicine include botanical medicine, phytomedicine, phytotherapy, and herbology. Pharmacognosy is the discipline covering all areas of medicinal plant research.

There are many different approaches to the use of plants as medicines. For example, traditional Chinese doctors and practitioners of Ayurvedic (i.e., East Indian) medicine would prescribe different herbs than Western herbalists. This is based on different health beliefs or paradigms regarding the mechanism of disease or origin of the patient's symptoms.

In pharmacies today, products used both by Eastern and Western practitioners can be found. This can present the pharmacist with many challenges, including inconsistent dosage regimens and unfamiliar dosage forms.

3. Special dosage forms

Herbal medicines may not always come in typical tablets, capsules, or suspensions familiar to pharmacists. While manufacturers have found methods to incorporate traditional dosage forms into preparations resembling modern medicines, it is important to understand the intended dosage form so that the proper dose can be established. Some of the more popular dosage forms of herbal medicines are summarized below.

3.1 Herbal teas

Herbal teas can be prepared as either a decoction or an infusion. Decoctions are reserved for bulky or fibrous plant materials like roots or barks. A product like licorice is prepared as decoction by directly boiling the plant matter in water. Infusions are used for delicate plant materials such as leaves or flowers (e.g., peppermint, lemon).

3.2 Tinctures

A tincture is prepared by macerating or percolating plant material in a mixture of water and alcohol. Changing the ratio of water to alcohol can lead to more selective extraction of certain compounds based on their relative solubility in alcohol and water. Tinctures are popular with practitioners who use raw plant ingredients, since they allow for the formulation of combination products specific to an individual patient's needs. However, tinctures are not always appropriate formulations, as the extraction process may leave important ingredients behind. For example, while tablets made with powdered feverfew leaf are clinically proven to reduce the incidence and severity of migraine headaches, a tincture proved to be ineffective.[5]

3.3 Standardized extracts

A standardized extract is a commercial product in which a specific concentration or level of activity of a particular constituent or group of constituents is guaranteed. While all of the original constituents may still be present, they are often not in the same proportions found in the whole herb. Since herbal products have more than one active ingredient, it is impossible to standardize a product to a single active agent that is solely responsible for the herb's medicinal properties. More often, a "marker" constituent is chosen for standardization. The constituent chosen may be a biologically active agent contributing to the herb's effects, such as hyperforin in St. John's wort, or it may be an inactive agent characteristic of the correct species or variety of the herb, such as echinacoside in echinacea. The aim of standardizing to a measurable single constituent is to ensure product identity, quality, and reproducibility.

4. Distinguishing between herbal medicines and other forms of complementary and alternative medicine

Pharmacists often need to teach patients how to distinguish between the different therapies included under the umbrella term CAM. It is important to realize that the term "complementary/alternative medicine" is primarily a political rather than a practical identification.[6] As more scientific evidence becomes available to support the safety and efficacy of some agents and therapies previously identified as complementary/alternative (e.g., St. John's wort in mild-to-moderate depression) and the number of CAM courses offered in North American medical and pharmacy schools increases, the definition of CAM is becoming more difficult. Despite the lack of precision in the definitions of CAM, most people (especially Western health care practitioners) find it easy to distinguish therapies considered to be CAM from therapies used in conventional medicine. It is more challenging to distinguish between therapies included within the practice of CAM. To the community pharmacist, one of the most confusing is distinguishing herbal medicine from homeopathic medicine, nutritional supplements, and naturopathic medicine.

4.1 Homeopathy

The practice of homeopathy is essentially based on the philosophy of *similia similibus curentur*, or "like cures like."[7] Simply put, a substance that in a high dose causes a particular physiological action (e.g., bee venom) can be used in smaller doses to treat a condition with similar presenting symptoms (e.g., inflammation, skin redness, throbbing pain).[8] Homeopathic medicines (or remedies) are made by systematically diluting the raw (base) material in a series of either 1 in 10 (decimal or X, D, DH), 1 in 100 (centesimal or C, CH, K), or 1 in 1000 (millesimal or M) dilutions. For example, a product that is labelled as 6X, 6D or 6DH has undergone a 1 in 10 dilution six times. Similarly, a product labelled as 2C, 2CH or 2K has undergone a 1 in 100 dilution twice. A major controversy is that remedies made by 12 centesimal dilutions (12CH or 10^{-24}) or greater will not contain any of the original raw material because they have been diluted beyond Avogadro's number (6.02×10^{23}, the number of molecules in a mole).[8] This fact negates the comparison made by many between immunization and high-dilution homeopathic preparations.

Most commercial homeopathic remedies are made according to the established manufacturing procedures from the French, German, or US homeopathic pharmacopœias. Hence, the quality and reproducibility of homeopathic products is excellent, which is not always the case with botanical preparations.[8] While homeopathic remedies were originally given as single remedies (classical homeopathy), current commercially available homeopathic self-medication products often contain more than one homeopathic medicine and may be combined with herbal medicines.[8]

The exact mechanism of action of homeopathy is unclear. Many homeopathic practitioners believe that the remedies do not act on the disease process but rather encourage the body's own defensive healing ability. This is commonly referred to as the "vital force."[7] According to this philosophy, patients' symptoms are considered to be a result of specific "imbalances" in this vital force. The lack of a plausible explanation is a major stumbling block to wide acceptance of homeopathy, especially among conventional health care practitioners in Western countries. However, it is important to note that no satisfactory biomedical model has been developed to explain clinically meaningful responses to some conventional medicines. Most recent research has focused on evaluating the effectiveness of homeopathy. While a number of clinical trials have shown that homeopathic medicine is superior to placebo,[7,9–13] the quality of trials and conclusions drawn have often been questioned.[7,14] A meta-analysis of 89 trials in 1997

reported that homeopathy, as a discipline, was probably superior to placebo.[15] However, this effect could partly be due to the larger benefits reported from trials with poorer study design.[16] Also, the relevance of this study has been questioned, since it is comparable to reviewing all conventional drug trials and claiming that drugs work better than placebos.[17] Indeed, a more recent meta-analysis comparing 110 homeopathy trials and 110 matched conventional-medicine trials (all placebo-controlled) reported that the clinical effects of homeopathy are likely placebo effects after biases in the trials were accounted for.[18]

Adverse effects directly attributed to homeopathic medicines have been very rare and were associated with adulterated products.[19] In addition, allergic reactions to homeopathic products of low dilutions (i.e., that still contain small amounts of the original base product) have been noted.[7] Finally, a review of adverse effects attributed to CAM conducted in the United Kingdom identified a number of cases of indirect problems resulting from poor advice given by homeopathic practitioners.[20]

4.2 Nutritional supplements

The use of nutritional supplements constitutes a large part of complementary/alternative medicine in North America. While no universally accepted definition of nutritional supplements exists, they are generally considered to include agents such as vitamins, minerals, amino acids, essential fatty acids, digestive enzymes, and derivatives of these substances.[6] Examples include vitamin C, vitamin E, zinc, magnesium, glucosamine salts, coenzyme Q10, and bromelain. A term becoming more popular among CAM practitioners to describe this therapy is *orthomolecular medicine*, which can be defined as the use of nutritional substances given in high pharmacologic doses to alter specific biochemical functions in the body.[6] While the basic mechanisms of action of these various agents are generally more widely accepted by conventional health care practitioners than those of homeopathic medicine, their safety and efficacy is still the subject of much debate. The quality of evidence supporting the use of these agents varies greatly between different supplements.[21] Generally, these supplements lend themselves well to conventional clinical evaluation methods such as randomized controlled trials, although relatively few such trials have been conducted to date.

Some products marketed as nutritional supplements are derived from plant sources and therefore are often confused with herbal medicine. Examples include the proanthocyanidin-rich extracts such as pycnogenol and grape-seed extract; flavonoids such as quercetin and rutin; and digestive enzymes such as bromelain (from pineapple) and papain (from papaya). In general, while whole plant products are not considered to be nutritional supplements, there are some exceptions such as herbs widely used in cooking (i.e., garlic and ginger).

4.3 Naturopathic medicine

Naturopathic medicine (or naturopathy) is a discipline rather than a specific kind of supplement. Naturopathic medicine is an eclectic practice regulated in 4 provinces (Ontario, British Columbia, Saskatchewan, and Manitoba). Naturopathic practitioners are generalists who use a number of CAM therapies, including herbal medicine. In fact, naturopathic practitioners are the only clinicians that are required to pass licensing exams in this discipline. Many CAM products are referred to as naturopathic products, which provides little or no indication of the type of product being described. This term is not specific to botanical medicine and should not be used due to the confusion it creates. More information about naturopathic medicine in Canada can be obtained from the Canadian College of Naturopathic Medicine (CCNM) website, www.ccnm.edu, or from the Canadian Association of Naturopathic Doctors (CAND) website, www.cand.ca.

5. Regulation of herbal medicine in Canada[22]

The Natural Heath Products Directorate (NHPD) has recently been formed as part of the Health Products and Food branch of Health Canada to regulate natural health products for sale in Canada. Under the Natural Health Products Regulations, which came into effect on January 1, 2004, natural health products are defined as:

- vitamins and minerals
- herbal remedies
- homeopathic medicines
- traditional medicines such as traditional Chinese medicines and Ayurvedic medicines
- probiotics
- other products such as amino acids and essential fatty acids

The natural health products can be manufactured, sold, or represented like a regular drug for use in:

- the diagnosis, treatment, mitigation, or prevention of a disease, disorder, or abnormal physical

state or its symptoms in humans (*therapeutic claims*)
- restoring or correcting organic functions in humans (*risk reduction claims*)

However, they can also be made and sold for use in modifying organic functions in humans, such as modifying those functions in a manner that maintains or promotes health (structure-function claims).

Natural health products must be safe for consideration as over-the-counter products, be available for self-care and self-selection, and not require a prescription to be sold. Products requiring a prescription will continue to be regulated under the Food and Drug Regulations.

The Natural Health Products Regulations provide a staged approach over a 6-year period beginning in January 2004, with a 3-phase transition over the following schedule:

- Beginning on January 1, 2004, all natural health products with a product licensed as a Drug Identification Number (DIN) were transferred to have an NPN or a DIN-HM (homeopathic medicine); all new products that fit the natural health products definition had to comply with the *Natural Health Products Regulations* immediately and obtain a product licence before being sold in Canada.
- Beginning on January 1, 2006, all manufacturers, importers, packagers, and labellers were required to employ good manufacturing practices (GMPs) and have site licences.
- All natural health products must comply with all the Regulations by January 1, 2010.

During this transition period, Health Canada is prioritizing on a risk-mitigation basis and applying focused compliance efforts against categories of natural health products without product licences.

5.1 Evidence to support claims

The Natural Health Products Regulations require that applicants for a natural product licence must submit an overall analysis of all the relevant evidence relating to the proposed claim for the natural health product and provide appropriate references. A wide range of evidence can be considered and can include the following (in descending order of quality [strength]):

- references to scientific evidence (in descending order of strength):
  - systematic reviews and meta-analyses of randomized controlled clinical trials
  - randomized controlled clinical trials
  - studies without randomization and/or control groups[235]
  - descriptive and observational studies (e.g., correlational studies, cohort studies, case-control studies)
  - peer-reviewed published articles, reputable regulatory authority reports, previous marketing experience, expert reports
- references to traditional use:
  - one pharmacopœial reference (e.g., *Pharmacopœia of the People's Republic of China* or the *State Drug Standard*, or the *Ayurvedic Pharmacopœia of India*),[235] or
  - at least two independent references to traditional use, or
  - one independent reference and an expert opinion report

When claims of traditional use are made for a natural health product, lower levels of evidence may be used to support the claim. However, the NDPD requires that the natural health product have at least 50 consecutive years of traditional use. Traditional use claims can be supported by pharmacopœial evidence relevant to the origin of the traditional use. For example, a product used in traditional Chinese medicine may use either the *Pharmacopœia of the People's Republic of China* or the *State Drug Standard* as a reference. To use a pharmacopœial reference, the natural health product must be identical to the pharmacopœial reference for the following items: medicinal ingredients, quantity of crude material equivalent, use or purpose, dose, route of administration, duration of use, dosage form, directions, risk information, and preparation. Traditional use products that do not meet the pharmacopœia requirements must provide at least two references that do not reference the same source or each other. If only one reference exists, or if several references refer back to a single source, an expert opinion report based on at least 50 years' experience could serve as the second reference.[235]

5.2 Quality control

One of the aims of the Natural Health Products Regulations is to address the problem of poor quality control. This involves requiring all manufacturers of natural health products to obtain site licences and to follow the GMPs beginning January 1, 2006. This is a crucial element of the Natural Health Products Regulations, since previously many consumers assumed that just because herbal products were bottled in packaging like a pharmaceutical there must have been standards in place to assure quality. Unfortunately, there was no guarantee that a bottle contained the product it claimed to contain.

Worse yet, there was no assurance that the product was manufactured according to safe, acceptable standards. Poor quality control could lead to inaccurate dosing or to contamination. Contaminants could make their way into natural product packages as microbes from poor plant processing, as misidentified plants, and even as pharmaceutical products either inadvertently contaminating products made using the same equipment as pharmaceuticals or from purposeful addition (adulteration) to substantiate claims of product efficacy. Indeed, contamination from pesticides and herbicides has been linked with cases of natural product toxicity. This may be especially true for imported products or products made from imported raw plant material.

One group of investigators published a study in 1994 examining 50 ginseng products sold in 11 countries at pharmacies or reputable stores for natural remedies. Each preparation was analyzed blind and in triplicate. In 44 of these preparations, the concentration of ginsenosides ranged from 1.9% to 9.0% (recommendations suggest at least 7.0% ginsenosides). Five products did not contain any ginsenosides, and one contained ephedrine instead.[23]

In a well-publicized example in 2002, Health Canada released a warning to avoid 7 herbal products manufactured in the United States, but popular among Canadians, because they contained undeclared prescription drugs including indomethacin, diethylstilbestrol, and alprazolam.[24] There is clearly a need for independent quality control of commercial herbal products. Currently, more than 500 commercial ginseng products sold throughout North America are being evaluated by the American Botanical Council's Ginseng Evaluation Program.[25]

Table 1. Potential mechanisms of adverse results from herbal medicines

Worsen an underlying condition	Interact with drugs	Cause toxicity
E.g., ginger being used as an antiemetic may affect diabetic control by causing hypoglycemia.[46]	E.g., St. John's wort can reduce the plasma level of the active metabolite of irinotecan, a chemotherapy agent.[42]	E.g., PC-Spes, once a popular herbal formulation for prostate health, contained estrogenic and warfarin-like contaminants[24]; kava may cause liver damage.[27]

Table 2. Examples of potential adverse events with herbal products

aristolochic acid[46]	nephrotoxicity and uroepithelial cancers[26]
pyrrolizidine alkaloids	hepatotoxicity and carcinogenicity[26]
kava	hepatoxocitiy[27]
ginkgo	increased risk of bleeding[28–33]

6. Herbal safety

It is a common misconception to believe that natural products should generally be safe. However, such products may potentially pose three major issues (see Table 1).

As with the evidence to support efficacy claims, it is unclear how one may identify authoritative evidence on pre-marketing safety of natural products under the Natural Health Products Regulations. Nevertheless, the need to follow the GMPS can address some of the dangers of the lack of quality control outlined above. Also, safety is often assumed based on the generally low number of reported cases of adverse reactions on natural products. However, "no reported toxicity" does not mean evidence of "no toxicity." Even with conventional drugs, the rate of post-marketing voluntary adverse reaction reporting is inherently low. Prior to the Natural Health Products Regulations, there was no mandated requirement to report adverse reactions if a natural product was marketed as a food. It is therefore noteworthy that documented cases of adverse reactions are reported even when the herbal product is prepared and used correctly. Over time, some herbal remedies have even been banned from sale in Canada and other parts of the world.

Like most drugs, herbal medicines have side effects. Most common are the "nuisance" side effects like nausea or diarrhea.[34] Some herbal products may cause photosensitivity reactions or dermatitis if patients come into contact with the raw plant material. Other side effects are natural extensions of the herb's pharmacologic action—excessive somnolence from herbs used for sleep, for example. While a review of adverse reactions to herbal medicines is beyond the scope of this CE module, it is important for pharmacists to know that it is their responsibility to understand the possible risks of any natural product they sell. These

include some risks which may be theoretical but potentially serious. For example, one may need to discuss the possibility that some phytoestrogens may stimulate estrogen-dependent breast cancer and antagonize tamoxifen therapy.[35–38,236,237]

While the direct adverse effects of natural products may be predicted based on the pharmacodynamics of the herb, the indirect adverse effects cannot. Indirect adverse effects arise from how the herbal product is used rather than from the herbal product itself. Patients who inappropriately use a product or who use a natural product with marginal efficacy for a serious disorder when an alternative proven therapy exists put themselves at risk. These are realities that come with self-medication and the consumer's right to choose.

7. Drug-herb interactions

A drug interaction can be defined as any modification in the action of a drug caused by another exogenous chemical like another drug, herb, or food. Drug-herb interactions may be either pharmacokinetic (related to absorption, distribution, and metabolism) or pharmacodynamic (related to enhanced or diminished activity) in nature (see Table 1 above). While a detailed discussion of drug-herb interactions is not the goal of this CE module, it is important to introduce these concepts with a few examples.

7.1 Pharmacokinetic interactions

Psyllium, flaxseed, and aloe contain large amounts of gums and mucilage that can prevent the absorption of a variety of drugs. Drugs such as lithium may not be properly absorbed when taken with psyllium.[39] Herbs like meadowsweet and willow contain salicylates that can displace drugs that are highly protein bound.

An interaction involving drug distribution is important because it can increase toxicity of protein-bound drugs such as warfarin and carbamazepine. There is a great deal of experimental data to suggest that a variety of herbs can affect the cytochrome p450 enzymes and thus lead to herb-drug interactions with drugs that rely on hepatic metabolism via the p450 enzymes. Herbal medicines that influence the cytochrome p450 system by inhibiting CYP 3A4 include goldenseal, cat's claw, St. John's wort, echinacea, chamomile, and licorice.[40,238] St. John's wort, for example, can interact with cyclosporine, indinavir,[41] warfarin,[239] and gliclazide,[240] as well as irinotecan, a commonly used intravenous cancer chemotherapy agent.[42]

7.2 Pharmacodynamic interactions

Coumadin is one of the best-studied medicines in terms of the potential for drug-herb interactions. Since ginkgo has some anti-platelet properties, the risk of bleeding may be increased when ginkgo is used with coumadin.[43] Although not all experts and studies agree with this increased risk, caution may still be warranted until more controlled studies are conducted.[241,242] The opposite effect occurs with alfalfa, which contains vitamin K—the antidote for coumadin. There are many other possibilities such as combining sedating or stimulating herbs with CNS-sedating medications, herbs that can increase or decrease blood glucose with insulin or oral hypoglycemics, and herbs that affect blood pressure with antihypertensive drugs.

Reports of suspected herb-drug interactions are not made as often as of drug-drug interactions. Until more case reports and controlled studies appear in the literature that can help pharmacists counsel patients about potential risks of herbal medicines, pharmacists will need to understand the pharmacology of natural medicines to try to predict interactions. Furthermore, pharmacists should report any suspicion of herb-drug interactions so that this crucial information can be disseminated. Previously, there were no formal agencies officially collecting this data, although adverse reactions to natural products could be submitted. This now falls under the umbrella of the Natural Health Products Directorate, and official reporting forms are available. It is important that pharmacists report any suspected interactions, since they may be the only health professionals aware that the patients are taking these agents concurrently.

8. Information sources for botanical medicine

Until recently, individuals interested in learning more about botanical medicine have experienced a great deal of difficulty in obtaining quality information. Currently, information about botanical medicine comes from a variety of sources, which Farnsworth argues should all be assessed when making decisions about botanical medicines.[44] Some standard references include the following free access websites:

- National Center for Complementary and Alternative Medicine, National Institutes of Health, USA
  www.nccam.nih.gov

- Integrative Medicine Service at Memorial Sloan-Kettering Cancer Center
  www.mskcc.org/mskcc/html/11570.cfm
- Medline Plus – Herbs and Supplements
  www.nlm.nih.gov/medlineplus/druginformation.html
- MayoClinic Drugs & Supplements
  www.mayoclinic.com/health/drug-information/DrugHerbIndex
- M. D. Anderson Cancer Center's Complementary/Integrative Medicine Education Resources (CIMER)
  www.mdanderson.org/departments/CIMER/

More information sources are outlined at the end of this lesson.

8.1 General approach to advising patients

In general, the same approach to over-the-counter medicines can be used to advise these patients, beginning with a basic work-up of drug therapy. For herbal medicines, the pharmacist may also need to address the following areas[3]:

1. Defining the role of the pharmacist

While not claiming specific expertise in the use of herbal medicine, the pharmacist may assess the available evidence on a particular herbal medicine and help the patients:

- make informed choices by providing objective information
- assess whether the product claims are credible
- weigh the possible benefits versus potential adverse effects
- devise a monitoring plan for efficacy and toxicity if patient wishes to try the product

Note that this differs from the usual role of the "drug expert," when the pharmacist is expected to recommend a drug of choice.

2. Evaluation of evidence

Given the difficulty in keeping up to date with herbal medicine products, the pharmacist may use a single reliable resource on the current evidence (e.g., the Natural Medicines Comprehensive Database – see Information Sources for Botanical Medicine above). Many references now also provide a patient version of the monographs.

3. Assessment of efficacy

Patients should be provided with an objective assessment of the available evidence. The efficacy of many herbal medicine products is based on evidence considered unproven by conventional standards. These data are often anecdotal, derived from preclinical and epidemiological studies, or pertaining to prevention rather than treatment. Until the recent introduction of the Natural Health Products Regulations, many products have been marketed without the need to provide substantiating evidence. Nevertheless, the pharmacist should appreciate that many patients may accept low levels of evidence because they have few options of standard treatments. It is important to keep an open mind to facilitate the discussion and to maintain the patient's hope for any potential benefit. It should be recognized that clearly defined mechanisms of action are not a necessary condition for a therapy to work – many things work without a satisfactory explanation. Moreover, herbal products may have poorly defined but active pharmacological effects (e.g., saw palmetto).

4. Assessment of safety

The patient should be informed of any known or potential harmful effects and provided information (if available) from standard references. Many herbal medicine products have doubtful efficacy, so a low threshold should be set for acceptable potential adverse effects ("first, do no harm"). As with efficacy, until recently the manufacturers of many natural health products have not been required to provide substantiating safety data and/or report adverse events. Hence, patients should be aware that absence of documented adverse effects may be a result of under-reporting rather than a lack of toxicity.

5. Therapeutic trial

Patients wanting a trial of a natural health product should be helped to develop a therapeutic monitoring plan similar to other self-care therapies. This includes clearly defined therapeutic endpoints, trial duration, and information on how to recognize and manage any potential adverse effects. Patients should also notify other health professionals about the use of herbal medicine products, which may affect other conventional treatments.

6. Closure

The motivation for patients to use natural health products is complex. Although most pharmacists have limited training in psychosocial counseling, it is worthwhile to explore the reasons behind the use of natural health products. Some of the general considerations include[45]:

- maintaining a sense of control
- misinformation about conventional treatment ("unnatural") and natural health products ("non-toxic, holistic")
- negative experience with conventional medicine

- emphasis on a close relationship between the body and the mind ("holistic")

In patients with serious illness (e.g., cancer), they may also feel the need to maintain hope that there may still be a cure or that more information is out there simply waiting to be discovered ("there's got to be something else").

The following 7 cases are designed to introduce some common herbs encountered in pharmacy practice. It is assumed that the usual patient work-up and therapeutic considerations would be carried out. These include, for example, verifying the proper use of prior conventional therapies and availability of conventional therapeutic options. The cases are structured in the following manner: introduction to the case; herbal monograph of relevant herb; and then a sample response to the clinical situation described in the case. It should be noted that conditions described in each case are not intended to be comprehensive reviews. Readers are encouraged to formulate their own response to the situation described in the introduction to the case as they read the herbal monograph and then to compare it with the sample response given. The responses outlined for each are examples only and are not meant to represent the only correct response to the case.

9. Case 1

Alice Gregory is a 27-year-old woman who is a regular customer. She is 2 months pregnant and comes in one day asking for something to help with her morning sickness. She has tried a number of agents and wonders if there is anything natural that she could use. She has tried ginger in the past and found that it successfully treated her motion sickness. She thinks it might help her now, but is afraid it might be harmful to her unborn child. She wants your advice.

1. Is there any evidence that ginger is effective for morning sickness?
2. Is ginger safe in pregnancy? If so, in what doses has it been shown to be safe?

9.1 Herbal monograph: Ginger (*Zingiber officinale* Roscoe, Zingiberaceæ)

Synonyms: zingiber, gan-jiang[46,47]

Active constituents: oleo-resin portion, notably gingerols, gingerdione, and shogaols (proportion of shogaols is significantly higher in dried than in fresh plant material)[46,48]

Standard doses:

- 2–4 g of dried powdered root or rhizome (or equivalent) daily[46,49]
- 1 g of dried powdered root before travel (for motion sickness) or induction of anesthesia (for postoperative nausea and vomiting)
- Weak ginger tincture B.P. (1:5, 90% ethanol) 1.5–3 mL three times daily[50]
- Strong ginger tincture B.P. (1:2, 90% ethanol) 0.25–0.5 mL[50]
- Dried ginger 250 mg 4 times daily[46,51]
- Dried ginger 500 mg at the onset of migraine headache and repeated every 4 hours up to 1.5–2 grams per day for 3–4 days

Very few herbal remedies have a more important history than ginger. The rhizome (underground stem) of this perennial herb, native to Southeastern Asia, plays a key role in a number of traditional forms of medicine.[48] Its important culinary and medicinal uses have led to its cultivation throughout the world, especially in the Caribbean and Australia.[52] Traditionally, ginger products have been used for a variety of conditions, including dyspepsia/gastrointestinal upset and microbial infections, notably of the gastrointestinal tract, as an anti-inflammatory in the management of arthritic and musculoskeletal conditions, as a tonic for the cardiovascular system, and to treat nausea.[47,48,53,54]

Pharmacology

Findings of a number of studies indicate that ginger extracts have an inhibitory action on platelet aggregation.[55,56] Randomized trials in humans[55,57] suggest that this effect only occurs at doses of greater than 2 grams daily.[57] Agents found in the oleoresin portion have been shown to inhibit both cyclo-oxygenase and 5-lipoxygenase.[58,59] This influence on prostaglandin and leukotriene synthesis is thought to account for the anti-platelet aggregatory action.

The exact mechanism of action of ginger's anti-emetic effects is unknown, but appears to be primarily due to a gastrointestinal action.[60] However, a centrally mediated mechanism has been noted at higher doses.[61,62] Originally, ginger's anti-emetic actions were thought to result from decreased gastric emptying rate. This theory has since been disproved.[63,64] One explanation that researchers are continuing to investigate is the possible antagonism of 5-HT_3 receptors found in parts of the brain and gastrointestinal tract.[62,65,243]

Human trials

While ginger has been used in a number of human trials for various conditions,[53,58,66] most interest has been focused on its use as an anti-emetic, especially in the management of motion sickness.[53] The clinical trials conducted to date have employed

a number of different designs with comparisons against not only placebo but also conventional pharmaceutical anti-emetics including scopolamine and dimenhydrinate.[63,67–71] While the results of most were promising,[67,68,70,71] a few well-designed studies failed to find any advantage in using ginger over either placebo or conventional pharmaceutical intervention.[63,69] Some possible reasons for these negative studies include insufficient dosage, possible use of poor-quality products, and the short duration of treatment.[72,73] It is important to note that a number of authoritative texts support the use of ginger in the prevention and management of motion sickness.[49,74]

Use of ginger in other types of nausea has also been investigated. In the case of nausea associated with anesthesia, a few clinical trials have noted that administration of dried ginger (0.5 g and 1 g respectively) before surgery decreased incidence of nausea and vomiting significantly more than placebo and comparably to metoclopromide.[64,75,244,245] Unfortunately, this finding was not supported by other studies.[76,246] However, a recent meta-analysis based on 5 randomized trials and 363 patients concluded that a fixed dose of at least 1 g of ginger was more effective than placebo for the prevention of post-operative nausea and vomiting.[247] It is important to note that the trials included in this analysis used minimal amounts of anesthesia. Debate exists over whether the beneficial effects of ginger postoperatively are seen when given with opioid analgesia.

Research with respect to the use of ginger in the management of nausea and vomiting in pregnancy has been conducted in several controlled studies. A Danish double-blind, placebo-controlled trial found that dried ginger (250 mg 4 times daily) was (statistically) significantly better than placebo in the management of women suffering from hyperemesis gravidarum.[77] A subsequent study also found a beneficial effect of dried ginger for nausea in pregnancy.[78] Systematic review of these and other randomized controlled studies[79–81] suggests that oral ginger may be more effective than placebo and probably similar to vitamin B_6 in reducing the severity of nausea and vomiting in some pregnant patients.[82,83] There were no significant side effects or bleeding risks, and the risk of major malformations in infants did not appear to be higher than the baseline rate.[82,83]

Adverse effects

Adverse effects from ginger appear to be rare and limited primarily to gastric burning and dyspepsia. These unwanted effects can be reduced by using encapsulated preparations and by not lying down soon after taking the product.

Cautions/contraindications

Given ginger's anticoagulant properties, concerns have been raised with regard to possible increased bleeding time after surgery. Also, given the herb's action on bile production, its use in cases of gallstones remains controversial.

The use of ginger in the management of morning sickness also remains controversial. While the clinical study identified above[77,82,83] found no teratogenic effects or increased rate of abortion, other traditional sources (traditional Chinese medicine) suggest that ginger should be avoided during pregnancy. In addition, *in vitro* data suggest that in large doses gingerol (a constituent of ginger) has a mutagenic effect.[84,85] These concerns have been challenged by experts who argue that ginger is used within traditional Chinese medicine in far higher does than in Western schools of herbalism (approximately 9 g daily compared to 3 g daily). Also, ginger has been found to contain anti-mutagenic constituents as well as the mutagenic one noted above.[86] Ginger appears to have no spermatotoxic properties.[87]

Drug interactions

There has been one case of a report indicating that ginger augments the international normalized ratio (INR) when taken with phenprocoumon, an agent with similar pharmacological effects to warfarin.[88] However, ginger was not shown to affect the pharmacokinetics or pharmacodynamics of warfarin in a small study of healthy subjects,[242] although the authors note that additional studies are needed in people who are taking anticoagulants. While no cases of ginger interacting with other conventional drugs could be found, it should be used with caution in situations of concurrent conventional cardiac, diabetic, anti-platelet, and anticoagulant therapy, or other herbal products with anticoagulant effects.[89] Because of its potential for increased bleeding, it is important to consider stopping ginger supplements before surgery.

Response

There is very little objective data assessing either the safety or the efficacy of herbal medicine therapy in cases of pregnancy.[90] The findings of a detailed literature review show there is only limited evidence for a small number of agents (ginger and vitamin B_6) in the management of this indication.[91]

The fact that there is any classically derived clinical evidence supporting the use of ginger in morning sickness is a rare occurrence. This is because pregnancy is often a contraindication for clinical studies—including those evaluating natural products.

While there is an abundance of anecdotal evidence for the safety and efficacy of ginger in pregnancy, the best evidence-based data come from several clinical trials.[82,83] Based on these data, when given in doses no greater than 1 g per day, ginger is safe and may be effective for nausea associated with pregnancy. The dose of ginger should be 250 mg qid or less. Ms. Gregory should be cautioned about the potential of ginger to increase bleeding and interact with other anticoagulant agents (including other herbal products such as ginkgo), as well as the need to consider stopping it before surgery (including major dental procedures). If Ms. Gregory wants to take ginger, it is important that she inform other members of her primary health care team and keep to doses lower than that stated above.

10. Case 2

Joan Chang is a perimenopausal 48-year-old woman who asks you about the use of natural progesterone cream. She has recently read in the newspaper that estrogen replacement therapy may be harmful and is wondering if there is an alternative that can be used to treat her hot flashes. She is unable to find the progesterone cream but has read in a magazine that "wild yam" cream was better since it is converted "in your body" to the actual human hormones. Is this the case and, if so, would eating yams have the same effect?

1. Is there evidence to support the use of wild yam in menopause?
2. Are wild yam and "natural progesterone" the same thing?
3. What "cream" is she likely talking about?

10.1 Herbal monograph: Wild yam (*Dioscorea villosa* L., Dioscoreaceæ)

Synonyms: colic root, rheumatism root[92]

Active constituents: steroidal saponins (based on the sapogenin diosgenin) including dioscin and dioscorin[92,93]

Standard doses: There is no typical established oral or topical dosage[46]; 2–4 mL of tincture (hydroalcoholic liquid preparation) taken 3 times daily has been used[94]

A number of members of the genus *Dioscorea* have been used medicinally. *Dioscorea villosa*, a perennial native to Eastern North America, is the one used most often by complementary practitioners.[95] The insipid-tasting fibrous root stock is the part used therapeutically. While the sweet potato (*Ipomœa batatas* (L.) Lam., Convolvulaceæ) is sometimes referred to as a yam, true vegetable yams (e.g., *Dioscorea alata* L.) are cultivated in the tropics and sold here mainly in ethnic grocery stores. Both of these vegetables possess nutritional value and are distinct from the medicinal wild yam.[96] Traditionally, wild yam was favored by the American eclectic physicians in the early part of the last century, where it was primarily used to treat diverticulitis, indigestion, and irritable bowel syndrome.[94,95,97] It was also used as an "anti-rheumatic" to treat joint inflammation and in the management of a number of gynecological problems such as dysmenorrhea.[94–96]

Pharmacology

As yet, little is known about the pharmacological action of the herb itself. Evidence from some *in vitro* trials dating back to the 1920s supports this herb's purported anti-rheumatic, antispasmodic, and digestive properties.[95,97]

Some of the constituents, on the other hand, have an established medicinal role. Diosgenin can be converted *in vitro* to a number of hormonal agents (e.g., progesterone, dehydroepiandrosterone) and was originally used as a raw starting material in the manufacture of a number of drug agents such as oral contraceptives and drugs used in hormone replacement therapy.[53] While it has been suggested that this conversion can occur *in vivo*, the existing objective evidence does not support this claim.[98,99]

Human trials

The majority of evidence supporting the use of wild yam is folkloric and traditional in nature. In one double-blind, placebo-controlled, cross-over study, wild yam cream or placebo was applied to 23 healthy women with menopausal symptoms.[100] There was no difference in symptom control or significant side effect observed between wild yam and placebo. Therefore, it seems that topical wild yam, although probably safe, is likely to be ineffective for troublesome symptoms of menopause.

Adverse effects

Few details exist with regard to the exact composition of this product.

Adverse effects seem to be quite rare for the herb itself. Hormonal actions such as early menopause and masculinization of females have been attributed to one commercial product.[101] High doses of wild yam have been associated with nausea and vomiting.[102]

Cautions/contraindications

Given this herb's action on smooth muscle, wild yam should be avoided in pregnancy.[53] Cases

of occupational asthma have been attributed to members of the genus *Dioscorea*.[103] Theoretical contraindications include cases of obstruction, inflammation, or cancer of the bile duct or gall bladder due to the herb's choleretic effects, and cases of liver disease including hepatitis, cirrhosis, and cancer due to its stimulation of liver function.[97]

Most concerns are about products usually referred to as "Mexican wild yam" or "wild yam" that have a strong hormonal action and thus have the potential to affect conditions such as prostate cancer.[101] Exact details of the composition of these products are uncertain, and the relevance of these concerns to *Dioscorea villosa* is unknown.

Drug interactions

No cases of drug interactions with wild yam could be found.

Response

Natural progesterone products are legally available only as prescription drugs in Canada because they are identical to that found in humans.[104] Many such products have been synthesized from members of the genus *Dioscorea* and are sold as wild yam products (which is illegal).[53] Natural progesterone applied topically is very often used by complementary and alternative health care providers for menopause, especially the vasomotor flushes.[105,106] There is also interest in their use for osteoporosis.[105,107–110] The evidence supporting this use has been criticized as being incomplete and too often extrapolated from the findings of studies that investigated synthetic progestins.[111] Also, some "natural progesterone" creams were found to contain no progesterone.[112]

Ms. Chang should be told that there is no evidence to support the use of topical wild yam in the management of menopause, and any evidence supporting its oral use is folkloric and empirical. Also, the human body cannot convert wild yam (taken in any form) into progesterone. While there is some evidence to suggest that natural progesterone may help, she should consult with an appropriately trained health care provider with prescribing rights in Canada to discuss the matter.

11. Case 3

John Smith, a 40-year-old regular customer, comes in one day requesting some information about valerian to help with anxiety and insomnia. He has been taking 15 mg of temazepam as required to help him get a good night's sleep for several months. Unfortunately, it makes him feel groggy in the morning. A friend recently told him that he got good results with valerian. John asks you if he could use the herb (valerian) with or instead of the drug (temazepam). What do you advise?

1. Is there evidence that valerian can help with insomnia or anxiety?
2. Are there risks of combining valerian with temazepam?
3. Are there risks to long-term use of valerian?

11.1 Herbal monograph: Valerian (*Valeriana officinalis* L. and other species of *Valeriana*, Valerianaceæ)

Synonyms: Belgian valerian, common valerian, fragrant valerian, garden valerian[46,113,114]

Active constituents: iridoids/valepotriates such as valerates, volatile oil components such as valerinic acid[53,115,116]

Standard doses:

- 2–3 g of root or rhizome orally three times daily or at bedtime
- 1–3 mL of tincture three times daily[117]
- Studies in the sleep literature have used valerian extract in doses of 400–900 mg

Valerian species have been used extensively within a number of healing traditions. The pungent, and somewhat malodorous, root is considered to have sedative-hypnotic qualities and is used in cases of insomnia and various nervous conditions. It is also purported to have a muscle-relaxing action and is often used in the management of conditions of the musculoskeletal system.[53,114]

Activity on the central nervous system

Constituents of valerian appear to have an affinity for a number of receptors found in the central nervous system, most notably 5-HT_{1A} and the GABA neurotransmitter system.[117–119] Evidence regarding the affinity of agents found in valerian for the $GABA_A$ (benzodiazepine) receptor is conflicting.[53] While the action of valerian is unlikely to be due to a single constituent or group of constituents, most attention has been focused on the presence of GABA itself. While water extracts of valerian appear to contain sufficient amounts of GABA to account for the release of GABA from synaptosomes and the inhibition of the GABA re-uptake which has been reported, GABA does not cross the blood-brain barrier following oral administration, making this proposed mechanism of action highly unlikely.[120,121] Valerenic acid, a constituent of valerian, seems to inhibit central GABA catabolism and thus increases central nervous system GABA levels.[122] Other agents in the herb, notably some of the sesquiterpenoids present, may inhibit catabolism of GABA in the periphery.[123]

Animal studies

Sedative properties have been demonstrated in a number of animal studies.[53] While these are not conclusive, valerian extracts have been shown to produce changes in behavioural tests and possibly to exert anticonvulsive effects.[53,117] Augmentation of barbiturate-induced sleep similar to changes seen following benzodiazepine administration has also been documented.[124–126] Agents found in valerian have potential antidepressant activity.[53]

Human trials

Some evidence exists to support the use of valerian as a hypnotic agent. Various extracts of valerian have been shown to improve sleep quality, decrease the latency of sleep onset, and improve a number of subjective measures of sleep.[53,113,127–129,130–134] A hypnotic action similar to that of triazolam 0.125 mg has been reported for a combination product containing valerian (160 mg per tablet) and lemon balm (80 mg per tablet).[135] Valerian extract (300 mg) in three divided daily doses also seems to improve the quality of sleep in insomniacs recently withdrawn from benzodiazepines.[132] It may need continuous daily use at night (from several days to four weeks) to achieve therapeutic effect.[130,131] Despite the positive findings of individual studies, a recent meta-analysis concluded that although valerian might improve sleep quality, there were significant methodological problems with most studies. The authors suggested that future research should assess various doses, use standardized preparations, and use standard measures for efficacy and safety.[249] In addition, authors of a systematic review of valerian used for sleep concluded that valerian is safe, but that the current evidence does not support the use of valerian for reducing general sleep disturbances or insomnia. The authors recommended that further studies are needed to adequately evaluate the usefulness of valerian with particular attention to the source of valerian, the form of valerian, doses, and patient samples.[250]

Subjective anxiolytic effects have also been noted under experimental conditions,[136] but currently there is not enough evidence to support the use of valerian for anxiety.[251,252]

Adverse effects

One study using a combination product (valerian and lemon balm) did not note any decrease in concentration or daytime sedation.[135] However, the pharmacology of valerian suggests that drowsiness is possible.

Valerian has an unpleasant taste and odour, which can well effect patient compliance.

Cautions/contraindications

Valerian should be used with caution in pregnancy, lactating women, and children under 3 years of age.[49,117] If valerian does cause sedation, it does not appear to influence normal mental and physical functioning during the day. Morning hangover effects also appear not to be a problem.[117,137]

Drug interactions

While evidence exists on only one case of minor drug interaction with alprazolam,[130] the potential exists for valerian to interact with other centrally acting agents such as conventional anxiolytics, antidepressants, and other drugs with sedative effects, including some analgesics, anesthetics, antiemetics, antiepileptics, alpha-blockers, and beta-blockers.[46,138] Studies using the combination product (lemon balm/valerian) identified above reported no potentiation of action when used in conjunction with alcohol.[135] Preliminary evidence suggests that valerian may inhibit cytochrome p450 3A4, so patients and clinicians should look out for, and report, any suspected interactions with other p450 3A4-metabolized drugs.[139,253]

Response

Although it appears that valerian may have some potential use as a sleep aid, the evidence is not yet conclusive. Further studies are needed to confirm the effect of valerian on improving sleep quality. The evidence supporting its use in cases of anxiety is even less clear. A problem faced here is the perception that natural remedies are safe and can be taken with conventional drugs. While only one case of drug interaction with alprazolam of minor clinical significance has been documented,[130] one should not infer that valerian can be taken safely with other conventional centrally acting medications. Also, there is insufficient quality evidence comparing valerian to conventional pharmacotherapy to suggest that they have comparable efficacy. It is also important to note that even though Mr. Smith only takes the temazepam on a prn basis, it should not be stopped suddenly or without consulting with his physician.

If Mr. Smith still wishes to stop his temazepam, he should be referred to his family physician so that he can stop his conventional medication in a controlled fashion. Unlike temazepam, valerian is not intended as a prn solution—some valerian supporters feel that it can take from 4 days to 4 weeks to attain the full therapeutic effect of valerian. Although there is only one known case report of a valerian withdrawal reaction,[153] patients should not stop using high doses of valerian suddenly after long periods of use. Despite the similarities to

benzodiazepines, patients who use valerian often report less morning grogginess, but this has not been verified in clinical trials. Knowing the evidence, if Mr. Smith decides to try valerian, suggest that he take his initial doses at a time when he is unlikely to need to be alert—such as days he is not at work or driving. This would allow him to safely assess the effects of valerian.

12. Case 4

Jean Hébert is a 35-year-old man. He explains to you that he is under a lot of stress at work at the moment and that this is making him edgy and he is having difficulty sleeping. In addition, he has developed a duodenal ulcer, which is being managed by conventional means. A colleague at work has suggested that chamomile tea can help with his ulcer and sleeping problem. He wants your advice before taking it. He tells you that he regularly takes antihistamines for seasonal allergies. How do you respond?

1. Is there any evidence that chamomile can help his stress or ulcer?
2. How is his history of seasonal allergies important to your discussion about chamomile?

12.1 Herbal monograph: German chamomile (*Matricaria recutita* L., Asteraceæ [also known as Compositæ])

Synonyms: *Matricaria chamomilla* L., single chamomile, pinheads, matricaria[52,53,140]

Active constituents: Terpenoids (including azulene, chamazulene, and α-bisabolol), flavonoids (including apigenin, quercetin, and rutin), coumarins, spiroethers, tannins, and polysaccharides[46,53,141]

Standard oral dose:

- 2–4 g of dried flower heads three times daily normally taken as a "herbal tea"[50]
- May also be used as 1–4 mL of 1:1 extract; 45% alcohol[46]

While often relegated to the status of a beverage in North America, this fragrant annual is highly prized in many parts of Europe for its medicinal properties.[54,140] It is native to much of Western Europe, but most commercial crops are now grown in the Balkans and parts of South America.[52] The flowers, preferably picked a few days before blooming, are the parts used medicinally.[53]

In many parts of the world, German chamomile is considered to have panacea-like properties and is used for so many conditions that it is often called confusingly "European ginseng."[140] German chamomile is usually taken orally as a herbal tea and is used typically for digestive upset, nervous tension, and insomnia and as an antispasmodic.[53] It seems particularly suited to conditions associated with stress or emotional tension. High-quality commercial topical products are also available and are used in a number of skin conditions such as eczema and minor abrasions.[53]

German chamomile is one of two kinds of chamomile used medicinally, the other being Roman or English chamomile (*Chamæmelum nobile* (L.) All., Asteraceæ).[142]

Pharmacology

Like most herbal medicines, German chamomile contains a number of medicinally active constituents. While most interest has been focused on the volatile oil portion, certain other constituents (such as the polysaccharides) have also been shown to have medicinal properties too.[53,141]

Many constituents found in the volatile oil portion, notably the azulene components such as chamazulene and its precursor matricin, spiroethers, and α-bisabolol, as well as the polysaccharides, exert an anti-inflammatory action.[140,141,143–147] This anti-inflammatory action may be due in part to an inhibition of leukotriene synthesis.[148] Powerful antispasmodic properties have also been demonstrated in animal and *in vitro* studies for the whole volatile oil fraction as well as the spiroethers and α-bisabolol, in addition to the polysaccharide fraction.[53,140,141,149] The antispasmodic action may be mediated through inhibition of cAMP phosphodiesterase.[254]

The α-bisabolol present has also been shown to prevent the formation of gastric ulcers in a number of experimental animal models.[53,150] Hepatoprotective, antioxidant, and anti-allergenic actions have also been identified.[53]

Findings of recent animal studies suggest that apigenin present in extracts of the flower has an affinity for the same receptors as benzodiazepines. This could be the mechanism of action of this herb's reputed anxiolytic and hypnotic properties.[151] The polysaccharide fraction also appears to have an anti-histaminic action.[152] Reports that German chamomile's tranquilizing effect could be due to the presence of tryptophan have yet to be confirmed by objective evidence.[140]

Clinical trials

Given German chamomile's widespread use, it is surprising to find relatively few clinical studies investigating this herb. A number of clinical trials have evaluated specific commercial extracts of German chamomile as an adjunct to conventional agents in the management of a number of skin

conditions, including stasis ulcers and wound care, with mixed results.[140,153,154]

There is some evidence that German chamomile, as part of a combination product (Iberogast, Enzymatic Therapy), may be more effective than placebo when taken as 1 mL three times daily over a 4-week period in improving dyspeptic symptoms (e.g., acid reflux, epigastric pain, cramping, nausea, vomiting). Other ingredients contained in this product include peppermint leaf, clown's mustard plant, caraway, licorice, milk thistle, celandine, angelica, and lemon balm.[156,157]

Results from an uncontrolled trial investigating the use of German chamomile mouthwash showed that its use could decrease stomatitis resulting from conventional chemotherapy.[158] These promising findings were not supported by a later, more sophisticated trial that reported that German chamomile mouthwash was no better than placebo in decreasing stomatitis caused by 5-fluorouracil.[159]

While German chamomile has been seen to have a sedative action when given during surgical procedures,[140] no controlled trials published in English investigating these reputed properties could be found.[53]

Adverse effects

Cases of adverse effects associated with German chamomile are exceedingly rare, with vomiting being noted when given in high doses.[53,54] However, a number of cases of allergic reactions, including situations of anaphylaxis, have been noted.[53,160–163] The sesquiterpene lactones present in German chamomile seem most likely to be responsible.[164,165] However, is important to note that many of these cases have occurred amongst people who come into frequent contact with the fresh herb, such as florists and horticulturalists.[162,166] Thus, the clinical significance of the medicinal use of German chamomile is unknown.[53]

Another complicating factor is that German chamomile products are often of low quality, and it has been suggested that adulterating agents may be responsible for the majority of reported allergic responses. One of the main culprits is stinking dog fennel (*Anthemis cotula* L., Asteraceæ). It is important to note that only in a minority of cases of alleged allergic reaction to German chamomile was the plant itself authenticated.[54,141,164]

Cautions/contraindications

Cross-sensitivity between different members of the sunflower (Asteraceæ) family has been noted and so it would seem prudent that people allergic to members of this family (e.g., ragweed, asters, chrysanthemums) avoid German chamomile products.[53,164,166,167]

Given the fact that resorption of fetuses and reduction of birth weight was noted in rats given German chamomile and that historically the herb is reputed to have emmenagogue properties, German chamomile should be used with caution in pregnancy.[168–170]

Given the potential for sensitizing newborns, German chamomile should be used with caution in lactation.[53]

Drug interactions

Despite *in vitro* data that chamomile may interact with drugs metabolized via cytochrome p450 3A4,[139] no documented cases could be found of interactions between German chamomile and conventional drug therapy. Given the herb's potential action on the central nervous system, high doses should be avoided with conventional drug agents as anxiolytics and antidepressants. *In vitro*, chamomile has been shown statistically to inhibit platelet activity. Although these findings have yet to be confirmed *in vivo*, Chamomile could theoretically interact with medications that affect platelets and clotting (e.g., acetylsalicylic acid, nonsteroidal anti-inflammatory drugs, warfarin).[153] Until clinical studies confirm or negate these effects, pharmacists should advise patients of the potential interaction, tell patients to watch for signs of bleeding and, if necessary, recommend additional monitoring by their physicians.

Response

Despite a significant amount of empirical and experimental evidence supporting the use of German chamomile, there have been only a limited number of conventional human trials supporting the use of German chamomile in cases of stress and stomach ulcers.[156,157] In addition, none of these trials compared German chamomile on its own or with conventional pharmacotherapy for duodenal ulcers. The latter is particularly important given the effectiveness of many current treatments for this condition, including eradication of any *Helicobacter pylori* infection. Therefore, after careful explanation of the type of evidence available to Mr. Hebert, this herb could be recommended. While adverse effects appear to be unlikely, his seasonal allergies complicate matters, especially if it is found that some of the plant pollens he is allergic to are from the Asteraceæ family. Even though the chance of an allergic reaction to German chamomile is slight, it is important to counsel Mr. Hebert appropriately. If anaphylaxis has occurred in the past, Mr. Hebert should be advised not to take this herb. It would be useful to note on Mr. Hebert's file if he does take this herb, since the potential exists for an interaction with some conventional centrally acting drugs.

13. Case 5

Mrs. Kaprovsky is a 49-year-old client of yours. She is entering perimenopause and is suffering from night sweats and irritability. Her doctor has confirmed that these "symptoms" are due to perimenopause. Her neighbour has been taking evening primrose oil (EPO) for her "moodiness" around menstruation and has suggested that Mrs. Kapovsky take some. Mrs. Kaprovsky wants to know your opinion before buying this product. When she sees how much she needs to take and the price of the supplement, she begins to have second thoughts. Does she need to take that much? She also asks if she can take flaxseed oil (a source of omega-3 fatty acids) instead. In fact, she has heard that fish oil is good for your health as well and asks if she could take cod liver oil instead. What is your response?

1. Is there evidence that evening primrose oil (EPO) is helpful in menopause?
2. Are the sources of omega-3 fatty acids that she mentioned similar in safety and efficacy?

13.1 Herbal monograph: Evening primrose (*Œnothera biennis* L., Onagraceæ)

Active constituents: fatty acids found in the fixed oil, notably cis-linoleic acid, cis-gamma linolenic acid, oleic acid, palmitic acid and stearic acid[52,171]

Standard doses: Adults: 2–8 grams daily in divided doses[46,172]

It is important to note that evening primrose oil supplements contain vitamin E as a pharmaceutical antioxidant and not necessarily as a therapeutic supplement.[53]

The first thing to realize is that evening primrose is not actually a primrose but rather a member of the fuchsia family. It is named evening primrose because the large yellow flowers open in the evening to allow pollination by insects, notably moths. While historically the whole plant (including the root) was used for both medicinal and culinary purposes, most attention now is focused on the fixed oil of the seeds. Evening primrose was one of the first natural health products to gain popularity in the developed world in the '70s and '80s.[52,171]

Pharmacology

The key to the medicinal action of evening primrose oil (EPO) is that it offers a rich source of gamma linolenic acid (GLA). Before describing this action in detail, it is important to review the basic points of essential fatty acid (EFA) biochemistry and nomenclature. The word "essential" refers to the fact that the body cannot manufacture these fatty acids and so must receive them from the diet. There are two basic types that will be discussed here, omega-3 (derived from alpha-linolenic acid) and omega-6 (derived from linoleic acid). Both types are polyunsaturated and so contain more than one double bond. The numbers refer to the number of carbon atoms the first double carbon-to-carbon bond is from the methyl end of the molecule.[53]

While these two types of EFA are not interchangeable, they do act as precursors to a number of biologically active moieties, including prostaglandins and leukotrienes. In addition, the EFAs and their metabolites play an important role in cell-membrane-based receptors, systems, and structure. The important constituent in evening primrose oil is gamma-linolenic acid (GLA), an omega-6 fatty acid. While GLA is not considered an essential fatty acid, since it is manufactured *in vivo* from linoleic acid, it has been suggested that the biosynthesis of GLA is inhibited in certain situations. The activity of the enzyme involved in this process, delta-6-desaturase, is thought to be affected in a number of conditions, including certain nutritional deficiencies (zinc, pyridoxine, and magnesium), diabetes, atopic eczema, aging, and viral infections.[53]

In simplified terms, it is argued that supplying preformed GLA will overcome this barrier and stimulate production of the beneficial members of the prostaglandin 1 series (notably PGE1). More detailed reviews of this exact process exist in other texts. For this lesson, it is important to realize that this premise for the medicinal effectiveness of evening primrose oil is not universally accepted.[53]

Clinical trials

Evening primrose oil is one of the most investigated natural health products on the market. Unfortunately, few definitive conclusions have been reached. Also, many studies used products combined with omega-3 fatty acids (marine fish oil), thus limiting the assumptions that could be made about EPO itself.[53]

Women's health care

Results from a number of trials support the use of EPO in cases of premenstrual syndrome.[172–176] However, in a recent review article, Budeiri et al. concluded that there was insufficient evidence from the existing literature to support this indication.[177] The short duration of some of the positive trials may have played a role in this conclusion.[53] When combined with omega-3 fatty acids, EPO has been shown to be beneficial in the treatment of endometriosis.[172]

Using EPO for mastalgia is an attractive option since EPO supplementation lacks the adverse

effects commonly associated with conventional pharmacotherapy (e.g., bromocriptine, tamoxifen, danazol).[179,183,256] A number of open and placebo-controlled trials support the use of EPO in cases of mastalgia.[178–182], but some of these trials had serious methodological problems (such as being open-label, not double-blinded) or were not published in peer-reviewed journals. Also, other placebo-controlled, randomized, double-blind studies have not shown EPO to improve cyclic mastalgia,[256–259] and a recent meta-analysis concluded that EPO did not improve pain scores compared to placebo.[260] The Society of Obstetricians and Gynaecologists of Canada's practice guidelines for mastalgia concluded that there was not enough evidence to support the use of EPO for mastalgia.[256]

While EPO is frequently used in the management of menopause, the little evidence that exists – dated back to 1994 – did not show EPO to be better than placebo.[184] While significant amounts of research have been performed using EPO supplementation, many authors comment that there is still a lack of rigorous clinical trials.[185,261–263]

Adverse effects

EPO appears to be very safe, with adverse effects limited to nausea, headache, and diarrhea. The nausea and diarrhea are reduced if EPO is taken with meals. It appears to have no carcinogenic properties.[53]

Cautions/contraindications

If given at normal therapeutic doses of less than 4 g per day, EPO supplementation is unlikely to cause problems in pregnancy.[90] Although the clinical impact associated with ingesting EPO during lactation is not known, maternal dietary supplementation with EPO has been documented to effect the composition of the breast milk.[53]

EPO may theoretically exacerbate cases of mania and should also be used with caution in some epileptic patients (see below).[46,186,187]

Drug interactions

Few cases of interactions between EPO and conventional drug therapy have been published. Theoretically, drugs affecting prostaglandin metabolism such as NSAIDs and corticosteroids will likely be enhanced by EPO. EPO should be used with caution in patients taking anticoagulant therapy.[53]

An increase in epileptic episodes was noted in schizophrenic patients taking phenothiazines when compared to placebo.[188] The schizophrenic patients in that report were taking EPO along with phenothiazines.

Response

Given the high daily dose and price of EPO supplements, inquiries occur quite frequently in community pharmacies. First, it is important to explain to Mrs. Kaprovsky that while there is some evidence to support the use of EPO in premenstrual syndrome, it is lacking in cases of menopause. So, EPO may not be the best course of action. If she does decide to purchase a supply, she should take it at the recommended dose of 4 grams daily. In addition, while flaxseed oil is significantly cheaper and has some benefits of its own, it is not interchangeable with EPO and does not contain appreciable amounts of GLA. Her question regarding cod liver oil is of more concern. While fish oil is rich in omega-3 fatty acids, it is distinct from EPO. Also, fish oil rich in these EFAs is not the same as cod liver oil and dosing may vary considerably.

14. Case 6

Mr. Black is a 56-year-old man who suffers from rheumatoid arthritis. His condition is currently controlled with 10 mg of prednisone daily. His chief concern is pronounced fatigue and lethargy. He is currently seeing a herbal practitioner who has suggested that he take a licorice product called DGL, which should help increase "his energy." He has now taken this product for 6 weeks and has not noticed any improvement. Recently he told his family physician about this and was advised to stop the licorice immediately since it can increase blood pressure and will interact with his medication. He is confused, since his holistic practitioner said the opposite—that DGL cannot interact with his medications or increase blood pressure. What do you advise?

1. Do licorice and DGL have different effects on blood pressure?
2. Will DGL help him with his fatigue?

14.1 Herbal monograph: Licorice (*Glycyrrhiza glabra* L., Fabaceæ)

Synonyms: liquorice, glycyrrhiza, sweetwood, liquiritiæ[72,189,190]

Active constituents: terpenoids (including glycyrrhizin, which yields glycyrrhetinic acid on hydrolysis), flavonoids, coumarins, and volatile oil[46,53,189]

Standard dosage:

- 5–15 g of the root, equivalent to 200–600 mg of glycyrrhizin daily[49]
- DGL tablets 380–1140 mg three times daily[191]
- Licorice products should not be taken for more than 6 weeks at a time[49]

Licorice has long been used within many healing traditions for its reputed medicinal properties. While *Glycyrrhiza glabra* L. is the species used within Western herbalism, another member of the genus, *Glycyrrhiza uralensis* Fisch. ex DC., is primarily used within traditional Asian healing models.[53] It has been used as an expectorant and antitussive in conditions of the upper respiratory tract, as a laxative, in cases of inflammation, and in gastric and duodenal ulcers.[52] It is also used as a tonic herb in cases of fatigue, since it is thought to strengthen adrenal function. The parts used medicinally are the roots and underground stems (rhizomes).[53]

Licorice is often used by herbal practitioners not as a pharmacological agent but as a sweetening agent to mask more unpleasant-tasting constituents in herbal formulae.[53] Glycyrrhizin is up to 100% sweeter than sucrose. While licorice candies are a popular confection, they generally contain little or no licorice (they are often flavoured with less-expensive anise seed oil) and therefore have few medicinal properties.[53,192]

Pharmacology

Unlike most herbal medicines, the pharmacology of licorice has been extensively studied.[53,189,193,194] While many constituents have been shown to have pharmacological actions, most attention has been paid to the terpenoid portion, notably glycyrrhizin and its aglycone glycyrrhetic acid. Glycyrrhizin has been shown to inhibit a number of enzymes involved in the metabolism of certain prostaglandins.[53] It has also been shown to affect endogenous steroid metabolism in many ways. Glycyrrhizin and glycyrrhetinic acid inhibit 11-beta-hydroxysteroid dehydrogenase (the enzyme that catalyzes the conversion of cortisol to inactive cortisone), bind weakly to both mineralocorticoid and glucocorticoid receptors, and influence aldosterone secretion and elimination.[53,72,193,195] Because of these actions, hypertension can possibly occur or be exacerbated. In addition, glycyrrhizin has been shown to suppress plasma renin activity and decrease angiotensin levels and anti-diuretic hormone levels.[53,194]

Due to the action of its constituents on cortisol and prostaglandin metabolism, it is not surprising to find that licorice has been shown to have anti-inflammatory properties.[53] The mechanism of action appears to be more complex than this, with glycyrrhetinic acid being shown to inhibit the classical complement cascade and glycyrrhizin selectively inhibiting the anti-inflammatory influence of thrombin.[196,197]

Human trials

While licorice has been the centre of much interest, few clinical trials have actually investigated the use of the herb itself. Most interest has been focused on the terpenoid constituents and commercial derivatives.[53]

Two commercial derivatives used primarily in the management of gastrointestinal conditions have been the most well studied. Carbenoxolone is a synthetic derivative of glycyrrhetinic acid used in the management of peptic ulcer disease. While an exact mechanism of action is not known, it is thought to exert its action by increasing synthesis and secretion of protective mucus.[189] A number of double-blind, placebo-controlled trials have demonstrated that carbenoxolone is more effective than placebo. Its use is now limited due to its associated adverse effects, including water retention and hypertension.[46,189]

The other primary commercial product is deglycyrrhizinated licorice (DGL), which was developed in order to address concerns raised about the adverse effects of carbenoxolone. DGL has little effect on blood pressure or adrenal function, since it has less than 3% glycyrrhizin content.[53,189] Most clinical studies have assessed two commercial brands of DGL. A number of controlled clinical trials of various designs have shown that DGL is superior to placebo and comparable to conventional pharmacotherapy (antacids or cimetidine) in the management of both gastric and duodenal ulcers.[53,198–201] There is also some evidence that licorice, as part of a combination product (Iberogast, Enzymatic Therapy), may be more effective than placebo when taken as 1 mL three times daily over a 4-week period in improving dyspeptic symptoms (e.g., acid reflux, epigastric pain, cramping, nausea, vomiting). Other ingredients contained in this product include peppermint leaf, clown's mustard plant, caraway, German chamomile, milk thistle, celandine, angelica, and lemon balm.[156,157]

Adverse effects

In small doses, licorice is generally considered to be relatively safe. In doses greater than 20 g, concerns arise, most notably from the mineralocorticoid action of the terpenoids.[202] Adverse effects include hypokalemia, headache, lethargy, sodium and water retention, and hypertension.[49,53] In the case of hypertension, there appears to be a dose-response relationship between the amount of licorice taken and the rise in blood pressure.[203] This collection of adverse effects is commonly referred to as pseudoaldosteronism. The low serum potassium can potentially result in cardiac arrhythmias and ECG abnormalities.[202] Situations of amenorrhea and hyperprolactinemia have also been described

due to the partial-agonist, antagonist effects of licorice on estrogen.[204,205] Licorice can also decrease serum testosterone and increase 17-hydroxyprogesterone. This may lead to reduced libido or sexual dysfunction in males.[206]

While fatalities have been reported following ingestion of licorice products, the clinical relevance of these cases to the use of licorice in herbal practice is unknown. This is due to the fact that most of these cases occurred following the ingestion of very large amounts of licorice normally taken in the form of candy.[53,207] One case of congestive heart failure occurred in a 53-year-old man who ate 700 g of licorice candy over an 8-day period.[208]

Since DGL contains such small amounts of glycyrrhizin, it is not associated with pseudoaldosteronism.[53]

Cautions/contraindications

Licorice should be used with caution in patients with high blood pressure, cardiovascular disease (particularly congestive heart failure), renal failure, or liver disease. Licorice should also be used with caution in pregnancy.[53]

Drug interactions

Licorice products should be used with caution in patients taking medication that can affect or depends on potassium levels, such as digoxin and diuretics.[49] This herb may also interfere with hormonal or hypoglycemic therapy.[46] Given that glycyrrhetinic acid decreases the metabolism of corticosteroids, it should be used with caution in patients taking agents such as prednisone.[53,209–211] DGL has been seen to increase the bioavailability of nitrofurantoin as well as to decrease the nausea often seen with this drug.[53] Grapefruit juice may enhance the mineralocorticoid activity of licorice.[212] As for many other herbal products, early laboratory information suggests that licorice can inhibit CYP450 3A4.[139]

Response

There are a number of things to bear in mind. Firstly, while fatigue may appear an insignificant symptom, it is important that Mr. Black determine its cause to rule out any more serious medical condition. Secondly, both his physician and herbal practitioner are partially correct. While licorice can result in hypertension and react with corticosteroids such as prednisone, DGL is unlikely to do so since it contains only small amounts of glycyrrhizin. Having said this, since DGL contains only small amounts of glycyrrhizin, it does not influence adrenal function and thus is unlikely to be of help in fatigue. To conclude, while DGL is unlikely to cause a problem, there is no evidence to support its use in this case.

15. Case 7

Mrs. Jones is a 52-year-old patient with a history of alcoholism. She also suffers from chronic migraines that are currently managed adequately with an acetaminophen/narcotic medication. Her naturopathic practitioner has recommended that she take a standardized milk-thistle product containing at least 70% silymarin. While she has confidence in her practitioner, the product that has been suggested is expensive and Mrs. Jones is wondering if she can use another kind of the herb. She has been looking at a herbal tea containing milk thistle that is almost half the price.

1. Can she replace one dosage form with the other?
2. What kind of evidence exists to support the use of this herb in patients taking acetaminophen?

15.1 Herbal monograph: Milk thistle (*Silybum marianum* (L.) Gaertn., Asteraceæ)

Synonyms: Mary thistle, St. Mary's thistle, Marian thistle, Lady's thistle, Holy thistle, Carduus marianus L.[213]

Active constituents: silymarin (a flavonolignan complex composed of silybin, silydianin, and silychristin)[52,213,214]

Standard dose: Milk thistle is poorly soluble in water, thus limiting the medicinal effectiveness of teas and infusions[53]

- 200 mg of a standardized extract (70% silymarin) three times daily[215]
- A milk thistle extract containing 70–80% silymarin (Legalon), 420 mg orally daily for hepatic cirrhosis[46]
- A milk thistle constituent, silibinin (Silibide), 240 mg twice daily for chronic hepatitis[46]

Milk thistle is a spiny leafed plant that is native to Europe. The white mottled appearance of the leaves was thought to have been caused by a drop of the Virgin Mary's milk, hence the specific epithet *marianum*. This folklore gave rise to the plant's use as a galactagogue (promoter of lactation).[213] Milk thistle is often confused with another member of the sunflower (Asteraceæ) family, blessed thistle (*Cnicus benedictus* L.). While they are both used as galactagogues, they are very different plants.[53] While milk thistle does have some historical uses, current uses are primarily supported by more recent scientific evaluations. The ripe seeds are the part used medicinally.

Pharmacology

The vast majority of interest has been focused on the actions of silymarin as a hepatoprotect-

ive agent. Silymarin is thought to work via three primary mechanisms of action: to stimulate cell development and regeneration by increasing synthesis of ribosome protein,[214,216,217] to competitively antagonize the action of certain hepatotoxic agents,[214] and to act as a powerful antioxidant decreasing cell destruction.[53,218] It has also been suggested that silymarin may decrease the production of potentially harmful leukotrienes,[219] inhibit neutrophil function,[220] and influence Kupffer cell (large macrophage) functions.[221]

Clinical trials/animal studies

A number of animal studies have demonstrated an ability of milk thistle products to protect the liver against a variety of toxins, including alpha-amanitin and phalloidin from the deathcap mushroom (*Amanita phalloides* Fr., Pluteaceæ), carbon tetrachloride, DL-ethionine, thioacetamide, and acetaminophen.[214,222–226] One double-blind, placebo-controlled trial of patients with hepatotoxicty resulting from neuroleptic medications found a decrease in serum levels of malondialdehyde (MDA).[227] Preliminary clinical research based on three double-blind, placebo controlled trials demonstrated improvement in alcohol-induced liver damage.[214,228,229] In addition, oral administration of a milk thistle extract standardized to silymarin to patients with cirrhosis was found to significantly lower the mortality rate. The best results were seen in patients with alcohol-induced cirrhosis.[230] However, a systematic review by the Cochrane Collaboration found limited beneficial effects of milk thistle for patients with alcoholic or viral hepatitis. This meta-analysis of 18 randomized trials involved a total of 1088 patients. Compared to placebo or observation, milk thistle did not appear to improve the overall mortality, complications of liver disease, or liver cirrhosis. Overall liver-related mortality was significantly reduced in patients taking milk thistle. However, the statistical significance of this benefit disappeared when only data from the high-quality trials were used. No significant side effects were observed amongst the trials.[231]

Results from studies investigating the use of silymarin in the management of hepatitis are inconclusive.[53] While a number of studies have noted an improvement in objective outcomes in both chronic and acute hepatitis,[214,232] a number have shown no significance difference between silymarin and placebo.[214] In addition, the majority of these studies assessed i.v. administration, limiting the applicability of this information to oral administration of milk thistle products.[53]

There have been attempts to improve oral absorption by converting milk thistle or its components to lipid-compatible complexes (e.g., milk thistle phytosome, silybin-phosphatidylcholine complex, Siliphos, Siliphost).[233] To date, however, this has not been shown to provide significant clinical effectiveness for any particular indication.[46] Also, there is some evidence that milk thistle, as part of a combination product (Iberogast, Enzymatic Therapy), may be more effective than placebo when taken as 1 mL three times daily over a 4-week period in improving dyspeptic symptoms (e.g., acid reflux, epigastric pain, cramping, nausea, vomiting). Other ingredients contained in this product include peppermint leaf, clown's mustard plant, caraway, licorice, German chamomile, celandine, angelica, and lemon balm.[156,157]

Adverse effects

Adverse effects of milk thistle may include nausea, dyspepsia, bloating, and flatulence, although all of these are less common than diarrhea.[53] Furthermore, there is a cross-sensitivity in patients allergic to other members of the Asteraceæ (also known as the Compositæ) family, such as ragweed and chrysanthemums.

Cautions/contraindications

Long-term safety has yet to determined in pregnancy and lactation.[53] It can also decrease elevated serum transminase levels caused by other medicines.[46]

Drug interactions

While no cases could be found, the hepatic properties of milk thistle may influence medications whose metabolism is heavily determined by liver function.[53] Milk thistle can inhibit hepatic glucuronidation as well as cytochromes P450 2C9[234] and 3A4.[40] However, one study in healthy volunteers showed no clinically relevant effects on 3A4.[255] This disparity may be a result of the specific milk thistle formulation used in these studies, and therefore caution is still warranted.

Response

An important point to explain to Mrs. Jones is the difference between milk thistle dosage forms. The vast majority of the information related to milk thistle comes from studies assessing standardized extracts. A standardized extract is one in which the product contains a specific amount of a particular agent, in this case silymarin. It is also important to note that silymarin (the most active agent) is not soluble in water, and so the cheaper tea would probably not be as effective. With regard to efficacy, there appears to be limited RCT information supporting the use of milk thistle products standardized to silymarin content in the management

of alcohol-induced liver conditions. Also, only animal data exist to support its use as a hepatoprotectant to acetaminophen. Thus, there is unlikely to be any benefit from the milk thistle tea and only a theoretical benefit of using a dosage form standardized to silymarin. It is important to note that many of these products are not available on the market.

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Appendix

Databases, the internet, journals, and texts/monographs all provide important details about botanical products. While a detailed description of all the relevant sources of information is beyond the scope of this education program, brief descriptions of each are listed below.

Databases

While specialty databases play a key role in any search, a significant amount of information can be found by searching databases commonly used in conventional medicine. These include MEDLINE, TOXLINE, Embase, condition-specific databases (CANCERLINE and TOXLINE), Chemical abstracts, and BIOSIS. Specialty databases include NAPRALERT (Natural Product Alert), AGRICOLA, AltHealth Watch, and CMI (Complementary Medical Index). A challenge faced when searching these databases is the lack of universally accepted key words specifically used to describe botanical medicine, which often necessitates multiple searches using a variety of different terms.[44] For example, when attempting to locate information about a specific botanical medicine, it is usually necessary to search the databases using the plant's common name(s), Latin binomial, and any commercial brand names.

Internet

While the internet contains significant amounts of information on various herbal products, it is often thinly disguised advertising used by herbal vendors or manufacturers with the intention of promoting product sales rather than educating consumers or health care practitioners. A number of websites containing useful information on herbal medicine are listed below.

- National Center for Complementary and Alternative Medicine, National Institutes of Health, USA
  www.nccam.nih.gov
- Integrative Medicine Service at Memorial Sloan-Kettering Cancer Center
  www.mskcc.org/mskcc/html/11570.cfm
- Medline Plus – Herbs and Supplements
  www.nlm.nih.gov/medlineplus/druginformation.html
- MayoClinic Drugs & Supplements
  www.mayoclinic.com/health/drug-information/DrugHerbIndex
- M. D. Anderson Cancer Center's Complementary/Integrative Medicine Education Resources (CIMER)
  www.mdanderson.org/departments/CIMER/
- Herb Research Foundation
  www.herbs.org

By subscription only:

- Natural Medicines Comprehensive Database
  www.naturaldatabase.com
- PhytoNet
  www.escop.com/phytonet.htm

Journals

A significant amount of information related to herbal medicine, especially with respect to evidence-based evaluation, can be found in mainstream peer-reviewed journals. These include *The Lancet*, the *British Medical Journal*, and the *New England Journal of Medicine*. The *Journal of the American Medical Association* (*JAMA*) and its sister publications (the *Archives* series) dedicated an entire volume to the subject of CAM in November 1998. A number of quality journals and periodicals now exist containing information useful to the community pharmacist in obtaining relevant information about herbal medicine. Examples of these are listed below.

Peer-reviewed dealing primarily with herbal medicine

- *Phytomedicine*
- *Fitotherapia*
- *British Journal of Phytotherapy*
- *European Journal of Herbalism*
- *Planta Medica*
- *Phytotherapy Research*
- *Pharmaceutical Biology*

Non peer-reviewed dealing primarily with herbal medicine

- *HerbalGram*
- *Australian Journal of Medical Herbalism*
- *Canadian Journal of Herbalism*

Journals dealing with CAM in general that contain information on herbal products

- *Health-Notes* (formerly *Quarterly Review of Natural Medicine*)
- *FACT* (*Focus on Alternative/Complementary Therapies*)
- *Complementary Therapies in Medicine*

Texts/monographs

Over the last several years, a number of referenced botanical monograph series have been published. Key series include those published by ESCOP (European Scientific Cooperative on Phytomedicine), the World Health Organization, and the American Herbal Pharmacopœia. A text

that has quickly become the gold standard for issues regarding dosage, indications, and cautions/adverse reactions is the Commission E monographs prepared by a department of the Federal German Government. This text was recently translated and modified by the American Botanical Council. Since it is an account of an expert committee, it is not referenced.

Pharmacognosy, the study of plant-based substances for medicinal use, has seen a revival in recent years. One standard pharmacognosy textbook is the 15th edition of *Trease & Evans' Pharmacognosy* (Bailliere Tindall). As a result of the increase in popularity of herbal medicine, a number of texts have also been written specifically for members of the primary health-care team. These include:

Barnes J, Anderson LA, Phillipson JD. *Herbal Medicines*, Third Edition (Pharmaceutical Press)

Boon H, Smith M. *Botanical Pharmacy* (Quarry Press)

Brinker F. *Herb Contraindications and Drug Interactions*, 3rd edition (Eclectic Medical Publications)

Kayne SB. *Complementary Therapies for Pharmacists* (Pharmaceutical Press)

Mason P. *Dietary Supplements* (Pharmaceutical Press)

Rapport L, Lockwood B. *Nutraceuticals* (Pharmaceutical Press)

Schulz V, Hansel R, Tyler V. *Rational Phytotherapy: A Physician's Guide to Herbal Medicine* (Springer Verlag)

Questions

1. Which of the following statements regarding the safety of ginger in pregnancy is most accurate?
   a. There have been no human safety data with the use of ginger in pregnancy.
   b. Doses of ginger used in clinical trials are far higher than those used in traditional Chinese medicine.
   c. The risk of major malformations in infants did not seem to increase in pregnant patients who took ginger for morning sickness.
   d. The safety data of ginger in pregnancy is generally based on doses of approximately 9 g daily.

2. Under the Natural Health Products Regulations, which of the following statements regarding herbal products in Canada is false?
   a. All herbal products must comply with good manufacturing processes.
   b. Herbal remedies currently issued with a Drug Identification Number (DIN) would be transferred to have a Natural Product Number (NPN) and treated as natural health products rather than drugs.
   c. Evidence for efficacy of herbal remedies must be substantiated with at least two randomized controlled clinical trials.
   d. Herbal products can be sold for use in modifying organic functions to maintain or promote health (i.e., structure-function claims).

3. Which of the following statements regarding drug-herb interactions is false?
   a. Interactions can occur between oral herbal medicine and intravenous drugs.
   b. The low number of cases reported means that herbal products are unlikely to interact with drugs.
   c. Pharmacists should report drug-herb interactions to the Natural Health Products Directorate.
   d. Drug-herb interactions can be either pharmacokinetic or pharmacodynamic in nature.

4. Which of the following statements regarding the clinical use of ginger is the most accurate?
   a. It has a limited number of indications.
   b. The use of ginger as an anti-emetic is based on its ability in inhibiting platelet aggregation.
   c. Ginger may increase bleeding and should be stopped before surgery.
   d. There is extensive evidence on the use of ginger and vitamin B_6 in the management of morning sickness.

5. Which of the following statements regarding the mechanism of action of the purported sedative effects of valerian is most accurate?
   a. The gamma-aminobutyric acid (GABA) neurotransmitter system may be involved.
   b. Valerian occupies the 5HT3 serotonin receptor.
   c. Central opioid receptors are stimulated by valerian.
   d. The sedative effect of valerian is consistent with an antihistamine effect.

6. Which of the following statements regarding the clinical use of licorice is false?
   a. Carbenoxolone is a synthetic derivative of glycyrrhetinic acid, which is contained in licorice.
   b. Deglycyrrhizinated licorice (DGL) is a concentrated licorice product with potent effect on blood pressure.
   c. Licorice candies are not effective in the management of peptic ulcer.
   d. Licorice is widely used as a sweetener in herbal formulae.

7. Which of the following statements regarding the safety of German chamomile is false?
   a. Some of the associated side effects may be due to adulterants.
   b. Nausea and vomiting is a common side effect.
   c. It should be avoided in patients allergic to members of the sunflower (Asteraceæ) family.
   d. It should be used with caution in pregnancy.

8. Which of the following statements regarding the use of licorice is true?
   a. DGL tablets contain amounts of glycyrrhizin equivalent to those in most other licorice products.
   b. Licorice products should not be taken for more than 6 weeks at a time.
   c. Licorice is commonly used as a colouring agent in herbal medicine.
   d. Licorice candies can have significant pharmacological activity.

9. Which of the following statements about information resources regarding botanical medicine is most accurate?
   a. All high-quality information can only be accessed by subscription only.
   b. It is relatively easy to locate relevant information on herbal medicine in conventional databases such as MEDLINE because they are well indexed.
   c. Herbal medicine has been evaluated and reported in various mainstream peer-reviewed medical journals.
   d. Pharmacognosy, the study of plant-based substances for medicinal use, is a relatively new discipline.

10. Which of the following statements regarding the effectiveness of wild yam is true?
   a. There has been no randomized controlled trial on the use of wild yam for menopausal symptoms.
   b. Wild yam taken orally has been shown to reduce hot flashes.
   c. Topical application of wild yam has not been shown to be better than placebo in controlling menopausal symptoms.
   d. Sweet potato can be as effective as wild yam for dysmenorrhea.

11. Which of the following statements regarding milk thistle is false?
   a. It is highly insoluble in aqueous solutions.
   b. It belongs to the sunflower (Asteraceæ) family.
   c. It contains carbenoxolone, which may have hepatoprotective effects.
   d. It contains ingredients that may have antioxidant properties.

12. Which of the following statements regarding the effectiveness of milk thistle is the most accurate?
   a. It is well established that milk thistle can significantly reduce liver cirrhosis in patients with alcoholic liver disease.
   b. The clinical evidence does not support the use of milk thistle as a hepatoprotectant against acetaminophen.
   c. Overall, milk thistle has been shown to reduce mortality in patients with viral hepatitis.
   d. The best available evidence suggests that milk thistle is likely effective in reducing liver-related mortality in patients with liver cirrhosis.

13. Which of the following is the most appropriate adult therapeutic dose of ginger for nausea and vomiting in pregnancy?
   a. 1000 mg qid
   b. 9000 mg daily
   c. 250 mg qid
   d. 250 mg prn up to a dose of 5000 mg over 24 hours

14. Which of the following is an active constituent present in licorice?
   a. gamma linolenic acid (GLA)
   b. DGL
   c. silymarin
   d. glycyrrhizin

15. Which of the following herbal products should be used with caution in people taking conventional antiplatelet medication?
   a. ginger
   b. German chamomile
   c. wild yam
   d. valerian

16. Which of the following statements regarding the clinical use of German chamomile is false?
   a. It has been studied extensively for stress and stomach ulcers.
   b. As a combination product (Iberogast), it has been shown to be more effective in placebo in reducing symptoms of dyspepsia.
   c. It has not been compared to conventional treatment of peptic ulcers in clinical trials.
   d. The sedative effect of German chamomile has not been well studied.

17. Which of the following statements regarding the mechanism of action for licorice is false?
   a. It contains glycyrrhizin, which may be involved in the metabolism of some prostaglandins.
   b. It contains glycyrrhizin and glycyrrhetinic acid, both of which may influence aldosterone secretion and elimination.
   c. It contains carbenoxolone, which may decrease synthesis and secretion of protective mucus in the gastrointestinal tract.
   d. Deglycyrrhizinated licorice (DGL) has little effect on adrenal function.

18. Which of the following statements regarding the Natural Health Products Regulations is false?
   a. Only natural health products manufactured according to the GMPs should be marketed.
   b. Herbal remedies are given a different identification number from other natural health products.
   c. Traditional medicines are governed by the Natural Health Products Regulations.
   d. The regulations will not come into effect until January 1, 2010.

19. A patient shows you a homeopathic medicine in a dilution of 4DH. Which of the following statements is true?
   a. It means the same as 4X.
   b. All homeopathic products are diluted to contain less than Avogadro's number.
   c. The product has been made by diluting the raw material by a series of 4 successive 1 in 100 dilutions.
   d. It is four times more potent than the usual strength of the product.

20. Which of the following statements regarding herbal efficacy is most accurate?
   a. Health Canada requires at least randomized controlled clinical data to license a herbal product.
   b. Testimonials of aboriginal leaders may be accepted as supportive evidence for efficacy of herbal products based on traditional use claims.
   c. A product can be sold based on traditional use claim if it has been used within a cultural belief system (e.g., traditional Chinese medicine) for at least 100 consecutive years.
   d. The strength of supportive evidence is the same whether the product is licensed for therapeutic claims (e.g., treatment of a medical condition) or structure-function claims (e.g., maintaining health).

21. Which of the following statements regarding the mechanism of action of homeopathy is true?
   a. The exact mechanism of action of homeopathy has been clearly establishe
   b. Many homeopathic practitioners believe that the remedies encourage the body's own defensive healing ability.
   c. Patients' symptoms are believed to be a result of specific infectious processes.
   d. The explanation of its mechanism of action is highly plausible within the conventional biomedical model.

22. Which of the following statements regarding the effectiveness of homeopathy is true?
   a. Many high-quality clinical trials have shown that homeopathic medicine is superior to placebo for a number of indications.
   b. A meta-analysis has shown that homeopathy, as a discipline, is probably superior to conventional medicine.
   c. A meta-analysis comparing homeopathy and conventional medicine trials has shown that the effectiveness of homeopathy may be due to placebo effects.
   d. Homeopathy has been shown to be highly effective in preventing morning sickness in pregnancy.

23. Which of the following statements regarding herbal medicine is false?

a. Herbal medicine refers to the use of a plant, alga, or fungus or their extracts for a therapeutic purpose.
b. Herbal remedies are not governed by the Natural Health Products Regulations of Health Canada.
c. Other terms used for herbal medicine include botanical medicine, phytomedicine, and herbology.
d. Both traditional Chinese medicine doctors and Western herbalists use very similar herbs for the same indication.

24. Which of the following statements regarding the safety of herbal medicine is true?

a. All currently marketed herbal products have undergone extensive toxicology studies.
b. Products such as ginger may increase bleeding.
c. Pharmacists should never discuss theoretical risks of herbal products with the patients.
d. No herbal products have ever been banned from sale in Canada.

25. Which of the following statements about advising patients on herbal products is most accurate?

a. The pharmacist should emphasize that he or she is an expert in the use of herbal medicine.
b. Information on the internet should be used as a basis to provide objective assessment of a particular product.
c. A herbal product without clearly defined mechanisms of actions may still be pharmacologically active.
d. If a patient wants a trial of a herbal product, all he or she needs to know is how to follow the instructions on the labelling.

26. Which of the following statements regarding the effectiveness of ginger for morning sickness in pregnancy is most accurate?

a. There has been more research in the use of ginger for morning sickness than in motion sickness.
b. Oral ginger may be more effective than placebo in reducing the severity of nausea and vomiting in pregnant patients.
c. Oral ginger may be more effective than vitamin B_6 in controlling morning sickness.
d. Our knowledge of the effectiveness of ginger is based on only one randomized controlled trial.

27. Which of the following statements regarding natural progesterone is most accurate?

a. Wild yam has been shown to be converted to progesterone after topical application in humans.
b. Natural progesterone is identical to that found in humans.
c. A number of natural progesterone cream products can be legally available in Canada without prescription.
d. Natural progesterone is safer than synthetic progesterone.

28. Which of the following statements regarding the clinical use of valerian is false?

a. Valerian extract may have some effect in improving the quality of sleep, but further studies are needed to confirm its effect.
b. Continuous use of valerian for at least several days may be needed before a therapeutic effect can be seen.
c. There have been several reports of valerian causing excessive sedation when used with benzodiazepines.
d. There are no clinical data that directly compare valerian and temazepam for insomnia.

29. Which of the following statements regarding the safety of licorice is true?

a. Deglycyrrhizinated licorice (DGL) can induce significant inhibition of the metabolism of corticosteroids.
b. Licorice should be used with caution in patients with high blood pressure.
c. Patients taking DGL tablets should follow the same cardiovascular precautions as other licorice products.
d. DGL has been associated with pseudoaldosteronism.

30. Which of the following statements regarding the safety of milk thistle is true?

a. Milk thistle should be avoided in patients who are allergic to German chamomile.
b. Milk thistle can be used safely in lactation since it has long been used as a promoter of lactation.
c. Milk thistle may stimulate the cytochrome P450 3A4 enzyme, which is commonly involved in drug metabolism.
d. One of the common side effects of milk thistle is itchiness.