Herbal Medications: An Evidence-Based Review

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- Read the enclosed course.
- Complete the questions at the end of the course.
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Faculty
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Faculty Disclosure
Contributing faculty, A. José Lança, MD, PhD, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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Division Planner/Director Disclosure
The division planner and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience
Considering the widespread availability and increased use of herbal medications, this course is designed for dental professionals who will benefit from the course.

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Course Objective

Considering the pharmacologic interactions between herbal medications (HMs) and conventional medications, it is paramount to increase the awareness and knowledge of dental professionals about HMs. The purpose of this course is to increase dental professionals' awareness of the potential risks and benefits of HMs from an evidence-based perspective and promote the planned inclusion of HM use in patients' medical history. This course should allow dental professionals to discuss HMs in a knowledgeable and succinct manner with patients and colleagues.

Learning Objectives

Upon completion of this course, you should be able to:

1. Discuss the prevalent current and historical use of HMs in North America.
2. Explain the need to inquire about the use of HMs during preparation of a patient's medical history, including components of a culturally sensitive assessment.
3. Discuss the pharmacology (i.e., pharmacokinetics, pharmacodynamics, drug interactions, adverse drug reactions, toxicology) of HMs.
4. Describe the differences between the process of development and approval of HMs versus conventional medications, and the implications of health claims and therapeutic efficacy of HMs.
5. Outline the merits and limitations associated with the application of contemporary scientific principles and methodologies (i.e., evidence-based medicine) to assess the efficacy and safety of HMs.
6. Discuss, based on scientific and conventional medical principles, the pharmacologic properties, efficacy, safety, toxicology, therapeutic indications, and recommended dosages of saw palmetto and St. John's wort.
7. Describe the potential risks and benefits of ginkgo.
8. Identify key characteristics of ginseng.
9. Discuss the use of echinacea and kava, including potential adverse effects.
10. Review the use of garlic and valerian as HMs.
11. Outline the potential medical uses of andrographis and English ivy leaf.
12. Analyze the available evidence for the use of peppermint, ginger, soy, and chamomile.

EVIDENCE-BASED PRACTICE RECOMMENDATION

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

DEFINITIONS

The National Center for Complementary and Integrative Health (NCCIH), a division of the U.S. National Institutes of Health, defines complementary and alternative medicine (CAM) as "health care approaches that are not typically part of conventional medical care or that may have origins outside of usual Western practice." [1]. Complementary medicine is non-mainstream practice used together with conventional medicine, and alternative medicine is non-mainstream practice used in place of conventional medicine. Integrative medicine attempts to bring together conventional and complementary approaches to health care [1]. CAM includes a wide range of products including natural health products (NHPs) and practices such as prayer, chiropractic, homeopathy, and massage therapy. In Canada, a similar definition is followed, and regulation of NHPs falls under the jurisdiction of the Natural and Non-Prescription Health Products Directorate (NNHPD), a branch of Health Canada [2].

Herbal medications (HMs), also known as phytochemicals or botanical medications, are considered an integral part of dietary supplements in the United States or natural health products in Canada [3]. Dietary supplements also include other natural compounds, such as vitamins, minerals, amino acids, and essential fatty oils [2].

PREVALENCE OF HERBAL MEDICATION USE

The desire to maintain and promote individual health has contributed to the prevalent use of natural health products, including herbal medications. In 2012, more than 3 out of 10 adults (33.2%) in the United States used complementary medicine approaches and 17.7% used natural products other than vitamin and mineral supplements [1]. In Canada, an estimated 18% of the population takes natural products other than vitamin and mineral supplements [4].

Data from the National Center for Health Statistics (NCHS) indicate that supplement use among U.S. adults 20 years of age and older increased from 48.4% to 56.1% during the period 2007–2008 and 2017–2018, with use more common among women (63.8%) than men (50.8%) [5; 6; 7; 8]. Nonvitamin, nonmineral natural products are the most commonly used category of CAM (17.7%), followed by deep breathing (10.9%), yoga, tai chi, and qi gong (10.1%), chiropractic care (8.4%), meditation (8.0%), and massage therapy (6.9%). The NCHS also found that approximately 12% of children 17 years of age or younger use some form of CAM [5]. Considering the aging of the "baby-boom" generation and increased incidence of chronic health issues, it is likely that the use of CAM, and HMs in particular, will continue to increase in this group. In 2017–2018, dietary supplement use increased with age, both overall and in both sexes, and was highest among women 60 years of age and older (80.2%). The most common types of dietary supplements used were multivitamin-mineral supplements, followed by vitamin D and omega-3 fatty acid supplements [8].

The use of CAM for general health and well-being is greater in people with higher education and income, rather than in individuals with lower education and lower socioeconomic status [5; 9]. However, the National Health Interview Survey revealed that poor adults were more likely to use megavitamin therapy and prayer specifically for a health reason than not poor adults [10]. An estimated 13% of adult CAM users have indicated that they used CAM because conventional medicine was too expensive [10].

It is particularly relevant for medical practitioners that several studies have shown that more than 50% of patients who require conventional health care use CAMs separately or in conjunction with conventional therapies [9; 11; 12]. A published study of men with prostate cancer revealed that one-third of the patients used CAM in conjunction with their conventional therapy [13]. Of those, approximately 30% were taking vitamin and mineral supplements, while 40% were taking herbal compounds either alone or in conjunction

with vitamins and antioxidants [13]. It has been estimated that 40% to 70% of patients using CAM fail to disclose this information to physicians or other healthcare professionals [5; 11]. Patients are more likely to disclose CAM use if it is provider-based rather than self-care use [9].

The prevalent use of herbal medications is particularly relevant to medical practice for three main reasons. First, it is commonly and erroneously assumed by patients that by being natural the compound is intrinsically beneficial and devoid of adverse effects. Second, patients often neglect to report to their physicians and other healthcare providers that they are taking HMs, as they think that it is not relevant. Third, pharmacologic interactions between compounds, regardless of whether they are from herbal or conventional origin, may alter therapeutic efficacies and cause negative interactions or serious adverse effects.

It is therefore essential to increase awareness regarding these issues and evaluate the pharmacologic profile and therapeutic properties of the most commonly used herbal medications based on scientific evidence, including clinical trials.

HISTORICAL OVERVIEW OF HERBAL MEDICATIONS IN NORTH AMERICA

Chemical compounds extracted from plants, animals, or micro-organisms, either in raw or purified form, have been used to treat disease for centuries and even millennia. Many of these substances are essential therapeutic tools and widely used in conventional medicine. Aspirin, digitalis, reserpine, morphine, most antibiotics, and anticancer drugs, to name but a few, are perfect examples of the long historical transition between natural medications and mainstream or conventional Western medications. The introduction of new and more effective conventional medications, such as statins, a class of drugs that inhibit 5-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase activity and effectively lower hyperlipidemia, and the antimalarial drug artemisinin, are pertinent examples of identification, extraction, and pharmaceutical application of natural compounds [14; 15]. In fact, it has been estimated that approximately 25% to 50% of marketed drugs are derived from natural sources [16]. One review found that almost 50% of the new small-molecule drugs introduced between 1981 and 2002 were natural products or their chemical derivatives [15]. Consequently, the difference between NHPs/HMs and conventional Western medications is not solely or primarily based on the origin of the compound (i.e., natural versus synthetic) but rather on the process of scientific evaluation of the pharmacologic and biologic properties, toxicologic profile, and therapeutic efficacy of a particular compound prior to its approval for marketing. In Western countries, the process of approval of new conventional drugs is tightly regulated. It falls under the jurisdiction of the U.S. Food and Drug Administration (FDA) in the United States; in Canada, it is regulated by Health Canada.

In the United States, herbal medications are considered dietary supplements and are regulated by the Dietary Supplement Health and Education Act (DSHEA) of 1994 [3]. Under this legislation, some claims, including structure and function, may be made by the manufacturer without requiring proof of safety and efficacy needed for conventional FDA-regulated medications. The product may be advertised as beneficial to maintaining or improving health of a particular organ or system, and the DSHEA states that the manufacturer is responsible for the safety of herbal products [3]. It is, however, the responsibility of the FDA to prove that an herbal compound is unsafe before a product is removed from the market [17]. This has been the case regarding the sale of dietary supplements, including HMs, containing ephedrine alkaloids (e.g., ephedra), which were prohibited in the United States by the FDA in April 2004 [18].

In Canada, herbal medications are classified as natural health products and fall under the jurisdiction of the Natural Health Products Regulations [19]. Canadian regulations provide a regulatory framework similar to the one existing in the United States. It is Health Canada's mandate to regulate the sale and safety of HMs, as illustrated by the ban on products containing ephedra in quantities greater than 8 mg per dose, 32 mg per day, or at any dose in combination with other stimulants, including caffeine.

MEDICAL AND PATIENT PERCEPTIONS AND MISCONCEPTIONS ABOUT THE USE OF HERBAL MEDICATIONS

The pharmacology, therapeutic properties, and toxicologic potential of herbal medications are often the object of inaccurate and biased assessment. Numerous factors contribute to this situation. In some cases, healthcare providers may have limited formal training in the area, which can result in a limited appreciation of the beneficial properties of some phytochemicals and of their potential health risks, including pharmacologic interactions with conventional medications [20]. A survey of community pharmacists in Texas showed that in spite of the fact that 70% of new patients use CAM, pharmacists rarely ask patients about CAM use. This is a particularly troublesome occurrence considering the role played by the pharmacist in assessing potential interactions with conventional drugs [21].

A 2010 United Kingdom-based *Drug and Therapeutics Bulletin* (DTB) survey of 164 healthcare professionals, consisting mostly of hospital physicians and general practitioners, found that while a majority of physician participants (75.3%) considered HMs to be helpful in some circumstances, 72% indicated that the general public had misplaced faith in HMs and 86% felt the general public was poorly informed about HMs [22].

Patients often use herbal compounds based on the misconception that due to being natural, these products are intrinsically beneficial, do not cause adverse effects, and are devoid of any serious toxicologic potential. This is a widespread and inaccurate assessment. Patients need a better understanding of why informing their healthcare providers about CAM, and especially HM, use will be beneficial to their health.

In response to the increasing interest in CAM, including HMs, the U.S. Federation of State Medical Boards has approved guidelines for the use of CAM in conventional medical practice. This document provides information regarding "clinically and ethically responsible use of CAM, within the boundaries of professional practice and accepted standard of care," and provides the methodology to evaluate physicians' adherence to standards of medical practice required by state legislation [23].

CULTURALLY SENSITIVE ASSESSMENT

Because the use of CAM, including HMs, may be tied closely to cultural or ethnic traditions, it is important that any assessment for use of these products be undertaken with an understanding of possible barriers to disclosure. Pachter developed a dynamic model to facilitate culturally sensitive assessments, which involves several tiers and transactions [24]. The first component of Pachter's model calls for the practitioner to take responsibility for cultural awareness and knowledge. The professional should be willing to acknowledge that he/she does not possess enough or adequate knowledge in health beliefs and practices among the different ethnic and cultural groups he/she comes in contact with. Reading and becoming familiar with medical anthropology is a good first step.

The second component emphasizes the need for specifically tailored assessment [24]. Pachter advocates the notion that there is tremendous diversity within groups. For example, one cannot automatically assume that a Nigerian immigrant adheres to traditional beliefs. Often, there are many variables, such as level of acculturation, age at immigration, educational level, and socioeconomic status, that influence health ideologies. Finally, the

third component involves a negotiation process between the patient and the professional [24]. The negotiation consists of a dialogue that involves a genuine respect of beliefs. The professional might recommend a combination of CAM and Western treatments. A knowledge of HMs commonly used in different cultures may allow healthcare professionals the opportunity to ask questions about specific products, as many patients do not volunteer information regarding their use of HMs.

DISCLOSURE AND CLINICAL NEED TO IDENTIFY THE USE OF HERBAL MEDICATIONS

As noted, an estimated 40% to 70% of patients fail to report the use of HMs to their physicians and other healthcare providers [5; 11; 13]. Some patients assume that reporting CAM use is not relevant because they are not mainstream medical products or procedures. In one literature review, the major reason for patients' failure to disclose the use of CAM was their concern of a negative reaction by the practitioner [11]. In the same study, lack of interest or assumed lack of knowledge by the medical practitioner were also reported among the main reasons for nondisclosure. This is supported by the 2010 DTB survey, which indicated physicians felt that their personal knowledge about HMs was "quite" or "very" poor (36.2% and 10.4%, respectively), and 89% conceded that their knowledge of herbal medications was "much poorer" than their knowledge of prescription drugs [22].

A number of patients do not disclose the use of HMs simply because their healthcare provider did not inquire [11]. While 77% of physicians worry that their patients may not be informing them about HM use, the DTB survey found that 9% never ask about HM use, 47% occasionally ask, 27% ask most of the time, and only 13% always ask [22]. Thus, considering the prevalent use and the common perception of healthcare professionals' attitudes toward herbal medications, it is essential to change these practices in order to safeguard patients' health.

CLINICALLY RELEVANT PHARMACOLOGY AND TOXICOLOGY OF HERBAL MEDICATIONS

In North America, regulation of HMs is not as strict as that applied to conventional medications. In fact, good manufacturing practices applicable to food manufacturing are some of the only regulations in place to assure standards and quality control of dietary supplements [25]. The concentration of active ingredients in HMs, however, is affected by numerous factors, including [11; 26; 27; 28]:

- The correct identification of the botanical source
- The presence of contaminants or substitution of the intended source or other plants of lower cost with potential toxicologic consequences
- Growing conditions, including temperature, geography and time of harvest, and possible contamination with micro-organisms, heavy metals, pesticides, or prescription drugs
- Collection of the appropriate plant part (e.g., leaves versus root)
- Preparation of specimens (e.g., drying, grinding)
- Laboratory processing (e.g., solvent used for extraction of active ingredients)
- Storage
- Formulation of the final product (e.g., liquid versus solid pill)

These processes vary considerably among manufacturers and influence product quality and concentration of active ingredients in the final product.

Unlike most conventional medications, herbal products often have numerous active ingredients. Pharmacologic and chemical interactions between ingredients may be required for the product to be effective. Accordingly, isolation and purification of a single individual chemical may not lead to the same therapeutic effect as the one described for the original product.

PHARMACOKINETICS

Pharmacokinetics is the study of the effects exerted on drugs by the body, namely the processes of drug absorption, distribution, biotransformation, and ultimate elimination of drugs and their metabolites. All drugs ingested for nutritional, therapeutic, preventive, or diagnostic purposes, regardless of being of natural or synthetic origin, undergo processes of absorption and eventual distribution throughout body tissues and systems prior to reaching their molecular target. Drug distribution does not occur homogeneously throughout the body. Effective availability and concentration of a drug in different organs and tissues is influenced not only by the chemical properties of the drug (e.g., molecular size, electrical charge, ability to bind to plasma proteins, affinity for transporters that will carry the drugs across cell membranes) but also by the anatomic and histologic properties of the tissues themselves (e.g., degree of vascularization and type of capillaries present, including the tightly sealed blood-brain barrier).

Subsequently, all drugs undergo chemical transformation by the body. Briefly, drug transformation is carried out by enzymes leading to the production of metabolites that are either water-soluble (hydrophilic) and excreted mainly through the kidney, or lipid-soluble (hydrophobic). The latter are further metabolized in the liver mainly by a large family of enzymes known as cytochrome P450 (CYP450). Selective CYP450 isoforms, such as CYP3A4 and CYP3A5, are particularly relevant for clinical practice. In fact, CYP3A4 and CYP3A5 account for the metabolism of about 50% of all known drugs. For example, drugs such as digoxin, warfarin, indinavir, cyclosporine A, statins, and some calcium channel antagonists and anticonvulsants are metabolized by these isoforms. Increases or decreases in CYP450 activity therefore influence the processes of drug transformation, alter drug availability, and can have serious clinical implications [29].

PHARMACODYNAMICS

The pharmacologic and therapeutic properties of HMs and conventional medications result from the biologic interaction between an active compound and its target. The mechanisms underlying the drug-target interactions are studied in pharmacodynamics. The precise molecular mechanisms underlying the actions of HMs are, however, more difficult to establish due to the complex composition and presence of numerous chemical elements. For the most commonly used HMs, certain chemical elements have been isolated, their effects studied in vitro, and their therapeutic properties clinically evaluated. Allicin, for example, has been identified as the chemical ingredient in garlic responsible for its cardioprotective and plasma lipid-lowering properties. This effect correlates with the inhibition of HMG-CoA reductase by allicin and other disulfides present in garlic, which is a mechanism of action shared with statins [30; 31; 32].

The beneficial effects of saw palmetto in the treatment of benign prostatic hyperplasia (BPH) have been obtained with standardized lipidosterolic extracts. Several mechanisms of action have been reported, in both in vitro and in vivo models. Although saw palmetto has alpha 1-adrenoceptor antagonistic properties, a mechanism of action common to tamsulosin (Flomax), and anti-inflammatory properties because it inhibits cyclooxygenase, its beneficial effects on BPH correlate with its inhibition of 5-alpha-reductase. This latter mechanism is shared with the conventional drugs finasteride (Proscar) and dutasteride (Avodart) [33; 34].

DRUG INTERACTIONS

Drug-drug interactions, herb-drug interactions, and food-drug interactions can occur when different compounds are concurrently present in the body. These interactions can be either of a pharmacokinetic nature (i.e., absorption, distribution, metabolism, excretion) or a pharmacodynamic nature (i.e., interfering with the interaction between the drug and its molecular target, such as a receptor). Rarely, both pharmacokinetic and pharmacodynamic interactions may occur at the same time.

The complex composition of HMs can, in principle, become the source of various interactions. Multiple chemical compounds can interact either synergistically (i.e., increase the activity of one or more of its chemical constituents) or antagonistically (i.e., decrease the activity of one or more of its components). Furthermore, herbal remedies may include complex mixtures of several herbs, thereby significantly increasing the number of active compounds in the preparation. This makes it particularly difficult to ascertain which of the chemicals is pharmacologically responsible for a particular biologic event. The co-administration of HMs and conventional drugs further increases the possibility of interactions, which can be manifested during experimental conditions or clinically.

Herb-drug interactions apparently occur less frequently and are less serious than drug-drug interactions. This is due to the weaker potency of the herbal medications; however, interactions and adverse events may also be under-reported and relevant information may not be collected [35; 36].

Pharmacokinetic Interactions

Pharmacokinetic interactions between chemical compounds can alter the therapeutic properties of a drug and either increase or decrease the effectiveness of one or both compounds. For example, compounds in grapefruit and grapefruit juice strongly inhibit the liver enzyme CYP3A4 in a dose-dependent manner, thus reducing or preventing the biotransformation of drugs metabolized by this enzyme. This leads to abnormally high and potentially serious or lethal concentrations of these drugs in the blood [35]. Some clinically relevant interactions take place when grapefruit (as well as some other citrus varieties, primarily sour types) are administered with statins, anxiolytic drugs, methadone, or calcium channel blockers [37]. This interaction has led to a ban of grapefruit products in many healthcare facilities.

Goldenseal, used topically as an antiseptic and systemically for the treatment of gastrointestinal disorders and menstrual pain, is also known to strongly inhibit CYP3A4, which prevents the metabolism of drugs such as erythromycin, leading to abnormally high blood levels of this antibiotic [38; 39].

An opposite effect is caused by other medications, including the herbal antidepressant St. John's wort (SJW). SJW induces both CYP3A4 and the intestinal drug transporter P-glycoprotein. Consequently, drugs transformed by CYP3A4 will be degraded faster and their blood levels quickly fall below therapeutic levels with foreseeable clinical implications [36]. These mechanisms have been linked to the low circulating levels of the antirejection drug cyclosporine in patients who received a kidney transplant and were also being treated with SJW [36]. A similar mechanism was reported in a heart transplant recipient and was responsible for the acute rejection of the transplant [40].

Other pharmacokinetic interactions between SJW and prescription drugs have been the subject of several clinical studies, including one that reported the interaction with the anxiolytic alprazolam [41]. Alprazolam is metabolized by CYP3A4 in the liver and intestinal mucosa, and SJW induced the activity of CYP3A4, shortening the elimination half-life of alprazolam from 12.4 to 6 hours.

Pharmacodynamic Interactions

Pharmacodynamic drug-drug or herb-drug interactions result from actions on molecular targets that mediate different processes of a physiologic response. The final result of these interactions can lead to an increase (i.e., synergism or potentiation) or decrease (i.e., inhibition or offset) of the expected response. For example, the antidepressant properties of SJW are associated with hypericin, pseudohypericin, and hyperforin. These compounds have a mechanism of action identical to fluoxetine (Prozac) and paroxetine (Paxil), and inhibit serotonin reuptake [42]. It is therefore not surprising that SJW, like the selective serotonin

reuptake inhibitors, has a pharmacodynamic synergistic interaction with drugs that further contribute to increases in serotonin concentration in the synapse, such as monoamine oxidase (MAO) inhibitors (e.g., phenelzine) [41; 43; 44]. The abnormal increase of serotonin resulting from the herb-drug interaction can cause a mild "serotonin syndrome," characterized by confusion, restlessness, high blood pressure, fever, and muscle spasms [45; 46; 47; 48].

Clinically relevant interactions also occur between HMs and conventional medications that affect hemostasis, such as antiplatelet drugs (e.g., acetylsalicylic acid, dipyridamole), anticoagulants (e.g., heparin and vitamin K antagonists such as warfarin), and fibrinolytic drugs (e.g., alteplase, reteplase). A number of HMs contain high amounts of coumarin, salicylates, or other compounds that interfere with hemostasis. Both red clover (*Trifolium pretense*) and sweet clover (*Melilotus alba*) are rich in coumarin. Mold contamination of these plants converts the coumarin into dicoumarol, the vitamin K antagonist from which the potent anticoagulant warfarin is derived. Toxicity has been reported in cattle grazing on moldy clover hay [49; 50; 51]. Although this interaction has not been reported in humans, due to the below-threshold effect of dicoumarol when the herb is administered at the recommended dosage, it is advisable to closely monitor hemostasis in patients undergoing anticoagulant therapy [50; 51].

Another potential herb-drug interaction exists between ginkgo biloba and conventional anticoagulants, as a few cases of hemorrhage have been reported in the literature. One German study, however, has shown that the inhibition of the platelet-activating factor by ginkgo biloba was only observed for amounts at least 100 times higher than the recommended dose [52]. Although, mechanistically, there is the potential for synergistic interaction between ginkgo biloba and anticoagulants, it seems unlikely. Interactions between various HMs and conventional cardiovascular pharmacotherapy, such as anticoagulants, antihypertensives, diuretics, statins, and digoxin, have been reported [53].

ADVERSE EFFECTS/ADVERSE DRUG REACTIONS

As discussed, the pharmacologic properties of HMs and their interactions with prescription drugs can cause adverse effects, also known as adverse drug reactions, and have the potential to cause toxicologic effects. The reporting of adverse effects is the most important tool in post-marketing drug surveillance and accounts for 60% of the data used for adverse effects assessment [54; 55]. In the United States, the FDA has the FDA Adverse Event Reporting System (FAERS). Adverse event reporting for dietary supplements, including HMs, should be directed to FDA's MedWatch. The equivalent agency in Canada is the Canada Vigilance Adverse Reaction Online Database. Reports should be made to MedEffect Canada. An adverse events reporting system, Natural MedWatch, has also been established by the Therapeutic Research Faculty, an independent publisher of evidence-based recommendations for pharmaceuticals (***Resources***).

In both the United States and Canada, adverse effects can also be reported to the manufacturer. In turn, the manufacturer should submit all the collected information to the regulatory agencies. The efficiency of this latter process, however, has been the subject of lengthy debate.

TOXICOLOGY OF HERBAL MEDICATIONS

Systematic analysis of the evidence-based toxicologic properties of HMs is scarce. Toxicologic effects of HMs can result from:

- Administration of a high dose of an HM and consequent abnormal exacerbation of the intended therapeutic effect or occurrence of a toxic effect unrelated to the original therapeutic effect
- Adulteration of the product either by contamination with other plants or with prescription medications illegally included in the product
- Interactions with conventional drugs or other HMs

There is a relationship between the administered amount of a drug and the effect obtained (dose-response curve). As for any drug, very low doses of HMs, below the intended therapeutic threshold, do not have a pharmacologic effect, whereas higher doses within the therapeutic range will elicit the intended effect (therapeutic dose). Above therapeutic doses, the compound may elicit unintended responses, which can result from the exacerbation of the therapeutic effect and the accompanying adverse effects. For example, high doses of an antihypertensive drug can cause abnormally low blood pressure. Alternately, it may stem from the occurrence of another adverse effect not directly related to the primary therapeutic action of the drug. Acetaminophen, the leading cause of acute liver failure in the United States, is a typical example to illustrate the latter type of event [56]. When administered at doses above the therapeutic threshold for analgesia and antipyresis, it causes liver toxicity and can eventually cause death due to liver failure. The smallest dose of a drug that elicits a toxic effect is known as the minimum toxic dose. The lowest drug dose that causes death is known as the minimum lethal dose.

Considering the fact that HMs have a complex and varied chemical composition, and due to the limited knowledge of the precise effects on different constituents of organ systems, healthcare providers should always be aware of their potential toxicity. A relevant example results from chronic ingestion of germander (*Teucrium chamaedrys*). In traditional Chinese medicine, it is used in the form of tea or extract for a variety of purposes, including weight loss. A number of germander-induced cases of severe hepatotoxicity have been reported in the scientific literature, leading to it being banned in France [57]. In 1996, two more cases of hepatotoxicity were reported in Canada [58]. It has been established that its toxicity is caused by the development of autoantibodies that cause immunoallergic hepatitis, and it is strongly advised that it should not be ingested for any reason [59].

Toxicity may also occur as the result of adulteration in the composition of HMs. This may occur by contamination with toxic plants or molds due to improper selection or storage. Adulterations of the intended product may occur either accidentally or deliberately when unscrupulous suppliers replace the intended plant for a cheaper one. Although this substitution may cause physiologic responses that resemble the ones intended, other effects, including toxicity, may occur. Widely reported cases have occurred in several countries, including the United States, where a mixture of plants used in traditional Chinese medicine to detoxify the body contained *Digitalis lanata* instead of plantain and caused digitalis intoxication in two patients. More numerous cases were prevented by the timely intervention of the FDA, leading to the immediate recall of the product [60]. Another well-known case occurred in Belgium, where more than 40 patients developed interstitial fibrosis and progressive renal failure when the nephrotoxic herb *Aristolochia fangchi*, known to contain potent carcinogens, was substituted for the intended *Stephania tetrandra* [61].

On several occasions, it has been found that an HM was deliberately adulterated by adding a prescription drug. Such was the case reported in England, when very high levels of the synthetic drug dexamethasone were found in an herbal cream used to treat eczema [62]. In Saudi Arabia, a complete toxicologic screening of more than 200 samples of traditional products revealed contamination by synthetic drugs (8 cases), micro-organisms (18 cases), toxic substances of natural origin (14 cases), or high heavy metals content (39 cases) [63]. These examples illustrate the need for an increased public and professional awareness, the implementation of appropriate quality control and exhaustive testing of supplies, adherence by the manufacturers to good manufacturing practices, and selection of products manufactured by reputable companies [64].

HERBAL MEDICATIONS: REGULATORY ASPECTS

COMPARISON OF THE PROCESSES OF APPROVAL OF HERBAL COMPOUNDS AND CONVENTIONAL DRUGS

As mentioned, the main difference between HMs and conventional Western medications is neither exclusively nor primarily based on the origin of the compound (i.e., natural versus synthetic) but rather on the process of evaluation regarding efficacy and safety, which the compound should undergo prior to being marketed. In fact, many conventional medications are extracted from natural sources or are the chemical derivatives of naturally occurring molecules.

In Western countries, the process of approval of new conventional medications is tightly regulated. New drugs undergo a process of detailed scrutiny and scientific evaluation prior to being released into the market. Briefly, during the preclinical stages, the physiopathologic mechanisms underlying the disease are identified, and biologic targets (e.g., enzyme, receptor, gene) are identified. Drugs aimed at biologic targets are tested in vitro, and in vivo experiments are conducted under controlled conditions. When the potential therapeutic benefit has been established based on the preclinical studies and the drug is considered ready for human studies, an elaborate application is then submitted to the appropriate regulatory institution: the FDA in the United States and Health Canada in Canada. The application includes:

- Composition and source of the drug
- Manufacturing information
- Data from in vitro and animal studies
- Detailed plans for proposed clinical trials
- Names and credentials of physicians responsible for conducting the clinical trials

If approved, human studies of the investigational new drug (IND) can be initiated. At the institutional level, interdisciplinary review boards are responsible for assuring the ethical and scientific integrity of the clinical trials.

Clinical studies are conducted in four stages or phases (I, II, III, and IV). Phase I is aimed at establishing drug safety, dosage, and pharmacokinetic properties of the drug (e.g., half-life, metabolism). These are open or nonblind studies, in which both investigators and healthy subjects (25 to 100) know what is being administered. Results of human studies are compared with animal studies.

The goal of Phase II is to study the effect of the drug on volunteer patients (100 to 200) with the disease for which the drug was developed. Subjects will either receive the drug, a placebo (negative control), or the standard drug (positive control) used in the treatment of the disease. Further toxicologic studies in animals will continue to assess chronic toxic potential.

Finally, in Phase III, double-blind or cross-over studies are conducted to further evaluate the efficacy of the drug in larger groups of thousands of patients. When Phase III is finished and if the results meet the goals initially established, a new drug application (NDA) will be submitted to the FDA or its congener in another country. After several years of preclinical research, four to six years of clinical trials, and as many as three years after the NDA has been submitted, the FDA may then approve marketing of the drug. At that point, Phase IV is initiated and a mechanism of post-marketing surveillance, including reporting of adverse effects, will be in place.

Compared with this elaborate process of approval, the mechanisms required for the marketing of HMs are extremely simple. To start, in many Western countries, including the United States and Canada, herbal medications are not legally considered drugs, but rather as dietary supplements and natural health products, respectively. Consequently, HMs are not legally required to undergo extensive preclinical investigation, and clinical trial evaluations are not required prior to the marketing of the herbal product. Rather, approval is based on traditional usage.

It should be noted that several herbal medications, namely in the European community, have been thoroughly evaluated, including safety and efficacy, product standardization, and well-conducted clinical trials with comparison to standard treatments (i.e., Phase III). These principles apply to the studies conducted to evaluate the efficacy of standardized preparations of saw palmetto (*Serenoa repens*) in the treatment of BPH [33; 34; 65].

SCIENTIFIC EVALUATION OF HERBAL MEDICATIONS

PRECLINICAL STUDIES AND EVALUATION IN CLINICAL TRIALS

The number of scientific studies aimed at unraveling the mechanism of action of HMs has undergone a remarkable growth in recent decades. Development of new legislation, availability of research funds to study the pharmacologic mechanisms of action and therapeutic efficacy of HMs, drug standardization, and implementation of clinical trials to assess HMs have played a central role in the development of an evidence-based approach to phytotherapeutics. The NCCIH in the United States and the NNHPD in Canada are pivotal in establishing advisory panels, coordinating scientific resources and expertise, and funding quality research on HMs [64; 66]. The American Society for Pharmacology and Experimental Therapeutics has long supported the increase in the National Institutes of Health's NCCIH budget for peer-reviewed research on botanical medications, particularly aimed at studying mechanisms of action and interactions with prescription drugs [67].

Scientific evidence on HMs should also be included in the basic curriculum in medical, pharmacy, dental, and nursing schools. Continuing education of healthcare professionals also contributes to a multidisciplinary and inclusive evidence-based assessment of HMs as part of a broader approach to maintenance of health and disease prevention.

IDENTIFICATION OF ACTIVE COMPOUNDS, ISOLATION, AND STANDARDIZATION

Standardization of the product and its individual chemical constituents is of major importance, and reliability of practices and procedures by the manufacturer is absolutely crucial. Several reports have analyzed the concentration of active ingredients present in herbal medications and compared the values obtained with those reported on the label by the manufacturer. Batch-to-batch variability has also been reported, and in one particular case of a compound containing ephedrine and methyl ephedrine, concentration of these substances varied by 180% and 1,000%, respectively [68].

The lack of standardization may also account for negative results obtained in some clinical trials [69]. One study revealed that, in the case of the antidepressant SJW (*Hypericum perforatum*), the amount of two of its most important chemical constituents, hypericin and pseudohypericin, can vary from 108% to 30% or even to as little as 0.1% of the amount reported on the label when a chemical analysis is conducted in a large number of samples from various manufacturers [70].

More reassuring results have been reported. The chemical composition of five of the most commonly used HMs was studied, and these results were compared to the information provided in the label by the manufacturer [71]. Results of this study, conducted by the University of California, Los Angeles (UCLA) Center for Human Nutrition, are encouraging and reflect a positive trend in increased quality and standardization of HMs by the manufacturers. For each product, three different samples from each of 12 bottles (6 bottles for each of the two separate batches) were collected. Five of the most commonly used HMs in North America were studied, specifically saw palmetto, SJW, echinacea, ginkgo biloba, and kava. Samples were purchased from 8 to 10 different suppliers nationally available in the United States. A greater consistency of composition was observed for samples purchased over the counter than for those purchased by mail order. A drastic decrease

in variability of the marker compound was observed between batches; saw palmetto and SJW were the least variable, and the most variable were ginseng and echinacea [71].

In fact, analysis of the saw palmetto specimens revealed that the concentration of the marker compound ranged from 77% to 106%, and for two of the manufacturers the values were within ±10% of their label claim. For SJW, the concentration of the marker compound hypericin ranged from 88% to 110%, and for two of the suppliers it was within ±10% of their claim. In the echinacea compounds studied, the concentration of the marker compound ranged from 78% to 173% of the reported value, and two of the manufacturers were within ±10% of the concentration claimed. Ginseng was the most variable HM, and the amount of the marker varied from 44% to 261% of the claim. Only for one of the manufacturers was the value within ±10% of the claim. For kava, the values were within ±10% of their claim for more than 70% of the suppliers [71].

In the United States, the National Institute of Standards and Technology (NIST), in collaboration with the National Institutes of Health Office of Dietary Supplements, the FDA, the Center for Drug Evaluation and Research, and the Center for Food Safety and Applied Nutrition, is developing procedures regarding the standardization of dietary supplements and natural health products [64; 72]. The development of standardization of active ingredients, accurate evaluation of chemical contaminants, such as toxic metals present in the soil and/or acquired during processing, and screening for microbiologic contaminants, such as *Escherichia coli*, will certainly contribute to an increase in consumer reassurance, and to the acceptance by larger numbers of conventional healthcare providers [73]. In 2007, the FDA issued guidelines to outline requirements and expectations regarding how dietary supplements are manufactured, prepared, and stored [74]. These practices are meant to reduce misidentification and contamination of dietary supplements by manufacturers and to reduce errors in purity, strength, and composition. The guidelines are updated periodically to ensure current safe practices, with the last update conducted in 2013 [74; 75]. Although the practices are expected to be adhered to, to date there is no FDA approval process [74]. Several organizations, including the U.S. Pharmacopeial Convention (USP), NSF International, and Consumerlab.com, offer voluntary dietary supplement verification programs that provide standards and monographs for determining product and ingredient identity, strength, quality, and purity, and award a seal of approval mark to dietary supplement products that meet their criteria [74; 76; 77; 78].

Legislation requiring the standardization of herbal medications has been successfully implemented in several countries of the European Union, with benefits regarding the scientific assessment of pharmacologic properties and conduction of well-controlled clinical trials and mandatory reporting of adverse effects [79]. It has often been argued that a stricter control of phytochemicals further enhances their role as useful complementary rather than alternative therapeutic tools to conventional medications [64; 74; 75].

EVIDENCE-BASED REVIEW OF THE MOST COMMONLY USED HERBAL MEDICATIONS

Considering the large number of available HMs, it is beyond the scope of this course to exhaustively review them all. Fourteen of the most commonly sold HMs will be reviewed following an evidence-based assessment of several parameters relevant to clinical practice (***Table 1***). For each phytomedicine, the following subjects will be presented:

- Common name and scientific name
- Historical and current use
- Pharmacology
- Evidence-based therapeutic use and effectiveness
- Adverse effects and drug interactions
- Toxicology
- Dosage

A REVIEW OF HERBAL MEDICATIONS				
Common Name	**Scientific Name**	**Typical Modern Uses**	**Efficacy**	**Safety**
Saw palmetto	*Serenoa repens* or *Sabal serrulata*	Treatment of benign prostatic hyperplasia (BPH)	★★E	S
St. John's wort	*Hypericum perforatum*	Treatment of mild-to-moderate depression	★★E	AEs/DIs
Ginkgo	*Ginkgo biloba*	Management of age-related memory loss, dementia, early stages of Alzheimer disease	★★E	S
Ginseng	*Panax ginseng*, *P. quinquefolius*, *P. japonicus*	Treatment of cardiovascular diseases, diabetes, immunomodulation, menopause	★E	No S data
Echinacea	*Echinacea angustifolia*, *E. pallida*, *E. purpurea*	Treatment of common-cold symptoms	★★E	S
Kava	*Piper methysticum*	Treatment of anxiety, stress, insomnia	★★★E	AEs/DIs/UnS
Garlic	*Allium sativum*	Prevention and treatment of hyperlipidemia, hypertension, cardiovascular disease	★★E	AEs/DIs
Valerian	*Valeria officinalis*	Treatment of insomnia, anxiety	★★E	S
Andrographis	*Andrographis paniculata*	Prevention of upper respiratory tract infections	★★E	AEs/DIs
English ivy leaf	*Hedera helix*	Treatment of bronchitis and asthma	★★★E	S
Peppermint	*Mentha x piperita* Lamiaceae	Management of irritable bowel syndrome, dyspepsia	★★E	S
Ginger	*Zingiber capitatum* or *Zingiber officinale*	Treatment and prevention of nausea	★★★E	S
Soy	*Glycine max*	Treatment of cardiovascular disease, osteoporosis	★E	No S data
Chamomile	*Chamaemelum nobilis* or *Matricaria recutita*	Management of inflammatory diseases	★★E	S

Source: Compiled by Author *Table 1*

The therapeutic effectiveness of each medication is based on published scientific data regarding in vitro and in vivo studies of the mechanism of action and clinical studies, including randomized clinical trials, clinical studies, and meta-analyses. Accordingly, each herbal product is ranked into one of the following four categories:

★★★E: Clinically effective: Demonstrated by multiple randomized clinical trials

★★E: Clinically beneficial: Demonstrated by several controlled clinical trials, although some studies show conflicting or inconclusive results

★E: Limited effectiveness: Demonstrated by controlled clinical trials

No E data: Nonexistent or minimal supporting scientific evaluation

Product safety guidelines follow the same general rules applicable to mainstream drugs, and use during pregnancy, lactation, and childhood should be restricted to compounds tested for teratogenicity, carcinogenicity, and general toxicity. Otherwise, it is not advisable for the patient to be exposed to an untested HM. As a guideline, a product is ranked as:

- **S**: Safe
- **AEs/DIs**: Reported adverse effects and/or drug interactions
- **UnS**: Unsafe
- **No S data**: Unknown or limited controversial safety data

SAW PALMETTO

Efficacy: ★★**E**

Safety: **S**

Common Name and Scientific Name

Saw palmetto (*Serenoa repens or Sabal serrulata*) is also known as American dwarf palm or cabbage palm. This abundant and scrubby palm is indigenous to Florida and other southeastern states of the United States.

Historical and Current Use

Saw palmetto berries collected in the autumn were used by southeastern Native Americans in the treatment of urinary disorders and as an antiseptic. Saw palmetto extracts are now used in the treatment of BPH. In several European countries, use of this herb has been approved for the treatment of mild-to-moderate BPH. In Germany and Austria, saw palmetto is the most common form of therapy for BPH and represents more than 90% of all drugs prescribed for the treatment of this disorder [51; 65].

Pharmacology

The beneficial effects of standardized liposterolic extracts (phytosterols) in the treatment of BPH are now well established. The extracts represent 85% to 95% of free fatty acids from saw palmetto berries. Although the mechanism of action of saw palmetto is not completely understood, both in vitro and in vivo studies have revealed that the beta-sitosterol component of the extract correlates with its efficacy in the treatment of BPH [80; 81; 82]. Saw palmetto inhibits 5-alpha-reductase, the enzyme responsible for the transformation of testosterone into dihydrotestosterone (DHT), its tissue-active form [82; 83]. This mechanism of action is similar to the one described for finasteride and dutasteride [34; 82; 84]. It should be noted, however, that finasteride only inhibits the type 1 isoform of 5-alpha-reductase responsible for the production of different testosterone metabolites in the tissues, whereas saw palmetto inhibits both type 1 and type 2 isoforms [82; 85].

Other pharmacologic mechanisms of action of saw palmetto have been reported in the literature, namely that it competes with DHT and blocks androgen receptor stimulation, although this mechanism does not seem to correlate with its clinical efficacy [82; 86]. In vitro, saw palmetto extracts have alpha-1 adrenoceptor blocking properties like the standard drug tamsulosin, albeit this mechanism does not seem to account for saw palmetto's therapeutic effects as it is not observed at the lower concentrations, which are equivalent to the doses used in humans [87]. Interestingly, saw palmetto also inhibits cell proliferation and promotes apoptosis (i.e., programmed cell death) of prostate cancer cells, and its anti-inflammatory properties have been linked to its inhibitory actions on cyclooxygenase and lipoxygenase [88; 89; 90]. Together, all of these mechanisms may synergistically contribute to the therapeutic efficacy of saw palmetto extracts.

Evidence-Based Therapeutic Use and Effectiveness

The clinical effectiveness of saw palmetto in the treatment of mild-to-moderate BPH has been extensively studied. A comprehensive review of clinical studies that assessed the efficacy of saw palmetto versus placebo and saw palmetto versus finasteride was published in 2002 [65]. Results from 21 clinical trials, with a total of more than 3,000 patients, were analyzed. Several clinical parameters were evaluated, including urinary symptoms (e.g., dysuria, fullness, bladder residual volume), nocturia, urine flow rate, and prostate size (Boyarsky score, American Urologic Association Score, and International Prostate Symptom Score). The authors concluded that, "men taking saw palmetto were nearly twice as likely to report improvement in symptoms than men taking placebo," [65]. Also, "when compared to finasteride, saw palmetto provided similar responses in urologic symptoms and flow measures and was associated with a lower rate of impotence" [65]. This review, however, lacks information regarding comparisons between saw palmetto and alpha-1 adrenoceptor antagonists such as tamsulosin. Updates of this review, pub-

lished in 2009 and 2012, found that saw palmetto was not more effective than placebo for treatment of urinary symptoms consistent with BPH [91; 92].

A large study of more than 2,500 patients suffering from mild-to-moderate BPH compared the effectiveness of saw palmetto versus tamsulosin (704 patients), saw palmetto versus finasteride (1,098 patients), and two different doses of saw palmetto (160 mg twice a day versus saw palmetto 320 mg once a day) [34]. The study demonstrated a better outcome for patients taking saw palmetto than those taking either of the conventional drugs. Also, unlike the conventional drugs, no negative impact on sexual function was reported by patients treated with saw palmetto. These results further support other well-conducted studies [84; 93; 94; 95; 96; 97; 98; 99; 100]. Interestingly, saw palmetto was less effective than finasteride in reducing prostate volume, although involution of the prostate epithelium and reduction of inflammation was observed [34; 101]. Co-administration of saw palmetto and finasteride did not improve the treatment outcome. A report in which saw palmetto efficacy was not observed may be attributable to the study being conducted in patients with moderate-to-severe BPH, as opposed to the beneficial effects on patients with a mild-to-moderate condition [102]. In addition to the population cohort difference, the study also failed to conduct an appropriate dose-response study or raise the dose of saw palmetto to adjust for the severity of the medical condition.

In conclusion, evidence demonstrates that saw palmetto is effective in the treatment of mild-to-moderate BPH, is less expensive, and is better tolerated than conventional medications [94; 103]. In addition, it is now well established that saw palmetto does not interfere with the laboratory measurements of prostate specific antigen (PSA), used to assess the progression of prostate cancer [83; 104]. This presents a considerable advantage over 5-alpha-reductase inhibitors finasteride and dutasteride, which are known to mask PSA readings and prevent an accurate assessment of the disease progression and concurrent development of prostate cancer [83; 104]. The efficacy of saw palmetto in the treatment of more severe BPH has not been established.

Saw palmetto has also been used to treat other genitourinary disorders, including chronic prostatitis. However, clinical studies have shown a lack of significant improvement in patients treated with saw palmetto for one year, contrasting with the benefits observed in the group treated with finasteride [103; 105].

It has also been advocated that saw palmetto, either alone or in conjunction with other nutraceuticals, may also play an important role in the prevention of BPH, although the results obtained are inconclusive [106; 107]. The effects of chronic saw palmetto administration on the organization of chromatin structure in patients with BPH provides an insight of the molecular effects of saw palmetto potentially relevant to gene expression and tissue differentiation [108].

Adverse Effects and Drug Interactions

Consistently, all studies revealed the absence of significant side effects. A 2008 meta-analysis of saw palmetto trials found that serious adverse effects (e.g., cancer, sexual dysfunction, hepatotoxicity, respiratory problems) were no more common in treatment groups than in placebo groups [109]. Gastrointestinal symptoms, including nausea or abdominal pain, may occur in less than 2% of patients but seem to decrease when doses are taken with a meal. Because of its antiandrogenic properties, women should not take saw palmetto for treatment of urogenital problems if they take contraceptives, hormone replacement therapy, have breast cancer, or are pregnant [65; 82]. Furthermore, there is no clinical evidence supporting a beneficial effect of saw palmetto in the treatment of urethritis in women. Interactions with anticoagulants are negligible and arise from a single reported case [110]. In clinical trials, 3% of the subjects developed hypertension, compared with 2% treated with finasteride; however, this difference was not statistically significant [84].

Toxicology

Saw palmetto is widely considered a safe phytomedicine, and no serious toxicologic effects are reported in the scientific literature [109]. Results of the Complementary and Alternative Medicine for Urological Symptoms (CAMUS) trial found no evidence of toxicity among 369 patients randomized to 320 mg, 640 mg, or 960 mg daily saw palmetto extract at doses up to three times the usual clinical dose during an 18-month period [111].

Dosage

Standardized lipophilic extracts of saw palmetto are administered at a dose between 100–400 mg twice daily for the treatment of BPH [33; 34; 51; 82]. A dose of 160 mg twice a day is the most commonly used dosage in clinical trials [82]. Therapeutic benefits are observed within three to four weeks after the initiation of treatment, which usually lasts for three to six months.

ST. JOHN'S WORT

Efficacy: **★★E**

Safety: **AEs/DIs**

Common Name and Scientific Name

St. John's wort (*Hypericum perforatum*) is also known as amber touch-and-heal, goatweed, and klamath weed.

Historical and Current Use

This perennial, native to Europe, Western Asia, and North Africa, is a resilient weed, widespread in parts of the United States and southern Canada. The plant has golden-yellow flowers that bloom in the summer, which are collected and dried. The medicinal use of SJW as a topical anti-inflammatory and for wound healing has been known since ancient Greece. Extracts have been used in folk medicine for the treatment of depression and other mood disorders and also as a diuretic. Today, SJW is used primarily for the treatment of mild-to-moderate depression and has traditionally been the most commonly prescribed antidepressant in Germany, where it is available as a prescription medication [79; 112].

Pharmacology

Several chemicals, including naphthodianthrones (e.g., hypericin, pseudohypericin), phloroglucinols (e.g., hyperforin), flavonoids (e.g., quercetin), and essential oils, are the primary constituents of SJW [82; 113]. Formulations are standardized to concentrations of hypericin, usually 0.3% to 0.4%, which is considered the active ingredient responsible for the antidepressant properties of SJW. Clinical and pharmacologic studies, however, have shown that hyperforin concentrations of 2% to 4% correlate closely with antidepressant efficacy [114; 115].

The pharmacologic mechanisms of action of SJW extracts relevant to its antidepressant effect are complex. Hypericin may have a minor role in MAO inhibition, a mechanism shared with the classical antidepressant phenelzine [82]. This mechanism, however, is not considered clinically significant because it is only observed at concentrations 100 times higher than those used to treat depression [33]. Hyperforin is generally agreed to be the active component [82]. Both hypericin and hyperforin inhibit synaptic reuptake of serotonin, which is the same action as fluoxetine and paroxetine, but they also inhibit the reuptake of dopamine and noradrenaline, like other antidepressants including venlafaxine [82; 116].

After a single dose, the half-life of hypericin is four to six hours, whereas after chronic administration, the half-life of hypericin is one to two days [117; 118]. These values are comparable to those observed for fluoxetine (one to three days) and the selective serotonin re-uptake inhibitor (SSRI) paroxetine (12 hours) [48].

Long-term administration of SJW extracts increase the synaptic density of serotonin receptors by 50%, whereas the receptor affinity remains unchanged [119]. The increase in number of serotonin receptors was observed after a minimum 10 to 12 days treatment, a time frame that correlates with the well-known therapeutic delay of standard antidepressant drugs [120]. Together, the increased number of serotonin receptors and the increase in synaptic concentrations of neurotransmitters provide a mechanistic explanation for the antidepressant effects of SJW [113; 117; 121].

SJW extracts also have antibacterial properties, accounting for the antiseptic and wound-healing properties of topical formulations. Hyperforin is effective in inhibiting gram-positive bacteria, including penicillin-resistant and methicillin-resistant *Staphylococcus aureus*, but it is not effective against gram-negative bacteria. One randomized trial showed the effectiveness of SJW topical application in the treatment of atopic dermatitis [122; 123; 124]. In one small pilot study, SJW significantly improved erythema, scaling, and thickness in plaques of patients with mild psoriasis [125].

Some in vitro studies have shown that SJW extracts have antiviral properties, namely against influenza virus, and one study has identified a novel protein in SJW that suppresses gene expression in human immunodeficiency virus (HIV) [122; 126]. However, a Phase I clinical trial provided negative results [127]. It is important to emphasize that SJW should not be administered to HIV or acquired immune deficiency syndrome (AIDS) patients because of the pharmacokinetic interactions with antiretroviral protease inhibitors, such as indinavir, saquinavir, and ritonavir, and non-nucleoside reverse transcriptase inhibitors, such as efavirenz, which are metabolized by CYP3A4. Induction of CYP3A4 by SJW drastically reduces drug concentrations in the blood by 50% to 80% with subsequent loss of HIV suppression [128].

Finally, in vitro studies have shown that hyperforin and hypericin inhibit tumor cell growth by induction of apoptosis [129; 130]. The use of SJW extracts in the treatment of triple-negative breast cancer is an area of ongoing research [131; 132]. Although these compounds seem to have high efficacy, their potential clinical usefulness as anticancer agents is, at this point, merely speculative.

Evidence-Based Therapeutic Use and Effectiveness

Several clinical trials have assessed the efficacy and safety of SJW preparations in the treatment of depression. A 2005 Cochrane Review extensively analyzed published randomized, double-blind trials comparing SJW with placebo (26 studies) or with standard antidepressants (14 studies) [133]. SJW was demonstrated to be "more effective than placebo and similarly effective as standard antidepressants for treating mild-to-moderate depressive symptoms" [133]. The treatment period lasted from 4 to 12 weeks.

Two large clinical trials conducted in the United States did not support these findings [134; 135]. Both studies were conducted on patients who suffered from moderate-to-severe depression, and many patents presented with a history of drug-resistant depression, which may have affected the outcomes. The Hypericum Depression Trial Study Group has also been criticized because the response rates for both the SJW-treated and the sertraline-treated groups were not different from the placebo-treated group. In another randomized study, conducted in Germany, the effect of SJW (900 mg/day standardized SJW extract) on moderate-to-severe depression was compared with paroxetine (20 mg/day) [42]. The treatment was continued for 6 weeks, and in initial non-responders, after 2 weeks of treatment the doses were increased by 100%.

The results indicated that, in the treatment of moderate-to-severe depression, hypericum extract was, "at least as effective as paroxetine" and was better tolerated [42]. A 2008 Cochrane Review of trials examining the treatment of severe depression with hypericum reached similar conclusions as to its efficacy in comparison to placebo and conventional antidepressants. Also, subjects in the SJW groups had a lower drop-out rate, possibly due to fewer side effects [136].

It is established in the scientific literature that standardized SJW extracts are effective and safe in the treatment of mild-to-severe depression [51; 122; 133; 136; 137; 138; 139].

Adverse Effects and Drug Interactions

SJW is well-tolerated and generally safe. Mild side effects include gastrointestinal symptoms, mild sedation or tiredness, dizziness, headache, and dry mouth. Incidence of side effects in SJW-treated patients (4% to 12%) is similar to that observed in the placebo-treated group and significantly lower than standard antidepressants [51; 82; 140; 141]. Two rare adverse events may occur after administration of SJW. First, transient photosensitivity may occur when administered in higher doses, and second, the occurrence of a serotonin syndrome when co-administered with SSRIs is possible [82; 142]. The latter results from the synergistic interaction between the drugs raising serotonin to abnormally high levels [45; 46; 47; 48; 143].

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the American Psychiatric Association, St. John's wort may be considered for patients with major depression who prefer complementary and alternative therapies, although evidence for its efficacy is modest at best and careful attention to drug-drug interactions is needed.

(https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf. Last accessed June 10, 2022.)

Strength of Recommendation: III (May be recommended on the basis of individual circumstances)

Pharmacokinetic interactions with SJW are rare and only occur at higher doses. Induction of cytochrome P450 isoforms, namely CYP3A4 and CYP1A2, by SJW results in a decreased bioavailability of drugs metabolized by this liver enzyme. These drugs include the immunosuppressant cyclosporine, the anticoagulant warfarin (bleeding), oral contraceptives (causing breakthrough bleeding), antiretroviral protease inhibitors, and theophylline [36; 51; 82; 128; 138]. A report has also shown a reduction in plasma levels of the HMG-CoA reductase inhibitor simvastatin [144]. Activation of the intestinal P-glycoprotein transporter also accounts for the reduction in plasma concentrations of digoxin [128].

In conclusion, although SJW has consistently been reported to be a safe drug when administered within its therapeutic range, its potential interactions with other drugs or herbs (e.g., kava) require caution and a thorough investigation during patient interview prior to use.

Toxicology

It is widely accepted in the literature that, when used within the normal therapeutic range, SJW is devoid of toxicologic properties. In high doses, SJW can elicit photosensitivity. Phototoxicity results from light-induced transformation of hypericin-derived pigments and has been reported in patients with HIV receiving high doses of intravenously administered SJW [127]. To date, only one study of potential teratogenicity during human pregnancy has been conducted, with data collected from the pregnancies of 54 SJW-treated women and 108 women either treated with conventional antidepressants or receiving no pharmacologic treatment. Rates of fetal malformations were similar among the three test groups and similar to rates of malformations in the general population; additionally, premature and live birth rates among the three test groups were similar [145]. Further research in this area is needed, and SJW administration in pregnant patients should therefore be avoided [82].

Dosage

Standardized preparations of SJW are usually administered from 500–1,800 mg per day [51; 122; 133; 137; 138]. In most studies, 900 mg was administered daily (450 mg twice a day, or 300 mg three times a day) [82].

GINKGO

Efficacy: ★★**E**

Safety: **S**

Common Name and Scientific Name

Ginkgo (*Ginkgo biloba*), also known as kew tree, ginkyo, or duck-foot tree (because of the characteristic fan-shaped leaves), is a large, resilient, and long-living tree cultivated by monks in China, where many individual specimens are documented to be more than 1,000 years old. Ginkgo trees, often known as living fossils, are the only survivors of the entire Ginkgoaceae family. Fossils of this tree that date back more than 200 million years have been identified in areas throughout the Northern Hemisphere, including Europe and North America. Ginkgo trees were brought into Japan and other East Asian countries around 1200 C.E., possibly in relation to the spread of Buddhism. In the seventeenth century, they were reintroduced in Europe and, more recently, in North America. Ginkgo is a resilient tree to parasites and diseases and, interestingly, also survived the Hiroshima atomic bombing.

Historical and Current Use

The designation originates from ginkgo, meaning silver apricot, and biloba, which describes the two-lobed shape of the leaf. Historically, leaf extracts have been used in traditional Chinese medicine to treat a variety of disorders, including asthma, allergies, premenstrual syndrome, tinnitus, cognitive impairments resulting from aging and dementia, and vascular diseases including central and peripheral vascular insufficiencies. Standardized leaf extracts are used based on their neuroprotective and vascular regulatory properties in the management of intermittent claudication, age-related memory loss, dementia, and early stages of Alzheimer disease [33; 146]. Plum-like fruits of the female tree are not edible and cause contact dermatitis. Ingestion of the seeds causes headache, nausea, diarrhea, and even seizures when ingested in larger amounts [51; 147].

Pharmacology

More than 40 chemical components of ginkgo have been isolated, including flavonoids, terpenoids, flavones, catechins, sterols, and organic acids. The two most important and active groups of chemicals are the flavonoids, such as quercetin and kaempferol, and the terpenoids, including ginkgolides A, B, C, J, and M and bilobalide. Ginkgo biloba extracts available in Europe and North America are standardized to 24% flavonoids and 6% terpenoids and have been used in hundreds of in vitro and in vivo studies and numerous clinical trials [33; 51].

The biologic properties of ginkgo biloba extract result from the complex interactions among chemical components, and it is therefore difficult to establish a well-defined cause-effect relationship between specific elements and biologic effect. Nevertheless, it is now well established that flavonoids have antioxidant and free-radical scavenger properties. They also have a protective effect against apoptosis and beta-amyloid neurotoxicity of Alzheimer disease and may play an important role in the prevention of neuronal degeneration in Parkinson disease [148; 149; 150; 151].

Terpenoids, particularly ginkgolides, inhibit the platelet activating factor (PAF), and therefore prevent platelet aggregation, have anti-inflammatory properties, and prevent contraction of smooth muscles in the respiratory tract [146]. The vasodilatory properties of standardized ginkgo biloba extract preparations are attributed to the stimulation of endothelium-derived relaxing factor and regulation of nitric oxide release [51].

Ginkgo biloba extract also stimulates receptor expression and neurotransmitter concentrations in the brain, particularly acetylcholine [152; 153; 154; 155]. This latter mechanism of action is similar to the cognitive enhancer, tacrine, previously used in the treatment of Alzheimer disease [156].

Evidence-Based Therapeutic Use and Effectiveness

There is scientific evidence supporting the beneficial use of standardized ginkgo biloba extract, 120–240 mg/day, in the treatment of mild-to-moderate cognitive impairment, such as age-related dementia, multi-infarct dementia, and possibly Alzheimer disease [33; 157; 158; 159]. Some studies show that ginkgo biloba extract is as effective as the acetylcholinesterase inhibitor donepezil (Aricept) in the treatment of patients with early stages of Alzheimer disease, although these findings are not supported by additional studies [160]. One study reported that the combination therapy of gingko biloba extract plus donepezil was more effective than either therapy alone [161]. A 2015 systematic review noted a positive response (defined as improvement in cognitive function and activities of daily living and reduced neuropsychiatric symptoms) to a 240 mg/day dose in study participants with neuropsychiatric symptoms related to a dementia diagnosis but not in individuals thought to have Alzheimer disease [159]. Although studies have shown that ginkgo biloba extract appears to be safe and with no excess side effects compared with placebo, the evidence that it has predictable and clinically significant benefit for people with dementia or cognitive impairment is inconsistent, and whether ginkgo biloba leaf extract is beneficial for the treatment of Alzheimer disease remains controversial. Researchers recommend that the findings be confirmed by larger clinical trials [33; 162; 163; 164; 165; 166; 167; 168].

Clinical trials have assessed the effectiveness of ginkgo biloba extract in the treatment of cerebral insufficiency, which is a syndrome combining mild cognitive impairment, headaches, confusion, poor concentration, fatigue, and dizziness, and is associated with mood disorders. Long-term treatment with ginkgo biloba extract at 120–150 mg/day reduced symptoms and improved short-term memory [169; 170].

Some evidence supports the effectiveness of ginkgo biloba extract in the treatment of peripheral vascular disorders, including intermittent claudication and, to a lesser degree, Raynaud syndrome [33; 171]. In fact, one clinical trial demonstrated that ginkgo biloba extract is as effective as pentoxifylline, the standard medication for the treatment of intermittent claudication [172]. Despite its ability to improve circulation, multiple clinical trials failed to show the efficacy of ginkgo biloba extract in the treatment of Raynaud disease compared with conventional therapy or placebo [173; 174]. One analysis concluded that while ginkgo biloba treatment did slightly increase treadmill walking time of participants with peripheral artery disease and led to a slight reduction of pain, the therapy produced only modest overall improvements [175].

The beneficial effects of ginkgo biloba extract in a variety of medical conditions, such as tinnitus, cochlear disorders, and vascular retinopathies (including macular degeneration), have also been reported in the scientific literature, although larger studies are required to confirm the clinical outcome. It is possible that in these conditions, ginkgo biloba extract is the most effective when administered in conjunction with standard therapies.

Adverse Effects and Drug Interactions

Consistently, ginkgo biloba extract is considered a safe and well-tolerated drug when used at the recommended dose for periods of up to six months. In most clinical studies, the incidence of adverse effects is similar to placebo. Less than 2% of patients develop side effects, namely headache, nausea, or mild gastrointestinal symptoms [51].

Two cases of subarachnoid bleeding have been reported in patients taking ginkgo biloba extract and warfarin, and one case of subarachnoid bleeding and intraocular hemorrhage has also been reported in a patient taking ginkgo biloba extract and acetylsalicylic acid concurrently. A case of postoperative bleeding has also been reported after laparoscopic surgery [176]. In these cases, however, the causal relationship between ginkgo biloba extract and bleeding was not clearly established. Furthermore, bleeding was not reported in any of the clinical trials involving hundreds of thousands of subjects [51]. Nonetheless, it is advisable to discontinue ginkgo biloba extract administration several days prior to surgery [82].

Toxicology

Although in vivo studies did not report either embryotoxic or teratogenic effects of ginkgo biloba extract, this phytomedicine should be avoided during pregnancy and breastfeeding [33; 82; 177]. As mentioned, severe contact dermatitis, similar to that caused by poison ivy, can result from direct contact with the pulp of ginkgo fruit of the female tree. Ingestion of ginkgo seeds, but not leaves, in large amounts (50 or more) causes headache, nausea, diarrhea, and even seizures. This condition is known in Japan as *gin-nan* [82; 147]. Pollen from the male tree can be allergenic for sensitive individuals [51].

Dosage

Standardized extracts are administered at a daily dose of 120–240 mg, in two or three equal doses, for periods of six months or longer [33; 82; 157; 158].

GINSENG

Efficacy: **★E**

Safety: **No S data**

Common Name and Scientific Name

Ginseng is a designation that applies to an HM that is prepared from the root of different plants of the Araliaceae family. Asian ginseng is obtained from *Panax ginseng,* American or Canadian from *P. quinquefolius*, and Japanese from *P. japonicus*. Siberian (Russian) ginseng is obtained from the root of *Eleutherococcus senticosus*, a plant that, although a member of the same Araliaceae family, is not a member of the *Panax* genus and, hence, is not considered a true ginseng. High-quality ginseng root is harvested in the autumn from plants that are 5 to 6 years old.

Historical and Current Use

The name *Panax* is derived from the Greek *panacea*, meaning cure-all. True to its etymology, the root of the plant has been historically used for a variety of purposes, such as improvement of cognitive and physical performance (i.e., ergogenic effect), cardiovascular diseases (e.g., hypertension), diabetes, cancer, immunomodulation, and menopause. Evidence-based knowledge regarding ginseng's medicinal properties is limited and has generally failed to support historical claims, possibly with the exception of clinical trials assessing the hypoglycemic properties of ginseng [33; 178; 179; 180; 181; 182].

Pharmacology

Several chemicals, including polysaccharides (e.g., ginsan, ginsenans) and a variety of saponins known as ginsenosides, are found in ginseng [82]. Ginsenosides, the most important bioactive compounds, are complex molecules with a steroidal skeleton and modified side chains. The concentration of different ginsenosides varies among species, age of plant, and season of harvest and contributes to the limited understanding of the pharmacologic and physiologic properties of each compound [82]. Adulterants are commonly found in ginseng preparations due to the high cost of authentic ginseng roots, and the presence of natural methylxanthines also may contribute to some reported physiologic effects [82].

Ginsenosides Rb1, Rg1, and Rg2 improve cognitive performance, a mechanism likely related to the stimulation of cholinergic activity implicated in the mechanisms of learning and memory [82; 183; 184]. Both in vitro and in vivo models of Parkinson disease have shown that ginseng extracts have a neuroprotective effect against 1-methyl-1-phenyl-

1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonism in rodents [185]. Gintonin, a novel glycolipoprotein, is a ginseng derivative found in the root of Korean ginseng [186]. Gintonin holds lysophosphatidic acid (LPA), a serum phospholipid that stimulates cell proliferation, migration, and survival [186; 187; 188]. It is thought that gintonin causes significant elevations in levels of intracellular calcium that promote calcium-mediated cellular effects. Research suggests that gintonin has antioxidant and anti-inflammatory effects against different models of neurodegeneration [186; 187; 189]. In studies of neurodegenerative diseases, such as Alzheimer disease and Parkinson disease, gintonin has demonstrated neuroprotective activity by providing action against apoptosis- and oxidative stress-mediated neurodegeneration [186; 187; 189]. In vitro and in vivo studies have demonstrated that ginseng polysaccharide GH1 and ginsenosides Rb2 and Re effectively reduce hyperglycemia and liver glycogen in genetically obese mice as well as in patients with and without type 2 diabetes [178; 190; 191]. Ginseng also stimulates insulin synthesis and release, an effect possibly caused by the increase in nitric oxide production by ginseng [192]. Preliminary results suggest that ginseng also regulates intestinal absorption of glucose and glycosylation of hemoglobin A1c (HbA1c) [179]. A variety of studies (human, animal, cell) have shown that different processed ginseng extracts and specific ginsenosides possess beneficial effects on type 2 diabetes. Most studies of individual ginsenosides have focused on Rb1, Re, or Rg1 as these are the main components of ginseng and easily obtained. However, their large molecule structure results in poor systemic bioavailability. It is thought that these large-molecule ginsenosides may be a form of storage for saponins in ginseng plants rather than the active form in vivo. The smaller molecule ginsenosides (Rg3, Rh1) may be the ingredient that exerts therapeutic effects [193; 194; 195].

In vitro studies have shown that ginsenosides cause vasodilation and lower blood pressure and that panaxynol, a potent inhibitor of thromboxane A2, prevents platelet aggregation [196; 197]. However, further scientific evidence of the antihypertensive effects of ginseng is required prior to considering its potential benefits in cardiovascular diseases. One double-blind controlled trial found that ginseng significantly improved arterial stiffness and systolic blood pressure but had no noted effect on diastolic blood pressure [198]. Research challenges to understanding the potential benefits of ginseng in cardiovascular disease include understanding and identifying the distinct cardiovascular properties of the different ginsenoside compositions, identifying what likely are multifaceted mechanisms that account for the effects of the distinct compositions, and determining which ginsenosides mediate which cardiovascular properties [199].The immunostimulatory and antiproliferative properties of ginseng have also been reported in the scientific literature, but further studies are required [200]. Ginseng has been studied for use in the treatment of menopause symptoms, due to the steroid-like chemical composition of ginsenosides, but the results were inconclusive.

The Society for Integrative Oncology recommends 2,000 mg daily of encapsulated American ginseng root powder can be considered to improve fatigue during chemotherapy and radiation for breast cancer.

(https://acsjournals.onlinelibrary.wiley.com/doi/full/10.3322/caac.21397. Last accessed June 10, 2022.)

Level of Evidence: C (Recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.)

Evidence-Based Therapeutic Use and Effectiveness

A Cochrane Review has concluded that the beneficial effects of ginseng preparations were "not established beyond reasonable doubt" [184]. Other literature reviews, however, have reported that ginseng extracts effectively reduced blood glucose levels in patients with type 2 diabetes, although information regarding dosage and long-term effects is still incomplete [33; 179; 201]. A modest improvement in cognitive performance has also been reported [33; 179]. Ginseng is also being investigated for use in the treatment of chronic fatigue, respiratory tract infections, stroke, dermatologic diseases, and as an adjuvant to chemotherapy in the treatment of non-small-cell lung cancer [202; 203; 204; 205; 206; 207; 208].

Adverse Effects and Drug Interactions

Ginseng preparations are generally well tolerated when administered within the recommended dosage, and the available animal and human studies suggest that it is safe [82]. As a result of its hypoglycemic properties, it should be used cautiously in patients with type 2 diabetes concurrently treated with oral hypoglycemic drugs. Improvements in blood glucose measures and glycemic control with ginseng use have been inconsistently reported [82].

Anticoagulant properties may also account for a few reports of epistaxis and vaginal bleeding. In contrast, a randomized, controlled clinical trial has shown that ginseng increases the risk of blood clotting in patients treated with warfarin. This pharmacokinetic interaction occurs only after long-term administration of ginseng and results from the induction of hepatic CYP450 isoforms responsible for warfarin metabolism [209].

Interactions between ginseng and MAO inhibitors have also been reported and may cause headaches, insomnia, nervousness, and mood disorders. Pharmacokinetic (e.g., CYP450 induction) and pharmacodynamic potentiation of antihypertensive drugs have also been reported, and it should not be administered to hypertensive patients [33; 82].

A few case reports describe the occurrence of diarrhea, unstable mood, skin rash, or itching after long-term administration. Ginseng has also been associated with loss of menstrual periods and vaginal bleeding in menopausal women. Therefore, ginseng should not be administered to patients with hormone-sensitive conditions, such as breast or uterine cancer and endometriosis [82]. In men, it may be associated with estrogen-like effects, such as reduced libido and gynecomastia [33].

Toxicology

At normal doses, ginseng is reported in the literature as being safe. Nevertheless, ginseng should be avoided during pregnancy and breastfeeding [33; 82; 137]. A case of reversible masculinization of a newborn girl when a mother allegedly took *Eleutherococcus senticosus* (Siberian ginseng) during pregnancy has been reported [210]. In fact, it resulted from the adulteration of the original product and substitution of *Periploca sepium*, a vine of the milkweed family, for ginseng. *Periploca sepium* has been used in traditional Chinese medicine for its stimulatory and libido enhancing effects. Accordingly, it should be emphasized that the mentioned report has been erroneously used as published evidence of ginseng toxicity [211; 212]. Pediatric safety concerns regarding ginseng treatment for upper respiratory tract infections were addressed in a 2008 Canadian trial involving 75 subjects (3 to 12 years of age) given standard doses, low doses, or placebo. The treatments were well tolerated, considered safe, and warrant additional research for use on these and other types of pediatric infections [213].

Dosage

Purified ginseng extracts are generally standardized to 4% or 7% ginsenoside contents. Usually, 100–200 mg of standardized 4% extract is administered orally once or twice daily, for as many as 12 weeks [82]. In traditional Chinese medicine, 0.5–2 g/day of dried ginseng root, equivalent to 200–600 mg of standardized extract, is commonly used.

Long-term administration of ginseng should not exceed 1 g/day of the dry root form or 400 mg/day in the extract form. It is administered daily for two to three weeks, then discontinued for one to two weeks. This treatment schedule may be repeated for several months [33; 137].

ECHINACEA

Efficacy: ★★E

Safety: S

Common Name and Scientific Name

The designation echinacea applies to several plants of the Asteraceae/Compositae family, including *E. angustifolia*, *E. pallida*, and *E. purpurea*. Echinacea, also known as coneflower, narrow-leafed cone-flower, or black-eyed Susan, is indigenous to North America. It adapts well and thrives in temperate climates, including Europe and Asia, where it has been planted for decorative and medicinal purposes.

Historical and Current Use

Echinacea was used by Native Americans for a wide variety of conditions, including chewing the roots for toothaches and gingivitis, root and leaf infusion for stomach pain, colds, and infections, and topically as a disinfectant and for wound healing. The use of echinacea was quickly adopted by early European settlers, and shortly thereafter, it became widely used by European herbalists and physicians. In Germany, it has been commonly used in mainstream medicine for almost a century. The German Commission E has approved the use of echinacea for the amelioration of common-cold symptoms, upper respiratory infections, and urinary tract infections, as well as topical administration for treatment of superficial wounds [214]. The scientific literature generally supports a beneficial effect of echinacea extracts in the treatment of cold symptoms, but evidence of its efficacy in the prevention of colds is still limited [215; 216]. Echinacea is the most widely sold HM in the United States and is the third most popular natural product overall (surpassed only by fish oil and glucosamine) [10].

Pharmacology

Preparations from different portions (e.g., root, leaves) of the echinacea plants (e.g., *E. angustifolia*, *E. purpurea*, *E. pallida*) are collected during the blooming season. The products are usually dried, and several chemical components, namely caffeic acid derivatives (e.g., echinacosides, cichoric acid derivatives), flavonoids (e.g., quercetin), alkylamides, and polysaccharides, are identified upon alcoholic extraction [51]. Laboratory analysis of echinacea extracts with high-pressure liquid chromatography provides the chemical fingerprint of different echinacea species. In fact, in *E. purpurea*, no echinacosides are detected, whereas they are abundant in *E. angustifolia* and *E. pallida*. On the other hand, the amount of cichoric acid present in *E. purpurea* is 40- to 60-fold higher than that present in *E. angustifolia* and *E. pallida*, respectively [217]. The relative concentration of various chemicals within the same species also varies in different plant parts. Echinacoside concentrations are higher in the root, whereas cichoric acid concentrations are higher in the flower of all echinacea species than in other plant parts.

Due to its complex chemical makeup, the precise pharmacologic and therapeutic properties of each compound remain to be determined. Naturally occurring phenols, such as the caffeic acid derivatives, are potent antioxidants due to the presence of hydroxyl groups on aromatic rings that scavenge tissue-damaging free radicals [217]. In vitro experiments revealed that alkylamides from echinacea inhibit cyclooxygenase and 5-lypoxygenase, accounting for its anti-inflammatory properties [218; 219].

The immunostimulatory properties of echinacea have been demonstrated both in vitro and in vivo. Nonspecific effects, such as macrophage proliferation, stimulation of interleukin-1, tumor necrosis factor, and interferon stimulation, as well as specific effects, such as increase in numbers of T lymphocytes and natural killer cells, have been reported in several studies [33]. Because the total immunostimulatory effect of echinacea in humans remains to be established, the German Commission E discourages the use of echinacea in patients with autoimmune diseases.

Many preparations are standardized to 4% to 5% echinacosides, while others also report the concentration of cichoric acid. A detailed study conducted by investigators from the University of Colorado Health Sciences Center analyzed 59 samples of echinacea-only preparations purchased from 11 retail outlets in the Denver area [220]. Ten percent of the samples did not contain measurable amounts of echinacea, and the species content only agreed with the label in 52% of the cases. Twenty-one preparations claimed to be standardized, but only nine met the composition reported on the label. Although the efficacy of echinacea in the treatment of some medical conditions has been reasonably established, the lack of species identification and standardization, as well as product contamination/adulteration, should be thoroughly investigated prior to being administered. The poor quality of many available products certainly contributes to, or may account for, the conflicting results and significant number of negative reports published in the scientific journals.

Evidence-Based Therapeutic Use and Effectiveness

The therapeutic effectiveness of echinacea preparations in prevention and treatment of the common cold has been extensively studied. Several extensive reviews and meta-analysis studies have been published, and some have provided conflicting or inconclusive results.

Researchers evaluated the therapeutic effectiveness of echinacea in the treatment of the common cold based on nine placebo-controlled clinical trials and concluded that its effectiveness has not been established [221].

Three randomized, double-blind, and placebo-controlled trials assessed the effectiveness of echinacea on the avoidance of and severity of colds. Consistently, they all revealed that subjects preventively treated with standardized echinacea extracts acquired fewer colds (22%, 58%, 49%) than the placebo group (33%, 82%, 56%) [222; 223; 224]. However, due to the small number of subjects studied in each trial, the decreases were not statistically significant. A meta-analysis evaluated these three clinical trials, and due to the common methodology used, the results of almost 400 subjects were combined [215]. The meta-analysis suggests that the risk of developing a cold was 55% higher in the placebo than in the echinacea-treated group, a statistically significant difference.

A 2014 Cochrane review also evaluated the effects of echinacea on naturally acquired colds [225]. Twenty-four published trials met their inclusion criteria. In the treatment of colds, echinacea was not effective in most clinical trials and beneficial or marginally better than the placebo group in only one trial. In the 12 prevention clinical trials, no significant difference was observed between echinacea and placebo groups, but a later analysis found a 10% to 20% reduction in cold risk [225]. Interestingly, the authors also commented on the pervasive issue of lack of standardization, the variability in bioactive composition of echinacea preparations, and the likelihood that they may contribute to, or account for, the lack of consistency in treatment and prevention outcomes.

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the Institute for Clinical Systems Improvement, the evidence on the efficacy of *Echinacea* for the prevention of viral upper-respiratory infection is limited. The studies are either small or of low quality, or the evidence is insufficient to make conclusions. More studies are needed.

(https://www.icsi.org/wp-content/uploads/2019/01/RespIllness.pdf. Last accessed June 10, 2022.)

Level of Evidence: Expert opinion

In vitro and in vivo studies, and in some cases preliminary clinical evidence as well, support other possible therapeutic applications of echinacea preparations (e.g., immunostimulant, anti-infective, wound-healing) [82]. However, due to the limited data, the actual therapeutic outcome is inconclusive.

Adverse Effects and Drug Interactions

In clinical trials, echinacea preparations are generally well tolerated, and the number of patients dropping out of studies is similar to the placebo group. A single study conducted in children 2 to 11 years of age reported the occurrence of an allergic rash [226]. In adults, one review found that the most common adverse effects were nausea and vomiting (<1%), abdominal pain (<1%), and mild drowsiness and headache (<1%) [33]. One case of anaphylaxis has been reported in a patient with a history of atopic reactions [227]. Echinacea should not be administered to individuals with allergies to other plants of the Asteraceae family, including daisies, ragweed, marigolds, and chrysanthemums. It is also recommended to avoid echinacea if currently on immunosuppressants [82].

Toxicology

Both in vitro and in vivo studies suggest that, even when administered at doses several-fold higher than the ones normally used, echinacea is devoid of toxicity. Analysis of 112 pregnant women who were exposed to echinacea preparations during the first trimester of pregnancy showed no difference in fetal health when compared with the nonechinacea-exposed group [228]. Although other studies seem to confirm safety, echinacea preparations should be avoided during the first trimester due to lack of definitive evidence.

Dosage

For treatment of cold symptoms and upper respiratory infections, an initial 300–1,000 mg titrated dose of powdered herb in capsules or its equivalent (tincture or juice) is administered for five to seven days [33; 51; 137; 179]. Use for more than eight weeks at a time should be avoided because of the potential for immunosuppression [82]. Preparations containing 15% pressed herb are used topically as disinfectants.

KAVA

Efficacy: ★★★**E**

Safety: **AEs/DIs/UnS**

Common Name and Scientific Name

Kava (*Piper methysticum*), a member of the pepper family, is a widely cultivated shrub indigenous to the South Pacific islands. It is also known as kava-kava, kawa, or ava pepper [82].

Historical and Current Use

A drink prepared from the root of the kava plant has been used traditionally in the South Pacific for ceremonial, social, and medicinal purposes for several centuries, if not millennia. It is used for its mild relaxing and calming properties, culturally comparable to alcohol use in Western societies. Following the European trend, the use of kava for the treatment of anxiety has become popular in the United States. In some countries, including Germany, it has been commonly prescribed to treat anxiety, stress, and insomnia, although very serious concerns regarding potential hepatotoxicity have led to warnings and bans in North America.

Pharmacology

The lipid-soluble extract of kava is rich in kava pyrones, including kavain, dihydrokavain, and methysticum [82; 229]. Kava pyrones block voltage-dependent sodium channels, a mechanism responsible for the local anesthetic properties of kava drinks, which causes numbness and tingling of the mouth. Kava also contains antioxidant flavonoids and alkaloids. It has been reported that kava has a direct effect on limbic structures, particularly the amygdala. It does not bind to the gamma-aminobutyric acid $(GABA)_A$ receptors, unlike benzodiazepines, which target the $GABA_A$ receptors abundantly distributed in the cerebral cortex. This may account for the difference in anxiolytic properties of kava, which, unlike benzodiazepines, does not cause sedation [230].

At higher doses, kava lactones also have muscle-relaxant and anticonvulsant properties, which are possibly related to the stimulation of the glycine receptor [231]. Kavain has dose-dependent antiplatelet aggregation and anti-inflammatory properties [232].

Evidence-Based Therapeutic Use and Effectiveness

The clinical effectiveness of kava has been widely studied, and clinical studies strongly support its efficacy in the treatment of moderate and mild cases of anxiety. One meta-analysis included data from 11 double-blind, controlled clinical trials, and the authors concluded that kava, when compared with placebo, is effective in the symptomatic treatment of anxiety [233]. A standardized preparation of kava (LI 150) was as effective as the anxiolytic drugs buspirone and opipramol [234; 235]. An extensive literature review also confirmed the clinical effectiveness of kava preparations in the treatment of anxiety [33].

Several clinical studies assessed the effect of kava on memory and compared it with both the anxiolytic oxazepam and placebo [230]. The studies concluded that kava, unlike oxazepam, does not impair cognitive performance and memory. In fact, an improvement in memory was observed in the kava-treated group, but these interesting results wait for confirmation [33; 236]. A review of at least 10 studies on the effects of kava on cognition have been published, but the heterogeneity of dosages/potency and preparations used precludes meta-analysis. At higher dosages, reaction time may be impaired [237; 238; 239]. Kava has been promoted for use in attention deficit hyperactivity disorder; however, clinical trials are lacking and such use is not recommended [239; 240].

EVIDENCE-BASED PRACTICE RECOMMENDATION

A Cochrane Review found that, compared with placebo, kava extract is an effective symptomatic treatment for anxiety, although, at present, the size of the effect seems small. The effect lacks robustness and is based on a relatively small sample. The data available from the reviewed studies suggest that kava is relatively safe for short-term treatment (1 to 24 weeks), although more information is required.

(https://www.cochrane.org/CD003383/DEPRESSN_kava-extract-for-treating-anxiety. Last accessed June 10, 2022.)

Level of Evidence: Meta-analysis

Adverse Effects and Drug Interactions

In clinical trials, the side effects of kava preparations were rare and mild, with gastrointestinal discomfort, restlessness, headache, and dizziness reported in about 2% of patients. Kava dermatitis, a yellow discoloration of the skin accompanied by scaly dermatitis, is only observed in chronic heavy kava drinkers and reverses after discontinuation of kava administration. This skin condition resembles pellagra but is resistant to niacin treatment [82].

Neurotoxicity, pulmonary hypertension, and choreoathetosis have also been reported in chronic heavy drinkers in the Australian Aboriginal population [241]. A few rare cases of kava-induced Parkinson-like extrapyramidal disorders have been reported, as well as the aggravation of existing Parkinson disease in one patient and one case in the United States of rhabdomyolysis related to the ingestion of a large amount of kava [51; 235]. There are some reports suggesting that kava may cause severe and, in some cases, irreversible liver damage. As a result, the FDA issued an advisory letter to healthcare professionals stating possible health risks [242].

Kava extracts interact with and potentiate the effects of anxiolytic and depressant drugs, such as benzodiazepines, barbiturates, and alcohol. Due to its antiplatelet properties, kavain-containing preparations should not be administered to patients undergoing anticoagulant therapy, although the clinical relevance of this potential interaction has not been established. Kava preparations should also be avoided in patients with extrapyramidal disorders, including Parkinson disease. Finally, due to the potential hepatotoxicity, kava should not be administered to patients with liver disease or those treated with potentially hepatotoxic medications such as acetaminophen, anabolic steroids, or the anticancer agent methotrexate [33; 82; 243]. As a precautionary measure, kava should not be administered during pregnancy and lactation due to the lack of safety studies [82]. Kava administration should be discontinued at least 24 hours prior to surgery because of possible potentiation of the sedative effect of anesthetics [244].

Toxicology

More than 30 cases of kava-induced hepatotoxicity, ranging from hepatitis and cirrhosis to acute liver failure and death, have been reported in the literature. One study of lipid-extractions of kava led researchers to state that rather than being caused by directly toxic mechanisms, reactions to kava likely stemmed from immunologically mediated idiosyncratic mechanisms; therefore, the hepatotoxicity of kava may be similar to benzodiazepines [245]. An Australian trial concluded that water-extracted kavalactones, using dried roots sourced from the island of Vanuatu and prepared in a controlled pharmaceutical manufacturing facility, caused neither an increase in liver enzymes nor hepatotoxic symptoms [246]. Other studies have shown that kava suppresses CYP450 enzymes in the liver, leading to hepatotoxic concentrations of concurrently administered drugs [82; 247]. Although no cases of hepatotoxicity were reported in any of the clinical trials included in a Cochrane Review, it is not recommended for use in the United States [137; 233].

Dosage

Standardized products are available, and the usual recommended daily dose of kavalactones ranges from 120–250 mg/day, divided in two to three equal doses [33; 51]. In the United States, most formulations are standardized to 30% or 55%, meaning that a 100 mg tablet contains 30 mg or 55 mg of kavalactones, respectively. Usually, kava use should be limited to three months to avoid potential habituation, and patients should be advised of the potential adverse effects on motor coordination and capacity to drive or operate heavy machinery [51].

GARLIC

Efficacy: ★★**E**

Safety: **AEs/DIs**

Common Name and Scientific Name

Garlic (*Allium sativum*), also known as allium, is related to chives (*Allium schoenoprasum*) and onions (*Allium cepa*), and all belong to the Liliaceae family, which also includes lilies.

Historical and Current Use

The recorded medicinal use of garlic goes back to ancient Egyptian, Greek, and Roman civilizations. It was used for the treatment of a variety of conditions, including heart problems, headaches, intestinal parasites, and tumors, and as a local disinfectant. In the nineteenth century, Louis Pasteur also reported the antimicrobial properties of garlic. It is now used for its effectiveness in

reducing cholesterol and for its antithrombotic and antioxidant properties, as well as for its ability to lower blood pressure. Together, these properties have also provided some support for the use of garlic in the prevention of cardiovascular diseases, including atherosclerosis [33; 37; 51]. The benefits of garlic in the treatment of certain cancers, specifically stomach and colorectal, have also been investigated [248; 249].

Pharmacology

The beneficial effects of garlic have been related to its sulfur compounds. More than 20 different sulfur compounds have been identified in garlic. The sulfur compound allinin (S-allyl-l-cysteine sulfoxide) is transformed to allicin (diallyl thiosulfinate) via the enzyme alliinase when the bulb is crushed or ground. Allicin is an unstable molecule that is converted into more stable compounds. Other sulfur compounds, such as peptides, steroids, terpenoids, flavonoids, and phenols, derive from allicin metabolism and have been the subject of investigations aimed at identifying their biologic role [250]. In vitro and in vivo studies have associated allicin with the antibacterial properties of garlic. Commercially available garlic extracts are standardized to the allicin content. Three water-soluble allicin derivatives, s-allylcysteine (SAC), s-ethylcysteine (SEC), and s-propylcysteine (SPC), are the most effective in reducing in vitro cholesterol synthesis in hepatocytes by 42% to 55% [251].

Methyl-allyl trisulfide (MATS), a lipid-soluble allicin derivative, inhibits cyclooxygenase activity and prostaglandin synthesis and is responsible for the antithrombotic and antiplatelet aggregation properties of garlic [252]. Another sulfur compound, diallyl trisulfide (DATS), is a potent inhibitor of colon and lung human cancer cell proliferation in cell cultures and is at least partially responsible for the anticancer properties of garlic [253; 254; 255; 256].

The antioxidative properties of garlic are exerted indirectly through the sulfur compound-induced stimulation of protective antioxidant enzymes present in the body, including glutathione-S-transferase, superoxide dismutase, and catalase [37; 252].

Evidence-Based Therapeutic Use and Effectiveness

Several clinical trials have reported that garlic lowers total cholesterol levels by 8% to 15% [257; 258]. This effect results from the lowering of the low-density lipoprotein (LDL) and triglycerides, while the high-density lipoprotein (HDL) values remain unchanged. A meta-analysis confirmed that, after 10 to 12 weeks, garlic lowers plasma cholesterol, although the benefits (4% to 6%) were less pronounced than previously reported, and this effect was not statistically significant after a six-month period [259]. In 2001, an extensive meta-analysis of 34 randomized clinical trials including almost 2,000 patients confirmed the previous assertions [260]. A meta-analysis of 26 studies found that, overall, garlic is superior to placebo in reducing serum total cholesterol and triglyceride levels [261]. Compared with placebo, serum total cholesterol and triglyceride levels in the garlic group were reduced by 0.28 mmol and 0.13 mmol, respectively. Garlic powder and aged garlic extract were more effective in reducing serum total cholesterol levels; garlic oil was more effective in lowering serum triglyceride levels. Garlic did not lower LDL cholesterol, HDL cholesterol, apolipoprotein B, or the total cholesterol/HDL ratio [261]. Results of a 2018 meta-analysis found that garlic can reduce total cholesterol and LDL levels, but not HDL and total triglyceride levels [262]. In conclusion, garlic preparations are moderately effective in lowering LDL and triglycerides and do not change the HDL concentration in the plasma [33].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American College of Physicians, the American College of Cardiology Foundation, the American Heart Association, the American Association for Thoracic Surgery, the Preventive Cardiovascular Nurses Association, and the Society of Thoracic Surgeons recommend that treatment with garlic should not be used with the intent of reducing cardiovascular risk or improving clinical outcomes in patients with stable ischemic heart disease.

(http://www.onlinejacc.org/content/64/18/1929. Last accessed June 10, 2022.)

Strength of Recommendation: Strong

The effects of garlic on blood pressure have been studied in several clinical trials. Some studies have shown a small (6%) yet statistically significant effect, although these findings were not replicated by other studies [33]. Garlic is not recommended for the management of hypertension [82; 263].

Garlic has also been shown to inhibit platelet aggregation, as expected by its inhibitory effects on cyclooxygenase and prostaglandin synthesis. The effective dosages are not well established, and comparison with other antiplatelet aggregation drugs is not yet available. Because several reports have associated garlic with bleeding accidents, administration should be limited to lower dosages and co-administration with drugs that affect hemostasis, including antiplatelet aggregation drugs (e.g., aspirin) or anticoagulants (e.g., warfarin), should be avoided [33; 144].

Some clinical studies suggest that garlic preparations slow the progression of atherosclerotic plaques [264]. Although encouraging, these results are preliminary and further studies are required [82].

The anticancer properties of garlic compounds have been reported both in vitro and in vivo, but their clinical effectiveness remains to be established [265]. One small trial in mice showed that garlic extract inhibits growth of certain cancer cells, particularly multiple myeloma. Researchers indicated that the reduced proliferation of cancer cells is at least partly mediated by increased endoplasmic reticulum stress [265]. Another small trial with mice indicated that anticancer properties of garlic are more effective when introduced directly to the cancer cells by injection rather than via oral ingestion [266]. Epidemiologic studies suggest that regular consumption of garlic may be associated with a lower risk of developing gastric and colorectal malignancies [267]. A review of 14 studies of the anticancer properties of garlic and onion supports this association [249]. While the results of one systematic review and meta-analysis suggest a significant inverse correlation between the intake of garlic and the risk of gastric cancer, an analysis of health claims provided to the FDA found no credible evidence supporting the use of garlic for prevention of gastric cancer or breast, lung, or endometrial cancers [261; 268]. Although the epidemiologic evidence is cautiously positive, well-designed clinical trials are needed before a conclusion can be reached [269].

Adverse Effects and Drug Interactions

The most common adverse effects reported are bad breath and body odor [82]. Less commonly, dyspepsia and flatulence are also reported. In rare cases, dermatitis and respiratory difficulty can occur in hypersensitive patients [51]. The highest risk of herb-drug interaction is between garlic and anticoagulant drugs, such as the vitamin K inhibitor warfarin, and antiplatelet aggregation agents, such as ticlopidine and clopidogrel, and results from the pharmacodynamic potentiation of mechanisms of action [144].

Toxicology

Garlic preparations administered within the recommended dosages are safe, although they should not be administered to patients allergic to garlic or to other members of the Liliaceae family, namely chives, onions, leek, or lilies [33; 82; 144]. A dangerous pharmacokinetic interaction between garlic and the protease inhibitor saquinavir has been reported, as it reduces the plasma concentration of the anti-HIV drug by 50% [270].

Dosage

Administration of garlic preparations varies greatly according to the preparation used (i.e., fresh, powder, oil extracts). Standardized preparations to 1.3% allinin or 0.6% allicin are usually administered at 600–900 mg per day. This is considered equivalent to one small clove of fresh garlic [51].

VALERIAN

Efficacy: ★★E

Safety: S

Common Name and Scientific Name

Valerian (*Valeria officinalis*), also known as baldrian, is a member of the Valerianaceae family. Other species of the same family that are also used for medicinal purposes include *V. wallichi* and *V. sambucifolia.*

Historical and Current Use

Historical documents from ancient Greece, China, and India widely report the use of preparations from valerian root and rhizome in the treatment of insomnia and anxiety. This herb, native to Asia and Europe, is found throughout the world. Topically, it has been used in the treatment of acne and wound healing. It has also been used traditionally for the treatment of a variety of disorders, including digestive problems, flatulence, congestive heart failure, urinary tract disorders, and angina pectoris. For the past 200 years, valerian has been widely used in Europe and North America for its mild sedative properties [37; 51].

Pharmacology

A large number of chemicals, including monoterpenes, sesquiterpenes, valepotriates, amino acids, and alkaloids, have been extracted from valerian. Although no single component has been shown to account for its pharmacologic properties, the biologically active valerenic acid has been used as the constituent for standardization. In vivo studies have confirmed the sedative, anxiolytic, and anticonvulsant properties of valerian preparations. Studies have also shown the agonistic effect of valerian and some of its individual compounds on the $GABA_A$ receptors and on the 5-HT5a serotonin receptors [271; 272; 273]. Other studies have revealed that valerian extracts inhibit the presynaptic GABA carrier, further contributing to an increased GABAergic inhibitory activity in the brain [274]. Valerenic acid also inhibits GABA transaminase, the enzyme responsible for GABA metabolism [275]. Together, these findings contribute to a better understanding of the molecular mechanisms underlying the sedative and anticonvulsant properties of valerian. More recently, research has identified valerenic acid and its modulation of the $GABA_A$-ergic system as probable cause of the anxiolytic effects, a mechanism similar to benzodiazepines (e.g., diazepam) [276]. In addition to valerenic acid, isovaleric acid, didrovaltrate, borneol, and some lignans have also been proposed to contribute to the anxiolytic effect of the plant [277].

Evidence-Based Therapeutic Use and Effectiveness

A systematic review of nine randomized clinical trials found that results regarding the effectiveness of valerian in the treatment of insomnia were inconclusive [278]. Some benefits were reported within one to two days, but benefits on sleep were observed only after four weeks of treatment. A larger European clinical trial reported that the valerian had minimal or no effect on sleep regulation [279]. Unfortunately, patients were treated for only two weeks, a time period considered too

short when compared with previous studies, which may account for the negative outcome. A 2011 systematic review of CAM practices on insomnia reached a similar conclusion as the European clinical trial regarding valerian [280]. The American Academy of Sleep Medicine suggests that valerian not be used for sleep-onset or sleep-maintenance insomnia as the benefits are considered to be approximately equal to the risks [281].

No well-designed trials of valerian in the treatment of anxiety in humans have been published to date. An investigation of the effect of valerenic acid on rats concluded that valerian use was related to a reduction of anxious behavior, and a small-scale study found that valerenic acid was effective for reducing anxiety before a medical procedure [276; 282].

Adverse Effects and Drug Interactions

In clinical trials, valerian side effects were minor, most commonly headache, stomach upset, or dizziness, and were usually reported as frequently as in the placebo group. Adverse effects on reaction time and alertness were much lower than benzodiazepines. Dependence and withdrawal have not been reported in any of the clinical trials, although a single case report of withdrawal symptoms after discontinuation has been published [283]. As valerian and benzodiazepines similarly target the $GABA_A$ receptor, it is possible that the patient may develop physical dependence after lengthy administration. It is therefore advisable to discontinue valerian administration progressively. Valerian potentiates the effects of other sedatives, such as benzodiazepines, barbiturates, alcohol, kava, and chamomile, and should not be co-administered in conjunction with these drugs or phytomedicines [33].

Toxicology

Valerian is considered safe by the FDA, but administration during pregnancy and breastfeeding is not advised due to the limited availability of safety data [82].

Dosage

In clinical trials, for the treatment of insomnia, 900 mg of a standardized solution equivalent or 1.5–3 grams of dried root was administered 30 minutes to 1 hour before bedtime [51]. Valerian extract, in doses of 400–600 mg, has been used in clinical trials evaluating valerian in insomnia [284; 285].

ANDROGRAPHIS

Efficacy: **★★E**

Safety: **AEs/DIs**

Common Name and Scientific Name

Andrographis (*Andrographis paniculata*) is also known as *Justicia paniculata*, green chiretta, king of bitters, kan jang, and sambiloto. It is an herb naturally found in Asia, including India, Southeast Asia, and southern China, and it is also cultivated for commercial use in the preparation of traditional HMs. Andrographis is an annual tall herb, up to one meter high, with small white flowers. It thrives in humid climates and shady areas.

Historical and Current Use

The bitter-tasting leaves of andrographis have been used for centuries in traditional Indian and Chinese medicine in the preparation of an infusion used for the treatment of digestive ailments and fever. In Malaysia, andrographis has also been traditionally used for the treatment of hypertension [286]. In northern European countries, andrographis is used for the prevention of upper respiratory tract infections [33].

Pharmacology

Andrographis is rich in diterpenoids and flavonoids. At least nine diterpenoids, including andrographolide, 14-deoxyandrographolide (DA), and 14-deoxy-11-oxoandrographolide (DDA), have been isolated.

In vitro studies revealed that andrographolide has anti-inflammatory, antiapoptotic, and immunomodulatory properties. In vivo studies demonstrated that both DA and DDA effectively lower blood pressure, decrease heart rate, and cause vasodilation [287]. DA and DDA block calcium channels, increase nitric oxide synthesis, and inhibit ß-adrenergic receptors. All of these actions provide the mechanistic explanation for the hypotensive properties of andrographis [287].

Evidence-Based Therapeutic Use and Effectiveness

Several clinical trials, including almost 900 subjects, have assessed the effectiveness of andrographis in the treatment and prevention of upper respiratory tract infection. Two meta-analyses concluded that andrographis was significantly more effective than placebo for the treatment of upper respiratory tract infection symptoms [288; 289]. A 2017 systematic review and meta-analysis also found that andrographis (*A. paniculata*) improved overall symptoms of upper respiratory tract infection compared to placebo, usual care, or other herbal therapies. Andrographis also shortened the time to symptom resolution [290]. Limited evidence also suggests that andrographis preparations may be effective in the prevention of upper respiratory tract infection [291; 292]. Two clinical studies concluded that andrographis is also effective in the treatment of influenza symptoms, although larger and better-designed studies are needed to confirm the results [33].

One randomized controlled trial of 60 patients with mild hypertriglyceridemia found that *A. paniculate* extract reduced triglyceride levels comparable to the effect of 300 mg/day of gemfibrozil, an LDL-lowering agent [293].

Adverse Effects and Drug Interactions

Andrographis is considered safe and well tolerated. Headache, nausea, vomiting, abdominal discomfort, and nasal congestion are the most commonly reported adverse effects [33; 82]. Although data regarding andrographis interactions with other drugs is still limited, due to andrographis' hypotensive and hypoglycemic properties, concurrent administration with antihypertensive and hypotensive drugs should be avoided.

Toxicology

In clinical trials, a dose-response dependent toxicity of andrographis has been identified, and fatigue, headache, and lymphadenopathy have been described [291; 294; 295]. Three cases of anaphylactic reaction have also been reported [288].

Dosage

Usually, 300 mg of standardized preparations of andrographis (4% andrographolides) is taken four times per day, for as long as two weeks [33].

ENGLISH IVY LEAF

Efficacy: ★★★**E**

Safety: **S**

Common Name and Scientific Name

English ivy (*Hedera helix*), also known as common ivy, is an evergreen climbing vine. It is native to Europe and Central Asia, grows easily, and is commonly found in humid environments and in forests. It is often used for decorative purposes. It is different from ground ivy (*Glechoma hederacea*) and American ivy (*Parthenocissus quinquefolia*). It is particularly important not to confuse it with poison ivy (*Rhus toxicodendron*).

Historical and Current Use

The glossy and dark green leaves of common ivy have been traditionally used for the treatment of a wide variety of disorders, including respiratory disease, arthritis, fever, burns, and infections. It is now used as an expectorant and in the treatment of bronchitis and asthma [51].

Pharmacology

Ivy leaves are rich in saponins (e.g., hederin, hederacoside) but also contain sterols, flavonol glycosides, and polyalkenes among other chemicals. Saponins stimulate secretion of mucus in the upper respiratory tract and have a mucokinetic and mucolytic effect [229]. They also prevent acetylcholine-induced bronchospasm [296]. Hederacoside C has antifungal and antibacterial properties [214]. Together, these bronchodilatory and antimicrobial properties of ivy leaf extracts provide the pharmacologic evidence to support their beneficial effects in the treatment of upper respiratory tract infections.

Evidence-Based Therapeutic Use and Effectiveness

The clinical efficacy of ivy leaf extracts has been the subject of one meta-analysis [297]. Five clinical trials, three of which measured its effect on children, indicated that the treated group showed an improvement in chronic bronchial asthma. In another study not included in the previous review, 1,350 children with chronic bronchitis were treated with standardized ivy leaf extracts for four weeks. A significant improvement or cure of the following symptoms was observed, when compared with the baseline: cough (92%), expectoration (94%), dyspnea (83%), and respiratory pain (87%) [298]. A postmarketing study of almost 10,000 patients with bronchitis showed that, after a seven-day treatment with ivy leaf extracts, 95% of the patients had improved significantly [299]. One 2021 systematic review found that while ivy leaf preparations are safe for use in cough due to acute upper respiratory tract infections, the effects are minimal at best and of uncertain clinical importance [300].

Adverse Effects and Drug Interactions

Ivy leaf extracts are generally considered safe. Mild adverse effects, such as gastrointestinal discomfort, eructation, or nausea, are observed in 0.2% to 2.1% of patients [298; 299]. No drug interactions have been reported. Considering the detergent-like actions of saponins, it has been suggested that ivy leaf extracts should not be ingested at the same time as other drugs, considering the unlikely possibility that ivy leaf extracts may facilitate the absorption of the other drugs. However, this warning is not supported by any evidence and should be considered as speculative.

Toxicology

Ingestion of ivy berries can be toxic, and falcarinol present in cut ivy leaves may cause contact dermatitis, particularly in sensitive individuals [144]. In a bizarre case, ingestion of ivy leaves caused mechanical obstruction and suffocation [301]. Toxicology tests confirmed the cause of death as being suffocation, and no toxin was detected in cardiac blood, femoral blood, or urine of the deceased [301].

It has been suggested that ivy leaf products should be avoided during pregnancy because the emetine content in ivy leaf may cause uterine contractions [302]. Data on the effects of ivy leaf extracts during lactation are not yet available, and as a result, ingestion of ivy leaf extracts in these cases should be avoided.

Dosage

Standardized ivy leaf extracts are available as a hydroalcoholic extract syrup (105 mg/day of dried ivy leaf extract), ethanolic extract drops (35–40 mg/day of dried ivy leaf extract), or suppositories (160 mg/day of dried ivy leaf extract) [297].

PEPPERMINT

Efficacy: ★★**E**

Safety: **S**

Common Name and Scientific Name

Peppermint (*Mentha x piperita L.*) is a hybrid of *Mentha spicata L.* (spearmint) and *Mentha aquatica L.* of the Lamiaceae (mint) family. It is also known as peppermint oil, menthol, mint, balm mint, brandy mint, and green mint. The plant is native to Europe but is widely cultivated in the United States and Canada [82; 303].

Historical and Current Use

Peppermint leaf and peppermint oil have a history of use for digestive orders that dates back to ancient Egypt. The plant was first described in England in 1696, and both the leaf and the oil have been used in Eastern and Western traditional medicine as antispasmodics, aromatics, and antiseptics. Peppermint oil is used in herbal remedies, cosmeceuticals, personal hygiene products, foods, and pharmaceutical products. Topical preparations have traditionally been used to calm pruritus and relieve irritation and inflammation [303; 304; 305; 306; 307]. Peppermint oil is widely used as a spasmolytic agent in irritable bowel syndrome (IBS) [307; 308; 309].

Pharmacology

Peppermint oil is complex and highly variable, with more than 100 components isolated from the oil. Relative concentrations vary depending on climate, cultivar, and geographic location. Peppermint yields 0.1% to 1% of volatile oil composed primarily of menthol (29% to 48%), menthone (20% to 31%), and menthyl acetate (3% to 10%) [82]. Menthol is rapidly absorbed following oral administration, and elimination is mainly via bile [82; 307]. Peppermint oil has a demonstrated dose-related antispasmodic effect on gastrointestinal smooth muscle, attributed to calcium channel blockade [82; 310; 311]. It reduces intragastric pressure, phasic contractility of the proximal stomach, and appetite, with negligible effects on gastric sensitivity, tone, and nutrient tolerance in health [309].

Evidence-Based Therapeutic Use and Effectiveness

Irritable Bowel Syndrome

The clinical effectiveness of peppermint oil in the treatment of IBS has been extensively studied. A Cochrane review of clinical studies that evaluated the efficacy of bulking agents, antispasmodics (e.g., peppermint oil), and antidepressants for the treatment of IBS was published in 2013 [312]. The review included 56 randomized controlled trials published between 1966 and 2009 involving 3,725 patients with IBS who were older than 12 years of age. The primary outcomes evaluated were improvements of abdominal pain, global assessment, and symptom score. Both antidepressants and antispasmodics demonstrated improvement in outcome measures. Abdominal pain improved in 58% of antispasmodic patients compared with 46% with placebo. Global assessment showed 57% improvement in patients taking antispasmodics compared with 39% with placebo; and 37% of patients taking antispasmodics showed improved symptom score compared with 22% with placebo [313]. A subgroup analysis of different types of antispasmodics, including peppermint oil, revealed statistically significant benefits [312]. Evidence suggests that enteric-coated peppermint oil may be effective in relieving some of the symptoms of IBS [82; 307; 314].

Dyspepsia/Functional Abdominal Pain

The use of peppermint in combination with other herbals for treatment of functional dyspepsia in adults and children has been reviewed in the literature [315; 316; 317]. A study published in 2000 evaluated the safety and effectiveness of enteric-coated capsules containing a fixed combination of 90 mg peppermint oil and 50 mg caraway oil [315]. The study included 96 patients who received either one capsule twice daily or placebo for 28 days. Outcomes measured included change in pain intensity, change in sensation of pressure, heaviness and fullness, and global improvement as rated by the investigators. On the 29th day, the average intensity of pain was reduced by 40% with peppermint use, compared with 22% with placebo; pressure, heaviness, and fullness was reduced by 43%, compared with 22% with placebo; and 67% of patients were very much improved, compared with 21% with placebo.

One randomized trial investigated the pharmacokinetics of menthol use in children 7 to 12 years of age with functional abdominal pain [318]. Thirty children underwent wireless motility capsule testing, and approximately one week later, they were randomized to 180, 360, or 540 mg of enteric coated peppermint oil. The researchers observed a direct linear relationship between peppermint oil dose and menthol systemic exposure with mean elimination half-life 2.1, 3.5, and 4.6 hours for the 180-, 360-, and 540-mg doses, respectively, suggesting that a higher dose of peppermint oil may be needed to achieve maximal response [318].

A choleretic action of peppermint oil has been described, with possible applicability in the management of gallstones [82; 307]. Its antispasmodic action makes it useful in patients with colonic and esophageal spasm and in endoscopy [319; 320; 321; 322; 323].

Adverse Effects and Drug Interactions

Menthol, the major component of peppermint oil, may cause contact dermatitis in some individuals. Mucosal burns and swelling of the tongue and oral cavity have been reported following ingestion of peppermint oil. Other reported incidences include stomatitis and vulval allergic contact; however, such reactions appear to be rare [82; 304; 324; 325; 326].

Toxicology

Peppermint is generally recognized as safe. Comprehensive reports on its safety have identified the constituents pulegone and menthofuran as being of toxicologic concern [327; 328]. Use in pregnancy should be avoided due to emmenagogue effects [82].

Dosage

Doses of peppermint oil of up to 1,200 mg in enteric-coated tablets are used to treat IBS [82]. The tablets should be swallowed whole, not crushed, broken, or chewed, to avoid irritation to the mouth, esophagus, and stomach, and they should be taken 30 to 60 minutes prior to meals on an empty stomach [82; 321; 329]. Doses of 0.1–0.24 mL of peppermint oil have been used as a carminative (relieving flatulence) in clinical studies [82; 313; 330; 331].

GINGER

Efficacy: ★★★**E**

Safety: **S**

Common Name and Scientific Name

Ginger (*Zingiber capitatum, Zingiber officinale*) is also known as black ginger, ginger root, and zingiberis rhizoma. Ginger is native to tropical Asia and is a perennial that is cultivated in Australia, Brazil, China, India, Jamaica, West Africa, and parts of the United States. The rhizome is used both medicinally and as a culinary spice [82].

Historical and Current Use

The medicinal use of ginger dates back to ancient China and India. It is referred to in Chinese pharmacopeias, Ayurvedic medicine scriptures, and Sanskrit writings. Its culinary properties were discovered in the 13th century, leading to its widespread use in Europe. Apothecaries in the Middle Ages recommended ginger for travel sickness, nausea, hangovers, and flatulence. Other uses include for the common cold, fever, sore throat, gastrointestinal complications, and indigestion. Ginger is referenced in the official pharmacopeias of more than one dozen countries. It is approved by Germany's Commission E for indigestion and to help prevent motion sickness. In the United States, ginger is approved as a dietary supplement and commonly used as a treatment for nausea [82; 332; 333; 334].

Pharmacology

Only unbleached ginger is a medicinal-grade drug, containing 1.5% or more volatile oil. More than 400 different compounds have been identified in ginger. The major constituents are carbohydrates (50% to 70%), which are present as starch. Amino acids, raw fiber, protein, phytosterols, vitamins and minerals are among the other constituents. Gingerols, a class of structurally related compounds, form shogaols, the pungent constituents of ginger. The primary shogaols are (6)-gingerol and (6)-shogaol [82; 335; 336]. Ginger exerts in vitro antioxidative, antitumorigenic, and immunomodulatory effects and is an effective antimicrobial and antiviral agent [336].

Evidence-Based Therapeutic Use and Effectiveness

Clinical trials in humans have examined the antiemetic effects of ginger as they relate to nausea of various etiologies (e.g., motion sickness, postoperative, pregnancy-related, chemotherapy-related). In particular, ginger has been found to be more effective than placebo in controlling pregnancy-related nausea and vomiting in randomized controlled trials. The mechanism by which this occurs is unclear, but enhanced gastrointestinal transport, antiserotonin activity, and possible central nervous system effects have been described in animal studies [82]. Although ginger has been shown to be effective in ameliorating pregnancy-related nausea and vomiting, its safety during pregnancy has not been established. In one randomized clinical trial, 102 participants randomly received either 500-mg ginger or placebo two times per day, 30 minutes prior to each dose of antiretroviral therapy for 14 days [337]. Forty-six (90.2%) of the patients in the placebo group and 29 (56.4%) of the patients in the ginger group experienced some degree of nausea, but the frequency of any degree of nausea was significantly lower in the ginger than the placebo group. Results from published studies on the use of ginger for chemotherapy-related nausea are equivocal [82].

Adverse Effects and Drug Interactions

Ginger may enhance the adverse/toxic effect of agents with anticoagulant/antiplatelet properties; bleeding may occur [82]. Adverse reactions reported in trials are uncommon [82]. Case reports of arrhythmia and IgE allergic reaction have been documented [334; 338].

Toxicology

Because there are little data on the toxicity of ginger in humans, there is no consensus on use during pregnancy and lactation [82]. One study found no adverse effects on pregnancy outcomes, and systematic reviews in 2013 and 2018 concurred with this conclusion [339; 340; 341].

Dosage

Ginger has been used in clinical trials in doses of 250 mg to 1 g, repeated three to four times daily [82].

SOY

Efficacy: **★E**

Safety: **No S data**

Common Name and Scientific Name

Soy (*Glycine max*), a plant in the pea family, is also known as soy isoflavones, soya, and soybean. Soy is a common source of dietary phytoestrogens found in American diets as either a food or a food additive [82; 303; 342].

Historical and Current Use

Traditional and folk uses of soy products include for menopausal symptoms, osteoporosis, memory problems, high blood pressure, high cholesterol, and breast and prostate cancer. Soy may be taken as a dietary supplement. Some studies suggest that daily intake of soy protein or soy isoflavones supplements may reduce LDL cholesterol and menopausal symptoms (e.g., hot flashes) in women; however, not enough evidence exists to determine whether soy supplements are effective for any other health uses [342].

Pharmacology

The isoflavones in soybean (i.e., genistein, daidzein, glycitein) have a chemical structure similar to estrogen. They bind to both estrogen receptors (ER alpha and ER beta) and exert estrogen-like effects under some experimental conditions [343]. Genistein, daidzein, and glycitein undergo metabolism to the isoflavandiols, equol, and p-ethylphenol. The metabolism is highly variable (i.e., dependent upon the effect of carbohydrate intake on intestinal fermentation). The isoflavones are secreted into bile via the enterohepatic circulation and eliminated in urine [82].

Evidence-Based Therapeutic Use and Effectiveness

Although soy protein has gained considerable attention for its potential role in improving risk factors for cardiovascular disease, the American Heart Association (AHA) and an expert panel from the American College of Cardiology (ACC) found that the evidence of benefit is uncertain, with a relatively small decrease (3%) in LDL cholesterol concentrations and no effect on other lipid risk factors with soy protein consumption, as compared with milk or other proteins [344].

To assess the effectiveness of phytoestrogens, including soy and soy extracts, for reducing hot flushes and night sweats in postmenopausal women, the authors of a Cochrane review evaluated the results of 30 randomized trials that had a duration of at least 12 weeks and in which the intervention for symptom relief was the use of a food or supplement with high levels of phytoestrogens [345]. However, a strong placebo effect was reported in most of the trials, with a reduction in symptom frequency ranging from 1% to 59%. The authors of the review found no evidence of effectiveness with phytoestrogen use for relief of menopausal symptoms. Authors of other studies confirm this conclusion [346; 347]. In 2017, as a result of inconclusive evidence, the FDA proposed a rule to prevent companies from claiming soy protein can reduce heart disease risk [348].

Several meta-analyses of clinical trials have evaluated the effectiveness of soy preparations in protecting against decreases in bone mineral density (BMD). Some report small improvements in BMD; others report no effect [349; 350]. Soy isoflavones, but not soy protein, may have a beneficial effect on bone turnover during early menopause and in postmenopausal women [351; 352].

Adverse Effects and Drug Interactions

Soybeans and soy products, including supplements, are generally well tolerated.

Toxicology

Concern has been expressed that feeding infants soy formula may adversely affect development of the reproductive system due to the estrogen-like activity of isoflavones; however, data are inconclusive to permit a firm conclusion [353]. In addition, some organizations, such as the American Academy of Pediatrics, assert that "isolated soy protein-based formulas are a safe and nutritionally equivalent alternative to cow milk-based formula for term infants whose nutritional needs are not met from breast milk" [354]. More research and long-term studies are necessary to determine the effects of soy-based formula.

Dosage

The effects of daily doses (40–120 mg) of isoflavones for a variety of conditions have been studied in a large number of clinical trials [82]. A dose of 20–50 g soy protein taken daily by mouth has been studied in individuals with high cholesterol. Isoflavones content has ranged from 60 mg to more than 100 mg daily [355].

CHAMOMILE

Efficacy: ★★**E**

Safety: **S**

Common Name and Scientific Name

Chamomile (*Chamaemelum nobilis*, *Matricaria recutita*) has a variety of common names, including common, English, garden, genuine, German, Hungarian, lawn, Roman, Scotch, sweet, true, and wild types [82].

Historical and Current Use

C. nobilis is a slow-growing perennial; *M. recutita* grows as an upright annual. The fragrant flowering heads of both plants are collected and dried for use as teas and extracts [82]. Both plants have been used since Roman times as antispasmodics and sedatives in the treatment of digestive and rheumatic disorders and as a wash to cleanse wounds and ulcers. Various formulations have been used to treat colic, cystitis, fever, flatulence, and vomiting [356; 357]. German chamomile flower is approved by the German Commission E for use as an inhalant in skin and mucous membrane inflammations, bacterial skin diseases (including those of the oral cavity and gums), and respiratory tract inflammations and irritations. It is also the variety most commonly used in the United States. The flower is approved for use in baths, as irrigation for anogenital inflammation, and for internal use to treat gastrointestinal spasms and inflammatory diseases [358]. *M. recutita* is widely used in Europe as a botanical for wound care. Aqueous extracts are used as washings or wet packs for fresh wounds. Alcoholic extraction yields the most complete blend, which can be transferred to aqueous formulations or ointments [359]. In Europe, traditional phytomedicines such as chamomile play an adjuvant role in acne therapy, either in addition to or in combination with intensive cosmetic care. After cleaning, creams or aqueous decoctions are applied topically [335].

Pharmacology

The chemical compounds of *C. nobilis* and *M. recutita* are similar. Chamomile tea, brewed from dried flower heads, contains 10% to 15% of the plant's essential oil. The blue-colored volatile oil is a complex mixture of sesquiterpenes, sesquiterpene lactones, and acetylene derivatives. Phenolic compounds found in the flowers include hydroxycinnamic acid derivatives, caffeic acid, and flavonoids (i.e., apigenin, luteolin, chamaemeloside). A novel and potent NK1 receptor antagonist has been identified in *Matricaria* flowers. Coumarin has also been identified [82]. The chemical constituents of chamomile (e.g., bisabolol, chamazulene) and the flavonoids apigenin and luteolin possess anti-inflammatory properties. Apigenin has also been shown to reversibly inhibit irritant-induced skin inflammation in animals and to exert antispasmodic effects in the intestines [360]. Bisabolol and the flavonoids have demonstrated antispasmodic effects [82].

Evidence-Based Therapeutic Use and Effectiveness

The chemical components in chamomile (i.e., bisabolol, flavonoids) have demonstrated antispasmodic effects in animal experiments. Chamomile infusions have been used traditionally as gastrointestinal antispasmodics despite the lack of rigorous trials to support this use [82]. Commercial preparations of creams containing chamomile are also widely available despite the paucity of trials to support their use [361; 362].

It has been suggested that chamomile might provide clinically meaningful antidepressant activity [363]. The authors of a Canadian study examined whether commercially available botanicals directly affect the primary brain enzymes responsible for GABA metabolism [364]. Approximately 70% of all extracts tested showed little or no inhibitory effect. However, both *M. recutita* and *Humulus lupulus* (hops) showed significant inhibition of GAD enzyme activity in animals.

Adverse Effects and Drug Interactions

Allergic reactions to chamomile are commonly reported and may be dependent on the route of ingestion. Hypersensitivity reactions include anaphylaxis, dermatitis, gastrointestinal upset, lacrimation, and sneezing. The dried flowering heads may induce vomiting in large amounts. Eye drops containing chamomile have caused allergic conjunctivitis [82]. Chamomile may potentiate the anticoagulant effects of warfarin. No coagulation disorders have been reported, but close monitoring of patients on anticoagulants is advised. In vitro, chamomile has been shown to be bactericidal to some *Staphylococcus* and *Candida* species [365].

Chamomile is considered safe by the FDA, but it should be used with caution in individuals who are allergic to ragweed, as cross-allergenicity may occur. Symptoms include abdominal cramping, tongue thickness, tight sensation in the throat, angioedema of the lips or eyes, diffuse pruritus, urticaria, and pharyngeal edema [366; 367].

Toxicology

Bisabolol toxicity in animal studies is reported to be low following oral administration with no noted teratogenic or developmental abnormalities [82].

Dosage

Because of the sedative effects of chamomile, caution should be used in conjunction with medications with sedative side effects or with alcohol. The oral dose is 400–1,600 mg/day in divided doses, standardized to 1.2% apigenin per dose. Chamomile is commonly consumed as a tea for its calming effect. It can be brewed using one heaping teaspoon of dried flowers steeped in hot water for 10 minutes and may be consumed up to three times per day [368].

CONCLUSION

Herbal medications have become an important issue in North America for a variety of social, economic, and medical reasons, and the use of HMs continues to increase. Data from the National Center for Health Statistics indicates that supplement use among U.S. adults 20 years of age and older increased from 48.4% to 56.1% during the period between 2007–2008 and 2017–2018, with use more common among women (63.8%) than men (50.8%) [8].

In 2012, out-of-pocket expenditures for CAM in the United States were $30.2 billion; this accounts for 1.1% of total national healthcare spending and 8.4% of total out-of-pocket expenditures [369]. The cost of dietary supplements alone was $12.8 billion, or about one-quarter of the $54.1 billion that U.S. adults spent out-of-pocket on prescription drugs [369]. Considering the high price of health insurance and changing attitudes towards CAM, the expenditures today are most likely greater.

In addition, more than 50% of patients receiving conventional medical care also use CAM [11]. An estimated 40% to 70% of patients fail to disclose the use of CAM to their healthcare providers, and concern regarding a possible negative reaction or perceived lack of interest by the healthcare provider have been identified as the main reasons for limited disclosure of CAM use [5; 11; 13]. It is commonly believed by the population in general, and by many healthcare providers as well, that due to their natural origin, these products are intrinsically safe and devoid of adverse effects or toxicity, or that the worst possible outcome is lack of therapeutic effectiveness. This has been proven false.

It is vital that healthcare providers have an understanding of the pharmacologic properties and evidence-based therapeutic efficacy of HMs. Healthcare providers should be aware of the need to inquire about and include current or past use of HMs in the patient's medical history and discuss relevant information with their patients. Providers also should be aware of the possible interactions with conventional medications and evaluate the potential therapeutic benefits of HMs when appropriate.

RESOURCES

MedWatch: The FDA Safety Information and Adverse Event Reporting Program
https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program
1-888-INFO-FDA

MedEffect Canada: Adverse Reaction and Medical Device Problem Reporting
https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html
1-866-234-2345

Natural Medicines
https://naturalmedicines.therapeuticresearch.com/

National Center for Complementary and Integrative Health: Dietary and Herbal Supplements
https://nccih.nih.gov/health/supplements

FACULTY BIOGRAPHY

A. José Lança, MD, PhD, received his Medical Degree at the University of Coimbra in Coimbra, Portugal, and completed his internship at the University Hospital, Coimbra. He received his PhD in Neurosciences from a joint program between the Faculties of Medicine of the University of Coimbra, Portugal, and the University of Toronto, Toronto, Canada. He was a Gulbenkian Foundation Scholar and received a Young Investigator Award by the American Brain & Behavior Research Foundation.

Dr. Lança participated in international courses and conferences on neurosciences. He has contributed to a better understanding of the mechanisms underlying the ontogenetic development of the brain opiatergic system. As a research scientist at the Addiction Research Foundation (ARF) in Toronto, he initiated research on the functional role played by dopaminergic cell transplants on alcohol consumption, leading to the publication of the first research reports on cell transplantation and modulation of an addictive behavior. Subsequently, he also investigated the role played by other neurotransmitter systems in the limbic system and mechanisms of reward, co-expression of classical neurotransmitters and neuropeptides and potential role in neuropsychiatric disorders.

He is an Assistant Professor in the Department of Pharmacology and Toxicology at the Faculty of Medicine and at the Faculty of Dentistry at the University of Toronto, where he lectures and directs several undergraduate and postgraduate pharmacology and clinical pharmacology courses. He was the Program Director for Undergraduate Studies in the Department of Pharmacology and Toxicology of the University of Toronto. He has developed clinical pharmacology courses for the Medical Radiation Sciences and Chiropody Programs of The Michener Institute for Health Sciences at the University of Toronto.

Dr. Lança's commitment to medical education started while a medical student, teaching in the Department of Histology and Embryology, where he became cross-appointed after graduation. In Toronto, he has contributed extensively to curriculum development and teaching of pharmacology to undergraduate, graduate, and medical students.

He has authored research and continuing education in peer-reviewed publications and is the author of six chapters in pharmacology textbooks. Dr. Lança has conducted research in various areas including neuropharmacology, pharmacology of alcoholism and drug addiction, and herbal medications.

He has developed and taught courses and seminars in continuing medical education and continuing dental education. His commitment to continuing education emphasizes an interdisciplinary approach to clinical pharmacology.

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