

Review Article

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Use of Herbal Medicines and Implications for Conventional Drug Therapy Medical Sciences

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Herbal medicines are an important part of healthcare throughout the world. In many countries including the U.S., herbal medicines are not regulated as extensively as conventional drug therapy. At present, there is a dearth of research evaluating the use of herbal medicines, especially in clinical trials. This, together with the ongoing development of new conventional drug therapies, compounds the number of unknown outcomes when using elements of these two treatment approaches together. Although many benefits can be derived from the use of herbs, potential areas of concern include possible product contamination and/or adulterations, potential toxicity, high potential of known and unknown drug/herb interactions, and substituting proven conventional medicine with herbal medicine. Mechanisms involved in herb-drug interactions are not fully understood, but both pharmacokinetic and pharmacodynamic processes may play a role. Because these can occur in 30-40% of older adults, health care providers and patients must be aware of potential interactions in order to monitor for alterations in therapeutic efficacy and/or potential toxicity. With the advances of the internet and increased emphasis on a global economy, consumers have much greater access to herbal products from anywhere in the world. A number of concerns arise when obtaining herbal medicines from the internet, as currently there is no system in place to verify legitimacy of sites. Additionally, there are cost implications with a worldwide herbal medicine market estimated at US \$83 billion annually. The worldwide implementation of standards for growing, selecting, manufacturing, conducting appropriate clinical trials, and treating patients with herbal medicines is necessary. The World Health Organizations has provided a number of technical guidelines to standardized herbal medicines throughout the world. Pharmacists are in prime position to help and monitor the use of herbal medicines, especially in older adults. Strategies for the safe use of herbs should include educational efforts directed at both the consumers and healthcare providers about the benefits and dangers of herbs and encouraging providers to ask their patients about their use of herbs without being judgmental, ensuring open communication with patients. *Integrative Medicine*, which is defined in the U.S. by the National Center for Complementary and Alternative Medicine as "a practice that combines both conventional and CAM treatments for which there is evidence of safety and effectiveness" has been gradually gaining acceptance within conventional medicine and should be considered the model of the future of healthcare.

Keywords: Herbal medicine; Conventional medicine; Safety; Herb/drug interactions; Integrative medicine

Introduction

Herbal medicines have been widely utilized as effective remedies for the prevention and treatment of multiple health conditions for centuries by almost every known culture. The first documented records of herbal medicine use date back 5,000 years [1] in China. Similarly, India's Ayurvedic medicine tradition is thought to be more than 5,000 years old and herbal medicines remain an essential component of its practice [2]. Today, the populations of certain countries still depend on herbal medicines to address their healthcare needs. In the U.S. the use of herbal medicines continues to grow since Eisenberg et al. [3,4] conducted the first national study of complementary and alternative medicine use.

Additionally, as a general rule, older adult populations are more likely to use both conventional drug therapy and herbal medicines. This population is also more likely to have a higher incidence of chronic disease, which more often than not requires the use of increasingly complex conventional drug therapy. As such, the potential for herb-disease and herb-drug interactions increases with older adult populations. At present, there is a dearth of research evaluating the use of herbal medicines, especially clinical trials. This, together with the ongoing development of new conventional drug therapies, further compounds the number of unknown outcomes when using elements of these two treatment approaches together. In many countries,

including the U.S., herbal medicines are not regulated as extensively as conventional drug therapy. Also, globalization has greatly increased accessibility of herbal medicines from all parts of the world to any single consumer. Clearly there is a great need for coordinated efforts to conduct the necessary clinical trials to study the efficacy and safety of herbal medicines, both alone and in conjunction with conventional drug therapies.

Regulations of herbal medicines

One of the most basic problems with the use of herbs is that there is lack of consistent terminology when describing what category herbs fall under. For example, a single product may be classified as a food product by some and as a dietary supplement by others. Therefore, this product may have multiple concurrent regulations depending on how it is classified. In the United States, the 1994 Dietary Supplement Act

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(DSHEA) [5] provides the regulatory framework for herbal medicines. This Act is considered to be industry friendly and does not apply Good Manufacturing Products (GMP) standards that are required for conventional drug therapy. This law classifies herbal products as dietary supplements; therefore, they are not considered drugs or prescribed substances, allowing the American public greater access to herbal products, but in effect remove the role of herbalists from the practice of medicine and sees them functioning and being regulated more like small businesses. Regulations and laws that apply to any and all healthcare providers, which have the safety of consumers in mind, do not apply to those involved in the manufacture and provision of herbal products. The DSHEA's definition of what constitutes the practice of medicine is the "diagnosis, treatment or cure of disease." Herbalists who claim to do any of these can be considered guilty of practicing medicine without a license. In reality, it is commonplace for a person selling herbs to recommend a specific herbal product that may help a given condition, and in essence circumvent the definition. Furthermore, regulations under this act allow great variation in product integrity by different manufacturing companies. Recent attempts to tighten these loose standards and improve safety were unsuccessful; the Dietary Supplement Safety Act of 2010, which proposed higher safety standards, was referred to committee for further evaluation.

The manufacturing, provision and use of herbal medicines are regulated differently in other parts of the world. In some countries, attempts to prove efficacy and safety of herbal medicines are considered to be superior to those in the U.S. The Commission E monographs in Germany [6] are an example of a more scientific approach to evaluating efficacy and safety of herbs in Western medicine. These monographs were developed by many stakeholders who combined the scientific, healthcare, and industry leaders; their guidelines are more grounded in evidence-based knowledge and seemingly more respected within the practice of medicine. In fact, prescribing of herbal medicines among providers in Germany is common.

In Europe, the "Traditional Herbal Medicinal Products Directive" (THMPD), [7] also known as the EC Directive 2004/24/EC is an attempt by the European Commission to further regulate the market for traditional herbal medicines. The THMPD, which became effective in early 2011, required a higher standard of scientific evidence. These changes were not without controversy and Britain has defied the implementation of this directive.

China has a long and rich history of traditional medicine use which includes the common use of herbs. Traditional Chinese Medicine (TCM) is an accepted medical system that runs parallel to the use of conventional medicine in China. Since 2004 [8], herb manufacturers are required to meet GMP standards; one of the reasons why the industry has put forth a major effort to implement information systems models. The extent to which Chinese manufacturers comply is unknown. Attempts to implement GMP standards for herbal medicines in other countries with similarly long standing traditions of herbal use (Africa, India, and Brazil) are ongoing.

Culture and traditional medicine

It is known that culture plays an important role in the manner in which a given people use herbs. In recognition of this, in 2009 the world health assembly passed resolution 62.13 urging national governments to respect, preserve, and widely communicate traditional medicine knowledge [9].

When asked, many patients who drink herbal teas will indicate

that they do not use herbal medicines. In our studies with Mexican-Americans we have found that patients who use herbs in this form do not report them as herbal medicine use, unless specifically asked in surveys (Rivera) [10]. The number one reason for using herbal teas in our region was for gastrointestinal ailments or discomfort.

Herbal medicine research

There are limited clinical trials to determine efficacy and safety of traditional herbal medicines. This lack of research does not impede most from using them, given that these remedies are often grounded in long standing cultural traditions. When trials are conducted, the Western-defined disease classification may not be appropriate to measure efficacy and safety in relation to the use of herbs in other countries. Tylburt and Kaptchuk [11] recently published an ethical analysis of global herbal medicine research. They pose multiple scientific questions that shed light on the difficulties of conducting research with herbal medicines worldwide. Finding appropriate ways to conduct this type of research is an ongoing challenge.

Trends in herbal medicine use

Worldwide it is estimated that 80% of the population uses herbs; in the developing world rates could be as high as 95% [12]. The U.S. continues to see an increase in the use of herbs [3]. The most recent national survey conducted in 2007 by the National Center for Complementary and Alternative Medicine (NCCAM) [13] showed that 17.7% of adults have used natural products (primarily herbs) in a one year period. Complementary and alternative medicine (CAM) was used most commonly by whites (43.1%) followed by Hispanics (23.7%). In the El Paso region studies, use of herbs by Hispanics, including older adults was much higher (between 59-70%) [10,14]. It is possible that certain methodologies may underestimate rates of use. In most studies, disclosure rates of herb use to providers are very low (a major concern). We found two main reasons for such low rates: providers did not ask about herb use or they showed displeasure with use of herbs. Our experience indicates that in some countries, herbs more commonly used vary depending on which products are marketed and on regional practices. Another recent trend in Western countries involves adding herbs to energy drinks and weight loss and nutritional products.

Global herbal market

It is extremely difficult to calculate sales data regarding the use of herbs worldwide; these calculations are likely underestimated. This is due in part to the varied ways in which herbs are used (e.g. food products, energy drinks, multivitamins, raw form). The World Health Organization (WHO) estimates that the global market is approximately US \$83 billion annually [12]. In some countries, marketing and sales of some herbs is driven primarily by profits. However, in other countries, herbs can serve as a major way of treating certain conditions or diseases more cost effectively, especially if the herb can be grown locally or regionally.

Raw versus commercial products

Local or regional herbs in raw form are typically more affordable. In some cases, consumers may prefer packaging that resembles that of pharmaceuticals (neutraceutical). It is imperative that standards are followed for both the growing and the manufacturing of herbs. The WHO has published guidelines [15,16] for the growing, collecting and manufacturing of herbs that should be considered by all countries as a template for global standardization of herbs.

Potential negative outcomes

While many benefits can be derived from the use of herbs, potential negative outcomes cannot be ignored. Saper et al. [17] reported that 20% of Ayurvedic medicines purchased via the Internet contained detectable levels of lead, mercury, and arsenic. Many herbal product adulterations have been detected primarily containing drugs like sildenafil (Viagra®), lovastatin (Mevacor®, and others), estrogen, alprazolam (Xanax®, and others), indomethacin (Indocin®, and others), and warfarin (Coumadin®, and others) [18]. There is an apparent trend of adding drugs or analogues to herbs to make them more effective, especially for weight loss and enhanced sexual function [19]. Herbs that have caused major adverse events include creosote bush (hepatotoxicity), [20] ephedra or Mau Huang (cardiovascular complications and hepatotoxicity), [21] and kava (hepatotoxicity) [22]. Using the proper parts of the plant and the appropriate processes for obtaining the ingredients could prevent toxicity, as seen in kava-induced toxicity [23]. Herbs that may alter bleeding are also of importance especially in patient populations with coagulopathies, on antiplatelet or anticoagulant drugs, or in surgical patients. We reported a case of a surgical patient with a prolonged unexplained bleeding after taking large quantities of an herbal tea that contained Mexican arnica [24]. Keep in mind that many medications used today may cause similar adverse events if not monitored or used correctly.

Selected herb/drug interactions

The potential for interactions between medications and herbs is one of the significant consequences resulting from the use of several medications, herbal products and supplements. Unfortunately, many consumers of herbal products assume that because these products are “natural” they are also safe [25]. However, there are a variety of case reports and clinical observations in literature documenting the occurrence of clinically significant interactions between herbs and medications [26]. There are other reports of interactions that are theoretically possibly based on preclinical data [26].

The mechanisms for these herb/drug interactions are not fully understood, but both pharmacokinetic and pharmacodynamic processes have been identified as playing a role [25,26]. In general, herbal products may mimic, increase, or decrease the effects of medications [26]. It is possible that the herbal product itself has therapeutic properties that are synergistic or an additive to the medication being used. Examples of herbs that enhance the therapeutic effect of a medication include Ephedra used with amphetamines, valerian or Kava with benzodiazepines. This may lead to supratherapeutic effects or toxicities, complicating the management of medical conditions and the corresponding medications. Similarly, an herb may counteract the desired effect of a medication, as in use of Ephedra with antihypertensive medications. Pharmacokinetic drug interactions can lead to alterations in the absorption, distribution, metabolism and excretion of medications. Studies revealed that these interactions occur through the induction or inhibition of drug metabolizing enzymes (cytochrome P 450) or alteration of drug transporters (P-glycoproteins) [26]. Herbal products that inhibit the metabolism of medications will result in higher medication levels, which can increase efficacy or risk for toxicity. Herbs that induce metabolism of medications can lead to decreased medication levels, which may result in decreased efficacy of the medication or therapeutic failure. Herbs that cause p-glycoprotein alterations can have an impact on the absorption and bioavailability of the medication and either reduce or potentiate the effects of the medication [27-29].

Studies have researched the prevalence of interactions between medications and herbs in the elderly. Most of these studies report that 30-40% of older adults had a potential interaction between their medication and herbs [30-32]. We conducted a survey of medication and herbal product use in 130 older adults living on the US-Mexico border [30] and potential interactions were found in 31.5% of these participants. Most of the interactions that were documented in this study involved herbal products causing potential alterations in the levels of medication, including statins, digoxin, benzodiazepines, bisphosphonates, thyroid hormones, H2-antagonists, and aspirin. These findings suggest that patients may have clinically relevant alterations in the efficacy of their medication (if medication levels are decreased) or potential toxicity (if medication levels are increased).

Although drug interactions can occur as a result of an herbal product's ability to influence the pharmacokinetics (e.g. metabolism) of a medication, other interactions result from the direct pharmacologic activity of the herb in the presence of an additional pharmacologic effect from medications [25,26]. Other potential interactions we identified were due to the herbal product's ability to alter glucose levels and blood pressure, which may result in clinically significant problems in patients already taking medications that affect glucose and blood pressure control [30]. Ten percent of the interactions identified were related to an increased risk of bleeding due to the combination of herbs and medications. Patients who are taking herbal products that have additional pharmacologic activity will need to be closely monitored to prevent adverse outcomes.

The literature includes a number of reports on herb/drug interactions. Table 1 summarizes some documented interactions between medications and commonly used herbs. It is important to note that most of the evidence is from case reports and not randomized controlled clinical trials. Additionally, for many reported herb/drug interactions, there is conflicting evidence on whether or not there is a true interaction. These factors should be taken into consideration when analyzing the literature and drawing conclusions on the potential for herb/drug interactions.

The clinical relevance of herb and drug interactions depends on the individual characteristics of the medication and herb (source of herb, product standardization) as well as on a variety of patient factors including comorbidities, additional medications and genetic differences. Although there are data in the literature to describe herb/drug interactions and the possible mechanisms involved, it should be emphasized that there is still a lack of information on this topic. Additionally, it is important to consider that herbal medicines can be a mixture of active ingredients that can increase the likelihood of the potential for interactions [25,26].

It is important for health care providers and patients to be aware of the potential for herb/drug interactions in order to monitor for alterations in therapeutic efficacy or potential toxicity. Studies have documented that one-third of patients or less disclose to their provider that they are taking herbal products [33]. As a result, it is left to the healthcare provider to specifically ask what herbs and supplements the patient is taking when obtaining medication history.

Integrative Medicine

In the U.S., the NCCAM was established in response to the wide utilization of CAM therapies by the population. The mission of NCCAM is “to define, through rigorous scientific investigation, the usefulness and safety of complementary and alternative medicine

Herb	Potential Interactions/Mechanism	Outcomes	Study Type
Dong Quai (<i>Allium sativum</i>)	Warfarin (additive effects)	Increased INR and risk of bleeding	Case report [34]
Garlic (<i>Allium sativum</i>)	Chlorpropamide (additive effect on glucose levels)	Hypoglycemia	Case report [35]
	Saquinavir, ritonavir (decreased AUC and Cmax by induction of 3A4 and P-glycoprotein)	Decreased antiretroviral efficacy	Pharmacokinetic trial [36,37]
	Warfarin (additive effect; evidence suggests no effect on PK and PD)	Increases INR and clotting time, risk of bleeding	Two clinical trials (evaluating PK and PD); case reports [38-40]
Ginkgo (<i>Ginkgo biloba</i>)	Thiazide diuretics (unknown)	Increased blood pressure	Case report [41]
	Warfarin (additive effect)	Increased risk of bleeding; conflicting evidence—no effect on INR and platelet aggregation	Case report [42], clinical trials [43,44]
	Aspirin (additive effect)	Increased risk of bleeding; one trial documents no effect on platelet aggregation	Case report [45], pharmacokinetic trial [46]
	Digoxin (Increases AUC by modulation of P-glycoprotein)	Increased efficacy/potential toxicity	Open label, crossover [47]
Kava (<i>Piper methysticum</i>)	Alprazolam (additive effect on GABA receptors)	Increased efficacy/potential toxicity	Case report [48]
	Levodopa (reduced efficacy)	Increased off period	Case report [49]
St. John's wort (<i>Hypericum perforatum</i>)	Additive effect on serotonin reuptake or signaling (buspirone, eletriptan, nefazodone, paroxetine, sertraline, venlafaxine)	Potential for serotonin syndrome	Case reports [50-56]
	Induction of 3A4 and/or p-glycoprotein (alprazolam, amitriptyline, atorvastatin, erythromycin, fexofenadine, imatinib, indinavir, nifedipine, omeprazole, oral contraceptives, simvastatin, verapamil)	Decreased efficacy	Pharmacokinetic trials [57-72]

Abbreviations: AUC: Area Under The Curve; INR: International Normalized Ratio; PK: Pharmacokinetic; PD: Pharmacodynamic

Table 1: Selected herb-drug interactions.

interventions and their roles in improving health and health care.” *Integrative Medicine*, which is defined by the NCCAM [12] as “a practice that combines both conventional and CAM treatments for which there is evidence of safety and effectiveness” has been gradually gaining acceptance within conventional medicine. There are currently at least 47 academic medical centers that are recognized as providing instruction [73]. Integrative medicine should be considered the model of the future of healthcare.

Role of Internet and the Global Economy

With the advances of the internet and increased emphasis on a global economy, consumers have much greater access to herbal products from anywhere in the world. Furthermore, industries are using internet sites as a vehicle to increase sales with most companies being less concerned with protecting the public as with making a profit. While many of these sites may claim that their products are safe, effective, standardized, pure, etc., such claims cannot be verified. The burden of investigation lies on the consumer, who should first research the company and its reputation in addition to looking into the product of interest before making a purchase. The international community needs a system for monitoring the legitimacy of internet sites that sell herbs similar to those of internet pharmacies verified by the National Association of Boards of Pharmacy [74].

Role of the Pharmacist in the Use of Herbal Medicine

The practice of pharmacy has evolved into a role that includes an expanded clinical application of pharmacotherapy knowledge as a member of the healthcare team. In many settings the pharmacist is in an ideal position to advise/monitor the use of herbs, especially in older adults. Recognizing this expanded role, in 1998 the WHO provided a technical document entitled “the role of the pharmacists in self care and

self medication” [75]. This document explains the role of the pharmacist in self care and self treatment of patients, one of the four elements of good pharmacy practice.

Strategies for the safe use of herbs

Perhaps the most important strategy for the safe use of herbs is to integrate evidence-based herbal medicine knowledge into the Western medicine healthcare curriculum. Several strategies may help with the management of herbs. They include: educating providers and patients about the possible benefits and risks of herbs, encouraging providers to ask their patients about their use of herbs without being judgmental, ensuring open communication with patients. Patients should also be careful when claims are made for a particular herb and should only purchase herbs from a reputable provider, company, or internet site.

Conclusion

Older adults are more likely to encounter potential problems with the use of herbs in conjunction to conventional drug therapies. Worldwide standardization of herbal medicines and adequate clinical trials are necessary to understand the potential benefits and risks of these products. Supporters of western medicine and traditional medicine should work together to incorporate best practices verified by sound scientific methods.

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