

EDUCATIONAL OBJECTIVES

After completing this continuing education activity, pharmacists will be able to

- List herbal products associated with liver, kidney, and heart damage
- Describe potential drug interactions with herbal medications
- Discuss the potential for contaminants in herbal products

After completing this continuing education activity, pharmacy technicians will be able to

- List herbal products associated with liver, kidney, and heart damage
- Recognize the potential for herbal products to be unsafe
- Describe certificates of analysis and how to retrieve them from manufacturers



The University of Connecticut School of Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Pharmacists and pharmacy technicians are eligible to participate in this knowledge-based activity and will receive up to 0.2 CEU (2 contact hours) for completing the activity, passing the quiz with a grade of 70% or better, and completing an online evaluation. Statements of credit are available via the CPE Monitor online system and your participation will be recorded with CPE Monitor within 72 hours of submission

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Patient Safety: Herbal Products and Potential Organ Dysfunction

ABSTRACT: As part of complementary and alternative medicine, herbal products are gaining popularity in the United States. Approximately one in five Americans use herbal products. Although people may perceive them as harmless due to their "natural" origin, studies and case reports on herbal toxicity dispute that belief. Injuries to liver, kidney, and heart; herb-drug interactions; and contamination and mislabeling are grave health risk concerns with some herbal products. Although non-prescription, herbal products' ubiquitous presence in all kinds of shops, pharmacies, and Internet vendors causes many people to consider them important to their overall well-being. Pharmacists and technicians can help patients reduce health risks associated with herbal products. Ample knowledge of popular herbal products will help pharmacy teams identify health risks quickly.

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FACULTY DISCLOSURE: The authors have no actual or potential financial conflicts of interest associated with this article.

DISCLOSURE OF DISCUSSIONS OF OFF-LABEL and INVESTIGATIONAL DRUG USE: This activity may contain discussion of off label/unapproved use of drugs. The content and views presented in this educational program are those of the faculty and do not necessarily represent those of the University of Connecticut School of Pharmacy. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

INTRODUCTION

Complementary and alternative medicine (CAM) use is on the rise in the United States (U.S.). One study estimated at least a quarter of Americans used CAM in 2014.¹ As a subset of CAM (see **Table 1**), herbal products, are popular. The same study showed around one in five Americans use herbal products.¹ Most people use herbal products either for general well-being or chronic health conditions. Nowadays, thanks to Internet and a dynamic demographic in the U.S., Americans are learning about new herbal products from all over the world.¹ Since the U.S. Food and Drug Administration (FDA) does not review or inspect herbal products before marketing, unchecked and unregulated herbal medicine presents risk.² A different federal agency, the National Center for Complementary and Alternative Medicine, sponsors and conducts research using scientific methods and advanced technologies to study CAM. It also has no role in these products' approval but has standardized much language associated with these

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PAUSE AND PONDER: How many times have patients asked you about herbal medicine? Are you familiar with the active herbal ingredients?

products. While pharmacists and pharmacy technicians generally should avoid promoting or dissuading patients from CAM, their knowledge about herbal products will ensure patient safety.

HERBAL PRODUCTS AND HEALTH RISKS

Herbal products have documented health risks, yet these risks are not well known publicly. For example, in the United Kingdom, a woman continued to bleed from abdominal site 10 months after an abdominoplastic surgery to remove excess skin after weight loss surgery. The bleeding caused the development of abdominal seroma (sterile accumulation of serum), requiring surgical drainage. Later, the doctors discovered she was taking an herbal product for menopause that contained bitter melon extract, hops, soya extract, and kelp. Kelp has anticoagulant effects, and probably contributed to the excess bleeding.⁴ This exemplifies the need to record all herbals that patients take on patient profiles.

This activity will discuss herbal products' health implications. Hopefully, the materials will help identify the "red flag" contraindications in patients visiting pharmacies. Overall, this activity focuses on three types of potential harm by herbal products:

- Potential organ toxicity
- Interaction with prescription medications
- Contamination with substances harmful to humans

Note that in many cases, we are unable to provide a recommended "dose," since limited evidence is available for many of these products. Often, the doses are unclear or just suggested. Additionally, any uses listed are suggested, not FDA-approved indications.

Liver and Kidney Injuries

Some herbal products are known to cause herb-induced liver injury (HILI). In some cases, liver injuries require liver trans-

plantation, which burdens patients and healthcare systems. Although not all cases are severe, pharmacy staff should always be vigilant about herbal products' ingredients. Past case reports and studies have linked several plants that are sources of active herbal ingredients to severe liver injuries. Let's review HILI's most common causes.

Greater celandine (*Chelidonium majus*), usually present in botanic extracts, may soothe gastrointestinal disorders and dyspepsia (indigestion).⁵ It contains isoquinoline alkaloids, which may cause several adverse effects in humans. Most commonly, it elevates transaminases. Uncommonly, case reports show it could cause liver injury requiring hospitalization.⁶ Iberogast, an over-the-counter (OTC) syrup available on the Internet, contains greater celandine. The manufacturer claims that this herb is useful for stomach upset and irritable bowel syndrome.⁷ Pharmacists should educate patients with liver disease that this product may exacerbate liver injury.

Chaparral (*Larrea tridentate*), used for skin disorders and cancer, originates from a shrubby heartland plant used in Native American medicine. Chemically, it contains nordihydroguaiaretic acid (NDGA), which may be hepatotoxic.⁸ Case reports over several years link chaparral extract to hepatitis. Rarely, it may cause liver failure that requires transplantation.⁹

Germander (*Teucrium chamaedrys*), taken as extract or tea, is promoted as a fever remedy and weight loss aid.¹⁰ Its hepatotoxicity manifests as non-specific symptoms, typically including fatigue, nausea, and jaundice associated with marked serum aminotransferase level elevation and sometimes fulminant hepatitis. This resolves without treatment upon herb discontinuation. Since germander causes glutathione depletion, N-acetylcysteine (typically used for acetaminophen poisoning) is an antidote in case of acute hepatotoxicity.¹⁰

Table 1. Definitions from National Center for Complementary and Alternative Medicine (NCCAM)³

Terminology	NCCAM Definition
Complementary and alternative medicine (CAM)	"A group of diverse medical and healthcare systems, practices, and products that are not presently considered to be part of conventional medicine" NCCAM classifies CAM into four domains: <ul style="list-style-type: none"> ● Biologically-based practices* ● Energy therapies ● Manipulative and body-based methods ● Mind-body medicine
Biologically-based practices	Includes, but is not limited to, "amino acids, animal-derived extracts, botanicals, fatty acids, functional foods, minerals, prebiotics and probiotics, proteins, vitamins, and whole diets"
Botanical (herbal) products	May be regulated as drugs, cosmetics, dietary supplements, or foods, depending on their intended uses

*The only one of the domains discussed here

Comfrey (*Symphytum officinalis*) is a leafy herb. Western folk medicine practitioners indicate that it may treat pain and aid in fracture healing.¹¹ Patients can administer comfrey topically or orally. Oral comfrey intake is associated with liver damage, liver cancer, and even death due to pyrrolizidine alkaloids. Therefore, the FDA prohibits oral use of comfrey-containing products in the U.S.. Its external use is still legal in the U.S. but requires warning labels describing adverse effects.¹¹

Impila (*Callilepis laureola*) is an herb extracted from a black-eyed Susan type flower. Research has described its use in several conditions (e.g., fertility, impotence, congestion). Case reports show impila poisoning mostly occurs in South Africa, where the plant originates. Poisoning by impila develops rapidly. Often, patients die before reaching the hospital.^{12,13} It contains atractyloside, a compound that induces cytotoxicity in liver cells. An *in vitro* study of impila poisoning indicates it involves glutathione depletion, suggesting N-acetylcysteine as a possible antidote.¹⁴

In addition to hepatotoxicity, impila also increases kidney injury risk.¹⁵⁻¹⁹ Researchers have found that mortality is highest among those who ingest the herb. It contains carboxyatractyloside, which inhibits mitochondrial adenosine triphosphate (ATP) synthesis (the energy source of living cells), causing renal tubular necrosis (acute kidney injury).²⁰ In the past, South African parents used impila to ward off evil spirits that might hurt their children; impila is the Zulu word for "health." Parents administer impila to their children orally or rectally via enema. It's unclear how often this herb is used today.¹⁶⁻¹⁹

Toothed clubmoss (*Huperzia serrata*) is an herb that is believed to help patients with dementia.²¹ This herb contains huperzine A, an anticholinesterase that decreases the breakdown of chemical messengers in the brain. Traditional Chinese medicine uses a similar herb called Jin Bu Huan (*Lycopodium serratum*) for sleep and arthritic pain. Both herbs are in the same plant category, but they have different levels of evidence for toxicity. For toothed clubmoss, no human study or case report shows its toxicity.

However, case reports show long-term use (a term poorly defined in studies) of Jin Bu Huan causes hepatitis in adults. Some traditional Chinese medicine (TCM) products containing Jin Bu Huan may mislabel the ingredients, hindering the herb's identification.²¹

Kava (*Piper methysticum*) is an herb popular in South Pacific cultures and used around the world for its anxiolytic (antianxiety) effect.²² The plant's root contains kavalactones, which show psychotropic effect in both *in vitro* and *in vivo* studies. Kava use in the West has caused sporadic cases of liver injuries since the 1990s. In response to the health risk, the FDA issued a warning on kava products, but people continue to use it. To ensure safety, patients should not consume more than 150 to 300 mg twice daily with food.^{22,23}

Pennyroyal (*Mentha pulegium*) is an herb used in Western folk medicine for repelling insects, inducing abortion, and regulating the menstrual cycle. Nowadays, manufacturers market both tea and oil versions of the herb. Case studies have connected oral pennyroyal essential oil intake to multiple cases of severe, life-threatening HILI.²⁴ While pennyroyal tea is relatively safer, children and patients with liver disease should avoid its long-term use.²⁵ Pharmacists should inform patients never to ingest pennyroyal essential oil orally.

Guang Fang Ji (*Aristolochia fangchi*) is an herb that has caused numerous kidney injuries since its introduction as a weight loss supplement. The herb contains aristolochic acid, which causes cancer and kidney damage. The associated renal adverse event is aristolochic acid nephropathy, a progressive renal interstitial fibrosis (excessive accumulation of collagen and related molecules). Guang Fang Ji caused multiple kidney injuries in Belgium after dozens of people used it as a weight loss aid, therefore many Western countries have prohibited its sale.¹⁹ The FDA has recalled products containing aristolochic acid. Currently, the FDA bans import of any products containing Guang Fang Ji or aristolochic acid.²⁶



Mentha pulegium, commonly called pennyroyal, also called squaw mint, mosquito plant, and pudding grass.

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PAUSE AND PONDER: How confidently can you answer patients' questions about herb-drug interactions?

Cardiotoxicity

Chuan wu (*Aconitum carmichaeli*) is an herb used in TCM to treat inflammation and musculoskeletal problems. However, ingestion of raw chuan wu plant causes aconitine poisoning, characterized by arrhythmia (irregular heartbeat) symptoms. Patients with severe aconitine poisoning could develop potentially fatal ventricular arrhythmia.²⁷

Henbane (*Hyoscyamus niger*) is an herb found in many folk medicines around the world, usually employed for insomnia and pain.²⁸ It contains many types of alkaloids, such as hyoscyamine, atropine, tropane, and scopolamine. Henbane overdose could cause myriad health problems. A primary adverse effect of acute overdose is cardiotoxicity, marked by tachycardia (rapid heartbeat) and arrhythmia.²⁸

Licorice (*Glycyrrhiza glabra*), the flavor found in candy, is also a common herb used in many folk medicines to alleviate heartburn and bronchitis. The FDA classifies licorice as “generally recognized as safe.”²⁹ Despite its widespread use, licorice still presents health risks in case of overdose. Glycyrrhizin in licorice can decrease serum potassium. Adverse effects include hypertension and arrhythmia. Licorice’s health risk depends on the dose.³⁰ Patients should limit licorice root intake to 1 to 5 grams three times daily for up to six weeks.²⁹

Lily of the valley (*Convallaria majalis*) is a decorative plant, but patients also use it to mitigate congestive heart failure.³¹ The plant, however, is poisonous; the cardiac glycoside convallatoxin found in this herb is functionally similar to digoxin. Therefore, lily of the valley has a digitalis-like effect, inhibiting the sodium-potassium pump in heart tissue and causing a positive inotropic effect (strengthening the force of the heart beat).³² Symptoms of poisoning include nausea, tachycardia, and confusion.³¹ Another case report showed a dog experienced a fatal cardiac shock after ingesting the herb.³³

Ephedra is a plant found in many folk medicines used for cold, allergy, and flu.³⁴ It has a variety of biological functions. Specifically, ephedrine—one of ephedra’s bioactive alkaloid compounds—has an amphetamine-like effect. The chemical can cause various adverse effects in humans (e.g., palpitations, nausea, vomiting). It may also trigger heart attack, stroke, seizure, and even death. Due to health problems caused by ephedra, the FDA prohibits the sale of the herb and any extract containing it. However, ephedra extract that does not contain ephedrine is not prohibited. If patients want to use ephedra extract, the extract should not include ephedrine in its ingredients.³⁴

Licorice root



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Before ephedra’s ban, it was included in some dietary supplements to promote weight loss, increased energy, and enhanced athletic performance. Consequently, herbal medicine manufacturers are looking for a substitute.³⁴ Bitter orange (*Citrus aurantium*) extract is replacing ephedra for its proposed ability to promote weight loss. The plant contains chemical *p*-synephrine, which is structurally similar to ephedrine. This similarity raises concern about bitter orange’s safety. Therefore, many studies intend to investigate the oral extract’s biological effects. So far, human studies show bitter orange and *p*-synephrine are safe for the heart.³⁵ As a result, bitter orange containing products are still legal in the U.S. Studies indicate that it is safe provided patients take the commonly recommended dose (not to exceed 70 mg/day).³⁶

Herb-Drug Interactions

Herbal products can interact with prescription medications. Depending on the medication, the interaction’s consequence can range from mild to severe. Since many herbal products exist on the market, a good starting point for spotting herb-drug interactions is to examine the 10 most commonly-used remedies in the U.S. (Table 2, page 6).³⁷

Since current evidence-based medicine cannot prove herbal products’ numerous alleged health benefits, the healthcare system may view herbal products as pseudoscience. Creating a genuinely evidence-based, scientific curriculum on herbal products is challenging. However, more and more people are starting to use herbal products or other CAM. Sometimes, pharmacists cannot answer questions regarding herb-drug interactions confidently.³⁸

The known interactions to each of the top 10 herbals used in the U.S. are shown in Table 2 (page 6). For some herbs, clinical trials

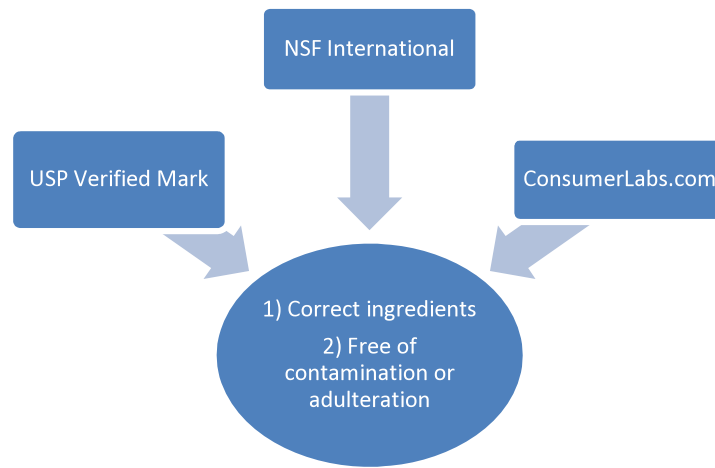


Figure 1. Inspecting Organizations for Herbs and Other CAM Products

are lacking, which challenges the translation of animal models or *in vitro* data to humans. Additionally, not all herbs are created equal; St John’s wort, for example, interacts significantly with drugs that undergo CYP3A4 metabolism. Some herbal products, like soy and garlic, deserve attention if patients overdose on them.

Tainted Herbal Products and Supplements

In addition to prescription medications, a majority of pharmacies also offer OTC herbal products.⁴⁵ While prescription medication goes through rigorous safety checks, CAM products, in general, are not held to the same standards.⁴⁵

Metal contamination is a primary concern regarding herbal products. In 2012, a study showed 121 natural health products made outside of the U.S. contained various heavy metals.⁴⁶ In 2019, the FDA issued a warning about a U.S. dietary supplement brand, advising consumers not to use their products due to lead contamination.⁴⁷

Microbial contamination is also concerning. A 2009 study showed 138 herbal products, including alfalfa, echinacea, garlic, ginger, and ginkgo, and other products contained unsafe levels of fungi and bacteria.⁴³ Kratom is an herb that some people use to reduce anxiety. In 2018, the FDA issued mandatory recalls for kratom products due to outbreaks of *Salmonella* infection.⁴⁸

Mislabeled Herbal Products

Looking at herbal ingredients on product packaging isn’t always reliable.⁴⁹ Some herbal products may not contain the exact ingredients listed on the label. Unknown ingredients in these products present a significant health risk to patients. In 2019, The U.S. Drug-Induced Liver Injury Network used chemistry instruments to identify mislabeling in more than half (51%) of 272 herbal products.⁴⁹ Among the products tested, those marketed for appearance enhancement, sexual performance, and weight loss were most likely to be mislabeled.⁴⁹ This finding should raise a question about current regulation of herbal products, or lack thereof.

NOTES TO PHARMACISTS

Due to current regulations and practical reasons, the FDA does not take action against an herbal product unless it’s *proven* unsafe.² Pharmacists can protect patients from harmful herbals by answering questions and monitoring what patients take.

One way to examine an herbal product’s legitimacy is through its labeling. An inspecting organization for herbal products will put its seal on the package. Such organizations include the United States Pharmacopeia (USP), NSF International, and ConsumerLabs. These organizations inspect herbals and other CAM consumables thoroughly during the manufacturing process. **Figure 1** shows organizations that have established processes to verify product and labeling integrity.



Table 2. Pharmacokinetic herb-drug interactions for top 10 herbals in the United States³⁹⁻⁴⁵

Herbal product	Mechanism of Interaction	Affected Medications/Adverse
American ginseng (<i>Panax quinquefolius</i>)	Unknown	Reduced effects of warfarin (0.2-point decrease in INR, increased clot risk)
Asian ginseng (<i>Panax ginseng</i>)	CYP3A4 inducer	Decreased levels of CYP3A4 substrates (e.g., calcium channel blockers, chemotherapy, HIV antivirals, statins)
Chamomile	No human data, but animal and <i>in-vitro</i> models show CYP1A2 inhibition	Increased levels of CYP1A2 substrates (e.g., caffeine, clozapine, fluvoxamine, haloperidol, olanzapine)
Echinacea	CYP1A2 and CYP3A inhibitor	Increased levels of CYP1A2 substrates (e.g., caffeine, clozapine, fluvoxamine, haloperidol, olanzapine) Increased levels of CYP3A substrates (e.g., alprazolam, amlodipine, citalopram)
Garlic	P-gp inducer	Decreased levels of P-gp substrates (e.g., colchicine, digoxin, doxorubicin, quinidine, rosuvastatin, tacrolimus, verapamil)
Ginger	Weak CYP2C19 inhibitor	Increased levels of CYP2C19 substrates (e.g., clopidogrel, cyclophosphamide, warfarin)
Ginkgo biloba	Unknown	Increased INR, and therefore increased bleeding risk
Kava	No human data, but animal and <i>in-vitro</i> models show CYP1A2 inhibition	Increased levels of CYP2E1 substrates (e.g., acetaminophen, chlorzoxazone, eszopiclone, ethanol, theophylline, verapamil)
Peppermint	No human data, but animal model shows CYP1A2 inhibition	Increased levels of CYP1A2 substrates (e.g., caffeine, clozapine, fluvoxamine, haloperidol, olanzapine)
Soy	UGT2B15 inducer	No significant drug interactions
St. John's wort	Potent CYP3A4 and P-gp inducer	Decreased levels of many drugs <i>General advice:</i> Avoid concurrent use of St. John's Wort with all prescription medications

CYP=cytochrome P450; HIV=human immunodeficiency virus; INR= international normalized ratio; P-gp=P-glycoprotein; UGT=uridine 5'-diphospho-glucuronosyltransferase

PAUSE AND PONDER: When should you help patients obtain a certificate of analysis, and how would you do it?

NOTES TO PHARMACY TECHNICIANS

Patients often underreport herbal product use, making it difficult to identify health risks.⁵⁰ Since patients may think herbal products are innocuous, they don't understand the need to disclose them. Often, pharmacy technicians can be instrumental in identifying a patient's herbal use. Patients may ask about herbal use during checkout for their prescriptions or request assistance in the CAM aisles. Technicians can also make it a point to ask patients what herbals or CAM they take. Pharmacy technicians should refer patients to pharmacists about herbals whenever possible. The **SIDEBAR** provides some tips for technicians.

CONCLUSION

Patients take herbals for general well-being and for some diseases or conditions, but unsafe herbal products can make matters worse. Current regulations do not require every herbal product on the market to be inspected, so some risks are hidden until harm is done. Pharmacists and pharmacy technicians can educate patients and recognize harmful herbal products. The take-home message is that patients should know that herbal products are not as safe as they may appear to be. While patients have the right to use any CAM, including herbals, our responsibility is to address any harmful products and repercussions as soon as possible. **Figure 2** (next page) summarizes key points to remember from this activity, and how you can step up your practice to broaden your skills and increase safety for patients who use herbals.

Additional Resources for Pharmacy Teams
<p>National Center for Complementary and Integrative Health https://www.nccih.nih.gov/</p> <ul style="list-style-type: none">• The nation's leading health agency investigating the evidence behind complementary and alternative medicines.
<p>Johns Hopkins Herbal Medicine https://www.hopkinsmedicine.org/health/wellness-and-prevention/herbal-medicine</p>

SIDEBAR: TECH TALK: Herbal Products in Pharmacy Settings⁵¹⁻⁵³

What is a certificate of analysis (CoA)? A CoA is a document attesting that certain goods (e.g., chemicals and pharmaceuticals, food products, wines and spirits) have undergone specified testing and achieved acceptable results in an accredited laboratory.

What will a CoA tell the customer and me? CoAs confirm that a product meets its product specifications. Most CoAs follow a template that includes spaces to record the levels of the purported active ingredient, bacterial levels, and possible contaminants (e.g., pesticides, solvent residue, heavy metals). It looks at purity, strength, composition, and contaminants. In short, it lists the product's contents.

How can I obtain a CoA? There are several ways to obtain CoAs, and you will need the exact product name, the lot number, and the expiration date:

- Contact companies directly by phone or by e-mail and ask for the CoA and other information that you need.
- Search the Internet. Many companies post information online.
- Look for third-party laboratories that publish their CoAs.

How can I be certain that a CoA is reliable? Always examine information provided by supplement manufacturers and sellers carefully. Unscrupulous manufacturers create CoAs that do not accurately reflect their product's quality. In rare cases, they have issued reports even though they have not conducted any tests (which is called "dry labbing"). "Reg flags" about CoAs include the following:

- It is not issued by an independent third-party laboratory
- It does not list the specific product in question and the exact lot
- It does not employ an appropriate test method. You can identify appropriate tests at ConsumerLab.com for many products (<https://www.consumerlab.com/methods/>, click on "How Products were Evaluated").

What if a company says they do not have or do not release CoAs? Think about it...what does that tell you? What it suggests is that they do not have a quality assurance process. You cannot verify the product's contents or possible contaminants. Convey that information to your customer.

Figure 2. Helping Patients Understand the Need to Take Medication as Recommended

Best

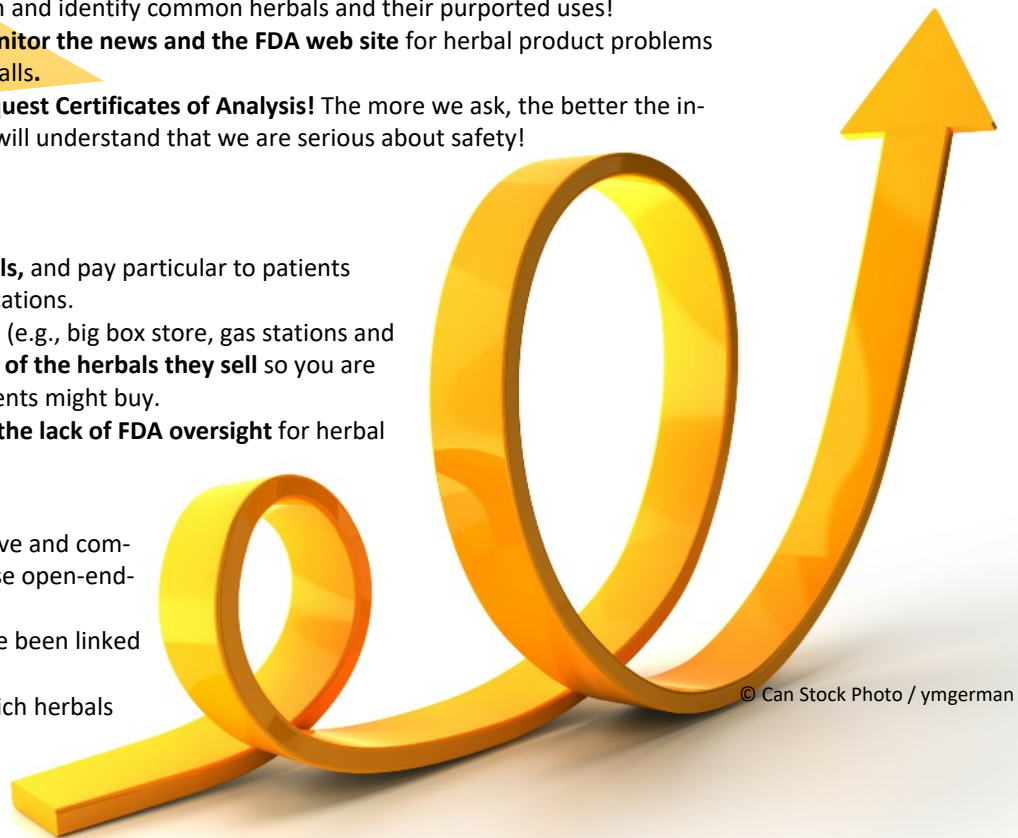
- ① **BE COMMUNITY CHAMPIONS.** Learn your community's cultural composition and identify common herbals and their purported uses!
- ② **Monitor the news and the FDA web site** for herbal product problems and recalls.
- ③ **Request Certificates of Analysis!** The more we ask, the better the industry will understand that we are serious about safety!

Better

- ① **Know the top 10 herbals**, and pay particular to patients who take interacting medications.
- ② When you visit vendors (e.g., big box store, gas stations and grocery stores), **make note of the herbals they sell** so you are familiar with products patients might buy.
- ③ **Inform patients about the lack of FDA oversight** for herbal products.

Good

- ① **Always ask patients** what alternative and complementary medicines they use—and use open-ended questions when you do!
- ② **Know which herbal medicines** have been linked to organ damage.
- ③ **Inspect your shelves** and know which herbals you stock.



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