

**The 'Dirty Dozen' – Herbal Products To Stay Away From**

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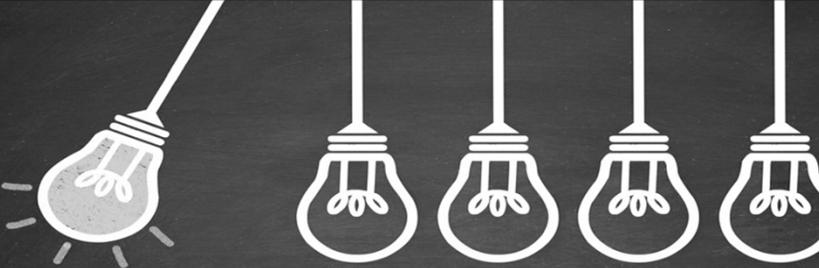
**I have no relevant financial relationships with ineligible companies to disclose.**

**Experimental or Off-Label Drug/Therapy/Device Disclosure**

I will be discussing experimental or off-label drugs, therapies and/or devices that have not been approved by the FDA.

**Professional Practice Gap**

Hundreds to thousands of herbal products exist and are advertised as natural, safe, and effective. In reality, however, they are largely unregulated and have no quality control process inherent in their production to protect consumers. The general public look to pharmacists as experts when it comes to herbal and dietary supplements, so it is the responsibility of the pharmacist to be aware of potential toxic active ingredients in herbal products.



## WHAT WILL I LEARN?

1. Define the Dietary Supplement Health and Education Act of 1994
2. Identify three general mechanisms underlying why an herb might be toxic
3. Distinguish the toxic active ingredient in three specific herbal products

### Pre-Assessment Question 1

When poll is active, respond at [pollev.com/ou321](https://pollev.com/ou321)  
Text **OU321** to **37607** once to join

#### Which of the following is true about The Dietary Supplement Health and Education Act (DSHEA) of 1994?

- Gives the manufacturer liberty to claim the ability to affect the body's structure or function in positive ways.
- Gives the manufacturer liberty to claim the ability to cure a disease or illness.
- Ensures that the dietary supplements are produced under sanitary conditions.
- Guarantees the purity or efficacy of herbal products.

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### Pre-Assessment Question 2

When poll is active, respond at [pollev.com/ou321](https://pollev.com/ou321)  
Text **OU321** to **37607** once to join

**Kristie is scheduled for knee replacement surgery Tuesday. It is now Saturday, and she read that taking ginkgo biloba may help to improve her memory. She is thinking about starting a daily dose of garlic today. Why might this not be a good idea?**

Kristie is going to surgery in only three days, and ginkgo biloba may increase the risk of bleeding during surgery.  
The surgeon may be easily agitated and distracted by Kristie's amazing improvement in her memory.  
Kristie may have to postpone her surgery if she discovers she is allergic to ginkgo biloba.  
Garlic biloba may give Kristie a very upset stomach prior to her surgery.

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### Pre-Assessment Question 3

When poll is active, respond at [pollev.com/ou321](https://pollev.com/ou321)  
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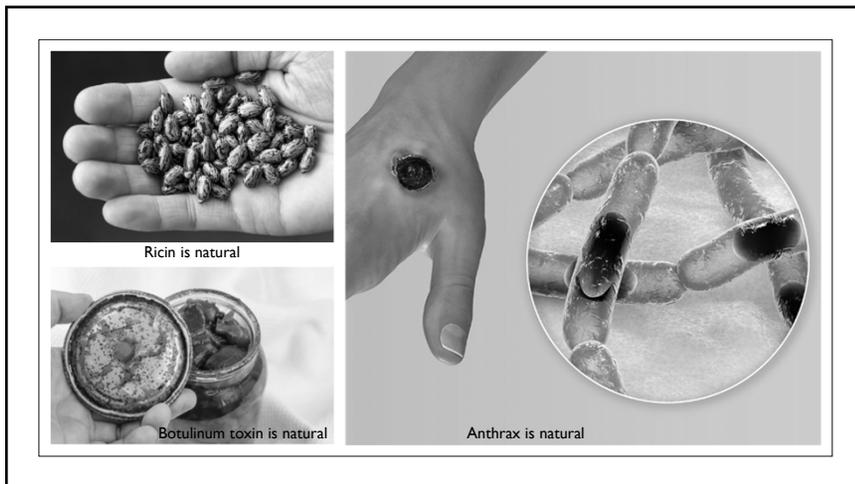
#### Which of the following herbal products was banned by the FDA in 2004 due to increased risk of heart attack, seizure, stroke, and sudden death?

- Kratom
- Pennyroyal
- Kava Kava
- Ephedra

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“If it’s natural, it must be safe!”



## Background

- Herbal medicines are crude drugs of vegetable origin used for the treatment of disease states, often ones of a chronic nature, or to attain or maintain a condition of improved health.
- Because most herbal products in the United States are considered dietary supplements, they are not required to meet the standards for drugs specified in the Federal Food, Drug and Cosmetic Act of 1938.



### Current Good Manufacturing Practice (CGMP) Regulations

- Herbal products can be marketed without any proof of testing for efficacy or safety.
- These products are governed by the Current Good Manufacturing Practice (CGMP) Regulations for foods, which are designed to ensure that dietary supplements are produced under sanitary conditions, but these regulations do not guarantee the purity or efficacy of the product.



### The Dietary Supplement Health and Education Act of 1994 (DSHEA)

- Packages containing herbals are not permitted to claim any ability to cure or prevent specific diseases but are allowed to declare the ability to affect the body's structure or function in positive ways.
- The Dietary Supplement Health and Education Act of 1994 (DSHEA) gives the herb manufacturer liberty to claim that their product "stimulates cardiovascular health" or "enhances sex drive" but opposes statements claiming "cures arteriosclerosis" or "cures impotence."



### Billion Dollar Industry

- Before the COVID-19 pandemic, 58% of American adults used vitamins, minerals, botanicals, live microorganisms, or other dietary supplements to prevent or treat various conditions including viral infections, memory loss, and heart disease.<sup>1</sup>
- Many people sought out supplements (and non-traditional treatment modalities) to prevent or treat COVID-19.
- Americans spent an estimated \$55 billion on dietary supplements in 2020.<sup>2</sup>



### Dietary Supplements vs. Prescription Medications

#### Prescription Medications

- Considered **unsafe until proven safe**
- All prescription and non-prescription drugs are regulated by the FDA



#### Dietary Supplements – vitamins, minerals, herbs, food substances or extracts

- Considered **safe until proven unsafe**
- FDA can stop a company if they can prove it poses a significant risk.



1. Mishra S, Sierrman B, Ganche JJ, Potischman N. Dietary supplement use among adults: United States, 2017-2018. NCHS Data Brief 2021; 399:1-8.

2. Cohen PA, Avorn J, Kesselheim AS. Institutionalizing Misinformation – The Dietary Supplement Listing Act of 2022. NEJM 2022; 387:3-5.

## 2020 Annual Report of the America's Poison Centers

|  | No. of Case Mentions | No. of Single Exposures | Adverse Reactions | Moderate/Major Outcomes |
|--|----------------------|-------------------------|-------------------|-------------------------|
| <i>Citrus Aurantium</i><br>(single ingredient)   | 9                    | 8                       | 1                 | 1                       |
| Ginkgo Biloba                                    | 78                   | 48                      | 8                 | 1                       |
| Ginseng  | 107                  | 67                      | 26                | 8                       |
| Kava Kava  | 114                  | 63                      | 24                | 12                      |
| Ma Huang/Ephedra<br>(single ingredienc)          | 23                   | 13                      | 1                 | 5                       |
| Multi-Botanicals with<br><i>Citrus Aurantium</i> | 34                   | 23                      | 8                 | 4                       |
| Multi-Botanicals with<br>Ma Huang                | 24                   | 16                      | 4                 | 3                       |
| St. John's Wort                                  | 160                  | 101                     | 8                 | 4                       |
| Valerian   | 195                  | 101                     | 27                | 4                       |
| Yohimbe  | 135                  | 99                      | 48                | 40                      |



## Ephedra

## Ephedra - Background

- Ephedra is a low evergreen shrub with small scaly leaves.
- Toxic Active Ingredient – ephedrine, pseudoephedrine
- Long history of medicinal use in China and India to treat colds, fever, headaches, coughing, wheezing, etc.
- FDA banned the sale of supplements containing ephedrine alkaloids in the United States in 2004.

**BANNED**

## Ephedra - Background

End of Summer Deal 20% Off w/code: FATBURN20

**Lipodrene with Ephedra - Hi-Tech Pharmaceuticals - 90 Tablets**  
SKU# 107-0001  
Hi-Tech Pharmaceuticals

**\$39.95**

Buy 2 for \$37.49 Each + Free Shipping USA  
Buy 3 for \$34.95 Each + Free Shipping USA

**Benefits and Results†:**

- Increased Energy
- Appetite Control
- Overall Improved Mood
- Weight Loss
- With DMAA and Ephedra

- Marketed as/also called ma huang
- Brand names include:
  - Metabolife®
  - Ripped Fuel®
  - Ultimate Orange
  - Purple Blast
  - Yellow Jackets
  - Xenadrine
  - Lipodrene
- Claimed benefits
  - Weight loss aid
  - Stimulant
  - Energy booster
  - Exercise enhancer

## Ephedra – What Have We Learned?

Prior to the ban, research showed that dietary supplements containing ephedra/ephedrine (usually in combination with caffeine) had modest short-term effects on weight loss.

However, this benefit was considered insufficient to outweigh the serious risks of these supplements.

No studies had assessed long-term effects on weight.

The evidence regarding athletic performance was insufficient to allow any conclusions to be reached.

Shelke GP, Hardy ML, Horton SC, et al. *Efficacy and safety of ephedra and ephedrine for weight loss and athletic performance: a meta-analysis*. JAMA. 2003;289(12):1537-1545.

## Ephedra – What Do We Know About Safety?

- The FDA banned dietary supplements containing ephedrine alkaloids because of their serious safety risks.
- The supplements were associated with cases of heart attack, seizure, stroke, and sudden death.
- People with a history of cardiovascular disease, those taking high doses of ephedra, and those taking it in combination with other stimulants such as caffeine would be expected to be at increased risk.
- Some of the severe events occurred in people with no preexisting medical problems, people taking relatively low doses of ephedra, or people taking ephedra alone.
- Taking ephedra may also cause anxiety, dizziness, dry mouth, headache, irritability, nausea, personality changes, insomnia, and other symptoms.

Steve Bechler collapsed on the field during spring training in 2003. At the hospital he was found to have temperature of 108 degrees. He was only 23 years old.

## Ginkgo Biloba

## Ginkgo Biloba - Background

- One of the oldest living tree species in the world, has a long history in traditional Chinese medicine.
- Members of the royal court were given ginkgo nuts for senility.
- Other historical uses for ginkgo were for asthma, bronchitis, and kidney and bladder disorders.
- Today, the extract from ginkgo leaves is promoted as a dietary supplement for many conditions, including anxiety, allergies, dementia, eye problems, peripheral artery disease, tinnitus, and other health problems.
- Toxic active ingredient – Ginkgo flavone glycosides and terpene lactones (ginkgolides and bilobalide)



## Ginkgo Biloba – What Have We Learned?

- There's no conclusive evidence that ginkgo is helpful for any health condition.
- Some studies suggest that ginkgo may help to slightly improve some symptoms of dementia, but the findings have been described as unreliable.
- Ginkgo neither helps prevent dementia or cognitive decline nor prevents Alzheimer's-related dementia from getting worse
- For various health conditions, a small amount of evidence suggests a benefit from taking ginkgo, but the overall evidence is not conclusive.
  - These conditions include anxiety, diabetic retinopathy, glaucoma, peripheral artery disease, premenstrual syndrome (PMS), schizophrenia, and vertigo.
- Research seems to suggest that ginkgo doesn't help with memory enhancement in healthy people, high blood pressure, tinnitus, multiple sclerosis, seasonal affective disorder, or the risk of having a heart attack or stroke.

Yang G, Wang Y, Sun J, et al. Ginkgo biloba for mild cognitive impairment and Alzheimer's disease: a systematic review and meta-analysis of randomized controlled trials. *Current Topics in Medicinal Chemistry*. 2016;16(5):570-578.

## Ginkgo Biloba – What Do We Know About Safety?

- For most people, ginkgo leaf extract appears to be safe when taken by mouth in moderate amounts.
- Side effects of ginkgo may include headache, stomach upset, dizziness, palpitations, constipation, and allergic skin reactions.
- In a 2013 research study, rodents given ginkgo leaf extract had an increased risk of developing liver and thyroid cancer at the end of the 2-year tests. Whether these results apply to humans is unclear.



## Ginkgo Biloba – What Do We Know About Safety?

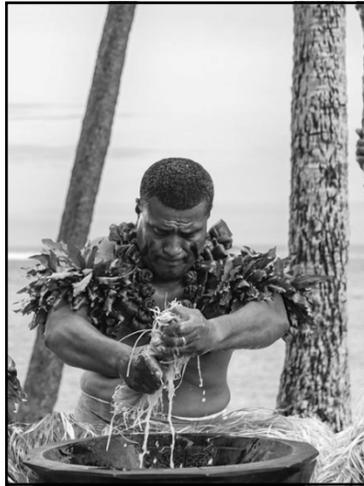
- Ginkgo may interact with some conventional medications, including anticoagulants.
- The active component of ginkgo includes a terpenoid called Ginkgolide B, which is a potent inhibitor of platelet activating factor.
- Fifteen published case reports described a temporal association between using ginkgo and a bleeding event.
  - Most cases involved serious medical conditions, including 8 episodes of intracranial bleeding.
- Fresh (raw) or roasted ginkgo seeds and the unprocessed ginkgo leaves can contain dangerous amounts of 4-methoxypyridoxine (MPN), which can precipitate seizure activity.



Bent et al. Spontaneous Bleeding Associated with Ginkgo biloba. *J GEN INTERN MED* 2005; 20:657-661.



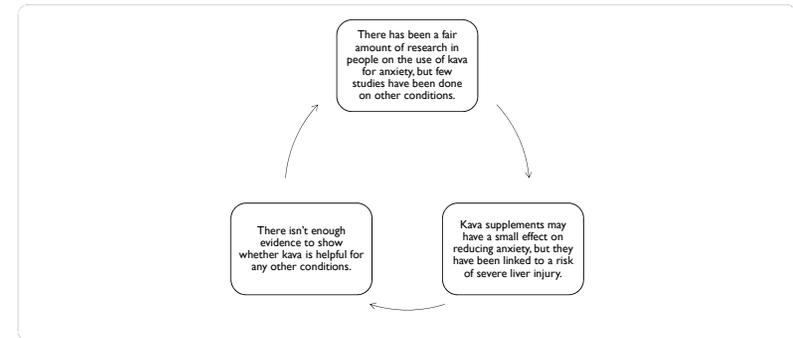
## Kava Kava



## Kava - Background

- Kava is native to the islands of the western Pacific and is a member of the pepper family.
- Derived from *Piper methysticum*, which means "intoxicating pepper."
- Pacific islanders have used kava for thousands of years as a medicine and for ritual purposes.
- Today, kava is promoted as a dietary supplement for anxiety, insomnia, and other conditions.
- Toxic active ingredient – kava lactones, flavokwain A and B

## Kava – What Have We Learned?



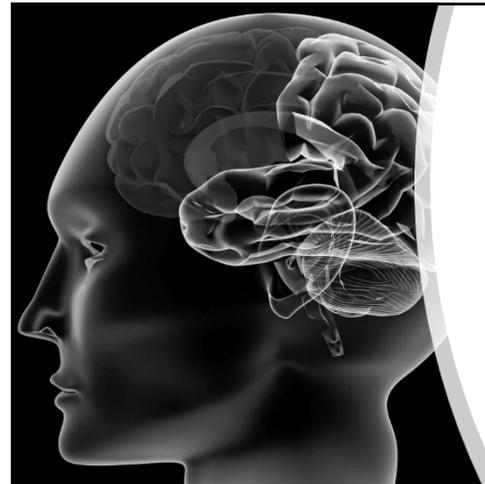
## Kava – Dermatologic Toxicity

- Long-term use of high doses of kava may cause kava dermopathy, a condition that involves dry, scaly, flaky skin with a yellow discoloration.
- Has been described in Pacific Islanders who consume large concentrations of kava.
- Chiefs and priests on pacific islands consider the dermopathy as a sign of nobility and privilege.
- Prompt reversal of effects are seen after abstinence.



## Kava – Neurologic Toxicity

- The use of kava may affect the ability to drive or operate machinery.
- Kava has been shown to potentiate the effects of certain sedative hypnotics.
  - Patients already on barbiturates or benzodiazepines are especially susceptible to CNS sedation if concomitant kava is used.
- Choreoathetoid movement disorders have been reported after kava use.



## Kava – Liver Dysfunction

- The use of kava has been linked to liver injury that is sometimes serious or even fatal.
  - The exact cause and frequency of the liver damage are unclear.
- 14-year-old girl developed fulminant hepatitis and hepatic failure requiring liver transplantation.
- MMWR also reported two US cases of liver failure associated with kava-containing dietary supplement products and summarizes cases from Germany and Switzerland commenting that a total of 11 patients had undergone subsequent liver transplantation.



## St. John's Wort



**St. John's Wort**

- A plant with yellow flowers that has been used in traditional European medicine as far back as the ancient Greeks.
- The name refers to John the Baptist, as the plant blooms around the time of the feast of St. John the Baptist in late June.
- Historically has been used for a variety of conditions, including kidney and lung ailments, insomnia, and depression, and to aid wound healing.



**St. John's Wort**

- Promoted for:
  - depression
  - menopausal symptoms
  - attention-deficit hyperactivity disorder (ADHD)
  - somatic symptom disorder
  - obsessive-compulsive disorder
- Topical use is promoted for various skin conditions, including wounds, bruises, and muscle pain.
- Toxic active ingredients –
  - hyperforin – induces P450 enzymes used for metabolism of medications
  - Hypericin – antiviral activity



## St. John's Wort – How Much Do We Know?

- There has been extensive research on the use of St. John's wort for depression and on its interactions with medications.
- **It has been clearly shown that St. John's wort can interact in dangerous, sometimes life-threatening ways with a variety of medicines.**

## St. John's Wort – What Have We Learned?



- Appears to be more effective than a placebo and as effective as standard antidepressant medications for mild and moderate depression.
  - It's uncertain whether this is true for severe depression and for time periods longer than 12 weeks.
- Has been studied for conditions other than depression.
  - For some, such as irritable bowel syndrome, chronic hepatitis C virus (HCV) infection, HIV infection, and social anxiety disorder, current evidence suggests that St. John's wort isn't helpful.

## St. John's Wort – What Have We Learned?



- Might be helpful for menopausal symptoms, wound healing, and somatic symptom disorder, but there's not enough evidence to know for certain.
- There's not enough reliable evidence to know whether it is beneficial for quitting smoking or improving memory or for many conditions, including anxiety, ADHD, and seasonal affective disorder.

## St. John's Wort – What Do We Know About Safety?



- In research studies, taking St. John's wort by mouth for up to 12 weeks has seemed to be safe. But because St. John's wort interacts with many drugs, it might not be safe for many people, especially those who take conventional medicines.
- St. John's wort can weaken the effects of many medicines, including crucially important medicines such as:
  - Antidepressants
  - Birth control pills
  - Cyclosporine
  - Some heart medications, including digoxin and ivabradine
  - Some HIV drugs, including indinavir and nevirapine
  - Some cancer medications, including irinotecan and imatinib
  - Warfarin
  - Certain statins, including simvastatin
- Taking St. John's wort with certain antidepressants or other drugs that affect serotonin, a substance produced by nerve cells, may lead to increased serotonin-related side effects, which may be potentially serious.



## St. John's Wort – What Do We Know About Safety?

- St. John's wort may cause increased sensitivity to sunlight, especially when taken in large doses.
- Other side effects can include insomnia, anxiety, dry mouth, dizziness, gastrointestinal symptoms, fatigue, headache, or sexual dysfunction.
- There isn't enough reliable information available to know if St. John's wort is safe when it's used topically.
  - It may cause severe skin reactions to sun exposure.
- It may not be safe to use St. John's wort during pregnancy or while breastfeeding.
  - It has caused birth defects in laboratory animals.
  - Breastfeeding infants of mothers who take St. John's wort can experience colic, drowsiness, and fussiness.



## Ginseng

## Ginseng

- The Greek term Panax ginseng literally means "all-healing man root."
- Asian native perennial herb has been a part of traditional Chinese medicine for 2000 years.
- Ginseng has become a choice for those treating sexual dysfunction, cardiovascular disease, immune suppression, cancer, and enhancing cognitive and physical performance.
- Topical ginseng is touted to enhance breasts and increase tightness.
- Toxic active ingredient – ginsenosides: panaxin, ginsenin



## Ginseng Safety

- Adverse reactions and toxicity from ginseng use are mainly limited to drug-drug interactions and chronic use of the supplement.
- A relationship between manic episodes and ginseng use in patients with known psychiatric disorders has been reported.
- Vaginal bleeding following ginseng use has been reported.



## Ginseng Safety

- Insomnia is the herb's most common side effect.
  - Others include menstrual problems, breast pain, increased heart rate, high or low blood pressure, headache, loss of appetite, and digestive problems.
- Some evidence suggests that Asian ginseng might affect blood sugar. If you have diabetes, consult your health care provider before using Asian ginseng.
- There are uncertainties about whether ginseng might interact with certain medications, such as calcium channel blockers and other high blood pressure medications, as well as statin medications and some antidepressants.
  - Studies on the effect of Asian ginseng on the anticoagulant (blood thinner) warfarin (Coumadin) have had mixed results.



Ginseng Safe?



Valerian

## Valerian - Background

- A plant native to Europe and Asia; it also grows in North America.
- Has been used medicinally since the times of early Greece and Rome.
- Historically was used to treat insomnia, migraine, fatigue, and stomach cramps.
- Today is promoted for insomnia, anxiety, depression, premenstrual syndrome (PMS), menopause symptoms, and headaches.
- The roots and underground stems of valerian are used for medicinal purposes.
- Toxic active ingredients – valpotriates, valerenic acid



## Valerian – What Have We Learned?

- Knowledge is limited because a relatively small amount of research has looked at valerian's effects on various conditions.
- Evidence on whether it is helpful for sleep is inconsistent.
  - In its 2017 clinical practice guidelines, the American Academy of Sleep Medicine recommended against using valerian for chronic insomnia in adults.
- Two small studies suggest that valerian might be helpful for menopausal symptoms, but there is not enough evidence to know for certain.
- There's not enough evidence to allow any conclusions about whether it is helpful for anxiety, depression, premenstrual syndrome, menstrual cramps, or stress.



Journal of Clinical Sleep Medicine, Vol. 13, No. 2, 2017



## Valerian – What Do We Know About Safety?

- Research suggests that valerian is generally safe for short-term use by most adults.
  - It has been used with apparent safety in studies lasting up to 28 days.
  - The safety of long-term use of valerian is unknown.
- Side effects of valerian include headache, stomach upset, mental dullness, excitability, uneasiness, heart disturbances, and even insomnia in some people.
  - A few people feel drowsy in the morning after taking valerian, especially at higher doses.
  - Some people experience dry mouth or vivid dreams.
- Because it is possible (though not proven) that valerian might have a sleep-inducing effect, it should not be taken along with alcohol or sedatives.



## Comfrey

Use externally as needed or as directed by a health care professional

**Warning: External Use Only**  
Consuming this product may cause liver damage. This product contains Comfrey. Comfrey contains pyrrolizidine alkaloids, which may cause serious illness or death. This product should not be taken orally used as a suppository, or applied to broken skin. For further information contact the Food and Drug Administration.

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### Comfrey Root Extract

**Supplemental Facts**  
Serving size: 10 Drops  
Servings per container: 110

| Amount per Serving | %Daily Value |
|--------------------|--------------|
| 10 Drops           |              |

Ingredients:  
Organic Comfrey Root

\*Daily Value not established

Other Ingredients: A base of pure vegetable glycerine and distilled\*  
No Fillers or Chemicals  
Store in a cool, dry place

\* This statement has not been evaluated by the Food and Drug Administration. This product is

## Comfrey

- Used for the treatment of fractures, tendon injuries, GI ulceration, and lung congestion.
- Toxic active ingredient - contains pyrrolizidine alkaloids and may predispose a user to the development of veno-occlusive hepatic disease.



## Chamomile

## Chamomile - Background

- Chamomile was described in ancient medical writings and was an important medicinal herb in ancient Egypt, Greece, and Rome.
- Today, chamomile is promoted for sleeplessness, anxiety, and gastrointestinal conditions such as upset stomach, gas, and diarrhea.
- It is also used topically for skin conditions and for mouth sores resulting from cancer treatment.
- Toxic active ingredient – none, but can be an allergen.



## Chamomile – What Have We Learned?

- Some preliminary studies suggest that a chamomile might be helpful for generalized anxiety disorder.
- Some research has found that products containing certain combinations of herbs that include chamomile may be of benefit for upset stomach, for diarrhea in children, and for infants with colic.
  - Chamomile alone has not been shown to be helpful for these conditions.
- There's very little information on chamomile's effect on insomnia.
  - A 2019 review of six small studies included only one study on insomnia.
  - That one study found that chamomile had no benefit for insomnia.
  - The same 2019 review looked at five studies on chamomile's effect in non-insomnia populations.
  - The review concluded that chamomile might help improve the individual component of sleep quality over a 4-week period in people without insomnia.



Phytotherapy Research 2019;33:1604–1615

## Chamomile – What Do We Know About Safety?

- Likely safe when used in amounts commonly found in teas.
- Might be safe when used orally for medicinal purposes over the short term.
- The long-term safety of using chamomile on the skin for medicinal purposes is unknown.
- Side effects are uncommon and may include nausea, dizziness, and allergic reactions.
  - Rare cases of anaphylaxis (a life-threatening allergic reaction) have occurred in people who consumed or came into contact with chamomile products.
- People are more likely to experience allergic reactions to chamomile if they're allergic to related plants such as ragweed, chrysanthemums, marigolds, or daisies.
- Interactions between chamomile and cyclosporine and warfarin have been reported, and there are theoretical reasons to suspect that chamomile might interact with other drugs as well.
- Little is known about whether it's safe to use chamomile during pregnancy or while breastfeeding.



**Citrus aurantium  
(bitter orange)**

## Bitter Orange - Background

- Native to eastern Africa, the Arabian Peninsula, Syria, and Southeast Asia,
- Now is grown throughout the Mediterranean region and elsewhere, including California and Florida.
- Has been used in traditional Chinese medicine for indigestion, nausea, and constipation.
- Today, various products are promoted for heartburn, nasal congestion, weight loss, appetite stimulation or suppression, and athletic performance.
- Applied to the skin for pain, bruises, fungal infections, and bedsores.
- Used in cooking and for adding flavor to beer and spirits.



## Bitter Orange – What Have We Learned?

- Toxic active ingredient - *p*-synephrine, which is structurally similar to ephedrine.
  - Commonly used as a substitute for ephedra in dietary supplements.
- The National Collegiate Athletic Association (NCAA) has placed "synephrine (bitter orange)" on its list of banned drugs, listing it as a stimulant.
- A small number of studies have investigated the usefulness of bitter orange for health purposes in people.
- Applying bitter orange oil to the skin may help with ringworm, jock itch, and athlete's foot infections.
- There's not enough scientific evidence to show whether bitter orange is helpful for other health purposes, such as weight loss, anxiety, and premenstrual syndrome.



## Bitter Orange – What Do We Know About Safety?

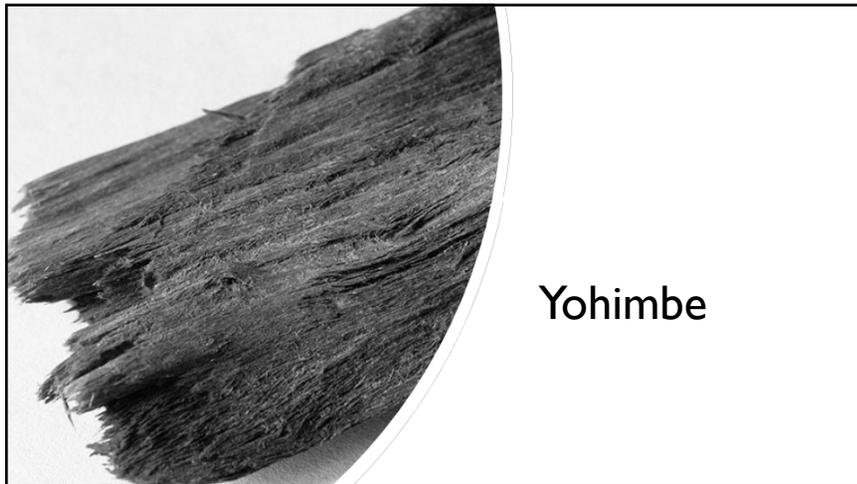
- Likely safe when used orally in amounts found in foods.
- There is one case report of a woman having a faster-than-normal heart rate at rest after taking a dietary supplement that contained only bitter orange.
- There are other case reports of healthy people experiencing fainting, angina, heart attack, and stroke after taking bitter orange as part of multicomponent products.
  - Because these products contained multiple ingredients, it is difficult to know the role that bitter orange played.
- Evidence regarding the effects of bitter orange (alone or combined with other substances, such as caffeine and green tea) on the heart and cardiovascular system is inconclusive.
  - Some studies showed that bitter orange raised blood pressure and heart rate, but other studies showed that bitter orange didn't have this effect at commonly used doses.
- Some sources list bitter orange as a stimulant whereas other sources say that it's not a stimulant at commonly used doses.



Pennyroyal

## Pennyroyal

- Traditional and Popular Usage – abortifacient, regulate menstruation, digestive tonic
- Toxic Active Ingredient – cyclohexanone: pulegone
- Adverse Effects – highly hepatotoxic!
- Death can occur with ingestions as little as 15-30 mL of pennyroyal oil in adults.



Yohimbe



### Yohimbe - Background

- An evergreen tree native to central and western Africa.
  - It has a compound called yohimbine in its bark.
  - The bark has been used traditionally as an aphrodisiac and to enhance sexual performance.
- Promoted for erectile dysfunction, athletic performance, weight loss, angina, high blood pressure, diabetic neuropathy, and more.
- Yohimbine hydrochloride is an  $\alpha^2$ -antagonist available in both prescription and herbal supplement products.

## Yohimbe – What Have We Learned?

- There is very little research in people on the effects of yohimbe as a dietary supplement.
- The amount of yohimbine in dietary supplements may vary; some yohimbe products contain very little yohimbine.
  - Yohimbe sold as a dietary supplement may not work like the prescription medication that contains yohimbine.
- It is illegal in the US to market an over-the-counter product containing yohimbine as a treatment for erectile dysfunction without getting approval from the FDA to do so.
- There is not enough research to say whether yohimbe as a dietary supplement is helpful for any condition, including erectile dysfunction, athletic performance, or weight loss.

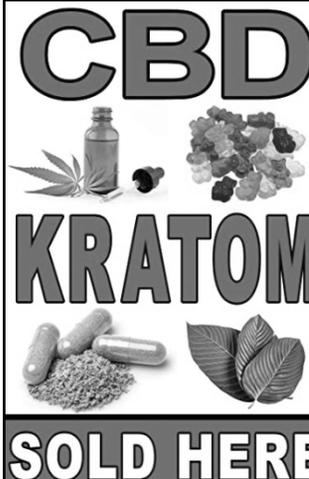


## Yohimbe – What Do We Know About Safety?

- Yohimbe has been associated with heart attacks and seizures.
- Because of inaccurate labeling and potential for serious side effects, yohimbe supplements have been restricted or banned in many countries.
- The California Poison Control System reported common adverse effects as gastrointestinal distress (46%), tachycardia (43%), anxiety/agitation (33%), and hypertension (25%)
- According to a 2015 analysis of 49 dietary supplements, the quantity of yohimbine ranged from none to 12.1mg.
  - Only 22% listed a specific quantity of yohimbine on the label and most of these were inaccurately labelled.
  - Of the 49 supplement brands only 4.1% (2/49) provided consumers with both accurate information about the quantity of yohimbine as well as information about yohimbine's known adverse effects.



## Kratom



## Kratom

- Kratom (*Mitragyna speciosa*) is used as an analgesic, antidepressant, anti-diarrheal, euphoriant, stimulant, and opioid replacement.
- Kratom contains the alkaloids mitragynine and 7-hydroxymitragynine, which are mu-opioid receptor agonists, and additionally have activity on adrenergic, serotonergic, and dopaminergic receptors.
- Mitragynine also appears to interfere with rectifier potassium currents, presenting a risk for sudden cardiac death.
- A study of mitragynine kinetics in 10 chronic kratom users found that 30 mg of mitragynine was enough to produce desired kratom effects without undesired side effects.



**Kratom**

- Mitragynine concentration varies greatly in kratom products, and kratom users have been documented to use as much as 275 mg of mitragynine to produce desired effects.
- The toxic and lethal doses of mitragynine are not well-defined.
- Kratom has potential for abuse given its mu-opioid activity and sometimes produces a withdrawal syndrome when discontinued after chronic use.
- However, despite kratom's opioid agonism, it has not been reported to cause respiratory depression.



**Kratom**

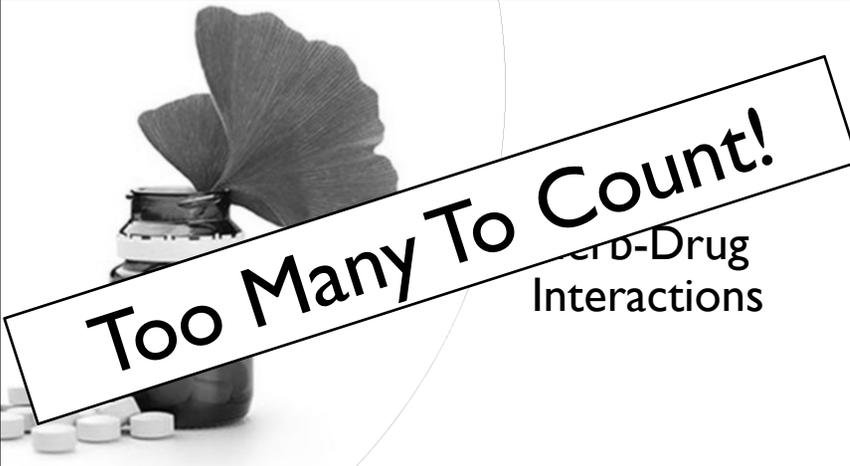
- Kratom use has been associated with hepatotoxicity, psychosis, seizure, coma, and death.
- The United States Drug Enforcement Agency has considered classifying kratom as a controlled substance.
- At this time, it remains unscheduled and is regulated as a standard dietary supplement.

## Herbs and Extracts Associated with Hepatotoxicity

black cohosh  
 Chaparral  
*Garcinia cambogia*  
 Germander  
 green tea extract  
 kava extract  
 linoleic acid  
 ma huang  
 Pennyroyal  
 usnic acid  
 1,3-dimethylamylamine

In addition, products with the following names have been associated with liver toxicity:

- Herbalife
- Hydroxycut
- LipoKinetic
- OxyELITE

**Too Many To Count!**

Herb-Drug Interactions

### St. John's Wort is the Biggest Culprit!

| Drug  | Effect   |
|---|--|
| Aminocaulmic acid   | Increase skin sensitivity  |
| Amiripryline  | Decrease efficacy by enhancing the elimination of drug   |
| Contraceptive pills   | Decreased efficacy of drug   |
| Cyclosporine  | Decreased efficacy of drug   |
| Digoxin   | Decreased absorption   |
| Fenfluramine  | Combination may increase the serotonin level in brain which leads to anxiety, heart problems and headache. |
| Imanifib  | Increases elimination rate of drug   |
| Irinotecan  | Decreased efficacy   |
| Anti-depressants (Flouoxetine, Amityrptiline, etc)                            | Increased level of serotonin which leads to heart problem, anxiety and shivering.                          |
| Narcotic Drugs  | Increases side effects of narcotic drugs   |
| Photosensitizing drugs  | Increases skin sensitivity   |
| Meperidine  | Combination may increase the serotonin level in brain which leads to anxiety, heart problems and headache. |
| Nefazodone; Paroxetine; Pentazocine; Sertraline                               | Combination may increase the serotonin level in brain which leads to anxiety, heart problems and headache. |
| Nortriptyline; Phenobarbital; Phensprocoumon; Phenytoin; Tacrolimus; Warfarin | Increases elimination rate of drug   |
| Reserpine   | Decreased efficacy   |
| Clopidogrel; Simvastatin; Theophylline  | Decreased efficacy and increased elimination rate  |
| Dextromethorphan  | Combination may increase the serotonin level in brain which leads to anxiety, heart problems and headache. |
| Fexofenadine  | Increased side effects   |

“Thou shall not commit adulteration.”



Adulteration Can Come in Many Flavors!



### Adulteration – Heavy Metals

- In one study, 20% of surveyed Ayurvedic products produced in South Asia and sold on a nonprescription basis in stores in the Boston area contained potentially harmful concentrations of lead, mercury, or arsenic.
- A follow-up study determined that a similar 21% of Ayurvedic products sold through the Internet also contained potentially harmful concentrations of these metals irrespective of whether manufacture occurred in the United States or India.



Saper, RB, et al. Heavy metal content of ayurvedic herbal medicine products. JAMA. 2004;292:2868-2873.  
Saper, RB, et al. Lead, mercury, and arsenic in US- and Indian-manufactured Ayurvedic medicines sold via the Internet. JAMA. 2008;300:91-97.

**NEWS**

## Dietary supplement recalled over undisclosed erectile dysfunction drug

by: Jacob Burbrink - Digital Investigative Reporter and Producer, Nexstar Media Wire  
 Posted: Sep 30, 2022 / 07:36 AM CDT  
 Updated: Sep 30, 2022 / 07:36 AM CDT

(File: Getty)



September 30, 2022

Supplement recalled because it is tainted with the active ingredient in the prescription drug Cialis.

**Supplement Facts**  
 Serving Size: 2 Capsules  
 Servings Per Container: 30

| Amount Per Serving                  | % DV    |    |
|-------------------------------------|---------|----|
| Horny Goat Weed (epimedium extract) | 1000 mg | ** |
| Extract (aw/aw) (tongkat ali)       | 250 mg  | ** |
| Maca Root Powder (androsynon)       | 30 mg   | ** |
| Mucuna Pruriens (seed) 15% L-Dopa   | 30 mg   | ** |
| Polypodium Vulgare Powder (leaf)    | 30 mg   | ** |
| Tongkat Ali Root Powder             | 100 mg  | ** |
| Shyama leaf/leaf                    | 100 mg  | ** |
| Saw Palmetto Berry Powder           | 100 mg  | ** |
| Sonchus oleraceus                   | 30 mg   | ** |
| Mulberry Fruit Powder (fruit)       | 30 mg   | ** |
| L-Arginine HCL (leaf)               | 30 mg   | ** |
| Panax Ginseng Root Powder           | 30 mg   | ** |

**Other Ingredients:** Gelatin Capsule, Rice Flour, Vegetable Magnesium Stearate.

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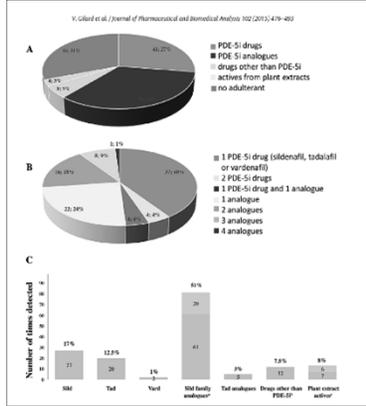
**Stellar**  
 Where Miracles Happen

Strength Energy Confidence

DIETARY SUPPLEMENT 60 CAPSULES

## Phosphodiesterase-5 Inhibitors as Adulterants

- 150 supplements marketed to increase sexual performance were analyzed
- 61% were adulterated with phosphodiesterase-5 inhibitors (PDE-5i)
- 25% contained a dose of PDE-5i that were higher than the maximum recommended dose
- Only 31% of the samples could be considered as true herbal/natural products.



V. Gilard et al. / Journal of Pharmaceutical and Biomedical Analysis 102 (2015) 476-493



## Human Use of Veterinary Products

## Ivermectin

---



**Heartgard (ivermectin)**  
Treat once a month to prevent heartworm disease in dogs.  
For Dogs 27-100 lbs  
6 chewables

**soolantra (ivermectin cream, 1%)**

**Ivermectin Tablets USP**  
3mg

## What is Ivermectin?

FDA approved broad spectrum antiparasitic agent

- Typical Dosage: 150-200 mcg/kg/day x 1 dose
- 14mg in a 70kg patient (package insert recommends 5 tablets = 15mg)
- Additional doses are not necessary

For humans:

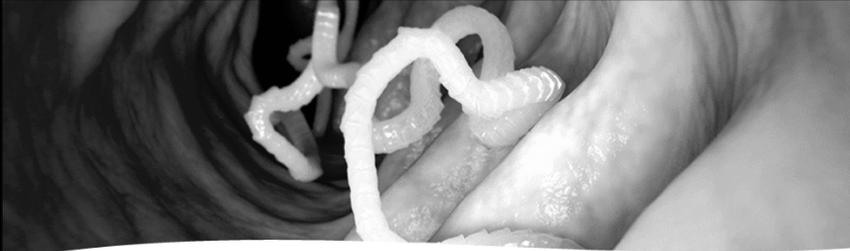
- Ivermectin Topical
- Indications include head lice and rosacea
- Formulations include 1% cream and 0.5% lotion
- Ivermectin Oral -
- Indications include onchocerciasis and intestinal strongyloidiasis (parasitic infections)
- Formulations include 3mg tablets

For animals:

- Heartgard (ivermectin) chewables for dogs
- Ivermectin Paste 1.87% for horses
- Ivomec (ivermectin) injection for cattle and swine 1% sterile solution
- Ivermectin topical solution pour-on for cattle 5mg/mL

1. Gonzalez Canga, A. The AAPS Journal, Vol. 10, No. 1, March 2008; 2. Ivermectin Package Insert

## Ivermectin Mechanism of Action for Parasites



- Ivermectin binds to glutamate-activated chloride channels on nerve and muscle cells paralyzing the creature exposed to it.
- These channels are present in worm and insect nervous systems, which is why the drug works.
- Humans have these chloride channels too, but only in our brain and spinal column, and since ivermectin can't cross the blood-brain barrier, we are spared from it's effects.
- You may note that SARS-CoV-2 has no muscles or nerves, so why the interest in this drug for this virus???

## Why Ivermectin for COVID?

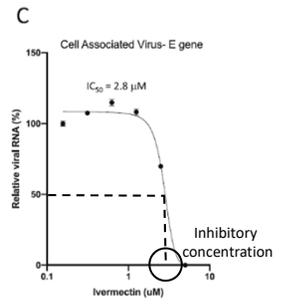
- Several groups have shown that ivermectin has antiviral activity against a broad range of viruses *in vitro*.
- The antiviral mechanism of ivermectin in COVID-19 is attributed to inhibition of the protein importin (IMP)  $\alpha/\beta$  receptor, which is responsible for transmitting viral proteins into the host cell nucleus.
- Researchers infected a cell culture with SARS-CoV-2 and added various concentrations of ivermectin.
- They then measured viral replication and found that the drug, *in vitro*, could inhibit the ability of the virus to reproduce.



Antiviral Research 179 (2020) 104767  
Contents lists available at ScienceDirect  
**Antiviral Research**  
Journal homepage: www.elsevier.com/locate/antiviral

**The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 *in vitro***

Leon Caly<sup>a</sup>, Julian D. Druce<sup>a</sup>, Mike G. Catton<sup>a</sup>, David A. Jans<sup>b</sup>, Kylie M. Wagstaff<sup>b,c</sup>  
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<sup>b</sup> Queensland Biomedical Institute, Monash University, Clayton, Vic, 3168, Australia



C  
Cell Associated Virus- E gene

Relative viral RNA (%)

IC<sub>50</sub> = 2.8  $\mu$ M

Inhibitory concentration

Ivermectin ( $\mu$ M)

## The Problem...

The inhibitory concentration of the drug is around 2.8 *micro*Molar

**• This concentration is not achievable in humans**

Standard ivermectin dosing achieves blood concentrations of about 25 *nano*Molar

**• 100 fold less than what was needed *in vitro***

## Meta-analysis of randomized trials of ivermectin to treat SARS-CoV-2 infection

Andrew Hill<sup>1</sup>, Anna Garratt<sup>2</sup>, Jacob Levi<sup>3</sup>, Jonathan Falconer<sup>4</sup>, Leah Ellis<sup>5</sup>, Kaitlyn McCann<sup>5</sup>, Victoria Pilkington<sup>6</sup>, Ambar Qavi<sup>5</sup>, Junzheng Wang<sup>5</sup>, Hannah Wentzel<sup>5</sup>

### THE FACTS

Seemed to show that ivermectin has pretty remarkable efficacy against COVID-19

## Expression of Concern

- The authors learned that one of the studies on which this analysis was based was withdrawn due to fraudulent data.
- Meta analysis is only as good as the information that you put into it.
- If the studies included in a meta analysis are found to be misleading or false, then the analysis itself will be full of flaws and inaccurate conclusions.

**Expression of Concern: "Meta-analysis of Randomized Trials of Ivermectin to Treat SARS-CoV-2 Infection"**

Andrew Hill<sup>1</sup>, Anna Garratt<sup>2</sup>, Jacob Levi<sup>3</sup>, Jonathan Falconer<sup>4</sup>, Leah Ellis<sup>5</sup>, Kaitlyn McCann<sup>5</sup>, Victoria Pilkington<sup>6</sup>, Ambar Qavi<sup>5</sup>, Junzheng Wang<sup>5</sup>, Hannah Wentzel<sup>5</sup>

Open Forum Infectious Diseases, Volume 8, Issue 8, August 2021, e160394.  
<https://doi.org/10.1093/ofid/ofab394>

Published: 03 August 2021 | [Article history](#)

This is a correction to Open Forum Infectious Diseases, e160358.  
<https://doi.org/10.1093/ofid/ofab358>

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**Issue Section:** EXPRESSION OF CONCERN

Open Forum Infectious Diseases, e160358, <https://doi.org/10.1093/ofid/ofab358>

Published: 06 July 2021

On July 6, 2021, Open Forum Infectious Diseases published the article "Meta-analysis of Randomized Trials of Ivermectin to Treat SARS-CoV-2 Infection" by Hill, et al. Subsequently, we and the authors have learned that one of the studies on which this analysis was based has been withdrawn due to fraudulent data. The authors will be submitting a revised version excluding this study, and the currently posted paper will be retracted.

© The Author(s) 2021. Published by Oxford University Press on behalf of Infectious Diseases Society of America.

## Retracted Articles

- This particular article was a review article cited in the introduction of the previous meta analysis.
- A few other articles have also been retracted for making false claims about the clinical evidence of the effect of ivermectin for the treatment of COVID-19.

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Review Article | Published: 15 June 2021

**RETRACTED ARTICLE: The mechanisms of action of ivermectin against SARS-CoV-2: An evidence-based clinical review article**

Asiya Kamber Zaidi<sup>1</sup> & Puya Dehghani-Mobaraki

*The Journal of Antibiotics* (2021) | [Cite this article](#)

591k Accesses | 2 Citations | 10609 Altmetric | [Metrics](#)

The Editor-in-Chief has retracted this article. Following publication, concerns were raised regarding the methodology and the conclusions of this review article. Postpublication review confirmed that while the review article appropriately describes the mechanism of action of ivermectin, the cited sources do not appear to show that there is clear clinical evidence of the effect of ivermectin for the treatment of SARS-CoV-2. The Editor-in-Chief therefore no longer has confidence in the reliability of this review article. None of the authors agree to this



Cochrane Database of Systematic Reviews

## Ivermectin for preventing and treating COVID-19 (Review)

### Main Results/Conclusions:

- Of the 41 study results contributed by included studies, about one third were at overall high risk of bias.
- Based on the current very low- to low-certainty evidence, we are uncertain about the efficacy and safety of ivermectin used to treat or prevent COVID-19.
- The completed studies are small and few are considered high quality. Several studies are undersay that may produce clearer answers in review updates.
- Overall, the reliable evidence available does not support the use of ivermectin for treatment or prevention of COVID-19 outside of well-designed randomized trials.

## Conclusion and Clinical Pearls

- The use of herbal remedies is exploding in the general population.
- Many of these preparations are manufactured with variable levels of quality control.
- These products have a myriad of pharmacological and toxicological properties.
- It is useful for the practicing pharmacist to have familiarity with some of the more common herbal products: ephedra, ginkgo biloba, kava kava, St. John's wort, ginseng, valerian and comfrey.



- Pharmacists should be aware of the potential for herb-drug interactions.
- Recognize the likelihood of adulterants and undeclared pharmaceuticals to be in herbal products.
- As pharmacists, we should obtain a history of use of herbal or other alternative therapies, in order to routinely recognize these potential problems.

## Post-Assessment Question 1

When poll is active, respond at [pollev.com/ou321](https://pollev.com/ou321)

Text **OU321** to **37607** once to join

### Which of the following is true about The Dietary Supplement Health and Education Act (DSHEA) of 1994?

- Gives the manufacturer liberty to claim the ability to affect the body's structure or function in positive ways.
- Gives the manufacturer liberty to claim the ability to cure a disease or illness.
- Ensures that the dietary supplements are produced under sanitary conditions.
- Guarantees the purity or efficacy of herbal products.

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## Post-Assessment Question 2

When poll is active, respond at [pollev.com/ou321](https://pollev.com/ou321)

Text **OU321** to **37607** once to join

**Kristie is scheduled for knee replacement surgery Tuesday. It is now Saturday, and she read that taking ginkgo biloba may help to improve her memory. She is thinking about starting a daily dose of garlic today. Why might this not be a good idea?**

As a pharmacist, you should be aware of the potential for herb-drug interactions. Recognize the likelihood of adulterants and undeclared pharmaceuticals to be in herbal products. As pharmacists, we should obtain a history of use of herbal or other alternative therapies, in order to routinely recognize these potential problems.

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## Post-Assessment Question 3

When poll is active, respond at [poll.com/ou321](https://poll.com/ou321)

Text **OU321** to **37607** once to join

**Which of the following herbal products was banned by the FDA in 2004 due to increased risk of heart attack, seizure, stroke, and sudden death?**

Kratom  
Pennyroyal  
Kava Kava  
Ephedra

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Start the presentation to see live content, for screen share software, share the entire screen. Get help at [poll.com/app](https://poll.com/app)

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## The 'Dirty Dozen' – Herbal Products To Stay Away From

Kristie Edelen, Pharm.D., DABAT

Assistant Managing Director

Oklahoma Center for Poison & Drug Information