



HERB-DRUG INTERACTIONS: MECHANISMS AND CLINICAL IMPLICATIONS

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Disclosure Declaration

- I do not have (nor does any immediate family member have) a vested interest in or affiliation with any cooperate organization offering financial support or grant monies for this continuing education activity, or any affiliation with an organization whose philosophy could potentially bias my presentation.

Disclosures

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Other Financial Support	None
Other Affiliation	None

Pharmacist Objectives

- Interpret common mechanisms of herb-drug interactions
- Identify the interaction potential of commonly used herbs
- Describe the potential complications associated with common herb-drug interactions

Technician Objectives

- Define traditional medicine
- List commonly used herbal products
- Describe concerns with concomitant use of herbal products with prescription medications

Definition of Traditional Medicine.

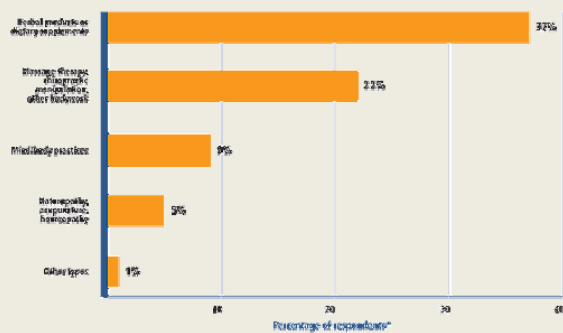
- The WHO definition...
 - ...traditional medicine (including herbal drugs) is comprised of therapeutic practices that have been in existence, often for hundred of years, before the development and spread of modern medicine and are still in use today.
- The earliest recorded evidence of herbal use dates back to 5000 years
 - Indian, Chinese, Egyptian, Greek, Roman and Syrian texts.

How Many Herbal Products Are Available?

- Estimated 11,000 species of herbal plants are in use worldwide
- Worldwide, 80% of the population uses herbs!

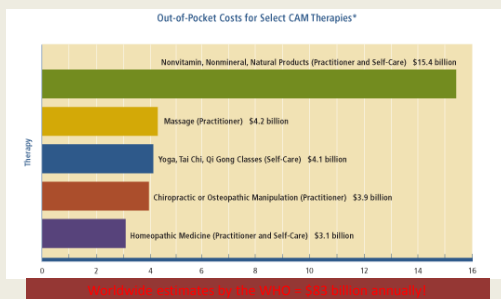
Chen XW, Sneed KB, Pan SY, et al. Herb-drug interactions and mechanistic and clinical considerations. *Curr Drug Metab* 2012;13:640-51.

Type of complementary and alternative medicine (CAM) used in the Past 12 Months (2010)



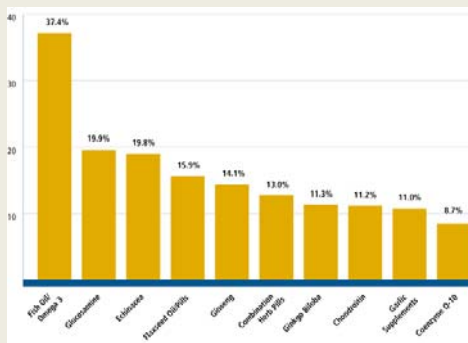
AARP, NCCAM. *Complementary and Alternative Medicine: What People Aged 50 and Older Discuss With Their Health Care Providers*. Consumer Survey Report; April 13, 2010.

What are Patients Spending CAM?



Nahin, RL et al. *National health statistics reports; no 18*. Hyattsville, MD: National Center for Health Statistics. 2009.
Rivera JO, Loya AM, Ceballos R. Use of Herbal Medicines and Implications for Conventional Drug Therapy Medical Sciences. *Altern Integ Med* 2013;2:6

Top 10 Most Commonly Used Herbs in Adults (2007)



Barnes PM et al. CDC National Health Statistics Report #12. Complementary and Alternative Medicine Use Among Adults and Children: United States, 2007. December 2008.

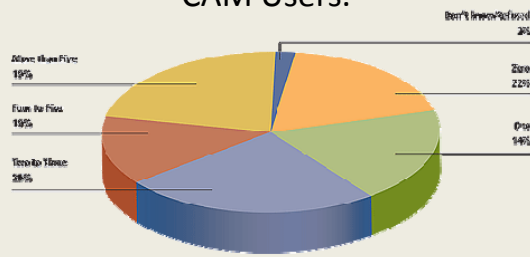
The 10 Top-Selling Herbal Products in the United States (2011)

Herb	Latin Name	U.S. Dollar Sales
Cranberry	Vaccinium macrocarpon	\$40,112,500
Soy	Glycine max	18,611,700
Saw palmetto	Serenoa repens	18,055,930
Garlic	Allium sativum	15,218,730
Ginkgo	Ginkgo biloba	14,628,650
Milk thistle	Silybum marianum	12,834,460
Echinacea	Echinacea spp.	10,914,500
Black cohosh	Actaea racemosa	10,319,990
St. John's wort	Hypericum perforatum	8,439,300
Ginseng	Panax ginseng	6,596,372

based on sales from chain drug and food stores, and other mass-market retailers, but do not include herb supplement sales in Wal-Mart, warehouse buying clubs (e.g., Costco, Sam's), or convenience stores (e.g., 7-Eleven).

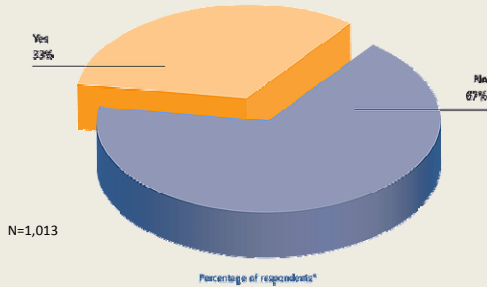
Blumenthal M, Lindstrom A, Ooyen C, Lynch ME. Herbal supplement sales increase by 4.5% in 2011. HerbalGram: The Journal of The American Botanical Council. 2012;95:60-

Number of Prescription Medications Currently Taken by CAM Users.

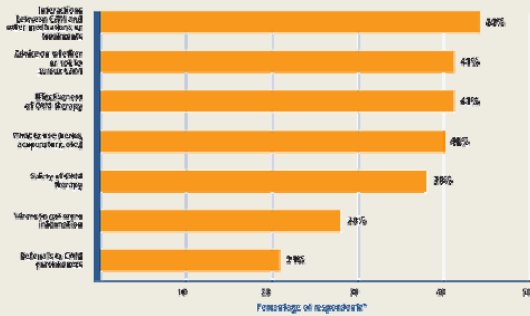


So What's the Big Deal?

Do you discuss CAM with your health care provider?



Topics Discussed by Healthcare Provider



Is There Evidence for Herb-Drug Interactions?

- Case reports
 - Voluntary reporting
- Lab studies
 - Used to define mechanisms
 - Not tested in a randomized controlled fashion
- Human studies
 - May be done on healthy population
 - Genetic polymorphisms
 - What about polypharmacy?
 - Studies are too short

De Smet P. Clinical risk management of herb-drug interactions. Br J Clin Pharm 2006; 63:258-67.

Is There Evidence Herbals Are Harmful?

- In an 8 year study (2004 – 2012) evaluating the Drug Induced Liver Injury Network database
 - Hepatotoxicity by any type of drug (herbs, Rx drugs, etc...) more than doubled
 - Cases caused by dietary and herbal products
 - Jumped from 7% to 20% ($p < 0.001$)
 - 16% of cases were attributed to an herbal product

Navarro V. Presented at the American Association for the Study of Liver Disease Annual Meeting 2014

Who Uses Herbs?

- In a NCCAM survey, CAM was most commonly used by:
 - Caucasians (43.1%)
 - Hispanics (23.7%)
- Another study found use in older Hispanics much higher (59 – 70%)

Rivera JO, Loya AM, Ceballos R. Use of Herbal Medicines and Implications for Conventional Drug Therapy Medical Sciences. Altern Integ Med 2013;2:6

Is there Risk for Iatrogenic Events: Case Example – Warfarin?

Herb	Result	Recommendation
Cranberry	Elevated INR	Caution
Soy	Decreased effect	Caution
Saw palmetto	Increased bleeding	Caution
Garlic	Elevated INR	Caution
Milk thistle	Elevated INR	Caution
Echinacea	Elevated INR	Caution
Black cohosh	No interaction	None
St. John's wort	Decreased INR	AVOID
Ginseng	Decreased INR	AVOID

Natural Medicines Comprehensive Database. Stockton, CA: Therapeutic Research Faculty. [Updated September 13, 2013; Accessed October 14, 2014].

Potential Problems with Herbal Medicines

- Adulterants and contaminations that can affect the quality of herbal remedies
 - Plants containing belladonna or pyrrolizidine alkaloids, microorganisms, aflatoxins, bacterial endotoxin, pesticides, fumigation agents, toxic metals and drugs
- Adverse effects of herbal remedies and their major constituents
 - Cardiotoxicity: aconite root ruber
 - Hepatotoxicity: certain herbs rich in anthranoids and protoberberine alkaloids, green-tea leaf
 - Neurotoxicity or convulsions: Kava rhizome
 - Renal toxicity: β -Aescin (saponin mixture from horse-chestnut seed)

De Smet PA. Herbal remedies. New Engl J Med 2002;347:2046-56.

Potential Problems with Herbal Medicines

- What's in the product?
- One report found that 20% of Ayurvedic medicines purchased via the Internet contained
 - Lead
 - Mercury
 - Arsenic
- Other reports have found detectable levels of prescription medications
 - Sildenafil, lovastatin, estrogen, alprazolam, indomethacin, warfarin

Saper RB, Phillips RS, Sehgal A, et al. Lead, mercury, and arsenic in Indian manufactured Ayurvedic medicines sold via the Internet JAMA 2008;300:915-23.
Anonymous. Herbal Warning. Medical Letter 2008;50:9.

Newmaster et al. BMC Medicine 2013, 11:222
<http://www.biomedcentral.com/1741-7015/11/222>



RESEARCH ARTICLE

Open Access

DNA barcoding detects contamination and substitution in North American herbal products

Steven G Newmaster^{1*}, Meghan Grguric², Dhivya Shanmuganandhan³, Sathishkumar Ramalingam³ and Subramanyam Ragupathi^{4*}

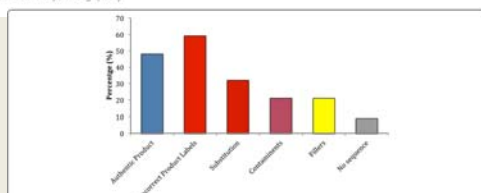
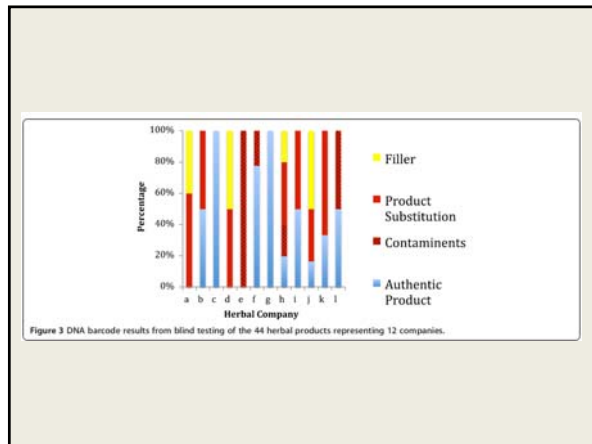


Figure 2 DNA barcode results from blind testing of the 44 herbal products representing 30 medicinal species of plants.



Select Herbs Associated with Major Adverse Effects

Herb	Adverse Effect
Creosote bush	Hepatotoxicity
Ephedra	Cardiovascular
Mau Huang	Cardiovascular
Kava	Hepatotoxicity
Mexican Arnica	Bleeding

Natural Medicines Comprehensive Database. Stockton, CA: Therapeutic Research Faculty. [Updated September 13, 2013; Accessed October 14, 2014].

How Often are Herb-Drug Interactions Encountered?

- Survey of 132 Canadian pharmacists were asked on whether they have ever encountered a patient with a herb-drug interaction
 - 47% responded yes
 - ONLY 1.5% reported the interaction to Health Canada

Charrois TL, Hill RL, Vu D, et al. Community identification of natural health product drug interactions. Ann Pharmacother 2007;41:1124-9

Pharmacokinetics versus Pharmacodynamics

Pharmacokinetic

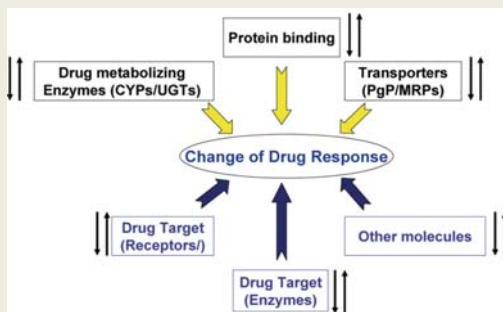
- Effects of the body on the drug
 - Cytochrome P450
 - P-glycoprotein

Pharmacodynamic

- Effects of the drug in the body
 - Alteration of GI flora
 - Inhibition of platelet aggregation

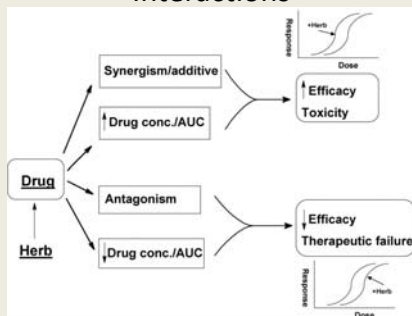
Elmer GW, Lafferty WE, Tyree PT et al. Potential interactions between complementary/alternative products and conventional medicines in a Medicare population. *Ann Pharmacother* 2007;41:1617-24.

Mechanisms of Herb-Drug Interactions



Zhou SF, Zhou ZW, Li CG, et al. Identification of drugs that interact with herbs in drug development. *Drug Disc Tod* 2007;12:664-73.

Potential Consequences of Drug-Herb Interactions



Zhou SF, Zhou ZW, Li CG, et al. Identification of drugs that interact with herbs in drug development. *Drug Disc Tod* 2007;12:664-73.

Effects of St John's Wort Constituents on Cytochrome Activity

CYP isoenzyme	Constituents	Inhibition				Mechanism
		Inhibitor	Assay system	K_i (μ M)	IC_{50} (μ M)	
CYP1A2	CME	+	POD-cYP		520 μ M	
	Hyperforin	+	POD-cYP		>100	
	13,13-Bi-6-gingerol	+	POD-cYP	0.95	3.7	Competitive
	Quercetin	+	POD-cYP	3.3	7.5	Noncompetitive
	Chlorogenic acid	+	POD-cYP		>100	
CYP2C9	Hyperforin	+	DH-cYP		19 μ M	
	CME	+	DH-cYP	1.8	4.4	Competitive
	13,13-Bi-6-gingerol	+	DH-cYP	0.32	4.0	Competitive
	Quercetin	+	DH-cYP		40	
	Chlorogenic acid	+	DH-cYP		>100	
CYP2C19	Hyperforin	+	SMH-cYP	1.4	3.4	Competitive
	CME	+	SMH-cYP		600 μ M	
	13,13-Bi-6-gingerol	+	SMH-cYP		31	
	Quercetin	+	SMH-cYP		5-100	
	Chlorogenic acid	+	SMH-cYP		24	
CYP2D6	Hyperforin	+	BH-cYP		9.1 μ M	
	CME	+	BH-cYP	1.5	16	Noncompetitive
	13,13-Bi-6-gingerol	+	BH-cYP	2.3	5.7	Competitive
	Quercetin	+	BH-cYP		26	
	Chlorogenic acid	+	BH-cYP		>100	
CYP3A4	Hyperforin	+	TGH-cYP	2.6	8.7	Competitive
	CME	+	TGH-cYP		67 μ M	
	13,13-Bi-6-gingerol	+	TGH-cYP	0.60	2.3	Competitive
	Quercetin	+	TGH-cYP	0.038	0.082	Competitive
	Chlorogenic acid	+	TGH-cYP		22	
	Hyperforin	+	TGH-cYP	4.2	8.7	Competitive

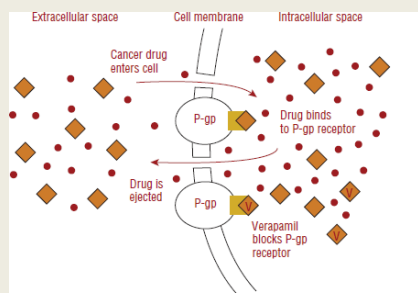
Zhou S, Gao Y, Jiang W, et al. Interactions of herbs with cytochrome P450. Drug Metabolism Reviews 2003;35:35-98.

St John's Wort Interactions

Drug	CYP	Effect
HIV protease inhibitors	Induce 3A4	↓
HIV NNRTI	Induce 3A4	↓
Warfarin	Induce 2C9	↓
Cyclosporine	Induce PGP	↓
Contraceptives	Induce 3A4	↓
Anticonvulsants	Induce 3A4	↓
Digoxin	Induce PGP	↓
Theophylline	Induce 1A2	↓
Triptans	Increase 5HT	↑
SSRI	Increase 5HT	↑

Henderson L, Yue QY, Bergquist C, Gerden B, Arlett P. St John's wort (*Hypericum perforatum*): drug interactions and clinical outcomes. Br J Clin Pharmacol 2002;54:349-56.

P-glycoprotein: Underappreciated Source of Interactions



Source: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM: Pharmacotherapy: A Pathophysiologic Approach, 8th Edition: www.accesspharmacy.com
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Selected Herb-Drug Interactions

Fish Oil / Omega 3 Fatty Acids

- Effective for lowering triglycerides and likely effective for cardiovascular disease
 - Recent data from the Alpha Omega trial suggest no cardiovascular benefit.
- Dose: 1 – 4 grams per day
- Generally well tolerated
 - Common ADRs include gastrointestinal including “fish burp”

Fish Oil / Omega 3 Fatty Acids

Drug	Description of Interaction
Antihypertensives	Additive effects
Contraceptives	Decreased efficacy of fish oil
Orlistat	Decreased absorption of fish oil
Anticoagulants Antiplatelets	High doses of fish oils have an antiplatelet effect; conflicting data on whether INR is increased

Glucosamine / Chondroitin

- Often used for osteoarthritis
 - Likely effective
- Dose: 500 mg/400 mg three times daily
- Generally well tolerated
 - Anecdotal reports of renal toxicity and glucose dysregulation

Glucosamine / Chondroitin

Drug	Description of Interaction
Warfarin	Several cases have reported elevated INRs
Antimitotic chemotherapy	May induce resistance to etoposide and doxorubicin by reducing inhibition of topoisomerase II



Echinacea

- Mixed data on the treatment and prevention of upper respiratory tract infections
- Dose: Highly variable, one brand –
 - 2 tablets three times daily
 - Each tablet ~ 7 mg
- Well tolerated but may worsen asthma or increase the risk hypersensitivity reactions.

Echinacea

Drug	Description of Interaction
Immunosuppressant	Decreased effectiveness. Stimulates the immune system.
CYP1A2 substrates, clozapine, benzodiazepines, theophylline	Inhibition of CYP1A2 results in increased object drug
CYP3A4 substrates, Diltiazem, cyclosporine, and many others	Inhibition of CYP3A4 results in increased object drug

Flaxseed Oil

- Possibly effective when used for cholesterol lowering
- Dose: Highly variable, for DM 600 mg three times daily
- Has laxative properties therefore, gastrointestinal discomfort is a common side effect
 - Should space from conventional medications

Flaxseed Oil

Drug	Description of Interaction
Anticoagulants	Decreases platelet aggregation
Hypoglycemic agents	Additive hypoglycemia
Estrogens	May decrease effects including oral contraceptives
Oral medications	Flaxseed has bulk forming laxative properties and may decrease drug absorption

Ginseng

- Possibly effective for diabetes and respiratory tract infections
- Dose: 200 mg twice daily
- Can cause gastrointestinal, nervous and cardiovascular system adverse effects
 - But in studies similar to placebo

Ginseng

Drug	Description of Interaction
Warfarin	Reduced INR
Hypoglycemic agents	Additive hypoglycemia
MAOIs	Decreased effectiveness of the MAOI

Ginkgo

- Possibly effective for age related memory impairment, cognitive impairment, and dementia
- Dose: 120 – 240 mg divided 2 -3 x/day
- Common side effects include GI upset, headache, dizziness, palpitations, constipation, and allergic skin reactions

Ginkgo

Drug	Description of Interaction
Anticoagulants Antiplatelets	Ginkgo may inhibit platelet aggregation
Anticonvulsants	Ginkgotoxin can cause seizures and reduce effectiveness of anticonvulsants
Buspirone, Fluoxetine	Decreased effectiveness
Inhibits CYP1A2, 2D6, 3A4, 2C9	Exaggerated response
Induce CYP2C19	Decreased effectiveness or conversion to active form.

Garlic

- Possibly effective for atherosclerosis, prevention of colorectal and gastric cancers?
- Dose: 600 - 1200 mg divided 3 x/day
- Common side effects include breath and body odor, mouth and gastrointestinal burning or irritation, heartburn, flatulence, nausea, vomiting, and diarrhea

Garlic

Drug	Description of Interaction
P-gp substrates; NNRTI, protease inhibitors	Induces P-gp?; Induces CYP3A4; Stimulates the immune system.
CYP2E1 substrates, clozapine, benzodiazepines, theophylline	Inhibition CYP2E1
Anticoagulants, antiplatelets	Additive effects

Coenzyme Q10

- Possible effective for myopathy, heart failure, cardiovascular disease
- Dose: 100 – 2400 mg in divided doses
- Well tolerated. Common side effects include gastrointestinal side effects such as nausea, vomiting, diarrhea, appetite suppression, heartburn, and epigastric discomfort in less than 1% of patient

Coenzyme Q10

Drug	Description of Interaction
Chemotherapy	Concern that antioxidants might protect tumor cells, may decrease efficacy of doxorubicin, cyclophosphamide, and radiation therapy
Warfarin	CoQ10 may have Vitamin K like procoagulant properties, decreased efficacy
Antihypertensives	Additive effects

Milk Thistle

- Possible effective for dyspepsia, allergic rhinitis, diabetes
- Dose: 400 – 600 mg in divided doses
- Generally well tolerated. May has gastrointestinal effects and laxative effects.

Milk Thistle

Drug	Description of Interaction
CYP 2C9 substrates	Enzyme inhibitor
CYP 3A4	Enzyme inhibitor
Glucuronidated drugs i.e., morphine	Inhibits beta glucuronidation
Organic anion transporting polypeptide 1B1 (OATP1B1) dependent; i.e., statins	Decreased activity of transporter reducing drug to active site

Black Cohosh

- Possibly effective for postmenopausal symptoms
- Dose: 40 – 80 mg twice daily
- Possibly safe, there is concern that long term use may cause liver damage
- Potential adverse effects include rash, headache, dizziness, weight gain, feeling of heaviness in the legs, cramping, breast tenderness, and vaginal spotting or bleeding, endometrial hyperplasia?, thromboembolism?

Black Cohosh

Drug	Description of Interaction
Statins	Increased liver enzymes
Cisplatin	May decrease cytotoxic effects
CYP 2D6 substrates	Inhibits activity
Hepatotoxic drugs	Additive toxicity

Herbals and Perioperative Care

- Several herbal medications can have an impact on surgical care
- Platelet Aggregation
 - Gingko, saw palmetto
- CNS Depression
 - Kava, valerian, skullcap, melatonin
- Blood Glucose
 - Fenugreek, bitter lemon, gymnema, cinnamon
- Blood Pressure

Ang-Lee MK, Moss J, Yuan CS. Herbal medicines and perioperative care. JAMA 2001;286:208-16.

Questions that Help Avoid Clinically Significant Herb-Drug Interactions

- Is the patient taking any herbal, natural, or alternative medicines/products?
- Is the patient on narrow therapeutic index drugs?
- Is the patient on 5 or more medications?
- Is the patient on drugs that are substrates of cytochrome p450?
- Is the patient on drugs that are transported by p-glycoprotein?
- Is the herbal product safe and effective?

General Recommendations

- Ask the patient
 - Follow up herb use found in case histories
 - Explain importance of potential interactions
- Avoid SJW and warfarin interactions
- Patients on complicated medical regimens should avoid herbs and supplements unless carefully screened/supervised, but prioritize drugs with narrow therapeutic index
 - Carbamazepine, **cyclosporine**, **digoxin**, levothyroxine, novel anticoagulants, phenytoin, procainamide, theophylline and **warfarin**

Resources for Evaluating Herbal Medicines

Free

- NIH – NCCAM
- American Botanical Council
- Office of Dietary Supplements

Subscription required

- National Medicines Comprehensive Database
- Natural Standard
- Lexi-Interact
- Micromedex – Altmedex

What is the Pharmacist Role

- Counsel patients
- WHO released technical document titled
 - “The Role of the Pharmacist in Self Care and Self Medication”
 - 1998, written to recognize the expanding role of the pharmacist
 - Communicator
 - Quality drug supplier
 - Trainer and supervisor
 - Collaborator
 - Health promoter

Case 1: What is the National Drink of Fiji?

- JY is a 56 year old male that suffers from severe anxiety which he medicates with alprazolam. He is on vacation and is offered Kava to help him relax a bit more. After consuming his Kava he becomes lethargic and disoriented.
- What is the mechanism of this interaction?

Case 2: How Much Warfarin Is the Patient On!

- LK is a 48 year old female with a mechanical mitral valve. She is on warfarin to prevent thromboembolic events. She has been on warfarin 25 mg daily for 2 weeks and her INR has been between 1.5 to 2.0; her INR goal is 2.5 to 3.5. She reports taking CoQ10 to help reduce statin related myopathy.
- Could CoQ10 decrease INR levels?

Case 3: Hypoglycemia


- MW is a 68 year old male with T2DM, HTN, and dyslipidemia. He takes several supplements including flaxseed oil, ginkgo, garlic, and vitamin E. Do any of these products have the potential to have additive effects with his glipizide?

Herbal Use and Concerns

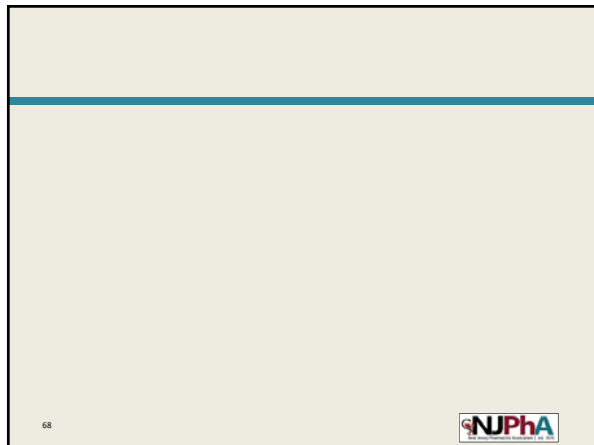
- What types of therapies are considered traditional medicine?
- Based on the lecture, what are 3 of the most commonly used herbal products?
- What can herb-drug interactions result in?
 - A. Increased drug levels
 - B. Decreased drug levels
 - C. Either A or B

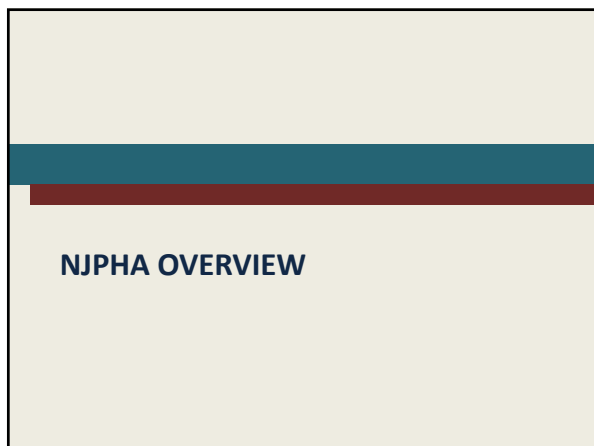
Conclusions

- Herbal products are not devoid of interaction potential
- Interactions may increase the risk for iatrogenic events
- Ultimately, when reconciling patient medications it is prudent to ask about herbal medicines

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NJPhA Mission

To advance the profession of pharmacy and pharmacists as health care providers while providing optimal care to the patients they serve. NJPhA is active at all levels of government protecting the interests of pharmacists and the patients that they serve.

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NJPhA Membership

Becoming an Active Member

- Founded in 1870 as a not-for-profit corporation to represent pharmacists in the State of New Jersey who practice in all areas of pharmacy.
- Get involved in ways that meet your specific goals:
 - Write for our **peer reviewed journal**
 - **Submit a poster** to our annual convention
 - Join one of our **Academies** (Consultant, Compounding, Disaster Management)
- Learn skills outside of the office that hasten your development:
 - Network and Make Connections
 - Be Recognized
 - Advance Your Expertise
 - Champion the Profession

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NJPhA Legislative Representation

- Organizational leadership and support has led to the development of many **legislative reforms** on a **state and federal** level. Some include:
 - 1965: NJPhA proposed limited quantity of children's aspirin
 - Saved lives, national recognition, President Johnson signed law, FDA action
 - 1969: First public anti-smoking campaign
 - 1970: First mandatory patient profile
 - 1975: Concern for senior citizens health prompted development of PAAD law in NJ
 - First in US, has helped millions, now has 200,000 beneficiaries
 - 1994: Pharmacists may be reimbursed as Diabetes Educators by NJ
 - 1999: Insurance audits must be performed at a mutually agreeable time
 - 2000: Mandatory Mail Order is not permitted for NJ State Regulated Plans.
 - 2005: Modernization of the Practice of Pharmacy
 - 2009: Pharmacists immunize patients in New Jersey; 2013: bill was amended to lower the age for flu vaccine administration
 - 2013: Collaborative Practice between Physicians and Pharmacists
 - 2014: Separation between consultant and provider extended

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NJPhA Federal Advocacy

Strength in Numbers!

- This year, APhA has dedicated 1.5 million dollars to advocate for pharmacists gaining **healthcare provider status** on a national level. This will allow **pharmaCISTS**, not just **pharmaCIES**, to bill and receive reimbursement for patient care related services (NJPhA has agreed to support this initiative on a state and national level).

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NJPhA Regulation Representation

Influence Laws and Regulation to Impact Change

- NJ Board of Pharmacy
- NJ Board of Medical Examiners
- NJ Drug Utilization Review Board
- NJ Health Information Technology Committee
- National Organizations
 - NABP
 - APhA
 - CMS

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In Summary...

We are committed to...

- Presenting a unified voice for NJ pharmacists and pharmacy technicians.
- Providing a forum for exchange of innovative ideas to establish progressive health systems.
- Promoting the optimization of drug therapy for the patients our members serve.
- Anticipating future information and professional development needs.
- Strengthening relationships between practitioners, student pharmacist, pharmacy technicians, and other health professionals.


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Becoming an Active Member
Sign up at today's event – see the registration desk for details

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- The online evaluation code will be sent from the office tomorrow morning:
- This code will be active for one week from the date of the lecture.
 - Deadline: **November 21, 2014**
- **NOTE: your credits will be posted to CPE monitor within 45 days of program date**

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