

# Herbal Medicines and the Clinical Laboratory

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# Alternative Medicine

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**Mending a  
Broken Heart**  
with Alternative  
Therapies

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**Anti-Aging  
Formula  
for MALE  
MENOPAUSE**

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**Pharmaceuticals: Your Money and Your Life**



**Ginkgo**



**Ephedra**



**St. John's Wort**



**Kava**



**Garlic**

# How Popular?



- Survey of 369 patient-escort pairs and reported that 174 patients (47.2%) used herbs
- Most common herbal products:
  - Ginseng (20%)
  - Echinacea (19%)
  - Ginkgo biloba (15%)
  - St John's wort (14%)

**Table 1**  
**Intended Uses of Common Herbal Medicines**

Herbal Medicine	Intended Use
Ginseng	Tonic capable of invigorating users physically, mentally, and sexually; also used for dealing with stress; used in China for more than 5,000 y
Siberian ginseng	Similar to ginseng
St John's wort	Treatment of mood disorders, particularly depression
Ginkgo biloba	Mainly to sharpen mental focus in otherwise healthy adults and also in people with dementia; improvement of blood flow in the brain and peripheral circulation; treatment of diabetes mellitus–related circulatory disorders, impotence, and vertigo
Kava	Relief of anxiety and stress; sedative
Valerian	Treatment of insomnia
Echinacea	Immune stimulant that helps increase resistance to colds, influenza, and other infections; wound healing
Saw palmetto	Treatment of benign prostatic hypertrophy
Feverfew	Relief from migraine headache and arthritis
Garlic	To lower cholesterol levels and blood pressure; prevention of heart attack and stroke
Ginger	Prevention of motion sickness, morning sickness, and nausea
Cranberry	Treatment of urinary tract infection; decrease kidney stone formation
Aloe	To heal wounds, burns, skin ulcers; also used as a laxative
Senna	Laxative
Dong quai	To alleviate problems associated with menstruation and menopause
Cat's claw	Immunostimulant with antiviral activity; also used by people with AIDS; prevention of colds and influenza; treatment of chronic fatigue syndrome
Hawthorn	For heart failure, hypertension, and angina pectoris
Pokeweed	Antiviral and antineoplastic; eating uncooked berry or root may cause serious poisoning



# Not a Drug but a Dietary Supplement

- FDA mandates that only medicines have to be proven to be safe before being released into the market
- Not a drug as long as they are not marketed for the prevention of any diseases
- Classified as "dietary supplements" and are marketed pursuant to the Dietary Supplement Health and Education act of 1994

# Types of Abnormal Lab Results

- Direct interference of a component of the herbal medicine with the assay
- Unexpected concentration of a therapeutic drug due to drug-herb interactions
- Toxic effects of the herbal product



**Table 2**  
**Interference of Herbal Products in Therapeutic Drug Monitoring of Digoxin\***

Herbal Product	Level of Interference	Comments
Chan Su	High	Chan Su has active components such as bufalin, which cross-react with digoxin assays; only Bayer assay has no interference; monitoring free digoxin also eliminates interference
Dan Shen	Moderate	Falsely elevated (FPIA) or falsely low (MEIA) digoxin level; no interference with EMIT, Bayer, Randox, Roche, or Beckman assays; monitoring free digoxin eliminates interference
Uzara root (diuretic)		Additive effect with digoxin; also interferes with digoxin assay
Siberian ginseng	Moderate	Falsely elevated (FPIA) or falsely low (MEIA) digoxin level; no interference with EMIT, Bayer, Randox, Roche, or Beckman assays; monitoring free digoxin does not eliminate interference
Asian ginseng	Moderate	Falsely elevated (FPIA) or falsely low (MEIA) digoxin level; no interference with EMIT, Bayer, Randox, Roche, or Beckman assays; monitoring free digoxin does not eliminate interference

FPIA, fluorescence polarization immunoassay; MEIA, microparticle enzyme immunoassay.

\* Bayer Diagnostics, Tarrytown, NY; Roche Diagnostics, Indianapolis, IN; Beckman Coulter, Fullerton, CA.

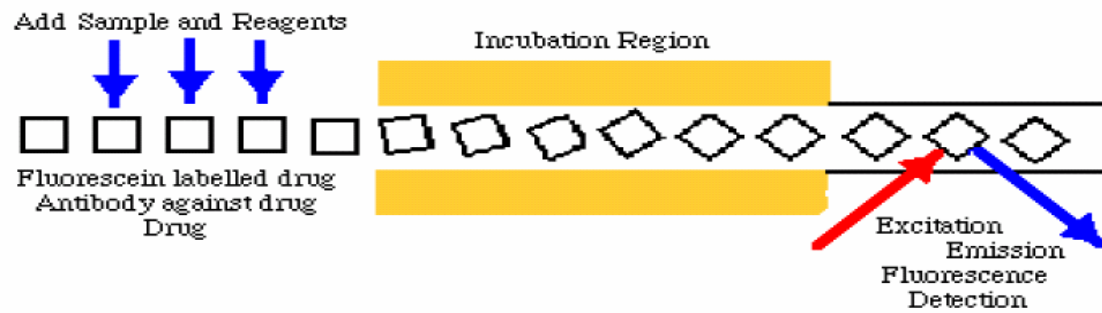


# Chinese Herbals-Chan Su

- Prepared from the dried white secretion of the auricular glands and the skin glands of Chinese toads (*Bufo melanostictus Schneider* or *Bufo bufo gargarzinas Gantor*)
  - In Chinese medicines Lu-Shen-Wan and kyushin used for tonsillitis, sore throat, furuncle, and palpitations
  - Stimulation of myocardial contraction and pain relief
  - At high dosages, causes cardiac arrhythmia, breathlessness, seizure, and coma
- Structural similarity between bufadienolides and digoxin accounts for the toxic effects and serum digoxin-like immunoreactivity of Chan Su
  - Falsely elevates the serum digoxin concentration when the FPIA is used
  - Negative interference of Chan Su in serum digoxin measurement has been reported with the microparticle enzyme immunoassay (MEIA)
  - Interfering components in Chan Su are bound very strongly to serum proteins, while digoxin is only 25% protein bound
  - Monitoring the free digoxin concentration eliminates this interference
  - Another way to eliminate this interference is to use the chemiluminescent assay

# Digoxin Measurement

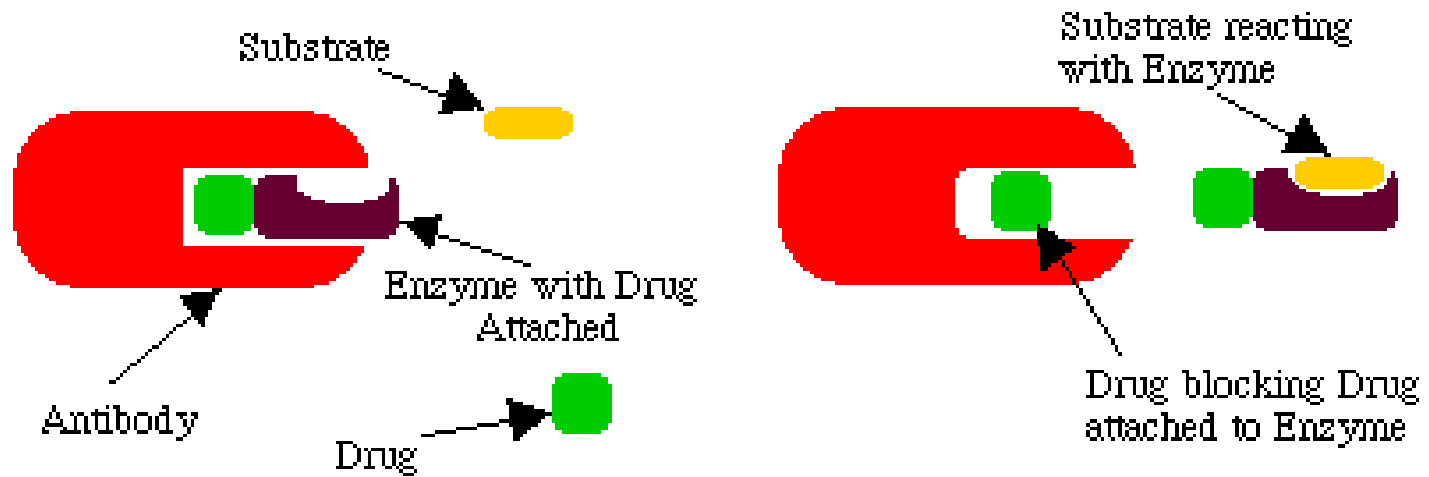
- FPIA (Fluorescent Polarization Immunoassay)
- MEIA (Microparticle enzyme immunoassay)
- EMIT (Enzyme Multiplied Immunoassay- Dade-Behring)
- Chemiluminescent assay (Elecsys)



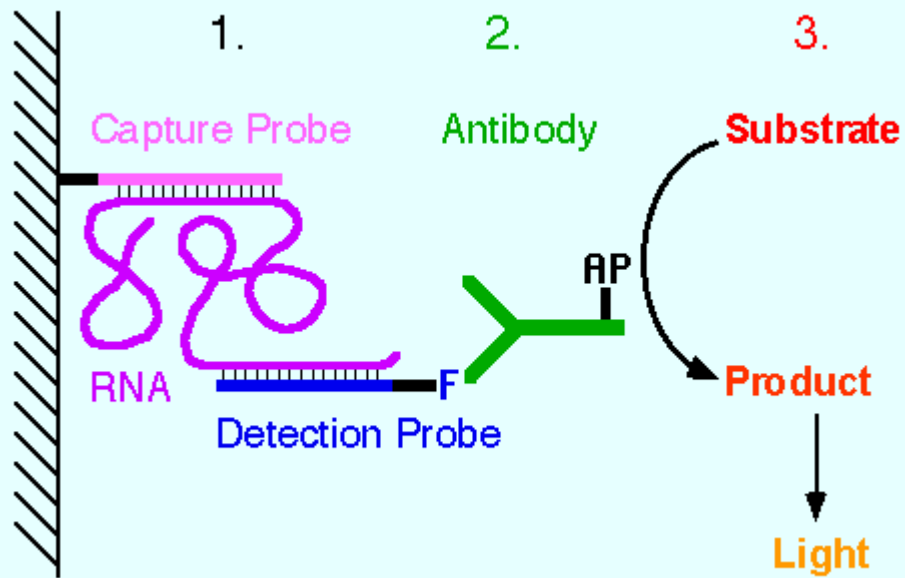
**Fig 3.9.1 FPIA Equipment Set-up**

# MEIA

- Solid-phase support consists of very small microparticles in liquid suspension
- Specific reagent antibodies are covalently bound to the microparticles
- Antigen, if present, is then "sandwiched" between bound antibodies and antigen-specific, enzyme-labelled antibodies
- Antigen-antibody complexes are detected and quantitated by analysis of fluorescence from the enzyme-substrate interaction



## Enzyme Multiplied Immunoassay





# Chinese Herbals-Dan Shen



- Prepared from the root of plant *Salvia miltiorrhiza*
  - Treating various cardiovascular diseases, including angina pectoris
- >20 diterpene quinones known as "tanshinones" have been isolated, structural similarity with digoxin
- Falsely elevated serum digoxin concentrations (FPIA)
- Falsely lowered the digoxin (MEIA)
- No interference with chemiluminescent assay
- Interference of Dan Shen in the FPIA and MEIA eliminated by measuring free digoxin because the digoxin-like immunoreactive components of Dan Shen have much higher serum protein binding than digoxin
- EMIT 2000 digoxin assay and a recently FDA-approved turbidimetric digoxin immunoassay also are free from interference from Dan Shen

# Chinese Herbals-Siberian Ginseng



- Ingestion of Siberian ginseng was associated with elevated digoxin concentrations
- Produces only modest interference in the digoxin FPIA and MEIA
- Asian ginseng also showed modest positive (FPIA) and modest negative (MEIA) interference

**Table 3**  
**Common Drug-Herb Interactions**

Herbal Product	Interacting Drug	Comments
Ginseng	Warfarin	Ginseng may decrease effectiveness of warfarin
	Phenelzine	Toxic symptoms, eg, headache, insomnia, and irritability
St John's wort	Paroxetine hydrochloride	Lethargy, incoherence, nausea
	Digoxin	Decreased AUC; peak and trough concentration of digoxin; may reduce effectiveness of digoxin
	Cyclosporine	Lower cyclosporine concentration due to increased clearance may cause transplant rejection
	Theophylline	Lower concentration, thus decreases the efficacy of theophylline
Ginkgo biloba	Indinavir	Lower concentration may cause treatment failure in patients with HIV
	Aspirin	Bleeding; ginkgo can inhibit PAF
	Warfarin	Hemorrhage
	Thiazide	Hypertension
Kava	Alprazolam	Additive effects with CNS depressants, alcohol
Garlic	Warfarin	Increased effectiveness of warfarin; bleeding
Ginger	Warfarin	Increased effectiveness of warfarin; bleeding
Feverfew	Warfarin	Increased effectiveness of warfarin; bleeding
Dong quai	Warfarin	Dong quai contains coumarin; dong quai increases INR for warfarin, causes bleeding
Dan Shen	Warfarin	Increased effectiveness of warfarin owing to reduced elimination of warfarin
Soy milk	Warfarin	Causes decline in INR
Comfrey	Phenobarbital	Increased metabolism of comfrey producing a lethal metabolite from pyrrolizidine; severe hepatotoxic effects
Borage oil	Phenobarbital	May lower seizure threshold, requiring dosage increase
Evening primrose oil	Phenobarbital	May lower seizure threshold, requiring dosage increase
Licorice	Spiro lactone	May offset the effect of spiro lactone
Shankhapushpi	Phenytoin	Lower phenytoin level and loss of seizure control

# Unexpected Concentrations



- Dong quai used for treatment of menstrual cramps, irregular menses, and menopausal symptoms
  - Elevate INR and increase bleeding time in patients taking warfarin
- Licorice
  - Anti-inflammatory herb and also as a remedy for gastric and peptic ulcers
  - Carbenoxolone, one of the components of licorice, can elevate blood pressure and cause hypokalemia
  - May offset the ability of spironolactones

# Unexpected Consequences



- St John's wort is prepared from *Hypericum*
  - Many chemicals have been isolated from St John's wort, including hypericin, pseudohypericin, quercetin, isoquercitrin, rutin, amentoflavone, hyperforin, other flavonoids, and xanthenes
- Activates cytochrome P-450 mixed-function oxidase liver enzymes (CYP3A4)
- Decrease concentrations of digoxin, cyclosporine, indinavir, theophylline

# Unexpected Consequences

- Of 2,069 samples of traditional Chinese medicines obtained from 8 hospitals in Taiwan, 23.7% contained pharmaceuticals
  - Caffeine
  - Acetaminophen
  - Indomethacin
  - Hydrochlorothiazide
  - Prednisolone
  - NSAIDS
  - Heavy metals

# Unexpected Consequences

- Kava-Kava
  - Abnormal Liver Function Test results
  - Additive effects with central nervous system depressants
  - Severe hepatitis
- Chaparral
  - Abnormal Liver Function Test results
  - Antioxidant and an anticancer herbal product
  - Chaparral-associated hepatitis
- Mistletoe
  - Liver Damage
  - Digestive aid, heart tonic, and sedative. Mistletoe berries are poisonous.
  - Hepatitis probably due to mistletoe
- Germander
  - Elevated Liver Enzyme Levels
  - Remedy for weight loss and as a general tonic
  - Germander-induced hepatotoxicity Acute cholestatic hepatitis

# Unexpected Consequences

- Kelp
  - Abnormal Thyroid Profile
- Ginseng
  - Hypoglycemic properties
- Fenugreek, ginger, nettle, sage, and devil's claw
  - Hypoglycemic



# Unexpected Consequences

- Licorice and Hypokalemia
  - Fifty-nine licorice-induced hypokalemic myopathy cases
  - Renin activity and aldosterone concentrations in serum usually decrease.
- Lead Poisoning Due to Herbs
  - Herbal medicines contaminated with
  - Patient was taking an herb purchased in India
  - Chinese herbal medicine Cordyceps
    - Lead content in the Chinese medicine was found to be as high as 20,000 ppm

**Table 4**  
**Potentially Toxic Herbs**

<b>Herb</b>	<b>Toxic Effect or System Affected</b>	<b>Intended Use (Should Anyone Use?)</b>
Comfrey	Hepatotoxic	Repairing of bone and muscle; prevention of kidney stones
Ephedra	Cardiovascular	Herbal weight loss
Chan Su	Cardiovascular	Tonic for heart
Borage oil	Hepatotoxic; hepatocarcinogenic	Source of essential fatty acids; rheumatoid arthritis; hypertension
Calamus	Carcinogenic	Psychoactive, not promoted in the United States
Chaparral	Hepatotoxic; nephrotoxic; carcinogenic	General cleansing tonic; blood thinner; arthritis remedy; weight loss product
Licorice	Pseudoaldosteronism (sodium and water retention, hypertension, heart failure)	Treatment of peptic ulcer; flavoring agent

# Toxic Effects



- Ginseng
  - In 1979, the term *ginseng abuse syndrome* was coined as a result of a study of 133 people who took ginseng for 1 month
  - Central nervous system stimulation ranging from depersonalization and confusion to symptoms of hypertension, nervousness, sleeplessness, skin eruption, and morning diarrhea

# Toxic Effects



- Ginkgo Biloba
  - Sharpen mental focus and to improve diabetes mellitus–related circulatory disorders
  - May cause gastric disturbances, headache, and dizziness
  - Bleeding with one case of spontaneous intracerebral hemorrhage and postoperative bleeding after laparoscopic cholecystectomy

# Toxic Effects

- Echinacea
  - Hepatitis, asthma, rash, myalgia, and nausea
- Garlic
  - Chopped garlic-and-oil mixes left at room temperature can result in fatal botulism food poisoning according to the FDA.
- Ma Huang (Ephedra-Containing Herbal Diet Pills)
  - Herbal weight-loss products that often are referred to as herbal fen-phen
  - May contain St John's wort and are sold as "herbal Prozac."
  - "Herbal ecstasy" another ephedrine-containing product, can induce a euphoric state
  - Contraindicated use of ephedra by patients with high blood pressure, glaucoma, or thyrotoxicosis

# Surgical Procedures

- American Society of Anesthesiologists
  - Patients should discontinue their herbal medicines at least 2 weeks before surgery
- Other recommendations
  - Garlic and ginseng should be discontinued at least 7 days before surgery
  - Ginkgo biloba should be discontinued 3 days before surgery because it inhibits platelet aggregation, causing bleeding
  - Kava should be discontinued at least 24 hours before surgery because kava can increase the sedative effect of anesthetics
  - Ma huang (ephedra) should be discontinued 24 hours before surgery because ma huang increases the blood pressure and the heart rate
  - St John's wort should be discontinued 5 days before surgery



**Ginkgo**



**Ephedra**



**St. John's Wort**



**Kava**



**Garlic**

# Questions



- Health nuts are going to feel stupid someday, lying in hospitals dying of nothing.

Redd Foxx (1922 -1991)



# References

- Dasgupta A. Am J Clin Pathol 2003;120:127-137.