Pharmacokinetics
of Herbal Active Constituents

Christopher Hobbs, Ph.D., L.Ac., A.H.G.

from Ancient Greek
pharmakon "drug" and
kinetikos "moving, putting in
motion" (Wikipedia)

The use of traditional cooking
with oil and spices led the way
for absorption-enhancement of
the medicinal qualities of
herbal medicines
Pharmacokinetics Overview

Pharmacokinetics

From: Psychopharmacology, Fig. 1.1
2006. Sinauer Associates
Pharmacokinetics & Pharmacodynamics of Herbal Active Constituents

• Pharmacokinetics
  – “the branch of pharmacology concerned with the movement of drugs within the body.”

• Pharmacodynamics
  – “the branch of pharmacology concerned with the effects of drugs and the mechanism of their action.”

1. First, the active constituents need to be identified, characterized
2. First, the active constituents have to be absorbed
3. Second, the ingredients in supplements or herbs need to have active constituents
4. The product has to have enough of the ingredients that have constituents to do anything (pixie dust)
Why Study Herbal Pharmacokinetics?

- **Efficacy**—helps determine
  - The best type of preparation (tincture, water-based extract, enhanced extract)
  - How the body’s organs, tissues, and cells are affected by the herb
  - The dose and dosage!

- **Safety**—a better understanding of the pharmacokinetics of herbal medicines is needed to support the predictability of botanical–drug interactions.

- How to maximize herbal formulas to increase effectiveness

- Why study pharmacodynamics? Efficacy, safety, identify biological activity, the mechanisms by which it acts
Scientific Basis—Herbal Research
Research articles on Scholar with key words related to pharmacokinetics

Original Research, C. Hobbs, 3-25-16
Pharmacodynamics
Agonists & Antagonists

- Agonist—increases
- Antagonist—blocks
- Agonist+antagonist = herbs and herb formulas
- Herbs bind more reversibly than designed drug monosubstances
- Herbs—more complex actions
Basics of Pharmacodynamics

- Drugs affect only the rate at which existing biologic functions proceed.
- Drugs do not change the basic nature of these functions or create new functions.
- Drugs can speed up or slow down the biochemical reactions:
  - muscles to contract
  - kidney cells to regulate the volume of water and salts retained
  - Hormone secretion
  - Nerve transmission
- Drugs cannot restore structures or functions already damaged beyond repair by the body.
- Most interactions between a drug and a receptor or between a drug and an enzyme are reversible.
- Sometimes an interaction is largely irreversible, and the drug’s effect persists until the body manufactures more enzyme.
- For instance, omeprazole, a drug used in the management of gastroesophageal reflux and ulcers, irreversibly inhibits an enzyme involved in the secretion of stomach acid.
- However, eventually the body will create more of the enzyme.
- **Active transport**
  - Requires the use of energy to move an active chemical
  - Carrier-mediated diffusion or facilitated diffusion—i.e. a carrier protein
- **Passive transport**—diffusion osmosis
From: Munira et al., 2015. Physiological Factors Affecting Drug Absorption.
http://www.slideshare.net/sirazummunira/physiological-factors-of-drug-absorption-45020626
Active Transport

- Against the concentration gradient
- Energy (ATP) is required
- Shape change transports solute from one side of membrane to other
- Protein “pump” conformational change
- Active transport, other examples:
  - Pinocytosis
  - Endocytosis
  - Phagocytosis
Phagocytosis, Pinocytosis, Endocytosis

From: Reece et al., 2011. Campbell Biology
Membrane Structure and Function:
slideshare.net
Example-Mushroom beta-glucans

- β-glucans dock to immune receptors including Dectin-1, complement receptor (CR3) and TLR-2/6
  - Trigger a group of immune cells including macrophages, neutrophils, monocytes, natural killer cells and dendritic cells
  - Fungal beta-glucans are taken up by macrophages
  - Then digested to fragments
  - Taken up and distributed inside the body
  - These bind to CR3 receptors
  - Inducing granulocytes to produce

Source: Chan et al., 2009
Cross-section of fungal cell wall

Source: Chan et al., 2009
β-glucans can act on a variety of membrane receptors found on the immune cells.

- may act singly or in combine with other ligands.
- Various signaling pathway are activated and their pathways are shown.
- Reactor cells include monocytes, macrophages, dendritic cells, natural killer cells and neutrophils.
- Corresponding surface receptors are listed.
- Immunomodulatory functions induced by β-glucans involve both innate and adaptive immune response.
- β-glucans also enhance opsonic and non-opsonic phagocytosis and trigger a cascade of cytokines release:
  - tumor necrosis factor(TNF)-α and various types of interleukins (ILs).

(From: Chan et al., 2009)
Blood serum levels and Tissue Levels
A study in itself

- Active compounds are absorbed into the blood
- Metabolized by the liver to some degree
- Then migrate to the tissues
- Low blood serum levels may not indicate low bioactivity!
- Look at the curves—the second of two peaks might indicate the start of elimination through urine and feces
CRM-LF consists of:

- CRM (6.17% w/w)—excipient
- Gelucire® 44/14 (16.46% w/w)—excipient
- Labrasol (5.76% w/w)—emulsifier
- Vitamin E TPGS (3.29% w/w)—antioxidant
- PEG 400 (55.55% w/w)—solubility enhancer
- Ethanol (8.23% w/w)—solvent
- Anhydrous citric acid (2.88% w/w)—preservative
- HPMC E5 (1.64% w/w)—coating

Pawar et al., 2012
Liver Enzymes & Drug Metabolism

- Most drugs, other chemicals that enter the blood are metabolized by the liver.
- Although metabolism typically inactivates drugs, some drug metabolites are pharmacologically active—sometimes even more so than the parent compound.
- Drug (or active herbal compound metabolism) by the liver and body’s cells—the goal is to make the drug easier to excrete.
Differences in Drug Metabolism—People

- PM means poor metabolizer
- EM means extensive metabolizer, which is the normal or usual phenotype
- URM means ultra-rapid metabolizer
- Approximately 7% of the U.S. population has a genetic defect in CYP2D6 that results in a poor metabolizer phenotype
- People that have usual drug metabolizing ability (EM) can become phenotypic poor metabolizers if they are given a substance (drug or food as we will see later) that inhibits the enzyme
### Active constituent metabolism—elderly

- With aging, the liver’s capacity for metabolism through the CYP450 enzyme system is reduced by $\geq 30\%$
- Drugs reach higher levels and have prolonged half-lives in the elderly

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**Comparison of pharmacokinetic outcomes for **diazepam** in a younger man (A) and an older man (B).**

Diazepam is metabolized in the liver to desmethyl-diazepam through P-450 enzymes. Desmethyldiazepam is an active sedative, which is excreted by the kidneys. Elimination half-life is inversely proportional to the terminal slopes of the curves, flat slopes correspond to long half-lives. $0 = $ time of dosing. (Adapted from Greenblatt DJ, Allen MD, Harmatz JS, Snader RI: *Diazepam* disposition determinants. Clinical Pharmacology and Therapeutics 27:301–312, 1980.)

![Graph A: Plasma concentration vs. time for Diazepam in a younger man](image1)

![Graph B: Plasma concentration vs. time for Desmethyldiazepam in an older man](image2)
Food-Drug Interactions (grapefruit) affecting Bioavailability serum drug levels

- furanocoumarins from grapefruit juice such as bergamottin can cause irreversible inhibition of the cytochrome P450 enzyme, CYP3A4
- resulting in an increase in systemic exposure, leading to adverse drug reactions and toxicity
- flavonoids in grapefruit juice, naringin and hesperidin, reduce bioavailability of some drugs (Dolton et al. 2012).
- Inhibition of CYP3A4 is irreversible and it can last for longer than 3 days after ingestion of grapefruit juice until new enzyme has been synthesized in the gut wall (Pirmohamed 2013)
Herbs are not Drugs

- Animals co-evolved with plants for millions of years!
- A drug’s action is affected by the quantity of drug that reaches the receptor and the degree of attraction (affinity) between it and its receptor on the cell’s surface.

- Herbs have many weaker chemicals that bind to receptor sites on and in cells.
- They usually are not as tightly-binding as drugs that are specifically designed to bind and have a dramatic effect.
Herbal inhibitors—Cytochrome P450 Enzymes

Table 1. Herbal remedies that are inhibitors of cytochrome P450 activity in vitro.

<table>
<thead>
<tr>
<th>CYP</th>
<th>Herbal Remedies</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A2</td>
<td>Black/green tea, dan shen, devil’s claw, Echinacea, fo-ti, ginkgo, ginseng, grapefruit juice, kava, licorice, resveratrol, St. John’s wort, wu-chu-yu tang</td>
</tr>
<tr>
<td>CYP2B6</td>
<td>Licorice, luteolin</td>
</tr>
<tr>
<td>CYP2C8</td>
<td>Devil’s claw, fo-ti, ginkgo, usnic acid</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Cranberry, devil’s claw, Echinacea, eucalyptus oil, evening primrose, fo-ti, garlic, genistein, ginger, ginkgo, ginseng, goldenseal, grapefruit juice, grapeseed extract, green tea, kava, licorice, luteolin, milk thistle, saw palmetto, St. John’s wort, soy, tumeric, usnic acid, valerian</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Devil’s claw, Echinacea, eucalyptus oil, evening primrose, fo-ti, garlic, ginko, ginseng, kava, milk thistle, St. John’s wort, usnic acid, valerian</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Black cohosh, black pepper, C. roseus, devil’s caw, dong quai, Echinacea, eucalyptus oil, evening primrose, fo-ti, genistein, ginger, ginkgo, goldenseal, grapefruit juice, grapeseed extract, green tea, kava, luteolin, milk thistle, saw palmetto, St. John’s wort, soy, yohimbine</td>
</tr>
<tr>
<td>CYP2E1</td>
<td>Echinacea, garlic, ginseng, kava, resveratrol, St. John’s wort, watercress</td>
</tr>
<tr>
<td>CYP3A4</td>
<td><em>A. dahurica</em>, β-carotene, black cohosh, black pepper, black mulberry, black raspberry, <em>C. aurantium</em>, cat’s claw, chamomile, cranberry, dan shen, devil’s claw, dong quai, Echinacea, eluthero, eucalyptus oil, evening primrose, feverb, fo-ti, garlic, genistein, ginkgo, ginseng, goldenseal, grapefruit juice, grapeseed extract, green tea, kava, licorice, luteolin, milk thistle, oregano, pomegranate, pomelo, red clover, resveratrol, sage, saw palmetto, schisandra fruit, St. John’s wort, soy, tumeric, valerian, wild grape</td>
</tr>
</tbody>
</table>

Source: Foti & Wahlstrom, 2008. role of dietary supplements in cytochrome P450-mediated drug interactions
# Herbs Affecting P450 Enzymes

<table>
<thead>
<tr>
<th>Herbals CYP1A2</th>
<th>Herbal CYP2B6</th>
<th>Herbals CYP2C8</th>
<th>Herbals CYP2C9</th>
<th>Herbals CYP2C19</th>
<th>Herbals CYP2D6</th>
<th>Herbals CYP2E1</th>
<th>Herbals CYP3A4</th>
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</thead>
<tbody>
<tr>
<td><strong>Genetic Polymorphisms</strong></td>
<td><strong>Genetic Polymorphisms</strong></td>
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<tr>
<td>Allium sativum</td>
<td>Allium sativum</td>
<td>Alpinia galanga</td>
<td>Piper Methysticum</td>
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<tr>
<td>Bergamottin</td>
<td>Harpagophytum procumbens</td>
<td>Alstonia scholaris</td>
<td>Allium sativum</td>
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<tr>
<td>Harpagophytum Procumbens</td>
<td>阳雀花</td>
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<td>Ammi visnaga</td>
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<td>Lycium barbarum</td>
<td>阳雀花</td>
<td>Andrographis paniculata</td>
<td>Azadirachta indica</td>
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<td></td>
<td></td>
<td>Catharanthus roseus</td>
<td>Cinnamomum burmannii</td>
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<td></td>
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<td>Cinmiciafuga racemosa</td>
<td>Eleutherococcus senticosus</td>
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<td>Gynostemma pentaphyllum</td>
<td>Gynostemma pentaphyllum</td>
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<td>Melaleuca leucadendron</td>
<td>Melaleuca leucadendron</td>
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<td>Panax ginseng</td>
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<td>Panax quinquefolius</td>
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<td></td>
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<td>Piper nigrum</td>
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<td>Punica granatum</td>
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<td>Rheum palmatum</td>
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<td>Salvia officinalis</td>
<td>Salvia officinalis</td>
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<td>Strychnos nux vomica</td>
<td>Strychnos nux vomica</td>
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<td></td>
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<td>Syzygium aromaticum</td>
<td>Syzygium aromaticum</td>
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<td></td>
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<td>Tinospora crispa</td>
<td>Tinospora crispa</td>
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<tr>
<td></td>
<td></td>
<td>Zingiber aromaticum</td>
<td>Zingiber aromaticum</td>
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</tr>
</tbody>
</table>

Source: EBM Consult
St. John’s Wort Induces CYP3A

- CYP3A is responsible for metabolizing the greatest number of marketed drugs
- Inhibitors of CYP3A
  - Grapefruit juice
  - Some pharmaceutical drugs (antifungals, erythromycin)
- Inducers of CYP3A
  - St. John’s wort
  - Mean plasma concentration time course of indinavir in 8 healthy volunteers with indinavir alone or after taking indinavir with St. John’s wort.¹ (57% reduction in AUC)
St. John’s wort has effects on the cytochrome P450 system (induction of CYP 3A4 and 2C9) as well as the major drug transport protein – P-glycoprotein.

Effect of SJW on drug metabolism of Xanax (14-day administration (JAMA. 2003. 290:1500-1504.)
Table 5. IC₅₀ values (μM) for kava compounds obtained using cryopreserved human hepatocytes.

<table>
<thead>
<tr>
<th>Test Compound</th>
<th>CYP1A2</th>
<th>CYP2A6</th>
<th>CYP2C9</th>
<th>CYP2C19</th>
<th>CYP2D6</th>
<th>CYP2E1</th>
<th>CYP3A4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methysticin</td>
<td>2.4</td>
<td>NI</td>
<td>5.5</td>
<td>4.8</td>
<td>NI</td>
<td>7.2</td>
<td>7.1</td>
</tr>
<tr>
<td>Desmethoxyyangonin</td>
<td>1.4</td>
<td>NI</td>
<td>NI</td>
<td>9.4</td>
<td>NI</td>
<td>NI</td>
<td>NI</td>
</tr>
<tr>
<td>Yangonin</td>
<td>12.1</td>
<td>NI</td>
<td>NI</td>
<td>58.9</td>
<td>NI</td>
<td>NI</td>
<td>NI</td>
</tr>
<tr>
<td>Kava Extract</td>
<td>4.4</td>
<td>NI</td>
<td>18.4</td>
<td>3.8</td>
<td>NI</td>
<td>18.0</td>
<td>15.1</td>
</tr>
</tbody>
</table>

Positive Control

<table>
<thead>
<tr>
<th>% Inhibition</th>
<th>Furfurylline</th>
<th>Tranylcypromine</th>
<th>Sulfinpyrazone</th>
<th>Omeprazole</th>
<th>Quinidine</th>
<th>4-Methylpyrazole</th>
<th>Ketoconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration</td>
<td>2 μM</td>
<td>2 μM</td>
<td>20 μM</td>
<td>50 μM</td>
<td>5 μM</td>
<td>500 μM</td>
<td>2 μM</td>
</tr>
</tbody>
</table>

Values shown represent the mean of three determinations. NI indicates no inhibition at the highest concentration tested. *Micromolar concentrations for the kava root extract are estimated from the amounts of the six kava lactones present in the extract as shown in Table 3.

Traditional herbal formulas in traditional Chinese medicine (for instance) often includes 3-12 different herbs
- Some are used to enhance the bioactivity of major actives
- Also to act on different aspects of a disease process or symptom
  - For instance, URI—antiviral, enhance host immunity, relieve symptoms
- Some are added for flavor and taste (“harmonize”)
- Other herbs can reduce toxicity
- Others are added to enhance bioavailability of actives
  - Studies show that in the presence of anthocyanins, other compounds, the major actives are better absorbed!
Examples of traditional formulas that include bioavailability enhancers

- **Fu gan feng** (contains active hepatoprotective compounds that are better absorbed within the context of the formula)
- **San huang xie xin tang** (rhubarb and coptis tea pills)
  - Rhein, known active bowel-enhancer is better absorbed—in the rhubarb herb, but even more from the formula
Pharmacokinetics, Pharmacodynamics of major compounds from Fugan Fang (tx hepatic diseases)

- Fugan Fang (FGF) is an effective traditional Chinese medicine (TCM) prescribed for the clinical treatment of hepatic diseases

- Pharmacokinetic parameters of:
  - calycosin-7-O-β-D-glu (isoflavone)
    - Hormone modulator, phytoestrogen
  - ononin (isoflavone)
    - Hormone modulator, phytoestrogen
  - gentiopicroside (iridoid glycosides)
    - Bitter, digestive enzyme activator, immune
  - Sweroside (iridoid)
    - Bitter, digestive enzyme activator, immune
  - ferulic acid (phenolic acid)
    - Abundant in fruits, veggies, mint family
    - Potent antioxidant, antiinflammatory
  - p-coumaric acid (phenolic acid)
    - Immunomodulator, antiinflammatory
Pharmacokinetics of Rhubarb Actives

- Cofactors increase absorption of rhein
- San-Huang-Xie-Xin-Tang (SHXXT)
- Coptis and rhubarb tea pills
- Contains coptis stem, rhubarb root, scute Root (*Scutellaria baicalensis*)
- Chinese patent for treating constipation
- Conclusion: “the herbal formulae (SHXXT) are more efficient than the single herb (rhubarb) or the pure compound (rhein) in rhein absorption”

Hou *et al.*, 2014
Pharmacokinetics of Curcumin

Figure 3. Mean plasma CRM concentration vs. time profile obtained after oral administration of CRM-LF to human volunteers at a dose of 750 mg.

Pawar et al., 2012
Products
Commercial Products--Issues

- FDA does have regulatory control over dietary supplements
- Claims and quality are main concerns
- Still, some unproven ingredients are marketed
- No licensure required, like Canada, most European countries
- Products should meet GNPs, identity, purity, potency, consistency
- Still some problems with substitution, reduced actives, testing, purity, but many improvements made
• Tinctures vs. powdered extracts
  – Tinctures
    • + Cold process, increased absorption, good shelf life
    • Some “farm to bottle”
    • - Contains alcohol, highly diluted
  – Powdered extracts
    • + Up to 25x more concentrated
    • - Extraction can hide poor quality, filth
    • Fillers have to be tested for

• Carriers are often necessary, but they can also be “fillers”
• They become fillers when in excess for the purpose of helping the ingredient to “flow” and to help avoid caking because ingredients are too hydroscopic
## Selecting the Best Preparation—Absorption

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Extraction of actives</th>
<th>Bioavailability of actives</th>
<th>Potency</th>
<th>Shelf-life</th>
<th>Compliance</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teas</td>
<td>good-excellent</td>
<td>good-excellent</td>
<td>good, depends on extraction time</td>
<td>2-4 days in 'fridge</td>
<td>fair-good; taste</td>
<td>Self-made, takes time</td>
</tr>
<tr>
<td>Tinctures</td>
<td>good-excellent</td>
<td>excellent</td>
<td>Fair (1:5 extract)</td>
<td>ca. 3 years</td>
<td>fair-good; taste</td>
<td>contains alcohol</td>
</tr>
<tr>
<td>Creams</td>
<td>fair-good</td>
<td>fair-good</td>
<td>fair-good</td>
<td>&lt;1 year</td>
<td>good</td>
<td>external</td>
</tr>
<tr>
<td>Salves</td>
<td>good</td>
<td>good</td>
<td>good</td>
<td>&lt;1 year</td>
<td>fair-good</td>
<td>external</td>
</tr>
<tr>
<td>Capsules</td>
<td>good-excellent</td>
<td>good-excellent</td>
<td>Capsules should contain extracts, not powders (4:1, 5:1)</td>
<td>&lt;2 years</td>
<td>good</td>
<td>check extraction ratio and standardization</td>
</tr>
<tr>
<td>Tablets</td>
<td>good-excellent</td>
<td>good</td>
<td>Capsules should contain extracts, not powders (4:1, 5:1)</td>
<td>&lt;3 years</td>
<td>good, size of tablet, coating</td>
<td>more concentrated than capsules</td>
</tr>
<tr>
<td>Syrups</td>
<td>good</td>
<td>good</td>
<td>fair-good</td>
<td>&lt;2 years</td>
<td>good, depends on taste</td>
<td>may contain alcohol, sugar</td>
</tr>
<tr>
<td>Baths</td>
<td>good</td>
<td>fair-good</td>
<td>fair</td>
<td>short</td>
<td>good</td>
<td>make a strong tea, add to bath</td>
</tr>
</tbody>
</table>
Quality—a course in itself

- GIGO (herb quality)
  - cultivated, “wild”
  - Parts collected (barks, roots)
  - How processed, dried, stored
- Fumigation, other chemicals
- Storage of herbs (years?)
- Extraction (solvents?)
- Standardization
- Manufacturing process
- Spiking, purity
  - Maltodextrin levels
- Micro
Standardization

- Plants vary considerably in types and levels of actives
- Identify known actives
- Doesn’t lead necessarily to purification and isolation of active constituents
- Insure sufficient and consistent levels based on studies
- Stability
- Recommended dose should follow clinical trials
- “pixie dust” effect
Standardization
Quality Assurance of Phytopharmaceuticals

- Growing methods
- Harvesting, processing
- Identification
- Determination of active compounds
- Purity considerations
- Product manufacture
- Efficacy, safety testing
Current Problems with Quality, Efficacy

- Farm to medicine chest?
- Dose—not enough actives
  - Tinctures (1:5), dry-weight basis
- Powdered extracts
  - 5:1, but often cut with maltodextrin
- Identification
  - Species ID
    - DNA vs. chromatography
    - Microscopic, organoleptic
Dose and Dosage

- **Dose depends on concentration of the herbs in the product**
  - level of active constituents
  - Tinctures from fresh herbs
  - ... from dried herbs
  - Dried herbs in capsules
  - Powdered extracts using water, alcohol, other solvents (acetone, hexane)

- **TCM, average dose**
  - Single herb in a blend = 5-20 g
  - 3-15 herbs in a blend (5-10 typical)
  - Typically in decoction, or water-extracted tea pills
  - Some alcoholic extracts, typically single herbs

- **Western herbs**
  - Dose and dosage varies widely
Dose and Dosage Regimen

- Adjust for body weight, age
- Adjust for patient vitality, sensitivity, age
- Consider level of purification and concentration
- Most constituents are usually at active levels in serum between 0.75-6 hours
- Usually take herb capsules, tablets with meals, b.i.d., morning and evening (compliance)
- Curcumin pharmacokinetics—rapid glucoronidation by liver

Anand et al., 2007
Storage of chemicals in Cell

Chloroplast (cp)
- some alkaloids (coniine, quinolizidines, caffeine)
- some terpenes

Mitochondrium (mt)
- some amines
- Conium alkaloids

Endoplasmic reticulum
- hydroxylation steps
- lipophilic compounds

Cytoplasm
- most hydrophilic compounds

Vesicles
- some alkaloids (protoberberines)

Vacuole
- storage of alkaloids, NPAAs, cyanogens, glucosinolates, glycosides, saponins, anthocyanins, flavonoids, cardenolides, sugars

ATP
ADP
H^+
Cell Compartments

Hydrophilic compounds:
- Vacuole: most alkaloids, NPAAs, saponins, glycosides, flavonoids, anthocyanins, tannins, cyanogens, glucosinolates, amines
- Laticifer: some alkaloids (Lobelia, Papaver, Chelidonium), cyanogens, NPAAs, cardiac glycosides (Nerium)
- Apoplas: tannins

Lipophilic compounds:
- Cuticle: waxes, lipophilic flavonoids, terpenoids
- Trichomes: monoterpens, sesquiterpens
- Resin ducts: terpenes (C10, C15, C20, C30), lipophilic flavonoids
- Laticifers: polyterpens, diterpens (phorbol esters), lipophilic flavonoids, quinones
- Oil cells: anthraquinones (hypericin, hyperforin), terpenoids
- Plastid membranes: ubiquinones, tetraterpenes
Four Major Chemical Pathways

- **Fatty Acids**
  - MeJA
  - cis-jasmone
  - GLVs e.g. hexenal
  - JA
  - OPDA
  - AOC
  - AOS
  - HPL
  - Lipase (DAD)
  - Lipoxigenase (LOX)
  - Fatty acids

- **Terpenes**
  - Diterpenes
  - Sesquiterpenes
  - Monoterpenes
  - Mevalonate pathway
  - Mevalonate pathway
  - Mevalonate pathway
  - Pyruvate
  - Acetyl CoA

- **Phenyl Propanoids**
  - MeSA
  - SAMT
  - Indole
  - SA
  - PAL
  - Shikimate pathway
  - Erythrose phosphate
  - Cinnamic acid
  - Phenolic acids
  - Quinones
  - Coumarins
  - Flavonoids
  - Coumarins
  - Anthocyanins
  - Tannins
  - Lignin

**Chemical Pathways**

- Phenylpropanoids
- Terpenes
- Fatty Acids

**Key Reactions**: Acetyl CoA, Pyruvate, Mevalonate pathway, Erythrose phosphate, Shikimate pathway, GLVs e.g. hexenal, Lipase (DAD), Lipoxigenase (LOX), MeJA, cis-jasmone, OPDA, AOC, AOS, HPL.
Shikimic Acid Pathway—Phenolics, Alkaloids

- Salicylates
- Serotonin, auxin
- Alkaloids
- betalains
- Tocopherols
- Cinnamates
- Coumarins
- Flavonoids
- Anthocyanins
- Tannins
Terpenes, Mevalonic Pathway
Essential Oils

- Complex mixtures of monoterpenes (middle notes, moderately volatile), esters (high notes, very volatile), sesquiterpenes (low notes, not too volatile)
- Some essential oils contain several hundred identified compounds
- Families commonly containing essential oils include the parsley family (Apiaceae), mint family (Lamiaceae), laurel family (Lauraceae), and the eucalyptus family
- Essential oils penetrate the skin, are used topically as antiinflammatory and antimicrobial agents, internally as mild sedatives (lemon balm, chamomile), antiinflammatory and antispasmodics (chamomile, yarrow) and flavor ingredients
Further Reading

- Best book:
- Pharmacognosy—the study of herbal “drugs”
- Potter’s Herbal has a concise review of major constituents found in most medicinal plants:
- http://www.gis.usu.edu/Geography-Department/utgeog/utvatlas/index.html (online flora for Utah)
Pharmacokinetics—Practical Aspects

- Absorption co-factors
  - Phenolic compounds
  - Spicy foods
    - Black pepper
    - Ginger
    - Cinnamon
  - Glycoside form?
    - Sugars attached, higher water-solubility
Herbal Bioenhancers

- Black pepper extract (Piperidine)
- Phospholipid (Phosphatidylcholine)
- Quercetin (onion)
- Ginger
- Cumin
- Licorice
- Naringin (grapefruit only)

(Dudhatra et al., 2012)
# Herbal Liposomal Formulations

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Active ingredient</th>
<th>Application</th>
<th>Biological activity</th>
<th>Method of preparation</th>
<th>Percent entrapment efficiency</th>
<th>Route of administration</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quercetin Liposome</td>
<td>Quercetin</td>
<td>Reduced dose, enhanced penetration in blood brain barrier</td>
<td>Anti-oxidant</td>
<td>Reverse evaporation technique</td>
<td>60%</td>
<td>Intranasal</td>
<td>68</td>
</tr>
<tr>
<td>Liposome encapsulated</td>
<td>Silymarin</td>
<td>Improve bioavailability</td>
<td>Hepato-protective</td>
<td>Reverse evaporation technique</td>
<td>69.22±0.6%</td>
<td>Buccal</td>
<td>69</td>
</tr>
<tr>
<td>Artemisia arborescens</td>
<td>Artemisia arborescens</td>
<td>Targeting of essential oils to cells, enhance penetration into cytoplasmic barrier,</td>
<td>Antiviral</td>
<td>Film method and sonication</td>
<td>60–74%</td>
<td>In–vitro</td>
<td>70</td>
</tr>
<tr>
<td>Ampelopsin Liposome</td>
<td>Ampe–lopsin</td>
<td>increase efficiency</td>
<td>Anti-cancer</td>
<td>Film ultrasound method</td>
<td>62.30%</td>
<td>In–vitro</td>
<td>71</td>
</tr>
<tr>
<td>Paclitaxel Liposome</td>
<td>Paclitaxel</td>
<td>High entrapment efficiency and pH sensitive</td>
<td>Anti-cancer</td>
<td>Thin film hydration method</td>
<td>94%</td>
<td>In–vitro</td>
<td>72</td>
</tr>
<tr>
<td>Curcumin Liposome</td>
<td>Curcumin</td>
<td>Long circulation with high entrapment efficiency</td>
<td>Anti-cancer</td>
<td>Ethanol injection method</td>
<td>88.27±2.16%</td>
<td>In–vitro</td>
<td>73</td>
</tr>
<tr>
<td>Garlicin Liposome</td>
<td>Garlicin</td>
<td>increase efficiency</td>
<td>Lungs</td>
<td>Reverse phase evaporation</td>
<td>90.77%</td>
<td>In–vitro</td>
<td>74</td>
</tr>
</tbody>
</table>

Source: Kesarwani & Gupta, 2013
Microspheres—between 0.1 and 100 μm in size

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Active ingredient</th>
<th>Application</th>
<th>Biological activity</th>
<th>Method of preparation</th>
<th>Size in μm</th>
<th>Route of administration</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rutin–alginate</td>
<td>Rutin</td>
<td>Targeting into cardiovascular and cerebrovascular system</td>
<td>Cardio–vascular and cerebro–vascular</td>
<td>Complex coacervation method</td>
<td>165–195</td>
<td>In–vitra</td>
<td>75</td>
</tr>
<tr>
<td>chitosan microspheres</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zedoary oil</td>
<td>Zedoary</td>
<td>Sustained release and higher bioavailability</td>
<td>Hepato–protective</td>
<td>Quasi emulsion solvent diffusion method</td>
<td>100–600</td>
<td>Oral</td>
<td>76</td>
</tr>
<tr>
<td>microspheres</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPT loaded microspheres</td>
<td>Camptothecin</td>
<td>Prolonged release of camptothecin</td>
<td>Anti–cancer</td>
<td>Oil in water evaporation method</td>
<td>10</td>
<td>Intraperitoneal or intravenously</td>
<td>77</td>
</tr>
<tr>
<td>Quercetin microspheres</td>
<td>Quercetin</td>
<td>Significantly decreases the dose size</td>
<td>Anti–cancer</td>
<td>Solvent evaporation</td>
<td>6</td>
<td>In–vitra</td>
<td>78</td>
</tr>
<tr>
<td>Cynara scolymus</td>
<td>Cynara scolymus</td>
<td>Controlled release of nutraceuticals</td>
<td>Nutritional supplement</td>
<td>Spray drying technique</td>
<td>6–7</td>
<td>Oral</td>
<td>79</td>
</tr>
</tbody>
</table>

Source: Kesarwani & Gupta, 2013
Nanoparticles—between 1 and 100 nm (under 0.1 μm)

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Active ingredient</th>
<th>Application</th>
<th>Biological activity</th>
<th>Method of preparation</th>
<th>% entrapment efficiency</th>
<th>Route of administration</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triptolide nanoparticles</td>
<td>Triptolide</td>
<td>Enhance the penetration of drug through stratum corneum by increased hydration</td>
<td>Anti-inflammatory</td>
<td>Emulsification ultrasound</td>
<td></td>
<td>Topical</td>
<td>80</td>
</tr>
<tr>
<td>Nanoparticle of <em>Cascuta chinensis</em></td>
<td>Flavonoids and Lignans</td>
<td>Improve water solubility</td>
<td>Hepato-protective and anti-oxidant activity</td>
<td>Nano-suspension method</td>
<td>90%</td>
<td>Oral</td>
<td>81</td>
</tr>
<tr>
<td>Artemisinin nanocapsules</td>
<td>Arte-misinin</td>
<td>Sustained drug release</td>
<td>Anti-cancer</td>
<td>Self assembly procedure</td>
<td>90–95%</td>
<td>In-vitro</td>
<td>82</td>
</tr>
<tr>
<td><em>Radix salvia</em> miltiorrhiza nanoparticles</td>
<td><em>Radix salvia</em></td>
<td>Improve the bio-availability</td>
<td>Coronary heart diseases, angina pectoris and myocardial infarction</td>
<td>Spray drying technique</td>
<td>96.68%</td>
<td>In-vitro</td>
<td>83</td>
</tr>
<tr>
<td>Taxol loaded nanoparticles</td>
<td>Taxol</td>
<td>Improve the bioavailability and sustained drug release</td>
<td>Anti-cancer</td>
<td>Emulsion solvent evaporation method</td>
<td>99.44%</td>
<td>In-vitro</td>
<td>84</td>
</tr>
<tr>
<td>Berberine loaded nanoparticles</td>
<td>Berberine</td>
<td>Sustained drug release</td>
<td>Anti-cancer</td>
<td>Ionic gelation method</td>
<td>65.40%</td>
<td>In-vitro</td>
<td>85</td>
</tr>
<tr>
<td>Naringenin loaded nanoparticles</td>
<td>Naringenin</td>
<td>Improve the release of NAR and improv its solubility</td>
<td>Hepato-protective</td>
<td>Nano-precipitation method</td>
<td></td>
<td>Oral</td>
<td>86</td>
</tr>
</tbody>
</table>

Source: Kesarwani & Gupta, 2013
Transferosomes—Lipophilic vesicles containing a hydrophilic drug as a delivery system

Table 4
Transferosomes

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Active ingredient</th>
<th>Application</th>
<th>Biological activity</th>
<th>Droplet size</th>
<th>Route of administration</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capsaicin transferosomes</td>
<td>Capsaicin</td>
<td>Increase skin penetration</td>
<td>Analgesic</td>
<td>150.6 nm</td>
<td>Topical</td>
<td>90</td>
</tr>
<tr>
<td>Colchicine transferosomes</td>
<td>Colchicine</td>
<td>Increase skin penetration</td>
<td>Antigout</td>
<td>—</td>
<td>In-vitro</td>
<td>91</td>
</tr>
<tr>
<td>Vincristine transferosomes</td>
<td>Vincristine</td>
<td>Increase entrapment efficiency and skin penetration</td>
<td>Anticancer</td>
<td>120 nm</td>
<td>In-vitro</td>
<td>92</td>
</tr>
</tbody>
</table>

- Transferosomes are a special type of liposomes, consisting of phosphatidylcholine and an edge activator. They are soft malleable vesicles tailored for enhanced delivery of active agents.
- The reason for using vesicles in transdermal drug delivery is based on the fact that they act as drug carriers to deliver entrapped drug molecules across the skin, as well as penetration enhancers because of their composition.
- Avoid liver metabolism

Source: Kesarwani & Gupta, 2013
Table 5
Lipid-based herbal formulations (with a phospholipid)

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Active ingredient</th>
<th>Application</th>
<th>Biological activity</th>
<th>Method of preparation</th>
<th>Dose</th>
<th>Route of administration</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ginkgo biloba lipid based systems</td>
<td>Flavonoids</td>
<td>Stabilizes ROS</td>
<td>Cardio-protective antioxidant activity</td>
<td>Phospholipid complexation</td>
<td>100 mg</td>
<td>Subcutaneous</td>
<td>93</td>
</tr>
<tr>
<td>Silybin lipid based systems</td>
<td>Flavonoids</td>
<td>Inhibits lipid peroxidation and stabilizes ROS</td>
<td>Hepatoprotective antioxidant</td>
<td>Phospholipid complexation</td>
<td>120 mg</td>
<td>Oral</td>
<td>94</td>
</tr>
<tr>
<td>Ginseng lipid based systems</td>
<td>Flavonoids</td>
<td>Increases absorption</td>
<td>Nutra-ceutical immune-modulator</td>
<td>Phospholipid complexation</td>
<td>150 mg</td>
<td>Oral</td>
<td>95</td>
</tr>
<tr>
<td>Greentea lipid based systems</td>
<td>Ginsenoside</td>
<td>Increases absorption</td>
<td>Nutra-ceutical, systemic antioxidant and anticancer</td>
<td>Phospholipid complexation</td>
<td>50–100 mg</td>
<td>Oral</td>
<td>95</td>
</tr>
<tr>
<td>Grapeseed lipid based systems</td>
<td>Epigallocatechin</td>
<td>Increases absorption</td>
<td>Systemic antioxidant</td>
<td>Phospholipid complexation</td>
<td>50–100 mg</td>
<td>Oral</td>
<td>95</td>
</tr>
<tr>
<td>Hawthorn lipid based systems</td>
<td>Procynidins</td>
<td>The blood TRAPn significantly elevated</td>
<td>Cardio-protective and anti-hypertensive</td>
<td>Phospholipid complexation</td>
<td>100 mg</td>
<td>Oral</td>
<td>96</td>
</tr>
<tr>
<td>Quercetin lipid based systems</td>
<td>Flavonoids</td>
<td>Exerted better therapeutic efficacy</td>
<td>Anti-oxidant and anticancer</td>
<td>Quercetin Phospholipid complexation</td>
<td></td>
<td>Oral</td>
<td>97</td>
</tr>
<tr>
<td>Curcumin lipid based systems</td>
<td>Curcumin</td>
<td>Increases antioxidant activity and increases bioavailability</td>
<td>Antioxidant and anticancer</td>
<td>Curcumin Phospholipid complexation</td>
<td>360 mg/kg</td>
<td>Oral</td>
<td>98</td>
</tr>
</tbody>
</table>

Source: Kesarwani & Gupta, 2013
Examples—How to increase blood levels

- Phytosomes, liposomes
- Black pepper extract (piperine)
- Liver metabolism modulators
- Micro-, nanoencapsulation
  - Ginkgo
  - Curcumin
  - Milk thistle
  - Green tea (ECGC)
Phytosome vs. Liposome
Pharmacokinetics of Gingko-Phytosome

- Ginkgolide A, Ginkgolide B and Bilobalide
- 12 healthy volunteers
- Oral, 60 mg standardized
- Taking with meals increases Tmax, but not AUC quantitatively (Fourtillan et al., 1995)
- Elimination half-lives vary in the 3 compounds (4.5, 10.57, 3.21 h)

Pharmacokinetics
Green tea EGCG and Milk Thistle, Phytosomes

Time course of epigallocatechin gallate (EGCG) after ingestion of Greenselect® and Greenselect® Phytosome® (Pietta et al., 1998)

Healthy volunteers

Patients with cirrhosis

Schreiber et al., 2008.
Curcumin from Turmeric

- Curcumin is very poorly absorbed orally, and the liver metabolizes what is absorbed rapidly to a more inactive form.
- Products aim to increase absorption and slow liver metabolism:
  - Phospholipid complexes
  - Microencapsulation, nanoencapsulation
  - Complex with black pepper extract (piperidine)
Curcumin blood levels with nanoemulsion

![Curcumin concentration in blood (ng/mL) vs. Time (h)](chart1)

- 50-nm curcumin emulsion
- 100-nm curcumin emulsion
- 200-nm curcumin emulsion
- Curcumin suspension

![Plasma Curcumin Concentration (ng/mL) vs. Time (h)](chart2)

- Curcumin aqueous suspension
- Curcumin-loaded PLGA nanoparticles
- Curcumin-loaded PLGA-PEG nanoparticles
Curcumin and Bioperine

Curcumin blood concentration (in humans with oral administration)

Anand et al., 2007
Chitosan coated curcumin nanocrystals for the treatment of sepsis

- chitosan coated curcumin nanocrystals (Chi-CUR-NC-4b)
- parenteral therapeutic approach against endotoxemia-induced sepsis
- curcumin-bearing nano-formulation could serve as a valuable option for the therapeutic intervention of sepsis and associated hyper-inflammatory disorders.

(Shukla et al., 2015)
Solubility of curcumin powder vs. nanocrystals

- Free curcumin (a)
- Curcumin nanoparticles (b)

Ravichandran, 2013
Traditional delivery systems

• Traditional way to use turmeric and enhance absorption
• Curry!
• Stir-fry veggies, meat, and spices
• Heat, bio-enhancers (pepper, ginger), oil

Jim Duke:
“I’d rather enjoy my medicine!”
Blood levels of 4 related compounds from TCM Formula

- Lonicera japonica
- Isatis indigotica
- Rheum palmatum
- Phellodendron chinense
- Scutellaria baicalensis

Significant pharmacokinetic differences were observed between the African and Chinese subjects. The \( AUC \)s of the African is about 4–10 fold higher than that of the Chinese for the three benzylisoquinoline alkaloids

Researchers argue that diet and microflora may be responsible

Aolga et al., 2015
Milk Thistle-Siliphos

- Kid et al., 2005