Pharmacokinetics
of Herbal Active Constituents

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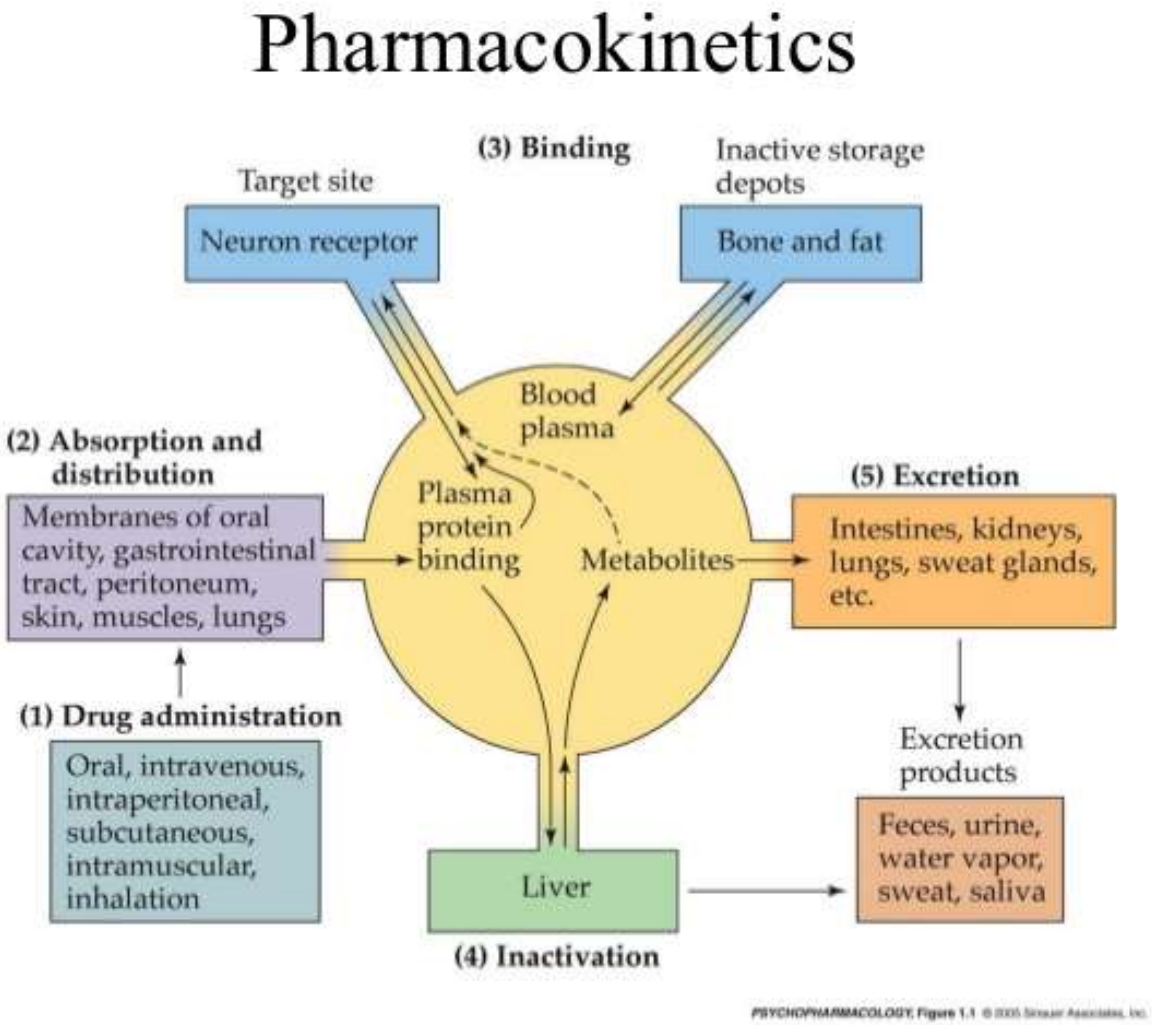
from Ancient Greek *pharmakon* "drug" and *kinetikos* "moving, putting in motion“ (Wikipedia)

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

Pharmacokinetics Overview

From: Psychophrmacology,
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."

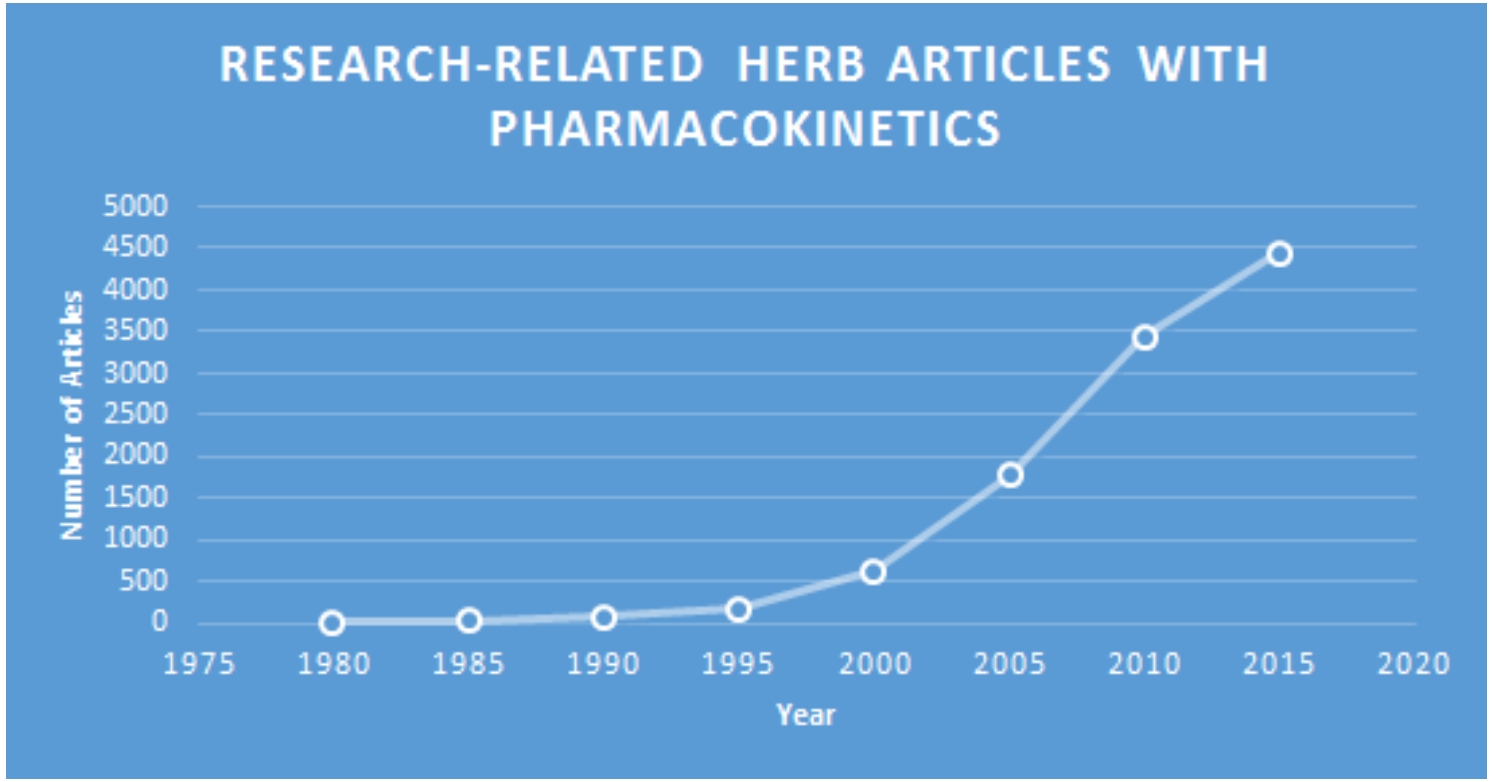
1. First, the active constituents need to be identified, characerized
2. First, the active constituents have to be absorbed
3. Second, the ingredients in supplements or herbs need to have active constituents
4. The product has to have enough of the ingredients that have constituents to do anything (pixie 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

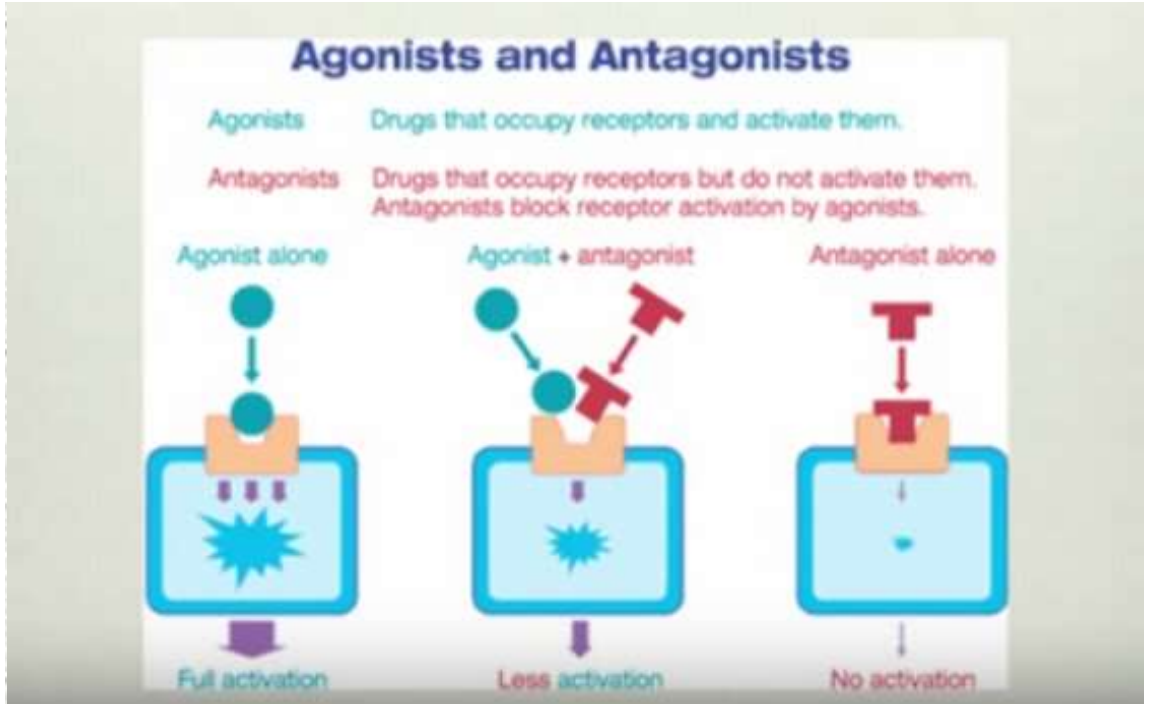
Scientific Basis—Herbal Research

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

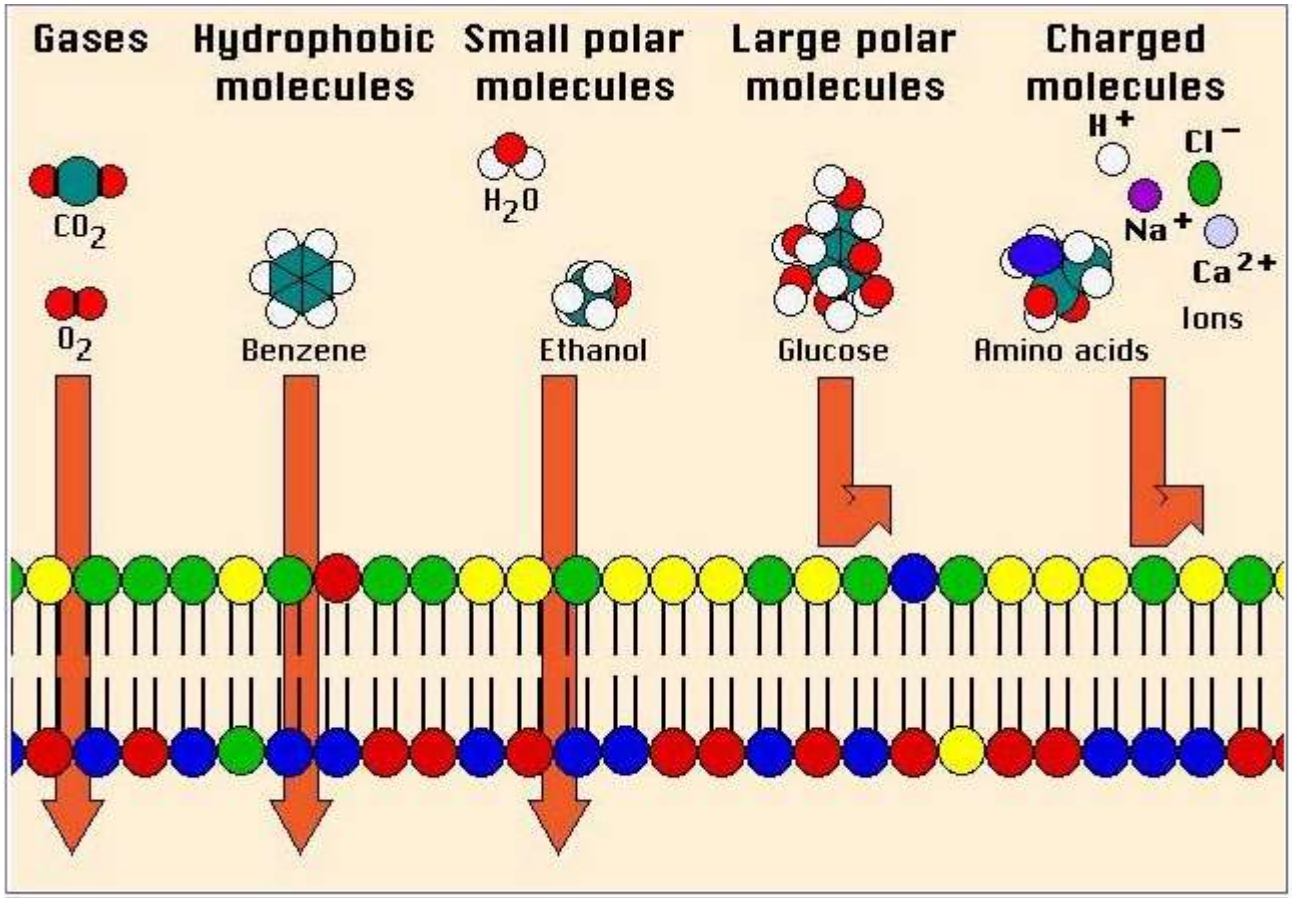
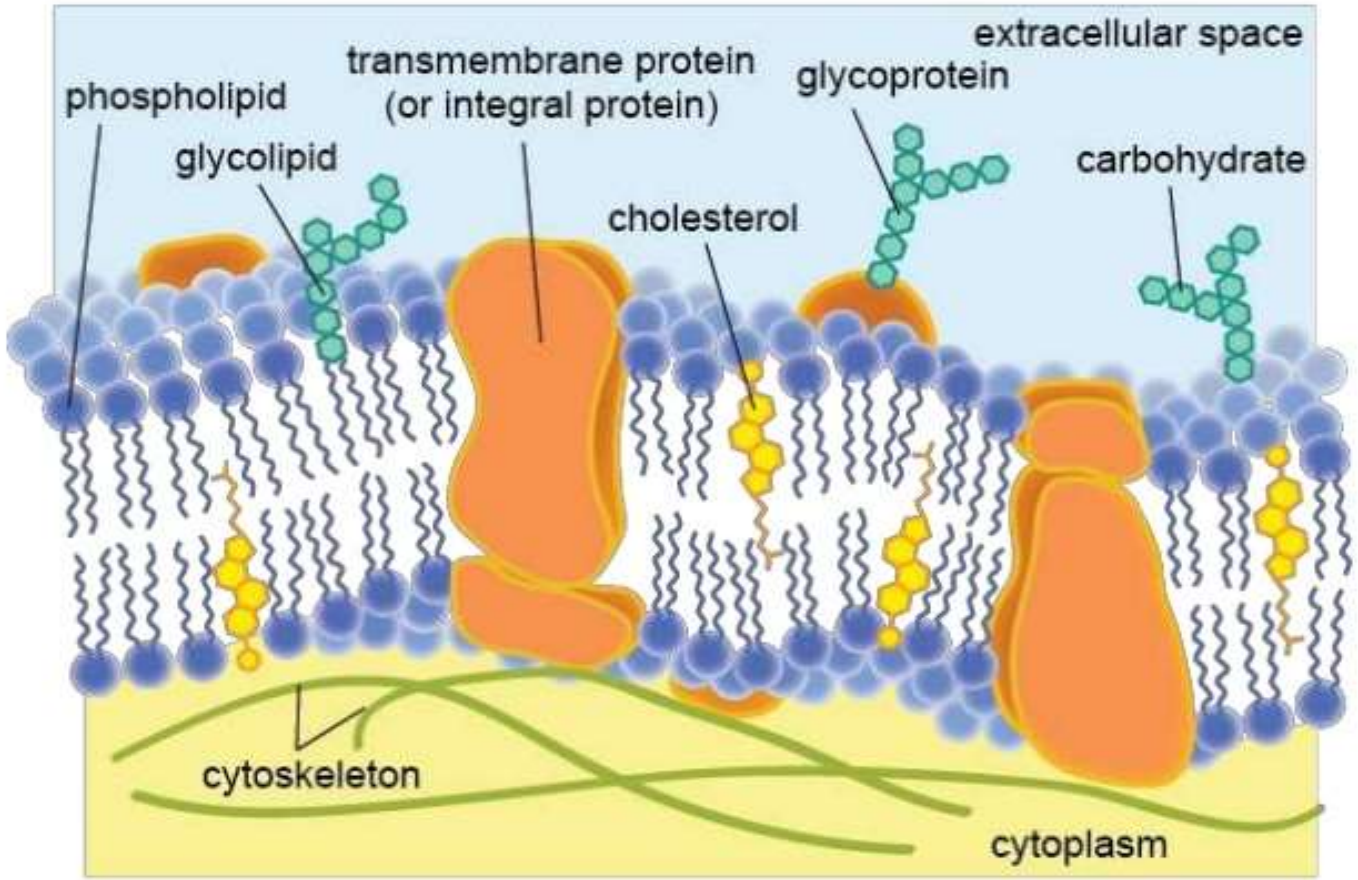


Figure Developed by Dr. Steve Downing, University of Minnesota

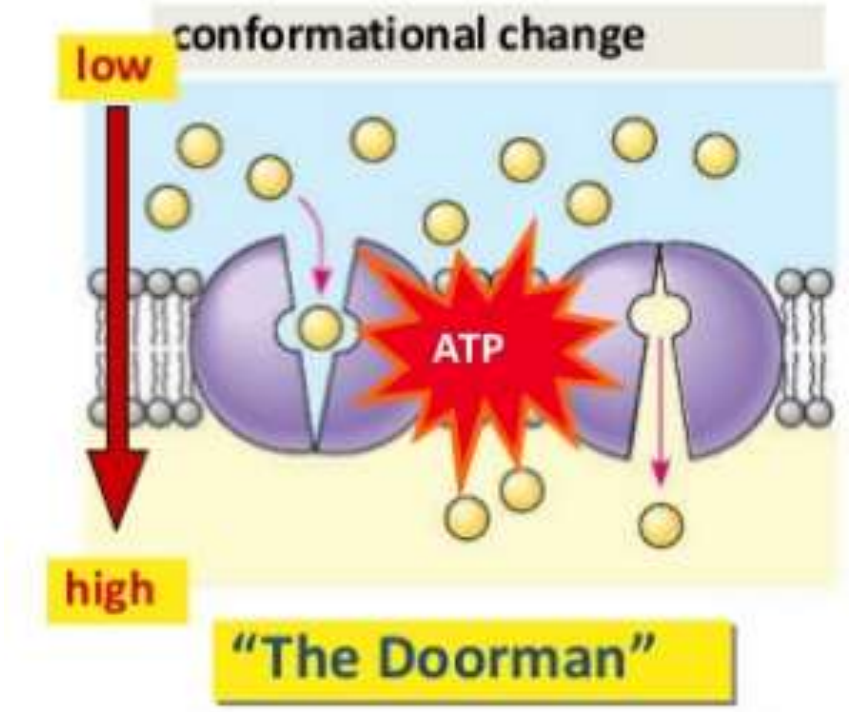
- Active transport
  - Requires the use of energy to move an active chemical
  - Carrier-mediated diffusion or or facilitated diffusion—i.e. a carrier protein
- Passive transport—diffusion osmosis

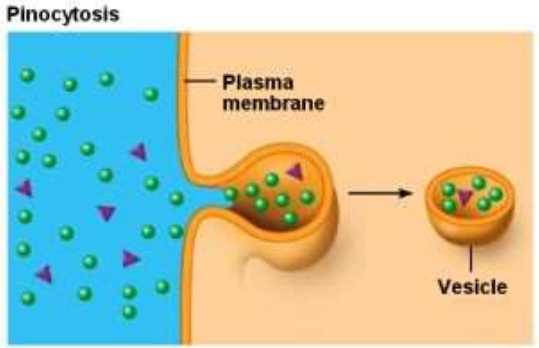
Source: YouTube standard license (ParaCarell)

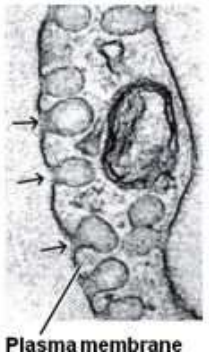


From: Munira *et al.*, 2015. Physiological Factors Affecting Drug Absorption. http://www.slideshare.net/sirazummunira/physiological-factors-of-drug-absorption-45020626

Active Transport



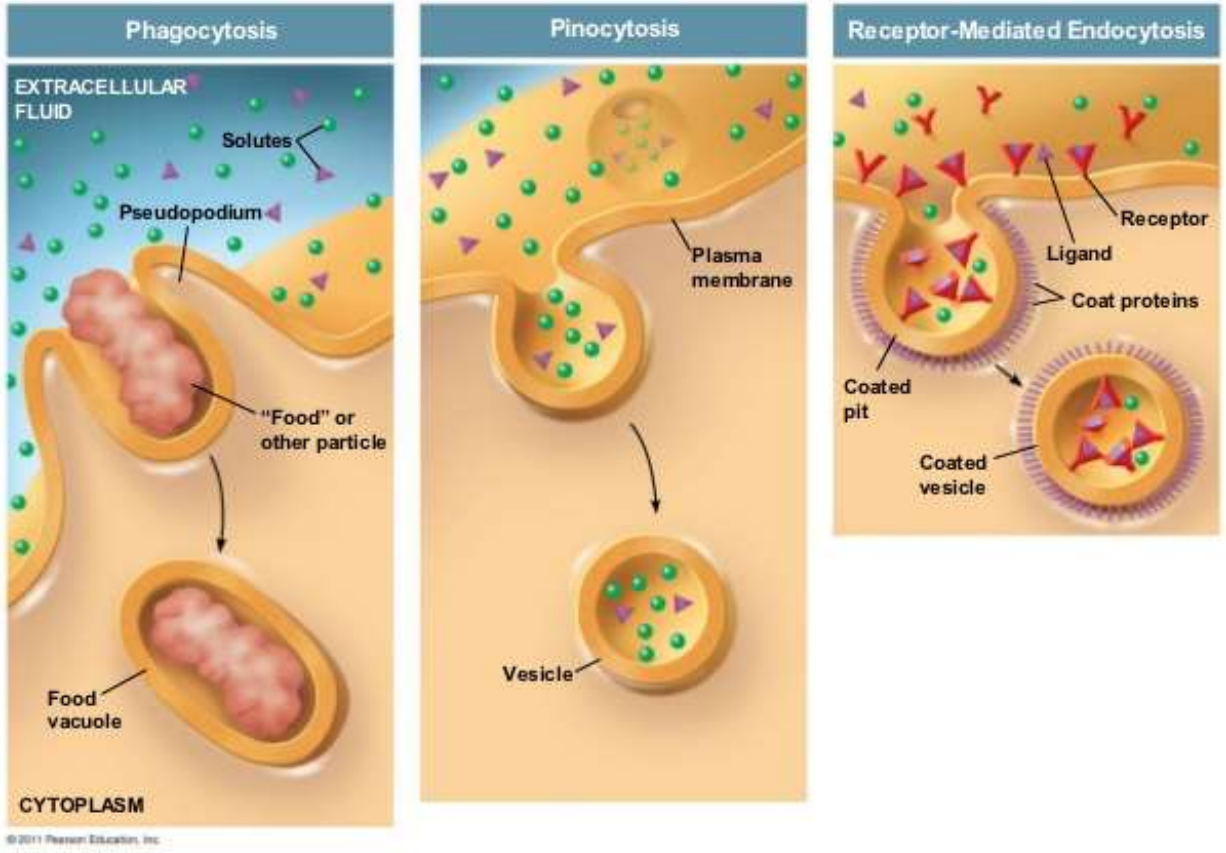




- Against the concentration gradient
- Energy (ATP) is required
- shape change transports solute from one side of membrane to other
- protein "pump" conformational change
- Active transport, other examples:
  - Pinocytosis
  - Endocytosis
  - Phagocytosis

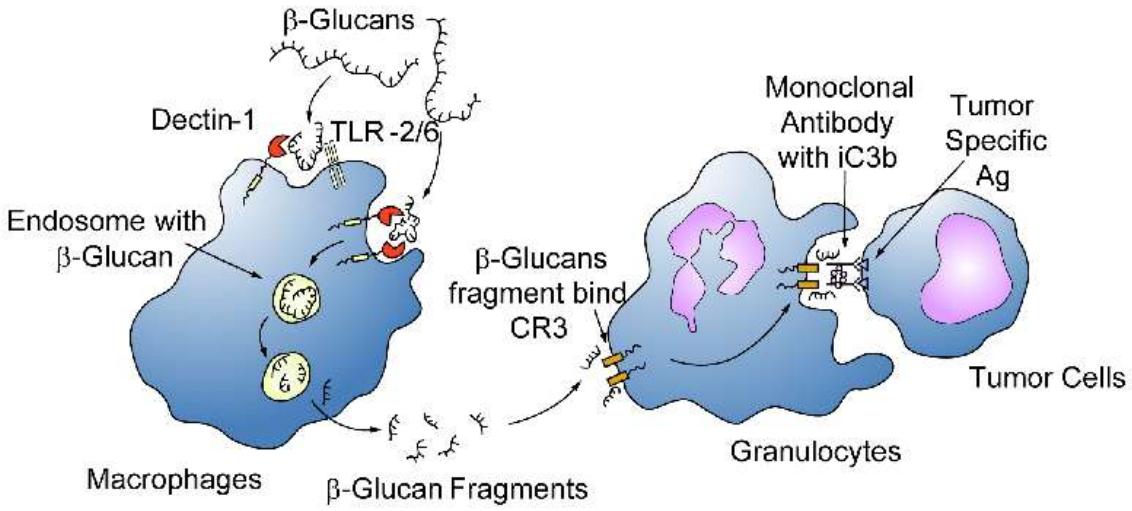
Phagocytosis, Pinocytosis, Endocytosis

Figure 7.22



From: Reece *et al.*, 2011. Campbell Biology
Membrane Structure and Function:
slideshare.net

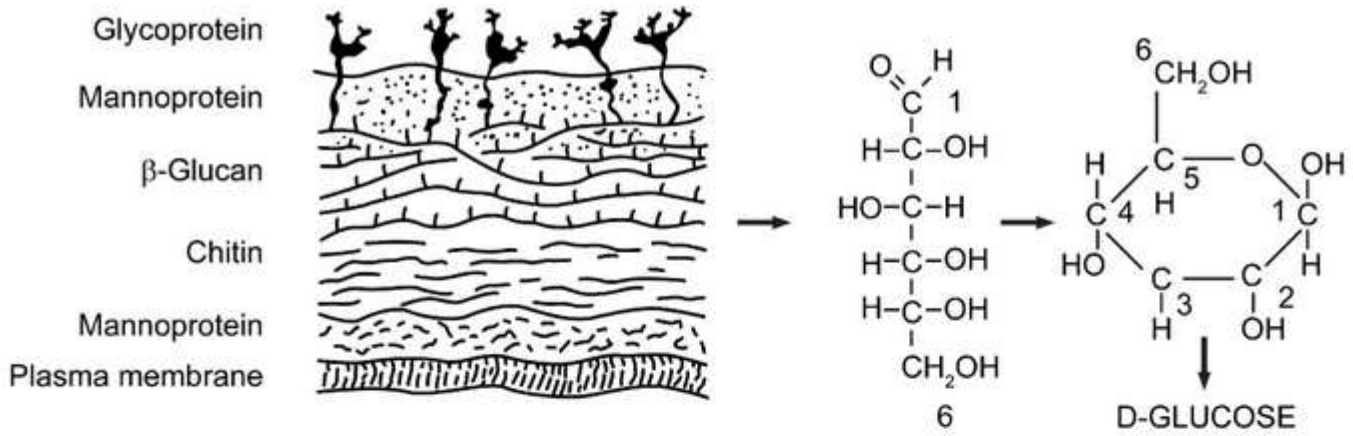
Example-Mushroom beta-glucans



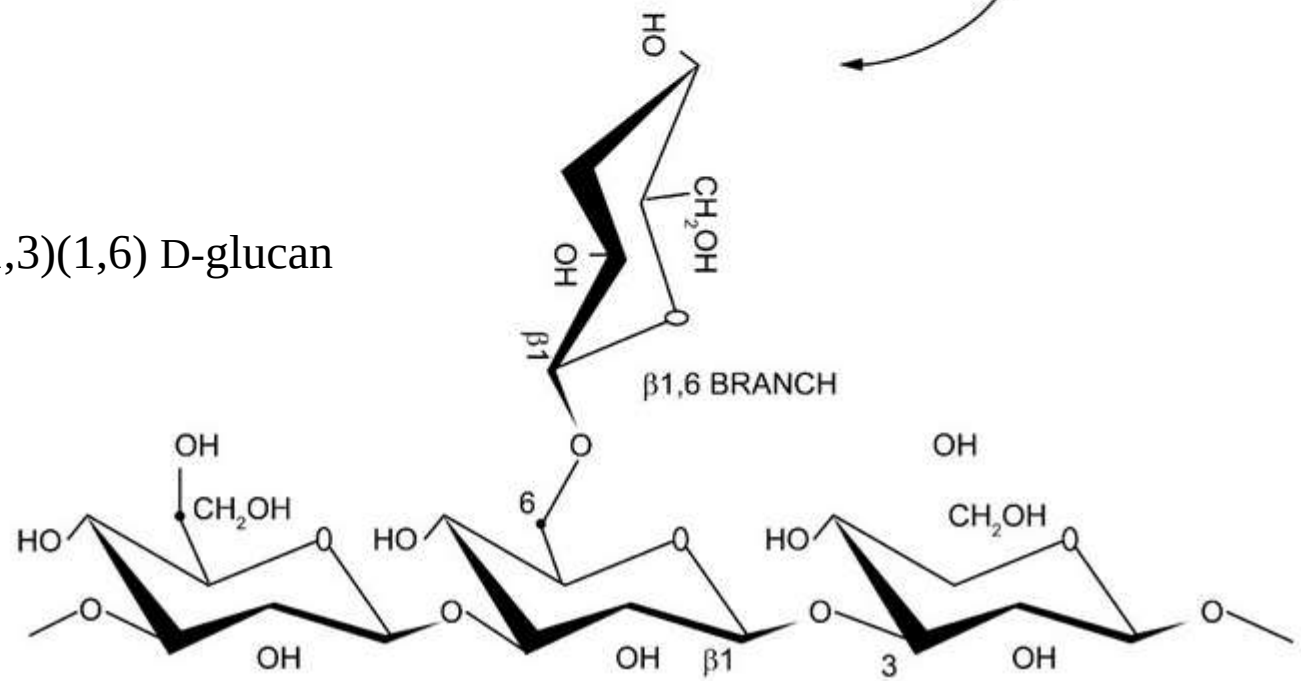
- β-glucans dock to immune receptors including Dectin-1, complement receptor (CR3) and TLR-2/6
  - Trigger a group of immune cells including macrophages, neutrophils, monocytes, natural killer cells and dendritic cells
  - Fungal beta-glucans are taken up by macrophages
  - Then digested to fragments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



(β(1,3)(1,6) D-glucan



Source: Chan *et al.*, 2009

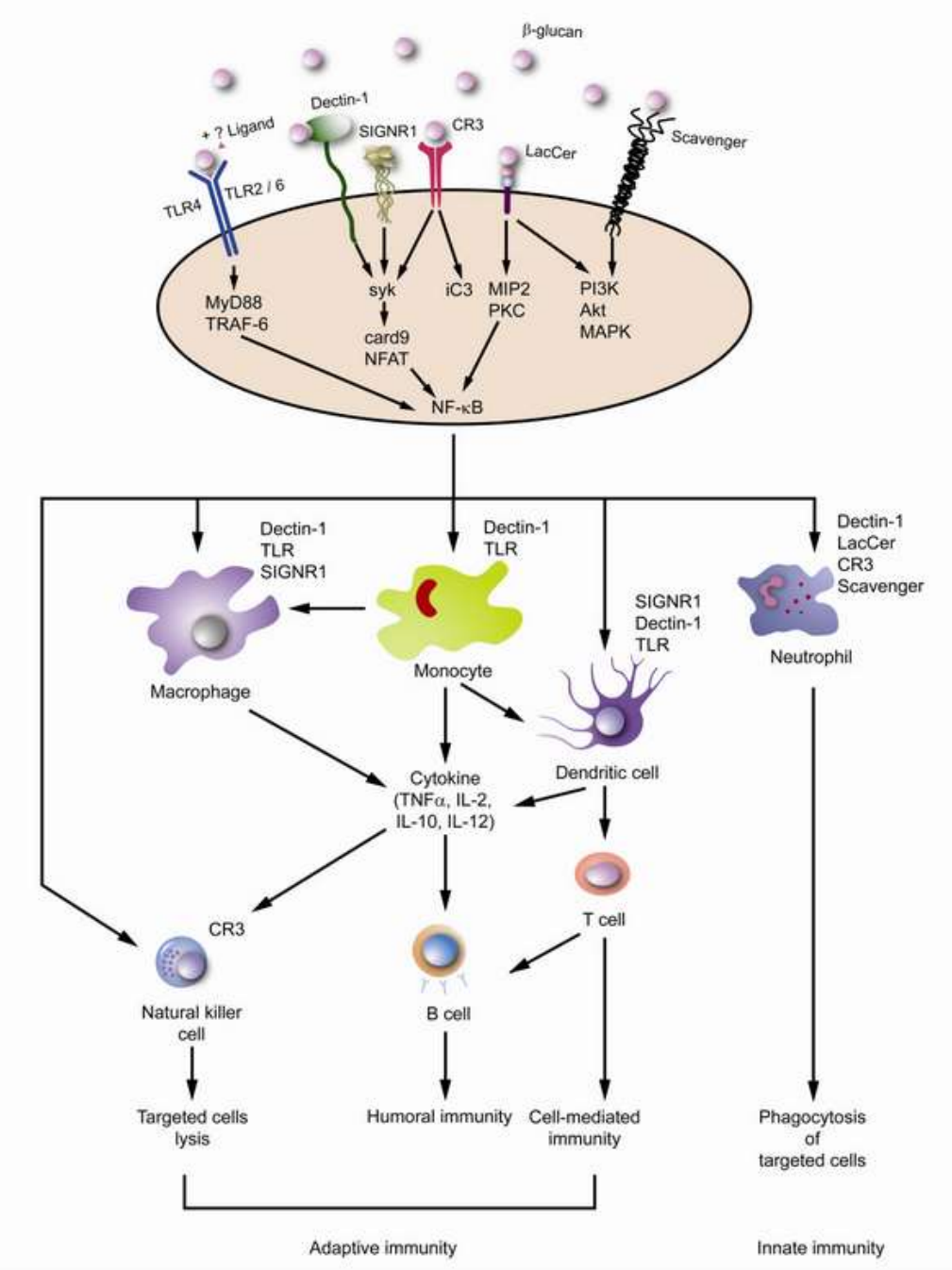


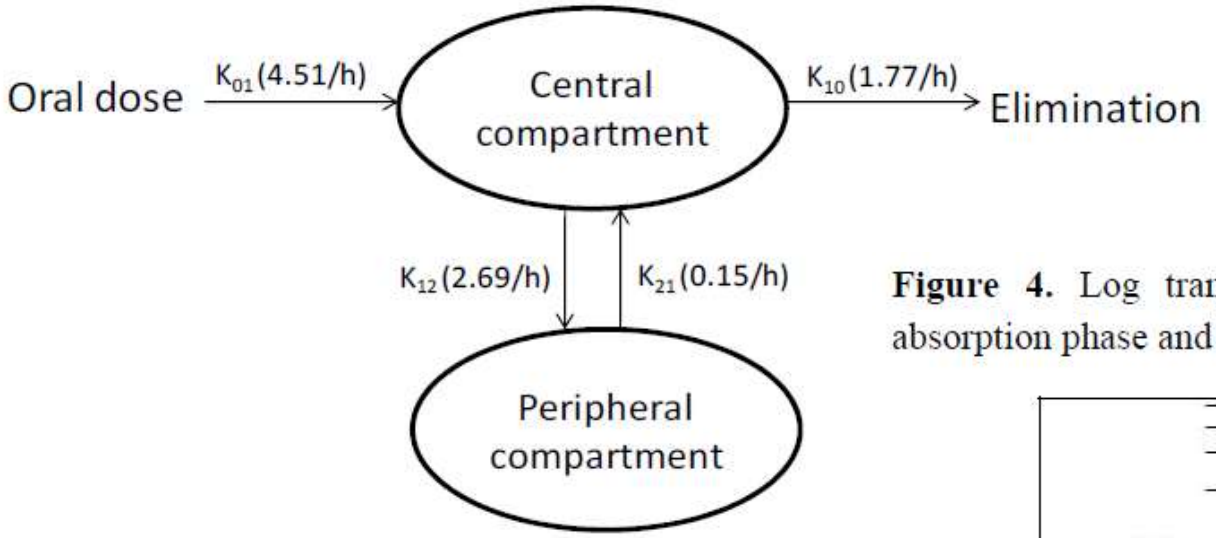
Figure 3 **Immune activation induced by β-glucans (From: Chan *et al*., 2009)**

- 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).

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

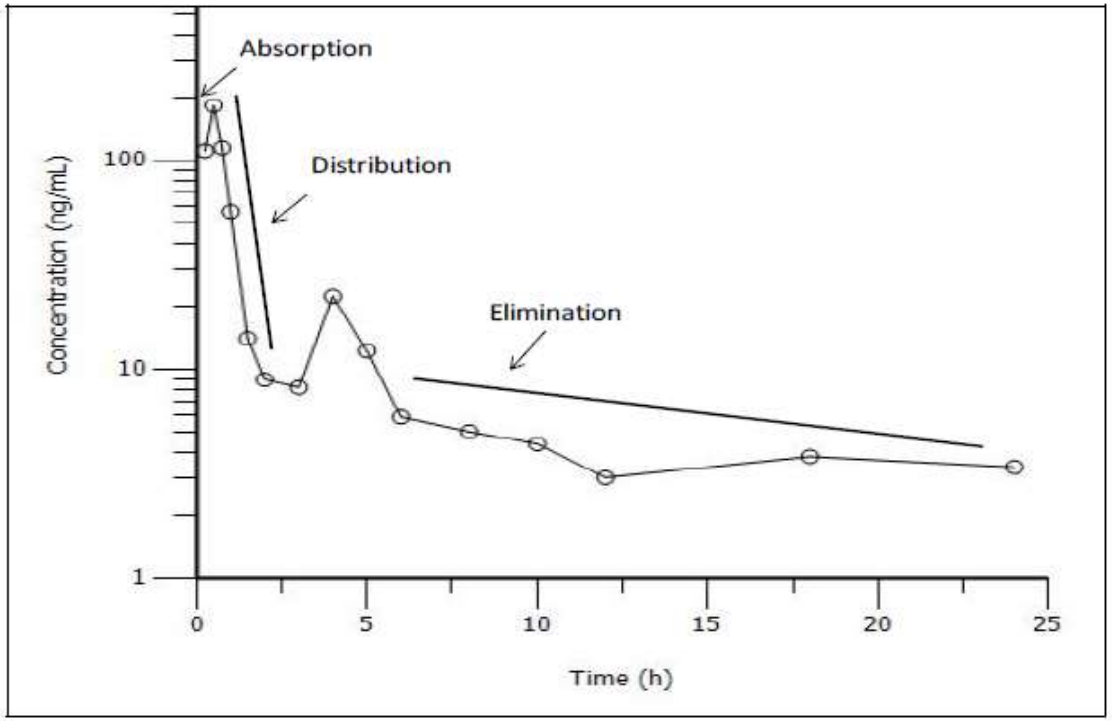
Figure 7. Pharmacokinetic model developed to describe the plasma concentration-time profile in human volunteers after oral dosing of CRM-LF.

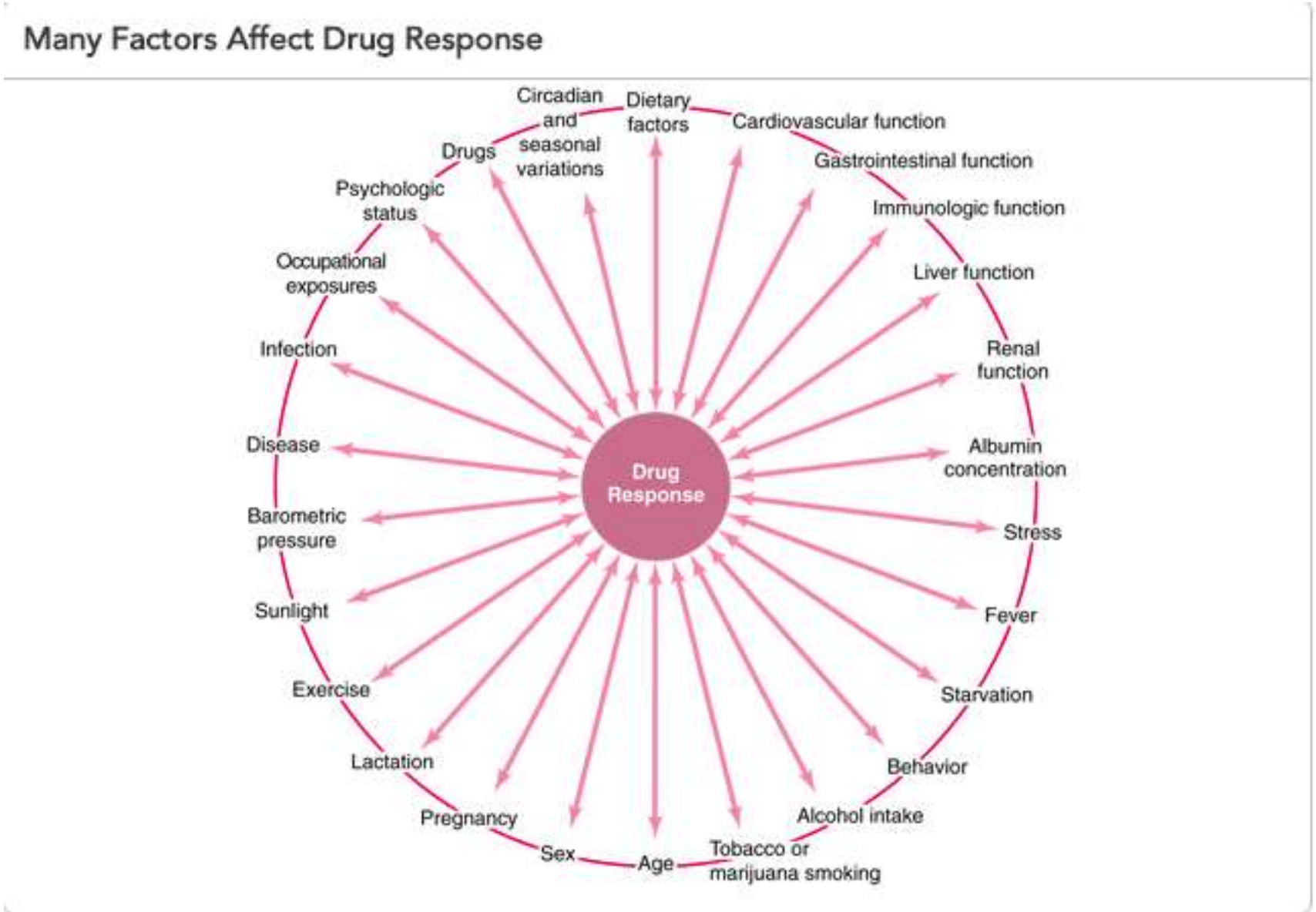


CRM-LF consists of:
CRM (6.17% *w*/*w*)—excipient
Gelucire® 44/14 (16.46% *w*/*w*)—excipient
Labrasol (5.76% *w*/*w*)—emulsifier
Vitamin E TPGS (3.29% *w*/*w*)--antioxidant
PEG 400 (55.55% *w*/*w*)—solubility enhancer
Ethanol (8.23% *w*/*w*)—solvent
Anhydrous citric acid (2.88% *w*/*w*)preservative
HPMC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

Pawar *et al.*, 2012

Figure 4. Log transformed plasma concentration profile of CRM-LF showing the absorption phase and rapid distribution phase followed by the slower elimination phase.

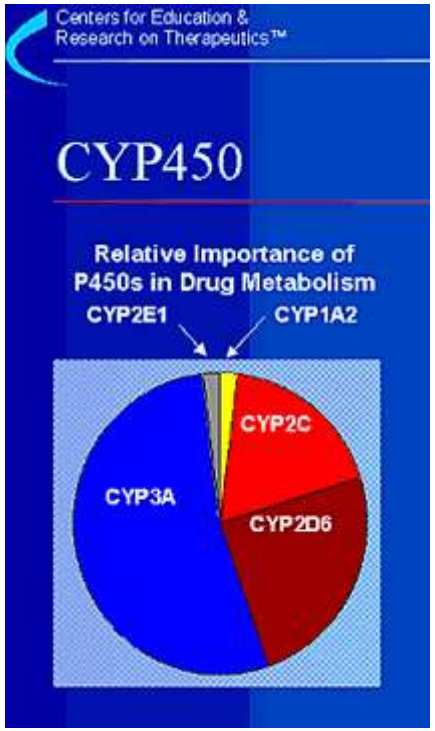




From: Hussar, Merck Manual, Consumer version

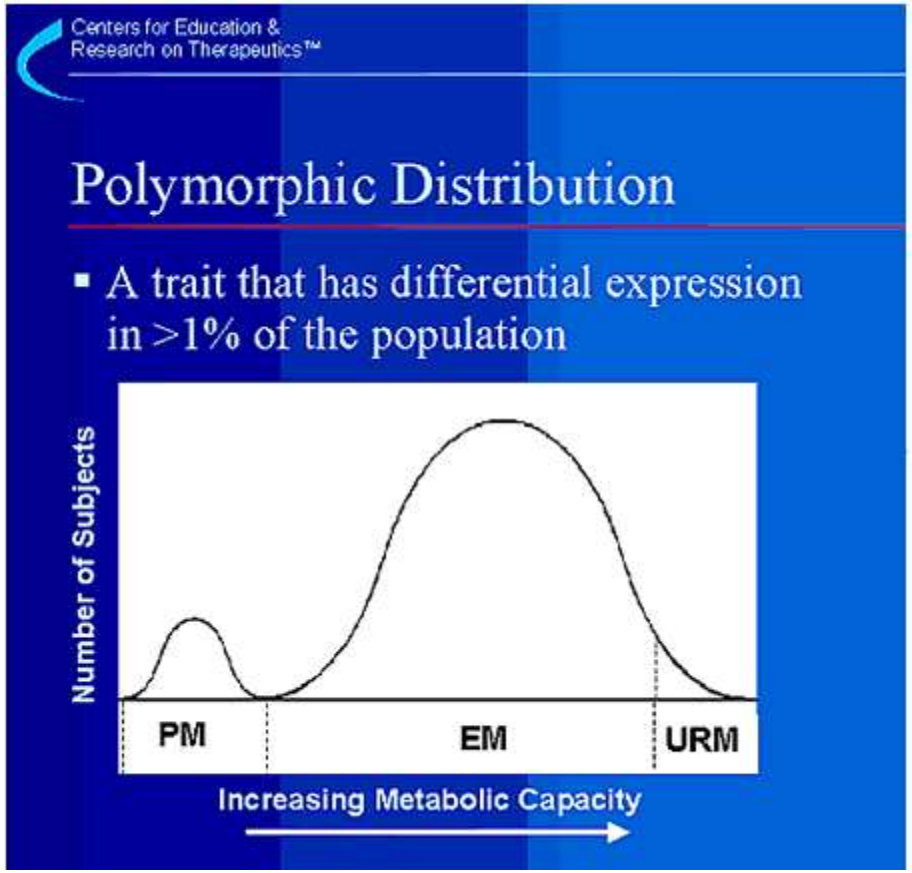
Liver Enzymes & Drug Metabolism

- 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



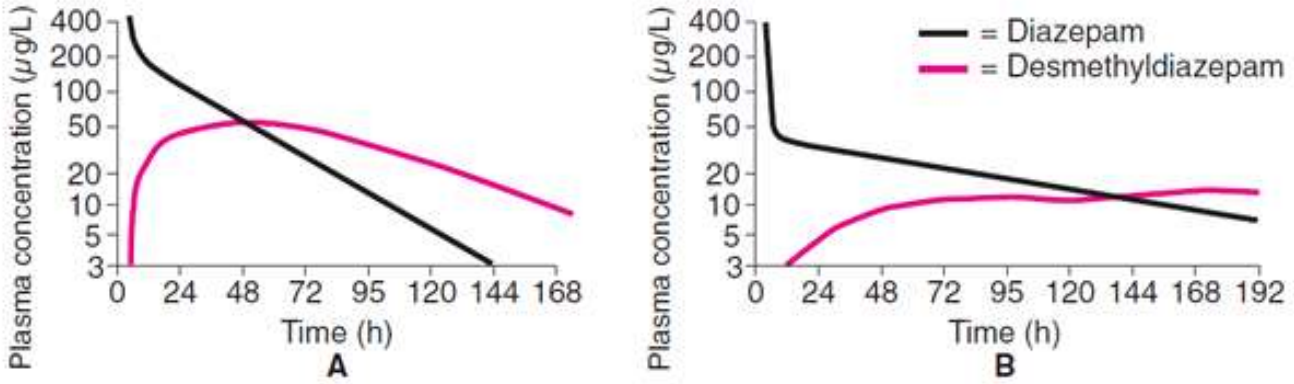
Active constituent metabolism—elderly

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

Le--Overview of Pharmacokinetics

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

Diazepam is metabolized in the liver to desmethyldiazepam 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, Shader RI: Diazepam disposition determinants. Clinical Pharmacology and Therapeutics 27:301–312, 1980.)



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 grape fruit 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*.

CYP	Herbal Remedies
CYP1A2	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
CYP2B6	Licorice, luteolin
CYP2C8	Devil's claw, fo-ti, ginkgo, usnic acid
CYP2C9	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
CYP2C19	Devil's claw, Echinacea, eucalyptus oil, evening primrose, fo-ti, garlic, ginko, ginseng, kava, milk thistle, St. John's wort, usnic acid, valerian
CYP2D6	Black cohosh, black pepper, *C. roseus*, devil's caw, dong quai, Echinacea, eucalyptus oil, evening primrose, fo-ti, genistein, ginger, ginseng, ginkgo, goldenseal, grapefruit juice, grapeseed extract, green tea, kava, luteolin, milk thistle, saw palmetto, St. John's wort, soy, yohimbine
CYP2E1	Echinacea, garlic, ginseng, kava, resveratrol, St. John's wort, watercress
CYP3A4	*A. dahurica*, β-carotene, black cohosh, black pepper, black mulberry, black raspberry, *C. aurantium*, cat's claw, chamomile, cranberry, dan shen, devil's claw, dong quai, Echinacea, eluthero, eucalyptus oil, evening primrose, feverfew, 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

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

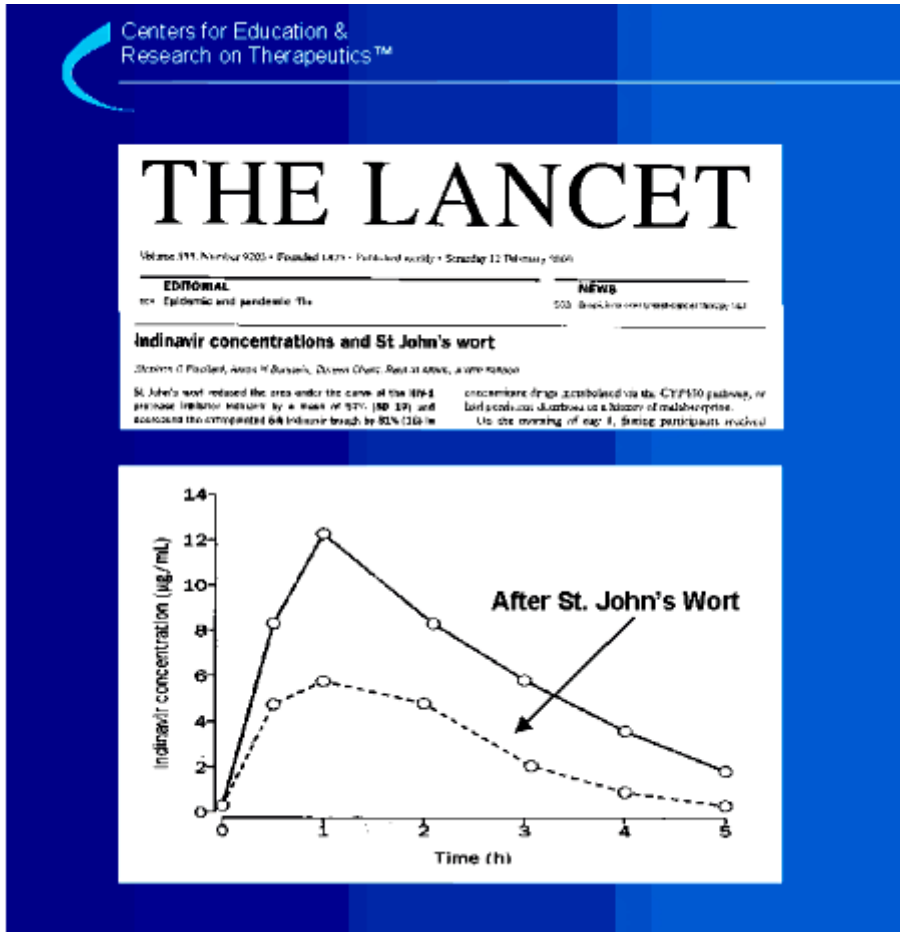
Herbs Affecting P450 Enzymes

Source: EBM Consult http://www.ebmconsult.com/content/pages/medications-herbs-cytochrome-p450-cyp-enzyme-inhibitors

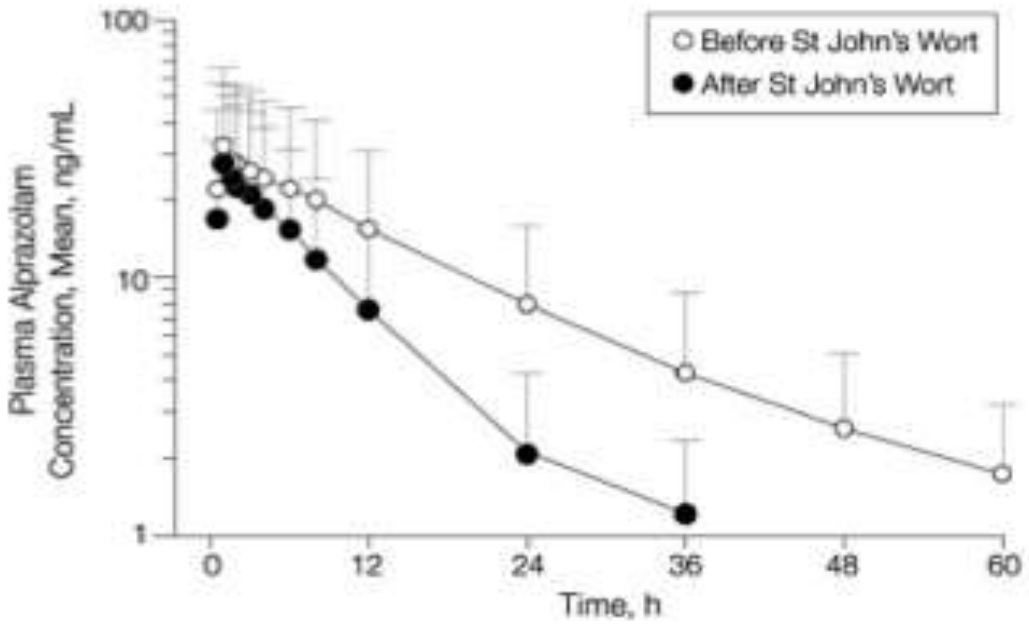
Herbals CYP1A2	Herbal CYP2B6	Herbals CYP2C8	Herbals CYP2C9	Herbals CYP2C19	Herbals CYP2D6	Herbals CYP2E1	Herbals CYP3A4
			Genetic Polymorphisms	Genetic Polymorphisms			
			Allium sativum *Bergamottin* *Harpagophytum Procumbens* *Lycium barbarum*	*Allium sativum* *Harpagophytum procumbens*	*Alpinia glanga* *Alstonia scholaris* *Andrographis paniculata* *Catharanthus roseus* *Cimicifuga racemosa* *Cinnamomum burmannii* *Eleutherococcus senticoccus* *Gycyrrhiza glabra* *Hydrastis canadensis* *Melaleuca leucadendron* *Panax ginseng* *Panax quinquefolius* *Piper nigrum* *Punica granatum* *Rheum palmatum* *Santalum album* *Strychnos ligustrina* *Syzygium aromaticum* *Tinospora crispa* *Zingiber aromaticum*	*Piper Methysticum*	*Allium sativum* *Ammi visnaga* *Azadirachta indica* *Cimicifuga racemosa* *Harpagphytum procumbens* *Hydrastis canadensis* *Naringenin compounds* *Panax ginseng* *Panax quinquefolius* *Strychnos ligustrina* *Uncaria tomentosa*

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



Effect of SJW on drug metabolism of Xanax (14-day administration (JAMA. 2003. 290:1500-1504.

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

Kava—Hepatotoxicity?

Table 5. IC_{50} values (μM) for kava compounds obtained using cryopreserved human hepatocytes.

Test Compound	CYP1A2	CYP2A6	CYP2C9	CYP2C19	CYP2D6	CYP2E1	CYP3A4
Methysticin	2.4	NI	5.5	4.8	NI	7.2	7.1
Desmethoxyyangonin	1.4	NI	NI	9.4	NI	NI	NI
Yangonin	12.1	NI	NI	58.9	NI	NI	NI
Kava Extract[a]	4.4	NI	18.4	3.8	NI	18.0	15.1
Positive Control	Fura-fylline	Tranyl-cypromine	Sulfa-phenazole	Omepera-zole	Quinidine	4-Methyl-pyrazole	Keto-conazole
% Inhibition	87	12	88	22	57	77	92
Concentration	2 μM	2 μM	20 μM	50 μM	5 μM	500 μM	2 μM

Values shown represent the mean of three determinations. NI indicates no inhibition at the highest concentration tested
[a] 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.

Source: Henderson *et al.*, 1999. Phytomedicine 11(4):285.

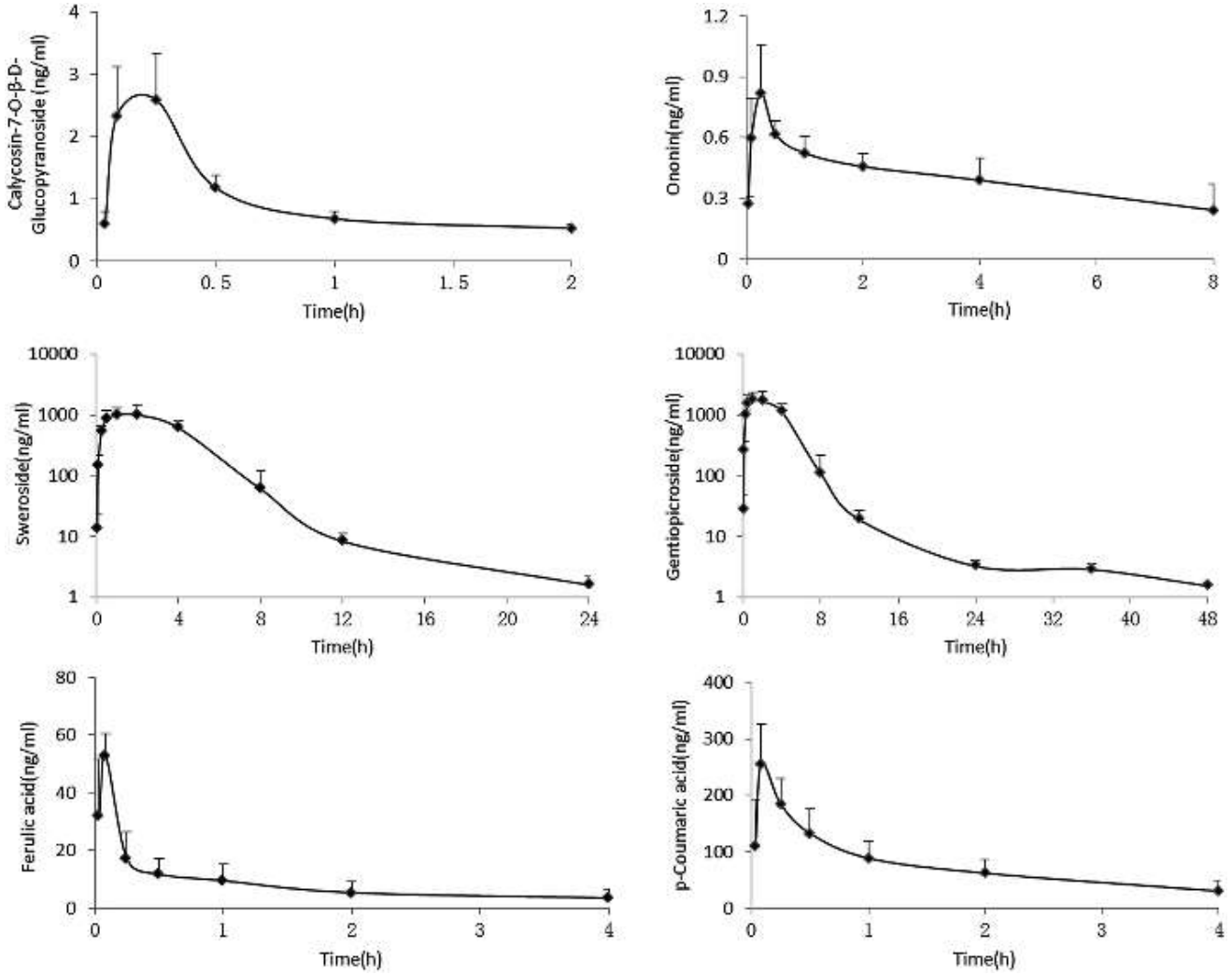
Traditional Herbal Formulas—Absorption

- 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 symtpoms
  - 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

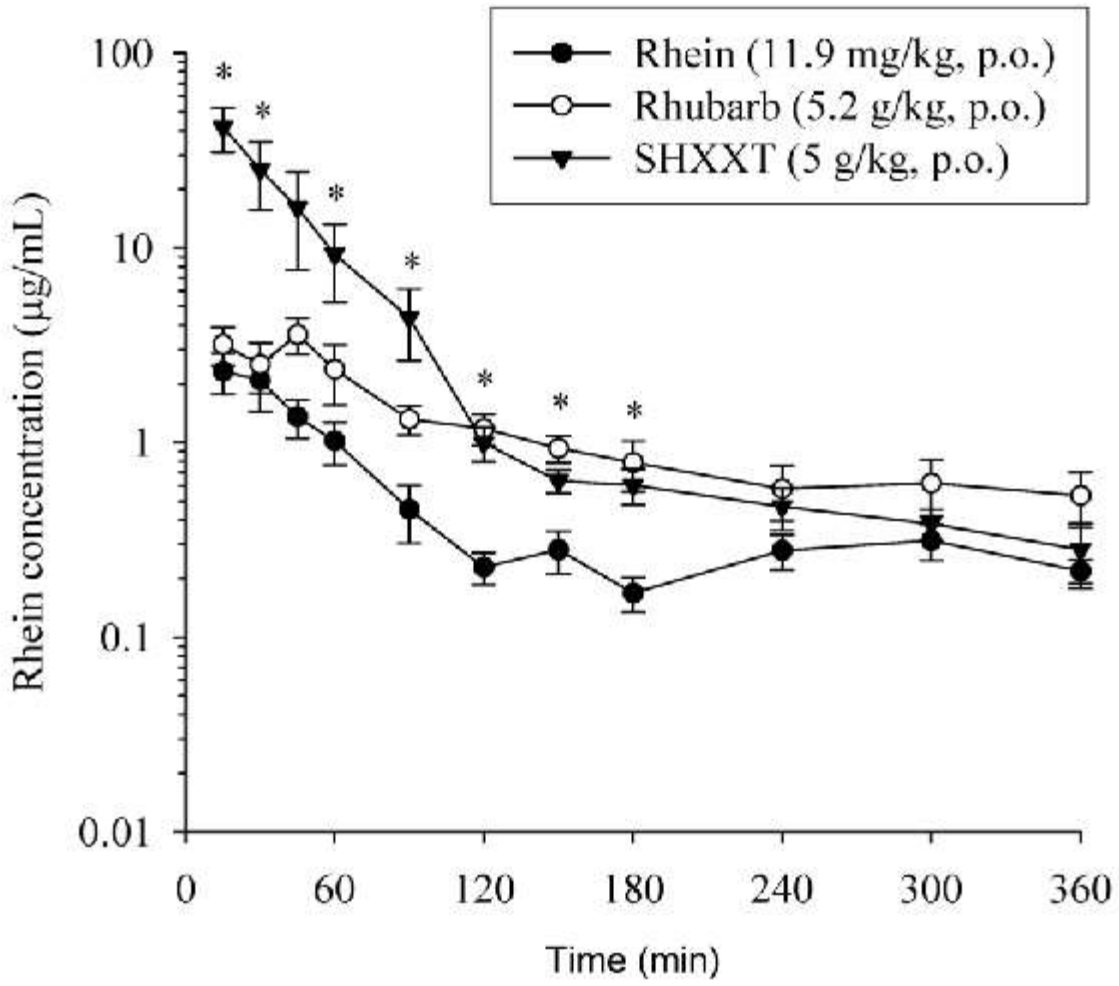
- Fu gan feng (contains active hepatoprotective compounds that are better absorbed within the context of the formula
- San huang xie xin tang (rhubarb and coptis tea pills)
  - Rhein, known active bowel-enhancer is better absorbed—in the rhubarb herb, but even more from the formula

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)
    - Immunomodudlator, antiinflammatory

Pharmacokinetics of Rhubarb Actives

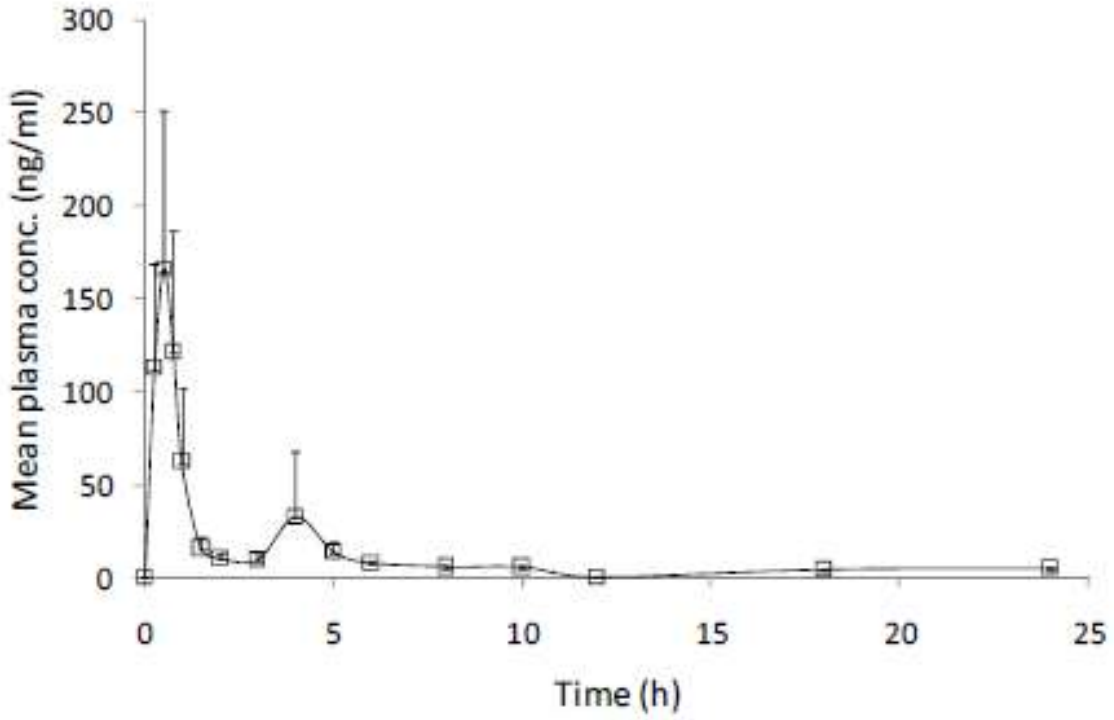


- Cofactors increase absorption of rhein
- San-Huang-Xie-Xin-Tang (SHXXT)
- Coptis and rhubarb tea pills
- Contains coptis stem, rhubarb root, scute Root (*Scutellaria baicalensis*)
- Chinese patent for treating constipation
- Conclusion: “the herbal formulae (SHXXT) are more efficient than the single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

- 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

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

Quality—a course in itself

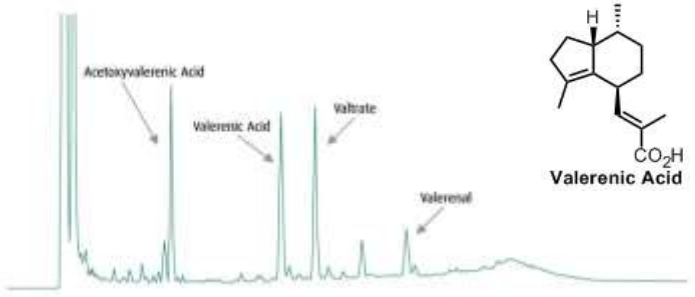
- GIGO (herb quality)
  - cultivated, “wild”
  - Parts collected (barks, roots)
  - How processed, dried, stored
- Fumigation, other chemicals
- Storage of herbs (years?)
- Extraction (solvents?)
- Standardization
- Manufacturing process
- Spiking, purity
  - Maltodextrin levels
- Micro

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



Valerenic Acid

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

Current Problems with Quality, Efficacy

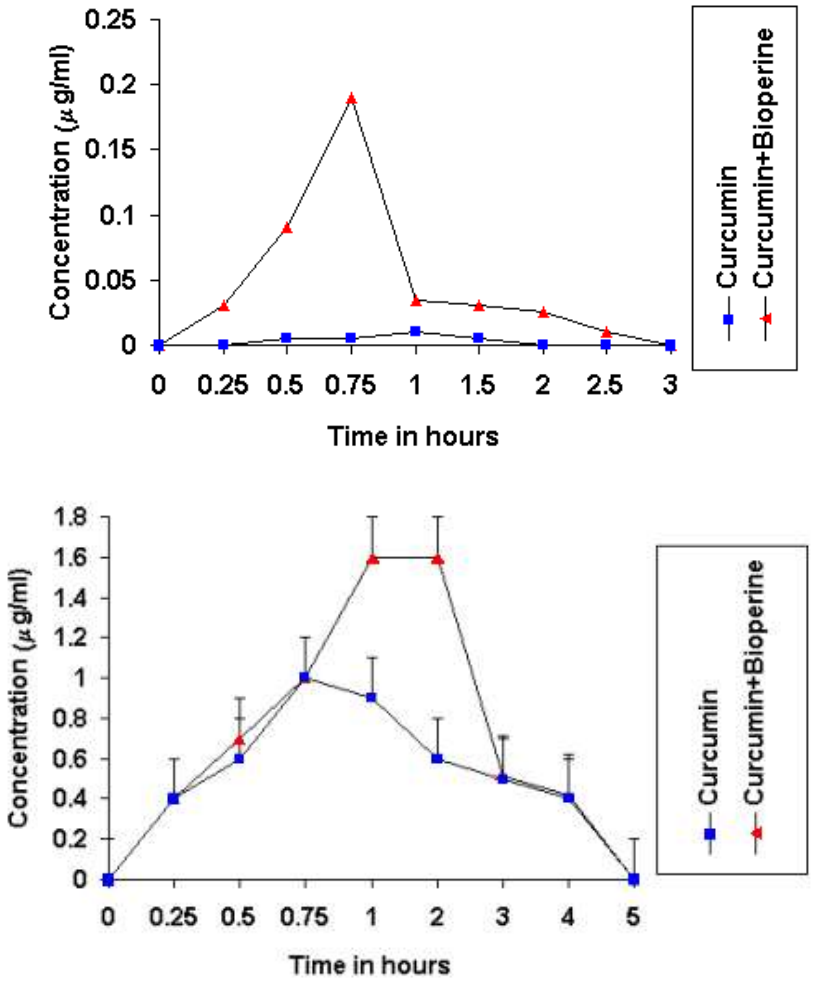
- Farm to medicine chest?
- Dose—not enough actives
  - Tinctures (1:5), dry-weight basis
- Powdered extracts
  - 5:1, but often cut with maltodextrin
- Identification
  - Species ID
    - DNA vs. chromatography
    - Microscopic, organoleptic

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, typicaly single herbs
- Western herbs
  - Dose and dosage varies widely

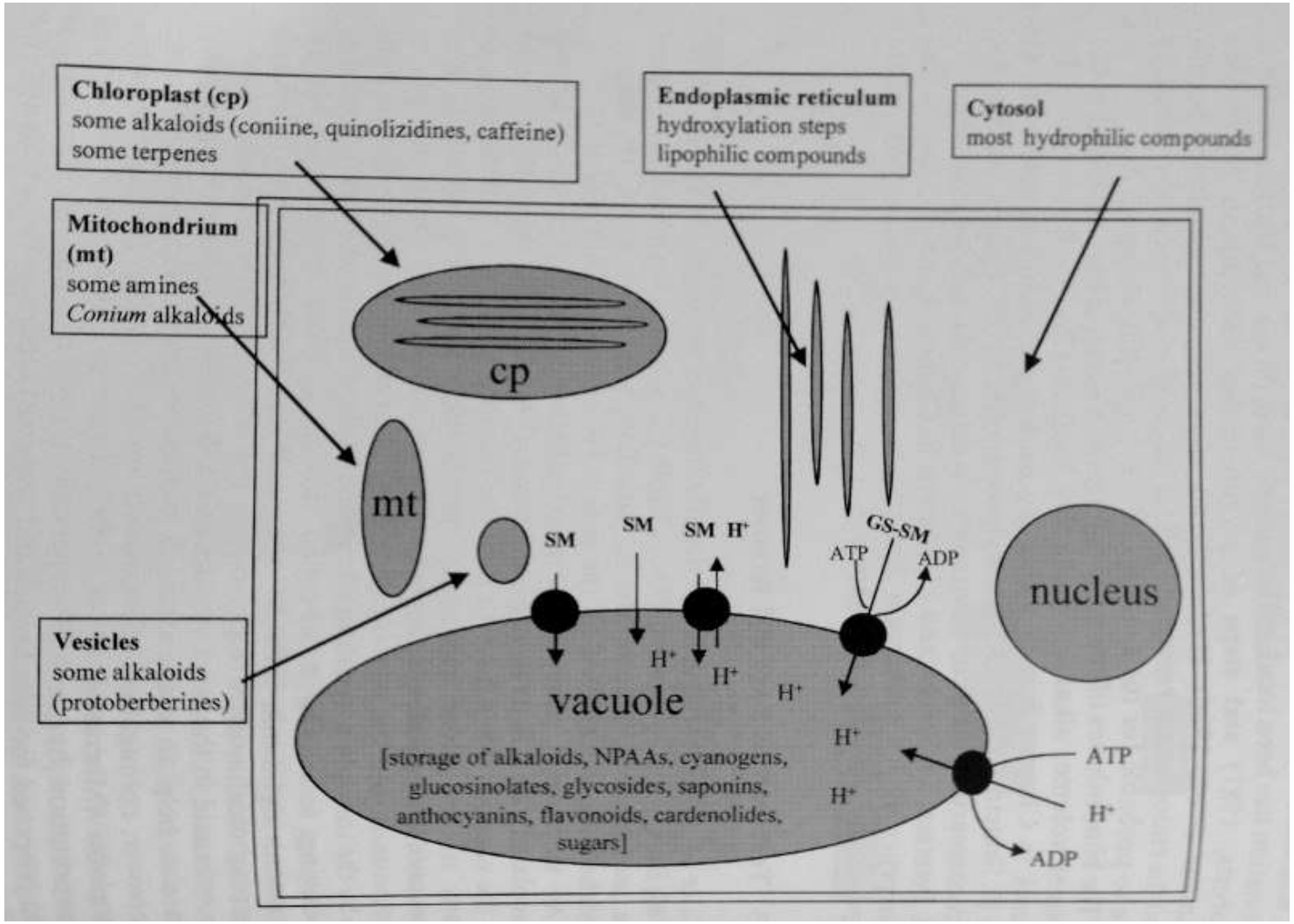
Dose and Dosage Regimen



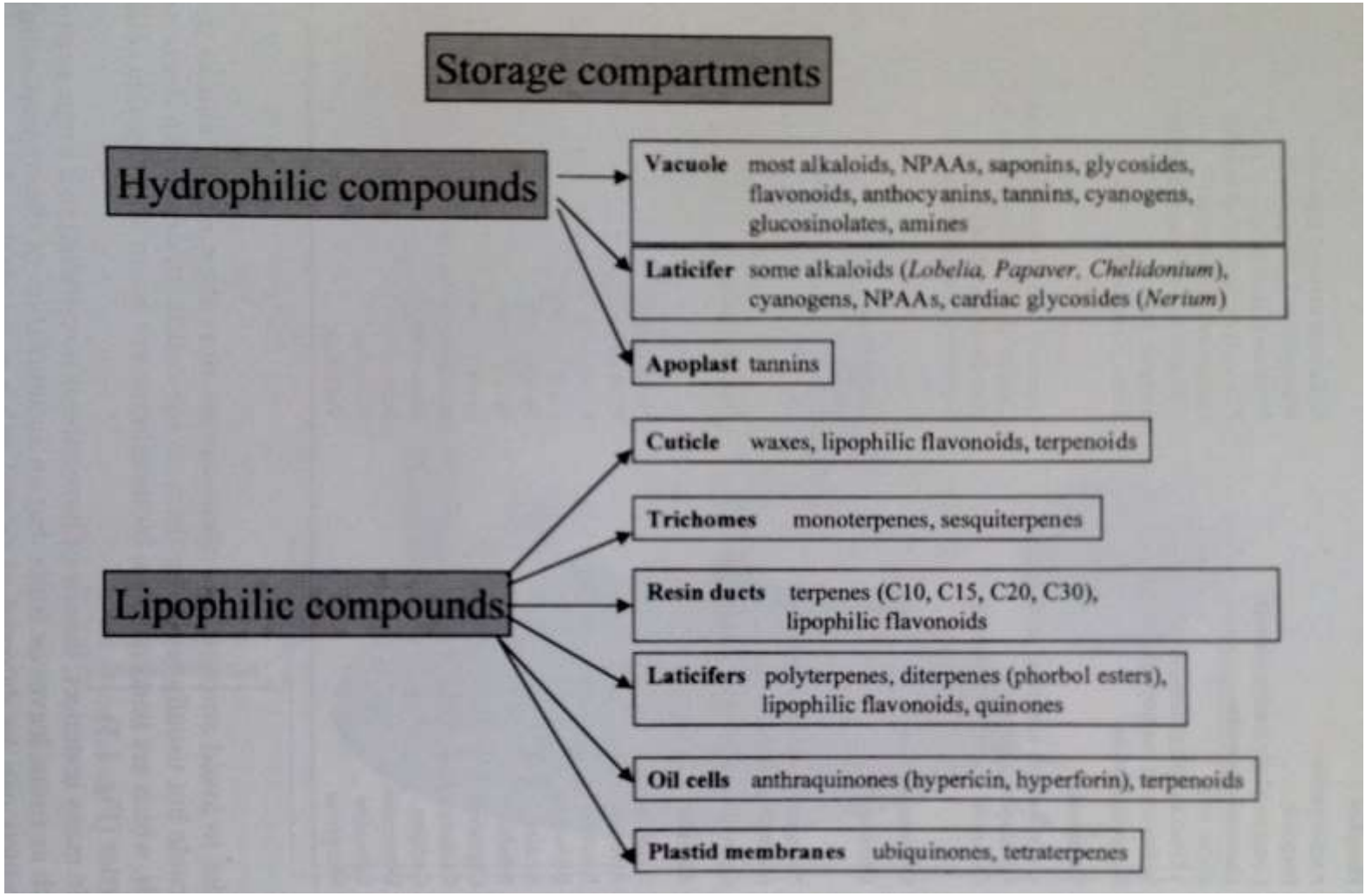
Anand *et al.*, 2007

- 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

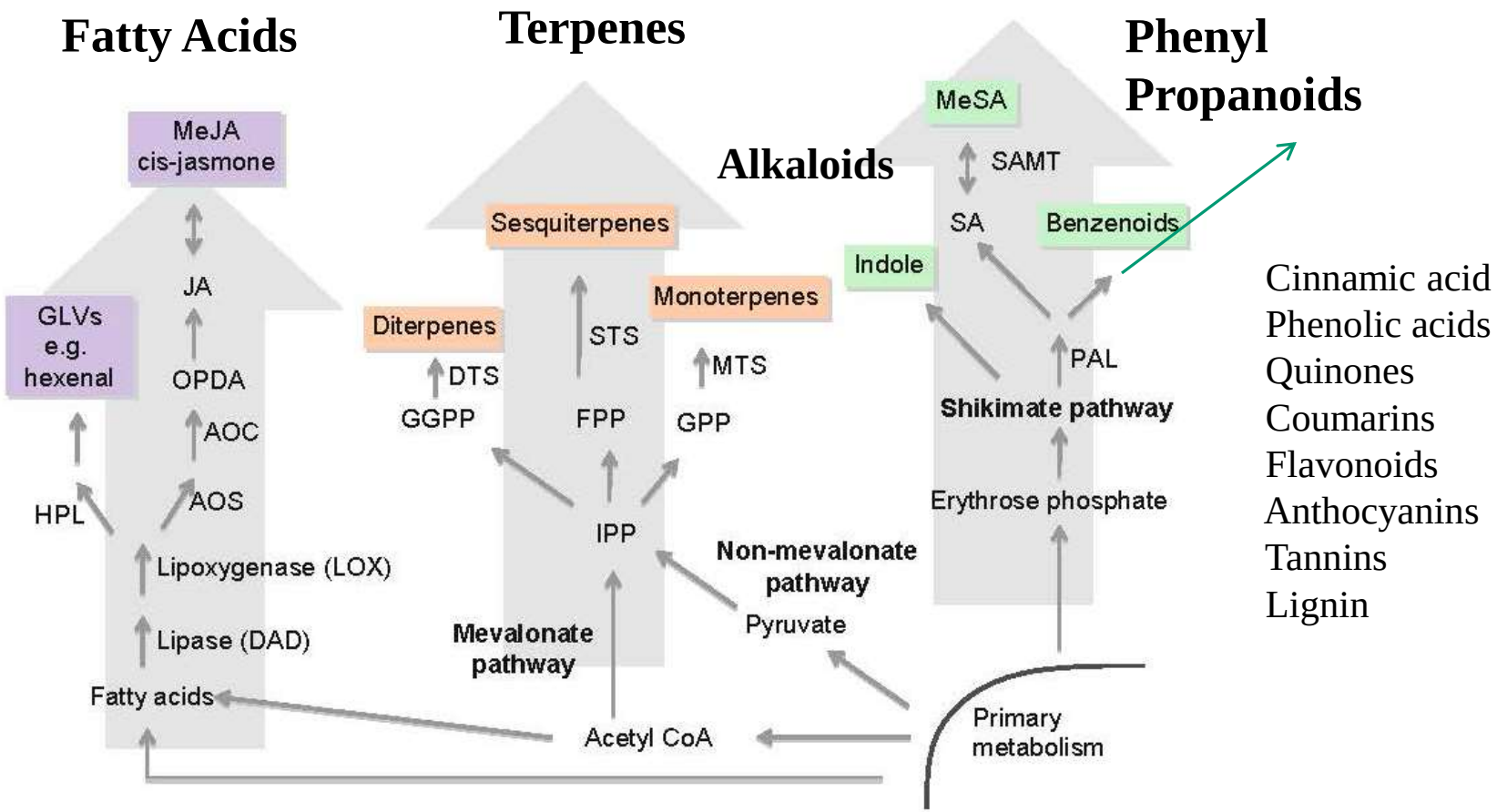
Storage of chemicals in Cell



Cell Compartments

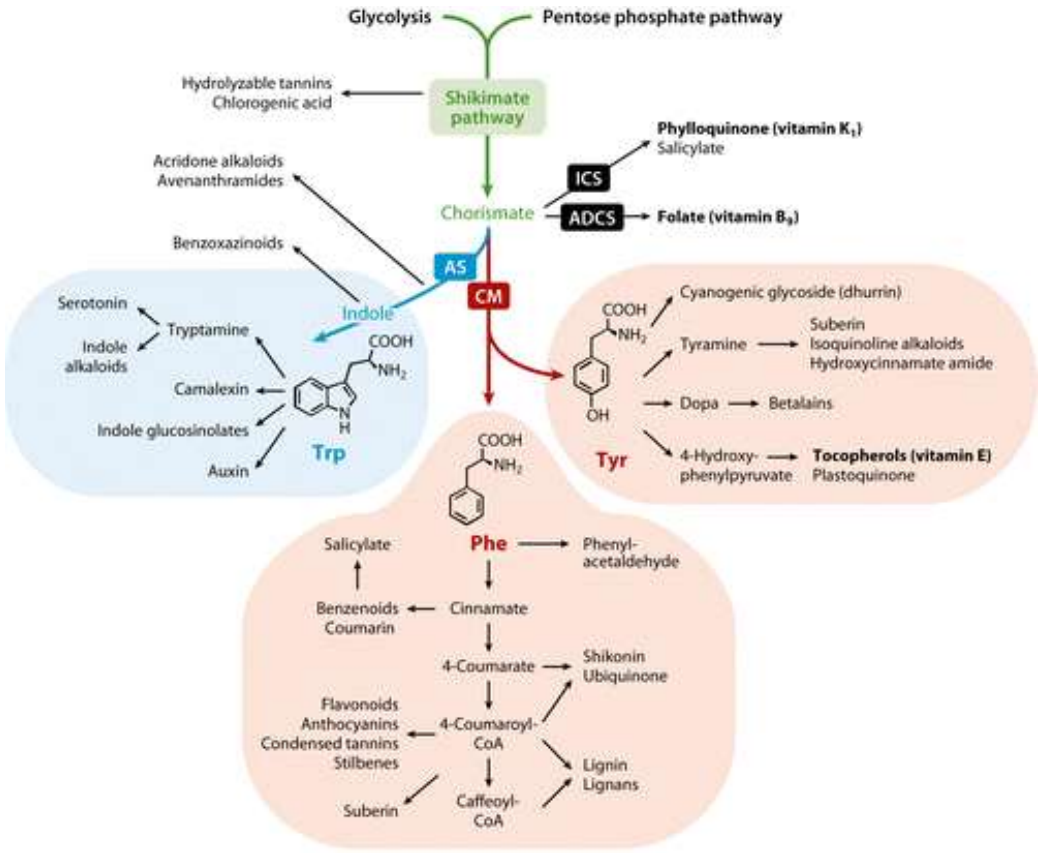


Four Major Chemical Pathways



Cinnamic acid
Phenolic acids
Quinones
Coumarins
Flavonoids
Anthocyanins
Tannins
Lignin

Shikimic Acid Pathway—Phenolics, Alkaloids



Maeda H, Dudareva N. 2012.
Annu. Rev. Plant Biol. 63:73–105

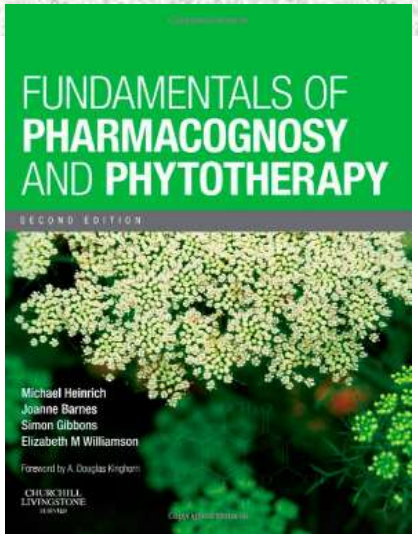
Salicylates
Serotonin, auxin
Alkaloids
betalains
Tocopherols
Cinnamates
Coumarins
Flavonoids
Anthocyanins
Tannins

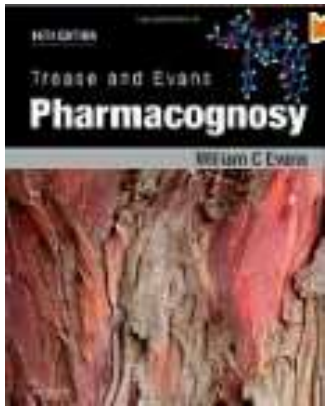
Terpenes, Mevalonic Pathway
Essential Oils

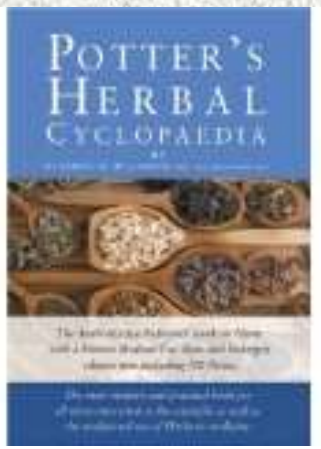
- Complex mixtures of monoterpenes (middle notes, moderately volatile), esters (high notes, very volatile), sesquiterpenes (low notes, not too volatile
- Some essential oils contain several hundred identified compounds
- Families commonly containing essential oils include the parsley family (Apiaceae), 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:
  - Bruneton J. Pharmacognosy, Phytochemistry, Medicinal Plants. 2nd ed. Paris, France: Technique & Documentation-Lavoisier, 2005, 487–9. (Order from www.herbalgram.org) Pricy, but great! ($122)
- Pharmacognosy—the study of herbal "drugs"
  - Fundamentals of Pharmacognosy and Phytotherapy, Barnes et al, 2012 ($40, Kindle edition, $50)
- Potter's Herbal has a concise review of major constituents found in most medicinal plants:
  - Potter's New Cyclopaedia of Botanical Drugs and Preparations. Williamson, E.M., Evans, F.J. London: C.W. Daniel Company Ltd. 1988.
- 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 1
Herbal liposomal formulations.

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

Source: Kesarwani & Gupta, 2013

Microspheres—between 0.1 and 100 μm in size

Table 2
Microspheres.

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

Source: Kesarwani & Gupta, 2013

Nanoparticles—between 1 and 100 nm (under 0.1 μm)

Table 3
Nanoparticles.

Formulation	Active ingredient	Application	Biological activity	Method of preparation	% entrapment effeciency	Route of administration	Ref.
Triptolide nanoparticles	Triptolide	Enhance the penetration of drug through stratum corneum by increased hydration	Anti–inflam–matory	Emulsi–fication ultrasound		Topical	80
Nanoparticle of *Cuscuta chinensis*	Flavonoids and Lignans	Improve water solubility	Hepato–protective and anti–oxidant activity	Nano–suspension method	90%	Oral	81
Artemisinin nanocapsules	Arte–misinin	Sustained drug release	Anti–cancer	Self assembly procedure	90–93%	*In–vitro*	82
Radix salvia miltiorrhiza nanoparticles	*Radix salvia*	Improve the bio–availability	Coronary heart diseases, angina pectoris and myocardial infraction	Spray drying technique	96.68%	*In–vitro*	83
Taxol loaded nanoparticles	Taxol	Improve the bioavailability and sustained drug release	Anti–cancer	Emulsion solvent evaporation method	99.44%	*In–vitro*	84
Berberine loaded nanoparticles	Berberine	Sustained drug release	Anti–cancer	Ionic gelation method	65.40%	*In–vitro*	85
Naringenin loaded nanoparticles	Naringenin	Improve the release of NAR and improv its solubility	Hepato–protective	Nano–precipitation method		Oral	86

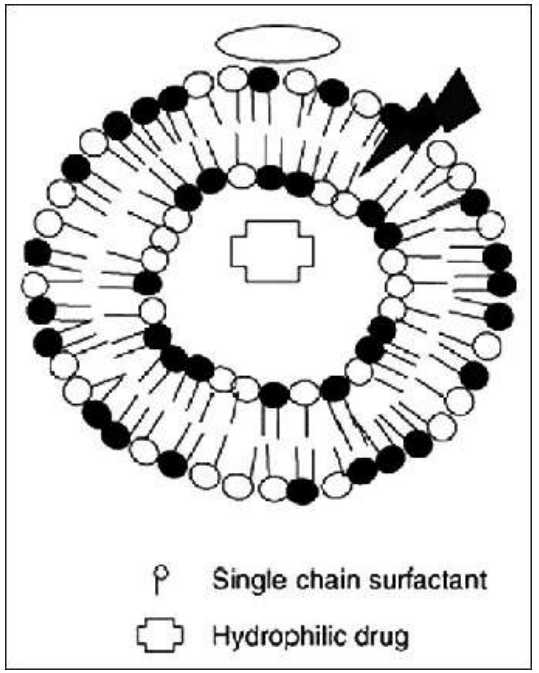
Source: Kesarwani & Gupta, 2013

Transferosomes—Lipophilic vesicles containing a hydrophilic drug as a delivery system

Table 4
Transferosomes.

Formulation	Active ingredient	Application	Biological activity	Droplet size	Route of administration	Ref.
Capsaicin transferosomes	Capsaicin	Increase skin penetration	Analgesic	150.6 nm	Topical	90
Colchicine transferosomes	Colchicine	Increase skin penetration	Antigout	_	*In–vitro*	91
Vincristine transferosomes	Vincristine	Increase entrapment efficiency and skin penetration	Anticancer	120 nm	*In–vitro*	92

- 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

Lipid-based herbal formulations (with a phospholipid)

Table 5
Lipid based herbal formulations.

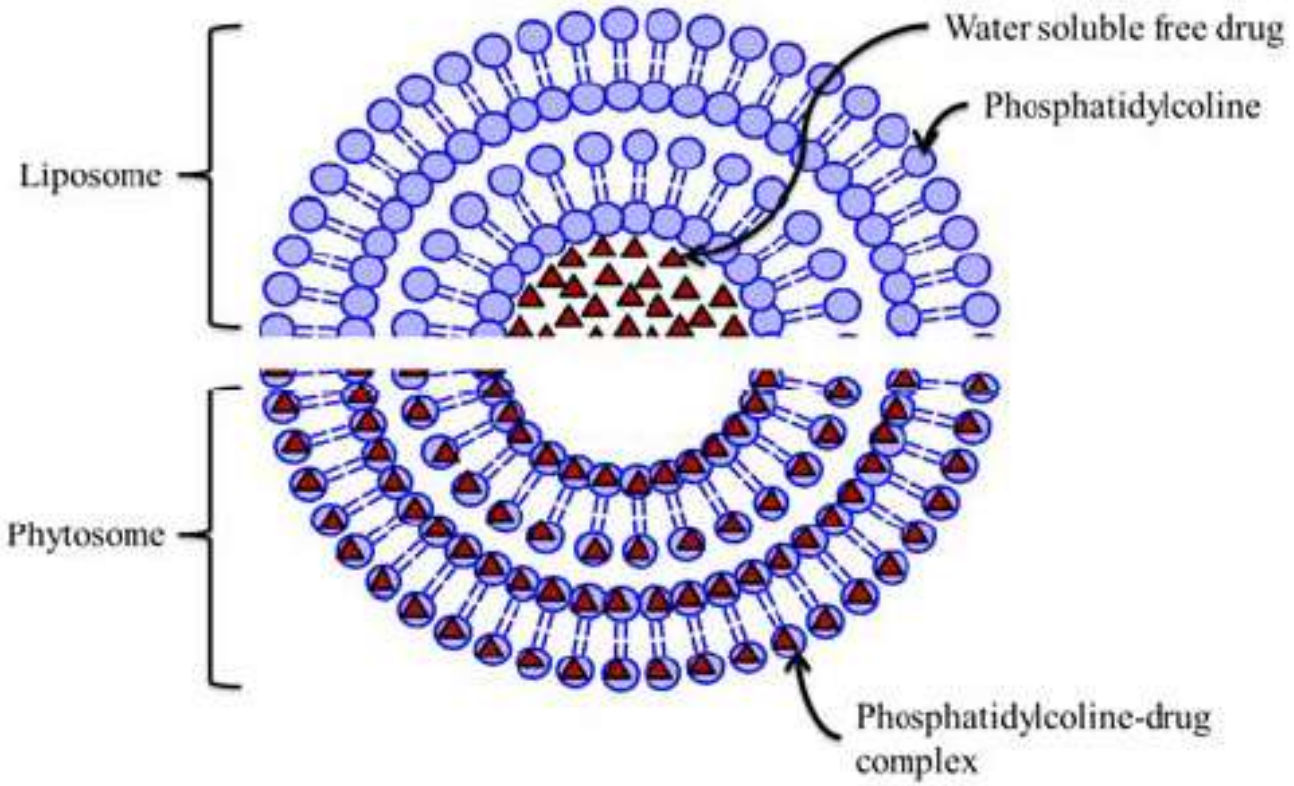
Formulation	Active ingredient	Application	Biological activity	Method of preparation	Dose	Route of administration	Ref.
Ginkgo biloba lipid based systems	Flavonoids	Stabilizes ROS	Cardio–protective antioxidant activity	Phospholipid complexation	100 mg	Subcutaneus	93
Silybin lipid based systems	Flavonoids	Inhobits lipid peroxidation(LP) and stabilizes ROS	Hepatoprotective antioxidant	Phospholipid complexation	120 mg	Oral	94
Ginseng lipid based systems	Flavonoids	Increases absorption	Nutra–ceutcal immune–modulator	Phospholipid complexation	150 mg	Oral	95
Greentea lipid based systems	Ginsenoside	Increases absorption	Nutra–ceutcal, systemic antioxidant and anticancer	Phospholipid complexation	50–100 mg	Oral	95
Grapeseed lipid based systems	Epigallo–catechin	Increases absorption	systemic antioxidant	Phospholipid complexation	50–100 mg	Oral	95
Hawthorn lipid based systems	Procynidins	The blood TRAPn significantly elevated	Cardio–protective and anti–hypertansive	Phospholipid complexation	100 mg	Oral	96
Quercetin lipid based systems	Flavonoids	Exerted better therapeutic efficacy	Anti–oxidant and anticancer	Quercetin Phospholipid complexation		Oral	97
Curcumin lipid based systems	Curcumin	Increases antioxidant activity and increases bioavailability	Antioxidant and anticancer	Curcumin Phospholipid complexation	360 mg/kg	Oral	98

Source: Kesarwani & Gupta, 2013

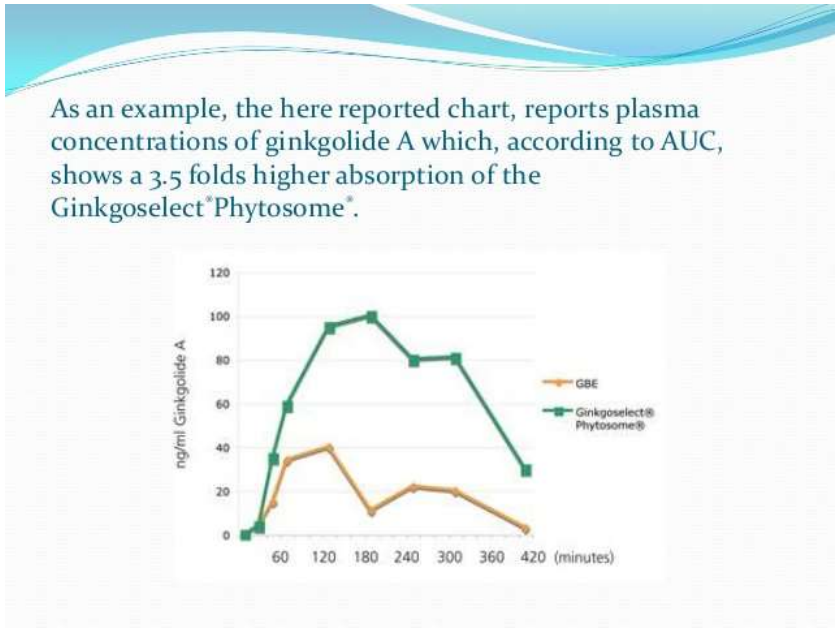
Examples—How to increase blood levels

- 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

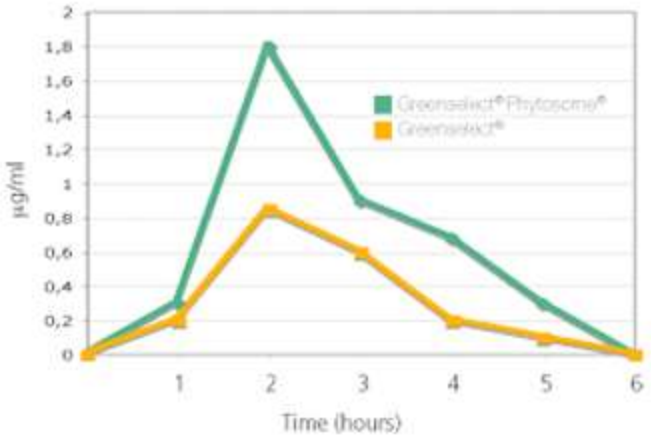


Mauri P, *et* al. 2001. Liquid chromatography/atmospheric pressure chemical ionization mass spectrometry of terpene lactones in plasma of volunteers dosed with Ginkgo biloba L. extracts, Rapid *Commun. Mass Spectrom.* 15, 929-934.

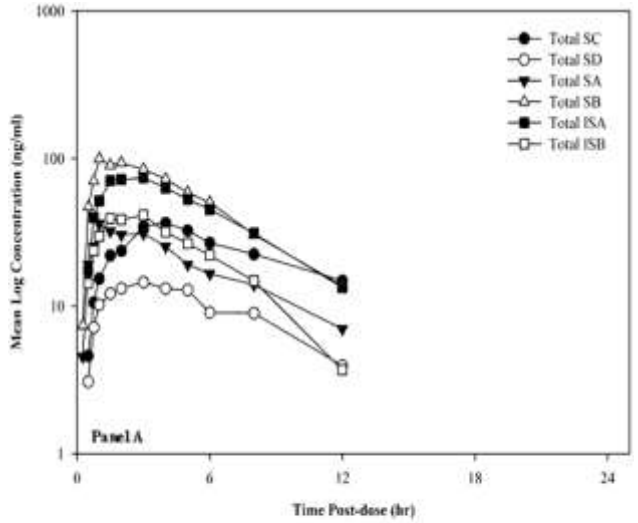
- Ginkgolide A, Ginkgolide B and Bilobalide
- 12 healthy volunteers
- Oral, 60 mg standardized
- Taking with meals increases Tmax, but not AUC quantitatively (Fourtillan *et al.*, 1995)
- Elimination half-lives vary in the 3 compounds (4.5, 10.57, 3.21 h)

Pharmacokinetics

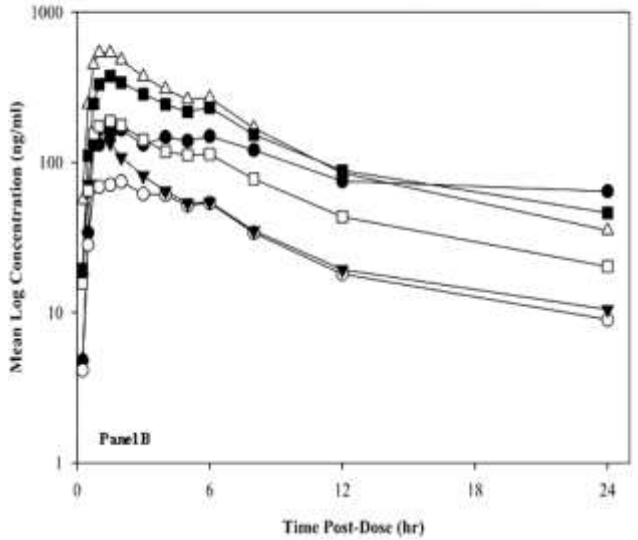
Green tea EGCG and Milk Thistle, Phytosomes



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



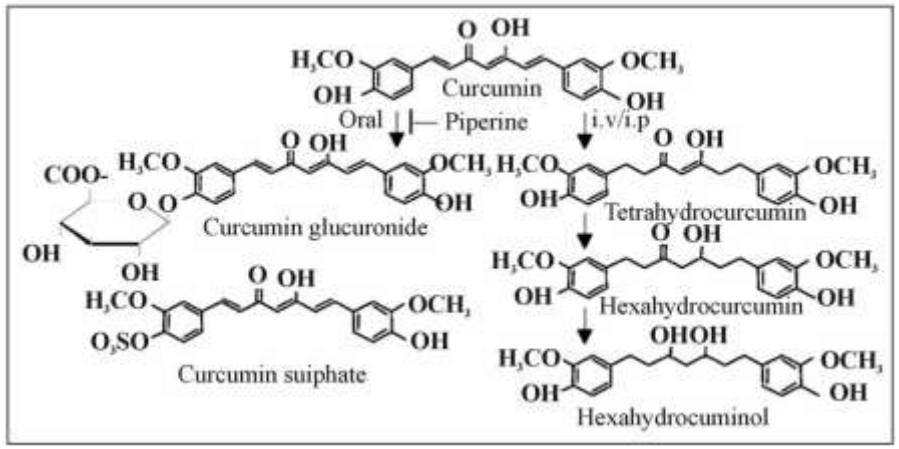
Healthy volunteers



Patients with cirrhosis

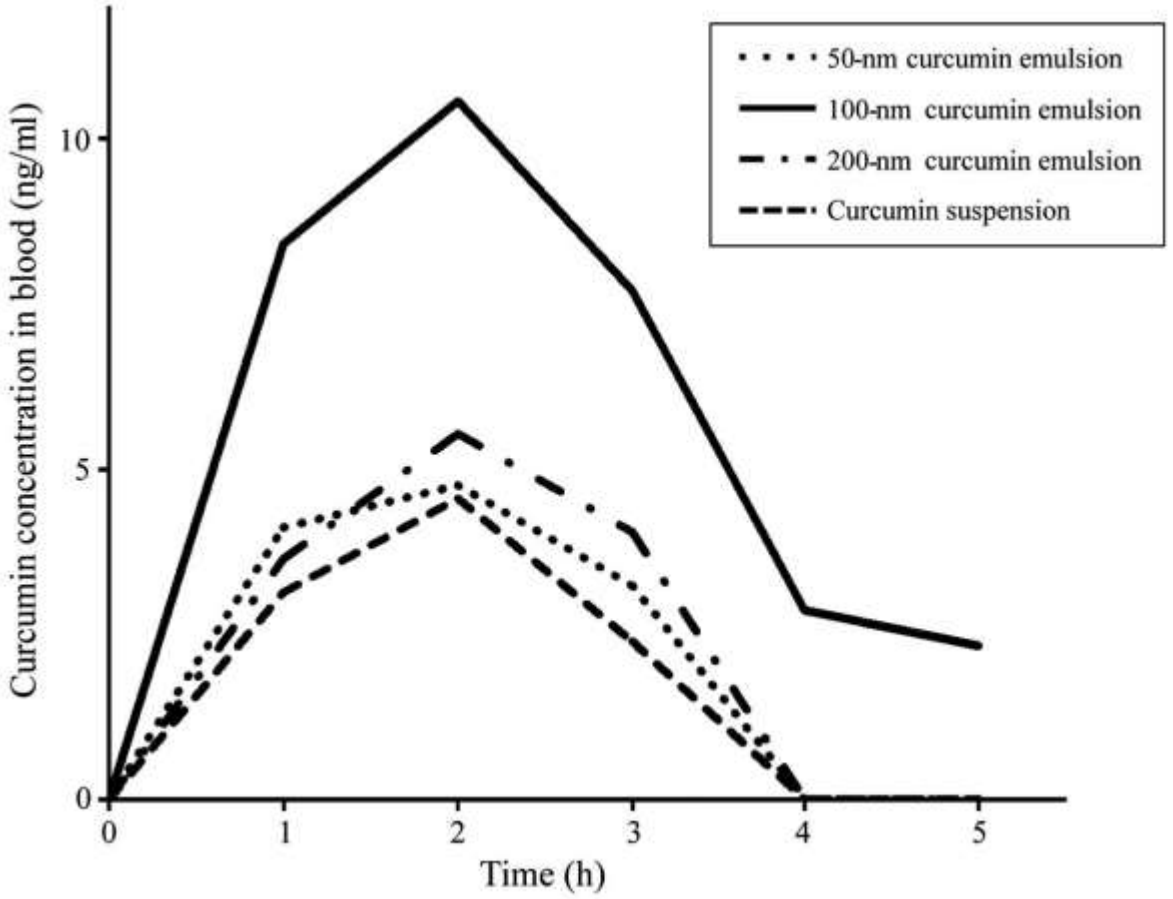
Schreiber *et al.*, 2008.

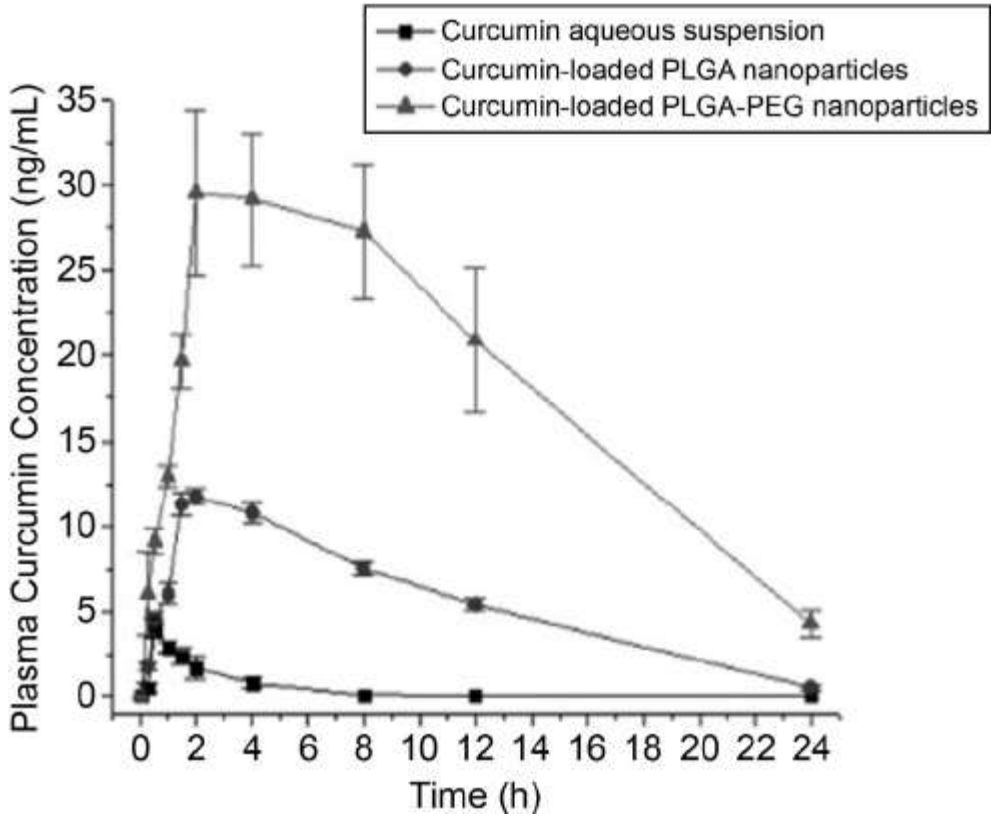
Curcumin from Turmeric



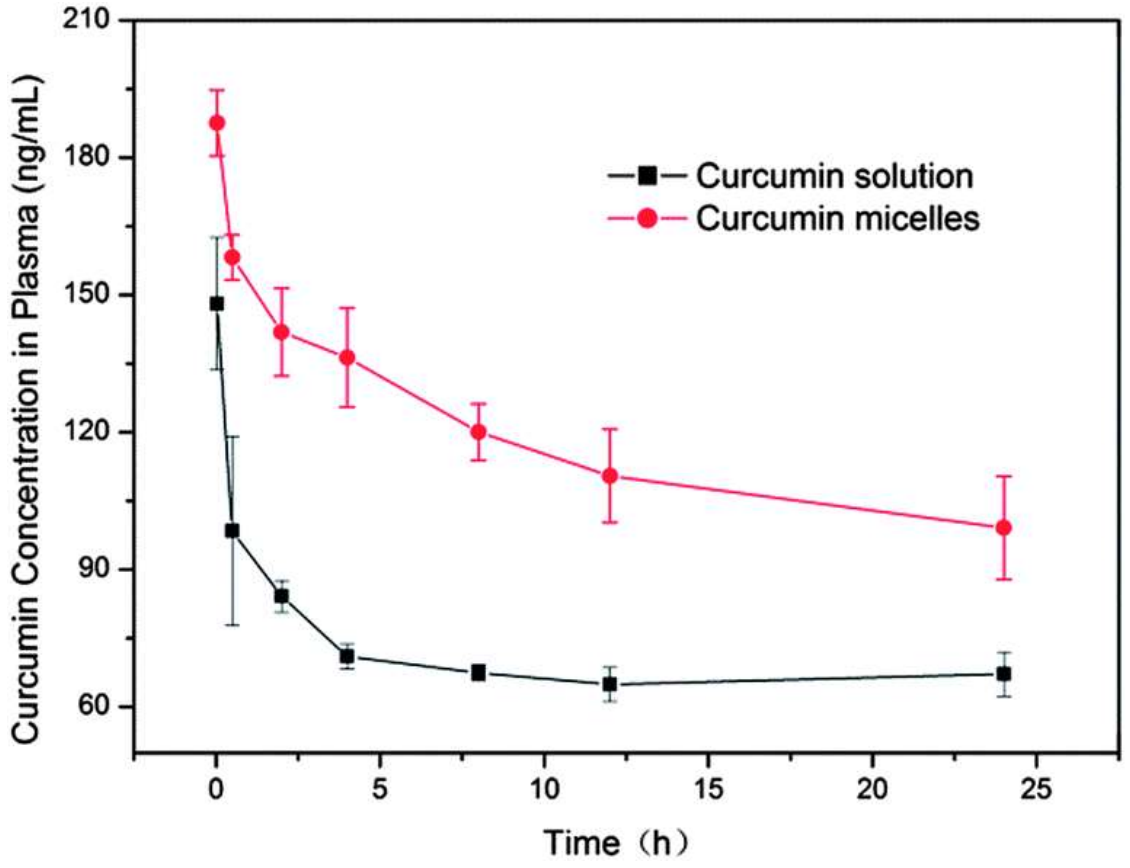
- Curcumin is very poorly absorbed orally, and the liver metabolizes what is absorbed rapidly to a more inactive form
- Products aim to increase absorption and slow liver metabolism
  - Phospholipid complexes
  - Microencapsulation, nanoencapsulation
  - Complex with black pepper extract (piperidine)

Curcumin blood levels with nanoemulsion



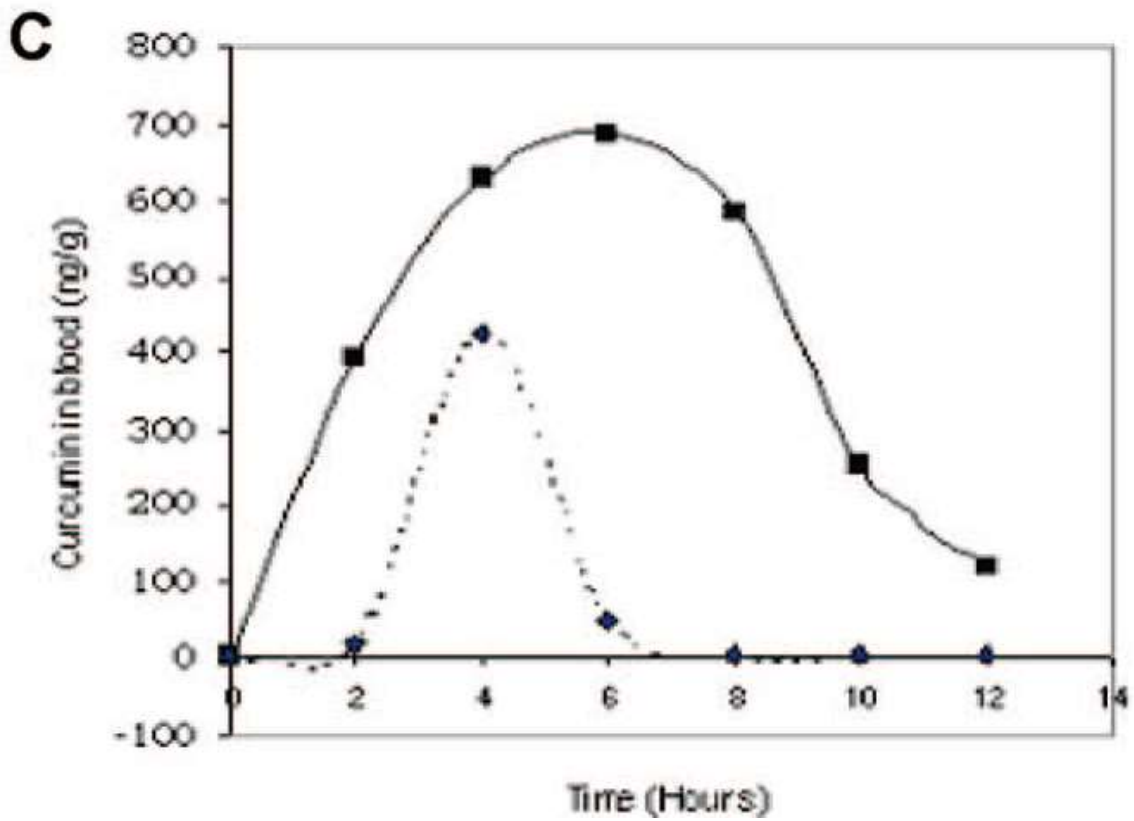


Curcumin micelles--absorption



Hsieh et al., 2014. Oral intake of curcumin.

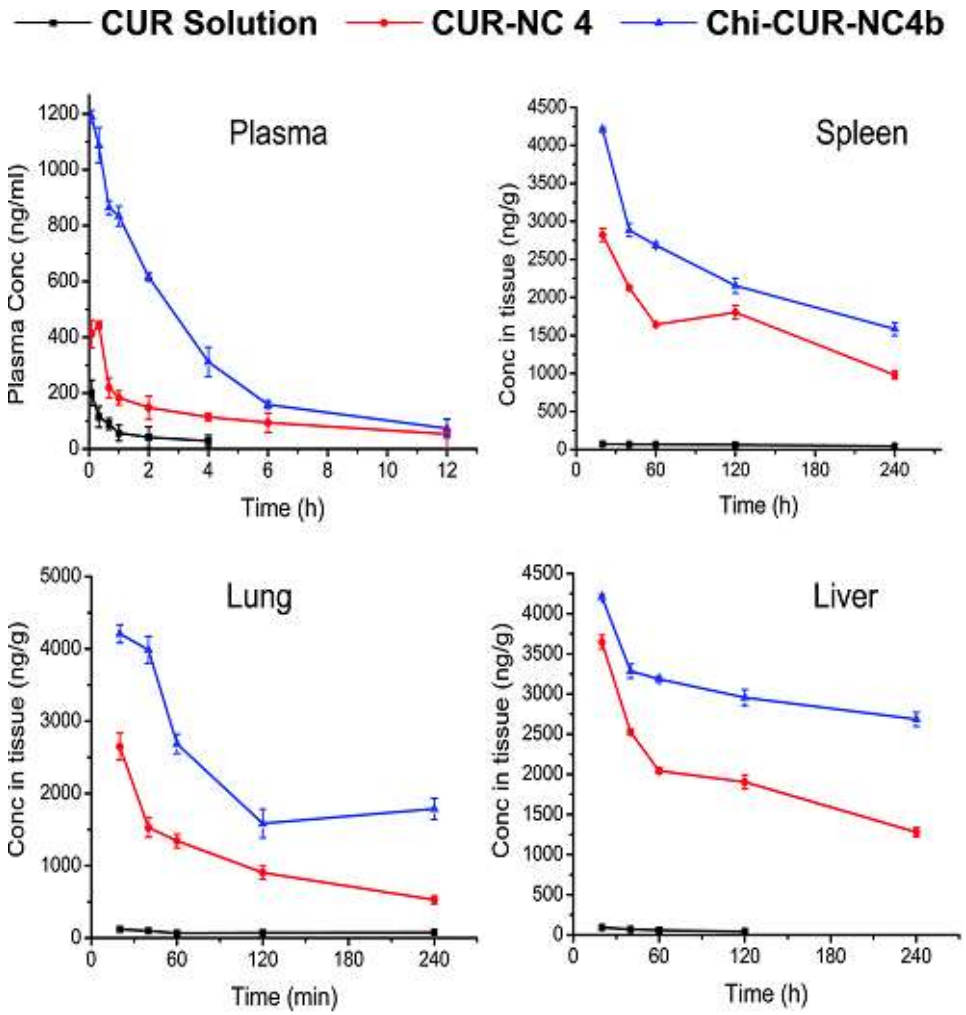
Curcumin and Bioperine



Curcumin blood concentration (in humans with oral administration)

Anand *et al.*, 2007

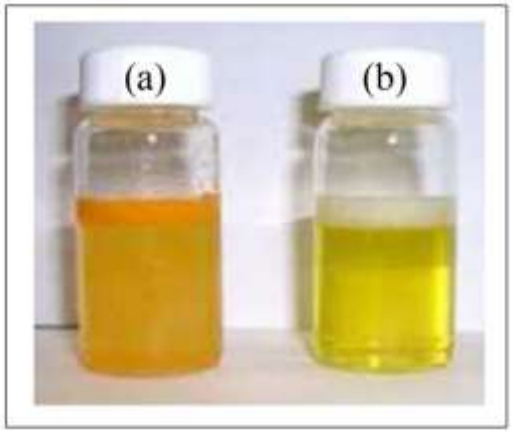
Chitosan coated curcumin nanocrystals for the treatment of sepsis



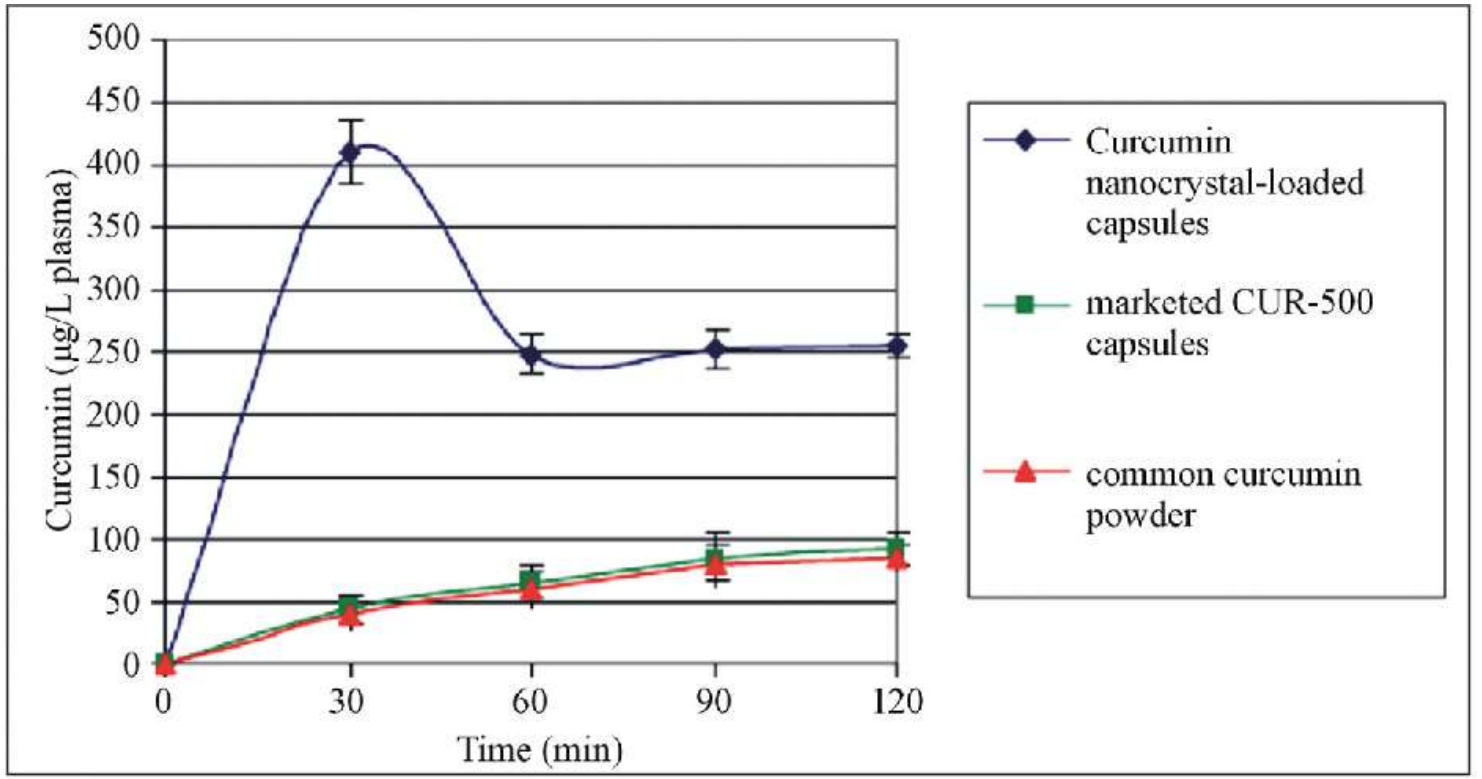
- chitosan coated curcumin nanocrystals (Chi-CUR-NC-4b)
- parenteral therapeutic approach against endotoxemia-induced sepsis
- curcumin-bearing nano-formulation could serve as a valuable option for the therapeutic intervention of sepsis and associated hyper-inflammatory disorders.

(Shukla *et al.*, 2015)

Solubility of curcumin powder vs. nanocrystals



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



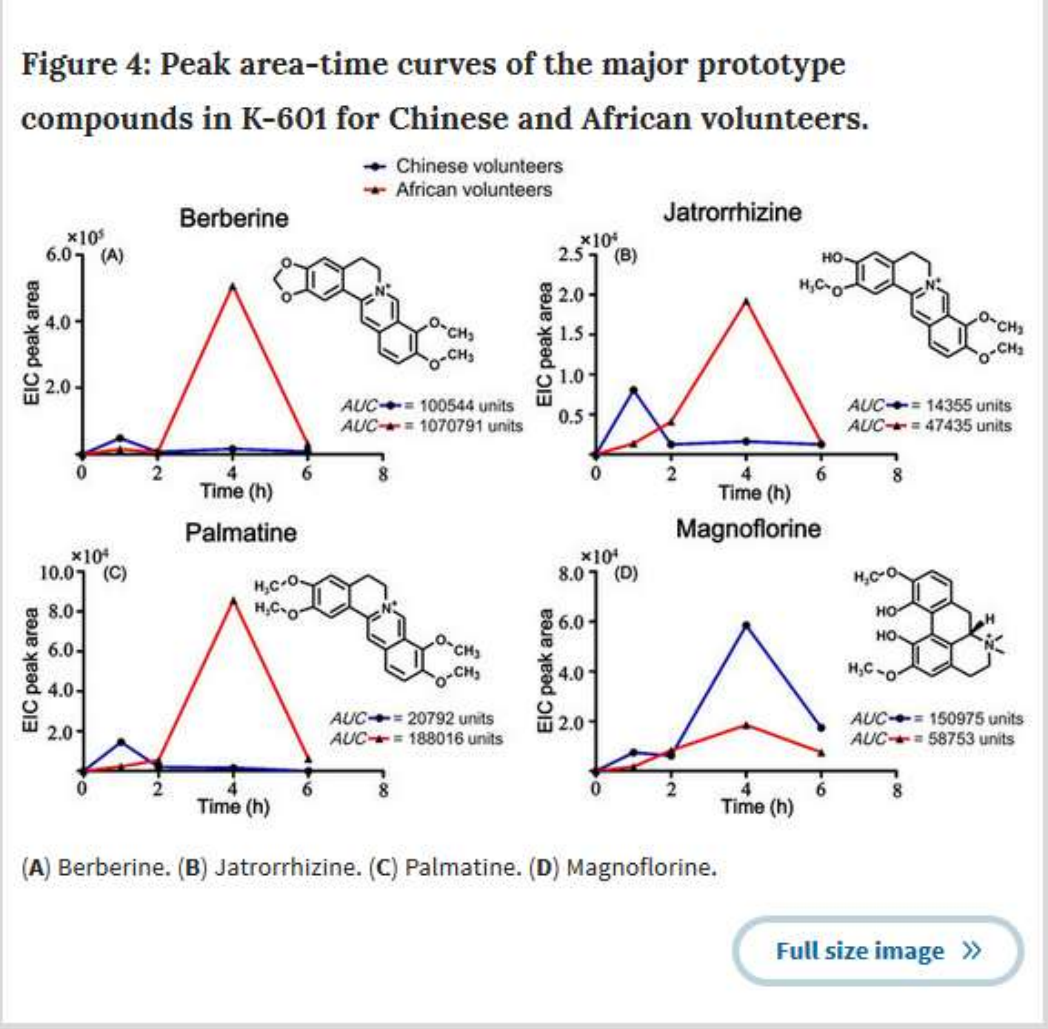
Ravichandran, 2013

Traditional delivery systems

Jim Duke:
"I'd rather enjoy my medicine!"

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

Blood levels of 4 related compounds from TCM Formula

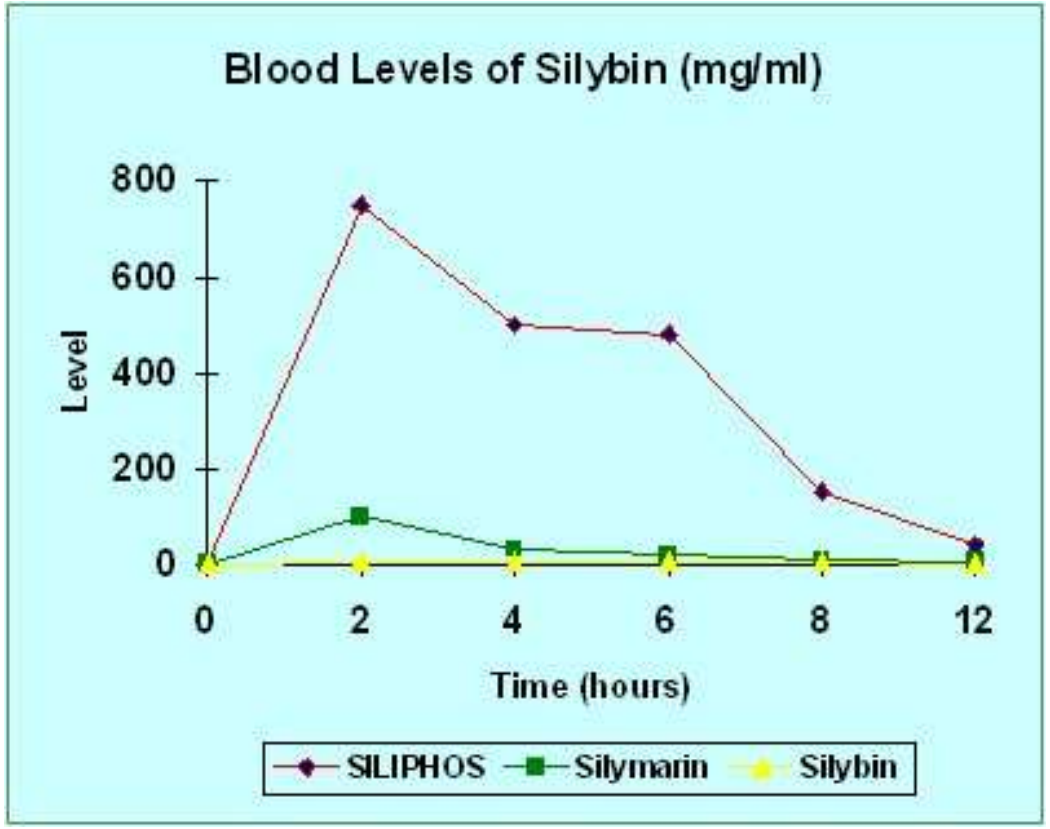


- Lonicera japonica
- Isatis indigotica
- Rheum palmatum
- Phellodendron chinense
- Scutellaria baicalensis

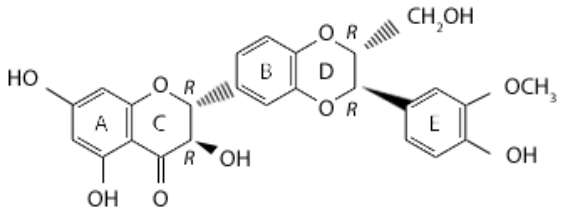
- Significant pharmacokinetic differences were observed between the African and Chinese subjects. The *AUC*s of the African is about 4–10 fold higher than that of the Chinese for the three benzylisoquinoline alkaloids
- Researchers argue that diet and microflora may be responsible

Alolga *et al.*, 2015

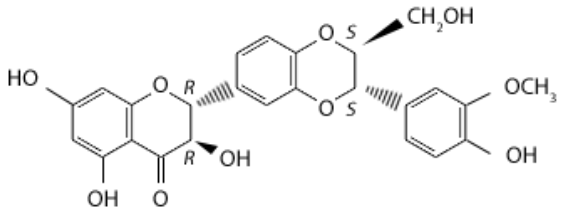
Milk Thistle-Siliphos



- Kid *et al.*, 2005



1a) Silybin A



1b) Silybin B