Nutrient/ Herbal - Drug Interactions

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Nutrient – Drug Interactions?
Case Study

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42 year old female with a history of migraine was rushed to the hospital

- slow heart rate and low blood pressure
- Patient had to be intubated

Husband reported:
Use of Verapamil (blood pressure medication) to prevent migraine

Blood Tests

- No sign of sepsis, myocardial ischemia, acute coronary syndrome or drug abuse
- **Verapamil** levels were **5x higher than the upper therapeutic limit?**
  → Accidental or planed overdose?

Patient recovered after two days and denied overdose.

Patient consumed 3-4 l **grapefruit juice** in the preceding 7 days

Pillai et al, Grapefruit juice and verapamil: a toxic cocktail, Southern Medicine, 2009 Mar, 102(3): 308-9

Some drugs and some foods don‘t mix

Pharmacodynamic vs. Pharmacokinetic

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Pharmacodynamics

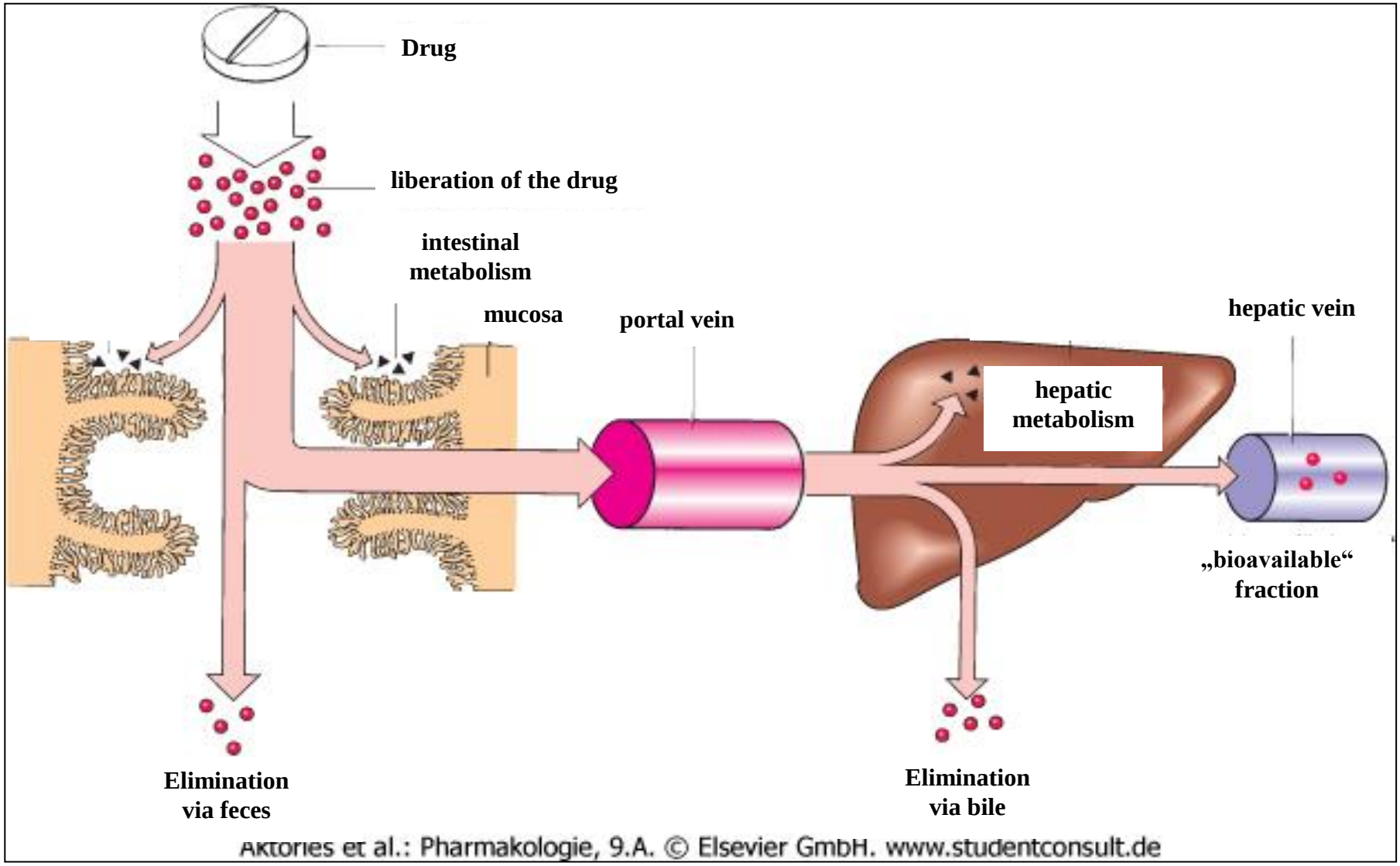
What the drug does to the body

Pharmacokinetics

What the body does to the drug

LADME

- **L**iberation
- **A**bsorption
- **D**istribution
- **M**etabolism
- **E**xcretion


Drug
liberation of the drug
intestinal metabolism
mucosa
portal vein
hepatic vein
hepatic metabolism
„bioavailable“ fraction
Elimination via feces
Elimination via bile
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Physiological Barriers

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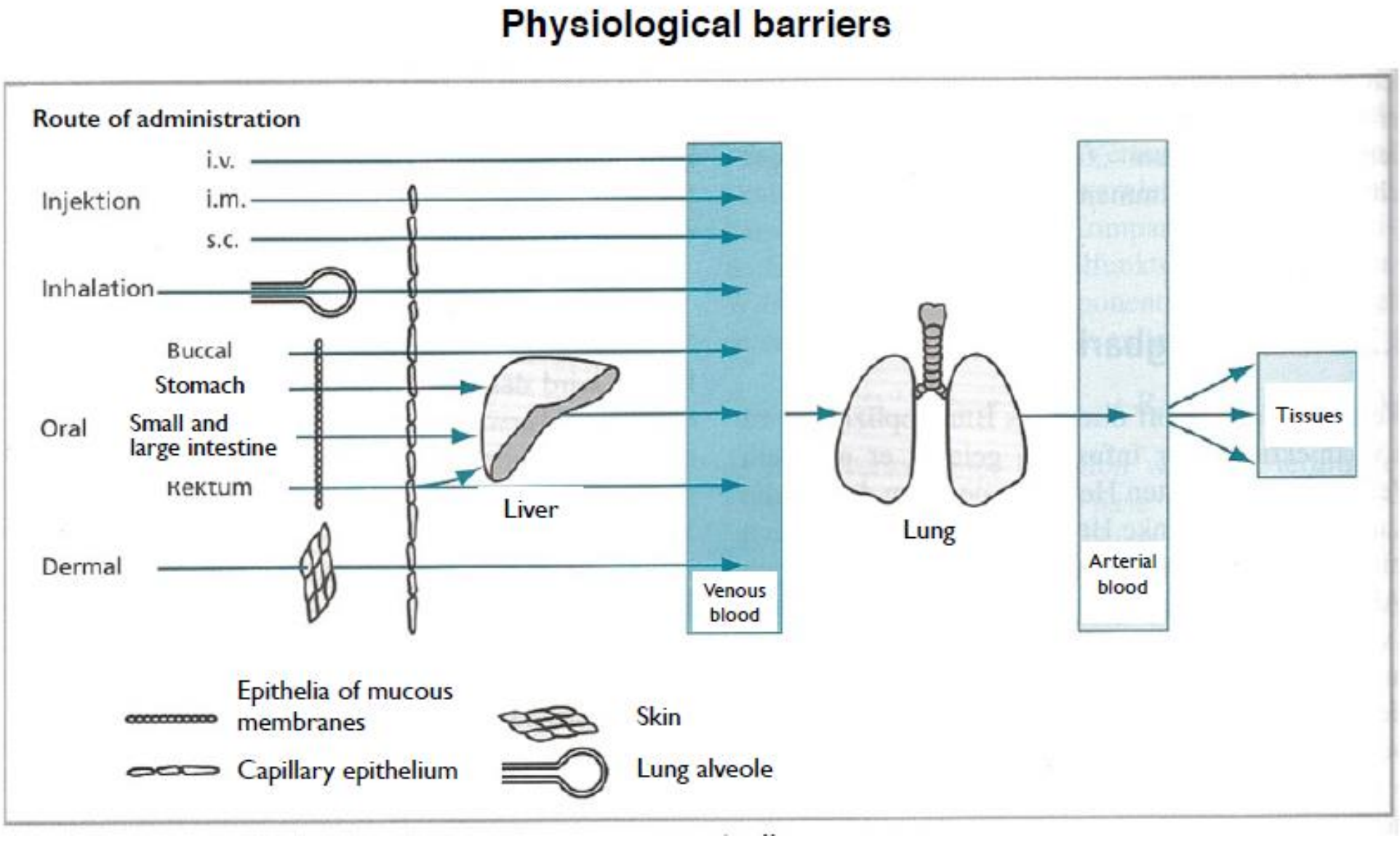

Quelle: Marquardt/Schäfer/Barth, Toxikologie, 3. Aufl.

Xenobiotic metabolism

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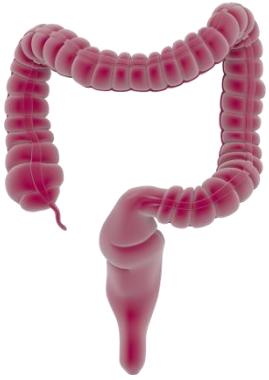
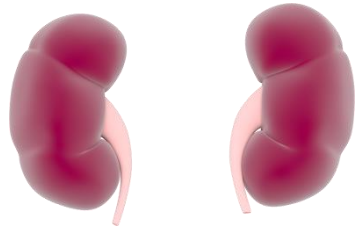
- Xenobiotic = substance foreign to the body
- Organism takes up significant amounts of materials that are neither energy substrates or building material
- To prevent accumulation the “junk” needs to be excreted
- The two major elimination pathways are via urine (renal) and bile (faeces)
- Both pathways require hydrophilicity for excretion

Metabolism



and/ or



biliar/ feces

renal/ urine

Characteristics of enzymes involved in the xenobiotic metabolism

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- Formation of sufficiently water soluble metabolites for excretion (urine, bile)
- Formation of biologically inactive but non-toxic metabolites
- Enzymes should have a broad specifity → even newley encountered xenobiotics should be metabolized

→ Almost impossible to fulfill all three conditions at the same time

→ The metabolism is facilliated by many enzymes and reactions are divided into different phases

Metabolism →

lipophilic substance **hydrophilic substance**

Xenobiotic metabolism

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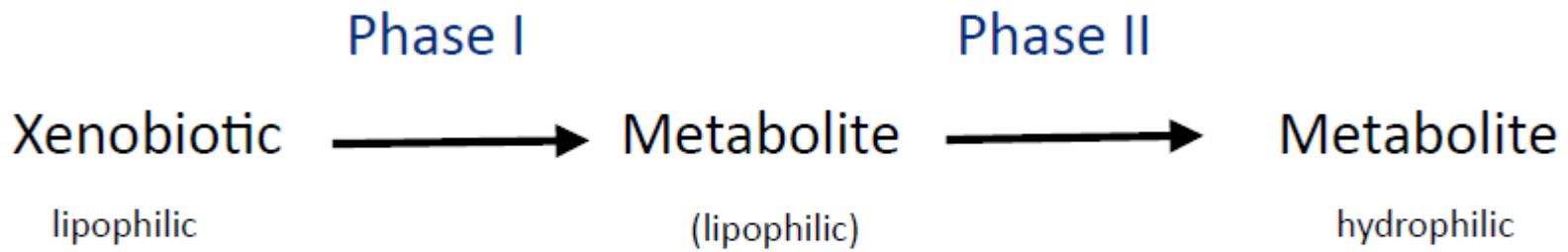
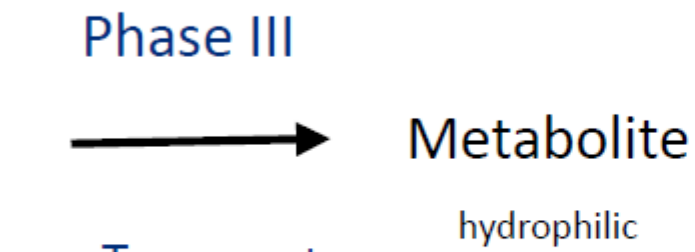
Biotransformation



Functionalisation
(„preparation“; oxidation, reduction, hydrolysis)

Conjugation
(glucuronidation, sulfation, methylation)



Transporters
(ATP-binding cassete and multidrug resistance-transporters ➜ excretion)

First-pass effect
Some compounds are completely converted to metabolites during their first passage through the liver

Phase I - Functionalization

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Oxidoreductases:

- Cytochrome P450-dependent monooxygenases (CYP)
- Flavin-containing monooxygenases (FMO)
- Monoamine oxidases (MAO)
- Cyclooxygenases (COX)

→ **introduce oxygen into or remove electrons from their substrates**

- Dehydrogenases and reductases
- e.g. alcohol and aldehyde dehdrogenases

→ **remove or introduce hydrogen to their substrates**

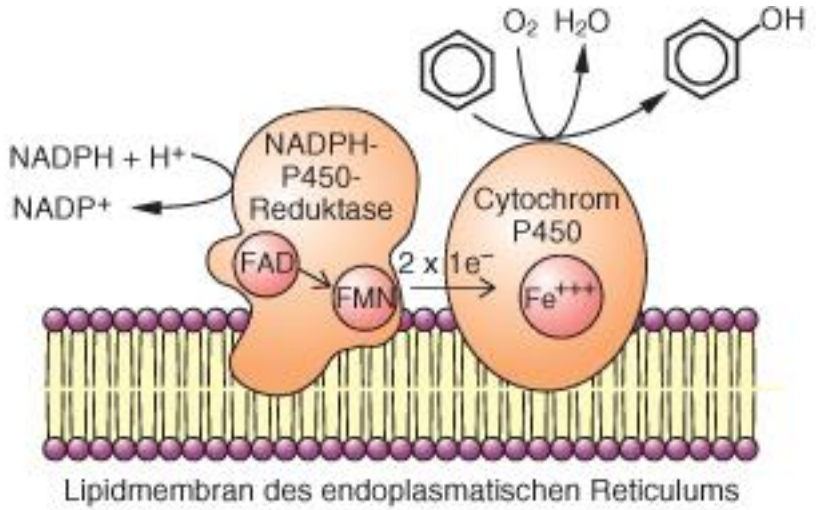
Hydrolases:

- Enzymes that reversibly hydrolyse esters, ethers, peptides, glycosides, organic acid anhydrides or C-C-bonds
- e.g. epoxide hydrolases, esterases, glycosidases, β-glucuronidases, sulfatases, amidases

Cytochrome P450 enzymes

- **Monooxygenases**

  transfer a single oxygen atom from molecular oxygen to an acceptor molecule
- Iron in the active centre of the reduced form of the enzyme can complex carbon monoxide ➔ complex UV absorption max. 450 nm
- CYP are expressed in all tissues, but primarily in the liver and intestine
- Membrane-bound to the endoplasmic reticulum (ER)
- Present in the ER as complex with NADPH-P_{450}-reductase



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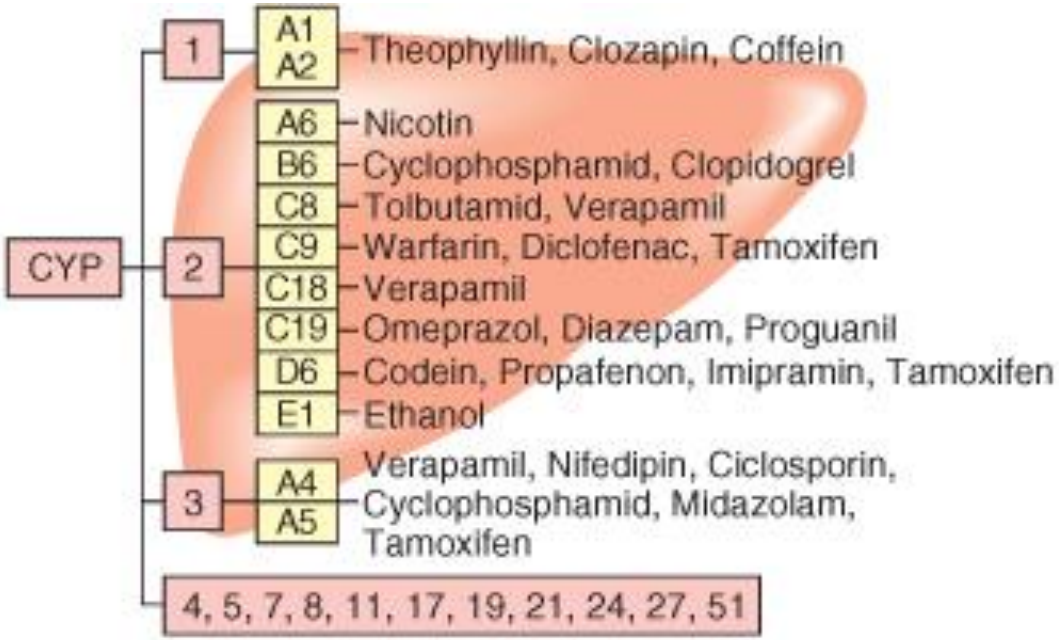
Cytochrome P450 enzymes

Nomenclature
Sequence similarity of >40% → family
Sequence similarity of >55% → sub-family

In humans, 57 **families** are currently known
Subfamilies: A-Z
Arabic numeral denotes **isoenzymes**

CYP3A4 **family: 3**
subfamily: A
isoenzyme: 4



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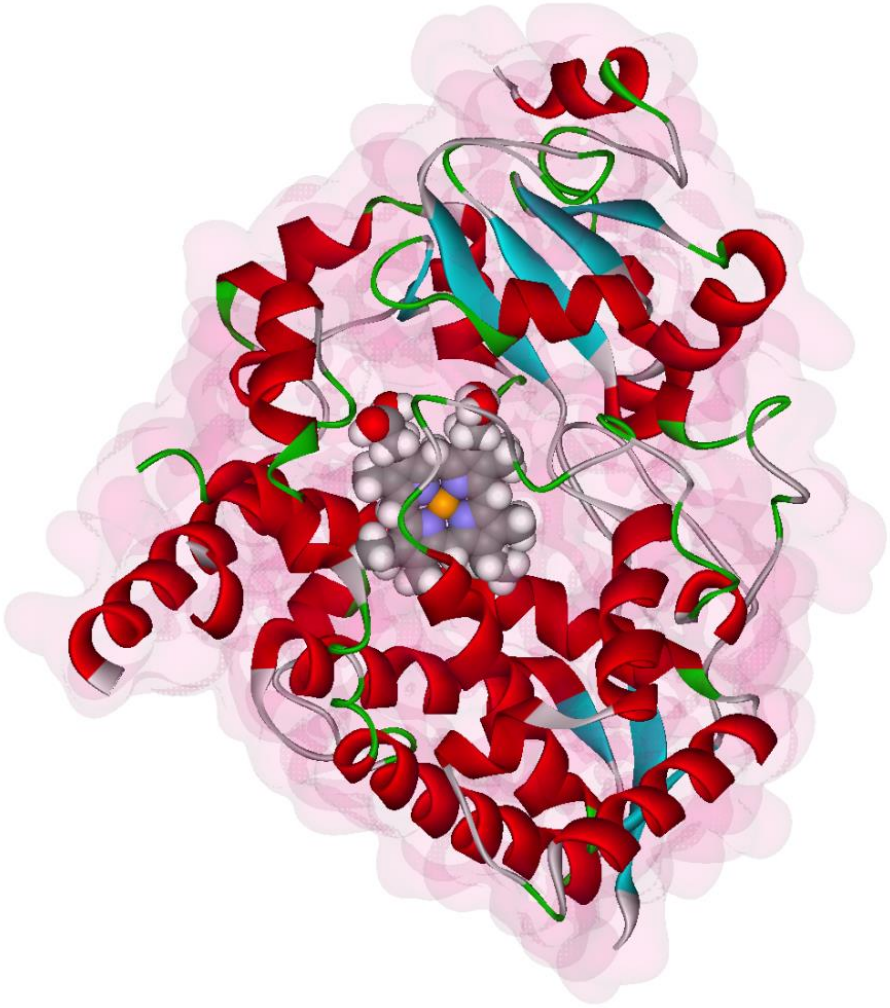
CYP3A4

- Member of the cytochrom P450 (CYP) superfamily of enzymes
- Most important CYP in liver and intestine
- metabolizes approx. 50% of all prescribed drugs



Phase I - functionalization

Phase I of xenobiotic metabolism catalyses

A. Introduction/insertion (R–H → R–OH)
B. Conversion (R_2CH–OH → R_2C=O)
C. Unmasking/uncovering (RCOOR‘ → RCOOH + HOR‘)

of functional groups.

Phase I reactions facilitate

A. biologic inactivation
B. preparation for phase II

Phase II - conjugation

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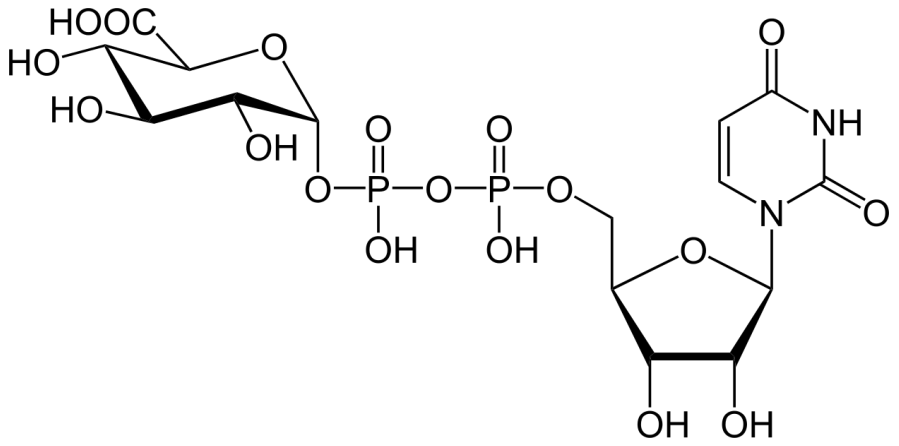
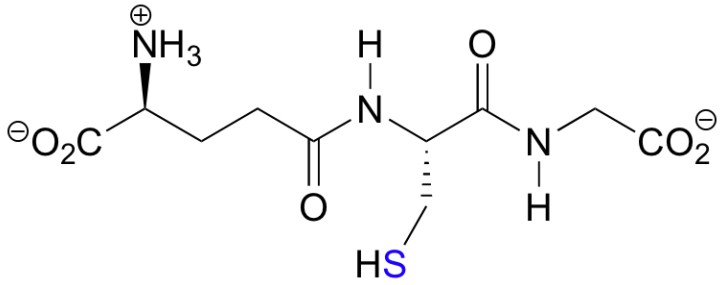
Phase II enzymes

- Glutathione-S-Transferases (GST)
- UDP-Glucuronosyltransferases (UGT)
- Sulfotransferases (SULT)
- N-Acetyltransferases (NAT)
- Methyltransferases
- Amino acid transferases



UDP glucuronic acid



Glutathione (GSH)

Phase II - conjugation

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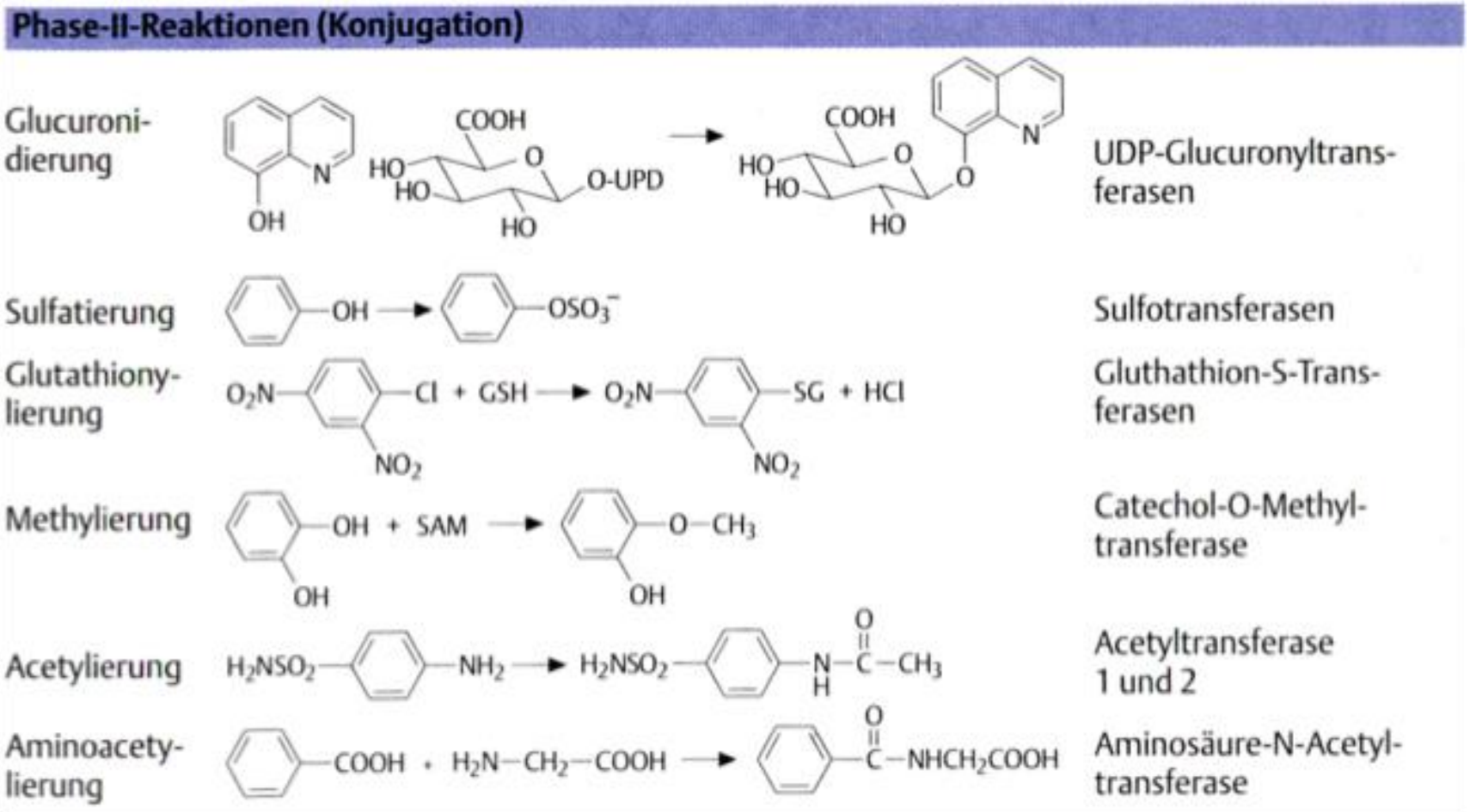
- Phase II reactions inactivated xenobiotics
- And/or increase solubility and thereby elimination of xenobiotics
- In some cases, bioactivation of xenobiotics may occur



Phase III - export

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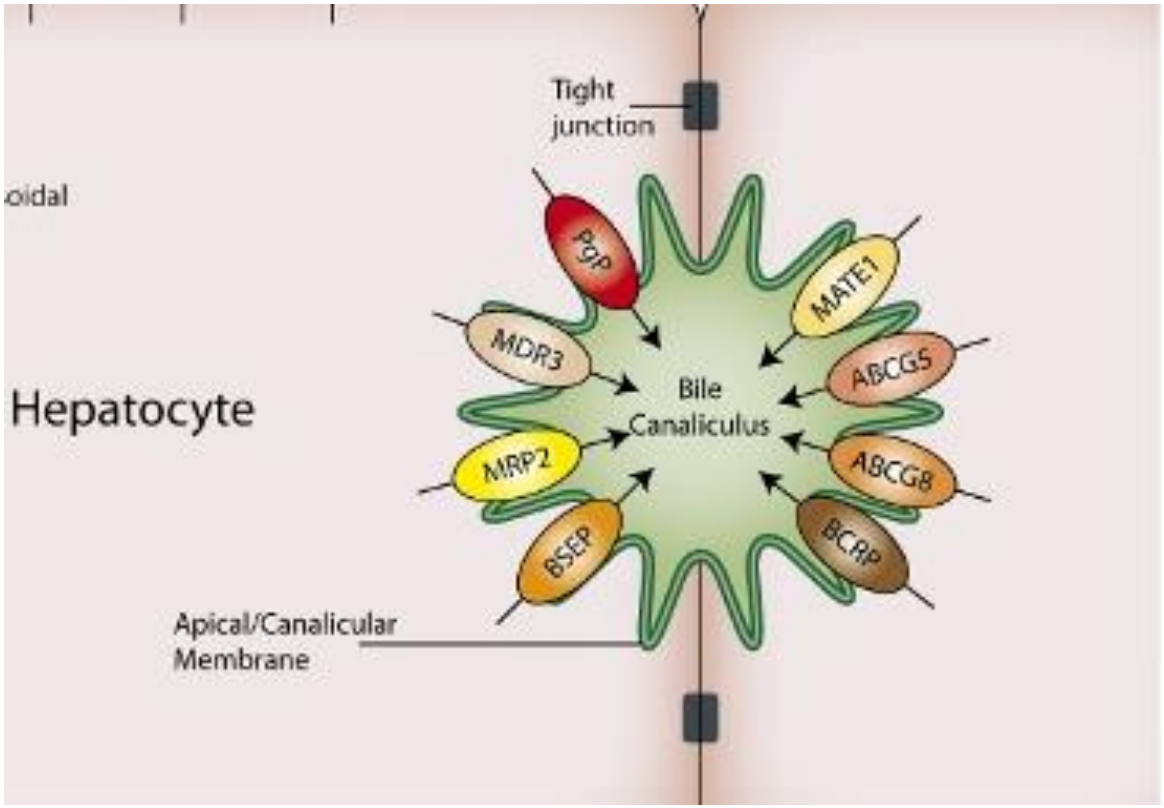
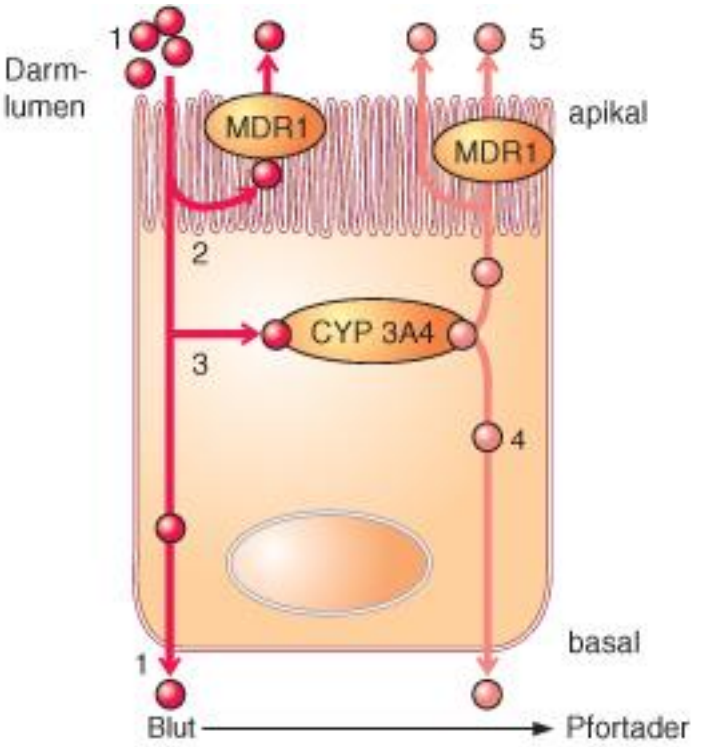
- Phase II Conjugates / parent compound can be actively excreted from cells
- Examples: P-gp (P-glycoprotein)
  BSEP (bile salt export pump)
  BCRP (breast cancer related protein)



http://www.solvobiotech.com/images/uploads/Human_Hepatocyte_ok.jpg

P-glycoprotein (MDR-1)

- ABC-Transporter (ATP-binding casette)
- expression in the intestine, liver, kidney and brain
- MDR-1 = multi-drug-resistant protein 1 discovered in cancer cells that overexpres this protein and are therefore resistent against a range of cytostatika
- expressed in the apical membrane of enterocyte
- eliminates in combination with CYP3A4 many drugs before absorption
- best characterized substrate: digoxin



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Xenobiotic metabolism - Summary

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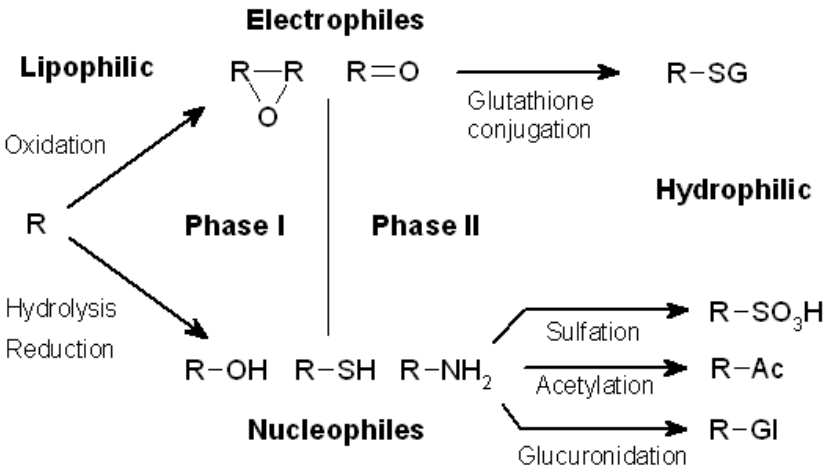

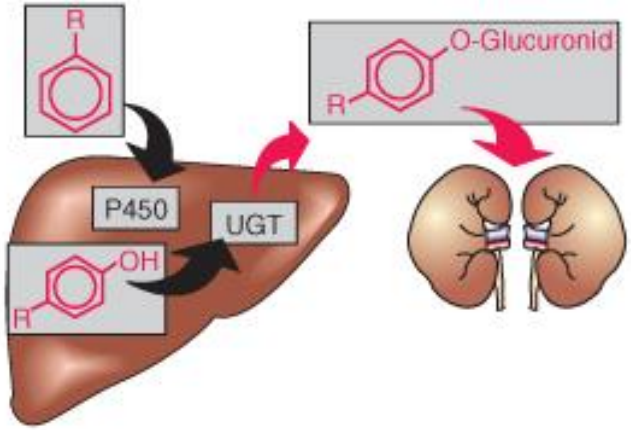

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Phase I – modification

- introduces reactive or polar groups by oxidation, reduction or hydrolysis
- Examples: cytochrome P_{450} enzymes (e.g. CYP3A4), alcohol dehydrogenase, monoamine oxidase

Phase II – conjugation

- conjugates drug or metabolite with a watersoluble, polar substance like glutathione (glutathione-S-transferase) or glucuronic acid (UDP-glucuronosyltransferase; UGT)

(Phase III)

- transporter, carrier that faciliate excretion e.g. MDR-1/ p-glycoprotein into the bile

Bioavailability

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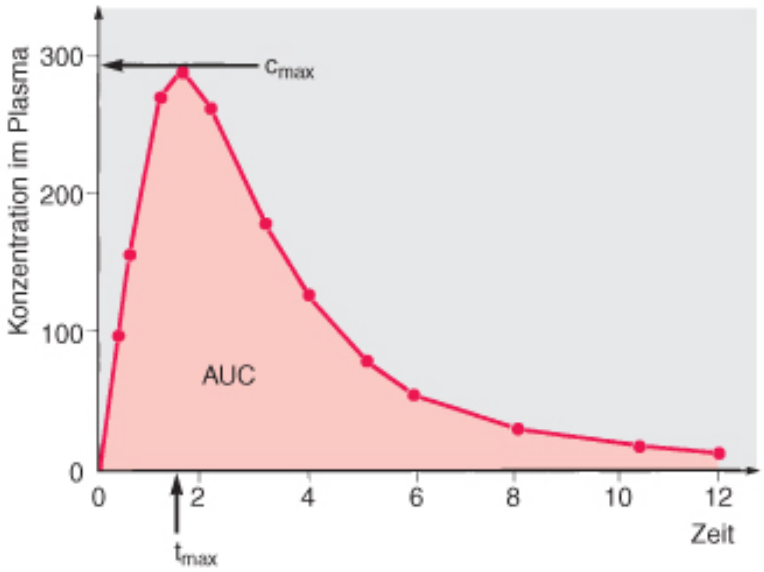

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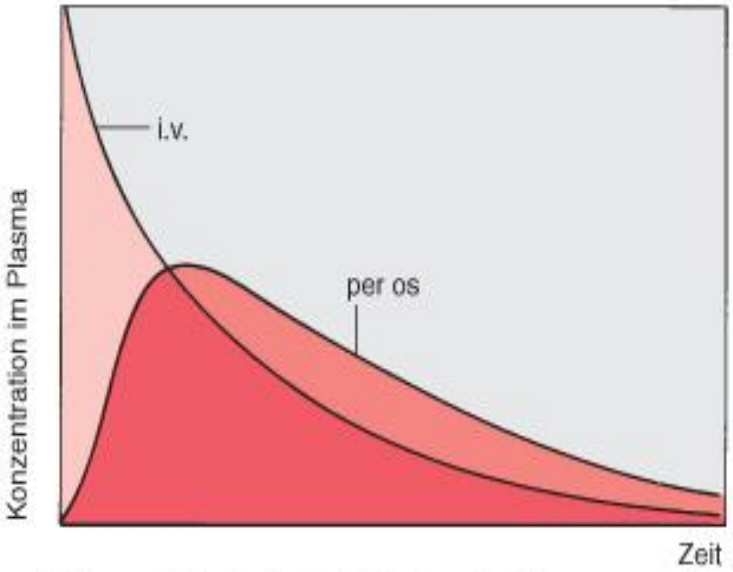

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- unchanged fraction of a drug that reaches systemic circulation after „first pass“ metabolism in intestine and liver

- the bioavailibility of an intravenously administered drug is 100% by definition

Factors influencing bioavailability

- **physical properties of the drug**
  e.g. lipophilic
- **galenics**
  liberation of the drug
- **anatomy, physiology**
  e.g. gastric emptying rate, intestinal transit time, presystemic metabolism and transport
- **interaction with other substances**
  e.g. drugs or nutrients

Gastric emptying rate

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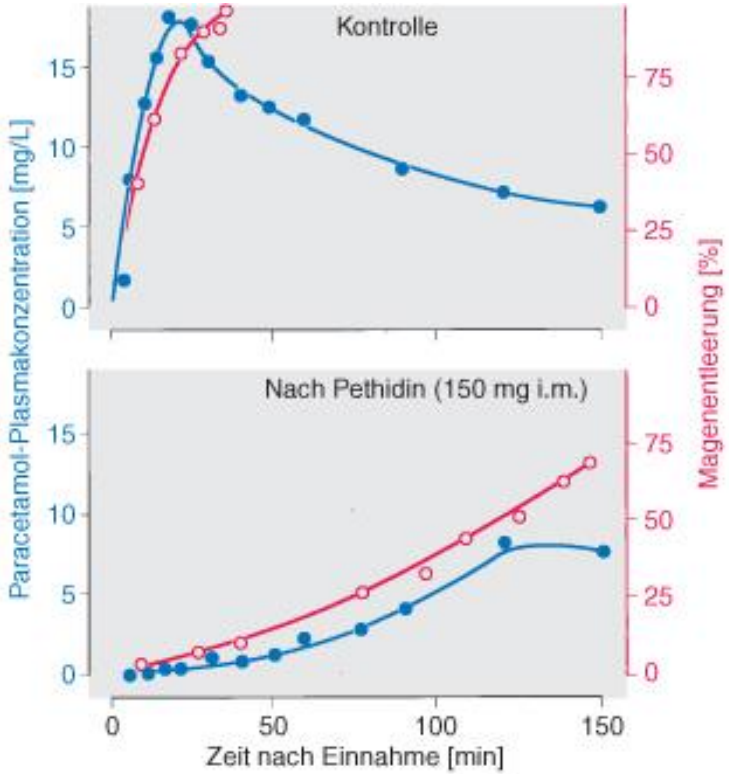

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slowed by	increased by
• fatty diet • solid food • hot food • obesity • migraine • heart attack • labor • pain	• consumption of large quantities of liquid

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Complexation

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- **complexation of the active compound in the gastrointestinal tract**
  some antibiotics from the tetracycline and quinolone family + Ca^{2+} (+ milk)

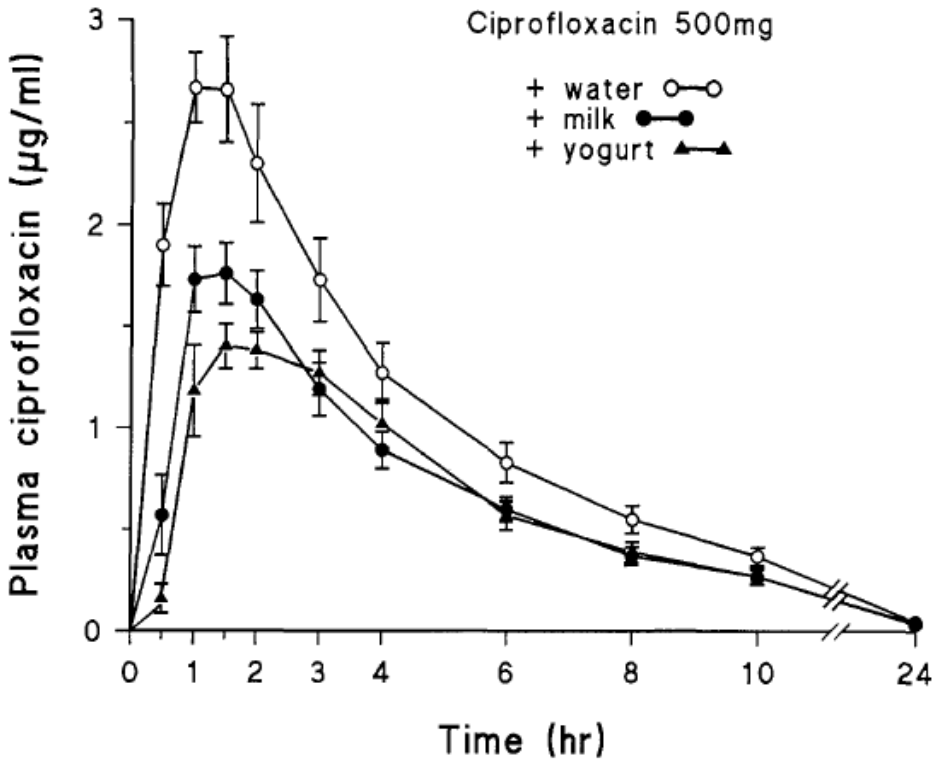

Fig. 1. Effect of concomitant ingestion of milk (300 ml) or yogurt (300 ml) on the absorption of ciprofloxacin (500 mg), reflected as plasma ciprofloxacin concentrations (mean ± SE) in seven subjects. The concentrations with milk and yogurt are significantly ($p < 0.05$) lower from ½ to 10 hours than with water, and with yogurt the concentrations are lower ($p < 0.05$) at 1 and 1½ hours than with milk.

Neuvonen et al. **Interference of dairy products with the absorption of ciprofloxacin**Clin Pharmacol Ther 50: 498-502, 1991

Interactions mediated by enzyme inhibition or induction

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enzyme inhibition

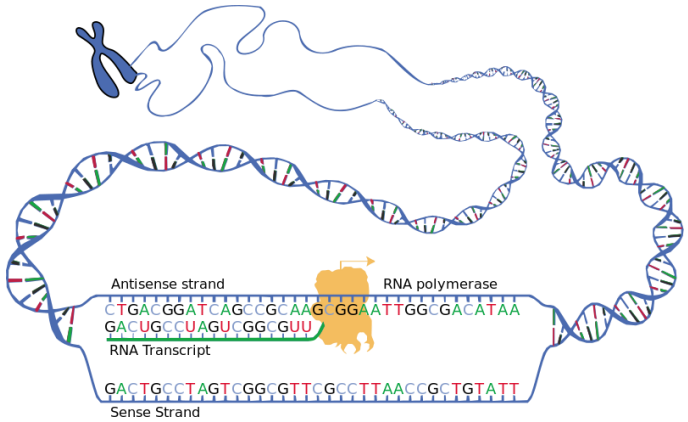
- reversible → inhibitor non-covalently binds to the enzyme

- irreversible → inhibitor covalently binds to the enzyme
  special case of irreversible inhibitor : „suicide inhibitors“
  → enzyme converts the inhibitor to an active form

enzyme induction

→ increase of the enzyme by increasing amount of protein

- increase of transcription/translation
- decrease of protein degradation



Enzyme Inhibition

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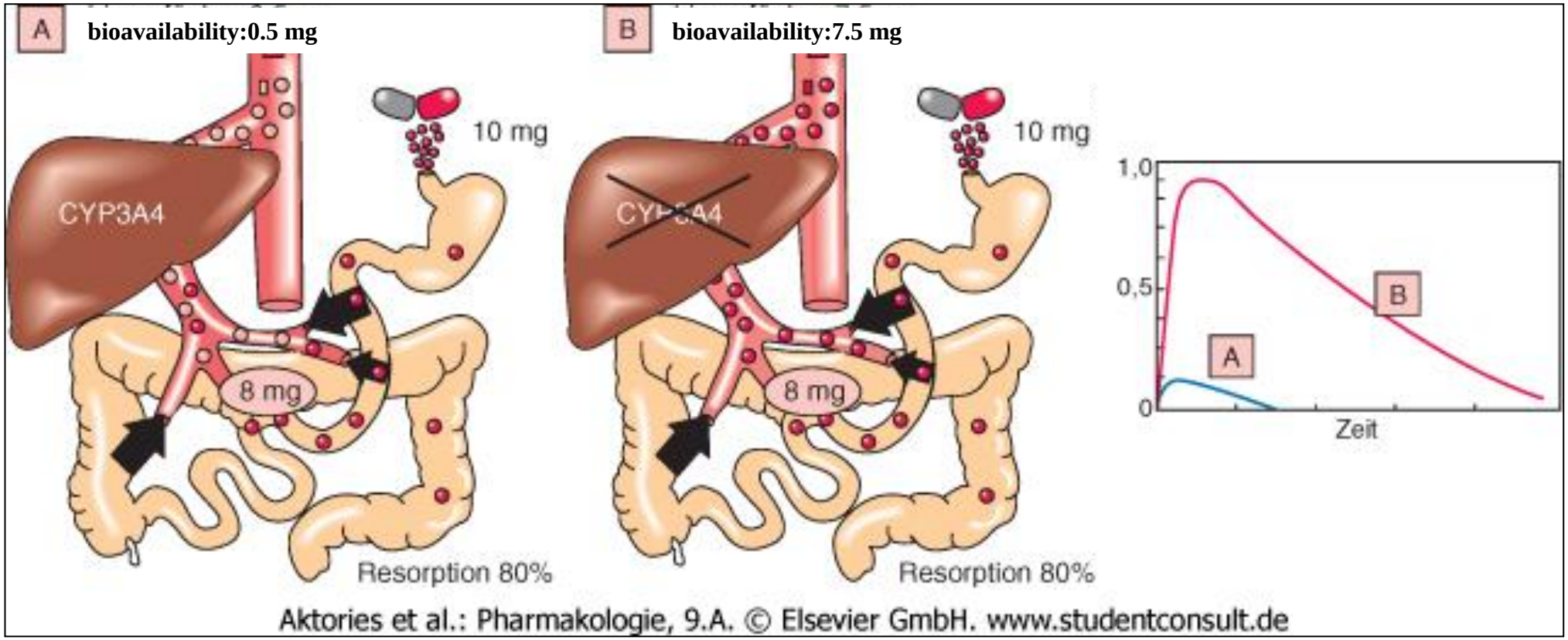

Grapefruit (*Citrus Paradisi*)

an unexpected discovery...

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Display Settings: Abstract

Clin Invest Med. 1989 Dec;12(6):357-62.

Ethanol enhances the hemodynamic effects of felodipine.

Bailey DG, Spence JD, Edgar B, Bayliff CD, Arnold JM.

Department of Pharmacy Services, Victoria Hospital, London.

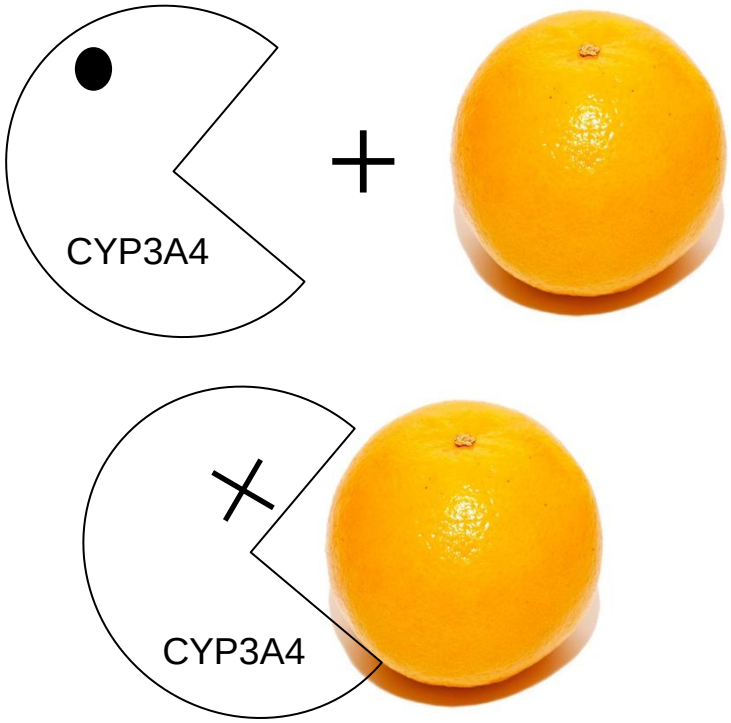
Abstract

The acute hemodynamic and pharmacokinetic interactions between the vasodilating/diuretic drugs ethanol and felodipine, a 1,4-dihydropyridine calcium entry blocker, were assessed in 10 patients with untreated borderline hypertension. A non-intoxicating dose of ethanol or placebo was administered in a randomized, crossover, double-blind manner followed by felodipine 5 mg. Maximum hemodynamic effects occurred at four hours. Felodipine plus ethanol decreased mean (+/- SE) supine total peripheral resistance (13 +/- 2 vs 17 +/- 2 mmHg/L/min, p = 0.05) and diastolic blood pressure (68 +/- 3 vs 75 +/- 2 mmHg, p less than 0.05) associated with increased heart rate (72 +/- 3 vs 67 +/- 2 bpm, p less than 0.05) and cardiac index (3.7 +/- 0.4 vs 3.0 +/- 0.3 L/min/m2, p less than 0.05) more than felodipine alone. Greater differences were apparent in standing blood pressure. Co-administration of ethanol decreased standing systolic (113 +/- 8 vs 126 +/- 5 mmHg, p less than 0.01) and diastolic (69 +/- 5 vs 82 +/- 3 mmHg, p less than 0.01) blood pressure to a greater degree, but heart rate was not altered (87 +/- 6 vs 84 +/- 3 bpm). Substantial four hour diuresis occurred with both treatments (807 +/- 126 vs 806 +/- 169 ml). Adverse effects were frequent but most often occurred with felodipine plus ethanol (17 vs 11) as a result of postural lightheadedness (5 vs 1) related to hypotension. Felodipine bioavailability was not influenced by ethanol. However felodipine plasma concentrations greatly exceeded the expected concentrations, possibly due to a pharmacokinetic interaction with the grapefruit juice vehicle. Ethanol can enhance felodipine hemodynamics to produce clinically relevant adverse effects.

PMID: 2612087 [PubMed - indexed for MEDLINE]

Grapefruit (*Citrus Paradisi*)

intestinal inhibition of CYP3A4



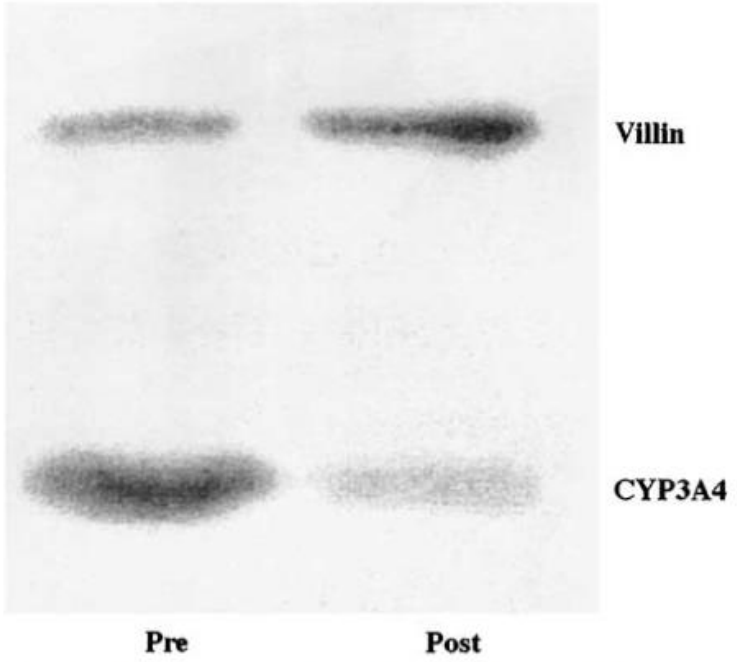


Figure 1 Determination of CYP3A4 concentration by immunoblot analysis of endoscopic duodenal biopsies before (Pre) and 4 h after (Post) drinking one glass of grapefruit juice. Villin, an enterocyte protein, served as a control.

irreversible inhibition „suicid substrate“

→ complex is rapidly degraded

→ inhibiton can only be overcome by producing new enzyme

Dahan und Altman. Food-drug interaction: grapefruit juice augments drug bioavailability-mechanism, extent and relevance. Eur J Clin Nutr (2004) vol. 58 (1) pp. 1-9

Grapefruit (*Citrus Paradisi*)

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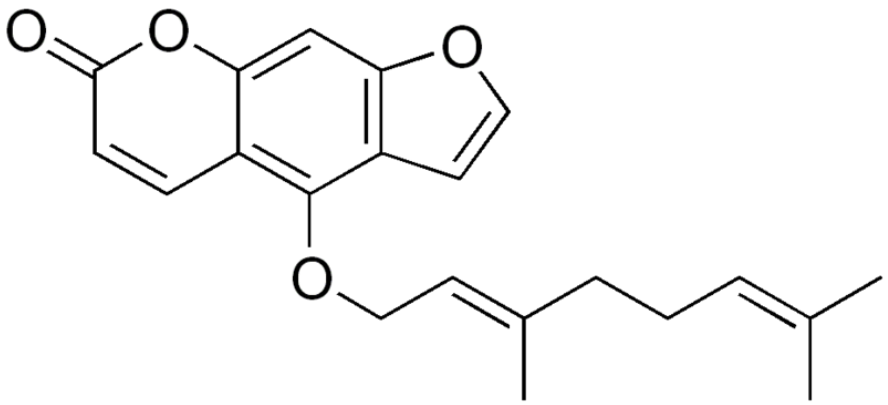
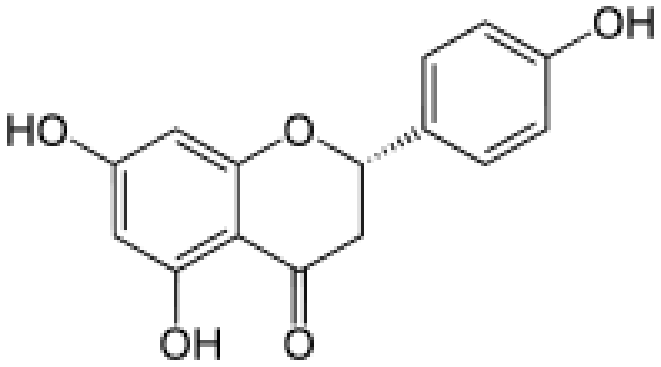


bergamottin
(furanocoumarin)

↓

strong inhibition of
Intestinal CYP3A4



naringenin
(flavenoid)

↓

weak inhibition of
Intestinal CYP3A4

Postranslational inhibition of CYP3A4 protein in the intestine

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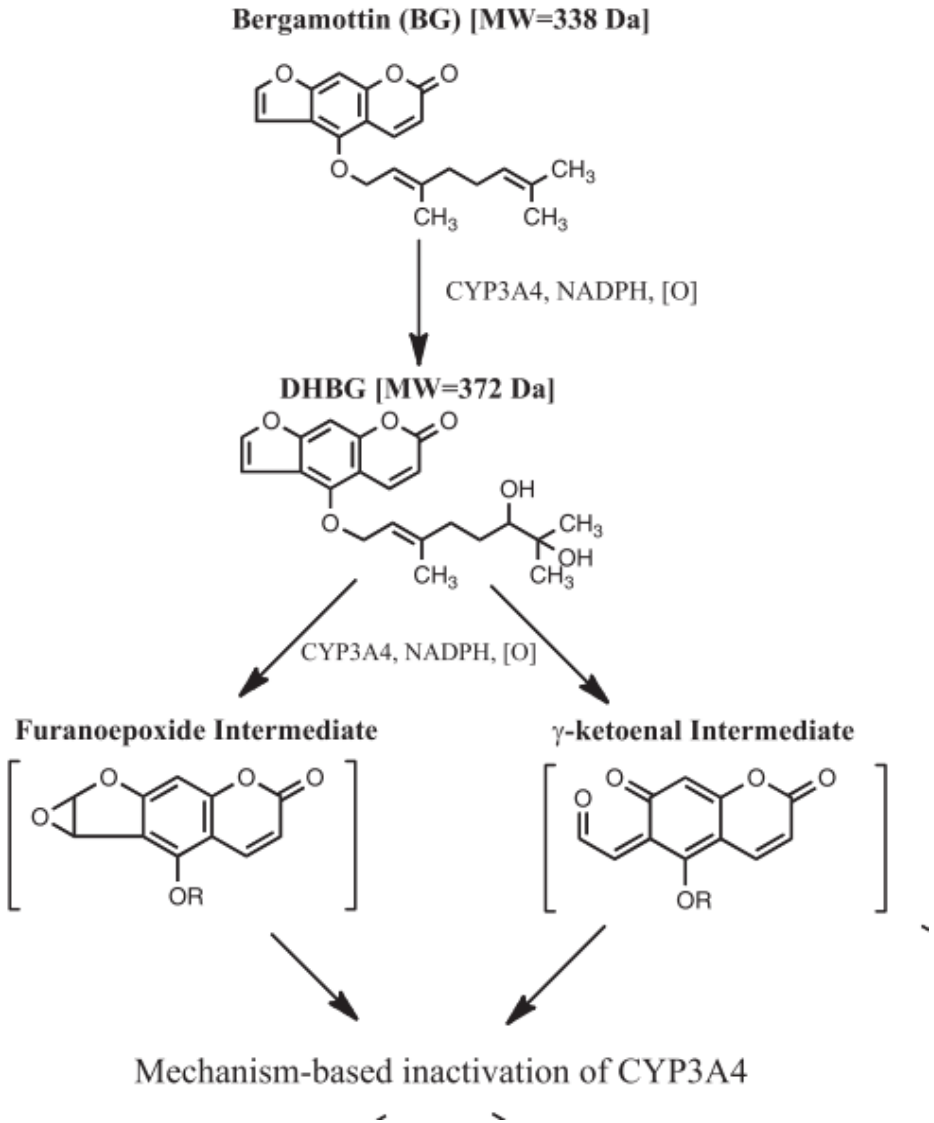

•Hsia-lien Lin,et al. Identification of the Residue in Human CYP3A4 That Is Covalently Modified by Bergamottin and the Reactive Intermediate That Contributes to the Grapefruit Juice EffectDrug Metab Dispos May 2012 40:998-1006;

Grapefruit (*Citrus Paradisi*)

effective dose

<u>1 grapefruit or 200 ml grapefruit juice</u>

→ Contains enough furanocoumarins to significantly increase the bioavailability of some drugs and cause **adverse reactions**

→ **seville oranges (bitter oranges)**,**lime** and **pomelo** contain similar levels of furanocoumarin !

Grapefruit – interactions with drugs

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Characteristic of drugs that interact with grapefruit

- administered orally
- low (<10%) to intermediate (> 30-70%) bioavailability
- metabolized by CYP3A4

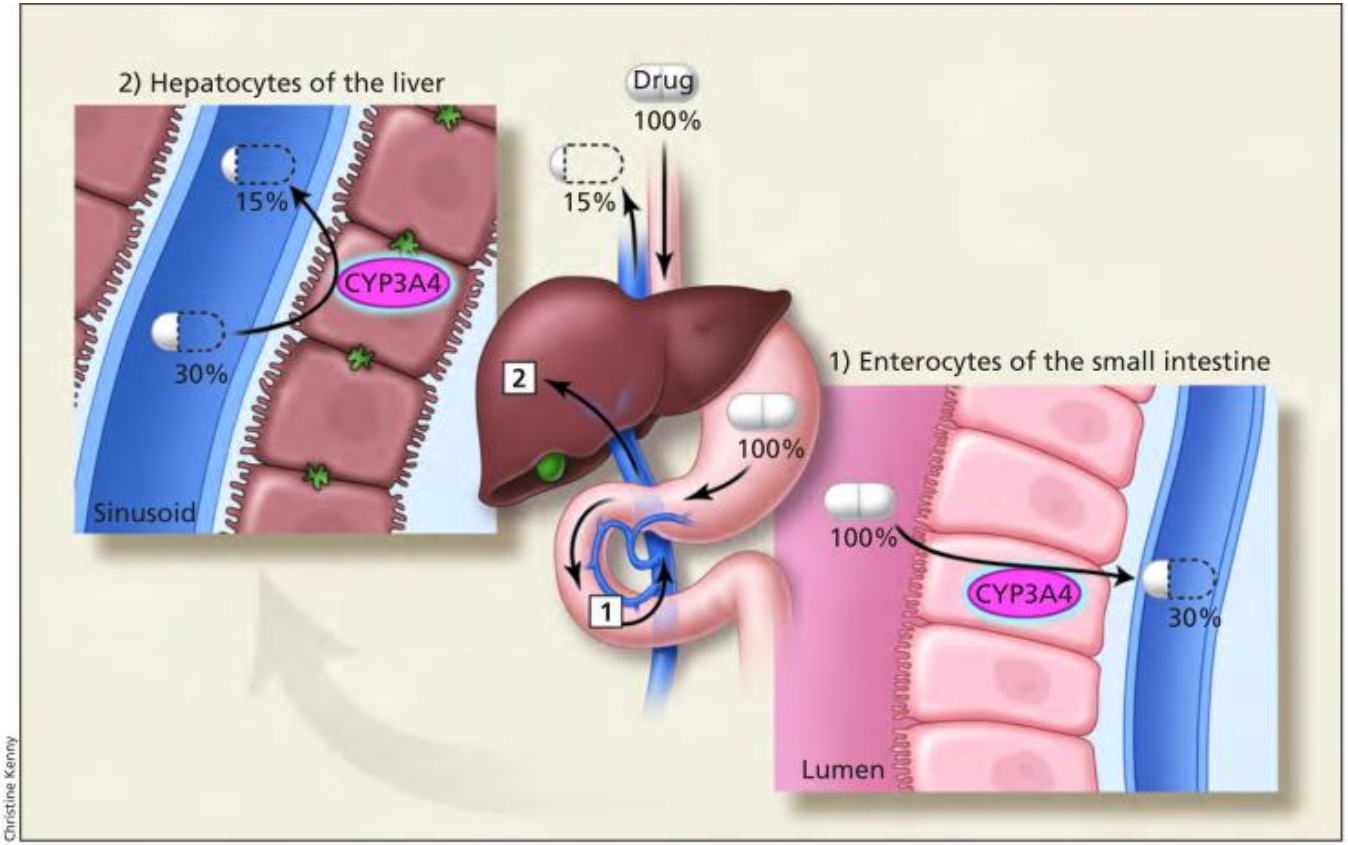

Figure 1: Sequential first-pass elimination of a drug, such as felodipine, through metabolism in enterocytes of the small intestine, then hepatocytes of the liver. The percentages of the initial dose that are available before and after passage through the gut wall and liver are shown. Although felodipine is 100% absorbed from the gastrointestinal tract, its bioavailability is only 15% after oral administration. CYP3A4 = cytochrome P450 enzyme 3A4.

Bailey, D. G., Dresser, G., & Arnold, J. M. O. (2013). Grapefruit-medication interactions: forbidden fruit or avoidable consequences? *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne*, *185*(4),

Grapefruit – interactions with drugs

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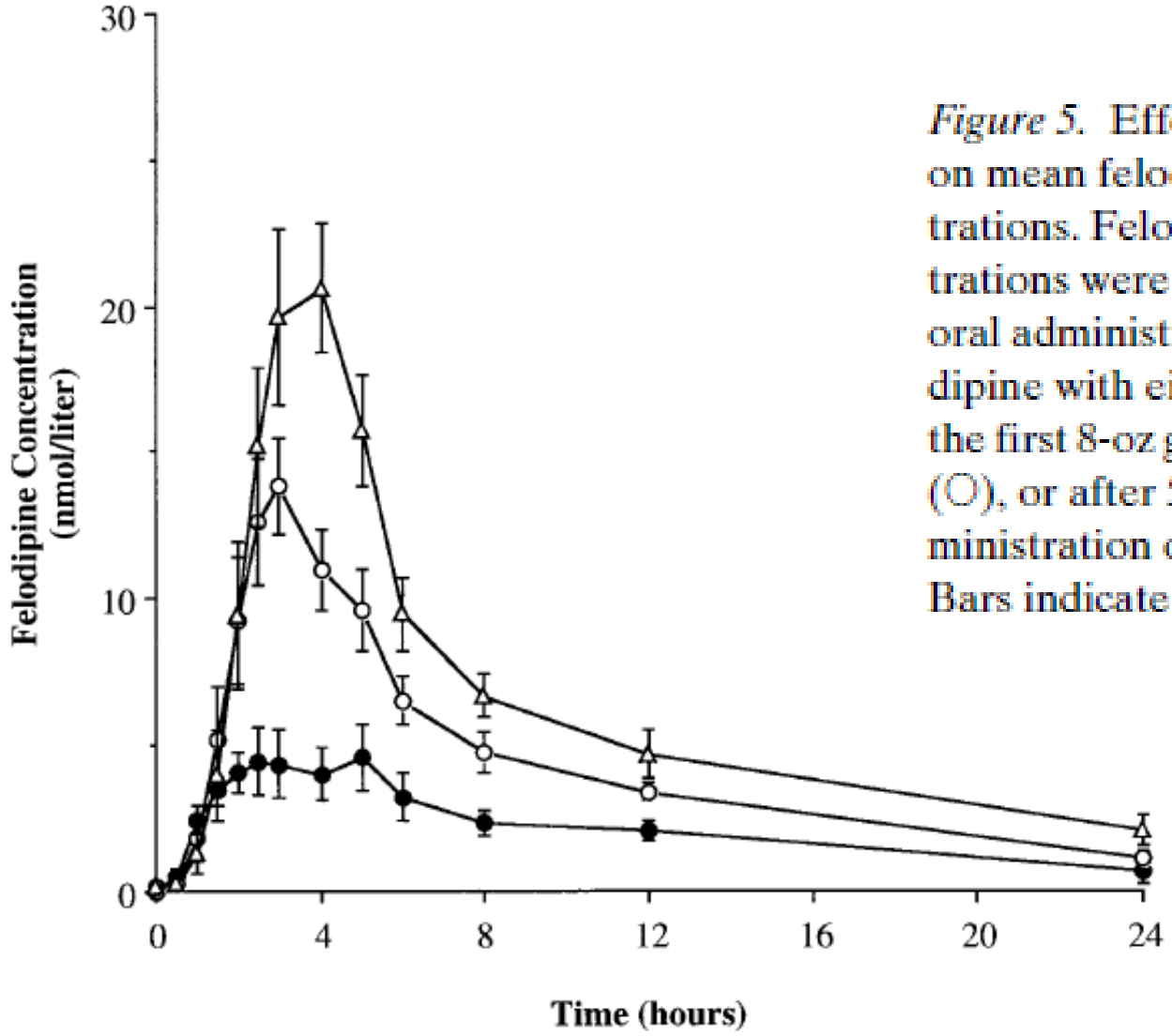

Figure 5. Effect of grapefruit juice on mean felodipine plasma concentrations. Felodipine plasma concentrations were measured after the oral administration of 10 mg felodipine with either water (●), after the first 8-oz glass of grapefruit juice (○), or after 5 d of thrice daily administration of grapefruit juice (△). Bars indicate standard errors.

Lown, K. S., Bailey, D. G., Fontana, R. J., Janardan, S. K., Adair, C. H., Fortlage, L. a, … Watkins, P. B. (1997). Grapefruit juice increases felodipine oral availability in humans by decreasing intestinal CYP3A protein expression. *The Journal of clinical investigation, 99*(10), 2545–53.

Grapefruit – interactions with drugs

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Drug class	drug	bioavailability	adverse events (dose-related)	predicted interaction risk
Anticancer agents	Crizotinib	Intermediate	Torsade de pointes, myelotoxicity	High
	Everolismus	Low	Myelotoxicity, nephrotoxicity	High
Antilipemic agents	Atorvastatin	Low	Rhabdomyolysis	High
	Simvastatin	Very low	Rhabdomyolysis	Very high
Cardiovascular agents	Felodipine	Low	Hypotension, peripheral edema	Intermediate
Gastrointestinal agents	Domperidon	Low	Torsade de pointes	Very high
Immuno-suppressants	Cyclosporine	Low	Nephrotoxicity	High

Bailey, D. G., Dresser, G., & Arnold, J. M. O. (2013). Grapefruit-medication interactions: forbidden fruit or avoidable consequences? *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne*, *185*(4),

Grapefruit – interactions with drugs

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Table 2: Case reports of serious adverse events related to grapefruit–drug interaction[18–26]

Serious adverse event	Drug	Amount of grapefruit consumed
Torsade de pointes	Amiodarone[18]	Juice, 1–1.5 L/d on a regular basis
	Quinine in tonic water[19]	Juice, high volume during preceding days
Complete heart block	Verapamil[20]	Juice, high volume during preceding days
Rhabdomyolysis	Atorvastatin[21,22]	Juice, 1–2 glasses/d for 5 d; juice from fresh grapefruit daily for 2 mo
	Simvastatin[23]	Whole fruit, 1 fruit/d for 2 wk
Nephrotoxicity	Tacrolimus[24]	Marmalade, 1.5 kg eaten during preceding 1 wk
Myelotoxicity	Colchicine[25]	Juice, 1 L/d for preceding 2 mo
Venous thrombosis	Ethinylestradiol[26]	Whole fruit, 1 fruit/d for breakfast for preceding 3 d

Bailey, D. G., Dresser, G., & Arnold, J. M. O. (2013). Grapefruit-medication interactions: forbidden fruit or avoidable consequences? *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne*, *185*(4),

Induction of enzymes and transporters

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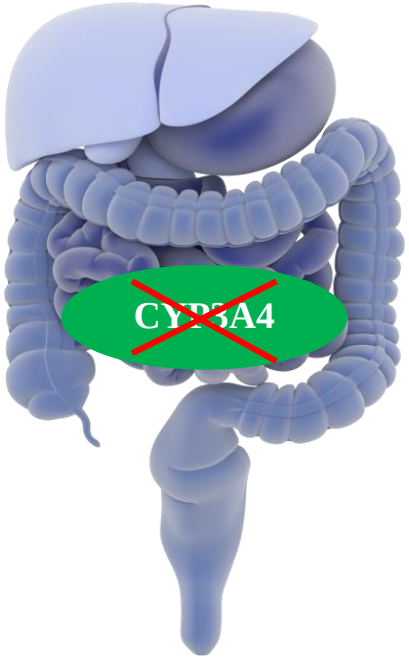
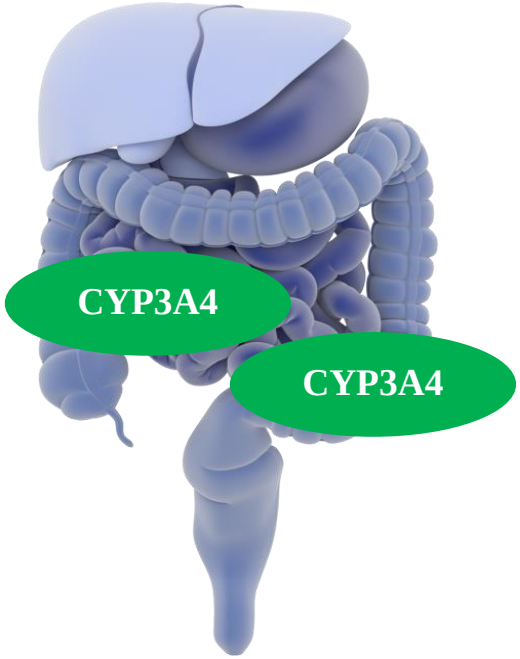
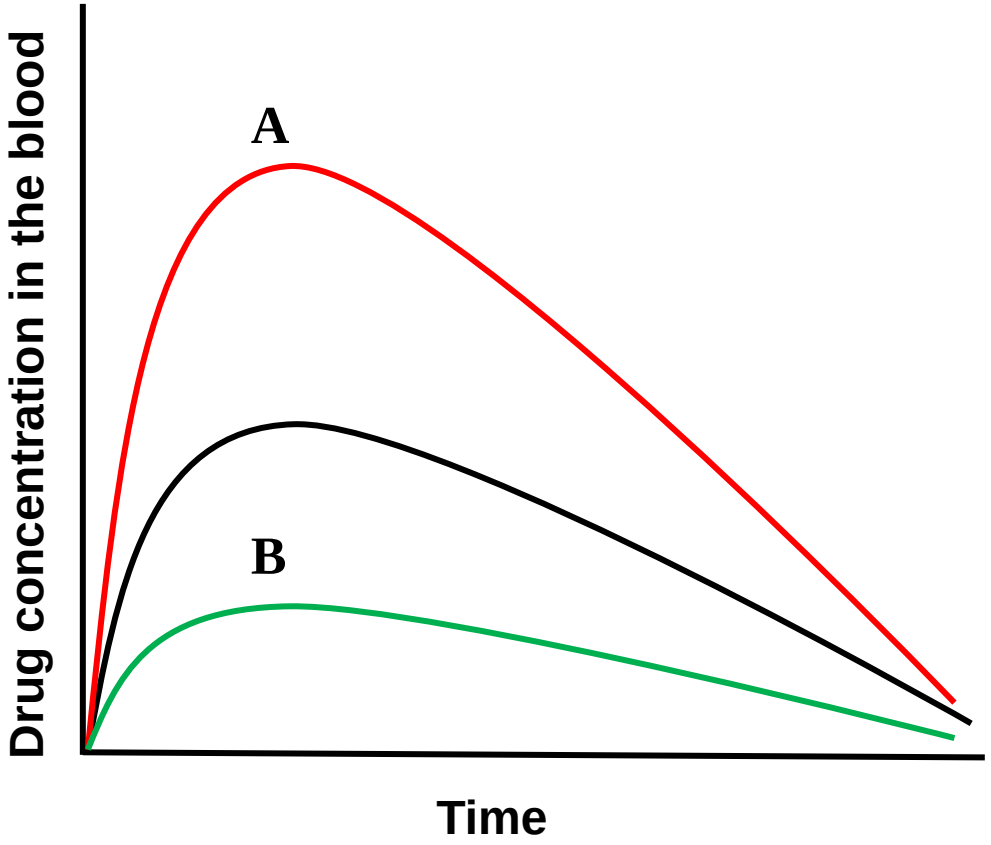
A) Inhibition CYP3A4



B) Induction CYP3A4





St John‘s wort
Hypericum perforatum

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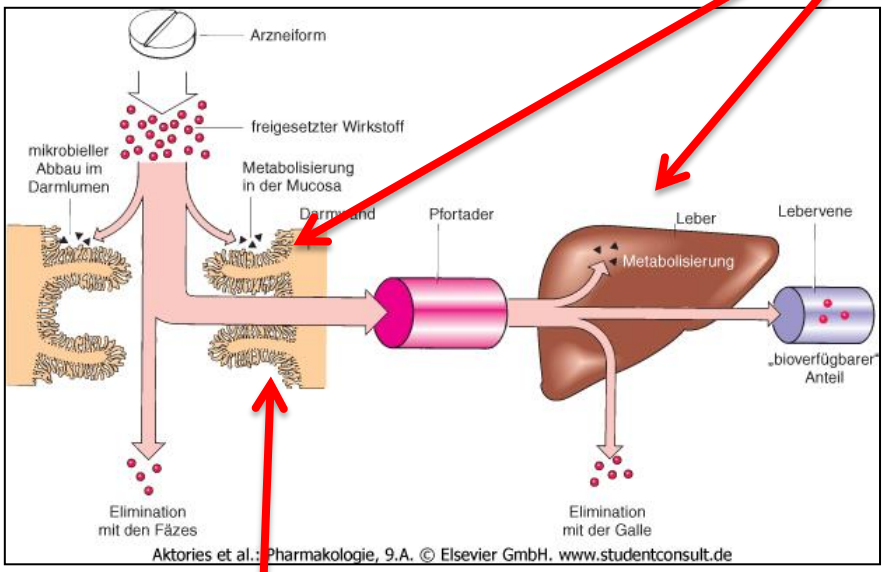
Traditional medicinal herbal product sold over-the-counter as a treatment for mild depression

St John‘s wort

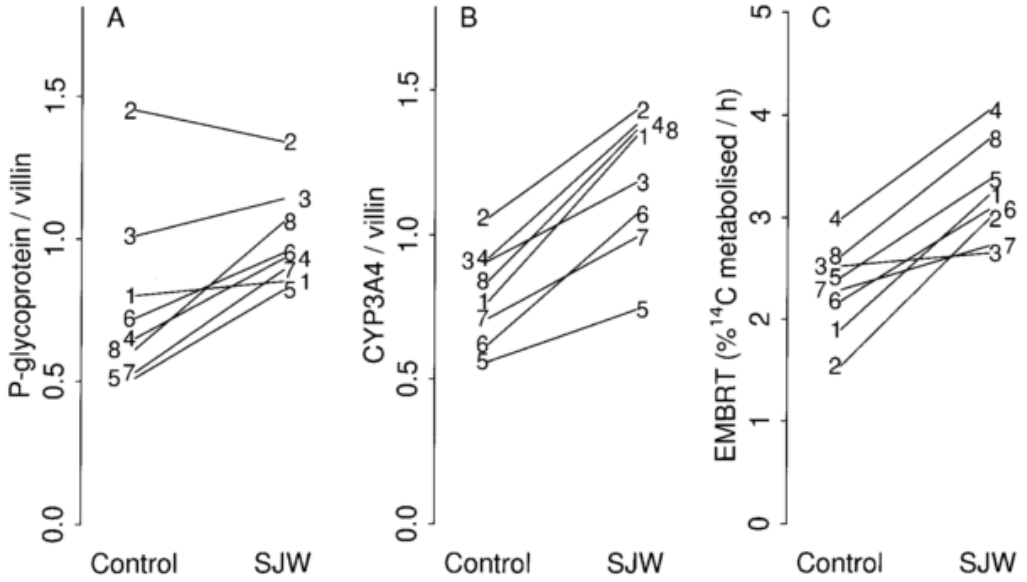
UNIVERSITÄT HOHENHEIM

active compound: hyperforin

CYP3A4



P-glycoprotein



Dürr et al. St John's Wort induces intestinal P-glycoprotein/MDR1 and intestinal and hepatic CYP3A4.

St John‘s wort – described interactions

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Table 5 The St John's Wort-drug interactions with major severity*

HDS	Drugs	Potential consequences/reactions†
St John's wort	Amiodarone (20,37)	↓Effect of amiodarone
	Benzodiazepine: alprazolam, clonazepam, diazepam, midazolam, triazolam (20,36,37,49,59,62,64,65,76,77,80,81,87,93,97,99,103)	↓Benzodiazepine effectiveness
	Bupropion, buspirone, eletriptan, meperidine, trazodone (17,31,37,39,65,69,99,103)	↑Risk of serotonin syndrome
	MAOI: isocarboxazid, phenelzine, tranylcypromine (17,33)	
	SSRI: citalopram, duloxetine, fluoxetine, fluvoxamine, nefazodone, paroxetine, sertraline, venlafaxine (12,16–18,20,31,32,35–37,47,52,59,64,65,69,72,77,81,87,99,103)	
	TCA: amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine (12,16,17,20,36,37,59,64,65,69,72,76, 77,80,81,85,87,93,97,99,103)	
	Busulfan (39)	↓Effect of busulfan
	Calcium channel blockers: diltiazem, felodipine, nicardipine, nifedipine, nitrendipine, verapamil (16,20,37,59,65,76,79–81,99,102,103)	↓Effect of calcium channel blockers
	Carbamazepine (32,37,99)	↓Effect of carbamazepine
	Cyclophosphamide (16,37,93)	↓Effect of cyclophosphamide
	Cyclosporin (12,16–18,20–22,30–32,34–37,47,49–51,59,64,65,69,72,76,77, 79–81,92,93,97,99,102,103)	↓Effect of cyclosporine
	Dapsone (37)	↓Effect of Dapsone
	Dexamethasone (39)	↓Effect of dexamethasone
	Digoxin (12,16–18,20,22,30–32,34,36,37,47,51,59,64–66,69,72,76,77, 79–81,87,90,92,93,97,99,102,103)	↓Effect of digoxin
	Docetaxel (39,74)	↓Effect of docetaxel
	Dolasetron (39)	↓Effect of dolasetron
	Doxorubicin (39,81)	↓Effect of doxorubicin
	Erlotinib (20)	↓Effect of erlotinib
	Erythromycin (103)	↓Effect of erythromycin
	Estrogens/progestogens: estradiol, gestodene, levonorgestrel, norethindrone (37,39,50,72)	↓Effect of contraceptive
	Etoposide (39,81)	↓Effect of etoposide
	Exemestane (20)	↓Effect of exemestane
	Fentanyl, Morphine, Oxycodone (21,37,99,111)	↑Sedation
	Fexofenadine (20,44,59,64,65,76,77,79,80,93,97,99,103)	↓Effect of fexofenadine
	Finasteride (39)	↓Effect of finasteride
	Flutamide (32,39)	↓Effect of flutamide
	Gliclazide (103)	↓Effect of gliclazide
	Haloperidol (37)	↓Effect of haloperidol
	Ifosfamide (39)	↓Effect of ifosfamide
	Imatinib (20,59,76,77,79,80,97,99,103)	↓Effect of imatinib
	Irinotecan (12,16,20–22,49,59,64,65,76,77,80,81,97,103)	↓Effect of irinotecan
	Ivabradine (103)	↓Effect of ivabradine
	Ixabepilone (20)	↓Effect of ixabepilone
	Lapatinib (20)	↓Effect of lapatinib
	Lidocaine (37)	↑Risk of cardiovascular collapse
	Loperamide (21,30,35,36,64,77,99,103)	↓Effect of loperamide
	Maraviroc (20)	↓Effect of maraviroc
	Mephenytoin (76,97,99,103)	↓Effect of mephenytoin
	Methadone (20,21,37,64,65,77,92,93,99,103)	↓Effect of methadone
	NNRTI: delavirdine, efavirenz, nevirapine (16,18,20,32,37,69,76,77,80,99,103)	↓NNRTI concentrations
	Omeprazole (17,20,65,76,77,80,92,93,103)	↓Effect of omeprazole
	Ondansetron (39)	↓Effect of ondansetron
	Paclitaxel (37,39)	↓Effect of paclitaxel

Table 5 Continued

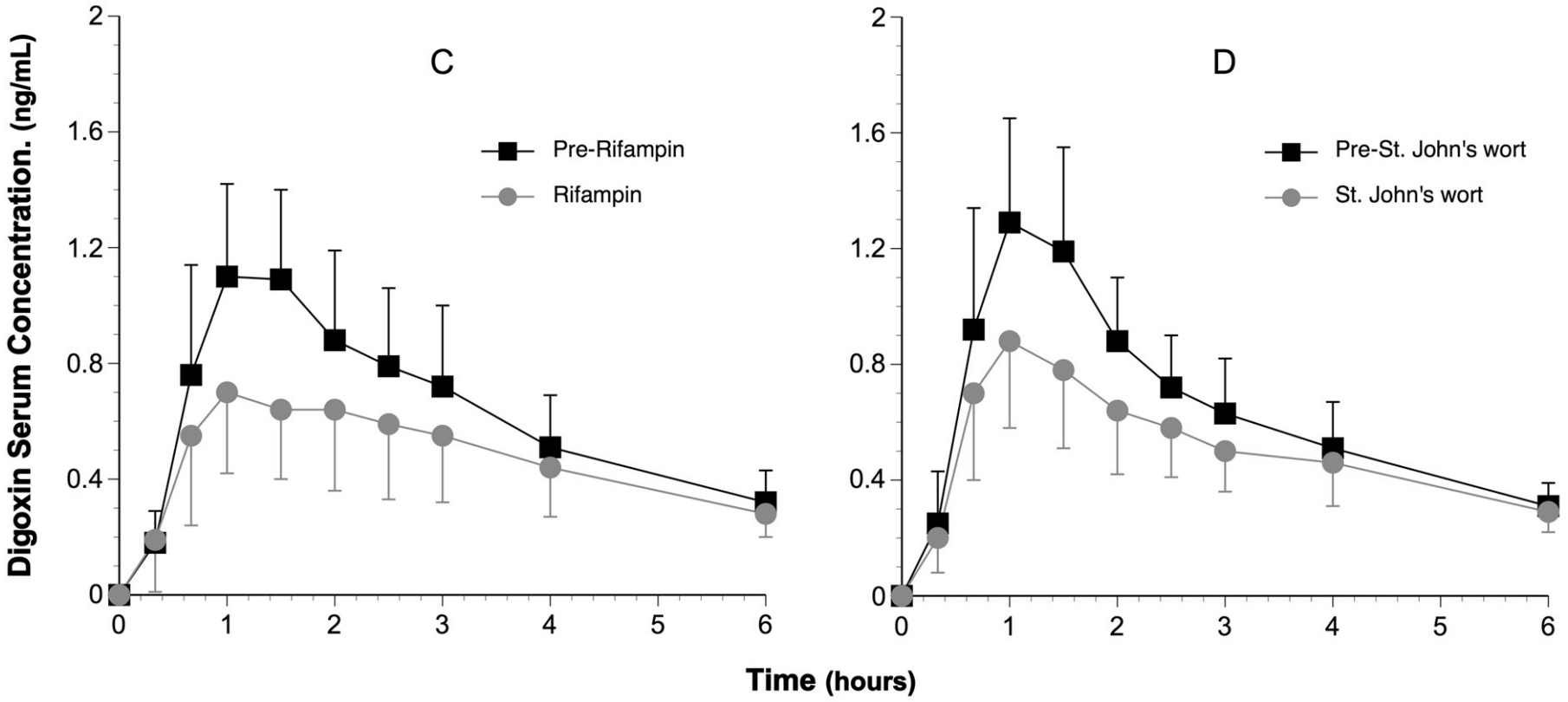
HDS	Drugs	Potential consequences/reactions†
	Phenprocoumon (12,18,31,35–37,47,65,66,77,80,81,97,103)	↓Effect of phenprocoumon
	Phenytoin (32)	↓Effect of phenytoin
	Piroxicam, rasagiline, risperidone, tetracycline, tolbutamide, tretinoin (20,37,39,77,102,103)	↑Photosensitivity reactions
	Propofol, sevoflurane (20,99,103)	↑Risk of cardiovascular collapse
	Protease inhibitors: amprenavir, atazanavir, darunavir, fosamprenavir, indinavir, nelfinavir, ritonavir, saquinavir, tipranavir (12,16–22,32,34,36,37,47,49,51,64,65,69,72, 76,77,79–81,93,97,103)	↓Effect of protease inhibitor
	Quetiapine (37)	↓Effect of Quetiapine
	Quinidine (37)	↓Effect of Quinidine
	Sildenafil (37,50,93)	↓Effect of Sildenafil
	Sirolimus (20)	↓Effect of Sirolimus
	Sunitinib (20)	↓Effect of sunitinib
	Tacrolimus (12,16,20,37,59,64,65,76,77,79–81,92,93,97,99,103)	↓Effect of tacrolimus
	Tamoxifen (16,37,39)	↓Effect of tamoxifen
	Temsirolimus (20)	↓Effect of sirolimus, the active metabolite of temsirolimus
	Teniposide (39)	↓Effect of teniposide
	Tramadol (96)	↓Effect of tramadol
	Vinblastin (37,39,81)	↓Effect of vinblastin
	Vincristine (39)	↓Effect of vincristine
	Voriconazole (20,76,77,99,103)	↓Effect of voriconazole
	Warfarin (16–18,20,22,32,35–37,43,47,51,59,64–66,69, 70,72,73,75–77,79–81,85,87,97,99,102,103)	↓Effect of warfarin

*Any HDS–drug interactions with severity rated as contraindicated or major in either database of MicroMedex® or NMCD® were included in this table. †Potential consequences or reactions were documented according to either aforementioned database with severity rating as major or contraindicated. ↑, increasing; ↓, decreasing. MAOI, monoamine oxidase inhibitors; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; NNRTI, non-nucleoside reverse transcriptase inhibitors.

Tsai, H-H at al.
Evaluation of documented drug interactions and contraindications associated with herbs and dietary supplements: a systematic literature review.

St John‘s wort

induction of intestinal P-glycoprotein (MDR-1)



Gurley, B. J., Swain, A., Williams, D. K., Barone, G., & Battu, S. K. (2008). Gauging the clinical significance of P-glycoprotein-mediated herb-drug interactions: comparative effects of St. John’s wort, Echinacea, clarithromycin, and rifampin on digoxin pharmacokinetics. *Molecular nutrition & food research*, *52*(7), 772–9:

Induction of P-glycoprotein (MDR-1) genexpression

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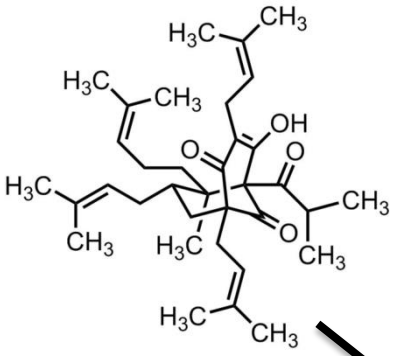

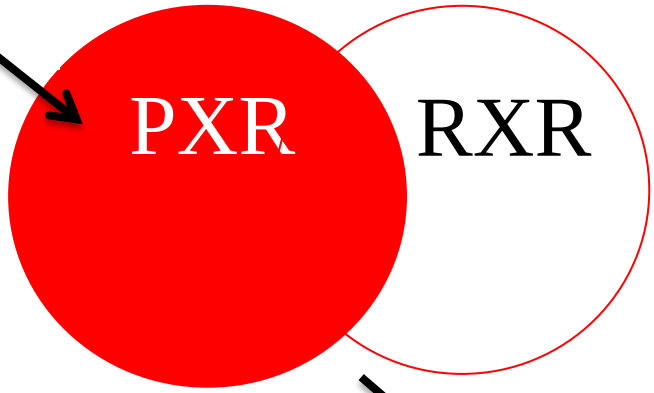

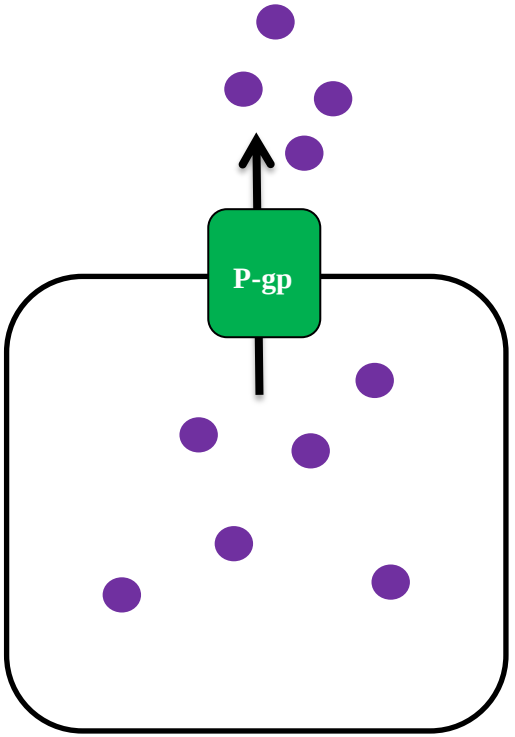

Induction of CYP3A4 genexpression

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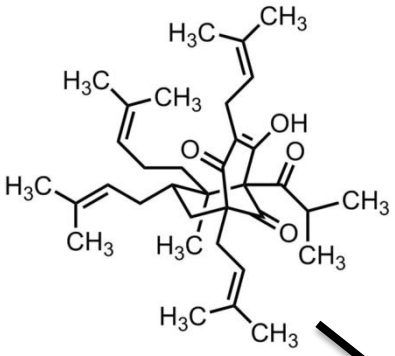

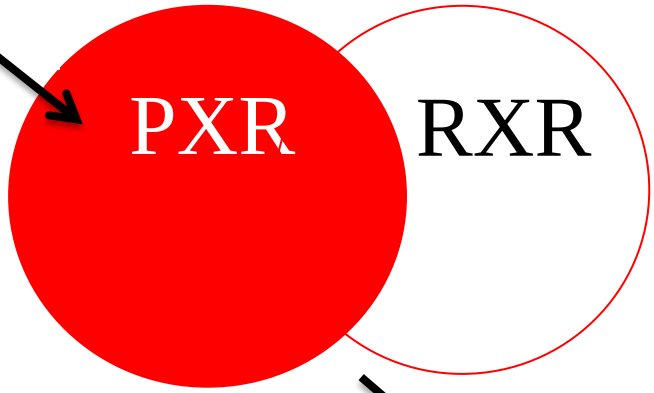

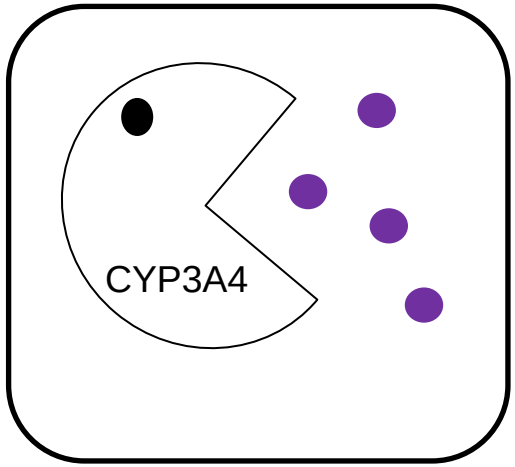

XREM (Xenobiotic Response Element) CYP3A4

St John‘s wort induction of CYP3A4

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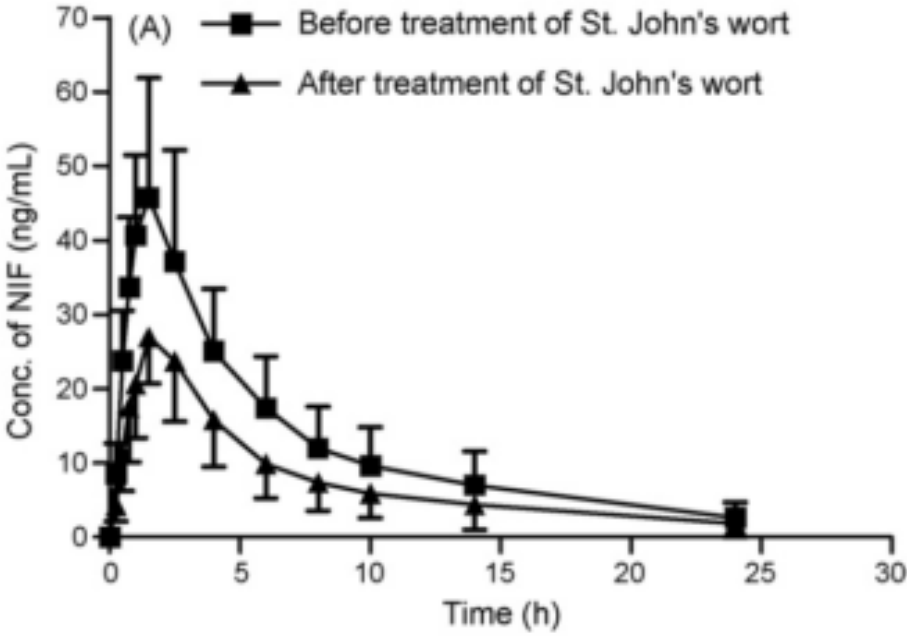
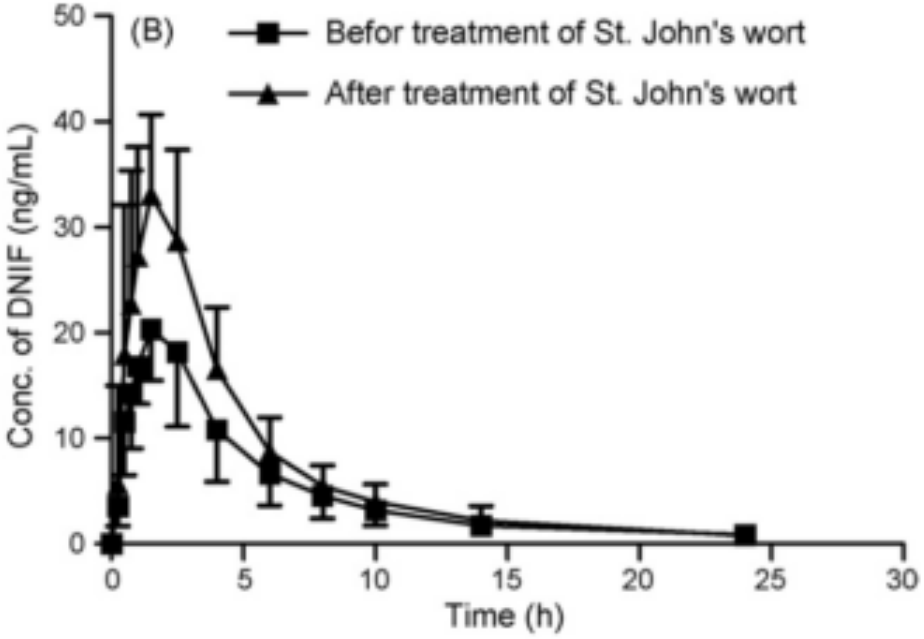
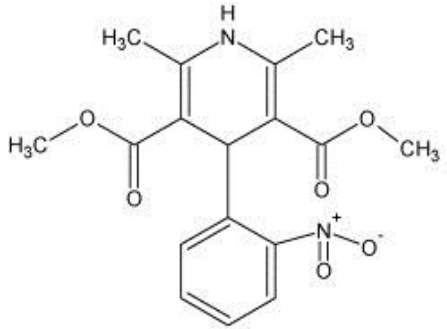
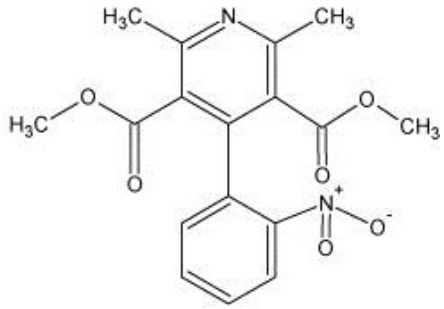






I (Nifedipine)

CYP3A4



II (Dehydronifedipine)

Wang, X.-D., Li, J.-L., Lu, Y., Chen, X., Huang, M., Chowbay, B., & Zhou, S.-F. (2007). Rapid and simultaneous determination of nifedipine and dehydronifedipine in human plasma by liquid chromatography-tandem mass spectrometry: Application to a clinical herb-drug interaction study. *Journal of chromatography. B, Analytical technologies in the biomedical and life sciences, 852*(1-2), 534–44..

St John‘s wort

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The interaction between St John’s wort and an oral contraceptive

Objectives: The popular herbal remedy St John’s wort is an inducer of cytochrome P450 (CYP) 3A enzymes and may reduce the efficacy of oral contraceptives. Therefore we evaluated the effect of St John’s wort on the disposition and efficacy of Ortho-Novum 1/35 (Ortho-McNeil Pharmaceutical, Inc, Raritan, NJ), a popular combination oral contraceptive pill containing ethinyl estradiol (INN, ethinylestradiol) and norethindrone (INN, norethisterone).

Conclusion: St John’s wort causes an induction of ethinyl estradiol–norethindrone metabolism consistent with increased CYP3A activity. Women taking oral contraceptive pills should be counseled to expect breakthrough bleeding and should consider adding a barrier method of contraception when consuming St Johns wort. (Clin Pharmacol Ther 2003;74:525-35.)

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Vitamin E induction CYP3A4?

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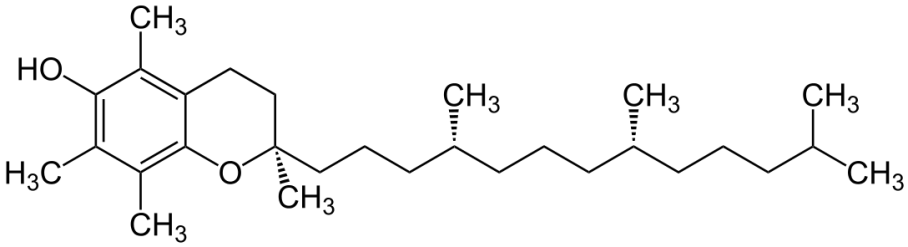
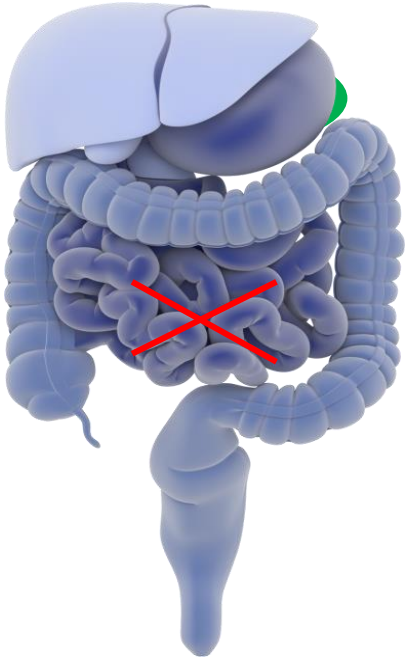
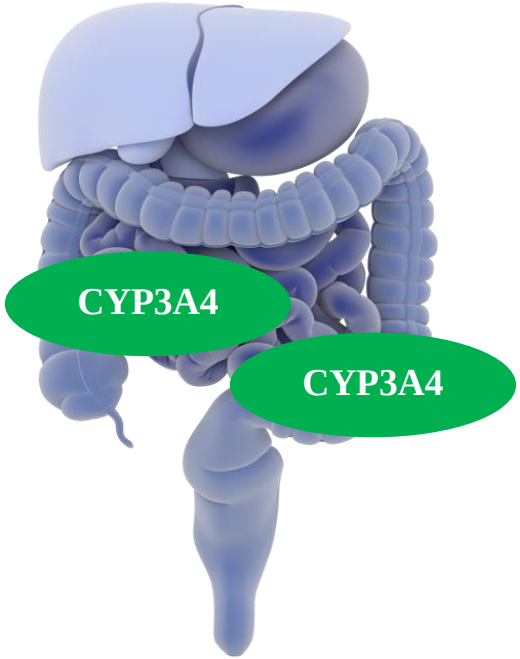
?

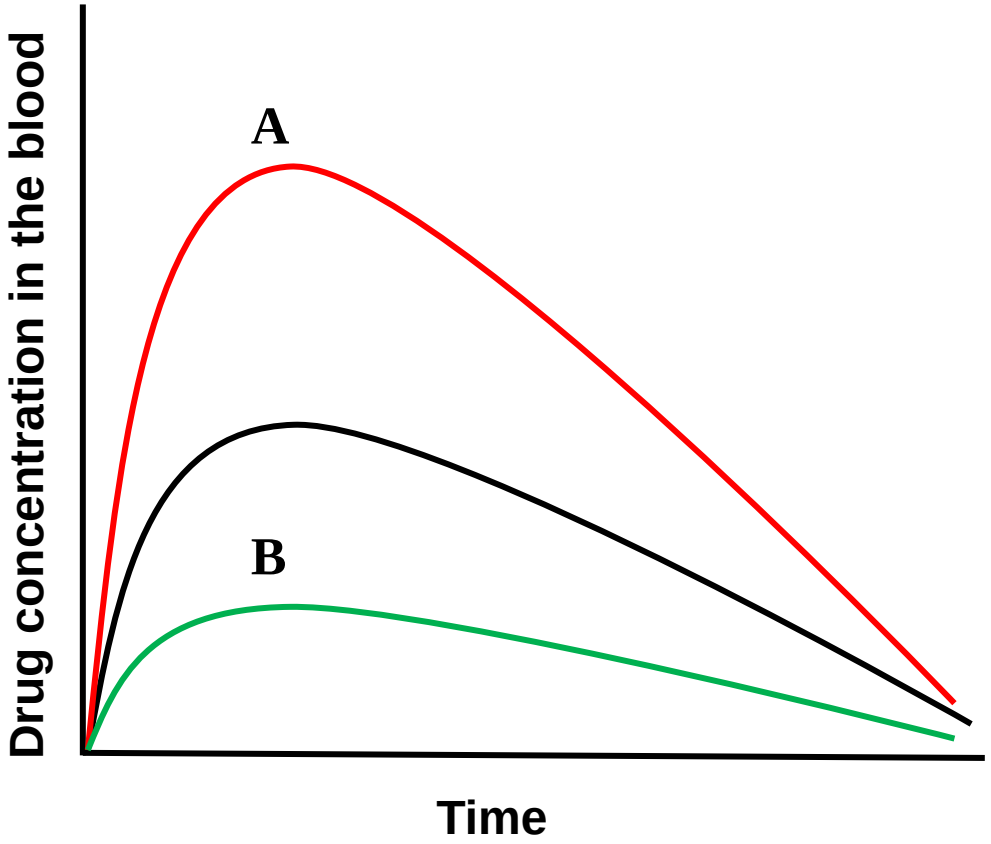


A) Inhibition CYP3A4



B) Induction CYP3A4





Vitamin E induction CYP3A4?

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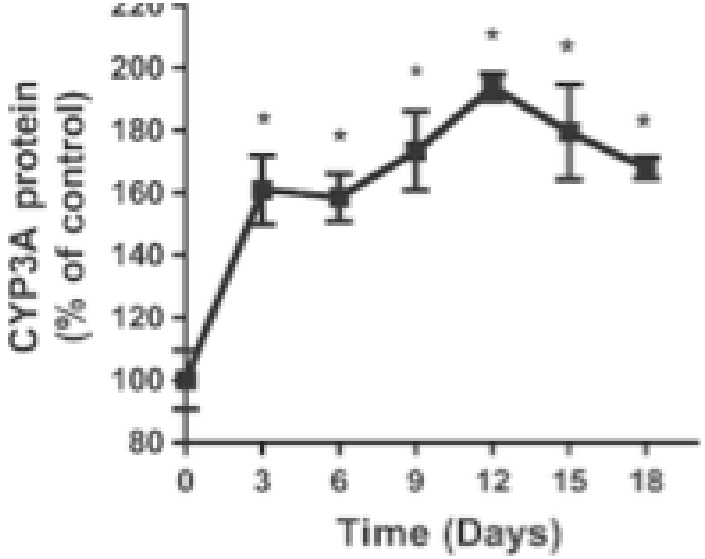

Rats were injected daily with 100 mg/kg BW αT for 18 d

Injection solution contained 20% ethanol

Mustacich et al. 2006 Free Radic Biol Med 41:1069-78.

Research in our lab:

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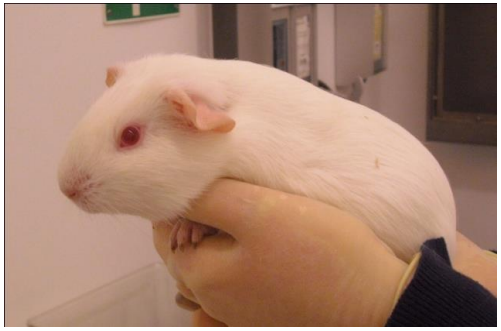
Influence of Vitamin E on CYP3A4

- 50 female Dunkin-Hartley guinea pigs
- 10 animals per group
- 1 week acclimatisation phase / 6 weeks feeding the respective test diet

Group	Diet
Control	5% Coconut and milk fat
High-fat control	21% Coconut and milk fat + 0.15% cholesterol
Atorvastatin	21% Coconut and milk fat + 0.15% cholesterol + 300 mg/kg atorvastatin
Vitamin E	21% Coconut and milk fat + 0.15% cholesterol + 250 mg/kg α-Tocopherol
Atorvastatin + Vitamin E	21% Coconut and milk fat + 0.15% cholesterol + 300 mg atorvastatin + 250 mg/kg α-Tocopherol



Influence of Vitamin E on the pharmacodynamics of atorvastatin

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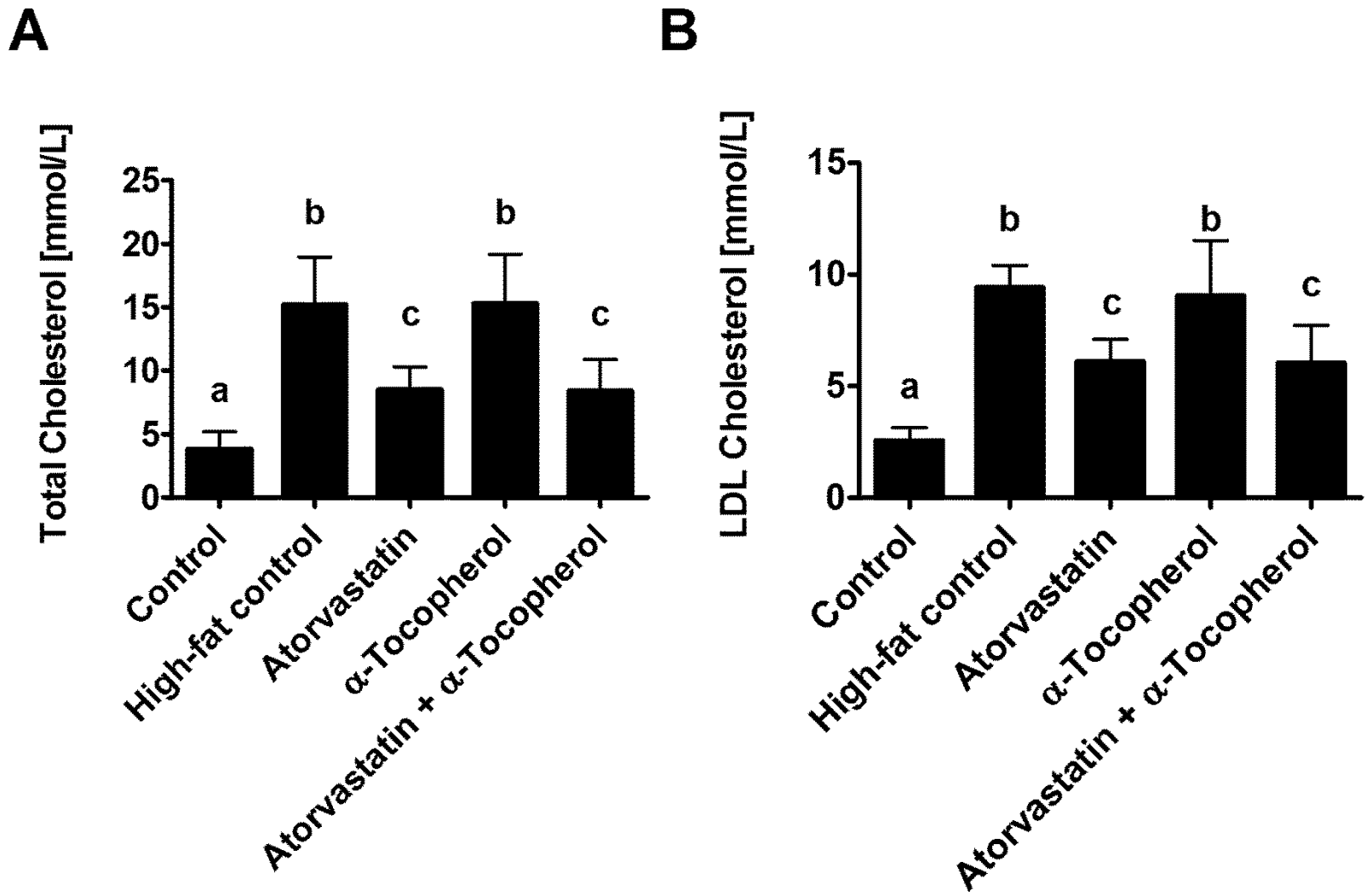

Podszun, M. C., Grebenstein, N., Hofmann, U., & Frank, J. (2013). High-dose supplementation with natural α-tocopherol does neither alter the pharmacodynamics of atorvastatin nor its phase I metabolism in guinea pigs. *Toxicology and applied pharmacology*, *266*(3), 452–8.

Influence of Vitamin E on CYP3A4 hepatic and intestinal protein expression

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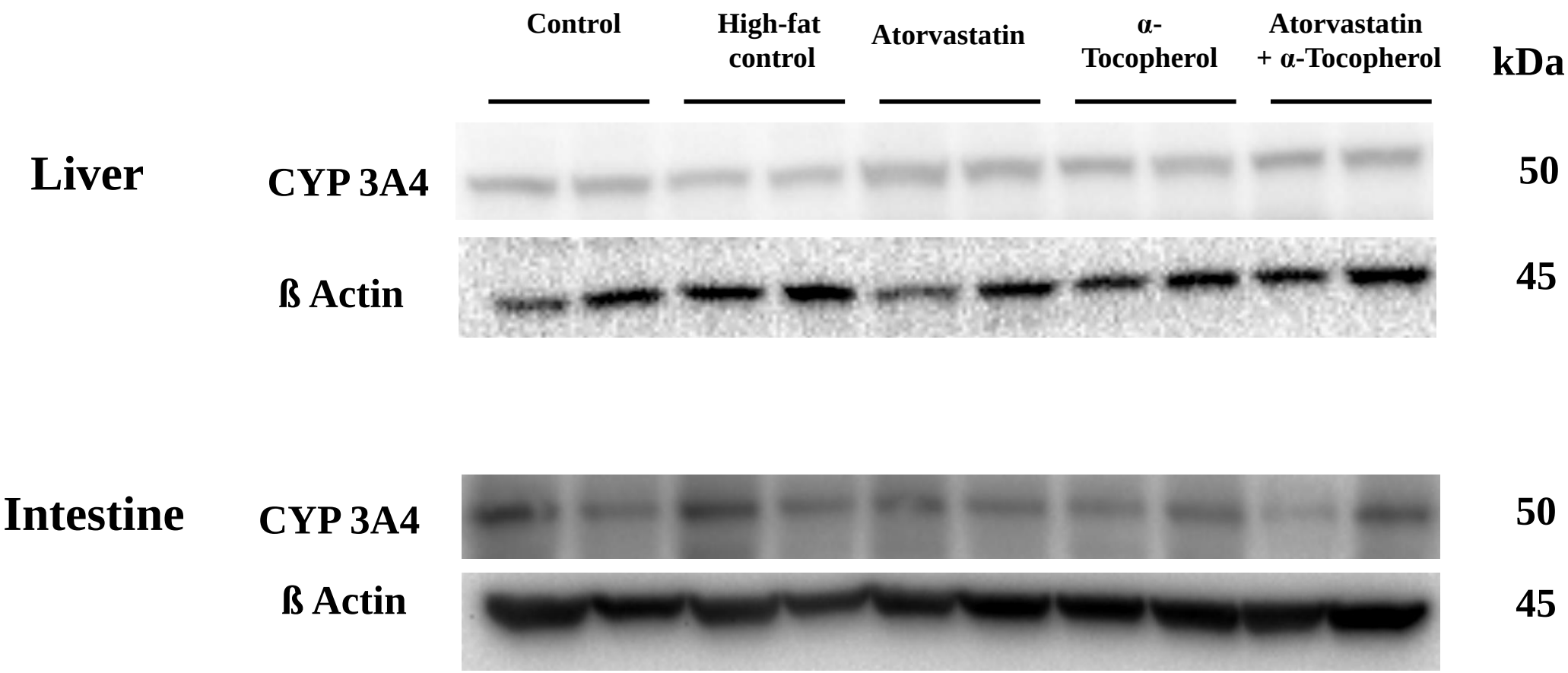

Podszun, M. C., Grebenstein, N., Hofmann, U., & Frank, J. (2013). High-dose supplementation with natural α-tocopherol does neither alter the pharmacodynamics of atorvastatin nor its phase I metabolism in guinea pigs. *Toxicology and applied pharmacology*, *266*(3), 452–8.

Influence of Vitamin E on the plasma concentration of atorvastatin and metabolites

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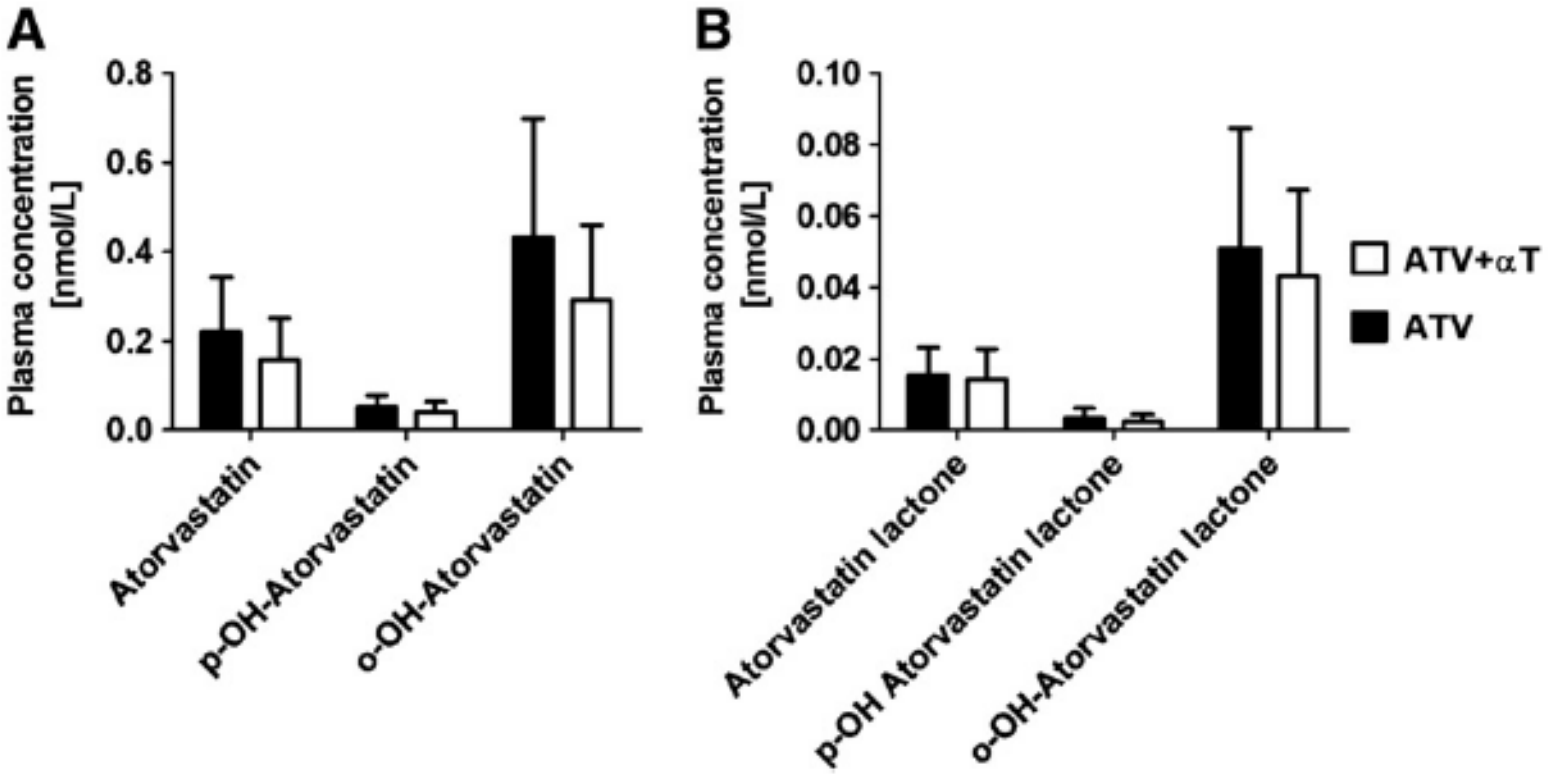

Podszun, M. C., Grebenstein, N., Hofmann, U., & Frank, J. (2013). High-dose supplementation with natural α-tocopherol does neither alter the pharmacodynamics of atorvastatin nor its phase I metabolism in guinea pigs. *Toxicology and applied pharmacology*, *266*(3), 452–8.

How about some green tea?

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Green Tea

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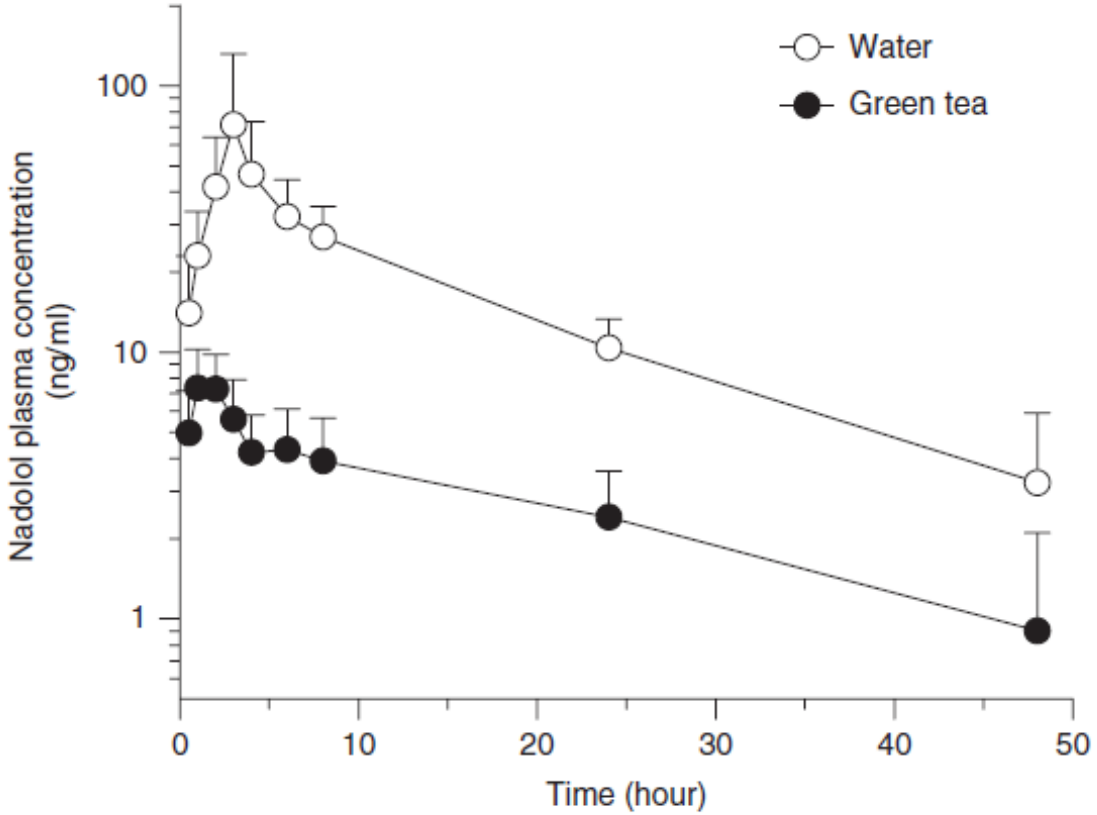
- 14 days either 700 ml commercially brewed green tea or water
- Single oral dose of the blood pressure medication nadolol (30 mg) after 14 days
- C_{max} of nadolol 85 % lower with green tea



Misaka, S. *et al.* Green tea ingestion greatly reduces plasma concentrations of nadolol in healthy subjects. *Clin. Pharmacol. Ther.* **95,** 432–8 (2014).

Green Tea

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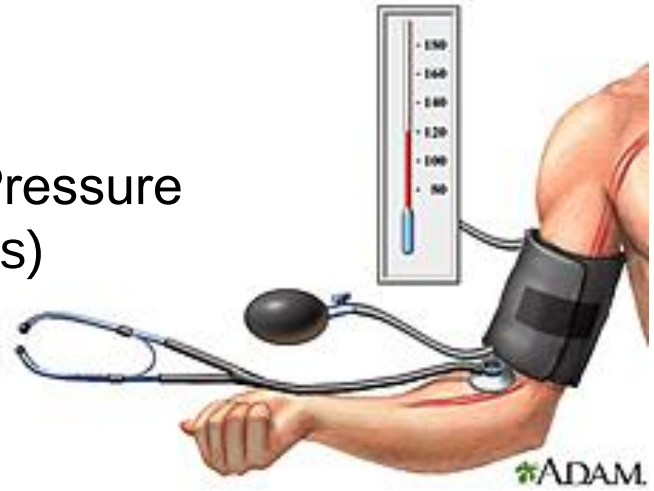
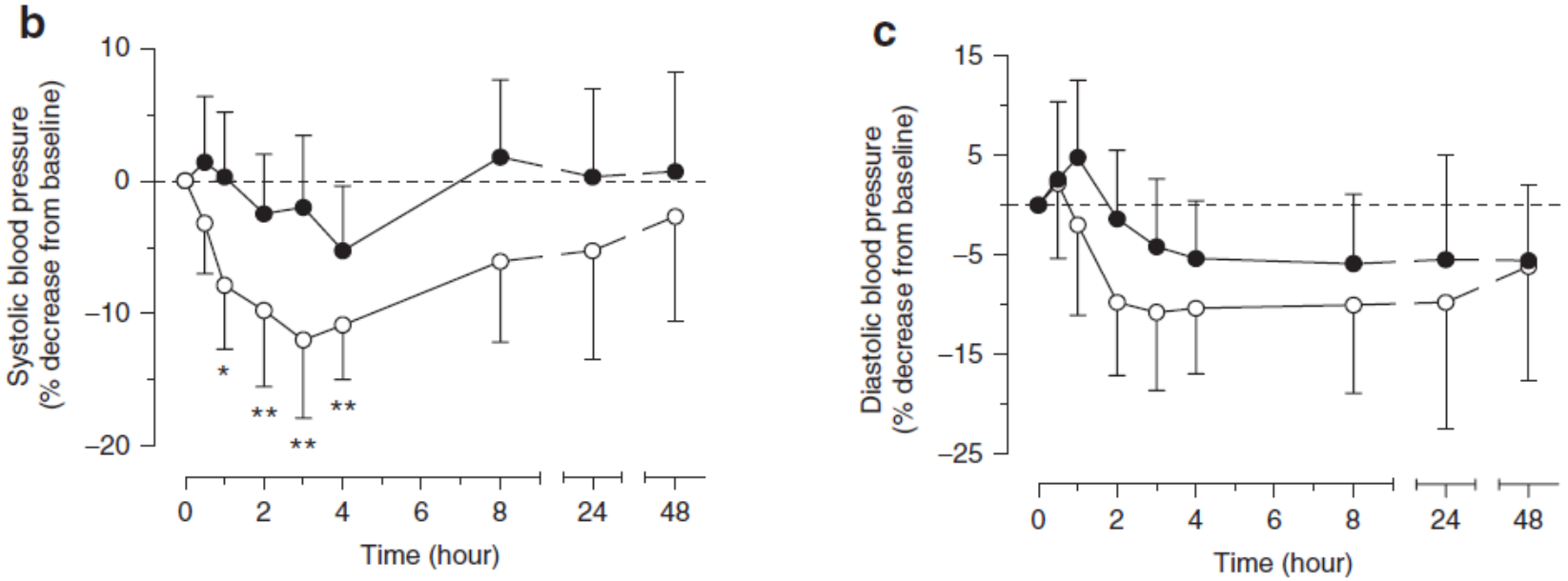
Nadolol ↓ Blood Pressure
(white circles)



Nadolol + Green Tea
↔ Blood Pressure
(black circles)



Misaka, S. *et al.* Green tea ingestion greatly reduces plasma concentrations of nadolol in healthy subjects. *Clin. Pharmacol. Ther.* **95,** 432–8 (2014).

Green Tea

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700 ml (daily doses) contains

- 56 mg epicatechin (EC) (8 mg/ 100ml)
- 168 mg epigallocatechin (EGC) (24 mg/ 100 ml)
- 91 mg epichatechin gallate (ECG) (13 mg/ 100 ml)
- 322 mg epigallocatechin gallate (EGCG) (46 mg/ 100 ml)

Table 2b. Determination of Catechin Content of 8 Green Teas

Tea Catechin	Bigelow Green Tea	Celestial Seasoning Green Tea	Uncle Lee's Green Tea	Salada Green Tea Earl Green	Lipton Green Tea	Stash Premium Green Tea Decaf	Salada Green Tea Decaf	Celestial Seasoning Decaf Green Tea
				mg/100 ml				
Gallic acid	1.5 ± 0.1	0.6 ± 0	1.0 ± 0.1	0.8 ± 0.1	1.2 ± 0	0.7 ± 0.1	2.0 ± 0	1.8 ± 0.1
Caffeine	23.6 ± 1.5	33.6 ± 0.2	29.4 ± 2.7	21.8 ± 1.8	33.1 ± 0.7	5.8 ± 0.6	3.8 ± 0	0.7 ± 0
EGC	30.9 ± 1.5	79.7 ± 1.0	49.2 ± 2.3	38.7 ± 2.9	76.4 ± 1.8	22.0 ± 1.5	23.8 ± 0.3	22.2 ± 0.4
Catechin	0.0 ± 0	4.4 ± 0.1	3.6 ± 0.5	0.0 ± 0	5.8 ± 0.9	0.0 ± 0	3.4 ± 0.5	0.0 ± 0
Epicatechin	6.5 ± 0.4	13.3 ± 0.1	15.4 ± 1.2	7.0 ± 0.6	11.9 ± 0.1	0.0 ± 0	4.1 ± 0	2.9 ± 0
EGCG	42.5 ± 2.5	99.3 ± 1.8	65.0 ± 7.1	49.8 ± 3.6	83.9 ± 2.8	20.7 ± 1.8	46.3 ± 0.7	37.7 ± 0.8
GCG	4.1 ± 0.2	5.4 ± 0.3	4.3 ± 0.4	3.1 ± 0.3	1.1 ± 0.1	3.6 ± 0.6	6.2 ± 0.1	3.4 ± 0
ECG	3.6 ± 0	4.0 ± 1.6	15.9 ± 1.5	9.5 ± 0.8	13.7 ± 0.3	6.1 ± 0.6	2.0 ± 0.1	5.2 ± 0.3
Catechin gallate	0.0 ± 0	10.0 ± 1.2	2.4 ± 0.2	0.3 ± 0.5	3.1 ± 0.1	0.4 ± 0.5	1.1 ± 0	0.9 ± 0
Total catechin	87.5 ± 4.6	216.2 ± 0.5	155.7 ± 13.2	108.5 ± 8.6	196.6 ± 5.2	52.7 ± 5.0	86.8 ± 0.7	72.3 ± 0.7
Total catechin + gallic acid	89.0 ± 4.6	216.7 ± 0.5	156.8 ± 13.3	109.3 ± 8.7	197.8 ± 5.2	53.3 ± 5.0	88.8 ± 0.7	74.1 ± 0.6
Total catechin + gallic acid/g tea	59.3 ± 3.1	103.2 ± 0.3	78.4 ± 6.6	60.7 ± 4.8	82.4 ± 2.2	26.7 ± 2.5	52.2 ± 0.4	39.0 ± 0.3

Henning et al. "Catechin Content of 18 Teas and a Green Tea Extract Supplement Correlates with the Antioxidant Capacity." *Nutrition and Cancer* 45 (2): 226–35.

Green Tea

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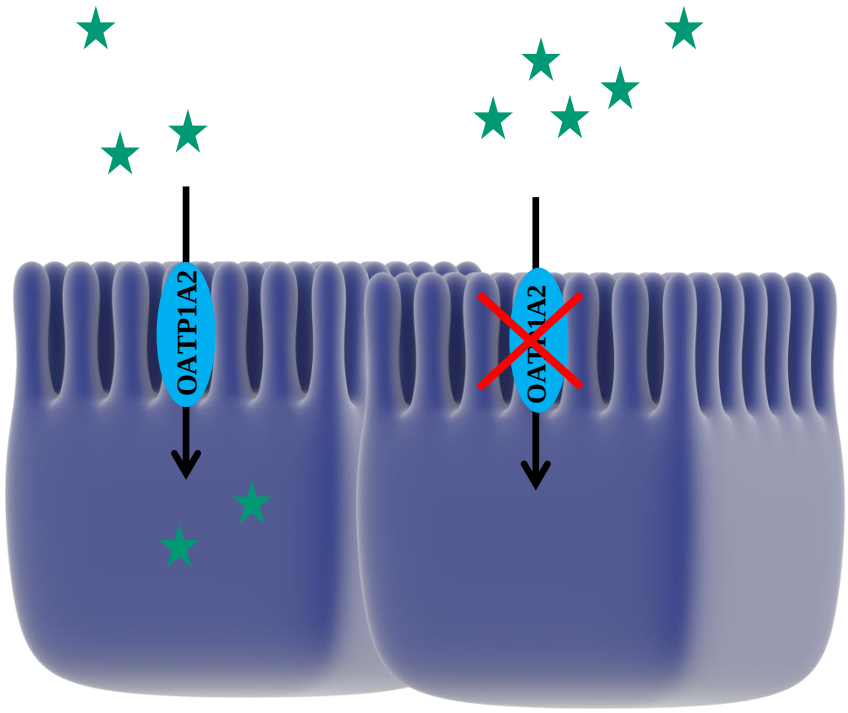
Nadolol is not metabolized by intestinal or hepatic enzymes but excreted unchanged in the urine

→ Inhibition of the transporter OATP1A2 in the intestine

Other OATP1A2 Substrates:

- fexofenadine (antihistamine, allergy treatment)
- levofloxacin (antibiotic)



Influence of green tea on CYP activity ?

14 days of green tea extract (844 mg green tea catechins/day) did not alter the activity of CYP3A4 and CYP2D6 in healthy humans.

Donovan et al. 2004 "Green Tea (Camellia Sinensis) Extract Does Not Alter Cytochrome P450 3A4 or 2D6 Activity in Healthy Volunteers :" Pharmacology 32 (9): 906–8

Nutrient-Drug Interactions: A word of Caution

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- **Caution: Isolated Nutrients**
  In most cases the danger lies in concentrated “pills” or a high consumption of a certain food (green tea), the exception is grapefruit!

- **Caution: Functional Food**
  Product formulation with high amounts of isolated nutrients, plant extracts, … could potentially alter the pharmacokinetics of drugs and thereby their effect.
  Special Concern: aging population with multiple medications

Nutrient-Drug Interactions: A word of Caution

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Caution: Novel Food

Unknown herbal extracts with unknown consequences

CASE REPORT

Acute drug toxicity related to drinking herbal tea in a kidney transplant recipient

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Abstract

Calcineurin and mTOR inhibitors are commonly used immunosuppressive agents with narrow therapeutic range. As the drugs are mainly metabolized by the P450 cytochrome system, the interaction between food and herbs are also commonly seen and affect the drug levels. We present a case of a kidney transplant recipient with toxic therapeutic levels of cyclosporine A and sirolimus due to interaction between the immunosuppressive agents and Chinese herbal tea. Ingredients within the herbal tea were reported to have inhibitory effect on cytochrome CYP3A4 *in-vitro* studies. Transplant recipients should be alert that there may be potent interaction between the immunosuppressive drugs and herbs resulting in adverse effect on allograft function.

Keywords

Drug interaction, drug toxicity, herbal tea, kidney transplantation

History

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Summary

- enzymes and transporters can be **inhibited (grapefruit)** or **induced (St John‘s wort)**
- interaction can occure **postranslational (grapefruit)** or can **affect gene expression (St John‘s wort)**
- **inhibition** of the intestinal/hepatic first pass metabolism of drugs with a low bioavailability leads to **increased** plasma concentrations → higher risk for adverse events
- **induction** of transporters and/or metabolizing enzymes leads to **reduced** plasma concentrations → loss of effectivity

Exception: pro-drugs !

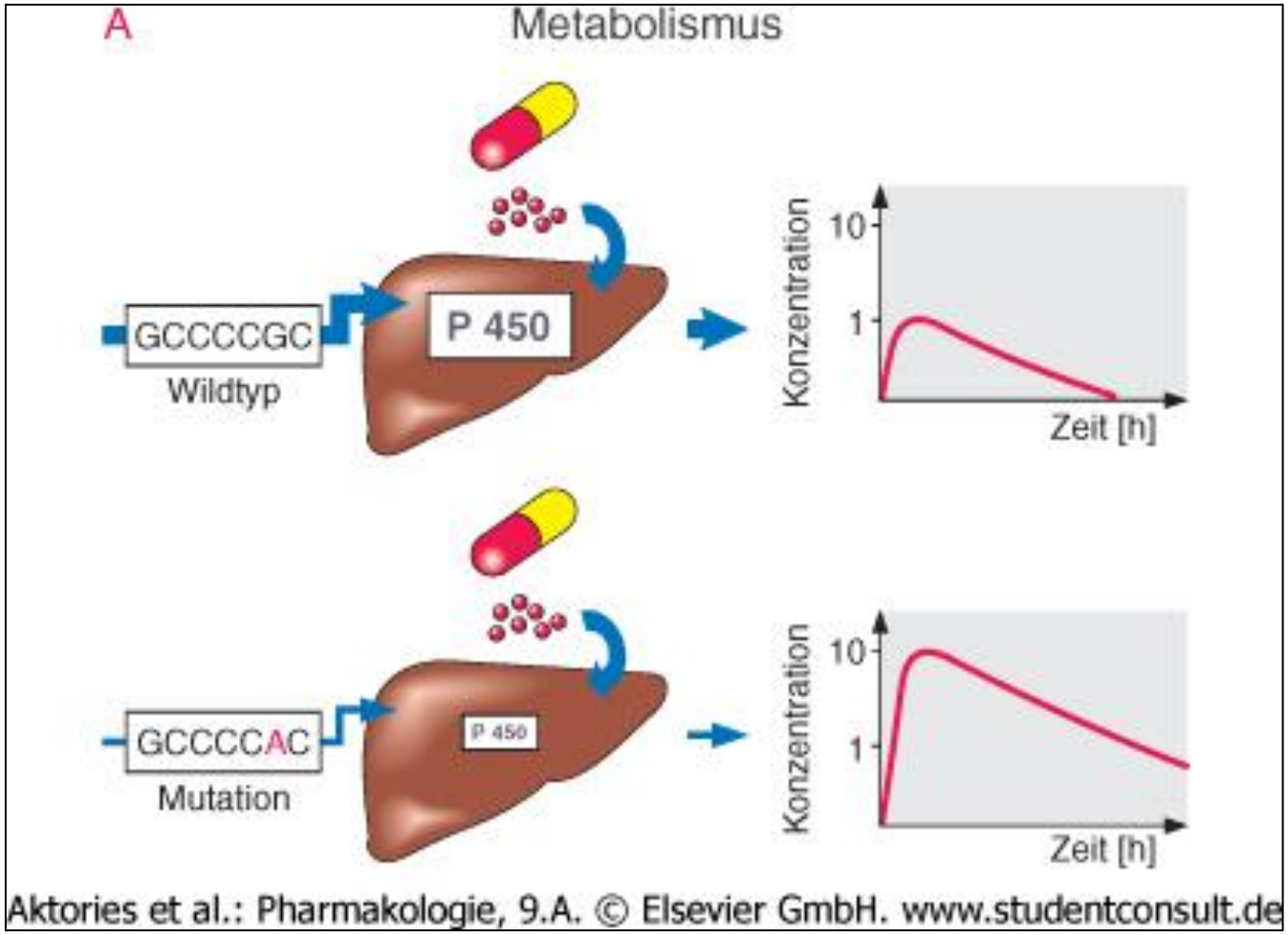
increased metabolism → more active compound

decreased metabolism → less active compound

Questions?

Pharmacogenetik

Die individuelle Wirkung



Aktories et al.: Pharmakologie, 9.A. © Elsevier GmbH. www.studentconsult.de