



# Predicting Drug-Nutrient Interactions: State of the Science & Time-Saving Tips

ACPE # 0130-9999-24-346-H01-P&T

Presented by

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## Disclosure

Sponsorship support for this program was provided by Pure Encapsulations®, and I serve as a medical consultant for Pure Encapsulations® and Douglas Laboratories®. Although I receive renumeration for my services, the information that I am sharing with you represents my own professional experience.

# Learning Objectives

At the completion of this activity, you will be able to: (pharmacists & technicians):

- Explain why many interactions are not contraindications and how to tell the difference.
- Identify four factors that determine whether a drug-nutrient interaction will occur in a patient, and how it may present clinically.
- Recognize major interactions between dietary supplements and the top 50 most prescribed drugs in the U.S.

**66%**

of adults  
take prescription  
drugs<sup>1</sup>

**89%**

of adults 65+  
take prescription  
drugs<sup>2</sup>

**80%**

regularly use  
OTC drugs<sup>3</sup>

**4 in 5**

use dietary  
supplements<sup>4</sup>

1. Health Policy Institute, 2021

2. Statistics on OTC use. Consumer Healthcare Products Association website. [chpa.org/MarketStats.aspx](http://chpa.org/MarketStats.aspx). Accessed 19 Dec 2022)

3. Kaiser Family Foundation (KFF) Health Tracking Poll, 2019

4. CRN survey

1	Atorvastatin	11	Hydrochlorothiazide	21	Trazodone	31	Citalopram	41	Methylphenidate
2	Levothyroxine	12	Sertraline	22	D-Amphetamine	32	Insulin glargine	42	Allopurinol
3	Metformin	13	Simvastatin				Potassium Cl	43	Venlafaxine
4	Lisinopril	14	Montelukast				Pravastatin	44	Clonazepam
5	Amlodipine	15	Escitalopram				Tramadol	45	Ethinyl estradiol
6	Metoprolol	16	APAP				Aspirin	46	Ergocalciferol
7	Albuterol	17	Rosuvastatin				Alprazolam	47	Zolpidem
8	Omeprazole	18	Bupropion	28	Meloxicam	38	Ibuprofen	48	Apixaban
9	Losartan	19	Furosamide	29	Clopidogrel	39	Cyclobenzaprine	49	Glipizide
10	Gabapentin	20	Pantoprazole	30	Prednisone	40	Amoxicillin	50	HCT/Lisinopril

100%

may interact with dietary  
supplements

1. ClinCalc DrugStats Database (2019 calendar year)

# “Prescriber paralysis”



## Food



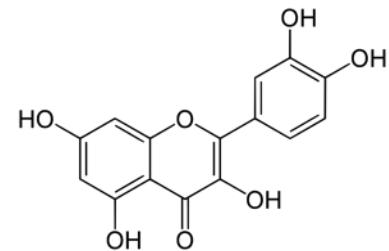
## Vitamins, minerals



## Herbs



## Nutraceuticals



# Drug Interaction Checker

Enter a drug, OTC or herbal supplement:

melatonin

Print

Add a second drug, OTC, or herbal

Possible drug interactions include:

- **Anticoagulants and anti-platelet drugs.** These types of drugs, supplements reduce blood clotting. Combining melatonin with them might increase the risk of bleeding.
  - **Anticonvulsants.** Melatonin might interact with anticonvulsants and increase the frequency and severity of seizures, particularly in children with neurologic disorders.
  - **Blood pressure drugs.** Melatonin might increase blood pressure in people taking blood pressure medications.
  - **Central nervous system (CNS) depressants.** Melatonin might interact with these medications and cause a sedative effect.
  - **Diabetes medications.** Melatonin might affect sugar levels. If you take diabetes medications, talk to your doctor before using melatonin.
- A  Avoid**
  - B  Be cautious**
  - C  Change dose/timing**
  - D  Dismiss**

drugs. Use of contraceptive drugs with melatonin might cause an additive sedative effect and increase the side effects of melatonin.

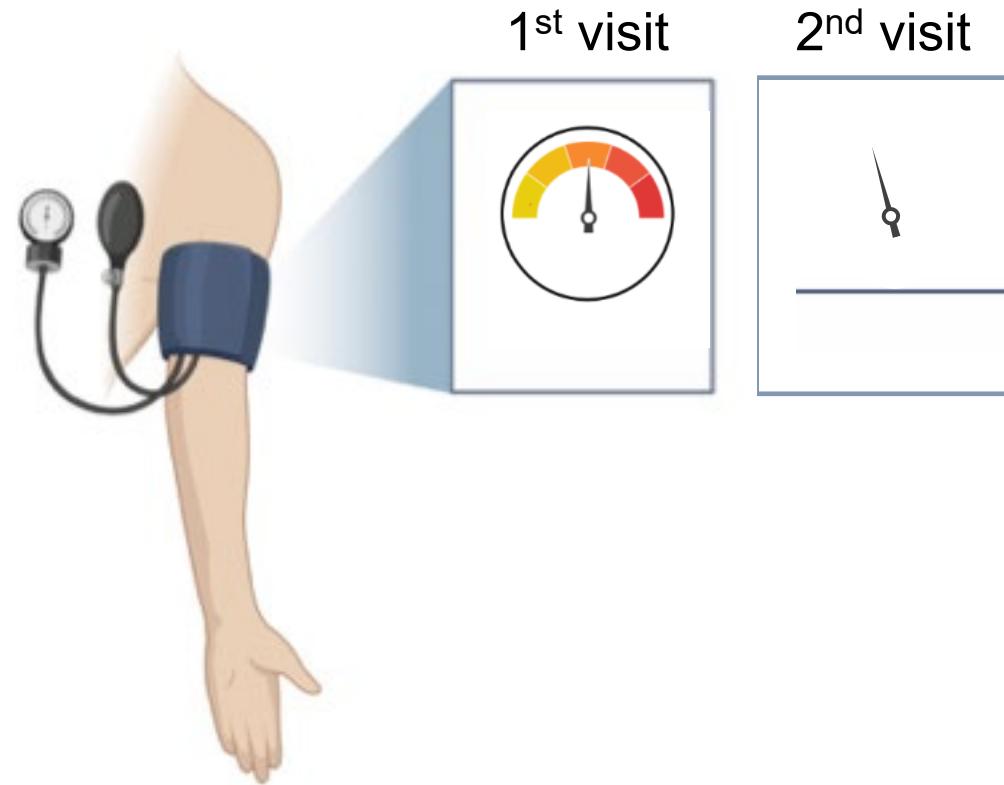
• **Enzyme inducers.** Melatonin might increase the metabolism of certain drugs by CYP3A4 (CYP3A4) and cytochrome P450 2D6 (CYP2D6) substrates. Use melatonin cautiously if you are taking drugs that are affected by these enzymes, such as diazepam (Valium, Valtoco, others) or phenytoin (Dilantin, Phenytek, others).

• **Sedatives.** Melatonin might increase the sedative effects of sedatives. This medication used to treat insomnia can increase melatonin levels and cause unwanted excessive drowsiness.

• **Immunosuppressive drugs.** Melatonin can stimulate the immune system and interfere with immunosuppressive therapy.

• **Seizure threshold lowering drugs.** Taking melatonin with these drugs might increase the risk of seizures.

Most interactions are undetectable, subtle and/or variable



# Imagine 3 situations

1. Loss of efficacy
2. Gain of efficacy
3. Gain of toxicity



**Know the drug**

Adverse effects profile

Therapeutic window

Dose adjustment risks

**REMEMBER!**

# Two types of interactions

## Pharmacodynamic

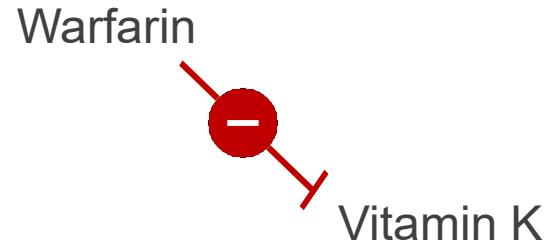
Modify the ***pharmacological or clinical effects***

## Pharmacokinetic

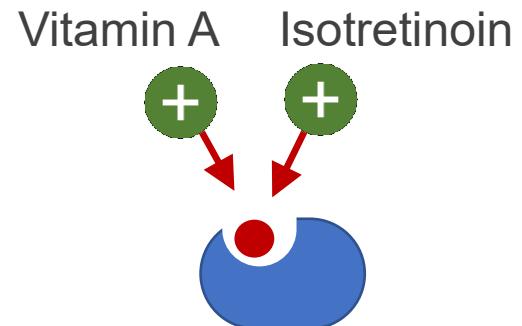
Modify the ***absorption, distribution, metabolism or elimination (ADME)***

*Includes drug-nutrient depletions*

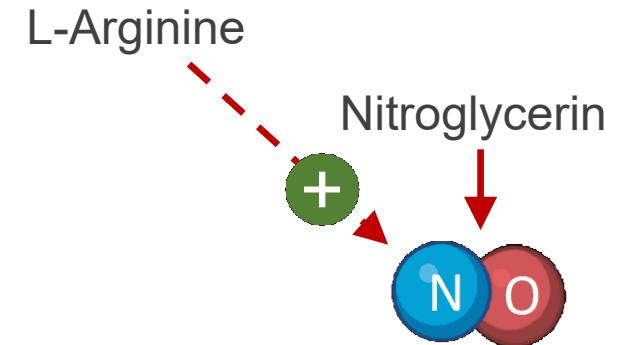
### ANTAGONISTIC



### ADDITIVE



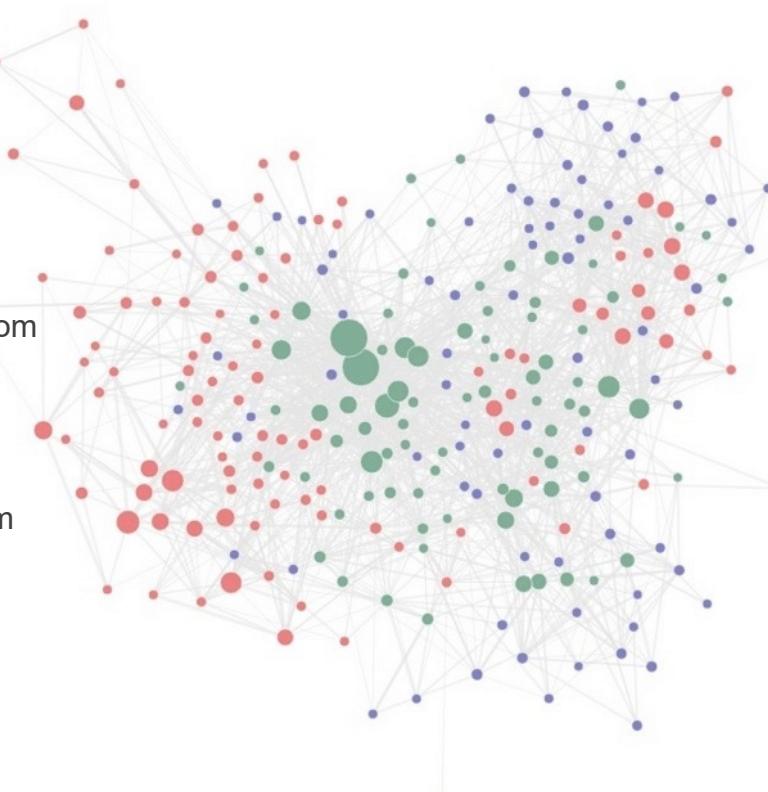
### SYNERGISTIC



Acai  
Aloe  
Artichoke  
Ashwagandha  
Bilberry  
Carnosine  
DHA  
EPA  
Eleuthero  
Garlic  
Ginkgo  
Gymnema  
L-arginine  
Melatonin



Berberine  
Bitter melon  
BCAA  
Chromium  
Panax ginseng  
Ribose  
Vanadium  
Maitake mushroom  
Maritime pine  
Niacin  
Policosanol  
Quercetin  
Reishi mushroom  
Rhodiola  
Zeaxanthin  
Inositol  
Milk thistle  
Krill oil



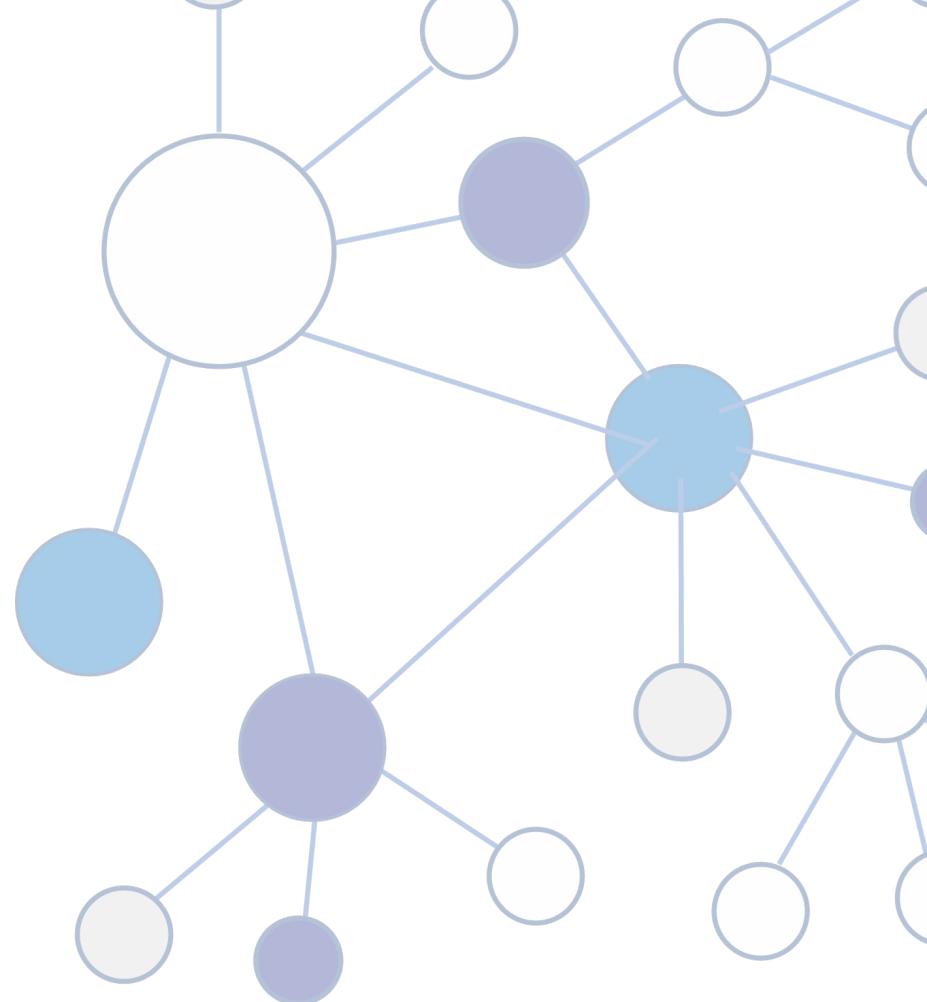
Glucophage	Tolinase	Novolin	Humalog Kwikpen
GlucoNorm	Glyset	NovoLog	Synjardy
Precose	Hypurin Bovine	NPH Iletin	Saxenda
Dymelor	Neutral	Regular Iletin	Ryzodeg 70/30
Diabinese	Hypurin Porcine	Velosulin	Tresiba
Chlorpropam	Neutral	Glucagon	Jentadueto XR
Glucotrol	Pork Actrapid	IV Glucose	Adlyxin
Glucotrol XL	Actrapid	Novolog Mix 70/30	Xultophy 100/3.6
Diabeta	Insuman Rapid	NPH Iletin II	Soliqua 100/33
Amaryl	Janumet	Regular Iletin II	Synjardy XR
Micronase	Diamicron	Prandase	Lusduna
Glynase	Onglyza	Apidra	Invokamet XR
Glucovance	Kombiglyze	Byetta	Qtern
Glycron	Juvisync	Symlin	Admelog
Micronized	Tradjenta	Levemir	Fiasp
Glynase PresTab	Janumet XR	Pargluva	Bydureon BCISE
Albert Glyburide	Jentadueto	Exubera	Ozempic
Starlix	Metformin	Avandaryl	Steglatro
Actos	Bydureon	ActoPlus Met	Admelog Solostar
Prandin	Nesina	NovoRapid Insulin	Segluromet
Avandia	Oseni	Januvia	Qternmet XR
Orinase	Kazano	Galvus	Myxredlin
Mobenol	Invokana	Glucobay	Baqsimi
Rezulin	Jardiance	Rybelsus	Riomet ER
Metaglip	Invokamet	Trijardy XR	Afrezza
Avandamet	Glyxambi	Semglee	Trulicity
Humalog	Basagliar	Lyumjev	Xigduo XR
Humulin	Farxiga	Zegateglouge	Toujeo Solostar
	Tanzeum	Wegovy	Lantus
	Victoza		Lente Iletin II



If it works...



and it's highly efficacious...



# Two types of interactions

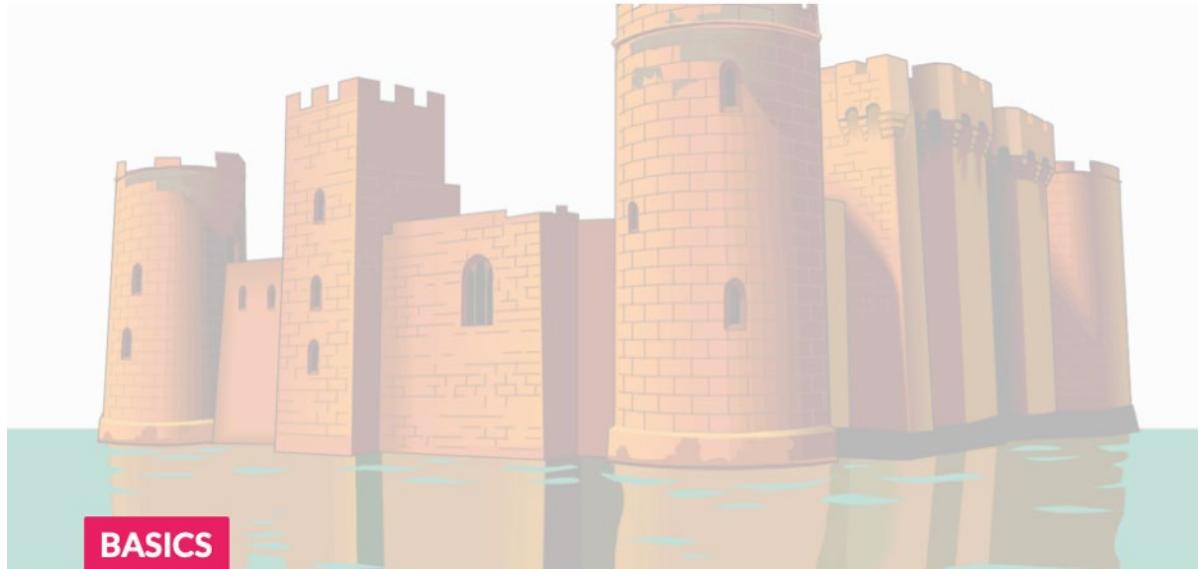
## Pharmacodynamic

Modify the *pharmacological or clinical effects*

## Pharmacokinetic

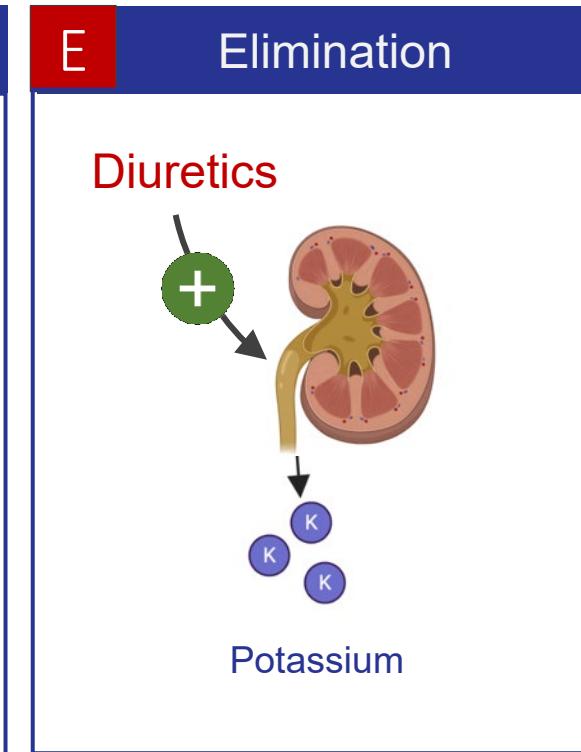
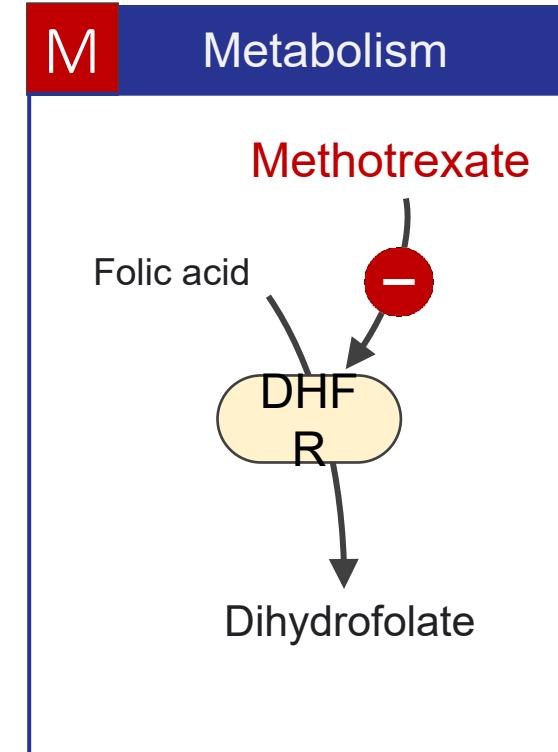
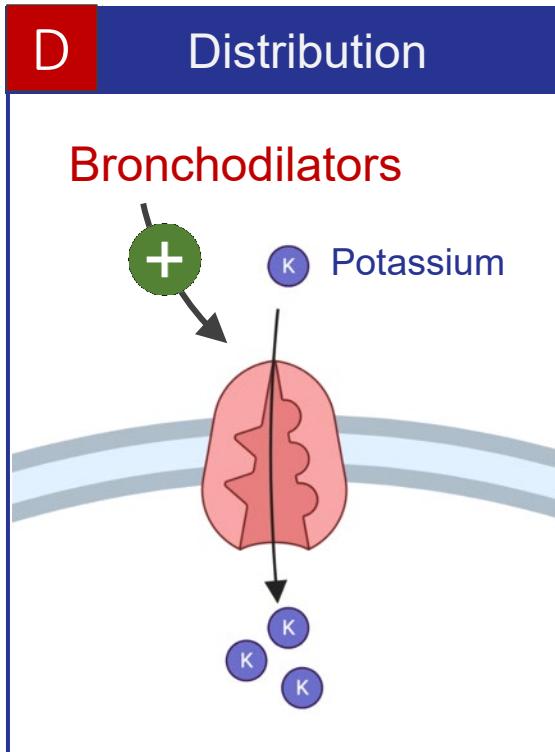
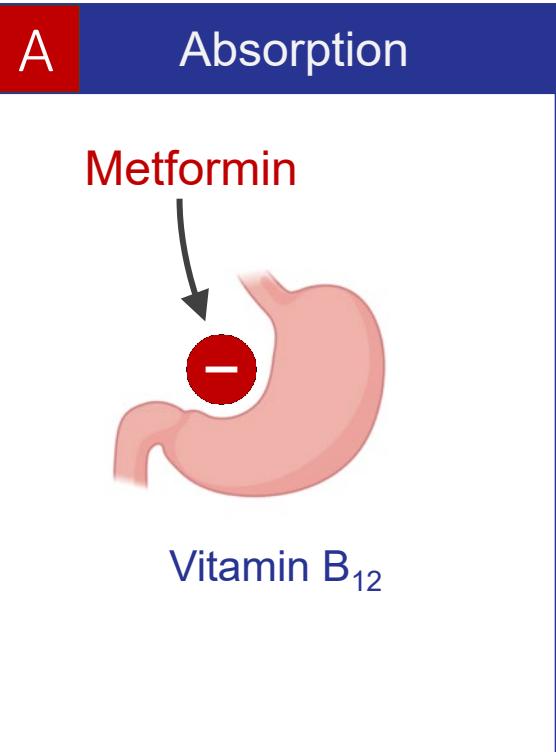
Modify the ***absorption, distribution, metabolism or elimination (ADME)***

A | D | M | E



## A Medicine's Journey: A Visual Introduction to Pharmacokinetics

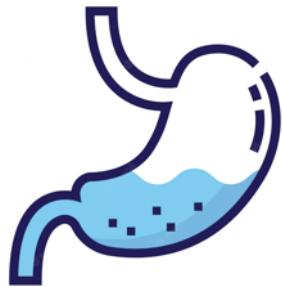
[IntegrativePharmacology.com](http://IntegrativePharmacology.com)



Nutrient	Drugs (Top 50)
Vitamin B12	Metformin, PPIs (proton pump inhibitors)
Coenzyme Q10	Statins
Potassium	Beta blockers, diuretics, corticosteroids
Magnesium	PPIs, diuretics, corticosteroids
Calcium	PPIs
Vitamin D	Corticosteroids

A

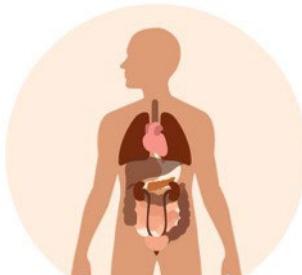
Absorption



Calcium, iron  
↓ Ciprofloxacin

D

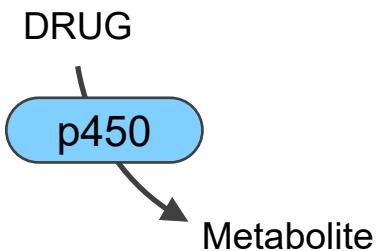
Distribution



Vitamin B6  
↓ Levodopa

M

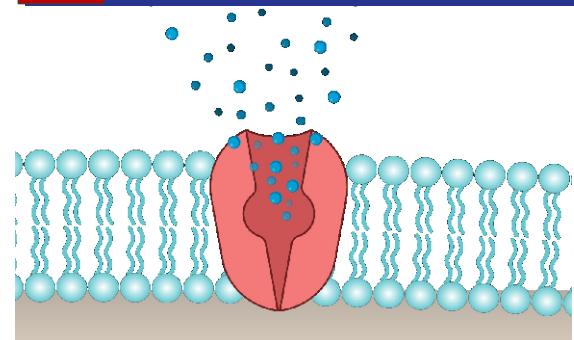
Metabolism



Berberine  
↓ CYP3A4

E

Elimination

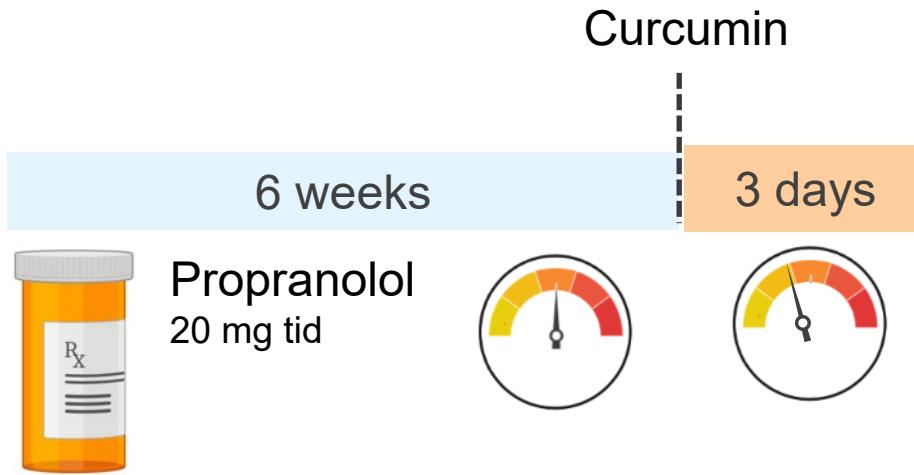


St. John's Wort  
↑ P-glycoprotein

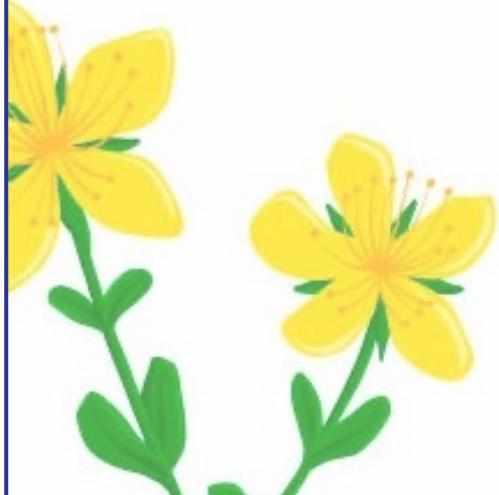


George

Recent knee pain  
**New onset fatigue**



**St. John's Wort**

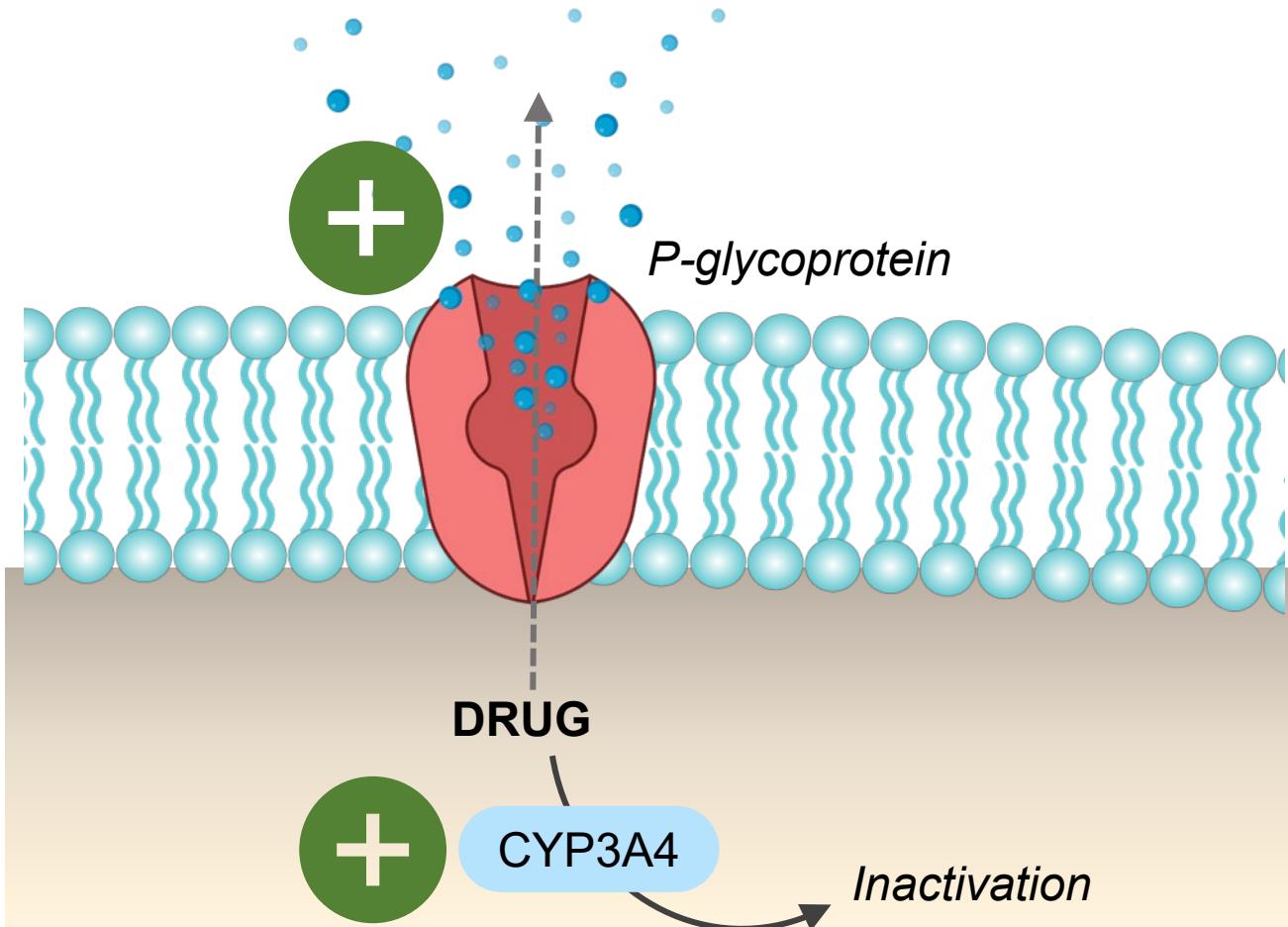
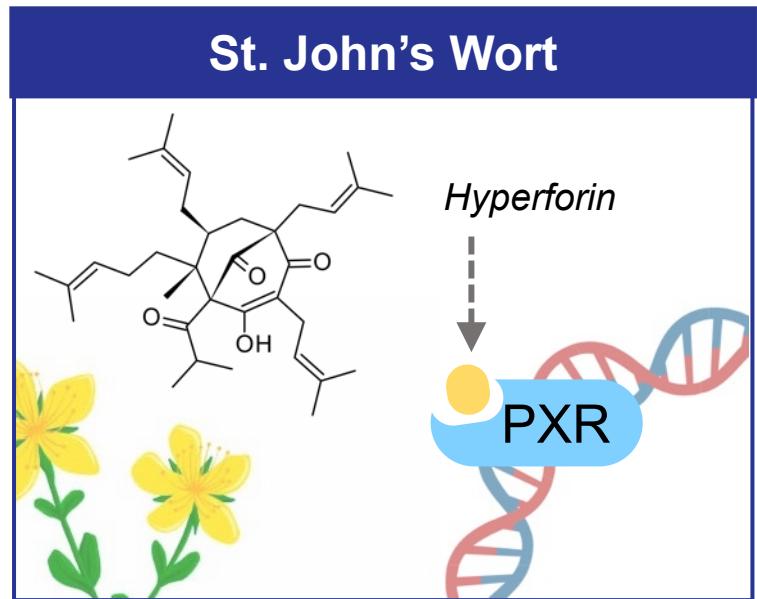


**Grapefruit**



**Green tea**

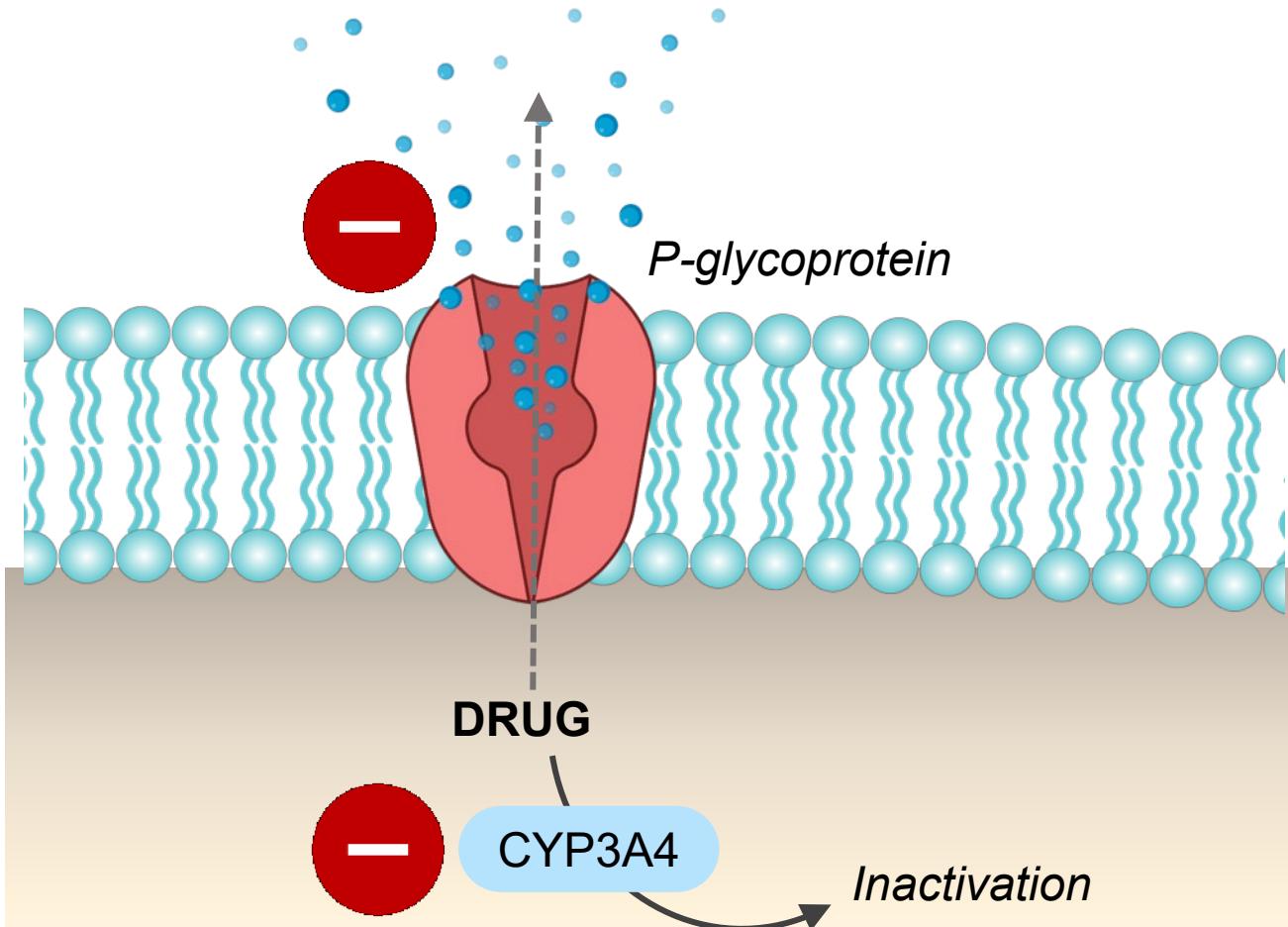
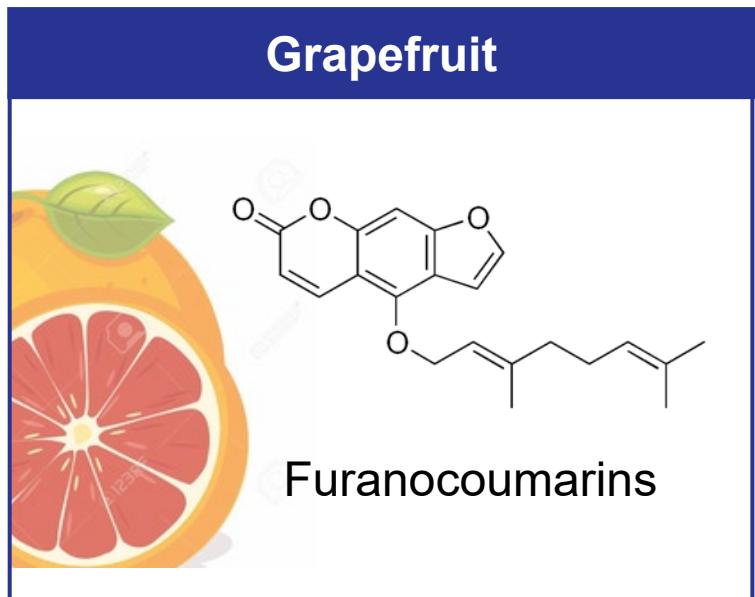


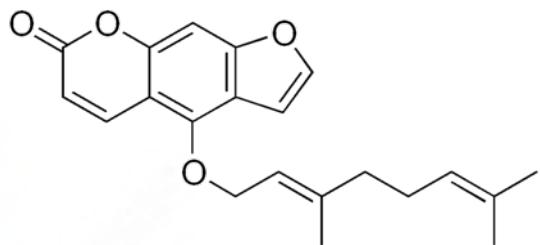
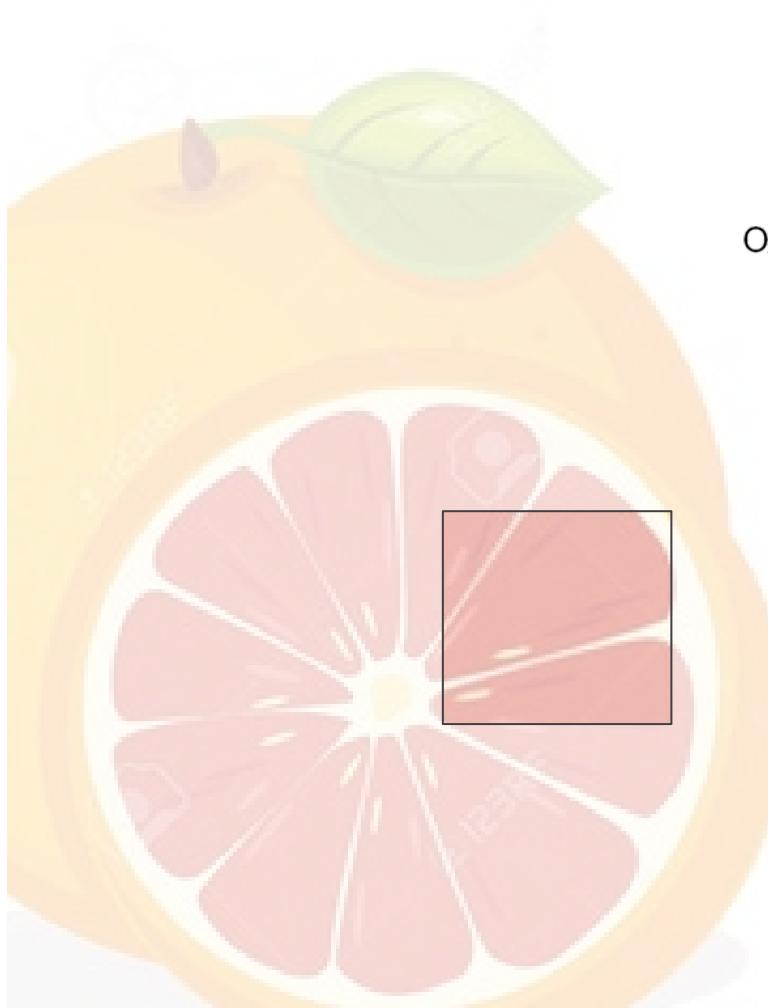


Nicolussi S, et al. Clinical relevance of St. John's wort drug interactions revisited. *Br J Pharmacol.* 2020 Mar;177(6):1212-1226.

## Pharmacokinetic

## Grapefruit



**Furanocoumarins**

- Bergamottin (pulp)
- **Dihydrobergamottin (pulp, seed)**

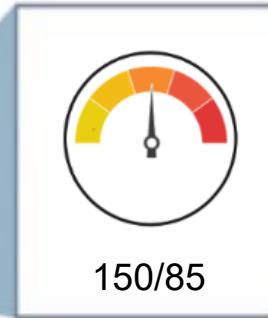
ALISKIREN  
AMIODARONE  
ARTEMETHER  
BENZODIAZEPINES  
BUDESONIDE  
BUSPIRONE  
CAFFEINE  
**Ca<sup>2+</sup> CHANNEL BLOCKERS**  
CARBAMAZEPINE  
CARVEDILOL  
CELIPROLOL  
CISAPRIDE  
CLOMIPRAMINE  
CLOPIDOGREL  
COLCHICINE  
CYCLOSPORINE  
CYP2C19 SUBSTRATES  
CYP3A4 SUBSTRATES  
DEXTROMETHORPHAN  
ERYTHROMYCIN  
ESTROGENS  
ETOPOSIDE  
FEXOFENADINE  
HALOFANTRIN  
STATINS  
ITRACONAZOLE



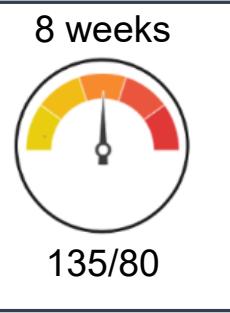
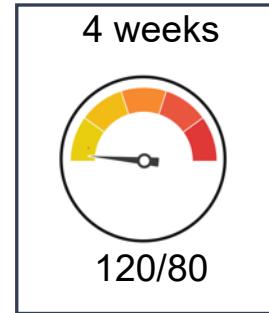
LEVOTHYROXINE  
LOSARTAN  
METHADONE  
METHYLPREDNISOLONE  
NADOLOL  
NILOTINIB  
OATP SUBSTRATES  
OXYCODONE  
PITAVASTATIN  
PRASUGREL  
PRAZIQUANTEL  
PRIMAQUINE  
QUINIDINE  
SAQUINAVIR  
SCOPOLAMINE  
SERTRALINE  
SILDENAFIL  
SUNITINIB  
Tadalafil  
TALINOLOL  
TERFENADINE  
THEOPHYLLINE  
TICAGRELOR  
TOLVAPTAN  
WARFARIN

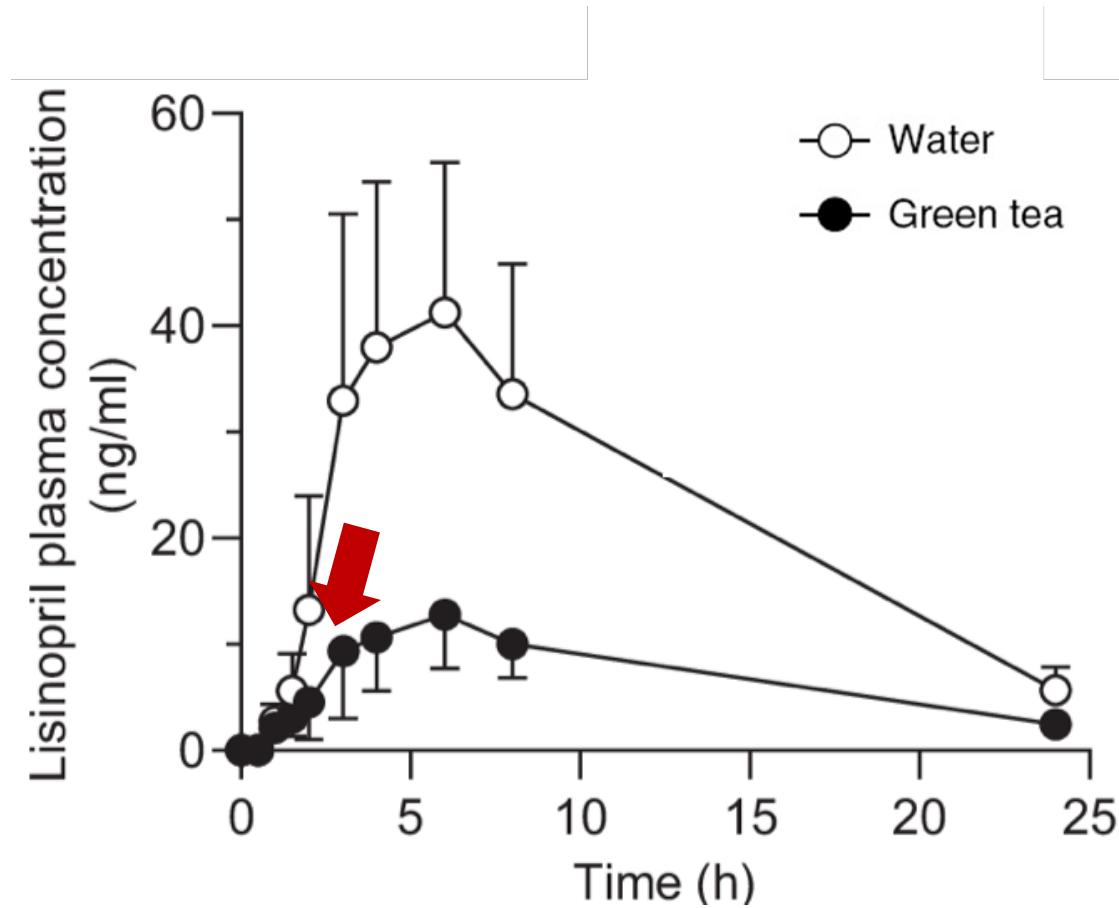


First visit

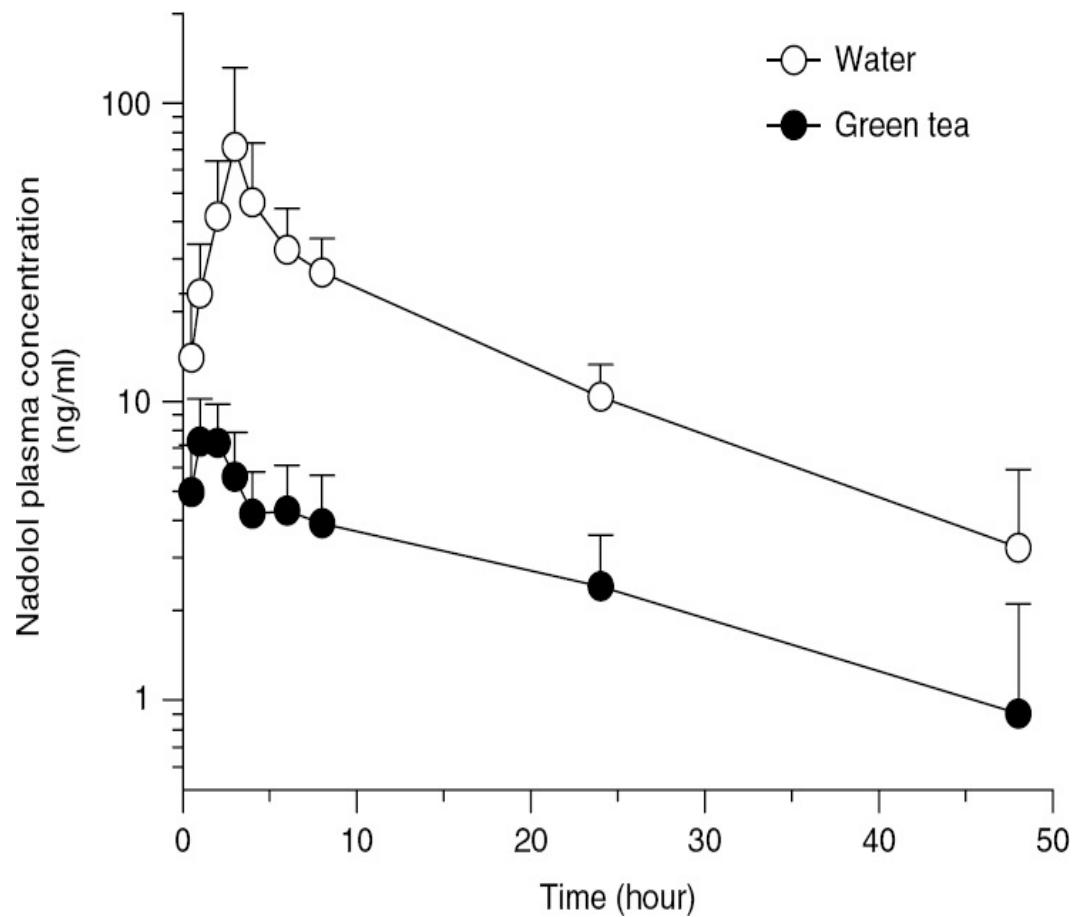


Lisinopril 10 mg





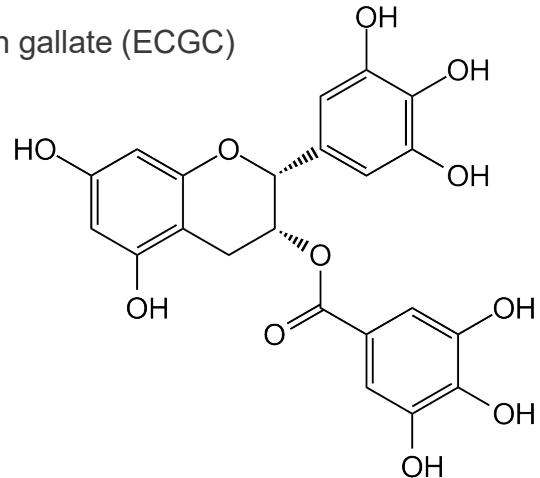
Misaka S, et al. Clin Transl Sci. 2021 Mar;14(2):476-480.



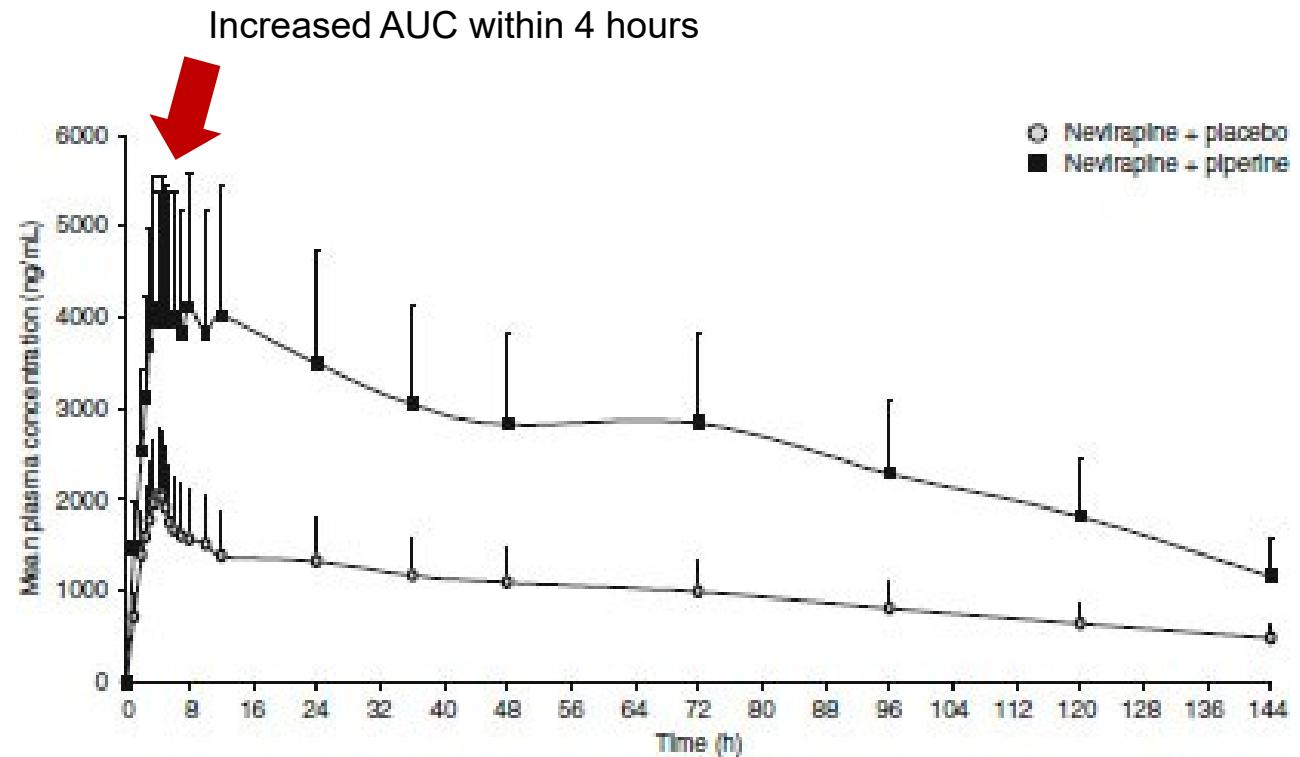
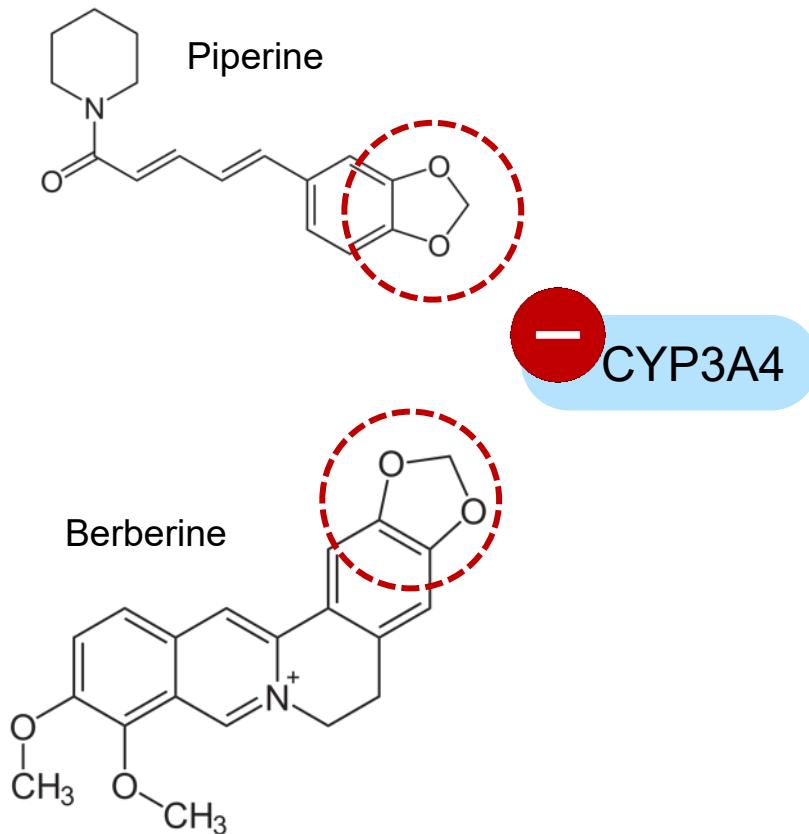
Misaka S, et al. Clinical Pharmacology & Therapeutics (2014); 95 4, 432–438.



Epicatechin gallate (ECGC)

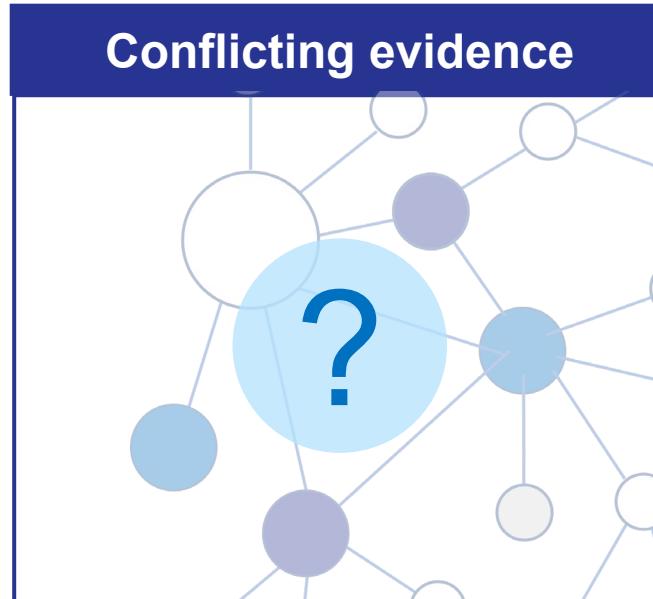


- ↓ Atorvastatin (Lipitor)
- ↓ Rosuvastatin (Crestor)
- ↑ Simvastatin (Zocor)



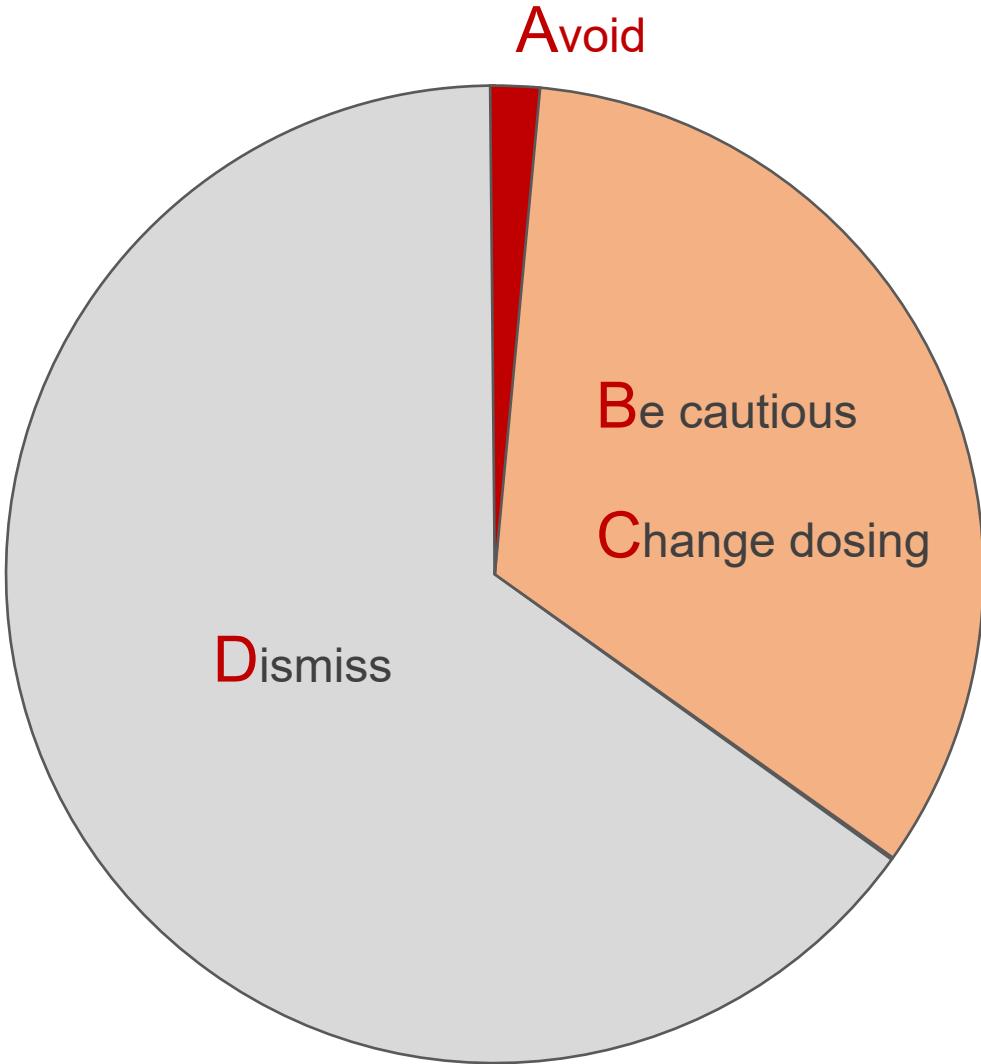
Kasibhatta, R., Naidu, M.U.R. Influence of Piperine on the Pharmacokinetics of Nevirapine under Fasting Conditions. *Drugs R D* 8, 383–391 (2007).

# Practical problems

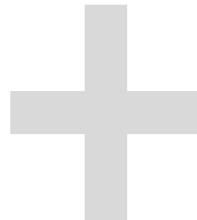


- Taking action**
- A  Avoid
  - B  Be cautious
  - C  Change dose/timing
  - D  Do nothing

Most interactions are not contraindications.



Potassium-sparing  
diuretics



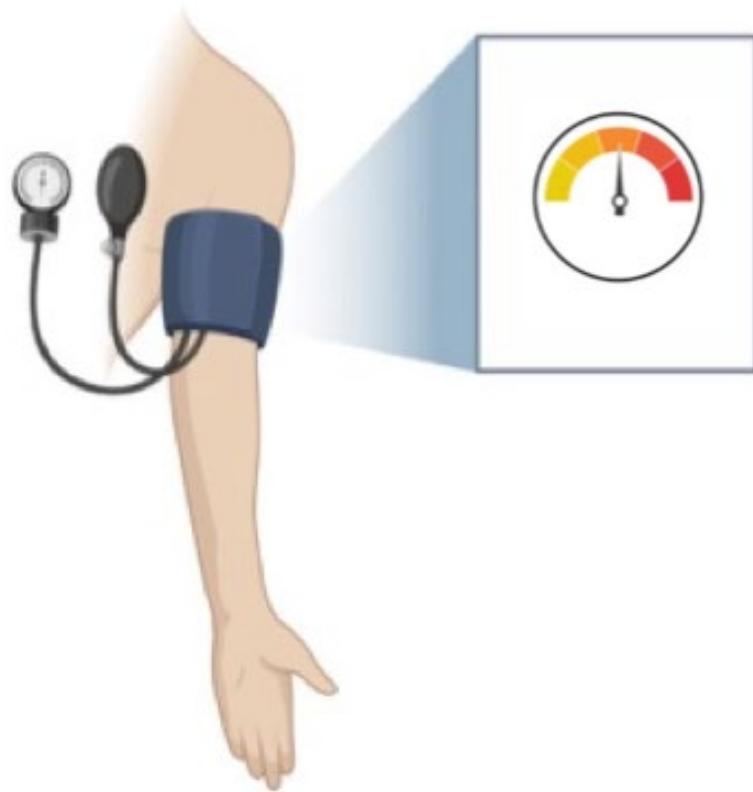
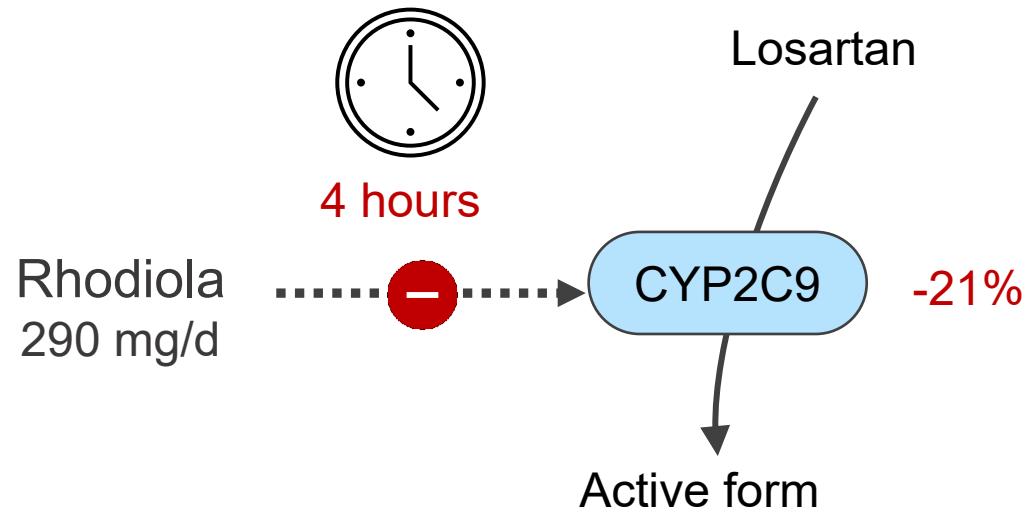
Potassium supplements  
Salt substitutes  
Renal insufficiency

A  Avoid

B  Be cautious

C  Change dose/timing

D  Dismiss



		Monitoring
Antihypertensives	L-arginine	BP
Antidiabetic drugs	Berberine	Glucose
Anticoagulant/antiplatelet	Vitamin E	INR

69 year-old woman  
Hx: Ischemic stroke

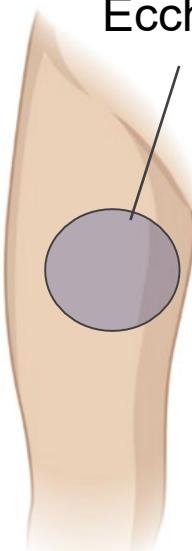
Warfarin  
Atenolol  
Digoxin  
Aspirin  
Omeprazole  
Simvastatin

INR = 1.4



1 day

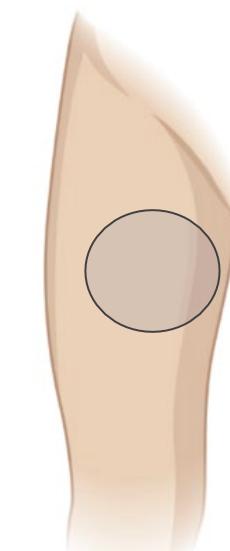
Ecchymosis



Stopped astaxanthin  
Added K1

2 days

INR = 10.38



INR = 1.43

Santiyanon N and Yeephu S. Interaction between warfarin and astaxanthin: A case report. J Cardiol Cases. 2019 Feb 18;19(5):173-5.

A  Avoid

B  Be cautious

C  Change dose/timing

D  Dismiss

PDR Search

- Inform patients that agents such as iron and calcium supplements and antacids can decrease the absorption of levothyroxine. Instruct patients not to take SYNTHROID tablets within 4 hours of these agents.

## Calcium or iron supplements



Tetracyclines & fluoroquinolones  
Separate dosing by 2-6 hours<sup>1-3</sup>



Levothyroxine (Synthroid, others)  
Separate dosing by 2 hours<sup>4</sup>



1. Product Information: Vibramycin, doxycycline. Pfizer Laboratories, New York, NY, 1990.
2. Product Information: Cipro, ciprofloxacin. Bayer Corporation, West Haven, CT, 2002.
3. Greenberger NJ. Absorption of tetracyclines: interference by iron. Ann Intern Med. 1971;74:792-793.
4. Product Information: Synthroid, levothyroxine. Abb Vie, Inc. North Chicago, IL, 2017.

A  Avoid

B  Be cautious

C  Change dose/timing

D  Dismiss

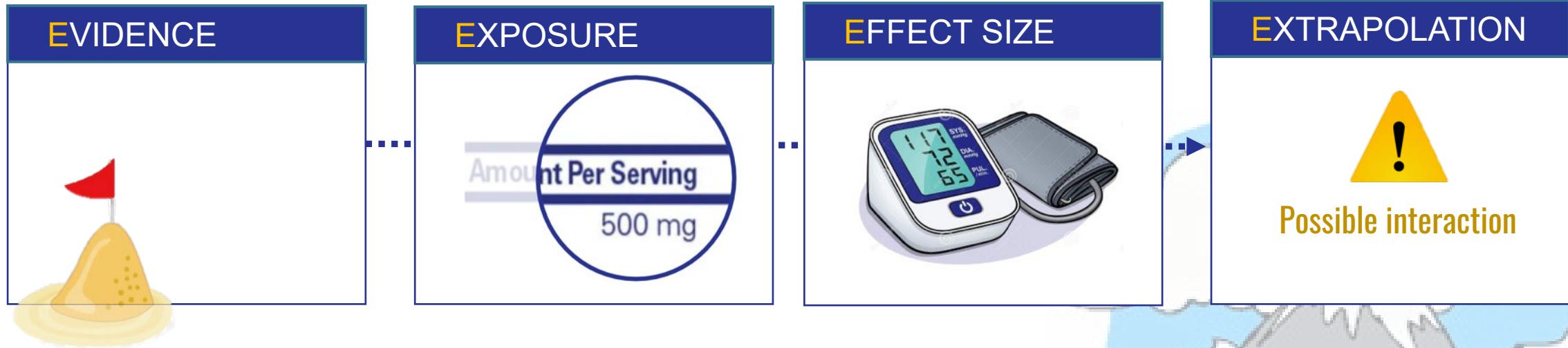


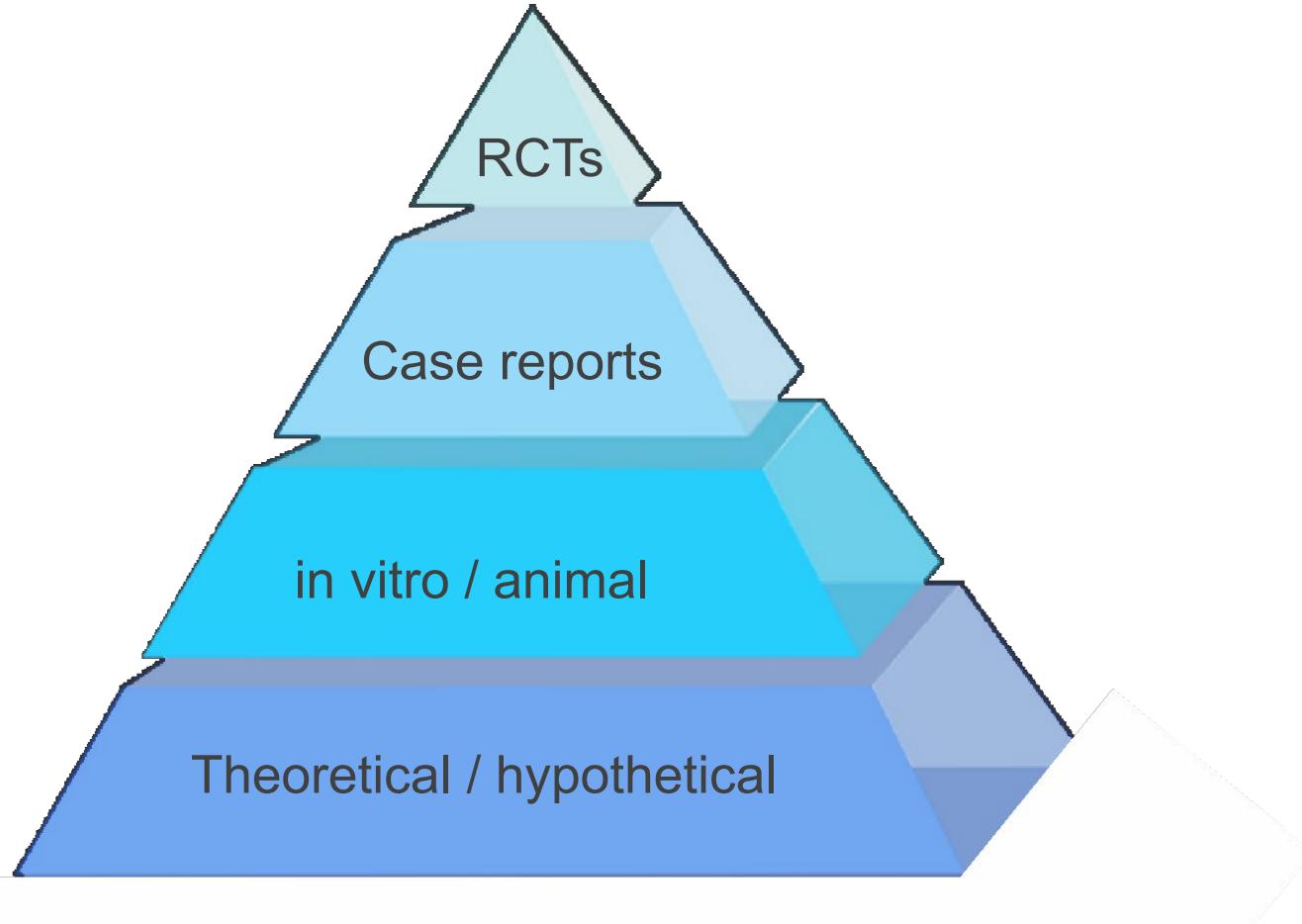
### Testosterone + L-Arginine

"This combination may have additive effects. L-arginine may increase the level of testosterone in men."



# Why many interactions are clinically irrelevant







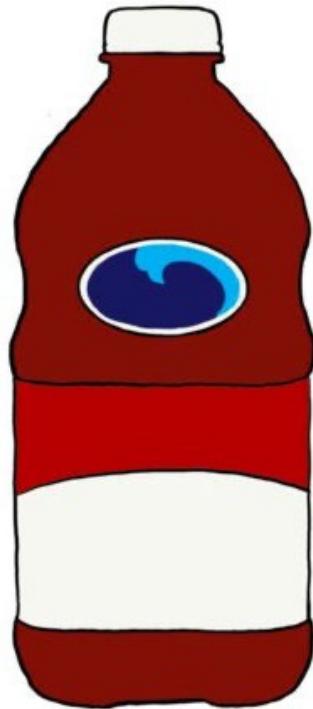
## Warfarin + Cranberry

EVIDENCE

EXPOSURE

EFFECT SIZE

EXTRAPOLATION



REVIEW | VOLUME 123, ISSUE 5, P384-392, MAY 01, 2010

### Cranberry Juice and Warfarin: When Bad Publicity Trumps Science

Jennifer Zikria, MD • Raimonda Goldman, MD • Jack Ansell, MD

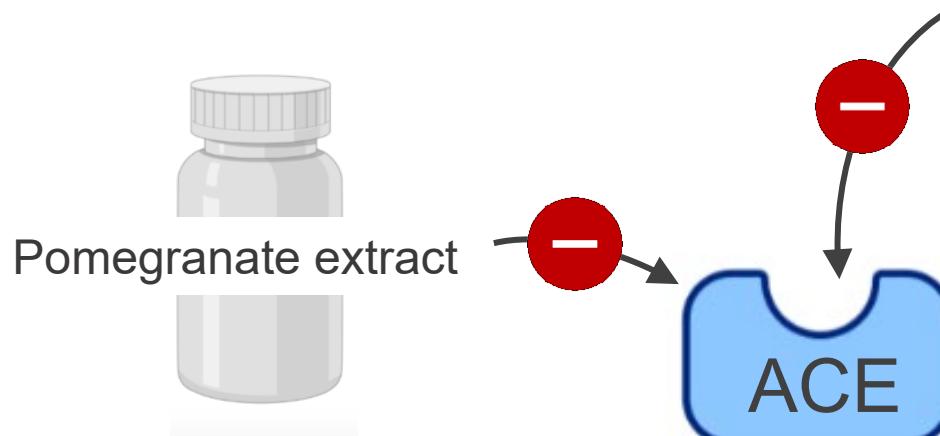
DOI: <https://doi.org/10.1016/j.amjmed.2009.08.019>

*Am J Med.* 2010 May;123(5):384-92.



## Pomegranate + ACE Inhibitors

Pomegranate may block ACE. Use caution when combining with ACE inhibitors.



## ACE Inhibitors

Benazepril (Lotensin)  
Captopril (Capoten)  
Enalapril/Enalaprilat (Vasotec)  
Fosinopril (Monopril)  
Lisinopril (Zestril, Prinivil),  
Moexipril (Univasc)  
Perindopril (Aceon)  
Quinapril (Accupril)  
Ramipril (Altace)

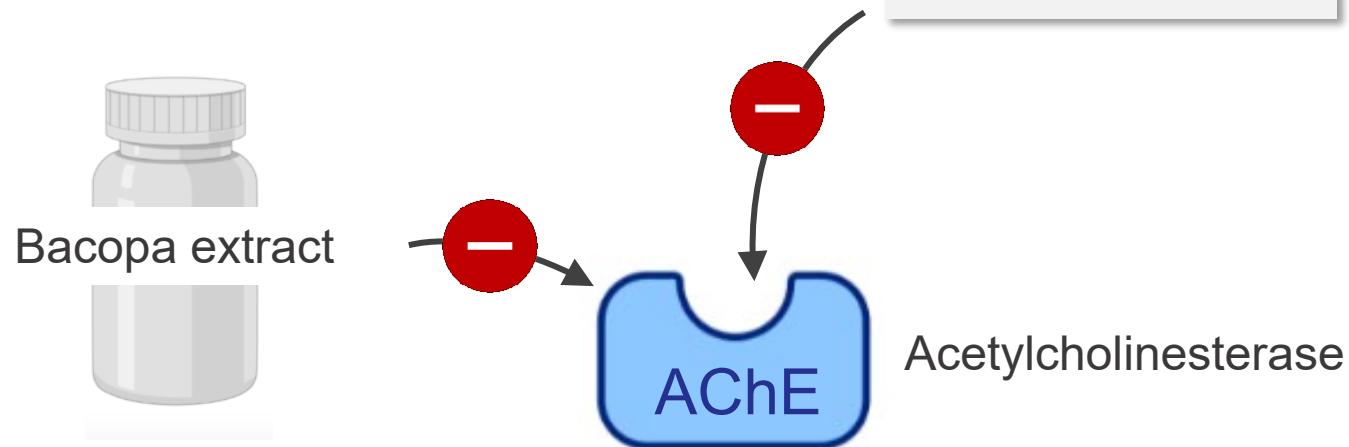
Warning can be dismissed. Error in extrapolation



## Bacopa + Acetylcholinesterase inhibitors

"Bacopa may inhibit acetylcholinesterase, increasing acetylcholine levels. This could have additive effects with other cholinergic drugs."

Adlarity  
Donepezil  
Exelon  
Galantamine

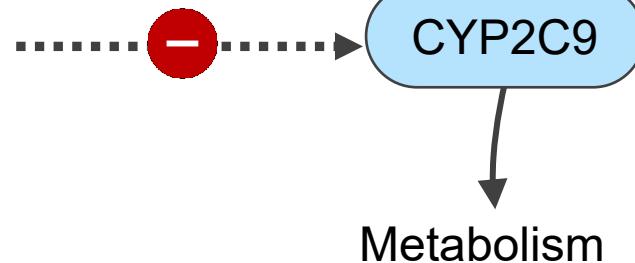
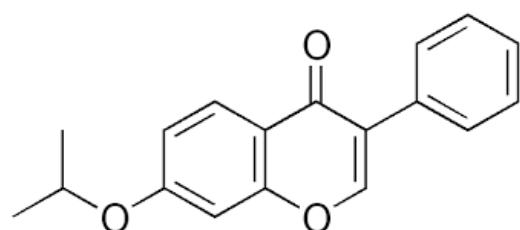


Warning can be dismissed. Inhibitory exposure can't be reach in tissue.



## Ipriflavone + CYP2C9 Substrates

**Ipriflavone** inhibits CYP2C9. Taking it with drugs that require CYP2C9 for metabolism may magnify their adverse effects."



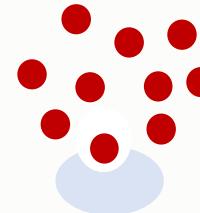
Warfarin (Coumadin)  
NSAIDS  
Amitriptyline (Elavil)  
Diazepam (Valium)  
Estradiol (Estrace)  
Tacrine (Cognex)  
Verapamil (Calan)  
Zileuton (Zyflo)

Warning can be dismissed. Ipriflavone not bioavailable enough

Amount in the blood



Amount needed to inhibit

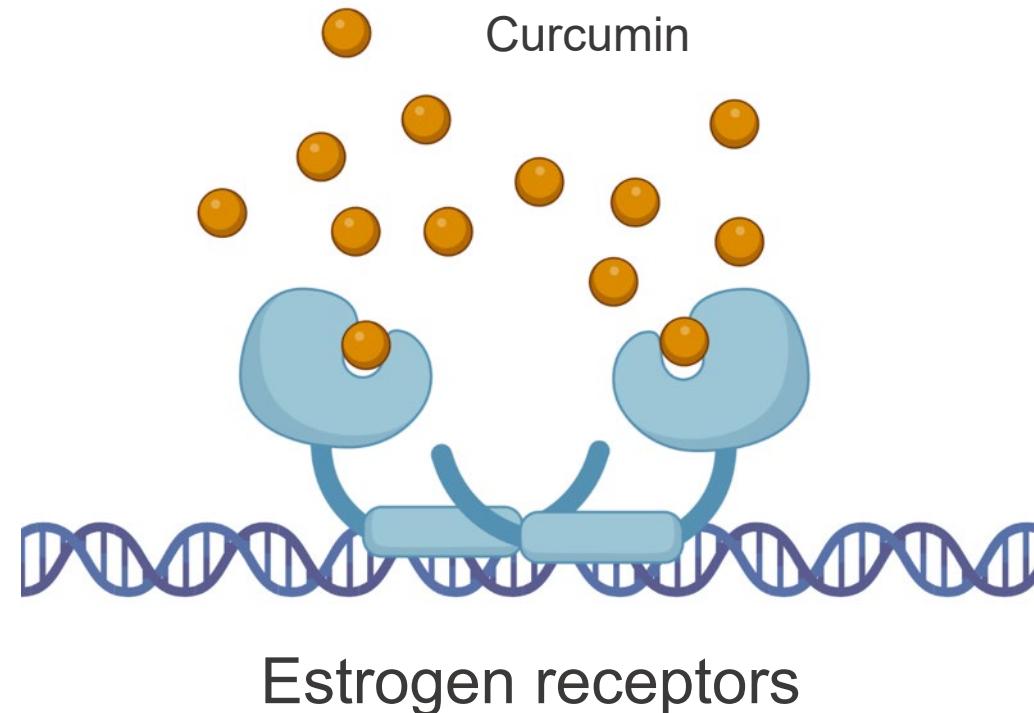


EVIDENCE

EXPOSURE

EFFECT SIZE

EXTRAPOLATION  
N



Geetha et al. J Biomol Struct Dyn. 2019 Mar;37(5):1189-1203.

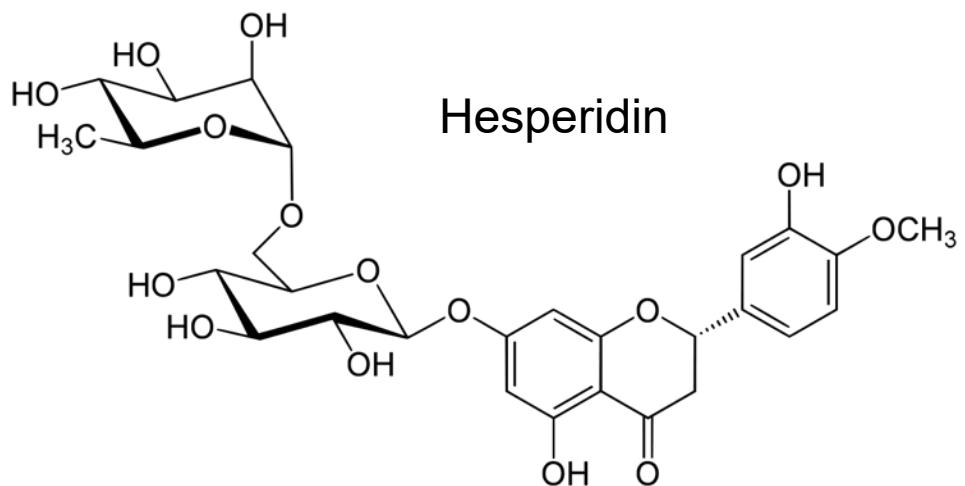


EVIDENCE

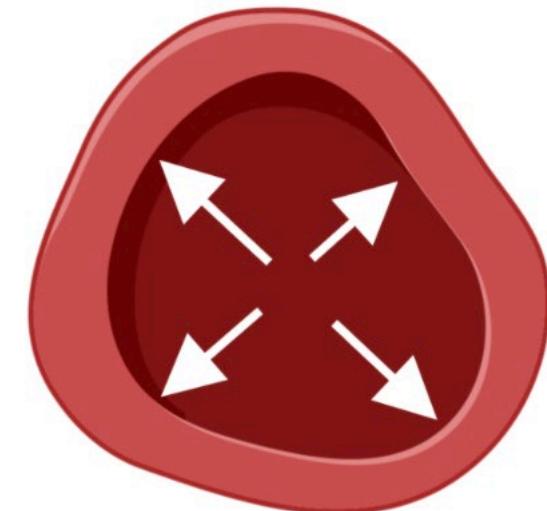
EXPOSURE

EFFECT SIZE

EXTRAPOLATION  
N



Hesperidin

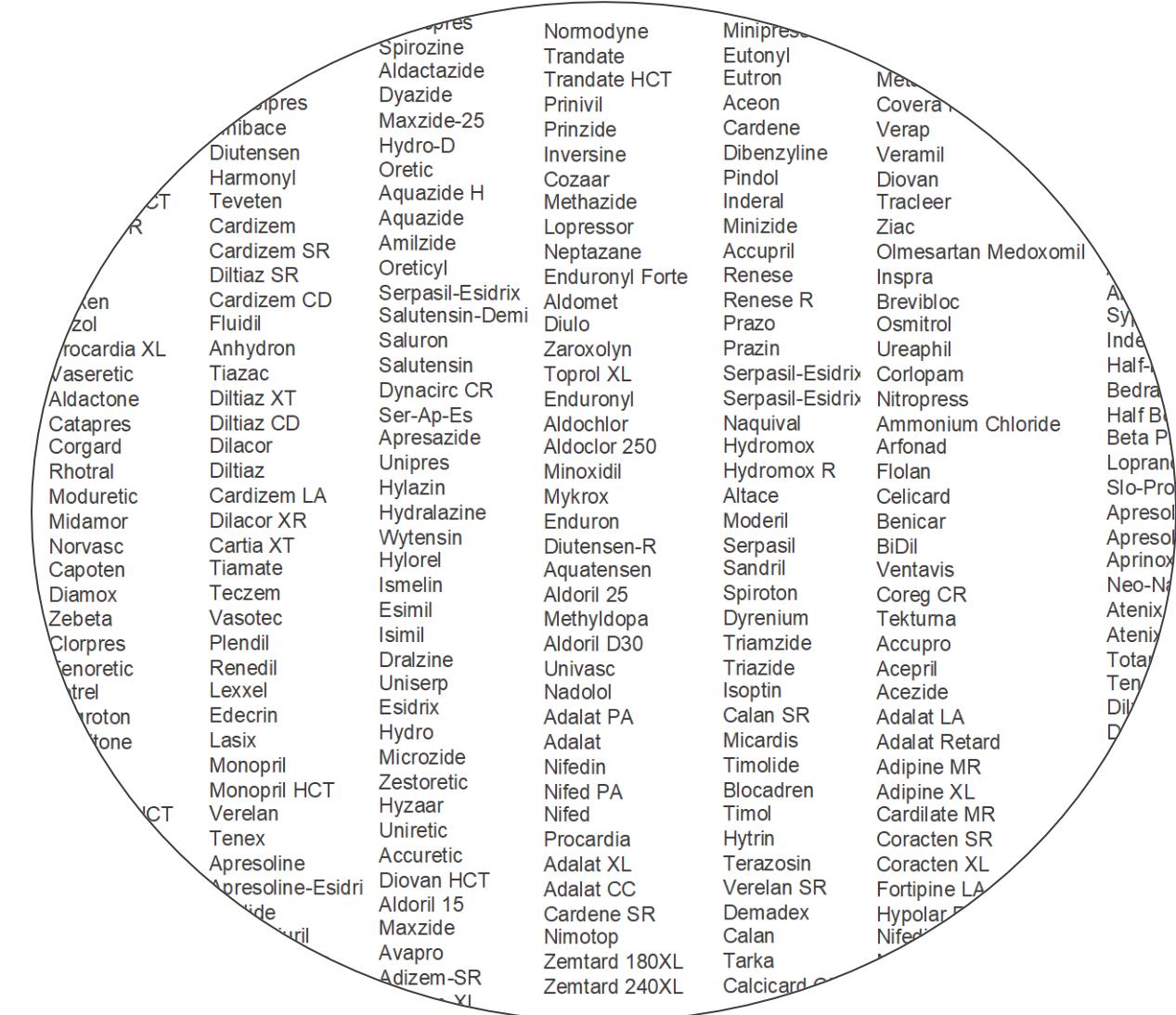
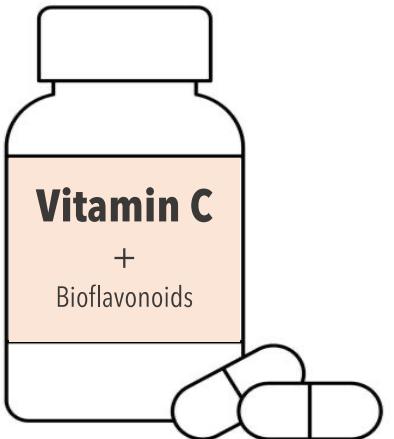


## EVIDENCE

## EXPOSURE

## EFFECT SIZE

## EXTRAPOLATION



## EVIDENCE

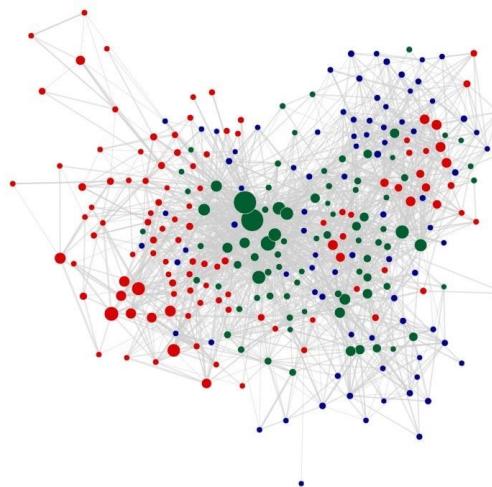
## EXPOSURE

## EFFECT SIZE

## EXTRAPOLATION

Acai  
Aloe  
Artichoke  
Ashwagandha  
Bilberry  
Carnosine  
DHA  
EPA  
Eleuthero  
Garlic  
Ginkgo  
Gymnema  
L-arginine  
Melatonin

**Berberine**  
**Bitter melon**  
**BCAA**  
**Chromium**  
Panax ginseng  
Ribose  
Vanadium  
Maitake mushroom  
Maritime pine  
Niacin  
Policosanol  
Quercetin  
Reishi mushroom  
Rhodiola  
Zeaxanthin  
Inositol  
Milk thistle  
Krill oil

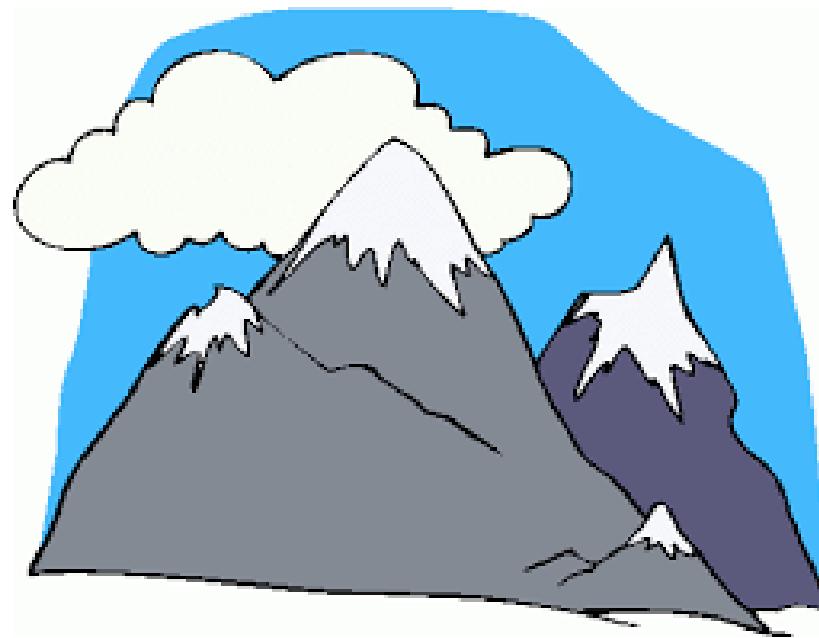


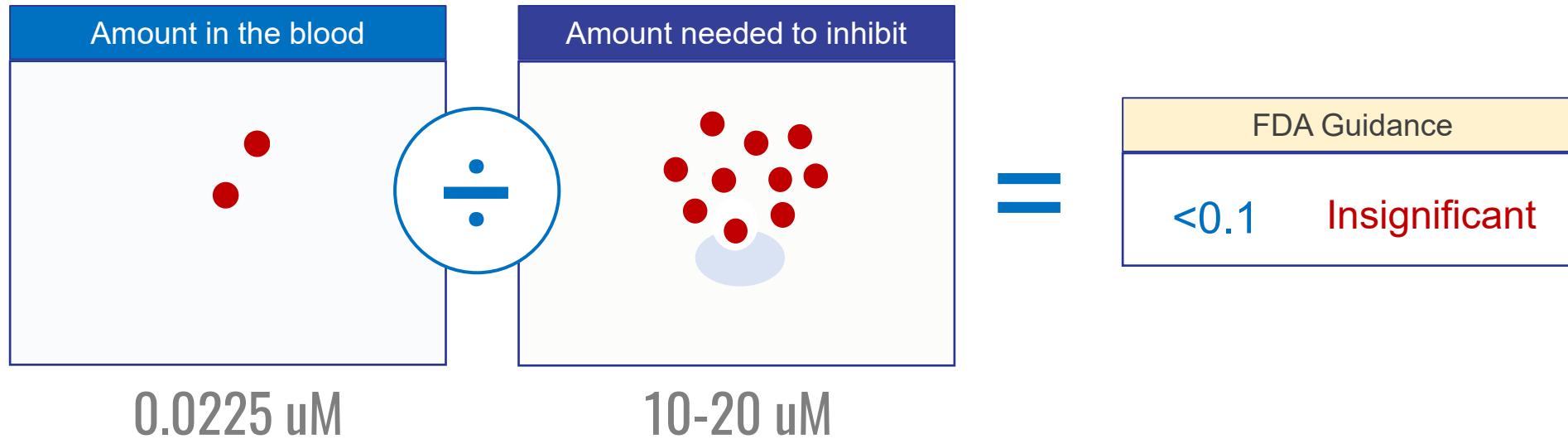
Glucophage  
GlucoNorm  
Precose  
Dymelor  
Diabinese  
Chlorpropam  
Glucotrol  
Glucotrol XL  
Diabeta  
Amaryl  
Micronase  
Glynase  
Glucovance  
Glycron  
Micronized  
Glynase PresTab  
Albert Glyburide  
Starlix  
Actos  
Prandin  
Avandia  
Orinase  
Mobenol  
Rezulin  
Metaglip  
Avandamet  
Humalog  
Humulin  
Tolinase  
Glyset  
Hypurin Bovine  
Neutral  
Hypurin Porcine  
Neutral  
Pork Actrapid  
Actrapid  
Insuman Rapid  
Janumet  
Diamicron  
Onglyza  
Kombiglyze  
Juvisync  
Tradienta  
Janumet XR  
Jentadueto  
Metformin  
Bydureon  
Nesina  
Oseni  
Kazano  
Invokana  
Jardiance  
Invokamet  
Glyxambi  
Basagliar  
Farxiga  
Tanzeum  
Victoza  
Novolin  
NovoLog  
NPH Iletin  
Regular Iletin  
Velosulin  
Glucagon  
IV Glucose  
Novolog Mix 70/30  
NPH Iletin II  
Regular Iletin II  
Prandase  
Apidra  
Byetta  
Symlin  
Levemir  
Pargluva  
Exubera  
Avandaryl  
ActoPlus Met  
NovoRapid Insulin  
Januvia  
Galvus  
Glucobay  
Rybelsus  
Trijardy XR  
Semglee  
Lyumjev  
Zeglogue  
Wegovy  
Humalog Kwikpen  
Synjardy  
Saxenda  
Ryzodeg 70/30  
Tresiba  
Jentadueto XR  
Adlyxin  
Xultophy 100/3.6  
Soliqua 100/33  
Synjardy XR  
Lusduna  
Invokamet XR  
Qtern  
Admelog  
Fiasp  
Bydureon BCISE  
Ozempic  
Steglatro  
Admelog Solostar  
Segluromet  
Qternmet XR  
Myxredlin  
Baqsimi  
Riomet ER  
Afrezza  
Trulicity  
Xigduo XR  
Toujeo Solostar  
Lantus  
Lente Iletin II

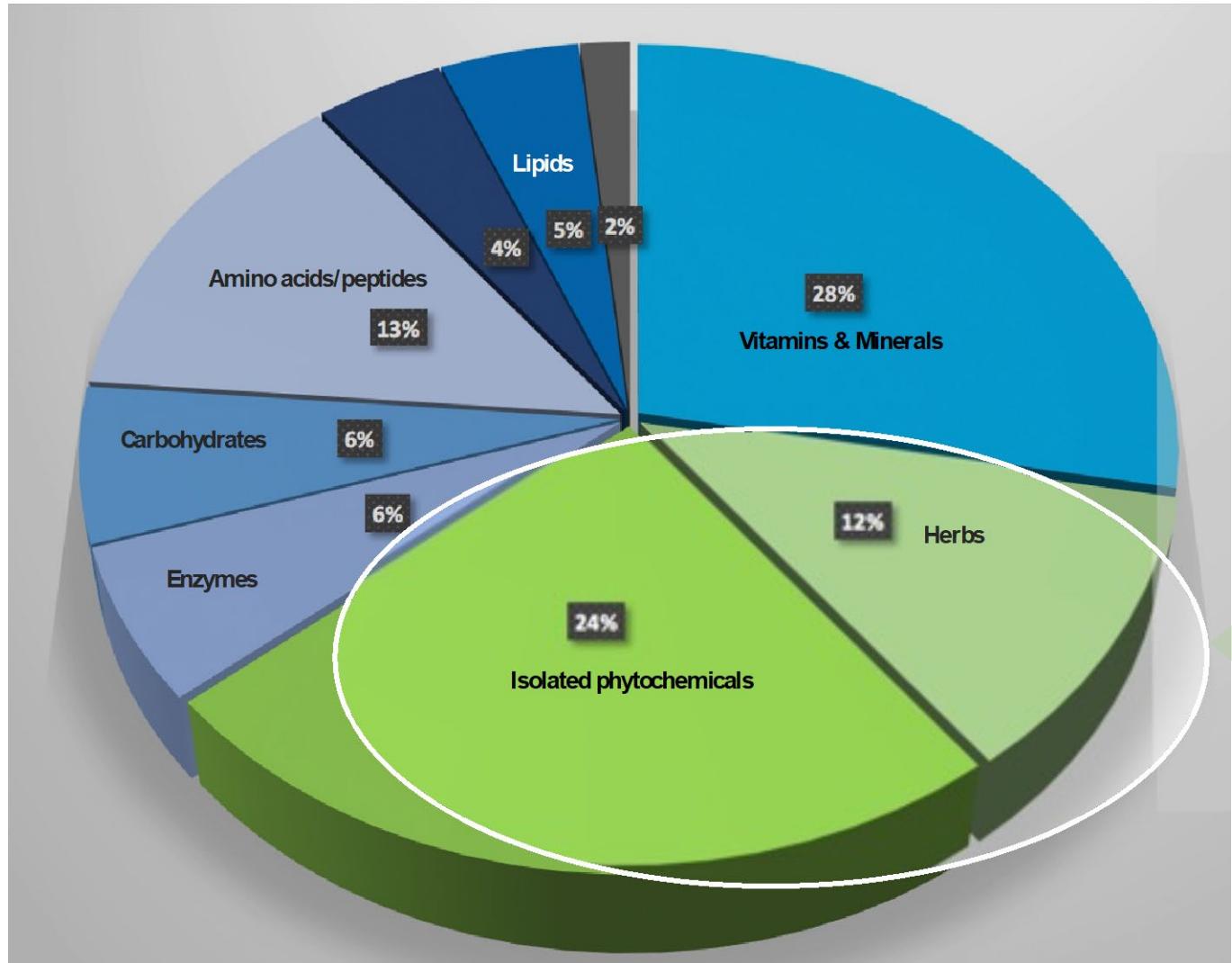
The evidence



The warnings







Alpha lipoic acid  
Astaxanthin  
Berberine  
Caffeine  
Curcumin  
Diindolylmethane  
Hesperidin  
Hesperetin  
Indole-3-carbinol  
Ipriflavone  
Luteolin  
N-acetyl cysteine  
Pterostilbene  
Quercetin  
Resveratrol  
Vinpocetine

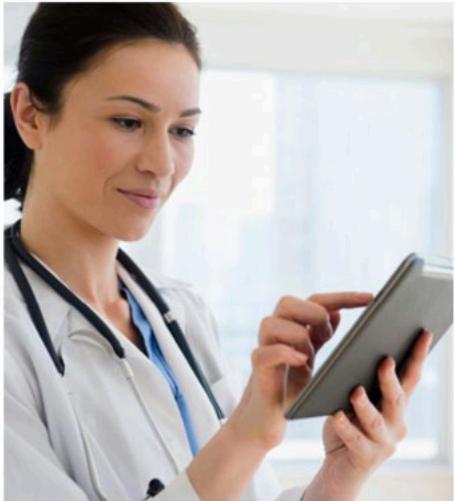
Let the experts do the work for you



# Real world navigation



# 1. Know the drug (even if you're not the prescriber)



## Know the drug

Adverse effects profile

Therapeutic window

Dose adjustment risks

REMEMBER!

## 2. Encourage full disclosure



3. When in doubt, read up.

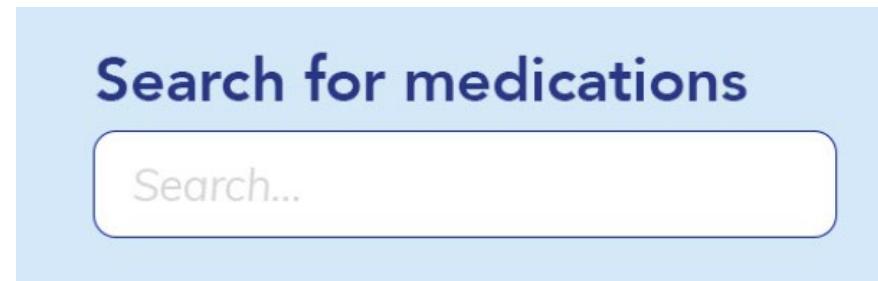


Google Scholar



## 4. Interaction checkers: Big advantages

- 1. Save time**
- 2. Avoid errors**
- 3. Stay current**



The Drug-Nutrient Inter action Checker is for general wellness informational purposes only and is not a substitute for medical, diagnosis, treatment or other professional advice or the independent clinical judgment of a healthcare professional.

# Interaction checkers: Common limitations

## 1. Most interactions are clinically insignificant

Evidence, Exposure, Effect size, Extrapolation

## 2. It's hard to know what to do

Avoid, Be cautious, Change dosing, or Dismiss

## 3. What's covered? Is the drug list up to date?

## 4. Patient accessibility

Pure Encapsulations®

# Drug-Nutrient Interaction Checker

**LESS NOISE. MORE CLINICAL RELEVANCE.**

Unlike other Drug-Nutrient Interaction checkers, we provide a unique experience by **reducing noise** and **delivering clinically relevant interactions** that can:

- 1. Happen in real life**
- 2. Occur at typical doses**
- 3. Affect the body in a significant way**

**Search for Medications Now:**

<https://www.pureencapsulationspro.com/drug-nutrient-interactions>

The Drug-Nutrient Interaction Checker is for educational and general wellness information purposes only and is not intended to provide any diagnosis, cure, mitigation, prevention or recommendation for medical treatment of any disease. It is not a substitute for medical, diagnosis, treatment or other professional advice or the independent clinical judgment of a healthcare professional.

Thank You