

Dietary Supplement Use in the Elderly

National Institutes of Health

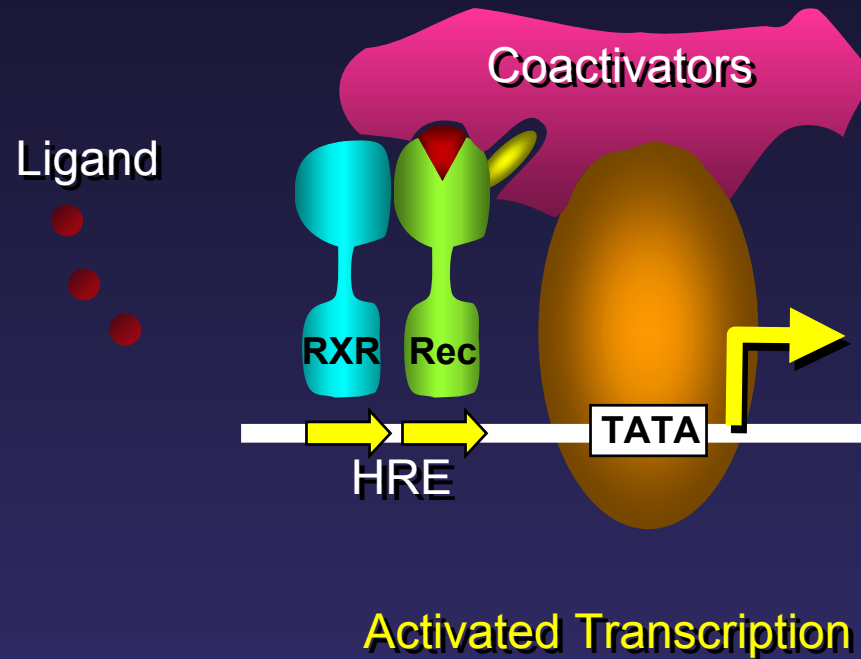
Polypharmacy & OTCs: Impact of Dietary Supplements on Gene Networks that Regulate Drug Clearance

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City of Hope National Medical Center
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Nuclear Hormone Receptors

Coactivator Recruitment



Orphan Nuclear Receptors

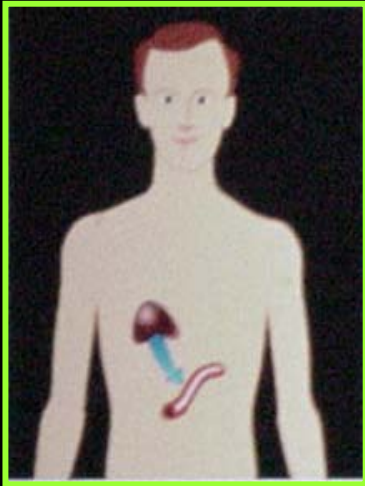
A New Endocrinology



Steroid
Thyroid
Retinoid
Vitamin D

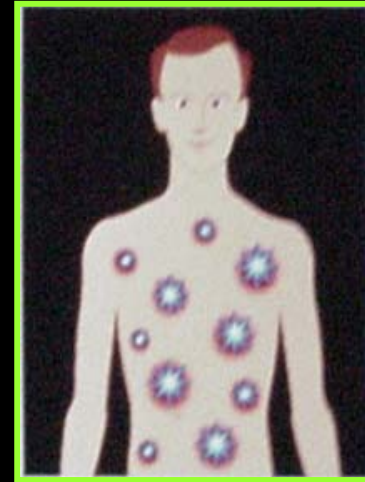
Hormonal Ligands

Classical Receptors



Steroids
Thyroid
Retinoids
Vitamin D

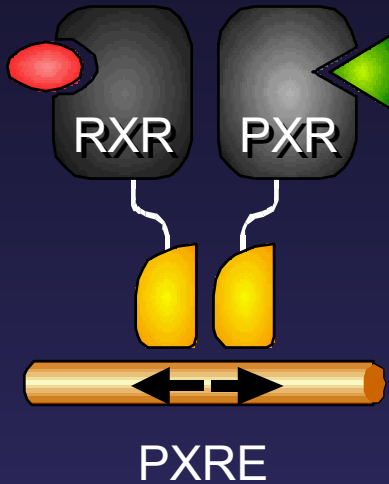
Orphan Receptors



Metabolites
Lipids
Fatty acids
Sterols
Bile Acids
Xenobiotics

SXR / PXR

A steroid & xenobiotic receptor



Expression: Liver & Intestine

Target Genes: Cyp3A4

Ligands: Phenobarbital
Rifampicin
Clotrimazole

Function: Protection from Xenotoxins

Enhancement of Drug Metabolism
Mediator of Drug-Drug Interactions

Cyclosporin
HIV Protease Inhibitors
Birth Control "Pill"

Taxol

Chemotherapeutic agent

Efficacy:

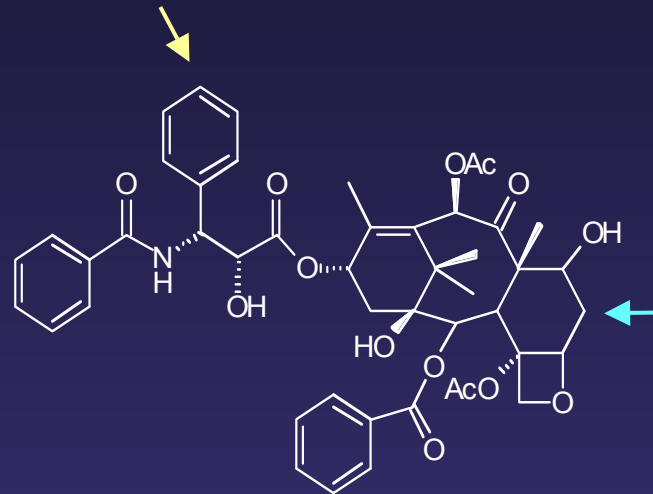
Breast & Ovarian Cancers

Activity:

Microtubule Stabilization

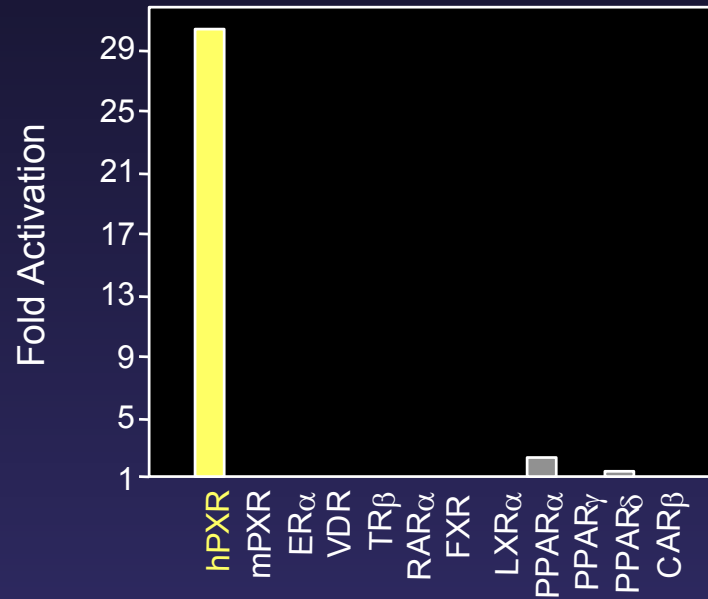
Metabolism:

Cyp3A4 & Cyp2C8



Taxol is a Specific Activator of hPXR

PXR vs other receptors



PXR & Taxol Degradation

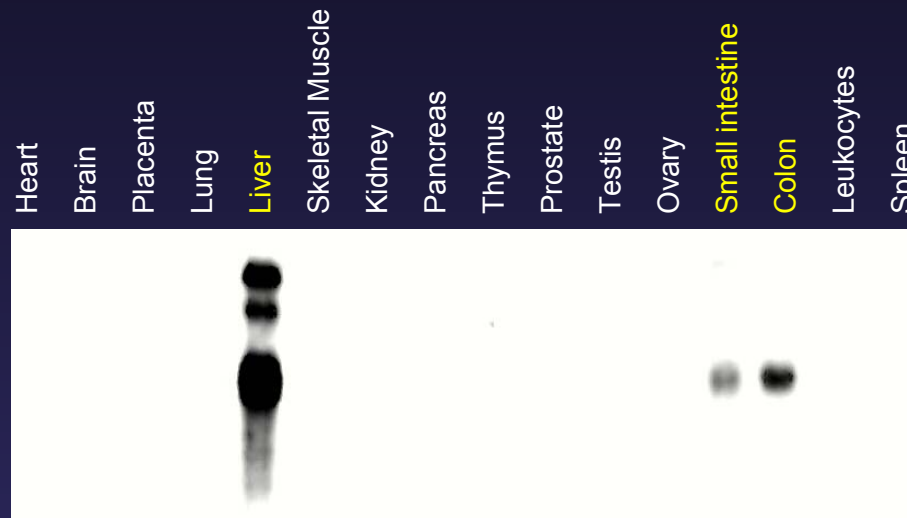
Cyp3A4 & Cyp2C8

Primary Human Hepatocytes



hPXR Expression

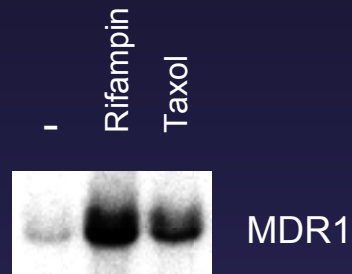
Liver & Intestine



Adapted from
Blumberg et al. , Lehmann et al. , & Bertilsson et al.

PXR Function in the Intestine?

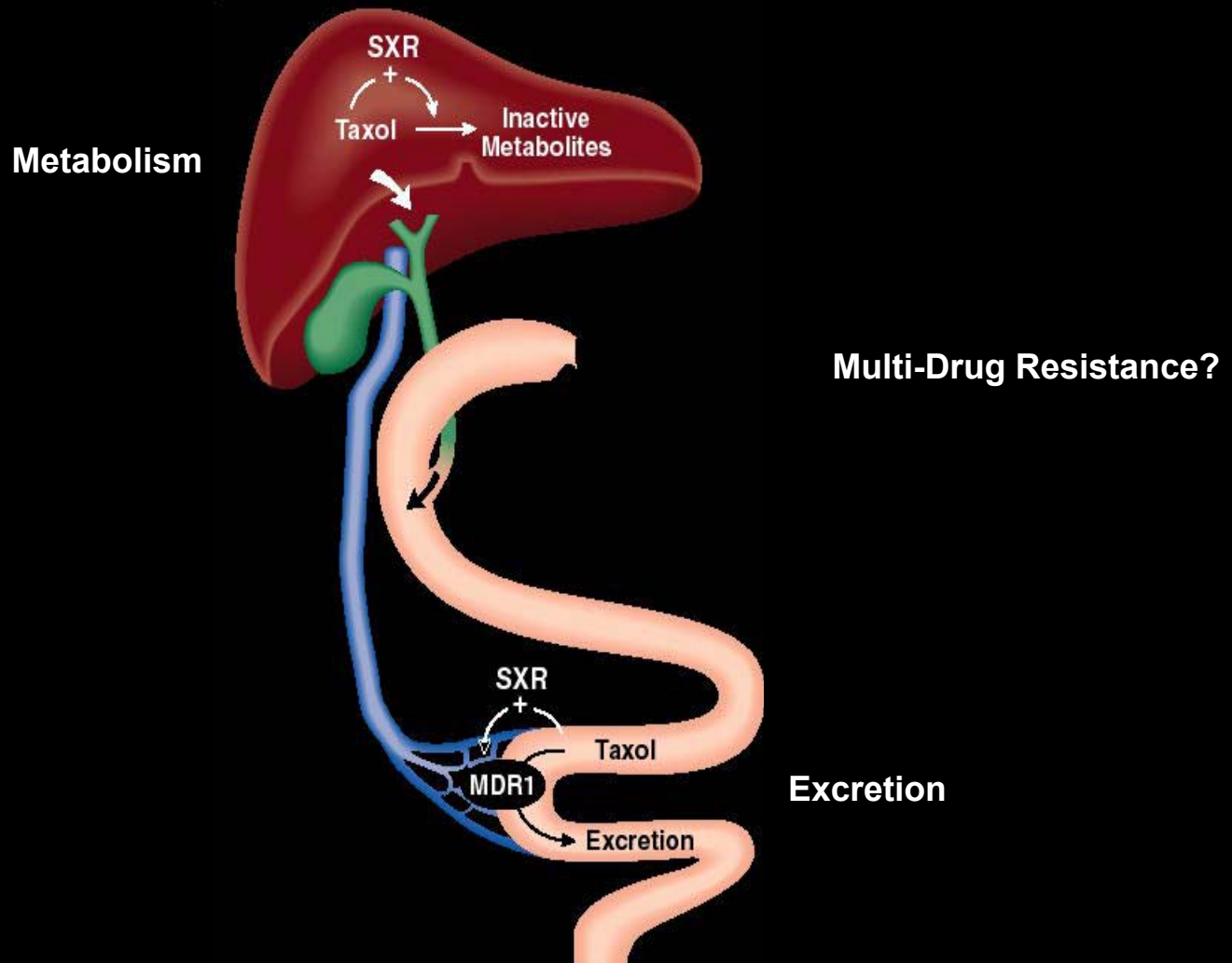
Regulation of MDR1



Human Intestinal Cells
LS180

PXR

A master regulator of drug clearance

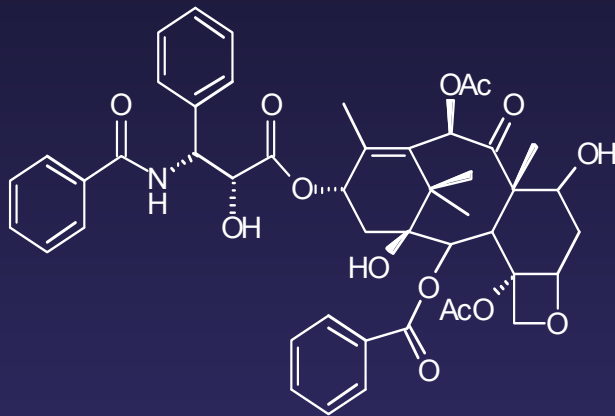


Taxol & Taxotere

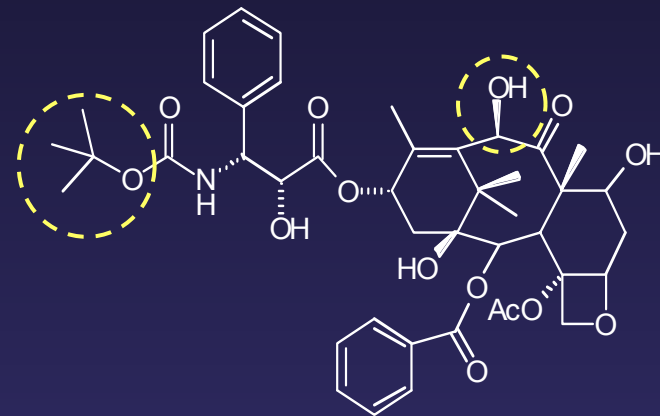
Related chemotherapeutic agents

Efficacy:
Activity:

Breast & Ovarian Cancers
Microtubule Stabilization



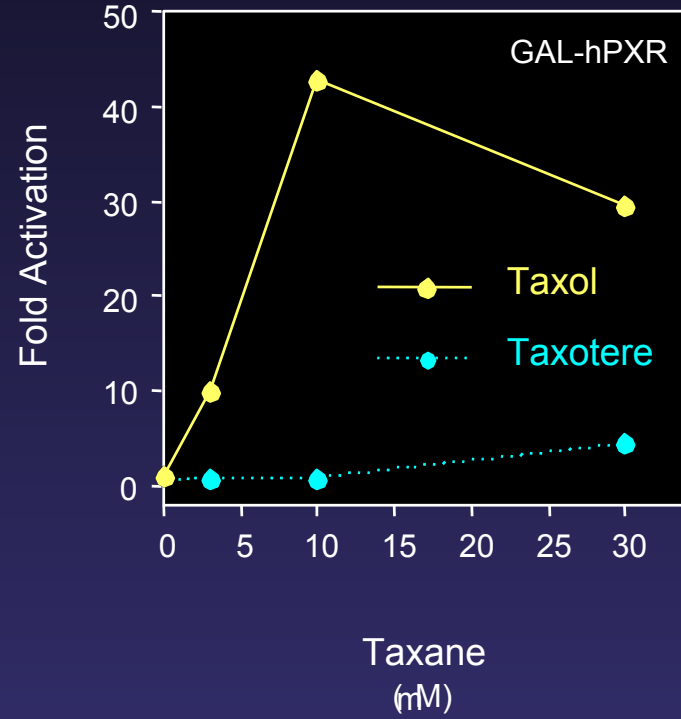
Taxol



Taxotere

Taxol vs Taxotere

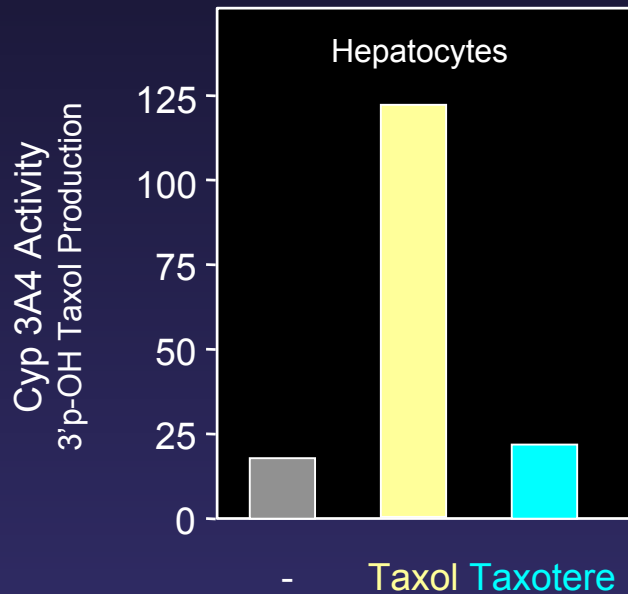
Taxotere does NOT activate hPXR



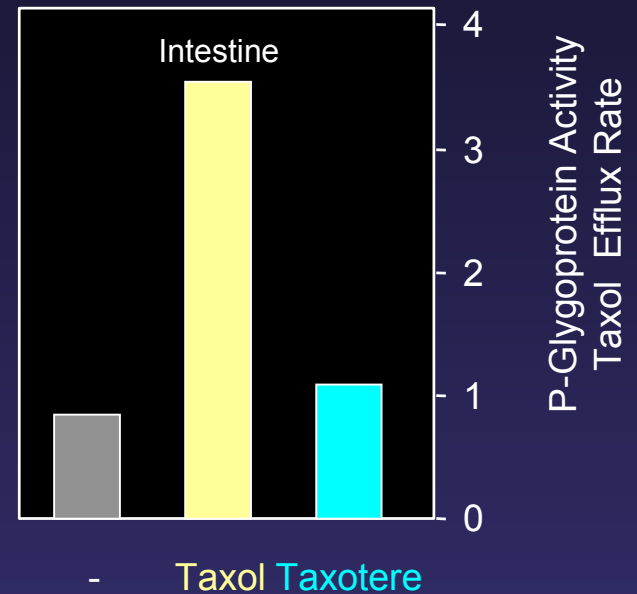
Taxol vs Taxotere

Taxotere does NOT induce drug clearance

Metabolism



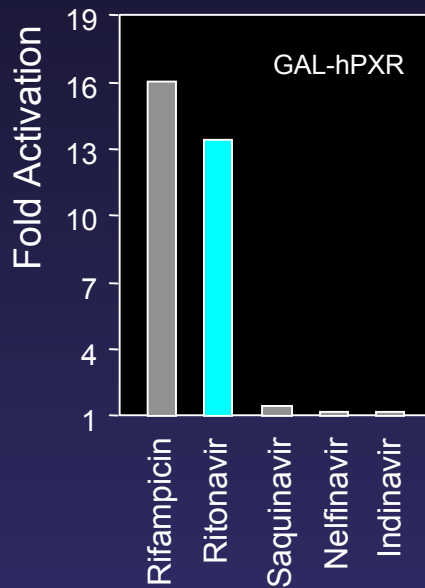
Efflux



HIV Protease Inhibitors & PXR

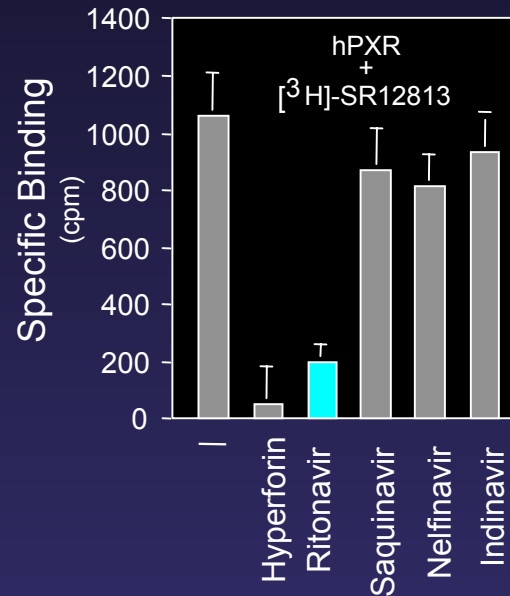
Ritonavir is a PXR ligand

Transfection
hPXR



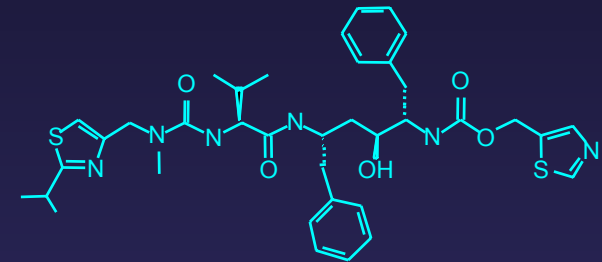
Protease Inhibitor

Ligand Binding
hPXR



Unlabeled
Protease Inhibitor

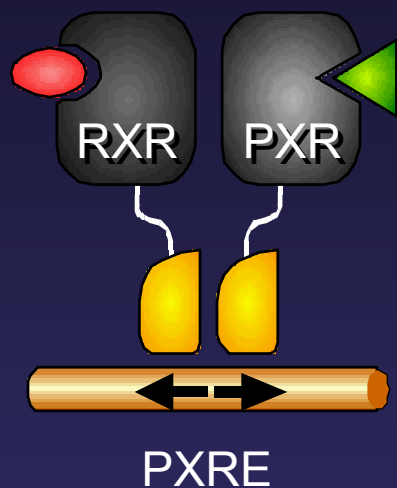
Structure



Ritonavir

Steroid & Xenobiotic Receptor (PXR/SXR)

PXR ligands are Cyp3A4 substrates



Expression: Liver & Intestine

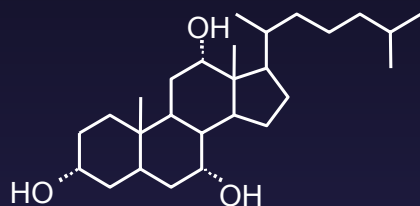
Function: Master regulator of drug & xenobiotic clearance

Target Genes: *MDR1, MRP2, OATP2*
Cyp3A4, Cyp2C8, Cyp2B
GSTa1, UGT1A, CAR
Aminolevulinate synthase (ALAS), Por

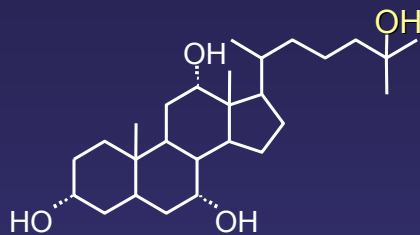
Ligands: Common Drugs & Xenobiotics
Endogenous Ligands?
Dietary Supplements?

Triol: a Potent PXR Agonist

Cyp3A4 & PXR utilize common sterol substrates

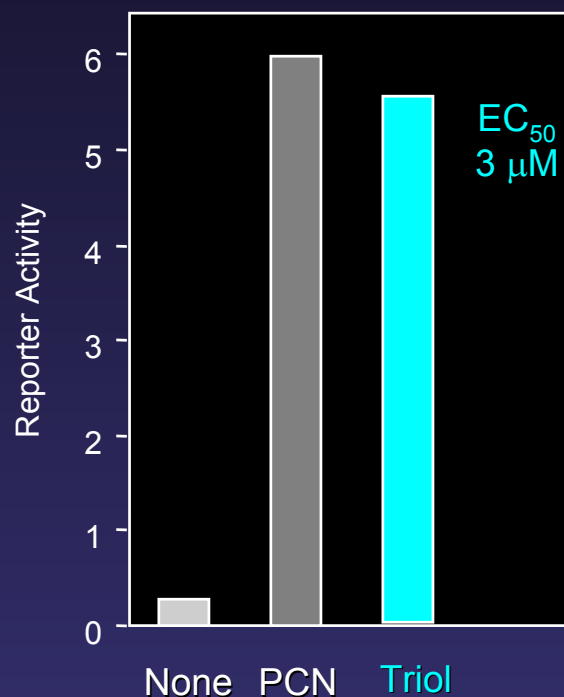


5 β -cholestane-3 α ,7 α ,12 α -Triol



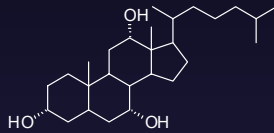
5 β -cholestane-3 α ,7 α ,12 α ,25-Tetrol

Transfection Assay
Mouse PXR



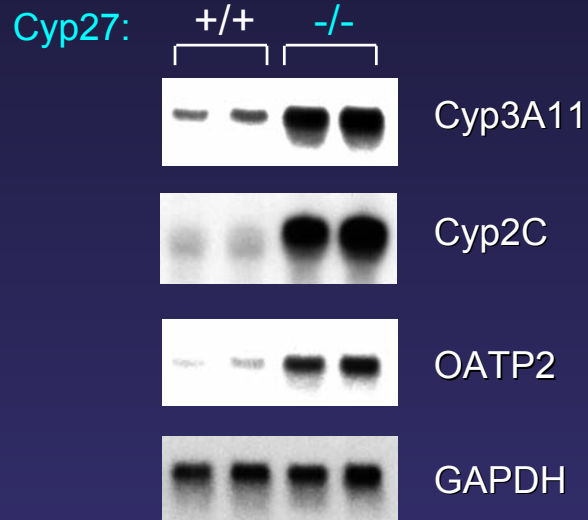
Cyp27 KO: Triol Accumulation & PXR Activation

Triol

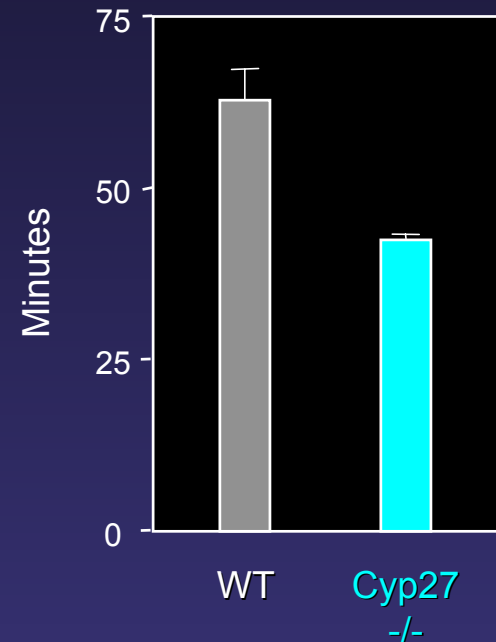


Cholic Acid

Hepatic Target Genes

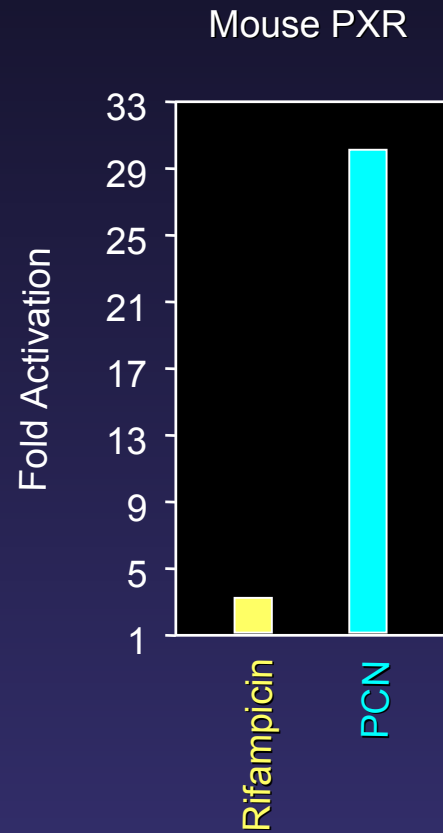
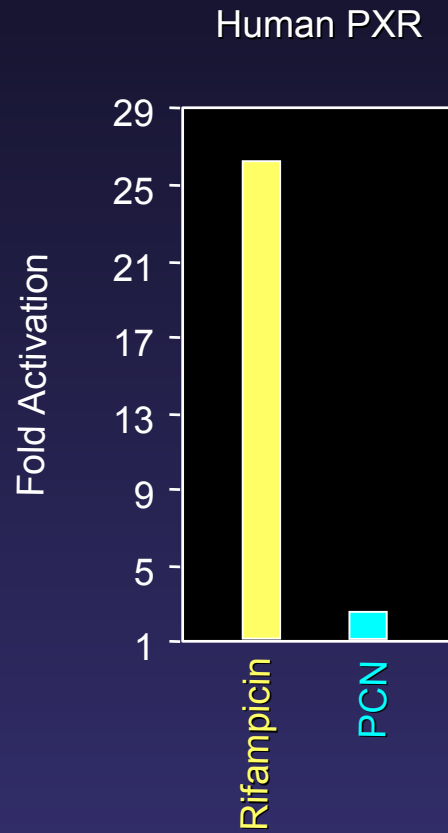


Tribromoethanol
Sleep Time



PXR

Species-specific responses



Widespread Use of Dietary Supplements



Widespread Use of Dietary Supplements



Widespread Use of Dietary Supplements



The image is a screenshot of the Jamba Juice website's 'jambacard! menu guide'. At the top, there is a red banner with the Jamba Juice logo on the left, a 'jambacard' image in the center, and the text 'give a jambacard! menu guide' on the right. Below the banner is a yellow navigation bar with links for 'smoothies', 'boosts', 'juices', and 'baked goods'. The main content area is divided into two columns. The left column is titled 'smoothies' and lists 20 different smoothie options. The right column features a large illustration of a smoothie cup with a swirl of fruit and a banana. To the right of the illustration is the 'Coldbuster!' product description, which includes a list of ingredients and a note. The word 'Echinacea' in the ingredients list is circled in blue. At the bottom of the page, there is a small graphic with the text 'jambalms #5... your body is a temple, littering is strictly prohibited.'

smoothies | boosts | juices | baked goods

smoothies

- seasonal smoothie
- Jamba Powerboost®
- Coldbuster!®
- Kiwi Berry Burner™
- Bounce Back Blast™
- Orange Dream Machine®
- Protein Berry Pizzazz™
- Chocolate Moo'd™
- Peanut Butter Moo'd™
- Strawberries Wild®
- Banana Berry™
- Razzmatazz®
- Berry Lime Sublime™
- Cranberry Craze®
- Orange Berry Blitz™
- Caribbean Passion™
- Mango-A-Go-Go™
- Citrus Squeeze™
- Orange-A-Peel™
- Aloha Pineapple™
- Peenya Kowlada®
- Peach Pleasure®

Coldbuster!®

The name says it all... the taste is all that! Coldbuster is loaded with over 2000% RDI of vitamin C! Whenever you feel the need, this cold-fighting blockbuster is high in vitamins A, E, B1, folic acid and zinc, plus it's boosted with **Echinacea*** and other herbs to combat free radicals and enhance your immune system.

Ingredients: Freshly Squeezed Orange Juice, Orange Sherbet, Frozen Peaches, Frozen Bananas, Ice, Vibrant C Boost, Immunity Boost.

*Note: For Echinacea, best results are obtained when used consecutively, not to exceed a duration of 2 weeks. Choose your boosts according to your daily nutritional needs! However, please consult your physician before starting any supplement program, especially if you have an autoimmune disorder, are pregnant, nursing, or taking other medications.

jambalms #5...
your body is a temple,
littering is strictly prohibited.

Future Research Needs & Resources

Predict and prevent herbal-drug interactions

❖ *Require comprehensive study of herbal meds for effects on:*

- PXR activation
- Endogenous PXR ligands
- Expression of genes involved in drug clearance
- Activity of P450 enzymes and transporters
- Drug clearance in humanized mice
- Human trials using non-invasive measures of drug clearance
- Similar studies on related receptor CAR

❖ *Teach clinicians & patients*

- Natural product ≠ Safety
- Medical histories should document use of drug supplements
- Create online database
- Modify supplement use is counterindicated
- FDA-like regulation? Standardize potency, efficacy, safety?

❖ *Explanation of interindividual differences in drug clearance?*

- Polymorphisms in PXR
- Polymorphisms in CAR

City of Hope

National Center for Complementary and Alternative Medicine
National Institutes of Health

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