Drug-Herbal Interactions

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Safety
Western Medicine
Traditional Chinese Medicine

Primum Non Nocere
First Do No Harm

Hippocratic Corpus

World Health Organization (WHO)

- WHO: >80% world's population uses CAM for their health care needs and particularly in western countries.
- CAM has become increasingly popular over the last few decades.

Borse SP, Singh DP, Nivsarkar M. Understanding the relevance of herb-drug interaction studies with special focus on interplays: a prerequisite for integrative medicine. Porto Biomed J. 2019 Mar 1;4(2):e15.

PORTO BIOMEDICAL JOURNAL
WHERE SCIENCE MEETS KNOWLEDGE

Review Article

OPEN

Understanding the relevance of herb–drug interaction studies with special focus on interplays: a prerequisite for integrative medicine

Swapnil P. Borse, BPharm, PhD[a,b], Devendra P. Singh, MPharm, PhD[a,b], Manish Nivsarkar, PhD[a,*]

Abstract

Integrative medicine refers to the blending of conventional and evidence-based complementary medicines and therapies with the aim of using the most appropriate of either or both modalities for ultimate patient benefits. One of the major hurdles for the same is the chances of potential herb–drug interactions (HDIs). These HDIs could be beneficial or harmful, or even fatal; therefore, a thorough understanding of the eventualities of HDIs is essential so that a successful integration of the modern and complementary alternative systems of medicine could be achieved. Here, we summarize all the important points related to HDIs, including types, tools/methods for study, and prediction of the HDIs, along with a special focus on interplays between drug metabolizing enzymes and transporters. In addition, this article covers future perspective, with a focus on background endogenous players of interplays and approaches to predict the drug–disease–herb interactions so as to fetch the desired effects of these interactions.

Keywords: Ayurveda, drug metabolizing enzymes–transporter interplays, herb–drug–disease interactions, integrative medicine

Herb-Drug Interactions

- Pharmacokinetic Interactions
  - Absorption
  - Distribution
  - Metabolism
  - Elimination

- Pharmacodynamic Interactions
  - Synergistic
  - Antagonistic
  - Complementary

Pharmacokinetic Interactions

- Absorption
- Distribution
- Metabolism
- Elimination

Absorption Interactions

- Binding in the gastrointestinal tract
- Change in pH in the stomach
- Change in intestinal motility
- Change in enzymes / normal flora

Binding in the GI Tract: Drugs

- Cholestyramine (Questran)
- Colestipol (Colestid)
- Ezetimibe (Zetia)
- Orlistat (Xenical)

Review > Drug Saf. 2008;31(1):53-65. doi: 10.2165/00002018-200831010-00005.

Orlistat-associated adverse effects and drug interactions: a critical review

Theodosios D Filippatos [1], Christos S Derdemezis, Irene F Gazi, Eleni S Nakou, Dimitri P Mikhailidis, Moses S Elisaf

metabolism. No significant effect on cancer risk has been reported with orlistat. Orlistat interferes with the absorption of many drugs (such as warfarin, amiodarone, ciclosporin and thyroxine as well as fat-soluble vitamins), affecting their bioavailability and effectiveness. This review considers orlistat-related adverse effects and drug interactions. The clinical relevance and pathogenesis of these effects is also discussed.

Filippatos TD, Derdemezis CS, Gazi IF, Nakou ES, Mikhailidis DP, Elisaf MS. Orlistat-associated adverse effects and drug interactions: a critical review. Drug Saf. 2008;31(1):53-65. doi: 10.2165/00002018-200831010-00005. PMID: 18095746.

Binding in the GI Tract: Herbs

- *Cha Ye*
  (Folium Camelliae)
  - Green Tea
  - *Oolong* Tea
  - Black Tea
  - *Pu-er* Tea

Chen J, Chen T. Chinese Medical Herbology and Pharmacology. Art of Medicine Press. 2004.

Cha Ye (Folium Camelliae)

- **Nadolol (Corgard)**: Coadministration of green tea extract (400 mg/kg) in rats significantly reduced C_{max} (85%) and AUC (74%) of nadolol (10 mg/kg), possibly through the inhibition of its intestinal absorption mediated by uptake transporters.

Misaka S, et al. Effects of green tea extract and (−)-epigallocatechin-3-gallate on pharmacokinetics of nadolol in rats. Phytomedicine, 2013, 20(14), 1247-1250.

Suggestion

- Take herbs and drugs separately by 2 hours

Pharmacokinetic Interactions

- Absorption
- Distribution
- Metabolism
- Elimination

Distribution

- Two factors that contribute to distribution interactions:
  - Narrow range of safety index
  - Highly protein bound (> 95%)

- No documented herb-drug interactions due to distribution

Mangoni AA, Jackson SH. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. Br J Clin Pharmacol. 2004;57:6–14.

Pharmacokinetic Interactions

- Absorption
- Distribution
- Metabolism
  - Cytochrome (CYP450) induction
  - Cytochrome (CYP450) inhibition
- Elimination

Cytochrome (CYP450) Induction

- Increased metabolism of herbs/drugs
- Decreased therapeutic effect
- Gradual onset of enzyme induction (takes about 1-2 month before effect is observed)

Cytochrome (CYP450) Inducers: Drugs

- Anticonvulsants: phenytoin (Dilantin), carbamazepine (Tegretol), phenobarbitone
- Steroids: dexamethasone, prednisolone, glucocorticoids
- Antibiotics: rifampicin, griseofulvin
- Others: alcohol, nicotine, cigarette smoke, St. John’s Wort

Cytochrome (CYP450) Inducers: Herbs

- *Guan Ye Jin Si Tao* (Herba Hyperici Perforati) - St. John's Wort
- *Ku Shen* (Radix Sophorae Flavescentis)
- *Ge Gen* (Radix Puerariae Lobatae)

Guan Ye Jin Si Tao (Herba Hyperici Perforati)

- Clears heat, eliminates toxins
- Stops bleeding
- Dispels wind-damp
- Spreads the Liver, regulates qi circulation

Chen J, Chen T. Chinese Medical Herbology and Pharmacology. Art of Medicine Press. 2004.

Guan Ye Jin Si Tao (Herba Hyperici Perforati)

- St. John's Wort induces the cytochrome P-450 system of the liver, leading to increased metabolism and reduced plasma concentration of many drugs, such as cyclosporine (Sandimmune/Neoral), ethinyloestradiol and desogestrel (combined oral contraceptive), theophylline (Theo-Dur), digoxin (Lanoxin), and indinavir (Crixivan).

PDR for Nutritional Supplements 1st Edition, Medical Economics, 2001.
Wang Z, et al. The effects of St John's wort (Hypericum perforatum) on human cytochrome P450 activity. Clin Pharmacol Ther. 2001 Oct;70(4):317-26.

Cytochrome (CYP450) Inhibition

- Decreased metabolism of herbs/drugs
- Increased therapeutic effect
- Rapid onset of enzyme inhibition (takes about 2 weeks before effect is observed)

Cytochrome (CYP450) Inhibitors: Drugs

- Antifungal: fluconazole (Diflucan), ketoconazole (Nizoral).
- Antibiotics: metronidazole (Flagyl), ciprofloxacin (Cipro), clarithromycin (Biaxin), sulfonamides, chloramphenicol, isoniazid.
- Antiulcer: cimetidine (Tagamet), omeprazole (Prilosec).
- Other: valproate sodium, grapefruit.

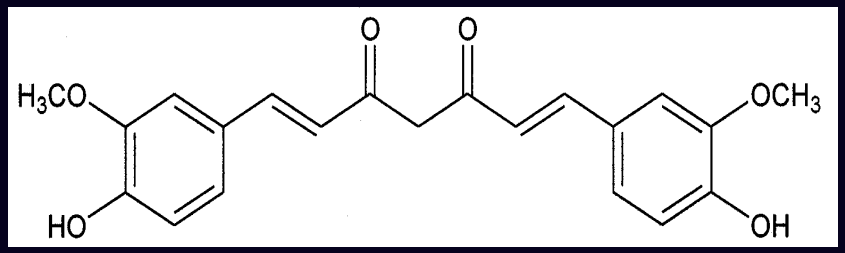
Cytochrome (CYP450) Inhibitors: Herbs

- *Jiang Huang* (Rhizoma Curcumae Longae)
- *Xin Yi Hua* (Flos Magnoliae)
- *Hu Zhang* (Rhizoma et Radix Polygoni Cuspidati)
- *Gan Cao* (Radix et Rhizoma Glycyrrhizae)
- *Dan Shen* (Radix et Rhizoma Salviae Miltiorrhizae)

Curcumin

- Curcumin is present in
  - *Jiang Huang* (Rhizoma Curcumae Longae)
  - *Yu Jin* (Radix Curcumae)
  - *E Zhu* (Rhizoma Curcumae)

– Note: Curcumin is also sold as is OTC



Chen J, Chen T. Chinese Medical Herbology and Pharmacology. Art of Medicine Press. 2004.

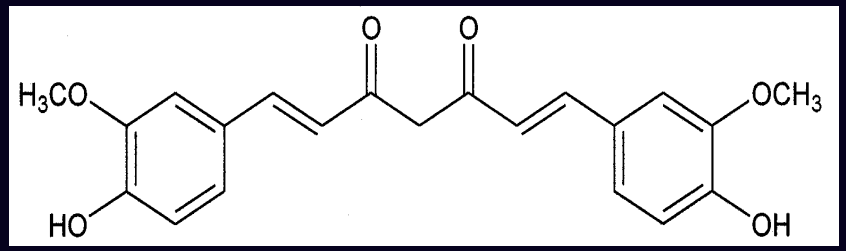
Curcumin

- Co-administration of curcumin in animal subjects has been shown to inhibit CYP3A, leading to an increase in C_{max} and AUC of rosuvastatin (Crestor),[1] docetaxel (Taxotere),[2] tacrolimus (Prograf).[3]

1. Zhou X, et al. Impact of curcumin on the pharmacokinetics of rosuvastatin in rats and dogs based on the conjugated metabolites. Xenobiotica. 2017 Mar;47(3):267-275.
2. Yan YD, et al. Effect of dose and dosage interval on the oral bioavailability of docetaxel in combination with a curcumin self-emulsifying drug delivery system (SEDDS). Eur J Drug Metab Pharmacokinet. 2012 Sep;37(3):217-24.
3. Egashira K, et al. Food-drug interaction of tacrolimus with pomelo, ginger, and turmeric juice in rats. Drug Metab Pharmacokinet. 2012;27(2):242-7.

Curcumin

- Note: These are studies done with one compound, at a high dosage, in animals.
- Acutal effect of the herb/formula, at a normal dosage, in humans, is not known at this time.



Chen J, Chen T. Chinese Medical Herbology and Pharmacology. Art of Medicine Press. 2004.

Suggestion

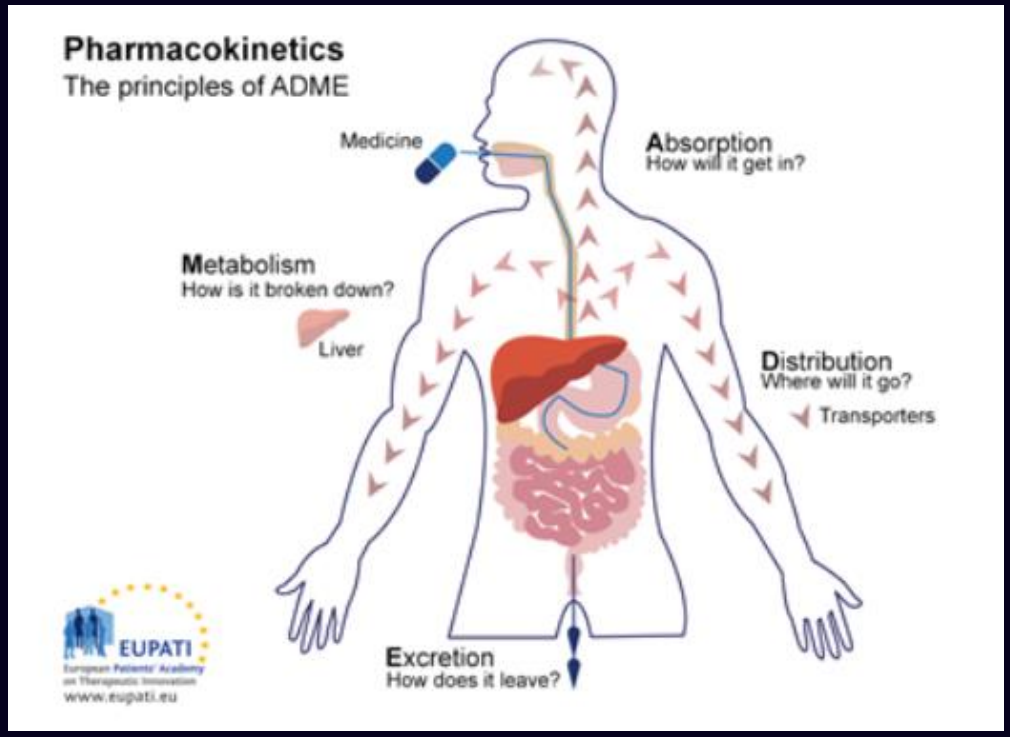
- Monitor the patient carefully
- Adjust the dosage of herbs as needed
- Select another herb without interaction

Pharmacokinetic Interactions

- Absorption
- Distribution
- Metabolism
- Elimination

Pharmacokinetic Interactions

- Absorption
- Distribution
- Metabolism
- Elimination



https://genomind.com/providers/introduction-to-pharmacokinetics-four-steps-in-a-drugs-journey-through-the-body/

Pharmacodynamic Interactions

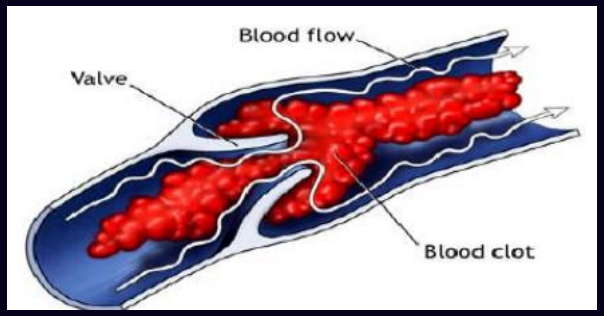
- Synergistic
- Antagonist
- Complementary

Pharmacodynamic Interactions

- Synergistic
- Antagonist
- Complementary

Clotting Disorders – Thrombus

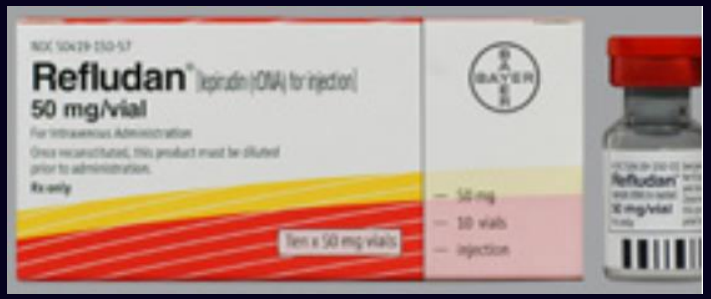
- Thrombolytic drugs:
  - Streptokinase
- Anticoagulant drugs:
  - Heparin
  - Warfarin (Coumadin)
- Antiplatelet drugs:
  - Aspirin
  - Dipyridamole (Persantine)
  - Clopidogrel (Plavix)



Clotting Disorders – Blood Stasis

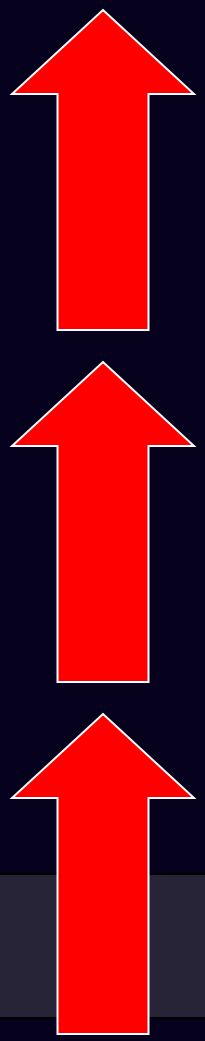
- *Dan Shen* (Rx et Rz Salviae Miltiorrhizae)
- *Dang Gui* (Radix Angelicae Sinensis)
- *Chuan Xiong* (Rhizoma Chuanxiong)
- *Tao Ren* (Semen Persicae)
- *Hong Hua* (Flos Carthami)
- *Shui Zhi* (Hirudo)

***Shui Zhi* (Hirudo)**



Herb-Drug Interactions

- Herbs that activate blood circulation and resolve blood stasis



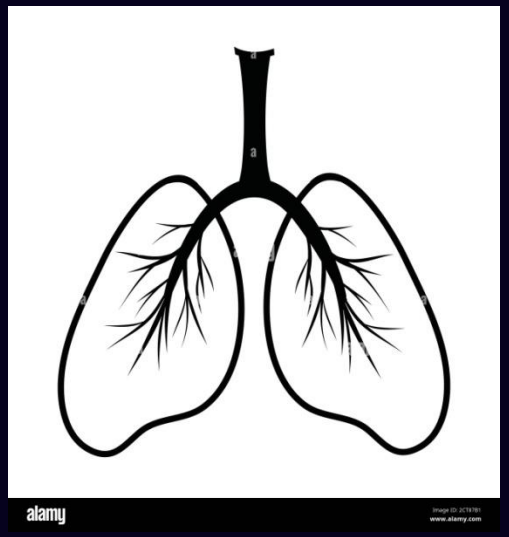
- Thrombolytic drugs
- Anticoagulant drugs
- Antiplatelet drugs

Pharmacodynamic Interactions

- Synergistic
- Antagonist
- Complementary

Antiasthmatic Drugs

- Bronchodilators
  - Beta-agonists (ie, albuterol (Proventil, Ventolin), epinephrine (Primatene Mist))
- Anti-inflammatory Drugs
  - Corticosteroids
  - Mast cell stabilizers (ie, cromolyn**)**
  - Leukotriene Inhibitors (ie, montelukast (Singulair), zafirlukast (Accolate), zileuton (Zyflo))



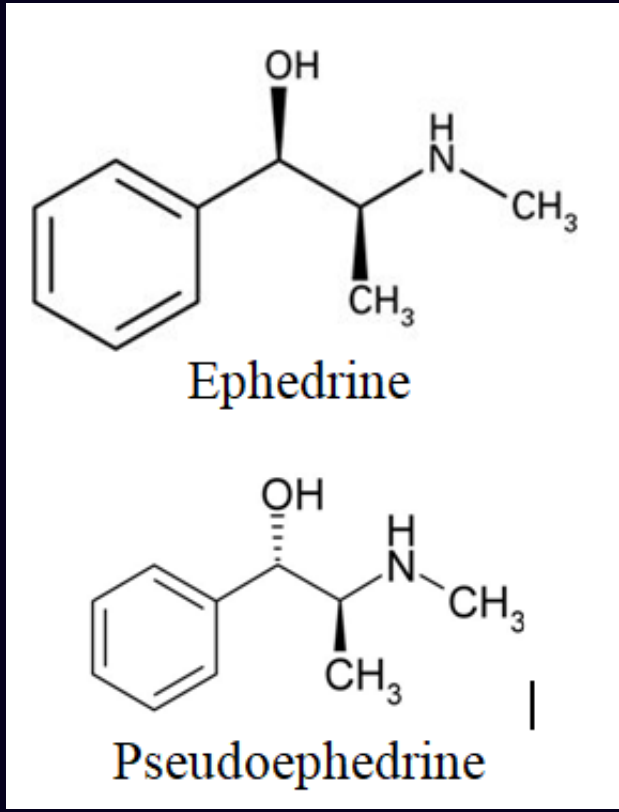
Ma Huang (Herba Ephedrae)

- Releases the exterior through diaphoresis
- Relieves wheezing and dyspnea, stops cough
- Regulates water circulation and relieves edema
- Warms and disperses cold

Chen J, Chen T. Chinese Medical Herbology and Pharmacology. Art of Medicine Press. 2004.

Ma Huang (Herba Ephedrae)

- Ephedrine alkaloids 0.481-2.47% (l-ephedrine, d-pseudoephedrine, l-norephedrine, l-methylephedrine, d-norpseudoephedrine, d-methyl-pseudoephedrine), essential oil 0.25% (l-alpha-terpineol, hexadecanoic acid; 1,4-cineole; 2,3,5,6-tetramethylprazine), ephedroxane, 2,3,4-trimethyl-5-phenyloxazolidine benzylmethylamine, 2,3,5,6-tetramethylpyrazine.



Xian Dai Zhong Yao Yao Li Xue (Contemporary Pharmacology of Chinese Herbs) 1997;32-33.
The Merck Index 12th edition. Chapman & Hall/CRCnetBASE/Merck, 2000.

Pseudoephedrine Interactions

- 181 medications interactions
  - albuterol, duloxetine, levothyroxine
- 1 alcohol/food interactions
  - caffeine
- 6 disease interactions
  - cardiovascular disease

https://www.drugs.com/drug-interactions/pseudoephedrine,sudafed-congestion.html

Ma Huang (Herba Ephedrae)

- **Beta blockers**: The effect of beta blockers may be reduced when combined with *Ma Huang* because of increased levels of norepinephrine caused by the herb.
- Examples of beta blockers: metoprolol (Toprol), propranolol(Inderal), atenolol(Tenormin), acebutolol (Sectral), bisoprolol (Ziac), esmolol (Brevibloc), labetalol (Normodyne) and carvedilol (Coreg).

Pharmacodynamic Interactions

- Synergistic
- Antagonist
- Complementary

Huang Qin Tang (Scutellaria Decoction)

- *Huang Qin* (Rx Scutellariae), 9g
- *Bai Shao* (Rx Paeoniae Alba), 6g
- *Gan Cao* (Rx et Rz Glycyrrhizae), 6g
- *Da Zao* (Fr Jujubae), 12 pcs

- Damp-heat dysentery: mild fever, a bitter taste in the mouth, abdominal pain, diarrhea, dysentery, a red tongue with a yellow tongue coating, and a rapid pulse.

Chen J, Chen T. Chinese Herbal Formulas and Applications. Art of Medicine Press. 2009.

THE WALL STREET JOURNAL.
U.S. EDITION Monday, April 2, 2012 As of 6:56 PM EDT

Chinese Medicine Goes Under the Microscope

Scientists studying a four-herb combination discovered some 1,800 years ago by Chinese herbalists have found that the substance enhances the effectiveness of chemotherapy in patients with colon cancer.

Photo Researchers Inc.

Early studies show a traditional four-herb combination has cancer-treatment benefits. The herbs are Chinese peony (pictured), Chinese jujube, Chinese licorice and baikal skullcap.

The mixture, known in China as huang qin tang, has been shown in early trials to be effective at reducing some side effects of chemotherapy, including diarrhea, nausea and vomiting. The herbs also seem to bolster colon-cancer treatment: Tests on animals with tumors have shown that administering the herbs along with chemotherapy drugs restored intestinal cells faster than when chemo was used alone.

The herb combination, dubbed PHY906 by scientists, is a rare example of a plant-based product used in traditional folk medicine that could potentially jump the hurdle into mainstream American therapy. A scientific team led by Yung-Chi Cheng, an oncology researcher at Yale University, and funded in part by the National Cancer Institute, is planning to begin Phase II clinical trials to study PHY906's effectiveness in people with colon cancer.

Clinical Trial > Clin Colorectal Cancer. 2011 Jun;10(2):85-96. doi: 10.1016/j.clcc.2011.03.003. Epub 2011 Apr 22.

A phase I study of the chinese herbal medicine PHY906 as a modulator of irinotecan-based chemotherapy in patients with advanced colorectal cancer

Shivaani Kummar [1], M Sitki Copur, Michal Rose, Scott Wadler, Joe Stephenson, Mark O'Rourke, Wayne Brenckman, Robert Tilton, Shwu-Huey Liu, Zaoli Jiang, Tahmun Su, Yung-Chi Cheng, Edward Chu

Affiliations + expand

PMID: 21859559 DOI: 10.1016/j.clcc.2011.03.003

Abstract

PHY906 is a novel Chinese herbal preparation that has been used in the Orient for over 1800 years to treat a wide range of gastrointestinal side effects including diarrhea, abdominal cramps, vomiting, fever, and headache. Preclinical and clinical studies were conducted to further investigate the biologic and clinical activities of this herbal medicine. To ensure standardization and maintain interbatch reliability of PHY906, high performance liquid chromatography (HPLC) was used to establish a "chemical fingerprint" of PHY906. In vivo preclinical studies using the murine Colon 39 tumor model showed that PHY906 protected against the weight loss associated with irinotecan treatment. In the presence of PHY906, mice were able to tolerate otherwise lethal doses of irinotecan. Significantly improved antitumor activity and overall survival were observed in animals treated with the combination of irinotecan and PHY906 versus irinotecan alone. The combination of PHY906 with irinotecan, 5-fluorouracil (5-FU), and leucovorin (LV) also resulted in at least additive antitumor activity with no increased host toxicity. Based on these in vivo studies, a phase I multicenter, double-blind, randomized, placebo-controlled, dose escalation, cross-over study of PHY906 as a modulator of the

Kummar S, Copur MS, Rose M, Wadler S, Stephenson J, O'Rourke M, Brenckman W, Tilton R, Liu SH, Jiang Z, Su T, Cheng YC, Chu E. A phase I study of the chinese herbal medicine PHY906 as a modulator of irinotecan-based chemotherapy in patients with advanced colorectal cancer. Clin Colorectal Cancer. 2011 Jun;10(2):85-96.

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determine the safety and tolerability of PHY906 when administered concomitantly with the bolus, weekly IFL regimen. Treatment with PHY906 did not alter the pharmacokinetics of 5-FU, irinotecan, or the irinotecan metabolite SN-38.

Kummar S, Copur MS, Rose M, Wadler S, Stephenson J, O'Rourke M, Brenckman W, Tilton R, Liu SH, Jiang Z, Su T, Cheng YC, Chu E. A phase I study of the chinese herbal medicine PHY906 as a modulator of irinotecan-based chemotherapy in patients with advanced colorectal cancer. Clin Colorectal Cancer. 2011 Jun;10(2):85-96.

The Oncologist

OXFORD UNIVERSITY PRESS

Oncologist. 2021 Mar; 26(3): e367–e373.
Published online 2020 Nov 25. doi: 10.1002/onco.13582

PMCID: PMC7930412
PMID: 33140457

A Phase II Clinical Trial on the Combination Therapy of PHY906 Plus Capecitabine in Hepatocellular Carcinoma

Chun A. Changou,[1,2,3] Her-Shyong Shiah,[1] Li-Tzong Chen,[4] Servina Liu,[5] Frank Luh,[5] Shwu-Huey Liu,[6] Yung-Chi Cheng,[7] and Yun Yen[1]

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This study aimed to evaluate efficacy and safety of capecitabine combined with a PHY906 (a pharmaceutical-grade formulation of four traditional Chinese herbs) in the treatment of advanced hepatocellular carcinoma (HCC) in Asian patients who were positive for hepatitis B virus (HBV).

Conclusion

Our data showed that PHY906 increases the therapeutic index of capecitabine by enhancing its antitumor activity and reduces its toxicity profile in advanced HCC.

Changou CA, Shiah HS, Chen LT, Liu S, Luh F, Liu SH, Cheng YC, Yen Y. A Phase II Clinical Trial on the Combination Therapy of PHY906 Plus Capecitabine in Hepatocellular Carcinoma. Oncologist. 2021 Mar;26(3):e367-e373. doi: 10.1002/onco.13582. Epub 2020 Nov 25. PMID: 33140457; PMCID: PMC7930412.

NIH NATIONAL CANCER INSTITUTE

Clinical Trials Using Chinese Herbal Formulation PHY906

YIV-906 (Formerly PHY906/KD018) With Sorafenib in HBV(+) Hepatocellular Carcinoma (HCC)

The aim of this study is to compare the efficacy and safety of YIV-906 plus standard-of-care sorafenib versus those of sorafenib alone as a first-line systemic treatment for patients with Hepatitis B (+) associated advanced hepatocellular carcinoma. YIV-906 (PHY906, KD018) is an immune system modulator. Clinical and preclinical research suggests that YIV-906 could act to enhance the body's immune response to fight cancer and increase the anti-tumor activity of sorafenib and protect and repair the gastrointestinal tract by reducing inflammation and promoting tissue regeneration. Inspired by a 1,800-year-old traditional medicine still in use today, YIV-906 is a botanical drug candidate, composed of an extract of four herbs and administered in oral capsule form. The CALM (Combination of YIV-906 and Sorafenib to treat Advanced Liver cancer in a Multi-center study) trial is a multi-regional, randomized, placebo-controlled study.

https://www.cancer.gov/research/participate/clinical-trials/intervention/chinese-herbal-formulation-phy906

Huang Qin Tang (Scutellaria Decoction)

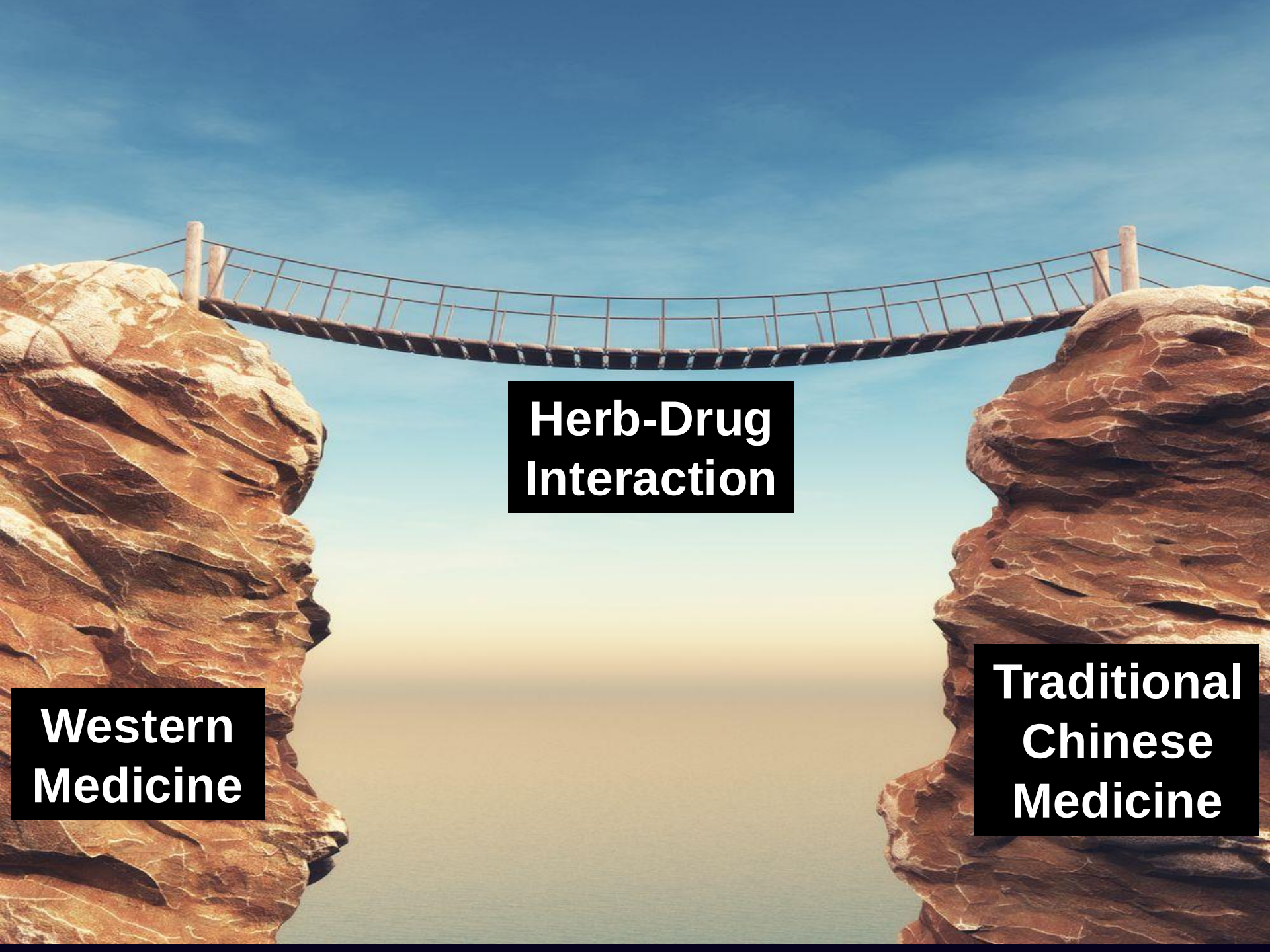
- PHY906 exhibited anti-inflammatory effects by decreasing the infiltration of neutrophils or macrophages, tumor necrosis factor–α expression in the intestine, and proinflammatory cytokine concentrations in plasma.
- Chemical constituents of PHY906 potently inhibited nuclear factor κB, cyclooxygenase-2, and inducible nitric oxide synthase.
- PHY906 had restored the intestinal epithelium by promoting the regeneration of intestinal stem cells

Lam W, Bussom S, Guan F, Jiang Z, Zhang W, Gullen EA, Liu SH, Cheng YC. The four-herb Chinese medicine PHY906 reduces chemotherapy-induced gastrointestinal toxicity. Sci Transl Med. 2010 Aug 18;2(45):45ra59. doi: 10.1126/scitranslmed.3001270. PMID: 20720216.

Huang Qin Tang (Scutellaria Decoction)

Herb	TCM function	WM function
Huang Qin (Rx Scutellariae)	Clears damp-heat	Antibiotic Anti-inflammatory Anticancer
Bai Shao (Rx Paeoniae Alba)	Nourishes yin	Restores the “form”
Gan Cao (Rx et Rz Glycyrrhizae) *Da Zao* (Fr Jujubae)	Tonifies qi	Restores the “function”

Chen J, Chen T. Chinese Herbal Formulas and Applications. Art of Medicine Press. 2009.


Herb-Drug Interaction
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Traditional Chinese Medicine

Additional Resources

- NIH's Office of Dietary Supplements https://ods.od.nih.gov
- U.S. Pharmacopeial Convention http://www.usp.org
- PubMed http://www.ncbi.nlm.nih.gov/pubmed

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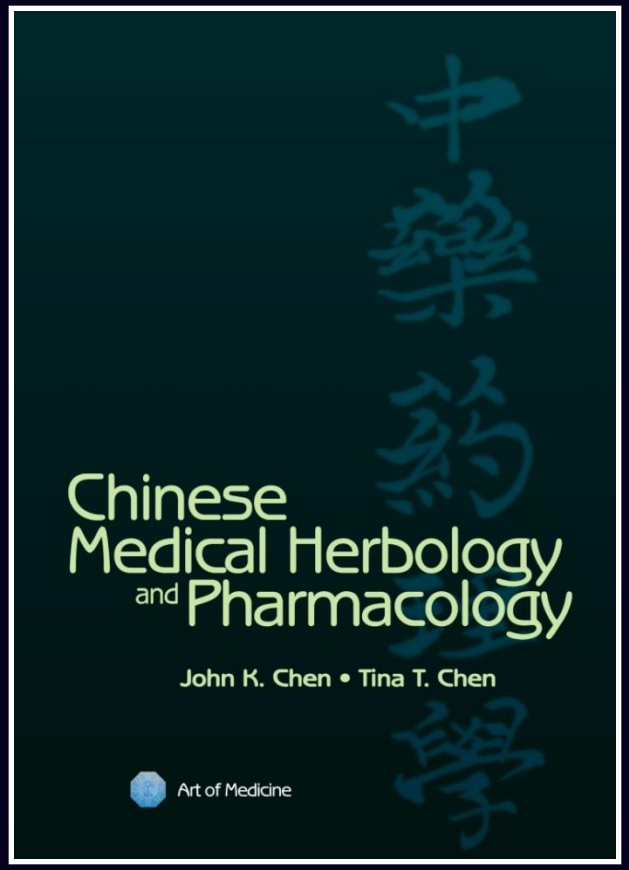
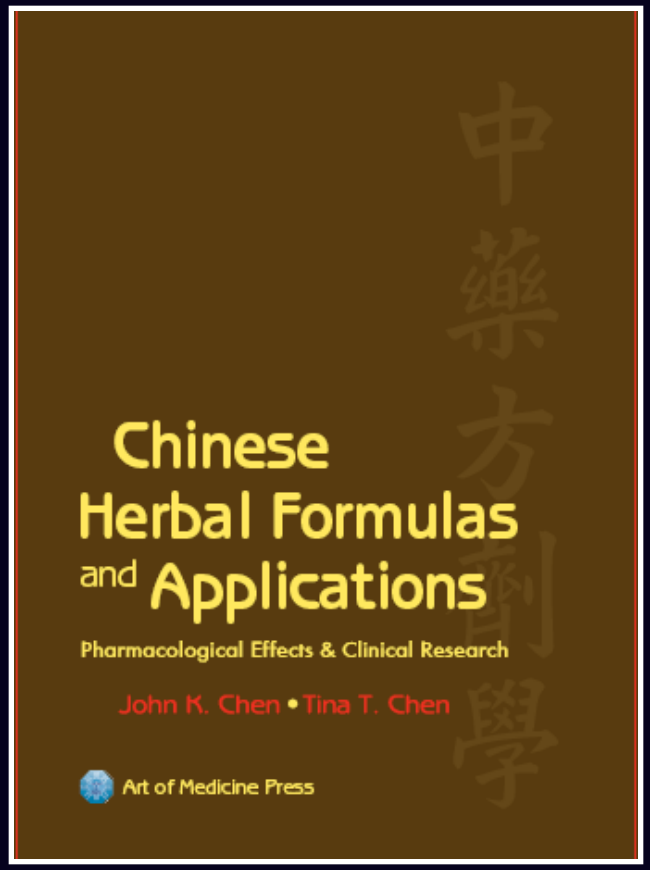
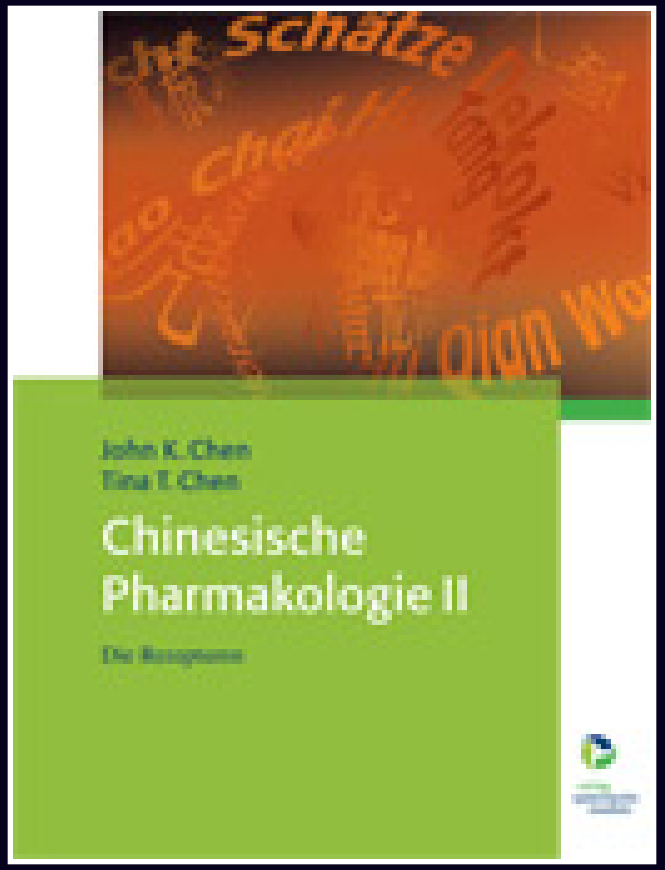




Art of Medicine Press



Safety on Drug-Herbal Interactions

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Question

- *Ma Huang* (Herba Ephedrae) should be used with caution in patients who take
  - A. alpha-blockers
  - B. beta-blockers
  - C. both

Answer

- *Ma Huang* (Herba Ephedrae) many compounds, such as ephedrine and pseudoephedrine, that have a stimulant effect and may antagonize the effects of alpha- and beta-blockers.