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# Interaction of Herbal Constituents with Cytochrome P450 Enzymes

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## Abstract

This article provides a review of the many facets of interactions between herbal constituents and cytochrome P450 (CYP450) enzymes. While stressing potential drug–herb interactions, the article also reviews information about how CYP450 enzymes participate in activating (for better or for worse) botanical constituents, and suggests circumstances in which the individual expression of patients' CYP450 enzymes can influence the activity of botanical medicines affected by these enzymes.

The article reviews the effect of *Hypericum perforatum* (St. John's wort) and *Citrus decumana* (grapefruit) on CYP3A4, and the potential influence of this effect on the metabolism of certain drugs. The article discusses the toxic activation by CYP3A4 of unsaturated pyrrolizidine alkaloids from plants such as *Symphytum officinale* (comfrey) and of alkylbenzenes such as safrole from *Sassafras* spp. (sassafras) and *Areca catechu* (areca or betel nut), and estragole from *Foeniculum vulgare* (fennel), *Pimpinella anisum* (anise), *Ocimum basilicum* (basil), and *Artemisia dracunculus* (tarragon). The effects of piperine from *Piper nigrum* (black pepper) and *Piper longum* (long pepper) on CYP3A4, as well as its interactions with *Curcuma longa* (turmeric), are surveyed. The effect of cruciferous vegetables, including *Nasturtium officinale* (watercress), and their isothiocyanate constituents (sulforaphane, phenylethyl isothiocyanate [PEITC], and most notably indole-3-carbinole) with CYP1A1, 1A2, and 2E1 are discussed in the context of carcinogenesis, induction of beneficial estrogen metabolism, and the ways in which the individual patient's glutathione enzyme systems can alter the efficacy of these vegetables and isothiocyanates. The pharmacokinetics of *Artemisia annua* (sweet Annie, *qing hao*) and artemisinin are discussed in light of CYP450 interactions. The article also presents minor relationships involving plants and plant constituents and CYP450 enzymes, such as that of grapefruit with CYP2A6, the activation of resveratrol to its more active metabolite piceatannol, and interactions of artemisinin and *Ginkgo biloba* with CYP2C19.

## Introduction

The CYP450 enzyme system plays a critical role in the metabolism of endogenous and exogenous compounds both in the intestinal lining and in the liver. Drugs are commonly metabolized by this major enzyme system, as are many herbal constituents. This is a cause for concern, since constituents metabolized through the CYP450 pathway may influence it in such a way as to alter the absorption, metabolism, toxicity, and excretion of each constituent. Typically, research focuses on herb–drug interactions that may be detrimental to the proper delivery of drugs. However, knowledge of interactions of herbs and herbal constituents with enzymes of the CYP450 pathway is also important in terms of understanding the pharmacokinetics of herbs, and may shed light on their mechanisms of action and how to enhance their effectiveness, as well as clarify any potential toxicity. In this article we review what is known about clinically relevant herbal interactions with CYP450, and discuss how these interactions may be problematic or useful to the clinician.

## The CYP450 Enzymes

CYP450 enzymes are a family of iron-containing molecules that act by oxidizing various organic molecules (particularly lipophilic ones; see Fig 1). The oxidation causes the molecule to become more polar and therefore more water soluble. This process generally requires energy provided by reducing equivalents or nicotinamide adenine dinucleotide phosphate (NADPH). When this process is coupled with various phase 2 enzyme reactions the result is improved excretion of unwanted compounds (usually potential toxins) by the kidney. CYP450 enzymes are also vital to numerous physiochemical processes inherent to the body, including the metabolism of endogenous steroid hormones and formation of cholesterol-derived eicosanoids. Many CYP450 genes are polymorphic, having multiple forms or alleles that can give rise to slightly variant forms of the enzymes. This can lead to distinct individual metabolic differences and helps to account for variability in patients' response to many herbal constituents.

The expression "P450" in the term CYP450 signifies a pigment that absorbs light having a wavelength of 450 nm. Genes encoding CYP enzymes, and the enzymes themselves, are designated with the abbreviation "CYP," followed by an Arabic numeral

**Table 1. Drugs Whose Absorption Is Known to Be Decreased by St. John's Wort[a]**

| Drug categories | Specific drug(s) |
|---|---|
| Immunosuppressives | Cyclosporin, azathioprine, tacrolimus |
| Oral birth control pills | Estrogen analogues |
| Chemotherapy drugs | Imatinib, irinotecan |
| Positive inotropes | Digoxin |
| Anticoagulants | Warfarin |
| Protease inhibitors | Indinavir |
| Antiasthmatics[b] | Theophylline |
| Tricyclic antidepressants | Amitriptyline |
| Antianginal | Ivabradine |
| Benzodiazepine anxiolytics | Midazolam, quazepam |

Source: Ref. 64.

[a]Latin binomial is *Hypericum perforatum*.

[b]Effect very minor.

**Table 2. Drugs Whose Absorption Is Known to Be Increased by Grapefruit[a]**

| Drug Category | Specific drug(s) |
|---|---|
| Immunosuppressive | Cyclosporin, tacrolimus, sirolimus |
| Benzodiazepine anxiolytics | Triazolam (probably not clinically significant) |
| Nonsedating antihistamine | Terfenadine[b] |
| Antimalarial | Primaquine |
| Calcium channel blockers | Felodipine |
| Statin; cholesterol lowering | Atorvastatin, simvastatin |
| Antiseizure | Carbamazepine |

Source: Ref. 64.

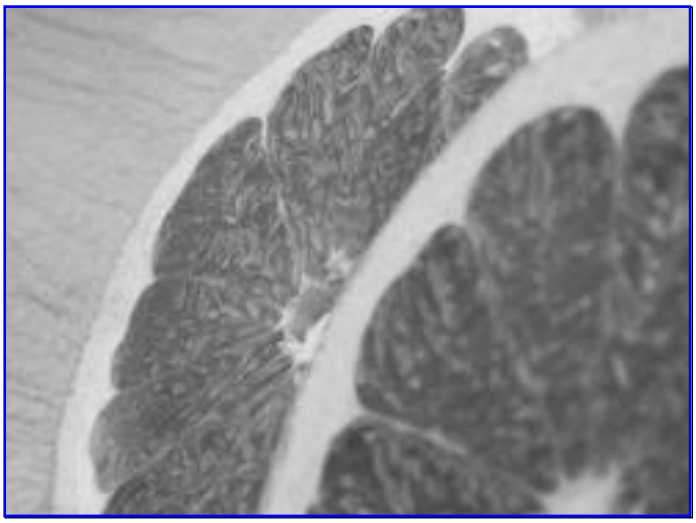
[a]Latin binomial *is Citrus decumana*.

[b]Though unlikely, this interaction could be lethal. Terfenadine has been removed from the market because of this interaction and similar interactions with cytochrome enzyme 3A4–inhibiting drugs such as ketaconazole.

indicating the gene family, a capital letter indicating the subfamily, and another numeral for the individual gene. In the liver, CYP enzymes act on drugs and toxic compounds as well as metabolic products such as bilirubin. The hepatic CYP enzymes are the most widely studied members of the enzyme family, but CYP enzymes are also present in the mucosa of the gastrointestinal tract, where they have important physiologic functions. We consider each of the major CYP450 enzymes and their relationships to herbs.

## CYP3A4, St. John's Wort, and Grapefruit

More than half of all drugs and chemicals are metabolized by the cytochrome enzyme CYP3A4, making it by many accounts the most important member of the CYP450 family.[1] Therefore, great concern has been raised about herbal compounds that undergo metabolism by this enzyme and the potential for drug–herb interactions to change the CYP3A4-mediated metabolism of certain drugs. Polymorphisms of 3A4 occur but are of unknown relevance. Two herbs having highly documented effects on drug-metabolic processes involving CYP3A4 are *Hypericum perforatum* (St. John's wort), which induces CYP3A4, and *Citrus decumana* (grapefruit), a CYP3A4 inhibitor. St. John's wort is a native Eurasian perennial plant that has become a weedy invader in North America, but is an effective treatment for many cases of mild to moderate depression. Grapefruit is produced by a hybrid tree that likely originated in Barbados and has become a major fruit crop centered in Florida, widely consumed in the United States and elsewhere.



***Citrus decumana* (grapefruit).**

Although the major CYP3A4-inducing constituent of St. John's wort is hyperforin, recent trials show that low-hyperforin extracts of St. John's wort have little or no effect on CYP3A4 in humans.[2–4] St. John's wort acts primarily on CYP3A4 in the intestines, although it may have some effects in the liver, since some studies show the herb to affect the metabolism of intravenously administered drugs in humans.[5,6] The major constituents of concern in grapefruit are furanocoumarins such as bergamottin, polymers of furanocoumarins, and flavonoids such as quercetin and naringen.[7] Grapefruit inhibits CYP3A4, as well as P-glycoprotein, in the intestines, but not in the liver.[8–11] Thus, grapefruit extracts for oral consumption have no effect on drugs administered intravenously.[12]

Numerous trials confirm that St. John's wort and grapefruit have clinically significant effects on drug metabolism in humans. Tables 1 and 2 summarize the major interactions of these two botanicals as shown in clinical trials or multiple case studies. The list is limited to interactions likely to be clinically relevant. Because of St. John's wort's broad effects on CYP450, this herb should not be administered simultaneously with any drug that is metabolized to a large extent by CYP3A4. It is also important to point out that many of the clinical trials in which the aforemen-

tioned interactions were observed were conducted in healthy volunteers, and that the demonstration of changes in pharmacokinetics does not always translate into changes in efficacy or toxicity. Thus, for instance, although St. John's wort was shown to decrease the absorption of quazepam, the herb had no effect on the pharmacodynamics of this drug.[13]

In the case of grapefruit and related bitter citrus fruits, their use with drugs metabolized by CYP3A4 should not be considered as absolutely contraindicated, at least when there is close clinical supervision. However, the effects of these two fruits are somewhat unpredictable, in part because they may affect other drug transport proteins and CYP450 enzymes that offset their effects on CYP3A4.[14,15] Grapefruit shows significant potential as a dose-sparing agent, allowing expensive or toxic drugs to be given at smaller doses than usual with no loss of activity. This has been most thoroughly studied with cyclosporin, a drug that is both toxic and expensive.[16] However, research on this issue is incomplete, making it difficult to control the interactions that may affect cyclosporin metabolism and keep the drug dose correct and safe.[17]

Case studies have been published of other instances in which grapefruit juice has beneficially augmented the effects of drugs that are substrates for CYP3A4, such as felodipine.[18] Clinicians need to be aware that any patient who takes grapefruit or other bitter citrus fruits, but who does not take drugs metabolized by CYP3A4 in reduced doses, risks serious harm, as has been shown in case studies. While the intentional use of grapefruit as a dose-sparing agent is intriguing, it is also tricky at best with drugs that have narrow therapeutic windows, and should be attempted only by physicians highly experienced with the drugs in question and only with very diligent, compliant patients.

Grapefruit inhibits CYP3A4 for 2–4 hours after ingestion in many people, though there is wide interindividual variation in this, and some people have minimal or no inhibition.[19] Consumption of grapefruit concurrently with a drug may affect absorption of the drug. Generally, the increase in absorption of the drug does not exceed 50%, although this does vary among drugs and among patients.

***Ocimum basilicum* (basil).**

Although they act primarily as inhibitors of CYP3A4, grapefruit and other bitter citrus fruits may improve the absorption of some natural substances that are substrates of CYP2A6 by also blocking this enzyme. Two studies have found that grapefruit juice increases the bioavailability of coumarin, a very

**Table 3. Critical Natural Product–Cytochrome Enzyme P450 Interactions**

| Agent | Common name (for herbs only) | Induces | Inhibits |
|---|---|---|---|
| Grapefruit,[a] pomelo,[b] bitter orange[c] | — | — | CYP3A4 (intestinal) |
| Berberine | — | — | CYP3A4 (intestinal)[f,g] |
| Isothiocyanates (I3C, DIM, PEITC) | — | CYP1A1, 1A2 | CYP2E1 |
| *Hypericum perforatum* | St. John's wort | CYP3A4 (intestinal) | — |
| *Allium sativum* | Garlic | CYP3A4 (dissenting study[d] | — |
| *Piper longum* (piperine) | Long pepper | — | CYP3A4 (intestinal) |
| *Ginkgo biloba* | Ginkgo | CYP2C19, negative trial on 3A4 and 2D6[e] | — |

[a]Latin binomial is *Citrus decumana*. [b]Latin binomial is *Citrus x aurantium*. [c] This agent is much less potent than grapefruit. [d]Markowitz JS, Devane CL, Chavin KD, et al. Effects of garlic (*Allium sativum* L.) supplementation on cytochrome P450 2D6 and 3A4 activity in healthy volunteers. Clin Pharmacol Ther 2003;74:170–177. [e]Markowitz JS, Donovan JL, Lindsay DeVane C, et al. Multiple-dose administration of *Ginkgo biloba* did not affect cytochrome P-450 2D6 or 3A4 activity in normal volunteers. J Clin Psychopharmacol 2003;23:576–581. [f]Wu X, Li Q, Xin H, et al. Effects of berberine on the blood concentration of cyclosporin A in renal transplanted recipients: Clinical and pharmacokinetic study. Eur J Clin Pharmacol 2005;61:567–572. [g]Xin HW, Wu XC, Li Q, et al. The effects of berberine on the pharmacokinetics of cyclosporin A in healthy volunteers. Methods Find Exp Clin Pharmacol 2006;28:25–29.

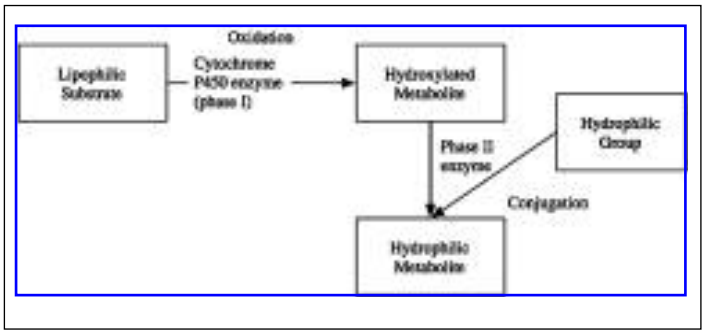



**Figure 1. Basic overview of cytochrome P450 (CYP450).**

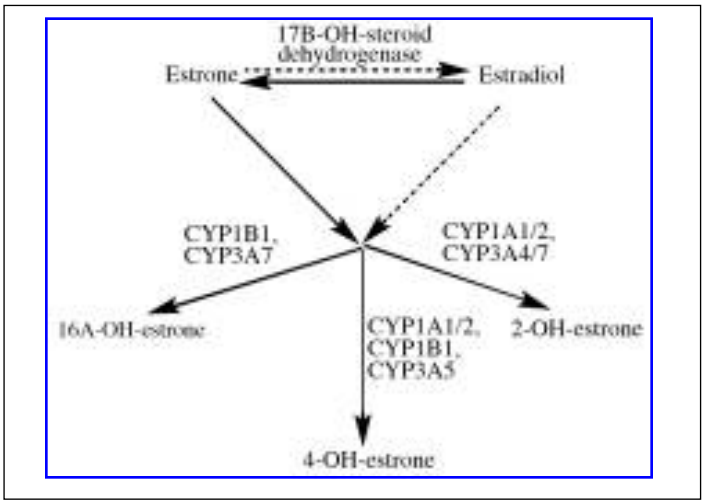



**Figure 2. Estradiol catabolism.**

common plant constituent with venoprotective and inflammation-modulating effects, and which is normally degraded by CYP2A6.[20,21] An inhibitory effect against CYP2A6 has also been observed with nicotine, which, like coumarin, is also catabolized by this enzyme. In a trial involving healthy volunteers, grapefruit juice significantly reduced the CYP2A6-mediated conversion of nicotine to its metabolite cotinine.[22] Consequently, grapefruit may be a useful dose-sparing agent in nicotine substitution.

## CYP450 and Activation of Plant Toxins

CYP450 enzymes can occasionally convert harmless plant compounds into dangerous toxins. Members of the Boraginaceae and Asteraceae families are those that most commonly contain the potentially hepatotoxic, nephrotoxic, and carcinogenic substances known as unsaturated pyrrolizidine alkaloids (uPA).[23] These substances are not inherently toxic, but become harmful after undergoing phase I hepatic metabolism. Studies of multiple animal models as well as human liver microsomes confirm that CYP3A enzymes are principally responsible for activating uPA to their toxic intermediates, consisting either of *N*-oxides or related molecules.[24,25]

**Table 4. Herbs Shown to Not Interact with Cytochrome Enzyme P450 in Clinical Trials**

| Latin binomials | Common names |
|---|---|
| *Actaea racemosa* | Black cohosh |
| *Berberis* spp., *Mahonia* spp., *Hydrastis* spp., *Coptis* spp., etc.; berberine | Barberry, Oregon grape, goldenseal, gold thread |
| *Camellia sinensis* | Green tea |
| *Echinacea purpurea* | Echinacea |
| *Eleutherococcus senticosus* | Eleuthero |
| *Serenoa repens* standardized extract | Saw palmetto |
| *Silybum marianum* silymarin extract | Milk thistle |
| *Vaccinium macrocarpon* juice | Cranberry |
| *Valeriana officinalis* | Valerian |

Source: Ref. 64.

Clinicians have observed that some people exposed to uPA-containing medicinal plants, such as *Symphytum officinale* (comfrey), do not develop toxicity.[26] That CYP3A enzymes may be critical in transforming uPA of comfrey to a harmful state, and that these enzymes can vary in activity from one person to another, may help explain this variable tendency to toxicity. It is also possible that administering CYP3A4 inhibitors, such as grapefruit juice, would reduce the toxicity of uPA, although this has not been investigated.

Another group of plant substances that can be transformed by CYP450 to toxic intermediates are alkylbenzenes. Safrole and estragole are probably the two best known botanical alkylbenzene toxins. Safrole is found in *Sassafras* spp. and *Ocimum basilicum* (basil), as well as in the fruit of *Areca catechu* (areca or betel nut), chewed as a stimulant in north Africa, the Middle East, and parts of Asia. Estragole is found in small quantities in common medicinal spices including *Foeniculum vulgare* (fennel), *Pimpinella anisum* (anise), basil, and *Artemisia dracunculus* (tarragon). Both safrole and estragole are metabolized by multiple CYP450 enzymes—most notably including CYP2A6, CYP2C9, CYP2D6, and CYP2E1—into carcinogenic 1′-hydroxy metabolites.[27,28] The presence of 1′-hydroxysafrole correlates to some degree with development of esophageal cancer in Taiwanese who chronically chew areca nuts.[29] This line of research also suggests that people who exhibit weak catalytic activity of CYP2A6 may have relative resistance to the carcinogenicity of betel nut.

The role of the CYP3A4 enzymes in potentially toxic reactions is an area in need of greater study and understanding, so that such reactions can be better treated or avoided.

## Piperine and Curry

Piperine is an alkaloid found in various species of *Piper*, including the fruits of *P. nigrum* (black pepper) and *P. longum* (long pepper). It inhibits CYP3A4, and may have other effects on CYP450 enzymes.[30] Piperine has been shown to increase the absorption in humans of the drugs phenytoin, propranolol, and

theophylline, which are metabolized by CYP3A4,[31,32] and therefore shows some of the same potential as grapefruit to act as a dose-sparing agent for some medications.

In Asia, piperine-containing herbs have long been added in small amounts to herbal formulas to make these formulas work better.[33] That piperine and possibly other substances in species of *Piper* enhance the absorption of other compounds gives a firm footing to this traditional belief. Piperine has specifically been shown to greatly (by 2000%) enhance the absorption of curcumin, a key antioxidant component of turmeric, as noted earlier.[31] Both black and long pepper and turmeric are key ingredients of curries, as well as of herbal formulas for arthritis and a host of other inflammatory diseases. While it is not clearly known how piperine causes such a profound increase in curcumin absorption, the effect may be partly related to CYP450. Some clinical trials have exploited this potential by combining curcumin and piperine as isolated constituents of their respective botanicals. However, this approach ignores other unknown but possibly beneficial interactions with other constituents present in the whole plants.[34]

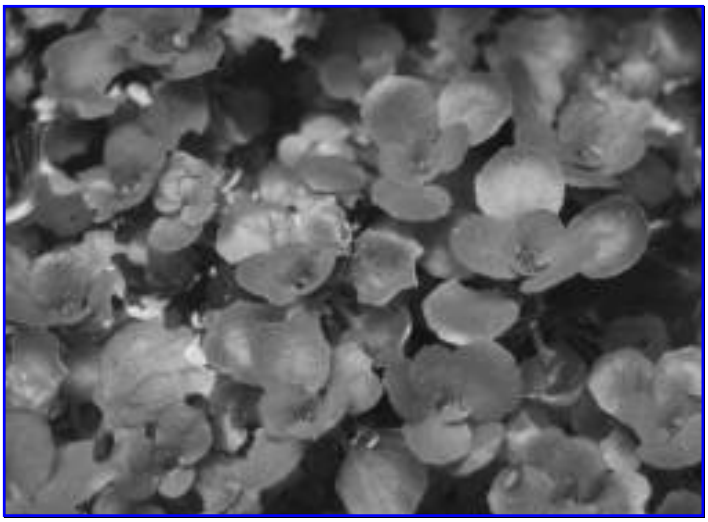
Curcumin itself has been shown to inhibit several CYP450 enzymes, including CYP1A1, CYP3A4, and CYP2B6 in vitro.[35] Surprisingly, curcumin was reported to decrease blood levels of the beta-blocker talinolol by about 33% on average in one clinical trial.[36] The authors suggested that this could be due to inhibition of p-glycoprotein (Pgp) by curcumin, although again this should have theoretically increased the absorption of talinolol. Further research is needed to determine whether turmeric or curcumin pose a risk of drug–herb interactions through effects on CYP450 enzymes, especially since turmeric, like grapefruit, is widely consumed in the diet.

## Crucifers, CYP450, Toxins, and Estrogen Metabolism

Cruciferous vegetables and medicinal plants such as *Brassica oleracea italica* (broccoli) contain isothiocyanates. These compounds or their metabolites have been shown to inhibit CYP2E1 while stimulating CYP1A1 and CYP1A2.[37,38] Sulforaphane, phenylethyl isothiocyanate (PEITC), and indole-3-carbinol (I3C) are three compounds in this group that have received extensive scrutiny. Many studies have confirmed the generally anticarcinogenic nature of foods that contain these compounds, though the protection they afford is imperfect.[39] Much of the protection they do provide is believed to derive from an enhancement of the body's ability to eliminate carcinogenic toxins, in part by accelerating the breakdown of these toxins by inducing CYP1A1/2.[40] The true mechanisms of action of the botanical isothiocyanates are almost certainly more complex than this, and are likely to involve mechanisms unrelated to CYP450 or the metabolism of carcinogens.[41]

Charred or well-done meats contain elevated levels of carcinogenic heterocyclic amines (HA). It appears that eating broccoli with such meats can reduce the potential harm done by these HA.[42,43] HA are substrates of CYP1A1/2, and their accelerated removal by concomitant consumption of CYP1A-inducing cruciferous vegetables appears to be protective. Much more work remains to be done to completely prove this hypothesis.

***Foeniculum vulgare*** **(fennel).**



***Nasturtium officinale*** **(watercress).**

Complicating the picture is that isothiocyanates are removed from the body in large part by the action of glutathione *S*-transferase mu-1 (GSTM1), an enzyme that appears to directly inhibit the ability of crucifers to induce CYP1A2. Some people lack the gene for this enzyme (a state called the "null genotype") and do not produce GSTM1. This means that less efficient, alternate metabolic pathways are responsible for excreting isothiocyanates

***Artemisia annua* (sweet Annie).**

in such people, resulting in increased blood and body levels of these substances and, at least according to some studies, giving cruciferous vegetables a greater importance in preventing cancer in these people.[44]

*Nasturtium officinale* (watercress), another member of the Brassicaceae family—which comprises the crucifers—is also rich in isothiocyanates that inhibit CYP2E1, and particularly PEITC. In one trial involving healthy adults, 50 g of watercress effectively halved the activity of this enzyme, showing twice the effect in this regard of isoniazid, an antitubercular drug well known to inhibit CYP2E1.[45] The effects of watercress on CYP2E1 lasted at least 10–12 hours according to a study of its effect on the pharmacokinetics of acetaminophen, another CYP2E1 substrate, in healthy adult volunteers.[46]

The catabolism of estradiol critically involves CYP450 enzymes (Fig. 2). Of particular importance in this regard are CYP1A1 and CYP1A2, because these enzymes are highly inducible. CYP1B1, another CYP450 enzyme involved in the catabolism of estradiol, is not dietarily inducible, although some synthetic chemicals may induce it.[47] 16-Alpha-hydroxyestrone also stimulates human papilloma virus (HPV). CYP1A2 catabolizes the formation of 2- and 4-hydroxyestrones, which not only carry less of a potential than 16-alpha-hydroxyestrone for generating carcinogens, but also do not stimulate HPV. Because CYP1B1 is difficult to inhibit, much research has gone into using isothiocyanates to instead induce CPY1A2, reducing the risk of creating potentially pathogenic metabolites of estrogen, and representing an interesting alternative to the traditional approach of suppressing injurious metabolic pathways.[48]

The major isothiocyanate studied for beneficially inducing estrogen metabolism is I3C. I3C has been examined in many clinical trials for its effects on estrogen-related diseases. *Brassica oleracea cabitata* (cabbage) juice has been studied to a lesser extent, although about one third to half a head of cabbage contains as much I3C as is used in most trials. One clinical trial found that 400 mg/day of I3C taken orally completely cured cervical intraepithelial dysplasia.[49] A more recent trial showed that 200 or 400 mg/day of I3C taken orally eased symptoms and shrank the lesions of vulvar intraepithelial neoplasia without altering the grades of the lesions.[50] I3C at a dose of 200 mg twice daily was also extremely effective in preventing the need for surgery in adults with HPV-mediated recurrent laryngeal papillomatosis.[51] These doses of I3C clearly shift the metabolism of estradiol away from its 16-alpha-hydroxyestrone metabolite and toward the more benign 2-hydroxyestrone.[52] Side effects at these doses of I3C have been minimal.

## Sweet Annie and CYP450

*Artemisia annua* (sweet Annie) is a weedy herb of the Asteraceae family found around the world. The herb contains artemisinin and other compounds that are potently destructive of the schizont form of the *Plasmodium* parasites that cause malaria—the form of the organism found in the blood of those it infects. A small clinical trial has shown that purified artemisinin at a single dose of 500 mg can significantly inhibit CYP1A2 by an average of 66% in healthy human volunteers.[53]

The metabolism of artemisinin, both as an isolated drug and as a tea of the crude herb, has been extensively studied. Artemisinin is primarily metabolized by the enzyme CYP2B6, and also induces—or autoinduces—higher levels of this same enzyme.[54] Artemisinin is also metabolized, to a less significant extent, by CYP2A6 and CYP3A4 (the latter being more important in patients with poor CYP2B6 activity). Repeated administration of artemisinin over a period of days clearly leads to its reduced absorption because of the autoinduction of CYP2B6 noted above.[55,56] Because women tend to have higher baseline clearance rates of artemisinin, it does not work as long in women as in men.[57] Absorption of artemisinin from an infusion of the crude leaf has also been studied and shown to have similar pharmacokinetics to those of the isolated drug.[58]

The clinical implication is that sweet Annie or artemisinin should not be prescribed continuously for malaria or cancer, but should instead be pulse dosed, being given for about 5–7 days, followed by a hiatus of 5–7 days, as it will not be absorbed in useful amounts after about a week of continuous use. This also suggests that in order to achieve optimal efficacy, sweet Annie or artemisinin should be coupled with other anti-

malarial agents that do not present this problem. Furthermore, sweet Annie and artemisinin are unlikely to be useful for preventing malaria, both because they cannot be effectively taken continuously and because they do not attack the *Plasmodium* sporozoites that mosquitoes carry and inject into the blood to generate human malaria.

## Activation of Resveratrol

Resveratrol, an antioxidant congener of stilbene, is found in *Vitis* spp. (grapes), *Arachis hypogaea* (peanuts), and other foods. Reports differ with regard to which of the CYP450 enzymes are involved in its metabolism, but they clearly play a role in the hydroxylation of resveratrol to its more active metabolite piceatannol. One report has suggested the CYP1B1 is the enzyme responsible for this hydroxylation, while others say that it is CYP1A2.[59,60] Although resveratrol itself appears to have antineoplastic and cardioprotective activity, this antioxidant's metabolites may be even more potent than the parent compound in these respects, or may have synergistic benefits.[61] Piceatannol has been shown to inhibit the multidrug resistance (MDR) protein-1, an important cause of multidrug resistant cancer, while resveratrol does not show this effect.[62] This is but one example of many probable instances in which precursor substances in medicinal plants are transformed by CYP450 into more potently beneficial metabolites.

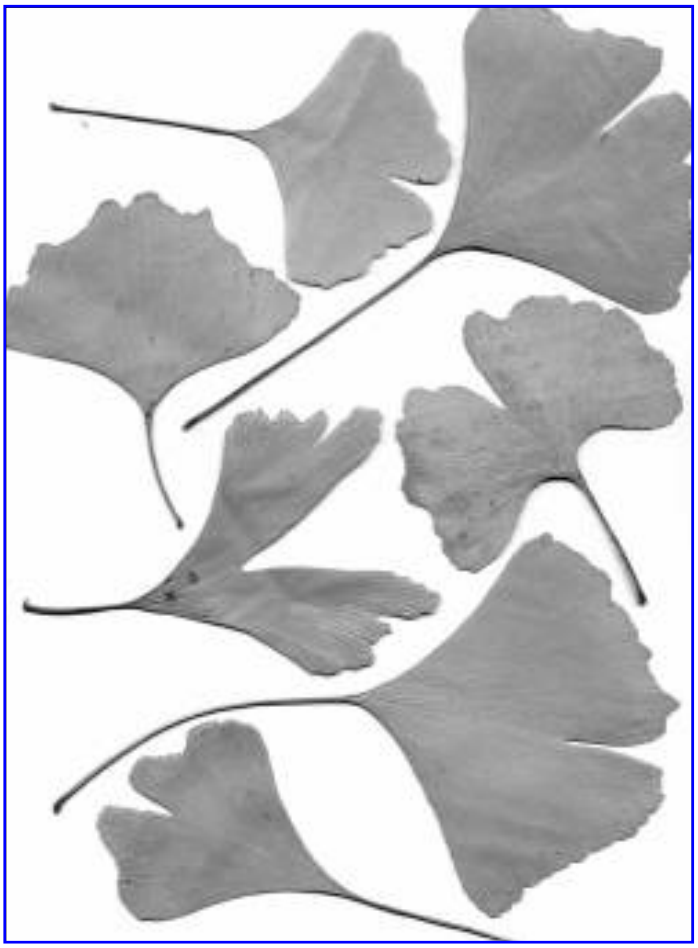
## Ginkgo, Artemisinin, and CYP2C19

CYP2C19 is a minor metabolizing enzyme in humans, but does affect the disposition of a few drugs. A small clinical trial in China found that an extract of the leaf of *Ginkgo biloba* at 140 mg given twice daily decreased serum levels of omeprazole.[63] Because omeprazole is a substrate of CYP2C19, and there were no other clear reasons for the observed effect of *G. biloba* on its serum levels, it is possible that ginkgo induces CYP2C19.[63]Artemisinin has also been reported to increase the elimination of omeprazole, which accords with it, too, having a CYP2C19-inducing effect.[64] Whether either *G. biloba* or artemisinin may pose a problem in clinical medicine is not yet known.

## Conclusion

Botanical medicines interact with CYP450 in many ways. The focus of this concern has largely been on the potential for interference with drugs metabolized by the same enzyme that metabolizes a botanical medicine. Although a serious and in many cases a valid concern, this has unfortunately overshadowed the converse potential of drugs to adversely affect the healing potential of herbal treatments. Although no research appears to have been done on this topic, it is high time that studies begin to determine the degree to which drugs may compromise this potential.

Botanical constituents can also interact with one another via CYP450 enzymes. The effects of such interaction include changes in the absorption and possibly in the clinical effects of botanical medicines. The CYP450 enzymes can also transform herbal constituents into more potent healing agents, as well as into toxic metabolites. Genotypic and phenotypic differences in the CYP450 enzyme system may determine an individual's reaction to botanical medicines, both favorably and adversely. This clearly illustrates the need for more research and wider knowledge of the relationships between botanical products and the CYP450 system. □



***Ginkgo biloba* (ginkgo).**


**References**

**1.** Bertz R, Granneman G. Use of in vitro and in vivo data to estimate the likelihood of metabolic pharmacokinetic interactions. Clin Pharmacokinet 1997;32:210–258.

**2.** Whitten DL, Myers SP, Hawrelak JA, Wohlmuth H. The effect of St. John's wort extracts on CYP3A: A systematic review of prospective clinical trials. Br J Clin Pharmacol 2006;62:512–526.

**3.** Mai I, Bauer S, Perloff E, et al. Hyperforin content determines the magnitude of the St John's wort–cyclosporin drug interaction. Clin Pharmacol Ther 2004;76:330–340.

**4.** Arold G, Donath F, Maurer A, et al. No relevant interaction with alprazolam, caffeine, tolbutamide, and digoxin by treatment with a low-hyperforin St John's wort extract. Planta Med 2005;71:331–337.

**5.** Mathijssen RH, Verweij J, de Bruijn P, et al. Effects of St. John's wort on irinotecan metabolism. J Natl Cancer Inst 2002;94:1247–1249.

**6.** Schwarz UI, Hanso H, Oertel R, et al. Induction of intestinal P-glycoprotein by St John's wort reduces the oral bioavailability of talinolol. Clin Pharmacol Ther 2007;81:669–678.
**7.** Mertens-Talcott SU, Zadezensky I, De Castro WV, et al. Grapefruit–drug interactions: Can interactions with drugs be avoided? J Clin Pharmacol 2006;46:1390–1416.
**8.** Lown KS, Bailey DG, Fontana RJ, et al. Grapefruit juice increases felodipine oral availability in humans by decreasing intestinal CYP3A protein expression. J Clin Invest 1997;99:2545–2553.
**9.** Kane GC, Lipsky JJ. Drug–grapefruit juice interactions. Mayo Clin Proc 2000;75:933–942.
**10.** Culm-Merdek KE, von Moltke LL, Gan L, et al. Effect of extended exposure to grapefruit juice on cytochrome P450 3A activity in humans: Comparison with ritonavir. Clin Pharmacol Ther 2006;79:243–254.
**11.** Charbit B, Becquemont L, Lepere B, et al. Pharmacokinetic and pharmacodynamic interaction between grapefruit juice and halofantrine. Clin Pharmacol Ther 2002;72:514–523.
**12.** Kupferschmidt HH, Fattinger KE, Ha HR, et al. Grapefruit juice enhances the bioavailability of the HIV protease inhibitor saquinavir in man. Br J Clin Pharmacol 1998;45:355–359.
**13.** Kawaguchi A, Ohmori M, Tsuruoka S, et al. Drug interaction between St John's wort and quazepam. Br J Clin Pharmacol 2004;58:403–410.
**14.** Soldner A, Christians U, Susanto M, et al. Grapefruit juice activates P-glycoprotein-mediated drug transport. Pharm Res 1999;16:478–485.
**15.** Dresser GK, Kim RB, Bailey DG. Effect of grapefruit juice volume on the reduction of fexofenadine bioavailability: Possible role of organic anion transporting polypeptides. Clin Pharmacol Ther 2005;77:170–177.
**16.** Brunner LJ, Pai KS, Munar MY, et al. Effect of grapefruit juice on cyclosporin A pharmacokinetics in pediatric renal transplant patients. Pediatr Transplant 2000;4:313–321.
**17.** Fuhr U. Drug interactions with grapefruit juice: Extent, probable mechanism and clinical relevance. Drug Saf 1998;18:251–272.
**18.** Pisarik P. Blood pressure–lowering effect of adding grapefruit juice to nifedipine and terazosin in a patient with severe renovascular hypertension. Arch Fam Med 1996;5:413–416.
**19.** Bailey DG, Bend JR, Arnold JM, et al. Erythromycin–felodipine interaction: Magnitude, mechanism, and comparison with grapefruit juice. Clin Pharmacol Ther 1996;60:25–33.
**20.** Runkel M, Tegtmeier M, Legrum W. Metabolic and analytical interactions of grapefruit juice and 1,2-benzopyrone (coumarin) in man. Eur J Clin Pharmacol 1996;50:225–230.
**21.** Merkel U, Sigusch H, Hoffman A. Grapefruit juice inhibits 7-hydroxylation of coumarin in healthy volunteers. Eur J Clin Pharmacol 1994;46:175–177.
**22.** Hukkanen J, Jacob P 3rd, Benowitz NL. Effect of grapefruit juice on cytochrome P450 2A6 and nicotine renal clearance. Clin Pharmacol Ther 2006;80:522–530.
**23.** Liddell JR. Pyrrolizidine alkaloids. Nat Prod Rep 2001;18:441–447.
**24.** Fu PP, Xia Q, Lin G, Chou MW. Pyrrolizidine alkaloids—genotoxicity, metabolism enzymes, metabolic activation, and mechanisms. Drug Metab Rev 2004;36:1–55.
**25.** Wang YP, Yan J, Fu PP, Chou MW. Human liver microsomal reduction of pyrrolizidine alkaloid N-oxides to form the corresponding carcinogenic parent alkaloid. Toxicol Lett 2005;155:411–420.
**26.** Anderson PC, McLean AEM. Comfrey and liver damage. Human Toxicol 1989;8:68–69.
**27.** Jeurissen SM, Bogaards JJ, Awad HM, et al. Human cytochrome p450 enzyme specificity for bioactivation of safrole to the proximate carcinogen 1′-hydroxysafrole. Chem Res Toxicol 2004;17:1245–1250.
**28.** Jeurissen SM, Punt A, Boersma MG, et al. Human cytochrome P450 enzyme specificity for the bioactivation of estragole and related alkenylbenzenes. Chem Res Toxicol 2007;20:798–806.
**29.** Lee JM, Liu TY, Wu DC, et al. Safrole-DNA adducts in tissues from esophageal cancer patients: Clues to areca-related esophageal carcinogenesis. Mutat Res 2005;565:121–128.
**30.** Bhardwaj RK, Glaeser H, Becquemont L, et al. Piperine, a major constituent of black pepper, inhibits human P-glycoprotein and CYP3A4. J Pharmacol Exp Ther 2002;302:645–650.
**31.** Pattanaik S, Hota D, Prabhakar S, et al. Effect of piperine on the steady-state pharmacokinetics of phenytoin in patients with epilepsy. Phytother Res 2006;20:683–686.
**32.** Bano G, Raina RK, Zutshi U, et al. Effect of piperine on bioavailability and pharmacokinetics of propranolol and theophylline in healthy volunteers. Eur J Clin Pharmacol 1991;41:615–617.
**33.** Johri RK, Zutshi U. An Ayurvedic formulation "Trikatu" and its constituents. J Ethnopharmacol 1992;37:85–91.
**34.** Durgaprasad S, Pai CG, Vasanthkumar, et al. A pilot study of the antioxidant effect of curcumin in tropical pancreatitis. Indian J Med Res 2005;122:315–318.
**35.** Appiah-Opong R, Commandeur JN, van Vugt-Lussenburg B, Vermeulen NP. Inhibition of human recombinant cytochrome P450s by curcumin and curcumin decomposition products. Toxicology 2007;235:83–91.
**36.** Juan H, Terhaag B, Cong Z, et al. Unexpected effect of concomitantly administered curcumin on the pharmacokinetics of talinolol in healthy Chinese volunteers. Eur J Clin Pharmacol 2007;63:663–668.
**37.** Nakajima M, Yoshida R, Shimada N, et al. Inhibition and inactivation of human cytochrome P450 isoforms by phenethyl isothiocyanate. Drug Metab Dispos 2001;29:1110–1113.
**38.** Petri N, Tannergren C, Holst B, et al. Absorption/metabolism of sulforaphane and quercetin, and regulation of phase II enzymes, in human jejunum in vivo. Drug Metab Dispos 2003;31:805–813.
**39.** Higdon JV, Delage B, Williams DE, Dashwood RH. Cruciferous vegetables and human cancer risk: Epidemiologic evidence and mechanistic basis. Pharmacol Res 2007;55:224–236.
**40.** Fowke JH. Head and neck cancer: A case for inhibition by isothiocyanates and indoles from cruciferous vegetables. Eur J Cancer Prev 2007;16:348–356.
**41.** Juge N, Mithen RF, Traka M. Molecular basis for chemoprevention by sulforaphane: A comprehensive review. Cell Mol Life Sci 2007;64:1105–1127.
**42.** Hamilton SM, Teel RW. Effects of isothiocyanates on cytochrome P-450 1A1 and 1A2 activity and on the mutagenicity of heterocyclic amines. Anticancer Res 1996;16:3597–3602.
**43.** Felton JS, Knize MG, Bennett LM, et al. Impact of environmental exposures on the mutagenicity/carcinogenicity of heterocyclic amines. Toxicology 2004;198:135–145.
**44.** Probst-Hensch NM, Tannenbaum SR, Chan KK, et al. Absence of the glutathione S-transferase M1 gene increases cytochrome P4501A2 activity among frequent consumers of cruciferous vegetables in a Caucasian population. Cancer Epidemiol Biomarkers Prev 1998;7:635–638.
**45.** Leclercq I, Desager JP, Horsmans Y. Inhibition of chlorzoxazone metabolism, a clinical probe for CYP2E1, by a single ingestion of watercress. Clin Pharmacol Ther 1998;64:144–149.
**46.** Chen L, Mohr SN, Yang CS. Decrease of plasma and urinary oxidative metabolites of acetaminophen after consumption of watercress by human volunteers. Clin Pharmacol Ther 1996;60:651–660.
**47.** Fishman J, Osboren MP, Telang NT. The role of estrogen in mammary carcinogenesis. Ann NY Acad Sci 1995:768:91–100.
**48.** Lord RS, Bongiovanni B, Bralley JA. Estrogen metabolism and the diet–cancer connection: Rationale for assessing the ratio of urinary hydroxylated estrogen metabolites. Altern Med Rev 2002;7:112–129.
**49.** Bell MC, Crowley-Nowick P, Bradlow HL, et al. Placebo-controlled trial of indole-3-carbinol in the treatment of CIN. Gynecol Oncol 2000;78:123–129.
**50.** Naik R, Nixon S, Lopes A, et al. A randomized phase II trial of indole-3-carbinol in the treatment of vulvar intraepithelial neoplasia. Int J Gynecol Cancer 2006;16:786–790.
**51.** Rosen CA, Bryson PC. Indole-3-carbinol for recurrent respiratory papillomatosis: Long-term results. J Voice 2004;18:248–253.
**52.** Wong GY, Bradlow L, Sepkovic D, et al. Dose-ranging study of indole-3-carbinol for breast cancer prevention. J Cell Biochem 1997;Suppl 28–29:111–116.
**53.** Bapiro TE, Sayi J, Hasler JA, et al. Artemisinin and thiabendazole are potent inhibitors of cytochrome P450 1A2 (CYP1A2) activity in humans. Eur J Clin Pharmacol 2005;61:755–761.

**54.** Svensson US, Ashton M. Identification of the human cytochrome P450 enzymes involved in the in vitro metabolism of artemisinin. Br J Clin Pharmacol 1999;48:528–535.
**55.** Ashton M, Hai TN, Sy ND, et al. Artemisinin pharmacokinetics is time-dependent during repeated oral administration in healthy male adults. Drug Metab Dispos 1998;26:25–27.
**56.** Ashton M, Sy ND, Huong NV, et al. Artemisinin kinetics and dynamics during oral and rectal treatment of uncomplicated malaria. Clin Pharmacol Ther 1998;63:482–493.
**57.** Gordi T, Xie R, Jusko WJ. Semi-mechanistic pharmacokinetic/pharmacodynamic modelling of the antimalarial effect of artemisinin. Br J Clin Pharmacol 2005;60:594–604.
**58.** Rath K, Taxis K, Walz G, et al. Pharmacokinetic study of artemisinin after oral intake of a traditional preparation of *Artemisia annua* L (annual wormwood). Am J Trop Med Hyg 2004;70:128–132.
**59.** Potter GA, Patterson LH, Wanogho E, et al. The cancer preventative agent resveratrol is converted to the anticancer agent piceatannol by the cytochrome P450 enzyme CYP1B1. Br J Cancer 2002;86:774–778.
**60.** Piver B, Fer M, Vitrac X, et al. Involvement of cytochrome P450 1A2 in the biotransformation of *trans*-resveratrol in human liver microsomes. Biochem Pharmacol 2004;68:773–782.
**61.** Ovesná Z, Kozics K, Bader Y, et al. Antioxidant activity of resveratrol, piceatannol and 3,3′,4,4′,5,5′-hexahydroxy-*trans*-stilbene in three leukemia cell lines. Oncol Rep 2006;16:617–624.
**62.** Bobrowska-Hägerstrand M, Lillas M, Mrówczyñska L, et al. Resveratrol oligomers are potent MRP1 transport inhibitors. Anticancer Res 2006;26:2081–2084.
**63.** Yin OQ, Tomlinson B, Waye MM, et al. Pharmacogenetics and herb–drug interactions: Experience with *Ginkgo biloba* and omeprazole. Pharmacogenetics 2004;14:841–850.
**64.** Svensson US, Ashton M, Trinh NH, et al. Artemisinin induces omeprazole metabolism in human beings. Clin Pharmacol Ther 1998;64:160–167.

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