Review Article

# อันตรกิริยาระหว่างสมุนไพรและยาจากการเปลี่ยนแปลงการทำงานของเอนไซม์ไซโตโครมพี 450

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## บทคัดย่อ

**อันตรกิริยาระหว่างสมุนไพรและยาจากการเปลี่ยนแปลงการทำงานของเอนไซม์ไซโตโครมพี 450**

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ปัจจุบันในขณะที่อาหารเสริมสมุนไพรกำลังเป็นที่นิยมเพิ่มขึ้นกลับพบรายงานการเกิดอันตรกิริยาระหว่างสมุนไพรและยาที่เพิ่มมากขึ้นเช่นกัน กลไกหนึ่งที่สำคัญที่ทำให้เกิดอันตรกิริยาระหว่างสมุนไพรและยาคือการที่สมุนไพรบางชนิดมีความสามารถในการเปลี่ยนแปลงระดับการทำงานของเอนไซม์ไซโตโครมพี 450 ซึ่งเป็นกลุ่มของเอนไซม์ที่มีบทบาทหลักในการเปลี่ยนแปลงสารหรือยาเพื่อการขับออกจากร่างกาย รายงานฉบับนี้กล่าวถึงตัวอย่างสมุนไพรที่ได้รับความนิยมที่พบรายงานความสามารถในการเปลี่ยนแปลงระดับการทำงานของไซโตโครมพี 450 ได้แก่ เซนต์จอห์นเวิร์ต เกรปฟรุ๊ต แปะก๊วย พริกไทยดำ และทับทิม โดยเซนต์จอห์นเวิร์ตเป็นสมุนไพรที่นิยมใช้ร่วมกับยาในการรักษาผู้ป่วยที่มีภาวะซึมเศร้าที่มีความสามารถในการเหนี่ยวนำการทำงานของ CYP3A4, CYP2E1 และ CYP2C19 น้ำเกรปฟรุ๊ตที่บริโภคอย่างแพร่หลายทั่วโลกเนื่องมาจากรสชาติ คุณค่าทางอาหาร และสรรพคุณทางยาก็จัดเป็นสารที่มีความสามารถในการยับยั้งการทำงานของ CYP3A4 ในขณะที่แปะก๊วยซึ่งเป็นหนึ่งในสมุนไพรที่ถูกใช้เป็นยาทางเลือก โดยเฉพาะในผู้สูงอายุและผู้ป่วยที่มีอาการความจำเสื่อม ก็มีรายงานถึงความสามารถในการยับยั้ง CYP3A4 พริกไทยดำเป็นเครื่องเทศที่นิยมใช้ในการปรุงอาหารหลายชนิดเนื่องจากมีกลิ่นและรสชาติเฉพาะ จัดเป็นตัวยับยั้ง CYP3A4 ที่แรงและถูกใช้เป็นสารเร่งชีวภาพ (bioenhancer) ทับทิมเป็นผลไม้ที่นิยมรับประทานเนื่องจากรสชาติอร่อยและมีชีวประโยชน์หลากหลาย ก็มีรายงานว่าสามารถยับยั้ง CYP3A4 ได้ใกล้เคียงกับน้ำเกรปฟรุ๊ต ดังนั้นทั้งแพทย์และผู้ป่วยควรตระหนักและใส่ใจข้อมูลอันตรกิริยาระหว่างสมุนไพรและยา เนื่องจากการเพิกเฉยหรือละเลยอาจนำไปสู่ผลกระทบต่อชีวิตได้ ผู้ป่วยควรรับทราบผลกระทบที่เป็นไปได้จากการบริโภคสมุนไพรควบคู่กับยาแผนปัจจุบัน ในขณะเดียวกันแพทย์ควรให้ความใส่ใจต่ออาหารเสริมสมุนไพรที่ผู้ป่วยบริโภคทั้งโดยตั้งใจหรือไม่ตั้งใจ ซึ่งอาจกระทบต่อสัมฤทธิ์ผลในการรักษาหรือก่อให้เกิดพิษหรืออาการที่ไม่พึงประสงค์ได้

**คำสำคัญ** : อันตรกิริยาระหว่างสมุนไพรและยา, ไซโตโครมพี 450, เซนต์จอห์นเวิร์ต, เกรปฟรุ๊ต, แปะก๊วย, พริกไทยดำ, ทับทิม

# Herb-drug interactions via modulation of cytochrome P450 enzymes

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## Abstract

**Herb-drug interactions via modulation of cytochrome P450 enzymes**

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Nowadays, whereas herbal supplements are becoming increasingly popular worldwide, the incidence of herb-drug interaction is being reported spontaneously. One main mechanism causing herb-drug interactions is the potential of an herb to modulate capacity or ability of drug-metabolizing enzymes, specifically cytochrome P450 (CYP450), a major superfamily of enzymes responsible for biotransformation in order to excrete xenobiotics out of the body. Herewith, cases of famous herbs, e.g., St. John's wort, grapefruit, *Ginkgo biloba*, black pepper, and pomegranate, and their potential in modulating CYP450 activities are reviewed. St. John's wort, a popular remedy for patients with depression, is a potent inducer of CYP3A4, CYP2E1, and CYP2C19. Grapefruit juice, extensively consumed due to its taste, nutritive value, and biological benefits, is a potent CYP3A4 inhibitor. *G. biloba*, one of the most consumed ethnomedicines, especially in senior people and patients suffering from dementia, has been reported to inhibit CYP3A4. Black pepper, well known for its pungent taste and extensively used in numerous dishes, is a potent CYP3A4 inhibitor. Pomegranate, a fruit popularly consumed globally due to its delicious taste and biological benefits, is reported to inhibit CYP3A4 similarly to grapefruit juice. Both health practitioners and patients should be interested and concerned about herb-drug interaction, as ignorance can cause fatal consequences. Patients should acknowledge the impact of coadministered therapies while practitioners should consider how these supplements, either intentionally or unintentionally, may convey an effect on the therapeutic outcome and adverse toxicity.

**Keywords**: herb-drug interaction, cytochrome P450, St John's wort, grapefruit, *Ginkgo biloba*, black pepper, pomegranate

## Introduction

To date, the use of herbal medicines as complimentary or alternative medicines has become increasingly common worldwide (Zhou *et al*., 2003; Foti and Wahlstrom, 2008; Wanwimolruk *et al*., 2014). Traditional herbal remedies are perceived as harmless owing to the fact that they are natural (Ernst, 1998; Izzo, 2012). As a result, herbal products are being increasingly taken together with or replacing conventional medications (Zhou *et al*., 2003; Wanwimolruk *et al*., 2014). A recent study estimated that approximately 20% of the population consumed herbal supplements as alternative medicines (Wu *et al*., 2014). As a result of the increased consumption of these herbs concomitant with modern drugs, there has been an increased awareness in herb-drug interactions, which can result in unwanted adverse effects (Foti and Wahlstrom, 2008).

Herb-drug interactions occur through several possible mechanisms. However, the most common mechanism responsible for these interactions involves modulation of the concomitant clinical drug's pharmacokinetics, including absorption, metabolism, or elimination, by the herb (Zhou *et al*., 2003; Wanwimolruk *et al*., 2014). In most cases, herbs which cause herb-drug interactions are inducers or inhibitors of the cytochrome P450 (CYP450) enzymes which are responsible for the metabolism of the clinical drug (Zhou *et al*., 2003; Izzo, 2012).

### Cytochrome P450

Cytochrome P450 (CYP450) is a superfamily of heme-proteins which play an important role in metabolism of drugs, toxic chemicals, and xenobiotics by adding an oxygen-containing group, mostly a hydroxyl group, to increase its solubility to be easily excreted (Hasler *et al*., 1999). The first discovery of this heme-protein was in rat liver microsomes which were found to be catalyzing oxidation reactions (Hasler *et al*., 1999). Therefore, it was named microsomal monooxygenase system (MMO), in which the so-called oxygenase enzyme was CYP450. CYP450s is highly abundant in the liver (Zangar *et al*., 2004), followed by intestinal and adrenal tissues (Hasler *et al*., 1999). Other tissues that contain CYP450s include lungs, brain, lymphocytes, endothelial smooth muscle, and nasal mucosa (Zangar *et al*., 2004). Induction of CYP450s can occur through prolonged exposure to their substrates, such as drugs, foods, herbs, and chemicals (Hasler *et al*., 1999; Wu *et al*., 2005) which can result in increased metabolism and, thus excretion, of its substrate. Inhibition of CYP450s results in decreased excretion of its substrate and, as a result, prolonged elimination time. Hence, herbs which are CYP450 inducers tend to decrease the concentration of the co-administered drug, reducing its pharmacological effects while herbs with CYP450 inhibitor properties tend to slow down the elimination rate of the co-administered drug which may result in adverse effects or toxicity of the clinical drug (Wanwimolruk *et al*., 2014).

CYP450s are grouped into different families and subfamilies according to similarity in their gene sequences (Martignoni *et al*., 2006; Cui *et al*., 2012). To date, 57 human genes have been discovered to play roles in the expression of CYP450 enzymes, resulting in a total of 57 isoforms, while 102 isoforms have been discovered in mice. These genes can be grouped into subfamilies, namely CYP1A, CYP2B, CYP2C, CYP2D, CYP2E, CYP3A, and CYP4A (Minamiya *et al*., 2004; Gonzalez, 2005; Eid *et al*., 2009; Flachsbart *et al*., 2011; Qi *et al*., 2013). Each subfamily is further classified into several isoforms in which each individual isoform varies in its contribution to drug metabolism as shown in Fig. 1 (Zanger *et al*., 2014).

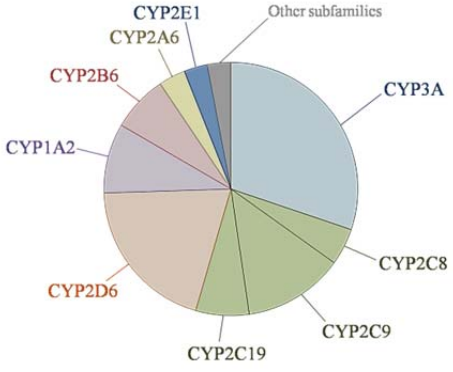



**Fig. 1** Individual cytochrome P450 isoforms to major drug metabolism's contribution

CYP1A is a subfamily of CYP450s, consisting of two isoforms, CYP1A1 and CYP1A2. In mouse, rat, dog, monkey, and human, CYP1A1 is mainly expressed in extrahepatic tissues while CYP1A2 is constitutively expressed in the liver (Martignoni *et al*., 2006). CYP1A is responsible for the metabolism of chemicals, including caffeine, carcinogenic polycyclic aromatic hydrocarbons, nitrosamine, and aflatoxin, and therapeutic drugs such as paracetamol, theophylline, and imipramine (Hasler *et al*., 1999; Martignoni *et al*., 2006). The induction of CYP1A occurs via the aryl hydrocarbon receptor (AhR) which is a cytosolic receptor. This involves heterodimerization of AhR and AhR nuclear translocator (AhRNT) along with upstream enhancer elements which transmits induction signals to the promoter, resulting in the transcription and translation processes (Fig. 2) (Martignoni *et al*., 2006).

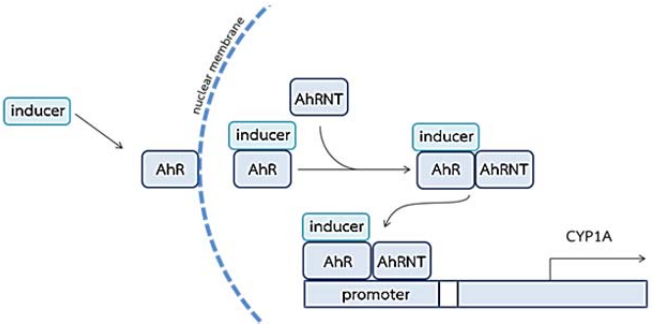



**Fig. 2** Mechanism of CYP1A induction via AhR

Human CYP2B enzymes consist of 2 isoforms, CYP2B6 and CYP2B7. These two isoforms have almost identical coding sequences. CYP2B6 is involved in the metabolism of 12-25% of clinical drugs while comprising 2-10% of hepatic CYP450 content (Wang and Tompkins, 2008). CYP2B6 is reported to have a large inter-individual variability in both expression and activity (Lamba *et al.,* 2003). CYP2B genes are known to be induced or inhibited by the nuclear constitutive androstane receptor (CAR) in response to various compounds (Negishi and Honkakoski, 2000). Phenobarbital is one of the important CYP2B inducers (Iwata *et al*., 2002). Recent studies have shown that mechanisms of CYP2B induction occur via the dimerization of CAR with retinoid X receptor (RXR) (Fig. 3) (Iwata *et al*., 2002).

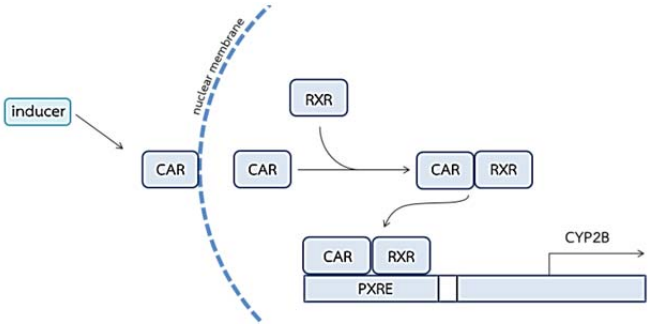



**Fig. 3** Mechanism of CYP2B induction via CAR

CYP2C is a subfamily responsible for metabolism of 16% of clinical drugs, and found mostly in the liver, followed by the heart, and cardiac tissue (Martignoni *et al*., 2006; Flachsbart *et al*., 2011). Common drugs metabolized by CYP2C are (*S*)-mephenytoin, omeprazole, tricyclic antidepressants, proguanil, sulfamethoxazone, dapsone, warfarin, some NSAIDs, tolbutamide, nelfinavir, paclitaxel, and carisoprodol (Hasler *et al*., 1999; Martignoni *et al*., 2006). Human CYP2C comprises 4 isoforms, namely, CYP2C8, CYP2C9, CYP2C18, and CYP2C19, while mice have as much as 15 isoforms (Nelson *et al*., 2004; Martignoni *et al*., 2006). Induction of CYP2C19, which is the main human CYP2C isoform, occurs via the nuclear receptors, namely, CAR and pregnane X receptor (PXR) (Pascassi *et al*., 2000; Chen *et al*., 2003). When a substrate is bound to CAR or PXR, CAR or PXR migrates to the nucleus and binds to the nuclear RXR, forming a heterodimer of CAR-RXR or PXR-RXR before binding to the CAR-responsive element (CAR-RE) or PXR responsive element (PXRE) which is a promoter, resulting in gene transcription (Chen *et al*., 2003). Another induction pathway occurs via substrate binding of glucocorticoid receptor (GR) which activates PXR or CAR to bind RXR as described above (Pascassi *et al*., 2000; Chen *et al*., 2003; Molnar *et al*., 2013).

The CYP2D gene is known for its polymorphism; however, CYP2D6 is the only isoform in humans responsible for drug metabolism (Teh *et al*., 2012). Even though its proportion of the total CYP450 is low, CYP2D metabolizes as much as 20 to 50 % of clinical drugs (Sundberg, 2005). Substrates of CYP2D are basic lipophilic nitrogen-containing molecules and alkaloids

(Dickmann *et al*., 2008). CYP2D is classified as a non-inducible gene by xenobiotics (Lee *et al*., 2008; Teh *et al*., 2012; Cederbaum, 2015). Therefore, drug interactions due to CYP2D induction do not normally happen. However, epigenetic variations of CYP2D enzymes can occur (Dickmann *et al*., 2008). It has been found that CYP2D activity is directly related to the amount of hepatocyte nuclear factor-4 alpha (HNF4α), which is a transcription regulator of genes contributing to glucose and lipid metabolism. The promoter of CYP2D is bound to HNF4α, hence, without HNF4α, the promoter cannot function properly, making HNF4α an important regulator in CYP2D expression (Lee *et al*., 2008).

CYP2E1 is the most important isoform in the CYP2E subfamily and is the main cause of hepatic oxidative injury. Mice, rats, and rabbits have been reported to have CYP2E1 genes quite similar to humans, meaning *in vivo* studies of CYP2E1 activity in animals reliably represent human CYP2E1 (Freeman *et al*., 1992; Cui *et al*., 2012). There is no report of changes to CYP2E1 expression in mice lacking CAR or PXR, confirming that CYP2E1 is not regulated in the same way as CYP2C (Wolf *et al*., 2005; Yamazaki *et al*., 2005). CYP2E1 expression is inducible by both ethanol and acetone, and also by diabetes and starvation via post-transcription and post-translation pathways (Ioannides, 2008; Bogacz *et al*., 2012; Cederbaum, 2015). This can be via stabilization of mRNA and enzyme proteins in order to facilitate the transcription process (Tompkins *et al*., 2007; Bogacz *et al*., 2012; Cederbaum, 2015) and inhibition of the ubiquitin degradation pathway, which plays a role in the degradation of proteins required in transcription and translation (Tompkins *et al*., 2007).

CYP3A is the main subfamily of CYP450 enzymes found in the liver. It is responsible for metabolizing glucocorticoid and anti-glucocorticoid hormones, macrolides, imidazole, phenobarbitals, and phenobarbital-like agents. The majority of CYP3A is found in the liver and intestines (Quattrochi and Guzelian, 2001; Wang *et al*., 2012). The human CYP3A subfamily comprises of 4 isoforms, namely CYP3A4, CYP3A5, CYP3A7, and CYP3A43 (Wang *et al*., 2012). CYP3A4 is the most dominant isoform of CYP3A in human. It makes up 30% of all CYP450 proteins in the liver, metabolizing 50% of clinical drugs (Basheer and Kerem, 2015). This makes it necessary to evaluate the metabolism of new drugs via CYP3A4 during development to avoid or minimize drug interactions. CYP3A4 enzyme has low substrate specificity, meaning it can bind to substrates of various sizes, shapes, and chemical properties. This means CYP3A4 metabolizes a wide variety of substrates including drugs, chemicals, and food compounds such as polyphenols, which are commonly found in fruits and vegetables (Basheer and Kerem, 2015). The induction of CYP3A occurs via the heterodimerization of PXR and RXR, before binding to PXRE, which is a promoter, resulting in the gene transcription process (Cheng *et al*., 2009; Istrate *et al*., 2010). A classic example of a herb substrate that can induce CYP3A is quercetin found in St. John's wort. (Basheer and Kerem, 2015).

PXR is a nuclear receptor protein responsible for the regulation of mRNA expressions of several CYP450 isoforms, including CYP2C, CYP3A, and CYP4A (Pascassi *et al*., 2000; Chen *et al*., 2003; Tompkins *et al*., 2007; Ioannides, 2008; Cheng *et al*., 2009; Istrate *et al*., 2010; Molnar *et al*., 2013). When a substrate binds to PXR in the cytosol, the PXR-substrate complex migrates into the nucleus and binds with RXR, becoming a PXR-RXR heterodimer. The heterodimer will further activate its responsive elements, PXRE, leading to transcription process of the genes (Chen *et al*., 2003) as shown in Fig. 4.

The CYP4A subfamily is responsible for physiologically catalyzing the ω- and ω-1-hydroxylation reactions of fatty acids, including arachidonic acid, as well as its epoxidation reactions (Nguyen *et al*., 1999). One important function of CYP4A is to catalyze the formation of 20-hydroxyeicosatetraenoic acid (20-HETE), an endogenous compound regulating renal vasculature and tubular ion transport (Kroetz *et al*., 1997). CYP4As in rodent livers and kidneys are induced by peroxisome proliferators (Sharma *et al*., 1989) and by physiological conditions where fatty acid levels are elevated (Kroetz *et al*., 1998). Fatty acids and peroxisome proliferators bind

and activate peroxisome proliferator-activated receptor alpha (PPARα), a member of the steroid hormone receptor superfamily (Wahli *et al*., 1999). PPARα heterodimerizes with RXR and activates enhancer elements of the genes, resulting in the activation of gene transcription (Johnson *et al*., 1996).

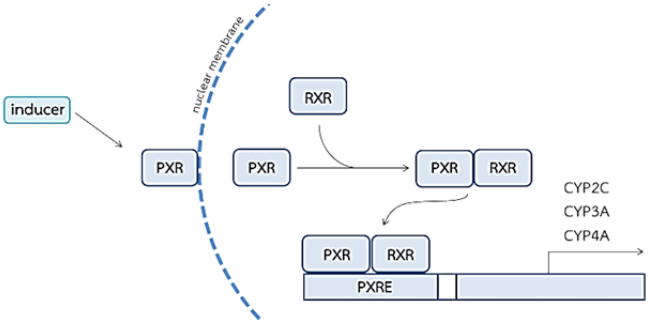



**Fig. 4** Mechanism of CYP450 induction via PXR

As herbal supplements are increasingly popular and the incidence of herb-drug interactions are being reported spontaneously, the mechanisms/pathways regarding how various herbs affect the activity of CYP450 enzymes have been herewith reviewed, including cases of famous herbs, e. g., St. John's wort, grapefruit, *Ginkgo biloba*, black pepper, and pomegranate.

**Herb – drug interaction and cytochrome P450**

***St. John's wort***

St. John's wort or *Hypericum perforatum* Linn. (Fig. 5), is a native herbal plant in Europe. It has been extensively used in several traditional remedies and is known to accelerate wound healing when applied topically and as an antidepressant and anti-insomnia agent when ingested orally (Wentworth *et al.,* 2000). The most common indication of St. John's wort is as an antidepressant, either self-medicated or prescribed. (Wentworth *et al.,* 2000; Wang *et al.,* 2004; Hellum *et al.,* 2009). It has been increasingly consumed as a health supplement in Europe and the United States. According to several studies, the antidepressant potency of St. John's wort is comparable to that of the conventional mild antidepressant drug, fluoxetine (20 mg/d) (Fava *et al.,* 2005).

**Fig. 5** St. John's wort or *Hypericum perforatum* Linn.

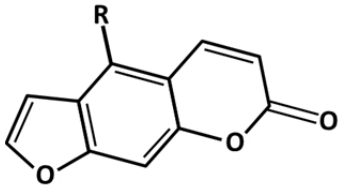
The main active constituent accounting for the antidepressant activity of St. John's wort is hyperforin, which is an acylphloroglucinol-derivative. Hyperforin inhibits neurotransmitters such as serotonin, dopamine, norepinephrine, and gamma-aminobutyric acid (GABA) from entering the synapse (Wonnemann *et al.,* 2000). Hyperforin activates PXR, which binds to several CYP450 gene-promoters (Wang *et al.,* 2004; Hellum *et al.,* 2009), modulating the gene expression of CYP450 enzymes, and therefore requiring care when used together with drugs metabolized by CYP450s such as warfarin or digoxin. Hyperforin was found to induce the expression of CYP3A4, CYP2C19 and CYP2E1 with no effect on CYP1A2, CYP2C9, and CYP2D6 (Izzo, 2012).

Important CYP450 isoforms that were reported to be induced by hyperforin are CYP3A4 and CYP2C9 (Komoroski *et al*., 2004). In an *in vitro* study in human hepatocytes, hyperforin induced CYP3A4 to an extent comparable to rifampicin, a typical CYP3A4 inducer (Komoroski *et al*., 2004). Expression of CYP3A4 was elevated in Sprague-Dawley rats receiving St. John's Wart extraction (Dürr *et al*., 2000). In addition, hyperforin was reported to induce CYP2C9 in human hepatocytes (Komoroski *et al*., 2004). Though St. John's Wart's effect on CYP4A is not yet available, it is also possible to induce CYP4A expression via binding to PXR.

***Grapefruit***

**Fig. 6** Grapefruit or *Citrus paradise* Macf.

Grapefruit or *Citrus paradise* Macf. (Fig. 6), a possible hybrid between pomelo (*Citrus grandis*) and sweet orange (*Citrus sinensis*), belongs to the family Rutacaeae. Grapefruit is extensively consumed worldwide due to its taste, nutritive value, and biological benefits including preventing cardiovascular disease, improving insulin sensitivity, and weight loss (Owira and Ojewole, 2010). Grapefruit juice is one of the widely studied natural products regarding drug interactions due to its potential to modulate CYP450 enzymes (Foti and Wahlstrom, 2008). Grapefruit juice has been reported as a potent inhibitor of intestinal CYP3A4 but hepatic CYP3A4 was unaffected (Lown *et al*., 1997; Bailey *et al*., 1998; Foti and Wahlstrom, 2008; Hanley *et al*., 2011). Therefore, patients with high intestinal CYP3A4 content or hepatic insufficiency appear to be more susceptible to drug-grapefruit interactions (Zhou *et al*., 2003). Grapefruit juice contains a variety of phytochemicals, including flavonoids and furanocoumarins (Hanley *et al*., 2011). Furanocoumarins (Fig. 4) in grapefruit juice, namely bergamottin and 6',7'-dihydroxybergamottin (DHB), are reported to inhibit intestinal CYP3A4, which results in increased levels of drugs metabolized by CYP3A4 enzymes when taken together with grapefruit juice (Zhou *et al*., 2003; Guo and Yamazoe, 2004; Lin *et al*., 2005; Hanley *et al*., 2011). Furanocoumarins are a class of compounds containing three aromatic rings and an aliphatic tail (except for bergaptol and bergapten) (Fig. 7) (Guo and Yamazoe, 2004). The variety in aliphatic tails results in different furanocoumarin molecules with different CYP3A inhibitory potency (Hanley *et al*., 2011). The most abundant furanocoumarins found in grapefruit juice are bergamottin and DHB (Guo and Yamazoe, 2004; Lin *et al*., 2005) and these are the most studied regarding their CYP3A inhibition. However, another low abundance furanocoumarin, namely paradisin, which is a dimer of furanocoumarins, showed more potent inhibitory activity (Ohta *et al*., 2002; Guo and Yamazoe, 2004; Hanley *et al*., 2011).




| | |
|---|---|
| Bergamottin | R=$OCH_2CHC(CH_3)CH_2CH_2CHC(CH_3)_2$ |
| 6', 7'-Dihydroxybergamottin (DHB) | R=$OCH_2CHC(CH_3)CH_2CH_2CH(OH)C(CH_3)_2OH$ |
| Bergaptol | R=OH |
| Bergapten | R=$OCH_3$ |

**Fig. 7** Chemical structure of furanocoumarins

Naringin, the most abundant flavonoid found in grapefruit juice, showed an inhibitory effect on CYP3A4. However, administration of naringin capsules equivalent to the amounts of naringin in grapefruit juice to healthy volunteers did not alter the pharmacokinetics of nisoldipine, a CYP3A4 substrate (Bailey *et al*., 1993). A similar study was conducted using quercetin, a flavonoid known to inhibit CYP3A *in vitro*. Administering quercetin equivalent to the amounts found in grapefruit juice to healthy volunteers did not affect the pharmacokinetics of nifedipine, another CYP3A4 substrate (Rachid *et al*., 1993). A more recent *in vitro* study on inhibition of CYP3A4 activity by furanocoumarins (bergapten), and flavonoids (quercetin, narigenin, and naringin) using human liver microsomes has shown that the flavonoids in grapefruit juice exhibited an inhibitory effect on CYP3A4 activity. Interestingly, in the amount actually found in grapefruits, bergapten was responsible for most of the CYP3A4 inhibitory activity (Ho *et al*., 2001).

The inhibitory effect of grapefruit juice on CYP3A was observed from clinical evidence showing interactions between drugs and grapefruit juice. This clinical interaction only occurs when an oral drug is significantly first-pass metabolized by enteric CYP3A enzymes, particularly CYP3A4 and CYP3A5 (Soldner *et al*., 1999; Hanley *et al*., 2011). These characteristics pinpoint the ability of grapefruit juice to inhibit intestinal CYP3A but not hepatic CYP3A enzymes.

The inhibition of CYP3A4 by furanocoumarins demonstrates either competitive or mechanism-based

patterns (Guo and Yamazoe *et al*., 2004). Furanocoumarins rapidly reduced the capacity of CYP3A4 enzymes to metabolize other substrates by competing for and occupying the active site of the enzyme, thereby lowering its ability to metabolize and eliminate other substrates (Muntingh, 2011). This form of inhibition is rapid and reversible. However, grapefruit juice was found to inhibit CYP3A4 catalytic activity in Caco-2 cells (Schmiedlin *et al*., 1997) through an irreversible inactivation of the CYP3A enzymes (Lin *et al*., 2005). The inactivation mechanism occurred via both destruction of the CYP450 heme structure and the covalent binding of mono-oxygenated metabolites of furanocoumarins to the CYP450 apoprotein (Lin *et al*., 2005). Thus, consuming large amounts of grapefruit juice leads to a rapid competitive inhibition followed by a suicide inactivation of CYP3A4. The irreversible inhibitory effect lasts up to 3 days, until the enterocytes regenerate.

Besides CYP3A4, *in vitro* studies of grapefruit juice have reported its inhibitory potential on CYP1A2, CYP2A6, CYP2C9, and CYP2D6 (Hukkanen *et al*., 2006; Girennavar *et al*., 2007). The inhibition of these CYP450 enzymes may occur through similar mechanism as CYP3A4. However, these effects may not be as prominent as those for CYP3A4 due to their lower abundance in enterocytes.

***Ginkgo biloba***

*Ginkgo biloba* Linn. (Fig. 8) is an ancient Chinese seed plant belonging to the family Ginkgoaceae that may live up to 1,000 years and can become up to 40 meters tall (Brondino *et al*., 2013). Even though it originated in China, *G. biloba* is now cultivated globally due to its well-known health benefits (Yan *et al*., 2007; Brondino *et al*., 2013). It is known to have antioxidant and vasoactive benefits for patients with ischemia, epilepsy, and peripheral nerve damage. However, its most popularly used benefit is to enhance cognitive ability in patients suffering from neurodegenerative diseases such as Alzheimer's disease (Yan *et al*., 2007; Brondino *et al*., 2013; Jiang *et al*., 2013). Today, *G. biloba* leaf extracts are one of the most consumed ethnomedicines, especially in senior people and patients suffering from dementia (Brondino *et al*., 2013).

**Fig. 8 *Ginkgo biloba* Linn. leaves**

Ginkgolides and bilobalide are terpenetrilactones found in *G. biloba* (Fig. 9) (van Beek and Montoro, 2009; Lau *et al*., 2012). Ginkgolides can be classified into 6 compounds, namely, ginkgolide-A, -B, -C, -J, -K, and -L, according to their side chains (van Beek and Montoro, 2009). Ginkgolides were reported to have several pharmacological activities, including peripheral vasoregulation, inhibition of platelet-activating factor (PAF), and neuroprotection (Liu *et al*., 2012; Huang *et al*., 2014). Ginkgolide-A, -B, and -C are potent antagonists of PAF and, therefore, are promising compounds in the development of drugs to prevent thrombus formation, bronchoconstriction, and allergic reactions (Huang *et al*., 2014). In addition, ginkgolide-C was also reported to increase lipolysis and inhibit adipogenesis in adipocytes, making it a promising candidate in improving metabolic syndromes such as obesity and insulin resistance (Liou *et al*., 2015). Bilobalide was reported to have several pharmacological activities that contribute to the biological benefits of *G. biloba*. Its activities include acting as a $GABA_A$ receptor antagonist (Kiewert *et al*., 2007), decreasing amyloid proteins (Shi *et al*., 2011), and preventing brain edema induced by ischemia (Mdzinarishvili *et al*., 2007). Hence, bilobalide is a potential candidate for development as a drug beneficial for patients with cerebral ischemia and Alzheimer's disease (Lau *et al*., 2012).

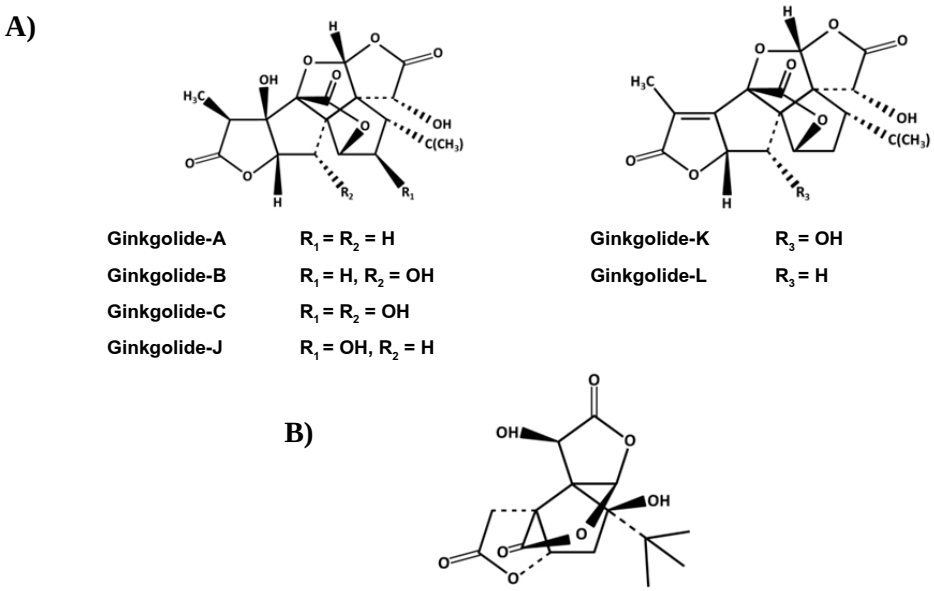



**Fig. 9** Chemical structure of ginkgolides (A) and bilobalide (B)

As described previously, CYP2C and CYP3A genes are regulated by CAR and PXR (Pascassi *et al*., 2000; Chen *et al*., 2003; Cheng *et al*., 2009). *G. biloba* extract was reported to activate PXR and increase the expression of CYP3A4 in cultured human hepatocytes (Deng *et al*., 2008; Yeung *et al*., 2008; Lau *et al*., 2010). However, when the ginkgo terpenetrilactones, namely ginkgolide-A, -B, -C, -J, and bilobalide, were evaluated individually, only ginkgolide-A was found to activate PXR in human HepG2 cells (Lau *et al*., 2010). In another *in vitro* study, bilobalide was reported to activate CAR in rat hepatocytes, but not in human hepatocytes (Lau *et al*., 2012), indicating a species-specific induction of CYP450 enzymes. It can be concluded that *G. biloba* induces human CYP3A4 activity via ginkgolide-A by binding to PXR.

***Black pepper***

**Fig. 10** Black pepper or *Piper nigrum* Linn.

Black pepper or *Piper nigrum* Linn. (Fig. 10), is a member of the family Piperaceae and is well known as the king of spices due to its pungent quality (Ahmad *et al*., 2012). Its fruit, the peppercorn, is extensively used in numerous dishes. In addition to its kitchen value, black pepper is also known for its medicinal value. Black pepper is used to relieve digestive disorders, such as diarrhea and indigestion, and respiratory disorders, such as cold, fever, and asthma (Ahmad *et al*., 2012). Studies have shown that *P. nigrum* exhibits numerous biological activities, including antimicrobial (Arslan *et al*., 2009; Ahmad *et al*., 2012), analgesic (Parmar *et al*., 1997), antidepressant (Li *et al*., 2007), antidiarrheal (Kumar *et al*., 2007), anti-inflammatory (Parmar *et al*., 1997; Fan *et al*., 2011), antioxidative (Ahmad *et al*., 2012), and immunomodulatory (Sunila and Kuttan, 2004) activities. Piperine, or (1-[5-(1,3-benzodioxol-5-yl)-1-oxo-2,4-pentadienyl]piperidine (Fig. 11), is one of the main components in pepper and gives the pungency of black pepper (Wadhwa *et al*., 2014). Piperine is classified according to its chemical structure as a cinnamamide alkaloid. It was shown to exhibit antipyretic, analgesic, insecticidal, anti-inflammatory, immunomodulatory, antitumor, and antidepressant activities (Ahmad *et al*., 2012). In addition to its own biological activity, piperine is also used as a bioavailability enhancer, or bioenhancer. This means it promotes and enhances biological activities or bioavailability of drugs, at doses that do not have their own biological activity, when used in combination (Wadhwa *et al*., 2014). Studies indicated that piperine at a dose of 10% w/w or at least 15-20 mg/day is an appropriate bioenhancing dose for most drugs (Wadhwa *et al*., 2014).

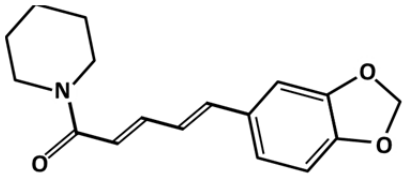



**Fig. 11** Chemical structure of piperine ([1-[5-(1, 3-benzodioxol-5-yl)-1-oxo-2, 4-pentadienyl] piperidine)

The bioenhancing property of piperine is due to 1) its inhibitory effect on drug-metabolizing enzymes, specifically CYP3A4 (Wadhwa *et al*., 2014); 2) its ability to increase gastrointestinal blood flow and membrane fluidity, and to enhance enteric absorption (Khajuria *et al*., 2002); and 3) its ability to enhance drug transport across cell membranes by modulating cell membrane dynamics (Wadhwa *et al*., 2014).

Piperine is a selective non-competitive inhibitor of CYP3A while having lowering effects on other CYP450 enzymes (Rezaee *et al*., 2014). A molecular docking study showed the ability of piperine to conjugate with iron in CYP3A4 molecules, leading to inhibition of enzyme activity (Alugolu *et al*., 2013). The strong binding of piperine with CYP3A4 resulted in reduction or inhibition of the piperine-Fe conjugate metabolizing ability of CYP3A4 (Alugolu *et al*., 2013).

***Pomegranate***

Pomegranate or *Punica granatum* Linn. (Fig. 12), of the family Punicaceae, is a seeded or granular apple popularly consumed worldwide. Pomegranate is native to Afghanistan, Iran, China and the Indian sub-continent (Ismail *et al*., 2012). Its delicious fruit has been extensively used in traditional remedies for treatments of acidosis, dysentery, microbial infections, diarrhea, helminth infection, hemorrhage, and respiratory disorders (Rahimi *et al*., 2012). Other parts of pomegranate were also shown to possess several biological activities. Its seeds exhibited estrogenic activity via estrogenic compounds contained in the seeds (Kim and Choi, 2009). Dried pericarp and fruit juice have been known to treat colic, colitis, headache, as a diuretic, menorrhagia, oxyuriasis, acne, piles, some oral diseases, and allergic dermatitis (Ricci *et al*., 2006). Further scientific studies revealed the biological activities of pomegranate as antioxidative, anti-inflammatory, anticancer, and antimutagenic (Hidaka *et al*., 2005; Faria *et al*., 2007; Rahimi *et al*., 2012).

**Fig. 12** Pomegranate or *Punica granatum* Linn.

Besides its biological activities, pomegranate fruit juice was reported to inhibit CYP3A activity similarly to grapefruit juice (Hidaka *et al*., 2005; Adukondalu *et al*., 2010). However, despite the well documented mechanism of grapefruit juice to inhibit CYP3A activities via furanocoumarins, the data of pomegranate CYP3A inhibition is still limited. It is possible that the main constituents responsible for CYP3A inhibition in pomegranate are furanocoumarins, as in grapefruit, or similar compounds. However, a recent study found that consumption of pomegranate juice decreased hepatic CYP3A expression in mice (Faria *et al*., 2007) which indicated a different inhibitory mechanism to that of grapefruit juice.

## Conclusion

While alternative medicines are becoming increasingly popular people, including both physicians and patients, are increasingly interested and concerned about drug-herb interactions. One main mechanism causing drug-herb interactions is modulation of drug-metabolizing enzymes, specifically CYP450, a major superfamily of enzymes responsible for biotransformations in order to excrete xenobiotics out of the body. Increased activity of these enzymes results in an increased rate of drug metabolism and a shorter half-life, thereby decreasing therapeutic potency. Decreased activity of these enzymes results in a decreased rate of drug metabolism, prolonging the drug's half-life and resulting in an increased potential of drug toxicity.

Herewith, some CYP450 modulatory herbs are reviewed. St. John's wort is a potential inducer of CYP3A4, CYP2E1, and CYP2C19 while, at the same time, being widely used as a combination therapy in patients with depression. Grapefruit juice, extensively consumed worldwide due to its taste, nutritive value, and biological

benefits, is a potent CYP3A4 inhibitor. *G. biloba,* one of the most widely consumed ethnomedicines in senior people and patients suffering from dementia, has been reported to inhibit CYP3A4. Black pepper, well known for its pungent taste and extensively used in numerous dishes, is a potent CYP3A4 inhibitor and therefore known and used as a bioenhancer. Pomegranate, a fruit popularly consumed worldwide due to its delicious taste and biological benefits, is reported to inhibit CYP3A4 similarly to grapefruit juice. These are only a few examples of CYP450 modulatory herbs which are numerous and extensively consumed worldwide. This information should provide a warning to health practitioners, patients and consumers as ignorance can cause fatal consequences. Patients should acknowledge the impact of taking co-administered therapies while practitioners should be aware of how these co-administered remedies can affect therapeutic outcome or cause adverse toxicity. Further studies of herb-drug or food-drug interactions are of great importance as the increasing trend of ethnomedicine usage is increasing case reports of these interactions.

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