FOOD-DRUG INTERACTIONS VIA HUMAN CYTOCHROME P450 3A (CYP3A)

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SUMMARY

Food-drug interactions have been reported to occur in various systems in the body. The causes of these interactions are mainly divided into pharmacodynamic and pharmacokinetic processes. Among these processes, drug metabolism plays a crucial role in drug interactions. Metabolic food-drug interactions occur when a certain food alters the activity of a drug-metabolizing enzyme, leading to a modulation of the pharmacokinetics of drugs metabolized by the enzyme. A variety of interactions have been documented so far. Foods consisting of complex chemical mixtures, such as fruits, alcoholic beverages, teas, and herbs, possess the ability to inhibit or induce the activity of drug-metabolizing enzymes. According to results obtained thus far, cytochrome P450 3A4 (CYP3A4) appears to be a key enzyme in food-drug interactions. For example, interactions of grapefruit juice with felodipine and cyclosporine, red wine with cyclosporine, and St John's wort with various medicines including cyclosporine, have been demonstrated. The results indicate the requirement of dosage adjustment to maintain drug concentrations within their therapeutic windows. The CYP3A4-related interaction by food components may be related to the high level of expression of CYP3A4 in the small intestine, as well as its broad substrate specificity, as CYP3A4 is

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responsible for the metabolism of more than 50% of clinical pharmaceuticals. This review article summarizes the findings obtained to date concerning food-drug interactions and their clinical implications. It seems likely that more information regarding such interactions will accumulate in the future, and awareness is necessary for achieving optimal drug therapy.

KEY WORDS

CYP3A4, inhibition, induction, grapefruit, herb, star fruit

INTRODUCTION

Cytochrome P450 (CYP) is a heme-containing enzyme that catalyzes the oxidation of a wide variety of endogenous and exogenous compounds, including drugs, carcinogens, and other xenobiotic chemicals /1/. CYP superfamilies are composed of families, and four of the families have been demonstrated as having the ability to catalyze the oxidation of foreign chemicals /1/. The human CYP3A subfamily consists of at least four members: CYP3A4 /2,3/, CYP3A5 /4,5/, CYP3A7 /6,7/, and CYP3A43 /8/. Among these CYP3As, CYP3A4 is the most abundant CYP expressed in the human liver as well as in the small intestine, and is involved in the metabolism of more than 50% of therapeutic drugs, such as dihydropyridines, cyclosporine, erythromycin and barbiturates /9/. CYP3A4 is also responsible for the bioactivation of carcinogens including aflatoxin B_1 /10/.

Inhibition of a drug-metabolizing enzyme by a certain drug results in the modulation of the pharmacokinetics of other drug(s) that are metabolized by the same enzyme, resulting in drug interaction(s). Various interactions have been reported thus far. For example, the metabolism of terfenadine catalyzed by human CYP3A is known to be inhibited by azole antifungal drugs, causing a notable increase of the plasma concentration of the parent drug to induce severe adverse drug reactions of terfenadine, such as a significant prolongation of the corrected QT interval in humans /11-14/. The interactions related to the inhibition of CYP3A activity occur not only with drugs but also with food constituents.

CYP3A4 transcription has been shown to be induced by a range of xenobiotics, including drugs such as the antibiotic refampicin, the antimycotic clotrimazole, the insulin-sensitizer troglitazone and the barbiturate phenobarbital /15,16/. Increments in CYP3A4 expression represent the basis for drug interactions /15/. Recent studies have demonstrated a new member of the steroid/thyroid hormone receptor family, termed the pregnane X receptor (PXR), that serves as a key regulator of CYP3A4 transcription /17-21/. PXR binds to the CYP3A4 promoter and is activated by the range of xenobiotics known to induce CYP3A4 expression. Drugs as well as food constituents have been known to interact with PXR to induce CYP3A4.

Since the finding of a grapefruit-drug interaction /22/, more attention has been paid to CYP3A-related food-drug interactions that occur through the inhibition of drug metabolism and the induction of protein expression. Besides the traditional foods, such as fruits, alcoholic beverages and teas, interest has rapidly grown in complementary and alternative medicine (CAM), especially in industrialized countries. Biologically based therapies in CAM use natural products such as herbs. Herbal remedies include dietary supplements intended for ingestion as a supplement to the diet (including vitamins, minerals, antioxidants, herbal products, and metabolites), phytomedicine (the use of plant parts to achieve a therapeutic effect) and botanical medicine. Herbs generally contain a vast array of complex constituents. So far, the modulation of CYP3A activity or expression by components of herbal products has been considerably evaluated.

The aim of this review is to briefly summarize reports on the effects of ingredients present in traditional foods as well as in herbal products on the activity or the expression of CYP3A4. Furthermore, the results obtained by the author and colleagues on the inhibition of CYP3A activity by tropical fruits and locally produced citrus fruits are described.

INHIBITION OF CYP3A4 ACTIVITY BY FOODS AND HERBAL PRODUCTS

Foods

Grapefruit juice

In early 1990s, grapefruit juice was documented to increase the oral bioavailability of felodipine by over 250% compared to that seen with water /22/. Adverse experiences, mainly accounted for by headaches, facial flushing and lightheadedness, were reported to be more frequent after intake of grapefruit juice than water.

Subsequently, various drugs which were orally administered have been shown to interact with grapefruit juice component(s) /23-25/. These drugs differ in their chemical structures and pharmacological properties, but are commonly metabolized by CYP3A4. Studies have shown that the furanocoumarin derivatives identified from grapefruit juice strongly inhibit the catalytic activity of CYP3A4, and cause the decrease of first pass metabolism of orally administered therapeutic drugs catalyzed by CYP3A4 /26-29/. The furanocoumarins appear to inhibit CYP3A4 activity in a competitive (reversible) manner and mechanism-based (irreversible) fashion /28,29/. An actual loss of CYP3A4 enzyme was revealed in biopsy specimens obtained from the small intestine in healthy volunteers after drinking grapefruit juice /30/. It was noted that the intestinal CYP3A4 content fell by more than 50% after consumption of even a single glass of grapefruit juice /26/. It was reported that enhanced oral drug bioavailability can occur 24 hours after the juice consumption /31/. Interestingly, pretreatment with grapefruit juice did not alter the pharmacokinetics or pharmacodynamics of drugs administered intravenously, indicating that the ingredients of grapefruit were not sufficiently absorbed into the body to inhibit the metabolism of CYP3A4 in hepatocytes /24,25/.

Among furanocoumarins present in grapefruit juice, bergamottin (BG) and 6′,7′-dihydroxybergamottin (DHB) are the most abundant components. Recently, these two prominent furanocoumarins in the juice, DHB and BG, have been documented as important contributors to grapefruit juice-drug interactions /32,33/.

Red wine

Like grapefruit juice, red wine contains a complex mixture of molecules. A wide variety of flavonoids and polyphenolics have been assumed to be inhibitors of CYP3A activity. *In vitro* experiments with B-lymphoblast cells expressing CYP3A4 have demonstrated that the components of red wine prepared at 8% of natural strength inhibited CYP3A4-catalyzed testosterone 6β-hydroxylation to almost the same extent as grapefruit juice at similar concentration to the red wine preparation /34/. The reversible inhibition observed in this study suggests that red wine does not contain mechanism-based inhibitor(s), unlike the case of grapefruit juice. Subsequently, a randomized, 2-way crossover study of 12 healthy individuals was performed /35/. Subjects received a single 8 mg/kg dose of oral cyclosporine with 12 oz of red wine (Blackstone Merlot, 1996; Blackstone Winery, Graton, CA, USA) or water (control). The red wine was shown to cause 50% increase in the oral clearance of cyclosporine. Systemic exposure as measured by the AUC and peak concentration were significantly decreased by the red wine treatment. However, the half-life was not affected, suggesting that red wine decreased cyclosporine absorption through the inhibition of intestinal CYP3A4 activity. Red wine has also been shown to affect the pharmacokinetics of felodipine, a marker substrate of CYP3A4 /36/. The mean time to plasma peak concentration of felodipine was prolonged. Caution may be warranted with concomitant intake of red wine and drugs with narrow therapeutic ranges such as cyclosporine.

Tea

There are various teas all over the world. Among teas, green tea has been especially consumed by the Japanese for many years. This beverage has been reported to contain various ingredients including catechins which are potent chemopreventive agents against cancers caused by chemical carcinogens in rodents. The effects of four of major epicatechin derivatives, epigallocatechin gallate (EGCG), epicatechin gallate, epigallocatechin and epicatechin, on the oxidative metabolism catalyzed by CYP3A4 were evaluated /37/. Among the epicatechin derivatives, EGCG was found to be the most potent CYP3A4 inhibitor. In contrast to this *in vitro* finding, green tea (*Camellia sinensis*) extract did not alter CYP3A4 activity as

monitored by alprazolam pharmacokinetics in healthy volunteers, even though the plasma concentration of EGCG reached 1.3 ± 1.8 μM 2 h after the green tea administration /38/.

Herbal products

Evening primrose

Evening primrose *(Oenothera binnis)* is used to treat premenstrual syndrome /39/, chronic mastalgia, diabetic peripheral neuropathy /40/, atopic eczema, rheumatoid arthritis /41/ and schizophrenia /42/. Evening primrose oil contains a complex mixture of essential fatty acids including linoleic acid, oleic acid, palmitic acid, stearic acid and gamma linolenic acid /43/. *Cis*-linoleic acid inhibited the *in vitro* activities of CYP3A4 in a dose-dependent manner /44/. However, no case has been reported on interactions of evening primrose with conventional medications.

Ginkgo

Ginkgo (*Ginkgo biloba*) has been used in traditional Chinese medicine for millennia. It is applied for various ailments and has multiple actions /45/. In some European countries, ginkgo has been approved for dementia, intermittent claudication, memory improvement and tinnitus /45/. However, a recent trial on normal healthy volunteers has demonstrated that ginkgo extract did not produce any significant improvement in cognitive effects /46/. Ginkgo is composed of several flavonoids, terpenoids (e.g. ginkgolides) and organic acids.

Studies using *in vitro* human models have indicated that components of ginkgo, ginkgolides A and B, did not appreciably affect the activity of CYP3A4 /47/. The administration of ginkgo to volunteers had no effect on the 1′-hydroxymidazolam/midazolam concentration ratio, a marker of CYP3A activity /48/, supporting the results of *in vitro* study. However, in another study, ginkgo increased the plasma concentrations of the CYP3A4 substrate nifedipine by 53% /49/. The contradictory findings for ginkgo's effects on CYP3A4 observed in these trials are possibly related to the highly variable phytochemical composition of commercially available ginkgo extracts /50/, as well as applied dose regimens and the duration of exposure to ginkgo.

Ginseng

Ginseng (*Panax ginseng*) is a perennial herb native to Korea and China which has been used as a herbal remedy in eastern Asia for thousands of years. The demonstrated properties of ginseng include sedative, hypnotic, aphrodisiac, antidepressant and diuretic effects /51/. The efficacy of ginseng in the treatment of physical performance, psychomotor performance, cognitive function, immune modulation, diabetes mellitus and herpes simplex type 2 infection has been reviewed recently /52/. Based on this analysis, it seems likely that the efficacy of ginseng has not been established beyond doubt for these indications. However, a retrospective trial suggested a relationship between ginseng consumption and a decrease in the risk of cancer, with a relative risk reduction of 40% /53/. Ginsenosides, the presumed active constituents in ginseng extracts, may play key roles in the adverse reactions and drug interactions with ginseng.

In vitro studies with human liver microsomes have suggested that crude extracts of ginseng as well as the various ginsenosides inhibited the testosterone 6β-hydroxylase activity of CYP3A4 /47/. An extract of ginseng did not induce CYP3A4 in human hepatocytes /54/. The *in vitro* inhibition of CYP3A4 /47/ is consistent with the finding that an 18-day course of ginseng treatment significantly increases the peak plasma concentration of nifedipine metabolized by CYP3A4 /49/. As predicted by *in vitro* data /54/, phenotype-probe nifedipine observations in humans indicated a lack of CYP3A4 induction /49/.

Kava

Kava (*Piper methysticum*), a member of the pepper family, has been used in the Pacific islands for centuries /55/. Kava is a herbal anxiolytic /56-59/, and supplements containing kava are promoted for relaxation, insomnia and menopausal symptoms /45/. The major constituents of commercially available kava are kavalactones /60/. *In vitro*, extracts of kava and several kavalactones were shown to be inhibitors of CYP3A4 /61,62/. Since a case report described coma in a woman after simultaneous ingestion of kava and the CYP3A4 substrate alprazolam /63/, an *in vitro-in vivo* correlation may be possible. Although direct evidence for this relationship is lacking, caution is warranted when kava is used in combination with CYP3A4 substrates.

Milk thistle

Milk thistle (*Silybum marianum*) is one of the most common herbal therapies and has been used for more than 2,000 years /64/. The most important medical use of milk thistle today is for liver protection from poisonous mushrooms, and for treatment of such hepatic ailments as cirrhosis, hepatitis and fatty infiltration due to alcohol consumption /65,66/. The principal components of milk thistle are silymarin, a mixture of flavonoids and phenylpropanoids found in the fruit of the plant, and silybin. The minor ingredients are silychristin, silydianin and other flavonoligans /67/. Inhibition of *in vitro* activities of CYP3A4 by milk thistle components has been reported /68,69/. However, in the clinically achievable peak concentration of about 0.6 μM /70,71/, silybin, dehydrosilybin, silydianin and silycristin did not substantially inhibit the activities of human liver microsomal CYP3A4 /72/. The effects of milk thistle on the pharmacokinetics of the HIV protease inhibitor indinavir were recently studied /73,74/. In accordance with the *in vitro* findings, milk thistle did not significantly alter exposure to indinavir, although the mean trough concentrations were 25% /73/ and 32% /74/ decreased in the two studies.

Soy

The use of soy (*Glycine max*) and soy-derived products for the treatment of menopause in women is growing with the fear of possible adverse drug reactions of traditional hormone replacement therapy /75/. The major components of soy, the isoflavones genistein and daizein, are structurally similar to 17β-estradiol and produce weak estrogenic effects (i.e., phytoestrogens) /76/. These isoflavones can also inhibit oxidative metabolism *in vitro* and *in vivo* /77/. Seven soybean varieties tested, as well as daidzein and genistein isolated from soybean, have been found to inhibit CYP3A4-mediated metabolism. In 20 healthy volunteers, a 14-day course of soy extract containing 50 mg of isoflavones twice daily did not alter the ratio of the amounts of 6β-hydroxycortisol and cortisol excreted in the urine, suggesting that the components of soy were not inducers of CYP3A4 in humans /78/.

INDUCTION OF CYP3A4 BY HERBS

Echinacea

Echinacea is one of the most commonly used alternative medicines in the world, representing 10% of the herbal market /79/. The most common and widespread species are *Echinacea angustifolia*, *E. purpurea* and *E. pallida*, each of which has a long history of medical use. Hundreds of studies have been performed on the use of echinacea in the stimulation of the immune system /80-84/. The major putative mechanisms of action include increase of granulocytes, enhanced phagocytic performance, inhibition of virus proliferation, cytokine activation, production of T-lymphocytes and an increase in the T4/T8 cell ratio /84,85/. Thus, echinacea is currently used to assist the prevention of cold and influenza symptoms /86/.

A wide variety of chemicals have been isolated and identified from *Echinacea* spp. Constituents that have been identified include volatile oil, caffeic acids, polysaccharides, polyines, polyenes, isobutylamides and flavonoids of quercetin and kaempferol. Both an extract of echinacea /87/ as well as quercetin /88/ have been shown to inhibit the activity of CYP3A4. However, a recent study has demonstrated that the intravenous intake of echinacea induced the activity of hepatic CYP3A in healthy volunteers /89/. When midazolam, which was a substrate for CYP3A4, was systemically administered, the chemical was cleared 42% faster during an 8-day treatment of echinacea in 12 volunteers than in controls, and 23% reduction was observed in the midazolam AUC /89/. On the other hand, the oral bioavailability of midazolam was significantly increased from 24% to 36% in the presence of echinacea, indicating that the intestinal CYP3A was inhibited by the components of echinacea /89/, consistent with the results obtained by Budzinski *et al.* /87/.

Grape seed

Grape seed (*Vitis vinifera*) is a naturally occurring plant substance. It contains a concentrated source of potent antioxidants /90/. Grape seed extracts are used mainly in the treatment of peripheral venous insufficiency, respiratory conditions, allergic rhinitis /91/, and as a cardioprotectant /92/. A wide variety of flavonoids are present in grape seed /93,94/. In human hepatocytes, grape seed extract at a concen-

tration of 600 ng/ml increased CYP3A4 mRNA by 270% /54/, indicating the ability to induce CYP3A4 expression. At present, there is no report on the pharmacokinetic interaction of grape seed components with therapeutic drugs.

St John's wort

St John's wort (*Hypericum perforatum*), a perennial plant native to Europe, North America and western Asia, is one of the most extensively studied herbal products /95/. It has been used for treatment of psychiatric disorders /96/. Currently, St John's wort is still widely used for the treatment of mild to moderate depression and other nervous conditions /97,98/. Varying results of therapy with St John's wort for depressive disorders have been reported; however; recent randomized, double blind, placebo-controlled trials evaluating the safety and efficacy of St John's wort in the treatment of patients with major depressive disorders revealed that St John's wort was no more effective than placebo /99,100/.

St John's wort contains a complex mixture including catechin-type tannins and condensed-type proanthocyanidins, flavonoids (mostly hyperoside, rutin, quercetin and kaempferol), bi-flavonoids (biapigenin), phloroglucinol derivatives such as hyperforin, phenolic acids, volatile oils, and naphthodianthrones, including hypericin and pseudohypericin /101-103/. With regard to the antidepressant effects of St John's wort, many of the pharmacological activities appear to be attributable to hypericin and hyperforin, which inhibit the reuptake of neurotransmitters in synapses /104/, although a contribution of other constituents has been postulated /105/.

Various *in vitro* studies have shown that St John's wort is a potent inducer of CYP3A4 /106,107/. The inducing effects on CYP3A4 have been related to hyperforin-induced ligand activation of the steroid and xenobiotic-regulated transcription factor known as PXR /18,19,108,109/. Hyperforin was a more potent activator of PXR (median effective concentration, 23 nM) than the well-known CYP3A4 inducer rifampin. The clinical exposure to hyperforin associated with the ingestion of available formulations of St John's wort (plasma hyperforin concentration, 200 to 400 nM) is sufficient to activate PXR and subsequent induction of CYP3A4.

Human studies indicated that long-term (more than 2 weeks) administration of St John's wort significantly induced intestinal and

hepatic CYP3A4 /48,109-117/. CYP3A4 induction by St John's wort has been implicated in the loss of efficacy of various drug therapies. Especially in the case of drugs having narrow therapeutic windows, such as cyclosporine, the alteration of pharmacokinetics by treatment with St John's wort may by crucial. A study performed by Bauer *et al.* /117/ has revealed that the administration of St John's wort extract to patients receiving cyclosporine treatment resulted in a rapid and significant reduction of plasma cyclosporine concentrations. Warning should be given to patients receiving cyclosporine therapy against the intake of St John's wort. CYP3A4 induction by the administration of St John's wort is subject to the dosing regimen, and schedules involving treatment with the herb for fewer than 8 days are unlikely to activate PXR /118,119/. St John's wort extracts have been documented to inhibit the activity of CYP3A4 /87,120,121/. According to the extent of inductive and inhibitory effects of St John's wort, the results observed *in vivo* depend on the dose, duration of administration, formulation and the source of the herb. Clinical trials are now reporting significant pharmacokinetic interactions with St John's wort of drugs from a variety of therapeutic classes /115-117,122/.

SCREENING OF FOODS FOR INHIBITION OF HUMAN CYP3A

Evidence for the inhibition or the induction of human CYP3A by constituents of foods has been accumulating. However, at present, most foods have not been evaluated for their effects on human CYP3A activity. To avoid adverse clinical outcomes caused by food-drug interactions via CYP3A, it is important to predict these interactions.

So far, a variety of *in vitro* and *in vivo* methods to assess food-drug interactions through CYP3A have been established. For the screening of certain foods as inhibitors or inducers of CYP3A, *in vitro* models appear to have advantages compared to the *in vivo* system in terms of short period of experiment and ease of use. The *in vitro* systems developed to date include subcellular fractions (liver microsomes, cytosol and homogenates), precision-cut liver slices, isolated and cultured hepatocytes, and cDNA-expressed enzymes /123-131/. All of the systems mentioned above can be applied for inhibition studies. On the other hand, hepatocytes are usually provided as a valuable tool to assess the effects of foods on CYP3A induction. The mechanisms for

CYP regulation by food component(s) can also be investigated with hepatocytes containing nuclear PXR regulating CYP3A /132,133/.

Recently, the author and colleagues screened several foods for inhibitor(s) of human CYP3A with liver microsomal systems. The results are described below.

Tropical fruits

In areas with a warm climate, a wide variety of fruits are grown. The author and colleagues investigated whether the components present in tropical fruits inhibited the midazolam 1′-hydroxylase activity of CYP3A with human liver microsomes /134/. Eight tropical fruits, common papaw, dragon fruit, kiwi fruit, mango, passion fruit, pomegranate, rambutan and star fruit, were tested. Filtered extracts of star fruit were found to inhibit human CYP3A activity *in vitro*, and the inhibition potency was almost the same as that of grapefruit components (Fig. 1). In contrast to the case with grapefruit, the inhibition potency of the juice from star fruit was not altered by lengthening the preincubation period, suggesting that star fruit does not contain a mechanism-based inhibitor.

Star fruit originated in Ceylon and the Moluccas, but it has been cultivated in southeastern Asia and Malaysia for many centuries. It is commonly grown in south China, Taiwan and India, and also in the southern part of Japan. Star fruit was introduced into southern Florida before 1887 /135-137/. It is highly popular in Brazil, the Philippines and Queensland (Australia), and moderately so in some South Pacific islands, in Central America and in tropical western Africa. Star fruit can be eaten whole or sliced and added to salads. Star fruit juice is used in tropical drinks and 'smoothies'. In Brazil, star fruit juice is served as a fresh beverage, *in natura*, or as an industrialized juice, as it is also served all over the world. Brazilians sometimes drink up to 500 ml of star fruit juice per day /136,137/.

Inhibition of CYP3A by star fruit juice may not occur *in vivo*. However, the results described here raised the hypothesis that filtered extracts of star fruit are capable of altering the pharmacokinetics of co-administered therapeutic drugs, through CYP3A inhibition, as occurs with grapefruit juice.

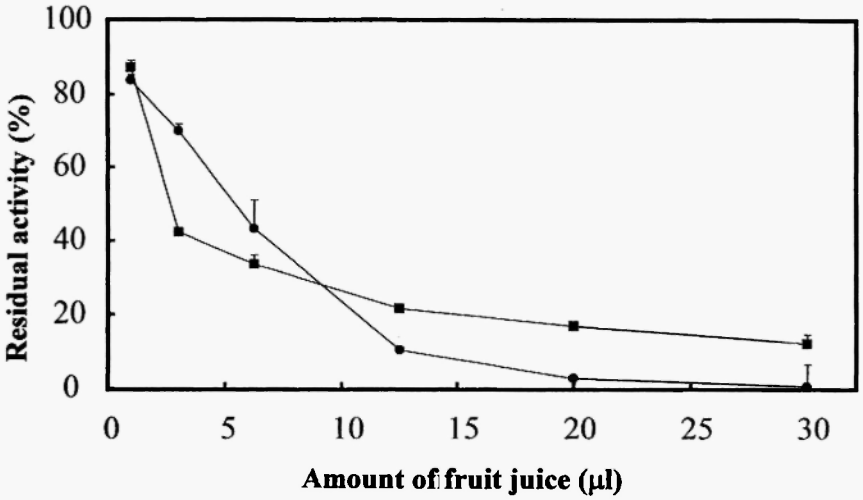

Fig. 1: Inhibition of human CYP3A activity by star fruit juice or grapefruit juice. The inhibitory effects of fruit juice on midazolam 1′-hydroxylation are expressed as a percentage of the residual activity compared with the control in the absence of juice. The amount of fruit juice added to the incubation mixture was 1.0, 3.0, 6.25, 12.5, 20, 30 μl (0.2, 0.6, 1.25, 2.5, 4.0, 6.0%, v/v), respectively. Star fruit (●); grapefruit (■). Each point represents the means of three independent assays.

Citrus fruits

The inhibition of human CYP3A activity by the locally produced citrus fruits in the southern part of Japan has been investigated /138/. Natsudaidai, banpeiyu, dekopon, hassaku orange, new summer orange, kumquat, pomelo, and satsuma mandarin were tested. Among the citrus fruits, banpeiyu juice showed the most potent inhibition; however, the inhibition was somewhat less than that of grapefruit juice. Lengthening of the preincubation period of the juice from banpeiyu with the microsomal fraction led to enhancement of the CYP3A inhibition. Thus, the ingredient(s) of banpeiyu is(are) inhibitor(s) or mechanism-based inhibitor(s) of human CYP3A activity, but the potency was somewhat less than that of grapefruit.

CONCLUSION AND PERSPECTIVES

Since the knowledge of food-drug interactions via CYP3A is now evolving, further research is needed to determine the scope, magnitude and clinical importance of food effects on this drug-metabolizing enzyme. As mentioned above, previous studies have demonstrated several clinically important interactions. These findings have now been recognized by many medical staff, including physicians and pharmacists, leading to the prevention of some adverse food-drug interactions. However, various potentially hazardous foods still remain untested for drug interactions. These foods have to be found by screening them. High throughput methods may be necessary to screen a range of foods in a relatively short period. For this purpose, an *in silico* model may be appropriate. Beside studies with *in vitro* and *in vivo* methods, analysis with *in silico* models has been increasingly performed to study CYP inhibition by xenobiotics /139,140/. Since the accuracy of the *in silico* analysis depends on the three-dimensional structural model of the CYP enzyme, the crystallization of CYP has been awaited. Subsequent to the crystallization of human CYP2C9 by Williams *et al.* /141/, CYP3A4 has recently been successfully crystallized by the same researchers /142/. Furthermore, the three-dimensional structure of the enzyme has been elucidated /142/. This landmark finding should improve the accuracy of the *in silico* model, and could lead to a further acceleration of the use of this model to study food-drug interactions.

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