REVIEW

Interactions between medicines and functional foods or dietary supplements

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Abstract. Recently, the demand for supplements has steadily been increasing with the diffusion of alternative and supplemental medicines throughout the world. Therefore, the supplements have frequently been taken with many drugs. Here, we have introduced the pharmacokinetic and pharmacological interactions between them. (Keio J Med 53 (3): 137–150, September 2004)

Key words: drug interaction, functional food, dietary supplement, cytochrome P450 (CYP), P-glycoprotein

Introduction

Recently, so-called health foods, including functional foods and dietary supplements, are being increasingly used world-wide as part of complementary and alternative medicine or self-medication (Fig. 1). With this prevalence of health foods, the possibility of their concomitant use with synthetic chemicals (medicines) in general has also increased (Fig. 2).[1] However, there is little information based on scientific evidence concerning the interactions between medicines and health foods.

Concerning mechanisms of interactions among medicines, pharmacokinetic interactions are the most frequent, and interactions in the metabolic processes are particularly important. Most of such metabolic interactions are considered to be related to inhibition or induction of the drug metabolizing enzyme cytochrome P450 (CYP).[2] In addition, there are many isoforms of CYP. CYP3A4, in particular, is present at high levels in the intestines and liver, and is involved in the metabolism of about 50% of the clinically used drugs, so that it is an isoform that needs particular attention in drug interactions.[3]

By setting the establishment of combination therapy using medicines and effective and safe traditional herbal medicines as the final goal, our laboratory has conducted basic research on pharmacokinetic interactions between them in which CYP3A4 is involved. As part of our research accomplishments, we could demonstrate an enhancement of metabolism of carbamazepine, an antiepileptic drug and a substrate of CYP3A after 1-week repeated oral administration of Shoseiryu-to in rats.[4] We have also reported that the possibility of the occurrence of interactions among these drugs is small in humans.[5] Moreover, we are continuing research on pharmacokinetic interactions between medicines and various health foods (*i.e.*, *Ginkgo biloba* leaf extract, *Agaricus blazei* Murill extract, propolis extract, and pomegranate juice) with the same objective as our study of traditional herbal medicines.

The Ministry of Health and Welfare (presently Ministry of Health, Labor and Welfare) announced in the ''Information concerning the safety of drugs and medical instruments No. 160 (May, 2000)'' that the plasma concentrations of various medicines that are substrates of CYP3A are reduced with consequent reductions in their effects by the ingestion of St. John's wort (*Seiyo-otogiri-so* in Japanese) extract. We believe that this announcement is of profound significance in that it urges keen awareness of physicians, pharmacists, and nutritionists about the necessity for attention to interactions not only among medicines but also between medicines and health foods.

In this article, we first explain the definition and classification of so-called health foods. Next, we de-

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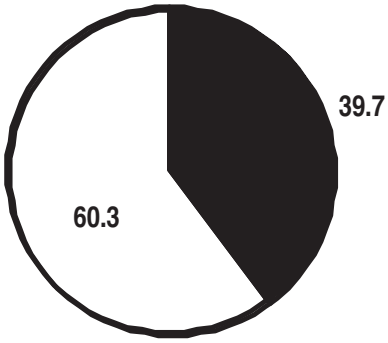

Fig. 1 Results of a questionnaire about the percentage of health-food users in the opinion pole about health by the Tokyo Metropolitan Government. Subjects: 2,113 males and females aged 20 years and above living in Tokyo (September, 2000). A question: Are you taking health foods (drinking health beverages) besides conventional foods? ■, Yes; □, No.

scribe cases of interactions between medicines and St. John's wort or grapefruit juice, and interactions between medicines and other typical health foods and the management of patients in case of such interactions.[6] Finally, we will present part of the results of basic research concerning pharmacokinetic interactions between medicines and health foods obtained at our laboratory.

Definition and Classification of Health Foods

Most of so-called health foods are foods manufactured and sold by business enterprises claiming that they are "better for the health than regular foods". Among those available in this country are St John's wort extract, grapefruit juice, *Ginkgo biloba* leaf extract, *Agaricus blazei* Murill extract, *Phellinus linteus* Aoshima extract, propolis extract, pomegranate juice, chlorella, collagen, Curcuma Longa L., Ginseng, royal jelly, vitamins, and minerals. The Ministry of Health, Labor and Welfare defines health foods as foods sold for supplementation of nutritional elements or for specific health uses, composed of conventional foods, and prepared in the forms of conventional foods or tablets, and capsules. Presently, however, there is no particular law that systematically controls or regulates health foods, and they are dealt with by multiple related laws similarly to conventional foods. Also, it is well-known that health foods cannot claim to be effective for particular indications, and they are treated as unapproved/unauthorized medicines and are regarded as violations of the Pharmaceutical Affairs Law once the product is purport to have a particular effect.

The Ministry of Health, Labor and Welfare started the "Health and Functional Foods System" in April, 2001, and so-called health foods came to be classified into health-protecting or health-promoting functional foods and health foods or supplements, which are regarded as conventional foods. Furthermore, health-protecting or health-promoting functional foods were classified into (1) conventional foods for specific health uses (individually approved type) and (2) newly categorized nutritional functional foods (specified and standardized type) (Fig. 3 and Table 1). Also, of these so-called health foods, those in the forms of tablets or capsules are categorized as dietary supplements. Many dietary supplements that contain herbs, vitamins, and minerals are put on the market, and are used by a large number of people.

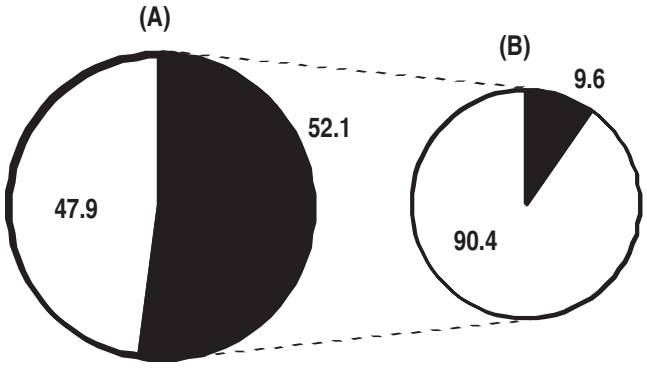

Fig. 2 Results of two questionnaires about the percentages of users experiencing the history of concomitant intake of health foods and medicines.[1] Period, May–June, 2000; Subjects: 453 outpatients at Tsukuba University Hospital. (A) The first question: Have you taken medicines prescribed by hospitals or clinics with health foods? ■, Yes; □, No. (B) The second question for the persons who answered "yes" in the first question: Did you tell it to the physician? ■, Yes; □, No.

Interactions Between Medicines and St. John's Wort (SJW) and Their Management

SJW is an erect perennial plant of the family Guttiferae distributed primarily from Europe to Central Asia. Its scientific name is *Hypericum perforatum*. SJW has also been used in Europe from ancient times for insominia and depression, and as it has recently been reported to have an effect similar to those of existing antidepressants,[7,8] it is popular particularly in the United States and Europe. In Japan, also, SJW is sold as a health food by many companies. SJW contains more than 20 natural components, and hyperforin has been shown to have the strongest antidepressant activity among them.[9]

Although no clinical case that suggests interaction between SJW and medicines has been reported to date in our country, caution against the concomitant use with SJW was added in 2000 to the precautions for use of the following medicines. SJW has been reported to reduce

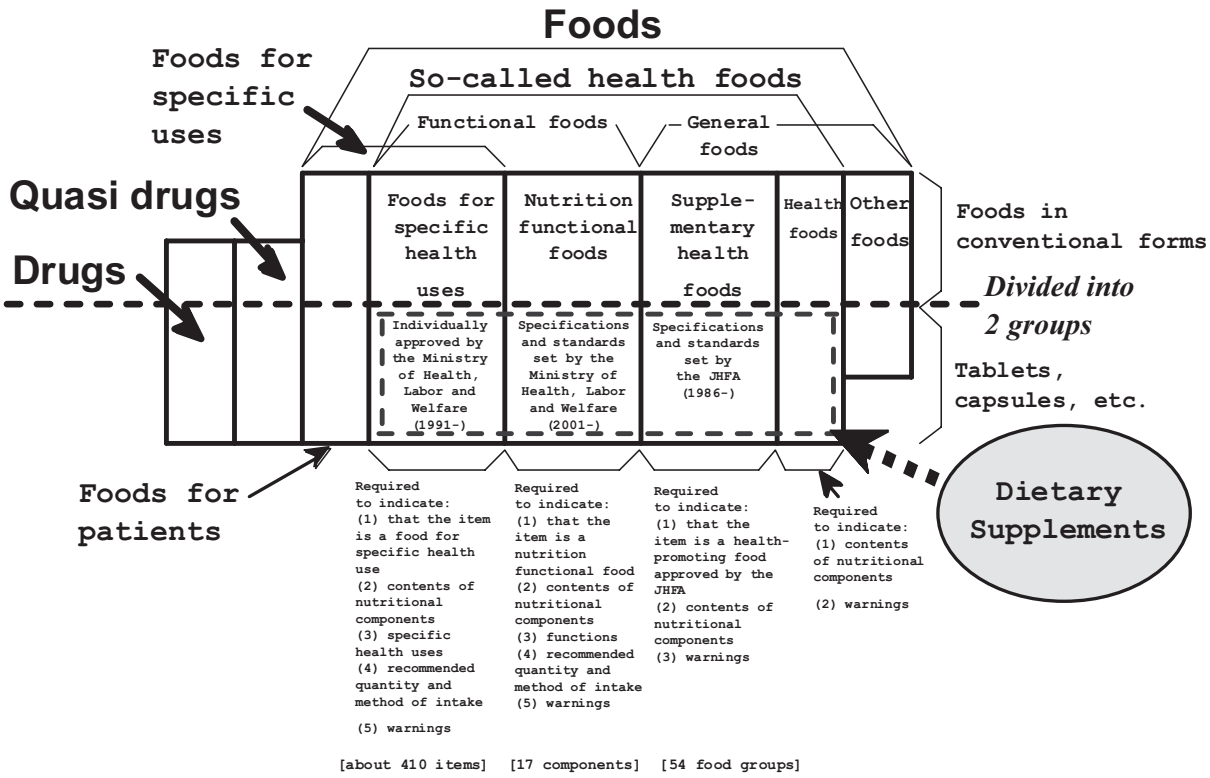

Fig. 3 Definitions and classification of health foods in our country (4/'04).[23] Forms of drugs generally include powder, granules, tablets, troches, capsules, ointment, cream, and liquids. Among them, Ensure Liquid®, an enteral nutritional preparation in a liquid form, appears identical with canned soft drinks sold as conventional foods. Moreover, Vicks Medicated Drops® and Asada Ame®, which are OTC drugs, look exactly the same as drops and candies prevalent as foods. Lipovitan D®, which is a quasi drug, is sold in a form difficult to distinguish from bottled beverages in general. Among foods other than health foods, some (*e.g.*, lemonade-flavored candies) are sold in the forms of tablets, troches, *etc.* ∗ Presently, warning against the concomitant use of St. John's wort is printed on packages and package inserts.

Table 1 Outline of Foods for Specific Health Uses and Nutrition Functional Foods

		Foods for specific health uses	Nutrition functional foods
Definition (Partially omitted)		Foods that are indicated on their packages that they are expected to produce specific health-promoting or health-protecting objectives for those who consume them for the stated objectives according to a nutritional regimen	Foods that are indicated on their packages to have the functions of the specific nutritional components that the foods are stated to contain according to the standards set by the Minister of Health, Labor and Welfare (fresh foods other than chicken eggs excluded)
Sales regulations		Individually approved (scientific data needed)	Regulated by specifications or standards (Upper and lower limits of the intake determined)
Number of items [Components]		About 410 (4/'04)	[Vitamins 12, Minerals 5]
Examples		Amyl S®, Yakulut 400, Bansorei-cha, Econa® Cooking Oil	Vitamins A, B, C, D, and E, foric acid, pantothenic acid, biotin, niacin, Ca, Fe
Specific examples	Commercial name	Origo-de-shikkari-Ca (Meiji Seika)	Tennen-koka-karushiumu (House Foods)
	Active components	Fructooligosaccharides, Ca	Ca
	Description	Fructooligosaccharides promote the absorption of Ca and make strong bones and teeth	Calcium is a nutrient necessary for the formation of bones and teeth

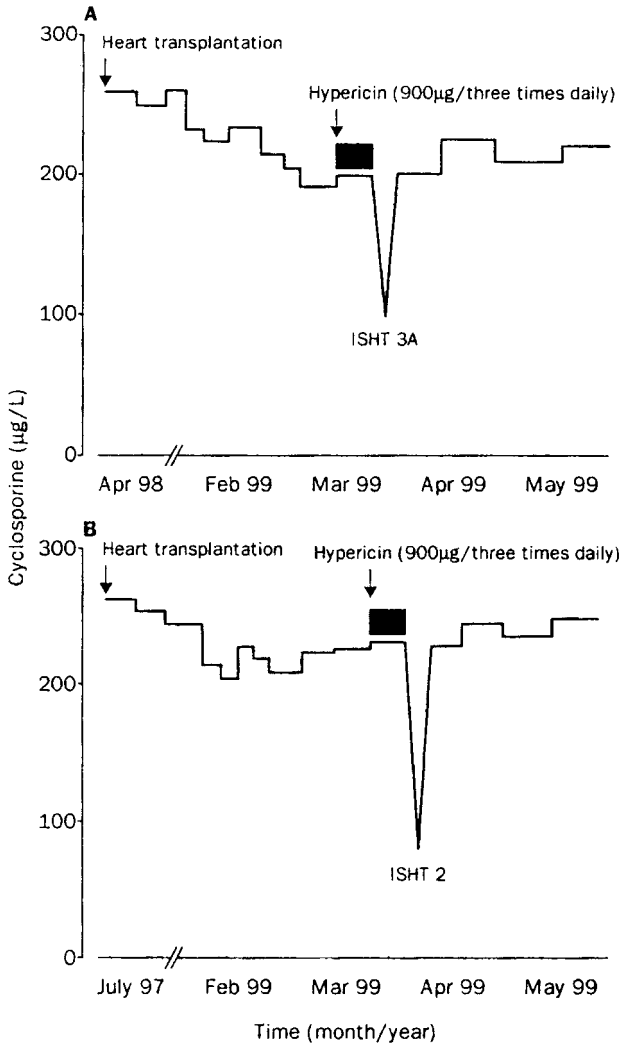

Fig. 4 Ciclosporin concentrations in two patients after heart transplantation. Treatment with St John's wort was associated with a drop in ciclosporin values below the therapeutic range and acute transplant rejection. Hypericin, one of the biologically active constituents of St John's wort extract, which is an antidepressant chemical compound; ISHT, the grading determined by International Society of Heart and Lung Transplantation. (Reproduce from, Ruschitzka F, *et al*: Lancet 2000; 355: 548–549, Copyright © (2000), with permission from THE LANCET Publishing Group, Elsevier Ltd.)

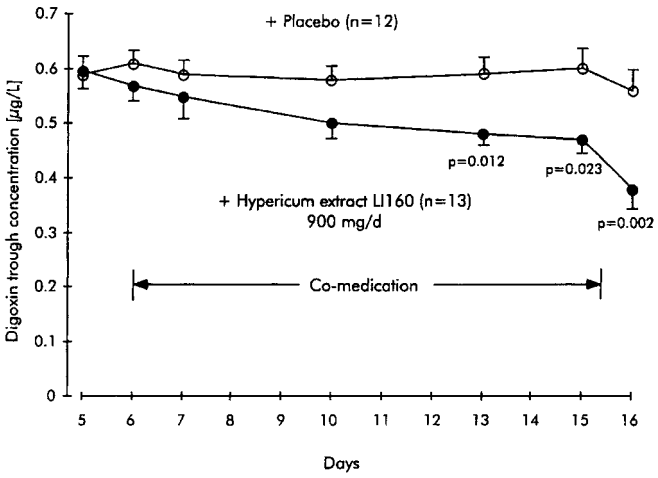

Fig. 5 Course of digoxin trough levels in 25 healthy volunteers treated either with hypericum extract (L1160) or placebo (mean ± SEM). Daily oral digoxin dose was 0.25 mg. *P* Values represent statistical significance between the two medication groups. (Reproduce from, Johne A, *et al*: Clin Pharmacol Ther 1999; 66: 338–345, Copyright © (1999), with permission from Mosby, Elsevier Ltd.)

the plasma concentrations of ciclosporin (Fig. 4),[10] indinavir,[11] and ethynylestradiol, which are metabolized by CYP3A4, theophylline,[12] which is metabolized by CYP1A2, and warfarin, which is metabolized by both of these isozymes.[13] Moreover, it has been concluded that CYP3A4 is induced by hyperforin as it directly binds with hormone receptor pregnane X receptor (PXR) to activate PXR.[14] SJW has also been reported to induce not only some CYP isoforms but also P-glycoprotein (MDR1), which is a drug efflux transporter and involved in multiple drug resistance of cancer cells.[15] Indeed, reductions of the plasma concentration of digoxin, which is a substrate of MDR1, have been reported (Fig. 5).[15]

For the above reasons, the concomitant use of SJW-containing foods and medicines should be avoided, in principle. Also, when physicians and pharmacists prescribe or prepare and dispense such medicines, they must check whether the patients consume SJW-containing foods. If they do, the physicians and pharmacists must try to persuade the patients to immediately stop consuming the SJW-containing foods and start the medication after a period. If they discover patients who have been concomitantly using SJW-containing foods and the above medicines over a relatively long period, they must lead the patients to eventually give up consuming the SJW-containing foods while paying sufficient attention to the patients, because if the patients suddenly stop consuming the SJW-containing foods on their own judgments, adverse reactions associated with rapid increases in the plasma concentrations of the medicines may appear. Therefore, providing sufficient information from physicians or pharmacists to patients is indispensable, and accumulation of reliable information is an urgent requirement.

Interactions Between Medicines and Grapefruit Juice (GFJ), and Their Management

Increases in the blood drug concentrations due to the intake of GFJ

When particular medicines metabolized by CYP3A4 are taken simultaneously with GFJ, their plasma con-

centrations may increase, occasionally causing unexpected adverse reactions. This interaction is mentioned in the package inserts of a total of 26 drugs as of the end of September, 2002. They include calcium blockers (nisoldipine, felodipine, and nifedipine), antipsychotics (pimozide), antiplatelet agents (cilostazol), immunosuppressants (ciclosporin and tacrolimus), anticancer drugs (gefitinib and imatinib), and antiviral agents (saquinavir). Also, GFJ increases the plasma concentrations of the antihyperlipidemic agents simvastatin, atorvastatin, and lovastatin, but it shows no interaction with pravastatin (which is not a substrate of CYP3A4 or MDR1). Figure 6 shows a typical case of interaction, in which the plasma concentration of simvastatin was increased by the concomitant intake of GFJ.[16] As shown in this figure, the peak concentration increased about 12-fold, indicating great danger of the concomitant use. As for the mechanism of inhibition by GFJ, it has been concluded that frunocoumarins, particularly their dimers, contained in GFJ inhibit CYP3A4 in intestinal epithelial cells, causing a marked increase in the intestinal absorption of the drug.[17] Moreover, by this inhibition mechanism, which is called mechanism-based inhibition (inhibition by direct binding of a metabolite or intermediate metabolite of the inhibitor with CYP3A4), intestinal CYP3A4 is inactivated, or irreversibly inhibited, and its protein level is reduced.

In addition, the degree of interaction between GFJ and medicines not only vary widely among medicines of the same categories (*e.x.* calcium blockers) but also are markedly affected by factors such as the quantity of intake, brand, and timing of intake of GFJ. Even worse, as GFJ irreversibly inhibits CYP3A4, a single dose of GFJ has been shown to produce an inhibitory action that may continue for several days (Table 2).[18]

Therefore, this interaction cannot be prevented by avoidance of simultaneous intake of GFJ, and it is best to completely abandon all intake of GFJ. However, only simultaneous intake is prohibited, and concomitant use is not, in many package inserts. Moreover, despite the presence of reliable literature that indicates the danger of concomitant use, it is not reflected in many package inserts. Therefore, utmost caution based on the latest information is required to physicians and pharmacists.

Decreases in the blood drug concentrations due to the intake of GFJ

Recently, there has been a very shocking report of interactions of GFJ. The plasma concentration of fexofenadine, an antiallergic agent, after its oral administration decreases markedly by a massive intake of GFJ (Fig. 7).[19] Moreover, this decrease has been shown to occur even with an intake of GFJ at a conventional

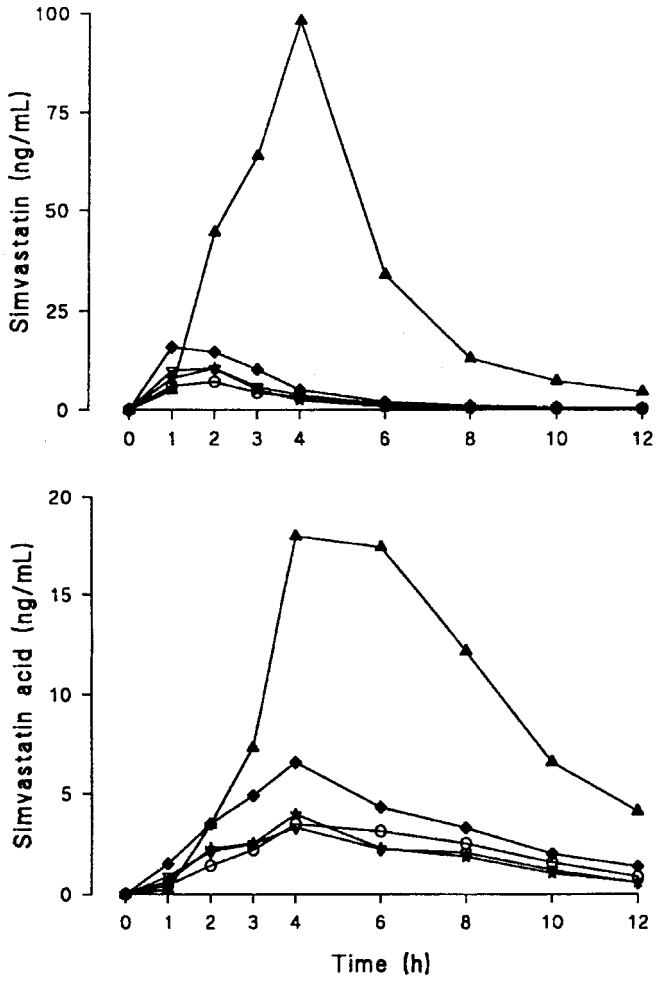

Fig. 6 Mean serum concentrations of simvastatin (**upper panel**) and simvastatin acid (**lower panel**) in 10 healthy volunteers after single oral doses of 40 mg simvastatin. Simvastatin was taken with 200 mL water (*open circles*), with 200 mL double-strength grapefruit juice after ingestion of 200 mL grapefruit juice three times daily for 2 days (*solid triangles*), or with 200 mL water 24 hours (*solid diamonds*), 3 days (*open triangles*), or 7 days (*solid stars*) after last dose of grapefruit juice. *Error bars* were omitted for clarity. (Reproduce from, Lilja JJ, *et al*: Clin Pharmacol Ther 2000; 68, 384–390, Copyright © (2000), with permission from Mosby, Elsevier Ltd.)

quantity (300 mL). Such decreases in the absorption of fexofenadine are caused also by an intake of orange juice or apple juice (Fig. 7).[19] Results similar to those of fexofenadine have been obtained in the concomitant intake of celiprolol, a β-blocker, with GFJ.[20]

One of the mechanism of these decreases is estimated to be inhibition of some organic anion transporting polypeptide (OATP-A, -B, -C, *etc.*) in intestinal epithelial or hepatic cells by a common component in fruit juices, because fexofenadine and celiprolol are substrates of some OATP and not of CYP3A4, but both drugs are substrates of MDR1.[19–21] Moreover, some medicines are considered to be substrates of both CYP3A4 or MDR1 and OATPs, in which case predic-

Table 2 Pharmacokinetic Parameters of Nisoldipine in Each Experiment

	Control	*G0*	*G14*	*G38*	*G72*	*G96*
AUC(0-∞) ($\times 10^{-6}$% of dose · h/mL)	78.1	321	181	132	107	108
Dose (mg)	10.0	5.0	5.0	5.0	5.0	5.0
AUC(0-∞) (mg · h/mL)	7.81	16.0	9.04	6.59	5.33	5.39
CL_{oral} (L/h)	1281	312	553	758	939	928
CL_{iv} (L/h)	49.9	49.9	49.9	49.9	49.9	49.9
$CL_{H,int}$ (L/h)	144	144	144	144	144	144
F_{liver} (%)	34.8	34.8	34.8	34.8	34.8	34.8
F and F′ (%)	3.9	16.0	9.03	6.59	5.32	5.38
F_{GI} (%)	11.2	46.0	26.0	18.9	15.3	15.5
$CL_{GI,int}$ (L/h)	427	63.2	154	231	299	295
ε	1.00	0.148	0.360	0.541	0.699	0.690
t_{max} (h)	1.50	1.69	1.00	1.50	0.875	1.19
t (h)	–	1.688	169	194	217	241
Ratio of AUC	1.00	4.11	2.32	1.69	1.36	1.38

F′ is availability after intake of grapefruit juice; ε is the ratio of active CYP3A4 to total CYP3A4. AUC and oral clearance (CL_{oral}) were calculated. Control nisoldipine bioavailability (F) was 3.9%,[38] then intravenous clearance (CL_{iv}) was calculated. Intrinsic hepatic clearance ($CL_{H,int}$) and hepatic bioavailability (F_{liver}) were calculated from the CL_{iv} and $Q_H = 76.62$ L/h.[36] F was calculated from CL_{oral} and CL_{iv}, gastrointestinal bioavailability (F_{GI}) was calculated form F and F_{liver}, then the intrinsic gastrointestinal clearance ($CL_{GI,int}$) was calculated from $Q_{GI} = 53.9$ L/h.[36] t_{max} (h) is the time of maximum plasma concentration, and t (h) is t_{max} + (time after grapefruit juice ingestion). (Reproduce from, Takanaga H, *et al*: Clin Pharmacol Ther 2000; 67, 201–214, Copyright © (2000), with permission from Mosby, Elsevier Ltd.)

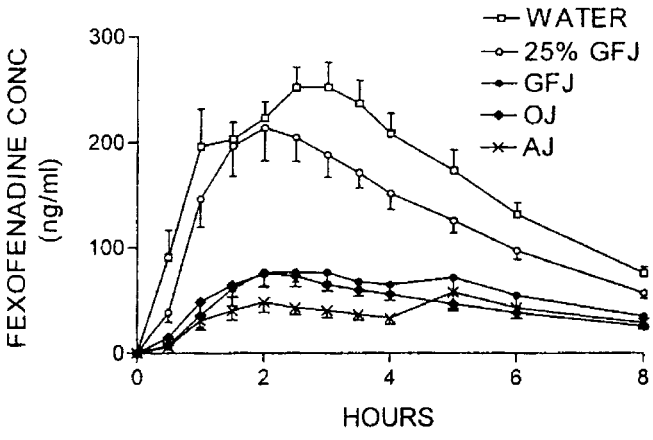

Fig. 7 Mean plasma fexofenadine concentration-time profiles for persons (n = 10) orally administered fexofenadine (120 mg) with 300 ml water, grapefruit juice at 25% of regular strength (25% GFJ), grapefruit juice (GFJ), orange juice (OJ), or apple juice (AJ) followed by 150 ml of the same fluid every 0.5 to 3 hours (total volume, 1.2 L). (Reproduce from, Dresser GK, *et al*: Clin Pharmacol Ther 2002; 71, 11–20, Copyright © (2002), with permission from Mosby, Elsevier Ltd.)

tion of interactions is very difficult. It should be noted that GFJ also inhibits MDR1.

From these observations, GFJ induces opposite interactions depending on the type of medicine, so that even greater caution than has been exercised is required. Especially, it is necessary to instruct patients who are taking medicines that are metabolized by CYP3A4 or those absorbed through the intestines *via* OATP (fexofenadine and celiprolol) to avoid the intake of GFJ. Among the many HMG-CoA reductase inhibitors, the bioavailability of pitavastatin, which is not a substrate of either CYP3A4 or MDR1 is completely unaffected by the concomitant intake of GFJ,[22] unlike simvastatin, atorvastatin, or lovastatin. Therefore, pharmacokinetic interactions are expected to be very rare with pitavastatin, and the agent is considered to be highly useful in the treatment of hyperlipidemia.

Noted Interactions between Medicines and Functional Foods (Herbs, Vitamins, Minerals, Amino Acids or Catecholamines) and Their Management

Problematic interactions of various health foods (herbs, vitamins, minerals, amino acids, or catecholamines) other than SJW and GFJ with medicines and their management are described.[6,23] Medicines with which concomitant use of vitamins and minerals is recommended because of possible vitamin or mineral deficiency on long-term administration are also touched on briefly.

Interactions with herbs

Since the number of herb-related health foods have recently increased, needs for them have grown, and they are likely to contain components with strong inductor or inhibitor activities against functional proteins in the body (enzymes and transporters), utmost caution is necessary concerning herb-drug interactions. Also, as multiple herbs are often blended in recent products, careful reading of package inserts is needed. Unfortunately, herbs are a category that most lack scientific evidence because of their uniqueness, *e.g.* (1) they are mixtures of many components, (2) they are a kind of prodrugs (many of their components are absorbed after they are transformed by the intestinal flora), (3) many of their active components are unknown, and (4) the contents of active components in herbs are variable. Here, typical examples of herb-drug interactions reported to date are shown in Table 3.[6,23]

Interactions with vitamins

Most of the vitamins have been used as medicines, and information about most interactions between herbs

Table 3 Representative Interactions between Medicines and Herbs[6,23]

Food	Drug	Side-effect	Package insert	Management
Fig	methoxsalen	phototoxity	Precaution in combination	Avoid the intake of a lot of fig
Ginkgo biloba leaf	warfarin	Intracerebral hemorrhage	Not mentioned	Avoid concomitant use
	aspirin	Spontaneous hyphema		
Plantain, seed	lithium carbonate	Decreases in plasma drug concentrations		Avoid simultaneous use
Tamarind	aspirin	Increases in plasma drug concentrations Possible increased risk of bleeding		Avoid concomitant use
Chlorella Ginseng	warfarin	Increased platelet aggregation	Precaution in combination	
Red wine	ciclosporin	Decreases in *plasma* drug concentrations	Not mentioned	Avoid simultaneous use
Garlic	warfarin	Possible increased risk of bleeding		Avoid concomitant use
	saquinavir	Decreases in plasma drug concentrations	Precaution in combination	

and vitamins has become available with clarification of their mechanisms. Table 4 summarizes part of them.[23]

Interactions with minerals

As shown in Table 5, many of the interactions between medicines and minerals occur as they form poorly soluble complexes such as chelates in the digestive tract, causing a decrease in their absorption.[23] Therefore, they are often manageable by avoiding their simultaneous intake such as by taking one at an appropriate interval after the intake of the other.

Interactions with amino acids or catecholamines

Table 6 shows examples of interactions between amino acids or catecholamines and medicines, and their management. The concomitant use of SSRI and SNRI, which are attracting attention as antidepressants, with foods with high L-tryptophan contents should be avoided to prevent serotonin syndrome.

Interactions that cause vitamin or mineral deficiency

Caution is needed in long-term administration of medicines or simultaneous intake of vitamins or minerals with drugs, because it may cause vitamin or mineral deficiency (Table 7). In such cases, vitamins or minerals should be supplemented to prevent their deficiency or to treat existing symptoms of their deficiency.

Basic Studies on Pharmacokinetic Interactions between Medicines and Functional Foods

Ginkgo biloba leaf extract

In our country, the market size of *Ginkgo biloba* leaf extract (GBE) is estimated to be 11 billion yen (2001),

Table 4 Representative Interactions between Medicines and Vitamins[23]

Food	Drug	Side-effect	Package insert	Management
Vitamin A	paclitaxel	Reduced function in bone marrow	Precaution in combination	Reduce the drug dose or lengthen the dosing interval during concomitant use
	etretinate	Hypervitaminosis	Contraindication in combination	Avoid concomitant use
Vitamin C	acetazoramide	Renal or urinary calculus	Contraindication in combination	
	deferoxamine	Reduced function in heart	Precaution in combination	Be careful of reduced function in heart during concomitant use
	warfarin	Increased platelet aggregation	Not mentioned	Avoid concomitant use
Vitamin D	alfacalcidol	*Hypercalcemia*	Precaution in combination	Desirable to avoid concomitant use
Vitamin E	warfarin	Possible increased risk of bleeding	Not mentioned	Avoid concomitant use
Folic acid	phenytoin	Convulsions		Desirable to avoid concomitant use

Table 5 Representative Interactions between Medicines and Minerals[23]

Food	Drug	Side-effect	Package insert	Management
Ca	digoxin	Digitalis toxity	Precaution in combination	Avoid the intake of a lot of Ca
Fe	cefdinir penicillamine	Decreases in gastrointestional drug absorption		Avoid simultaneous use (Keep a dosing interval for 2–3 h)
Ca, Fe, Mg, Al, Zn, etc.	tetracyclines new quinolones sodium risedronate hydrate, alendronate sodium hydrare	Decreases in drug concentrations		Avoid simultaneous use of all foods except water (Take drugs before the ingestion of breakfast at rising, and avoid all foods except water at least 30 min after drug intake)

Table 6 Representative Interactions between Medicines and Amino Acids or Catecholamines[23]

Food	Drug	Side-effect	Package insert	Management
L-tryptophan (serotonin precursor)	fluvoxamine paroxetine	serotonin syndrome	Not mentioned Precaution in combination	Desirable to avoid concomitant use
Yogurt (tyramine)	isoniazid	hypertension, *etc.*		

and it is among very popular items of health foods. Therefore, the possibility of concomitant use of GBE with various medicines is very high. The calcium blocker diltiazem (DTZ) is a typical highly extracted drug and has been shown to be metabolized into *N*-demethyldiltiazem (MA), an active metabolite, by CYP3A in humans and rats.[24–26] Similarly to DTZ, nifedipine (NFP) has also been shown to be metabolized primarily by CYP3A and to have a very low bioavailability.[27,28] Therefore, we selected DTZ and NFP as model substrates of CYP3A and studied the effects of concomitant administration of GBE on the absorption or metabolism of these drugs in rats.

First, we evaluated the effect of the addition of GBE on the DTZ *N*-demethylation reaction (CYP3A activity) using intestinal and hepatic microsomes derived from rats or humans. GBE inhibited the CYP3A activity in a manner dependent on the concentration (50% inhibition concentration: about 50 μg/mL in the rat intestine, about 182 μg/mL in the rat liver, 159 μg/mL in the human liver).[29] In NFP, the 50% inhibition concentrations in the rat intestine and liver were about 33 and 107 μg/mL, respectively.[30] Moreover, evaluations using rat intestinal or hepatic microsomes indicated that the mechanism of at least part of this inhibition was mechanism-based inhibition (Fig. 8).[29] Also, the

Table 7 Representative Interactions That Vitamins or Minerals is Possible to be Decreased by Taking Medicines

Category	Drug (Brand name)	Food	Side-effect, *etc.*	Package insert	Management
OTC drug	aspirin (Bufferin®)	folic acid	Elevated excretion in folic acid due to displacement between folic acid and aspirin, deficiency of folic acid	Not mentioned	Desirable to take each supplement
Ethical drug	famotidine (Gaster® 10)	Food-derived VB_{12}, folic acid, Fe	Reduced gastrointestinal absorption in each nutritional supplement due to the decrease in gastric acids, deficiency of each nutritional supplement		
	omeprazole	Food-derived VB_{12}			
	colestyramine	VA, VD, VE, VK, folic acid	Reduced gastrointestinal absorption in each nutritional supplement due to adsorption to drug, deficiency of each nutritional supplement	Important basic precautions	Avoid simultaneous use (Keep a dosing interval for 4–6 h)

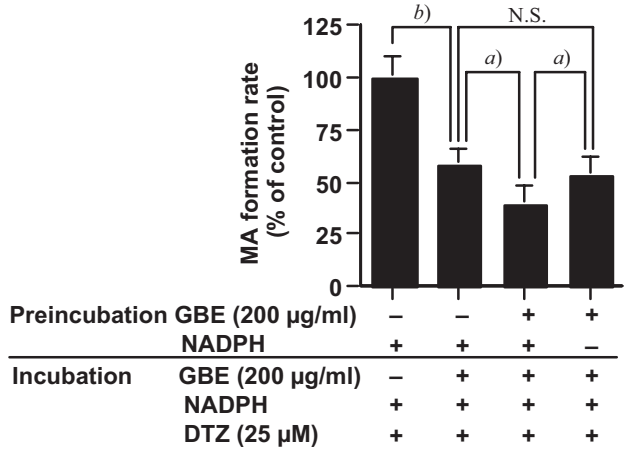

Fig. 8 Effects of the Preincubation under Various Conditions on the Formation of MA from DTZ by Rat Liver Microsomes.[29] Each column represents the mean ± S.E. of 3 rats. *a*) and *b*) $p < 0.05$ and $p < 0.01$, respectively (repeated measures ANOVA and Fisher's PLSD test). After preincubation for 10 min, the incubations were performed in an NADPH-generating system containing microsomes (150 μg) and DTZ (25 μM) without or with GBE (200 μg/ml) at 37°C for 3 min. (Reproduce from, Ohnishi N *et al*: Biol Pharm Bull 2003; 26, 1315–1320, Copyright © (2003), with permission from The Pharmaceutical Society of Japan)

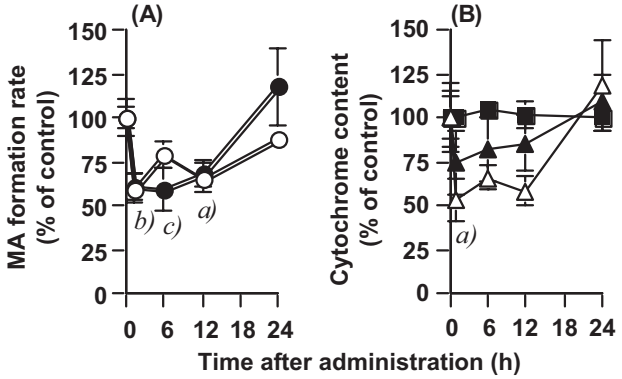

Fig. 9 Effects of Single Oral Pretreatment with GBE on the Formation of MA from DTZ (A) and Cytochrome Content (B) in Rat Small Intestine and Liver Microsomes.[29] Each point represents the mean ± S.E. of 3–6 rats. *a*) and *b*) $p < 0.05$ and $p < 0.01$ *vs.* each point at 0 h for small intestine, respectively, and *c*) $p < 0.05$ *vs.* the point at 0 h for liver (non-repeated measures ANOVA and Fisher's PLSD test). The GBE suspension (20 mg/kg) was administered orally to unanesthetized rats, and then the small intestine and liver were excised at indicated time points. (A) The reactions were performed in an NADPH-generating system containing small intestine or liver microsomes (300 or 150 μg) and DTZ (25 μM) at 37°C for 5 or 3 min, respectively. ○, small intestine (MA formation); ●, liver (MA formation); △, small intestine (CYP content); ▲, liver (CYP content); ■, liver (cytochrome b_5 content). (Reproduce from, Ohnishi N, *et al*: Biol Pharm Bull 2003; 26, 1315–1320, Copyright © (2003), with permission from The Pharmaceutical Society of Japan)

CYP3A activity in intestinal and hepatic microsomes was temporarily reduced after a single oral administration of GBE (20 mg/kg) in rats. Furthermore, this decrease corresponded with the decrease in the total CYP content. The cytochrome b5 content in hepatic microscomes showed no change (Fig. 9).[29]

Next, we evaluated the effects of the concomitant use of GBE on the pharmacokinetics of DTZ in rats after intravenous administration and observed significant decrease in the elimination rate constant (λ) and significant prolongation of the mean residence time (MRT) of DTZ by the concomitant use. Also, the peak plasma MA concentration was significantly lower in concomitant use of GBE than in the control. We also evaluated whether the concomitant use with GBE affects the pharmacokinetics of DTZ after oral administration and showed significant increases in the area under the plasma concentration-time curve (AUC) and bioavailability (F) of DTZ by the concomitant administration (Fig. 10 and Table 8).

These results indicate that GBE concomitantly administered with DTZ inhibits the metabolism of DTZ at least partly by inhibiting intestinal and hepatic CYP3A and increases the plasma DTZ concentration.

Although the metabolic clearance of DTZ is markedly greater in rats than in humans, the bioavailability after its oral administration is low in both species. The drug is also known to be metabolized primarily by CYP3A and esterases by nearly the same route in both species.[24,25] Therefore, the above results are considered be useful basic information for the evaluation of pharmacokinetic interactions of GBE with highly extracted drugs including DTZ, which are substrates of CYP3A.

We, therefore, carried out a study of interactions between GBE and NFP on simultaneous administration in 8 healthy adult males. The results suggested the possible occurrence of pharmacokinetic interactions also in humans despite individual variation.[31] A report of this study is under review for publication.

Agaricus blazei Murill extract

When we performed an *in vivo* study similar to that of GBE in rats, the absorption of DTZ was delayed by concomitant administration of *Agaricus blazei* Murill (ABM) extract (200 mg/kg: about 10 times a standard dose) contrary to GBE (Fig. 11A).[32] There were no significant differences in plasma MA concentrations and its pharmacokinetic parameters among the three groups (Fig. 11B).

Propolis extract

Simultaneous administration of propolis extract (20 mg/kg: about 10 times a standard dose) with DTZ

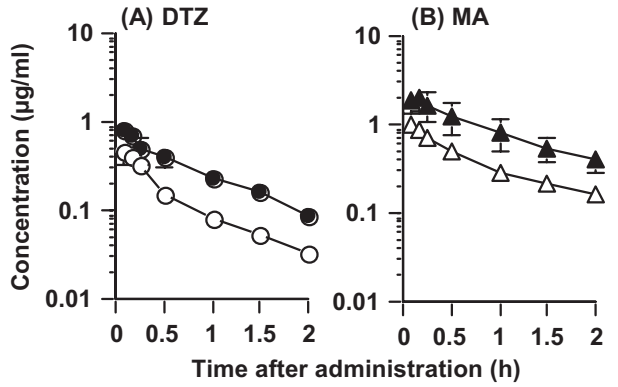

Fig. 10 Effects of Single Oral Pretreatment with GBE on the Plasma DTZ and MA Concentrations after Oral Administration of DTZ to Rats.[29] Each point represents the mean ± S.E. of 5 or 6 rats. The vehicle (control) or GBE suspension (20 mg/kg) was administered orally to unanesthetized rats, and then the DTZ solution (30 mg/kg) was administered orally 1 h later. ○, control (DTZ); ●, GBE (DTZ); △, control (MA); ▲, GBE (MA). (Reproduce from, Ohnishi N, *et al*: Biol Pharm Bull 2003; 26, 1315–1320, Copyright © (2003), with permission from The Pharmaceutical Society of Japan)

Table 8 Effects of Single Oral Pretreatment with GBE on the Pharmacokinetic Parameters of DTZ and MA after Oral Administration of DTZ to Rats[29]

Parameter	DTZ		MA	
	Control	GBE	Control	GBE
C_{max} (μg/ml)	0.55 ± 0.06	0.92 ± 0.19	1.11 ± 0.21	2.24 ± 0.66
T_{max} (h)	0.12 ± 0.02	0.13 ± 0.02	0.12 ± 0.02	0.14 ± 0.02
λ (/h)	0.96 ± 0.08	1.11 ± 0.09	0.61 ± 0.06	0.68 ± 0.10
$t_{1/2(\lambda)}$ (h)	0.75 ± 0.06	0.65 ± 0.05	1.20 ± 0.15	1.28 ± 0.35
$AUC_{0-\infty}$ (μg·h/ml)	0.30 ± 0.04	0.67 ± 0.14[a)]	1.03 ± 0.18	2.63 ± 0.80
MRT (h)	0.90 ± 0.07	1.02 ± 0.13	1.57 ± 0.16	1.77 ± 0.48
F (%)	2.0 ± 0.3	4.6 ± 0.9[a)]	–	–

Each value represents the mean ± S.E. of 5 or 6 rats. *a*) $p < 0.05$ *vs.* each control value (unpaired Student's *t*-test). The vehicle (control) or GBE suspension (20 mg/kg) was administered orally to unanesthetized rats, and then the DTZ solution (30 mg/kg) was administered orally 1 h later. The peak plasma concentration (Cmax) and the time to reach Cmax (Tmax) of DTZ and MA were determined from the actual data obtained after intravenous or oral administration. The terminal elimination rate constant (λ) was calculated by fitting individual data for three terminal points of the plasma concentration profile with a log-linear regression equation using the least-squares method. The corresponding elimination half-life ($t_{1/2(\lambda)}$) was calculated by dividing ln 2 by λ. The areas under the plasma concentration-time curves from zero to infinity ($AUC_{0-\infty}$) for DTZ and MA were calculated by means of the trapezoidal rule with extrapolation to infinity with λ. The mean residence time from zero to infinity (MRT) for DTZ and MA was estimated by moment analysis.[24] The absolute bioavailability of DTZ after oral administration (F) was estimated as follows: (AUCp.o. × Di.v.)/(AUCi.v. (DTZ alone) × Dp.o.) × 100. (Reproduce from, Ohnishi N, *et al*: Biol Pharm Bull 2003; 26, 1315–1320, Copyright © (2003), with permission from The Pharmaceutical Society of Japan)

increased the absorption of DTZ in rats, but the increase was not significant.[32]

Pomegranate juice

Pomegranate extract is a health food popular primarily among women for the alleviation of menopausal syndrome, because its seeds contain a factor resembling the female hormone, estrogen. When DTZ was orally administered to rats after the administration of pomegranate juice (5 mL/kg; 3-fold concentrate: about 10 times the conventional dose), little change was observed in the pharmacokinetics of DTA or its metabolites.[33]

The above results are useful basic information for the evaluation of pharmacokinetic interactions of these 4 health foods with liver-blood-flow-dependent drugs, which are CYP3A substrates, in humans.

Problems with Health Foods and Measures for Their Management

Distressing health damage caused by health foods for dieting that contained thyroid powder or *N*-nitrosofenfluramine (a possible carcinogen that accumulates in the liver) occurred in our country from the middle of 2000 to the fall of 2002. This incidence seems to be a natural consequence of the circumstances. As the products were popular dieting items among health foods, the number of victims amounted to 833 (including 4 deaths) (as of October 30, 2002).

In addition, in August, 2003, there were emergency admissions of people who took health foods (such as Tojigen), which were alleged to be effective for the treatment of diabetes mellitus, due to hypoglycemia, because they contained the oral hypoglycemic drug glibenclamide. The occurrence of health damages of this kind seems endless. Various problems emerge from these instances. I will summarize such problems and present measures that are being taken by the administration.

Quality of health foods

No strict GMP (Good Manufacturing Practice) has been established by the legislation for health foods as has been for medicines. Moreover, the system to prevent entry of non-approved medicines, or components the use of which in health foods is not approved by the Pharmaceutical Affairs Law (Food-Drug Discrimination: amended in April, 2001), is not functioning adequately. For these reasons, the quality and safety of all health foods are not guaranteed.

In summer, 2002, the Japan Health Food & Nutrition Food Association (JHFA) independently drafted and

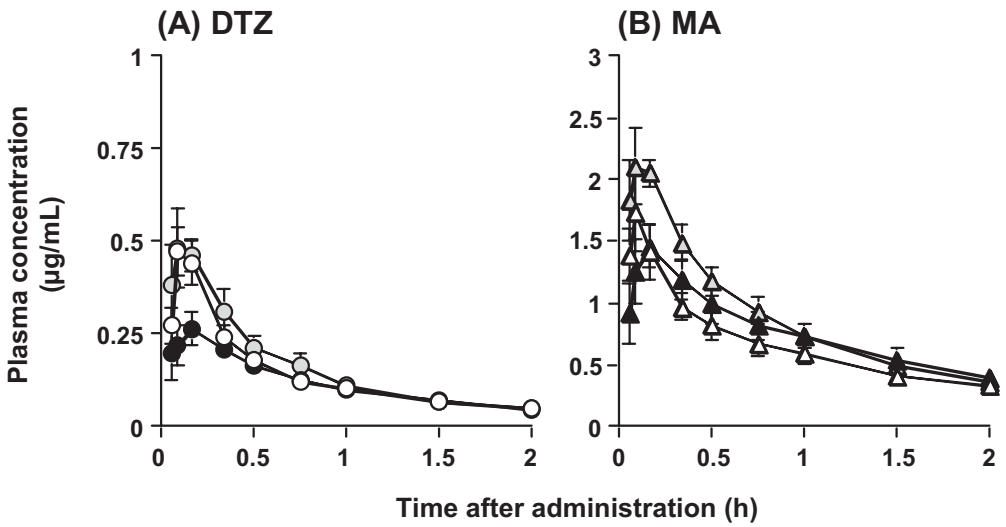

Fig. 11 Effects of Simultaneous Oral Administration of ABM Extract on the Plasma Concentrations of DTZ (A) and MA (B) after Oral Administration of DTZ to Rats.[32] Each point represents the mean ± S.E. of 5–8 rats. The DTZ solution (30 mg/2.5/kg) was administered simultaneously with water (control, 2.5 mL/kg) or ABM extract (40 or 200 mg/2.5 mL/kg) to unanesthetized rats. ○, control (DTZ); ●, 40 mg/kg ABM (DTZ); ●, 200 mg/kg ABM (DTZ); △, control (MA); ▲, 40 mg/kg ABM (MA); ▲, 200 mg/kg ABM (MA). (Reproduce from, Ohnishi N, *et al*: FFI J Jpn 2003; 208, 353–360, Copyright © (2003), with permission from FFI Journal)

announced the ''Supplementary Health Foods GMP'' to ensure the quality and safety of health supplements and to pave the way to further development of the industry. Relevant legislative actions are urgently needed.

Safety of health foods

The tolerable daily intakes based on scientific evidence have been decided for only a handful of items (*e.g.* foods for specific health uses and nutrition functional foods) among health foods for their safe use. Presently, the National Institute of Health Sciences is conducting chronic toxicity studies of some food items.

Effectiveness of health foods

The effectiveness of health foods remains to be evaluated. It is no exaggeration to say that reliable data concerning the effectiveness are available only for health functional foods among health foods. Believing whatever mass media and advertisements say is very dangerous.

Quality of information about health foods and systems for its distribution

Necessary and proper information about matters such as the effectiveness of health foods, adverse reactions, and interactions between medicines and health foods to be provided to consumers is markedly deficient compared with information about medicines (Table 9). Therefore, their collection, sorting, assessment, accumulation, and use are important problems for the future. To cope with this need, the National Institute of Health and Nutrition started to operate the ''Health Foods Safety Information Network (http://humpty.nih.go.jp/food/)'' in March, 2003, and collection of data and construction of a database are in progress. The Ministry of Health, Labor and Welfare is also working to develop a similar system, and I am looking forward to their completion.

Distribution of health foods

The health foods that were identified as the cause of the above health damage were primarily purchased by individual import, but it was later revealed that they were also sold by domestic agents over the Internet, by mail-order systems, and at retail stores. To prevent such incidents, the ability of consumers to critically select goods must be improved.

To summarize the above 5 points, the formulation and enforcement of a ''Food Health Protection Law'' (tentative naming), which systematically regulates health foods, are urgently needed to prevent recurrence of similar incidents. Presently, the Ministry of Health, Labor and Welfare is evaluating such a law at the Evaluation Committee of Systems Related to Health Foods and other organizations. Also, the Fundamental

Table 9 Comparison of Information Provided as Package Inserts between Medicines and Health Foods (multiple vitamin preparations)

Description (Excerpt)	OTC drug	Nutrition functional food	Health food (Dietary supplement)
Brand name	Shin-Popon®-S	Multiple Vitamin	Multiple Vitamin
Components	10 vitamins and others	13 vitamins	10 vitamins
Indications or functions	Nutritional supplementation, weak constitution, nourishing and strengthening of the body	Vitamin C is a nutrient that supports the health of the skin and mucosa	Not mentioned
Dosage regimen or recommended dose	2 tablets at a time, once a day (Vitamin A: 2000 units)	1 tablet/day (Vitamin A: 1800 units)	2 tablets/day (Vitamin A: 1800 units)
Contraindica-tions	Pregnant women within 3 months of pregnancy and women who expect pregnancy must consult a pharmacist, *etc.* before they start taking this drug	Pregnant or breast-feeding women must consult a physician before they start taking this product	Not mentioned
Interaction, duplicated administration	who are being treated by physicians must consult with them	Those who are being medicated or treated on the outpatient basis must consult with their physicians	
Adverse reactions	If nausea, vomiting, diarrhea, and itching appear, stop taking the drug and consult a physician	If any physical abnormality is felt, stop taking the product	
Overdosing	Not mentioned	Intake of the product in large quantities does not contribute to the healing of the disease or promotion of the health	
Period of use	Consult a pharmacist or physician if no improvement is observed after taking the drug for about 1 month	Not mentioned	
Others	Yellowing of urine is no problem (Vitamin B_2)		

Law of Food Safety was established in May, 2003 although the law is not focused on health foods. In August, 2003, the Amended Health Promotion Law was enforced, and legislative control of announcements and advertisements that induce excessive expectations and disclosure of commercial names of the health foods that have caused serious health damages has been introduced. Thus, consumer-protection systems are being improved though slowly.

Conclusion

Diverse health foods are distributed in our country as well as in the United States and Europe. Also, along with the policies to reduce government control and the review of food-drug discrimination currently advanced by the administration, the numbers of health foods and their categories are expected to increase further. The occurrence of interstitial pneumonia due to concomitant use of *sho-saiko-to* and interferon-α, interaction between drugs including calcium blockers and GFJ, and the above pharmacokinetic interactions between medicines and SJW, which became topics in the late 1990's, are only the tip of the iceberg, and the advent of the second and third SJW is considered to be highly likely.

Therefore, in addition to scientific demonstration of functions and safety of health foods themselves, how quickly to accumulate and utilize information based on scientific evidence concerning interactions between medicines and health foods, which is particularly deficient, is expected to be a key to the ''proper use of health foods''. Moreover, the author believes that pharmacists are the most appropriate human resources that can play this role (advisory staff) (Table 10). Pharmacists are considered to be responsible for protecting people from the risk of health foods as well as medicines by appropriately distributing such information to a wide range of people *via* hospital pharmacies, community pharmacies, and drugstores. I would like to close this article by showing 6 points to be observed not only by medical professionals to do their duties but also patients and consumers in general to protect themselves from health damages associated with health foods in Table 11.

Table 10 Basic Concepts of Training of the Advisory Staff Concerning the Use of Functional Foods

Definition of the advisory staff	Individuals who can provide appropriate information concerning functional foods to consumers and whom consumers feel close and easy to talk to.
Persons who implement training	Private bodies appropriate in organization and management
Intended trainees	Management nutritionists, pharmacists, public health nurses, doctors, other specialists
Knowledge to be acquired by the advisory staff	(1) Proper methods for use or intake (2) Differences from medicines (3) Interactions among foods and between medicines and foods (4) Emphasis on health and nutrition in notes and descriptions (5) Basic knowledge for understanding of scientific evidence (6) Knowledge about foods and food additives (7) Knowledge about health and nutrition (8) Related laws (9) Viewpoints and protection of consumers (10) Market and overseas information

Excerpts from Shokuhatsu No. 0221002, Ministry of Health, Labor and Welfare (February 21, 2002).

Table 11 Six Items That Medical Professionals, Patients, and Consumers Must Observe for the Prevention of Health Damages Due to Health Foods

1. To eliminate products that are, or are suspected to be, unapproved or unauthorized medicines!
   1) Doesn't the product contain raw materials of medicines?
   2) Isn't the product prepared in the form of an ampoule, sublingual tablet, *etc*.?
   3) Doesn't the product claim to have indications?
   4) Isn't dosage regimen resembling that of a medicine mentioned?
2. To judge whether the health food is really necessary for the patient!
3. To have medical professionals to become familiar with differences between medicines and health foods and also to have patients understand them.
4. If the patient's condition permits, to recommend general medicines, functional foods, and supplements (JHFA) in this order (if there are products with the same active components).
5. To monitor health foods that patients report are very effective with particular attention.
6. To try to minimize the possibility of interactions between medicines and health foods and duplicated intake of the same active components.

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