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Tissue Distribution and Cytochrome P450 Inhibition of Sesaminol and Its Tetrahydrofuranoid Metabolites

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ABSTRACT: Sesame lignans such as sesamin, sesaminol, and sesamolin are major constituents of sesame oil, and all have a methylenedioxyphenyl group and multiple functions in vivo. It was previously reported that sesaminol, a tetrahydrofurofuran type lignin, was metabolized to mammalian lignans. The present study examined the tissue distribution of sesaminol in Sprague−Dawley (SD) rats. Changes in the concentration of sesaminol and its metabolites (sesaminol glucuronide/sulfate, hydroxymethylsesaminol-tetrahydrofuran, enterolactone, and enterodiol) were determined in tissues within a 24 h period after tube feeding (po 220 mg/kg) to SD rats. The concentrations of enterodiol and enterolactone were significantly higher than those of sesaminol and its tetrahydrofuranoid metabolites in the organs (liver, heart, brain, and kidney). This study demonstrates that sesaminol has potent inhibition of cytochrome P450 (CYPs), compared to tetrahydrofuranoid metabolites. The IC_{50} values of CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 for sesaminol were determined as 3.57, 3.93, 0.69, 1.33, and 0.86 μM, respectively. In addition, hydroxymethylsesaminol-tetrahydrofuran and enterodiol were weak inhibitors of CYP2C9 and CYP1A2, respectively.

KEYWORDS: *sesaminol, tetrahydrofuranoid lignans, tissue distribution, cytochrome P450*

INTRODUCTION

Lignans are phenolic compounds with a 2,3-dibenzylbutane structure formed from the dimerization of two cinnamic acid residues.[1] Sesame seeds contain very high levels (up to 2.5%) of furofuran lignans such as sesamin, sesamolin, and sesaminol glucosides. Sesame seed lignans have been reported to have health beneficial activities including modulation of fatty acid metabolism, inhibition of cholesterol absorption and biosynthesis, antioxidant and vitamin E-sparing effects, hypotensive effect, improvement of liver functions in connection with alcohol metabolism, and an antiaging effect.[2] Sesame lignans were converted to physiologically beneficial metabolites by intestinal microflora; they may exert antioxidative, anti-inflammatory, and estrogenic activities.[3]

Various xenobiotic-metabolizing enzymes and xenobiotic transporters, including cytochrome P450 (CYP), UDP-glucuronosyltransferase (UGT), and sulfotransferase (SULT), play major roles in the metabolism and disposition of xenobiotics such as environmental contaminants and therapeutic drugs. In general, CYPs carry out the oxidative metabolism of lipophilic compounds, and UGTs and SULTs convert the compounds into hydrophilic conjugates.[4] According to in vitro studies, when the lignans most commonly found in food (secoisolariciresinol, matairesinol, pinoresinol, lariciresinol, sesamin, and sesaminol triglucoside) are incubated with human fecal microflora, they are transformed to the tetrahydrofuranoid metabolites or enterolignans.[5−7] On the other hand, sesaminol, having methylenedioxyphenyl moieties in its structure, may require an additional oxidative demethylenation of the methylenedioxyphenyl ring for conversion to tetrahydrofuranoid lignans, sesaminol-6-catechol, methylated sesaminol-6-catechol, enterolactone (ENL), and enterodiol (END) (Figure 1).[7,8]

Natural products that cause induction or inhibition of metabolizing enzymes can result in drug interactions. For example, compounds that induce CYP3A will increase detoxification of CYP3A substrates, resulting in decreasing systemic drug concentrations and pharmacological effect. Alternatively, drugs such as flucloxacillin, which undergo bioactivation by CYP3A, will have enhanced toxicity.[9] Similar alterations in drug concentration and/or bioactivation are possible with enzyme inhibition. Inhibition of intestinal CYP3A4 by grapefruit can lead to increased circulation levels of amiodarone and other CYP3A4 substrates that have high first-pass metabolism.[10] The potential for drug interactions is of particular importance with lignan supplementation, because the target population (patients with cardiovascular disease, cancer, and diabetes) are likely on other medications as well. Cytochrome P450 enzymes, such as CYP3A4, have decreased activity in the elderly and patients with certain diseases.[11] Interindividual differences, due to differential exposure to environmental inducers and inhibitors, occur with both CYP and phase II enzymes.[12,13] Certain drug interactions do not manifest immediately, leading to missed adverse drug reaction diagnoses.[11] Interactions can occur at the hepatic or intestinal

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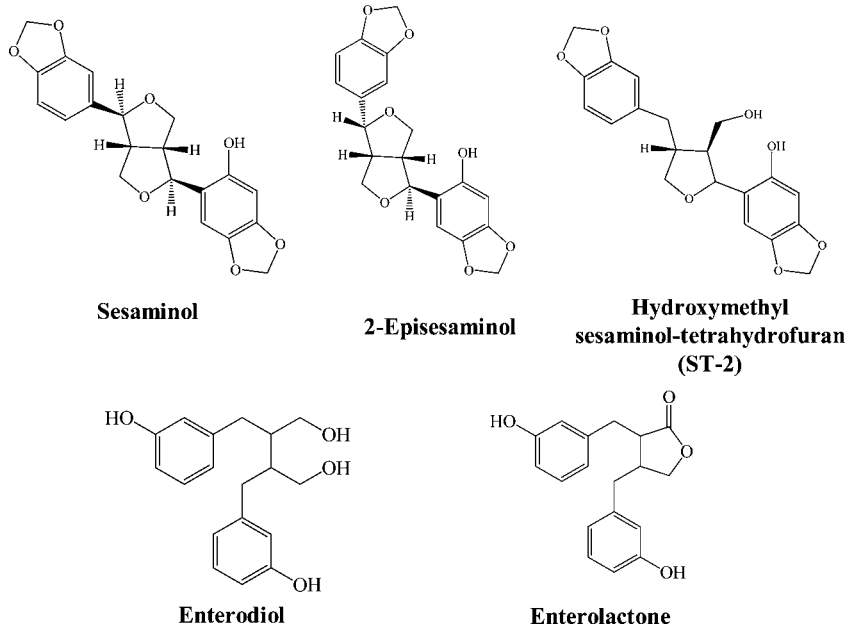

Figure 1. Chemical structures of sesaminol and its metabolites.[12]

enzyme level,[10,14] depending on the route of administration and substrate used. Phase II enzyme induction and inhibition is less often associated with negative drug interactions. However, such interactions can also alter systemic drug concentrations and toxic metabolite production. Unfortunately, drug-metabolizing enzyme interactions are not always predictable for a number of reasons: location of interaction, interindividual differences, and delayed onset of effect. Consequently, food−drug interactions involving sesame lignans may not be identified as such.

The bioavailability of sesaminol needs to be determined to clarify the function of the distributed and metabolized sesame lignans in vivo. However, few studies have attempted to measure the distribution and CYP inhibition of sesaminol and its metabolites. Methylenedioxyphenyl lignans (sesamin and episesamin) were previously reported as mechanism-based inhibitors of CYP 450 in rat bile and human liver microsomes.[15−17] In this study, sesaminol and its metabolites have methylenedioxyphenyl and tetrahydrofuranoid groups. We speculate that sesaminol and tetrahydrofuranoid type metabolites could interact with the P450 isozymes and affect xenobiotic metabolisms in vivo. Thus, we propose that the methylenedioxyphenyl and tetrahydrofuranoid type lignans in sesame could be potent inhibitors or inactivators of some CYP isoforms. The degree of inhibition could be closely related with the consumption amount of sesaminol and its metabolites. Nevertheless, there are no data available in the literature on the inhibition of sesaminol and its metabolites. In this study, we investigated the distribution of sesaminol and its main transformation metabolites in various parts of tissues. Tetrahydrofuranoid type metabolites of sesaminol present in the tissues were measured by LC-MS/MS. To understand the interference from metabolites in vivo, we also used pure individual compounds to study their effects on CYP450s.

MATERIALS AND METHODS

Materials and Chemicals. Cellulase (from *Aspergillus niger*), β-glucosidase (from almond), and sulfatase (type H-1, from *Helix pomatia*, containing sulfatase and β-glucuronidase) were obtained from Sigma-Aldrich (Poole, Dorset, UK). HPLC grade solvents were obtained from Mallinckrodt Baker (Phillipsburg, NJ, USA). All other chemicals were of analytical grade. Triply deionized water was used for all preparations. Enterolactone and enterodiol of 95% purity were purchased from ChromaDex (Santa Ana, CA, USA). Sesaminol, sesaminol triglucoside, and the major metabolite of 2-episesaminol and *R,R*-hydroxymethylsesaminol-tetrahydrofuran were extracted and purified as described previously.[4,18,19]

Animals and Diets. The experimental protocol was approved by the National Laboratory Animal Center (Taipei, Taiwan). Inbred male Sprague−Dawley (SD) rats [body wt 275 ± 25 g, mean ± SD] were purchased from the BioLASCO Experimental Animal Center (Taipei, Taiwan). Rats were housed in pairs in cages in a room with controlled temperature (20−22 °C), relative humidity (50−70%), and a 12−h light/dark cycle). Rats consumed their food (AIN 93 M diet, Purina Mills, St. Louis, MO, USA) ad libitum and had unlimited access to water. Their weight and food consumption were recorded weekly.

Distribution Experiment. Sesaminol was dissolved in 50% propylene glycol at 733 mg/mL. SD rats (n = 6) were orally administered via gastric gavage at a dose level of 220 mg/kg three times daily. At the end of the study, rats were anesthetized in the morning of the fourth day (2200 mg/kg, 10 doses) without overnight fasting. Rats were fully bled via the abdominal aorta. Liver, heart, lung, brain, and kidney were collected at 1, 3, 6, 9, and 24 h on the fourth day after administration, dissected, weighed, and immediately frozen in liquid nitrogen. The contents of sesaminol conjugated metabolites were processed and analyzed as plasma and tissues and then hydrolyzed by sulfatase; the termination of hydrolysis was accomplished by adjusting the pH to 7.4. The assays used in this study for analyses of sesaminol and its metabolites in the tissues have been validated in our laboratory.[20,21]

Determination of Sesaminol and Its Metabolites in Tissues. Identification of sesaminol metabolites was accomplished using LC-MS/MS with a Thermo HPLC system equipped with electrospray−ionization ion trap mass spectrometer (ThermoFinnigan LXQ Advantage, San Jose, CA, USA). Separation was achieved using a YMC Hydrosphere C18 column (2.0 × 150 mm i.d.; 5 μm, YMC, Tokyo, Japan). During the analyses, the ESI parameters were set as follows: capillary voltage, −49 V for negative mode; source voltage, 4.5 kV; source current, 100 μA; sheath gas flow rate, 35 au; capillary temperature, 350 °C; and tube lens voltage, −110 V.

MS/MS product ions were produced by the collision-activated dissociation of selected precursor ions in the collision cell of a two-dimensional linear ion trap mass spectrometer and the mass analyzed

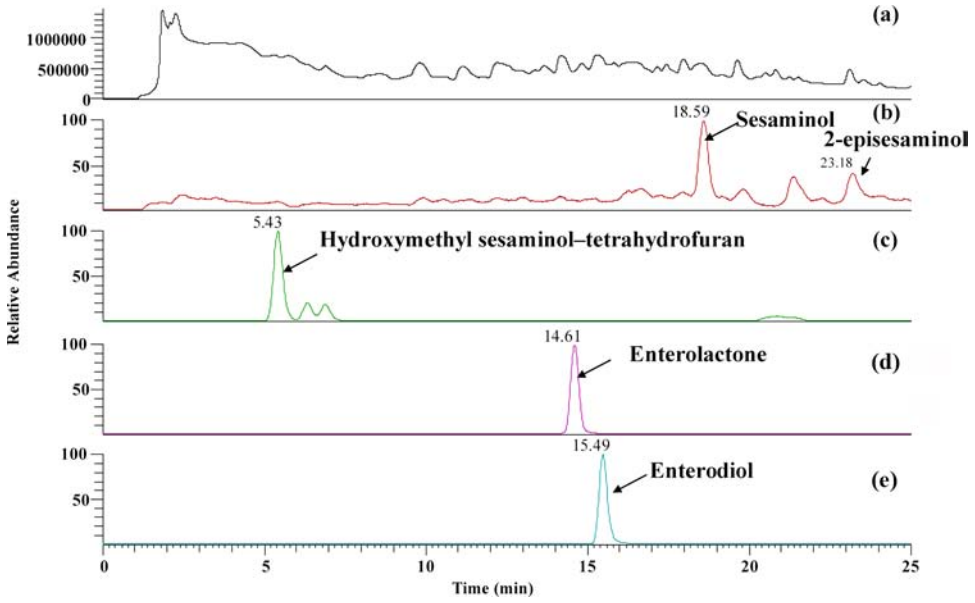

Figure 2. HPLC and SRM chromatograms of the analyzed sesaminol and its metabolites in rat liver: (a) A280; (b) sesaminol [m/z 369 → 271]; (c) hydroxymethylsesaminol-tetrahydrofuran [m/z 359 → 221]; (d) enterolactone [m/z 297 → 253]; (e) enterodiol [m/z 301 → 253].

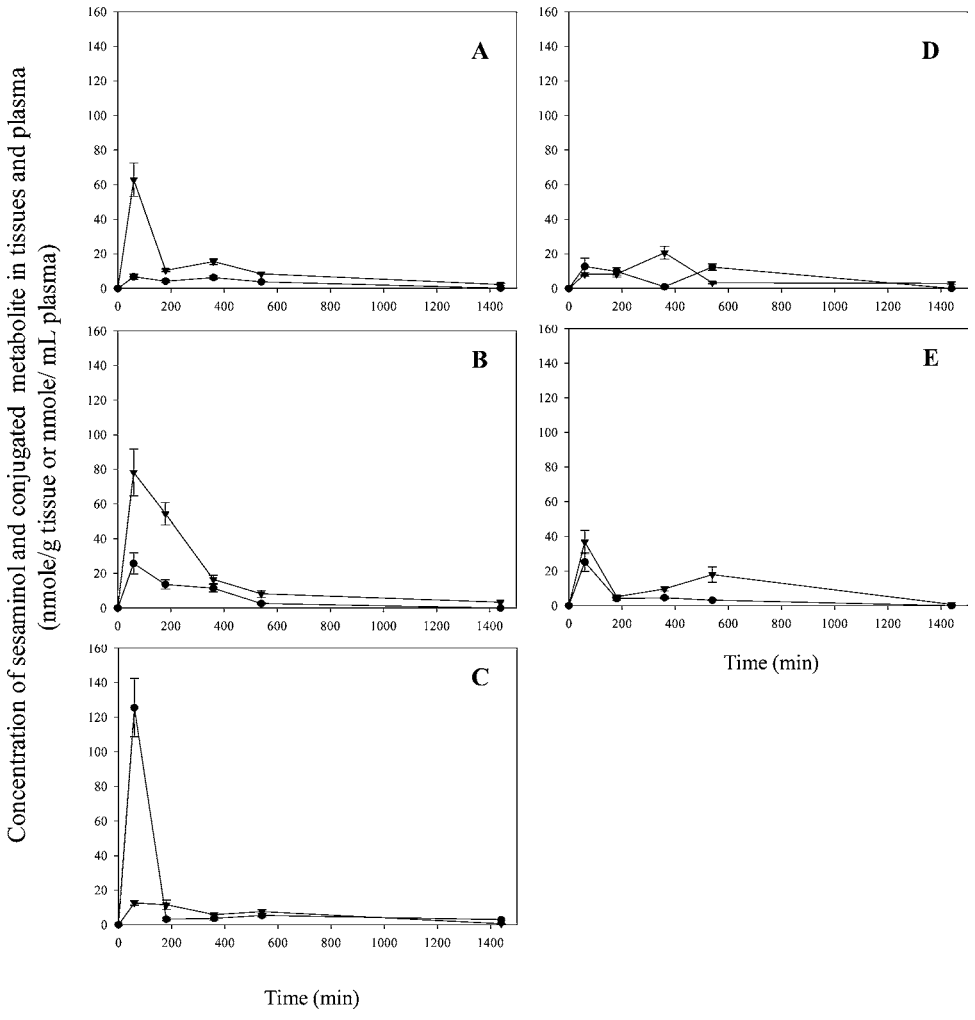

Figure 3. Time-dependent changes of sesaminol (●) and sesaminol glucuronide/sulfate (▼) concentrations in different rat tissues after oral administration of sesaminol (220 mg/kg): (A) liver; (B) heart; (C) lung; (D) brain; (E) kidney.

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Table 1. Pharmacokinetic Parameters of Sesaminol Free and Conjugated Forms in Rat Tissue[a]

	liver	lung	kidney	heart	brain
AUC[b] (min·μmol/mL or min·μmol/g)					
sesaminol	4.6 ± 1.3	18.0 ± 7.0	5.7 ± 2.9	8.2 ± 4.5	9.0 ± 7.1
sesaminol glucuronide/sulfate	19.5 ± 8.4*	11.3 ± 5.6	16.9 ± 14.2*	30.8 ± 14.8*	11.4 ± 7.3
C_{max}[c] (nmol/g)					
sesaminol	6.8 ± 1.4	126 ± 16.9	25.3 ± 5.6	25.8 ± 6.1	12.8 ± 4.9
sesaminol glucuronide/sulfate	62.9 ± 9.6*	12.7 ± 1.4*	36.8 ± 6.7	78.2 ± 13.5*	20.6 ± 3.7*
t_{max}[c] (min)					
sesaminol	60	60	60	60	60
sesaminol glucuronide/sulfate	60	60	60	60	360

[a]Data are expressed as the mean ± SD (n = 6). *, P < 0.05 compared with group sesaminol. [b]The area under the concentration−time curve (AUC) was calculated by conventional linear trapezoidal summation and was extrapolated to infinity. [c]The maximum concentration (C_{max}) and the time to reach the maximum concentration (t_{max}) were read directly from the concentration−time data for each subject in the tissues.

using the second analyzer of the instrument. Selected reaction monitoring was used to monitor five transitions for each analysis: sesaminol, m/z 369 → 271; hydroxymethylsesaminol-tetrahydrofuran m/z 359 → 221; enterodiol, m/z 301 → 253; enterolactone m/z 297 → 253, sesaminol-6-catechol, 357 → 207. All LC-MS/MS data were processed by Xcalibur version 2.0 data acquisition software.

The analytical methods for determining sesaminol and its metabolites (sesaminol glucuronide/sulfate, hydroxymethylsesaminol-tetrahydrofuran, enterolactone, and enterodiol) in tissues were developed and validated in a previous study.[22] Coefficients of variation of intraday and interday assays were <5% in the concentration range of 0.5−20.0 μg/mL. For the analysis of sesaminol, hydroxymethylsesaminol-tetrahydrofuran, enterolactone, and enterodiol, the lower limits of quantization were 0.2, 0.3, 0.1, and 0.3 μg/mL and the limits of detection were 0.05, 0.07, 0.03, and 0.04 μg/mL, respectively.

CYP450 Inhibition Assay. Five microliters of 3× P450 Baculosomes/Vivid Substrate or 3× control Baculosomes/Vivid Substrate in assay buffer (0.2× assay buffer for CYP1A2, 2C9, 2C19, 2D6, and 3A4 assays) was dispensed to the assay plate. The concentration of each test compound (sesaminol, episesaminol, hydroxymethylsesaminol-tetrahydrofuran, enterolactone, enterodiol, and sesaminol triglucoside) was tested in duplicate, in the presence of P450, to assess inhibition, as well as in the presence of control to detect autofluorescent compounds. In the control wells 1% DMSO in the control wells was used in the presence of P450 (n = 16) to represent 100% activity or in the presence of control (n = 16) to represent 0% activity. Plates were incubated with 5 μL of 3× Regeneration System/NADP$^+$ added to all wells for 10 min prior to the start of the reactions. Plates were shaken for 30 s as above and incubated for 25 min. The reaction was stopped by the addition of 5 μL of 0.5 M Tris base (pH 10.5) to all wells and shaken for 30 s as above. Plates were then read on a Safire (Tecan, Durham, NC, USA) plate reader using the fluorescent excitation and emission settings indicated.

IC_{50} Determination. Sesaminol and sesaminol triglucoside were tested in a 10-dose IC_{50} mode with 3-fold serial dilutions starting at 100 μM. Ketoconazole and furafylline were used as positive controls in a 10-dose IC_{50} mode with 5-fold serial dilutions starting at 20 μM. Percent activity of sample wells was plotted versus the log value of each test compound concentration to generate a 10-point dose−response curve. IC_{50} values (the concentration of the inhibitor causing 50% inhibition of the original enzyme activity) were calculated on the basis of the curves of mean enzyme activity versus inhibitor concentration.

Statistical Analysis. All samples were extracted and analyzed in triplicate. Tissues of six rats were pooled before analysis. Sesaminol and its metabolite concentrations were expressed as nanomoles per gram of tissue. Data were analyzed by ANOVA and Tukey's analysis of variance. Differences were considered to be statistically significant at P < 0.05.

RESULTS

Tissues Distribution Study of Sesaminol. Determination of sesaminol and its metabolites was conducted using LC-MS. The chromatograms show that sesaminol in liver was largely present as phase II conjugates. The conversion to other metabolites was detected as 2-episesaminol, sesaminol-6-catechol, methylated sesaminol-catechol, hydroxymethylsesaminol-tetrahydrofuran, enterolactone, and enterodiol (Figure 2). To investigate the distribution of sesaminol and conjugated metabolites in rats, we administered sesaminol and conjugated metabolites to rats and determined their concentrations in tissues within 24 h after administration. In the tissues, the concentrations of sesaminol and conjugated metabolites reached a maximum at 60 min after administration and were rarely found after 9 h (Figure 3). It is interesting that the concentrations of sesaminol conjugated metabolites were significantly greater than free form in the brain and liver, despite equal amounts being administered. In the lung, the concentrations of sesaminol were also significantly greater than that of the conjugated form the tissues, and the AUCs of sesaminol metabolites (glucuronide/sulfate) were significantly greater than that of sesaminol. The conjugated metabolites of sesaminol reached the highest peak of concentration (C_{max}) in both liver and heart. The free form sesaminol also reached high peak concentrations in the lung (126 ± 16.9 nmol/g), as high as the conjugated metabolites of sesaminol. Peak concentration values were recorded 60 min (t_{max}) after administration for sesaminol (Table 1). In the liver, kidney, heart, and brain, the sesaminol concentration value was low at 60 min except in lung (Figure 3). Thereafter, a gradual decrease in this concentration was observed during the course of the experiment. The highest concentrations of peak were detected at 60−180 min after administration. Sesaminol and conjugated metabolites were rarely found in these tissues after 9 h.

An important parameter for pharmacokinetic analyses of a drug is the area under the curve (AUC), which represents the total drug exposure integrated over time. After administration, the AUCs of sesaminol were in the following order: lung > brain > heart > kidney > liver (Table 1). It is important to note that AUCs of sesaminol metabolites (glucuronide/sulfate) in kidney, liver, and heart were increased remarkably. However, the AUC of free form sesaminol was higher than that of the conjugated metabolites in lung.

In addition, sesaminol was metabolized to hydroxymethylsesaminol-tetrahydrofuran, END, and ENL by intestinal microflora. In the liver and kidney, END and ENL concentrations were also significantly greater than in the lung (Table 2). A

Table 2. Tissue Concentration (Nanomoles per Gram) of Sesaminol and Its Tetrahydrofuranoid Metabolites in Rat at 24 h[a]

	liver	lung	kidney	heart	brain
sesaminol	21.3 ± 0.6cd	141 ± 3.3c	37.1 ± 1.3d	53.5 ± 1.9cd	35.9 ± 1.5cd
episesaminol	2.31 ± 0.6e	3.0 ± 0.1e	0.7 ± 0.1e	3.4 ± 0.2e	2.9 ± 0.3e
hydroxymethylsesaminol-tetrahydrofuran	143 ± 80.4c	132 ± 112bc	213 ± 23.7c	133 ± 52.9c	131.2 ± 111.5c
enterodiol	751 ± 122b	361 ± 93.5b	754 ± 21.3b	491 ± 54.1ab	430.5 ± 23.2ab
enterolactone	1910 ± 144a	583 ± 20.5a	1144 ± 73.7a	542 ± 30.4a	483.4 ± 54.1a

[a]Data are expressed as the mean ± SD. Data in the same row with different letters are significantly different at $P < 0.05$.

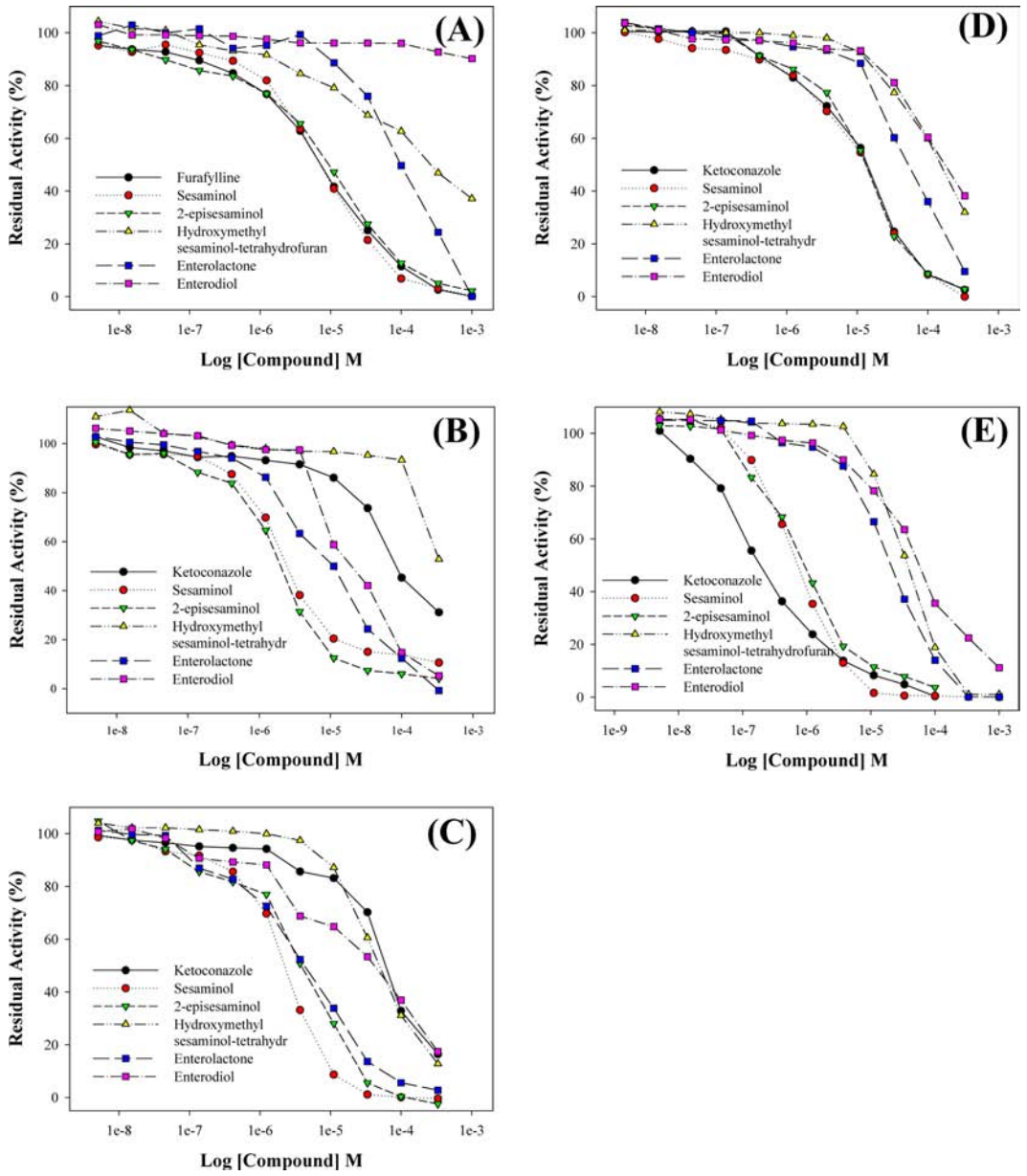

Figure 4. Dependence of inhibition activities catalyzed by CYP1A2 (A), 2C9 (B), 2C19 (C), 2D6 (D), and 3A4 (E) on the concentrations of sesame lignans and its metabolites.

significant diversity of ENL and END concentrations was observed in the tissues. Peak values were reached at 24 h after administration, with the liver and kidney exhibiting higher concentrations than the lung, heart, and brain (Table 2).

CYP 450 Inhibitory Effect of Sesaminol and Sesaminol Triglucoside in Vitro. Phytochemicals may interact with cytochrome P450 and thus raise the potential of food−drug interactions. To determine whether sesaminol or its metabolites are inhibitors of CYP1A2, 2C9, 2C19, 2D6, and 3A4 activity, experiments were carried out in a microsomal test system to determine the mechanism. IC_{50} values of positive controls, ketoconazole and furafylline, ranged between 0.13 and 3.54 μM. Sesaminol and its metabolites showed a concentration-dependent inhibitory effect on CYP1A2, 2C9, 2C19, 2D6, and 3A4 activity (Figure 4). However, sesaminol and its epimer showed a strong inhibitory effect on CYP3A4 and 2C9 with

Table 3. Cytochrome P450 Inhibitory Activities (IC_{50}) of Various Tetrahydrofuranoid Metabolites from Sesaminol[a]

lignan	Cyp450 IC_{50} (μM)				
	CYP1A2	CYP2D6	CYP2C9	CYP2C19	CYP3A4
sesaminol	0.9 ± 0.4b	4.0 ± 1.2a	0.9 ± 0.2a	0.8 ± 0.2a	0.7 ± 0.2b
episesaminol	3.6 ± 1.5c	3.9 ± 1.0a	0.7 ± 0.1a	1.3 ± 0.3a	0.9 ± 0.2b
hydroxymethylsesaminol-tetrahydrofuran	73.6 ± 3.2d	46.1 ± 3.4c	>10000	16.1 ± 2.4d	33.6 ± 3.1d
enterolactone	3.4 ± 1.0c	18.5 ± 1.2b	3.1 ± 0.4b	1.3 ± 0.5a	19.4 ± 1.2c
enterodiol	>10000	58.5 ± 3.4d	6.5 ± 0.8c	9.9 ± 1.8c	52.2 ± 4.2e
ketoconazole	ND	3.5 ± 0.8a	3.5 ± 0.7b	2.2 ± 0.2b	0.1 ± 0.1a
furafylline	0.3 ± 0.1a	ND	ND	ND	ND

[a]Data are expressed as the mean ± SD. Data in the same row with different letters are significantly different at $P < 0.05$.

IC_{50} values of 0.86 ± 0.17 and 0.69 ± 0.14, respectively (Table 3). This result shows the mechanism-based inhibitory effect of CYP 450s from a methylenedioxyphenyl group. In sesame lignans, sesaminol had a higher inhibitory activity than its metabolites. IC_{50} values of episesaminol obtained ranged between 0.69 and 3.93 μM. Sesaminol and its epimer showed the strongest inhibition of CYPs (CYP1A2, 2C9, 2D6, 2C19, and 3A4) and its metabolites (hydroxymethylsesaminol-tetrahydrofuran and enterodiol), the weakest.

DISCUSSION

In a previous study, we found that sesaminol triglucoside (hydrophile) was administered through gastric and small intestinal walls because the sesaminol triglucoside concentrations were extremely high not only in the plasma but also in the heart and liver.[15] In this study, we show that sesaminol may be incorporated into the liver and then transported to other tissues such as the lung, heart, kidney, and brain. Sesaminol might be able to change permeability (higher lipophilicity) via the lymphatic system without being metabolized by liver phase II enzyme. However, the absorbability conditions for sesaminol triglycoside and sesaminol were significantly different. Sesaminol conjugated metabolites (glucuronide/sulfate) were widely distributed in rat tissues, with the highest concentrations in liver and heart and the lowest in brain. Sesaminol may be, at first, incorporated into the liver and then transported to other tissues (lung, kidney, and brain) via the hematological system, whereas others were transported by lymphatic absorption. Sesaminol is removed from tissues within 24 h after oral administration in rats in a route and phenomenon similar to those of sesamin. Furthermore, metabolites of sesaminol may be further converted to mammalian lignans by intestinal microbiota. A previous study reported that sesaminol triglucoside and sesaminol were converted, by fermentation with fecal microbiota, to hydroxymethylsesaminol-tetrahydrofuran, ENL, and END.[4,23] In healthy humans, the consumption of sesame seed increased plasma END and ENL concentrations; ENL was the major metabolite of sesame lignans.[23] A previous study reported that sesaminol was metabolized by cytochrome P450 in rat liver, which converted it to methylenedioxyphenyl to a hydrophenyl (catechol) moiety.[24] These metabolites (hydroxymethylsesaminol-tetrahydrofuran, END, and ENL) appeared to be absorbed and metabolized in the distal intestine (cecum, large intestine, and rectum), where hydroxymethylsesaminol-tetrahydrofuran might undergo very limited metabolism.[22] The results indicated that a low amount of hydroxymethylsesaminol-tetrahydrofuran was detected, reflecting its low concentration by the tail end of intestine. These metabolites were absorbed from the intestines into the body. According to the data presented in the present study, ingestion of sesaminol by experimental animals results in elevated hydroxymethylsesaminol-tetrahydrofuran, END, and ENL levels in tissues.

Interactions between drugs and coadministered compounds are a major concern in food−drug interactions. The most common type of pharmacokinetic-based interactions involves drug-metabolizing enzyme induction and inhibition. A preliminary screening of CYP enzyme interactions is the first step in predicting the potential for drug interactions. CYP1A2, 2C9, 2C19, 2D6, and 3A4 were the major targets in humans for drug interactions.[25] Drug interactions resulting from CYP inhibition and induction can cause increased toxic metabolite formation and increased/decreased detoxification, leading to an altered circulatory drug concentrations. Phytochemicals may lead to alterations in stable drug concentrations as well, resulting in potentially serious consequences.[26] For the lignans to be used therapeutically, the safety of administration alone and in conjunction with other drugs must be determined. The primary cause of drug interactions was induction and inhibition of CYPs and phase II enzymes. Previously reported methylenedioxyphenyl lignans were mechanism-based inhibitors of CYP3A4.[27] Preliminary studies indicate that lignans in sesame inhibit CYP3A in vivo.[28,29] The flavonolignan Silybin shows mechanism-based inhibition of CYP3A4 and CYP2C9 as well as potent anti-CYP1A activity.[30,31] Nordihydroguaiaretic acid, a structurally similar lignan, also shows broad-spectrum inhibition against CYPs, particularly CYP1A.[32] Lignans isolated from Schizandrae Fructus also inhibit CYP enzymes.[33] Mammalian lignans undergo enterohepatic circulation. Consequently, the liver is exposed to prolonged and high levels of lignans that may be significantly greater than systemic levels. Sesamin contains two methylenedioxyphenyl groups; it is likely that sesamin displays a mechanism-based inhibition of CYP2C9 and 1A2;[14] furthermore, sesaminol, indeed, exhibited a mechanism-based inhibition of CYPs. Similarly to sesamin, sesaminol was further metabolized to 2-episesaminol; however, the contribution of each inhibition was significantly different between 2-episesaminol and sesaminol. Sesaminol was further metabolized to tetrahydrofuranoid lignans; however, the contribution of each inhibition was significantly different among hydroxymethylsesaminol-tetrahydrofuran, END, and ENL. Interestingly, the tetrahydrofuranoid lignans from intestinal metabolism showed significant amounts of END and ENL in the tissues. In this study, we have revealed significantly different metabolites by microflra for sesaminol, resulting in different inhibition of CYP effects.

A preliminary screening to determine if sesaminol and its metabolites interact with key drug-metabolizing enzymes was pertinent to predicting the potential for drug interactions. The concentrations of sesaminol and its metabolites in liver were needed for the determination of their potential to cause enzyme

interactions. The concentrations of sesaminol in the liver and kidneys have been clearly determined in rats. Irregular absorption of sesaminol and phase II metabolites may result in the appearance of double peaks (1 and 6 h) in liver concentration−time profiles after oral administration of sesaminol and phase II metabolites. Possible reasons for the double-peak phenomenon have been proposed, such as enterohepatic circulation and an irregular gastric emptying pattern.[34] However, the levels of sesaminol and phase II metabolites in liver and kidney can be hypothesized from CYP inhibition. Tissue distribution results in the lowest levels of sesaminol in the liver and kidney, but sesaminol and its epimer have potent inhibition of CYPs. Sesaminol can cause inhibition of CYP enzymes in the gastrointestinal tract or liver and have the greatest impact on absorption by increasing the bioavailability of orally coadministered CYP substrates. Inhibition of hepatic and intestinal enzymes can also alter elimination through metabolism. Hydroxymethylsesaminol-tetrahydrofuran and enterodiol were not inhibitors of CYP1A2 and CYP2C9, respectively. The inhibitory effects of sesaminol and part of its metabolites were determined on the basis of potential inhibitory effect of P450 isozymes on CYP 1A2, 2C9, 2C19, 2D6, and 3A4.

In conclusion, this study demonstrates that, with intragastric administration, sesaminol inhibited the activity of CYP. Intragastric administration of sesaminol to rats increased the $AUC_{0-\infty}$ and C_{max} values in lung, compared with other tissues. Therefore, sesaminol crosses the lymphatic system into the body. However, sesaminol was metabolized to tetrahydrofuran metabolites by microflora and absorbed from intestinal mucosa to hepatocytes. Sesaminol and its metabolites inhibited the activity of CYP, and the concentrations of these lignans in the tissue distribution might have altered. In addition, sesaminol exerted a much stronger inhibiting effect on CYP than its metabolites. Sesaminol and its epimer are potent mechanism-based inhibitors of CYP, which in turn interfered with methylenedioxyphenyl and tetrahydrofuran groups, simultaneously. The present findings suggest that it is critical to assess the potential interactions between sesaminol and its metabolites to avoid clinically unwanted food−drug interactions in sesame lignan-rich diets.

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Notes

The authors declare no competing financial interest.

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