Metabolism of Sesamin by Cytochrome P450 in Human Liver Microsomes

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ABSTRACT:

Metabolism of sesamin by cytochrome P450 (P450) was examined using yeast expression system and human liver microsomes. Saccharomyces cerevisiae cells expressing each of human P450 isoforms (CYP1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, 2E1, and 3A4) were cultivated with sesamin, and monocatechol metabolite was observed in most of P450s. Kinetic analysis using the microsomal fractions of the recombinant S. cerevisiae cells revealed that CYP2C19 had the largest k_cat/K_m value. Based on the kinetic data and average contents of the P450 isoforms in the human liver, the putative contribution of P450s for sesamin metabolism was large in the order of CYP2C9, 1A2, 2C19, and 2D6. A good correlation was observed between sesamin catecholization activity and CYP2C9-specific activity in in vitro studies using 10 individual human liver microsomes, strongly suggesting that CYP2C9 is the most important P450 isoform for sesamin catecholization in human liver. Inhibition studies using each anti-P450 isoform-specific antibody confirmed that CYP2C9 was the most important, and the second-most important P450 was CYP1A2. We also examined the inhibitory effect of sesamin for P450 isoform-specific activities and found a mechanism-based inhibition of CYP2C9 by sesamin. In contrast, no mechanism-based inhibition by sesamin was observed in CYP1A2-specific activity. Our findings strongly suggest that further studies are needed to reveal the interaction between sesamin and therapeutic drugs mainly metabolized by CYP2C9.

Introduction

Sesamin is a major lignan in sesame, and its biological effects, such as antioxidant effect (Ikeda et al., 2003; Nakai et al., 2003), anticarcinogenic effects (Hirose et al., 1992; Miyahara et al., 2000), and suppression of hypertension (Miyawaki et al., 2009), have been extensively studied by many researchers. Thus, sesamin seems to be one of the most reliable food factors, the physiological effects of which can be expected by individuals taking it as a supplement or remedy. Meanwhile, some food factors are known to affect the xenobiotic metabolism. For example, some flavonoids show potent inhibitions of cytochromes P450 (P450s) and interfere with the metabolism of therapeutic drugs (Cermak and Wolffram, 2006). Furthermore, there have been some reports of mechanism-based inhibition (MBI) of P450s by methylenedioxyphenyl (MDP) compounds (Nakajima et al., 1999; Murray, 2000; Chatterjee and Franklin, 2003; Usia et al., 2005). Usia et al. (2005) demonstrated that some lignans that contain the MDP group have potent MBI of CYP3A4. Because sesamin has two MDP groups, it might cause MBI of some P450s. However, to the best of our knowledge, no reports on MBI of P450s by sesamin have been published. Thus, in this study, we examined whether sesamin could cause MBI.

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ABBREVIATIONS: P450, cytochrome P450; MBI, mechanism-based inhibition; MDP, methylenedioxyphenyl; DMSO, dimethyl sulfoxide; HPLC, high-performance liquid chromatography.

Nakai et al. (2003) demonstrated that sesamin was metabolized to mono- and dicatechol metabolites in rat liver. They assumed that some P450s were involved in sesamin catecholization, because MDP compounds were demethylated by P450-dependent oxidation (Kumagai et al., 1991; Murray, 2000). Sesamin was also converted to some metabolites, including mono- and dicatechol metabolites, by in vitro fermentation of human feces or in vivo administration (Penalvo et al., 2005; Liu et al., 2006). Moreover, the monocatechol compound was also detected as a human urinary sesamin metabolite (Moazzami et al., 2007). Liu et al. (2006) proposed tentative metabolic pathways of sesamin. Among the 11 kinds of the metabolites, mono- and dicatechol metabolites, which appear to be metabolized by P450s, are known to have high antioxidative activities (Nakai et al., 2003; Miyake et al., 2005). It was reported that sesamin elevated CYP2B and CYP4A mRNA levels in rats (Tsurukoa et al., 2005; Ikeda et al., 2007) and CYP1A activity in rainbow trout (Trattner et al., 2008). In addition, sesamin inhibited CYP4F2 to elevate tocopherol levels (Sonntag and Parker, 2002). However, to the best of our knowledge, there is no report to identify the P450 isoforms responsible for sesamin metabolism in humans or to estimate the drug-sesamin interaction.

To predict drug metabolism in the human body, we established a yeast expression system for human P450s and showed its usefulness for the prediction of drugs or environmental contaminants (Imaoka et al., 1996; Hayashi et al., 2000; Sakaki and Inouye, 2000; Inouye et al., 2002). In this study, the yeast expression system and human liver microsomes were used to identify a P450 isoform responsible for the
metabolism of sesamin in the human body. In addition, we describe the mechanism-based inhibition of CYP2C9 by sesamin.

Materials and Methods

Materials. Sesamin, sulfaphenazole, and (+)-N-3-benzylirinanol were purchased from Sigma-Aldrich (St. Louis, MO). NADPH was purchased from Oriental Yeast Co., Ltd. (Tokyo, Japan). Human single donor liver microsomes (HG43, HH47, HH18, HH74, HH77, HG95, HH715, HH581, HG3, and HH714) and a 50 donor human liver microsome pool were purchased from BD Gentest (Woburn, MA). Polyclonal antibodies against each of four human P450s (1A2, 2C9, 2C19, and 2D6) were purchased from Nihon Nosan Kogyo (Yokohama, Japan). The recombinant Saccharomyces cerevisiae AH22 cells expressing each of 11 human P450s (CYP1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, 2E1, and 3A4) with the vector pGyr were kindly provided by Sumitomo Chemical Co., Ltd. (Osaka, Japan). The vector pGyr is an episomal S. cerevisiae/Escherichia coli shuttle vector that contains a 2 μM DNA ori, a Leu2 gene as a marker, an S. cerevisiae NADPH-P450 reductase gene, a Puc ori, an Amp’r, and a glyceraldehyde-3-phosphate dehydrogenase primer and terminator derived from Zygosaccharomyces rouxii. The microsomes prepared from the recombinant S. cerevisiae cells expressing human P450s were purchased from Sumika Chemical Analysis Service (Osaka, Japan). Sesamin monocatechol and dicatechol were obtained by using rat liver microsomes and were used as authentic standards. All other chemicals were purchased from standard commercial sources of the highest quality available.

Methods. Measurement of P450 Hemoproteins. The contents of P450 hemoprotein in the recombinant yeast cells were measured as described previously (Oeda et al., 1985). Yeast cells (100-ml culture) were harvested during logarithmic growth phase, washed twice by suspension in 100 mM potassium phosphate buffer (pH 7.4), and then suspended in 5 ml of the buffer. The concentration of P450 hemoprotein in the whole-cell fraction or microsomal fraction was determined from the reduced CO-difference spectrum using a difference of the extinction coefficients at 450 and 490 nm of 91 mM⁻¹ cm⁻¹ (Omura and Sato, 1964).

Results

Identification of the Metabolite of Sesamin. Figure 1A shows the HPLC profiles of sesamin and its metabolite by the recombinant yeast cells expressing CYP2C19. One major metabolite, M1, was observed at a retention time of 25.3 min, and eluted with authentic sesamin monocatechol with cochromatography (data not shown). The same metabolite (M1) was detected in microsomes of recombinant yeast cells expressing CYP2C19 (Fig. 1B). To confirm the chemical structures of the metabolites, we collected the metabolites in the effluents from HPLC and subjected them to mass spectrometric analysis. Relative intensities (percent) of major ion fragments of the authentic standard of sesamin and its metabolite were as follows: sesamin, m/z
319 (M+H-2H2O), 4%; m/z 337 (M+H-H2O), 100%; m/z 355 (M+H) 55%; and the metabolite M1, m/z 307 (M+H-2H2O), 4%; m/z 325 (M+H-H2O), 100%; m/z 343 (M+H) 43%. These results strongly suggest that M1 was monocatechol metabolite of sesamin (Fig. 1). Other metabolites, such as the dicatechol metabolite, were not detected.

Sesamin Catecholization by Human P450s. Table 1 shows the conversion ratio of sesamin catecholization by recombinant yeast cells expressing each of human P450 isoforms. Only monocatechol was detected as a metabolite of sesamin for different P450 isoforms. It is noted that all of the human P450s except for CYP2E1 showed activity. Specific activity per P450 molecule based on the normalized conversion ratio in Table 1 indicated that CYP1A1, 1A2, 2B6, 2C9, 2C19, and 2D6 had high activity. Of these P450s, however, CYP1A1 and 2B6 are considered to be minor P450s whose contents in human liver are lower than the other four P450s. Thus, we selected CYP1A2, 2C9, 2C19, and 2D6 to identify essential P450s that are responsible for sesamin catecholization in human liver.

Kinetic Parameters of CYP1A2, 2C9, 2C19, and 2D6 for Sesamin Catecholization. Table 2 shows kinetic parameters determined by using microsomes of recombinant yeast cells expressing each of four P450s, CYP1A2, 2C9, 2C19, and 2D6. The kcat/Km value was high in order of CYP2C19, 2D6, 2C9, and 1A2, suggesting that CYP2C19 is the most efficient enzyme for monocatecholization of sesamin among the 11 human P450s examined in this study. However, the average content of CYP2C19 in human liver is only 1% from the previous reports (Shimada et al., 1994; Inoue et al., 1997), and our Western blots analysis of 50-donor pooled human liver microsomes confirmed these results (data not shown). To predict contribution of each P450 for sesamin metabolism in human body, we consider the value of (kcat/Km) × (the relative content (percent) of each P450 in human liver). The relative contents are 1% for CYP2C19, 2% for CYP2D6, 13% for CYP1A2, and 20% for 2C9 (Shimada et al., 1994; Inoue et al., 1997). Table 2 demonstrates that the putative contribution

### Table 1

<table>
<thead>
<tr>
<th>P450</th>
<th>Conversion Ratio</th>
<th>P450 Conc.</th>
<th>Normalized Conversion Ratio</th>
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<tr>
<td>1A1</td>
<td>0.040</td>
<td>2.6</td>
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<td>1A2</td>
<td>0.56</td>
<td>10</td>
<td>0.054</td>
</tr>
<tr>
<td>2A6</td>
<td>0.053</td>
<td>64</td>
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</tr>
<tr>
<td>2B6</td>
<td>0.30</td>
<td>17</td>
<td>0.017</td>
</tr>
<tr>
<td>2C8</td>
<td>0.068</td>
<td>99</td>
<td>0.001</td>
</tr>
<tr>
<td>2C9</td>
<td>3.4</td>
<td>104</td>
<td>0.033</td>
</tr>
<tr>
<td>2C18</td>
<td>0.56</td>
<td>170</td>
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</tr>
<tr>
<td>2C19</td>
<td>5.9</td>
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</tr>
<tr>
<td>2D6</td>
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<td>35</td>
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</tr>
<tr>
<td>2E1</td>
<td>0.00</td>
<td>88</td>
<td>0.000</td>
</tr>
<tr>
<td>3A4</td>
<td>0.16</td>
<td>51</td>
<td>0.003</td>
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*This value is the conversion ratio per nanomolar of P450.

### Table 2

<table>
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<tr>
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<th>km</th>
<th>kcat/km</th>
<th>Contribution</th>
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<td>1A2</td>
<td>3.6</td>
<td>1.5</td>
<td>0.24</td>
<td>38</td>
</tr>
<tr>
<td>2C9</td>
<td>2.2</td>
<td>0.11</td>
<td>0.41</td>
<td>100</td>
</tr>
<tr>
<td>2C19</td>
<td>5.0</td>
<td>1.8</td>
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<td>27</td>
</tr>
<tr>
<td>2D6</td>
<td>2.8</td>
<td>0.48</td>
<td>0.48</td>
<td>12</td>
</tr>
</tbody>
</table>

*Kcat and km values represent mean ± S.D. from three separate experiments.

*Putative contributing ratio is the value of (kcat/km) × (the relative content (percent) of each P450 isoform in human liver). The average contents of each P450 isoform in human liver are 1A2:13, 2C9:20, 2C19:1, 2D6:2%, respectively (Shimada et al., 1994; Inoue et al., 1997).
Correlation between Sesamin Catecholization Activity and Each P450-Specific Activity in Human Liver Microsomes. To confirm the prediction that CYP2C9 is essential for the metabolism of sesamin in human liver, we examined the correlation between sesamin catecholization activity and each P450-specific activity using human single donor liver microsomes. Figure 2 shows sesamin catecholization activity. Activity range was 2.5-fold in sesamin catecholization (Fig. 2) and 6.3-fold in diclofenac 4'-hydroxylation among 10 human liver microsomes, respectively. These data suggest that the interindividual difference of sesamin catecholization is not so large. As shown in Fig. 3A, good correlation was observed between sesamin catecholization activity and diclofenac 4'-hydroxylation activity, which is known to be a CYP2C9-specific activity ($r = 0.94$). On the other hand, phenacetin $O$-deethylolation activity, which is known to be a CYP1A2-specific reaction, showed a little correlation ($r = 0.33$) with sesamin catecholization (Fig. 3B). Both $S$-mephenytoin 4'-hydroxylation activity and bufuralol 1'-hydroxylation activity, which are known to be CYP2C19- and CYP2D6-specific reactions, respectively, showed almost no correlation with sesamin catecholization (data not shown). These results clearly demonstrate that CYP2C9 is a major P450 isoform of sesamin catecholization in human liver.

Inhibition of Sesamin Catecholization in Human Liver Microsomes by Anti-P450 Antibody. Figure 4 shows the effect of antibodies against human P450s on sesamin catecholization in the pooled human liver microsomes at different sesamin concentrations, 5 μM (Fig. 4A) or 50 μM (Fig. 4B). At 5 μM sesamin, catecholization was significantly inhibited by anti-CYP2C9 antibody. In contrast, at 50 μM sesamin, catecholization was significantly inhibited by anti-CYP2C9 antibody as well as anti-CYP1A2 antibody, indicating that the contribution of CYP1A2 is larger at 50 μM than at 5 μM. These results seem to be consistent with the fact that the $K_m$ value of CYP1A2 is significantly larger than that of CYP2C9 (Table 2). At both 5 and 50 μM, catecholization was slightly inhibited by anti-2C19 antibody but was not inhibited by anti-2D6 antibody. It should be noted that the anti-CYP2C19 antibody has some cross-reactivity with CYP2C9, judging from Western-blot analysis using the recombinant yeast microsomes (data not shown). Thus, the effect of anti-CYP2C9 antibody in Fig. 4 appears to be overestimated because of its cross-reactivity with CYP2C9.

Inhibition of Sesamin Catecholization in Human Liver Microsomes by CYP2C9- or CYP2C19-Specific Inhibitor. To confirm that CYP2C9 is the most essential P450 isoform but CYP2C19 is not, we examined the effect of chemical inhibitors for human CYP2C9 (sulfaphenazole) and CYP2C19 [(+)-N-3-benzyl nirvanol]. The $K_i$ values of sulfaphenazole and (+)-N-3-benzyl nirvanol in the human liver microsomes were reported to be 0.12 μM (Miners et al., 1988) and 0.24 μM (Suzuki et al., 2002), respectively. As expected, sulfaphenazole showed a remarkable inhibition of sesamin catecholization activity in pooled human liver microsomes. The $K_i$ value was estimated to be $0.24 \pm 0.03$ μM, regarding sulfaphenazole as a competitive inhibitor. In contrast, the activity was hardly reduced even in the presence of 5 μM (+)-N-3-benzyl nirvanol. These results strongly suggest that CYP2C9 is the most essential P450 isoform for sesamin monocatecholization in human liver, whereas the contribution of CYP2C19 is much lower than CYP2C9.

Correlation between Sesamin Catecholization Activity and Each P450-Specific Activity in the Presence of Anti-CYP2C9 Antibody. To examine a contribution of other P450 isoforms, we further examined the correlation between sesamin catecholization activity and each P450 activity in the presence of anti-CYP2C9. As shown in Fig. 3C, sesamin catecholization activity and phenacetin $O$-deethylolation activity, which is known to be a CYP1A2-specific
reaction, showed a considerable correlation \((r = 0.86)\). However, both \(S\)-mephenytoin 4'-hydroxylation activity and bufuralol 1'-hydroxylation activities showed little correlation with sesamin catecholization activity (data not shown). These results indicate that CYP1A2 is also involved in sesamin catecholization in human liver, although its contribution is smaller than that of CYP2C9.

Inhibition of the P450 Isoform-Specific Activity by Sesamin.

Because sesamin is a substrate of most of the P450 isoforms examined in this study (Table 1), it seems likely that a competitive inhibition is observed in the drug-metabolizing activities of those P450 isoforms. The effect of sesamin on CYP3A4 was also examined, because CYP3A4 metabolizes a large number of medicines and is the most essential P450 isoform in drug metabolism. Note that most of the severe drug-drug and drug-food factor interactions are related to CYP3A4. Thus, inhibitory effects of sesamin on each of the CYP2C9-, 1A2-, and 3A4-dependent activities were examined in this study. As expected, competitive inhibition by sesamin was observed in these P450s-dependent activities. The apparent \(K_i\) values of sesamin were estimated to be 24, 75, and 4.2 \(\mu M\), respectively. Thus, it was found that sesamin was a potent inhibitor of CYP3A4.

Mechanism-Based Inhibition of P450s.

To examine MBI by sesamin, first we used the microsomal fraction of the recombinant yeast expressing CYP2C9, CYP1A2, and CYP3A4. Although CYP1A2 and CYP3A4 showed no MBI, CYP2C9 showed time- and concentration-dependent MBI (Fig. 5). The apparent \(K_i\) and \(k_{\text{inact}}\) values of sesamin in CYP2C9-dependent diclofenac 4'-hydroxylation were estimated to be 1.6 \(\mu M\) and 0.22 min\(^{-1}\), respectively. Next, a similar experiment was performed with human liver microsomes using diclofenac as a substrate to confirm the sesamin-dependent MBI of CYP2C9 in human liver. The apparent \(K_i\) and \(k_{\text{inact}}\) values were estimated to be 22 \(\mu M\) and 0.13 min\(^{-1}\), respectively, for CYP2C9-specific diclofenac 4'-hydroxylation in human liver microsomes (Table 3).

Discussion

To the best of our knowledge, this is the first report to identify the human P450 isoforms responsible for sesamin metabolism, although some previous studies have demonstrated that sesamin appears to be catecholized by several types of P450s (Nakai et al., 2003; Penalvo et al., 2005; Liu et al., 2006). First, we used the recombinant yeast expression system, which had been used as a tool for prediction of drug metabolism in human body (Imaoka et al., 1996; Hayashi et al., 2000; Sakaki and Inouye, 2000; Inouye et al., 2002), to identify the
human P450 isoforms responsible for sesamin metabolism. We were surprised to find that most human P450s examined in this study showed sesamin catecholization (Table 1). In particular, four kinds of P450s (CYP1A2, 2C9, 2C19, and 2D6) had high ability to catecholize sesamin, compared with other P450s. The kinetic studies suggested that CYP2C19 had the highest turnover for sesamin catecholization among human P450s (Table 2). However, based on their average contents in human liver, we predicted that the contribution in human liver is large in order of CYP2C9, 1A2, 2C19, and 2D6.

To examine our assumption, we performed experiments using individual human single donor liver microsomes (Figs. 2 and 3) and a 50-donor human liver microsome pool (Fig. 4). The experimental data strongly suggested that CYP2C9 was largely responsible for sesamin catecholization in human liver, whereas CYP1A2 also made a small contribution. A significant inhibitory effect of the CYP2C9-specific inhibitor, sulfaphenazole, on sesamin catecholization in the pooled human liver microsomes confirmed that CYP2C9 was the most essential P450 isoform. However, the fact that interindividual difference in sesamin catecholization activity (activity range: 2.5-fold) was smaller than that of diclofenac 4′-hydroxylation activity (activity range: 6.3-fold) might be related to the contribution of CYP1A2. Contribution of CYP2C19 for sesamin catecholization in human liver seems to be small, although CYP2C19 has the largest turnover (Table 1). No significant inhibitory effect of the CYP2C19-specific inhibitor, (+)-N-3-benzyl nirvanol, on sesamin catecholization in the pooled human liver microsomes confirmed that the contribution CYP2C9 is small. The contribution of CYP2D6 is also quite small, although some kind of methylenedioxyphenyl compounds such as methylenedioxymethamphetamine is metabolized to catechol metabolites mainly by CYP2D6 (Tucker et al., 1994; Lin et al., 1997; Keeth et al., 2000). Both of CYP2C19 and CYP2D6 are known to have genetic polymorphisms. The frequency of CYP2C19 poor metabolizer in Japanese and Koreans is approximately 20% and that of CYP2D6 poor metabolizer in whites is approximately 7–10%. Thus, our conclusion that CYP2C19 and CYP2D6 are not essential for sesamin catecholization may predict a small interindividual difference in sesamin metabolism.

One of the most important findings in this study is that sesamin is a mechanism-based inhibitor of CYP2C9. Figure 6 shows a putative reaction mechanism of sesamin catecholization proposed by Murray (2000). A part of the metabolite (I) produced by CYP2C9 could be converted spontaneously to form a reactive carbene compound (II) that probably covalently binds to a heme iron of CYP2C9. Because MI inactivates the enzyme irreversibly, it is a remarkably severe inhibition compared with a reversible competitive inhibition. The $k_i$ and $k_{inact}$ values of sesamin were estimated to be 22 μM and 0.13 min$^{-1}$, respectively, in human liver microsomes. Usia et al. (2005) demonstrated that some lignans that contain MDP groups inhibit CYP3A4 irreversibly ($k_i$, 0.082–0.37 μM; $k_{inact}$, 0.23–0.32 min$^{-1}$). Bergamottin in grapefruit juice is a well known mechanism-based inhibitor of CYP3A4 with the $K_i$ value of 4.2 μM and the $k_{inact}$ value of 0.30 min$^{-1}$ (Zhou et al., 2004). Judging from $k_{inact}/K_i$ value, sesamin is a weak inhibitor compared with these inhibitors (Table 3). However, CYP2C9 is a major P450 isoform to metabolize therapeutic drugs such as diclofenac, phenytoin, and S-warfarin. These results suggest that a drug-sesamin interaction should be evaluated on these therapeutic drugs. On the other hand, sesamin did not irreversibly inhibit CYP1A2, which is the second most important P450 isoform for sesamin catecholization. Conversion from (I) to (II) or (III) is a spontaneous reaction (Fig. 6). Thus, it is possible that the reactive metabolite (II) is also produced in the substrate-binding pocket of CYP1A2, but the metabolite (II) may not rapidly attack a heme iron of CYP1A2. Otherwise, MI-complex with CYP1A2 might be much less stable than that with CYP2C9 on the basis of different stabilities of the MI-P450 complexes formed (Murray 2000). The difference between CYP2C9 and CYP1A2 seems to originate from the difference of the structures and microenvironment of their substrate-binding pockets.

Sesamin monocatechol is known as a compound that has a potent antioxidative activity different from that of sesamin (Nakai et al., 2003). In addition, recent studies suggested that sesamin monocatechol has the ability to induce enhancement of endothelium-dependent vasorelaxation (Nakano et al., 2006) and neuronal differentiation (Hamada et al., 2009). Thus, conversion from sesamin to its monocatechol is considered to be a useful reaction to produce antioxidant or other bioactive compound in the human body. Previous studies demonstrated that sesamin is metabolized to sesamin dicatechol via sesamin monocatechol in rats (Nakai et al., 2003; Peñalvo et al., 2005; Liu et al., 2006). It is noted that sesamin dicatechol is a more potent antioxidant than sesamin monocatechol (Nakai et al., 2003; Miyake et al., 2005). Thus, the conversion from monocatechol to dicatechol is pharmacologically important. We examined the conversion of monocatechol into dicatechol by adding sesamin monocatechol to human liver microsomes as a substrate. However, only a small amount of dicatechol was detected (data not shown). These results demonstrate that sesamin monocatechol is not a good substrate of P450s compared with sesamin itself.

In this study, we examined the metabolism of sesamin and revealed P450 isoforms involved in sesamin metabolism by combination of the

**TABLE 3**

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>P450</th>
<th>$k_{inact}$</th>
<th>$K_i$</th>
<th>$k_{inact}/K_i$</th>
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<tr>
<td>Sesamin</td>
<td>2C9</td>
<td>0.13 ± 0.01</td>
<td>22.0 ± 2.8</td>
<td>0.0059 ± 0.0004</td>
</tr>
<tr>
<td>Lignane</td>
<td>3A4</td>
<td>0.23–0.32</td>
<td>0.082–0.37</td>
<td>0.84–5.7</td>
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<td>Bergamottin</td>
<td>3A4</td>
<td>0.30</td>
<td>4.2</td>
<td>0.071</td>
</tr>
</tbody>
</table>

$K_i$ and $k_{inact}$ values represent mean ± S.D. from three separate experiments.

$^{a}$Usia et al., 2005.

$^{b}$Zhou et al., 2004.
yeast expression system for human P450s and human liver microsomes. In particular, the whole-cell system of the reconstituent yeast cells is useful for screening of P450 isoforms involved in the metabolism, and production of the metabolite to identify its chemical structure. We found that CYP2C9 was the most important P450 isoform in sesamin catalytization in human liver, but we also found that sesamin was a mechanism-based inhibitor of CYP2C9. At the present time, it is difficult to regard the MBI of CYP2C9 by sesamin as a serious problem, because no severe drug-sesamin interaction has been reported to the best of our knowledge. Pehalvo et al. (2005) reported that the peak plasma concentration of sesamin was only 0.1 μM after a single serving of sesame seeds containing 170 mg of sesamin. Thus, a much lower concentration of sesamin in vivo than the apparent inhibitor constant (K_{app}) shown in Table 3 might lead us to the conclusion that MBI of CYP2C9 by sesamin could be negligible. However, our findings suggest that in vivo studies would be required to reveal the interaction between sesamin and therapeutic drugs metabolized by CYP2C9.

References

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