


 Cite this: *RSC Adv.*, 2026, 16, 12570

# Sesamin exhibits potential food–drug interactions through the inhibition of cytochrome P450s and human UDP-glucuronosyltransferases *in vitro*

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As a natural plant active ingredient, sesamin has the following nutritional values: anti-inflammatory, antioxidant, anti-hypertension, liver protection, and cholesterol reduction, and has been developed for dietary supplements to assist clinical drug therapy. However, it is not known whether it inhibits the catalytic activities of drug-metabolizing enzymes. Hence, the objective of this research was to assess the inhibitory effects of sesamin on cytochrome P450s (CYPs) and UDP-glucuronosyltransferases (UGTs) and to predict the risk of inducing food–drug interactions (FDIs). The results indicated that sesamin had no significant inhibitory effects on UGTs. However, since people may take sesame in excessive amounts, the FDIs mediated by UGTs still cannot be ignored. Sesamin could increase the potential risk of FDIs by inhibiting the activities of CYP2C9 and CYP2C19. It is worth noting that for phenytoin, a CYP2C9 substrate with a narrow therapeutic window, sesamin can significantly inhibit the formation of its hydroxylation products and cause clinically significant FDIs. Therefore, when patients are being treated with CYP2C9 and CYP2C19 substrate drugs with narrow therapeutic windows, high doses of sesame or other sesamin-rich substances should be avoided.

 Received 9th January 2026  
 Accepted 28th February 2026

DOI: 10.1039/d6ra00237d

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## 1. Introduction

Sesamin is a naturally occurring lipid-soluble furfuran lignan and a member of the benzodioxole family.<sup>1</sup> Although sesame is still the best source of sesamin, sesamin is actually very widely distributed in plants and is not limited to a specific species.<sup>2</sup> It has been reported that sesamin possesses several pharmacological activities, including anti-cancer, neuroprotective, anti-oxidative, and anti-cardiovascular diseases, and is expected to be used in the treatment of cardiovascular disorders, neurodegenerative diseases, and other diseases.<sup>3–5</sup> In recent years, studies have suggested that sesamin is capable of improving diabetes-associated behavioral deficits (DABD) and may be effective as a novel drug to treat diabetes patients.<sup>6,7</sup> Given the many pharmacologically beneficial activities, sesamin is often found in people's diets and is often used clinically as a natural supplement in combination with other medications.<sup>8</sup> As a result, food–drug interaction (FDI) issues may subsequently arise.<sup>9</sup>

As a serious threat to the safety of drug therapy, FDIs have received increasing attention in recent years. However, compared with drugs, people tend to be less vigilant about food

and less aware of FDIs, easily ignoring this risk factor. Therefore, it is necessary to conduct in-depth and systematic research and prediction of FDIs. Inhibition of the activities of drug-metabolizing enzymes is the main mechanism of FDIs.<sup>10,11</sup> Cytochrome P450s (CYPs) are the major phase I metabolic enzymes responsible for the oxidative metabolism of various drugs, steroids, and carcinogens.<sup>12</sup> Approximately 90% of human drug oxidation is carried out by CYPs of the CYP1, CYP2, and CYP3 families,<sup>13</sup> and members of other CYP families are involved in the metabolic process of endogenous compounds, including bile acids, steroids, and leukotrienes.<sup>14,15</sup> After entering the human body, sesamin is first catalyzed into monocatechol metabolites with higher antioxidant activity by CYP1A2, 2C9, 2C19, and 2D6, among which CYP2C9 is the most important P450 subtype of sesamin catecholization in human liver.<sup>16</sup> As a substrate of CYPs, the efficacy of sesamin nutrients may be affected by inhibitors or inducers of the enzymes. In addition, whether sesamin can inhibit the activity of the CYP enzyme is also worth further investigation. Previous studies have shown that sesamin has inhibitory activities of CYP2C9, CYP2C19, and CYP3A in human liver microsomes (HLMs) using specific substrates of flurbiprofen, *s*-mephenytoin, and triazolam with the half-maximal inhibitory concentration (IC<sub>50</sub>) values of 21.1 μM, 6.2 μM, and 7.3 μM, respectively.<sup>17</sup> However, the inhibitory effect of sesamin on enzymes is substrate-dependent, and studies using different substrates may lead to completely different conclusions. Furthermore, existing research has only studied the inhibitory effects of metabolic

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enzymes, but has not fully and deeply explored the possible FDIs caused by sesamin.

Except for CYPs, UDP-glucuronosyltransferases (UGTs) occupy essential positions in the drug metabolic process as well.<sup>18</sup> As phase II metabolic enzymes, UGTs can catalyze the binding reaction between the drug and glucuronic acid, making it more hydrophilic and easier to be excreted from the body. The inhibition of the activities of UGTs can lead to the decrease of glucuronidation degree, leading to the decrease of drug clearance, and the accumulation of drugs in the human body to produce toxicity. It has been reported that 82% of monocatechol metabolites converted from sesamin by CYPs in HLMs are further metabolized by UGTs and converted into glucuronide, and this process is mainly mediated by UGT2B7.<sup>19</sup> The glucuronidation can significantly reduce the antioxidant activity of the phase I metabolites. Therefore, when the activity of UGT2B7 changes, the plasma exposure and pharmacological activity of sesamin may change significantly. Besides, for all we know, there is no research on whether sesamin has inhibitory effects on UGTs.

The objective of this study was to assess the inhibitory effects of sesamin on CYPs and UGTs *in vitro* and to determine the corresponding inhibitory types and inhibitory constants. The potential risk of FDIs induced by sesamin combined with CYPs or UGTs substrates was further quantitatively predicted.

## 2. Materials and methods

### 2.1 Chemical and reagents

Phenacetin, coumarin, bupropion, trifluoperazine (TFP), and sesamin were obtained from Selleck Chemicals (Houston, USA). 4-Methylumbelliferone (4-MU), 4-methylumbelliferone- $\beta$ -*D*-glucuronide (4-MUG), midazolam (1.0 mg mL<sup>-1</sup> in methanol), umbelliferone, phenytoin, *p*-hydroxyphenytoin, uridine 5'-diphosphoglucuronic acid tri-ammonium salt (UDPGA), and nicotinamide adenine dinucleotide phosphate (NADPH) were obtained from Sigma-Aldrich Co. (Missouri, USA). Tolbutamide and omeprazole were obtained from Aladdin (Shanghai, China). Dextromethorphan was purchased from Glpbio (USA). Pooled HLMs were obtained from the Research Institute for Liver Diseases (RILD, Shanghai, China). Recombinant human UGT isoforms were obtained from BD Gentest Corp. (Woburn, MA, USA).

### 2.2 Preliminary screening of the inhibition capability of sesamin towards recombinant human UGTs

4-MU is a non-specific probe substrate of UGTs except UGT1A4, which was utilized to investigate the inhibition of sesamin towards UGTs. When measuring the activity of UGT1A4, TFP was selected instead of 4-MU as the specific substrate. The incubation conditions for each enzyme were slightly modified according to the conditions described in the published literature.<sup>20–22</sup> A typical incubation system (200  $\mu$ L) contained different concentrations of sesamin, recombinant UGT isoforms, 4-MU/TFP, Tris-HCl buffer (pH 7.4, 50 mM), 5 mM MgCl<sub>2</sub>, and 2.5 mM UDPGA. The concentrations of 4-MU

corresponding to UGT1A1, 1A3, 1A6, 1A7, 1A8, 1A9, 1A10, 2B4, 2B7, 2B15, and 2B17 were 110, 1200, 110, 30, 750, 30, 30, 1200, 350, 250, and 2000  $\mu$ M, respectively. And the concentration of TFP was 40  $\mu$ M for UGT1A4. The reaction time was determined based on the literature published previously.<sup>23,24</sup> 200  $\mu$ L ice-cold acetonitrile containing the internal standard (18  $\mu$ M umbelliferone) was used as the termination solution. The incubation system with a sesamin concentration of 0  $\mu$ M was the negative control. After the reaction stopped, the mixture was centrifuged (12 000 rpm, 15 min), and 10  $\mu$ L of the supernatant was absorbed and transferred for HPLC analysis (Waters Alliance HPLC 2695). The samples were separated using 0.5% formic acid in water and acetonitrile as the mobile phase, and the flow rate was 1.0 mL min<sup>-1</sup>. The UV detection of 4-MUG and TFP was 316 nm and 254 nm, respectively. All incubations were performed in two independent experiments in duplicate and data were reported as the mean  $\pm$  standard error.

### 2.3 Preliminary screening of the inhibition capability of sesamin towards CYPs in HLMs

The activities of seven CYP enzymes were assessed by simultaneous determination of the production of metabolites from different specific substrates using a cocktail method according to FDA guidelines. Different concentrations of probe substrates for each CYP were used: CYP1A2 (by 20  $\mu$ M phenacetin), 2A6 (by 10  $\mu$ M coumarin), 2B6 (by 50  $\mu$ M bupropion), 2C9 (by 75  $\mu$ M tolbutamide), 2C19 (by 25  $\mu$ M omeprazole), 2D6 (by 5  $\mu$ M dextromethorphan), 3A4 (by 5  $\mu$ M midazolam), to explore the inhibitory effects of sesamin on CYPs *in vitro*.<sup>25–27</sup> The reaction system (200  $\mu$ L) was established in phosphate buffer (100 mM, pH 7.4). The system included HLMs (0.25 mg mL<sup>-1</sup>), a mixture of cocktail probe substrates, 5 mM MgCl<sub>2</sub>, sesamin (0  $\mu$ M, 1  $\mu$ M, 10  $\mu$ M, or 100  $\mu$ M), and 0.5 mM NADPH. After the reaction at 37  $^{\circ}$ C for 40 min, the ice-cold acetonitrile (containing 0.2  $\mu$ M carbamazepine as internal standard) was used to terminate it. The samples were centrifuged twice at 12 000 rpm at 4  $^{\circ}$ C for 15 min each to precipitate the proteins. Finally, the supernatant (100  $\mu$ L) was transferred to an auto-injector vial, and the sample (2  $\mu$ L) was injected for LC-MS/MS analysis (Waters ACQUITY UPLC interfaced with Applied Biosystems Qtrap 6500). 0.1% formic acid in water and acetonitrile were used as mobile phase and the flow rate was 0.3 mL min<sup>-1</sup> which formed the following gradient: 0–2.2 min, 8% B; 2.2–2.4 min, 40% B; 2.4–3.5 min, 85% B; 3.5–5 min, 8% B. Multiple reaction monitoring (MRM) method was used to analyze metabolites and carbamazepine in positive mode. Detailed MS/MS parameters were as follows: curtain gas 35, IS voltage 5500 V, temperature 500  $^{\circ}$ C, GS1 50, GS2 30. All incubations were performed in two independent experiments in duplicate, and data were reported as the mean  $\pm$  standard error.

### 2.4 Enzyme inhibition studies of sesamin on CYP2C9 and CYP2C19

According to the inhibitory effects of sesamin, the IC<sub>50</sub> value was measured for CYPs whose activity was potentially inhibited. The reaction mixtures similar to Section 2.3 containing



substrates, HLMs, and NADPH were reacted with a series of different concentrations of sesamin solutions (0, 0.01, 0.1, 0.5, 1, 5, 10, 25, 50, 100  $\mu\text{M}$ ). In addition, since phenytoin is mainly metabolized in the human body by CYP2C9 and CYP2C19, and its therapeutic window is narrow, phenytoin was added as an additional probe substrate in the experiments. The final concentration of phenytoin was 20  $\mu\text{M}$ . The experimental method was the same as that described in Section 2.3. The concentration-dependent inhibition curve was plotted using the GraphPad Prism 9 software. All incubations were performed in two independent experiments in duplicate, and data were reported as the mean  $\pm$  standard error.

## 2.5 Inhibition kinetics analysis

The inhibition kinetics experiments were conducted with the appropriate drug concentration range according to the  $K_m$  values for probe substrates and  $\text{IC}_{50}$  values for sesamin. A range of concentrations of probe substrates was used: 12.5–150  $\mu\text{M}$  tolbutamide for CYP2C9, 10–30  $\mu\text{M}$  phenytoin for CYP2C9, and 5–50  $\mu\text{M}$  omeprazole for CYP2C19. The inhibition constant ( $K_i$ ) was calculated by fitting the expressions for competitive inhibition (eqn (1)), noncompetitive inhibition (eqn (2)), uncompetitive inhibition (eqn (3)), or mixed inhibition (eqn (4)).<sup>28,29</sup>

$$v = (V_{\max}S)/(K_m(1 + I/K_i) + S) \quad (1)$$

$$v = (V_{\max}S)/(K_m + S)(1 + I/K_i) \quad (2)$$

$$v = (V_{\max}S)/(K_m + (1 + I/K_i)S) \quad (3)$$

$$v = (V_{\max}S)/(K_m(1 + I/K_i) + S(1 + I\alpha K_i)) \quad (4)$$

where  $v$  represents the reaction velocity;  $V_{\max}$  is the maximum velocity;  $I$  and  $S$  are the concentrations of inhibitor and substrate, respectively.  $K_m$  is the Michaelis constant;  $\alpha$  reflects the effect of the inhibitor on the affinity of the enzyme for its substrate. The  $K_i$  values of sesamin were calculated by nonlinear regression analysis using GraphPad Prism 9 software.

The unbound fraction of the inhibitor ( $f_{u,\text{inc}}$ ) was calculated using eqn (5), and the value of  $K_{i,u}$  was calculated using eqn (6).<sup>30</sup>

$$f_{u,\text{inc}} = 1/(C \times 10^{0.561\log P/D-1.41} + 1) \quad (5)$$

$$K_{i,u} = f_{u,\text{inc}} \times K_i \quad (6)$$

where  $C$  represents the concentration of HLMs in this research. If the inhibitor is alkaline, the  $\log P$  value is selected; conversely, when the inhibitor is neutral or acidic, the  $\log D$  value is used for calculation. All incubations were performed in two independent experiments in duplicate, and data were reported as the mean  $\pm$  standard error.

## 2.6 Prediction of FDI risk

Since the concentrations of sesamin at CYP active sites were not available experimentally, the concentrations of sesamin were calculated by using the following equations: the average ( $[I]_{\text{av}}$ ) and maximum ( $[I]_{\text{max}}$ ) systemic plasma concentration (eqn (7)

and (8)), and the maximum unbound systemic plasma concentration ( $[I]_{\text{max,u}}$ ) (eqn (9)).<sup>31–33</sup>

$$[I]_{\text{av}} = (D \times F)/(V_L \times \text{MW}) \quad (7)$$

$$[I]_{\text{max}} = ([I]_{\text{av}}k\tau)/(1 - \exp(-k\tau)) \quad (8)$$

$$[I]_{\text{max,u}} = ([I]_{\text{av}}k\tau f_u)/(1 - \exp(-k\tau)) \quad (9)$$

where  $D$  and  $F$  are oral dose and oral bioavailability of sesamin, respectively ( $D = 10$  mg,  $F = 0.54$ ).  $V_L$  is the blood volume in humans ( $V_L = 5.6$  L/70 kg);  $\text{MW}$  is the molecular weight of sesamin ( $\text{MW} = 354.35$ ); and  $\tau$  is the dosing interval ( $\tau = 24$  h).  $k$  and  $f_u$  denote the elimination rate constant and unbound fraction of sesamin, respectively ( $k = 0.33$  h<sup>-1</sup> and  $f_u = 0.01$ ).<sup>34,35</sup>

The value of  $R_1$  was calculated to estimate the risk of sesamin or sesamin-rich foods causing FDIs by inhibiting the activities of human hepatic CYPs (eqn (10)).<sup>36</sup>  $R_1 \geq 1.02$  suggests a high DDI risk, and it is necessary to conduct further research.

$$R_1 = 1 + [I]_{\text{max,u}}/K_{i,u} \quad (10)$$

The  $R_{1,\text{gut}}$  value was used to assess the risk of FDIs caused by inhibition of intestinal metabolic enzymes *in vivo* (eqn (11)).<sup>36</sup>

$$R_{1,\text{gut}} = 1 + [I]_{\text{gut}}/K_{i,u} \quad (11)$$

where the value of  $[I]_{\text{gut}}$  was calculated as the dose/250 mL, representing the intestinal luminal concentration after a single oral administration. If the value of  $R_{1,\text{gut}}$  is greater than 11, further clinical drug interaction studies are recommended.

## 3. Results

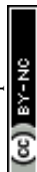
### 3.1 Inhibition effects of sesamin towards UGTs

The preliminary screening was first conducted to test the inhibitory effects of sesamin on various human UGT isoforms. Sesamin at 100  $\mu\text{M}$  had significant inhibitory effects on UGT1A7, 1A9, 2B4, 2B7 and 2B15 (residual activity < 50%), and inhibited the activities of UGT1A1, 1A3, 1A4, 1A6, 1A8, and 1A10 weakly (residual activity > 50%), as shown in Fig. 1. On the other hand, sesamin at 100  $\mu\text{M}$  presented induction on UGT2B17. However, sesamin had no significant inhibitory effects on all UGTs at low concentrations.

### 3.2 Inhibition effects of sesamin towards CYPs

In the CYP cocktail assay, the inhibition of sesamin towards CYP enzymes in the HLMs was shown in Fig. 2. At a concentration of 100  $\mu\text{M}$ , sesamin significantly inhibited the activities of CYP2B6, 2C9, 2C19, 2D6, and 3A4 (residual activity < 50%), and can significantly inhibit the activities of CYP2C9 and CYP2C19 even at 10  $\mu\text{M}$ .

The results of concentration-dependent experiments showed that when tolbutamide and phenytoin were used as probe substrates, sesamin could significantly inhibit the activity of CYP2C9, with  $\text{IC}_{50}$  values of  $5.83 \pm 0.45$   $\mu\text{M}$  and  $8.13 \pm 0.92$   $\mu\text{M}$ , respectively. Sesamin also showed a potent inhibitory effect on CYP2C19 with an  $\text{IC}_{50}$  value of  $6.17 \pm 1.01$   $\mu\text{M}$  (Fig. 3).



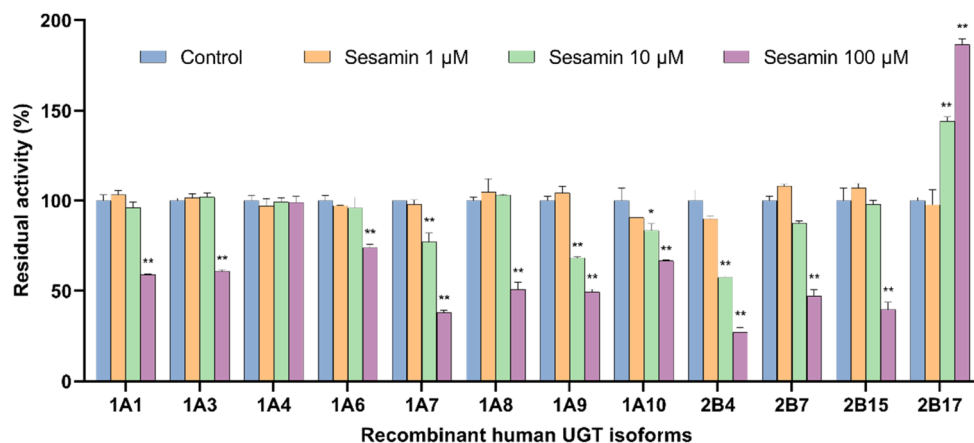


Fig. 1 Inhibition of human recombinant UGTs by sesamin (0, 1, 10, 100  $\mu\text{M}$ ). Each column represents the mean  $\pm$  standard error of duplicate experiments. Compared with the control group, \* means  $P < 0.05$ ; \*\* means  $P < 0.01$ .

### 3.3 Kinetic analysis for inhibition of CYP2C9 and CYP2C19

Inhibition kinetic studies were further conducted, and the  $K_i$  values and the inhibition mechanism of sesamin were determined for CYP2C9 and CYP2C19 in HLMs. As shown in Fig. 4, the representative Lineweaver-Burk plot and Dixon plot indicated that sesamin effectively inhibited the hydroxylation reaction of tolbutamide catalyzed by CYP2C9 through a non-competitive mechanism, with a  $K_i$  value of  $7.60 \pm 0.98 \mu\text{M}$ . When using phenytoin as the probe substrate, sesamin showed a potent mixed inhibitory effect on the activity of CYP2C9, with a  $K_i$  value of  $14.11 \pm 0.96 \mu\text{M}$ . Sesamin competitively inhibited the activity of CYP2C19 with a  $K_i$  value of  $5.38 \pm 0.96 \mu\text{M}$ . The  $f_{u,inc}$  value of sesamin was 0.66, and the calculated  $K_{i,u}$  values were  $5.02 \pm 0.65 \mu\text{M}$ ,  $9.31 \pm 0.63 \mu\text{M}$ , and  $3.55 \pm 0.63 \mu\text{M}$ , respectively.

### 3.4 Prediction of FDI risk *in vivo*

At the oral dose (10 mg per day) of sesamin, the values of  $[I]_{av}$ ,  $[I]_{max}$ , and  $[I]_{max,u}$  were calculated as  $2.72 \mu\text{M}$ ,  $21.55 \mu\text{M}$ , and  $0.22 \mu\text{M}$ , respectively. The risks of FDIs when sesamin was co-

administered with drugs mainly cleared by CYP2C9 or CYP2C19 were evaluated by estimating  $R_1$  and  $R_{1,gut}$ . When the oral dose of sesamin was 10 mg per day, and the substrate was tolbutamide, the values of  $R_1$  and  $R_{1,gut}$  were 1.043 and 23.48 for CYP2C9, respectively. The prediction results using phenytoin as the probe substrate showed that the values of  $R_1$  and  $R_{1,gut}$  were 1.023 and 13.12 for CYP2C9, respectively. For CYP2C19, the values of  $R_1$  and  $R_{1,gut}$  were 1.061 and 32.79, respectively. In view of the fact that  $R_1 > 1.02$  or  $R_{1,gut} > 11$  were considered as warning values for drug interactions in FDA guidance, the data suggested that sesamin was associated with a high risk of drug interactions when it was co-administered with tolbutamide, phenytoin, or omeprazole.

## 4. Discussion

FDIs can unintentionally alter the efficacy of a drug, and most clinically relevant FDIs result from changes in food-induced drug exposure.<sup>37</sup> Ignoring the interactions between drugs and nutrients in food can lead to serious adverse consequences. A well-known example of FDIs is the mechanism-based inhibition

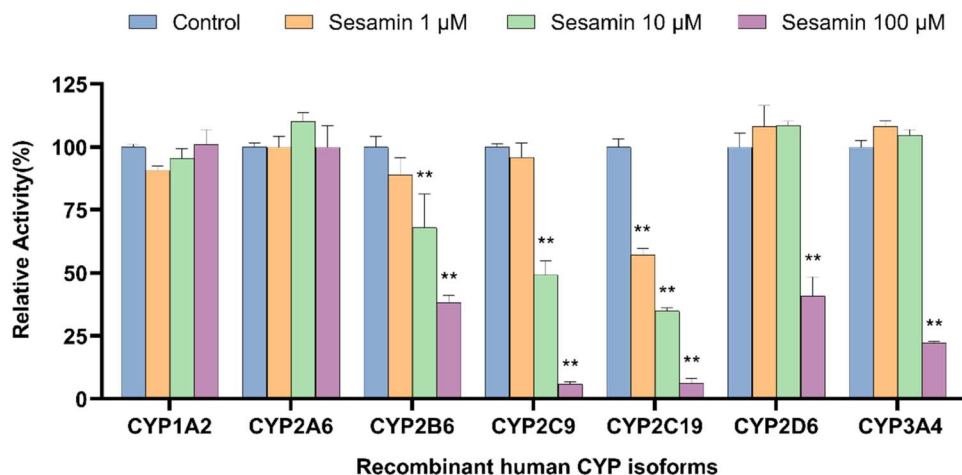


Fig. 2 Inhibition of CYPs by sesamin (0, 1, 10, 100  $\mu\text{M}$ ). Each column represents the mean  $\pm$  standard error of duplicate experiments. Compared with the control group, \* means  $P < 0.05$ ; \*\* means  $P < 0.01$ .

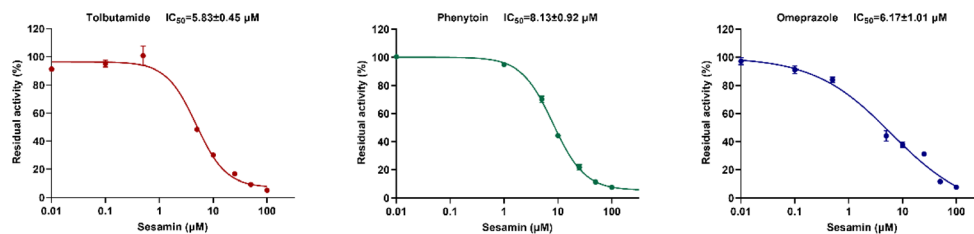


Fig. 3 Concentration-dependent inhibition of sesamin on CYP2C9 (tolbutamide and phenytoin) and CYP2C19 (omeprazole). All data points shown represent the mean  $\pm$  standard error of duplicate experiments.

of furanocoumarins in grapefruit that causes a permanent loss of CYP3A4 activity, triggering interactions between grapefruit and felodipine or other CYP3A4 substrate drugs.<sup>38,39</sup> This results in a more than five-fold increase in the overall exposure to certain drugs when taken with grapefruit juice, and significantly increases the risk of adverse reactions, seriously threatening the lives of patients.<sup>40</sup> Therefore, predicting FDIs and avoiding adverse reactions is one of the key problems to be solved in clinical medicine.

According to the Statement on Reforming FDA Oversight to Enhance Regulation of Dietary Supplements, safety is one of the FDA's top concerns in the area of dietary supplements and other natural products. It is necessary to perform *in vitro* research to assess whether dietary supplements or foods are involved in metabolism-mediated FDIs or which CYPs are warranted.<sup>41</sup> Our data offer *in vitro* evidence that sesamin is an inhibitor of CYPs, including CYP2B6, CYP2D6, CYP2C9, CYP2C19, and CYP3A4. Among these, sesamin can potently inhibit the activities of CYP2C9 and CYP2C19. Compared with the previously published literature,<sup>17,42</sup> this study selected several different specific substrates (tolbutamide, phenytoin, omeprazole, and midazolam) to investigate the effects of sesamin on the activities of CYP2C9, 2C19, and 3A4. The  $IC_{50}$  value of sesamin on CYP2C19 was consistent with that reported in the literature. The difference in the inhibition effects of CYP2C9 and CYP3A4 may be caused by different experimental conditions and specific substrate selection. Moreover, due to the inadequacy of existing studies, this study further used the *in vitro*–*in vivo* extrapolation methods to predict the risk of FDIs when sesamin is taken with CYP substrates. The results suggested that sesamin had a high risk of clinical FDIs when taken in conjunction with CYP2C9 or CYP2C19 substrate drugs.

The intake of sesamin by the human body can be achieved through consuming sesame seeds, sesame oil, or sesame supplements. Previous studies have shown that each 100 g of sesame seeds contains approximately 60–940 mg of sesamin,<sup>43–45</sup> while the same amount of sesame oil contains about 190–720 mg of sesamin.<sup>46–48</sup> In a study on the effects of sesame on lipid profile and oxidative stress biomarkers in patients with knee osteoarthritis, the subjects consumed 40 g of sesame daily.<sup>49</sup> Calculated at the lowest concentration, the amount of sesamin was approximately 24 mg per day. It is recommended that the daily intake of edible oil should be 27 g per day.<sup>50</sup> After calculation, as one of the healthiest and most popular edible oils in the world, sesame oil contains approximately 51.3–194.4 mg per day of sesamin. However, the actual

daily intake of edible oil in most countries may be much higher than the recommended amount. In some studies exploring the pharmacological activity of sesamin, the daily dosage of sesamin supplement taken by the patients was 200 mg per day.<sup>51,52</sup> The content of sesamin in all of the above three intake ways is much higher than 10 mg per day. The results of this study indicated that sesamin could trigger FDIs by inhibiting the activities of CYP2C9 and CYP2C19 at low doses. If more sesamin is consumed on a daily basis, there would be a higher risk of FDIs.

CYP2C9 catalyzes the metabolic process of a variety of endogenous and exogenous substrates in the human body, including steroids, tolbutamide, diclofenac, and *S*-warfarin.<sup>53</sup> CYP2C9 is mainly located in the liver and intestine and plays important roles in drug oxidation, adverse drug reactions, and genetic and pharmacological variation, and it has become one of the most studied human P450s.<sup>54,55</sup> Phenytoin is a typical CYP2C9 substrate drug with a narrow therapeutic window. Due to the neuroprotective effects of both phenytoin and sesamin, patients may take them simultaneously. The inhibitory effects of food or drugs on CYP2C9 can affect the catalytic function of the enzyme, resulting in an increase in the blood concentration of phenytoin or a decrease in its clearance rate. Therefore, the inhibition of phenytoin hydroxylation by sesamin may increase the risk of related adverse reactions. Additionally, when 5–500 nM of sesamin is present, the 7-hydroxylation rate of warfarin is significantly reduced.<sup>56</sup> Similar to phenytoin, warfarin is also a drug that is mainly metabolized by CYP2C9 and has a narrow therapeutic window.<sup>57,58</sup> Since sesamin can significantly affect the warfarin metabolism process catalyzed by CYP2C9, patients who require anticoagulant therapy with warfarin should avoid taking sesamin as much as possible.

CYP2C19 is mainly found in the cellular structure of the endoplasmic reticulum of hepatocytes, and its metabolic rate is as high as 26% in 110 commonly used drugs, including drugs with narrow therapeutic windows such as clopidogrel, warfarin, and carbamazepine that are often used clinically.<sup>59</sup> When patients take these drugs, it is not recommended to take sesame and other sesamin-rich substances. In addition, several clinical trials have shown that sesamin supplements can effectively relieve rheumatoid arthritis (RA).<sup>51,60</sup> Commonly used clinical drugs for RA patients include diclofenac, ibuprofen, and omeprazole.<sup>61–63</sup> This study found that when omeprazole acts as a substrate for CYP2C19, sesamin could significantly decrease the metabolic activity of CYP2C19, preventing omeprazole from normal conversion to its product. If patients taking omeprazole



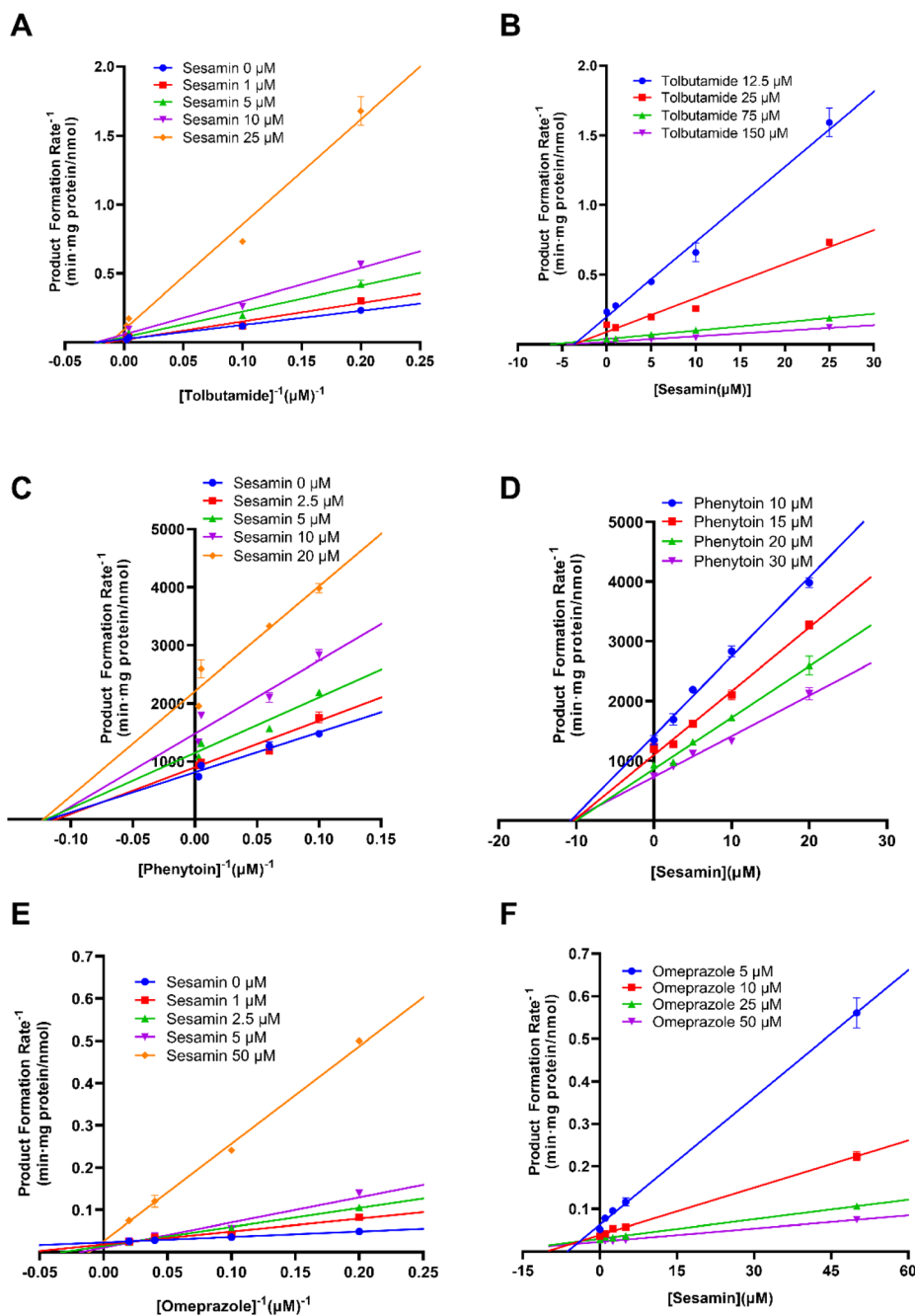


Fig. 4 Lineweaver–Burk and Dixon plots for sesamin inhibition of tolbutamide hydroxylation in CYP2C9 (A and B), phenytoin hydroxylation in CYP2C9 (C and D), and omeprazole hydroxylation in CYP2C19 (E and F). All data points shown represent the mean  $\pm$  standard error of duplicate experiments.

also take sesame or sesamin supplements, it may cause accumulation of omeprazole in the body, and in severe cases, it can lead to adverse events.

UGTs have received extensive attention in recent years as important phase II metabolic enzymes. Although the activities of UGTs were also examined in this study, the results showed that sesamin had no obvious inhibitory effect on UGTs, and it was less likely to cause FDIs by inhibiting the activities of UGTs. However, this does not mean that vigilance should be relaxed. UGTs play very important roles in the metabolic process of

sesamin in the human body. Moreover, as a food or dietary supplement, people often do not consider sesame to be toxic and may take excessive amounts. If 40 grams of sesame are consumed daily, the content of sesamin in it can reach over 1000  $\mu\text{M}$ . Therefore, the FDIs mediated by UGTs still require additional attention. In addition, the monocatechol metabolites of sesamin can also be further catalyzed by catechol *O*-methyl transferase (COMT) into methylation products.<sup>19</sup> Therefore, it is necessary to explore the effect of sesamin on the



activity of COMT and whether it can induce clinical FDIs by inhibiting COMT activity in the future.

The mechanism of FDIs is complex, and the evaluation of FDI based on inhibition of CYPs-catalyzed drug metabolism is a challenging process. *In vitro* prediction is a good foundation for evaluating the risk of clinical FDIs, but there are still many factors that may influence it. For example, CYP2C9 is highly polymorphic, and the distribution frequency of CYP enzyme alleles varies greatly among different races. CYP2C9\*2 and CYP2C9\*3 are the most common mutant alleles,<sup>64</sup> both of which are associated with decreased enzyme activity and impaired drug metabolism phenotype, reducing *S*-warfarin metabolism by 30% and 80%, respectively.<sup>65</sup> Therefore, the occurrence of FDIs needs in-depth and accurate analysis according to the actual situation.

## 5. Conclusion

Sesamin potently decreased the activities of CYP2C9 and CYP2C19 *in vitro* and may inhibit hepatic and intestinal CYP2C9 and CYP2C19 metabolism to the extent of clinical relevance. This may be a warning sign of possible FDIs between sesamin and substrate drugs with narrow therapeutic windows of the two enzymes mentioned above. However, factors such as individual differences, substance concentration at the active site, and the distribution of transporters in tissues may also affect the prediction results. The results obtained from *in vitro* experiments should be treated with caution. Further *in vivo* studies will be conducted in the future to explore the significance of the sesamin–CYP interactions.

## Author contributions

Hang Yin: writing – original draft, data curation, formal analysis, software. Lei Zhu: investigation, writing – original draft, data curation, formal analysis. Xiaoyu Wang: visualization, methodology, software. Zhen Wang: investigation, methodology. Hecheng Wang: validation, supervision, project administration. Yong Liu: funding acquisition, writing – review & editing.

## Conflicts of interest

The authors declare that there are no conflicts of interest.

## Data availability

The supporting data has been provided as part of the supplementary information (SI). Supplementary information: Table S1, Fig. S1–S4. See DOI: <https://doi.org/10.1039/d6ra00237d>.

## Acknowledgements

This work was supported by the National Natural Science Foundation of China (82274006).

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