SHORT COMMUNICATION

Chiral resolution and bioactivity of enantiomeric furofuran lignans from *Juglans mandshurica* Maxim

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**ABSTRACT**

Enantiomers have generally been reported mostly for racemic mixtures with a 1:1 ratio, as in that case there were weak Cotton effects in the ECD spectrum and negligible optical rotations. A furofuran lignan (sesamin), with a remarkable rotation and significant Cotton effects, was isolated from *Juglans mandshurica* Maxim. Subsequently, sesamin was resolved by chiral HPLC to afford a pair of enantiomers, \((+)-sesamin\) (\(a\)) and \((-)-sesamin\) (\(b\)), in a ratio of approximately 1:3. Their absolute configurations were determined by computational analysis of their electronic circular dichroism (ECD) spectrum. In addition, the pair of enantiomers were evaluated for the inhibition of self-induced \(A\beta\) aggregation. Interestingly, \((+)-sesamin\) (67.7%) and \((-)-sesamin\) (80.6%) exhibited different degrees of anti-\(A\beta\) aggregation activity. The different inhibition profiles were further explained by molecular dynamics and docking simulation study.

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1. Introduction
In nature, lignans with chiral carbon atoms are usually composed of a pair of enantiomers or several pairs of stereoisomers with different amounts (Pereira et al. 2011). In general, biological effects of enantiomers are not identical owing to the chiral nature of the biological receptors (Crossley 1995). It is essential to obtain optically pure compounds and evaluate their pharmacological effects. Herein, chiral column chromatography analysis is regarded as a powerful and effective method to obtain pure enantiomers.

*Juglans mandshurica* Maxim., belonging to the *Juglans* genus of the Juglandaceae family, is widely distributed in China and Korea (Chen et al. 2015; Diao et al. 2017; Jiang et al. 2017). In our present study, a furofuran lignan (sesamin) was obtained as a scalemic mixture from *J. mandshurica* that was resolved by HPLC analysis using a chiral column to afford a pair of enantiomers. The inhibitory activity on Aβ aggregation of optical pure compounds was tested by ThT assay.

2. Results and discussion
The concentrated 75% ethanol extract of the bark of *J. mandshurica* was subjected to a series of chromatographic separations to afford a furofuran lignan. The chemical structure was characterized as sesamin by NMR data analyses (Pelter et al. 1976). The relative stereochemistry of H-7/H-8 and H-7'/H-8' were established as the trans configuration based on the chemical shift differences of H2-9 and H2-9' (0.36 ppm in CDCl3) (Shao et al. 2018). Sesamin exhibited a specific rotation [α]D 10.0 and obvious Cotton effects in the ECD spectrum (Figure S10). Interestingly, the enantioseparation of sesamin by HPLC using a Daicel Chiralpak IC column provided the enantiomers (+)-sesamin (a) and (−)-sesamin (b) with a ratio about 1:3 (Figure S7). Generally, purification of enantiomers has been reported mostly for fully racemic mixtures, which were specific rotation approaching zero and no significant Cotton effects in ECD spectrum (Li et al. 2016) In addition, their absolute configurations were determined by comparison of its experimental and calculated ECD spectrum (Wu et al. 2016). The calculated ECD curve of (7S,8R,7'S,8'R)-sesamin at the B3LYP/6-31G(d, p) level with the Gaussian 09 package in methanol solution matched with the experimental ECD curve of (+)-sesamin (a) (Figure S8). Thus, (+)-sesamin (a) and (−)-sesamin (b) were unambiguously determined as (+)-(7S,8R,7'S,8'R)-sesamin and (−)-(7R,8S,7'R,8’S)-sesamin, respectively.

On the basis of obtaining optically pure compounds, (+)-sesamin (a) and (−)-sesamin (b) were evaluated for their ability of inhibiting Aβ1-42 aggregation by ThT assay, taking curcumin as the positive control. The result (Figure S11) showed that (−)-sesamin (b) exhibited significant inhibition of Aβ1-42 aggregation at the concentration of 20 μM (80.6 ± 1.53%), which was higher than that of curcumin (75.6 ± 1.52%). However, (+)-sesamin (a) showed moderate Aβ1-42 aggregation activity (67.7 ± 2.04%). As mentioned above, the difference of inhibitory activities caused by chirality is quite attractive.

To explore the interaction of the enantiomers in structural terms, molecular dynamics simulations were performed using the GROMACS5 simulation package to relax the structure and dynamics of protein (Manouchehri et al. 2016). The result was used for
further docking simulations. Analysis for optimized binding conformation of (−)-sesamin (b) in Figure 1 displayed that methylenedioxy group interacts with Lys16 residue and the Leu17 residue of Aβ1–42 via hydrogen bonding (distance 2.76 Å, 1.96 Å). However, (−)-sesamin (a) can only interact with Ser26 residue through a hydrogen bond with a distance of 2.42 Å. In addition, Lys16 (Yu et al. 2019) and Leu17 (Liu et al. 2004) were also considered as key active residues interacting with natural ligands. Overall, the results in docking study were consistent with ThT assay, and further proved that (−)-sesamin (b) showed optical selectivity on Aβ1–42 aggregated inhibition.

3. Conclusions

In this paper, a pair of furofuran lignan enantiomers, (−)-sesamin (a) and (−)-sesamin (b), were successfully achieved with a ratio of 1:3 by a chiral chromatographic column. Interestingly, this pair of enantiomers exhibited the influence of different stereochemistries on anti-Aβ aggregation activity. This work described here will be of particular value for the enantioselectivity of furofuran lignans.

Disclosure statement

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