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## Inhibition of Adenosine 3',5'-Cyclic Monophosphate Phosphodiesterase by Lignan Glucosides of *Eucommia* Bark<sup>1)</sup>

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Studies were conducted on adenosine 3',5'-cyclic monophosphate (cyclic AMP) phosphodiesterase inhibition by lignan glucosides from bark of *Eucommia ulmoides* OLIV. (Eucommiaceae). Various lignan diglucosides, (+)-syringaresinol di-*O*- $\beta$ -D-glucopyranoside (**1c**), (+)-medioresinol di-*O*- $\beta$ -D-glucopyranoside (**2c**), (+)-pinoresinol di-*O*- $\beta$ -D-glucopyranoside (**3c**) and (+)-1-hydroxypinoresinol 4',4''-di-*O*- $\beta$ -D-glucopyranoside (**4d**), showed strong inhibitory activity.

The structure-inhibitory activity relationships of the aglycone and its glucosides are discussed. The order of inhibitory effect was diglucoside  $\cong$  aglycone > monoglucoside.

**Keywords**—cyclic AMP phosphodiesterase; inhibitor; *Eucommia ulmoides*; lignan glucoside; (+)-syringaresinol di-*O*- $\beta$ -D-glucopyranoside; (+)-medioresinol di-*O*- $\beta$ -D-glucopyranoside; (+)-pinoresinol di-*O*- $\beta$ -D-glucopyranoside; (+)-1-hydroxypinoresinol 4',4''-di-*O*- $\beta$ -D-glucopyranoside; structure-inhibitory activity relationship

The adenosine 3',5'-cyclic monophosphate (cyclic AMP) phosphodiesterase inhibition test provides a useful means for the screening of biologically active compounds contained in medicinal plants. Nikaido *et al.* reported on cyclic AMP phosphodiesterase inhibitors contained in various medicinal plants.<sup>2)</sup> In the previous papers,<sup>3)</sup> Nishibe *et al.* isolated a series of lignans from barks of *Olea europea* L., *O. africana* MILL., *O. capensis* L., *Fraxinus japonica* BLUME and *F. mandshurica* RUPR. var. *japonica* MAXIM. (Oleaceae), and reported on the inhibition of cyclic AMP phosphodiesterase by these lignans.<sup>2)</sup>

Recently Deyama *et al.* isolated a series of lignans from bark of *Eucommia ulmoides* OLIV. (Japanese name: tochu) (Eucommiaceae), which is one of the longest-known tonic drugs in China.<sup>4)</sup>

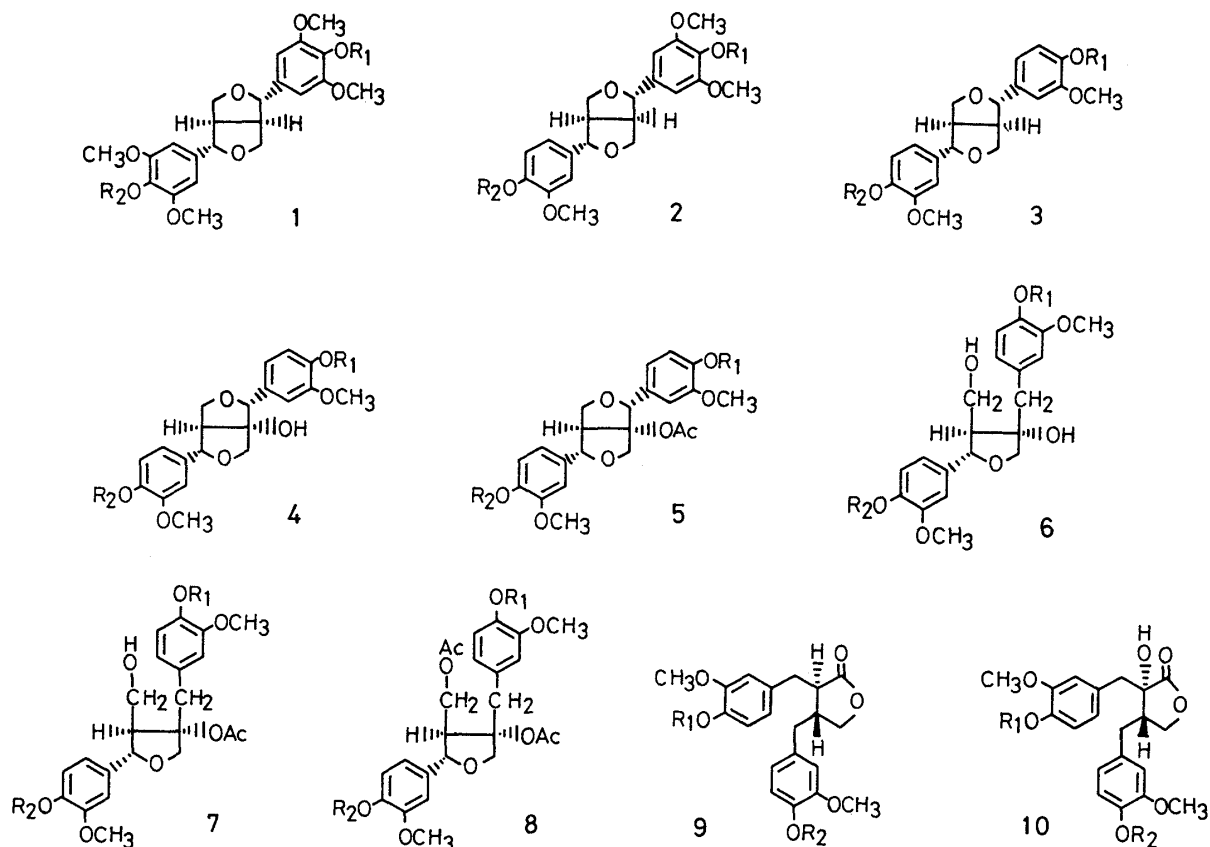
As a continuation of our studies on cyclic AMP phosphodiesterase inhibition by lignans contained in medicinal plants, this paper deals with the inhibitory effect of lignan glucosides from *Eucommia* bark. The structure-inhibitory activity relationships of the aglycone and its glucosides are also discussed.

## Results and Discussion

Lignan glucosides from *Eucommia* bark were tested for inhibitory activity against beef

heart cyclic AMP phosphodiesterase using the method reported in the previous papers.<sup>2)</sup> The assay consisted of a two-step isotopic procedure. Tritium-labelled cyclic AMP was hydrolyzed to 5'-AMP by phosphodiesterase and the 5'-AMP was then further hydrolyzed to adenosine by snake venom nucleotidase. The hydrolyzate was treated with an anion-exchange resin to adsorb all charged nucleotides and to leave [<sup>3</sup>H]adenosine as the only labelled compound to be counted.

TABLE I. Inhibitory Activity of Lignan Glucosides on Cyclic AMP Phosphodiesterase



| Compound No. | R <sub>1</sub> | R <sub>2</sub> | IC <sub>50</sub> (× 10 <sup>-5</sup> M) | Compound No. | R <sub>1</sub> | R <sub>2</sub> | IC <sub>50</sub> (× 10 <sup>-5</sup> M) | Compound No. | R <sub>1</sub> | R <sub>2</sub> | IC <sub>50</sub> (× 10 <sup>-5</sup> M) |
|--------------|----------------|----------------|-----------------------------------------|--------------|----------------|----------------|-----------------------------------------|--------------|----------------|----------------|-----------------------------------------|
| 1a           | H              | H              | 17.5                                    | 4a           | H              | H              | 21.3                                    | 7a           | H              | H              | > 50                                    |
| 1b           | Glc            | H              | > 50                                    | 4b           | Glc            | H              | 28.6                                    | 7b           | Glc            | Glc            | 16.5                                    |
| 1c           | Glc            | Glc            | 12.7                                    | 4c           | H              | Glc            | 33.2                                    | 8a           | H              | H              | > 50                                    |
| 2a           | H              | H              | 12.1                                    | 4d           | Glc            | Glc            | 10.0                                    | 9a           | H              | H              | 9.8                                     |
| 2b           | Glc            | H              | 29.7                                    | 5a           | H              | H              | 3.2                                     | 9b           | Glc            | H              | > 50                                    |
| 2c           | Glc            | Glc            | 6.3                                     | 5b           | Glc            | H              | 4.4                                     | 9c           | Glc            | Glc            | 11.1                                    |
| 3a           | H              | H              | 7.5                                     | 5c           | Glc            | Glc            | 1.1                                     | 10a          | H              | H              | 19.5                                    |
| 3b           | Glc            | H              | 14.2                                    | 6a           | H              | H              | 20.1                                    | 10b          | Glc            | H              | > 50                                    |
| 3c           | Glc            | Glc            | 8.9                                     | 6b           | Glc            | H              | 35.8                                    | 10c          | Glc            | Glc            | 14.3                                    |
|              |                |                |                                         | 6c           | H              | Glc            | 40.1                                    |              |                |                |                                         |
|              |                |                |                                         | 6d           | Glc            | Glc            | 23.7                                    |              |                |                |                                         |

IC<sub>50</sub> (× 10<sup>-5</sup> M) value of papaverine as a reference inhibitor: 3.0. All the lignan samples were isolated from *Eucommia* bark except the following samples: 5a and 5b, isolated from *Olive* bark<sup>3)</sup>; 5c, prepared from 4d; 7a and 8a, prepared from 6a; 7b, prepared from 6d; 9a—9b and 10a—10c, isolated from *Trachelospermum asiaticum* var. *intermedium*.<sup>5)</sup>

Major lignan diglucosides, (+)-syringaresinol di-*O*- $\beta$ -D-glucopyranoside (**1c**), (+)-medioresinol di-*O*- $\beta$ -D-glucopyranoside (**2c**), (+)-pinoresinol di-*O*- $\beta$ -D-glucopyranoside (**3c**) and (+)-1-hydroxypinoresinol 4',4''-di-*O*- $\beta$ -D-glucopyranoside (**4d**), showed strong inhibitory effects.

Previous studies on lignans having a 2,6-diarylated 3,7-dioxabicyclo[3.3.0]octane ring indicated that the presence of two *p*-hydroxyl groups is essential for the phosphodiesterase inhibitory activity, and both *O*-methylation and *O*-glucosylation of free hydroxyl groups generally decrease the activity.<sup>2b, j)</sup>

In the case of the lignan diglucosides of *Eucommia* bark, **1c**, **2c**, **3c**, **4d** and **6d**, no decrease in the inhibitory effect, compared with that of their aglycones, **1a**, **2a**, **3a**, **4a** and **6a**, was observed. The structure-inhibitory activity data for the aglycone and its glucosides are summarized in Table I. The order of inhibitory effect was shown to be diglucoside  $\cong$  aglycone > monoglucoside. Similar relationships were also observed among lignan diglucosides having a 2,3-dibenzylated butyrolactone ring, **9c** and **10c**, isolated from stems of *Trachelospermum asiaticum* NAKAI var. *intermedium* NAKAI (Apocynaceae).<sup>5)</sup> These results suggested that lignan diglucosides derived from aglycones which have strong inhibitory activity might be potent cyclic AMP phosphodiesterase inhibitors.

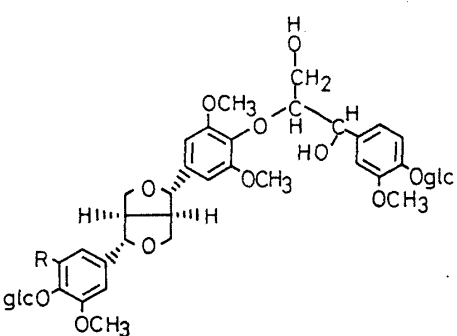
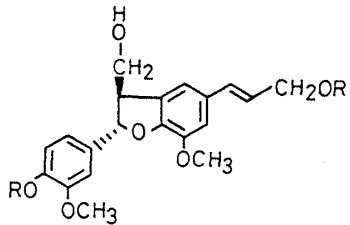
From this point of view, (+)-1-acetoxypinoresinol 4',4''-di-*O*- $\beta$ -D-glucopyranoside (**5c**) was newly prepared from **4d** as described in Experimental.

As expected, **5c** showed strong inhibitory activity. The newly prepared lignan diglucoside **7b** also showed inhibitory activity.

However, the sesquiliglan and neolignan diglucosides, **11a**, **11b** and **12b**, showed no inhibitory effect (Table II).

Weinryb *et al.* reported that a considerable number of therapeutic agents used as antipsychotics, antianxiety agents, antihypertensives and the like showed strong inhibitory effects on phosphodiesterase *in vitro*, though it is not necessarily the case that the pharmacological activity is due to some alteration of cyclic AMP metabolism.<sup>6)</sup> Recently it was reported that **1c** and **3c** protect animals from stress-induced decreases in sexual activity and in rectal temperature, stress-induced decreases in exploratory and spontaneous movements, and stress-induced failure of memory retrieval.<sup>7)</sup> Thus, there may be some correlation

TABLE II. Inhibitory Activity of Sesquiliglan and Neolignan Glucosides on Cyclic AMP Phosphodiesterase

|  |                  |                                           |  |     |                                           |
|-------------------------------------------------------------------------------------|------------------|-------------------------------------------|--------------------------------------------------------------------------------------|-----|-------------------------------------------|
| <b>11</b>                                                                           |                  |                                           | <b>12</b>                                                                            |     |                                           |
| Compound No.                                                                        | R                | IC <sub>50</sub><br>( $\times 10^{-5}$ M) | Compound No.                                                                         | R   | IC <sub>50</sub><br>( $\times 10^{-5}$ M) |
| <b>11a</b>                                                                          | H                | > 50                                      | <b>12a</b>                                                                           | H   | > 50                                      |
| <b>11b</b>                                                                          | OCH <sub>3</sub> | > 50                                      | <b>12b</b>                                                                           | Glc | > 50                                      |

IC<sub>50</sub> ( $\times 10^{-5}$  M) value of papaverine as a reference inhibitor: 3.0.

between the pharmacological effect and the cyclic AMP phosphodiesterase-inhibitory activity of these lignan diglucosides. Therefore, it is noteworthy from a medicinal viewpoint that major lignan diglucosides from *Eucommia* bark, used as a tonic, were shown to be strong cyclic AMP phosphodiesterase inhibitors.

### Experimental

The following instruments were used: optical rotations, Yanaco OR-50D; ultraviolet (UV) spectra, Shimadzu UV 210; infrared (IR) spectra, Hitachi 270-30; proton nuclear magnetic resonance ( $^1\text{H-NMR}$ ) spectra, JEOL JNM-FX 60 equipped with a JEC-980 computer with tetramethylsilane (TMS,  $\delta=0$ ) as an internal reference; mass spectrum (MS), JEOL JMS-DX 303 and Shimadzu LKB-9000. The abbreviations used are as follows: s, singlet; m, multiplet. Precoated thin-layer chromatography (TLC) plates, Silica gel 60F<sub>254</sub> (Merck), were used for TLC and preparative TLC. The spots were detected under UV (254 nm) illumination as dark, absorbing spots or by spraying the plates with 10%  $\text{H}_2\text{SO}_4$  solution and heating.

**Assay Method for Cyclic AMP Phosphodiesterase**—Samples were tested for cyclic AMP phosphodiesterase activity in duplicate by the method described in the previous papers.<sup>21</sup> All the inhibitors were added as solutions in dimethylsulfoxide (DMSO). The presence of DMSO in the assay medium at up to 2% concentration is known to have no effect on the enzyme activity. The  $\text{IC}_{50}$  value is the concentration of a compound required to give 50% inhibition of cyclic AMP phosphodiesterase activity.

**Enzymes and Chemicals**—Beef heart phosphodiesterase was purchased from Boehringer. Snake venom nucleotidase and cyclic AMP were obtained from Sigma, and [ $^3\text{H}$ ]cyclic AMP from the Radiochemical Centre. Papaverine, a reference inhibitor, was purchased from Tokyo Kasei Kogyo Co., Ltd. (Tokyo).

**(+)-1-Acetoxypinoresinol 4',4''-Di-O- $\beta$ -D-glucopyranoside (5c)**—**4d** (50.6 mg) was acetylated with acetic anhydride–pyridine in the usual way. The crude acetate was purified by preparative TLC using  $\text{CHCl}_3$ –AcOEt (1 : 2) as a developer to give (+)-1-acetoxypinoresinol 4',4''-di-O- $\beta$ -D-glucopyranoside octaacetate (**5d**) (36.9 mg) as an amorphous powder.  $^1\text{H-NMR}$  (in  $\text{CDCl}_3$ )  $\delta$ : 1.67 (3H, s, tertiary alcoholic  $\text{OCOCH}_3$ ), 2.03, 2.07 (24H, each s,  $8 \times$  alcoholic  $\text{OCOCH}_3$ ), 3.81, 3.84 (6H, each s,  $2 \times \text{OCH}_3$ ), 6.80–7.20 (6H, m, arom. H).

**5d** (36.9 mg) was deacetylated with ammonia in methanol. The crude product was purified by preparative TLC using the lower layer of  $\text{CHCl}_3$ –MeOH– $\text{H}_2\text{O}$  (65 : 35 : 10) as a developer to give **5c** (9.9 mg) as an amorphous powder.  $[\alpha]_D^{24} -25.9^\circ$  ( $c=0.33$ , MeOH). UV  $\lambda_{\text{max}}^{\text{EtOH}}$  nm: 229.5, 277. IR  $\nu_{\text{max}}^{\text{KBr}}$   $\text{cm}^{-1}$ : 3436 (OH), 1740 (C=O), 1596, 1514 (aromatic ring). FAB-MS  $m/z$ : 763  $[\text{M}(\text{C}_{34}\text{H}_{44}\text{O}_{18}) + \text{Na}]^+$ .  $^1\text{H-NMR}$  (in  $\text{CD}_3\text{OD}$ )  $\delta$ : 1.66 (3H, s, tertiary alcoholic  $\text{OCOCH}_3$ ), 3.86, 3.88 (6H, each s,  $2 \times \text{OCH}_3$ ), 6.80–7.20 (6H, m, arom. H).

**(-)-Olivil Monoacetate (7a) and (-)-Olivil Diacetate (8a)**—**6a** (94.6 mg) was acetylated with acetic anhydride–pyridine in the usual way. The crude acetate was purified by preparative TLC using  $\text{CHCl}_3$ –AcOEt (1 : 1) as a developer to give (-)-olivil tetraacetate (**8b**) (27 mg) as an amorphous powder.  $^1\text{H-NMR}$  (in  $\text{CDCl}_3$ )  $\delta$ : 1.82 (3H, s, tertiary alcoholic  $\text{OCOCH}_3$ ), 2.07 (3H, s, alcoholic  $\text{OCOCH}_3$ ), 2.29, 2.30 (6H, each s,  $2 \times$  phenolic  $\text{OCOCH}_3$ ), 3.79, 3.82 (6H, each s,  $2 \times \text{OCH}_3$ ), 6.60–7.10 (6H, m, arom. H).

**8b** (27 mg) was deacetylated with ammonia in methanol to give a mixture of **7a** and **8a** (22.5 mg). Separation and purification of the products by TLC afforded **7a** (7.2 mg) as an amorphous powder and **8a** (13.9 mg) as an amorphous powder.

**7a**:  $[\alpha]_D^{24} -49.0^\circ$  ( $c=0.08$ , MeOH). UV  $\lambda_{\text{max}}^{\text{MeOH}}$  nm: 223, 280.5. IR  $\nu_{\text{max}}^{\text{KBr}}$   $\text{cm}^{-1}$ : 3444 (OH), 1732 (C=O), 1606, 1516 (aromatic ring). MS  $m/z$ : 418 ( $\text{M}^+$ ,  $\text{C}_{22}\text{H}_{26}\text{O}_8$ ).  $^1\text{H-NMR}$  (in  $\text{CDCl}_3$ )  $\delta$ : 1.97 (3H, s, tertiary alcoholic  $\text{OCOCH}_3$ ), 3.86, 3.88 (6H, each s,  $2 \times \text{OCH}_3$ ), 6.50–7.00 (6H, m, arom. H).

**8a**:  $[\alpha]_D^{24} -45.5^\circ$  ( $c=0.32$ , MeOH). UV  $\lambda_{\text{max}}^{\text{MeOH}}$  nm: 229, 281. IR  $\nu_{\text{max}}^{\text{KBr}}$   $\text{cm}^{-1}$ : 3444 (OH), 1732 (C=O), 1608, 1516 (aromatic ring). MS  $m/z$ : 460 ( $\text{M}^+$ ,  $\text{C}_{24}\text{H}_{28}\text{O}_9$ ).  $^1\text{H-NMR}$  (in  $\text{CDCl}_3$ )  $\delta$ : 1.90 (3H, s, tertiary alcoholic  $\text{OCOCH}_3$ ), 2.04 (3H, s, alcoholic  $\text{OCOCH}_3$ ), 3.86, 3.87 (6H, each s,  $2 \times \text{OCH}_3$ ), 6.50–7.00 (6H, m, arom. H).

**(-)-Olivil 4',4''-Di-O- $\beta$ -D-glucopyranoside Monoacetate (7b)**—**6d** (58.2 mg) was acetylated with acetic anhydride–pyridine in the usual way. The crude acetate was purified by preparative TLC using  $\text{CHCl}_3$ –AcOEt (1 : 3) as a developer to give (-)-olivil 4',4''-di-O- $\beta$ -D-glucopyranoside decaacetate (**8c**) (35.6 mg) as an amorphous powder.  $^1\text{H-NMR}$  (in  $\text{CDCl}_3$ )  $\delta$ : 1.87 (3H, s, tertiary alcoholic  $\text{OCOCH}_3$ ), 2.03, 2.07 (27H, each s,  $9 \times$  alcoholic  $\text{OCOCH}_3$ ), 3.79 (6H, s,  $2 \times \text{OCH}_3$ ), 6.50–7.20 (6H, m, arom. H).

**8c** (35.6 mg) was deacetylated with ammonia in methanol. The crude product was purified by preparative TLC using the lower layer of  $\text{CHCl}_3$ –MeOH– $\text{H}_2\text{O}$  (65 : 35 : 10) as a developer to give **7b** (4.1 mg) as an amorphous powder.  $[\alpha]_D^{24} -64.3^\circ$  ( $c=0.13$ , MeOH). UV  $\lambda_{\text{max}}^{\text{MeOH}}$  nm: 226, 278. IR  $\nu_{\text{max}}^{\text{KBr}}$   $\text{cm}^{-1}$ : 3428 (OH), 1730 (C=O), 1596, 1512 (aromatic ring). FAB-MS  $m/z$ : 765  $[\text{M}(\text{C}_{34}\text{H}_{46}\text{O}_{18}) + \text{Na}]^+$ .  $^1\text{H-NMR}$  (in  $\text{CD}_3\text{OD}$ )  $\delta$ : 1.83 (3H, s, tertiary alcoholic  $\text{OCOCH}_3$ ), 3.84 (6H, s,  $2 \times \text{OCH}_3$ ), 6.70–7.20 (6H, m, arom. H).

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- 1) This paper forms Part XIV of "Inhibitors of Cyclic AMP Phosphodiesterase in Medicinal Plants." Part XIII: T.

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