



IgE-Suppressive Activity of (–)-Matairesinol and Its Structure-Activity Relationship

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The IgE-suppressive activity of (–)-matairesinol is demonstrated, and the structure-activity relationship of (–)-matairesinol clarified. 3',4-Dihydroxy-3,4'-dimethoxylignano-9,9'-lactone showed higher IgE-suppressive activity than (–)-matairesinol without any cytotoxic activity. Some derivatives bearing a longer and more bulky alkoxy group at the 3 or 4 position showed IgE-accelerative activity.

Key words: lignan; matairesinol; IgE-suppressive activity

(–)-Matairesinol, α,β -dibenzyl- γ -butyrolactone lignan, is one of the well-known lignans contained in food plant.¹⁻⁴ Although many α,β -dibenzyl- γ -butyrolactone lignans have been isolated from plants,⁵ a detailed study on the relationship between the structure and biological activity and the effect of the stereochemistry on the biological activity has not been conducted. Our interest is the chemical function of the food plant and the structure-activity relationship of the biologically active compounds contained in the food plant. Antibody-productive activity was selected to clarify the effect of food plants on the human health in this study. Since the biosynthesis as an enantiomeric mixtures has been reported in the biosynthetic research on lignan,⁶ (–)-matairesinol and its stereoisomers were examined at first, and then the derivatives were applied to the biological testing. The stereoisomers of matairesinol and derivatives were synthesized by the previously described method.⁷⁻¹⁰ Since IgE is an antibody for allergy, suppressing the activity of IgE-production would decrease the allergic symptoms, while promotive compounds would contribute to research into allergy. The IgM- and IgE-productive activities of secoisolariciresinol, which is a butanediol type of lignan contained in food plant, were examined in our previous study, and the IgM-accelerative production of (–)- and (+)-secoisolariciresinol was observed; however, none of the stereoisomers of secoisolariciresinol affected the IgE-productive activity.¹¹ In this article, the IgE-productive activity of four stereoisomers of matairesinol is compared, and the structure-activity relationship of (–)-matairesinol is described. The results of this study should contribute to the development of new medicines and the utilization of natural resources.

Material and Methods

Melting point (mp) data are uncorrected. NMR data were measured by a JNM-EX400 spectrometer, using TMS as a standard (0 ppm), MS data were measured with a JMS-MS700V spectrometer, and optical rotation values were evaluated with a Horiba SEPA-200 instrument. The nomenclature of compounds follows the literature for lignans.¹² All stereoisomers and derivatives were prepared by the previously described method.⁷⁻¹⁰ The enantiomeric excess of all stereoisomers of matairesinol prepared by the previous method was determined as more than 99%ee by using a chiral column.^{9,13}

(7S,8S,8'R)-4,4',7-Trihydroxy-3,3'-dimethoxylignano-9,9'-lactone (**12**). The title compound was obtained from (2S,3R)-3-(4-benzyloxy-3-methoxybenzyl)-2-[(S)-(4-benzyloxy-3-methoxyphenyl)hydroxy]-methyl-4-butanolide by hydrogenolysis.⁸ Colorless oil, $[\alpha]_D^{20}$ –48 (c 0.6, CHCl₃). NMR δ_H (CDCl₃): 2.27 (1H, dd, J = 13.7, 8.2 Hz), 2.48 (1H, dd, J = 13.7, 7.7 Hz), 2.62 (1H, dd, J = 5.7, 3.1 Hz), 2.74 (1H, m), 2.96 (1H, d, J = 4.8 Hz), 3.74 (3H, s), 3.78 (3H, s), 3.96 (1H, dd, J = 8.8, 5.3 Hz), 4.35 (1H, dd, J = 8.8, 8.8 Hz), 5.25 (1H, dd, J = 4.8, 3.1 Hz), 5.72 (1H, s), 5.61 (1H, s), 6.21 (1H, br. s), 6.35 (1H, br. d, J = 7.9 Hz), 6.58 (1H, br. s), 6.70 (1H, br. d, J = 7.9 Hz), 6.79 (1H, d, J = 7.9 Hz), 6.84 (1H, d, J = 7.9 Hz). NMR δ_C (CDCl₃): 36.5, 39.3, 52.7, 55.5, 55.7, 72.0, 73.0, 107.6, 110.7, 114.0, 114.1, 117.8, 121.3, 129.6, 132.8, 144.2, 144.9, 146.5, 146.6, 178.7. EIMS m/z : 374 (M⁺, 17), 153 (57), 133 (65), 89 (100). HRMS (EI) m/z (M⁺): calcd. for C₂₀H₂₂O₇, 374.1365; found, 374.1367.

(7R,8S,8'R)-4,4',7-Trihydroxy-3,3'-dimethoxylignano-9,9'-lactone (**13**). The title compound was obtained from (2S,3R)-3-(4-benzyloxy-3-methoxybenzyl)-2-[(R)-(4-benzyloxy-3-methoxyphenyl)hydroxy]-methyl-4-butanolide by hydrogenolysis.⁸ Colorless oil, $[\alpha]_D^{20}$ –37 (c 1.1, CHCl₃). NMR δ_H (CDCl₃): 2.12 (1H, dd, J = 13.8, 5.5 Hz), 2.23 (1H, dd, J = 13.8, 9.3 Hz), 2.43 (1H, m), 2.58 (1H, dd, J = 8.4, 8.4 Hz), 3.79 (3H, s), 3.86 (3H, s), 3.90 (1H, dd, J = 8.9, 8.9 Hz), 4.15 (1H, s), 4.15 (1H, dd, J = 8.9, 8.9 Hz), 4.77 (1H, d, J = 8.4 Hz), 5.65 (1H, s), 5.83 (1H, s), 6.27 (1H, d, J = 1.8 Hz), 6.38 (1H, dd, J = 8.0, 1.8 Hz), 6.74 (1H, d, J = 8.0 Hz), 6.86 (1H, d, J = 8.0 Hz), 6.89–6.91 (2H, m). NMR δ_C (CDCl₃): 38.3, 39.8, 51.2, 55.7, 55.9, 72.1, 74.3, 108.7, 110.8, 114.0, 114.4, 119.8, 121.0, 129.6, 132.0, 144.3, 145.9, 146.5, 147.0, 179.1. EIMS m/z : 374 (M⁺, 28), 153 (100), 137 (47). HRMS (EI) m/z (M⁺): calcd. for C₂₀H₂₂O₇, 374.1365; found, 374.1364.

(8R,8'R)-4'-Hydroxy-3',4'-dimethoxylignano-9,9'-lactone (**19**). Colorless oil, $[\alpha]_D^{20}$ –29 (c 1.0, CHCl₃). NMR δ_H (CDCl₃): 2.40–2.50 (2H, m), 2.54–2.60 (2H, m), 2.88 (1H, dd, J = 14.1, 7.2 Hz), 2.99 (1H, dd, J = 14.1, 5.3 Hz), 3.78 (3H, s), 3.82 (3H, s), 3.85 (1H, dd, J = 9.3, 6.3 Hz), 4.10 (1H, dd, J = 9.3, 7.0 Hz), 5.62 (1H, s), 6.43 (1H, d, J = 1.8 Hz), 6.50 (1H, dd, J = 7.9, 1.8 Hz), 6.80 (1H, d, J = 7.9 Hz), 6.81 (2H, d, J = 8.5 Hz), 7.05 (2H, d, J = 8.5 Hz). NMR δ_C (CDCl₃):

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34.1, 38.2, 41.2, 46.4, 55.1, 55.8, 71.1, 111.0, 113.9, 114.4, 121.2, 129.6, 129.7, 130.2, 144.3, 146.5, 158.4, 178.7. EIMS m/z : 342 (M^+ , 70), 121 (100). HRMS (EI) m/z (M^+): calcd. for $C_{20}H_{22}O_5$, 342.1467; found, 342.1466.

(8*R*,8'*R*)-3-Ethoxy-4,4'-dihydroxy-3'-methoxylignano-9,9'-lactone (**24**). Colorless crystals, mp 87–88 °C, $[\alpha]_D^{20}$ –22 (c 0.5, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.42 (3H, t, $J = 6.9$ Hz), 2.43–2.58 (3H, m), 2.61 (1H, dd, $J = 13.1$, 6.2 Hz), 2.87 (1H, dd, $J = 14.2$, 6.7 Hz), 2.93 (1H, dd, $J = 14.2$, 5.3 Hz), 3.81 (3H, s), 3.87 (1H, dd, $J = 9.1$, 7.2 Hz), 4.02 (2H, q, $J = 6.9$ Hz), 4.13 (1H, dd, $J = 9.1$, 7.3 Hz), 5.54 (1H, s), 5.61 (1H, s), 6.41 (1H, d, $J = 1.8$ Hz), 6.50 (1H, dd, $J = 8.0$, 1.8 Hz), 6.58–6.61 (2H, m), 6.79 (1H, d, $J = 8.0$ Hz), 6.82 (1H, d, $J = 7.9$ Hz). NMR δ_C ($CDCl_3$): 14.8, 34.5, 38.3, 41.0, 46.6, 55.8, 64.4, 71.3, 110.9, 112.4, 114.0, 114.4, 121.3, 122.0, 129.4, 129.8, 144.4, 144.6, 146.0, 146.6, 178.8. EIMS m/z : 372 (M^+ , 100), 151 (80), 137 (60). HRMS (EI) m/z (M^+): calcd. for $C_{21}H_{24}O_6$, 372.1573; found, 372.1572.

(8*R*,8'*R*)-3-Butoxy-4,4'-dihydroxy-3'-methoxylignano-9,9'-lactone (**25**). Colorless oil, $[\alpha]_D^{20}$ –23 (c 0.9, $CHCl_3$). NMR δ_H ($CDCl_3$): 0.98 (3H, t, $J = 7.3$ Hz), 1.48 (2H, m), 1.78 (2H, m), 2.43–2.57 (3H, m), 2.60 (1H, m), 2.87 (1H, dd, $J = 14.1$, 7.0 Hz), 2.94 (1H, dd, $J = 14.1$, 5.3 Hz), 3.81 (3H, s), 3.87 (1H, dd, $J = 9.1$, 7.3 Hz), 3.96 (2H, t, $J = 6.6$ Hz), 4.13 (1H, dd, $J = 9.1$, 7.1 Hz), 5.56 (1H, s), 5.60 (1H, s), 6.42 (1H, d, $J = 1.8$ Hz), 6.50 (1H, dd, $J = 8.1$, 1.8 Hz), 6.59 (1H, dd, $J = 7.9$, 1.9 Hz), 6.62 (1H, d, $J = 1.9$ Hz), 6.79 (1H, d, $J = 7.9$ Hz), 6.82 (1H, d, $J = 8.1$ Hz). NMR δ_C ($CDCl_3$): 13.9, 19.2, 31.3, 34.6, 38.3, 41.0, 46.6, 55.8, 68.7, 71.3, 111.0, 112.5, 114.0, 114.5, 121.3, 121.9, 129.5, 129.8, 144.5, 144.7, 146.2, 146.6, 178.8. EIMS m/z : 400 (M^+ , 46), 196 (75), 140 (100), 123 (97). HRMS (EI) m/z (M^+): calcd. for $C_{23}H_{28}O_6$, 400.1885; found, 400.1879.

(8*R*,8'*R*)-4,4'-Dihydroxy-3-isopropoxy-3'-methoxylignano-9,9'-lactone (**26**). Colorless oil, $[\alpha]_D^{20}$ –20 (c 4.4, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.31 (3H, d, $J = 6.1$ Hz), 1.33 (3H, d, $J = 6.1$ Hz), 2.43–2.57 (3H, m), 2.61 (1H, m), 2.87 (1H, dd, $J = 14.0$, 6.0 Hz), 2.92 (1H, dd, $J = 14.0$, 5.4 Hz), 3.80 (3H, s), 3.85 (1H, dd, $J = 8.8$, 7.4 Hz), 4.09 (1H, dd, $J = 8.8$, 7.0 Hz), 4.50 (1H, m), 5.76 (1H, s), 5.79 (1H, s), 6.45 (1H, d, $J = 1.7$ Hz), 6.50 (1H, dd, $J = 8.1$, 1.7 Hz), 6.59 (1H, dd, $J = 8.1$, 1.7 Hz), 6.68 (1H, d, $J = 1.7$ Hz), 6.79 (1H, d, $J = 8.1$ Hz), 6.82 (1H, d, $J = 8.1$ Hz). NMR δ_C ($CDCl_3$): 22.0, 22.2, 34.5, 38.2, 41.0, 46.6, 55.8, 71.3, 71.6, 111.2, 114.3, 114.4, 114.5, 121.3, 122.1, 129.4, 129.8, 144.5, 144.8, 145.5, 146.7, 178.9. EIMS m/z : 386 (M^+ , 41), 149 (57), 137 (100), 123 (66). HRMS (EI) m/z (M^+): calcd. for $C_{22}H_{26}O_6$, 386.1730; found, 386.1726.

(8*R*,8'*R*)-4-Ethoxy-3,4'-dihydroxy-3'-methoxylignano-9,9'-lactone (**27**). Colorless oil, $[\alpha]_D^{20}$ –23 (c 1.0, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.43 (3H, t, $J = 7.0$ Hz), 2.39–2.58 (4H, m), 2.81 (1H, dd, $J = 14.1$, 7.3 Hz), 2.98 (1H, dd, $J = 14.1$, 4.8 Hz), 3.83–3.87 (1H, overlapped), 3.84 (3H, s), 4.05–4.12 (3H, m), 5.59 (1H, s), 5.71 (1H, s), 6.47 (1H, br. s), 6.50 (1H, br. d, $J = 8.1$ Hz), 6.62 (1H, br. d, $J = 8.1$ Hz), 6.72–6.74 (2H, m), 6.79 (1H, d, $J = 8.1$ Hz). NMR δ_C ($CDCl_3$): 14.9, 34.6, 38.2, 41.5, 46.3, 55.9, 64.5, 71.2, 111.0, 111.7, 114.4, 115.4, 120.7, 121.3, 129.9, 130.8, 144.4, 144.7, 145.7, 146.6, 178.7. EIMS m/z : 372 (M^+ , 100). HRMS (EI) m/z (M^+): calcd. for $C_{21}H_{24}O_6$, 372.1573; found, 372.1566.

(8*R*,8'*R*)-4-Butoxy-3,4'-dihydroxy-3'-methoxylignano-9,9'-lactone (**28**). Colorless oil, $[\alpha]_D^{20}$ –21 (c 0.8, $CHCl_3$). NMR δ_H ($CDCl_3$): 0.98 (3H, t, $J = 7.4$ Hz), 1.49 (2H, m), 1.79 (2H, m), 2.40–2.59 (4H, m), 2.82 (1H, dd, $J = 14.1$, 7.3 Hz), 2.98 (1H, dd, $J = 14.1$, 4.9 Hz), 3.83–3.87 (1H, overlapped), 3.84 (3H, s), 4.01 (2H, t, $J = 6.5$ Hz), 4.10 (1H, dd, $J = 9.2$, 6.9 Hz), 5.56 (1H, s), 5.66 (1H, s), 6.47 (1H, s), 6.50 (1H, d, $J = 8.0$ Hz), 6.62 (1H, d, $J = 8.0$ Hz), 6.73–6.75 (2H, m), 6.80 (1H, d, $J = 7.9$ Hz). NMR δ_C ($CDCl_3$): 13.8, 19.2, 31.3, 34.6, 38.3, 41.5, 46.3, 55.8, 68.7, 71.2, 111.0, 111.7, 114.4, 115.4, 120.7, 121.3, 129.9, 130.7, 144.4, 144.9, 145.7, 146.6, 178.7. EIMS m/z : 400 (M^+ , 30), 167 (68), 149 (100). HRMS (EI) m/z (M^+): calcd. for $C_{23}H_{28}O_6$, 400.1885; found, 400.1884.

(8*R*,8'*R*)-3,4'-Dihydroxy-4-isopropoxy-3'-methoxylignano-9,9'-lactone (**29**). Colorless oil, $[\alpha]_D^{20}$ –25 (c 0.9, $CHCl_3$). NMR δ_H ($CDCl_3$):

1.35 (6H, d, $J = 6.0$ Hz), 2.40–2.60 (4H, m), 2.82 (1H, dd, $J = 14.0$, 7.3 Hz), 2.98 (1H, dd, $J = 14.0$, 4.9 Hz), 3.83–3.87 (1H, overlapped), 3.84 (3H, s), 4.09 (1H, dd, $J = 6.9$, 4.7 Hz), 4.54 (1H, m), 5.56 (1H, s), 5.72 (1H, s), 6.48 (1H, d, $J = 2.0$ Hz), 6.50 (1H, br. d, $J = 7.9$ Hz), 6.62 (1H, dd, $J = 7.9$, 2.0 Hz), 6.74–6.77 (2H, m), 6.80 (1H, d, $J = 7.9$ Hz). NMR δ_C ($CDCl_3$): 22.2, 34.6, 38.2, 41.5, 46.3, 55.9, 71.2, 71.8, 111.1, 113.5, 114.5, 115.6, 120.6, 121.3, 129.9, 130.9, 143.5, 144.4, 146.6, 178.7. EIMS m/z : 386 (M^+ , 41), 149 (57), 137 (100), 123 (66). HRMS (EI) m/z (M^+): calcd. for $C_{22}H_{26}O_6$, 386.1730; found, 386.1724.

(8*R*,8'*R*)-4,4'-Dihydroxy-3,3',5'-trimethoxylignano-9,9'-lactone (**31**). Colorless oil, $[\alpha]_D^{20}$ –32 (c 1.2, $CHCl_3$). NMR δ_H ($CDCl_3$): 2.48 (1H, ddd, $J = 13.4$, 6.1, 6.1 Hz), 2.54–2.62 (3H, m), 2.86 (1H, dd, $J = 14.1$, 7.0 Hz), 2.96 (1H, dd, $J = 14.1$, 5.1 Hz), 3.80 (3H, s), 3.82 (6H, s), 3.90 (1H, dd, $J = 7.8$, 7.3 Hz), 4.18 (1H, dd, $J = 7.8$, 7.8 Hz), 5.48 (1H, s), 5.64 (1H, s), 6.17 (2H, s), 6.59–6.60 (2H, m), 6.81 (1H, d, $J = 8.5$ Hz). NMR δ_C ($CDCl_3$): 34.6, 38.8, 41.0, 46.5, 55.8, 56.2, 71.4, 105.2, 111.4, 114.1, 122.0, 129.0, 129.5, 133.5, 144.6, 146.8, 147.1, 178.8. EIMS m/z : 388 (M^+ , 100), 167 (63), 137 (75). HRMS (EI) m/z (M^+): calcd. for $C_{21}H_{24}O_7$, 388.1522; found, 388.1525.

(8*R*,8'*R*)-4-Hydroxy-3,4'-dimethoxylignano-9,9'-lactone (**33**). Colorless oil, $[\alpha]_D^{20}$ –24 (c 3.3, $CHCl_3$). NMR δ_H ($CDCl_3$): 2.43–2.56 (3H, m), 2.59 (1H, dd, $J = 9.5$, 7.4 Hz), 2.87 (1H, dd, $J = 14.2$, 6.5 Hz), 2.92 (1H, dd, $J = 14.2$, 5.1 Hz), 3.76 (3H, s), 3.80 (3H, s), 3.84 (1H, dd, $J = 9.1$, 3.2 Hz), 4.07 (1H, dd, $J = 9.1$, 6.7 Hz), 5.84 (1H, s), 6.61 (1H, dd, $J = 8.1$, 1.8 Hz), 6.64 (1H, d, $J = 1.8$ Hz), 6.77–6.83 (3H, m), 6.90 (2H, d, $J = 8.1$ Hz). NMR δ_C ($CDCl_3$): 34.3, 37.4, 40.8, 46.4, 55.0, 55.7, 71.1, 111.6, 113.9, 114.2, 121.9, 129.3, 129.4, 129.8, 144.4, 146.6, 158.1, 178.7. EIMS m/z : 342 (M^+ , 88), 137 (100), 121 (61). HRMS (EI) m/z (M^+): calcd. for $C_{20}H_{22}O_5$, 342.1467; found, 342.1470.

(8*R*,8'*R*)-4,4'-Dihydroxy-3-methoxylignano-9,9'-lactone (**34**). Colorless oil, $[\alpha]_D^{20}$ –22 (c 0.7, $CHCl_3$). NMR δ_H ($CDCl_3$): 2.44–2.52 (2H, m), 2.52–2.62 (2H, m), 2.88 (1H, dd, $J = 13.8$, 6.7 Hz), 2.91 (1H, dd, $J = 13.8$, 5.4 Hz), 3.81 (3H, s), 3.86 (1H, dd, $J = 9.0$, 9.0 Hz), 4.11 (1H, dd, $J = 9.0$, 7.2 Hz), 5.70 (1H, s), 5.88 (1H, s), 6.60 (1H, d, $J = 8.4$ Hz), 6.63 (1H, s), 6.73 (2H, d, $J = 8.4$ Hz), 6.81–6.84 (3H, m). NMR δ_C ($CDCl_3$): 34.4, 37.6, 40.9, 46.6, 55.8, 71.5, 111.6, 114.2, 115.5, 122.1, 129.4, 129.6, 129.7, 144.4, 146.7, 154.6, 179.4. HRMS (EI) m/z (M^+): calcd. for $C_{19}H_{20}O_5$, 328.1311; found, 328.1312.

(8*R*,8'*R*)-3'-Ethoxy-4,4'-dihydroxy-3-methoxylignano-9,9'-lactone (**37**). Colorless oil, $[\alpha]_D^{20}$ –24 (c 0.6, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.43 (3H, t, $J = 6.9$ Hz), 2.42–2.62 (4H, m), 2.87 (1H, dd, $J = 14.1$, 6.9 Hz), 2.94 (1H, dd, $J = 14.1$, 5.2 Hz), 3.81 (3H, s), 3.87 (1H, dd, $J = 9.0$, 7.0 Hz), 4.00 (2H, q, $J = 6.9$ Hz), 4.13 (1H, dd, $J = 9.0$, 7.1 Hz), 5.59 (1H, s), 5.61 (1H, s), 6.40 (1H, d, $J = 1.8$ Hz), 6.49 (1H, dd, $J = 8.1$, 1.8 Hz), 6.59–6.62 (2H, m), 6.80 (1H, d, $J = 8.1$ Hz), 6.81 (1H, d, $J = 7.7$ Hz). NMR δ_C ($CDCl_3$): 14.8, 34.5, 38.2, 41.0, 46.5, 55.8, 64.4, 71.3, 111.5, 111.8, 114.0, 114.3, 121.2, 122.0, 129.5, 129.6, 144.48, 144.52, 145.9, 146.7, 178.8. EIMS m/z : 372 (M^+ , 99), 137 (100). HRMS (EI) m/z (M^+): calcd. for $C_{21}H_{24}O_6$, 372.1573; found, 372.1572.

(8*R*,8'*R*)-3'-Butoxy-4,4'-dihydroxy-3-methoxylignano-9,9'-lactone (**38**). Colorless oil, $[\alpha]_D^{20}$ –26 (c 0.8, $CHCl_3$). NMR δ_H ($CDCl_3$): 0.99 (3H, t, $J = 7.4$ Hz), 1.50 (2H, m), 1.79 (2H, m), 2.43–2.63 (4H, m), 2.88 (1H, dd, $J = 14.1$, 6.7 Hz), 2.94 (1H, dd, $J = 14.1$, 5.3 Hz), 3.82 (3H, s), 3.87 (1H, dd, $J = 8.9$, 7.3 Hz), 3.94 (2H, t, $J = 6.6$ Hz), 4.13 (1H, dd, $J = 8.9$, 7.2 Hz), 5.59 (2H, s), 6.42 (1H, br. s), 6.50 (1H, br. d, $J = 7.8$ Hz), 6.60 (1H, br. d, $J = 8.0$ Hz), 6.62 (1H, br. s), 6.80 (1H, d, $J = 8.0$ Hz), 6.81 (1H, d, $J = 7.8$ Hz). NMR δ_C ($CDCl_3$): 13.9, 19.2, 31.3, 34.6, 38.3, 41.1, 46.6, 55.9, 68.6, 71.3, 111.6, 111.9, 114.1, 114.4, 121.2, 122.1, 129.5, 129.7, 144.56, 144.58, 146.1, 146.7, 178.8. EIMS m/z : 400 (M^+ , 54), 208 (59), 137 (91), 123 (100). HRMS (EI) m/z (M^+): calcd. for $C_{23}H_{28}O_6$, 400.1885; found, 400.1875.

(8*R*,8'*R*)-4,4'-Dihydroxy-3'-isopropoxy-3-methoxylignano-9,9'-lactone (**39**). Colorless oil, $[\alpha]_D^{20}$ –27 (c 1.0, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.33 (3H, t, $J = 6.0$ Hz), 1.35 (3H, d, $J = 6.1$ Hz), 3.42–2.51 (2H, m),

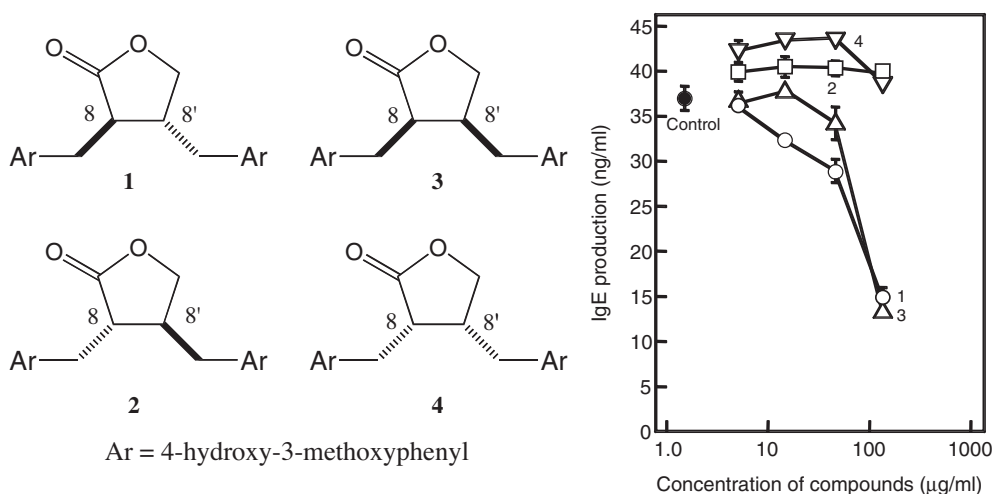


Fig. 1. IgE-Productive Activity of (–)-Matairesinol and Its Stereoisomers.

2.54–2.63 (2H, m), 2.61 (1H, dd, $J = 14.1$, 5.4 Hz), 2.95 (1H, dd, $J = 14.1$, 5.1 Hz), 3.83 (3H, s), 3.86 (1H, dd, $J = 7.7$, 7.7 Hz), 4.11 (1H, dd, $J = 7.7$, 7.7 Hz), 4.47 (1H, m), 5.59 (1H, s), 5.64 (1H, s), 6.46 (1H, br. s), 6.49 (1H, br. d, $J = 8.1$ Hz), 6.61 (1H, br. d, $J = 8.1$ Hz), 6.65 (1H, br. s), 6.81 (1H, d, $J = 8.1$ Hz), 6.82 (1H, d, $J = 8.1$ Hz). NMR δ_C (CDCl₃): 22.1, 22.2, 34.5, 38.2, 41.1, 46.6, 55.9, 71.3, 71.8, 111.6, 113.8, 114.2, 114.6, 121.3, 122.1, 129.5, 129.6, 144.59, 144.63, 145.4, 146.7, 178.8. EIMS m/z : 386 (M^+ , 16), 137 (49), 123 (100). HRMS (EI) m/z (M^+): calcd. for C₂₂H₂₆O₆, 386.1730; found, 386.1714.

(8*R*,8'*R*)-4'-Ethoxy-3',4-dihydroxy-3-methoxylignano-9,9'-lactone (40). Colorless oil, $[\alpha]_D^{20} -27$ (c 1.7, CHCl₃). NMR δ_H (CDCl₃): 1.43 (3H, t, $J = 7.1$ Hz), 2.41–2.52 (2H, m), 2.53–2.61 (2H, m), 2.89 (1H, dd, $J = 14.2$, 6.2 Hz), 2.93 (1H, dd, $J = 14.2$, 5.4 Hz), 3.81–3.85 (1H, overlapped), 3.84 (3H, s), 4.05–4.10 (1H, overlapped), 4.07 (2H, q, $J = 7.1$ Hz), 5.69 (1H, s), 5.78 (1H, s), 6.46 (1H, dd, $J = 8.1$, 2.0 Hz), 6.59 (1H, d, $J = 2.0$ Hz), 6.63 (1H, dd, $J = 7.9$, 1.9 Hz), 6.68 (1H, d, $J = 1.9$ Hz), 6.71 (1H, d, $J = 8.1$ Hz), 6.83 (1H, d, $J = 7.9$ Hz). NMR δ_C (CDCl₃): 14.8, 34.4, 37.8, 40.8, 46.5, 55.8, 64.5, 71.2, 111.6, 114.3, 114.7, 119.9, 122.0, 129.4, 131.0, 144.4, 144.6, 145.8, 146.6, 178.7. EIMS m/z : 372 (M^+ , 79), 137 (100). HRMS (EI) m/z (M^+): calcd. for C₂₁H₂₄O₆, 372.1573; found, 372.1575.

(8*R*,8'*R*)-4'-Butoxy-3',4-dihydroxy-3-methoxylignano-9,9'-lactone (41). Colorless oil, $[\alpha]_D^{20} -18$ (c 1.3, CHCl₃). NMR δ_H (CDCl₃): 0.98 (3H, t, $J = 7.4$ Hz), 1.49 (2H, m), 1.78 (2H, m), 2.42–2.51 (2H, m), 2.53–2.62 (2H, m), 2.89 (1H, dd, $J = 14.1$, 6.2 Hz), 2.94 (1H, dd, $J = 14.2$, 5.4 Hz), 3.81–3.85 (1H, overlapped), 3.84 (3H, s), 3.84 (2H, t, $J = 7.0$ Hz), 4.09 (1H, dd, $J = 9.2$, 7.0 Hz), 5.64 (1H, s), 5.72 (1H, s), 6.46 (1H, dd, $J = 8.2$, 2.0 Hz), 6.59 (1H, d, $J = 2.0$ Hz), 6.64 (1H, dd, $J = 8.0$, 1.7 Hz), 6.68 (1H, d, $J = 1.7$ Hz), 6.72 (1H, d, $J = 8.2$ Hz), 6.83 (1H, d, $J = 8.0$ Hz). NMR δ_C (CDCl₃): 13.8, 19.2, 31.3, 34.5, 37.9, 40.9, 46.6, 55.9, 68.7, 71.3, 111.69, 111.73, 114.3, 114.7, 120.0, 122.2, 129.5, 131.0, 144.5, 144.8, 145.9, 146.7, 178.8. EIMS m/z : 400 (M^+ , 67), 137 (100), 123 (61). HRMS (EI) m/z (M^+): calcd. for C₂₃H₂₈O₆, 400.1885; found, 400.1884.

(8*R*,8'*R*)-3',4-Dihydroxy-4'-isopropoxy-3-methoxylignano-9,9'-lactone (42). Colorless oil, $[\alpha]_D^{20} -24$ (c 0.8, CHCl₃). NMR δ_H (CDCl₃): 1.35 (6H, d, $J = 6.0$ Hz), 2.42–2.51 (2H, m), 2.53–2.62 (2H, m), 2.90–2.96 (2H, m), 3.82–3.86 (1H, overlapped), 3.85 (3H, s), 4.09 (1H, dd, $J = 9.1$, 7.0 Hz), 4.53 (1H, s), 5.56 (1H, s), 5.71 (1H, s), 6.46 (1H, dd, $J = 8.1$, 2.0 Hz), 6.60 (1H, d, $J = 2.0$ Hz), 6.64 (1H, br. d, $J = 8.1$ Hz), 6.69 (1H, br. s), 6.74 (1H, d, $J = 8.1$ Hz), 6.84 (1H, d, $J = 8.1$ Hz). NMR δ_C (CDCl₃): 22.2, 34.5, 37.9, 40.9, 46.6, 55.9, 71.3, 71.8, 111.7, 113.4, 114.3, 114.8, 120.0, 122.2, 129.5, 131.2, 143.4, 144.5, 146.7, 178.8. EIMS m/z : 386 (M^+ , 92), 344 (72), 137 (100). HRMS (EI) m/z (M^+): calcd. for C₂₂H₂₆O₆, 386.1730; found, 386.1729.

Assay of the IgM productive activity. The IgM concentration was measured by the same method as that previously described in the literature.¹¹⁾

Assay of cytotoxicity. The cytotoxicity of each compound was determined by a WST-8 assay (Kishida Reagents Chemicals, Osaka, Japan). Viable cells produce WST-8 formazan which is detectable by its absorbance at 450 nm. U266 cells were seeded in different culture media containing various concentrations of each MAT compound and cultured for 24 h. A WST-8 solution was added to the culture medium at 10%, and the mixture incubated for 2 h. The absorbance at 450 nm was measured after this incubation.

Assay of the IgE-productive activity. The IgE concentration was measured by the same method as that previously described in the literature.¹¹⁾

Results and Discussion

IgE-Productive activity of (–)-matairesinol

Although (–)- and (+)-secoisolariciresinol, which are butanediol-type lignans, showed accelerated IgM-production in our previous study,¹¹⁾ none of the stereoisomers of matairesinol, which is a γ -butyrolactone-type lignan, affected the IgM-production. It could be assumed that the butanediol structure was important for promoting IgM-production. In the case of the IgE-productive activity, no stereoisomer of secoisolariciresinol affected the IgE-productive activity;¹¹⁾ however, (8*R*,8'*R*) **1** and (8*R*,8'*S*) **3** isomers of matairesinol showed suppressive activity. Both the lactone ring and stereochemistry were important for this IgE-suppressive activity. Natural (8*R*,8'*R*)-(–)-matairesinol (**1**) showed higher activity than (8*R*,8'*S*) isomer **3** (Fig. 1), and no cytotoxic effect was apparent. Since the two 8*S* isomers **2** and **4** did not show activity, the 8*R* stereochemistry seems to have been more important than stereochemistry at the 8' position for the IgE-suppressive activity. The (8*R*,8'*R*)-(–)-matairesinol derivatives were then applied to the activity test to study the relationship between the structure of matairesinol and the IgE-productive activity.

Cytotoxic activity of the derivatives

U266 cells that produce IgE were used to evaluate the IgE (allergic antibody)-productive activity. The IgE-suppressive activity cannot be evaluated in the case of a cytotoxic compound. It can be said that IgE-suppressive

Table 1. Cytotoxic and IgE-Productive Activity of (–)-Matairesinol (**1**) and Its Derivatives

Compounds	Cytotoxic activity (IC ₅₀ , μ M)	IgE-Productive activity	Compounds	Cytotoxic activity (IC ₅₀ , μ M)	IgE-Productive activity
1	>30	suppressive	32	>30	suppressive
9	22 $\pm$ 0.082	—	34	25 $\pm$ 0.010	—
23	7.6 $\pm$ 0.042	promotive	35	>30	suppressive
24	>30	promotive	36	18 $\pm$ 0.051	—
25	8.6 $\pm$ 0.062	—	38	30 $\pm$ 0.091	—
26	>30	promotive	39	18 $\pm$ 0.032	—
27	>30	promotive	40	12 $\pm$ 0.041	—
28	19 $\pm$ 0.033	promotive	41	4.8 $\pm$ 0.054	—
29	28 $\pm$ 0.022	promotive	42	8.2 $\pm$ 0.092	—
30	6.8 $\pm$ 0.10	—			

The other compounds did not show activity.

activity was seen when no cytotoxic activity was apparent and a low IgE concentration was shown. Compounds showing both a high level of cytotoxic activity and high level of IgE concentration would accelerate the IgE production, because a small amount of cells produce a large amount of IgE. The derivatives that showed IgE-suppressive or -accelerative activity without cytotoxic activity would be the desired compounds, so the cytotoxic activity should be examined before evaluating the activity against IgE (Table 1).

Compounds **5–15** (Fig. 2) were tested to clarify the effect on activity of the oxidation degree of the α,β -dibenzyl- γ -butyrolactone structure. Only (8*S*,8'*S*)- α -hydroxy matairesinol (**9**) had cytotoxic activity, showing the effect of stereochemistry. Thus, no cytotoxic activity of (8*R*,8'*S*)- α -hydroxy matairesinol (**8**) was apparent. Oxidation at the 7 and 7' benzylic positions did not affect the cytotoxic activity. Neither the tetrahydrofuran ring nor lactone ring showed any activity. In the case of the derivatives of the aromatic ring, 3,4-dihydroxy derivative **23**, 3-butoxy-4-hydroxy derivative **25**, 3',4'-dimethoxy derivative **30**, 4'-butoxy-3'-hydroxy derivative **41**, and 3'-hydroxy-4'-isopropoxy derivative **42** showed especially high cytotoxic activity. These activities were weaker than that of podophyllotoxin (IC₅₀, 0.031–0.034 μ M).²⁵) 4-Butoxy-3-hydroxy derivative **28**, 3-hydroxy-4-isopropoxy derivative **29**, 4'-hydroxy derivative **34**, 3',4'-dihydroxy derivative **36**, 3'-butoxy-4'-hydroxy derivative **38**, 4'-hydroxy-3'-isopropoxy derivative **39**, and 4'-ethoxy-3'-hydroxy derivative **40** also showed cytotoxic activity. The longer and more bulky the alkoxy group on the aromatic ring, the greater the cytotoxic activity, and the catechol type of structure also had activity. The cytotoxic activities of **30** and **34** suggests that the 3'-methoxy group and 4'-hydroxy group of matairesinol were important for suppressing the cytotoxic activity. Even if the hydroxy group was not present, 3',4'-methylenedioxy derivative **32** and 4'-methoxy derivative **33** did not show any activity. These results mean that the less bulky group at the 3' and 4' positions than the 3',4'-dimethoxy group suppressed the activity. The positions of the methoxy group and hydroxy group at the 3' and 4' positions were not important for the activity, because the 3'-hydroxy-4'-methoxy **35** derivative did not show any activity. The derivatives on 7-phenyl group did not show the cytotoxic activity, except for catechol and the longer

alkoxy derivatives, suggesting the low contribution to this activity of the substituent on the 3 and 4 positions of matairesinol.

IgE-Productive activity of the derivatives

Table 1 and Fig. 3 show the IgE-productive activity. The loss of IgE-suppressive activity of **5–15** means that two free benzylic positions were necessary for the activity of matairesinol. No activity of tetrahydrofuran derivatives **10** and **11** suggest that the lactone structure was important for the IgE-suppressive activity. Derivatives **16–21** on the 7-phenyl group and 4,4'-dehydroxy derivative **22** did not show any activity. 3,4-Dihydroxy derivative **23** showed high cytotoxic activity, although the IgE concentration remained at a high level at 10 μ mol. This means that the IgE production was accelerated in this case. The result that the disappearance of IgE-suppressive activity of 4-hydroxy derivative **20**, which lacked the methoxy group at the 3-position of matairesinol, shows the importance of the 3-methoxy group of matairesinol for this activity. The inactivity of 3,4-dimethoxy derivative **16**, 3,4-methylenedioxy derivative **18**, and 4-methoxy derivative **19** suggests the importance of the phenolic hydroxy group on the 7-phenyl group of (–)-matairesinol. Even though the hydroxy group was present at the 3 position, 3-hydroxy-4-methoxy derivative **21** did not show any activity. The inactivity of compound **17** suggests that the increase of the substituent removed the activity. Several substitution derivatives on the 7-phenyl group for **16–23** did not result in IgE-suppressive activity. The substituents on the 7-phenyl group of natural matairesinol played an important role in both the low cytotoxic activity and IgE-suppressive activity of (–)-matairesinol.

The effect of the 3',4' positions of (–)-matairesinol was also evaluated. It is noteworthy that 3'-hydroxy-4'-methoxy derivative **35** showed higher IgE-suppressive activity than (–)-matairesinol at 10 μ mol and 30 μ mol. It could be assumed that the hydrophilic group at the 3' position and hydrophobic group in the 4' group would accelerate the IgE inhibition. 3',4'-Methylenedioxy derivative **32** also showed higher IgE-suppressive activity than (–)-matairesinol at 10 μ mol and same level of activity at 30 μ mol with none of the cytotoxic activity. The IgE-suppressive activity was removed by the increase of substituents on the 7'-phenyl group. Thus, 4'-hydroxy-3',5'-dimethoxy derivative **31** did not

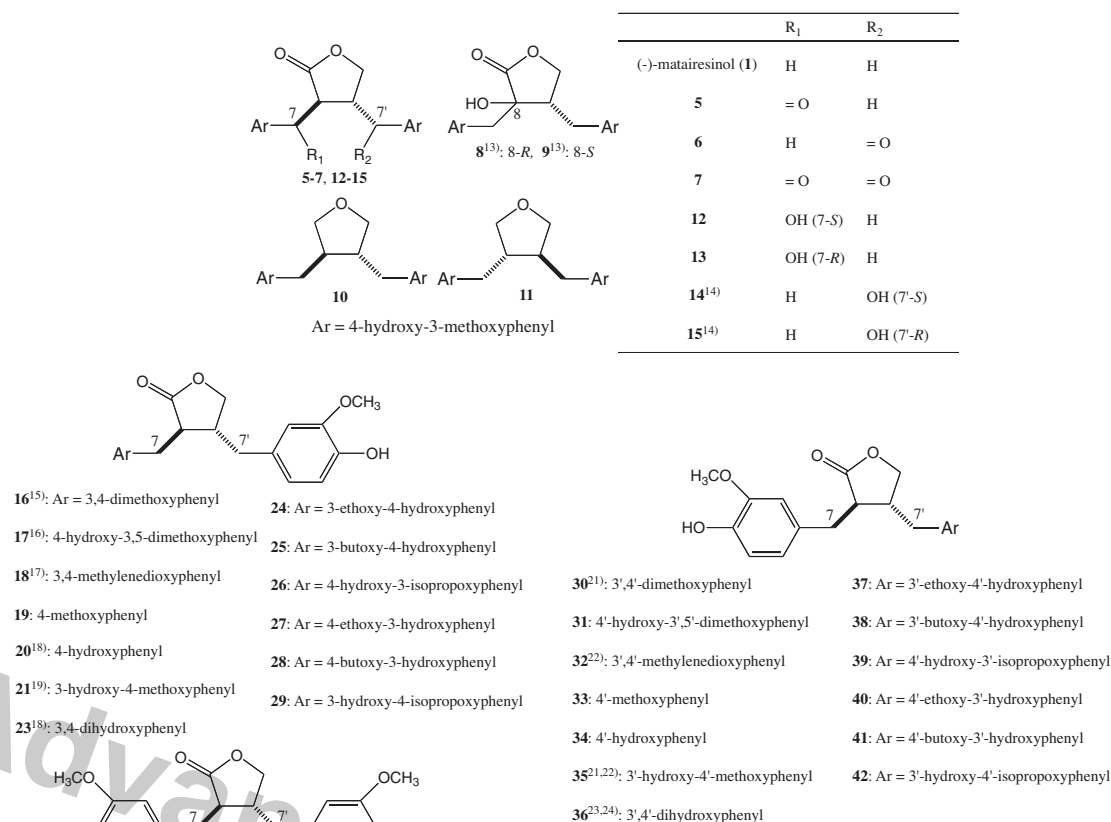


Fig. 2. (–)-Matairesinol and Its Derivatives.

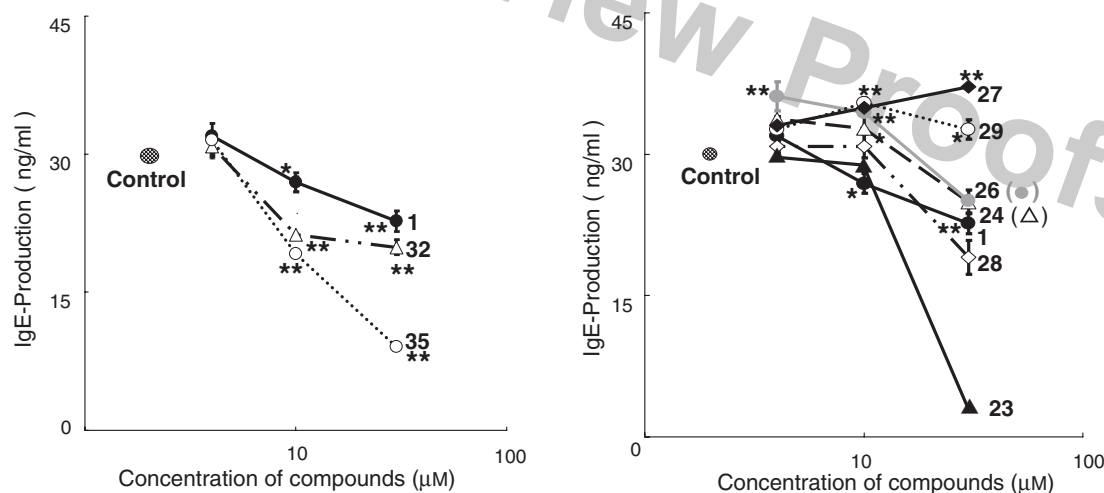


Fig. 3. IgE-Productive Activity of the (–)-Matairesinol Derivatives.

p* < 0.05, *p* < 0.01.

show any IgE-suppressive activity. Some derivatives of the 7'-phenyl group showed higher IgE-suppressive activity.

The effect of the length and bulky of alkoxy groups at the 3,4,3', and 4' positions on the IgE-productive activity was then examined. In the case of the 7-phenyl derivatives, 4-butoxy-3-hydroxy derivative **28** and 3-hydroxy-4-isopropoxy derivative **29** showed a high IgE concentration with their cytotoxic activity. 3-Ethoxy-4-hydroxy derivative **24**, 4-hydroxy-3-isopropoxy derivative **26**, and 4-ethoxy-3-hydroxy derivative **27** showed a high IgE concentration without cytotoxic activity. Conversions at the 3 or 4 position to a long or bulky

alkoxy group tended to accelerate the IgE-productive activity. The increase of hydrophobicity at the 3 or 4 position resulted in the acceleration of IgE production. In the case of 3',4'-derivatives **37–42**, no IgE-productive activity was apparent. The conversion at the 3' or 4' position to a long or bulky alkoxy group only resulted in the acceleration of cytotoxic activity. The 4'-methoxy group was found to be the best size for IgE-suppressive activity, 3'-hydroxy-4'-methoxy derivative **35** showing the highest activity in this study.

The results of this study reveal the relationship between the structure of (–)-matairesinol and the IgE-productive activity. 3'-Hydroxy-4'-methoxy derivative

35 showed higher IgE-suppressive activity than (–)-matairesinol. On the other hand, higher IgE-accelerative activity was observed in 4-ethoxy-3-hydroxy derivative **27**, with no cytotoxic activity being apparent at any concentration. Although the effect of γ -butyrolactone lignan on cytokines had been reported,²⁶⁾ the IgE-productive activity was shown for the first time.

Acknowledgments

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