ARYLTETRALIN LIGNANS FROM *Linum cariense*

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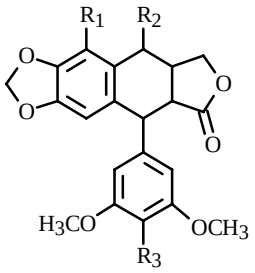
Four aryltetralin lignans and the glucoside of 6-methoxypodophyllotoxin and podophyllotoxin were isolated from the roots of Linum cariense *and identified.*

Key words: aryltetralin lignans, *Linum cariense*, podophyllotoxin, 6-methoxypodophyllotoxin.

Lignans possess interesting biological activities, their antitumor properties being most important. Podophyllotoxin (PTOX) is a starting compound for the chemical synthesis of the antitumour agents Etoposide, Teniposide, and Etopophos. Chemical synthesis of PTOX is possible but complex and uneconomical. Therefore, PTOX is isolated from plants grown in the Himalayas and converted chemically to a drug [1]. Due to the limited occurrence of this species, phytochemical studies have focused on the discovery of PTOX from other plant species. PTOX, however, is restricted to a few families only, such as Berberidaceae, Cupressaceae, Polygalaceae, and Linaceae. The genus *Linum* is known to contain aryltetralin group lignans [2–7]. In Turkey, the genus *Linum* is represented by 39 species, and *L. cariense* is one of the endemic species from the section Syllinum.

Linum, the largest genus of the family Linaceae, comprises about 230 species, and quite a number of these species produce 6-methoxypodophyllotoxin (**3**) and podophyllotoxin (**1**). The highest 6-methoxypodophyllotoxin contents are found in the roots of the *Linum* species from the section Syllinum, except *L. cariense*, with α-peltatin (**5**) as the major lignan in its roots [8]. This study describes the isolation and identification of four known aryltetralin type lignans and two glucosides from *L. cariense.*



1 - 6

1: R_1 = H, R_2 = OH, R_3 = OMe
2: R_1 = H, R_2 = O-Gl, R_3 = OMe
3: R_1 = OMe, R_2 = OH, R_3 = OMe
4: R_1 = OMe, R_2 = O-Gl, R_3 = OMe
5: R_1 = OH, R_2 = H, R_3 = H
6: R_1 = OH, R_2 = H, R_3 = OMe

EXPERIMENTAL

The plant material from *Linum cariense* was collected near Ankara, Turkey in July 2002. A plant specimen was deposited in the Herbarium of the Faculty of Pharmacy, University of Ankara.

Ten-gram root samples were extracted with hot ethanol (3×70 ml) by stirring on a hot plate (70°C) for about 10 min. The mixture was cooled, then filtered under vacuum. The combine extracts were evaporated to dryness under vacuum and redissolved in EtOH. This extract was separated using preparative TLC [$CHCl_3$/MeOH (10:1 v/v)]. Preparative TLC was achieved using 20×20 cm glass plates coated with 0.5 mm layers of silicagel (Merck Kieselgel GF 254). After developing the plates with the solvent system, six bands were located under UV light. These bands were scraped from the plates, and silica

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gel was packed into sintered glass columns and eluted with the appropriate solvents [for aglycones, acetone; for glycosides, acetone/methanol (1:1 v/v)].

6-Methoxypodophyllotoxin (**3**, R_f 0.89, band 1), β-peltatin (**6,** R_f 0.72, band 2), podophyllotoxin (**1**, R_f 0.65, band 3), α-peltatin (**5**, R_f 0.57, band 4), 6-methoxypodophyllotoxin glucosides (**4**, R_f 0.32, band 5), and podophyllotoxin glucosides (**2**, R_f 0.29, band 6) were isolated from root samples. Aglycone bands were further purified by TLC in CH_2Cl_2/EtOH (60:1v/v, band 1), hexane : acetone (1:1 v/v, band 2, 3), and petroleum ether (60–80°C): acetone : *n*-propanol (90 : 10 : 0.45 v/v/v, band 4). Identification of aglycones was achieved by comparison with standards on HPLC and by NMR data.

HPLC was performed as described by Smollny et al. [7]. 6-Methoxypodophyllotoxin and podophyllotoxin glucosides were hydrolyzed with β-glucosidase on the TLC surface to yield the aglycones. These were identified by comparison with standards on TLC and HPLC.

Podophyllotoxin (1): ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 6.51 (H-3), 6.37 (H-2′+ H-6′), 5.99 (d, J = 1.5, OCH_2O), 4.78 (d, J = 9.1, H-7), 4.61 (m, H-9a), 4.60 (d, H-7′, J = 1.6), 4.16 (OMe, H-6), 4.10 (dd, J_1 = 19.1, J_2 = 9.1, H-9b), 3.81 (OMe, H-4′), 3.75 (OMe, 3′,4′), 2.84 (dd, J_1 = 13.8, J_2 = 5.35, H-8′), 2.79 – 2.75 (m, H-8).

6-Methoxypodophyllotoxin (3): ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 6.43 (H-2′+H-6′), 6.29 (H-3), 5.96 (OCH_2O), 5.03 (d, J = 9.2, H-7), 4.63 (dd, J_1 = 6.9, J_2= 9.1, H-9a), 4.54 (d, J = 3.8, H-7′), 4.16 (H-6, OMe), 4.06 (H-9a), 3.81 (OMe, H-4′), 3.76 (OMe, 3′, 4′), 2.75 (dd, H-8′, J_1 = 4.6, J_2 = 14.9), 2.88 (m, H-8).

α-Peltatin (5): ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 6.23 (H-3), 6.36 (H-2′, 6′), 5.94 (d, J = 4.9, OCH_2O), 3.78 (3′,5′-OMe), 3.22 (J_1 = 13.4, J_2 = 3.6, H-7a), 2.5 (dd, J_1 = 12.4, J_2 = 8.5 H-7b), 4.59 (d, J = 3.6, H-7), 4.4 (dd, H-9, J_1 = 11.6, J_2 = 6.7), 3.93 (dd, H-9′, J_1 = 8.56, J_2 = 6.26), 2.6 (m, H-8, H-8′).

β-Peltatin (6): ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 6.23 (H-3), 6.35 (H-2′, 6′), 5.94 (d, OCH_2O, J = 2.4), 3.78 (4′-OMe), 3.75 (3′, 5′-OMe), 3.23 (J^1 = 16.4, J_2 = 5.2, H-7a), 2.5 (dd, J = 16.4, J_2 = 5.2, H-7b), 4.51 (dd, J_1 = 8.4, J_2 = 6.4, H-7′), 4.59 (d, J = 4, H-9), 3.98 (dd, J_1 = 10, J_2 = 9.2, H-9′), 2.5 (d, J_1 = 16.4, J_2 = 10.8, H-8), 2.7 (m, H-8).

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