

# The Importance of Aryltetralin (Podophyllum) Lignans and Their Distribution in The Plant Kingdom

Arltetralin Lignanların Önemli ve Bitkiler Alemindeki Dağılımı

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## SUMMARY

In the plant world lignans are natural products which occupy quite a large area. They have been identified in some 70 families, many of which have been used in folk medicine.

Lignans have gained increasing attention due to their biological effects; antimetabolic, antiviral, cathartic, allergenic and antitumour activity. The most important of these is their antitumour activity. The aryltetralin (Podophyllum) group lignans are important compounds showing this activity.

This review sets out cover literature on aryltetralin lignans from 1905-to Feb. 1995 and includes lists of the family, genus, species and chemical structure.

Key Words: Aryltetralin lignans, antitumour, Podophyllum lignans, lignans.

## ÖZET

Bitki dünyasında geniş bir alana sahip olan lignanlar doğal ürünlerdir. 70 familyada bulunmuş olup büyük bir kısmı halk ilacı olarak kullanılmaktadır. Lignanlar biyolojik etkileri nedeni ile büyük bir önem kazanmışlardır. Bunlar; antimetabolik, allerjik, kathartik, antiviral ve antitümör etkileridir. Şüphesiz antitümör etki en önemlileridir. Ariltetralin (Podophyllum) grup lignanlar bu aktiviteyi göstermeleri nedeni ile önemlidir. Bu derleme 1905- Şubat 1995 yılları arasında teşhis edilen ariltetralin

Redaksiyonun veriliş tarihi: 15.12.1995

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lignanlar, familya, genus ve türlerine göre sınıflanmış olup kimyasal formülleri de verilmiştir.

## INTRODUCTION

Lignans are a group of naturally occurring phenolic compounds that were first introduced in 1936 by Haworth who applied them to dimers consisting of two phenylpropanoid (C6-C3) units linked at the central carbons ( $\beta$ -carbon) (1, 2). In the classification of lignans, the aryltetralin group belongs to the cycloignans, together with aryl-naphthalene and dibenzocyclooctadiene (Fig.1).

The Podophyllum lignans are another important group of anticancer drugs investigated because of folklore reference. The drug Podophyllum is obtained from the dried root and rhizomes of two species of *Podophyllum* (Berberidaceae), the American species *P. peltatum* and the Indian species *P. hexandrum* (*P. emodi*). Podophyllum and the resin *podophyllin*, which is obtained after the ethanolic extraction of Podophyllum, have long been known as cathartics, emetics and cholagogue. As early as 1615 Camplain described the North American plant and spoke of the fruit as edible, however he did not mention medicinal properties of the root. The European settlers reported using the root extensively particularly as a cathartic and anthelmintic. It appears they learned these uses from the North American Indians who used it medicinally and as a poison. Podophyllum was included in the first U.S. Pharmacopoeia of 1820 and was retained until the twelfth revision in 1942. It has appeared at one time or another in most European, South American and Asian Pharmacopoeias. Indian Podophyllum has a similar long history of usage amongst natives of the Himalayas, an aqueous extract of the roots being a common cathartic. It has also been used as a remedy in ophthalmia. Resin from the Indian plant was analyzed by Thomson in 1890, who reported 56% podophyllo-toxin content. Podophyllotoxin was first shown to be the active principle of podophyllin by Podwysotzki and was obtained in a pure state in 1880.

Early pharmacological work focussed attention on the cathartic and irritant action of the resin. Ummey in 1892 concluded that podophyllo-toxin was the active principle (3). Scientific evidence for antitumour activity of podophyllotoxin was first found out by Kaplan in 1942 (4). These two *Podophyllum* species contain mainly podophyllotoxin, *a*-peltatin and  $\beta$ -peltatin. Through clinical trials, researchers found that podophyllotoxin, *a*-peltatin all have unacceptable side effects, so research focussed on semisynthetic derivatives and two compounds etoposide and teniposide were developed.

These two compounds have useful anticancer activity with minimal toxic side effects. In clinical trials etoposide has been found to be a valu-

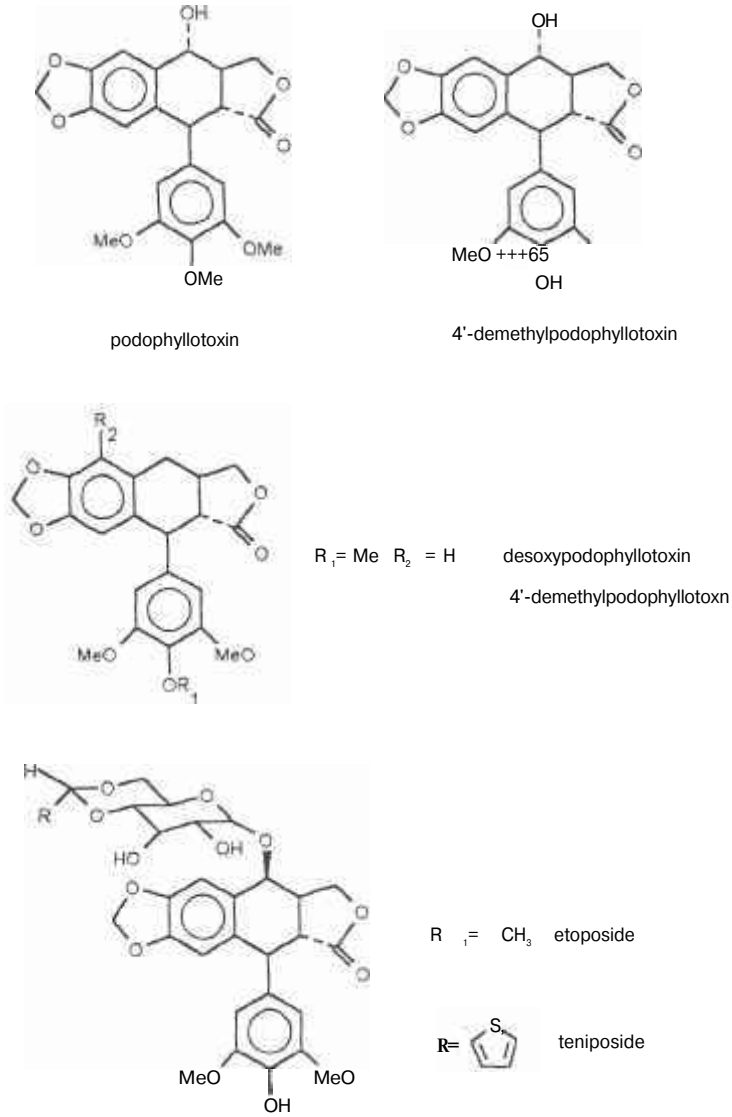


Fig. 1: Structures of four ariltetralin lignans, etoposide and teniposide.

able anticancer agent with activity against small cell lung cancer and testicular cancer. Clinical testing of teniposide and etoposide has shown that there is no significant clinical difference between them nor is there any superiority of one compound over the other in any tumour type. However etoposide has been employed mainly with adult tumours, whilst teniposide has been used more frequently against pediatric malignancies. Etoposide can be used both orally and intravenously (5).

A disadvantage is that the total synthesis is both complex and uneconomic, so natural podophyllotoxin is isolated from plants and converted chemically to the drug. Therefore phytochemical studies have focussed on the investigation of other plants, which provide sources of podophyllotoxin or its 4'-demethyl analogue. Researchers have examined other *Podophyllum* species as well as related plant genera. According to Cordell's data approximately 180, 000 plant extracts from 2500 genera had been systematically investigated for anticarcinogenic activity (6).

#### *Aryltetralin lignans in the plant kingdom*

The plant kingdom has so far yielded over 200 lignans from nearly 70 different families, but the aryltetralin group has only been found in a few. Nevertheless, as the result of continuing research, this number is increasing. Among the aryltetralin group, there are two lignans which have a special significance. These are podophyllotoxin and 4'-demethylpodophyllotoxin and their special importance lies in their anticancer activity.

Podophyllotoxin was the first crystalline compound to be isolated from the American species *Podophyllum peltatum* in 1880 by Podwysotzki. A few years later the same compound was found in the Indian plant *P. hexandrum* (7). Both species belong to the Family Berberidaceae.

Both species belong to the he Family Berberidaceae, subfamily Podophylloideae. In 1948 Hartwell and co-workers isolated a-peltatin and P-peltatin from *P. peltatum* but these compounds were not detected in *P. hexandrum* (9). Later on Jackson and Dewick's studies with the latter showed that they were present in the plant but in very small amounts (8).

Another *Podophyllum* lignan 4'-demethylpodophyllotoxin was found in *P. hexandrum* (10). Desoxypodophyllotoxin was isolated from two *Podophyllum* species, *P. peltatum* and *P. pleianthum* (10, 11). The earliest reference about desoxypodophyllotoxin in *P. hexandrum* was by Stahl (1973) who mentioned its presence according to TLC results (13). This conclusion was confirmed when desoxypodophyllotoxin was isolated from *P. hexandrum* root (and from *P. peltatum*) by Jackson and Dewick

Tablo 1: Plant species known to contain aryltetralin lignans.

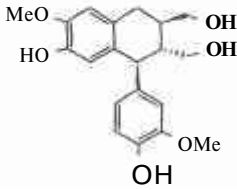
	p toxin	des.p toxin	4'-dem. p toxin	4'- dem des.p. toxin	others	ref
<b>Araucariaceae</b>						
<i>Araucaria angustifolia</i>					1,2,3,4	4
<b>Aristolochiaceae</b>						
<i>Aristolochia chilensis</i>					5	4
<b>Austrobaileyaceae</b>						
<i>Austrobaileya scandens</i>					6,7,8	4
<b>Berberidaceae</b>						
<i>Podophyllum peltatum</i>	+		+	+	9,10,11,12, 13,14	7,8,9,10, 11
<i>P. hexandrum</i>	+	+	+	+	9,10,11,12,13,14	8,9,10,11 .12
<i>P. pleianthum</i>	+	+	+	+	11,12,13,14	11,13
<i>P. versipelle</i>	+		+		9,10	8
<i>Dyosma aurantioaulis</i> ( <i>P. aurantiocaule</i> )	+				11,1,2,15,16	14
<i>D. veltschi</i>	+				10	15
<i>D. mayorensis</i>	+				11,12,15,16,17,18	16
<i>D. versipellis</i> var <i>tomentosa</i>	+		+		10,17	16
<i>Diphyleia cymosa</i>	+		+		10,11,17	7
<i>D. grayi</i>	+		+		10,11,17	7,17
<i>D. sinensis</i>					16	17,18
<b>Betulaceae</b>						
<i>Alnus glutinosa</i>					19,20	4
<b>Burseraceae</b>						
<i>Bursera microphylla</i>		+			21	19
<i>B. morensis</i>		+				20
<i>Commiphora incisa</i>		+				4
<b>Canellaceae</b>						
<i>Cinnamosma madagascariensis</i>					22	4
<b>Cupressaceae</b>						
<i>Austrocedrus chilensis</i>		+				21
<i>Callitris drummondii</i>	+					22
<i>C. columellaris</i>		+				23
<i>C. preisii</i>		+				21
<i>Chamaecyparis lawsonia</i>		+				24

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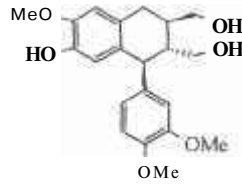
6

<i>Fitzrova cupressoides</i>					23	4
<i>Juniperus bermudiana</i>		+				25
<i>J. chilensis</i>	+					26
<i>J. formosa</i>					24	4
<i>J. lucayana</i>	+					24
<i>J.oxcedrus</i>	+	+				26
<i>J.phoenica</i>		+			25	28
<i>J sabina</i>	+	+			25.26.27	29
<i>J. scopulorum</i>	+					25
<i>J. silicicola</i>		+			27	30
<i>J. thurifera</i>		+				24.31
<i>J. virginiana</i>	+	+				24
<i>Libocedrus chinensis</i>	+					32
<i>L. decurrens</i>		+				26
<i>Thuja occidentalis</i>		+				4
<i>Thujopsis dolobrata</i>		+				4
<i>Thuja plicata</i>		+			28.29	4
<b>Euphorbiaceae</b>						
<i>Amanoa oblongifolia</i>						33
<i>Cleistanthus collinus</i>					30.31	4
<i>Phyllanthus niruri</i>					32.33,34	4
<b>Hernandiaceae</b>						
<i>Hernandia quiansis</i>		+			29	34
<i>H. ovigera</i>		+			35.36	35.36
<i>H. cordigera</i>		+			4	37
<b>Labiatae</b>						
<i>Hyptis tomentosa</i>	+					39
<i>H. verticillata</i>				+		40
<b>Lauraceae</b>						
<i>Cinnamomum laura</i>					37	4
<b>Linaceae</b>						
<i>Linum album</i>				+	9.10.40	7.41
<i>L. arboreum</i>	+				9.10.41.42	7
<i>L. flavum</i>	+				41.42	7
<b>Magnoliaceae</b>						
<i>Linodendron tulipifer</i>					43	4
<i>Magnolia salicifolia</i>					44	4
<i>Schizandra henryi</i>					45	4
<i>S. nigra</i>					46	4
<i>S. sphenathera</i>					47	4
<b>Meliaceae</b>						
<i>Toona cliata</i>					48	4
<b>Myristicaceae</b>						
<i>Dialvanthera otoba</i>					49	4
<i>Irtanthera grandis</i>					50	4
<i>Osteophyllum platypemum</i>					51.52,53	4
<i>Knema artenuata</i>					54.55.56.57.58	4
<i>Mvristiaca caganensis</i>					49.54.58.59	4

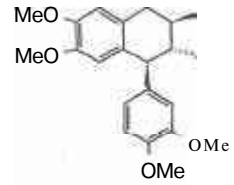
M. otoba					53.55.56	4
Viola calopylloideae					59.60	4
V. carinata					61.	4
V. cuspidata					49.62.63	4
V. sebifera					64.65.66.67.68	4
<b>Oleaceae</b>						
Olea africana					69	4
O. cuniunghami					70	4
<b>Podocarpaceae</b>						
Dacridium intermedium					23	4
Podocarpus spicatus					71	4
<b>Polygalaceae</b>						
Polygala macradaneia				+		40
P. paenea	+					40
P. polygama					72	42
<b>Polygonaceae</b>						
Polygonum aviculare					73	43
<b>Pinaceae</b>						
Abies sachaliensis					1.71	4
Picea ajanensis					71	4
Tsuga heteophylla					71	4
<b>Rosaceae</b>						
Pygenum acuminatum					74.75	4
Sorbus desora					19	4
<b>Rutaceae</b>						
Haplohyllum vulcanicum					76	4
<b>Taxodiaceae</b>						
Taxus baccata					22,37	4
<b>Umbellifereae</b>						
Anthnscus sylvestris		+				44
<b>Zygophylaceae</b>						
Guaiaicum officinale					78,79	4
Larrea tndentata					80.81	45



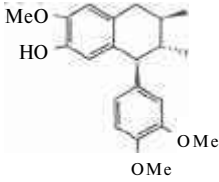
(+) -eyciolanciresinol (1)



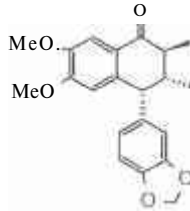
(+) -4'-O-methylcyclolanciresinol (2)



(-) -galbulin (3)



cyclogalgravtin (4)

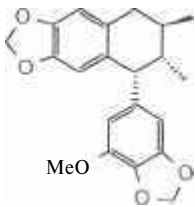


aristotetralone (5)

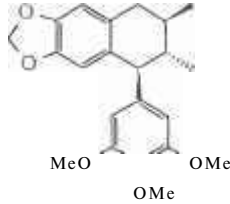
*C* *i*

MeO' O

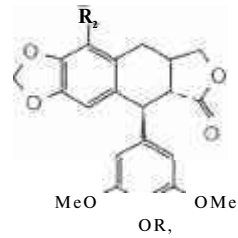
austrobailignan 1 (6)



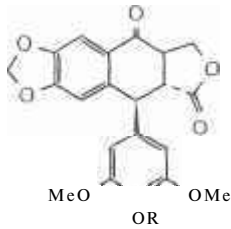
austrobailignan 3 (7)



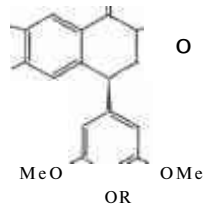
austrobailignan 4 (8)



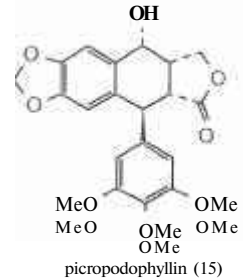
$R_1 = H$   $R_2 = OH$  a-peltatin (9)  
 $R_1 = Me$   $R_2 = OH$  o-peltatin (10)



$R = Me$  podophyllotoxone(11)  
 $R = H$  4'-demethylpodophyllotoxone (12)

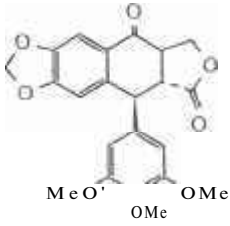


$R = Me$  isopodophyllone (13)  
 $R = H$  4'-demethylisopodophyllone (14)

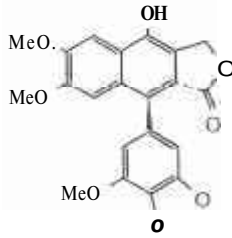


picropodophyllin (15)

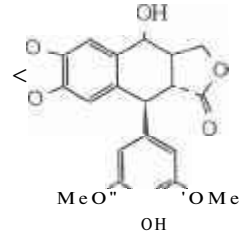




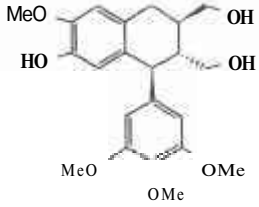
picropodophllone (16)



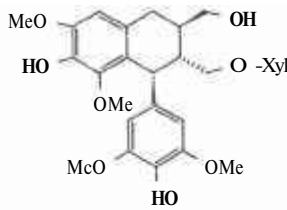
diphyllin (17)



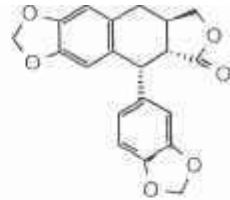
4'- demethyisopodophyllotoxin (18)



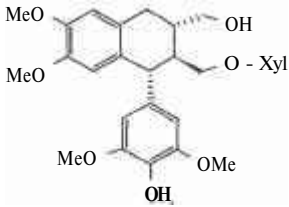
(+)-lyoresinol (19)



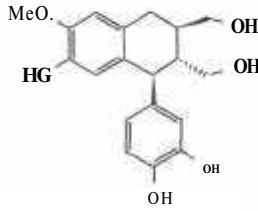
lyoniside (20)



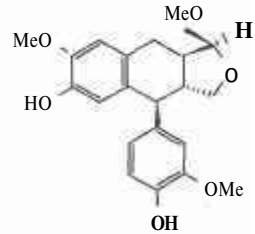
polygamain (21)



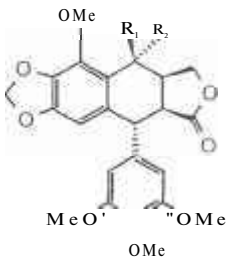
(-)- 5'- methoxycyclolanciresinol xyloside (22)



(+)- cyclolaxiresinol (23)

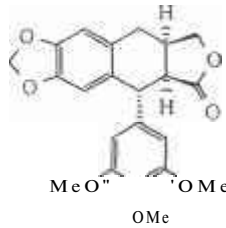


tsugacetal (24)

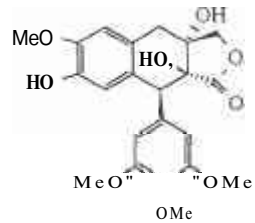


$R_1 = \text{QH}$   $R_2 = \text{H}$   
2'- methoxyepicropodophyllin (25)

$R_1 = \text{H}$   $R_2 = \text{OH}$   
2'- methoxycyclopodophyllin (26)



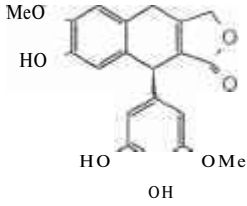
deoxycropodophyllin (27)



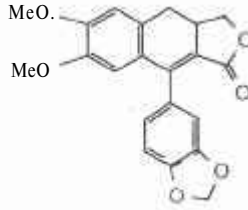
plicatin (28)

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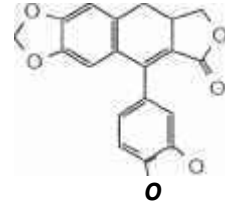
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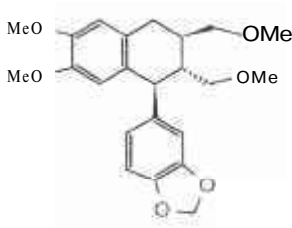
$\beta$  - apoplicatitoxin (29)



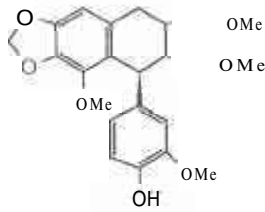
collinusin (30)



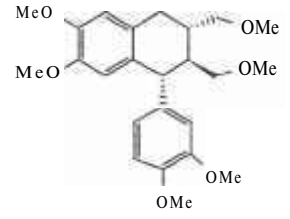
dihydrotaiwanin C (31)



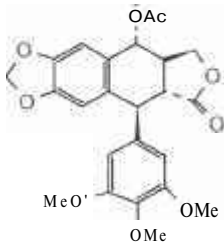
linetralin (32)



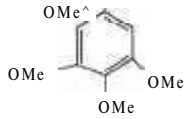
nirtetralin (33)



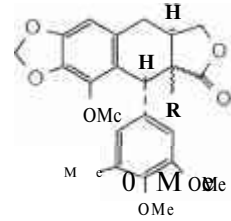
phyltetrahn (34)



podophyllotoxin acetate (35)

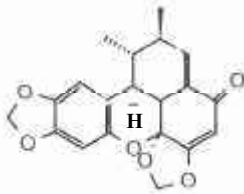


hernandin (36)

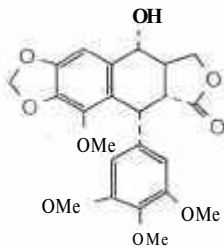


R=β OH 2-β- hydroxy-4-demethyl desoxypodophyllotoxin(37)

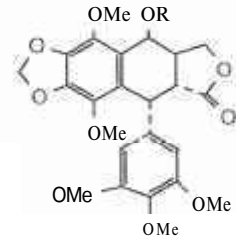
R= α OH 4'-demethyl desoxypicro podophyllotoxin(38)



carponone (39)

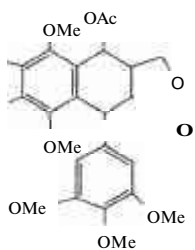


3'- demethylpodophyllotoxin (40)

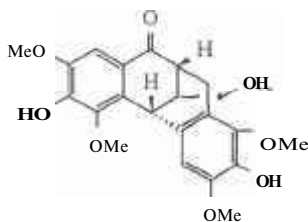


R=H 5-methylpodophyllotoxin (41)

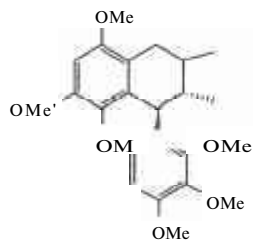
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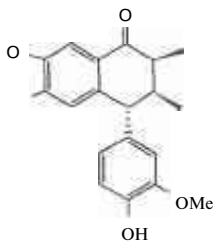
R=H 5-methylpiperophyllotoxin acetate (42)



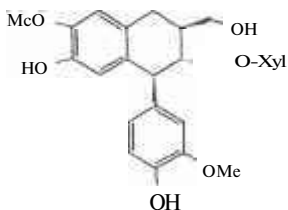
linonol (43)



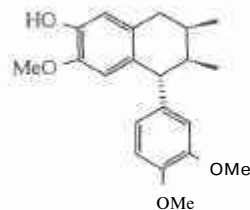
magnoshinin (44)



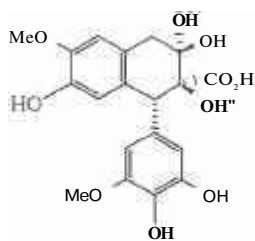
(-) -enshicine (45)



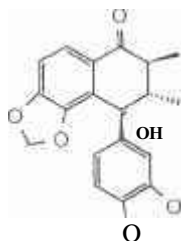
schi/andnside (46)



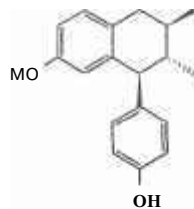
schisandrone (47)



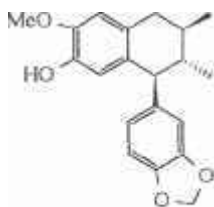
plicatic acid (48)



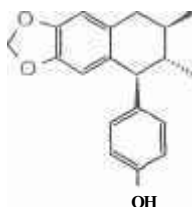
hydroxyotobain (49)



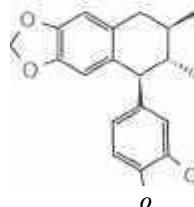
(50)



otobaphcnol(51)

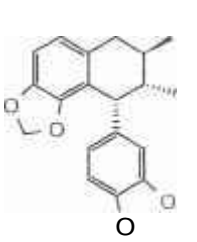


altcnuol (52)

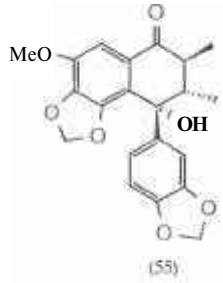


(-) - cagayanin (53)

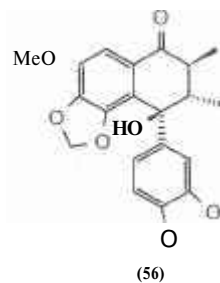
## 12



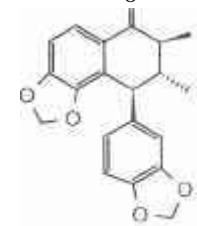
otobain (54)



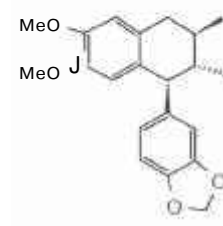
(55)



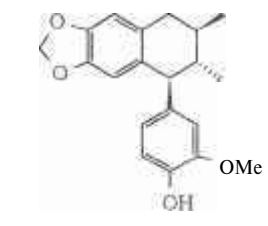
(56)



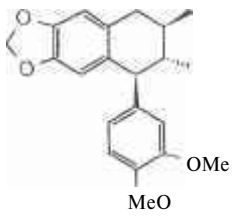
olobanone (57)



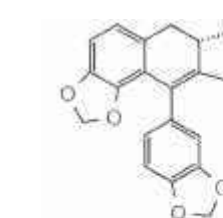
isootobatin (58)



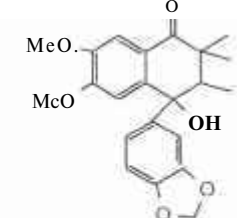
(-) - isootobaphenol (59)



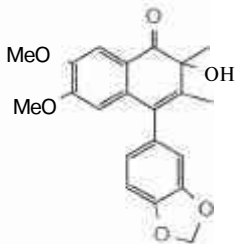
(-) - galcatin (60)



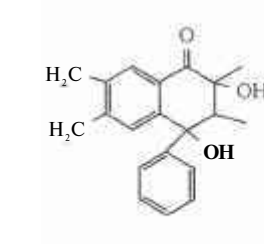
otobaene (61)



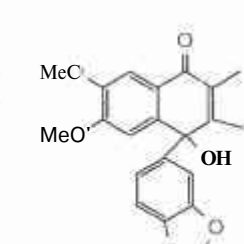
(62)



(63)

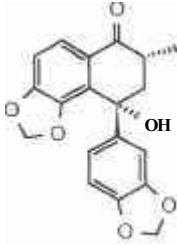


(64)

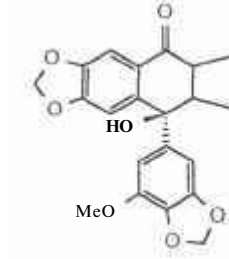


(65)

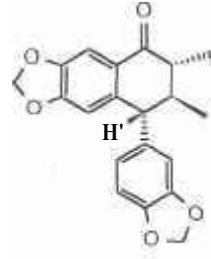
13



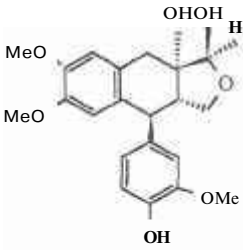
(66)



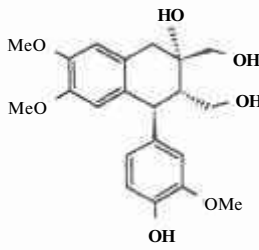
(67)



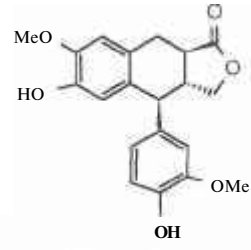
(68)



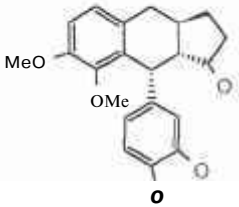
(+) - africanal (69)



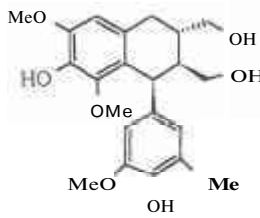
(+) - cycloolivil (70)



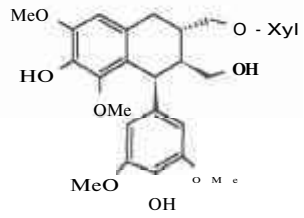
(-) -  $\alpha$ -condendrin (71)



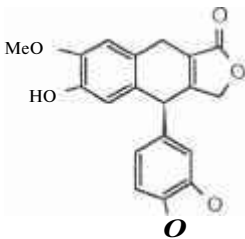
polygamatin (72)



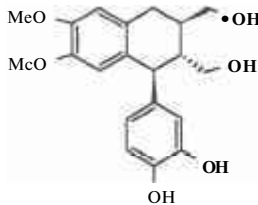
(-) - pygeoresinol (73)



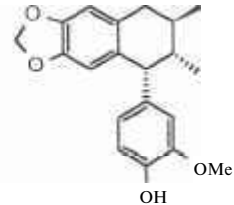
pygeoside (74)



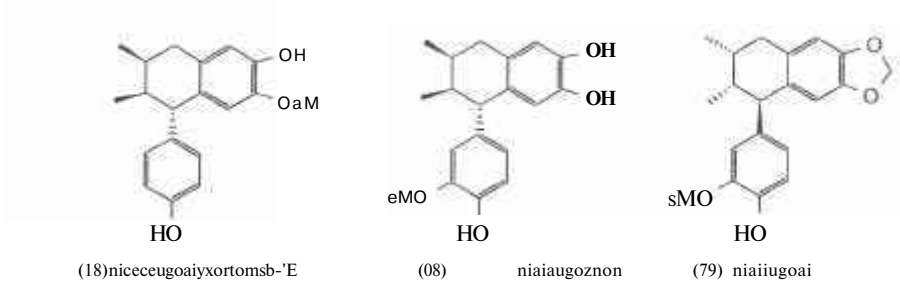
konyanin (75)



4 - O - methylcyclootaxiresinol (76)



(+) - guaiacin (77)



1985. A third species *P. pleianthum* was discovered in Formosa by Hance in 1883, and this plant yielded podophyllotoxin, desoxypodophyllotoxin and some flavonoids (12). Later on isopicropodophyllone was found in the same species (14).

In the continuing search for plants having tumour inhibitory constituents, it was found that some species of the following families contain aryteralin lignans (see Table 1).

## COCLUSION

Today podophyllotoxin is obtained from two species and its synthesis is complex and uneconomical. Therefore it will be worthwhile to investigate a variety of species in different families with a high percentage of podophyllotoxin content. Studies of this kind might lead to the discovery of new compounds which have anti-tumour activity. There has been an increase in cell-culture studies on podophyllotoxin lignans (44, 45, 46, 47, 48, 49, 50, 51). All these studies will contribute to our knowledge of podophyllotoxin and related lignans.

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