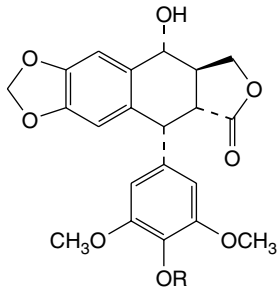
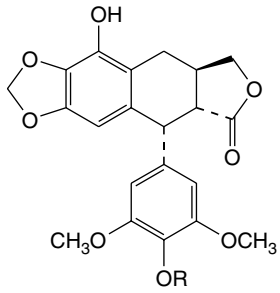
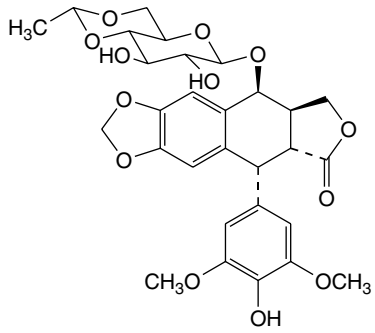


Podophyllotoxin, R = CH_3
Demethylpodophyllotoxin, R = H



β-Peltatin, R = CH_3
α-Peltatin, R = H



Etoposide

organic solvent extraction, gave yields of 5.2% podophyllotoxin exceeding levels previously reported from any source. This increase in yield resulted from hydrolysis of lignan 4-*O*-β-*O*-glucosides *in situ* during the rehydration period.

Uses. Podophyllum resin has long been used as a purgative but has largely been replaced by less drastic drugs. It has a cytotoxic action and is used as a paint in the treatment of soft venereal and other warts. Podophyllotoxin is also used for this purpose. Etoposide (4′-demethyl-epipodophyllotoxin ethylideneglucoside) is a lignan derivative obtained semi-synthetically from podophyllotoxin and used in the treatment of small-cell lung cancer and testicular cancer as well as lymphomas and leukaemias. The water-soluble pro-drug etopophos (etoposide 4′-phosphate) is also available. The related thenylidene derivative teniposide has similar anticancer properties and though not as widely used as etoposide has value in paediatric neuroblastoma, lymphocytic leukaemia, and brain tumours in children (see H. Stähelin and A. von Wartburg, *Cancer Res*., 1991, **51**, 5–15).

INDIAN PODOPHYLLUM

Indian podophyllum consists of the dried rhizome and roots of *Podophyllum hexandrum*, syn. *P. emodi* (Berberidaceae), a perennial herb found in Tibet, Afghanistan and the Himalayan areas of Pakistan and India. The drug is collected in India, Pakistan and China.

Macroscopical characters. The drug, at first glance, shows little resemblance to American podophyllum. The roots frequently break off and some samples consist almost entirely of rhizomes, while others consist largely of roots.

The rhizomes occur in much contorted pieces of an earthy brown colour, about 2–4 cm long and 1–2 cm in diameter. The internodes are much shorter than in the American drug, with the result that each piece bears the remains of about 3–6 branches ending in cup-shaped scars and about 20–40 roots or root scars. The rhizome is hard and somewhat difficult to break. Internally it is pale brown in colour and horny (usually) or starchy. The general arrangement of the tissues resembles that found in American podophyllum, but the vascular bundles are more elongated radially. The odour and taste resemble those of the American drug.

Microscopical characters. The calcium oxalate cluster crystals are fewer and smaller, 20–**30**–60 μm. The starch grains are simple or 2–20 compound; individual grains 2–**7**–34 μm (cf. American podophyllum).

Constituents. Indian podophyllum contains more resin (about 6–12%) than the American drug and the percentage of podophyllotoxin in the resin (up to 40%) is much higher. The root contains about 4% podophyllotoxin, 0.45% 4′-demethylpodophyllotoxin and smaller amounts of related lignans (see D. E. Jackson and P. M. Dewick, *Phytochemistry*, 1984, **23**, 1147–1152). Only traces of the peltatins are present, but the range of constituents is much the same as in the American resin.

Root cultures of *P. hexandrum* have been shown to contain higher proportions of podophyllotoxin than normal roots (B. P. S. Sagar and R. Zafar, *Pharm. Biol*., 2005, **43**, 404).

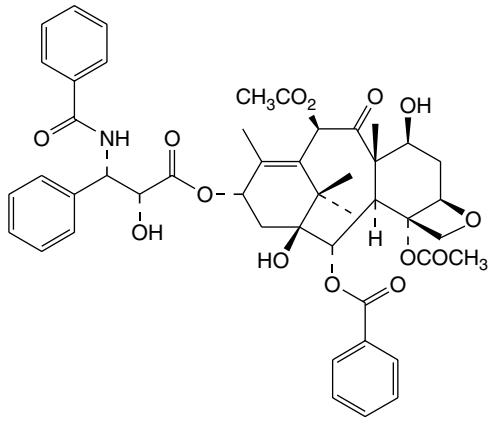
Uses. Indian podophyllum is used for the preparation of the resin and isolation of podophyllotoxin for drug use and semi-synthesis of etoposide. Other less common species of *Podophyllum* (e.g. *P. pleianthum*) and related genera (e.g. *Diphylleia*) also contain podophyllotoxin and structurally related lignans (see A. J. Broomhead and P. M. Dewick, *Phytochemistry*, 1990, **29**, 3831–3837).

TAXUS BREVIFOLIA AND TAXOL

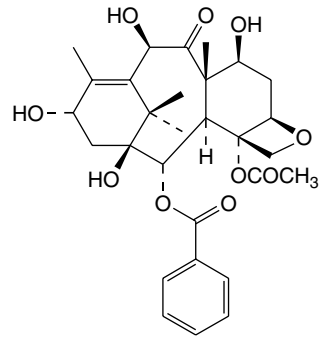
A note on nomenclature: the name taxol was given to a diterpene ester with anticancer properties when it was first isolated in 1971 from *Taxus brevifolia*. When this compound was subsequently exploited commercially as a drug, Taxol was registered as a trademark. Accordingly, the generic name paclitaxel has been assigned to the compound. The literature now contains an unhappy mixture of the two names, though the original name taxol is most often employed.

The Pacific yew, *Taxus brevifolia* (Taxaceae) is a slow-growing shrub/tree found in the forests of North-West Canada (British Columbia) and the USA (Washington, Oregon, Montana, Idaho and N. California). Although the plant is not rare, it does not form thick populations, and needs to be mature (about 100 years old) to be large enough for exploitation of its bark. At this age, the tree will be some 6–9 m high, and have a trunk of about 25 cm in diameter. The bark is removed from mature trees during the period May–August. The wood of *T. brevifolia* is not suitable for timber, and in some areas, plants have been systematically destroyed to allow cultivation of faster-growing commercially exploitable conifers. Harvesting is now strictly regulated. Although taxol is currently extracted from the dried bark, it is realized that this cannot be expected to provide a satisfactory long-term supply of the drug. It requires the bark from about three mature 100-year-old trees to provide one gram of taxol, and a course of treatment may need 2 grams of taxol. Current demand for taxol is in the region of 100–200 kg per annum.

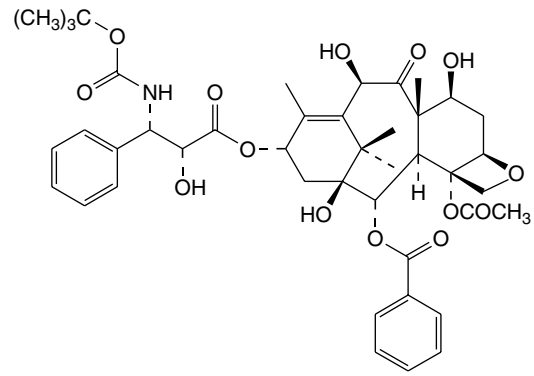
Constituents. All parts of *Taxus brevifolia* contain a wide range of diterpenoid derivatives termed taxanes, which are structurally related to the toxic constituents found in other *Taxus* species, e.g. the common yew, *Taxus baccata*. Over a hundred taxanes have been characterized



Taxol
(Paclitaxel)



10-Deacetylbaccatin III



Taxotere
(Docetaxel)

from various *Taxus* species, and taxol is a member of a small group of compounds possessing a four-membered oxetane ring and a complex ester side-chain in their structures, both of which are essential for antitumour activity. Taxol is found predominantly in the bark of *T. brevifolia*, but in relatively low amounts (0.01–0.02%). Up to 0.033% of taxol has been recorded in some samples of leaves and twigs (see N. C. Wheeler *et al*., *J. Nat. Prod*., 1992, **55**, 432–440), but generally the taxol content is much lower than in the bark. Significant variation in taxol content depending on season, geographical location, and environmental factors as well as individual populations of trees have been noted. The content of some other taxane derivatives in the bark is considerably higher, e.g. up to 0.2% baccatin III. Other taxane derivatives characterized include 10-deacetyltaxol, 10-deacetylbaccatin III, cephalomannine and 10-deacetylcephalomannine.

TAXUS BACCATA AND OTHER *TAXUS* SPP.

A more satisfactory solution now employed for the long-term supply of taxol and derivatives for drug use is to produce these compounds by semi-synthesis from more accessible structurally related materials. Both baccatin III and 10-deacetylbaccatin III may be efficiently transformed into taxol. 10-Deacetylbaccatin III is readily extracted from the leaves and twigs of *Taxus baccata*, and although the content is variable, it is generally present at much higher levels (up to 0.2%) than taxol can be found in *T. brevifolia. Taxus baccata*, the common yew, is widely planted as an ornamental tree in Europe and the USA and is much faster growing than the Pacific yew; it therefore provides a sustainable source of raw material. Five new taxanes and forty known ones have been reported from *T. baccata* grown in Israel (Q.-W. Shi *et al*., *J. Nat. Prod*., 2004, **67**, 168). *T. baccata* pollen contains taxine alkaloids (yield 0.08%) and the taxoids taxol, baccatin III and 10-deacetylbaccatin III (overall yield 0.004%). It is suggested that exposure to yew pollen could be the origin of the atopic manifestations attributed to the tree (M. Vanhaelen *et al*., *Planta Medica*, 2002, **68**, 36).

New taxane analogues have been reported from the needles of *T. canadensis* (J. Zhang *et al*., *J. Nat. Prod*., 2001, **64**, 450; Q.-W. Shi *et al*., *Nat. Prod*., 2003, **66**, 470). This species (Canada yew), occurring wild in the north-eastern United States and eastern Canada, is harvested commercially for its content of paclitaxel and 10-deacetylbaccatin III. S. L. Cameron and R. F. Smith (*Pharm. Biol*., 2008, **46**, 35) have reported on taxane levels in both older and younger components of twigs throughout a season and find that the lowest levels occur during periods of active growth (April–July), with peak levels following; overall, the preferable harvesting time is August and September. For a review of the chemistry and biological activity of the taxoids (120) of *T. cuspidata* (Japanese yew), see H. Shigemori *et al*., *J. Nat. Prod.*, 2004, **67**, 245. Three new oxetane-ring-containing taxoids have been isolated from *T. chinensis*; the availability of such C-14 oxygenated taxoids with an oxetane functionality has great potential, allowing the synthesis of additional oxygenated derivatives of taxol (F.-S. Wang *et al*., *J. Nat. Prod*., 2004, **67**, 905).

Advances in the identification of the genes involved in the biosynthesis of taxol have been reported. By 2001 five cDNA encoding pathway enzymes had been isolated from a *Taxus* cDNA library and functionally expressed from an appropriate vector or in bacteria or yeast as host (K. Walker and R. Croteau, *Phytochemistry*, 2001, **58**, 1).

Cell cultures of *Taxus* species also offer excellent potential for production of taxol of 10-deacetylbaccatin III; taxol yields of up to 0.2% dry weight cultured cells have been reported. *Taxus cuspidata* (Japanese yew): large-scale cell cultures have produced approximately 3 mg/1 of taxol and 74 mg/1 total taxanes after 27 days of growth (S. H. Son *et al*., *Plant Cell Rep*., 2000, **19**, 628).

A number of reports deal with the effect of various added precursors on taxol production; species so studied include *T. baccata*, *T. brevifolia*, *T. chinensis*, *T. cuspidata* and *T. wallichiana*, see C. Veersham *et al*., *Pharm. Biol*., 2003, **41**, 426. Abietane diterpenoids have been isolated from callus cultures of *T. baccata* (B. Monacelli *et al*., *Planta Medica* 2002, **68**, 764).

Uses. Taxol® (paclitaxel) is being used clinically in the treatment of ovarian cancers, breast cancers and non-small-cell lung cancer. It may also have potential value against other cancers. Taxotere® (docetaxel) is a side-chain analogue of taxol, which has also been produced by semi-synthesis from 10-deacetylbaccatin III. It has improved water-solubility and is used in treatment of breast cancers.