

THE YEW TREE (*TAXUS BACCATA*) IN MYTHOLOGY AND MEDICINE

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The yew has always held a special place in medicine and mythology (Figure 1). The Third Witch in *Macbeth* mentions, as a constituent of the cauldron's brew, 'slips of yew slivered in the moon's eclipse' (*Macbeth*: Act 4, Scene 1). Being an evergreen and famed for its longevity, it has been associated both with death and immortality. Within the last decade it has been recognised that the pseudoalkaloids of various species of yew are powerful antimitotic agents, useful in certain cancers which are refractory to other drugs. It is a slow-growing evergreen tree that may reach a height of 25 metres (80 feet). Its bark is rust red and its leaves needle-like and dark green.



FIGURE 1
The yew (*Taxus baccata*).

The taxonomy of the yew family is much disputed¹ but most authorities recognise the following: *Taxus baccata* (the European yew); *Taxus brevifolia* (the Pacific or Western yew); *Taxus cuspidata* (the Japanese yew) and *Taxus canadensis* (the American or Canadian yew). This last is often used to decorate North American homes at Christmas time (in comparison to the holly and the ivy in Britain).

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The first association of the yew was with immortality.² Indeed, the name 'yew' in its simple brevity has been compared with the name of God: Jahweh, Jehovah, the Immortal. This name then became variously *iva* (Latin); *iwa* (Old German); *eibe* (Modern German); *iw* (Old English); *id* (Swedish) and *iubhar* (Gaelic), thus leading to confusion with ivy, another long-lasting evergreen.

The yew is thought to be a species indigenous to Europe and has been widely distributed in this area for many thousands of years. It grows well in northern temperate zones. Latterly, its cultivation has become concentrated in churchyards, usually on the south or southwest side of the church (see below).³

CHRISTIAN ADOPTION OF PAGAN RITUAL

The yews predate the Christian tradition and its churches. The Celtic people may have brought the tree from Iberia (Spain), where it is abundant, to the south and west of Great Britain. Julius Caesar records that the Druids preached the doctrine of the immortality of the soul, and that the yew was their sacred tree and the symbol for immortality. Caesar also records what is perhaps the first case of poisoning by yew when Catibulus, king of the Eburones, died from drinking its juice. The Druid priest, as chief medicine man of the Celtic tribe, is said to have sat under the sacred tree and dispensed wisdom and justice. 'Slips of the yew, cut at the eclipse of the moon' were thought to convey powers of healing and to preserve the dead body for everlasting life. Yews were often planted on holy sites, a custom that was adopted by Christians.

The Christian Church commonly appropriated local traditions and folklore into its own traditions and liturgy. As the cypress tree became the symbol of immortality in Southern Europe, so did the yew in the North. The green boughs of the yew represent renewal and eternal youth. Christians took over the Spring Festival of Eostre and called it Easter, and this symbolised resurrection and life everlasting. Yew twigs were used to sprinkle holy water in the ancient service of 'Asperges' that immediately precedes the Latin High Mass (from the Latin *aspergere*: to scatter or sprinkle about). During Holy Week, if palm leaves were unavailable, yew twigs were worn in the cap of worshippers from Palm Sunday to Easter Sunday.

The yew has also gained a place in funeral solemnities. Shakespeare refers to its use when he talks in *Twelfth Night* of 'a shroud of white stuck all with yew'. The bodies of the dead were often rubbed with an infusion of yew leaves, presumably in an attempt both to preserve them and to guarantee their immortality.

Another legend which held sway in the Middle Ages came to associate the yew with both virginity and fertility, in rites associated with the Virgin Mary, the Holy Mother of God.³ The yew is prone to develop fibrous hair-like growths under the bark and on its roots. These growths were somehow likened to the hair of a virgin.

William Camden, a Tudor antiquary, recounts the story of a Yorkshire priest who severed the head of a virgin who had refused his sexual advances and subsequently hid her head in a yew. This tree thus became an object of veneration and pilgrimage. The pilgrims plucked hair-like filaments from between the bark and the wood and venerated these. The name of the village, Houton, was later changed to Halifax (holy hair). Pilgrims, by traffic and trading, contributed greatly to the development of the modern West Yorkshire town.

In many churches named after Saint Mary the Virgin, an honoured place was reserved for yew trees. At Saint Mary's Church, Painswick, Gloucestershire, there were 99 yews (a mystical number!) and at one time they were only clipped on 8 September, the feast of the Nativity of Our Lady, the Blessed Virgin.

In similar vein, Saint Winifred sheltered under the yews near Abergele in North Wales. She was subsequently beheaded by Caradoc for spurning his sexual advances and became the patron saint of virgins, a legend quite similar to that of the Houton woman.

With all such powerful associations, with death, life, immortality, fertility and the Blessed Virgin, it is not surprising that the local peasantry and farmers came to tolerate the yew, though fully aware of its toxic properties. They preferred it to be planted in the churchyard, out of the reach of their cattle and horses.

THE YEW AND THE BOW

The supernatural powers of the tree also led to its use in the manufacture of the wands of magicians, but the yew tree was to feature more prominently later in the development of the long bow. It is not clear from which part of the yew tree the wood for the bow was cut; some argue that the bows were made from the branches, some from the boles. The best yew bows were not derived from trees grown in Britain but were imported, along with wine shipments, from Spain and Venice. The export of yew was forbidden by statute. In addition, for every butt of wine imported ten bow staves of yew had to come as well.

From the thirteenth century, archery practice was required by Royal command or by Act of Parliament. It is thought that the use of yew in the bow may have given rise to its Latin name, *Taxus*. There are obvious similarities between *Taxus* and toxophily; arrow poison and archery.

Why are yews positioned to the south or south west of the church and how long do they live? The planting of the yew tree certainly often predated the church, and when the church came to be built it was placed to the north or the north east side of the tree (or trees). Robert Turner in his *Botanologia*, 1664, says that the yew is 'hot and dry' and 'will attract poysonous vapours and imbibe them'. He thought that it was at the south and west sides of the church that gases were released ('will o' the wisps' he called them) from the putrefaction of decaying corpses. These vapours, he also surmised, could be dead bodies walking abroad! The gases would gather under the branches of the yew before they were imbibed by the tree. It was thought that this concentration of poison could be deadly to both man and beast.² Turner goes on to quote both Galen and Dioscorides who had stated previously that lying under the branches of the yew could lead to death. There were contrary views. Gerard in his *Herball* (1579) rashly denied all such claims stating that he had eaten his fill of the berries and slept under the branches, not once, but often, and had not come to any harm!

A yew tree stands for many centuries but it is very difficult to estimate the age of a particular specimen accurately. Suckering and intertwining are common, and these render the usual technique of ring counting very inaccurate. As a result, figures of two-to-three thousand years are probably an overestimate, and a truer figure might be one-to-two thousand. A classical specimen has stood for many centuries in the village of Fortingall, Glen Lyon, Perthshire. Local folklore had it that it was an ancient preaching site (which is probably true) and that Pontius Pilate had been suckled beneath it when his father served as a Roman legionary in Scotland (which is probably false!). In 1796 it was measured by Pennant at 57 feet. It was visited subsequently by the eminent French botanist, Baron Humboldt, and, in 1870, by Sir Robert Christison, Professor of Medical Jurisprudence of the University of Edinburgh; the latter pronounced its age to be 3,000 years (approximately). It stands to this day, although badly damaged by the fire on Beltane (1 May) in 1825.

TOXICOLOGY OF THE YEW

Farmers must have been aware for many centuries of the toxic effects of yew on their livestock. In the nineteenth century the tree reappeared in large gardens and was valued for its evergreen leaves and attractive red 'berries' (botanically they are referred to more accurately as fruit arils). The Japanese yew *Taxus cuspidata* was also introduced to Europe and America.

The pseudo-fruit (or aril) may be swallowed, and as a result the seeds contained in it are ingested. The contents are very bitter and if children ingest them accidentally, they will usually spit them out. Individuals intending suicide however tolerate the bitter taste. The seeds and leaves are the most dangerous parts of the plant due to their content of the diterpenoid alkaloids, Taxine A and Taxine B. (Figure 1) It is thought that Taxines A and B can inhibit calcium and sodium transport in myocardial cells. It is of great interest therefore that the therapeutic compounds derived from yew, the taxels, can on occasion cause cardiac toxicity.

The first description of yew poisoning in the British literature appears to be that by Hurt in the *Lancet* in 1836.⁴ A child aged three years ingested yew berries. He vomited up some of them, then convulsed and died. At post-mortem examination there were changes in the stomach and gut. Four other children had also swallowed berries, but recovered after a strong emetic. Hurt reported that there had been three fatal cases in Manchester where yew leaves were used therapeutically for eradicating worms!

Since Hurt's original description, sporadic cases of poisoning have been described. The estimated lethal dose given by Cooper⁵ is 50 to 100 gms of the leaves but less of the seeds. Poisoning is manifest first by nausea, vomiting and severe abdominal pain followed shortly by hypotension and fatal cardiac arrhythmias. Anaphylactic shock has also been described by Burke and Siegel.⁶

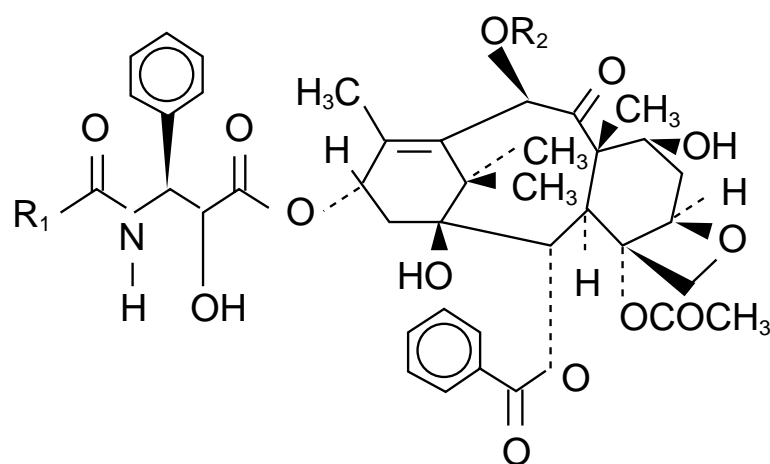
A more recent illustrative case is described by van der Werth and Murphy (1994).⁷ A sixteen-year-old female had been confined to a secure residential institution after several suicide attempts. The patient ate a handful of yew leaves from a tree in the grounds. Syrup of ipecacuanha was administered and vomiting occurred with yew leaves being recovered in the vomit. About three hours after ingestion she developed various cardiac arrhythmias including broad complex tachycardia, multiform ventricular tachycardia and self-limiting ventricular fibrillation. She was monitored intensively for three days and then discharged back to the institution, completely recovered. Meanwhile the yew had been felled and awaited removal. She and four other patients at the institution then ate leaves from the felled tree! Fortunately all five recovered after their immediate admission to hospital. This second event emphasises that the leaves should be burned, if there is any risk to man or the animal.

Sometimes the cardiac toxicity presents as a severe bradycardia. This is well illustrated by the patient of Cummins and co-workers.⁸ A five-year-old autistic child was brought into the Emergency Room having swallowed the leaves and berries of an ornamental shrub which was identified later as *Taxus brevifolia* (the Pacific yew). The pulse rate fell to 30 beats per minute and, later, complete heart block ensued. The heart rate did not respond to atropine, lignocaine, adrenaline or isoprenaline. Eventually the patient was paralysed with pancuronium, intubated, ventilated and his heart paced externally at a rate of 60 beats per minute (current, 40 milliamperes); subsequently transvenous pacing was substituted for transthoracic. On the second day the child recovered consciousness, was extubated and pacing was discontinued. By the third day the child had completely recovered and was discharged home. Friends of the family removed all the yew bushes from the yard.

Frohne and Pfander reported 356 incidents of yew ingestion.⁹ Only 4% resulted in symptoms, and these were usually minor.

THE YEW IN THERAPEUTICS

The yew is a veritable Pandora's box of compounds and many have been identified including taxines, taxols, taxusines, taxagifin, and baccatins I, II and III. Until 1971 the toxic effects of the various members of the yew family were medical curiosities seen occasionally in accident and emergency departments. Matters changed dramatically in 1971 when Wani and his colleagues¹⁰ isolated an antimetabolic compound from the bark of the Western or Pacific yew (*Taxus brevifolia* Nutt). The structure of the compound was subsequently elucidated (Figure 2) and it was named paclitaxel. A near congener, with similar antimetabolic activity has also been synthesised and named docetaxel (Figure 2).



	R ₁	R ₂
Paclitaxel		
Docetaxel		H-

FIGURE 2
The taxels.

Paclitaxel demonstrates unique antimetabolic activity promoting microtubule formation and inhibiting depolymerisation (Figure 3). The resulting accumulation of microtubules destabilises the cell, particularly if it is neoplastic, causing its death. The action of the taxels contrasts with those of colchicine and the vinca alkaloids which inhibit polymerisation, and cause death by accumulation of tubulin.

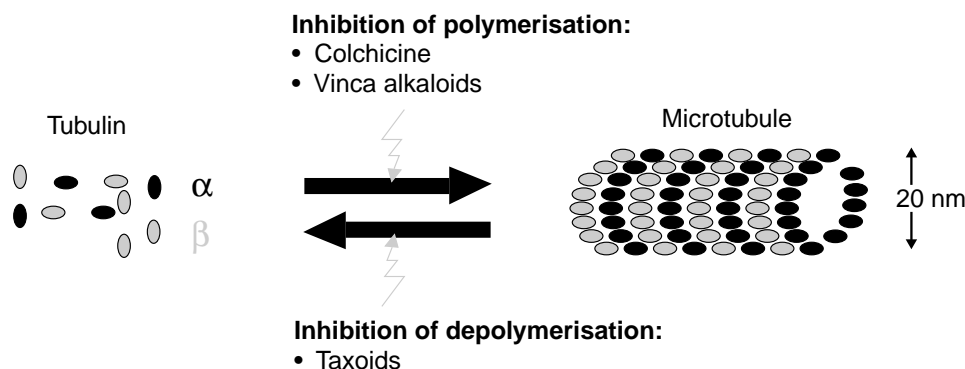


FIGURE 3
The effect of the yew on microtubule formation.

The main problem that faced investigators of these compounds in the initial period of research was the low concentration of taxel in the yew (0.01% w/w). To obtain 1 kg of taxel would have required approximately 30,000 kg of bark and, as a consequence, the tree would have been extinct in the Pacific North West within 10 years! However, the industry and ingenuity of the chemical engineer solved the problem.¹¹ At first the taxels were synthesised by a semi-synthetic route from 10-desacetylbaccatin. This is a renewable resource found in *Taxus baccata* and also in *Taxus wallichiana* Zucch (the Himalayan yew). Total synthesis from simple, readily available, organic compounds has now been achieved (Nicolau *et al*).¹²

The taxel molecules have very limited solubility and need to be administered in ethanol and polyethoxylated castor oil. This results in a high incidence of hypersensitivity reactions, and prophylactic treatment to counteract these should be given with diphenhydramine and cimetidine (H_1 and H_2 antagonists) together with dexamethasone.

The taxels have a broad spectrum of anti-cancer activity. Responsive cell lines have included those of human breast, colon and ovary. They are also effective in cell lines that have acquired resistance to 5-fluorouracil, cisplatin, vincristine, or etoposide. Paclitaxel has been evaluated in a clinical trial in metastatic ovarian and breast cancer.¹³ It showed definite activity in cancers progressing despite primary combination schedules. Response rates in such patients in relapse ranged from 20% to 50% depending on the clinical stage of the patient and the exact treatment regimen employed. Preliminary results have also shown significant response rates in cancer of the lung, head and neck, oesophagus and urinary bladder. The optimum regimens and combinations for the taxels have yet to be established.

Toxic side-effects that have been described include neutropenia (largely preventable by granulocyte colony stimulating factor, G-CSF) and peripheral neuritis.¹⁴ Many patients have also demonstrated asymptomatic bradycardia with occasional bursts of

ventricular tachycardia during the course of the intravenous infusion of the chemotherapeutic agent. These resolve spontaneously but are reminiscent of the poisonous effects of yew on the heart.

A lasting judgement on the place for the taxels in the modern treatment of neoplastic disease cannot yet be made but will emerge over the next 10-20 years. Suffice it to say that they represent some of the most promising agents to emerge since the advent of cis-platinum some years ago.

ENVOI

The rod of office in the Highlands was made of yew, a legacy of the Druids (*slatdhraoidheachd*) possessing as it did mystical authority. It carried also the power of death as we see in the murder of Hamlet's father (Act 1 Scene 5).

Upon my secure hour thy uncle stole,
With juice of cursed hebenon in a vial,
And in the porches of mine ears did pour
The leperous distilment; whose effect
Holds such an enmity with the blood of man,
That, swift as quicksilver, it courses through
The natural gates and alleys of the body;

Man was rightly frightened of the yew in ancient and medieval times with its powerful associations with death and poisoning. Now, with the application of science, we can look on it with new respect, whether in churchyard or hedgerow. The Tree of Death has become a Tree for Life!

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