Proceedings of CONF-MCEE 2026 Symposium: Advances in Sustainable Aviation and Aerospace Vehicle Automation
DOI: 10.54254/2755-2721/2026.KA29613

Paclitaxol: The Cornerstone of Modern Cancer Treatment

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Abstract. Paclitaxel (Taxol) is a widely used chemotherapeutic drug that inhibits cancer cell division by stabilizing microtubules. Unlike many other agents, it acts by stabilizing microtubules and preventing their depolymerization, effectively disrupting the normal process of mitosis and halting uncontrolled cell growth. Originally discovered in the 1960s from Taxus brevifolia (the Pacific yew tree), it is now produced semi-synthetically from yew needles, making it more sustainable and efficient. Administered intravenously, its employed in the treatment of various malignant cancers including ovarian, breast, and lung. Its unique mechanism of action coupled with its broad clinical use has made it a cornerstone in modern oncology and a critical component of many current chemotherapy regimens.

Keywords: Paclitaxol, microtubules, enzymes, synthesis

1. Introduction

Paclitaxol is one of the most important molecules involved in modern day cancer treatment, saving many lives from the fatal disease. This extremely important molecule was initially found as a substance coming from Pacific yew trees, eventually being collected and analyzed by scientists across decades. The molecular shape of paclitaxol is Figure 1:

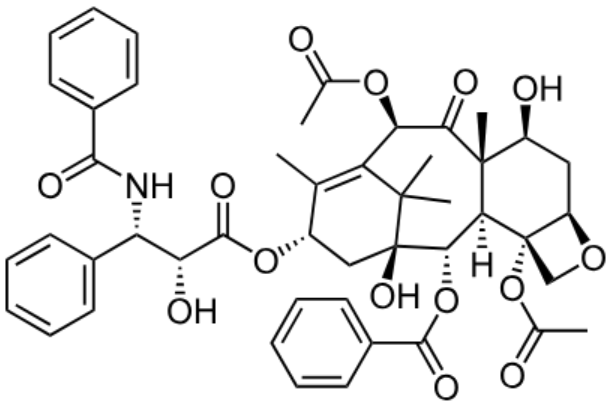


Figure 1. The molecular structure of Paclitaxol. The molecular formula is $C_{47}H_{51}NO_{14}$with a molar mass of 853.91 g/mol

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Paclitaxel is a small molecule, not a polymer. It is classified as a natural product because it was originally isolated from the bark of the Pacific yew tree (Taxus brevifolia), although it is now often produced by semi-synthesis from related natural precursors. It is a terpenoid, specifically a diterpene alkaloid with a highly complex, polycyclic structure. It includes many notable features: A fused tricyclic core: a taxane ring system, an oxetane ring, a benzoate ester side chain (which includes an aromatic ring), and multiple hydroxyl (-OH) groups. It also includes many functional groups, including esters, ethers, hydroxyl groups, aromatic rings , aliphatic chains etc (Fig 1).

Paclitaxel was first isolated from the bark of the Pacific yew tree (Taxus brevifolia) by Monroe Wall and Mansukh Wani at the Research Triangle Institute. The compound was named paclitaxel and reported in scientific literature. Its structure was elucidated, and its unusual mechanism of action became of interest. The complete chemical structure of paclitaxel was determined and published by Wall and Wani. Researchers did trials on Murine leukemia and xenograft models. Results led to the conclusion that paclitaxol is a promising candidate for clinical development. Initial human clinical trials were then conducted and demonstrated efficacy against advanced ovarian and breast cancers, but supply was limited due to reliance on harvesting bark from yew trees. In the 1990s, Holton's FSU group completed the first total synthesis. Environmental concerns and supply challenges prompted the development of semi-synthetic production methods from the needles of Taxus baccata (European yew), making large-scale production feasible.The FDA approved Taxol, the commercial name for paclitaxel, in 1992 for the treatment of ovarian cancer. Since the 2000s, innovations in paclitaxel include the development of Abraxane® and advances in biosynthetic engineering and cryo-EM imaging, which have improved drug delivery, reduced toxicity, and deepened mechanistic understanding.

2. Mechanism of action

Normally, microtubules undergo dynamic instability and constantly grow and shrink during mitosis to align and separate chromosomes (Fig 2). But when paclitaxel binds to the β-tubulin subunit of microtubules, the binding stabilizes microtubules, preventing their depolymerization. As a result, cells cannot complete mitosis because microtubules are "frozen" in a polymerized state. This leads to cell cycle arrest in the M phase and eventually apoptosis [1] (Fig 2).

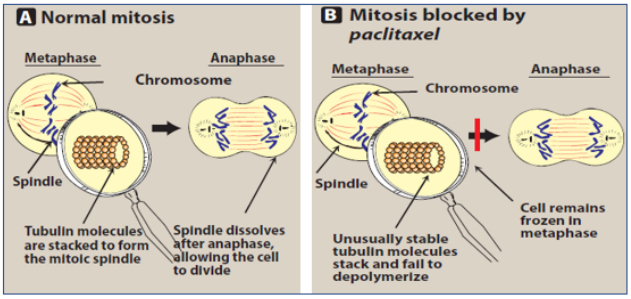


Figure 2. The image above shows a comparison between normal mitosis and mitosis blocked by paclitaxol, leading to apoptosis in harmful cancer cells

Along with causing the apoptosis of cancer cells, having Paclitaxol in the human body also has many side effects, among them including anti-angiogenic effects, where paclitaxel can inhibit endothelial cell proliferation, suppressing tumor neovascularization and immunogenic effects (at low doses) which may promote dendritic cell maturation and tumor antigen presentation, enhancing immune recognition.

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Looking into a stimulated model of Paclitaxol action, the microtubule fragment consists of two tubulin α/β heterodimers and two additional α-monomers to minimize potential end effects. The M-loop for this monomer is colored yellow and the interacting H1-S2 loop of the adjacent monomer is colored red. The M-loop is a flexible segment on β-tubulin that is critical for lateral contacts between protofilaments in the microtubule lattice(Fig 3). When paclitaxel binds, it promotes a structured conformation of the M-loop, locking it into a geometry that favors tight lateral binding to the adjacent protofilament [2].

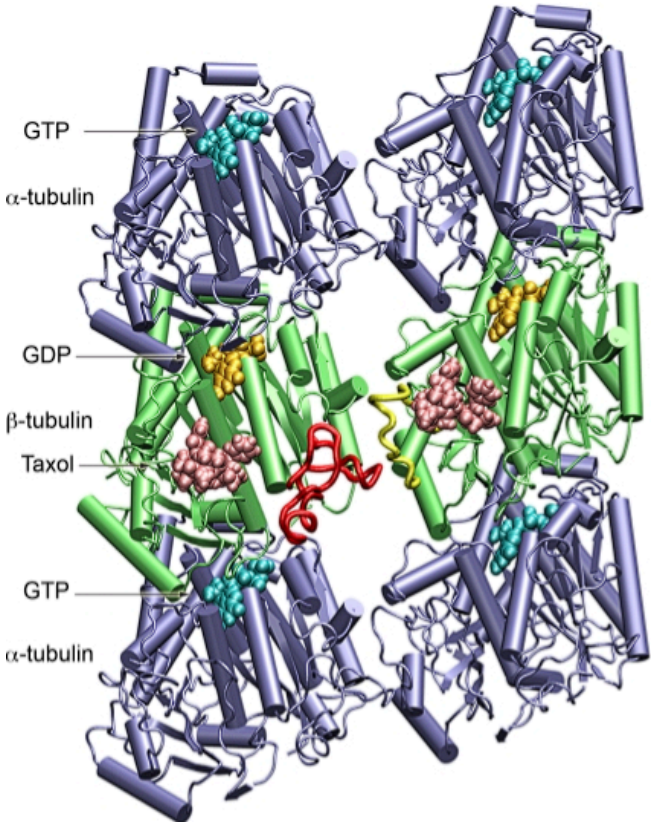


Figure 3. A stimulated mechanism of action of Paclitaxol on microtubules. The stimulation includes M-Loop and H1-S2 loops, both crucial to the action Paclitaxol has on microtubules [2]

By allosterically stabilizing the M-loop, paclitaxel indirectly increases the mechanical stability of the entire microtubule lattice. This reduces dynamic instability, leading to prolonged polymerized state and mitotic arrest in dividing cells [3].

3. Biosynthesis

Taxol is derived from the diterpenoid precursor geranylgeranyl diphosphate (GGPP). GGPP undergoes cyclization catalyzed by taxadiene synthase (TS) to produce taxa-4(5),11(12)-diene, the first committed step of Taxol biosynthesis. A series of P450-dependent monooxygenases modify taxadiene at different positions to form early oxygenated intermediates like taxadiene-5α-ol and taxadiene-13α-ol [3] (Fig 4).

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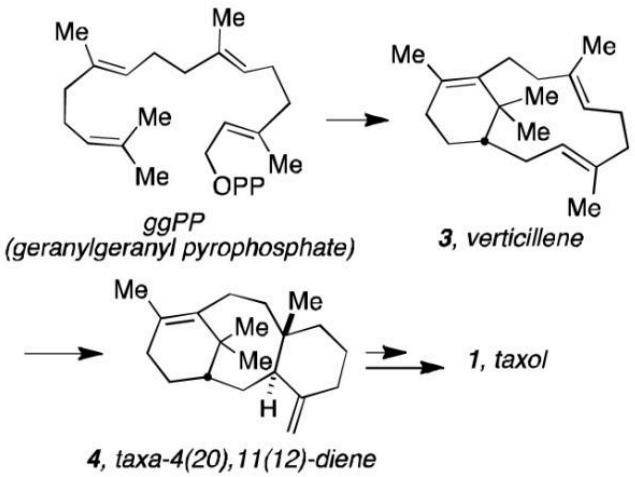


Figure 4. This is a shortened version of the biosynthesis of Taxol from ggPP (geranylgeranyl pyrophosphate) [4]

The researchers discuss their attempts to chemically synthesize and isolate early intermediates (e.g., taxadien-5α-ol, 10β-hydroxy-taxadiene) to confirm their structure and function through co-elution studies with natural plant extracts. Techniques like GC-MS and radioisotope labeling were used to confirm the identity of pathway intermediates and validate proposed biosynthetic steps(Fig 5). The pathway includes alternative or branched oxygenation patterns, suggesting enzyme promiscuity and the potential existence of non-linear routes to Taxol. Due to the complexity and low yield of Taxol in yew trees, understanding these early steps is crucial for developing biotechnological production strategies (e.g., metabolic engineering in microbes or plant cell cultures) [4].

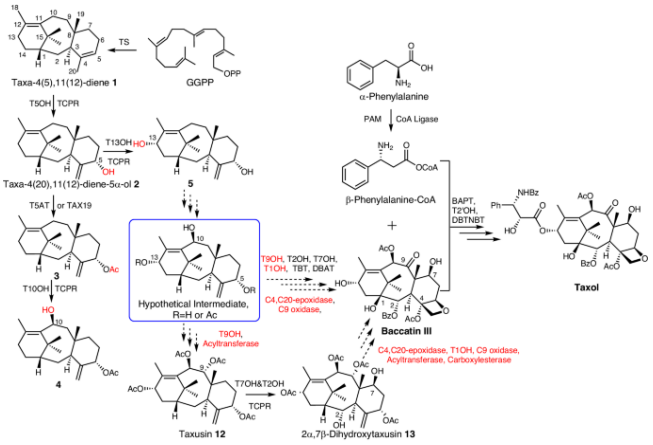


Figure 5. This is the step by step biosynthesis of Taxol with reaction conditions labeled and multiple intermediates identified [5]

Table 1. Table created by student researcher. Shows steps, in order, of paclitaxol bio-synthesis

Step	Transformation	Enzyme(s)
1	GGPP → taxa-4(5),11(12)-diene (1)	TS (taxadiene synthase) — cyclization

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Table 1. (continued)

2	(1) → taxa-4(20),11(12)-dien-5α-ol (2)	T5OH (+TCPR) — 5α-hydroxylation with Δ4(5)→Δ4(20) shift
3	(2) → 13-OH intermediate (order can swap with step 4)	T13OH (+TCPR) — installs 13-OH at C13
4	(2) → 13-OH intermediate → 5-O-acyl taxadienol	T5AT / TAX19 — 5-O-acetyltransferase (5-OAc)
5	"Hypothetical intermediate (R = H or Ac)" → +10-OH	T10OH (+TCPR) — introduces 10-OH
6	Optional oxidations on core: +7-OH, +2-OH, +1-OH	T7OH, T2OH, T1OH — hydroxylases
7	Formation of 4,20-epoxide (oxetane precursor)	C4,20-epoxidase — sets oxetane precursor
8	C9 oxidation (→ C9=O)	C9 oxidase — yields C9 carbonyl
9	2-O-benzoylation of core	TBT (C2 O-benzoyltransferase) — installs C2-Bz
10	10-O-acetylation	DBAT (10-deacetylbaccatin III 10-O-acetyltransferase) — gives 10-OAc
11	Final ester edits → Baccatin III	Final tailoring steps

From the biosynthesis of Taxol, researchers have also wondered what causes taxol to have these anti-cancer effects. So researchers have created two "deletion" PTX derivatives: 2′-deoxy-PTX, which lacks the 2′-OH group, and N-debenzoyl-2′-deoxy-PTX, which lacks both the 2′-OH and the 3′-benzoyl group [6] (Fig 6). Their affinities for GMPcPP-stabilized microtubules, their efficacies as promoters of pure tubulin assembly, and their cytotoxicities have been measured and compared with those of the parent molecule, PTX, and the paclitaxel derivative devoid of the side chain, baccatin III. It is found that the 2'-OH group is the most important component of the side chain, as it accounts for 80% of the binding free energy of the entire side chain. It can therefore be said that this hydrogen bonding interaction is the most important interaction that PTX forms with protein in the region of C-13 side chain [7] (Sharma, Lagisetti, Poliks, Coates, Kingston, & Bane, 2013).

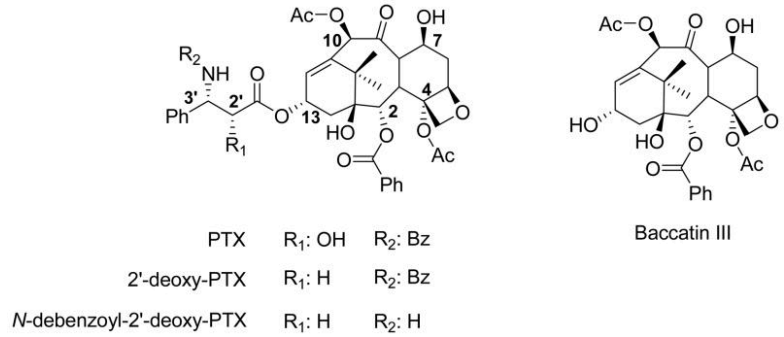


Figure 6. The molecule on the left is an image of potential replacements in the R1 and R2 groups, while the molecule on the right is the Baccatin III molecule devoid of the side chain [7]

4. Clinical use

Paclitaxel can only be obtained from prescriptions from a doctor, due to its harmful nature. It cannot be purchased over the counter or instantaneously from pharmacies. It is used in the treatment of various cancers, including ovarian, breast, and non-small cell lung cancer. It is supplied to pharmacies through specialty distributors and arrives in vials that are ready to use injectable

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solutions. Depending on the patient, the dosage or concentration of Taxol will vary. Taxol is administered by intravenous infusion under the supervision of professionals, as its use carries significant risks such as severe allergic reactions, myelosuppression, and peripheral neuropathy. To minimize harmful reactions, patients are typically given other drugs which protect their body before infusion. The clinical formulation contains paclitaxel dissolved polyoxyethylated castor oil and ethanol, since paclitaxel is unable to dissolve in water effectively. Because it is light-sensitive and temperature-sensitive, Taxol must be stored refrigerated at 2–8 °C in its original packaging to protect from light, and it must not be frozen to preserve solubility and stability.

5. Pharmacokinetics

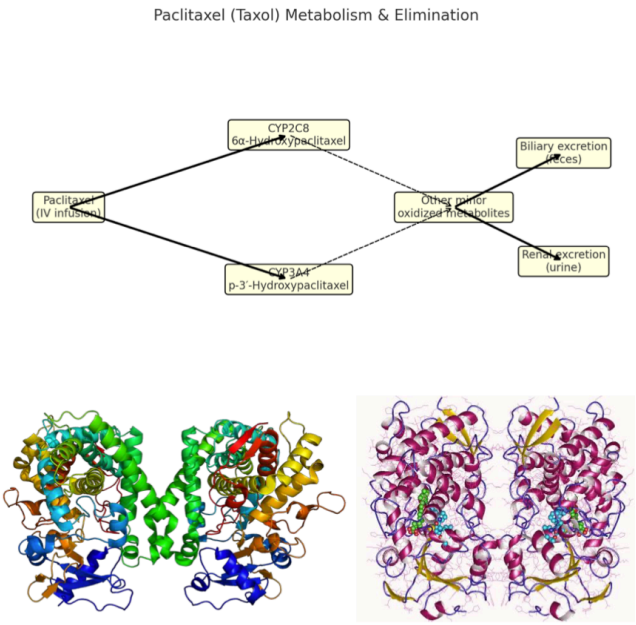


Figure 7. The first image is drawn by a student and is a pathway of excretion that paclitaxel goes through, with two different excretion paths: renal and biliary. The bottom left and bottom right are CYP2C8 and CYP3A4, respectively, representing an enzyme helping with excretion

5.1. Phase I metabolism – oxidation

CYP2C8 – produces 6α-hydroxypaclitaxel (major pathway).

CYP3A4 – produces p-3′-hydroxypaclitaxel (secondary pathway).

These products go through monooxygenation – the enzyme inserts an oxygen atom into specific carbon positions on paclitaxel. Hydroxylation increases polarity and makes the molecule more water-soluble, preparing it for excretion [8] (Fig 7).

5.2. Phase II metabolism – conjugation

UDP-glucuronosyltransferases (UGTs) – add glucuronic acid to hydroxylated metabolites.

Sulfotransferases (SULTs) – add sulfate groups to hydroxyls.

Conjugation greatly increases water solubility, enabling efficient biliary and renal excretion [8].

After metabolism in the liver, paclitaxel and its metabolites are actively transported into bile and then pass into the intestines for elimination in feces. P-glycoprotein (P-gp / ABCB1) is an ATP-

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binding cassette transporter that pumps paclitaxel and its hydroxylated metabolites into bile canaliculi. If bile flow is impaired (cholestasis or bile duct obstruction), clearance can be significantly reduced, increasing systemic exposure and toxicity risk [8] (Fig 7).

6. Conclusion

The analysis of paclitaxol is a landmark for oncological studies. From original natural isolation from Taxus brevifolia to semi-synthetic extension and formulation enhancement, paclitaxel has become more accessible to meet clinical demands and stimulate innovations in drug delivery and in cancer therapy. Increased exploration of resistance mechanisms, new analogs, and targeted delivery systems could enhance its effectiveness while reducing toxicity. As a cornerstone of modern oncology, paclitaxel is a testament to the potential of drug discovery from natural products to transform cancer chemotherapy.

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