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A COMPRESSIVE REVIEW ON TAXOL: OCCURRENCE, ISOLATION AND CHARACTERISTIC FEATURES

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ABSTRACT

Paclitaxel, another name for Taxol, is a popular chemotherapy drug used to treat a variety of malignancies. One of the most often used antitumor medications; Taxol has been used to treat more than a million patients since its antitumor activity was discovered. First, taxol was extracted from a *Taxus brevifolia* tree. It is one of the most prized natural substances that the Food and Drug Administration (FDA) in the USA has authorized for the treatment of many forms of cancer. In addition, the overuse of this natural tree species and its decreased taxol yield prompted researchers to look into other sources, such as semi-synthetic methods and other Taxus species. A better way to isolate taxol and its analogues from a crude extract of the Taxus plant is by using reverse phase liquid chromatography. In this method, Taxol and its analogues stick to its adsorbent, and then the eluent is used to wash them off, allowing Taxol and its natural analogues to be collected from the material.

KEYWORDS: *Taxus brevifolia*, Taxol, Anticancer, Isolation.

INTRODUCTION

African Fern Pine (*Podocarpus gracilior* Pilger) contains taxol, a tubulin-binding diterpene that was first identified from the Pacific Yew (*Taxus brevifolia* Nutt.) (Podocarpaceae). This is the first record of this compound's presence in plants unrelated to the Taxaceae family.[1] Taxol is a powerful cancer medicine, but it comes from the needles of a rare and endangered tree. The demand for this medicine might become too high. Scientists discovered a new way to get the cancer drug Taxol. They found it in hazelnut trees and fungi. This could: Provide a lot more of the drug and make it cheaper.

Taxol treats ovarian and breast cancer. Many survivors take it to prevent recurrence. For now, there's enough. But demand may rise as researchers explore its use for: Other cancers, Alzheimer's and Multiple sclerosis.[2] The entire market was still expected to grow at a rate well over $ 1 billion annually despite a 24% decline between 2006 and 2007 as a result of patent expiration and greater generic competition in Europe and Japan in the first quarter of 2006. This was attributed to new therapeutic use.[3]

Paclitaxel approved by the Food and Drug Administration for the treatment of ovarian, lung, breast cancer as well as Kaposi's sarcoma. Off label uses includes treating leukemia, sarcoma, lymphoma and gastric, endometrial, cervical, prostate and head and neck cancer.[4] The primary mechanism of taxol is to promote cellular death by attaching to tubulin and preventing microtubule disintegration. Taxol is therefore classified as microtubule targeting agent (MTAs). MTAs are categorized into two groups: those that stabilize microtubule like Taxol and those that destabilize them, such vinca alkaloid, which attach to alpha/beta tubulin to cause microtubule disintegration. Consequently despite the fact that they both induce cell death and are commonly used anticancer drugs, they have opposing mechanism of action.[5]

OCCURRENCE

Taxol was first found in the bark, roots, and branches of the *Taxus brevifolia* (yew) tree. Today, taxol comes from two main sources: Semi-synthetic materials from yew trees and the yew tree itself. Although yew trees contain very little taxol (only 0.01-0.05%), their bark remains the main source. The drug is expensive due to: Limited natural supply and increasing demand for cancer treatment.[6] To address the taxol shortage, researchers explored other plant sources beyond *Taxus brevifolia*. They studied other species within the Taxus family, which includes: *T. wallichiana, T. globosa, T. floridana, T. chinensis, T. Canadensis, T. baccata, T. cuspidate, T. fauna, T. sumatrana*.[3]

Microbial fermentation technology has surfaced as a substitute strategy for producing taxol at a lower cost and with a greater yield. In particular, a very promising and workable method for producing a significant amount of taxol is the isolation and identification of taxol-producing endophytic fungus.[7] It has been reported that a number of endophytes from various genera, including *T. Anderanae*, *Alternaria alternate*, and *Fusarium sp*., produce taxol.[8]

Many taxol-producing endophytic fungi have been isolated in the last few decades. However, due to the low level of taxol production, none of them were able to establish an industrial production platform. Since yew trees (Taxus spp.) are rare and grow slowly, they're looking for alternative sources. To address this, researchers are: Searching for fungi in nature that produce high amounts of taxol and using advanced technology to improve production.

In this study, researchers focused on a specific fungus, Aspergillus fumigatus, found on yew trees in the Himalayas. They aimed to: Isolate and identify this fungus and understand how it produces taxol outside its cells.
Goal: Find new ways to produce taxol on a large scale to meet increasing market demand.[9]

ISOLATION

Isolation of Taxol from *T. brevifolia*

Alcohol is used as a solvent to extract taxol from the dried, powdered bark of the yew tree (*Taxus brevifolia*). To obtain a mixture of taxol and cephalomannine, the alcoholic extract is concentrated, dried, and then separated using two types of chromatography (on silica gel and florisil). This mixture is further separated using chromatography with dichloromethane and 1-propanol. The first part of the process gives pure taxol, while the later parts contain both taxol and cephalomannine.

To fully separate cephalomannine from taxol, osmium tetroxide is used to turn cephalomannine into its diol form, which doesn't affect taxol. Afterward, flash chromatography is used to separate taxol from the diol.

Another method of extracting taxol from yew bark uses supercritical fluid extraction. By using a mix of carbon dioxide and ethanol at 318 K, this method recovers around 50-85% of the taxol. Supercritical fluid extraction can provide up to 1.5% of taxol compared to only 0.125% in an ethanol extract, making it a more efficient extraction method.[10]

Other Method

A structurally similar compound to taxol was extracted from European yew (*Taxus baccata*) needles and further converted into taxol using a four-step process. Since the needles are replenishable and harvesting doesn't harm the tree, the technique can provide significant amounts of semisynthetic taxol.[11]

CHEMICAL NATURE

The chemical formula of paclitaxel (PTX), a diterpenoid pseudoalkaloid, is $C_{47}H_{51}NO_{14}$. It is made up of an N-benzoylphenylisoserine group and a taxane ring.[12] Paclitaxel is typically found in relatively modest amounts in different areas of the yew tree. However, because of their potentially effective anti-cancer properties, they represent the most interesting class of taxanes. Typically, they have a complicated side chain at position C-13 instead of C-5, as is common with other groups of taxanes, and a ketone group at position C-9.

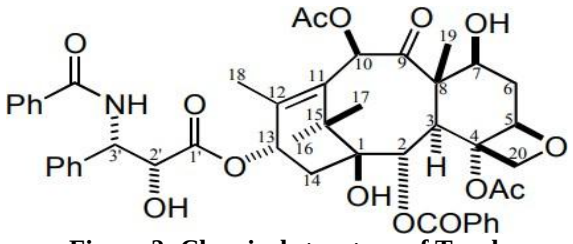
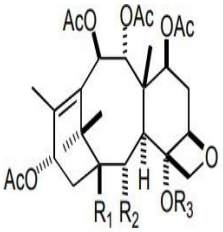


Figure 2: Chemical structure of Taxol.

The bark *of Taxus baccata, Taxus wallichiana,* or *Taxus brevifolia* has yielded a variety of compounds that vary only in the type of substituents present at positions C-1, C-2, and C-4.[13]



	R_1	R_2	R_3
1.17a	OH	OAc	Ac
1.17b	H	OAc	Ac
1.17c	OH	OCOPh	Ac
1.17d	OH	$OCOC_5H_{11}$	Ac
1.17e	H	OAc	H

Figure 3: Other taxanes having an oxetane ring at C-4 and C-5.

Table 1: Physical property of taxol.

Empirical formula	$C_{47}H_{51}NO_{14}$
Molar mass	853.91 g/mol
Appearance	White crystalline powder
Melting point	213–216 ºC
Water solubility	≈10–20 mg/L (est.)

BENEFITS OF PACLITAXEL

Paclitaxel is used to treat different kinds of cancer and is a member of the chemotherapeutic agent class. Paclitaxel is indicated for the treatment of a number of malignancies, such as melanoma, esophageal, breast, ovarian, bladder, lung, prostate, and other solid tumors.

Mechanism of action: *In vitro* paclitaxel interacts directly with microtubules and helps them form into stable structures. It prevents them from breaking down when exposed to cold or calcium, which usually cause normal microtubules to break apart. Paclitaxel is different from other chemotherapy drugs because it has a

specific spot where it binds to microtubules. It's also unusual because it can cause tubulin (a protein that makes up microtubules) to form without the help of other molecules like guanosine triphosphate (GTP) and proteins that are usually needed.

Paclitaxel binds strongly to the beta-subunit of tubulin when exposed to ultraviolet light along with microtubule protein. It has one main high-affinity binding site that allows it to attach to cells in a selective and controllable way. When paclitaxel is present, it causes the microtubule structure in cells to rearrange and form stable, large parallel arrays.[14]

Off label uses

Apart from the well-established indications, paclitaxel has proven to be adaptable in a range of off-label applications, indicating it's potential to treat difficult cancers, a few of which are included below.

- Metastatic bladder cancer: To treat metastatic or advanced bladder cancer, paclitaxel and gemcitabine are utilized in combination therapy.
- Advanced cervical cancer: Paclitaxel is used to treat advanced cervical cancer in conjunction with topotecan, bevacizumab, and/or cisplatin.
- Malignancies of the esophagus and stomach: When paired with carboplatin and radiation treatment, paclitaxel is an essential part of preoperative care for patients suffering from these types of malignancies.
- Advanced head and neck cance**r**: Cisplatin and paclitaxel are used together to treat advanced head and neck cancer.
- Neoadjuvant therapy for penile cancer: Paclitaxel is taken into consideration for treating penile cancer patients who have large regional lymph node metastases.
- Paclitaxel is used to treat small-cell lung cancer that has either relapsed or shown to be resistant to other forms of treatment.
- If angiosarcoma is advanced or incurable, paclitaxel may be used as a therapeutic intervention.
- Germ cell cancers in the testicles that have relapsed or are resistant to treatment: Paclitaxel is used in conjunction with gemcitabine and oxaliplatin or ifosfamide and cisplatin to treat these tumors.
- Advanced thymoma/thymic carcinoma: Paclitaxel and carboplatin are used in tandem to treat this condition.
- Unknown primary adenocarcinoma**:** Patients with unknown primary adenocarcinoma are treated with paclitaxel, frequently in conjunction with carboplatin and/or etoposide.
- Treatment for endometrial carcinoma**:** Paclitaxel is used in this situation.
- Malignancies of the stomach and esophagus that have spread or are incurable: Paclitaxel is used to treat these types of malignancies.
- Melanoma**:** Paclitaxel is taken into consideration when treating this condition.
- Paclitaxel may be utilized in the treatment of anaplastic thyroid cancer**.**

These varied off-label applications highlight paclitaxel's potential as a treatment choice in a range of difficult clinical situations.[15]

CONCLUSION

In recent years the use of medicinal plants and phytochemicals are increasing for the prevention and treatment of various diseases and conditions such as cancer and cardiovascular problems. Taxol is a diterpene phytochemical found in *T. brevifolia* and other Taxus species. So it is isolated from these Taxus species. The compound features a taxane ring system with a four-membered octane ring and an ester side chain at C-13, where the presence of an accessible moiety at C-2 of the ester side chain significantly enhances cytotoxic activity. This plant derived compounds have ongoing use for the variety of cancer treatments. Used in lung cancer and has demonstrable anticancer activity in advanced ovarian and breast malignancies. Taxol caused the formation of stable microtubule bundles, which disrupted the normal function of microtubules in the cell. Overall, Taxol represents a remarkable intersection of natural product chemistry and pharmacology, highlighting the need for sustainable practices in its sourcing and continued exploration of its full therapeutic potential.

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