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Taxol: A Chemotherapy Medication

Shweta Kamble[1], Dnyaneshwar Dhere[1], Priyanka Panmand[1]

[1]**IVM, Krishnarao Bhegade Institute of Pharmaceutical Education and Research, Talegaon Dabhade**

Corresponding Author E-mail: priyankapanmand92@gmail.com

ABSTRACT

Taxol, also known as paclitaxel, is a common chemotherapy medication utilised for treating a number of cancers. Since its anticancer efficacy was found, over 1 million patients have been treated with taxol, one of the most widely used antitumor drugs. First, a Taxus brevifolia plant was used to extract taxol. The Food and Drug Administration, or FDA, in the United States has approved it as one of the most valuable natural chemicals for the treatment of many types of cancer. The diterpene alkaloid taxol, which was extracted through the bark of the Taxus brevifolia plant, functions in a special way. One of the most often used antitumoural medications, taxol has been utilised to treat more than a million patients. The primary mode of action of taxol, the first filament targeting drug reported in the literature, is an interruption of microtubule dynamics, which results in mitotic arrest and cell death. Nevertheless, it has also been shown that secondary pathways can potentially induce apoptosis. The key features of this significant medication, from its invention to the present, are briefly described in this review. We point out the primary obstacles that need to be overcome in the upcoming years to improve Taxol's efficacy as an anticancer medication.

Key Words:

Taxol, Anticancer, Antitumor, Chemotherapy

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1. Introduction:

The tubulin-binding diterpene taxol, which is found in African Fern Pine (Podocarpus gracilior Pilger), was initially discovered in Ocean Yew (Taxus brevifolia Nutt.) (Podocarpaceae). The occurrence of this substance in plants unrelated with the Taxaceae family has never been documented before.[1] The needles from a rare and imperilled tree are the source of the potent cancer medication taxol. This medication may become overly popular. Researchers found a novel method of obtaining the cancer medication Taxol. Breast and ovarian cancer are treated with taxol. In order to avoid recurrence, many survivors take it. There's enough for now. However, as researchers investigate its potential applications for Alzheimer's, multiple sclerosis, and other malignancies, demand may increase.[2] The FDA has approved paclitaxel for the treatment of

Kaposi's sarcoma, lung, breast, and ovarian cancer.Leukaemia, sarcoma, lymphoma, and cancers of the stomach, endometrium, cervical region, prostate, and head and neck are among the off-label uses. [4]Despite a 24% drop between 2006 and 2007, the market as a whole was still anticipated to rise at a rate of well over $1 billion per year due to patent expiration and increased generic rivalry in Japan and Europe in the first three months of 2006. This was ascribed to novel therapeutic applications. [3] The FDA has approved the medication for use in the management of non-small cell lung, breast, and ovarian cancers. It is the initial natural substance to stabilise microtubules (Rowinsky, 1997). It has been possible to isolate several hundred distinct taxoid, lignan, flavonoid, steroid, and sugar derivatives from different sections of different Taxus species. [23]

Figure no. 1 (a) fruit of taxol (b) taxol bud

Taxonomical character:
Domain: Eukaryota
Kingdom: Plantae
Phylum: Pinophyta
Class: Pinopsida
Order: Pinales
Family: Taxaceae
Genus: Taxus
Species: Taxus brevifolia (Pacific yew)

Paclitaxel was originally derived from Taxus brevifolia but can now be synthesized semi-synthetically from precursors found in Taxus baccata (European yew). It is a key antineoplastic agent used in the treatment of various cancers, including ovarian, breast, and lung cancer.[12]

2. **History:**

Colchicine, or Colchicum atumnale, was the first known substance to bind to tubulin; nonetheless, it has not been utilised to treat cancer. Vinca alkaloids Vinblastine and Vincristine were the first anticancer medications authorised for clinical use in the 1960s. In 1958, the University of Western Ontario isolated them from the leaf tissue of the Cantharanthus roseus (Vinca rosea) plants. Researchers from the US Department of Agriculture (USDA) first gathered samples of Pacific yew bark in 1962 in an effort to identify a natural substance that might treat cancer. Additional bark samples were gathered in 1964 and 1965 in order to separate paclitaxol and determine its biological mechanism.Although Monrie Walls and Mansukh Wani found the first medication in 1967 in extracts from the outer bark from the Yew plant, Taxus brevifolia, coupled with the taxanes and paclitaxel, its ability to block tubulin (tumour) was not known until

1979. According to Jordan (2012), yews are an insufficient source of active agents, which hindered the invention of taxanes for more than 20 years until the synthesis method was discovered. "Taxol" was another marketing name for paclitaxel in 1977. Paclitaxel was authorised for use in chemotherapy in December 1992 (Gordoliza, 2008). The Food and Drug Administration, also known as the FDA, authorised taxol in 1984 for the treatment of breast cancer and ovarian cancer, respectively. The structure of paclitaxel, which USDA obtained from Taxus brevifolia, was described in 1992.In 2003, Schmidt-Sody showed that paclitaxel had anticancer and antiangiogenic properties. [5]

Names in Different Languages (Vernacular Name):

Paclitaxel, commonly known as Taxol, has different names in various languages based on regional pharmaceutical conventions:

English: Taxol / Paclitaxel
Spanish: Paclitaxel
French: Paclitaxel
German: Paclitaxel
Chinese (Simplified): 紫杉醇 (Zǐshānchún)
Japanese: パクリタキセル (Pakuritakiseru)
Russian: Паклитаксел (Paklitaksel)
Hindi: पैकलिटैक्सेल (Paiklitaxel)
Arabic: باكليتاكسيل (Baklitaksel)

The name generally remains "Paclitaxel" in most languages due to international medical nomenclature.[13]

3. Occurrence:

The bark, the roots, and twigs of the Taxus brevifolia (yew) tree were the first places where taxol was discovered. These days, there are two primary sources of taxol: the yew tree directly and semi-synthetic compounds derived from it. The primary source of taxol is still the bark of yew trees, despite the fact that they only contain 0.01–0.05 percent of it. Due to its limited nature supply and rising demand for cancer therapy, the medication is costly.[6] In recent decades, numerous endophytic fungi that produce taxol have been identified. However, neither of them were able to set up a commercial production platform because of the low level of taxes production. Since yew trees, or Taxus spp., are uncommon and develop slowly, they are searching for other sources. In order to solve this, scientists are looking for fungi in the wild that generate large quantities of taxoland enhancing production through the use of cutting-edge technologies. Researchers in this study concentrated on Aspergillus fumigatus, a particular fungus that grows on Himalayan yew trees. Their objectives were to: Separate and characterise this fungus and comprehend how it generates taxol outside of its cells.[7]

Sources and Production:

The bark of Taxus brevifolia was the original source of taxol, but because of supply issues and environmental concerns, other sources were investigated. Aspergillus terreus and other endophytic fungi have been discovered as possible manufacturers of taxol.Nowadays, 10-deacetylbaccatin III, a precursor present in Taxus baccata, is produced semi-synthetically.[22]

4. Extraction of taxol :

One gramme of soy tone/1 was added to 500 millilitres of MID medium in a two-litre Erlenmeyer flask.[8] The test fungi was injected into the medium and left for 21 days at 26 ± 1°C.

the incubation period was up, the culture was taken out and the culture supernatant was run through four layers of cheesecloth.

To prevent fatty acid contamination, 0.25 g of NaCO3 was added to the filtrate and taken out with two equal volumes of solvent Dichloromethane.

The organic phase was recovered and dried by evaporation at 35°C under decreased pressure.

After being redissolved in methanol, the solidified dry residue was put on a 1.5 × 30 cm silica gel column (Baker 40 μ). The column was eluted using a combination of organic solvents in varying amounts after 70 mL of 100% methylene chloridewas added.

The resulting fractions were gathered, dried by evaporation, and then put through thin layer chromatography (TLC). The presence of taxol in the fungal sample was examined using TLC, UV absorption spectrophotometry, IR spectroscopic inquiry, HPLC analysis, and MASS spectroscopy analysis.[9]

5. Chemical structure of taxol:

The components of paclitaxel include an eight-member taxane ring, a four-member oxetane ring, and a large esters side chain at C-13 that can be altered but is required for anticancer action [10] (Figure 1). Paclitaxel's molecular structure is 853.9 and its chemical formula is C47H51O14. It is insoluble in water and extremely lipophilic, but soluble in ethanol, methanol, chloroform, acetone, Cremophor EL, and polyethyleneglycols 300 and 400. 50% Cremophor EL and 50% dried alcohol are used in the formulation of paclitaxel for clinical application.[11]

Empirical formula: C47H51NO14
Molecular weight: 853.9g/mol
Average mass: 853.9D
Systemicname:(2α,4α,5β,7β,10β,13α)-4,10-bis(acetyloxy)-13-{[(2R,3S)-3-(benzoylamino)-2-hydroxy-3phenylpropanoyl]oxy}-1,7-dihydroxy-9-oxo-5,20-Epoxytax-11-en-2-yl benzoate.

Macroscopical Characteristic:

Taxol, also known as paclitaxel, is a highly potent chemotherapeutic agent originally derived from the bark of the Pacific yew tree (Taxus brevifolia). It is a diterpenoid compound with a complex molecular structure, widely recognized for its ability to stabilize microtubules and inhibit cell division, making it effective against various cancers.

- Macroscopical Characteristics of Taxol
- Physical Appearance: Taxol is a white to off-white crystalline powder.
- Solubility: It is insoluble in water but dissolves in organic solvents like ethanol, methanol, chloroform, and dimethyl sulfoxide (DMSO).
- Melting Point: The melting point of taxol is approximately 216–217°C.
- Odor and Taste: Taxol is odorless and has a bitter taste.
- Chemical Structure: It is a complex polycyclic diterpenoid, featuring an eight-membered taxane ring with multiple hydroxyl and ester functional groups. [21]
- Type: Taxol is a tetracyclic diterpenoid belonging to the taxane family.
- Key Features: Its structure includes a four-membered oxetane ring and a complex ester side chain, both of which are essential for its antitumor activity.
- Molecular Formula: C47H51NO14.

Detection of taxol using TLC:

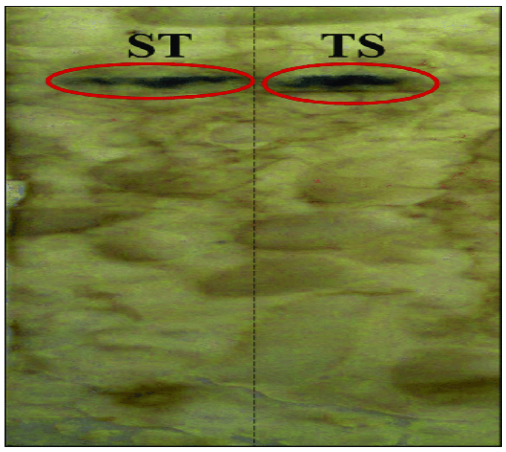

Figure no. 2 Detection of taxol using TLC;ST: Standard Taxol; and TS: Test Sample [24]

Phytoconstituents of Taxol:

Table no.1: Key Phytoconstituents of Taxol

Phytoconstituents	Information
Paclitaxel	The main bioactive compound responsible for its anticancer properties
10-Deacetylbaccatin III	A precursor used in the semi-synthetic production of paclitaxel.
Cephalomannine	A taxane derivative with structural similarities to paclitaxel.
Baccatin II	Another taxane compound involved in biosynthesis.
Taxane Alkaloids	A group of related compounds that contribute to the pharmacological effects.

6. Pharmacological activities:

1. Antioxidant effect:

Although studies indicates that taxol (paclitaxel) may possibly have antioxidant qualities, its primary function is as an anticancer drug. Research has examined the effects of taxol on antioxidant activity and oxidative stress, especially in plant cell cultures. For instance, studies on hazel (Corylus avellana L.) cell cultures have demonstrated that specific precursors, such as phenylalanine, can boost the formation of taxol and increase antioxidant activity. Similarly, benzoic acid dramatically increased antioxidant activity and Taxol levels in hazel cell cultures, according to another study. Furthermore, in Taxus baccata callus cultures, stress caused by polyethylene glycol (PEG) resulted in elevated activity of antioxidant enzymes like catalase and guaiacol peroxidase, which assisted in reducing oxidative damage. [14]

2.Anti-inflammatoryaction:

TNF-α, IL-6, and IL-1β are important mediators of inflammation, and taxol has been demonstrated to affect these inflammatory cytokines by decreasing their expression. According to certain research, taxol may be able to block the inflammatory response-related pathway NF-κBsignaling. In order to balance immunological responses, Taxol may also encourage the secretion of anti-inflammatory cytokines.[14]

3.Analgesiceffect :

The potential of taxol to reduce neuropathic pain, especially in cancer patients receiving chemotherapy, has been studied. It might lessen pain sensitivity by adjusting the central nervous system's microglial activity. Certain formulations have been created to improve its analgesic and anti-inflammatory properties, such as Taxol-liposome gel.

4.Antimicrobial action:
When it comes to some harmful fungus, taxol has demonstrated strong antifungal properties. According to research, endophytic fungi that may produce Taxol may have antifungal qualities that could prevent the growth of fungi. Furthermore, Aspergillus flavus, a common fungal pathogen, has been shown to be susceptible to the effects of Taxol, which is generated from Aspergillus niger, an endophyte of Encephalartos whitelockii.[16]

5.Antifungal Characteristics:
Research on taxol generated from fungi indicates that it might have antibacterial qualities, preventing some bacterial strains from growing. Using agar well diffusion techniques, the antibacterial activity of fungi that produce taxol has been assessed and found to be effective against bacterial infections that affect humans.[17]

6.Benefits of Cardioprotection:
The cardioprotective effects of taxol (paclitaxel) have been investigated, especially in relation to chemotherapy-induced cardiotoxicity. Although its main function is anticancer, scientists have looked into how it can lessen the negative effects of chemotherapy on the heart. Possible Cardioprotective Benefits:
1. Reduction of Oxidative Stress: One of the main causes of chemotherapy-induced cardiotoxicity is oxidative damage to cardiac cells, which taxol may help prevent.
2.Anti-inflammatory Properties: Taxol may lessen heart problems associated with inflammation by modifying inflammatory pathways.
3.Microvascular Protection: According to certain research, Taxol may help maintain vascular integrity, which could lower the chance of heart damage brought on by chemotherapy. Even so, not many people consider taxol to be a cardioprotective substance.[18]

7.Antidiabetic Effect:
Although studies have examined its possible antidiabetic effects, taxol (paclitaxel) is most recognised for its anticancer effects. Despite not being a traditional diabetic medication, some research indicates that Taxol may have an impact on insulin sensitivity and glucosemetabolism.[19]

Typical Side Effects:
• Fatigue and weakness
• Joint or muscle discomfort
• Temporary hair loss
• Darkening of the skin or nails
• Nausea, vomiting, diarrhoea, or constipation [20]

Extreme Adverse Reactions:
- Blood conditions include anaemia, thrombocytopenia, and neutropenia (low white blood cell count).
- Hypersensitivity reactions include anaphylaxis, dyspnoea, hypotension, angioedema, and urticaria.

Neuropathy: tingling, burning, numbness, or discomfort in the limbs
Severe infections: fever, chills, sore throat, and unusual bleeding or bruising;

- Cardiovascular problems: slow heartbeat, lightheadedness, fainting, and dyspnoea [13]

Additional Uses of Taxol:

Table no.2: Additional Uses of Taxol

Use of taxol	Description
Head and Neck Cancers	Used in combination therapies for treating advanced head and neck cancers.
Glioblastoma (Brain Cancer)	Being studied for its effectiveness in treating aggressive brain tumors.
Prostate Cancer	Investigated for potential use in hormone-resistant prostate cancer.
Bladder Cancer	Sometimes used in cases where other treatments have not been effective.
Pancreatic Cancer	Often combined with other chemotherapy drugs like gemcitabine toimprove treatment outcomes.
Anti-inflammatory Properties	Some research suggests Taxol may have applications in treating inflammatory diseases.

Marketed formulation:

Paclitaxel, a chemotherapy medication used to treat a variety of malignancies, is marketed under the name Taxol. Although many areas have stopped using the original Taxol formulation, there are still a number of branded and generic forms of paclitaxel accessible worldwide.

India:

Paclitaxel is sold in India under a number of brand names, such as:

1.CiplaL td. (Paclitax)
2.Dr. Reddy's Laboratories Ltd.'s Mitotax
3.Sun Pharmaceutical Industries Ltd.'s Oncotaxel
4.(Intas Pharmaceuticals Ltd.) Cytax
5.Taj Pharmaceutical's Paclitaxel
6.PM Genexol (Lupin Ltd.)
7.Panacea Biotec Ltd.'s Pacliall
8.Biochem Pharmaceutical Industries' Petaxel
9.(Celon Laboratories Ltd.) Celtax
10.Taj Pharmaceutical's Paclitaxel

these medicines come in a variety of formulations and strengths, including injections of 260 mg/43.4 ml and 100 mg/16.7 ml.

America**:**

Paclitaxel, an albumin-bound version, is marketed under the Abraxane trademark in the United States. Companies such as Breckenridge Pharmaceutical, Mylan Pharmaceuticals, Pfizer, Teva Pharmaceuticals, NorthStar, and Fresenius Kabi market other generic versions.

WorldwideAccess**:**

Paclitaxel is marketed internationally under a number of brand names, including Abraxane, Onxol, Taxol, and Taxol-A. Manufacturers such as Accord Healthcare, Actavis, Alembic, Fresenius Kabi, Gland Pharma, Hikma, Hospira, MSN, and Teva produce generic versions.

6. Conclusion:

The fight against cancer is and, for decades to come, will probably continue to be, one of the primary human battles. In this way, although the effectiveness of new drugs is increasing, cancer continues to be very lethal. Taxol, along with the rest of the compounds derived from PTX, have been and continues to be very useful in the fight against this disease. However, the two main disadvantages of its use remain unresolved: Its production is both expensive and unsustainable, and the mechanisms by which tumour cells develop resistance to it are not yet fully clear**.** Regarding the fight against resistance developed by many of the patients treated with PTX, the research currently underway is very intense. Much progress has been made towards understanding the PTX pathway, although it still remains unclear. According to the conclusions reached to date, this resistance may be due to the different pathways activated by the drug, which makes it more difficult to combat. To achieve this, it is necessary to continue developing research in this field and increase our knowledge, thereby improving the efficacy of Taxol, as well as other known anticancer agents.

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