Taxol (Paclitaxel): A Novel Alkaloid with Anticancer Potential

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ABSTRACT

Taxol, a widely used anticancer drug, is derived from the plant alkaloid paclitaxel. It functions as an antimicrotubular agent and a mitotic inhibitor, effectively blocking the division of cancer cells. Administered intravenously, Taxol's efficacy has been well-documented, particularly in treating solid cell tumors. Despite its success, the drug's effectiveness diminishes with prolonged use due to the development of resistance in cancer cells. Additionally, adverse effects can vary significantly based on patient-specific factors such as age, genetics, and overall health. To address these challenges, researchers have developed various conjugates, including nanocomplexes, aimed at overcoming resistance and minimizing side effects. These innovations have shown promise in enhancing the drug's therapeutic profile and extending its effectiveness. Beyond its primary role in cancer treatment, Taxol has also demonstrated potential in other therapeutic areas, broadening its clinical applications. This editorial highlights role of Taxol as an anticancer drug, emphasizing the need for continued research into overcoming resistance mechanisms and offering new avenues for this established therapeutic agent in modern oncology and beyond.

Key Words: *Paclitaxel, Taxol, Microtubule manipulation, Mitotic inhibitor, Cancer*

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Respected Editor-in-Chief,

Paclitaxel ($C_{47}H_{51}NO_{14}$) is a therapeutic agent used in cancer treatment, belonging to the taxane class, which is part of the diterpene family. Originally extracted from the bark of the Pacific yew tree (*Taxus brevifolia*), a member of the Taxaceae family, it received FDA (Food and Drug Administration) approval in 1993 and has been listed among the World Health Organization's (WHO) Essential Medicines since then. Marketed under the brand name Taxol, it has demonstrated effectiveness against a wide range of cancers, including those of the lung, breast, ovary, bladder, prostate, melanoma, cervix, esophagus, pancreas, and colorectal areas, as well as Kaposi sarcoma [1, 2].

Taxol, like other drugs in the taxane category, interferes with microtubule functions. Microtubules are essential intracellular structures involved in various critical processes in eukaryotic cells, such as cell movement, nuclear and cellular division, and the maintenance of cellular architecture. Taxanes stabilize tubulin bound to GDP, thereby preventing its depolymerization and disrupting the mitotic spindle formation, chromosome separation, and cell division. Like other anticancer alkaloids such as vincristine, vinblastine, and vinorelbine from the Vinca genus and colchicine from Colchicum, paclitaxel acts as a mitotic inhibitor. Although these substances have distinct effects on microtubule dynamics, they are all directed towards microtubules. Additionally, paclitaxel promotes apoptosis by inhibiting the apoptosis regulator protein Bcl-2 (B-cell leukemia 2) [3]. Paclitaxel induces apoptosis by blocking the apoptosis inhibitor protein Bcl-2 (B-cell Leukemia 2) [4].

Usually given intravenously, paclitaxel can be prepared with albumin, alcohol, and/or emulsifier. Its cytotoxic effects depend on time as well as concentration.

In an *in vitro* study, ascorbic acid improved the antineoplastic potential of paclitaxel in human breast carcinoma cells. Caffeic acid phenethyl ester (CAPE) has selective estrogen receptor modulators (SERM) activity, and it increases the proapoptotic effects effect of paclitaxel on prostate cancer cells (PC-3, DU-145 and LNCaP)

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prostate cancer cells [5]. A cell penetrating peptide (CPP)-taxol conjugate (Taxol–CPP) was synthesized, self-assembled nanospheres, and showed cytotoxicity against HepG2 cancer cells. Nanoxel, a nanoparticle formulation of the taxol has been approved by the Indian regulatory authority [4]. Mice bearing NSCLC (non-small cell lung cancer) xenografts, when administered with nanoparticles loaded with paclitaxel and cisplatin showed better control of tumor growth [6].

However, drug resistance is a deterrent in the prolonged usage of Taxol. The upregulated expression of TXNDC17 is associated with resistance in colorectal cancer cells. The high levels of phospho-STAT3 and TXNDC17 production are induced by taxol [6]. A study found that taxol-resistant cells expressed higher levels of TAK1 (transforming growth factor-β-activated kinase 1). Taxol-resistant human ovarian cancer specimens were more susceptible to taxol-oligoarginine conjugates [6]. Apart from drug resistance, taxol shows side effects, which can lead to patient non-adherence. Some of the adverse effects include hives, wheezing, poor hair quality, alopecia, muscle pains, arthralgia, tingling sensation, dizziness, peripheral neuropathy, diarrhea, female infertility, bone marrow suppression etc. In some patients, vascular issues can occur. The foetus may become teratogenic as a result of the administration to pregnant mothers. Due to its limited water solubility, taxol is frequently combined with the formulation vehicle cremophor, which might lead to unfavorable effects. Thus, ongoing pharmacovigilance regarding taxol, drug-herb interactions, and drug-drug interactions must be practiced [6]. Apart from the plant, taxol has been isolated from the endophytic fungus *Paraconiothyrium variabile* and *Epicoccum nigrum*. Other fungi such as *Metarhizium anisopliae*, *Pestalotiopsis microspora* NK17, and *Cladosporium* species also elaborated taxol in culture medium. *Cladosporium cladosporioides* MD2 produce taxol at levels up to 800 µg/L. *Aspergillus aculeatinus* Tax-6 also produced taxol on in culture conditions. The taxol biosynthetic gene has been identified to be dbat, pgα1 etc. Apart from different *Taxus* species, paclitaxel has been detected in hazel plants from the Betulaceae family. In the plants, paclitaxel is synthesized by the terpenoid pathway. Semisynthetic taxol is generated using plant metabolite baccatin III; plant cell culture techniques; and metabolic engineering of bacteria. Apart from the anticancer usage, paclitaxel is being used for other therapeutic purposes. Paclitaxel eluting stents are used for vascular diseases [6]. Hence, other taxol possibilities and scopes to circumvent its adverse effects ought to be explored. **Figure 1** illustrates the biological mechanism of taxol.

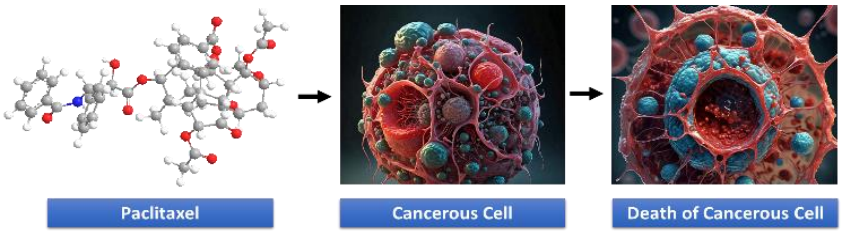

Figure 1. General mechanism of taxol anticancer mechanism

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