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Paclitaxel Against Cancer: A Short Review

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Abstract

Cancer is a life threatening condition. Though it has been immensely studied in the field of medical research, not all attempts have been fruitful. More than half the people diagnosed with cancer receive chemotherapy. One such effective discovery leads to Paclitaxel, a Pacific Yew tree isolate. This review makes attempt at understanding a few advancements in cancer treatment using Paclitaxel since its discovery. We await the discovery of many such compounds which make an impact in cancer treatment. This review tried to discuss the various research using Paclitaxel and its efficacy against various types of cancers and stresses on the need for the research in the field of Cancer Chemotherapy.

Keywords: Paclitaxel; Cancer; Chemotherapy

Introduction

Monroe E. Wall and Mansukh C. Wani in 1967 isolated a mitotic inhibitor from the bark of *Taxus brevifolia* (northwest Pacific Yew Tree) (Figure 1) and named this compound Taxol. It was later discovered that the Taxol was produced by a fungal endophyte when grown on semi-synthetic media. The fungal endophyte was isolated from the phloem tissue of the Pacific Yew Tree [1]. It was first commercially developed by Bristol-Myers Squibb Company with the generic name Paclitaxel and sold under the trademark Taxol. Several formulations were later developed in this field by conjugating Paclitaxel with albumin, Polycitrate etc., from each *Taxus* tree, 150 strains of endophytic fungi were isolated. The endophytic fungal population is varied. 105 out of 150 strains belonged to 25 different genera whereas one remains undetermined and 44 did not produce any reproductive structure in solid cultures [2].

Paclitaxel is a crystalline powder which is white to off-white in appearance. Its empirical formula is $C_{47}H_{51}NO_{14}$ (Figure 2) and is known to have a molecular weight of 853.9 units. It is highly lipophilic thus highly insoluble in water. Its melting point is around 216-217°C.

Mechanism of Action

Paclitaxel drug targets tubulin. Researchers have observed that Paclitaxel treated cells have difficulty with the spindle assembly, cell division and also chromosome segregation which is in opposing nature to Colchicine, a drug that targets tubulin. The major difference between Colchicine and Paclitaxel is that Colchicine inhibits the microtubule assembly whereas Paclitaxel stabilizes and protects microtubule against disassembly. At a higher dose, Paclitaxel is known to suppress microtubule minus ends detachment from centrosomes [3-5]. The beta-tubulin subunit is known to have the binding site for Paclitaxel [6].

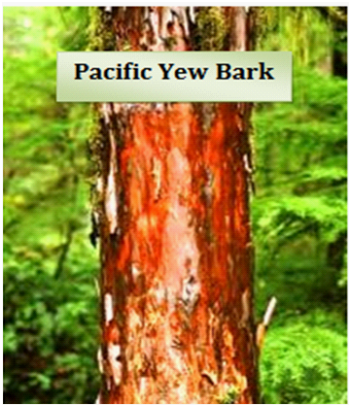

Figure 1: A glimpse of *Taxus brevifolia* bark.

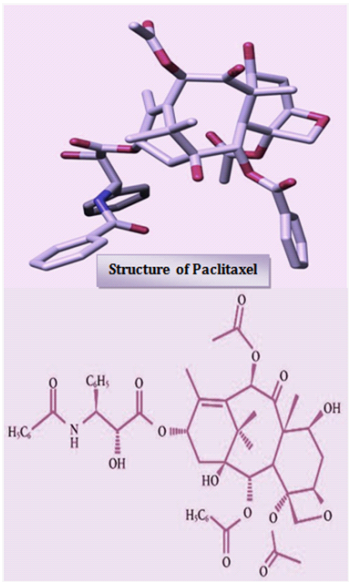

Figure 2: Structure of the drug Paclitaxel.

Role of Paclitexal in Inhibiting Various Types of Cancer

Extensive studies have been done in the field of cancer treatment, especially in the use of various chemotherapeutic agents.

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Nanoparticle assisted chemotherapeutic drug delivery has been used as it enhances therapeutic effectiveness. Studies on metastatic breast cancer demonstrates the inhibition of metastasis by co-delivering chemotherapeutic agent Paclitaxel and twist shRNA via complex nanoparticles thus affectively achieving cellular uptake, RNA interference and inhibited metastasis [7]. Administration of Paclitaxel-loaded expansile nanoparticles (pax-eNP) at the time of cytoreductive surgery effectively decreased local tumor recurrence in Ovarian Carcinoma [8]. Chemotherapeutic nanoparticles provide an advantage over free drugs as they achieve slower clearance and accuracy in target delivery [9]. However, chemoresistance has been observed in various cancer types, including breast, lung, prostate, ovarian, and neck carcinomas. Nanoparticles conjugated with Paclitaxels can also be delivered as nanomicelles and these formulations can be simply uptaken by intracellular endocytosis which showed higher rate of efficiency in drug delivery to the target tumor when compared to other formulations [10,11]. Multiwalled carbon nanotubes have also been used as potential drug delivery systems where Paclitaxel has been conjugated with poly citric acid.

Use of an inhibitor against an activating mutation of signaling molecule in combination with a standard chemotherapeutic agent such as Paclitaxel showed synergistic activity in mutant human endometrial cancer cell lines [12]. A study performed to evaluate the cytotoxic effects of Paclitaxel in combination with Etoposide in Osteosarcoma cells to thermochemotherapy showed that the apoptosis inducing capacity of the drug combination was stronger than the effect of drugs when used individually [13]. A study demonstrates an enhanced Paclitaxel activity in conjugation with gelomulide K, a caspase-independent cell death inducing agent providing an insight into the development of new caspase-independent cell death-inducing agents [14]. Involvement of many target signal transducers as targets to inhibit metastasis by a chemotherapeutic target is being studied for their ability to either mutate, activate or inhibit to suppress the tumor [15-20].

Despite various efforts, multiple myeloma remains incurable. Thus in most cases, combination of chemotherapeutic drugs have been used in order to increase the efficiency. Mostly Paclitaxel synergized with farnesyltransferase inhibitor R115777 (Zarnestra) was found effective enough to induce G2/M cell cycle arrest [21]. Due to hypersensitivity reactions and altered pharmacokinetics of Paclitaxel in combination with Cremophor EL, ABI-007, a Cremophor-free, albumin-stabilized, nanoparticle paclitaxel formulation was used and found to have less toxicity in comparison to Cremophor-containing Paclitaxel in mice [22]. In a study conducted, use of an oral paclitaxel formulation based on thiolated polycarbophil showed significant improved paclitaxel plasma levels and reduced tumor growth [23].

Paclitaxel in various studies is showed as effective anticancer agent against lung, breast, ovarian, leukopenia and liver cancer [24-29]. It is also known to produce macrophage IL-12 in tumor bearing hosts which down regulates the tumor growth significantly by selective dysregulation of IL-12 p40 expression [30]. It is also known to reduce glycolysis by specific mechanisms [31]. Paclitaxel has a role in treating various kinds of cancer by targeting tubulin or inducing cell cycle arrest or enhancing the signaling factors or mutating them [32-40]. Unfortunately the high demand for Taxol from the bark of Pacific yew is a challenging aspect for this new therapeutic weapon [41]. Therefore focus should be on developing this product by chemical/ synthetic methods in order to meet the growing need of this anticancer drug.

Conclusion

Paclitaxel is a very potent anticancer agent obtained from the Pacific Yew tree bark. It seems to raise its efficacy by having multi targets as described earlier, thus being effective against most cancers. This drug has been studied extensively since 1967, from the time of its discovery till date. The main drawback seems to be the mass production of this drug, which can be resolved by focusing more on either chemical/ microbial synthesis of Paclitaxel for the clinical use.

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