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FROM LAB TO PHARMACY SHELVES: THE STORY OF A PLANT DERIVED ANTICANCER DRUG, "PACLITAXEL"

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ABSTRACT

Paclitaxel (Taxol®) is a highly praised anticancer drug, known for its efficiency in treating different cancers. It belongs to a class of compounds called taxanes that are derived from the plants of the genus *Taxus.* This drug is now FDA approved, but there was a time when the name Taxol was less known to the scientific world. Taxol, being a unique molecule in its structure, properties and mechanism of action, has undergone more than 30 years of trials, and faced a lot of hurdles to leave the bench of a laboratory and reach the shelves of a pharmacy. This review focuses on the story of Taxol, how it began and how it achieved the status of Paclitaxel.
Key words: secondary metabolites, *Taxus brevifolia*, taxol, Paclitaxel.

INTRODUCTION

Secondary metabolites of plants have always fascinated scientists due to their unique and diverse properties that could be exploited for their usefulness for mankind. These compounds are involved in plant defense systems that respond to environmental aggressors, where they serve as the molecules of communication and defense warfare. Under the attack of a predator/pathogen, they make the plants unpalatable, toxic for the attacker and also play a role as warning signals for other plants present in close proximity (Rhoades 1979, Friedman 2007, Gershezon and Keris 1999). Applications of secondary metabolites in the plant defense system against predators/pathogens provided the researchers a clue to their possible pharmacological implications in combating human diseases. These molecules constitute a highly diversified group. According to a rough estimate, almost 40,000 different secondary metabolites of plants exist in nature (Denis RA Mans, 2013). Among them, only 10,000 have been chemically characterized, while a large number still remains to be explored for pharmaceutical implications (Firn and Jones 2003; Wink 2003). This concern triggered a significant report that was presented by the US National Institute of Cancer, in which 122 structurally different compounds were isolated from only 94 species of medicinal plants that had been used in traditional medicines in the past (Fabricant and Farnsworth 2001). In the present paper, we reviewed an important invention of cancer treatment, Taxol (commonly known as paclitaxel).

Paclitaxel (Taxol) occurs in the form of crystalline powder of white to off-white color with an empirical formula of $C_{17}H_{51}NO_{14}$ and is a plant derived anticancer drug that is the first drug of choice for chemotherapy in cancer treatment. It lies in the group of hydrophobic diterpenoids, which belong to a class of compounds called taxanes (Wani et al., 1971). It is derived from a plant named *Taxus brevifolia*, commonly known as "Pacific Yew" (Weaver 2014), which is an evergreen dioecious tree. Its bark, whose extract was used to isolate taxol, is dark reddish, groovy and grows 4-6 mm thick upon maturity. The variable size of its trees and the intermittent occurrence makes its wood of no commercial value. Many early tribes used the tree for making weapons, and treating injuries, wounds and pain (Taylor 1981).

Discovery of Taxol

It was an initiative by Dr. Jonathan L. Hartwell of the National Cancer Institute (NCI), with collaboration from the United States Department of Agriculture (USDA), in 1960 to screen as many plants as they could in search for antitumor agents. In their efforts to find novel antitumor agents, 15,000 plants and 115,000 extracts were screened. In 1962, Arthur S. Barclay, a botanist from the USDA, collected 650 plant samples with the help of three field assistants (Persinos 1990), that included *T. brevifolia*. The samples of *T. brevifolia* were tested for their cytotoxic activities by NCI researchers. It was then handed over to the Monroe Wall of the Research Triangle Institute (RTI) who, in 1964, along with Mansukh Wani, started working on the isolation of the active component in the *T. brevifolia* extract (Walsh and Goodman 2002). After three years of struggle, the active component of *T. brevifolia* was isolated in 1967 and named Taxol due to the evidence of hydroxyl groups in it (Wall and Wani 1995).

The isolation of taxol then raised another important question of its structure. It was a very difficult task at that time and techniques like mass spectrometry, hydrogen nuclear magnetic resonance (H'NMR) and X-ray analysis were applied. After a great deal of hard work, the structure of Taxol (Figure 1) was published in 1971 by Wani and coworkers (Wani et al., 1971). After the publication of Taxol's structure, it was quite clear that it was a unique compound with regards to its structure and properties.

Taxol falls in the class of anticancer drugs that target microtubules. Unlike any other anti-microtubule drug, it has a unique mechanism of action (Figure 2). In studies carried out by Fuchs and Johnson (Fuchs and Johnson 1978), it was indicated that taxol was an inhibitor of cell proliferation by blocking mitosis and arresting the cell in the G2 and M phase of cell cycle. A more detailed explanation of the mechanism of action of taxol was presented in 1979 by Schiff and coworkers (McGuire et al., 1989), which explained its uniqueness in stabilizing the microtubules to cause cell cycle arrest. Furthermore, it was observed that instead of inhibiting the formation of microtubules, taxol binds to the protein tubulin that promotes the formation of microtubules (Wall and Wani 1995; Schiff *et al.,* 1979 and Parness and Horwitz 1981). The microtubules thus produced are nonfunctional but highly stable. They hinder the spindle formation and cause failure in the cell to divide with an equal number of chromosomes. This activates apoptosis and results in cell death (Rowinsky and Donehower 1995). The discovery of its mechanism along with its unique structure and properties made it a very important candidate for anticancer studies.

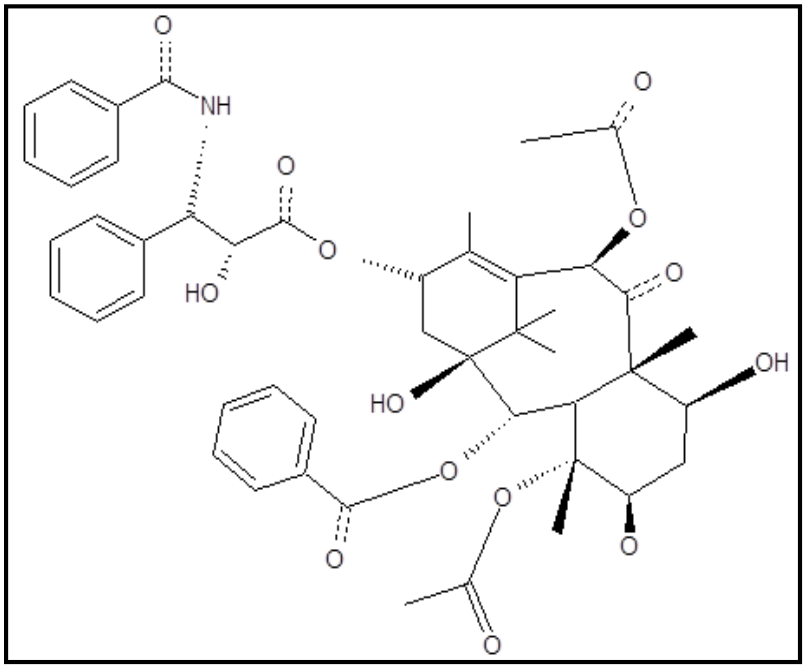

Figure 1: Structure of Taxol (Paclitaxel) (taken and modified from Rowinsky and Donehower 1995).

Before taxol could be exploited at a commercial level, development of a better understanding of biosynthetic pathways of

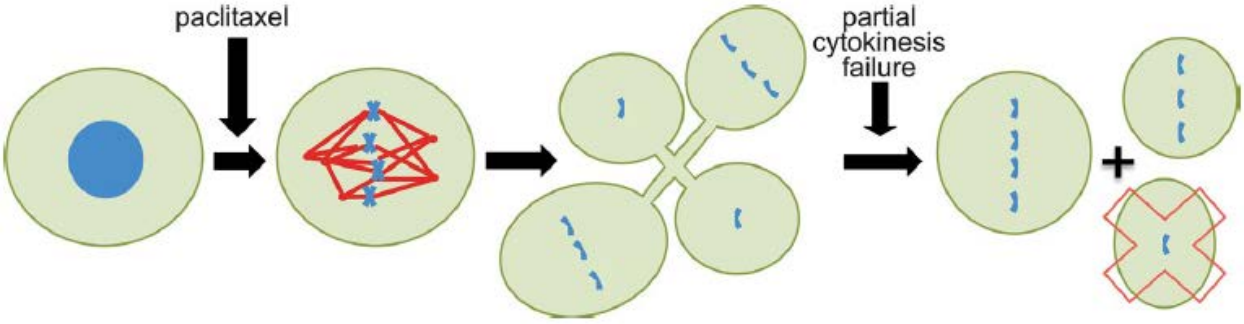

Figure 2: Mechanism of action of Taxol (Weaver, 2014).

taxol in plants was essential. This field grabbed the attention of researchers in the last decade of 20th century where they utilized various techniques, e.g., isotope labelled feeding precursors, cell free enzymology, cDNA library construction and pathway gene cloning techniques, to better understand the biosynthesis in plants. On the basis of feeding experiments, it was suggested that the carbon skelton of taxol could be produced either by mevalonic acid pathway (MVA) (Zamir et al. 1992), or by 2-C-methyl-D-erythritol-4-phosphate (MEP) pathway (*Eisenreich* et al. 1996). Recently, geranylgeranyl pyrophosphate (GGPP) was also suggested as a precursor of the taxane skeleton (Koepp et al., 1995), which was supported by another study of Hefner and colleagues (1996) where the feeding of *T. brevifolia* stem discs with cyclized di-terpenes resulted in production of radioactive 10-deacetyl baccatin III (intermediate product for taxol biosynthesis) and taxol. On a molecular basis, it has been noted that eight cytochrome p450-mediated, three CoA-dependent acyl/aroyl transferases-mediated and some simultaneous steps are involved in the formation of baccatin III. Moreover, the addition of side chain of C-13 is accomplished in 5 more steps (Figure 3) (Croteau *et al*. 2006).

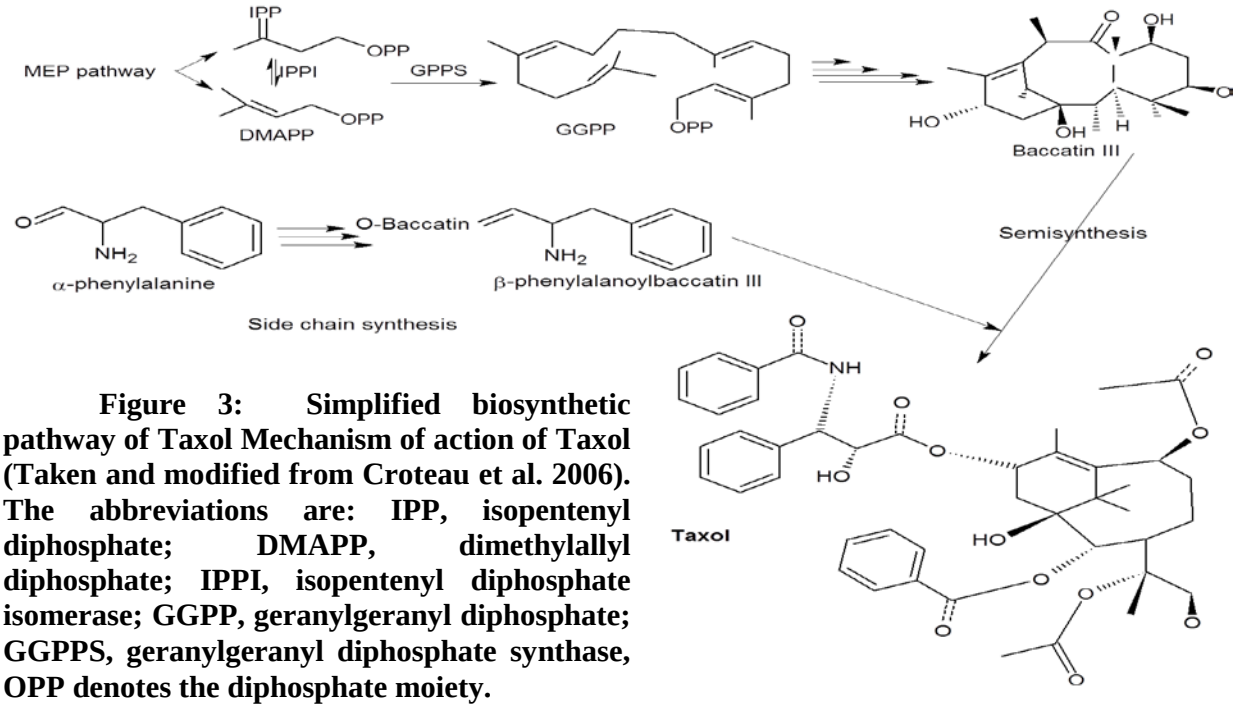

Figure 3: Simplified biosynthetic pathway of Taxol Mechanism of action of Taxol (Taken and modified from Croteau et al. 2006). The abbreviations are: IPP, isopentenyl diphosphate; DMAPP, dimethylallyl diphosphate; IPPI, isopentenyl diphosphate isomerase; GGPP, geranylgeranyl diphosphate; GGPPS, geranylgeranyl diphosphate synthase, OPP denotes the diphosphate moiety.

From Taxol to Paclitaxel

Although taxol (Paclitaxel) is a very important drug in cancer therapeutics, it took more than three decades for taxol to achieve the status of Paclitaxel. The drug entered its phase I trials almost 20 years after its discovery and was approved by the FDA five years after that.

Clinical Trials

Taxol entered its phase I clinical trials in 1984 (Figure 4) and only a year later it was going through phase II trials (Figure 4), but a lack of plant material contributed to taxol once again being delayed during the progress of creating this drug (Walsh and Goodman 2002). It was in 1988 when a complete successful trial of taxol on ovarian cancer was reported by William McGuire of the John Hopkins Oncology Center (McGuire *et al*. 1989). In 1989, when obtaining large quantities of taxol became almost impossible, it was evident that the 'ownership' of taxol was about to change and in 1991, NCI selected Bristol-Myers Squibb (BMS), a pharmaceutical company, for the commercialization of taxol (Weaver 2014).

A lot has happened since then. In 1992, BMS trade marked the name Taxol and assigned a new name "Paclitaxel". It made great progress in getting approval of Taxol for ovarian cancer from The Food and Drug Administration (FDA). Moreover, the Pacific Yew Act was passed that was to ensure the survival of *T. brevifolia,* and thus, would cause no hindrance to the supply of Taxol. Now that Paclitaxel had gained approval, its demand increased even more and forced its manufacturers and suppliers to find an alternative way of synthesizing it. It was mainly because of the shortage of the tree *T. brevifolia* that the suppliers could not meet the demands for this drug. Thus, in 1993, BMS announced its plan to abandon *T. brevifolia* for preparation of taxol and to adopt a semi-synthetic process to make taxol through 10-DAB. It was approved by the FDA in 1994, along with approval of its use in breast cancer treatment, and thus, after a year, the Pacific Yew Act was also ended. The clinical trials kept on going and due to its efficiency in remitting non–small cell lung cancer (NSCLC), the FDA approved Taxol for its treatment in 1999.

The studies on Paclitaxel are still ongoing and researchers are trying to make it even more efficient. Recent studies show the efficacy of nanoparticle bound paclitaxel (Sparreboom *et al*., 2005; Jia *et al.,* 2015 and Esfandyari-Manesh *et al*., 2015). Some studies are focused on finding a way to decrease paclitaxel associated adverse effects, such as the use of adjuvants for targeted drug delivery. One such study involves the use of a lectin, Maackia amurensis agglutinin (MAA), as an adjuvant and shows its efficacy in different cancers (Lalli et al., 2015). Other studies show combinations of different drugs with paclitaxel to enhance its efficacy, like dasatinib (Xiao et al., 2015) and carboplatin (Avelino et al., 2015).

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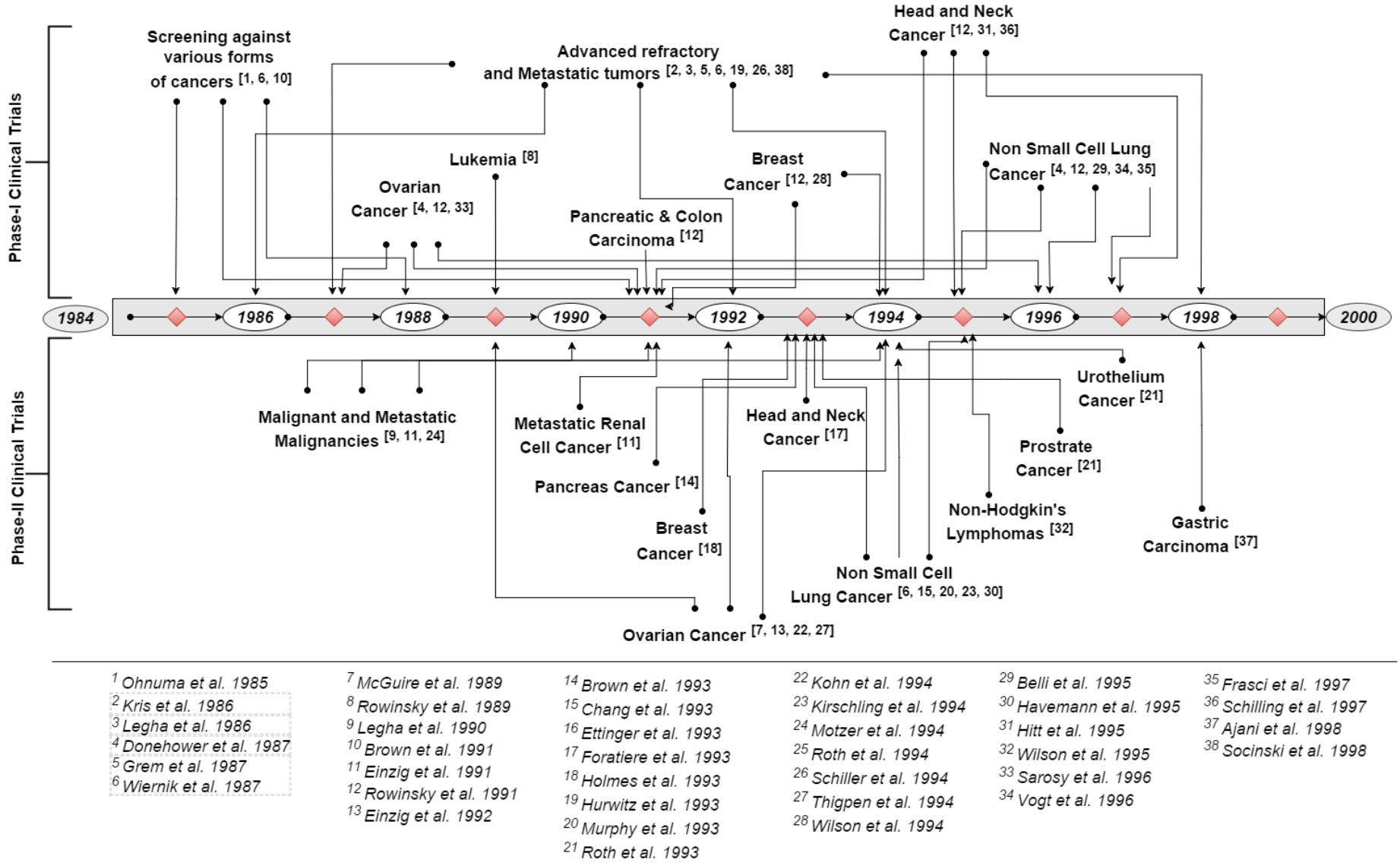

Figure 4: Summary of Phase I and Phase II clinical trials of Taxol.

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