Synthesis Method of Taxol And Its Application in Cancer Treatment

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Abstract. Taxol, also known as paclitaxel, it is a broad known anticancer compound. It is a medication that can be used to treat multiple cancer. Taxol comes mainly from the pacific yew tree bark and it is the first microtube agent. It has been approved that taxol is a significantly chemotherapeutic agent against many forms of cancer, it has been widely used on patients. Unfortunately, it has limited production amount, chemical and biological synthesis have been worldwide researched and tested to improve taxol production. Following the background and methodology of synthesis of taxol, the different methods and procedures investigated will have a brief explanation of some of the known processes. Also, summarization of paclitaxel anticancer mechanism, and immunomodulatory effects explained here. Taxol can be used to treat breast cancer as a first-line therapy. Here, the discussion centered around current research that focus on taxol treatment for breast cancer, its mechanisms of treating cancer and effects on breast cancer.

Keywords: Taxol, Synthesis, Application, Cancer treatment.

1. Introduction

Taxol, found in the Pacific yew tree, is useful in treating cancer, as it inhibited mitosis by increasing tubulin polymerization and stabilizing micro-tubules [1]. New forms of synthesis, such as chemical and biosynthesis, are necessary because of the shortage of mail material for taxol production. Taxol is a tricyclic diterpenoid that is composed of a taxane ring and has a complex chemical structure, with two main terpenoid biosynthetic pathways, including the mevalonate and the methylerythritol phosphate. The mevalonate pathway produces isopentenyl pyrophosphate and dimethyl pyrophosphate from three acetyl-CoA molecules that originate primarily from animals, plants, fungi, and archaea. And the methyl erythritol phosphate pathway produces isopentenyl pyrophosphate and dimethyl pyrophosphate primarily through eubacteria, green algae and upper plants.

The important to take into account that it is the low yield of taxol, where the little amount of taxol needs to take a long time and needs bark trees that exited more than 100 years. Taxus species have undergone many studies in the last 10-15 years because of the limited resources, but taxol is generally isolated initially from *T. brevifolia*. Genetically modified microorganisms or precursors that facilitate the production of taxol trough chemical semi-synthesis, even though taxadine's best synthesis has yet to be achieved. Taxadiene production has been made possible by the development of multiple methods. For instance, *Escherichia coli* has been successfully discovered for the production of taxadiene. Endophyte fungi have the highest taxol production, with approximately 200 endophyte fungi belonging to over 40 mushroom genera identified as taxol producers.

Taxol is microtubule targeting agents that bind to tubulin, paclitaxel stabilizes the microtubular polymer and prevents the breakdown of micro-tubules, blocks the progression of the cell cycle, prevents mitosis and inhibits cancer cell growth [2]. Taxol directly kills tumour cells and regulates different immune cells, increasing number of natural killer cells. As a result, taxol chemotherapy can be used to increase apoptosis levels in tumour cells and release tumor antigens. Taxol can be used as an antitumor drug for multiple cancers treatment, and it also obtained remarkable therapeutic effect on cancer treatment such as breast cancer. Of course, it can also be used to treat other diseases, such as cutaneous disorders. Following a series of clinical trials, it has also been used to treat head and neck cancers and AIDS.

The rise in cancer morbidity and mortality worldwide is a result of unhealthy lifestyles and environment effect such as pollution or exposure to hazardous chemicals [3]. It is essential of finding effective treatment for various type of cancer. In this research, mechanism of cancer therapy by using paclitaxel were described, as well as different ways of paclitaxel synthesis.

2. The Synthesis Method of Taxol

Taxol molecule consists of a tetracyclic core that contain ring A, ring B, ring C and ring D called Baccarin III and an amide tail. Taxol's synthesis is made up of three synthons that have already been assembled, cyclohexene rings A and C can be connected by using the Shapiro reaction. Here, the ring A and C are connected through pinacol coupling reaction to create an 8 membered B ring. The pre-assembled portion is an amide tail. And the ring C is fused to ring D, which is an oxetane ring.

A diverse of different synthesis method can be used to prepare taxol, such as Holton synthesis. The Holton synthesis can be used to prepared taxol. Wender synthesized taxol starting from bervenome. Mukaiyama used the linear strategy Kuwajima synthesis, and sythong A could be obtained. The C ring synthesis can be slightly modified, resulting in the formation of hydrazon, and at a later point, the diol group was protected [4]. Also, A new synthesis of hemiacetal 19 was developed through lactone 22 with a new synthesis. The enantiopure C ring of taxol was synthesized in six steps and coupling of C ring with A fragment can be successfully modelled using the Shapiro reaction. They developed a new synthesis process for Hamiacetal 19 and they slightly modified the synthesis for the C ring, and they carried out all the synthesis reaction under a desirable condition. However, they only tried on attempt in the Shapiro reaction after noticing it was successful.

The transannular strain has caused the generation of the eight-membered carbocyclic ring, and this is a challenge for the taxol synthesis [5]. Despite the various versions of Taxol synthesis that were proposed by various authors, the general synthetic remains the same. The total synthesis of taxol is comprised of six versions, including formal syntheses such as Holton, Wender, and Mukaiyama. The Taxol skeleton was built successively using a linear approach by all of them.

Total taxol synthesis for the eight membered B ring by the different scientists has been reported [6]. The results show a general basic way of the production of the eight membered ring and each of the percent yield in their processes. It can be seen that even though they carried out different reactions, the aim was to form the B ring. In Nicolaou's group, they used pinacol coupling to form B ring and they had 25% of yield of it. Danishefsky et al. improved the percent of yield to 59% by using Heck reaction. The most percentage of yield in the graph was from Chida et al which was 66% by reacting with Sml2. They compared in details of different reactions carried out in Taxol total synthesis of the eight membered B ring by different scientists 'groups, which organized the reaction and their strength and weakness for us to clearly understands what needs to be improved for the taxol synthesis.

There was no reaction of 75 with $KBrO_3/Na_2S_2O_3$, 56a,b, and the reaction with Ph 3CBF 4 56c caused the ring opening of oxetane. After removing the benzyl group, compound 81 is formed with a TES ether. The possible stereoisomers and the complex structure affording to the difficulty of the synthesis of the taxol. Biosynthesis of taxol is another way to improve taxol production. Studies also allow for more than chemical synthesis of taxol. Following this research will discuss the biosynthesis of taxol by using the semi-synthetic taxol. They use semi-synthesis in their experiment, and also the cell suspension cultures are used in this work, where the cell culture is a useful way for the synthesis of taxol.

The expression levels of taxol biosynthesis enzymes are enhanced by elictors, which are strong stimulators for producing taxol [7]. Genetic and metabolic engineering is the new approach to improving taxol biosynthesis. The production of taxol can be increased by overexpressing genes that control the limitation stages or by suppressing undesirable taxanes based on the developed antisense technology. Although the experiment employed innovative methods to enhance the taxol production, the developed genetic manipulation strategies are still not complete and it can only use high-value compounds.

For the production of taxol with the biosynthesis method, there is an experiment that enhances the production of taxol. A new copy number of GGPPS was added to the plant to produce taxol, which increased the size of the terpenoid pool in GGPP [8]. The terpenoid pool size was increased, as evidenced by an increase in carotenoid levels. It is a new approach was used to increase the production of taxol in the plant, the production improved by the experiment, but the best way to improve the production of taxol has yet to be demonstrated by them. Next, another experiment was carried out through several steps [9], where taxol contents can be collected in different samples (Fig. 1). First, the taxol standard solution used to create a normalized quantification curve followed by RNA extraction were RNase-free aragose gel electrophoresis was used to verify the quality of RNA in taxol determination. And then a real-time PCR validation was performed. The results show there is about 3-fold higher taxol in the needles. It's an illustrate regulatory of mechanisms to improve taxol synthesis. It explains specifically and reasonably of the variation of taxol content. Though low level of taxol was reported. In summary, all the various way of taxol synthesis that used and researched, and all different versions of synthesis of taxol had their own process that improved the taxol synthesis.

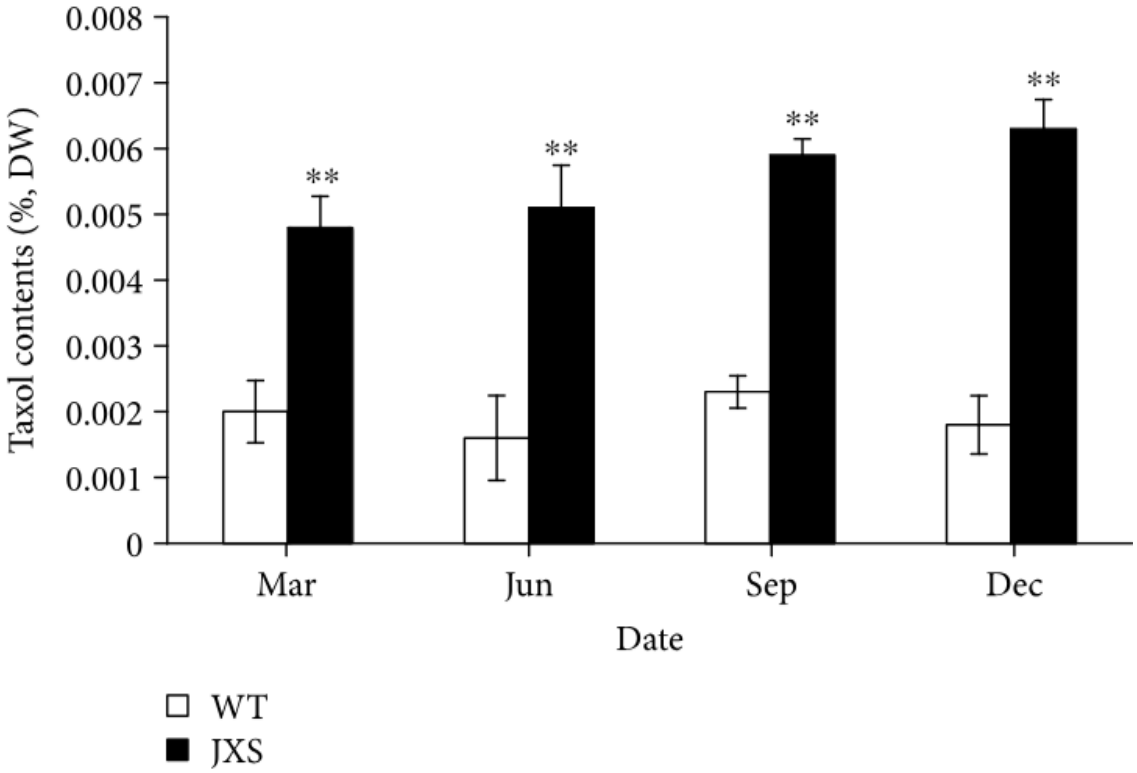

Fig. 1 The taxol contents in different samples [9].

3. Cancer Treatment

Taxol belongs to the most important natural drugs that can be able to treat various types of cancers. Taxol attaches to microtubules and maintains their stability and reduces tubulin concentration, which disrupts the process of that cell split up [10]. The immune cells have relationship with tumor growth are stimulated and suppressed by paclitaxel during immunomodulation. Tumor immunotherapy aids in body immunity by activating an immune response to tumors. It has been reported by many researchers that taxol can be used to kill tumor cells and regulate immune cells, natural cells, regulatory cells, and macrophages. Taxol chemotherapy is a second line chemotherapy regimen, which can be used to decrease the tregs number. In addition, it is proven that a low dose of taxol inhibits cell mitosis.

Taxol is a drug that treats breast cancer by affecting cellular processes that lead to cell death [8]. Breast cancer is the type of cancer that is most likely to affect females, leading to 24% of female malignancies. Breast cancer is classified into three main types and five subtypes and it affects approximately two million women around the world and causes more than 620,000 deaths every year, and mortality continues to increase. Breast cancer is a complicated disease to treat due to its inherent characteristics such as heterogeneous nature.

According to Susan Horwitz's report, paclitaxel facilitates the formation of microtubules and it also decreases the concentration of purified tubulin subunits, and also the proportion of tubulin subunits that assemble to grow [3]. In addition, microtubules that are polymerized with paclitaxel are protected by the normal disassembly. In living cells, paclitaxel is able to counteract the effects of colchicine and vinca alkaloids. In animal tumor models, paclitaxel treatment stops a wide range of cell types in mitosis as well as in cell culture. Taxol triggers mitotic arrest by activating the mitotic checkpoint. During mitosis, the way of cell cycle control is responsible for disrupting chromosome missegregation. The spindle microtubules connect with chromatids via kinetochores, and mitotic progression is delayed by the activation of a signal transduction cascade by unattached kinetochores, then cells in mitosis are halted by paclitaxel treatment. Taxol is commonly used in cell biology and can be advantageous in cancer treatment. Kinetochores interacted with spindle microtubules, and they stabilized by the sister chromatids attachment in untreated cells, which causes tension in kinetochores. Taxol alleviates the stress on kinetochores that sustain bipolar attachment and it is a useful for stopping cells in mitosis.

4. Conclusion

The production of taxol has been researched and improved over time, scientists fight against cancer for decades and will continue to be. Taxol has been very effective in cancer treatment and fight against many different types of cancers. However, the low production still be a main concern to scientist, and the mechanism of taxol synthesis still needs to be proved. With the improvement of biosynthesis technology, it is another practicable way of produce taxol, more research needs to be carried to enhance paclitaxel biosynthesis production. There is not real way to tell which one is the best way to synthesize taxol. In all the versions of taxol synthesis, what can be improved in the chemical methods to obtain taxol in the fastest way? Taxol can affect immunotherapy and play a crucial role in chemotherapy. It's crucial to acknowledge that the process of tumor immune is complex and cancer is a challenging disease to treat, further research is necessary to understand the role of taxol for cancer treatment. Moreover, resistance to chemotherapy is a serious problem for cancer treatment, it is very important to improve the properties of taxol as well as to reduce the resistance of cancer cells and improve its efficiency in cancer therapy and decrease the side effects.

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