Proceedings of the 4th International Conference on Biological Engineering and Medical Science
DOI: 10.54254/2753-8818/72/2024.19390

Review of the Research Progress of Paclitaxel

Ziyu Zhou[1,3,†], Ziqian Sang[2,4,*,†]

[1]Suzhou North America High School, Suzhou, China
[2]Nanjing Foreign Language School, Nanjing, China

[3]rafaelziyu@gmail.com
[4]ziqian_sang@163.com
*corresponding author
[†]These authors contributed equally to this work and should be considered co-first authors.

Abstract. Since its initial discovery in 1962, Paclitaxel has emerged as a highly esteemed drug in the realm of cancer therapy, garnering widespread attention owing to its potent anticancer properties. This paper delves into the pivotal milestones in the evolution of Paclitaxel, comprehensively outlining its historical context, manufacturing methodologies, mode of action, and clinical utilization. Originating from the bark of the Pacific yew tree, the drug was initially procured through natural extraction, posing challenges due to scarcity of raw material. Over time, advancements in biosynthetic and semi-synthetic production techniques have been implemented, mitigating reliance on natural resources and ensuring a more reliable and sustainable supply. Paclitaxel exerts its therapeutic effect by inhibiting cancer cell division during mitosis, thereby effectively halting the progression of various solid tumor types, including ovarian, breast, and lung cancers. Nevertheless, despite its established therapeutic merits, Paclitaxel is not devoid of adverse effects. Patients undergoing treatment with Paclitaxel may encounter a spectrum of side effects, such as neuropathy and immune system suppression, necessitating meticulous management to optimize its efficacy and mitigate complications during cancer therapy.

Keywords: Paclitaxel, biosynthesis, semi-synthesis, cancer therapy, mechanism of action.

1. Introduction

Paclitaxel is a chemotherapy drug that can treat different kinds of cancer. It is a white crystalline powder. Its molecular formula is C47H51NO14. Figure 1 shows the whole configuration of Paclitaxel, clearly demonstrating all of its functional groups. This includes aromatic rings, ester, ketone, alcohol, amide, and oxetone. It can treat cancers like ovarian, breast, bladder, and various other solid tumors. The melting point of Paclitaxel is 213°C, and it is insoluble in water because of aromatic rings which are non-polar. Paclitaxel is stable, and it is incompatible with a strong oxidizing agent.

DOI: 10.54254/2753-8818/72/2024.19390

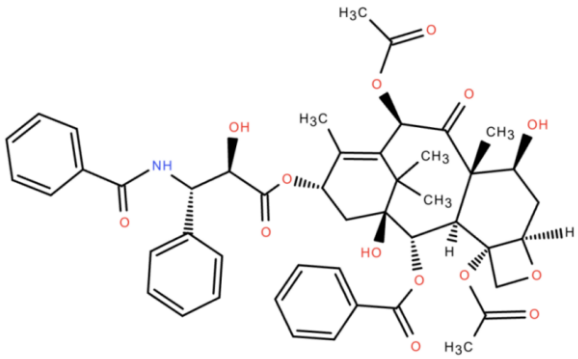

Figure 1. Structure of Paclitaxel.

2. History

1962, in a Pacific yew tree, a botanist called Arthur S. Barclay collected bark from it in the north of the town of Parkwood, Washington.

In 1964, Monroe Wall and Mansukh Wani at the Research Triangle Institute of North Carolina successfully isolated active compounds from the bark of the Pacific yew tree.

1971, Monroe Wall and Mansukh Wani revealed their discovery to the world, publishing the structure of Paclitaxel.

1990, Robert A. Holton and his group at Florida State University reported the semi-synthesis of Paclitaxel.

1991, the National Cancer Institute (NCI) selects Bristol-Myers Squibb (BMS) to commercialize taxol.

In 1992, the Food and Drug Administration (FDA) agreed on the marketing of paclitaxel injection for the therapy of advanced ovarian cancer.

In 1994, Robert A. Holton and his team reported their first total synthesis of Paclitaxel [1].

3. Bio-synthesis of Paclitaxel

The enzyme-catalyzed multi-step process is done in the cells of living organisms(see Figure 2).

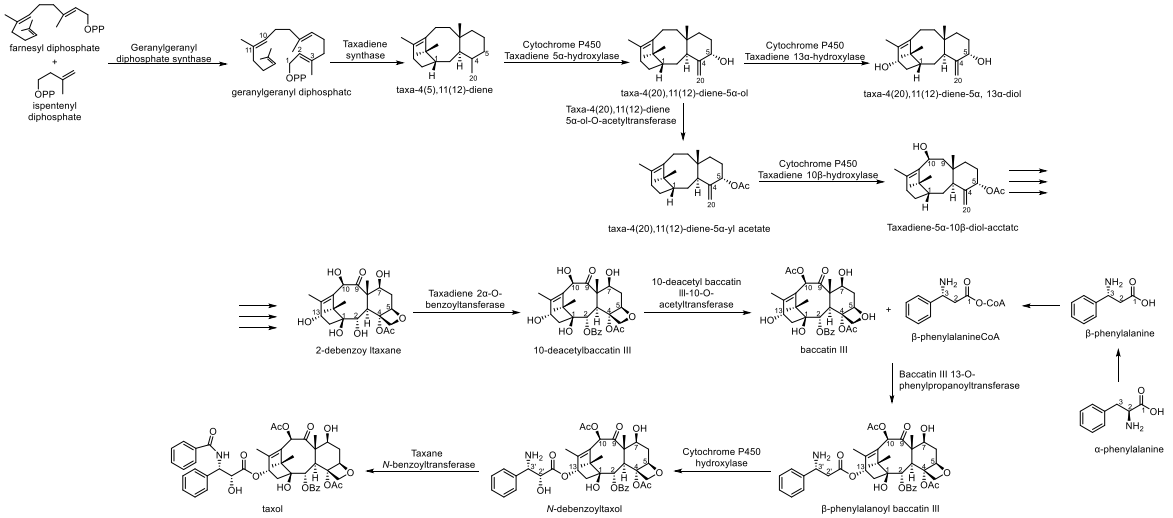

Figure 2. The biosynthesis of Paclitaxel [2].

Geranylgeranyl diphosphate synthase is an intermediate in the biosynthesis of diterpenes and diterpenoids (see Figure 3).

DOI: 10.54254/2753-8818/72/2024.19390

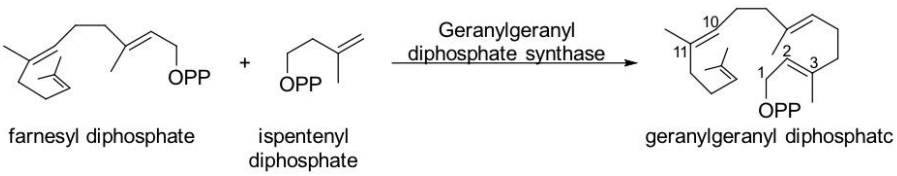

Figure 3. The substep of Paclitaxel biosynthesis.

This step is cyclization. Taxadienien can turn the geranylgeranyl diphosphate into taxa-4,11-diene and diphosphate (see Figure 4).

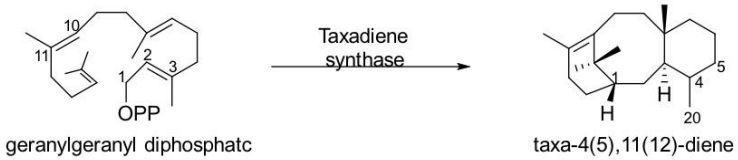

Figure 4. The substep of Paclitaxel biosynthesis.

This is acetylation and esterification. Most cytochrome P450 will reduce monooxygenase reaction to water (see Figure 5). This step adds a phenylalanine to make a side chain attachment.

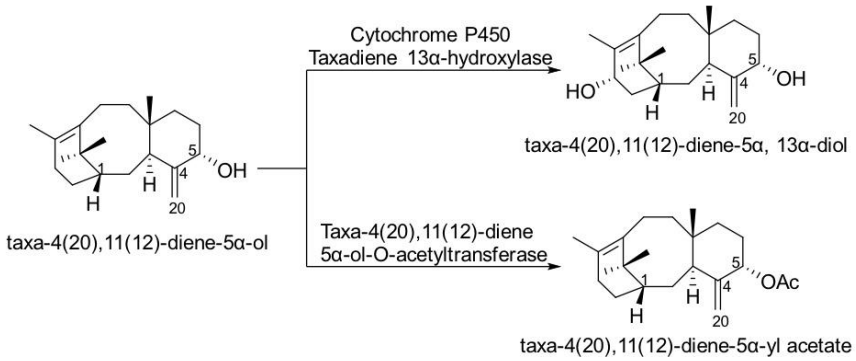

Figure 5. The substep of Paclitaxel biosynthesis.

Figure 6 shows the transfer of α-phenylalanine to β-phenylalanineCoA.

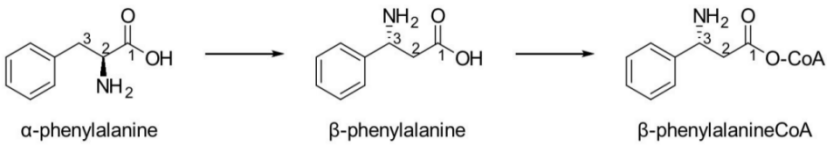

Figure 6. The substep of Paclitaxel biosynthesis.

4. Semi-synthesis of Paclitaxel

Figure 7 demonstrates the entire process of the production, starting from 10-DAB as an important material. The process begins with protecting the secondary alcohol (7) from reacting with compounds 2 and 1,1' -thiocarbonyldiimidazole and CHCl3 at room temperature. The next phase is acetylation; compound 3 reacts with acetic anhydride and pyridine at room temperature, facilitating the acetyl group to substitute the hydrogen in the hydroxyl group. The third step is esterification. Compound 5 reacts with compound 4 and DCC and DMAP in toluene-CH2Cl2 at room temperature, producing corresponding protected paclitaxel 6. The final stage of the process is deprotection, a mixture of p-toluenesulfonic acid (PTSA) and 0.1 mol/L aqueous hydrochloride with methanol at room temperature [3].

DOI: 10.54254/2753-8818/72/2024.19390

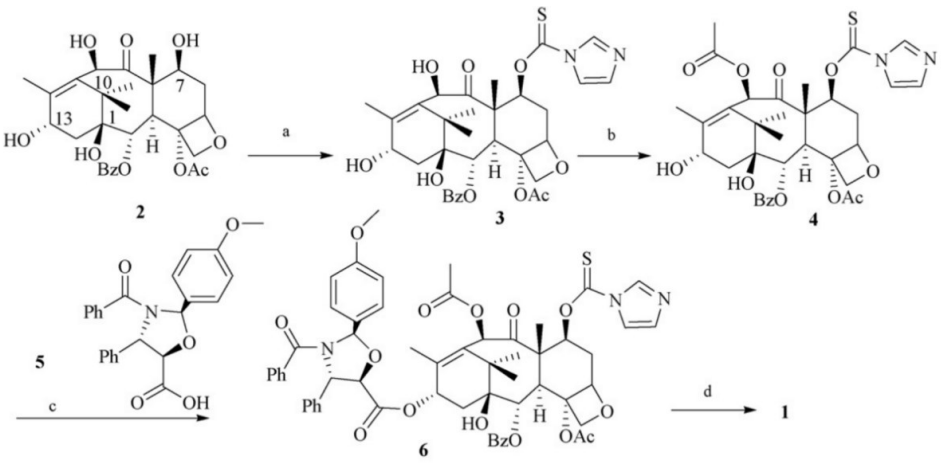

Figure 7. The semi-synthesis of Paclitaxel [3].

Figure 8 shows another semi-synthetic method that only needs three steps: redox, acetylation, and deacetylation. This synthetic process does not use 10-DAB precursors as a starting material, resulting in fewer reaction steps and significantly higher yields [4].

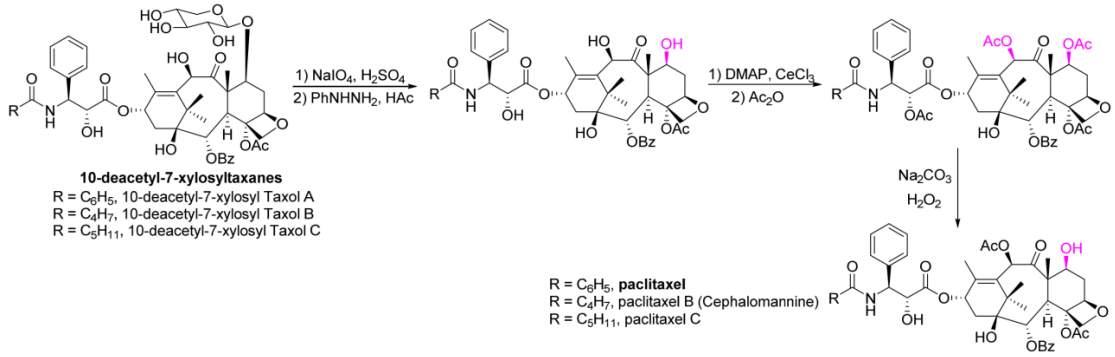

Figure 8. The semi-synthesis of Paclitaxel [4].

5. Mechanism of Paclitaxel

Paclitaxel acts on mitosis, which happens during the M phase. Paclitaxel is hydrophobic, so it can penetrate the cancer cell. Then, Paclitaxel binds with β-tubulin in the microtubule. The concatenation is connected to the chromosomes firmly and prevents the pulling of chromosomes, so the chromosomes cannot align in the middle of the cell. This leads to a mitotic arrest, which causes cell death, and the cancer cell cannot multiply.

6. Why is important

1984, Paclitaxel entered clinical trials. A clinical study on ovarian cancer showed that taxol therapy was useful to 30% of patients with advanced ovarian cancer. Moreover, it can treat breast, ovarian, bladder, lung, prostate, and various other solid tumors. As a result, Paclitaxel is effective and low toxicity.

7. Side effect of Paclitaxel

Bleeding, coldness, discoloration of the skin, feeling of infection, inflammation, itching, lumps, numbness, pain, scarring, ulceration, or warmth at the injection site, difficulty with swallowing, hair loss, numbness, burning or tingling in the hands or feet, pain in the joints or muscles, thinning of the hair [5].

DOI: 10.54254/2753-8818/72/2024.19390

8. Conclusion

Paclitaxel's synthetic pathways and medical value have been developed over the past few decades. Mass production is achieved through semi-synthesis to relieve pressure on raw materials. Paclitaxel has a remarkable effect in the treatment of tumors and cancers. However, the synthesis of Paclitaxel also requires taxus as a natural raw material. Hopefully, the Exogenous synthesis of Paclitaxel can be realized in the future.

Acknowledgment

Ziyu Zhou and Ziqian Sang contributed equally to this work and should be considered co-first authors.

References

[1] Weaver, B. A. (2014). How Taxol/paclitaxel kills cancer cells. Molecular Biology of the Cell, 25(18), 2677–2681.https://doi.org/10.1091/mbc.e14-04-0916

[2] Sonia Malika, Rosa M. Cusidób, Mohammad Hossein Mirjalilic, Elisabeth Moyanod, Javier Palazónb, Mercedes Bonfillb, Production of the anticancer drug taxol in Taxus baccata suspension cultures: A review, 2011, www.elsevier.com/locate/procbio

[3] Zhang, Hu, Li, Ou, Guo, Lin, Yong, Ping, & Yu. (2008). Regioselective protection of 10-deacetylbaccatin III and semi-synthesis of Paclitaxel. http://www.cqvip.com/QK/84039X/200802/26594308.html

[4] Zhang, S.; Ye, T.; Liu, Y.; Hou, G.; Wang, Q.; Zhao, F.; Li, F.; Meng, Q. Research Advances in Clinical Applications, Anticancer Mechanism, Total Chemical Synthesis, Semi-Synthesis and Biosynthesis of Paclitaxel. Molecules 2023, 28, 7517. https://doi.org/ 10.3390/ molecules28227517

[5] Paclitaxel (Intravenous route). 2024, July https://www.mayoclinic.org/drugs-supplements-paclitaxel-intravenous-route/side-effects/drg-20065247