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Advances in Taxol Biosynthesis Pathways and Regulatory Networks in Chinese Yew (*Taxus chinensis*)

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Abstract This study summarizes the main synthesis process of taxol in Taxus chinensis, sorts out the latest research progress of key structural genes such as TS, BAPT, and DBTNBT, and points out that some ring-limiting steps have not been fully resolved. It also sorts out the multilayer regulatory network involving transcription factors such as MYC, ERF, and WRKY. The significant roles of signals such as monosinic acid, ABA, and SA in inducing taxol synthesis were discussed. The potential influences of miRNA and epigenetic modifications in post-transcriptional regulation were introduced. Several key directions for increasing taxol yield were summarized, including the redistribution of metabolic flux, the synergistic enhancement of key enzymes, and the optimization of cell culture systems. This study aims to provide a theoretical basis and technical reference for the efficient biomanufacturing and sustainable resource utilization of taxol in Taxus chinensis.

Keywords Taxol; Taxus chinensis; Biosynthetic pathways; Molecular regulatory networks; Metabolic engineering and synthetic biology

1 Introduction

Taxol is the first type of anti-cancer drug that acts on microtubules. It can block the division of tumor cells and induce apoptosis, and thus is widely used as a first-line chemotherapy drug for various malignant tumors (Gallego-Jara et al., 2020). At present, there is a high demand for taxol in clinical practice, but its natural sources are very limited, mainly relying on extraction from the bark and needles of *Taxus chinensis*. *Taxus chinensis* has a slow growth rate and scarce resources. Moreover, treating one patient often requires the consumption of several trees. Therefore, the existing extraction methods have been difficult to meet the rapidly growing market demand (Mutanda et al., 2021).

Taxus chinensis is one of the important natural sources of taxol and is also a rare and endangered plant under key protection in China. It has significant medicinal value as well as ecological and economic significance (Hu et al., 2020). *Taxus chinensis* is rich in secondary metabolites and has unique genomic characteristics, which provide excellent materials for studying the synthesis mechanism and industrial development of taxol (Liao et al., 2017; Xiong et al., 2021). With the development of genomic, transcriptomic, metabolomic and other technologies, as well as the deepening of people's understanding of the taxol synthesis pathway, the key genes and regulatory networks have gradually become clear (Sun et al., 2024; Jiang et al., 2025). These advancements have laid the foundation for increasing taxol production and promoting its industrialization.

This study reviews the latest progress in taxol biosynthesis in *Taxus chinensis*, introduces the multi-layer regulatory contents such as key enzyme genes, important transcription factors and non-coding RNAs, and further explains the molecular mechanism of taxol synthesis by integrating the latest omics data and functional verification results, and explores its application directions in synthetic biology and metabolic engineering. This study aims to provide theoretical and technical support for alleviating the insufficient supply and demand of taxol, protecting *Taxus chinensis* resources, and promoting the development of related industries.

2 Taxol Biosynthesis Pathways in *Taxus chinensis*

2.1 Terpenoid backbone formation and early pathway steps

The synthesis of taxol begins with a common diterpene precursor, which is called geranylgeranyl diphosphate (GGPP). It is mainly formed in plastids through the methylerythritol phosphate (MEP) pathway. GGPP will be converted into taxa-4(5),11(12)-diene under the action of taxadiene synthase (TS). This step marks the beginning of the taxol skeleton and is also regarded as one of the rate-limiting steps in the synthetic pathway (Liao et al., 2017; Xiong et al., 2021). Subsequently, this taxadiene skeleton undergoes a series of modifications, including oxidation, hydroxylation and acylation, and eventually forms key intermediates such as baccatin III.

2.2 Key modification reactions and core enzymatic processes

The subsequent formation of taxol relies on the hydroxylation reaction of a large number of CYP450 enzymes. For instance, common ones include T5αH, T10βH, T13αH, T2αH, T7βH, T14βH, etc. These enzymes add hydroxyl groups at different positions of the skeleton. Subsequently, multiple acylation steps are required, which are accomplished by enzymes such as TAT, DBAT, BAPT, and DBTNBT (Mutanda et al., 2021). These modifications can affect the structure of taxol and directly determine its yield and activity. Existing studies have pointed out that CYP450 enzymes are very crucial in the entire pathway, and approximately half of the steps are accomplished by them (Liao et al., 2017; Xiong et al., 2021). In addition to CYP450 enzymes, acyltransferases (ACTs) of the BAHD family also play important roles in multiple acylation steps (Wang et al., 2021).

2.3 Current knowledge gaps and unresolved biosynthetic steps

There are still some enzymes in the synthesis of taxol that have not been fully clarified. Enzymes for key steps such as hydroxylation at the C1 position, formation of oxetane, oxidation at the C9 position, and hydroxylation of the C2' side chain have not been identified yet (Liao et al., 2017). The sequence of some hydroxylation steps, the specific mechanism of acylation, and substrate specificity are still controversial (Wang et al., 2021). The latest omics analysis has proposed possible candidate genes, but their functions and enzymatic properties still need further verification (Liao et al., 2017; Mutanda et al., 2021). This synthetic pathway is also affected by various regulatory factors such as transcription factors, miRNAs, and hormone signals, which makes the system analysis more complex (Chen et al., 2021; Sun et al., 2024; Ren et al., 2025).

3 Key Enzymes and Gene Families Involved in Taxol Production

3.1 Cytochrome P450 monooxygenases in hydroxylation steps

Cytochrome P450 monooxygenase (CYP450s) is of great significance in taxol biosynthesis. Approximately half of the oxidative modifications are accomplished by these enzymes, which are mainly responsible for adding hydroxyl groups to multiple positions of the taxane skeleton, including sites such as C-2, C-5, C-7, C-9, C-10, and C-13 (Wang et al., 2021; Li et al., 2022). Among them, members of the CYP725A family (such as T5αH, T10βH, T13αH, T2αH, T7βH, T14βH, etc.) showed obvious gene aggregation in *Taxus chinensis*, forming gene clusters closely related to taxol synthesis (Xiong et al., 2021; Yu et al., 2021). Transcriptome analysis identified a total of 118 complete CYP450 genes, belonging to 8 clans and 29 families. Some new members of the CYP725 family (such as TcCYP725A9, A11, A16, A20, A22, A23) are also considered candidate genes for taxol synthesis (Liao et al., 2017). Although these enzymes have similar structures, their substrate selection and catalytic abilities are not exactly the same. This has led to the branching of synthetic pathways and the formation of more diverse products (Wang et al., 2021; Yu et al., 2021).

3.2 Transferases and oxidoreductases in structural diversification

In the later stage of taxol synthesis, various transferases (such as acetyltransferase, benzoyltransferase, aroyltransferase, etc.) and some oxidoreductases are also required. These enzymes will further acylation, oxidation or side chain modification of the taxane skeleton. Among them, the more typical ones include DBAT, TAT, BAPT and DBTNBT, etc. These enzymes have all been identified and functionally verified in *Taxus chinensis* (Xiong et al., 2021; Yu et al., 2021). The substrate selection range of transferases is very wide. Coupled with different enzymatic activities, the structures of taxane compounds are also more diverse (Wang et al., 2021). In addition,

although some REDOX related enzymes (such as C-9 oxidase and cyclooxygenase) have not been fully determined yet, possible candidate genes have been identified through omics and biochemical analyses (Yu et al., 2021).

3.3 Enzyme functional characterization and evolutionary insights

Functional studies have shown that these enzymes involved in taxol synthesis are structurally conserved, but still significantly different in catalytic mode and substrate preference. This indicates that they have undergone gene duplication and functional differentiation during evolution to adapt to complex secondary metabolic requirements (Wang et al., 2021; Xiong et al., 2021; Yu et al., 2021). Phylogenetic analysis of the CYP725 family indicates that this family is specific to gymnosperms and has significant differences in P450 enzymes from angiosperms (Liao et al., 2017). The transferase family (such as the BAHD family) also shows diversity in substrate selection and catalytic mechanisms. Some members have completed functional verification through heterologous expression and in vitro enzymatic experiments (Wang et al., 2021). Furthermore, the formation of gene clusters and the induced expression by hormones (such as MeJA, SA) also provide a key regulatory basis for taxol biosynthesis.

4 Molecular Regulation of Taxol Biosynthesis

4.1 Transcription factor families regulating pathway genes

A variety of transcription factor families are involved in the regulation of taxol biosynthesis, and their roles are all crucial. TcMYC2a and TcJAMYC5 in the MYC family can directly bind to the promoters of key enzyme genes such as TASY, T5H, and DBTNBT, promoting the expression of these genes. They are induced by jasmonic acid (JA) signaling and are important nodes for JA signaling to downstream enzyme genes (Chen et al., 2022; Cai et al., 2025). The MYB family is also involved in regulation. For example, TcMYB29a can increase the expression of T5OH and T10OH under ABA signaling, while TcMYB73 works under SA signaling and can directly activate synthetic genes or indirectly regulate WRKY33, thereby increasing taxol production (Ren et al., 2025). Members of the WRKY family (such as TcWRKY1, TcWRKY33, TcWRKY26) can also bind the promoters of key genes such as DBAT, or regulate TASY by influencing ERF15, thereby participating in JA and SA signaling regulatory networks (Figure 1) (Chen et al., 2021; Chen et al., 2022). ERF68 and ERF15 in the AP2/ERF family can also activate genes such as T2H and TASY (Jiang et al., 2025).

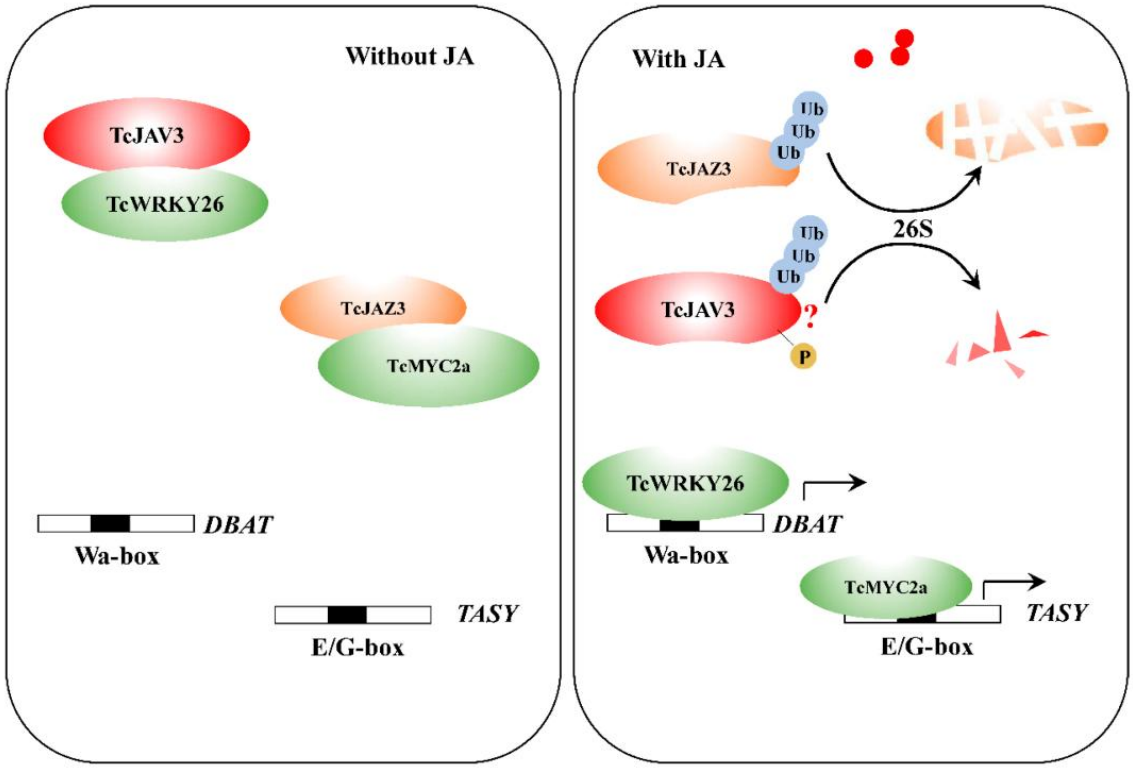

Figure 1 JA regulation mechanism of taxol biosynthesis (Adopted from Chen et al., 2022)

4.2 Hormonal and elicitor-mediated signaling mechanisms

Jasmonic acid (JA) and its derivatives are among the strongest known inducers for taxol biosynthesis. They can up-regulate the expression of almost all synthase genes at one time, mainly exerting their effects through signaling pathways such as JAZ-MYC2 and JAV3-WRKY26 (Chen et al., 2022; Sun et al., 2024; Cai et al., 2025). Salicylic acid (SA) enhances taxol accumulation by activating factors such as TcMYB73 and TcWRKY33 and increasing the expression of genes such as DBAT and TASY (Chen et al., 2021; Ren et al., 2025). Abscisic acid (ABA) can increase the expression of TcMYB29a and thereby activate enzyme genes such as T5OH. This pathway is independent of the regulation of JA. Exogenous inducers such as MeJA, coronatine and some endophytic metabolites of fungi can also synergistically enhance the expression of transcription factors and enzyme genes by stimulating signals such as JA and SA, and ultimately significantly increase taxol production.

4.3 Epigenetic, post-transcriptional, and miRNA-based regulation

Studies have found that multiple miRNAs act on hormone signaling, mRNA monitoring, and cell cyclin-related genes, thereby indirectly affecting taxol biosynthesis (Sun et al., 2024). miR5298b targets and degrades TcNPR3, thereby relieving the inhibition of TASY and T5H by TcNPR3 and TcTGA6, and ultimately promoting taxol synthesis (Chen et al., 2023). The miR858b-MYB1L module is particularly active in the endocortex. It can enhance the expression of enzyme genes such as TBT and BAPT, and increase taxol accumulation (Yu et al., 2025). Epigenetic regulation such as m6A methylation may also be involved in taxol biosynthesis, as the expression of YTH domain proteins changes significantly under stress conditions (Zhang et al., 2025). In addition, some miRNAs can indirectly affect the entire synthetic network by regulating transcription factors such as ERF and WRKY (Chen et al., 2020; Sun et al., 2024).

5 Multi-Omics Approaches to Pathway Discovery

5.1 Genomic resources and pathway gene cluster identification

In recent years, with the release of high-quality *Taxus chinensis* genomes, researchers have made significant progress in the mining of taxol-related genes. Chromosome-level genomic results show that many genes in the CYP725A family cluster together on the genome, and genes related to taxadiene synthesis have also formed gene clusters. Most of these gene clusters are formed by gene duplication and are of great significance for analyzing the complete taxol synthesis pathway and subsequent metabolic engineering (Li et al., 2022). Genomic data also helped researchers identify some previously unknown key enzyme genes and conduct new functional annotations for them, providing more clues for the reconstruction of synthetic pathways (Xiong et al., 2021; McClune et al., 2025).

5.2 Transcriptomic profiling under induced and stress conditions

Transcriptome sequencing (RNA-seq) is widely used to observe the expression changes of taxol synthesis genes in different tissues, at different developmental stages, and after treatment with exogenous hormones. For example, hormones such as MeJA, SA, and ABA can significantly induce the expression of related genes in the taxol pathway and activate multiple transcription factors, including MYB, WRKY, ERF, etc. (Zhou et al., 2019; Sun et al., 2024; Ren et al., 2025). These transcription factors directly or indirectly regulate key enzyme genes, such as DBAT, TASY, and T5OH, thereby controlling the synthesis rate and level of taxol. Transcriptome data also show that the contents of taxol and its derivatives vary in different tissues (such as roots, leaves, barks, and branches), and their regulatory networks are also different (Yu et al., 2021; Jiang et al., 2025).

5.3 Metabolomics and proteomics integration for pathway mapping

The combination of metabolomics and proteomics makes it easier for researchers to identify important intermediate products, key enzymes and regulatory factors in the taxol pathway. Yu et al. (2021) and Jiang et al. (2025) hold that by jointly analyzing the metabolome and transcriptome in different tissues and using methods such as WGCNA, possible regulatory genes can be screened out. Proteomic data can help identify which key enzymes are truly expressed and their regulatory methods, thereby promoting the reconstruction of the entire synthetic network. In addition, new technologies such as single-cell nuclear transcriptome (mpXsn) have also been applied in *Taxus chinensis* research. It can identify complex gene families and expression modules more accurately, accelerating the discovery and functional verification of new genes (McClune et al., 2025).

6 Biotechnological Strategies to Enhance Taxol Production

6.1 Cell culture optimization and elicitation strategies

Optimizing cell culture conditions and using exogenous inducers are common methods to increase the yield of taxol. Studies have shown that by adjusting the composition of the culture medium, supplementing carbon sources such as sucrose, or controlling the conductivity, cell growth can be significantly promoted and the accumulation of taxol can be increased. For example, by using the online conductivity monitoring system to regulate the culture environment in real time and adding MeJA induction, the taxol yield can reach 76.2 mg/L, and the production efficiency is also significantly improved (Wang et al., 2016). In addition, by combining ultrasonic treatment, MeJA induction and in-situ organic solvent extraction, the yield can even be increased to 17 times that of the control group. Fungal inducers (such as Aspergillus niger and Pseudodidymocyrtis lobariellae KL27) are equally effective. They can activate signaling pathways such as JA, ethylene, and ABA, and simultaneously up-regulate key genes in multiple taxol biosynthesis pathways, increasing the yield by more than three times. Some rare earth elements, such as La^{3+} , can also play an inducing role, increasing the output by approximately three times.

6.2 Metabolic engineering and synthetic biology applications

Metabolic engineering can effectively increase the accumulation of taxol and its precursors by regulating the expression of key enzyme genes and optimizing the underflow direction. In heterogeneous systems, the combined expression of taxadiene synthase (TS) and GGPP synthase from *Taxus chinensis*, along with the feedback inhibition of HMG-CoA reductase, can increase the yield of taxodiene by approximately 40 times. In *Taxus chinensis* cells, transcription factors such as TcMYB29a, TcMYB73, and TcWRKY33 activate key enzyme genes such as TS, T5OH, and DBAT, thereby significantly promoting taxol synthesis (Figure 2) (Chen et al., 2021; Ren et al., 2025). Furthermore, Newton et al. (2023) discovered that by regulating the direction of metabolic pathways, for instance, by inhibiting the PAL gene in the phenylpropane pathway, the bottom stream could be "directed" to the taxol synthesis pathway, thereby increasing the yield by 25 times.

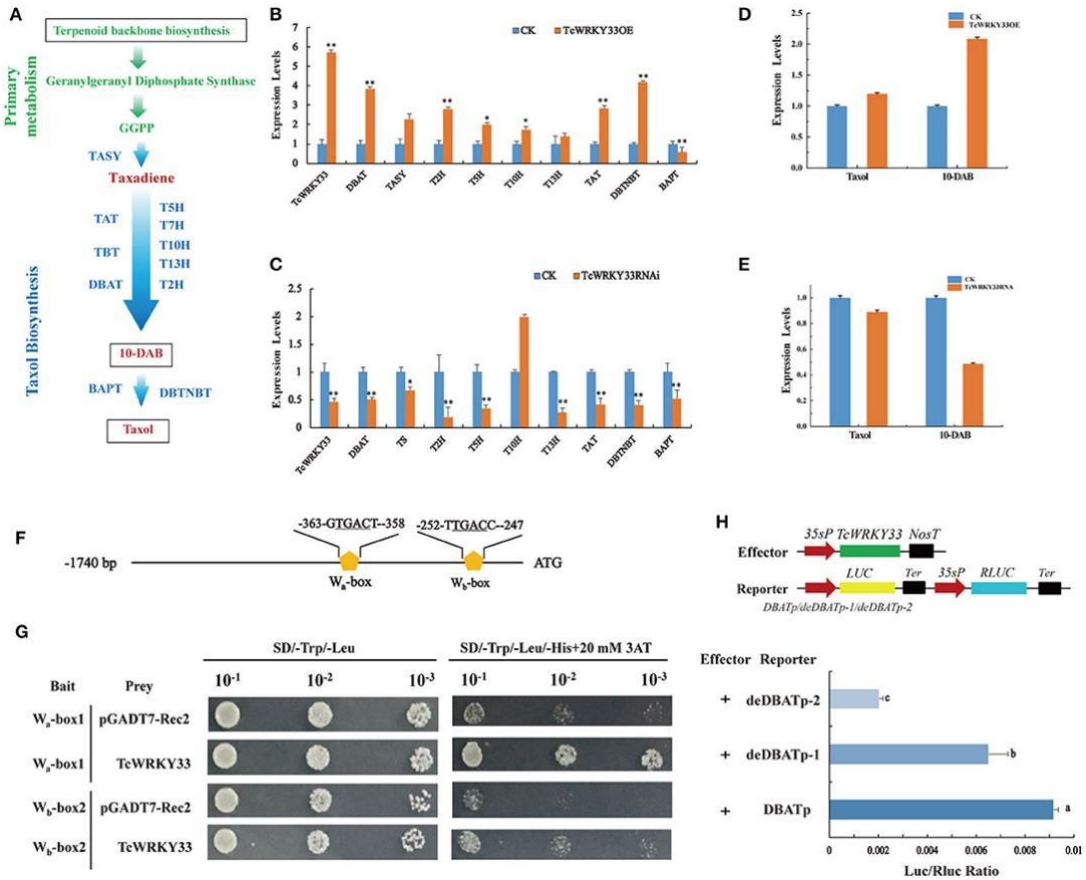

Figure 2 *TcWRKY33* promoted the biosynthesis of taxol and 10-DAB by directly activating *DBAT via* binding with the W-boxes in its promoter (Adopted from Chen et al., 2021)

6.3 CRISPR/Cas-based gene editing in Taxus and heterologous hosts

Inhibiting the PAL gene by CRISPR-mediated DNA methylation can increase taxol accumulation and reduce other by-products (Newton et al., 2023). CRISPR/Cas9 has also been used to knock out or regulate key genes related to taxol, or to reconstruct complete synthetic pathways in heterologous systems such as Arabidopsis thaliana, thereby achieving more efficient production (Cardi et al., 2023). CRISPR can also be used to edit cis-regulatory elements or non-coding regions, thereby more precisely regulating gene expression (Das et al., 2024). However, in non-model plants such as *Taxus chinensis*, low gene transformation efficiency and immature regeneration systems remain the main problems restricting their application (Cardi et al., 2023).

7 Case Study: Enhancing Taxol Yield in *Taxus chinensis* Cell Cultures

7.1 Background, initial production challenges, and research goals

Taxol is an important anti-cancer drug, mainly obtained from plants of the Taxus genus. However, Taxus trees like T. chinensis grow very slowly and have a very low content of taxol in their bodies. Therefore, extracting it from the bark or needles by traditional methods is far from meeting clinical needs and would also damage wild resources. The total chemical synthesis of taxol involves too many steps and is too costly, making it almost of no practical application value. Although semi-synthesis is feasible, the precursor substances need to be obtained from plants, and thus are still limited by raw material supply and the environment. In contrast, cell suspension culture provides a more sustainable approach, but there are still problems such as unstable cell lines, low metabolic flux, and low yield at present (Mutanda et al., 2021; Ren et al., 2025). Therefore, increasing the taxol yield in the cell culture system of T. chinensis has become the focus of current research.

7.2 Omics-guided identification of regulatory or enzymatic bottlenecks

Multi-omics analyses (such as transcriptomics and metabolomics) revealed that the synthesis of taxol depends on two metabolic pathways, diterpenoids and phenylpropanoids, requiring a total of more than 20 enzymes and at least 19 reactions. Among them, rate-limiting enzymes such as taxadiene synthase (TS) and taxane 5α-hydroxylase (T5OH) play a key role in the entire metabolic flux (Sun et al., 2024). The study also found that exogenous hormones such as MeJA, ABA, and SA can significantly induce key genes in the synthetic pathway, while transcription factors such as MYB, WRKY, ERF, etc. occupy core positions in the regulatory network (Chen et al., 2021; Ren et al., 2025). In addition, there is substrate competition between the phenylpropane pathway and taxol synthesis, among which PAL is a confirmed "bottleneck" node (Newton et al., 2023).

7.3 Engineering interventions and resulting improvements in Taxol yield

Researchers have attempted various engineering strategies to increase taxol production in response to these limitations. Chen et al. (2021) and Ren et al. (2025) demonstrated that overexpression of key enzyme genes (such as BAPT, TS, T5OH) or regulatory factors (such as TcMYB29a, TcMYB73, TcWRKY33) could significantly enhance the expression of downstream genes and increase taxol and its intermediates (such as 10-DAB, baccatin III) by 1.8 to 2.7 times. Inhibition of PAL by CRISPR-guided DNA methylation can reduce substrate inflow into the phenylpropane pathway and increase taxol accumulation to 25 times the original (Newton et al., 2023). In addition, inducers such as MeJA, ABA, and SA can up-regulate transcription factors such as TcMYB29a, TcMYB73, and TcWRKY33, further strengthening the synthetic pathway (Chen et al., 2021; Sun et al., 2024; Ren et al., 2025). Treatments such as ultrasonic stimulation, solvent extraction, fungal induction and nutritional supplementation, whether used alone or in combination, can significantly increase the yield by 5 to 17 times, with the maximum yield reaching approximately 67 mg/L.

8 Challenges and Future Perspectives

8.1 Technical limitations in pathway elucidation and genetic manipulation

The biosynthesis of taxol is very complex, requiring more than 20 enzymes and at least 19 reactions. Moreover, some key enzymes (such as several types of CYP450 hydroxylases and cyclooxygenases) have not been fully identified so far, which leaves a "gap" in the entire pathway. Traditional transcriptome and co-expression analyses are not very effective in large genomes such as *Taxus chinensis* because there are many related genes and significant expression differences, thus further increasing the difficulty of pathway analysis. In addition, the

expression efficiency of many functional enzymes (especially CYP450) in heterologous systems is very low, and the enzyme activity is also unstable, which brings great limitations to the construction of synthetic biology platforms. Although tools such as CRISPR have been used to regulate these pathways, there are still many difficulties in precisely regulating multiple metabolic branches simultaneously.

8.2 Need for computational modeling and AI-driven enzyme discovery

With the increasing amount of omics data, traditional bioinformatics methods have become inadequate in predicting enzyme functions and searching for unknown enzymes. Artificial intelligence (AI) and deep learning are now regarded as more powerful tools for predicting enzyme function, protein structure, and even for designing new enzymes. For example, AlphaFold has been used to predict the structure of enzymes related to taxol synthesis and assist in functional inference. AI-combined with protein engineering is expected to find unknown enzymes more quickly, improve catalytic efficiency, and provide more efficient enzyme elements for synthetic biology. In the future, the combination of multi-omics data, AI algorithms and experimental verification should fill the gap of the taxol synthesis pathway more quickly and be useful for constructing a more complete regulatory network.

8.3 Prospects for sustainable and scalable Taxol production

At present, taxol is mainly extracted from natural *Taxus chinensis*. However, due to slow tree growth, scarce resources and significant environmental influence, it is far from meeting the clinical needs (Mutanda et al., 2021). Cell suspension culture, co-culture with endophytic fungi, and new synthetic biology approaches have all provided new directions for continuous production. However, further breakthroughs are still needed in terms of yield, stability and scale-up production. In the future, cell activity and yield can be enhanced by optimizing the design of bioreactors, regulating metabolic flow, using a combination of multiple inducers, and adding microcarriers. Further exploration of key regulatory factors and development of new biosynthetic chassis will also provide a basis for the large-scale and sustainable production of taxol.

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Conflict of Interest Disclosure

The author affirms that this research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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