Advances in Biocatalysis for Sustainable Pharmaceutical Synthesis: Applications, Technological Progress, and Future Directions

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Abstract. Biocatalysis has emerged as a critical tool in pharmaceutical synthesis, offering a range of significant advancements in recent years. This paper provides a comprehensive review of biocatalysis applications in drug synthesis, emphasizing its role in enhancing the efficiency and environmental sustainability of producing complex pharmaceutical molecules. Through detailed case studies, including the biocatalytic synthesis of amoxicillin, paclitaxel, and ribavirin, the paper illustrates the superior reaction efficiency, selectivity, and reduced environmental impact achievable through biocatalysis. The technological advancements discussed include optimizing enzyme activity via genetic engineering, enhancing enzyme stability through covalent modification, and applying enzyme immobilization techniques. Furthermore, the integration of biocatalysis with green chemistry principles is explored, highlighting its potential to reduce harmful byproducts and energy consumption in industrial processes. The paper also delves into the future directions and challenges of scaling biocatalysis for broader industrial application. As an integral part of green chemistry, biocatalysis is poised to play a pivotal role in promoting sustainable development and minimizing environmental impact in the pharmaceutical industry.

Keywords: Biocatalysis, Pharmaceutical synthesis, Green chemistry, Enzyme immobilization.

1. Introduction

Pharmaceutical synthesis is a core aspect of the pharmaceutical industry. Through chemical synthesis and process control, it ensures the accuracy and quality of drug molecular structures, activity, and purity, while enabling large-scale production, shortening production cycles, and reducing costs. The application of chemical synthesis in the pharmaceutical industry provides foundational technology for new drug development, existing drug improvement, and quality control. By optimizing the molecular structure and properties of drugs, chemical synthesis allows for more effective treatments and improved production efficiency.

However, traditional chemical synthesis methods in drug synthesis have several limitations. These methods often have low selectivity, necessitating complex separation and purification steps to obtain the desired drug molecules, thereby increasing production costs and time. Additionally, high energy consumption and environmental pollution are major drawbacks of traditional methods [1]. A typical example is the synthesis process of sitagliptin. Initially, Merck used the Mitsunobu reaction to introduce chiral amines, but this method had low atom economy and produced a large amount of triphenylphosphine oxide as a byproduct due to the use of triphenylphosphine. To address these issues, Merck and Codexis developed an engineered transaminase to directly convert ketones into the desired chiral amines, avoiding high-pressure reactions and the use of heavy metals [2].

To overcome the limitations of traditional synthesis methods, biocatalysis has emerged as an alternative approach. Biocatalysis involves biochemical reactions catalyzed by enzymes, representing one of the most efficient, selective, and mild catalytic systems known, while also being environmentally friendly, thus promoting the development of "green chemistry." In the pharmaceutical industry, biocatalysis is primarily used to synthesize complex, chiral drugs with single conformations [3]. In recent years, chiral alcohols and amines, as key intermediates in chiral drugs, have seen significant success in the development of ketoreductases and transaminase families, and

they have been widely applied in pharmaceutical manufacturing [4]. Biocatalysis has also achieved breakthroughs in fields such as carbon-hydrogen bond activation, overcoming challenges that traditional catalysis struggles with [5]. Multi-enzyme cascade reactions can control or alter unfavorable reaction equilibria during synthesis, enabling efficient and green drug production [6]. Additionally, chemoenzymatic methods offer more diverse synthetic pathways for drug synthesis [7]. This paper systematically reviews the practical applications and future development directions of biocatalysis in drug synthesis, exploring its potential and prospects in the pharmaceutical industry.

2. Basic Concepts and Advantages of Biocatalysis

Biocatalysis is a core concept in biotechnology, referring to the use of biological systems (such as whole cells, cell extracts, or isolated enzymes) to catalyze specific biochemical reactions. In recent years, the field of industrial biocatalysis has rapidly developed, driven by the growing demand in the pharmaceutical industry for pure enantiomeric compounds, the urgent need for sustainable and environmentally friendly technologies, and the development of pure chemical strategies for the synthesis of complex glycoproteins, oligosaccharides, and lipids [8]. Thus, the application of microorganisms and enzymes has become indispensable in chemical drug manufacturing.

Enzymes are proteins or RNA produced by living cells, characterized by high specificity and catalytic efficiency toward substrates. Studies have shown that enzymes can maintain their natural folded structure in organic solvents, with similar catalytic mechanisms as in aqueous solutions, both following an "acyl-enzyme" catalytic mechanism. The core of biocatalytic reactions lies in the significant reduction of activation energy—the minimum energy required to initiate a reaction. Traditional chemical reactions often require high temperatures, high pressures, or strong acids and bases to provide this energy. In contrast, biocatalysts use their unique spatial structure to create specific active sites that precisely bind with substrates, altering their electronic distribution and lowering the transition state energy of chemical reactions [9]. Biocatalysis has several key advantages. First, biocatalysis typically involves enzymes or microorganisms as catalysts, which exhibit high specificity for particular substrates, enabling precise catalytic action on specific functional groups within substrate molecules [10]. Second, enzyme-catalyzed reactions generally occur under mild conditions (e.g., room temperature, atmospheric pressure, near-neutral pH), with high selectivity and minimal side reactions, leading to extremely high catalytic efficiency. For example, the hydrolysis rate of starch by β-amylase is 3×10^{11} times higher than acid- or base-catalyzed hydrolysis [11]. Furthermore, biocatalysts possess natural renewability, allowing them to be reused in reactions, which not only reduces production costs but also minimizes waste generation, aligning with the principles of green synthesis. Lastly, biocatalysis typically uses water as the reaction medium rather than harmful organic solvents, helping to reduce environmental pollution and supporting sustainable development [12].

3. Applications of Biocatalysis in Various Types of Drug Synthesis

3.1. Biocatalytic Synthesis of Amoxicillin

The aqueous-phase enzyme-catalyzed production of semi-synthetic antibiotics like amoxicillin is a classic example of biocatalysis. This process occurs in an aqueous phase where penicillin V is cleaved by penicillin V acylase (PVA), followed by the separation of immobilized enzymes. The reaction solution is then passed through a chromatographic column to remove side chains and impurities. The 6-aminopenicillanic acid (6-APA) core is eluted and directly combined with side chains under SPGA catalysis to form amoxicillin without requiring crystallization. This process reduces steps and material losses while significantly improving product quality and yield. Using penicillin V as the substrate, PVA-catalyzed antibiotic production offers several unique advantages: it can catalyze higher substrate concentrations, with penicillin V potassium salt reaching 25% and a conversion rate close to 99%, thus increasing 6-APA yield; the optimal pH range for PVA is 5.5-7.5,

where fewer byproducts are formed, and 6-APA is more stable; and the byproduct, phenoxyacetic acid, is easy to separate and odorless, resulting in high-purity 6-APA [13].

3.2. Biocatalytic Synthesis of Paclitaxel

The biosynthesis of paclitaxel can be divided into three parts: the formation of the taxane diterpenoid skeleton—baccatin III, the synthesis of the β-phenylalanoyl CoA side chain, and the acylation and modification of the side chain. The biosynthesis of the paclitaxel carbon skeleton begins with acetyl-CoA, which generates isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP) through the mevalonate pathway (MVA pathway) or methylerythritol phosphate pathway (MEP pathway). DMAPP and three IPP units condense to form the diterpene precursor geranylgeranyl pyrophosphate (GGPP). Under the catalysis of taxadiene synthase (TASY), GGPP is converted into taxadiene, forming the basic skeleton of paclitaxel, taxadiene-4(5),11(12)-diene. Subsequently, under the action of cytochrome P450 oxygenases, multiple hydroxylation reactions occur at the C5, C10, C2, C9, C13, C7, and C1 positions of taxadiene-4(5),11(12)-diene. The intermediate products undergo epoxidation, ketonization, benzoylation, and acetylation to produce baccatin III. The second step in paclitaxel synthesis is the formation of the side chain, primarily catalyzed by phenylalanine aminotransferase (PAM) and β-phenylalanoyl CoA ligase, which convert α-phenylalanine to β-phenylalanoyl CoA. The final step involves the modification of the carbon skeleton and side chain, assembling paclitaxel under the catalysis of baccatin III-13-O-transferase (BAPT), 3'-N-debenzoyl-2'-deoxytaxol-N-benzoyltransferase (DBTNBT), and other unidentified cytochrome P450 enzymes (Figure 1) [14,15].

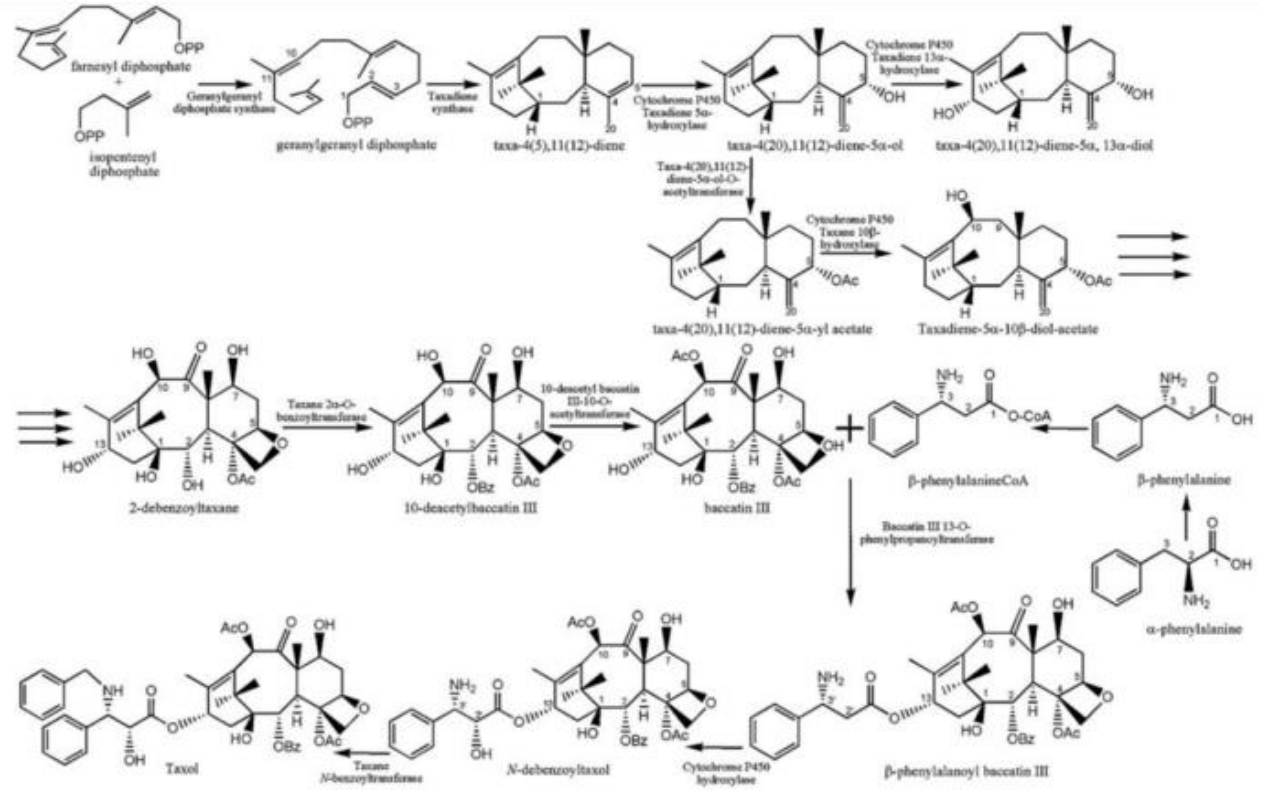

Fig. 1 Biocatalytic synthesis pathway of paclitaxel [15].

3.3. Biocatalytic Synthesis of Ribavirin

The Bacillus subtilis fermentation method for producing ribavirin involves several steps: the synthesis of purine nucleosides, the metabolism of nucleosides to 5-phosphoribosyl-1-pyrophosphate (PRPP), the reversible phosphorylation reactions catalyzed by purine nucleoside phosphorylase and phosphopentose isomerase, and the biotransformation of the exogenous substrate TCA (Figure 2)

[16]. Liu Li's experiments identified Springer 2506 as the optimal adenine donor for ribavirin fermentation, with the highest accumulation at a concentration of 15 g/L [17]. When the initial adenine concentration was 47.97 mg/L, adenine levels in the fermentation broth were maintained at 40-50 mg/L, resulting in maximum PRPP amidotransferase activity and the highest ribavirin synthesis.

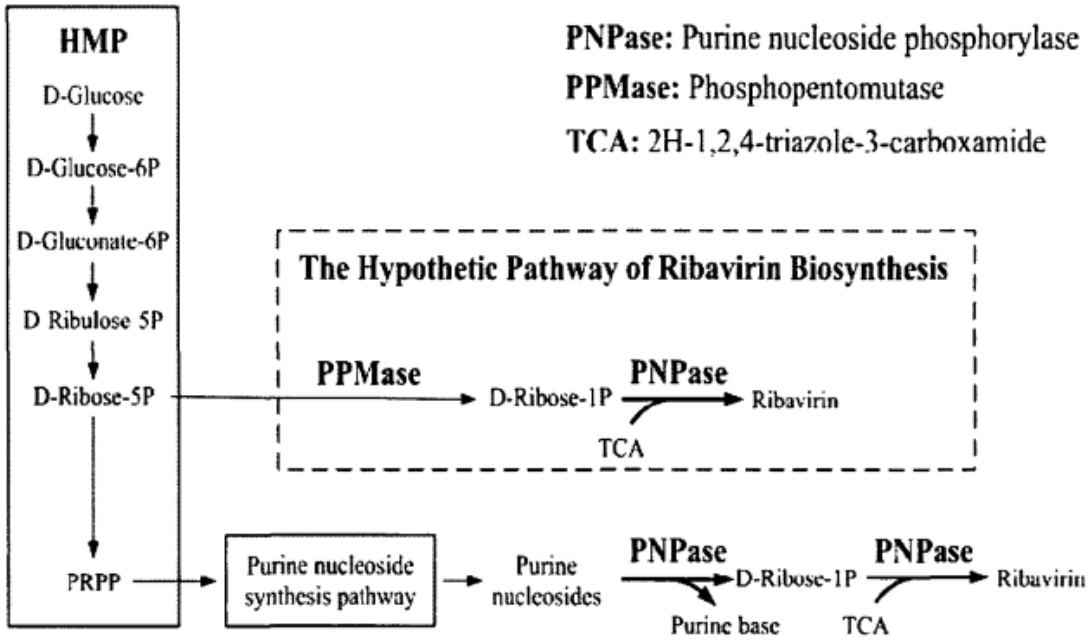

Fig. 2 Synthesis pathway of ribavirin [16].

These examples of biocatalysis demonstrate its broad prospects in drug synthesis, not only enhancing reaction efficiency but also reducing environmental pollution and achieving the goals of green chemistry.

4. Technological Progress in Biocatalysis for Drug Synthesis

4.1. Advances in Genetic Engineering for Optimizing Enzyme Activity and Stability

Chiral epoxides and diols are high-value multifunctional synthons widely used in pharmaceutical synthesis. Epoxide hydrolases (EHs) can specifically hydrolyze racemic or meso-epoxides to produce chiral epoxides and diols. However, limitations in enantioselectivity, product inhibition, and stability have restricted the industrial application of EHs. Hu Die [18] used Aspergillus usamii E001 as the starting strain and employed RT-PCR and THSO-PCR techniques to clone a novel Aueh2 gene from A. usamii. The gene was efficiently expressed heterologously in Escherichia coli BL21(DE3) using the pET28a(+) plasmid. Analysis showed that the activity of the recombinant strain was 400 times higher than that of the wild strain A. usamii E001. The hydrolysis process of this enzyme was optimized in a n-hexanol/buffer biphasic catalytic system, increasing the substrate concentration fivefold compared to a single aqueous phase. By using a semi-rational design strategy, the enantioselectivity of AuEH2 was improved, resulting in excellent mutant enzymes suitable for the preparation of chiral epoxides and diols with potential industrial applications.

4.2. Advances in Enhancing Enzyme Stability through Covalent Modification

PEGylation is a technique where polyethylene glycol (PEG) is covalently attached to proteins or peptides, significantly enhancing their activity. PEGylation offers advantages such as extended half-life, reduced immunogenicity, decreased side effects, and improved chemical and biological stability [19]. For example, interleukin-2 (IL-2) has shown remarkable efficacy in tumor immunotherapy, but its adverse side effects have limited its clinical use. In recent years, researchers have manipulated IL-2 receptor selectivity to favor binding to IL-2 receptor (IL-2R) βγ while avoiding binding to IL-2Rα,

selectively activating the tumor-killing function of CD8+ T cells and maximizing IL-2's immune activation potential. Combination therapy designs based on biased IL-2 receptor agonists like NKTR-214 and THOR-707, along with immune checkpoint inhibitors like PD-1/PD-L1, have shown enhanced anti-tumor immune responses, resulting in significant anti-tumor effects [20].

Additionally, Orlistat, developed by Roche, is a lipase inhibitor that prevents the hydrolysis of triglycerides by covalently binding to triacylglycerol lipase, thereby reducing fat absorption. The mechanism of Orlistat involves covalently binding to porcine pancreatic lipase as illustrated in Figure 3. The strained β-lactone ring in Orlistat's structure imparts electrophilicity to the acyl group, while the catalytic triad (Ser162, Asp176, and His263) in the lipase active site enhances the nucleophilicity of Ser162, leading to nucleophilic attack on Orlistat's β-lactone ring, acylating the Ser162 residue and inactivating the lipase [21].

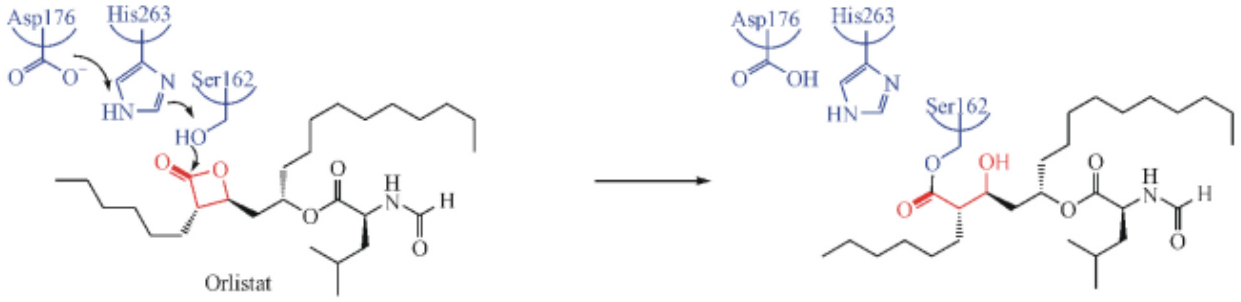

Fig. 3 Mechanism of pancreatic esterase inactivation by Orlistat[21].

4.3. Applications of Enzyme Immobilization Techniques in Drug Synthesis

Chemical cross-linking involves connecting enzymes to carriers using bifunctional reagents, forming covalent bonds between the enzyme, carrier, and functional reagent. However, conventional cross-linkers may have negative effects during immobilization. To address this, OUYANG [22] and colleagues proposed a new green and efficient enzyme immobilization method using enzymatic hydrolysates of geniposide as cross-linking agents for laccase immobilization. This method is green, safe, and applicable to industries requiring strict toxicity control, such as food and pharmaceuticals.

In nonsteroidal anti-inflammatory drugs, ibuprofen is the most commonly used. Research has shown that the two enantiomers of racemic ibuprofen have different effects: S-ibuprofen has better clinical efficacy, while R-ibuprofen is inactive and may even cause side effects [23]. Moguei et al. [24] used a multi-component reaction based on isocyanide to immobilize Thermomyces lanuginosus lipase onto epoxy-functionalized hydroxylated multi-walled carbon nanotubes. The immobilized enzyme exhibited higher thermal stability and was used to catalyze the esterification of ibuprofen with ethanol, achieving a substrate conversion rate of 49.9% and an E-value greater than 300.

Sertraline is a commonly used antidepressant with a chiral carbon atom in its structure, resulting in different enantiomers. Duleba [25] and colleagues immobilized Burkholderia cepacia lipase on a polyacrylic carrier (IB-150A) to catalyze the esterification of (R,S)-1-phenylethanol with an acyl donor to produce S-phenylethanol, an intermediate of sertraline. Under optimal conditions, the substrate conversion rate reached 49%, with an enantioselectivity of 800. Compared to free enzymes, this immobilized lipase demonstrated significantly improved activity in non-aqueous media, along with excellent stability, high enantioselectivity, high conversion rates, and faster product recovery.

Stiripentol is a novel anticonvulsant drug often used as an adjunct treatment with valproate and benzodiazepines. EI-Behairy [26] used different lipases to resolve (R,S)-4,4-dimethylpent-1-en-3-ol to obtain (R)-(+)-4,4-dimethylpent-1-en-3-ol, which was then coupled with 5-vinylbenzo[d][1,3]dioxole to yield (R)-stiripentol. The results showed that in n-hexane at 35°C, 2g of Antarctic pseudomonad lipase immobilized on Immobead 150 catalyzed the transesterification of (R,S)-4,4-dimethylpent-1-en-3-ol with vinyl butyrate, producing R-ester with an ee greater than 99% after 9 hours. The obtained R-ester was further hydrolyzed in a pH 7.0 phosphate buffer using lipase to produce R-alcohol with an ee greater than 99%.

5. Integration of Biocatalysis with Green Chemistry

The core goal of green chemistry is to reduce or eliminate the use and generation of substances hazardous to human health and the environment through chemical technologies and methods, aiming for more sustainable industrial production. Biocatalysis, as a crucial tool of green chemistry, significantly improves the efficiency and selectivity of chemical reactions, maximizes the utilization of atoms in raw materials, and reduces byproduct formation, thereby enhancing atomic economy and product purity, in full alignment with green chemistry principles [27]. For instance, in drug synthesis, traditional chemical catalysis often requires high temperatures, high pressures, or toxic organic solvents, whereas biocatalytic reactions can usually proceed at ambient temperature and pressure, using water or other environmentally friendly solvents, thus reducing energy consumption and minimizing the release of harmful substances. Moreover, enzymes as biocatalysts are non-toxic, biodegradable, and do not cause long-term environmental pollution. This inherent renewability makes enzyme catalysis more environmentally friendly and economically feasible for large-scale applications. Biocatalysts not only enable the reuse of catalysts during reactions, reducing production costs, but also minimize waste generation, further alleviating environmental burdens. This advantage is particularly important in large-scale drug synthesis, where it helps pharmaceutical companies adhere to stringent environmental regulations while maintaining efficient production.

To further advance the integration of biocatalysis with green chemistry, current research focuses on developing more efficient and stable biocatalysts, as well as exploring strategies for combining biocatalysis with traditional chemical catalysis. Through protein engineering and metabolic engineering, it is possible to design and produce enzyme catalysts with enhanced catalytic efficiency, selectivity, and tolerance. These improvements enable high-efficiency catalysis under a broader range of conditions, expanding the application scope of biocatalysis. Additionally, combining biocatalysis with chemical catalysis in multi-step integrated catalytic systems can optimize overall synthesis pathways, improving the efficiency and economy of drug synthesis. This approach not only better achieves the goals of green chemistry in industrial production but also promotes the pharmaceutical industry's progress toward more sustainable development. The integration of biocatalysis and green chemistry not only brings technological innovation to the pharmaceutical industry but also provides a crucial solution for balancing environmental and economic benefits. With the continued development of new biocatalysts and the advancement of biocatalysis technology, the prospects for applying biocatalysis in green chemistry will be even broader in the future.

6. Future Directions

The development of new biocatalysts is key to advancing biocatalysis technology. Through advanced protein engineering, scientists can improve enzyme performance and stability in synthetic biology, creating biocatalysts with higher catalytic efficiency and environmental tolerance. These improvements not only enable the efficient synthesis of natural medicinal products but also significantly reduce production costs and environmental impacts. Additionally, the combination of biocatalysis and chemical catalysis is another area worth exploring. In multi-step synthesis strategies, biocatalysis is renowned for its high selectivity and mild reaction conditions, while chemical catalysis offers shorter reaction times and broader applications [28]. Combining the two can optimize overall synthesis pathways, increase synthesis efficiency, reduce production costs, and minimize waste. This combined approach can allow biocatalysis to be more widely applied in drug synthesis, promoting the green development of the pharmaceutical industry.

Although biocatalysis has made significant progress at the laboratory stage, it still faces many challenges in industrial application. These challenges include the stability of catalysts, reusability, production costs, and maintaining performance during scale-up. To address these challenges, future research should focus on developing more stable and efficient biocatalysts, optimizing production processes, and innovating in separation, purification, and immobilization technologies. These efforts

will enable biocatalysis to better meet the demands of industrial production and fully realize its potential in drug synthesis.

7. Conclusion

Biocatalysis has shown immense potential and undeniable importance in drug synthesis. It not only improves the efficiency and selectivity of chemical reactions but also significantly reduces environmental pollution, making it an integral part of the green chemistry concept. By applying biocatalysis to drug synthesis, the pharmaceutical industry can achieve efficient production while better responding to environmental protection needs, thereby promoting the green transformation of the chemical industry. In the future, with the development of new biocatalysts and continuous optimization of production processes, the prospects for biocatalysis in drug synthesis will be even broader. Through the combination with chemical catalysis and innovation in industrial applications, biocatalysis is expected to play an increasingly crucial role in promoting the green upgrade and sustainable development of the chemical industry. This will not only help achieve dual goals of economic efficiency and environmental protection but also provide a cleaner and more efficient pathway for drug synthesis. In the future, biocatalysis technology is expected to showcase more advantages in broader industrial applications, driving the further development of green chemistry.

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