Advancements and Prospect in Microbial Pharmaceuticals

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Abstract. Microbial pharmaceuticals are a vital pillar of modern medicine, playing a critical role in the treatment of infectious diseases, cancer, and immune-related disorders. This paper systematically reviews advancements in microbial pharmaceuticals over the past decade, categorizing them into three main types based on their sources, with a focus on representative drugs such as antibiotics, amino acids, and nucleotides. While significant clinical successes have been achieved, challenges persist, including bacterial resistance, inefficiencies in drug screening, limited diversity, and concerns regarding side effects and toxicity. To address these issues, this paper outlines future development prospects, summarized into four key directions. By integrating multidisciplinary technological approaches and innovative strategies, microbial pharmaceutical research is poised to make transformative advances in addressing global health challenges.

Keywords: Microbial Pharmaceuticals; Antibiotic Resistance; Drug Development; Artificial Intelligence; Antibiotics.

1. Introduction

Microorganisms comprise approximately 60% of the Earth's total biomass, representing one of the most diverse groups of species[1]. In response to complex, harsh, and ever-changing natural environments, microorganisms have evolved a wide array of natural metabolites with diverse structures and functions. These metabolites act as chemical weapons, enabling survival and reproduction by defending against, attacking, or signaling to eliminate competitors[2]. Such natural metabolites also play a crucial role in disease treatment.

Microbial pharmaceuticals are drugs derived from microorganisms. As early as ancient civilizations, such as those in China, people utilized molds and fermentation products to treat infections. In the early 20th century, the discovery of penicillin, marked the dawn of the antibiotic era. Subsequently, Howard Florey and Ernst Chain advanced its purification and industrial production, making penicillin the first widely used clinical antibiotic. The extensive application of antibiotics significantly reduced mortality rates from infectious diseases and greatly improved global public health. However, the overuse of antibiotics has led to an escalating problem of resistance, with the emergence of multidrug-resistant and extensively drug-resistant bacteria posing a serious threat to global health. Consequently, the development of new antibiotics and alternative therapies has become a top research priority. Recent advancements in technologies such as genomics, synthetic biology, and microbiomics have accelerated research in microbial pharmaceuticals. Studies have identified an enzyme-active nanzyme that exhibits excellent antibacterial and antiviral activity under physiological conditions, enhancing therapeutic efficacy[3]. Additionally, research suggests that phage therapy can serve as an alternative to antibiotics, or that combining phages with antibiotics may yield promising results, with demonstrated synergistic antibacterial effects[4]. However, challenges remain, including narrow antibacterial spectra, unknown safety profiles, and bacterial resistance associated with phage therapy[5].

Despite these advancements, the research and application of microbial pharmaceuticals continue to face significant challenges. The widespread use of antibiotics has led to increased bacterial resistance, more adverse reactions, and the waste of pharmaceutical resources. Furthermore, microbial pharmaceuticals encounter hurdles in development and production, including high production costs, lengthy drug development cycles, and substantial risks.

In this context, this paper reviews the progress made in microbial pharmaceuticals over the past decade and proposes future research directions to address the challenges that have been faced.

2. Research Progress of Different Microbial Pharmaceuticals

Microbial pharmaceuticals can be classified into three categories based on their sources. The first category is derived from whole or partial microorganisms, which includes microbial strains, vaccines, diagnostic reagents, antigens, and antibodies used for diagnosis or treatment. These products have a long history of use and are collectively referred to as biological products. The second category is derived from primary metabolites of microorganisms. This includes substances such as amino acids, nucleotides, coenzymes, and alcohols that form the macromolecular framework of microorganisms. The third category is derived from secondary metabolites of microorganisms. These drugs, such as antibiotics, play a crucial role in controlling infections and treating cancer.

2.1 Biological Products

Biological products consist of drugs that feature intact microbial cells, specific components, or their derivatives as the primary active ingredients. These drugs exert therapeutic, preventive, or diagnostic effects primarily through the biological functions of the microorganisms or their components. They are widely used in treating infectious diseases, immune modulation, metabolic disorders, and cancer therapy. The sources of these drugs include bacteria, fungi, and archaea, primarily as microbial strains, diagnostic agents, or therapeutic antibodies.

2.2 Drugs Derived from Primary Metabolites of Microorganisms

2.2.1 Amino Acid-Based Drugs

Amino acids are small molecules that are widely present, characterized by the presence of both amino and carboxyl groups. Over the past decade, research on amino acid-based drugs has concentrated on developing new medications, optimizing formulation technologies, and investigating biosynthetic pathways.

In China, significant advancements have been made in the development of amino acid-based drugs. Novel amino acid medications have shown remarkable efficacy in treating neurological disorders, cardiovascular diseases, and diabetes. Antimicrobial peptides, a category of small peptides with diverse biological activities, include scorpion venom-derived peptides that play a crucial role in combating pathogenic infections[6]. Recent advancements in drug formulation technologies have led to the emergence of new dosage forms for amino acid-based drugs, such as injectables, sustained-release tablets, and nanoparticles. These innovative formulations enhance drug bioavailability, reduce side effects, and improve therapeutic outcomes for patients. In this regard, Ma Lei optimized the process for arginine glutamate injection, which not only improved the drug's quality but also reduced the incidence of adverse reactions and toxic side effects[7].

As biotechnology continues to advance rapidly, researchers are systematically exploring the biosynthetic pathways of amino acid-based drugs, laying the foundation for the application in their production. For example, Zhang identified the specific residue S441HP2 in the hEAAT2 protein, highlighting its critical role. This may uncover a class of residues associated with protein channel activity, thereby enhancing our understanding of diseases related to EAATs channel activity[8].

2.2.2 Nucleotide-Based Drugs

Nucleotide-based drugs are widely utilized in antiviral therapy and have been clinically proven effective against various viral diseases, including human immunodeficiency virus (HIV)[9] and hepatitis B virus (HBV)[10]. These drugs offer advantages such as good tolerability and convenient administration. However, challenges remain in their clinical use, including significant side effects, strong drug resistance, a tendency for relapse after treatment, and the inability to achieve a complete cure.

To further enhance the therapeutic effects of nucleotide-based drugs, current research primarily focuses on three areas: the novel nucleotides' synthesis, delivery systems, and mechanisms of action. In recent years, research teams have developed a series of new nucleotide-based drugs with broad therapeutic potential. These drugs target various therapeutic areas. For example, in the treatment of

chronic hepatitis B, the antisense oligonucleotide drug bepirovirsen has completed Phase II clinical trials. It effectively inhibits HBV-DNA replication and induces the clearance of hepatitis B surface antigen, demonstrating good safety and tolerability[11,12]. In terms of drug structure optimization, chemical modification strategies, such as linking through thiophosphate bonds, have significantly enhanced the serum stability and nuclease resistance of nucleotide-based drugs. Additionally, it has enabled precise delivery to target organs, such as the liver and brain. For instance, Huang's research team developed a biomimetic nanodelivery system for brain-targeting oligonucleotides. This system successfully breached the blood-brain barrier and achieved efficient oligonucleotide delivery to the striatum in a Parkinson's disease model, providing an innovative biomimetic delivery paradigm to improve the bioavailability of nucleotide-based drugs[13]. Furthermore, in exploring mechanisms of action, multidimensional approaches, including epigenetic regulation and RNA interference pathway activation, have revealed the key regulatory roles of nucleotide-based drugs in processes such as the degradation of HBV covalently closed circular DNA and the inhibition of α-synuclein aggregation. Structure-activity relationship analyses have also offered theoretical support for the rational design and high-throughput screening of the next generation of nucleotide-based drugs. These advancements are facilitating the transition of nucleotide-based therapies from traditional small-molecule treatments to precision-targeted therapies[9].

2.2.3 Therapeutic Enzymes

Therapeutic enzymes remain a key focus in the field of biopharmaceuticals, primarily used as pharmaceutical intermediates. These biocatalysts are specifically designed to treat diseases and improve medical conditions. Enzymes possess two notable characteristics as drugs: (1) they exhibit high affinity and specificity for their substrates, and (2) they can convert substrates into desired products with minimal side effects[14]. Therapeutic enzymes have become effective treatments for several major diseases, including congenital enzyme deficiencies, thrombosis, coronary heart disease, and cancer.

In recent years, research on therapeutic enzymes and enzyme-engineered products has concentrated on key areas such as enzyme screening, optimization, and applications in drug production. By integrating high-throughput screening platforms with computational biology techniques, researchers have successfully identified and characterized multiple novel therapeutic enzymes with clinical potential. For example, PEGylated kynureninase has effectively cleared kynurenine from the body, demonstrating significant synergistic therapeutic effects against various solid tumors, including melanoma, breast cancer, and colorectal cancer, when combined with immune checkpoint inhibitors and tumor vaccines[15]. Studies have shown that combining therapeutic enzymes with drug delivery systems, such as nanoparticles and liposomes, can simultaneously enhance the bioavailability and therapeutic efficacy of these enzymes. The development of new formulations for therapeutic enzymes and their increased utilization depend not only on the advancement of novel drug carriers but also on innovative techniques such as chemical modification and supercritical fluid technology[16].

2.3 Drugs Derived from Secondary Metabolites of Microorganisms

2.3.1 Antibiotic Drugs

Antibiotics are substances that interfere with cellular development functions and exhibit antibacterial and bactericidal effects[17].

2.3.1.1 Quinolone Antibiotics

Quinolone antibiotics represent a significant class of synthetic antibacterial agents that play an essential role in clinical antimicrobial therapy. Over the past decade, research on quinolone antibiotics has focused on their mechanisms of action, new drug development, resistance issues, clinical applications, and adverse effects.

Researchers have identified that the mechanism of action for quinolone drugs involves binding to bacterial topoisomerase II[18]. When quinolone antibiotics bind to this target, they inhibit normal

DNA replication in bacteria, making it difficult for the bacteria to divide and effectively leading to their death. Furthermore, quinolone drugs do not produce cross-resistance, resulting in low resistance rates among bacterial strains[19]. This research provides a theoretical foundation for the development of new quinolone antibiotics. As resistant strains continue to emerge, research on quinolone antibiotics has increasingly shifted toward the synthesis of novel structures and their antibacterial activity. To date, fourth-generation quinolone antibiotics, such as moxifloxacin and gemifloxacin mesylate, have been developed, demonstrating broader antibacterial activity and improved pharmacokinetic properties, while also exhibiting relatively fewer adverse reactions.

2.3.1.2 β-Lactam Antibiotics

β-lactam antibiotics represent a significant class of widely used antibiotics known for their strong bactericidal activity, low toxicity, broad range of indications, and favorable clinical efficacy. This category includes penicillins and cephalosporins. Since the introduction of penicillin, β-lactam drugs have remained first-line treatments due to their low incidence of adverse reactions and significant antibacterial effects. However, they do have some clinical limitations. For instance, penicillins require skin testing, and a small percentage of patients may experience severe anaphylactic shock during this procedure[20].

To address the issue of β-lactamase resistance, research has focused on the synthesis of novel β-lactam compounds and the exploration of β-lactamase activity. For example, researchers such as Hou, Xia and Li have reviewed the mechanism of action, pharmacological properties, and antibacterial activity of cefepime-tazobactam, providing valuable insights for its clinical application[21].

2.3.1.3 Macrolide Antibiotics

Macrolide antibiotics are widely utilized in clinical settings for the treatment of infectious diseases and are characterized by their lactone structures, which consist of 14 to 16-membered rings. As antibiotic resistance has become increasingly severe, research on macrolide antibiotics has gained prominence, focusing on the synthesis of new compounds and mechanisms of resistance.

Modified traditional macrolide antibiotics exhibit enhanced antibacterial activity, broader spectra, and improved drug properties. These advancements have significantly increased their efficacy against multidrug resistant strains. Notable examples include azithromycin, a 15-membered macrolide with an optimized structure that offers strong acid stability, improved oral bioavailability, and an extended elimination half-life, enabling once-daily dosing. Clarithromycin, a 16-membered macrolide, has become a first-line treatment for respiratory infections, skin infections, and Helicobacter pylori infections due to its excellent tissue penetration and broad-spectrum antibacterial activity[22].

2.3.1.4 Aminoglycoside Antibiotics

Aminoglycoside antibiotics, such as streptomycin and kanamycin, are invaluable for treating various infectious diseases. Both are concentration-dependent antibacterial agents, with aminoglycosides demonstrating a more negligible post-antibiotic effect (PAE) against Gram-positive cocci and a larger PAE against Gram-negative bacilli. Their administration is characterized by an initial exposure effect and dose-dependency[20].

To combat the growing challenge of bacterial resistance, current research on aminoglycoside antibiotics emphasizes the design of novel drug molecules and the elucidation of resistance mechanisms. For instance, plazomicin, a new aminoglycoside antibiotic, has been successfully used to treat infections caused by resistant bacteria, achieving favorable clinical outcomes[23]. Studies have shown that 16S rRNA methyltransferases are key contributors to high-level resistance to aminoglycosides. Inhibiting the activity of these enzymes can effectively combat resistant infections. Additionally, combination therapy can enhance antibacterial effectiveness and reduce resistance. When aminoglycosides are used in conjunction with β-lactam antibiotics, they disrupt the integrity of the cell wall, thereby increasing drug bioavailability and significantly improving the bactericidal activity against resistant bacteria..

3. Current Challenges

In recent years, the field of microbial drugs continues to face numerous challenges.

3.1 Antimicrobial Resistance

Since the discovery of penicillin, humanity has embarked on a journey to combat bacterial infections. However, the emergence of antimicrobial resistance has become a critical issue. This resistance arises from genetic mechanisms such as mutations and horizontal gene transfer, as well as the misuse of antimicrobial agents. As a result of selective pressure, bacteria continuously evolve, rendering many antimicrobial drugs ineffective[24]. Mechanisms of resistance include the production of inactivating enzymes, modifications to drug targets, and increased activity of efflux pumps, which can transform previously effective antibiotics into ineffective treatments. Furthermore, due to the rapid adaptability of microorganisms, many new antibacterial compounds are also at risk of having a short lifespan[25]. The rise of antimicrobial resistance not only complicates treatment strategies but also presents significant challenges to the development and application of antibiotics.

3.2 Drug Screening Efficiency and Diversity

The screening of microbial drugs is a crucial step in the research and development of new drugs.. Currently, it primarily relies on traditional screening methods based on microbial growth inhibition and specific bioactivity assays. While these methods have yielded some success over the past few decades, their limitations are becoming increasingly evident. Traditional screening approaches are time-consuming, often taking months or even years[26], and they tend to have low efficiency, making it difficult to meet the demands of large sample libraries. This is especially problematic in complex environmental samples, where potentially beneficial microorganisms may be overlooked due to constraints in cultivation conditions. With the development of various emerging technologies, screening methods have made significant breakthroughs, yet challenges remain. For instance, high-throughput screening technology[27] can rapidly test thousands or even millions of compounds, enhancing screening efficiency. However, it is costly and requires complex equipment and technical support.

Furthermore, the limited diversity of traditional screening methods has resulted in many microbial drugs with novel mechanisms of action remaining undiscovered. Currently, human understanding of the microorganisms inhabiting Earth is less than 3%, and the microbial drugs developed so far are largely based on known bioactive molecules such as antibiotics and immunomodulators, with insufficient exploration of new drug targets and structures[28]. Additionally, the development of microbial drugs often depends on cultivable microorganisms, while over 99% of environmental microbes have yet to be successfully cultured, severely limiting the diversity of drug development.

3.3 Side Effects and Toxicity

All medications come with inherent side effects and toxicity concerns. The potential side effects and toxicities of microbial drugs present significant challenges in both drug development and clinical applications.

The side effects and toxicity of microbial drugs primarily arise from the complexity of their mechanisms of action and their non-specific effects on host cells. For instance, while aminoglycoside antibiotics effectively eliminate pathogenic bacteria, they can also harm the host’s kidneys and auditory system, leading to nephrotoxicity and ototoxicity[29]. Additionally, mycotoxins produced by fungi can exert direct toxic effects on the liver and nervous system[30]. As immunomodulators and anticancer agents, these compounds may elicit excessive immune responses or cytotoxicity, resulting in tissue damage and inflammatory reactions. Such side effects not only diminish the therapeutic efficacy of the drugs but also increase risks for patients and elevate healthcare costs.

3.4 Microbial-Host Interactions

The host's genotype is a critical factor influencing the efficacy of microbial drugs. Genetic polymorphisms can lead to variations in drug-metabolizing enzymes, transport proteins, and drug targets, thereby affecting the ADME (absorption, distribution, metabolism, and excretion) processes. For example, the highly polymorphic CYP2C19 gene can impact the exposure levels of voriconazole, thus influencing the drug's blood concentration and therapeutic effects[31]. Furthermore, certain genetic variations may alter the structure or expression levels of drug targets, hindering effective binding and action.

The gut microbiome, as a vital component of the host, also plays a crucial role in the action of microbial drugs. It not only participates in the metabolic conversion of drugs but may also influence drug efficacy by modulating the host's immune system and metabolic state[32]. Its effects include: some gut microbes converting prodrugs into their active forms, enhancing therapeutic effects; while others may degrade drugs or produce competitive metabolites, thereby reducing drug efficacy. Additionally, disruptions to the gut microbiome caused by antibiotic use can increase the risk of side effects and even lead to secondary infections.

3.5 Drug Development Costs and Time

Statistics indicate that the average development cycle for a new drug, from laboratory to market, is 10 to 15 years and costs over $2 billion[33]. For microbial drugs, unique challenges such as high production difficulty, poor drug stability, and complex mechanisms of action contribute to high development costs and extended timelines.

Clinical trials represent the most expensive and time-consuming phase in the development of microbial drugs. Due to the complex mechanisms of action and the potential for multiple adverse reactions in the host, the design and implementation of clinical trials for these drugs require exceptional caution. For example, in the case of antibiotics, clinical trials must assess the drug's efficacy against different pathogens, the risk of resistance, and the safety of long-term use. This typically necessitates large sample sizes and extended follow-up periods, often subject to rigorous scrutiny by regulatory agencies. Furthermore, microbial drugs are highly susceptible to degradation and inactivation due to environmental factors during storage and transportation. To enhance drug stability, new formulations often need to be developed, which increases research costs and prolongs the development cycle.

4. Future Outlook

In response to the challenges outlined above, future research on microbial drugs is likely to focus on several key areas.

4.1 Development of Antimicrobial Drugs Targeting Resistant Microbes

As antimicrobial resistance continues to escalate, the development of new drugs targeting resistant microbes has become crucial. Future research will prioritize the creation of novel antibiotics, strategies to inhibit resistance mechanisms, and innovative antibacterial approaches to combat resistant microorganisms. Elarembase, the world's first fluorinated tetracycline antibiotic, features a broad antimicrobial spectrum, strong tissue penetration, high exposure levels, and potent antibacterial activity, making it an ideal candidate for combination therapy. As an innovative and highly effective antibacterial drug, it offers a powerful new option for treating infections caused by multidrug-resistant bacteria in clinical settings[34].

4.2 Development of New Drugs from Natural Products

Natural products continue to be a vital source of microbial drugs, with many effective antibiotics derived from microorganisms. Future research will focus on exploring untapped microbial resources, advancing synthetic biology techniques, and optimizing the structures of natural products.

Additionally, gene mining techniques will be employed to identify new biosynthetic gene clusters, thereby facilitating the synthesis of novel natural products that can serve as candidates for drug development.

4.3 Regulation of Microbial Communities

Microbial communities are closely linked to human health, and regulating their structure holds promise as a new strategy for treating certain diseases. Future research will concentrate on understanding the mechanisms behind microbial community interactions with hosts and how these communities can be modulated to treat diseases. This may include developing probiotics and prebiotics[35] or implementing fecal microbiota transplantation techniques[36].

4.4 Application of Artificial Intelligence and Big Data in Drug Development

With advancements in artificial intelligence and big data technologies, the development of microbial drugs is entering a transformative era. The application of AI can efficiently identify microbial products with potential therapeutic value. Additionally, big data analysis can help researchers discover new drug targets and mechanisms of action, as well as optimize chemical structures. The potential of AI to enhance target discovery efficiency, accelerate drug development processes, and reduce R&D costs is substantial, paving the way for innovative treatments for various complex diseases[37].

5. Conclusion

In recent years, significant advancements have been made in the research and application of microbial drugs, which include both whole microorganisms and their primary and secondary metabolites. Among these, as the important secondary metabolites, antibiotics have played a crucial role in controlling infections and treating cancer. However, the field still faces challenges, such as the rising incidence of bacterial resistance and increasing adverse reactions. Additionally, microbial pharmaceuticals face challenges such as like high production costs, lengthy drug development cycles, and substantial risks. Therefore, it is essential to pursue new drug development, structural optimization, research on stability and specificity, as well as the development of delivery systems. Efforts should also focus on optimizing production processes, discovering more bioactive substances, and utilizing gene editing techniques for strain selection to enhance efficacy and reduce resistance.

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