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Integrating Computational Methods into Antibacterial Drug Discovery and Development from Natural Products

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ABSTRACT: Natural products have long been pivotal in sustaining civilizations due to their medicinal properties and have served as a rich source of bioactive compounds for drug discovery. With the rise of antibiotic-resistant bacteria, there is an urgent need for new antibacterial agents. Natural products, with their diverse chemical structures, provide a promising reservoir for identifying new lead compounds. Historically, the discovery of bioactive natural products often relied on serendipity, but modern advancements in computational approaches, particularly computer-aided drug design (CADD), have revolutionized this process. In the modern era, vast data from advanced technologies can provide valuable insights through computational methods. These approaches enable the structural analysis of molecules and the prediction of their biological activities, accelerating drug discovery. Advances in molecular sciences have identified more antibacterial targets, further facilitating this process. Integrating computational drug design with the study of natural products allows for the efficient identification and optimization of potential antibacterial agents. Moreover, many medicinal plants harbor mechanisms of action that remain unexplored by conventional methods. By employing computational techniques, researchers can uncover these mechanisms and develop novel antibacterial drugs. This combined approach not only enhances our understanding of natural products but also addresses the critical need for new treatments in the fight against bacterial infections.

Keywords: **natural products; computational methods; in silico chemistry; antibacterial; drug discovery.**

Introduction

The rise of antibiotic-resistant bacteria is one of the most pressing threats to global public health today. The emergence of multidrug-resistant bacterial strains, including methicillin-resistant Staphylococcus aureus, carbapenem-resistant Enterobacteriaceae, and multidrug-resistant Mycobacterium tuberculosis, has rendered many currently available antibiotics ineffective [1]. This alarming trend is largely due to the overuse and misuse of antibiotics in human medicine, agriculture, and animal husbandry, accelerating the natural evolutionary processes that enable bacteria to adapt to antimicrobial agents [2]. Studies have shown that antimicrobial resistance (AMR) is widespread and has severe impacts, causing millions of deaths annually [3].

Compounding this crisis is the dearth of new antibiotics entering the market. The traditional drug development pipeline has struggled to keep pace with the rapid evolution of resistance mechanisms [4,5]. Despite significant advancements in basic life sciences and biotechnology, the process of drug discovery and development (DDD) remains slow and costly, typically requiring around 15 years and approximately up to $2 billion to bring a small-molecule drug to market [6]. There is an urgent need for new antimicrobial agents, necessitating innovative approaches, including the creation of new chemical entities and the repurposing of existing drugs to combat antibiotic resistance.

Natural products have long been a treasure trove for discovering bioactive compounds. The modern scientific exploration of natural products began in the 19th century with the isolation of morphine from the opium poppy and quinine from cinchona bark, marking the start of pharmacognosy [6]. This era laid the groundwork for future discoveries, including antimicrobials. The 20th century saw the discovery of numerous antibiotics such as penicillin and streptomycin, derived from microorganisms, which revolutionized the treatment of bacterial infections [7]. This ongoing search for novel bioactive compounds underscores the

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importance of natural products in drug discovery and development.

Computer-aided drug design (CADD) has transformed modern drug discovery by employing computational techniques to streamline the identification and optimization of potential therapeutic agents. Advances in high-performance computing and sophisticated algorithms have made it possible to rapidly analyze vast chemical libraries, reducing the time and cost associated with traditional drug discovery processes [8]. Key studies have demonstrated that CADD can effectively discover novel inhibitors for challenging targets, such as protein-protein interactions and allosteric sites, which were once considered undruggable [9]. The continuous advancements in computational power and machine learning are expected to further augment CADD's capabilities, solidifying its role as an indispensable tool in the pharmaceutical industry.

In this review, we aim to explore the potential of combining CADD with natural products in the discovery and development of new antibacterial agents. We will delve into the historical and contemporary contributions of natural products to antimicrobial therapy, the advancements in CADD techniques, and how merging these fields can accelerate the identification of novel compounds with potent antibacterial properties. We will also discuss recent findings on the use of natural products as potential candidates for antibacterial agents and how CADD has played a crucial role in enhancing their discovery and optimization. By integrating these approaches, we can address the urgent need for new antibiotics and improve the prospects for effective, accessible, and safer treatments against resistant bacterial infections.

Natural Products in Antimicrobial Drug Discovery

Throughout history, from ancient civilizations to the present day, natural products have played a crucial role in the treatment of infections. Historical records show the use of herbs, extracts, and other natural substances for this purpose [10]. A landmark discovery in 1928 by Alexander Fleming opened the door for the golden age of antibiotics in the mid-20th century, where subsequent antibiotics like streptomycin, isolated from soil bacteria,

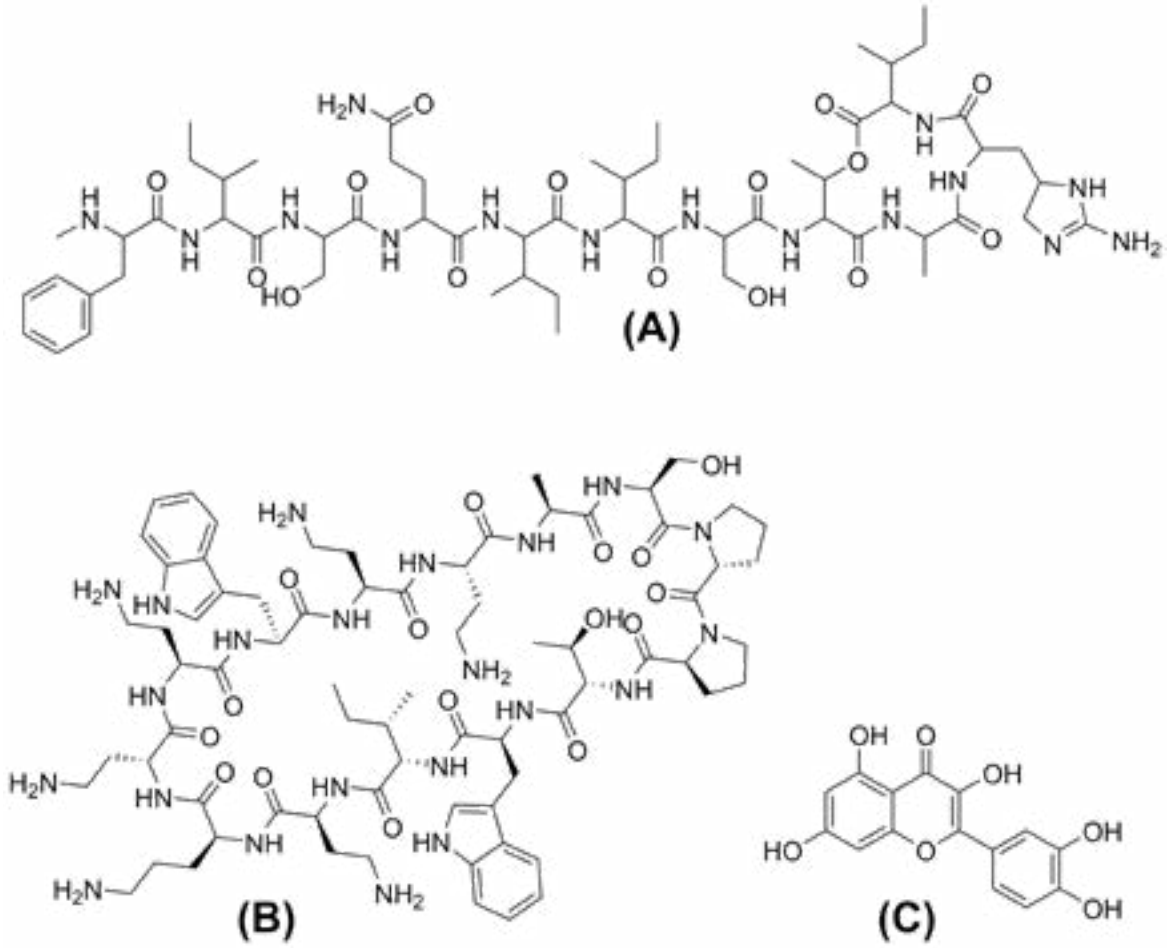

Figure 1. Chemical structures of (A) teixobactin, (B) murepavadin, and (C) quercetin.

further demonstrated the significance of natural sources in uncovering new antimicrobial agents [11]. These historical breakthroughs highlight the genetic and biochemical diversity found in nature, providing a prolific source of novel bioactive compounds. This ongoing exploration of natural products continues to yield promising candidates for antibiotic development, especially in the current context of rising antimicrobial resistance [12].

Success Stories of Antibacterial Agents from Natural Products

One of the most prominent success stories this century in the development of antibacterial drugs from natural products is the discovery of teixobactin [13]. Identified in 2015 and currently in the preclinical stages of development, teixobactin represents a breakthrough in antibiotic discovery as it is produced by a previously unculturable bacterium, Eleftheria terrae. Teixobactin has demonstrated efficacy against gram-positive pathogens, including drug-resistant strains such as MRSA and VRE, without detectable resistance development [14]. This natural product was isolated using innovative cultivation techniques that bypass traditional limitations in microbial cultivation. Teixobactin's unique mode of action, targeting lipid II and lipid III, essential precursors for bacterial cell wall synthesis, underpins its potent antibacterial activity and represents a significant step forward in antibiotic research [15].

Murepavadin, previously known as POL7080, is a peptidomimetic derived from the natural antimicrobial peptide protegrin-1. This compound exhibits potent antibacterial activity against Pseudomonas aeruginosa and has shown efficacy in a mouse septicemia model [16]. Importantly, murepavadin is non-hemolytic and has high plasma stability, overcoming limitations often associated with natural antimicrobial peptides. Murepavadin targets the LPS trafficking pathway in P. aeruginosa by binding to the essential outer membrane protein LptD [17]. In a murine lung infection model, intratracheal administration of murepavadin led to a greater than 2 log reduction in colony-forming units against multiple P. aeruginosa strains at doses below 1 mg/kg, and a greater than 1 log reduction at 1.25 mg/kg [18]. Murepavadin displays potent in vitro and in vivo activities against extensively drug-resistant P. aeruginosa strains, offering promise in addressing the unmet medical need for treating difficult-to-treat organisms, including those with limited treatment options [19].

Another story comes from quercetin, a flavonoid found in many fruits and vegetables that has shown significant potential as an antimicrobial agent. It inhibits the growth of both Gram-positive and Gram-negative bacteria by targeting multiple mechanisms. For instance, quercetin can inhibit the expression of blaNDM, enhancing the activity of meropenem, a carbapenem antibiotic. This combination disrupts bacterial cell morphology and integrity, leading to bacterial death [20]. Additionally, quercetin has been found to inhibit bacterial DNA gyrase and topoisomerase IV enzymes, which are crucial for bacterial DNA replication [21]. These properties make quercetin a promising candidate for developing new antibacterial therapies, especially against multidrug-resistant (MDR) bacteria.

Moreover, quercetin's ability to enhance the efficacy of existing antibiotics is noteworthy. Studies have shown that quercetin can potentiate the activity of tetracycline against Escherichia coli by increasing cell permeability and weakening the bacterial cell envelope [22]. This synergistic effect not only improves the antibiotic's effectiveness but also helps in reducing the required dosage, potentially minimizing side effects. Quercetin's low toxicity in animal models further supports its potential as a safe and effective antimicrobial agent [23].

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