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Utilization of Natural Products as a Source of Novel Antibiotics: A Literature Review

Nur Afni[1*]

[1]Department of Chemistry, Faculty of Mathematics and Natural Science, Universitas Negeri Makassar, Makassar, Jalan Mallengkeri Makassar, 90244, Indonesia

**Corresponding Address: nur.afni@unm.ac.id*

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ABSTRACT

Antibiotic resistance is a growing global health concern that threatens the effectiveness of current treatments against bacterial infections. Natural products have long served as essential reservoirs for the discovery of bioactive compounds, including antibiotics, owing to their structural diversity and ecological functions. This literature review highlights recent advances (2016–2025) in the identification and development of novel antibacterial compounds derived from natural sources such as medicinal plants, soil actinomycetes, marine organisms, endophytes, and extremophiles. It also discusses the molecular mechanisms underlying their antibacterial actions and addresses modern approaches in natural product-based drug discovery, including genome mining, metabolomics, artificial intelligence, and synthetic biology. Despite various challenges, such as the rediscovery of known molecules and low yields, innovative strategies continue to drive the development of promising antibiotic candidates. This review emphasizes the untapped potential of natural resources and advanced technologies in tackling the global antimicrobial resistance crisis.

Keywords: antibacterial compounds, antibiotic resistance, drug discovery, natural products, novel antibiotic

I. INTRODUCTION

Antibiotic resistance has become one of the most significant global health challenges today. The spread of bacteria resistant to multiple classes of conventional antibiotics has led to increased morbidity and mortality due to difficult-to-treat infections (WHO, 2022). Therefore, there is an urgent need to discover new antibiotic compounds with novel mechanisms of action. One promising approach is exploring natural products as a primary source of bioactive compounds, given their long-standing success in drug development (Newman & Cragg, 2020a).

Natural sources such as medicinal plants, endophytic microorganisms, marine fungi, and soil bacteria have been shown to produce various secondary metabolites with potential antibacterial activity. For instance, *Streptomyces* is well-known as a major producer of natural antibiotics like streptomycin and tetracycline (Barka et al., 2016). Moreover, recent studies highlight that marine microorganisms represent an important reservoir of novel antibacterial

compounds with unique chemical structures that remain largely unexplored (Barzkar et al., 2023; Choudhary et al., 2017). This biodiversity offers great opportunities for discovering new molecules capable of overcoming bacterial resistance.

However, the discovery and development process for antibiotics derived from natural products faces several technical and scientific challenges. Isolating pure active compounds requires advanced extraction and purification techniques alongside comprehensive bioactivity assays to confirm their effectiveness against clinical pathogens (Montalvão et al., 2014; Olaniyan et al., 2025)Furthermore, a deep understanding of molecular mechanisms is essential for developing these compounds into potential drug candidates. Therefore, this review aims to summarize recent advances in utilizing natural products as sources for new antibiotic compounds.

II. METHODS

This literature review was conducted using a systematic approach to collect, evaluate, and synthesize original research studies related to the utilization of natural products as sources of new antibiotic compounds. The literature search focused on scientific articles published between 2016 and 2025 to ensure up-to-date and relevant information. Primary data sources were reputable electronic databases, including PubMed, MDPI, and Google Scholar. Search keywords comprised combinations such as “natural products,” “antibiotic discovery,” “bioactive compounds,” “medicinal plants,” “marine microorganisms,” and “antimicrobial resistance.” Inclusion criteria encompassed original research articles that discussed the isolation, chemical characterization, antibacterial activity testing, and mechanisms of action of compounds derived from natural sources.

Following an initial screening based on titles and abstracts, selected articles were thoroughly analyzed to extract key data regarding types of natural materials studied, methods for isolating active compounds, results from in vitro or in vivo antibacterial assays, as well as potential for further development. The extracted data were thematically organized to provide a comprehensive overview of recent advances in antibiotic discovery based on natural products.

III. RESULTS AND DISCUSSION

A. Potential of Natural Products as Sources of New Antibiotic Compounds

Natural products have long served as a cornerstone in the discovery of bioactive compounds, particularly antibiotics, due to their vast chemical diversity and evolutionary optimization for biological activity. The urgency for discovering new antimicrobial agents has intensified with the rise of multidrug-resistant (MDR) pathogens. Natural sources, including medicinal plants, soil bacteria, marine organisms, fungi, endophytic microbes, extremophiles, and symbiotic bacteria offer promising reservoirs for novel antibiotic candidates that may bypass current resistance mechanisms.

1) Medicinal Plants and Phytochemicals

Medicinal plants are among the most extensively studied sources of antimicrobial agents due to their rich phytochemical profiles. Secondary metabolites such as alkaloids, flavonoids, terpenoids, phenolics, and saponins have been widely reported to possess significant antibacterial activity against Gram-positive and Gram-negative bacteria (Abdallah et al., 2023; Górniak et al., 2019). For instance, compounds from *Azadirachta indica* (neem), *Curcuma longa* (turmeric), and *Ocimum sanctum* (holy basil) exhibit bactericidal effects by disrupting membrane integrity or inhibiting essential metabolic enzymes.

2) Soil Microorganisms and Actinomycetes

Soil-derived actinomycetes, particularly from the genus *Streptomyces*, are well-known producers of clinically important antibiotics such as streptomycin, tetracycline, and erythromycin. Recent advances in genome mining and metabolomic profiling have enabled researchers to identify previously unexpressed biosynthetic gene clusters that encode structurally unique antibiotic compounds (Barka et al., 2016; Subramani & Sipkema, 2019). These approaches continue to uncover new molecules with broad-spectrum antibacterial activity and potential clinical applications.

3) Marine-Derived Natural Products

Marine environments, characterized by high biodiversity and unique ecological pressures, have emerged as prolific sources of novel bioactive compounds. Marine sponges and associated microbial symbionts produce unique antibacterial substances, including brominated alkaloids, polyketides, and peptides with potent activity against MDR bacteria (Barzkar et al., 2023; Blunt et al., 2016; Choudhary et al., 2017). For example, marine-derived fungi and bacteria have been found to synthesize rare metabolites like marinopyrrole A, which targets resistant strains such as Methicillin-Resistant *Staphylococcus aureus* (MRSA) and Vancomycin-resistant Enterococci (VRE) (Elmaidomy et al., 2022)

4) Endophytic Microorganisms

Endophytic microorganisms—residing asymptomatically within plant tissues—play a key role in antibiotic discovery due to their ability to produce secondary metabolites structurally similar or complementary to their host plants. These microorganisms, particularly endophytic *Streptomyces*, have yielded novel antibacterial compounds with activity against drug-resistant bacteria (Nurjannah et al., 2023). Such sources not only enhance chemical diversity but also offer sustainable alternatives for drug development without depleting plant populations (Atanasov et al., 2015; Chaachouay & Zidane, 2024).

5) Animal-Derived Compounds and Antimicrobial Peptides

Animals, including insects and fish, also produce antimicrobial peptides (AMPs) as part of their innate immune defense. Research has shown that peptides isolated from insect hemolymph possess significant antibacterial properties, offering a new class of potential antibiotic candidates. AMPs often act through mechanisms distinct from traditional antibiotics, such as disrupting bacterial membranes or modulating host immune responses. AMPs could become a promising option to tackle medically relevant biofilms, preventing resistance development, and combating multidrug-resistant bacteria, including ESKAPE pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa*, and Enterobacter species) (Guryanova et al., 2023; Mohideen & Louis, 2021; Sahoo et al., 2021)

6) Extremophiles and Chemically Unique Antibiotics

Microorganisms that thrive in extreme conditions, extremophiles, are gaining attention for their ability to produce thermotolerant and chemically novel antibiotics. These include bacteria from hot springs, acidic environments, and deep-sea hydrothermal vents. Such organisms possess unique biosynthetic pathways that have evolved to produce stable and potent antimicrobials under harsh conditions (Gallo & Aulitto, 2024; Marzban & Tesei, 2025; Tiwari & Gupta, 2012). For example, extremophilic *Bacillus* strains have been found to produce lipopeptides like surfactin and fengycin, which show broad-spectrum antimicrobial activity (Ongena & Jacques, 2008).

7) Symbiotic Bacteria and Emerging Leads

Symbiotic bacteria, especially those associated with insects and nematodes have recently gained interest as producers of antibiotics that serve protective roles for their hosts.

One of the most groundbreaking discoveries in this area is *darobactin*, a novel antibiotic isolated from *Photorhabdus khanii*, a bacterial symbiont of entomopathogenic nematodes. Darobactin exhibits selective activity against Gram-negative bacteria by targeting the BamA protein in the outer membrane, making it a rare example of a natural compound effective against these hard-to-treat pathogens (Imai et al., 2019).

Table 1. Natural Sources and Their Antibacterial Compounds

Natural Source	Example Antibacterial Compounds	Mechanism of Action	Target Pathogens	References
Medicinal Plants	Tea Tree Oil (Terpenoids), Berberine (Alkaloids), Curcumin (Polyphenol)	Cell membrane disruption, protein synthesis inhibition, biofilm supression	*S. aureus*, *E. coli, P. aeruginosa*	(Abdallah et al., 2023; Górniak et al., 2019)
Soil Actinomycetes	Streptomycin, Tetracycline, Actinomycin D	Ribosome binding (30S/50S), DNA intercalation	*Mycobacterium*, *Pseudomonas, Streptococcus*	(Barka et al., 2016; Subramani & Sipkema, 2019)
Marine Organisms	Marinopyrrole A, Brominated alkaloids	DNA gyrase inhibition, biofilm disruption	MRSA, VRE, *Acinetobacter*	(Barka et al., 2016; Blunt et al., 2016; Choudhary et al., 2017; Elmaidomy et al., 2022)
Animals	Antimicrobial Peptides (AMPs)	Disrupting bacterial membranes or modulating host immune responses	MDR, including ESKAPE	(Guryanova et al., 2023; Mohideen & Louis, 2021; Sahoo et al., 2021)
Endophytes	Darobactin, Padicamycin	Targets BamA protein (Gram-negative), cell wall synthesis	*E. coli*, *K. pneumoniae*	(Atanasov et al., 2015; Chaachouay & Zidane, 2024; Nurjannah et al., 2023)
Extremophiles	Lipopeptides (e.g., Surfactin)	Cell membrane disruption	*Bacillus*, *Staphylococcus*	(Gallo & Aulitto, 2024; Marzban & Tesei, 2025; Ongena & Jacques, 2008; Tiwari & Gupta, 2012)

Symbiotic Bacteria	Xenocoumacin (from *Xenorhabdus*)	Dual enzyme inhibition (protease + kinase)	*P. aeruginosa, Enterobacter*	(Imai et al., 2019)

B. Modern Approaches in Natural Product-Based Antibiotic Discovery

The persistent rise in antimicrobial resistance has necessitated the integration of advanced technologies into the antibiotic discovery pipeline. Traditional bioactivity-guided isolation methods, while effective in the past, are increasingly limited by the rediscovery of known compounds and the inability to culture many microbial species. Consequently, modern approaches involving genomics, metabolomics, artificial intelligence (AI), synthetic biology, and advanced cultivation strategies have been implemented to overcome these barriers and expedite the discovery of novel antibiotics from natural products.

1) Genome Mining and Biosynthetic Gene Cluster Activation

Genome mining is now a mainstream tool in natural product research, allowing researchers to identify cryptic biosynthetic gene clusters (BGCs) from sequenced microbial genomes (Covington et al., 2021). Tools such as antiSMASH and PRISM facilitate the prediction of potential secondary metabolites by annotating BGCs. However, many of these clusters are silent under standard lab conditions. To activate them, several strategies have been adopted:

- *Heterologous expression*: Transferring the entire BGC into a well-characterized host, such as *Streptomyces coelicolor*, can activate silent clusters (Fergusson et al., 2024)
- *CRISPR-based promoter engineering*: Tools like CRISPR-Cas9 have enabled targeted activation or editing of specific genes within BGCs (Baranova et al., 2023)
- *Elicitors and co-culturing*: Adding chemical inducers or cultivating microbes with other species can induce interspecies signaling that triggers antibiotic biosynthesis (Selegato & Castro-Gamboa, 2023).

These approaches have led to the identification of several novel compounds, such as darobactin from *Photorhabdus* species, which shows activity against Gram-negative pathogens (Imai et al., 2019).

2) Metabolomics and Molecular Networking

The application of metabolomics allows for the high-throughput identification and characterization of small molecules in complex extracts. Coupled with tandem mass spectrometry (MS/MS), molecular networking platforms such as GNPS (Global Natural Products Social) visualize related compounds in large datasets, facilitating dereplication and discovery (Nothias et al., 2020). Recent studies using metabolomic approaches have successfully identified new antimicrobial compounds from previously uncharacterized soil actinomycetes and marine bacteria (Fergusson et al., 2024).

3) Artificial Intelligence and Machine Learning

AI and machine learning are revolutionizing how natural products are prioritized for development. Algorithms can now predict antibacterial activity based on chemical structure and prioritize BGCs with the greatest potential for novel bioactivity (Szymczak & Szczurek, 2023). For example, deep learning models trained on known antimicrobial peptides have been used to design new synthetic antibiotics with promising preclinical efficacy. AI is also being applied to de novo molecular design and retrosynthetic analysis, streamlining the path from genome sequence to candidate drug (Schuh et al., 2025)

4) Advanced Cultivation Techniques

Many natural product-producing microbes are unculturable using standard techniques. Innovations such as the iChip device and simulated natural environments have enabled researchers to cultivate rare species directly in their natural habitats. The discovery of teixobactin, a new class of antibiotic, from an uncultured bacterium *Eleftheria terrae* using iChip technology is a landmark achievement in this area (Ling et al., 2015). Additionally, co-cultivation approaches stimulate microbial interactions that lead to the expression of otherwise silent metabolites (Baranova et al., 2023).

5) Synthetic Biology and Combinatorial Biosynthesis

Synthetic biology provides tools to redesign and construct new biosynthetic pathways by assembling genes from multiple organisms. This allows the production of novel "unnatural" natural products with enhanced stability, activity, or specificity. Combinatorial biosynthesis has yielded antibiotic analogs with improved pharmacological profiles, which would be challenging to derive via traditional means (Cravens et al., 2019; Winter & Tang, 2012).

Table 2. Modern Technologies in Natural Product-Based Antibiotic Discovery

Technology	Example Applications	Advantages	Example Discoveries	References
Genome Mining	CRISPR-Cas9 activation of silent BGCs, *in silico* BGC prediction	Identifies cryptic clusters, reduces trial-and-error	Darobactin (*Photorhabdus*)	(Baranova et al., 2023; Covington et al., 2021)
Metabolomics	GNPS-based molecular networking, isotopic labeling	High-throughput, detects minor metabolites	Lagriamide (soil Actinomycetes)	(Fergusson et al., 2024; Nothias et al., 2020)
Artificial Intelligence (AI)	Structure-activity prediction, *de novo* peptide design	Accelerates prioritization, reduces lab workload	AI-designed synthetic peptides	(Schuh et al., 2025; Szymczak & Szczurek, 2023)
Advanced Cultivation	iChip for unculturable microbes, co-culture systems	Accesses "dark matter" of microbial diversity	Teixobactin (*Eleftheria terrae*)	(Ling et al., 2015)
Synthetic Biology	Combinatorial BGC assembly, pathway optimization	Produces stable "unnatural" analogs, enhances yield	Engineered polyketides (*Streptomyces*)	(Cravens et al., 2019; Winter & Tang, 2012)

C. Mechanisms of Action of Natural Compounds Against Pathogenic Bacteria

Natural compounds derived from plants, microorganisms, and marine organisms exhibit diverse mechanisms to inhibit or kill pathogenic bacteria. These mechanisms include disruption of bacterial cell membranes, inhibition of protein synthesis, interference with nucleic acid synthesis, and prevention of biofilm formation, each contributing to overcoming bacterial resistance.

1) Disruption of Cell Membrane Integrity

Many natural compounds such as flavonoids, terpenoids, and phenolic acids exert antibacterial effects by targeting the bacterial cell membrane. They increase membrane

permeability causing leakage of cellular contents leading to cell death (Sawitri & Mahmuda, 2022; Yadav et al., 2023). For example, tannic acid has been shown to disrupt membrane integrity in *Staphylococcus aureus* and *Escherichia coli*, resulting in rapid bactericidal activity (Lorca et al., 2024).

2) Inhibition of Cell Wall Synthesis

Certain natural compounds interfere with the biosynthesis of peptidoglycan layers essential for bacterial cell wall integrity. For instance, some polyketides produced by *Streptomyces* species inhibit enzymes involved in cross-linking peptidoglycan strands (Alvarez et al., 2024; Harvey, 2008). Plant-derived alkaloids like berberine also show inhibitory effects on enzymes critical for cell wall synthesis (Qassadi et al., 2023; Yan et al., 2021).

3) Inhibition of Protein Synthesis

Certain alkaloids and peptides interfere with ribosomal function thereby inhibiting protein synthesis essential for bacterial growth. Antimicrobial peptides (AMPs) derived from natural sources can bind to ribosomes or interact with translation factors disrupting the elongation process (Xuan et al., 2023). This mechanism is effective against MDR strains by targeting conserved components not easily mutated.

4) Interference with Nucleic Acid Synthesis

Some natural products inhibit Deoxyribonucleic Acid (DNA) gyrase or topoisomerase enzymes critical for DNA replication and transcription. For instance, marine-derived compounds have demonstrated potent inhibition on DNA polymerases leading to halted bacterial proliferation (Sagar et al., 2010). Such interference prevents genetic material duplication necessary for survival.

5) Anti-Quorum Sensing and Anti-Biofilm Activities

Biofilms protect bacteria from antibiotics; thus disrupting biofilm formation is a promising strategy. Natural molecules like flavonoids can inhibit quorum sensing signaling pathways that regulate biofilm development (Mishra et al., 2020). By blocking these signals, these compounds reduce virulence factor expression and enhance antibiotic susceptibility.

D. Challenges in the Development of Antibiotics Based on Natural Products

Despite the immense potential of natural products as sources for new antibiotics, their development faces several significant challenges. One major obstacle is the complexity and low yield of bioactive compounds isolated from natural sources. Many studies report difficulties in isolating pure compounds due to complex mixtures and often minute concentrations of active molecules. This complicates large-scale production and further pharmacological evaluation. (Chinemerem Nwobodo et al., 2022; Silver, 2011; Simoben et al., 2023)

Another challenge lies in the rediscovery problem, where known compounds are repeatedly isolated, limiting novelty (Harvey et al., 2015). Advances in genome mining and metabolomics have helped address this by enabling targeted discovery of novel biosynthetic gene clusters; however, translating these findings into clinically useful antibiotics remains a bottleneck (Foulston, 2019).

Furthermore, comprehensive toxicity assessments and pharmacokinetic studies are essential but resource-intensive steps before clinical application can be considered (Atanasov et al., 2021; Newman & Cragg, 2020b). The complexity of natural product structures also poses synthetic challenges for modification or optimization to improve efficacy or reduce side effects (Li & Vederas, 2009).

Finally, regulatory hurdles and high costs associated with drug development discourage investment from pharmaceutical companies despite urgent medical needs. Collaborative efforts integrating traditional knowledge with modern biotechnological tools are crucial to overcome these barriers. (Renwick & Mossialos, 2018; Roope, 2022; Todd et al., 2021).

IV. CONCLUSION

Natural products continue to serve as a rich and diverse source of new antibiotic compounds, especially in the face of rising antimicrobial resistance. Various natural sources, such as medicinal plants, actinomycetes, marine organisms, endophytes, extremophiles, and symbiotic microbes, have yielded compounds with promising antibacterial properties and novel mechanisms of action. Recent innovations including genome mining, metabolomics, artificial intelligence, and synthetic biology have significantly enhanced the efficiency of identifying and developing these compounds. Despite these advancements, challenges remain, including low compound yields, rediscovery of known metabolites, and the complexity of translating findings into clinically approved drugs. Addressing these obstacles requires integrated multidisciplinary efforts and continued investment. Nevertheless, the synergistic use of natural product research and modern biotechnological tools holds strong potential to deliver effective antibiotics for combating multidrug-resistant pathogens.

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