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THE RENAISSANCE OF NATURAL PRODUCTS IN ANTI-INFECTIVE THERAPY: NOVEL ANTIMICROBIAL AND ANTIVIRAL STRATEGIES

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ABSTRACT

The escalating crisis of antimicrobial resistance (AMR) has renewed global interest in natural products as sources of novel anti-infective agents. Historically, natural products have served as the foundation of antimicrobial therapy, with penicillin, streptomycin, and tetracycline representing transformative discoveries. However, the drying of the natural product pipeline and the rise of synthetic chemistry led to reduced investment in natural product discovery. The current AMR crisis has catalyzed a renaissance in natural product-based anti-infective drug discovery, driven by advances in genomics, metabolomics, and screening technologies. This review critically examines the renewed exploration of natural products for antimicrobial and antiviral applications, focusing on novel molecular targets, strategies to overcome resistance, and synergistic combinations. We evaluate emerging discoveries from plants, fungi, bacteria, and marine organisms that exhibit activity against drug-resistant pathogens, including MRSA, ESKAPE pathogens, and multidrug-resistant fungi. Furthermore, we assess the potential of natural products to overcome resistance through novel mechanisms, including anti-virulence strategies, biofilm disruption, and efflux pump inhibition. Challenges including supply sustainability, clinical development, and rediscovery are critically examined. This review identifies promising research directions and proposes strategies for accelerating natural product anti-infective discovery.

Keywords: Antimicrobial Resistance; Natural Products; Anti-Infective; Synergistic Combinations; Antiviral; Drug Discovery

1 INTRODUCTION

Antimicrobial resistance (AMR) has been identified as one of the greatest threats to global health, with estimates suggesting 10 million annual deaths by 2050 if current trends continue. The emergence of multidrug-resistant pathogens, including methicillin-resistant Staphylococcus aureus (MRSA), carbapenem-resistant Enterobacteriaceae, and multidrug-resistant Pseudomonas aeruginosa, has rendered many conventional antibiotics ineffective. The pipeline of new antibiotics has been insufficient to meet clinical needs, with few novel classes developed in recent decades (Woo et al., 2023). An alarming treatment gap exists between highly drug-resistant gram-negative bacteria and the options now available, according to recent WHO assessments (Quercetin: Synergistic Interaction, 2023).

Natural products have historically been the most productive source of antibiotics, accounting for approximately two-thirds of all approved anti-infective agents (Newman and Cragg, 2020). Natural product-based antibiotics have been

exploited for more than eighty years and continue saving uncountable lives every year (Natural products in antibiotic development, 2022). However, the golden age of antibiotic discovery was followed by a period of declining investment in natural product research, as synthetic chemistry and target-based screening approaches became dominant. The currently lean antibiotic R&D pipeline shows a clear trend away from NP-based programs, and innovative compounds are also rare in early stages (Natural products in antibiotic development, 2022). The current AMR crisis has prompted a renaissance in natural product-based anti-infective discovery, driven by advances in genomics, metabolomics, and screening technologies (Atanasov et al., 2021).

Natural products obtained from plant sources can be identified as the next-generation antibacterial and antiviral alternatives (El-Saadony et al., 2023). The rising antimicrobial resistance and redundancy of antibiotic discovery platforms have highlighted the growing concern to discover new antibiotics, necessitating exploring natural products as effective alternatives to counter drug resistance (Sharma et al., 2022). This review examines the renewed exploration of natural products for antimicrobial and antiviral applications, focusing on novel molecular targets, strategies to overcome resistance, and synergistic combinations.

2 THE ANTIMICROBIAL RESISTANCE CRISIS

2.1 Scope and Impact

AMR is a global public health emergency affecting all regions and countries. The WHO Global Antimicrobial Resistance Surveillance System has documented widespread resistance across bacterial pathogens. The greatest burdens of AMR are in low- and middle-income countries, where limited healthcare infrastructure and antimicrobial stewardship exacerbate the problem.

Antimicrobial resistance poses a significant global health threat (Woo et al., 2023). There is a rising demand for innovative drug scaffolds and new targets to combat multidrug-resistant bacteria (Woo et al., 2023). According to recent estimates, if preventative measures are not adopted, there will be 10 million annual deaths from antibiotic resistance worldwide by 2050, surpassing the number of deaths from cancer, which is currently the leading cause of death (Quercetin: Synergistic Interaction, 2023).

2.2 Priority Pathogens

The WHO has published a priority pathogen list, categorizing bacteria based on the urgency of need for new antibiotics. Priority 1 (critical) pathogens include carbapenem-resistant Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacteriaceae. Priority 2 (high) pathogens include MRSA, vancomycin-resistant Enterococcus faecium, and drug-resistant Salmonella species.

Multi-drug resistant ESKAPE pathogens (Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species) represent a significant challenge in healthcare settings. The use of plants as a natural source of antimicrobial agents provides a solution as they are easily available and safe to use (Multi-drug resistant ESKAPE pathogens, 2023).

2.3 Mechanisms of Resistance

Resistance to antimicrobial agents occurs through multiple mechanisms, including drug inactivation, target modification, and reduced drug accumulation. Efflux pumps, enzyme-mediated inactivation, and target mutation are common mechanisms driving multidrug resistance. The horizontal gene transfer of resistance determinants accelerates the spread of AMR.

Table 1: Priority Pathogens and Resistance Mechanisms

Pathogen	Drug Resistance	Key Mechanism	Clinical Impact
MRSA *(Methicillin-resistant Staphylococcus aureus)*	Methicillin / β-lactams	Target alteration *(mecA-encoded PBP2a mutation)*	Severe skin, soft tissue, respiratory, and bloodstream infections
VRE *(Vancomycin-resistant Enterococcus)*	Vancomycin	Target modification *(vanA/vanB gene-mediated cell wall alteration)*	Nosocomial enterococcal infections, endocarditis, and UTIs
CRE *(Carbapenem-resistant Enterobacteriaceae)*	Carbapenems	Carbapenemase enzyme production *(e.g., KPC, NDM, OXA-48)*	High-mortality hospital-acquired infections, sepsis, and pneumonia
MDR *P. aeruginosa*	Multiple antimicrobial classes	Efflux pump overexpression, porin loss, and enzymatic inactivation	Severe opportunistic infections in immunocompromised and ICU patients
MDR *A. baumannii*	Multiple antimicrobial classes	Combined target mutations, efflux pump activity, and β-lactamases	Recalcitrant hospital-acquired pneumonia, bacteremia, and wound infections

3 NATURAL PRODUCTS IN ANTI-INFECTIVE DISCOVERY

3.1 Historical Successes

Natural products have contributed significantly to the antimicrobial pharmacopoeia, with penicillin, streptomycin, tetracycline, and erythromycin representing foundational discoveries (Newman and Cragg, 2020). The golden age of antibiotic discovery (1940s-1970s) yielded most of the antibiotic classes still in clinical use. Soil bacteria, particularly Streptomyces species, have been the most prolific sources of antibiotics. Before the advent of antibiotics, infections were treated with plants chosen from traditional medicine practices (Woo et al., 2023). Of Earth's 374,000 plant species, approximately 9% have been used medicinally, but most species remain to be investigated (Woo et al., 2023).

3.2 Plant-Derived Antimicrobial Natural Products

Recent discoveries of antimicrobial natural products from plants covering 2018 to 2022 have highlighted plant-derived natural products with antibacterial, antivirulence, and antibiofilm activity documented in lab studies (Woo et al., 2023). This review illuminates discoveries of antimicrobial natural products from plants and examines the development of novel derivatives from well-studied parent natural products, as natural product derivatives have often served as scaffolds for anti-infective agents (Woo et al., 2023).

The genus Nocardia has been identified as a source of new antimicrobials, illustrating the potential of microbial sources for anti-infective discovery (Nonthakaew et al., 2023). Plants are considered a wealthy resource of novel natural drugs effective in the treatment of multidrug-resistant infections (Ephedra foeminea, 2023).

3.3 The Rediscovery Problem

A significant challenge in natural product discovery is the rediscovery of known compounds, leading to diminishing returns from traditional screening. Dereplication strategies and culture-independent discovery approaches have been developed to address this problem. Advances in genomics have enabled the identification of biosynthetic gene clusters and the activation of silent pathways.

3.4 Emerging Sources

Novel sources, including marine organisms, extremophiles, and plant-associated microorganisms, have expanded the chemical diversity available for discovery. Marine natural products have yielded novel antibiotics. Endophytic microorganisms from medicinal plants represent an underexplored source of antimicrobial compounds. Latin American plants have been described as sources of natural products and extracts with antimicrobial activity against multidrug-resistant strains, as well as classes and subclasses of plant secondary metabolites with antimicrobial activity (Latin American Plants, 2023).

Table 2: Emerging Natural Product Sources for Anti-Infective Discovery

Source	Examples	Bioactive Compounds	Antimicrobial Activity & Target Scope
Marine Organisms	Sponges *(Porifera)*, tunicates, bryozoans *(Bugula neritina)*	Spongistatins, bryostatins, halichondrins, manzamines	Broad-spectrum cytotoxicity, antiviral, and potent antimitotic/antitumor activities
Endophytic Fungi	*Penicillium* species, *Aspergillus* species, *Fusarium* species	Novel polyketides, alkaloid-derived penicillins, peptides	Inhibits bacterial and fungal plant/human pathogens, including MDR strains (e.g., MRSA)
Plant Extracts	Ethnomedicinal plants, halophytes *(e.g., Salvadora species)*	Alkaloids, flavonoids, terpenoids, essential oils	Broad antibacterial, antifungal, and antiviral activities; biofilm disruption
Extremophiles	Deep-sea hydrothermal vent microbes, halophiles, psychrophiles	Unique polyketides, cyclic peptides, extremolytes	Multi-target antimicrobial activity under extreme physiological conditions
Microbial Communities	Uncultivated soil microbiomes, marine sediments	Novel non-ribosomal peptides, polyketide antibiotics	Highly active against drug-resistant ESKAPE pathogens and priority superbugs

4 ANTIVIRAL NATURAL PRODUCTS

4.1 Plant-Derived Antivirals

Viral infections have always been the main global health challenge, as several potentially lethal viruses, including the hepatitis virus, herpes virus, and influenza virus, have affected human health for decades (Ponticelli et al., 2023). Unfortunately, most licensed antiviral drugs are characterized by many adverse reactions and, in long-term therapy, also develop viral resistance; for these reasons, researchers have focused their attention on investigating potential antiviral molecules from plants (Ponticelli et al., 2023).

Natural resources indeed offer a variety of specialized therapeutic metabolites that have been demonstrated to inhibit viral entry into the host cells and replication through the regulation of viral absorption, cell receptor binding, and competition for the activation of intracellular signaling pathways (Ponticelli et al., 2023). Many active phytochemicals, including flavonoids, lignans, terpenoids, coumarins, saponins, alkaloids, etc., have been identified as potential candidates for preventing and treating viral infections (Ponticelli et al., 2023).

Phytochemicals including lycorine, capsaicin, rottlerin, piperine, and chebulinic acid have demonstrated inhibitory effects against HCoV-OC43 and SARS-CoV-2 in vitro and in vivo (Effective inhibition, 2023). Phenolic lipids from Clausena harmandiana have been identified as a source of new antiviral agents against human coronaviruses, inhibiting SARS-CoV-2 entry into host cells (New Phenolic Lipids, 2023).

4.2 Mechanisms of Antiviral Action

Natural products exert antiviral effects through diverse mechanisms including inhibition of viral entry, interference with viral replication, modulation of host immune responses, and direct inactivation of viral particles. The modern approach to antiviral drug discovery is to study the viral structure and replication details to find targets for new antiviral drugs (Ponticelli et al., 2023). Along with designing tailor-made drugs against specific viral proteins of defined species, a more traditional strategy to increase the number of drugs available to treat viral diseases is to screen natural compounds derived from plants (Ponticelli et al., 2023).

A systematic review of specialized metabolites from plants has summarized the knowledge obtained to date on the in vivo antiviral activity of specialized metabolites extracted from plant matrices by focusing on their mechanism of action (Ponticelli et al., 2023). Alkaloids have been identified as potential antivirals, with a comprehensive review providing a broad overview of numerous naturally occurring alkaloids (isolated from both terrestrial and aquatic species) along with synthetically produced alkaloid compounds having prominent antiviral properties (Alkaloids as potential antivirals, 2023).

4.3 Broad-Spectrum Antivirals

Broad-spectrum antivirals derived from natural products have been summarized, covering recently discovered antiviral drugs, mechanisms of action, and screening and design strategies for novel antiviral agents (Broad-Spectrum Antivirals, 2023). The development of broad-spectrum antivirals is particularly important for emerging viral threats where specific therapies are not yet available.

Table 3: Key Antiviral Natural Products and Mechanisms

Compound Class	Examples	Mechanism of Action	Target Viruses
Alkaloids	Lycorine, Piperine, Berberine	Blockade of viral entry, suppression of viral gene expression, and inhibition of RNA replication	SARS-CoV-2, HCoV-OC43, Influenza A, and Dengue virus
Flavonoids	Quercetin, Kaempferol, Epigallocatechin gallate (EGCG)	Prevention of viral attachment/adsorption, inhibition of viral 3CL^{pro} protease and RNA polymerase	SARS-CoV-2, Influenza, Herpes Simplex Virus (HSV-1), and Hepatitis C
Terpenoids	Triterpenoids *(e.g., Glycyrrhizin, Betulinic acid)*	Inhibition of early-stage viral replication, capsid assembly, and viral fusion	HIV-1, HSV-1, Hepatitis B, and Coronaviruses
Phenolic Lipids	*Clausena* compounds *(e.g., phenolic lipids from C. harmandiana)*	Disruption of viral envelope integrity, inhibition of viral entry into host cells	Human Coronaviruses *(e.g., SARS-CoV-2, HCoV-229E)*
Lignans	Nordihydroguaiaretic acid (NDGA), Schisandrin B, Arctigenin	Interference with host/viral intracellular signaling pathways *(e.g., NF-κB, MAPK/ERK)*	HIV-1, Influenza A, Hepatitis B, and Flaviviruses

5 NOVEL STRATEGIES FOR OVERCOMING RESISTANCE

5.1 Anti-Virulence Strategies

Anti-virulence strategies target bacterial virulence factors rather than essential functions, potentially reducing selective pressure for resistance development. Accumulated evidence suggests that plant-derived natural products that have been used for centuries to treat infectious diseases can be a rich source for screening potential virulence-arresting drugs (VADs) for developing advanced therapeutics for infectious diseases (Plant-derived virulence arresting drugs, 2023).

Plant-derived virulence arresting drugs as novel antimicrobial agents have been reviewed, summarizing virulence factors and their roles in various bacteria, as well as recent advances in plant-derived natural products as VAD candidates (Plant-derived virulence arresting drugs, 2023). Natural VAD-related clinical trials and patents, the perspective of VAD-based advanced therapeutics for infectious diseases, and critical challenges hampering clinical use of VADs have also been discussed (Plant-derived virulence arresting drugs, 2023).

Anti-quorum sensing strategies have emerged as promising approaches for combating bacterial infections. The evaluation of anti-quorum sensing and antibiofilm effects of secondary metabolites from various plant sources has been documented (Evaluation of anti-quorum sensing, 2023). Modulation of virulence factors in biofilm-forming Klebsiella pneumoniae via selected medicinal plants and phytochemical compounds has shown significant reduction in exopolysaccharide production (Modulation of virulence factors, 2023).

5.2 Biofilm Disruption

Biofilm formation contributes to antibiotic tolerance and persistent infections. Natural products with biofilm-disrupting activity have been identified, including plant phenolics and bacterial secondary metabolites. Novel perspectives on phytochemicals-based approaches for mitigation of biofilms in ESKAPE pathogens have been explored, emphasizing the pivotal role of phytochemicals in the fight against biofilm-associated infections and multidrug-resistant ESKAPE pathogens (Novel perspectives on phytochemicals-based approaches, 2023).

Natural medicine has been identified as a promising candidate in combating microbial biofilm, with a review summarizing and analyzing the efficacy characteristics and corresponding mechanisms of natural-product-based

antibiofilm agents, including phytochemicals, biosurfactants, and antimicrobial peptides, along with their mechanisms, quorum sensing signaling pathways, and disruption of extracellular matrix adhesion (Natural Medicine, 2023).

Ephedra foeminea has been identified as a novel source of antimicrobial and anti-biofilm compounds to fight multidrug resistance phenotype (Ephedra foeminea, 2023). Plant extracts have demonstrated antibiofilm activity against Staphylococcus aureus and Pseudomonas aeruginosa (In vitro biofilm inhibition, 2023).

5.3 Efflux Pump Inhibition

Efflux pump inhibitors can restore the activity of antibiotics that are substrates of efflux pumps. Natural products, including plant alkaloids and flavonoids, have demonstrated efflux pump inhibitory activity. Carvacrol from oregano has been shown to enhance the antimicrobial potency of berberine in Bacillus subtilis through efflux pump inhibition (Carvacrol Enhances, 2022). The inhibition of efflux pumps represents a promising strategy for overcoming multidrug resistance.

5.4 Synergistic Combinations

Synergistic combinations of natural products and antibiotics can enhance activity and overcome resistance. The synergistic effect of plant compounds in combination with conventional antimicrobials against biofilms of Staphylococcus aureus, Pseudomonas aeruginosa, and Candida albicans has been reviewed, analyzing and summarizing the current knowledge on the synergistic effects of plant metabolites in combination with conventional antimicrobials (Synergistic Effect of Plant Compounds, 2023). The synergism of conventional antimicrobials with plant compounds can modify and inhibit the mechanisms of acquired resistance (Synergistic Effect of Plant Compounds, 2023).

Medicinal plant Miconia albicans has been shown to synergize with ampicillin and ciprofloxacin against multi-drug resistant Acinetobacter baumannii and Staphylococcus aureus (de Jesus et al., 2023). Extracts and phases obtained from the medicinal plant demonstrated synergistic effects when combined with commercial antibiotics, restoring their antibacterial efficacy. Extracts and phases also exhibited antibiofilm property against S. aureus (de Jesus et al., 2023).

Quercetin has demonstrated synergistic interaction with antibiotics against colistin-resistant Acinetobacter baumannii (Quercetin: Synergistic Interaction, 2023). Quercetin combined with colistin and amikacin showed synergistic effects against colistin-resistant A. baumannii strains, causing a decrease in the MIC values of these antibiotics. The combination of quercetin with colistin resulted in MIC decreases of 4 to 16-fold, while combination with amikacin resulted in 16 to 64-fold decreases (Quercetin: Synergistic Interaction, 2023). The results from time-kill assays also showed the synergistic effect and bactericidal activity of these combinations (Quercetin: Synergistic Interaction, 2023).

Tamarindus indica extract has been identified as a promising antimicrobial and antivirulence therapy, demonstrating synergistic effects with conventional antibiotics (imipenem, amikacin, and ofloxacin) and reducing their MICs (Tamarindus indica Extract, 2023). Combinations of chloramphenicol with perillyl alcohol and hydrocinnamic acid have revealed synergism mainly at low concentrations of antibiotics, highlighting the potential of combinatorial therapies for microbial growth control (Combinations of chloramphenicol, 2023). Phytochemicals can play an important role as potentiators or resistance-modifying agents (Combinations of chloramphenicol, 2023).

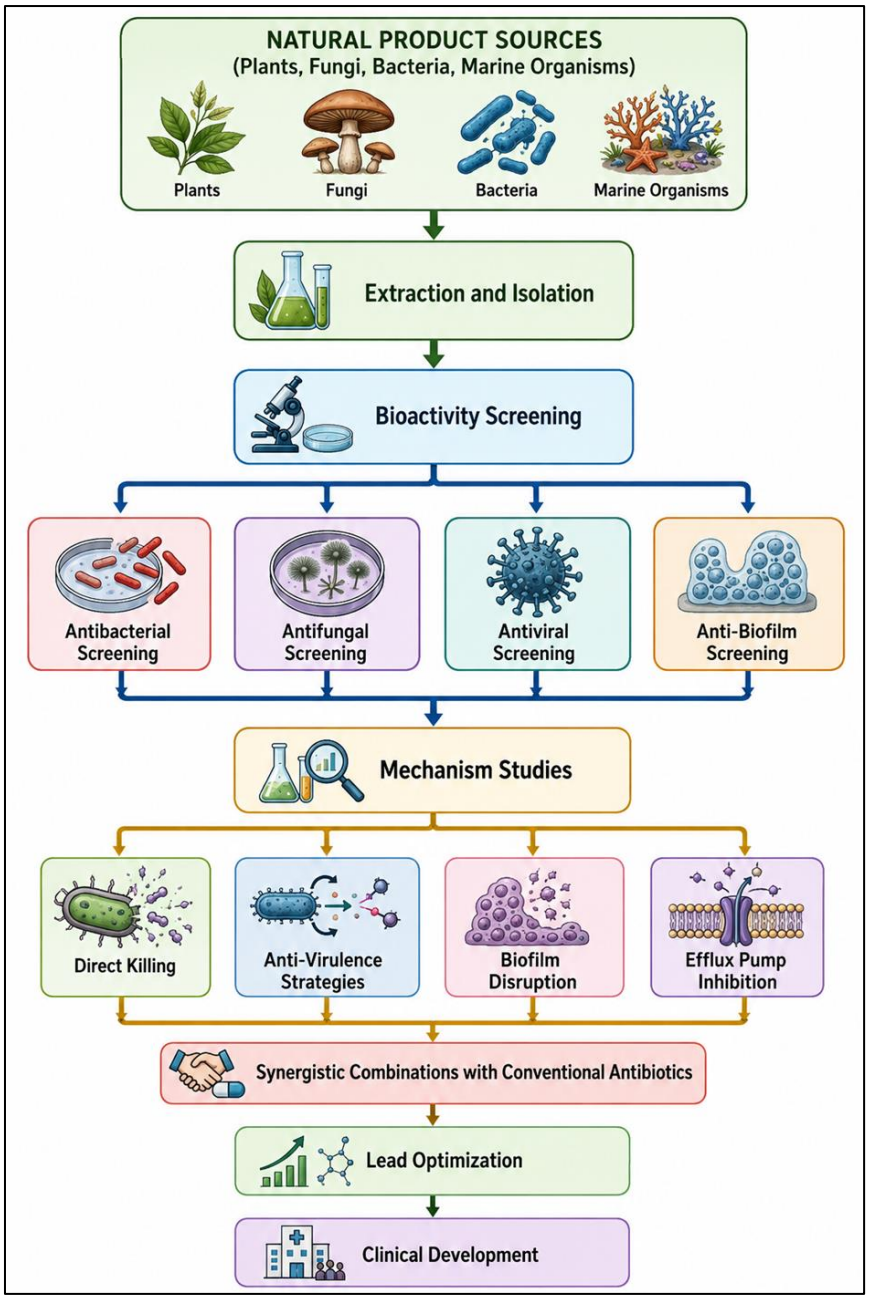

Figure 1: Strategies for Natural Product-Based Anti-Infective Discovery

6 CHALLENGES IN NATURAL PRODUCT ANTI-INFECTIVE DISCOVERY

6.1 Supply Sustainability

The sustainable supply of natural products is a significant challenge, particularly for compounds from rare or slow-growing organisms. Total synthesis and semi-synthesis are feasible for some compounds but may be economically challenging. Biotechnological production and synthetic biology approaches offer alternatives. The production of effective phyto-antimicrobials via metabolic engineering strategies has been explored as a means to address supply challenges (Sharma et al., 2022).

6.2 Clinical Development

Clinical development of natural product antibiotics faces challenges including toxicity, pharmacokinetics, and regulatory requirements. Critical challenges hampering the clinical use of plant-derived virulence-arresting drugs have been identified (Plant-derived virulence arresting drugs, 2023). The economic viability of natural product antibiotics is challenged by the limited return on investment. Public-private partnerships and push incentives are being explored to address this challenge.

6.3 Dereplication and Rediscovery

The rediscovery of known compounds remains a persistent challenge in natural product discovery. Advanced analytical techniques and databases have improved dereplication. Culture-independent approaches, including metagenomic screening, may identify novel compounds from unculturable organisms. The discovery of novel antimicrobials has significantly slowed down over the last three decades (Biological Dark Matter Exploration, 2022).

Here is Table 4, which outlines the major challenges, their impact, and potential strategies for overcoming obstacles in the discovery of new anti-infectives from natural products.

Table 4: Challenges and Strategies in Natural Product Anti-Infective Discovery

Challenge	Impact on Discovery Pipeline	Potential Solutions and Strategies
Supply Sustainability	Limited availability of raw source material, hindering large-scale production and development.	Sustainable cultivation practices, semi-synthesis or total chemical synthesis, large-scale microbial fermentation.
Rediscovery of Known Compounds	Diminishing returns from traditional screening methods, as known compounds are repeatedly isolated.	Advanced dereplication techniques (e.g., MS/MS networking), exploring unique/extreme ecological niches, utilizing genomic data.
Clinical Development Hurdles	Prohibitively high development costs, complex regulatory pathways, and market uncertainty for new antibiotics.	Increased public-private partnerships, specialized funding initiatives, regulatory incentives (e.g., market entry rewards).
Rapid Resistance Development	New compounds may face existing or rapidly emerging resistance, shortening their clinical lifespan.	Focus on novel targets/mechanisms, employing synergistic combinations, investigating resistance-modifying agents.
Poor Bioavailability	Excellent *in vitro* activity but failing *in vivo* due to poor solubility, stability, or absorption (pharmacokinetics).	Nanoparticle formulation and drug delivery systems, chemical derivatization to optimize drug-like properties.

7 FUTURE PERSPECTIVES

The future of natural product anti-infective discovery lies in the integration of emerging technologies and innovative strategies. Genomic approaches, including genome mining and bioinformatics, will enable the discovery of novel biosynthetic gene clusters. Metabolomic and chemical approaches will accelerate compound identification and dereplication. The application of artificial intelligence and machine learning will enhance predictive capabilities and accelerate lead optimization.

The development of predictive models for anti-infective activity and toxicity will facilitate lead optimization. The exploration of novel sources, including cultured organisms and synthetic biology, promises to expand chemical diversity. The integration of natural products with conventional antibiotics through synergistic combinations represents a promising direction for overcoming resistance. The development of anti-virulence strategies and biofilm-disrupting agents offers alternatives to traditional antibiotics that may reduce selective pressure for resistance development.

8 CONCLUSION

The AMR crisis has catalyzed a renaissance in natural product-based anti-infective discovery, driven by advances in genomics, metabolomics, and screening technologies. Natural products continue to offer the most promising source of novel antimicrobial agents, with historical successes including penicillin, streptomycin, and tetracycline. Emerging discoveries from plants, fungi, bacteria, and marine organisms exhibit activity against drug-resistant pathogens including MRSA, ESKAPE pathogens, and multidrug-resistant fungi. Antiviral natural products from diverse sources, including alkaloids, flavonoids, terpenoids, and phenolic lipids, have demonstrated activity against clinically significant viruses. Emerging strategies for overcoming resistance include anti-virulence approaches, biofilm disruption, efflux pump inhibition, and synergistic combinations with conventional antibiotics. Challenges including supply sustainability, clinical development, and rediscovery persist but are being addressed through technological advances and innovative approaches. Continued investment in natural product anti-infective research and development is essential for ensuring effective treatments for drug-resistant infections.

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