Chinese Journal of Natural Medicines

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Citation: Junbiao Yang, Jiwen Wang, Mengqun Liu, Xuzhe Zhou, Dong Feng, Hanxiang Jiang, Xinna Liu, Lu Chen, Ying Wang, Leveraging microbial natural products for pharmaceutical innovation: a vision of inspiration and future prospects, Chinese Journal of Natural Medicines, 2025, 23(9), 1047−1057. doi: 10.1016/S1875−5364(25)60971−X.

View online: https://doi.org/10.1016/S1875−5364(25)60971−X

Chinese Journal of Natural Medicines 23 (2025) 1047-1057

Contents lists available at ScienceDirect

Chinese Journal of Natural Medicines

journal homepage: www.cjnmcpu.com/

Review

Leveraging microbial natural products for pharmaceutical innovation: a vision of inspiration and future prospects

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ARTICLE INFO

Article history:
Received 6 July 2024
Revised 3 November 2024
Accepted 7 November 2024
Available online 20 September 2025

Keywords:
Microbial derivatives
Bioactive natural products
Marketed pharmaceuticals
Innovative biochemical entities
Pharmaceutical discovery

ABSTRACT

Microorganisms, abundant in nature, are prolific producers of a diverse array of natural products (NPs) that are fundamental in the development of innovative therapeutics. Despite their significant potential, the field faces considerable challenges, including the continuous emergence of potential health threats, as well as novel pathogen strains and viruses. The advent and implementation of advanced technologies, such as culture strategies, genomics mining, and artificial intelligence (AI), are facilitating a paradigm shift in pharmaceutical research, introducing innovative methodologies and perspectives. The development and maturation of these technologies have enhanced the exploration of microbial-derived NPs, thereby advancing pharmaceutical research and development. This review synthesizes recent developments in this context, emphasizing their applications in pharmaceutical discovery and development. Through systematic analysis and synthesis, it provides objective insights into the promising prospects and future direction of this essential field.

1. Introduction

Microorganisms, representing the most genetically and taxonomically diverse group of organisms on Earth, produce secondary metabolites that are essential in innovative pharmaceuticals [1, 2]. Since the discovery of penicillin by Alexander Fleming in 1928, microbial-derived natural products (NPs) have been widely applied in the treatment of infectious diseases [3]. Given the exceptional biological activity and broad applicability of microbial metabolites, microorganisms exceed other sources in the number of commercial drugs derived, establishing them as an indispensable resource in drug discovery [4–6].

However, the complex structure of most NPs presents significant challenges for chemical synthesis [7, 8], and the increasing incidence of drug resistance emphasizes the urgent need for novel natural drugs and advanced technologies [9]. The rapid advancement and comprehensive application of new technologies in NP discovery, analysis, identification, and synthesis—including nuclear magnetic resonance, omics, and data technology [10, 11]—has substantially accelerated the discovery of microbial NPs [12, 13]. Additionally, the exploration of diverse environments, such as marine and extreme ecosystems, has revealed abundant microbial resources and unique products [14, 15]. Currently, over 200 000 NPs have been identified, with microbial-derived entities comprising approximately 1/4, exceeding 48 000 [16], which demonstrates the substantial potential of microbial NPs. This review systematically examines the advancements in microbial NP research over the past decade, highlighting the essentia role of microbial resources and emerging technological innovations, which together provide objective and inspiring perspectives for practical applications in pharmaceutical discovery and development.

2. Microbial NPs: temporal dynamics and source analysis

From the perspective of resource acquisition, the ocean has emerged as a significant source of active NPs. Marine resources decreased from approximately 68% in 2015 to about 51% in 2023. Over the past decades, approximately half of the reported NPs have originated from the ocean, indicating that the exploration and utilization of marine microbial resources are increasingly becoming the primary pathway for discovering novel NPs [17, 18] (Fig. 1). This trend may be attributed to the saturation of terrestrial microbial resource exploration, with unexplored marine resources becoming a focus of research [19, 20]. Moreover, the ongoing development of deep-sea exploration has accelerated this transition [21].

Regarding species contributing to NP sources, fungi exhibit a marked upward trend. The proportion of reported NPs derived from fungi increased from approximately 40% in 2015 to about 84% in 2023. The similarities between marine and terrestrial fungi suggest their broad adaptability [22, 23]. The increase in fungal sources largely stems from the complexity and diversity of their metabolic pathways, providing the foundation for chemically and functionally diverse small molecule compounds [24, 25]. Conversely, bacterial-derived NPs show a significant decline, decreasing from approximately 54% in 2015 to about 4% in 2023 (Fig. 1). Al-

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https://doi.org/10.1016/S1875-5364(25)60971-X

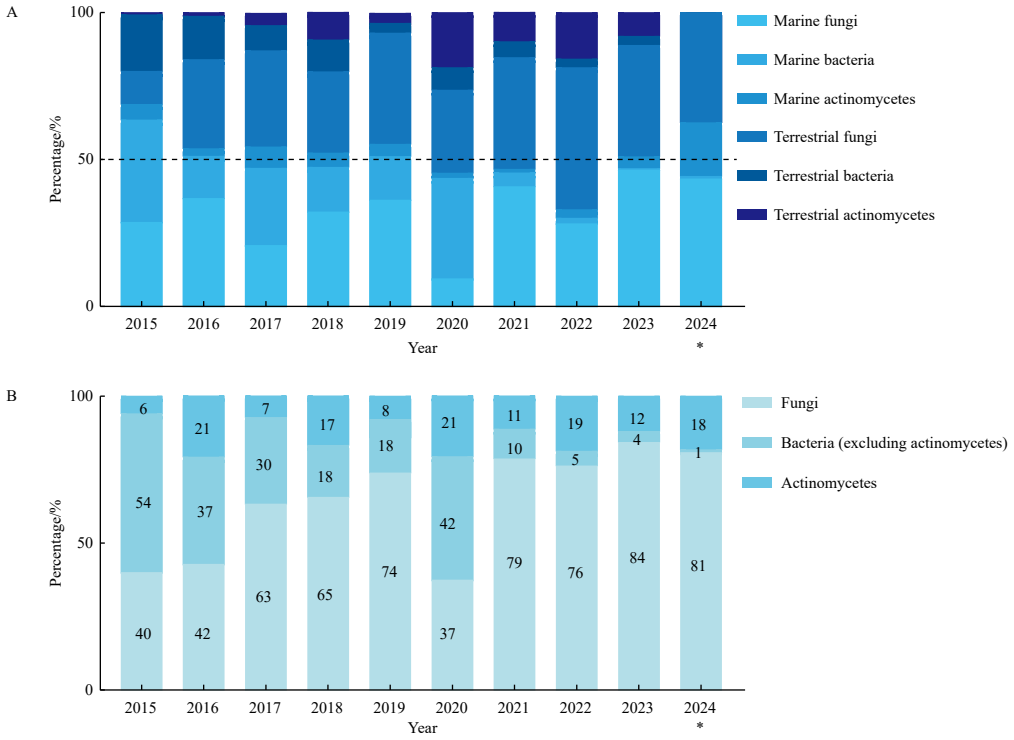

Fig. 1 (A) Microorganisms are categorized as marine or terrestrial and further classified by species into fungi, bacteria, and actinomycetes. A dotted line at the 50% mark is included for reference. (B) Distribution of fungi, bacteria, and actinomycetes as microbial sources of NPs over the past decade. The numbers in the figure represent the respective proportions. *: Data for 2024 were collected up to June.

though NPs of bacterial origin have decreased recently, they maintain promise as new technologies emerge [26]. Actinomycetes increased from approximately 6% in 2015 to about 12% in 2023. As an important source of antibiotics, actinomycetes continue to possess significant untapped potential and value [27].

3. Microbial sources: NPs and derived medicines

NPs from microbial sources demonstrate extensive bioactivities, encompassing antibiotics, antifungal, anti-cancer, anti-inflammatory, and anti-cardiovascular disease (CVD) properties [28–30]. Additionally, researchers continue to identify compounds with diverse pharmacological effects —spanning antiparasitic, anti-viral, and glycemic regulation—which expand the potential for translational applications [31] (Fig. 2).

3.1. Antibiotics

Pathogenic bacteria remain a significant threat to human health [32]. Antibiotics serve as compounds targeting bacteria for infection treatment and prevention. Although antibiotics have partially addressed infection concerns, the simultaneous rise in bacterial resistance and transmission rates poses an unprecedented challenge to global public health [33]. The proliferation of drug-resistant bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), and extended spectrum *β*-lactamase (ESBLs) producing bacteria, presents an urgent challenge requiring resolution, complicating treatment processes and increasing morbidity and mortality risks [34]. Statistics from 2019 reveal that bacterial infections ranked as the second leading cause of death globally, causing approximately 7.7 million deaths, representing 13.6% of total global mortality [35]. This situation underscores the critical need for coordinated international efforts to enhance infection prevention measures.

Microbial resources, particularly through their competitive ecological interactions, maintain a crucial position in antibiotic development. These organisms, through their NPs, establish an essential foundation for advancing new antibiotic therapeutics [36]. The distinctive molecular structures and bioactive mechanisms of these compounds, refined through evolutionary competition, enable them to address the significant clinical challenges posed by resistant strains, highlighting their importance in pharmaceutical research [37].

β-Lactams, representing the first discovered antibiotic class, maintain widespread clinical use due to their distinctive mechanism targeting bacterial cell walls through non-selective inhibition of penicillin-binding proteins crucial for peptidoglycan synthesis [38, 39]. This mechanism effectively compromises bacterial integrity, contributing to their efficacy while maintaining minimal side effects, establishing *β*-lactams as fundamental in anti-infective therapy [40]. Despite the global prevalence of *β*-lactam-resistant bacteria, microbial-derived NPs offer potential solutions. This prospect stems from microbial competition principles in ecological niches, suggesting NPs possess inherent mechanisms against these pathogens. Cephalosporins, comprising approximately half of these prescriptions, maintain their prominence through structural similarities and modifications that confer resistance to *β*-lactamase enzymes [41]. Cephalosporin C, a *β*-lactam antibiotic produced by *Mycobacterium acuminatum*, demonstrates notable stability and resistance to penicillinase degradation, potentially enhancing its effectiveness against various penicillin-resistant bacteria. Many current clinical cephalosporin antibiotics derive from natural cephalosporins. These semi-synthetic variants exhibit broader anti-bacterial spectra, enhanced activity, and improved pharmacokinetic properties. Such modifications improve stability and therapeutic effectiveness while fostering the development of diverse compounds with varying activity spectra, pharmacokinetic profiles, and clinical applications, expanding therapeutic options [42].

Ceftaroline fosamil, a fifth-generation cephalosporin prodrug, received Food and Drug Administration (FDA) approval for treating various infectious diseases in 2010. The FDA specifically authorized its use in adults with community-acquired bacterial

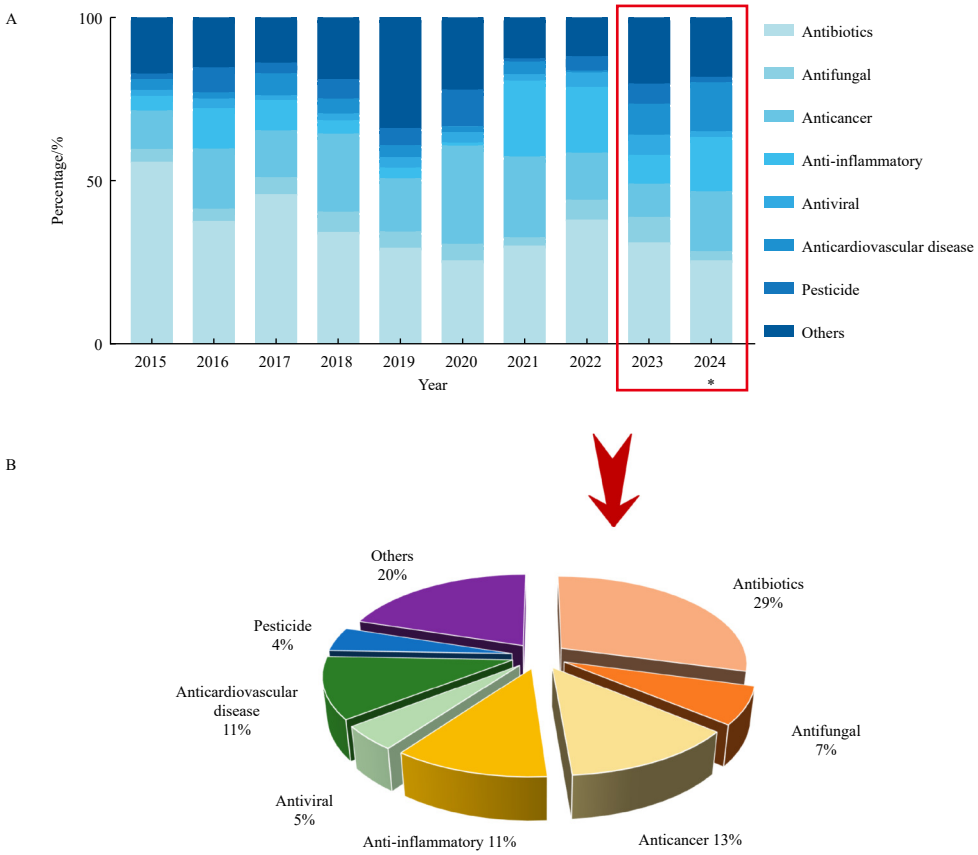

Fig. 2 (A) Analysis of biological activities of compounds. (B) Specific functions of compounds in 2023–2024. *Data for 2024 is up to June.

pneumonia (CABP) caused by *Streptococcus pneumoniae*, with or without bacteremia, based on clinical trial results. The European Medicines Agency (EMA) subsequently approved ceftaroline fosamil in 2012 for complicated skin and soft tissue infections, demonstrating its therapeutic versatility [43]. In 2024, the FDA approved Zevtera (ceftobiprole medocaril), a fifth-generation cephalosporin, for treating various infections, including *S. aureus* bacteremia (including right-sided infective endocarditis) in adults, acute bacterial skin and skin structure infections (ABSSSI), and CABP in pediatric patients aged 3 months to under 18 years [44]. This approval establishes Zevtera as the first *β*-lactam antibiotic specifically endorsed by the FDA for treating *S. aureus* infections, introducing a novel therapeutic option in clinical antibiotic therapy.

Combination therapy has gained increasing prominence, involving the concurrent or sequential administration of two or more drugs to achieve synergistic effects, expand the anti-bacterial spectrum, and combat drug-resistant bacteria [45,46]. Zerbaxa (ceftolozane/tazobactam), an antibiotic combination therapy, received FDA approval in 2014 and EMA approval in 2015. This combination incorporates fifth-generation cephalosporins and *β*-lactamase inhibitors, primarily indicated for treating complex abdominal and urinary tract infections. It exhibits effectiveness against Gram-positive bacteria and provides broad-spectrum coverage against Gram-negative pathogens, including multidrug-resistant and extensively drug-resistant strains of *Pseudomonas aeruginosa* and ESBLs-producing Enterobacteriaceae. However, its effectiveness against certain drug-resistant organisms such as *Staphylococcus*, *Enterococcus*, and *Acinetobacter* remains limited [47].

Exblifep (cefepime, emetazobactam) represents another combination of *β*-lactam/*β*-lactamase antibiotics that addresses resistance in Gram-negative bacteria, particularly resistance mediated by broad-spectrum *β*-lactamases. In 2024, both the FDA and the EMA approved Exblifep for treating adult urinary tract infections (including pyelonephritis) and hospital-acquired pneumonia (including ventilator-associated pneumonia), as well as for treating patients with bacteremia associated with these infections [48].

Glycopeptide antibiotics possess a highly modified heptapeptide structure, specifically targeting the bacterial cell wall component known as D-alanyl-D-alanine. Vancomycin, the first glycopeptide from *Streptomyces orientalis* for clinical treatment, effectively combats Gram-positive bacteria, including *S. pneumoniae*, *S. pyogenes*, and *Enterococcus* spp., with significant activity against MRSA [49]. In 2018, the FDA approved oral solution vancomycin hydrochloride (Firvanq, CutisPharma) for treating Clostridium difficile-associated diarrhea and enteritis caused by *S. aureus* (including methicillin-resistant strains). This oral formulation enhances treatment accessibility, potentially improving patient access to medical care [50].

Oritavancin, a semi-synthetic glycopeptide antibiotic derived from vancomycin's chloroeremomycin analog, functions through three bactericidal mechanisms: inhibiting transpeptidation, transglycosylation, and disrupting cell membrane integrity. Approved by the FDA in 2014 and the EMA in 2015, Orbactiv (oritavancin) represents the first FDA-sanctioned single-dose antibacterial drug for treating ABSSSI caused by susceptible Gram-positive bacteria in adults, including methicillin-sensitive and resistant *S. aureus*, various Streptococci, and *E. faecalis*. Orbactiv's single-dose efficacy matches traditional vancomycin treatment, reducing hospitalizations by 20% and significantly improving patient conditions within 48–72 h [51]. Following Dalbavancin and Sivextro, Orbactiv became the FDA's third approved antibiotic. Furthermore, another formulation of oritavancin, Kimyrsa (oritavancin), demonstrates rapid bactericidal activity against ABSSSI in adults caused by susceptible Gram-positive microorganisms, including MRSA. Compared to Orbactiv, Kimyrsa re-

duces infusion time substantially, thereby decreasing the incidence of infusion-related adverse reactions [52]. Given its exceptional therapeutic effectiveness, the FDA approved Kimyrsa in March 2021 for treating ABSSSI in adult patients, particularly those infected with MRSA [53].

Dalbavancin derives from a naturally occurring theophylline-like glycopeptide produced by the actinomycete *Nonomuria* spp. As a second-generation lipopeptide antibiotic, it exhibits potent anti-bacterial activity by inhibiting both cell wall synthesis and anchoring mechanisms simultaneously. In 2021, the FDA approved Dalbavancin for treating various Gram-positive microorganisms responsible for ABSSSI in both adults and children, including *S. aureus* (methicillin-sensitive and methicillin-resistant), *S. pyogenes*, *S. agalactiae*, *S. dysgalactiae*, the *S. anginosus* group (including *S. anginosus*, *S. intermedius*, and *S. constellatus*), and vancomycin-susceptible *E. faecalis* [54].

Macrolide antibiotics, characterized by 14 or 16-membered rings with lactone structures derived from *Streptomyces*, exert their anti-bacterial effects primarily through protein synthesis inhibition. Clarithromycin, a semi-synthetic macrolide antibiotic, demonstrates bacteriostatic activity against numerous Gram-positive bacteria, including *Streptococcus* spp., *S. aureus*, *Clostridium* spp., *Corynebacterium* spp., *Listeria* spp., *Haemophilus influenzae*, and *Neisseria meningitidis* [55]. Furthermore, it exhibits activity against *Chlamydia pneumoniae*, *Helicobacter pylori*, and several atypical mycobacteria. The FDA initially approved clarithromycin in 1993 [56]. In 2024, the FDA approved Voquezna Triple Pak (amoxicillin, clarithromycin, and vonoprazan) for preventing adult gastric ulcers caused by *H. pylori* infection [57]. The eradication of *H. pylori* presents significant challenges due to antibiotic resistance, insufficient acid suppression, and complex treatment protocols [58]. This combination therapy offers a promising approach to address current treatment limitations. However, studies indicate that dual therapy with vonoprazan and amoxicillin demonstrates comparable effectiveness in eradicating *H. pylori* as Voquezna Triple Pak [59].

Beyond *β*-lactams, glycopeptides, and macrolides, several other antibiotic types merit attention. Hetiamacin B, an amicoumacin group antibiotic isolated from *Bacillus subtilis*, demonstrated strong inhibitory activities against *S. aureus*, *S. epidermidis*, and *S. haemolyticus* including drug-resistant isolates, MRSA, methicillin-resistant *S. epidermidis* (MRSE), methicillin-susceptible *Staphylococcus aureus* (MSSA), methicillin-resistant *S. haemolyticus* (MRSH) and vancomycin-intermediate *S. aureus* (VISA), while showing minimal activity against Gram-negative bacteria [60]. Acremolin C, a novel alkaloid obtained from fungus *Aspergillus sydowii*, exhibited inhibitory activity against MRSA and MRSA, MRSE [61]. Additionally, 2-deoxy-sohirnone C, a sorbicillin derivative isolated from the mangrove endogenous fungus *Penicillium* sp. GD6, shows moderate anti-bacterial activity against MRSA [62]. Bionectin D, a rare diketopiperazine from the endophytic fungus Bionectria, demonstrated antibiotic activity against *Escherichia coli*, *S. aureus*, and *Salmonella typhimurium* ATCC6539 [63]. Beilunmycin, a novel virginiamycin antibiotic from *Streptomyces mangroveus* 2BBP-J2, exhibits inhibitory activity against Gram-positive bacteria MSSE, MRSE, MSSA, and VRE through protein translation inhibition [27].

3.2. Antifungal

Recent advances in medical technology have created conditions conducive to opportunistic pathogenic fungi, resulting in a significant increase in invasive fungal infections [64]. This increase encompasses established fungal diseases such as candidiasis, aspergillosis, cryptococcosis, and mucormycosis, while new pathogenic fungi continue to emerge, increasing the complexity and severity of these conditions. Annually, approximately 6.5 million cases of invasive fungal infections occur worldwide, leading to as many as 3.8 million deaths [65]. Antifungal drugs comprise a diverse class of medications designed to treat invasive fungal infections, encompassingvarious types, strengths, formulations, and applications. The eukaryotic nature of fungi, sharing similarities with human cells, limits the available molecular targets for drug development [66]. Consequently, comprehensive research into invasive fungal infections and the development of novel antifungal therapies have become critical priorities in modern medical research.

Candida infections represent substantial challenges regarding morbidity and mortality among immunocompromised patients, although natural bacteriostatic agents offer promising potential [67]. Echinocandins have established themselves as the primary therapeutic option for treating invasive candidiasis in current clinical practice, offering enhanced treatment safety and efficacy compared to polyenes or azoles [68].

Echinocandins constitute a novel class of antifungal agents produced by *Aspergillus* spp., which function by non-competitively inhibiting *β*-1,3-glucan synthase, thereby disrupting the synthesis of *β*-1,3-glucan in the fungal cell wall. Caspofungin emerged as the first approved echinocandin, followed by two additional echinocandin drugs, anifenzin and micafungin [69]. However, their clinical application remains limited due to poor oral bioavailability. This constraint led to the search for new compounds with similar glucan synthase inhibitory mechanisms and enhanced oral dosing capabilities.

Rezayyo (Rezafungin) represents a once-weekly intravenous echinocandin that inhibits 1,3-*β*-D-glucan synthase. The FDA approved it in March 2023 for treating candidemia and invasive candidiasis in patients aged 18 and above. Furthermore, it shows promise for preventing invasive fungal diseases in blood and bone marrow transplant recipients. That same year, the EMA approved Rezafungin for treating invasive candidiasis in adults [70].

Ibrexafungerp, derived from enfumafungin produced by the fungus *Hormonema carpetanum*, represents a first-in-class triterpenoid antifungal drug that inhibits the biosynthesis of fungal cell wall *β*-(1,3)-D-glucan similar to echinocandins. The FDA approved Brexafemme (ibrexafungerp) in 2021 as the first and only non-azole oral medication for treatingvaginal yeast infections, offering a crucial therapeutic option for patients with severe and frequently drug-resistant fungal infections [71].

Candida albicans colonizes mucosal surfaces, presenting a risk that can result in severe infections in both immunocompromised and healthy individuals [72]. In the search for effective antifungal treatments, Guignardone N, isolated from the endophytic fungus *Guignardia* spp., has shown activity against *C. albicans*. This compound inhibits *C. albicans* biofilms and enhances their susceptibility to fluconazole when used in combination with this antifungal agent [73].

3.3. Anti-cancer

Cancer persists as a leading cause of mortality worldwide, resulting in approximately 10 million deaths in 2020 [74]. The pursuit of anti-cancer agents remains a primary focus of medicine [75, 76], leading to substantial progress in discovering novel, potent, and safer therapeutic agents, while also reevaluating existing compounds with previously unrecognized anti-tumor properties [77, 78]. Research has identified numerous compounds with pronounced anti-cancer properties from natural sources, many of which have been incorporated into clinical therapies [79]. Microbial NPs contribute to over 60% of anti-cancer agents used in clinical practice [80]. These medications target various cancer hallmarks, including cellular immortalization, invasiveness, inflammation, evasion of programmed cell death (apoptosis), metabolic anomalies, resistance to multiple drugs, angiogenesis, genomic in-

stability, and circumvention of immune surveillance [81–83].

In the tumor microenvironment, cancer cells interact with immune cells *via* microfilament, suppressing immune cell cytotoxicity and enabling immune escape by cancer cells [84]. Consequently, microfilaments and their associated proteins present potential therapeutic targets. Cytolaxin, a fungal toxin, impedes polymerization through binding to filamentous (F) actin, thereby inhibiting cell division [85]. Eight cytolaxins extracted from the endophytic fungus *A. genus*, designated as asperchalasins A–H, exhibit cytotoxic effects on human lung cancer A-549 cells, indicating their potential as future anti-cancer therapeutics [86].

Cancer arises from uncontrolled cell growth caused by irregular expression of cell cycle proteins [87]. This understanding has made these regulators an attractive target for developing anticancer drugs [88, 89]. Midostaurin, an alkaloid derived from *Streptomyces* spp. was initially identified as a cell cycle protein inhibitor. The FDA approved it in April 2017 for treating adult patients with aggressive systemic mastocytosis, systemic mastocytosis with hematologic neoplasms, or mast cell leukemia [90].

During cancer progression, the overexpression of anti-apoptotic proteins and suppression of pro-apoptotic proteins inhibitcell apoptosis [85–87]. NPs that promote apoptosis present promising anti-cancer therapeutic options. Calicheamicins, enediyne anti-tumor antibiotics derived from *Micromonospora echinospora*, demonstrate anti-cancer effects by triggering DNA doublestrand breaks and apoptosis [91]. Additionally, several active compounds show potential for development into anti-cancer medications. Grincamycins, angucycline glycosides isolated from *S. griseus*, exhibit selective apoptosis induction in the human acute promyelocytic leukemia cell line NB4 through enhanced endoplasmic reticulum stress and increased intracellular reactive oxygen species, demonstrating significant anti-tumor activity [92].

Antibody drug conjugates (ADCs) represent innovative therapeutics utilizing monoclonal antibodies as carriers to deliversmall molecule cytotoxic drugs specifically to target tumor cells [93]. The distinctive combination of chemotherapeutic drugs and antibody drugs has led to significant ADC success in recent years [94]. In 2000, *N*-acetyl-gamma-calicheamicin, a cluster of differentiation 33 (CD33) antigen-targeted immunoconjugate, entered the market as a targeted therapy for acute myeloid leukemia. By 2017, the FDA approved Besponsa, the second calicheamicin-linked monoclonal antibody, an anti-CD22-directed antibody-drug conjugate for treating relapsed or refractory B-cell precursor acute lymphoblastic leukemia in adults [95].

Molecular chaperones, especially heat shock proteins (HSPs), participate in protein quality control under variousphysiological conditions [96]. HSP regulation is essential for cancer cell progression and invasion while contributing to resistance against anticancer therapeutic agents [97, 98]. Geldanamycin, obtained from *S. hygroscopicus*, represents a benzoquinone ansamycin anti-tumor antibiotic that inhibits HSP90 function by binding to its unique ADP/ATP binding pocket. Recent clinical trials have shown promising results, although HSP90 inhibitors have not yet received FDA approval [99]. Current research indicates that combining ADCs with free geldanamycin increases anti-cancer efficacy, potentiallyoffering a viable solution for improving ADC effectiveness in difficult-to-treat or resistant HER2-positive cancers [100].

Autophagy has emerged as a promising therapeutic strategy, garnering increased attention in clinical cancer research [101]. Chlorotheolides B, isolated from the endophytic fungus *Pestalotiopsis theae*, demonstrates anti-proliferative effects on human cervical cancer cell line HeLa through autophagy induction [102].

3.4. Anti-CVD

CVD represents a chronic condition affecting the heart and blood vessels, with atherosclerosis identified as its primarycause [103]. Atherosclerosis manifests as a chronic progressive disease characterized by lipid plaque accumulation within arterial walls, leading to arterial thickening, hardening, reduced elasticity, luminal narrowing, and disrupted lipid metabolism [104].

The past two decades have witnessed the emergence of various anti-atherosclerotic therapies, with lovastatin and its derivatives standing out as prominent lipid-lowering NPs [105]. Three lovastatin derivatives, aculeatones C, E, and F, derived from the endophytic fungus *A. aculeatus*, demonstratedsignificant inhibition of lipid accumulation in a human hepatoma HepG2 cell model [106]. Penihemeroterpenoids A–F, sesquiterpenoid compounds from the marine fungus *Penicillium herquei* GZU-31-6, showedminimal cytotoxicity against HepG2 cells while exhibiting lipid-lowering effects comparable to simvastatin through activation of the adenosine 5'-monophosphate-activated protein kinase (AMPK)/acetyl-CoA carboxylase (ACC)/sterol regulatory element binding protein 1c (SREBP-1c) signaling pathway [107].

Patients with CVDs exhibit vulnerability to thrombosis, which can lead to severe outcomes, including mortality [108]. Consequently, the development of novel anti-thrombotic drugs remains a priority. The marine-derived fungus *P. chrysogenum* Y19-1 yielded nine isolated compounds. Among these, ethyl formyltyrosinate, conidiogenone C, and dihydroresorcylide demonstrated anti-thrombotic activity, while ethyl formyltyrosinate, ergosterol peroxide, *N*-(2-hydroxypropanoyl)-2-aminobenzoic acid amide, and 4-methyl-5,6-dihydro-2*H*-pyran-2-one exhibited proangiogenic properties. Notably, ethyl formyltyrosinate emerges as the natural compound with the greatest potential for antithrombotic medication development [109].

Hypertension, the primary risk factor for CVDs, can be managed with angiotensin-converting enzyme inhibitors (ACEIs) [110, 111]. Six karnamicins, designated E1 through E6, extracted from *Lechevalieria rhizosphaerae* NEAU-A2, exhibited significant ACEI inhibitory activity, suggesting their potential efficacy in treating hypertension and related conditions [112].

3.5. Anti-inflammatory

Studies indicate that inflammatory diseases account for over 50% of deaths, encompassing ischemic heart disease, stroke, cancer, diabetes, chronic kidney disease, non-alcoholic fatty liver disease, autoimmune and neurodegenerative disorders [113]. Multiple safe and effective anti-inflammatory drugs are currently available, including aspirin and other non-steroidal anti-inflammatory drugs [114]. Furthermore, ongoing development of natural anti-inflammatory drugs continues to broaden treatment options [115, 116].

The endophytic fungus *Periconia* sp. TJ403-rc01 yielded two novel lanostane triterpenoids, pericinones A and B, which demonstrate moderate anti-inflammatory activity against nitric oxide production [117]. Additionally, seven novel indole diterpenoids, specifically penpaxilloids A–E, were isolated from marine fungus *Penicillium* sp. ZYX-Z-143. Among these compounds, penpaxilloid A functions as a non-competitive inhibitor of protein tyrosine phosphatase 1B, while penpaxilloid D demonstrates potent inhibition of nitric oxide production in lipopolysaccharide-stimulated RAW264.7 macrophages [118]. Moreover, streptinone, a novel naphthoquinone derivative isolated from *S. massiliensis*, was identified as an inhibitor of the Toll-like receptor-mediated nuclear factor-κB signaling pathway. It effectively suppresses the production of nitric oxide, prostaglandin E2, and pro-inflammatory cytokines include interleukin-1β (IL-1β), IL-6, and TNF-α. Thus, streptinone shows promise as a preventive and therapeutic agent for various inflammatory diseases [119].

3.6. Anti-viral

ificant threats, capable of triggering devastating global pandemics. During the initial two years of the Coronavirus disease 2019 (COVID-19) pandemic, approximately 14.9 million deaths

were attributed to the virus [120]. NPs continue to serve as essential reservoirs for developing prototype anti-viral agents [121–123].

The filamentous fungus *A. californicus* yielded two biogenetic intermediates, calipyridones B and C, which demonstratedmodest inhibition effects on SARS-CoV-2 plaque-forming ability [124]. Through global NP social molecular networking, a new triphenyl derivative, asperterphenyls A, was obtained from sponge-derived fungus *Aspergillus* sp. SCSIO41315. It exhibited potent inhibition against various H1N1 strains, indicating its potential as a pharmaceutical anti-viral agent. Furthermore, asperterphenyl A demonstrated neuraminidase inhibitory activity [125]. Similarly, three novel compounds, vanitaracin C, vanitaraphilone A, and 2-hydroxy-4-(hydroxymethyl)-6-methylbenzaldehyde were isolated from *Talaromyces* spp., all showing inhibitory effects against bovine leukemia virus [126].

4. NP mining: a nexus of technological innovation and accelerating exploitation

4.1. Microbial culture technology

Approximately 99% of microbial populations in nature cannot thrive under typical cultivation conditions, though they maintain metabolic activity and may eventually return to a cultivable state. Thus, developing microbial cultures remainsessential for drug discovery [127]. The challenges arise from the extensive numbers of uncultivated microbes in natural habitats, their competitive dynamics and prevalence, the complexity of simulating natural growth conditions, the slow growth rates of certain microbial species, and limitations in detection methodologies. These challenges are being addressed through emerging culture techniques [128].

4.1.1. Culturable microorganisms

The primary challenge in bacterial cultivation within laboratory settings stems from the inadequacy of growth environments and limited understanding of essential factors, including optimal breeding conditions, suitable temperatures, and required nutrients. Consequently, enhancing and modifying culture environments and techniques for microorganisms remains essential [129].

Ohmyungsamycins A and B are cyclic depsipeptides produced by *S. maritimus* strains *via* non-ribosomal peptide synthetases. Ohmyungsamycin A exhibits substantially higher activity against *Mycobacterium tuberculosis* and human cancer cells compared to Ohmyungsamycin B. To enhance Ohmyungsamycin A production, researchers optimized culture conditions, including sea salt concentration, inoculum size, and amino acid levels provided as building blocks. The A2-structural domain-engineered strain demonstrated a 3.8-fold increase in Ohmyungsamycin A yield and an 8.4-fold decrease in Ohmyungsamycin B yield under optimized conditions, relative to the wild-type strain under initial conditions [130].

4.1.2. Unculturable microorganisms

4.1.2.1 Co-culture

Co-cultures function as models to simulate interspecies competition among bacterial strains in natural habitats and stimulate the production of signaling molecules exchanged between bacteria, potentially generating novel compounds. A marine-derived *Streptomyces* spp., isolated from the periplasm of Panamanian organisms, underwent co-cultivation with human pathogens including *Bacillus subtilis*, MSSA, MRSA, and *Pseudomonas aeruginosa*. Co-cultivation of *Streptomyces* sp. PTY087I2 with these human pathogens resulted in increased yields of antibiotics granaticin, granatomycin D, and dihydrogranaticin B [131]. Furthermore, co-cultivation enhanced bioactivity against the Gram-positive human pathogens used in these experiments. *S. rhodochrous* MB037 was co-cultured with the fungus *Rhinocladiella similis* 35, derived from willow coral, leading tothe isolation of borrelidins J, which demonstrated significant antifungal activity against MRSA from the co-culture broth [132].

4.1.2.2 *In situ* culture

In situ culture encompasses diffusion chamber method, chip separation method, trap technique, Itip technique and capsule deposition.Throughadvanced diffusion chamber technology, a novel cultivation tool, the diffusion bioreactor, was effectively-developed for isolating and cultivating novel and previously difficult-to-cultivate bacteria [133].

For the first time, the technique of isolation microarrays was applied to marine sponges (*Xestospongia muta*), resulting in the discovery of a putative new bacterial species named *Alteromonas* sp. RKMC-009 [134]. This finding holds significant importance as *Alteromonas* sp. RKMC-009 demonstrates the ability to produce a novel *N*-acyl tyrosine with a rare *α*-methyl substituent within its aminoacyl portion, exhibiting anti-bacterial activity against gram-positive bacteria. Additionally, researchers have identified a novel depsipeptide antibiotic, teixobactin, derived from *Eleftheria terrae*, a *β*-proteobacterium previously challenging to cultivate. Teixobactin's unique feature lies in its unprecedented resistance profile, presenting promising prospects in antibiotic development [135].

4.1.2.3 *Microfluidics and cell sorting technology*

Cell sorting technology serves as an advanced biological tool frequently employed to isolate cells from complex microbial populations for subsequent culture. State-of-the-art technologies in this field include lasers and fluorescence-activated cell sorting (FACS), often integrated with microfluidics for enhanced performance and efficiency [136].

Microfluidics cultivation, based on distinct modes of microfluidic manipulation, comprises three categories of cell screening systems: perfusion flow mode, droplet mode and microarray mode [137]. Microfluidic technology has evolved into an essential platform for high-throughput experiments across various research fields, including microbiology [138]. Specializing in precise control, manipulation, and detection of complex fluids at the microscopic scale, the technology enables parallel detection of multiple uncultured microorganisms and successful acquisition of pure cultures of target microorganisms within brief periods. While microfluidic culture and analysis devices have become versatile tools for examining microbial interactions at the single-cell level, their manufacturing processes and technical requirements exceedthe complexity of traditional culture methods [139].

The utilization of a microfluidics-based high-throughput platform substantially increases the number and diversity of microbial cultures while enhancing the potential for cultivating and characterizing underexplored microorganisms [140]. Through the integration of microfluidics with FACS technology, microorganisms can be precisely and efficiently cultured in agarose-solidified droplets [141]. Additionally, a hybrid microfluidic chip constructed from surface-modified indium tin oxide glass and polydimethylsiloxane facilitates effective screening of thrombin inhibitors from NPs. These investigations collectively demonstrate the promising applications of microfluidics in exploring microbial-origin NPs [142].

4.2. Genome mining

Genome mining technology has evolved considerably over recent decades, driven by rapid developments in genome sequencing technology. It systematically identifies and analyzes biological genomes of compounds, connecting genes to molecules to discover novel or new secondary metabolites with desired biological activities [143]. These advances have become fundamental to drug

discovery efforts, particularly in microbial NP-derived technologies [144].

Currently, core enzyme mining serves as a primary tool for genome mining. Since the core enzyme catalyzing the formation of similar compound skeletons maintains sequence conservation, researchers can search for the gene encoding the core enzyme through homology comparison, followed by functional analysis of adjacent genes to identify complete biosynthetic gene clusters [145]. Gene-based mining represents another effective approach for discovering active NPs. Additionally, resistance genes provide valuable indicators for target discovery of NPs, bridging the connection between NPs, biosynthetic gene clusters and targets [146].

Heterologous expression of biosynthetic gene clusters represents a vital approach in NP mining and plays an essential role in studying and synthesizing marine microbial NPs. Through promoter engineering and heterologous expression of biosynthetic gene clusters, significant improvements in production yields have been achieved. For example, disorazol yield increased 7-fold [147], while the insecticidal macrolide spinosad, produced by *S. albus* J1074, achieved a substantial 328-fold increase in yield [148].

The development of new bioinformatics tools featuring enhanced search algorithms introduces novel approaches for genome mining. Antibiotic Resistance Targeted Searchers (ARTS), a notable web-based tool, specifically focuses ondiscovering NPs in bacteria through a targeted approach using self-resistance enzymes [149]. ClusterTools, another significant software, distinguishes itself by emphasizing computational identification of biosynthetic gene clusters using hidden Markov models of specific functional elements, particularly for antibiotic resistance gene-directed NP discovery [150]. Furthermore, a comparable pipeline to clusterTools is utilized for targeted genome mining of resistance genes from fungal species [151].

In contrast to existing bioinformatics tools, clusterTools aims to identify putative biosynthetic gene clusters of interest using hidden markov models of specific functional elements. Additionally, a similar pipeline to clusterTools is employedfor targeted genome mining of resistance genes from fungal species. Computational tools such as BiG-SCAPE facilitate sequence similarity analysis of biosynthetic gene clusters, while CORASON employs a phylogenomic approach tounderstand evolutionary relationships among gene clusters. These tools expand genome mining capabilities from individual genomes to entire genera, microbiomes, or strain collections [152].

4.3. Bioinformatics and artificial intelligence (AI)

AI methods have demonstrated remarkable progress in computational drug design, enabling bioactivity prediction and ab initio design of molecular targets [153]. Machine learning (ML), a subset of AI, has emerged as a powerful tool for discovering NPs, facilitating genome mining and biological activity prediction [154], thereby advancing drug discovery frontiers [155].

ML enables efficient exploration of chemical space, increasing the probability of discovering novel antibiotics compounds. A neural network trained on a growth inhibition dataset successfully predicted structurally novel molecules with anti-*Acinetobacter baumannii* activity, leading to the discovery of abaucin, an antibiotics compound demonstrating narrow-spectrum activity against *A. baumannii* [156]. Additionally, numerous studies have implemented integrated multi-omics approaches combined with ML to screen for novel NPs [157].

Deep neural network modeling successfully predicted molecules with antibiotics activity, leading to the identification ofhalicin through screening multiple chemical libraries [158]. This molecule, sourced from the center for drug repurposing, possesses a structure distinct from conventional antibiotics, yet demonstrates potent bactericidal activity against various pathogens, including *M. tuberculosis* and carbapenem-resistant Enterobacteriaceae (CRE) across a broad phylogenetic spectrum [159]. Notably, halicin effectively treated infections caused by Clostridium difficile and pan-drug-resistant *A. baumannii* (PDRAB) in a murine model, presenting promising potential for future antibiotics therapies.

Recent studies have introduced various methodologies to optimize ML model performance, including data augmentation, migration learning, comparative learning, and integration methods [160]. These methodologies enable ML models to effectively handle limited and imbalanced data distributions, thereby enhancing their predictive capabilities in NP discovery. Approaches such as transfer learning and multi-task learning have demonstrated particular effectiveness in improving the efficiency and performance of ML models for NP discovery [161]. The continuous evolution and implementation of ML technologies present significant opportunities and potential foridentifying novel NPs and understanding their biological mechanisms [162].

5. Discussion

The significance of microbial NPs in drug discovery has grown substantially in recent decades. Technological advances in resource development have established marine microorganisms, especially fungi, as vital sources of novel NPs. Thisdevelopment corresponds with the enhanced success rate of the global marine pharmaceutical pipeline, demonstrating the abundance; of marine microbial resources and the complexity of their metabolic pathways [163]. Beyond the conventional approach of screening antibiotic products from microorganisms, research in anti-cancer and cardiovascular therapeutic domains has produced significant outcomes [164]. A considerable proportion of active components in current cancer therapeutics derives from microorganisms, including anthracyclines, epothilones, bleomycins, and other antibiotic agents [165]. Additionally, progress in developing novel antithrombotic agents and ACEIs has improved the precision and effectiveness of CVD treatments.

The extension of microbial resource exploration from terrestrial to marine and extreme environments substantiallyincreases the diversity and accessibility of NPs for drug discovery [166, 167]. The distinctive conditions and intense competition in polar regions harbor numerous microorganisms producing diversenovel biologically active compounds. This expansion enhances the therapeutic arsenal against diseases while providingadditional combination possibilities for developing clinical treatment strategies [168, 169]. Notable examples include the β-lactam/β-lactamase inhibitor combination strategy (Table 1), partially driven by the prevalence of ESBLs-positive Gram-negative bacteria. This approach represents a crucialdevelopment in modern medicine, delivering enhanced therapeutic outcomes, decreased resistance development, improved patient compliance, and accelerated drug development progress [170].

The treatment of specific persistent diseases, including viral, fungal, and tumor-related conditions, remains heavily relianton extensive NP exploration [176–178]. This necessitates an expanded resource foundation for drug discovery, particularly considering microorganisms as a dominant group with considerable pharmaceutical production potential [179, 180]. Given the unique cultivation characteristics of microorganisms, improvements in cultivation methodologies are essentialfor comprehensive drug resource discovery [181]. Recent advances in co-culture, *in situ* culture, microfluidics, and cell sorting technologies have substantially enhancedtechnical capabilities and platforms for isolating and cultivating challenging microorganisms, including individual cells [158]. Additionally, interdisciplinary collaboration in NP discovery has gained significance, incorporating advancedtechnologies in bioinformatics, synthetic biology, and AI [182–184]. This collaborative ap-

Table 1 Representative applications of microbial-derived NPs between 2015 and 2024.

Brand name	Agent	FDA approval time	Activities	Sources
Avycaz	Ceftazidime/avibactam	February 2015	Antibiotic	*Acremonium chrysogenum* [171]
Zemdri	Plazomicin	June 2018	Antibiotic	*Micromonospora inositola* [172]
Fetroja	Cefderocol	November 2019	Antibiotic	*Acremonium chrysogenum* [171]
Brexafemme	Ibrexafungerp	June 2021	Antifungal	*Aspergillus* spp. [173]
Lupkynis	Voclosporin	January 2021	Immunosuppression	*Tolypocladium* [174]
Rezzayo	rezafungin	March 2023	Antifungal	*Aspergillus nidulans* [175]
Zevtera	ceftobiprole medocaril sodium	April 2024	Antibiotic	*Acremonium chrysogenum* [171]
Exblifep	cefepime, enmetazobactam	February 2024	Antibiotic	*Acremonium chrysogenum* [171]

proach facilitates genomic and metagenomic-driven NP discovery through the integration ofadvanced technologies. Moreover, the activation of dormant biosynthetic gene clusters and implementation of AI technologies for accurate prediction and discovery of novel NPs present new opportunities for disease treatment [185].

A critical challenge in the drug discovery process involves optimizing the balance between therapeutic efficacy of highly active microbial-derived NPs and their potential side effects [186]. Numerous microbial metabolites, including doxorubicin and bleomycin, have shown remarkable therapeutic potential in clinical cancer treatment. However, many promising compounds face limitations due to significant adverse effects or poor druggability. Targeted approaches, such as ADCs and precision drug delivery systems, present innovative solutions to these challenges. Notably, ADCs achieve targeted tumor cell destruction by utilizing antibody selectivity and employingmicrobial metabolites as "warhead" molecules to deliver cytotoxic drugs precisely to malignant cells [187]. These innovative therapeutic strategies have demonstrated significant clinical efficacy and show promise for improvingtreatments in refractory diseases through the incorporation of novel tumor antigen targets and more potent microbial NPs, potentially expanding the application scope of these leading compounds and enhancing therapeutic outcomes.

6. Conclusion

Research on microbial NPs represents a dynamic and continuously evolving field, where the development and application of novel technologies drive significant breakthroughs and discoveries. Sustained exploration and innovation continue to yield essential biological resources for medical science, advancing microbial NP-derived pharmaceuticals into a revolutionary era of healthcare innovation and revealing unprecedented therapeutic opportunities for diverse diseases.

Funding

This work was supported by Nanjing Science and Technology Bureau International, Hong Kong, Macao, and Taiwan Science and Technology Cooperation Program (No. 202401042).

Conflict of Interest

The authors report there are no competing interests to declare.

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