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•Commentary•

Natural products from untapped sources as a potent reserve against antimicrobial resistance crisis

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Since the discovery of penicillin in 1928, antibiotics have revolutionized modern medicine by effectively treating infectious diseases and saving countless lives. However, the widespread development of antimicrobial resistance (AMR) now threatens the efficacy and longevity of these critical drugs. A study published in The Lancet reported that bacterial AMR contributed to approximately 4.95 million deaths globally in 2019, with 1.27 million directly attributable to AMR (Fig. 1) [1]. Natural products (NPs) continue to play a crucial role in discovering new antibiotics, as they can bypass the penetration barriers of target bacteria in ways that synthetic methods cannot [2]. In the past two decades, traditional screening methods for antimicrobial drugs have become increasingly ineffective, underscoring the urgent need to identify novel molecules with unique mechanisms of action. Recently, Shukla *et al.* published a paper in *Cell*, unveiling clovibactin, a new antibiotic derived from an uncultured soil bacterium. This compound has shown efficacy in killing drug-resistant Gram-positive bacteria without promoting the development of resistance [3].

Most natural antibiotics are identified through the screening of laboratory-cultured, soil-dwelling strains. While sources such as actinomycetes have been extensively studied, approximately 99% of microbial species in various environments remain uncultured, representing a vast, untapped reservoir of potential novel antibiotics. In the referenced study [3], researchers overcame this challenge by incubating soil samples for 16 weeks under conventional culture conditions to facilitate the growth of previously uncultured bacterial species. The extracts from these cultures were then screened *in vitro* against *Staphylococcus aureus*, leading to the isolation of clovibactin, an antibiotic with significant antimicrobial activity. Clovibactin targets the pyrophosphate of multiple essential peptidoglycan precursors, including C55PP, lipid II, and lipid IIIWTA, thereby inhibiting cell wall synthesis (Fig. 2). In recent years, this research group discovered a series of natural antibiotics from uncultured bacteria, such as teixobactin (a cell wall synthesis inhibitor by binding to a highly conserved motif of lipid II and lipid III), lassomycin (an inhibitor of the ClpP1P2C1 protease), and amycobactin (an inhibitor of the SecY protein exporter) [4-6]. These discoveries highlight the potential of uncultured bacteria as sources of novel antibiotics, providing promising leads for developing treatments with a reduced risk of drug resistance.

Uncultured bacteria represent a vast, largely untapped chemical resource that often remains undetectable under conventional culture conditions. To address this challenge, the research group led by Kim Lewis developed the iChip, an innovative culturing device [4-6]. The iChip comprises multiple parallel chambers, each covered with a semi-permeable membrane and submerged in a suspension containing bacteria and their native environmental components. This design preserves the essential nutrients and growth factors necessary for bacterial growth. The iChip features numerous miniature openings, ensuring that each chamber isolates approximately one bacterial cell, thus facilitating simultaneous isolation and cultivation. Once colonies form—a critical step—they can be transferred to a conventional Petri dish for further incubation and extraction.

In addition to the traditional sources of NPs, such as plants, bacteria, and fungi, other resources like animal venoms have shown promise in antibiotic development due to their ability to disrupt bacterial membranes [7]. However, some potential sources remain underexplored due to accessibility challenges. Marine environments, for instance, are known to harbor diverse natural antibiotics, such as ilamycins [8]. Similarly, extreme environments like hypersaline hab-

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These authors have no conflict of interest to declare.

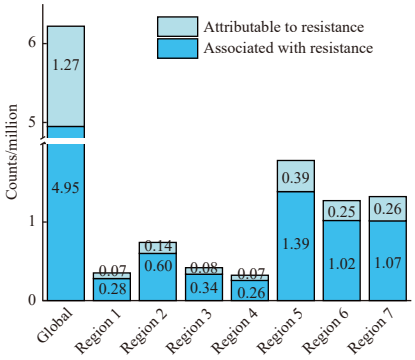

Fig. 1 The number of deaths attributable to and associated with bacterial AMR by regions (Region 1: Central Europe, Eastern Europe, and Central Asia; Region 2: High income; Region 3: Latin America and Caribbean; Region 4: North Africa and Middle East; Region 5: South Asia; Region 6: Southeast Asia, East Asia, and Oceania; Region 7: Sub-Saharan Africa).

itats, acid mine drainage, glaciers, and permafrost [9] are known to contain species that have developed specialized survival mechanisms in harsh conditions, potentially leading to the discovery of novel NPs. Exploring these unique environments is crucial, but it must be approached with caution to prevent anthropogenic impact and contamination. Further research is needed to replicate the conditions of these ecosystems in the laboratory effectively, which is essential for cultivating and studying the sampled species.

Additional methods to explore untapped natural sources include genome mining, which leverages existing knowledge to uncover biosynthetic gene clusters (BGCs) and corresponding natural antibiotics across different strains through phylogenomics-guided approaches. This strategy, when combined with unconventional cultivation techniques such as *in situ* cultivation, heterologous expression, and chemical synthesis, can significantly expand the chemical diversity of natural sources by activating silent operons typically dormant under the standard physical conditions. Furthermore, the branch points of phylogenetic trees offer opportunities to discover novel enzymes that mediate chemical modifications, potentially leading to the identification of new classes of natural antibiotics. Advanced tools in genome mining and deep learning are increasingly capable of predicting innovative antibiotics and their targets, enhancing the efficiency of these explorations [10-11]. An intriguing aspect of this research is that microorganisms producing antibiotics often co-express resistance genes for self-detoxification. These resistance-related genes can serve as valuable markers for identifying novel natural antibiotics and vice versa. Unlike traditional screening methods, these genome mining techniques can broaden the scope of antimicrobial discovery, offering potential relief from the pressures imposed by multidrug-resistant pathogens and the scarcity of viable antimicrobial targets.

Untapped natural resources represent a critical reservoir in the face of the urgent AMR crisis. The challenge lies not only in efficiently identifying these resources but also in avoiding the substantial effort involved in re-discovering

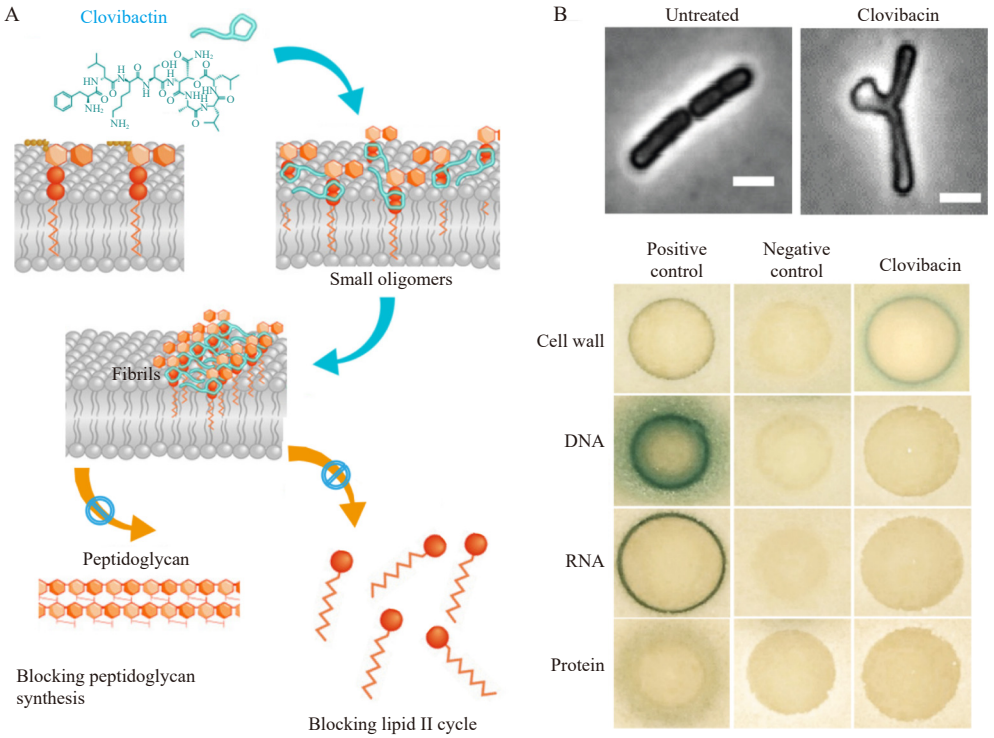

Fig. 2 The antibacterial mechanism of clovibactin. (A) Clovibactin sequestrated multiple essential peptidoglycan precursors by wrapping around the conserved pyrophosphate module and forming supramolecular fibrils on the cell membrane, which further interfered with the cycle of lipid II. (B) Expression of LacZ was specifically induced by clovibactin in *B. subtilis* P_{ypuA}-*lacZ*, indicative of interference with cell wall biosynthesis and treatment of *B. subtilis* with clovibactin induced cell-shape deformations as visualized by phase-contrast microscopy.

known compounds. To this end, dereplication methods are essential. By integrating these methods with transcriptome analysis, researchers can predict novel compounds in advance [12]. Another promising approach is differential screening, which compares different species or variations within the same species, focusing on differences in sensitivity and gene profiles [13]. This technique helps bypass the discovery of known NPs and those that are toxic, either selectively or universally. It also identifies selective antibiotics that could play a crucial role in circumventing the AMR crisis, especially those induced by broad-spectrum antibiotics.

Traditional screening platforms have generally failed to yield novel antibiotics from conventional sources. It is anticipated that the next generation of antibiotics, characterized by innovative structures and mechanisms of action, will be discovered by extensively mining vast gene pools, exploring uncultured bacteria, and tapping into other previously underexplored species. These advancements will be supported by an enhanced understanding of microbial biology and significant technological innovations (Fig. 3).

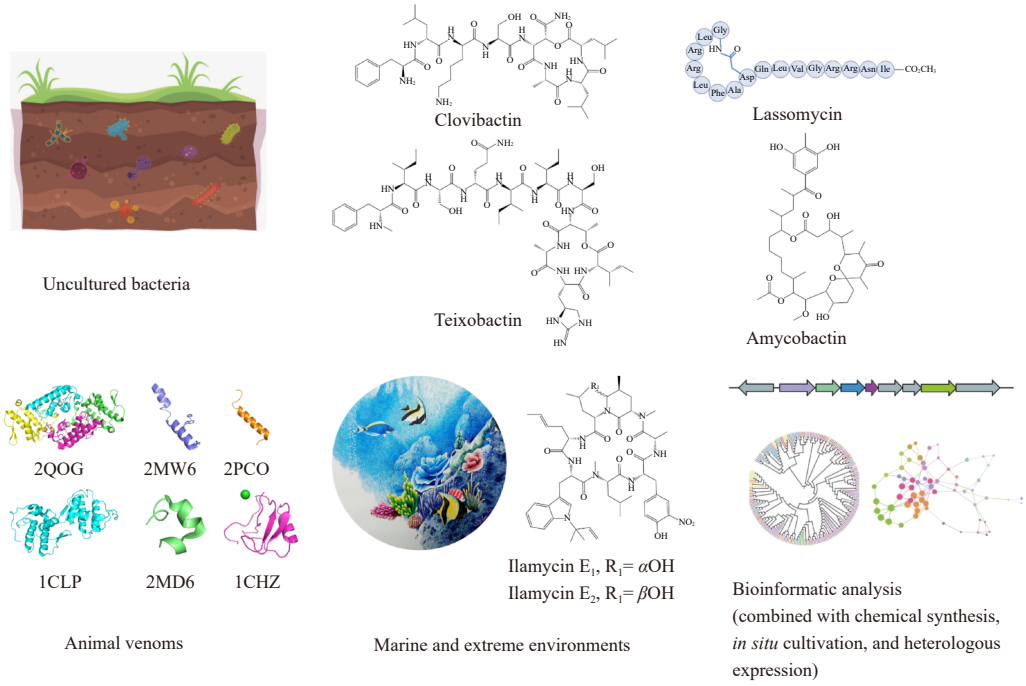

Fig. 3 NPs from untapped sources as a potent reserve against AMR crisis.

References

[1] Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis [J]. *Lancet*, 2022, **399**(10325): 629-655.

[2] Lewis K. Antibiotics: recover the lost art of drug discovery [J]. *Nature*, 2012, **485**(7399): 439-440.

[3] Shukla R, Peoples AJ, Ludwig KC, *et al*. An antibiotic from an uncultured bacterium binds to an immutable target [J]. *Cell*, 2023, **186**(19): 4059-4073.

[4] Ling LL, Schneider T, Peoples AJ, *et al*. A new antibiotic kills pathogens without detectable resistance [J]. *Nature*, 2015, **517**(7535): 455-459.

[5] Gavrish E, Sit CS, Cao S, *et al*. Lassomycin, a ribosomally synthesized cyclic peptide, kills *Mycobacterium tuberculosis* by targeting the ATP-dependent protease ClpC1P1P2 [J]. *Chem Biol*, 2014, **21**(4): 509-518.

[6] Quigley J, Peoples A, Sarybaeva A, *et al*. Novel antimicrobials from uncultured bacteria acting against *Mycobacterium tuberculosis* [J]. *mBio*, 2020, **11**(4): e01516-e01520.

[7] Samy RP, Stiles BG, Franco OL, *et al*. Animal venoms as antimicrobial agents [J]. *Biochem Pharmacol*, 2017, **134**: 127-138.

[8] Ma J, Huang H, Xie Y, *et al*. Biosynthesis of ilamycins featuring unusual building blocks and engineered production of enhanced anti-tuberculosis agents [J]. *Nat Commun*, 2017, **8**(1): 391.

[9] Shu WS, Huang LN. Microbial diversity in extreme environments [J]. *Nat Rev Microbiol*, 2022, **20**(4): 219-235.

[10] Alanjary M, Kronmiller B, Adamek M, *et al*. The antibiotic resistant target seeker (ARTS), an exploration engine for antibiotic cluster prioritization and novel drug target discovery [J]. *Nucleic Acids Res*, 2017, **45**: W42-W48.

[11] Stokes JM, Yang K, Swanson K, *et al*. A deep learning approach to antibiotic discovery [J]. *Cell*, 2020, **180**(4): 688-702.

[12] O'Rourke A, Beyhan S, Choi Y, *et al*. Mechanism-of-action classification of antibiotics by global transcriptome profiling [J]. *Antimicrob Agents Chemother*, 2020, **64**(3): e01207-e01219.

[13] Johnson EO, LaVerriere E, Office E, *et al*. Large-scale chemical–genetics yields new *M. tuberculosis* inhibitor classes [J]. *Nature*, 2019, **571**(7763): 72-78.

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