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Harnessing microbial secondary metabolites for modern medicine: A review

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Abstract

Microbial secondary metabolites have been an essential source of drug discovery for more than eight decades, and are currently influencing modern medicine, with an estimated half of all approved pharmaceuticals being of microbial natural product origin. Bacteria, fungi and actinomycetes produce these low-molecular-weight compounds, which exhibit remarkable chemical diversity and high biological activity, thus yielding clinically important antibiotics, antifungals, immunosuppressants and anticancer agents. Despite this achievement, therapeutic innovation has been limited by high rediscovery and an abysmal lack of contact between microbial genetic potential and experimentally observed metabolites. Genomic examination of biosynthetic gene clusters (BGCs) coded in microbial genomes indicates that most are silent or cryptic in standard laboratory environments, and that most environmental microorganisms are recalcitrant to growth, in total representing a huge pool of undiscovered chemical diversity. Recent developments in the field of genome mining, metagenomics, metabolomics, heterologous expression, epigenetic modulation, synthetic biology and gene-editing technologies like CRISPR-Cas9 have changed the discovery of secondary metabolites with systematic predictions, activation, and optimisation of these hidden pathways. This review attempts to synthesize vital insights along with recent computational and experimental studies to challenge microbial secondary metabolite biosynthesis, contemporary discovery strategies, and therapeutic uses.

Keywords: Secondary Metabolites; Biosynthetic Gene Clusters; Genome Mining; Synthetic Biology; Antimicrobial Resistance; Novel Therapeutics

1. Introduction

The secondary metabolites of microorganisms have had an immense impact on modern pharmaceutical research, occupying a significant percentage of the most effective agents in the treatment of infectious diseases, malignancies and immune-mediated syndromes [1][2][30][20]. In 1928, Alexander Fleming discovered penicillin in the filamentous fungus, *Penicillium notatum*, an event that transformed the treatment of bacterial infections and placed microorganisms as the leading sources of pharmaceutical agents [1][2][30]. Later systematic screening efforts, especially of the actinomycetes, produced antibiotics of the class streptomycin, tetracycline, erythromycin and chloramphenicol; these represent about 80% of clinically used natural antibiotics and represent a chemical diversity of structure and activity [2][3][7]. In addition to antibacterials, microbial secondary metabolites have also provided antifungal agents, immunosuppressants, as well as anticancer drugs and natural products or natural product derivatives now form one-half of all approved pharmaceuticals globally [2][4][30][20]. Over 35,000 microbial secondary metabolites have thus far been reported, and about 95% of them are biologically active and include remarkable chemical and pharmacological diversity [1][5][23][24].

Although this has been a historical success, pioneering new drugs being discovered by microbial sources have been found less often, thus creating a so-called discovery void, which is well known [20]. Global spread of antimicrobial

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resistance has never been this high and is itself a factor of critical concern in this crisis, with the estimates of the resistant infections causing 1.27 million deaths per year [6]. Though there were sixteen new antibiotic classes discovered in the period 1930-1960, only six new ones have been forthcoming in the last five decades, mainly because of scientific and economic limitations [7]. Culture-based screening has been impeded by large rediscovery rates, as well as because microbial genome has far more biosynthetic potential than can be observed by experimental measurements [1][20]. Genomic studies have shown that most microorganisms, specifically the Actinomycetes, harbor more than tenfold the biosynthetic gene clusters (BGCs) compared to known metabolites, with most of them being in an inactive state under typical laboratory conditions [1][8][23][37]. To make this task even more difficult, most microorganisms that inhabit the environment are unculturable, which makes their chemical repertoire largely inaccessible [9][37]. The intersection of silent BGCs, uncultured microbial diversity, and increasing multidrug resistance is an indicator of the urgency of discovery approaches [23][20].

The present changes in technology are fundamentally transforming microbial natural products investigation. The biosynthetic potential of cultured and uncultured microorganisms can now be interrogated on a high-throughput scale in terms of genome sequencing, metagenomics and metatranscriptomics [9][10][23][37]. AntiSMASH (version 8.0) represents a genome-mining platform, which supports systematic discovery and classification of BGCs in a wide range of taxa through profile hidden Markov models and curated biosynthetic rules [11][12][13]. In addition to these experimental methods, further complementary approaches to the study of metabolism have been used to access previously inaccessible metabolites and facilitate the rational design of new analogues with improved pharmaceutical properties: heterologous expression in genetically tractable hosts, epigenetic modulation to reactivate silent pathways in fungi, and metabolic engineering using synthetic biology [8][14][15][16][23].

This study reviews microbial secondary metabolites and their biosynthetic pathways, modern methods of their discovery, and treatment. Combining historical insights with state-of-the-art genomic, computational and engineering techniques, the review aims to elucidate how historical bottlenecks in discovery may be overcome, as well as provide a future roadmap on how microbial secondary metabolites can be used as a platform to develop new therapeutics [23][20][24].

2. Therapeutic Applications and Clinical Significance

2.1. Antimicrobial Agents and Response to Resistance Mechanisms

Microbial secondary metabolites remain the foundation of modern antimicrobial therapy, encompassing structurally diverse compounds that target bacterial, fungal, and parasitic pathogens through different mechanistic pathways. It has been demonstrated that habitat disturbance and effect on hostparasite interactions, e.g. in swamp rats, can be complicated and can affect both parasite abundance and host persistence, highlighting the ecological context of parasitic infections [50]. In Ghana, intestinal parasitic infection is a major health issue of concern, and the threat of zoonotic infection highlights the importance of sustaining surveillance and mass education to reduce disease burden [48]. Traditionally, the representatives of the genus *Streptomyces* have provided many historic antibiotics, including streptomycin, tetracyclines, macrolides, and chloramphenicol, which inhibit protein synthesis by binding complementary ribosomal interfaces [2][7]. The structural heterogeneity caused by nonribosomal peptide synthetases (NRPSs) and polyketide synthases (PKSs) has enabled the wide-ranging antimicrobial activity against both Gram-positive and Gram-negative bacteria [2][7][11].

The increase in multidrug resistance, particularly in methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci, has led to the development of next-generation therapeutics with engineered properties to avoid known resistance mechanisms. Improved accuracy and efficiency in outbreak management using artificial intelligence and genomic surveillance have been shown to be more effective and accurate when used to detect and respond to outbreaks of infectious diseases, which explains why technological innovations are so crucial to the practice of public health [47]. The recent findings in U.S. hospitals show that optimized antimicrobial stewardship initiatives enhance clinical outcomes and produce significant economic savings, and hence the necessity to develop strong stewardship initiatives to reduce the effects of antimicrobial resistance [42].

The examples of such strategic changes of vancomycin are lipoglycopeptides, such as dalbavancin and oritavancin, which have increased binding affinity with bacterial cell walls and strong activity against resistant Gram-positives [4][12]. Also, there are enzymatic approaches, including the MRSA-specific endolysin F12, a therapeutic that specifically cleaves unique cell-wall components, providing a reusable therapeutic option and initial promising efficacy [4].
The increase in the antimicrobial repertoire, recent studies of the previously uncultivated microorganisms have also provided new metabolites, such as kitamycobactin and amycobactin, that have potent activity against multidrug-

resistant *Mycobacterium tuberculosis* by disrupting the necessary protein-translocation and proteolytic pathways [4]. The metabolic state dependent potentiation of antibiotics has become a new paradigm of therapy; in this case, intracellular nutrient metabolites enhance antibiotic activity in persister cells and biofilm communities and generate significant improvements in bactericidal activity, with translational potential in preclinical animal models [15].

2.2. Anticancer and Immunomodulatory Metabolites

Microbial secondary metabolites have made enduring contributions to oncology, providing chemotherapeutic agents that interfere with genomic integrity, nucleic acid production, and cell viability. Doxorubicin, a byproduct of *Streptomyces peucetius* is one of the foundations of anticancer therapy, as it has been shown to work by intercalating DNA, inhibiting topoisomerase II, and leading to an oxidative stress that ultimately causes apoptosis [4][32][35][38]. Later structural modifications have produced derivatives like epirubicin, which mitigate the adverse effects of cardiotoxicity, and complex delivery vehicles, such as thermosensitive liposomal encapsulations, which increase intratumoral targeting and reduce systemic off-target delivery [4]. Bleomycin and actinomycin D are other microbial agents that also induce DNA strand scission and apoptotic cascades, and their therapeutic use in malignancies in both pediatric and adult malignancies has a long history [2][4][7]. In addition to the main cytotoxic processes, microbial metabolites are also recognized to possess an immunomodulatory potential. As an example, doxorubicin was reported to increase antitumor immunity through the upregulation of immune checkpoint signaling and improvement of T-cell cytotoxicity, which strengthens its therapeutic interaction with immunotherapeutic agents [32]. The cyclosporine family, which was identified in *Tolypocladium inflatum*, has essentially changed the immunosuppression realm by inhibiting the activation of T-cells by the calcium-regulated enzyme calcineurin, thereby enhancing the success of transplants and easing the treatment of autoimmune and hematological diseases [31][34].

2.3. Hypocholesterolemic and Metabolic Agents

Statins are commercially successful microbial secondary metabolites produced by the species of *Aspergillus* and *Trichoderma*, and are routinely used to reduce cardiovascular risk through competitive inhibition of 3-hydroxy-3-methylglutaryl-CoA reductase [4]. Besides lipid-lowering effects, statins also have pleiotropic immunomodulatory effects, and they are promising antimicrobial adjuvants. Modern studies have shown that statins undermine the integrity of the MRSA membrane and can reverse the resistance of 2-lactam antibiotics, therefore, supporting their repurposing in combination therapy programs [4]. Ongoing discovery of fungi secondary metabolites that regulate glucose homeostasis, lipid metabolism, and mitochondrial activity continues to increase the therapeutic options of metabolic disorders [3][4]. Combined, these results highlight the breadth of clinical and economic applicability of microbial secondary metabolism, not just in the traditional antimicrobial and oncologic uses [3][6].

3. Challenges and Limitations in Secondary Metabolite Development

3.1. Technical and Economic Barriers

Although there have been significant advances in genome mining, the synthesis of secondary metabolites into therapeutics which could be used clinically has been hindered significantly by large technical and financial obstacles. The elevated attrition rates in the development process are indicative of the strict specifications of the pharmacokinetics, pharmacodynamics, safety, and manufacturability [36]. Many natural products have sub-optimal physicochemical characteristics, such as low solubility, low permeability of the membrane, and high clearance by the metabolism, making them hard to use at a systemic level [36]. Although efforts in medicinal chemistry can alleviate these characteristics, these optimizations require special skills and resources that are not typically available in the academic research setting [36]. Manufacturing using fermentation is another area of complexity, as the best production parameters differ greatly amongst microbial producing strains and require significant strain and process optimization to reach commercially viable titers [22]. The regulatory requirements of natural product-derived therapeutics place more stringent demands than synthetic drugs that require extensive source characterization, identity testing, potency and batch-to-batch consistency analysis [36]. These obstacles are further aggravated by the unfavorable economic incentives to develop antibiotics, such as low market returns and shortened useful lifetime of effective patents, which have sparked a massive dumping of antibiotic research and development by the pharmaceutical industry [36][39]. As a result, academic and publicly funded organizations are currently producing large numbers of early-stage candidates but often do not have facilities to drive them towards late-stage preclinical and clinical development [36][39].

3.2. Silent BGC Activation and Production Optimization

Despite the huge discovery of biosynthetic potential by utilizing genome mining, a significant proportion of biosynthetic gene clusters (BGCs) exist as silent or inexpressible, thus restricting the quantity of metabolites available to perform

comprehensive characterization and further development. Heterologous expression remains a consistent problem due to the heterogeneity of the compatibility between donor pathways and hosts. For example, fungal BGCs do not express efficiently in bacterial hosts due to the differences in post-translational regulation and cellular structure [22][26]. Transfers and expression of large BGCs require the use of more sophisticated cloning systems, and expensive optimization of codons requires the synthesis of genes, which also limits scalability [22].

It is not uncommon to observe low metabolite titers even in cases where expression is attained, and strategies to employ epigenetic activation can result in the activation of multiple pathways at the same time, making it difficult to purify [26]. The processes that control silent BGC activation are not fully understood, and the environmental factors that initiate the process of metabolite production are hard to recreate in the laboratory cultures [26]. Based on this, optimization of conditions, culture and fermentation is still an extensive labor-intensive process that may need a significant amount of empirical screening to improve yield and selectivity [6][22].

3.3. Antibiotic Resistance and Loss of Efficacy

The emergence of antimicrobial resistance at a very rapid rate is one of the fundamental constraints to the long-term effect of antibiotics of the second generation that are derived through secondary metabolites. The resistance mechanisms include enzyme drug inactivation, alteration of targets, decreased intracellular accumulation, and horizontal gene transfer [33][39]. Worryingly, the emergence of resistance to new antibiotics is more common in years than decades, and it is influenced by the excessive use of antibiotics, environmental selection pressure, and effective genetic cross-contamination between bacteria [33][36][39].

Countermeasures efforts, including the use of β-lactamase inhibitors, have shown temporary results but often have the side effect of favoring new forms of resistance, thus requiring the maintenance of new classes of inhibitors [4][36]. Policy frameworks and advocacy strategies on federal, state and local levels have demonstrated the possibility to decrease unnecessary antibiotic use and improve prescribing patterns implying that interdisciplinary collaboration and consistent data gathering are key to long-lasting effectiveness [43]. The latest combinatorial therapies, such as sulbactam-durlobactam and diazabicyclooctane-based, portray advancements but also highlight the repetitive character of resistance control [4]. In conclusion, the evolution of resistance is inevitable, and there is a need to continue efforts on the discovery, optimization, and stewardship of secondary metabolites to maintain clinical activity [33][36][39]. The major efforts to encourage responsible antibiotic use and development of new antimicrobial agents, such as expanded stewardship programs and public-private partnerships, are essential for addressing the growing threat of antimicrobial resistance [46].

4. Advanced Screening and Identification Techniques

In addition to genetic manipulation, parallel advances in screening and identification technologies are required to hasten the discovery pipeline of microbial secondary metabolites. Modern screening techniques often go beyond the very high-throughput brute-force techniques to adopt more advanced, data-driven techniques [23]. New screening regimens currently emphasize the discovery of less familiar microorganisms, application of optimized growth and fermentation environments to induce the regioselective expression of cryptic biosynthetic pathways, the use of super-sensitive and highly selective bioassays, and early in vivo screening to focus on leads of interest [37][8]. For instance, cocultivation, when specific microbial species are grown together, can induce interspecies interactions that trigger the expression of silent BGCs and lead to the synthesis of non-accessible bioactive metabolites in monoculture [21]. Techniques Direct metabolite profiling (direct injection mass spectrometry or NMR), along with modern informatics software, is used regularly to chemotyping and metabolomics of culture collection-derived and natural sample-derived strains, thus enabling rapid identification and dereplication [23]. Techniques such as MALDI Imaging Mass Spectrometry (MALDI-IMS) and MALDI Fourier Transform Ion Cyclotron Resonance Mass Spectrometry (MALDI-FTICR MS) have significantly improved the spatial and temporal localization of emerging metabolites in microbial colonies and have provided real-time localization of the complex metabolic interactions [23]. By extension, the transcription of BGCs can be selectively targeted using small-molecule signalling compounds or environmental stimuli, which can be used to activate dormant pathways and increase natural product libraries by adding new chemical species to them [23]. These high-tech approaches, together with powerful computational strategies to determine the structure and computer-aided identification, are invaluable to study the enormity of the chemical space of microbial secondary metabolites and to rank the candidates with real therapeutic potential [23].

5. Recent Advances in Microbial Secondary Metabolite Discovery

5.1. Synthetic Biology and Rational Metabolite Engineering

Synthetic biology has emerged as a transformative framework for discovering and optimizing secondary metabolites, in many ways, but not limited to, facilitating the production of natural products efficiently, as well as providing a systematic approach to the creation of novel analogs with superior pharmacological qualities. The foundation of this method is the design–build–test (DBT) cycle, combining the design of pathways, genetic construction, and functional analysis in a cycle of refinement of the metabolite yield and structure [25]. DBT approaches work on scales ranging down to host strain optimization to supply precursors, through pathway selection and tuning at the level of biosynthetic pathways, and, at an enzyme level, to enhance catalytic performance and substrate specificity through rational design, directed evolution or machine learning-based approaches [25]. Developments in pathway engineering have made it easier to recreate more complex biosynthetic systems, such as the recent example of a twenty-five-enzyme pathway to produce the anticancer drug noscapine being engineered successfully [25]. Synthetic biology combined with computational modeling of metabolism also allows prediction of pathway fluxes, bottlenecks, and rational regulation of gene expression to obtain high productivity [25]. The creation of standardized genetic parts libraries has made the rapid assembly of pathways by providing highly characterized, modular assemblies to be assembled in a combinatoric manner [25][41]. In parallel, cell-free biosynthesis systems, which integrate purified enzymes with defined substrates, have also been developed as fast testing platforms that can be used to tune the pathway regardless of cellular limits [1].

5.2. Artificial Intelligence and Machine Learning Applications

Machine learning (ML) and artificial intelligence (AI) are increasingly advancing the field and the discovery of secondary metabolites by making it predictive and data driven. The trained ML models on the characterized biosynthetic gene clusters (BGCs) and their corresponding products can infer the metabolite structures using the genomic sequences, thus saving the time of identifying promising compounds without experimental isolation due to the prior availability of the models constructed on the BGCs [1]. The application of natural language processing to scientific text also reveals the patterns of connection between the biosynthetic pathways, chemical structures, and biological activity, which can guide the rational design of compounds [11][14]. Optimization of fermentation conditions based on AI has proven to be successful by mapping out the connections between culture parameters and the yield of metabolites, and high-productivity regimes can be predicted [1][11][14]. Deep learning models have expanded enzyme discovery by predicting new catalytic activity that is relevant in secondary metabolism [1][11][14]. Variational autoencoders and diffusion-based architecture are generative models that promise to be useful in designing new metabolite scaffolds with desired pharmacological properties. High-throughput experimental validation of AI-guided BGC prioritization is a new paradigm of rational natural product discovery that is rapidly emerging [1][11][14].

5.3. Integration of Genomics, Transcriptomics, and Metabolomics

The integration of multi-omics has provided an unprecedented insight into the biosynthesis of secondary metabolites. The identification of biosynthetic potential is defined as genome mining, and the identification of actively expressed clusters of genes under specific conditions is defined as transcriptomic profiling [29]. With high-resolution mass spectrometry and NMR, metabolomics provides a detailed and comprehensive description of generated metabolites, including new substances of all chemical classes [27][28][29]. The comparison of such datasets correlates expressed BGCs with measured metabolic identities and shows unforeseen metabolic functions and guides reasonable optimization of culture conditions [29]. A metatranscriptomic analysis has shown that around 30% of the total number of secondary metabolic genes are dynamically expressed in natural microbial communities, which highlights the utility of the predicted biosynthetic potential in natural ecological settings [29]. A combination of metabolomic and transcriptomic data also enlightens on environmental regulation and ecological functions of secondary metabolites [27][29]. New methodologies like phyloproteomics facilitate biosynthetic insights by connecting the predictions to proteomic findings of enzyme expression [29].

5.4. Clinical Translation Strategies and Future Therapeutic Applications

To achieve effective clinical translation of secondary metabolites, it is important to develop models to address specific properties of natural products. Reusing the available metabolites, as new therapeutic indications, is an effective route to clinical outcomes, including as antimicrobial adjuvants, antimicrobial combination agents, and immunomodulatory agents in cancer therapy [4][15][33]. Preclinical screening might be simplified in open-access libraries of characterized secondary metabolites and analogs, which could also lower the development cost [4]. Innovative methods like digital health tools and culturally sensitive education schemes have been demonstrated to considerably enhance patient adherence to prescribed treatment regimes which are vital in ensuring the transfer of new metabolites into clinical

practice [44]. The development of standardized bioassays in response to emerging pathogen and therapeutic requirements would also hasten the process of identifying high-value candidates [4][12][33]. A combination of secondary metabolites with immunotherapy approaches is especially promising, as there is growing evidence that most natural products regulate host immune responses [13][16]. Future applications are expected to surpass antimicrobials and anticancer agents to microbiome modulation, metabolic disease, and neuroinflammatory disorders [3][4][6]. Additional progress in heterologous expression, epigenetic activation, and synthetic biology will expand the available chemical space additional, thus leading to the creation of an ever-growing number of diverse and clinically relevant secondary metabolites [1][22][26].

6. Challenges and Future Directions

6.1. Overcoming Rediscovery and Accessing Cryptic Pathways

One of the long-term problems in the discovery of microbial drugs has been the high rediscovery rate, whereby, despite extensive screening of many compounds, already known compounds are found [20]. Since over 20,000 secondary metabolites of microbes are already known, random screening methods used in the traditional way have diminishing returns unless coupled with sophisticated prioritization methods [20]. This has led chemical dereplication to become a vital early-stage method that uses rapid analytical techniques and extensive databases to identify known molecules efficiently and focus resources on genuinely novel entities [23].

Another major problem is the abundance of transcriptionally silent or cryptic biosynthetic gene clusters (BGCs), the metabolites of which are not produced in standard laboratory reaction conditions [23][37]. Discovering these silent ways is one of the big breakthroughs in the field [23]. Current strategies include modulation of culture conditions, co-cultivation with other microorganisms, application of epigenetic modifiers, and targeted manipulation of pathway-specific or global regulatory genes [23][30][41][37]. A better understanding of the role of bacterial nucleoid-associated proteins in genome organization as well as transcriptional regulation, is proving to be a way forward in selective activation of silent clusters [23]. The combination of these activation strategies with high-throughput screening and genome-guided prioritization will be used more often in future discovery approaches to improve the efficiency of discovery [37].

6.2. Exploiting Microbial Diversity and Unculturable Microorganisms

Among the deepest constraints of microbial drug discovery is that only an estimated 1-10% of microorganisms can be successfully cultivated using current laboratory methods, leaving an enormous “unculturable majority” that represents a vast, untapped reservoir of novel secondary metabolites [23]. It is estimated that there is enormous, untapped chemical diversity in this “microbial dark matter”. To reach this reservoir, new methods of cultivation that more closely resemble natural habitats are under development, which allow them to grow hitherto unculturable species [21]. Metagenomics has become one of the most effective methods, as it has made it possible to recover and analyze directly in the environmental DNA, without cultivation of BGCs [20]. Such BGCs can then be heterologously expressed in tractable host organisms, avoiding the necessity of culturing original producers [23]. In extreme and biodiverse environments, such as marine systems, deep-sea habitats, polar systems, and geothermal systems, bioprospecting has further increased the chemical space of secondary metabolites, producing novel structures and bioactivities, including compounds [40]. The endophytic fungi have also become a notable source of structurally different metabolites with antimalarial and anticancer properties [40]. Continued investment in metagenomics, culturomics, and environmental sampling will be essential to fully exploit global microbial diversity [20].

6.3. Sustainable Production and Commercial Viability

Conversion of microbial secondary metabolites into clinically and commercially viable products entails significant issues of sustainable production and economic viability [23]. Although most natural products can be easily fermented by microbes, low intrinsic yields, downstream processing complexity, and variability in production usually limit them to large-scale use [23]. To overcome such problems, genetic engineering, metabolic engineering and synthetic biology have become central to the current development pipelines to perform strain optimization [23][17].

The methods allow the optimization of microbial cell factories by improving precursor supply, improving biosynthetic pathways and reducing competing metabolic fluxes [23]. Microbial assembly has turned out to be especially useful in long-term production of complex plant-based metabolites, such as terpenoids, flavonoids and alkaloids, which are generally hard to produce in large amounts [19]. Technological improvements in fermentation, process control and purification further enhance yield, consistency and cost-effectiveness, and the renewable feedstock improves the environmental sustainability [23]. The integration of microbial fuel cell technology can be seen as offering viable

solutions to sustainable development, serving a variety of objectives, such as clean energy, water, and sanitation and pointing to the larger scope of environmental implementation of microbial systems [49]. The green chemistry principles and advanced wastewater treatment are becoming widely accepted as elements of eco-friendliness in pharmaceutical production and sustainable production in the long term, as well as the sustainable environmental and long-term health of people [45]. Finally, to be drawn to commercial viability, a combined approach incorporating scientific innovation, economic and ecological concerns is needed throughout the drug development pipeline [23].

7. Conclusion

The microbial secondary metabolites comprise an unchanging and invaluable source of therapeutic innovation in that they have formed the basis of modern medicine over the decades yet represent an essential resource to meet the current medical demands of the global population. Innovations in genome mining, metagenomics, heterologous expression, epigenetic regulation, synthetic biology, and multi-omics integration have fundamentally altered streams of discovery, and these new approaches have allowed the identification of systematically accessible cryptic biosynthetic potentials beyond conventional culture-dependent approaches. Such innovations are especially important in the background of the growing antimicrobial resistance, continuing cancer burden, and broadening metabolic and immunological disease profiles. The translational capabilities of contemporary secondary metabolite research are evidenced by emerging clinical successes such as next-generation lipoglycopeptides, resistance-breaking enzyme inhibitors and engineered natural product analogs. However, there are still major obstacles to reaching unculturable microbial diversity, switchable silent gene sets, and a sustainable and economically viable production realm. Further interdisciplinary collaboration between microbiology, computational science, and bioprocess engineering will be needed to fully exploit the therapeutic potential of microbial secondary metabolites and to increase the future pharmacopeia.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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