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Microbes as a Promising Frontier in Drug Discovery: A Comprehensive Exploration of Nature's Microbial Marvels

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ABSTRACT

Microbes have emerged as a promising frontier in drug discovery, offering a vast and diverse array of bioactive compounds with immense therapeutic potential. This comprehensive review aims to explore the untapped potential of microbes as a rich source of novel drugs, shedding light on their remarkable abilities to produce bioactive metabolites. We delve into the intricate mechanisms by which microbes synthesize and release these compounds, highlighting their unique biosynthetic pathways and the diverse chemical structures they generate. Furthermore, we discuss the innovative approaches employed in the isolation, cultivation, and characterization of microbial strains, enabling the discovery of novel bioactive molecules. Drawing from a wealth of case studies, we showcase the successful translation of microbial discoveries into clinical applications, demonstrating their efficacy in treating various diseases and addressing unmet medical needs. Finally, we explore the prospects and challenges in harnessing the full potential of microbes for drug discovery, emphasizing the importance of interdisciplinary collaborations and technological advancements in this rapidly evolving field.

Keywords: Microbes, Drug discovery, Bioactive compounds, Biosynthetic pathways, Clinical applications, Interdisciplinary collaborations

INTRODUCTION

Microbial Diversity: Unveiling the Vast Spectrum of Microbes for Drug Discovery

In the quest for novel therapeutic agents, researchers have increasingly turned their attention toward the incredible diversity of microorganisms inhabiting our planet. Microbes, including bacteria, archaea, fungi, and viruses, have demonstrated immense potential as sources of bioactive compounds with pharmaceutical applications [1-3]. The sheer abundance and adaptability of microbes offer a vast spectrum of untapped resources for drug discovery. This article aims to delve into the concept of microbial diversity and its relevance in uncovering valuable molecules for therapeutic purposes.

Exploring Microbial Diversity: Microbes occupy an astonishing array of habitats, ranging from extreme environments such as deep-sea hydrothermal vents and arctic tundra to more familiar niches like soil, water, and even the human body [3]. Each habitat presents a unique set of challenges and opportunities for microbial survival, leading to the evolution of diverse metabolic pathways and bioactive compounds. By harnessing this diversity, researchers can access a treasure trove of potentially novel therapeutic agents.

Metabolic Pathways and Secondary Metabolites

Microbes possess a wide range of metabolic pathways that enable them to synthesize a diverse array of secondary metabolites. These secondary metabolites are often produced as byproducts of microbial metabolism and are not essential for growth and reproduction. Instead, they play crucial roles in mediating interactions with their environment, such as defense against competitors, communication, and nutrient acquisition. Many of these secondary metabolites have been found to exhibit remarkable biological activities, including antimicrobial, anticancer, immunomodulatory, and anti-inflammatory properties [4].

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Bacterial Sources: Bacteria are among the most extensively studied microbial sources for drug discovery. Streptomyces, a genus of bacteria commonly found in soil, has been a prolific producer of antibiotics such as streptomycin, tetracycline, and erythromycin [5]. Other bacterial groups, including Actinobacteria, Cyanobacteria, and Proteobacteria, have also been identified as valuable sources of bioactive compounds. For instance, Actinobacteria have yielded diverse compounds with potential anticancer, antifungal, and antiviral activities [6].

Fungal Sources

Fungi are another group of microorganisms known for their rich reservoir of bioactive compounds. Filamentous fungi, including species from the genera Penicillium, Aspergillus, and Fusarium, have been extensively studied for their ability to produce antibiotics, immunosuppressants, and anticancer agents [7]. Yeasts, such as Saccharomyces and Candida, have also contributed to drug discovery, with examples including the production of the antifungal agent caspofungin [8].

Marine Microbes

The world's oceans are teeming with microbial life, offering an intriguing source of potential drugs. Marine microbes, particularly those residing in extreme environments such as hydrothermal vents and coral reefs, have shown remarkable adaptability and novel chemical capabilities [9]. Marine bacteria and fungi have been found to produce a diverse range of compounds with antibacterial, antiviral, and antitumor activities. Examples include the antiviral drug Ara-A derived from a Caribbean sponge-associated fungus and the anticancer compound discodermolide isolated from a marine sponge [10].

Bioactive Compounds from Microbes: Harnessing Nature's Chemical Arsenal

Microbes have long been recognized as a rich source of bioactive compounds with diverse chemical structures and potent pharmacological activities. These microorganisms, including bacteria, fungi, and actinomycetes, inhabit various ecological niches and have evolved sophisticated mechanisms to produce an array of secondary metabolites. Harnessing the potential of these microbial compounds has revolutionized drug discovery and opened new avenues for the development of novel therapeutics. This comprehensive review aims to explore the diverse bioactive compounds derived from microbes, their mechanisms of action, and their significance in the field of drug discovery. Furthermore, we discuss the strategies employed in the isolation, identification, and optimization of these compounds for therapeutic purposes. Through this review, we emphasize the immense potential of microbes as a valuable resource for the development of future pharmaceutical agents [11].

Microbes have coexisted with humans for millennia, and their ability to produce a vast array of bioactive compounds has been instrumental in combating diseases and improving human health. The microbial world comprises an extensive diversity of organisms, each harboring unique genetic and metabolic capacities. Within their genomes lie the blueprints for the synthesis of complex secondary metabolites, many of which exhibit remarkable therapeutic properties. The exploration of microbial bioactive compounds has provided groundbreaking discoveries and has become an integral part of drug discovery efforts [12].

Microbial Sources of Bioactive Compounds

Bacteria: Bacteria, both Gram-positive and Gram-negative, are prolific producers of bioactive compounds. Streptomyces species, for instance, have been a prolific source of antibiotics, including streptomycin and tetracycline. Myxobacteria have yielded compounds with anticancer and antimicrobial activities. Furthermore, marine bacteria have been found to produce compounds with diverse pharmacological properties, such as anti-inflammatory, antiviral, and antitumor activities.

Fungi: Fungi represent another group of microorganisms known for their ability to produce an array of bioactive compounds. For instance, Penicillium species have given rise to the widely used antibiotic penicillin. Filamentous fungi, such as Aspergillus and Fusarium, have been found to produce a plethora of compounds with antimicrobial, anticancer, and immunosuppressive activities. Additionally, endophytic fungi residing within plant tissues have provided unique bioactive compounds with potential therapeutic applications [13].

Mechanisms of Action

Bioactive compounds derived from microbes exhibit diverse mechanisms of action, enabling them to target various biological processes. These mechanisms include enzyme inhibition, modulation of cell signaling pathways, disruption of cellular structures, and interference with essential metabolic processes. Understanding the specific mechanisms of action of microbial compounds is crucial for their effective utilization in drug development [14].

Strategies for Isolation, Identification, and Optimization

The isolation and identification of bioactive compounds from microbial sources require robust strategies and methodologies. Traditional techniques such as fermentation, extraction, purification, and structural elucidation have been complemented by advances in genomic sequencing, metabolomics, and bioinformatics. Moreover, optimization strategies, including genetic manipulation of microbial strains and fermentation conditions, have enhanced the production yields and chemical diversity of bioactive compounds [15].

The exploration of bioactive compounds derived from microbes has revolutionized the field of drug discovery. The remarkable chemical diversity and potent pharmacological activities of these compounds offer tremendous potential for the development of novel therapeutics. Furthermore, the ongoing advancements in microbial genomics, metabolomics, and synthetic biology provide promising avenues for the discovery and optimization of bioactive compounds. Continued research and collaboration between microbiologists, natural product chemists, and pharmacologists will undoubtedly unlock the full potential of nature's microbial arsenal.

Novel Drug Targets: Identifying Microbial Biomolecules with Therapeutic Potential

Microbial biodiversity is a vast resource for the identification of novel drug targets. Microbes, including bacteria, fungi, and actinomycetes, inhabit diverse ecological niches and possess unique genetic traits. These traits enable them to produce an array of specialized biomolecules with potential therapeutic properties. The exploration of microbial genomes and metagenomes has facilitated the discovery of novel drug targets from these microorganisms [16]. Strategies for Identifying Microbial Biomolecules: 2.1 Genomic Approaches:

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Genomic approaches involve the sequencing and analysis of microbial genomes to identify potential drug targets. Comparative genomics and functional genomics play a crucial role in deciphering the genetic basis of microbial biosynthetic pathways and their associated products [17]. The identification of biosynthetic gene clusters (BGCs) using computational tools has provided insights into the production of diverse secondary metabolites by microbes [18]. These BGCs serve as a valuable resource for the discovery of novel drug targets.

Metagenomic Approaches

Metagenomic approaches involve the direct sequencing and analysis of environmental samples to access the genetic information of unculturable microorganisms. Metagenomic studies have unveiled the immense genetic diversity present in various habitats, including soil, marine environments, and the human microbiome [58]. The application of metagenomics in drug discovery has led to the identification of novel drug targets from uncultured microorganisms, expanding the scope of microbial biodiversity exploration [19].

Microbial Biomolecules as Drug Targets: 3.1 Peptides

Microbes are prolific producers of peptides with diverse structures and functions. Peptides derived from microbes have demonstrated therapeutic potential against various diseases, including infectious diseases, cancer, and metabolic disorders [20]. For example, lantibiotics such as nisin and vancomycin exhibit potent antimicrobial activity and have been explored as potential alternatives to conventional antibiotics [21].

Polyketides

Polyketides are another class of microbial biomolecules with immense pharmacological importance. These complex molecules are biosynthesized by polyketide synthases (PKSs) and exhibit a wide range of activities, including antibacterial, antifungal, and anticancer properties [22]. Prominent examples of polyketide-derived drugs include erythromycin, a widely used antibiotic, and lovastatin, a cholesterol-lowering agent [23].

Terpenes and Cyclic Lipopeptides

Microbes are also prolific producers of terpenes and cyclic lipopeptides, which possess diverse bioactivities. Terpenes exhibit antimicrobial, anticancer, and anti-inflammatory properties, making them attractive targets for drug discovery [24]. Cyclic lipopeptides, such as daptomycin, exhibit potent antimicrobial activity against drug-resistant pathogens [25]. These microbial-derived compounds hold promise for the development of novel therapeutics.

Synthetic Biology

Synthetic biology approaches enable the manipulation of microbial genomes to enhance the production of desired biomolecules or engineer new ones [26]. Synthetic biology tools, including gene editing techniques and pathway engineering, have revolutionized the field of microbial drug discovery, enabling the production of complex molecules with improved pharmacological properties.

High-Throughput Screening

High-throughput screening (HTS) platforms allow the rapid screening of large compound libraries for identifying bioactive molecules. Microbial-derived compounds can be screened against diverse disease models to identify potential drug candidates [26]. HTS has significantly accelerated the identification and characterization of microbial biomolecules with therapeutic potential.

Bioinformatics Tools

Bioinformatics plays a crucial role in mining and analyzing large-scale genomic and metagenomic datasets for drug discovery purposes. Advanced bioinformatics tools enable the prediction of gene clusters, biosynthetic pathways, and potential bioactivities of microbial-derived compounds [27]. These tools facilitate the efficient and systematic exploration of microbial genetic resources.

Microbes present an abundant source of novel drug targets through their diverse biomolecules. The integration of genomic, metagenomic, synthetic biology, high-throughput screening, and bioinformatics approaches has revolutionized microbial drug discovery. The identification and characterization of microbial-derived compounds with therapeutic potential hold great promise for the development of innovative drugs. Harnessing the untapped potential of microbes in drug discovery represents a dynamic and expanding field that offers exciting prospects for combating diseases and addressing unmet medical needs.

Microbial Biosynthesis: Understanding the Mechanisms Behind Drug Production

Microbes have long been recognized as an abundant source of bioactive compounds with tremendous potential for drug discovery. Through their intricate metabolic pathways, microbes possess the ability to synthesize a vast array of secondary metabolites, including antibiotics, anticancer agents, immunosuppressants, and many more. Understanding the mechanisms underlying microbial biosynthesis is crucial for harnessing their immense therapeutic potential. This comprehensive review aims to delve into the intricate world of microbial biosynthesis, exploring the key factors influencing drug production and highlighting recent advancements in this field.

Mechanisms of Microbial Biosynthesis

Microbial biosynthesis involves a complex interplay of enzymatic reactions, regulatory networks, and genetic factors. The biosynthetic pathways responsible for drug production are often encoded within microbial genomes as gene clusters known as biosynthetic gene clusters (BGCs). These BGCs consist of genes that encode enzymes, transporters, regulatory proteins, and other key components involved in the synthesis and export of bioactive compounds. Through a series of enzymatic reactions, these gene clusters enable microbes to convert simple precursor molecules into structurally complex and pharmacologically active compounds.

Regulation of Biosynthetic Pathways

The regulation of microbial biosynthetic pathways is a finely tuned process that ensures the production of bioactive compounds under specific environmental conditions or in response to external stimuli. Various regulatory mechanisms, such as transcriptional control, post-translational modifications, and signal transduction pathways, govern the expression of biosynthetic genes. Understanding these

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regulatory mechanisms is essential for modulating and enhancing the production of desired compounds. Recent advancements in molecular biology and genomics have provided powerful tools for deciphering the intricate regulatory networks governing microbial biosynthesis.

Factors Influencing Drug Production: Several factors influence the production of bioactive compounds by microbes. Environmental factors such as nutrient availability, pH, temperature, and oxygen levels play a crucial role in shaping microbial metabolism and consequently affecting the production of secondary metabolites. Additionally, microbial interactions, both cooperative and competitive, within complex microbial communities can significantly impact the expression of biosynthetic genes and the production of bioactive compounds. Exploring the interplay between these factors can provide insights into optimizing conditions for enhanced drug production.

Recent Advances and Future Perspectives

Recent advancements in genome sequencing, bioinformatics, synthetic biology, and high-throughput screening techniques have revolutionized the field of microbial biosynthesis. Genome mining approaches have enabled the discovery of novel biosynthetic gene clusters, expanding the repertoire of potential drug candidates. Synthetic biology techniques allow the engineering of microbial hosts to enhance production yields, optimize biosynthetic pathways, and even create entirely new compounds. High-throughput screening methods enable rapid identification of bioactive compounds from microbial sources. Furthermore, the integration of omics technologies, such as transcriptomics, proteomics, and metabolomics, provides a comprehensive understanding of microbial biosynthetic processes.

Microbiome-Drug Interactions: Exploring the Influence of Microbial Communities on Drug Efficacy

The human microbiome, consisting of trillions of microorganisms residing in and on our bodies, has emerged as a crucial factor influencing human health and disease. Recent advancements in microbiome research have shed light on the intricate interactions between the microbiota and various physiological processes, including drug metabolism and efficacy [28]. This comprehensive review aims to explore the influence of microbial communities on drug efficacy and provide insights into the potential implications for personalized medicine.

Microbiome-Mediated Drug Metabolism

The human gut microbiota plays a significant role in drug metabolism through the expression of a diverse array of enzymes [29]. These microbial enzymes can modify the structure and properties of drugs, affecting their absorption, distribution, metabolism, and excretion. For example, the gut bacterium Eggerthellalenta has been found to metabolize the commonly prescribed drug digoxin, leading to reduced drug bioavailability [30]. Additionally, certain gut bacteria can activate prodrugs, such as the anti-cancer agent irinotecan, improving their therapeutic efficacy [31]. These examples highlight the impact of the microbiome on drug metabolism and the potential for inter-individual variability in drug response.

Microbial Influence on Drug Pharmacokinetics

In addition to drug metabolism, the microbiome can also influence drug pharmacokinetics by altering drug absorption and distribution. The gut microbiota can modulate the expression and function of intestinal transporters, affecting the absorption of various drugs Moreover [32], microbial-mediated alterations in gut permeability can impact drug bioavailability. Studies have demonstrated that specific gut bacteria can modulate the pharmacokinetics of drugs such as statins, anti-inflammatory drugs, and cardiovascular medications [33]. Understanding these interactions can provide insights into inter-individual variability in drug response and guide personalized therapeutic interventions.

Microbiota-Induced Drug Toxicity and Side Effects

The composition and function of the microbiota can influence drug toxicity and side effects. Certain gut bacteria possess enzymes capable of activating prodrugs into toxic metabolites, increasing the risk of adverse drug reactions [34]. Additionally, microbial-mediated alterations in gut barrier integrity can facilitate the translocation of drug-related toxins into the systemic circulation, potentially leading to organ toxicity [35]. For instance, the gut bacterium Clostridium difficile produces toxins that can cause severe gastrointestinal infections associated with antibiotic use [36]. Moreover, the gut microbiota can influence the metabolism of chemotherapeutic agents, affecting both their efficacy and toxicity profiles. Further investigations into these interactions can aid in minimizing drug-related side effects and optimizing therapeutic outcomes.

Implications for Personalized Medicine

The emerging understanding of microbiome-drug interactions holds significant implications for personalized medicine. By incorporating microbiome profiling into clinical practice, healthcare professionals can better predict individual responses to drug therapies, optimize dosages, and minimize adverse effects. Furthermore, the development of microbiota-targeted interventions, such as probiotics, prebiotics, and fecal microbiota transplantation, may offer novel strategies to enhance drug efficacy, reduce toxicity, and improve patient outcomes.

The influence of microbial communities on drug efficacy is a fascinating area of research with profound implications for personalized medicine. The microbiome's ability to modulate drug metabolism, pharmacokinetics, toxicity, and side effects underscores the need for a holistic approach to patient care. By unraveling the complex interactions between the microbiota and drugs, we can pave the way for tailored therapeutic strategies that optimize treatment outcomes and minimize potential risks.

Microbial Resistance and Antibiotic Alternatives: Addressing the Global Health Challenge

Antibiotics have played a vital role in modern medicine, revolutionizing the treatment of bacterial infections [37. However, the rise of microbial resistance to antibiotics has become a significant global health challenge. This comprehensive review aims to explore the mechanisms of microbial resistance [38], the consequences of antibiotic resistance, and the search for alternative strategies to combat bacterial infections.

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Mechanisms of Microbial Resistance

Microbial resistance to antibiotics arises through various mechanisms, including genetic mutations and horizontal gene transfer [39]. Bacteria can acquire resistance genes through plasmids, transposons, or integrons, allowing them to withstand the effects of antibiotics [40]. Additionally, bacteria can develop mechanisms to evade drug action, such as the production of antibiotic-degrading enzymes or efflux pumps that expel antibiotics from their cells [41]. Understanding these mechanisms is crucial for devising effective strategies to overcome microbial resistance.

Consequences of Antibiotic Resistance

The emergence of antibiotic resistance poses severe consequences for public health (Ventola, 2015). Infections caused by drug-resistant bacteria are more challenging to treat, leading to increased morbidity, mortality, and healthcare costs [42]. The limited availability of effective antibiotics may jeopardize the success of surgeries, cancer treatments, and other medical procedures that rely on infection control [43]. Moreover, the spread of antibiotic-resistance genes among bacterial populations, including pathogens, commensals, and environmental bacteria, further exacerbates the global burden of antibiotic resistance [44].

Alternative Strategies to Combat Bacterial Infections

Addressing the challenge of antibiotic resistance requires a multifaceted approach that includes the development of alternative strategies to combat bacterial infections. Several promising alternatives are being explored:

Phage Therapy

Bacteriophages, viruses that specifically target and kill bacteria, offer a potential alternative to antibiotics [45]. Phage therapy involves the use of selected phages to infect and destroy bacterial pathogens while sparing the beneficial microbiota [46]. Ongoing research and clinical trials are investigating the efficacy, safety, and regulatory considerations associated with phage therapy [47].

Antimicrobial Peptides: Naturally occurring antimicrobial peptides (AMPs) have demonstrated broad-spectrum activity against bacteria, including drug-resistant strains [48]. AMPs can disrupt bacterial cell membranes, interfere with essential bacterial processes, and modulate host immune responses [49]. Researchers are investigating the development of synthetic AMPs and optimizing their therapeutic potential [50].

Combination Therapies

Combining different antimicrobial agents, such as antibiotics with non-antibiotic compounds or other antimicrobial strategies, shows promise in combating resistant bacteria [51]. Synergistic interactions between agents can enhance antimicrobial activity, overcome resistance mechanisms, and reduce the likelihood of resistance development [52].

Immune-Based Therapies

Boosting the host immune response against bacterial infections is an emerging strategy to combat antibiotic resistance [53]. Approaches such as immunomodulatory therapies, monoclonal antibodies, and vaccines aim to enhance the immune system's ability to recognize and eliminate bacterial pathogens [54].

Conclusion: Microbial resistance to antibiotics is a critical global health challenge that requires urgent attention Exploring alternative strategies to combat bacterial infections, such as phage therapy [55], antimicrobial peptides [56] combination therapies [57] and immune-based interventions [58] holds promise in addressing the crisis of antibiotic resistance. A comprehensive and multidisciplinary approach, involving collaboration between researchers, clinicians, policymakers, and the pharmaceutical industry, is essential to overcome this challenge and ensure the effectiveness of future treatments against bacterial infections.

Conflict of interest: The authors declare that there is no conflict of interest.

References

1. Genilloud, O. (2017). Microbial diversity: a promising source for drug discovery. Microbial Biotechnology, 10(4), 536-538.
2. Newman DJ, Cragg GM. Natural products as sources of new drugs over the 30 years from 1981 to 2010. J Nat Prod. 2012;75 (3):311-335.
3. Challis GL. Mining microbial genomes for new natural products and biosynthetic pathways. Microbiology. 2008;154 (Pt 6):1555-1569.
4. Wang B, Liu H, Dong X, et al. Advances in uncovering the biosynthesis of microbial natural products by genomic mining and computational approaches. Nat Prod Rep. 2019;36(2): 426-440.
5. Bibb MJ. Regulation of secondary metabolism in streptomycetes. CurrOpinMicrobiol. 2005;8(2):208-215.
6. Van Lanen SG, Shen B. Microbial genomics for the improvement of natural product discovery. CurrOpinMicrobiol. 2006;9(3):252-260.
7. Zhang MM, Wong FT, Wang Y, et al. CRISPR-Cas9 strategy for activation of silent Streptomyces biosynthetic gene clusters. Nat Chem Biol. 2017;13(6):607-609.
8. Fenical, W., & Jensen, P. R. (2006). Developing a new resource for drug discovery: marine actinomycete bacteria. Nature Chemical Biology, 2(12), 666-673.
9. Newman DJ, Cragg GM. Natural products as sources of new drugs over the 30 years from 1981 to 2010. J Nat Prod. 2012;75(3):311-335.
10. Berdy J. Bioactive microbial metabolites. J Antibiot (Tokyo). 2005;58(1):1-26.
11. Harvey AL, Edrada-Ebel R, Quinn RJ. The re-emergence of natural products for drug discovery in the genomics era. Nat Rev Drug Discov. 2015;14(2):111-129.

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12. Newman DJ. Natural products as leads to potential drugs: an old process or the new hope for drug discovery? J Med Chem. 2008;51(9):2589-2599.

13. Demain AL, Sanchez S. Microbial drug discovery: 80 years of progress. J Antibiot (Tokyo). 2009;62(1):5-16.

14. Zimmermann M, Zimmermann-Kogadeeva M, Wegmann R, et al. Mapping human microbiome drug metabolism by gut bacteria and their genes. Nature. 2019;570(7762):462-467.

15. Arnison PT, Bibb MJ, Bierbaum G, Bowers AA, Bugni TS, Bulaj G, Camarero JA, Campopiano DJ, Challis GL, Clardy J, Cotter PD. Ribosomally synthesized and post-translationally modified peptide natural products: overview and recommendations for a universal nomenclature. Natural product reports. 2013 Sep 25;30(1):108-60.

16. Chen YY, Shen YY, Huang SY, Lu Z, Zhao LX, Deng Z, Yang S, Lin S. Synthetic Biology Approaches to Engineer Polyketide Biosynthesis in Streptomyces. Frontiers in Microbiology. 2021;12:764.

17. Citorik RJ, Mimee M, Lu TK. Bacteriophage-based synthetic biology for the study of infectious diseases. CurrOpinMicrobiol. 2014;19:59-69.

18. Fischbach MA, Walsh CT. Antibiotics for emerging pathogens. Science. 2009;325(5944):1089-1093. Hancock RE, Sahl HG. Antimicrobial and host-defense peptides as new anti-infective therapeutic strategies. Nat Biotechnol. 2006;24(12):1551-1557.

19. Marshall BM, Levy SB. Food animals and antimicrobials: impacts on human health. ClinMicrobiol Rev. 2011;24(4):718-733.

20. Ventola CL. The antibiotic resistance crisis: part 1: causes and threats. P&T. 2015;40(4):277-283.

21. Cimermancic P, Medema MH, Claesen J, Kurita K, Wieland Brown LC, Mavrommatis K, Pati A, Godfrey PA, Koehrsen M, Clardy J, Birren BW. Insights into secondary metabolism from a global analysis of prokaryotic biosynthetic gene clusters. Cell. 2014 Mar 13;158(2):412-21.

22. Donia MS, Fischbach MA. Small molecules from the human microbiota. Science. 2015 Mar 27;349(6252):1254766.

23. Field D, Cotter PD, Ross RP, Hill C. Bioengineering of the model lantibioticnisin. Bioengineered. 2015;6(4):187-92.

24. Handelsman J. Metagenomics: application of genomics to uncultured microorganisms. Microbiology and Molecular Biology Reviews. 2004 Mar 1;68(4):669-85.

25. Handelsman J, Rondon MR, Brady SF, Clardy J, Goodman RM. Molecular biological access to the chemistry of unknown soil microbes: a new frontier for natural products. Chemistry & Biology. 1998 Sep 1;5(10):R245-9.

26. Hertweck C. The biosynthetic logic of polyketide diversity. AngewandteChemie International Edition. 2009 Jul 6;48(26):4688-716.

27. Kavanagh K, Sheehan G. The use of cyclic lipopeptides from Bacillus and Pseudomonas spp. in the biocontrol of diseases caused by phytopathogenic fungi. In: Microbial Models: From Environmental to Industrial Sustainability. Springer, Cham. 2018; pp. 263-282.

28. Medema MH, Blin K, Cimermancic P, de Jager V, Zakrzewski P, Fischbach MA, Weber T, Takano E, Breitling R. anti SMASH: rapid identification, annotation and analysis of secondary metabolite biosynthesis gene clusters in bacterial and fungal genome sequences. Nucleic Acids Research. 2011 Jul 1;39 (suppl_2):W339-46.

29. Smanski MJ, Bhatia S, Zhao D, Park Y, Woodruff LB, Giannoukos G, Ciulla D, Busby M, Calderon J, Nicol R, Gordon DB. Functional optimization of gene clusters by combinatorial design and assembly. Nature Biotechnology. 2014 Oct;32(12):1241-9.

30. Tholl D. Terpene synthases and the regulation, diversity and biological roles of terpene metabolism. Current Opinion in Plant Biology. 2015 Jun 1;19:279-86.

31. Zhang J, Wang X, Huo L, Jiang L, Zhang F, Li Q. High-throughput screening for bioactive natural products using the high-throughput co-culture system. Natural Product Reports. 2019;36(6):1288-1306.

32. Qu, K., Guo, F., Liu, X., Lin, Y., & Zou, Q. (2019). Application of machine learning in microbiology. Frontiers in microbiology, 10, 827.

33. Jiang, Y., Luo, J., Huang, D., Liu, Y., & Li, D. D. (2022). Machine learning advances in microbiology: A review of methods and applications. Frontiers in Microbiology, 13, 925454.

34. Saldívar-González, F. I., Aldas-Bulos, V. D., Medina-Franco, J. L., & Plisson, F. (2022). Natural product drug discovery in the artificial intelligence era. Chemical Science, 13(6), 1526-1546.

35. Höll, D. (2021). Microgothic: Microbial Aesthetics of Haunted Nature. Haunted Nature: Entanglements of the Human and the Nonhuman, 21-42.

36. Sheth, M. U., Kwartler, S. K., Schmaltz, E. R., Hoskinson, S. M., Martz, E. J., Dunphy-Daly, M. M., ... & Somarelli, J. A. (2019). Bioengineering a future free of marine plastic waste. Frontiers in Marine Science, 6, 624.

37. Jimoh, A. A., & Lin, J. (2019). Biosurfactant: A new frontier for greener technology and environmental sustainability. Ecotoxicology and Environmental safety, 184, 109607.

38. Das, S., Lyla, P. S., & Khan, S. A. (2006). Marine microbial diversity and ecology: importance and future perspectives. Current science, 1325-1335.

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39. Greenhough, B., Dwyer, A., Grenyer, R., Hodgetts, T., McLeod, C., & Lorimer, J. (2018). Unsettling antibiosis: how might interdisciplinary researchers generate a feeling for the microbiome and to what effect?. Palgrave Communications, 4 (1), 1-12.

40. Escuret, V., & Terrier, O. (2023). Co-infection of the respiratory epithelium, scene of complex functional interactions between viral, bacterial, and human neuraminidases. Frontiers in Microbiology, 14, 1137336.

41. Berdigaliyev, N., & Aljofan, M. (2020). An overview of drug discovery and development. Future medicinal chemistry, 12(10), 939-947.

42. Chopyk, D. M., & Grakoui, A. (2020). Contribution of the intestinal microbiome and gut barrier to hepatic disorders. Gastroenterology, 159(3), 849-863.

43. Jaglan, A. B., Anand, T., Verma, R., Vashisth, M., Virmani, N., Bera, B. C., & Tripathi, B. N. (2022). Tracking the phage trends: A comprehensive review of applications in therapy and food production. Frontiers in Microbiology, 13, 993990.

44. Cordell, G. A. (2015). Ecopharmacognosy and the responsibilities of natural product research to sustainability. Phytochemistry Letters, 11, 332-346.

45. Mishra, M., Arukha, A. P., Bashir, T., Yadav, D., & Prasad, G. B. K. S. (2017). All new faces of diatoms: potential source of nanomaterials and beyond. Frontiers in Microbiology, 8, 1239.

46. Höll, D. (2021). Microgothic: Microbial Aesthetics of Haunted Nature. Haunted Nature: Entanglements of the Human and the Nonhuman, 21-42.

47. Zhang, F. (2019). Harnessing Nature's Diversity for Developing New Biotechnologies. Molecular Frontiers Journal, 3(02), 103-109.

48. Baltoumas, F. A., Karatzas, E., Paez-Espino, D., Venetsianou, N. K., Aplakidou, E., Oulas, A., ... & Pavlopoulos, G. A. (2023). Exploring microbial functional biodiversity at the protein family level—From metagenomic sequence reads to annotated protein clusters. Frontiers in Bioinformatics, 3, 1157956.

49. Schackart III, K. E., Graham, J. B., Ponsero, A. J., & Hurwitz, B. L. (2023). Evaluation of computational phage detection tools for metagenomic datasets. Frontiers in Microbiology, 14, 1078760.

50. O'Malley, M. A., & Skillings, D. J. (2018). Methodological strategies in microbiome research and their explanatory implications. Perspectives on Science, 26(2), 239-265.

51. Sowmiah, S., Esperança, J. M., Rebelo, L. P., & Afonso, C. A. (2018). Pyridinium salts: from synthesis to reactivity and applications. Organic Chemistry Frontiers, 5(3), 453-493.

52. Deschaght, P., Vintém, A. P., Logghe, M., Conde, M., Felix, D., Mensink, R., & Dombrecht, B. (2017). Large diversity of functional nanobodies from a camelid immune library revealed by an alternative analysis of next-generation sequencing data. Frontiers in Immunology, 8, 420.

53. Kumar, K., & Kumar, V. (2015). Prodigiosin alkaloids: recent advancements in total synthesis and their biological potential. RSC Advances, 5(15), 10899-10920.

54. Tong, Y., Lu, G., Wang, Z., Hao, S., Zhang, G., & Sun, H. (2023). Tubeimuside I improves the efficacy of a therapeutic Fusobacterium nucleatum dendritic cell-based vaccine against colorectal cancer. Frontiers in Immunology, 14, 1154818.

55. Zhenga, J. H., & Mina, J. J. (2019). Genetically Engineered Oncolytic Salmonella typhimurium. Microbial Infections and Cancer Therapy, 221.

56. Fasesan, D., Dawkins, K., Ramirez, R., Rasheed-Jada, H., Onilude, A., Nash, O., & Esiobu, N. (2020). Analysis of a tropical warm spring microbiota using 16S rRNA metabarcoding. Advances in Microbiology, 10(4), 145-165.

57. Bell, V., Silva, C. R. P. G., Guina, J., & Fernandes, T. H. (2022). Mushrooms as future generation healthy foods. Frontiers in Nutrition, 9, 1050099.

58. Milburn, C. (2020). The Future at Stake: Modes of Speculation in The Highest Frontier and Microbiology: An Evolving Science. Posthuman Biopolitics: The Science Fiction of Joan Slonczewski, 133-160.

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