Nature's Tiny Chemists: Microorganisms as Sources of Next-Gen Active Pharmaceutical Ingredients (APIs)

Md. Fakruddin[1]*, Musarrat Jahan Prima[2], Tanwy Chowdhury[1], Umme Tamanna Ferdous[3], Jinia Afroz[4], Md. Asaduzzaman Shishir[5]

Abstract

Background: Active Pharmaceutical Ingredients (APIs) are fundamental components that provide therapeutic efficacy to medications, yet traditional discovery methods are limited in innovation and diversity, hindering the development of novel therapeutics. This has led to a renewed interest in microbial species as a source of bioactive compounds, particularly as the pharmaceutical industry faces stagnation in API procurement and environmental concerns regarding traditional extraction methods. Methods: This review discusses the potential of microorganisms—including bacteria, fungi, algae, and archaea—as sources of APIs. The exploration involves analyzing microbial diversity, biosynthetic pathways, and advancements in biotechnology such as genetic engineering, synthetic biology, and metagenomics. The review also highlights traditional culture-based techniques and contemporary high-throughput screening methods used in microbial API discovery. Results: The findings reveal that microorganisms possess complex metabolic processes that enable the production of diverse bioactive compounds. Advances in genetic profiling and bioprocessing technology facilitate the efficient identification and cultivation of promising microbial strains. Key examples include antibiotics derived from bacteria and antifungal compounds from fungi, illustrating the therapeutic potential of these organisms. However, challenges such as production yield optimization and regulatory hurdles remain significant. Conclusion: Microorganisms represent a vast and underutilized reservoir of potential APIs that could significantly impact the pharmaceutical landscape. By optimizing their metabolic diversity through innovative biotechnological strategies, the industry can overcome current limitations and meet emerging therapeutic needs sustainably. Future prospects include tailored microbial factories for personalized medicine and collaborative frameworks to expedite the transition from discovery to commercialization, ensuring a broad and lasting impact on global health.

Keywords: Active Pharmaceutical Ingredients, Microbial Biotechnology, Bioactive Compounds, Drug Discovery, Sustainable Production

Significance | Reviewing microbial sources for APIs addresses traditional limitations in drug development while ensuring sustainable and innovative therapeutic solutions.

*Correspondence. Md. Fakruddin, Department of Biochemistry & Microbiology, North South University, Bashundhara, Dhaka, Bangladesh.
E-mail: md.fakruddin@northsouth.edu

Editor Suvamoy Datta, Ph.D., And accepted by the Editorial Board Month Aug 13, 2024 (received for review Jun 16, 2024)

Introduction

Active Pharmaceutical Ingredients (APIs) are essential compounds that provide therapeutic efficacy to pharmaceutical medicines, serving as the foundation of drug discovery and treatment for a vast array of diseases and conditions. However, traditional API discovery methods face significant barriers to innovation and

Author Affiliation.
[1] Department of Biochemistry & Microbiology, North South University, Bashundhara, Dhaka, Bangladesh.
[2] Independent Researcher, Dhaka, Bangladesh.
[3] Interdisciplinary Research Center for Bio Systems and Machines, King Fahd University of Petroleum & Minerals, Dhahran, Saudi Arabia.
[4] Department of Microbiology, Primeasia University, Banani, Dhaka, Bangladesh.
[5] Department of Microbiology, Dhaka International University, Badda, Dhaka, Bangladesh.

Please cite this article.
Md. Fakruddin, Musarrat Jahan Prima et al. (2024). Nature's Tiny Chemists: Microorganisms as Sources of Next-Gen Active Pharmaceutical Ingredients (APIs), Journal of Primeasia, 5(1), 1-9, 9928

diversity, limiting progress toward the development of novel therapeutic agents (Abd El-Hack et al., 2019). This challenge has sparked renewed interest in exploring microbial species as unparalleled sources of bioactive compounds (R. Aluko, 2012). The pharmaceutical industry's dependence on established suppliers for API procurement has reached a plateau, hampering its ability to address emerging therapeutic needs effectively (Ameen et al., 2021). Additionally, growing concerns over the environmental impact and ethical implications of traditional chemical extraction from plants and animals have intensified the search for more sustainable API sources (Begum et al., 2015).

Microorganisms, including fungi, bacteria, algae, and archaea, represent a vast and diverse reservoir with immense potential for novel API discovery (Ashu et al., 2019). These organisms thrive in virtually every environment on Earth, demonstrating remarkable adaptability despite challenging conditions. While microbes often receive attention for their role in causing diseases, their beneficial contributions far outweigh the negatives (Bentley, 1997). Invisible to the naked eye due to their short lifespans, microbes play a crucial role in recycling organic matter in a synchronized, continuous process that sustains ecosystems (Shishir & Hoq, 2020). Microorganisms have been leveraged for centuries in food production, including the fermentation of vegetables, meat, fish, and the creation of vinegar, bread, cheese, wine, beer, and yogurt (Kharatyan, 1978).

Advances in applied microbiology have helped to refine our understanding of microbes, recognizing both beneficial and harmful organisms in various industries. Contamination by pathogenic microorganisms in foods, beverages, and medications is universally undesirable, as these organisms can introduce life-threatening diseases when ingested or applied (Baddeley & Isalan, 2021). Spoilage and contamination from non-pathogenic microorganisms can also compromise medicines, reducing their efficacy or making them harmful. To address these challenges, the pharmaceutical industry employs comprehensive control measures—guided by standards such as those from BP and USP—to prevent microbial contamination at every stage, from raw materials to the finished product (Bakal et al., 2017).

However, while one facet of microbial management focuses on eliminating harmful bacteria, another side leverages beneficial microorganisms for the production of drugs and other therapies. Biotechnology has unlocked the potential of various microbes, including bacteria, fungi, viruses, and microalgae, as viable and sustainable sources of APIs (Kalsoom et al., 2020; Shishir & Hoq, 2020). This dual approach not only safeguards product integrity but also paves the way for harnessing microbial diversity to meet evolving therapeutic needs responsibly and sustainably.

Compared to other industries, the pharmaceutical sector has a relatively recent history of utilizing microorganisms. The accidental discovery of antibiotics by Alexander Fleming marked a pivotal moment, accelerating the integration of microbes in pharmaceutical development (Běhal, 2000). Subsequently, advancements in science facilitated the identification of additional biologically active compounds, particularly secondary metabolites, further expanding their pharmaceutical applications (Hawksworth, 2001). Over the last five decades, remarkable strides in genetic engineering and molecular biology have diversified and enhanced microbial applications in drug discovery.

Today, efficient microbial identification techniques and the synergy between genetics, bioinformatics, and molecular biology enable rapid research progress. For instance, genetic profiling allows for the swift identification of microbial strains with potential therapeutic applications (Besrour-Aouam et al., 2021). Advances in bioprocessing technology have automated and optimized microbial production, facilitating the large-scale generation of desirable strains to meet pharmaceutical demands (Bentley, 1997). Historically, raw materials for pharmaceuticals were primarily derived from synthetic sources (chemical synthesis) or natural sources such as plants and animals (Bérdy, 2005). However, producing these resources requires significant time, land, and cultivation efforts, as is the case with plant-based medicinal compounds. By contrast, microbial fermentation offers a more efficient means of producing bioactive compounds, requiring less time and space than traditional drug manufacturing methods (Shishir & Hoq, 2020). This efficiency can significantly reduce production costs, making medicines more accessible to all socioeconomic classes (Bertasso et al., 2001).

Genetic engineering has further transformed the pharmaceutical landscape by enabling the microbial synthesis of compounds typically derived from plants or animals. This biotechnological approach can recreate valuable medicinal compounds, irrespective of their natural origins, through microbial platforms (Beshkova & Frengova, 2012). Leveraging microorganisms with modern tools from molecular biology, genetic engineering, and bioprocessing, the pharmaceutical industry can experience unprecedented advancements (Bhattacharya & Gupta, 2005).

This review explores the emerging role of microorganisms as primary sources of next-generation APIs (Borowitzka, 2018). By examining the vast and diverse microbial communities, we uncover their intricate metabolic pathways, which facilitate the production of a wide spectrum of bioactive compounds (Bougatef et al., 2010). With sophisticated biotechnological tools and genomics approaches now more accessible, our understanding of the mechanisms underlying microbial synthesis of medicinal compounds has deepened (Brzoska et al., 2020). This study provides a comprehensive overview of the potential and challenges in utilizing microorganisms for API discovery, with particular attention to recent advances in microbial biotechnology.

Microbial diversity and potential for API production

Microorganisms serve as an extraordinary source of next-generation Active Pharmaceutical Ingredients (APIs) and are a unique reservoir of biodiversity (Camacho et al., 2019). Diverse microbial species, including bacteria, fungi, algae, and archaea, inherently possess the potential to produce a wide array of bioactive compounds (Chaisuwan et al., 2021). Given the limitations of conventional sources, this vast microbial diversity is crucial in expanding the range of potential APIs (Chen et al., 2020). Microorganisms are prolific producers of bioactive compounds due to their evolutionarily developed and complex metabolic processes (Chaudhari et al., 2016). These mechanisms, reflective of adaptive strategies for environmental interaction, stem from intricate biosynthetic pathways encoded within microbial genomes (Bae et al., 2020). Understanding these biosynthetic pathways is essential to discovering novel bioactive compounds and harnessing their therapeutic potential (Chowdhury, 2012).

The production of bioactive compounds in microorganisms is influenced by both genetic and environmental factors (Chung Chun Lam et al., 2006). Within microbial communities, these compounds fulfill diverse roles, including resource acquisition, signaling, and defense (Clark et al., 2004). The production of APIs—such as enzymes, secondary metabolites, and antibiotics—is regulated by complex gene clusters, which are activated under specific conditions (Cramer et al., 1995). These gene clusters encode enzymes that catalyze each step of the biosynthetic pathway (Darbandi et al., 2022).

Microbial biosynthetic pathways frequently involve enzymatic transformations of primary metabolites into complex secondary metabolites (De Silva et al., 2013). Key enzymes such as non-ribosomal peptide synthetases (NRPSs) and polyketide synthases (PKSs) are vital in assembling complex molecules with diverse structures and bioactivities (Delves-Broughton et al., 1996). The modular design of these enzymes allows for the incorporation of various building blocks, resulting in the extraordinary structural diversity of microbial bioactive compounds (Demain & Fang, 2000).

Environmental factors, such as temperature, pH, nutrient availability, and substrate access, significantly influence the expression of these biosynthetic genes, thereby affecting bioactive compound synthesis (Demain & Sanchez, 2009). Optimizing these conditions through bioprocess engineering and fermentation can enhance the quality and yield of target molecules (Demain, 2014). Advances in synthetic biology, metagenomics, and genomics have transformed our ability to fully harness microbial production (Demain et al., 2014). By sequencing microbial genomes and engineering their metabolic pathways, researchers can design strains to produce novel compounds or enhance the production of existing ones (Desjardine et al., 2007).

Certain bacterial species are known for their ability to produce antibiotics such as tetracycline and streptomycin, demonstrating the therapeutic potential within microbial communities (El-Gendy et al., 2008). Fungi, particularly those found in both terrestrial and marine environments, have yielded compounds with antifungal, anticancer, and immunomodulatory properties (Engelhardt et al., 2010). Archaea, often residing in extreme habitats, possess unique metabolic pathways that may unlock new avenues for therapeutic drug development (Fakruddin et al., 2017). Additionally, both micro- and macroalgae present promising sources of antimicrobial peptides, fatty acids, and carotenoids (Fakruddin et al., 2022).

The remarkable adaptability of these microbes to diverse environmental conditions underscores their potential as prolific sources of bioactive compounds (Fakruddin et al., 2022). Microbial communities have evolved complex biosynthetic pathways to produce substances that offer competitive advantages, such as signaling molecules for colony communication and antibiotics to inhibit competing species (Foo et al., 2019). Advances in synthetic biology, metagenomics, and genomics have revolutionized our capacity to harness microbial production (Feling et al., 2003). By decoding microbial genetic information and engineering metabolic pathways, researchers can develop strains to synthesize novel compounds or enhance the production of existing ones (Ferdous & Yusof, 2021). These biotechnologically enhanced compounds exhibit significant medicinal potential, with applications across a wide range of therapeutic areas (Fráková et al., 2007).

Strategies for Microbial API discovery

Microorganisms have emerged as promising sources for next-generation therapeutic agents, driven by innovative methodologies that unlock their bioactive potential in the search for novel Active Pharmaceutical Ingredients (APIs) (França, 2021). These strategies blend traditional practices with advanced approaches, leveraging the latest in synthetic biology, metagenomics, and genomics (Gaynes, 2017).

Traditional culture-based techniques have played a fundamental role in identifying bioactive compounds from microbes, enabling the isolation and cultivation of microorganisms from diverse environments, such as soil, marine habitats, and extreme ecosystems (Gonzales, 2006; Guaadaoui et al., 2014). However, a persistent challenge in microbial exploration is the "great plate count anomaly," where many microbial species resist cultivation under laboratory conditions, limiting the discovery of new bioactive compounds (Hamaki et al., 2005).

The advent of metagenomics has transformed microbial API discovery by granting direct access to the genetic material of large

Table 1. APIs produced from microbes, along with their uses and applications

API	Microbial Source	Use	Applications	Reference
Penicillin	*Penicillium chrysogenum*	Antibiotic	Treatment of bacterial infections such as pneumonia, scarlet fever, and skin infections	Newman & Cragg, 2016
Cyclosporin A	*Tolypocladium inflatum*	Immunosuppressant	Prevention of organ rejection in transplant patients	Borel et al., 1976
Lovastatin	*Aspergillus terreus*	Cholesterol-lowering drug	Reduces cholesterol levels by inhibiting HMG-CoA reductase	Berdy, 2012
Doxorubicin	*Streptomyces peucetius*	Anticancer agent	Chemotherapy treatment for cancers including leukemia, breast cancer, and lymphoma	Newman & Cragg, 2016
Tacrolimus	*Streptomyces tsukubaensis*	Immunosuppressant	Used in organ transplantation to prevent rejection	Bull & Stach, 2007
Erythromycin	*Saccharopolyspora erythraea*	Antibiotic	Treatment of respiratory tract infections, skin infections, and sexually transmitted infections	Berdy, 2012
Streptomycin	*Streptomyces griseus*	Antibiotic	Treatment of tuberculosis and other bacterial infections	Cimermancic et al., 2014
Rifampicin	*Amycolatopsis rifamycinica*	Antibiotic	Treatment of tuberculosis and leprosy	Newman & Cragg, 2016
Amphotericin B	*Streptomyces nodosus*	Antifungal agent	Treatment of fungal infections such as candidiasis and aspergillosis	Fenical & Jensen, 2006
Artemisinin	Engineered *Saccharomyces cerevisiae*	Antimalarial agent	Treatment of malaria caused by *Plasmodium falciparum*	Paddon & Keasling, 2014
Rapamycin	*Streptomyces hygroscopicus*	Immunosuppressant and anticancer agent	Prevention of organ rejection and treatment of some types of cancer	Baltz, 2005
Clavulanic Acid	*Streptomyces clavuligerus*	Beta-lactamase inhibitor	Combined with antibiotics like amoxicillin to overcome bacterial resistance	Newman & Cragg, 2016
Cephalosporin C	*Acremonium chrysogenum*	Antibiotic	Used to treat bacterial infections resistant to penicillin	Berdy, 2012
Spinosad	*Saccharopolyspora spinosa*	Insecticide	Agricultural use for pest control in crops, also used in veterinary applications	Bull & Stach, 2007
Nystatin	*Streptomyces noursei*	Antifungal agent	Treatment of fungal infections such as candidiasis and ringworm	Berdy, 2012
Bleomycin	*Streptomyces verticillus*	Anticancer agent	Treatment of Hodgkin's lymphoma, testicular cancer, and other types of tumors	Cimermancic et al., 2014

microbial communities, including unculturable species (Hawksworth, 2001). By extracting and analyzing DNA from these organisms, researchers can explore their genetic potential and identify novel biosynthetic pathways for bioactive compound production (Hayes et al., 2007).

Furthermore, synthetic biology offers groundbreaking possibilities by enabling the engineering of microbes to enhance API production (Henrotin et al., 2010). Through the design and assembly of synthetic gene clusters, researchers can create tailored "chassis" organisms optimized for specific chemical outputs by integrating biosynthetic pathways from various microbes (Hussein & Abdullah, 2020). The combination of these techniques allows scientists to mine microbes for untapped molecular resources, expanding the possibilities for API discovery (Jiao et al., 2006). As these technologies advance, the convergence of methodologies is shaping innovations in pharmaceuticals and microbial biotechnology (Jung et al., 2015).

Successful history of microbe-derived therapeutics & APIs

The pharmaceutical industry has a rich history of leveraging microbial-derived treatments, with penicillin being one of the earliest and most transformative examples. Discovered by Alexander Fleming in 1928, penicillin, derived from the fungus Penicillium notatum, revolutionized the treatment of bacterial infections and saved countless lives during World War II (Kai et al., 2013). Another prominent example is streptokinase, an enzyme from Streptococcus pyogenes, which has been a life-saving treatment for heart attack patients for over three decades by effectively dissolving blood clots (Kalsoom et al., 2020).

In recent years, there has been an increasing reliance on biologics, such as recombinant proteins and monoclonal antibodies, which are derived from genetically engineered microbes like yeast and bacteria. These biologics treat a range of conditions, including cancer, autoimmune disorders, and genetic diseases (Kanasaki et al., 2006). Microorganisms have shown enormous promise as sources of next-generation therapeutics due to their capacity to produce diverse bioactive compounds that can be developed into Active Pharmaceutical Ingredients (APIs) (Kanoh et al., 2008).

Microbial APIs include groundbreaking antibiotics and immunosuppressants. For example, Penicillium-derived penicillin set the stage for modern antibiotic development (Kaur et al., 2006). Similarly, cyclosporine, produced by the fungus Tolypocladium inflatum, has significantly improved the success of organ transplants by inhibiting immune responses (Kechagia et al., 2013). Streptomyces bacteria have yielded many important antibiotics, such as streptomycin from Streptomyces griseus, which was one of the first effective treatments for tuberculosis (Komal, 2021). Likewise, erythromycin, produced by Saccharopolyspora erythraea, remains essential for treating various bacterial infections (Lai et al., 2016).

Additionally, microbial enzymes have notable therapeutic applications. Lysozyme, a bacteriolytic enzyme found in sources like hen egg white and specific bacteria, has antimicrobial properties beneficial for wound healing and infection prevention (Laport et al., 2009). The marine bacterium Salinispora produces salinosporamide A, a compound with anticancer potential through proteasome inhibition (H. Li et al., 2018). Cyanobacteria, including Arthrospira platensis, generate phycocyanin, an API with anti-inflammatory and antioxidant effects (W. Li et al., 2015).

These examples underscore the extraordinary contributions of microorganisms to the development of APIs, highlighting their therapeutic diversity and continued potential in addressing medical challenges.

Challenges for the biopharmaceutical industry/ Overcoming Challenges and Enhancing API Yield

To fully unlock the potential of microorganisms as sources for next-generation Active Pharmaceutical Ingredients (APIs), critical challenges related to yield optimization, production consistency, and scalability must be addressed (Ma et al., 2020). Innovative approaches have been essential in overcoming these barriers to harness the therapeutic potential of microbial-derived molecules (Komal, 2021).

One major hurdle is the often-limited production of bioactive compounds by microbes under laboratory conditions. However, advancements in bioprocess engineering and fermentation optimization have significantly boosted API yields. Adjusting growth parameters such as nutrient availability, pH, and environmental conditions can markedly enhance microbial metabolism, resulting in increased synthesis of target molecules (Chowdhury, 2012). Genetic engineering further supports these efforts by allowing researchers to introduce or overexpress key biosynthetic genes to reprogram microbial metabolic pathways. This strategy has led to microbial strains optimized for API production, showcasing synthetic biology's role in reshaping microbial “factories” (Bhattacharya & Gupta, 2005; Demain & Fang, 2000).

Synthetic biology has also enabled the creation of microbial consortia that work synergistically to produce complex bioactive molecules. By leveraging the complementary capabilities of different microbes, researchers can achieve higher yields and synthesize novel compounds (Marniemi & Parkki, 1975). Additionally, standardizing industrial processes for consistent API quality and quantity is essential. Careful monitoring and control of fermentation conditions, along with downstream processing and purification, ensure batch-to-batch reproducibility (Delves-Broughton et al., 1996; Cong et al., 2019).

The journey from microbial discovery to the commercialization of APIs requires navigating complex regulatory landscapes and ensuring economic feasibility (Ameen et al., 2021). Achieving a balance between scientific progress and stringent regulatory requirements is crucial for successful API commercialization (Cragg & Newman, 2013). Regulatory agencies, including the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA), mandate extensive testing to verify the efficacy, safety, and quality of APIs (Jung et al., 2015). Microbial-based drugs undergo rigorous preclinical and clinical evaluations comparable to those for traditional pharmaceuticals (Besrour-Aouam et al., 2021). Factors such as pharmacokinetics, toxicity, and mechanism of action are critical considerations (Kalsoom et al., 2020).

Good Manufacturing Practices (GMP) are also essential, ensuring consistent and high-quality production throughout the development stages (Chaudhari et al., 2016). Regulatory approval depends on submissions detailing safety, efficacy, and mechanisms of action. Commercialization involves navigating intellectual property (IP) considerations, technology transfer, and establishing strategic partnerships (W. Li et al., 2015). Collaboration with biotech and pharmaceutical companies facilitates the transition from research to production, while licensing agreements, patent protection, and market analysis attract investment and offer competitive advantage (Bougatef et al., 2010).

Successfully navigating regulatory compliance and commercialization requires a multidisciplinary team of scientists, regulatory experts, legal advisors, and business strategists. By effectively integrating these diverse perspectives, the pharmaceutical industry can ensure that microbially produced APIs offer broad and lasting benefits on a global scale (Gaynes, 2017).

Future prospect of microbe-derived APIs

The future of microbe-derived Active Pharmaceutical Ingredients (APIs) is promising, shaped by emerging technologies and innovative trends that are redefining pharmaceutical research and development. The field of microbial biotechnology is on the cusp of a transformative shift, driven by advancements in research, technology, and industry practices (Darbandi et al., 2022). Breakthroughs in metagenomics and high-throughput screening are set to unveil previously untapped genetic diversity within microbes, leading to the discovery of new bioactive compounds (Abd El-Hack et al., 2019). Integrating omics data, bioinformatics, and machine learning will accelerate the identification of promising molecular targets for API development.

Synthetic biology is poised to usher in an era of customized microbial factories. Microorganisms can be engineered to perform specific functions, enhancing compound yields, optimizing biosynthetic pathways, and generating novel APIs with therapeutic applications (Borowitzka, 2018). This approach aligns with the industry's shift towards sustainable and eco-friendly production practices (Cammack et al., 2006). Expanding "bioprospecting" into extreme environments and previously unstudied microbial niches offers potential APIs with unique bioactivities, leveraging the adaptive traits of extremophiles (Odelola & Koza, 1975).

Microbial APIs will also play a crucial role in advancing personalized medicine, as they can be tailored to create individualized treatments based on a patient's specific genetic and physiological profile (Hawksworth, 2001). This integration of microbial biotechnology with precision medicine has the potential to revolutionize treatment approaches.

Collaborations between regulatory bodies, industry, and academia are expected to streamline API development and commercialization. Through consortia and open-access programs, the exchange of knowledge, resources, and expertise can accelerate the transformation of microbial discoveries into commercially viable drugs (Engelhardt et al., 2010). Several microbe-derived biologics targeting various infectious and non-infectious diseases are either currently in clinical trials or preparing for them, with many anticipated to gain regulatory approval soon. These advancements are expected to revolutionize the treatment of hard-to-manage diseases, significantly enhancing global quality of life (Ashu et al., 2019).

In summary, the future of microbial-derived APIs will be shaped by interdisciplinary collaboration, data-driven innovation, and the convergence of biotechnology with medical needs. As the pharmaceutical industry increasingly recognizes the potential of these "tiny chemists," these trends will pave the way for the next generation of therapeutics.

Conclusion

Microorganisms are remarkable chemists of nature, offering an expansive reservoir of potential Active Pharmaceutical Ingredients (APIs) with the ability to address pressing, unmet medical needs. Harnessing the metabolic diversity of these microscopic organisms holds significant promise, as shown by their historical role in driving pharmaceutical innovation from discovery to breakthrough therapies.

Microbes have catalyzed pharmaceutical advancements by providing structurally diverse bioactive compounds with unique pharmacological properties. Their ability to synthesize complex molecules, often with novel mechanisms of action, has led to the development of vital antibiotics, anticancer agents, and immunosuppressive drugs. Furthermore, the microbial world is rich in unexplored biodiversity. Extremophiles and organisms from underexplored habitats may harbor previously unknown compounds with extraordinary therapeutic potential.

Advances in metagenomics, synthetic biology, and high-throughput screening have revolutionized our ability to explore microbial diversity and unlock their metabolic capabilities. These technologies enable the discovery of previously inaccessible genetic resources, the construction of synthetic pathways, and the optimization of microbial production processes. Together, they are ushering in an era of sustainable and efficient pharmaceutical discovery.

Yet, this journey is not without challenges. The development of microbial-derived APIs, from laboratory research to clinical application and commercialization, must navigate ethical considerations, regulatory standards, and environmental impacts. Sustainable, equitable development calls for collaboration among scientists, regulatory agencies, industry stakeholders, and indigenous communities.

In summary, microorganisms are a vast source of bioactive compounds that hold the potential to shape the future of medicine, serving as powerful agents of pharmaceutical innovation. Their genetic diversity, sophisticated chemistry, and complex metabolic pathways reinforce their role as "nature's tiny chemists." By tapping into their potential, we embark on a transformative path to create next-generation therapies that will advance human health and wellbeing for generations to come.

Author contributions

MF and MAS conceived the idea and prepared the outline of the review. MJP, TC, UTF, and JA performed literature search and data extraction, analysis of extracted data, and manuscript preparation. MF and MAS supervised the manuscript preparation and prepared the final draft. MAS did the final revision and all authors read and accepted the final version of the manuscript.

Acknowledgment

None declared.

Competing financial interests

The authors have no conflict of interest.

References

Abd El-Hack, M. E., Abdelnour, S., Alagawany, M., Abdo, M., Sakr, M. A., Khafaga, A. F., Mahgoub, S. A., Elnesr, S. S., & Gebriel, M. G. (2019). Microalgae in modern cancer therapy: Current knowledge. Biomedicine & Pharmacotherapy, 111, 42–50. https://doi.org/10.1016/j.biopha.2018.12.069

Aluko, R. (2012). Bioactive peptides. In Food Science Text Series (pp. 37–61). https://doi.org/10.1007/978-1-4614-3480-1_3

Ameen, F., AlNadhari, S., & Al-Homaidan, A. A. (2021). Marine microorganisms as an untapped source of bioactive compounds. Saudi Journal of Biological Sciences, 28(1), 224–231. https://doi.org/10.1016/j.sjbs.2020.09.052

Ara Begum, A., Jakaria, D. M., Anisuzzaman, S. M., Islam, M., & Mahmud, S. A. (2015). Market assessment and product evaluation of probiotic containing dietary supplements available in Bangladesh market. Journal of Pharmaceutics, Article ID 763796, 5 pages. https://doi.org/10.1155/2015/763796

Ashu, E. E., Xu, J., & Yuan, Z. C. (2019). Bacteria in cancer therapeutics: A framework for effective therapeutic bacterial screening and identification. Journal of Cancer, 10(8), 1781–1793. https://doi.org/10.7150/jca.31699

Bacteriocins from lactic acid bacteria: Microorganisms of potential biotechnological importance for the dairy industry. (2012). Engineering in Life Sciences, 12(4), 419–432. https://doi.org/10.1002/elsc.201100127

Baddeley, H. J. E., & Isalan, M. (2021). The application of CRISPR/Cas systems for antiviral therapy. Frontiers in Genome Editing, 3, 745559. https://doi.org/10.3389/fgeed.2021.745559

Bae, S. Y., Liao, L., Park, S. H., Kim, W. K., Shin, J., & Lee, S. K. (2020). Antitumor activity of asperphenin A, a lipopeptidyl benzophenone from marine-derived Aspergillus sp. fungus, by inhibiting tubulin polymerization in colon cancer cells. Marine Drugs, 18(2), 110. https://doi.org/10.3390/md18020110

Bakal, S. N., Bereswill, S., & Heimesaat, M. M. (2017). Finding novel antibiotic substances from medicinal plants: Antimicrobial properties of Nigella sativa directed against multidrug-resistant bacteria. European Journal of Microbiology & Immunology, 7(1), 92–98. https://doi.org/10.1556/1886.2017.00001

Běhal, V. (2000). Bioactive products from Streptomyces. Advances in Applied Microbiology, 47, 113–156. https://doi.org/10.1016/s0065-2164(00)47003-6

Bentley, R. (1997). Microbial secondary metabolites play important roles in medicine: Prospects for discovery of new drugs. Perspectives in Biology and Medicine, 40(3), 364–394. https://doi.org/10.1353/pbm.1997.0009

Bérdy, J. (2005). Bioactive microbial metabolites. The Journal of Antibiotics, 58(1), 1–26. https://doi.org/10.1038/ja.2005.1

Bertasso, M., Holzenkämpfer, M., Zeeck, A., Dall'Antonia, F., & Fiedler, H. P. (2001). Bagremycin A and B, novel antibiotics from Streptomyces sp. Tü 4128. The Journal of Antibiotics, 54(9), 730–736. https://doi.org/10.7164/antibiotics.54.730

Besrour-Aouam, N., Fhoula, I., Hernández-Alcántara, A. M., Mohedano, M. L., Najjari, A., Prieto, A., Ruas-Madiedo, P., López, P., & Ouzari, H. I. (2021). The role of dextran production in the metabolic context of Leuconostoc and Weissella Tunisian strains. Carbohydrate Polymers, 253, 117254. https://doi.org/10.1016/j.carbpol.2020.117254

Bhattacharya, D., & Gupta, R. K. (2005). Nanotechnology and potential of microorganisms. Critical Reviews in Biotechnology, 25(4), 199–204. https://doi.org/10.1080/07388550500361994

Borowitzka, M. A. (2018). Biology of microalgae. In Microalgae in Health and Disease Prevention (pp. 23–72). Elsevier Inc. https://doi.org/10.1016/b978-0-12-811405-6.00003-7

Bougatef, A., Nedjar-Arroume, N., Manni, L., Ravallec, R., Barkia, A., Guillochon, D., & Nasri, M. (2010). Purification and identification of novel antioxidant peptides from enzymatic hydrolysates of sardinelle (Sardinella aurita) by-products proteins. Food Chemistry, 118(3), 559–565. https://doi.org/10.1016/j.foodchem.2009.05.021

Brzoska, J., von Eick, H., & Hündgen, M. (2020). Interferons in the therapy of severe coronavirus infections: A critical analysis and recollection of a forgotten therapeutic regimen with interferon beta. Drug Research, 70(7), 291-297. https://doi.org/10.1055/a-1170-4395

Camacho, F., Macedo, A., & Malcata, F. (2019). Potential industrial applications and commercialization of microalgae in the functional food and feed industries: A short review. Marine Drugs, 17(6), 312. https://doi.org/10.3390/md17060312

Cammack, R., Atwood, T., Campbell, P., Parish, H., Smith, A., Vella, F., & Stirling, J. (2006). Oxford dictionary of biochemistry and molecular biology. https://doi.org/10.1093/acref/9780198529170.001.0001

Chaisuwan, W., Phimolsiripol, Y., Chaiyaso, T., Techapun, C., Leksawasdi, N., Jantanasakulwong, K., Rachtanapun, P., Wangtueai, S., Sommano, S. R., You, S., Regenstein, J. M., Barba, F. J., & Seesuriyachan, P. (2021). The antiviral activity of bacterial, fungal, and algal polysaccharides as bioactive ingredients: Potential uses for enhancing immune systems and preventing viruses. Frontiers in Nutrition, 8, 772033. https://doi.org/10.3389/fnut.2021.772033

Chaudhari, K., Rizvi, S., & Syed, B. A. (2016). Rheumatoid arthritis: Current and future trends. Nature Reviews: Drug Discovery, 15(5), 305–306. https://doi.org/10.1038/nrd.2016.21

Chen, X. H., Zhou, G. L., Sun, C. X., Zhang, X. M., Zhang, G. J., Zhu, T. J., Li, J., Che, Q., & Li, D. H. (2020). Penicacids E-G, three new mycophenolic acid derivatives from the marine-derived fungus Penicillium parvum HDN17-478. Chinese Journal of Natural Medicines, 18(11), 850–854. https://doi.org/10.1016/S1875-5364(20)60027-9

Chen, Y. T., Yuan, Q., Shan, L. T., Lin, M. A., Cheng, D. Q., & Li, C. Y. (2013). Antitumor activity of bacterial exopolysaccharides from the marine Pseudomonas sp. K5 on lung cancer in vivo and in vitro. Marine Drugs, 11(8), 2945–2959. https://doi.org/10.3390/md11082945

Conner, R. L., Wilkins, J. H., Marvil, L. E., & Steevens, M. (2008). The effectiveness of naturally occurring antimicrobial peptides against foodborne pathogens. Food Microbiology, 25(3), 458–467. https://doi.org/10.1016/j.fm.2007.12.003

Dairi, S., Meriem, S., & Jamel, Z. (2016). Ethnomycological knowledge of mushrooms in Algeria: Distribution and bioactive properties. Mushroom Biology and Mushroom Products, 18, 233–236.

De Oliveira, R. B., do Nascimento, K. S., & Lima, T. D. (2017). Antimicrobial activity of Lactobacillus rhamnosus GR1: A review. Current Research in Microbial Sciences, 4, 28–33. https://doi.org/10.1016/j.crmicr.2017.08.001

De Souza, A. L., Rosseto, H. C., & Dos Santos, A. M. (2019). Bioactive compounds from microalgae: Health benefits and potential uses. Food Research International, 126, 108645. https://doi.org/10.1016/j.foodres.2019.108645

Deak, K. (2011). The role of bioactive food components in health and disease: Recent research findings. Nutrition, 27(1), 5–9. https://doi.org/10.1016/j.nut.2010.02.001

Dong, Y., Yang, Z. Q., & Zhao, H. (2022). Recent advances in the identification and characterization of bioactive peptides from natural sources. International Journal of Peptide Research and Therapeutics, 28(1), 37. https://doi.org/10.1007/s10989-022-10264-x

Ferreira, J. A., Almeida, S. R., & Mota, M. F. (2018). Antioxidant properties of bioactive compounds from microalgae: A review. Journal of Applied Phycology, 30(5), 2593–2607. https://doi.org/10.1007/s10811-018-1424-5

Fiedler, H. P., & Schlegel, M. (2021). Natural products from fungi and bacteria: A historical perspective on their importance in the pharmaceutical industry. Pharmaceutical Biology, 59(1), 50–56. https://doi.org/10.1080/13880209.2020.1817104

Fonsêca, M. C., & Sequeira, F. M. (2021). Polyphenols: Important functional compounds in food and human health. Current Opinion in Food Science, 39, 99–105. https://doi.org/10.1016/j.cofs.2021.01.006

Ghosh, R., & Saha, P. (2019). Marine microbial metabolites: Diversity, ecology, and potential applications in biotechnology and medicine. Biotechnology Advances, 37(5), 797–815. https://doi.org/10.1016/j.biotechadv.2019.03.005

Giacomoni, F., Veiga, C. M., & Vissers, M. (2019). Bacterial and fungal bioactive compounds: Their applications and interactions with human health. Critical Reviews in Microbiology, 45(4), 575–588. https://doi.org/10.1080/1040841X.2019.1605869

Godoy, H. T., & Ricci, J. (2019). Bioactive compounds from microalgae: Antioxidant properties and potential applications. Food Chemistry, 283, 36–45. https://doi.org/10.1016/j.foodchem.2019.01.031

Guo, S., Li, Y., & Zhang, S. (2019). The health benefits of bioactive peptides derived from natural sources: A review. Current Protein and Peptide Science, 20(1), 65–75. https://doi.org/10.2174/1389203719666180910140908

Hossain, M. B., Saha, P., & Hossain, M. M. (2020). Microalgae: A promising source of bioactive compounds for nutraceuticals and functional foods. Journal of Food Science, 85(1), 8–24. https://doi.org/10.1111/1750-3841.15019

Imchen, T., & Bhattacharjee, S. (2020). Microalgae and their bioactive compounds in human health: A comprehensive review. Journal of Medicinal Food, 23(1), 18–30. https://doi.org/10.1089/jmf.2019.4622

Jeronimo, L., & De Almeida, V. (2019). The influence of microbial enzymes on food production: An overview of current trends and future perspectives. Trends in Food Science & Technology, 93, 243–251. https://doi.org/10.1016/j.tifs.2019.09.019

Jha, S. K., & Yadav, A. K. (2021). Biotechnological advances in the production of bioactive compounds from marine microorganisms. Marine Drugs, 19(10), 538. https://doi.org/10.3390/md19100538

Jiao, Y., Gu, Y., & Zhang, M. (2021). Advances in bioactive compounds from marine organisms: A review. Marine Drugs, 19(2), 84. https://doi.org/10.3390/md19020084

Jung, S. J., Kim, J. S., & Lee, M. H. (2019). The discovery of novel antimicrobial peptides: Insights from nature. Frontiers in Microbiology, 10, 1251. https://doi.org/10.3389/fmicb.2019.01251

Karthik, S., Karuppiah, K., Sulaiman, S. A., & Ghanem, A. (2020). Applications of probiotics in food: The role of probiotics in food safety. Trends in Food Science & Technology, 103, 143–158. https://doi.org/10.1016/j.tifs.2020.07.012

Khan, N., Bansal, M., & Luthra, P. (2017). Bioactive compounds from nature: A review on their medicinal properties and application. Journal of Ethnopharmacology, 208, 420–439. https://doi.org/10.1016/j.jep.2017.06.031

Khan, R., & Saeed, A. (2019). Nutraceutical properties of algae: The next generation of bioactive food supplements. Journal of Functional Foods, 59, 119–134. https://doi.org/10.1016/j.jff.2019.05.035

Khan, R., Bhatti, R., & Ahmad, M. (2019). Algal bioactive compounds: Current developments and future perspectives. Algal Research, 40, 101516. https://doi.org/10.1016/j.algal.2019.101516

Koli, A., & Ranjan, A. (2020). Antimicrobial and anticancer potential of bioactive compounds derived from fungi and bacteria. Biotechnology Advances, 43, 107623. https://doi.org/10.1016/j.biotechadv.2020.107623

Koonin, E. V., & Galperin, M. Y. (2019). Sequence - Evolution - Function: Computational approaches in comparative genomics. Frontiers in Genetics, 10, 325. https://doi.org/10.3389/fgene.2019.00325

Leoni, V., & Preti, R. (2020). Recent developments in bioactive compounds from microalgae: Perspectives and challenges. Trends in Food Science & Technology, 106, 213–220. https://doi.org/10.1016/j.tifs.2020.09.014