CHAPTER 14

Microbial Natural Products: A Source of Novel Antibiotics and Immunomodulators

AMNA REHMAN[1*], FEHMEEDA NASEEM[1], SAWERA[1], ASMA ANWAR[1], HIFSA AHMAD[1], DILWASH QADIR[2], MUHAMMAD SAKANDAR MAJID[1], MUHAMMAD ZAID SALAR[1]

[1]Department of Zoology, Wildlife and Fisheries, University of Agriculture, Faisalabad, Pakistan
[2]Department of Computer Science, University of Agriculture, Faisalabad, Pakistan
[*]Corresponding author: amnarehman150@gmail.com

ABSTRACT: Natural products (NPs), especially those derived from microbes, have been important in serving as crucial sources of therapeutic agents because of their distinct bioactivities and structural variety. This chapter explores the historical, biological and pharmacological significance of microbial natural products, focusing on their roles in antimicrobial, anticancer, immunosuppressive, and anti-inflammatory therapies. Microorganisms such as bacteria and fungi produce secondary metabolites that demonstrate potent biological effects, including antibiotic, antiviral, antifungal, and immunomodulatory properties. With rising antimicrobial resistance, the need for novel treatments has led to emerging strategies like CRISPR-Cas gene editing, efflux pump inhibitors, and combination therapies. Commercial antibiotic development remains challenged by high costs and low profitability. Global collaboration and sustainable practices are essential to address the growing threat of antimicrobial resistance and to support future drug discovery from microbial sources.

Keywords: Microbes, Anti-inflammatory, Immunomodulatory, CRISPR-Cas, Antibiotic

The analysis of the effectiveness of bioactive compounds present in nature is of much interest for the drug-discovery (Ebada et al., 2008). Natural products are byproducts and/or metabolites of living organisms like animals, plants and microbes. The use of natural products as medication is based on the fact that the products are readily available and are cheap compared to modern medication, especially in underdeveloped countries. Moreover, they are of utmost value as drug research and discovery sources because of their unusual composition of chemicals and wide set of bioactivities (Shen et al., 2015).

Nature has been seen to possess very numerous structurally diverse secondary metabolites. The bioactive compounds can be immunosuppressive, anticancer and antibacterial drugs being of clinical significance (Ahmed et al., 2025). Moreover, they act as growth promoters, herbicides, insecticides and anti-parasitics in agricultural and veterinary applications. The reports by the World Health Organization (WHO) have shown that an average of 60 percent of the people in the world enjoy their health care services offered by traditional medicine (El-Naggar et al., 2021). The utilization of natural products as medicines by human beings has likely occurred since time immemorial, long before the first recorded instances. The earliest records are of the juice of the poppy seed, *Papaver somniferum,* and the oils of Cedrus species (cedar). About 1000 products of plant origin are covered in ancient Mesopotamia (2600 BC) in the first known records (Newman et al., 2000). The ancient Egyptian Ebers Papyrus (1550 BC) contains over 800 complex prescriptions along with more than 700 natural components, such as aloevera (aloe) and the oil of *Ricinus communis* (castor) (Zhong et al., 1999).

How to Cite: Rehman A, F Naseem, Sawera, A Anwar, H Ahmad, D Qadir, MS Majid & MZ Salar, 2025. Microbial Natural Products: A source of novel antibiotics and immunomodulators. In: Natural Products in Biomedical Research (Ijaz MU & A Ashraf, Eds.): FahumSci, Lahore, Pakistan, pp: 139-148. ISBN: 978-627-7745-15-8. https://doi.org/10.61748/NPBR.2025/14

Microorganisms have played a pivotal role in advancing natural product chemistry and revolutionizing medical therapeutics. Since the discovery of penicillin in 1929, microorganisms have been recognized as a valuable source of diverse and unique bioactive compounds (Fenical et al., 1993). A large number of antibiotics available today are derived from microbial sources, and more than 120 of the most important drugs in modern medicine originate from terrestrial microorganisms (Shaaban et al., 2012). The current chapter discusses the role of microbial natural products as promising therapeutic agents.

IMPORTANCE OF MICROBIAL NATURAL PRODUCTS IN MEDICINE

Natural products play promising role in medicine as immunosuppressive, anti-bacterial, anti-cancer, and anti-inflammatory agents (Fig. 1).

Antibiotic Agents

Penicillium notatum produces the well-known antibiotic penicillin, a secondary metabolite effective against various Gram-positive bacteria responsible for diseases such as scarlet fever, gonorrhea, diphtheria, meningitis, and pneumonia (Tan & Tatsumura, 2015).

Penicillin and vancomycin belong to the non-ribosomal peptide antibiotics (Fischbach & Walsh, 2006). Non-ribosomal peptides represent one of the most prevalent and structurally diverse groups of secondary metabolites. They are assembled by non-ribosomal peptide synthetases (NRPS) and possess potent bioactive properties with significant therapeutic potential. Another important antibiotic class, the aminoglycosides, functions by binding to the 30S rRNA subunit of bacterial ribosomes, thereby inhibiting protein synthesis and disrupting bacterial growth. The first aminoglycoside to be identified in 1944 was streptomycin, which is produced by *S. griseus* and helps treat pulmonary tuberculosis. Semi-synthetic derivatives of natural products have been developed into aminoglycoside antibiotics, including dibekacin, netilmicin, amikacin, and isepamicin (Pham et al., 2019).

Anticancer Agents

Polyketide actinomycin was the first antibiotic proven to have anticancer effects and was isolated originally in 1940 from *Streptomyces parvulus*

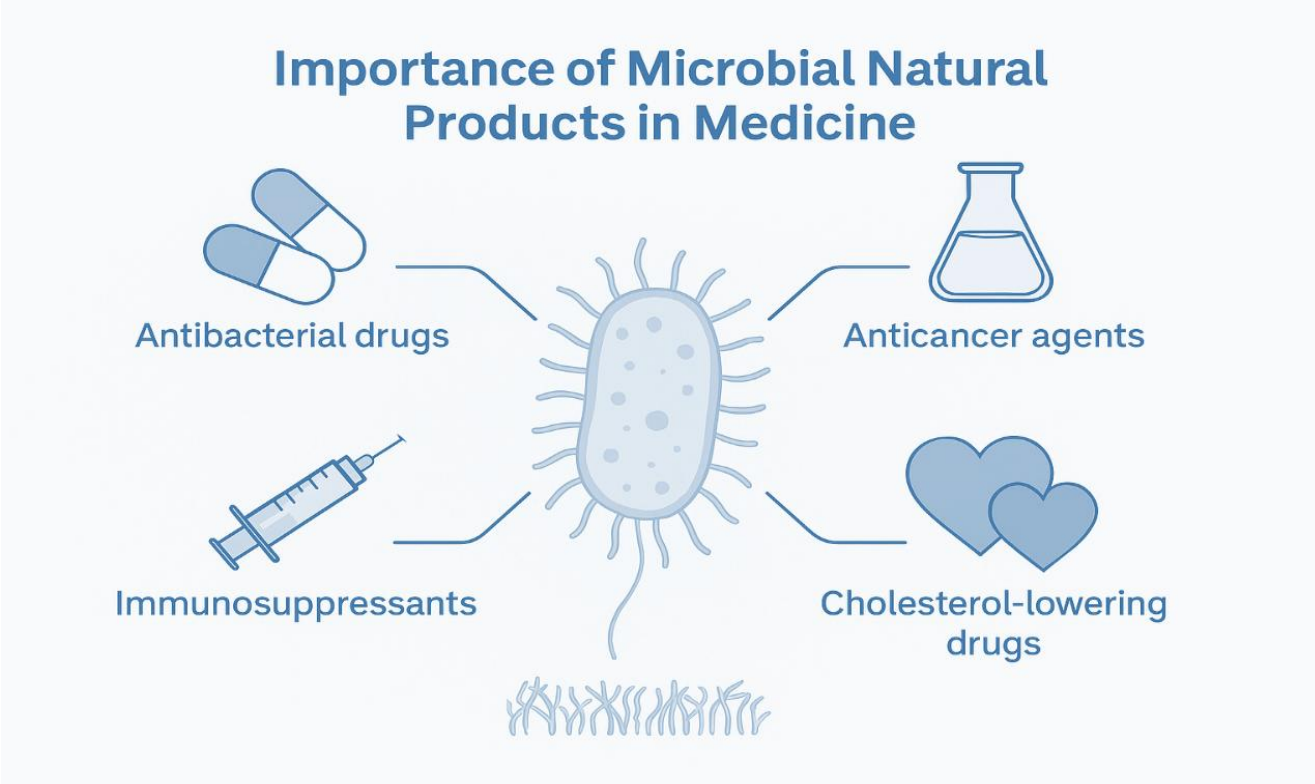

Fig. 1. Importance of microbial natural products

(Hollstein, 1974). Specifically, the FDA-approved actinomycin D, sometimes referred to as dactinomycin, has been clinically utilized widely as an anticancer medication to treat a variety of malignancies, namely, Ewing's sarcoma, pediatric rhabdomyosarcoma, and metastatic Wilms' tumor, non-seminomatous testicular cancer.

Immunosuppressive agents

FK506 (tacrolimus) and rapamycin (sometimes called sirolimus) are natural microbial substances that have immunosuppressive tendencies. Rapamycin suppresses the immune system by inhibiting cell cycle progression of lymphocytes and blocking the growth of platelet-derived growth factors, Interleukins-2, Interleukins-3 (IL-2, IL-3), and epidermal growth factors (Soliman, 2013). Additionally, rapamycin works in combination with other immunosuppressants, like cyclosporin, to lower acute renal allograft rejection and renal damage. Rapamycin has a number of biological activities in addition to its immunosuppressive action, including lifespan extension properties, antineoplastic, anticancer and neuroregenerative / neuroprotective (Yoo & Mazmanian, 2017). Fig. 2 shows the microbial natural products with immunosuppressive properties.

Anti-inflammatory properties

Additionally, several natural substances have anti-inflammatory properties. FK506 has also explained effectiveness in treating chronic inflammatory condition that is refractory rheumatoid arthritis. By reducing the proliferation and activation of inflammatory cells as well as the expression of inflammatory cytokines, rapamycin also has a neuroprotective effect by suppressing the inflammatory response resulting from spinal cord injury (Song et al., 2015).

BACTERIAL AND FUNGAL SECONDARY METABOLITES IN ANTIMICROBIAL THERAPY

Secondary metabolites found in bacteria, fungi, algae, plants and animals, examples include

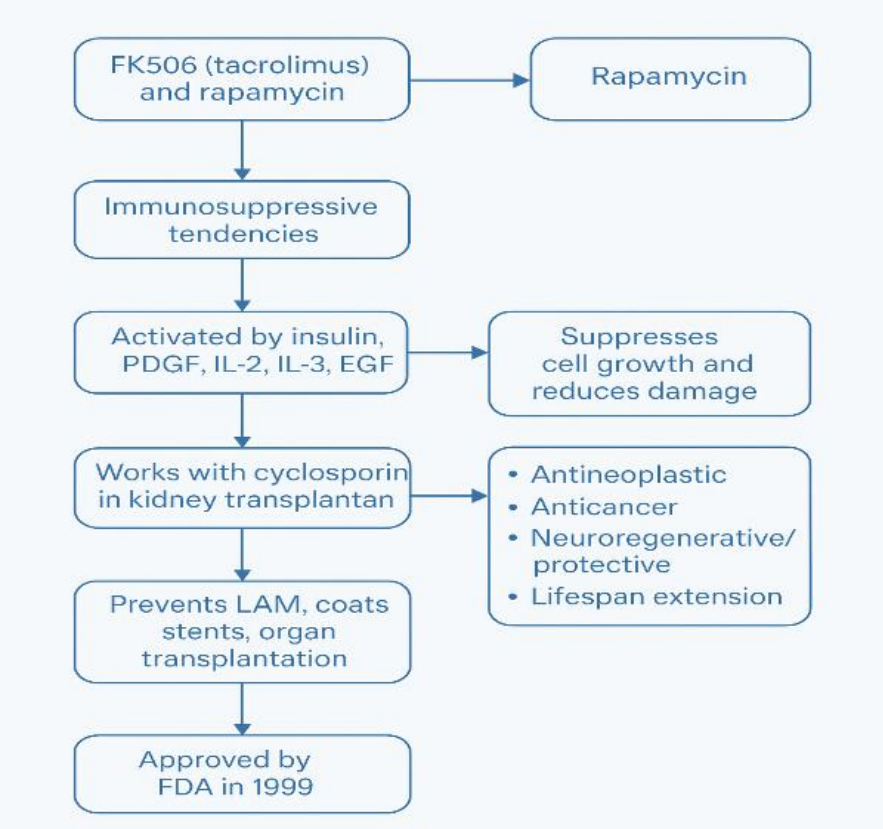

Fig. 2. Microbial natural products as immunosuppressive agents

terpenes, phenolics and alkaloids Fungi release secondary metabolites, known as “extrolites,” into the environment that are volatile, excreted compounds, incorporated into cell structures, or retained within the cell. Our consideration of secondary metabolites stems from screening in pharmaceuticals, agriculture and academia to identify beneficial small molecules. Bioassays help isolate compounds from fermentation extracts, which are then identified using techniques like NMR, mass spectrometry and X-ray crystallography. Fungi and bacteria also produce different polyketides. Some metabolites, like gibberellins, are found in both fungi and plants (Rodrigues et al., 2012).

Bacteria are considered a fascinating source of bioactive compounds, known for their remarkable structural diversity and wide range of biological activities. Bacteria that live in seawater and sediments and various aquatic organisms generate numerous special medicinal substances which exhibit multiple therapeutic functions (Piel, 2009). Marine bacteria produce active biological substances that enable them to defend against environmental dangers while they obtain nutrients (including carbon) from their host organism. These bacteria produce various bioactive substances (Alexpandi et al., 2019). Table 1 shows microbial secondary metabolites and their uses.

Antimicrobial Potential of Marine Actinobacteria

Phylum Actinobacteria synthesize a range of useful secondary metabolites. Actinobacteria play an essential role in ecology by decomposing and recycling complex organic nutrients. Additionally, they are recognized for producing a variety of novel bioactive secondary metabolites with significant pharmaceutical and medical potential (Bull & Stach, 2007). Chlorocatechelin, another compound isolated from microbial *Streptomyces* species, has demonstrated strong inhibitory effects against a wide range of bacterial and fungal pathogens. They are newly identified siderophores that feature chlorinated catecholate groups and an acylguanidine moiety in their structure (Kishimoto et al., 2014).

Fungal Secondary Metabolites as Antibiotics

Fungi exist as powerful producers of bioactive secondary metabolites which have helped scientists achieve new medical discoveries for animal and human health. The β-lactam antibiotics, which include penicillin and cephalosporin, stand out as the most important medical discoveries. Penicillin discovery brought a medical revolution which led to essential technological progress in microbiology, chemistry, biochemistry and engineering fields. Moreover, it laid the foundation for the emergence and growth of the modern pharmaceutical industry. Numerous secondary metabolites can be produced by fungi, and these are usually influenced by the fungus's developmental stage as well as environmental variables including temperature, light, and nutrient concentrations (Calvo et al., 2002). *Aspergillus* fungi, in particular, are capable of producing a great number of such chemicals. Over 226 known secondary metabolites are secreted by filamentous fungus, *Aspergillus fumigatus*, that belong to various classes i.e., polyketides, cyclic peptides, alkaloids and sesquiterpenoids (Frisvad et al., 2009). The best investigated representative of fungal secondary metabolites synthesized by *A. fumigatus* is gliotoxin, which consist of an intramolecular disulfide bond to a diketopiperazine backbone (Gardiner & Howlett, 2005).

Mechanisms of Action of Microbial Antibiotics

The β-lactam antimicrobials are also one of the oldest antimicrobial agents used in vast quantities. This is a very wide group with a β-lactam ring within their molecular structure, comprising penicillin derivatives (penams), cephalosporins (cephems), monobactams and carbapenems (Holten & Onusko, 2000). They irreversibly inhibit the enzyme transpeptidase used by bacteria to build their cell walls. The final stage in the peptidoglycan formation is carried out by transpeptidase, referred to as penicillin-binding proteins (PBPs). PBPs bind to the D-Ala-D-Ala peptidoglycan end located in the end of muropeptides, which are the precursors of the peptidoglycan. The β-lactam antibiotics are the type of antibiotic that mimics the site and inhibit PBP crosslinking of peptidoglycan (Vollmer et al., 2008).

Mechanism of action of aminopenicillins

The penicillin family of antibiotics includes the aminopenicillins. The β-lactam ring that contains nitrogen having four-membrane in the center of this category of antibiotics' structure, which is essential to their antibacterial activity, is what distinguishes them from other penicillins. Two examples of aminopenicillins are ampicillin and amoxicillin & clavulanic acid. Sometimes, the β-lactamase inhibitor clavulanic acid is used with amoxicillin. This combination helps overcome bacterial antibiotic resistance caused by β-lactamase synthesis and broadens the spectrum of action against germs. The bacterial β-lactamase enzyme from *Streptomyces clavuligerus* is significantly inhibited by clavulanic acid (Ser et al., 2016). Aminopenicillin has minimal antibacterial activity against the majority of entities when taken alone, but when combined with β-lactam antibiotics, it stops microbial lactamase from inactivating the antibiotic. By binding to and permanently blocking the β-lactamase, it restores the antibacterial action of β-lactam antibiotics against bacteria that secrete lactamases. Additionally, concomitant penicillin may become more effective by deactivating β-lactamase (Bush & Bradford, 2019).

MICROBIAL NATURAL PRODUCTS AS IMMUNOMODULATORS

An immune response is the host immune system's coordinated reaction to neutralize or eliminate the effects of any foreign substance or infection that is identified (Finlay & McFadden, 2006). It involves recognizing the invaders and developing defense strategies. Adaptive immunity relies heavily on lymphocytes, such as B-cells, T-cells, and the antibodies they secrete. The primary function of lymphocyte T-cells is cell-mediated immunity (Singh et al., 2017).

Immunomodulators are any biological or synthetic substances that can alter innate, adaptive, or both immune responses. These are classified as immunosuppressants and immunostimulants. Both stimulatory and suppressive effects are possible with certain immunomodulators.

Immunostimulation strengthens the immune system, while immunosuppression lowers the immune system. These are essential components for immunomodulation. In autoimmune diseases, an active immune system leads to the loss of self-entity (normal immune cells) by making it hard for the body to differentiate itself from the non-self (foreign antigens). In order to moderate the immune system to almost normal functioning, immunosuppressants are required. Additionally, immunomodulators have the ability to trigger several cellular processes, including protein synthesis, lipid peroxidation, free radicals and apoptosis. In addition, they target different transcription factors and immunological responses (Kumar et al., 2022).

Natural products made from microbial sources have shown the immunomodulatory effects through mounting research (Ramirez et al., 2022). Natural compounds that are produced by microbes could be utilized as new drugs. An innovative approach to this therapy is the use of immunomodulation to improve host immunity instead of just direct antibacterial action. Immunomodulators is one of the promising classes for treatments of infectious diseases (Ruh et al., 2017). To preserve homeostasis and improve all consequent immunological responses, immunomodulatory medications include synthetic, recombinant, and natural immunomodulatory preparations have been utilized to either activate or inhibit the immune system's defenses.

NEW STRATEGIES TO COMBAT ANTIMICROBIAL RESISTANCE (AMR)

The discovery of antibiotics was one of the most effective medical discoveries in the twentieth century. However, their utility is now being put at stake by the advent of antimicrobial resistance (AMR), which is a normal effect of nature where microorganisms develop resistance to medicine. In the first place, this opposition is advanced by excessive antibiotics use, patients' non-compliance with treatment and lack of new antibiotics (Annunziato, 2019). Treatment failure also happens because of sub-therapeutic exposure to drugs through improper dosing, organ pathophysiology and drug distribution.

AMR can either be intrinsic or acquired resistance. Intrinsic resistance belongs to the category where bacteria do not have the target of the

drug in the first place, whereas acquired resistance may happen as a result of mutation or a foreign genetic material (Blair et al., 2015). Plasmids and transposons aid in horizontal gene transfer, which disseminates the resistance genes in the bacterial population. They usually contain beneficial genes that can make bacteria durable and survive in harmful conditions and they allow transferring resistance between Gram-negative bacteria and Gram-positive bacteria (Aslam et al., 2018).

Limitations of current antibiotics and treatment failure

Antimicrobial resistance (AMR) poses a challenge to the efficacy of antibiotics and puts additional burdens on infectious diseases (Rafiq, 2025). Since the years of 2015 and 2025, the development of new technologies such as antibacterial peptides or phage therapy and CRISPR has gained significant attention (Czaplewski et al., 2016). Amplified diagnostics and WHO-approved stewardship initiatives encourage sensible practice of antibiotics in animal and human domains to stop resistance (WHO, 2020). The incidence of AMR factors increases the threat of smallpox. The new methods embrace a better diagnostics practice, population education and country-based plans in line with the WHO recommendations. Antarctic extreme habitats are promising sources of new antimicrobials, as environmental stress induces bacteria to produce unique bioactive metabolites. The search for new antibiotics focuses on *Streptomyces* and extremophiles from unexplored habitats (Mehetre et al., 2018).

MDR Bacteria Targeted Elimination Using the CRISPR-Cas System

Sublethal antibiotic doses allow bacteria to survive by altering phenotypes, driving drug-resistant infections. New antibacterial approaches must focus on narrow-spectrum antibiotics and rapid adaptation to resistant bacteria. The CRISPR-Cas system, consisting of Cas proteins and CRISPR arrays, creates complexes that target specific DNA or RNA sequences by modifying guide RNA. This method, promising for combating superbugs, uses delivery vectors like phages, nanoparticles, and plasmids to induce lethal DNA breaks in bacteria (Shafi et al., 2022).

Alternative methods for treating antibiotics

Combination Therapy I: Increases Membrane Permeability: Polymyxins kill Gram-negative bacteria by disrupting membranes. Tran et al. (2018) discovered that mitotane, a non-antibiotic drug, enhances polymyxin B's effect against resistant strains. The bacterial outer membranes undergo disruption by SPR741 which leads to improved antibiotic effectiveness. Scientists need more research to understand how this substance works with carbapenems against bacteria that resist treatment because of porin deficiencies (Streicher, 2021).

Combination Therapy II: Decreases Activity of Efflux Pump: Efflux pumps cause antimicrobial resistance by removing drugs from bacteria. The Resistance-Nodulation-cell Division (RND) family dominates multidrug resistance in gram-negative bacteria. Efflux pump inhibitors (EPIs) like phenylalanine-arginine β-naphthylamide (PaβN) block these pumps, increasing antibiotic levels inside bacteria, permeabilizing membranes, and reducing resistance, especially in P. aeruginosa (Ghosh et al., 2019).

Combination Therapy III: Prevents Kinase and Intrinsic Antibiotic Resistance: Two-component systems (TCS) help bacteria sense and adapt to environments, controlling virulence and resistance. PhoP/PhoQ in Salmonella regulates infection and is inhibited by quinazoline compounds. Eukaryotic-like serine/threonine kinases (eSTKs), including PASTA kinases, affect bacterial metabolism, pathogenicity, and antibiotic susceptibility, making them potential drug targets (Ianiro et al., 2018).

FUTURE PERSPECTIVES AND CHALLENGES

Exploring Microbial Biodiversity for Novel Compounds

Studies on marine-derived fungi showed that they have unique metabolic routes and the ability to yield various bioactive substances. The marine-derived natural products (marine fungi) have a wide range of classes, including polyketides, alkaloids, terpenoids and peptides. Therefore, marine-derived

microorganisms are a source of new antibiotic development (Pan et al., 2024).

Challenges in Commercial Antibiotic Development

The extensive money invested in research and development activities and low monetary gains have now compelled the big pharmaceutical companies to abandon the antibiotic development activities. Consequently, the pipeline for antibiotic innovation exhibits a precarious state, disproportionately affecting low-income countries where the commonness of antibiotic confrontation is most pronounced (Piddock et al., 2024). WHO reported in 2024 on antibacterial development underscores the imperative need for continued investment and enhancements in innovative strategies to combat the escalating menace of antimicrobial resistance (Mendelson et al., 2024).

Role of Artificial Intelligence in Natural Product Discovery

The emergence of artificial intelligence can examine a wide range of data records consisting of genomic and chemical information to determine potential bioactive natural substances. AI-driven methodologies have expedited the identification of novel antibiotics by harnessing the previously untapped genomic potential of diverse microbial populations. Machine learning algorithms have been utilized to forecast biosynthetic gene clusters and their associated metabolites, thereby optimizing the selection of promising candidates for further research and development (Gangwal & Lavecchia, 2025). Furthermore, the implementation of artificial intelligence models has facilitated the acceleration and refinement of structural elucidation processes for complex natural products, thereby augmenting the overall efficacy of the discovery process (Jiménez-Luna et al., 2021)

Global Collaboration for Sustainable Antibiotic Usage and Development

The approach to the mitigation of antimicrobial resistance requires international responses. The World Health Organization, Global Antibiotic Research and Development Partnership are notable institutions that have been catalyzing activities that would translate to sustainable development and usage of antibiotics. Among these, there is stimulation of research and development programmes, enhancement of regulatory tools, and universal access to efficient antibiotics (Mendelson et al., 2024).

CONCLUSION

Microbial natural products offer vast potential for drug discovery due to their diverse biological activities. Microbial natural products offer vast potential for drug discovery due to their diverse biological activities. They have been very useful in the cure of infections, cancer, inflammation, and immunological disorders. However, the resistance to antimicrobials is a major health risk in the global world. Innovative approaches such as CRISPR, AI-aided drug discovery, and marine bioprospecting play a significant role in addressing this challenge. Although science is catching momentum, the commercial development of antibiotics is held back by economic and policy barriers. To achieve the sustainable use and discovery of effective microbial therapies, a unified international strategy is essential.

Table 1. Microbial secondary metabolites and their uses

Metabolite	Source Species	Structural Classification	Commercial Products	Mode of Action	Indications / Uses	Reference
Penicillins G and V	*Penicillium rubens*, *P. chrysogenum*	Nonribosomal peptide	Benzylpenicillin, phenoxymethylpenicillin, ampicillin, amoxicillin	Inhibits bacterial cell wall	Gram-positive and some Gram-negative bacterial infections	Demain & Elander, 1999
Cephalosporin C	*Acremonium chrysogenum*	Nonribosomal peptide	Cephalexin, cefadroxil, cefuroxime, cefdinir, etc.	Inhibits the biosynthesis of cell wall	Gram-positive and Gram-negative	Demain & Sanchez, 2009

					bacterial infections	
Pleuromutilin	*Clitopilus passeckerianus*, other *Clitopilus* spp.	Diterpene	Retapamulin, tiamulin, valnemulin	Inhibits protein synthesis by targeting bacterial ribosome	Topical and veterinary bacterial infections	Hurdle et al., 2011
Fusidic acid	*Acremonium fusidioides*	Steroid-like structure	Sodium fusidate, Fucicort®	Blocks the elongation factor G (EF-G) in protein synthesis	Gram-positive bacterial infections, mostly topical	Collignon, 2002
Strobilurins A–D	*Strobilurus tenacellus*	Polyketide with benzoyl-CoA	Azoxystrobin, kresoxim-methyl, trifloxystrobin, etc.	Inhibits mitochondrial respiration via cytochrome bc1 complex	Agricultural fungicides	Balba, 2007
Pneumocandin B_0	*Glarea lozoyensis*	Lipopeptide	Precursor of caspofungin (Cancidas®)	Inhibits β-1,3-glucan synthase affecting fungal cell wall	Systemic fungal infections	Denning, 2003
FR901379	*Coleophoma cylindrospora* (*C. empetri*)	Acylated fatty acid	Precursor of micafungin	Inhibits β-1,3-glucan synthase	Systemic fungal infections	Espinel-Ingroff, 2003
Echinocandin B	*Aspergillus pachycristatus*, *A. rugulosus*	Acylated fatty acid	Precursor of anidulafungin (Eraxis®)	Inhibits β-1,3-glucan synthase	Systemic fungal infections	Balkovec et al., 2014

REFERENCES

Ahmed Z, M Baig, LN Khan et al., 2025. Anti-inflammatory and Antioxidant Properties of Herbal Extracts: Mechanism and Therapeutic Potential. Chronicles of Biomedical Sciences 2:50.

Alexpandi R, MI Prasanth, AV Ravi, et al., 2019. Protective effect of neglected plant Diplocyclos palmatus on quorum sensing mediated infection of Serratia marcescens and UV-A induced photoaging in model Caenorhabditis elegans. Journal of Photochemistry and Photobiology B: Biology 201:111637.

Annunziato G, 2019. Strategies to overcome antimicrobial resistance (AMR) making use of non-essential target inhibitors: a review. International Journal of Molecular Sciences 20:5844.

Aslam B, W Wang, MI Arshad et al., 2018. Antibiotic resistance: a rundown of a global crisis. Infection and Drug Resistance 11:1645-58.

Balba H, 2007. Review of strobilurin fungicide chemicals. Journal of Environmental Science and Health Part B, 42:441-51.

Balkovec JM, DL Hughes, PS Masurekar et al., 2014. Discovery and development of first in class antifungal caspofungin (CANCIDAS®)-A case study. Natural Product Reports 31:15-34.

Blair JMA, MA Webber, AJ Baylay et al., 2015. Molecular mechanisms of antibiotic resistance. Nature Reviews Microbiology 13:42-51.

Bull AT & JEM Stach, 2007. Marine actinobacteria: New opportunities for natural product search and discovery. Trends in Microbiology 15:491-99.

Bush K & PA Bradford, 2019. Interplay between β-lactamases and new β-lactamase inhibitors. Nature Reviews Microbiology 17:295-306.

Calvo AM, RA Wilson, JW Bok et al., 2002. Relationship between secondary metabolism and fungal development. Microbiology and Molecular Biology Reviews 66:447-59.

Collignon AM, HVD Sype & JM Favre, 2002. Geographical variation in random amplified polymorphic DNA and

quantitative traits in Norway spruce. Canadian Journal of Forest Research, 32:266-82.

Czaplewski L, R Bax, M Clokie, et al., 2016. Alternatives to antibiotics—a pipeline portfolio review. The Lancet Infectious Diseases 16:239-51.

Demain AL & RP Elander, 1999. The β-lactam antibiotics: past, present, and future. Antonie Van Leeuwenhoek 75:5-19.

Demain AL & S Sanchez, 2009. Microbial drug discovery: 80 years of progress. The Journal of Antibiotics 62:5-16.

Denning DW, 2003. Echinocandin antifungal drugs. The Lancet 362:1142-1151.

Ebada SS, RA Edrada, W Lin et al., 2008. Methods for isolation, purification and structural elucidation of bioactive secondary metabolites from marine invertebrates. Nature Protocols 3:1820-1831.

El-Naggar A, N Ahmed, A Mosa et al., 2021. Nickel in soil and water: sources, biogeochemistry, and remediation using biochar. Journal of Hazardous Materials 419:126421.

Espinel-Ingroff A, 2003. Medical Mycology and Training in the United States: A Historical Analysis (1894-1996). Springer Science & Business Media, New York, USA, pp: 18-20.

Fenical W, 1993. Chemical studies of marine bacteria: developing a new resource. Chemical Reviews 93:1673-83.

Finlay BB & G McFadden, 2006. Anti-immunology: evasion of the host immune system by bacterial and viral pathogens. Cell 124:767-82.

Fischbach MA, CT Walsh, 2006. Assembly-line enzymology for polyketide and nonribosomal peptide antibiotics: logic, machinery, and mechanisms. Chemical Reviews 106:3468-3496.

Frisvad JC, C Rank, KF Nielsen et al. 2009. Metabolomics of *Aspergillus fumigatus*. Medical Mycology 47:53-71.

Gangwal A, A Lavecchia, 2025. Artificial intelligence in natural product drug discovery: current applications and future perspectives. Journal of Medicinal Chemistry 68:3948-69.

Gardiner DM & BJ Howlett, 2005. Bioinformatic and expression analysis of the putative gliotoxin biosynthetic gene cluster of *Aspergillus fumigatus*. FEMS Microbiology Letters 248:241-48.

Ghosh C, P Sarkar, R Issa et al., 2019. Alternatives to conventional antibiotics in the era of antimicrobial resistance. Trends in Microbiology 27:323-38.

Hollstein U, 1974. Actinomycin. Chemistry and mechanism of action. Chemical Reviews 74:625-52.

Holten, KB & EM Onusko, 2000. Appropriate prescribing of oral beta-lactam antibiotics. American Family Physician. 62:611-20.

Hurdle JG, AJ O'neill, RE Lee et al., 2011. Targeting bacterial membrane function: an underexploited mechanism for treating persistent infections. Nature Reviews Microbiology, 9:62-75.

Ianiro G, M Maida, J Burisch et al., 2018. Efficacy of different faecal microbiota transplantation protocols for *Clostridium difficile* infection: a systematic review and meta-analysis. United European Gastroenterology Journal 6:1232-44.

Jiménez-Luna J, F Grisoni, N Weskamp, et al., 2021. Artificial intelligence in drug discovery: recent advances and future perspectives. Expert Opinion on Drug Discovery 16:949-59.

Kishimoto S, S Nishimura, A Hattori et al., 2014. Chlorocatechelins A and B from *Streptomyces* sp.: New siderophores containing chlorinated catecholate groups and an acylguanidine structure. Organic Letters 16:6108-11.

Kumar P., S Rai, S Verma et al., 2022. Classification, mode of action and uses of various immunomodulators. In: Immunomodulators and human health (Kesharwani RK, RK Keservani, AK Sharma, Eds): Springer, Singapore, pp: 3-38. ISBN: 978-981-16-6378-9.

Mehetre G, M Shah, SG Dastager et al., 2018. Untapped bacterial diversity and metabolic potential within Unkeshwar hot springs, India. Archives of Microbiology 200:753-70.

Mendelson M, JA Lewnard, M Sharland et al., 2024. Ensuring progress on sustainable access to effective antibiotics at the 2024 UN General Assembly: a target-based approach. The Lancet 403:2551-2564.

Newman DJ, GM Cragg & KM Snader, 2000. The influence of natural products upon drug discovery. Natural Product Reports 17:215-34.

Pan C, SSU Hassan, I Muhammad et al., 2024. Marine fungi as a goldmine for novel antibiotics: a 2024 perspective. Frontiers in Marine Science 11:1538136.

Pham JV, MA Yilma, A Feliz, et al., 2019. A review of the microbial production of bioactive natural products and biologics. Frontiers in Microbiology 10:1404.

Piddock LJV, Y Alimi, J Anderson et al., 2024. Advancing global antibiotic research, development and access. Nature Medicine 30:2432-43.

Piel J, 2009. Metabolites from symbiotic bacteria. Natural Product Reports 26:338-362.

Ramirez-Rendon D, AK Passari, B Ruiz-Villafan et al., 2022. Impact of novel microbial secondary metabolites on the pharma industry. Applied Microbiology and Biotechnolog 106:1855-1878.

Rafiq HA, 2025. Assessment of Antibiotic-Resistant Bacterial Contamination in Diverse Drinking Water Sources: Implications for Water Safety and AMR Control Strategies. Chronicles of Biomedical Sciences 2:PID56-PID56.

Rodrigues C, LPDS Vandenberghe, J de Oliveira, et al., 2012. New perspectives of gibberellic acid production: a review. Critical Reviews in Biotechnology 32:263-273.

Ruh C, R Banjade, S Mandadi et al., 2017. Immunomodulatory effects of antimicrobial drugs. Immunological investigations 46:847-863.

Ser HL, JWF Law, N. Chaiyakunapruk, et al., 2016. Fermentation conditions that affect clavulanic acid production in *Streptomyces clavuligerus*: a systematic review. Frontiers in Microbiology 7:522.

Shaaban HA, AH El-Ghorab & T Shibamoto, 2012. Bioactivity of essential oils and their volatile aroma components: Review. Journal of Essential Oil Research 24:203-12.

Shafi AH, ZA Qasim & LHA Al Obaidy, 2022. CRISPR-Cas system detection of *Escherichia coli* isolated from different clinical sources. Biochemical & Cellular Archives 22:2861-2869.

Shen Z, F Jin, F Wang et al., 2015. Sorption of lead by Salisbury biochar produced from British broadleaf hardwood. Bioresource Technology 193:553-56.

Singh T., S. Sharma & S. Nagesh, 2017. Socio-economic status scales updated for 2017. International Journal of Research in Medical Sciences 5:3264.

Soliman GA, 2013. The role of mechanistic target of rapamycin (mTOR) complexes signaling in the immune responses. Nutrients 5:2231-57.

Song D, X Zhou, Q Peng et al., 2015. Newly emerged porcine *deltacoronavirus* associated with diarrhoea in swine in China: identification, prevalence and full-length genome sequence analysis. Transboundary and Emerging Diseases 62:575-80.

Streicher LM, 2021. Exploring the future of infectious disease treatment in a post-antibiotic era: a comparative review of alternative therapeutics. Journal of Global Antimicrobial Resistance 24:285-295.

Tan SY, Y Tatsumura, 2015. Alexander Fleming (1881–1955): Discoverer of penicillin. Singapore Medical Journal 56:366-367.

Tran TB, PJ Bergen, DJ Creek, et al., 2018. Synergistic killing of polymyxin B in combination with the antineoplastic drug mitotane against polymyxin-susceptible and-resistant *Acinetobacter baumannii*: A metabolomic study. Frontiers in Pharmacology 9:359.

Vollmer W, D Blanot & MA De Pedro, 2008. Peptidoglycan structure and architecture. FEMS Microbiology Reviews 32:149-167.

Yoo BB & SK Mazmanian, 2017. The enteric network: interactions between the immune and nervous systems of the gut. Immunity 46:910-26.

Zhong J, AHFM Peters, K Lee et al., 1999. A double-stranded RNA binding protein required for activation of repressed messages in mammalian germ cells. Nature Genetics 22:171-74.