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Review Article

Microbial Natural Products and Biopharmaceuticals: From Antibiotic Discovery to Modern Therapeutic Applications

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Abstract

Microorganisms have long been known to be a source of biologically active molecules with great medical and pharmaceutical applications. The identification of penicillin opened the door to the development of drugs and stimulated a range of investigations into the microbial metabolites that could be used to treat disease. Since then, bacteria and fungi have been used to produce a variety of compounds with antibacterial, antifungal, anticancer, immunosuppressive, anti-inflammatory, and antibiofilm properties. The review highlights the significance of microbial natural products in drug discovery, particularly in the development of key therapeutic molecules from bacteria and fungi. Modern medicine was transformed by classical antibiotics, such as penicillin, streptomycin, tetracycline, erythromycin, and vancomycin, which greatly enhanced health worldwide by curing infectious diseases. Other compounds found in microbial metabolites have also been used in cancer therapy, including bleomycin, daunorubicin, doxorubicin, rapamycin, and geldanamycin that affect pathways that control cellular proliferation and tumor development. More recently, microbial compounds with antibiofilm, anti-inflammatory, antiparasitic, and metabolic regulatory activities have shown further therapeutic potential. The increasing global problem of antimicrobial resistance, however, has stimulated the search for new bioactive molecules that are produced by microorganisms that have not yet been characterized. The next generation of therapeutics discovery and optimization is being driven by emerging technologies such as genomics, synthetic biology, metabolic engineering, and production platforms based on biotechnology. In sum, microbial natural products are crucial to the development of pharmaceuticals and to solving today and tomorrow's global health needs.

Keywords: Microbial natural products; Antibiotics; Antimicrobial resistance; Biopharmaceuticals; Bioactive metabolites; Anticancer agents.

1- Introduction

Natural products are bioactive secondary metabolites produced by a wide range of living organisms, including plants, animals, microorganisms, terrestrial vertebrates, and invertebrates. Their remarkable structural and chemical diversity has made them an important source of compounds with therapeutic potential. The medicinal use of naturally derived substances has a long history, with evidence from ancient Mesopotamia dating to approximately 2900–2600 BCE. Their importance remained substantial into the

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modern era; by the beginning of the twentieth century, plant-derived preparations constituted more than 80% of the medicines used at that time (1).

In 1928, Alexander Fleming made the landmark discovery of penicillin, following his observation of the antibacterial activity of *Penicillium notatum*, which represented a major turning point in natural-product research and broadened the search for therapeutic compounds beyond plant-derived sources. Since that landmark discovery, microbial bioactive metabolites have found extensive applications in medicine, agriculture, food-related industries, and scientific research. The early period of antibiotic discovery was particularly productive, leading to the identification of several clinically important antimicrobial agents from microbial sources, especially species belonging to the genus *Streptomyces*. These discoveries established microorganisms as an important reservoir of chemically diverse compounds with considerable therapeutic value (2).

The remarkable success of naturally derived therapeutics has maintained considerable interest in natural products within pharmaceutical research and drug-development programs. A substantial proportion of approved small-molecule drugs and antibacterial agents are either natural products or compounds developed from natural-product scaffolds. Nevertheless, the discovery and development of these molecules can be challenging because many promising metabolites are produced naturally in very small quantities, making their isolation, characterization, and large-scale production both time-consuming and expensive. One strategy developed to overcome these limitations involves heterologous expression, in which biosynthetic genes or entire gene clusters from the original producing organism are introduced into suitable microbial hosts, such as bacteria or fungi. This approach can facilitate compound production and provide opportunities for further biosynthetic modification (3).

Advances in microbial engineering have provided efficient platforms for producing biologically active substances at larger scales. Engineered microorganisms can be used not only to increase the yield of naturally occurring compounds but also to generate modified molecules and facilitate investigation of their biological functions. The pharmaceutical importance of living systems, however, extends beyond microbial natural products and includes the broader field of biological products, or biologics. The rapid development of biologics has been strongly supported by advances in recombinant DNA technology and the use of both prokaryotic and eukaryotic expression systems. Unlike conventional small molecules that can often be manufactured through chemical synthesis, many biological products possess complex molecular structures that require living cells or biological materials for their production. Such products may originate from microorganisms, plants, animals, human cells, blood-derived materials, or tissues. Based on their biological characteristics and method of production, these therapeutic products can be classified into five principal categories (4).

After recombinant human insulin and human growth hormone received regulatory authorization and were introduced into clinical practice, which were among the earliest achievements of modern biopharmaceutical production, the field expanded considerably. Since then, diverse microbial expression platforms have been employed to manufacture numerous therapeutic biological products that have successfully reached clinical use and the pharmaceutical market. In parallel, continued advances in biotechnology and recombinant production systems have supported the development of many additional biopharmaceutical candidates that are currently progressing through different stages of research and clinical development (5).

During the emergence of the biopharmaceutical industry in the 1980s, *Escherichia coli* became one

of the most widely adopted microbial systems for recombinant protein expression, followed by the yeast *Saccharomyces cerevisiae*. Microbial hosts have since been extensively utilized for manufacturing recombinant therapeutic proteins, particularly when the target product does not require complex post-translational modifications. Their widespread application is supported by several advantages, including rapid growth, relatively simple cultivation requirements, well-characterized genetics, and the possibility of achieving high production yields. Nevertheless, recombinant expression in microbial cells may encounter limitations such as protein degradation, inadequate solubility, improper folding, and cellular stress associated with high-level expression. Despite these challenges, bacterial and yeast expression systems remain robust, practical, and efficient platforms for the production of many recombinant biopharmaceuticals (6).

2- Antibiotics

Natural products have been used to fight pathogenic bacteria and fungi for over 50 years. These secondary metabolites doubled our life expectancy in the twentieth century, reduced pain, and transformed medicine. The golden period of antibiotics was from 1940 to 1970. Despite the slower discovery pace, new antibiotics were launched in the 1980s and 1990s. These molecules are discussed, as well as some new antibiotics. Antibiotics are in danger due to pathogenic bacteria developing resistance and significant pharmaceutical corporations leaving the sector due to perceived economic issues (7). Fortunately, a few pharmaceutical corporations, tiny biotechnology companies, and academic laboratories are still searching for novel antibiotics. The most clinically relevant natural antibiotic scaffolds include polyketides, non-ribosomal peptides, and aminoglycosides. Polyketides represent a major and highly diverse class of secondary metabolites with considerable biological and economic importance. Their broad range of bioactive properties has contributed to their extensive applications in pharmaceutical development, agricultural practices, and various industrial processes (8).

A polyketide antibiotic from *S. venezuelae*, while pikromycin, was first discovered in 1950. Pikromycin is particularly effective against multidrug-resistant respiratory infections, according to studies. Erythromycin A, generated by *S. erythraea*, is another exceptional polyketide antibiotic having clinical potential.

Certain antibiotics can be used as alternatives for patients with penicillin allergy and are effective against infections involving the respiratory and gastrointestinal tracts, as well as conditions such as whooping cough, syphilis, and acne. Tetracyclines exhibit broad-spectrum antibacterial activity against both Gram-positive and Gram-negative bacteria. Several other antimicrobial agents are predominantly effective against Gram-positive bacterial pathogens responsible for various infectious diseases, including scarlet fever, pneumonia, meningitis, and diphtheria. Non-ribosomal peptides represent a structurally diverse group of secondary metabolites synthesized by non-ribosomal peptide synthetases (NRPSs). Vancomycin, a glycopeptide antibiotic synthesized through nonribosomal peptide synthetase (NRPS)-dependent pathways, demonstrates strong antibacterial activity against a broad range of Gram-positive bacteria, such as *Clostridioides difficile*, *Streptococcus pneumoniae*, *Listeria monocytogenes*, *Staphylococcus epidermidis*, and methicillin-resistant *Staphylococcus aureus* (MRSA) (9).

The antibacterial activity of amino-glycoside antibiotics is related to the ability to bind to the 30S ribosomal subunit of bacteria to disrupt normal protein synthesis. Streptomycin, a product of Streptomyces griseus, was discovered in 1944, and other members of the class of antibiotics have since been discovered, including kanamycin, gentamicin,

sisomicin, and lividomycin. The discovery of resistance to this group of antibiotics by bacteria led to the development of semi-synthetic versions. Later, chemically modified forms of naturally occurring aminoglycosides, known as semisynthetic derivatives, were produced, such as amikacin, netilmicin, dibekacin, and isepamicin (10).

The antimicrobial natural compounds are also of great importance in food preservation and safety. Lactic acid bacteria are able to release several antimicrobial products that inhibit the growth of other microorganisms. Nisin A is an antimicrobial bacteriocin naturally synthesized by *Lactococcus lactis* and is widely authorized for food-related applications across more than 50 countries. Its pronounced inhibitory effect against Gram-positive bacteria makes it particularly valuable for limiting the growth of foodborne pathogens and spoilage organisms in milk, dairy products, and processed meat products (11).

Table 1: Biological activities of microbial-derived natural products and biologics.

No.	Antimicrobial compound	Microbial source	Biological activity	Ref.
1.	Erythromycin A	Produced by *Saccharopolyspora erythraea*	Antibacterial	(12)
2.	Tetracycline	Derived from *Streptomyces rimosus*	Antibacterial	(13)
3.	Vancomycin	Produced by *Amycolatopsis orientalis*	Antibacterial	(14)
4.	Streptomycin	Produced by *Streptomyces griseus*	Antibacterial	(15)
5.	Nisin A	Biosynthesized by *Lactococcus lactis*	Antibacterial	(16)
6.	Reuterin	Produced by *Lactobacillus reuteri*	Antibacterial	(17)

3- Antifungal Agents

Nystatin, first identified in 1950, is a polyene antifungal produced by *Streptomyces noursei* and is widely used as a topical treatment for oral, gastrointestinal, and vaginal candidiasis. Amphotericin B, another polyene antifungal produced by *Streptomyces nodosus*, is commonly employed for severe *Aspergillus* infections, particularly in immunocompromised patients. A recent screening of naturally derived compounds against *Candida albicans* demonstrated that 71 out of 142 evaluated substances exhibited antifungal effects, with minimum inhibitory concentrations (MICs) of less than 8 mg/mL (18).

Bioactive metabolites derived from *Bacillus licheniformis* have exhibited notable antifungal activity against several fungal pathogens, including *Aspergillus niger*, *Rhizoctonia solani*, *Botrytis cinerea*, *Colletotrichum acutatum*, and *Candida albicans*. These metabolites have also demonstrated antibacterial effects against *Staphylococcus aureus*, *Bacillus subtilis*, *Bacillus cereus*, *Salmonella typhi*, *Escherichia coli*, and *Pseudomonas aeruginosa*. Reported minimum inhibitory concentrations (MICs) ranged from 0.01 to 0.05 M, highlighting these microbial metabolites as promising candidates for further investigation in the development of new antibacterial and antifungal agents (19).

Table 2. Microbial Sources and Biological Activities of Antifungal Compounds

No.	Name of antibiotics and origin	Biological activity	Ref.
7.	Amphotericin B originated from *Streptomyces nodosus*	Antifungal	(4)
8.	Ieodoglucomide C originated from *Bacillus licheniformis*	Antifungal	

4- Anticancer Agents

Numerous anticancer agents of microbial origin have been investigated clinically. Actinomycin, a polyketide isolated from *Streptomyces parvulus* in 1940, was among the earliest microbial antibiotics recognized for anticancer activity. It has been used in the treatment of several malignancies, including Wilms tumor, pediatric rhabdomyosarcoma, Ewing sarcoma, and metastatic non-seminomatous testicular cancer. Another important example is bleomycin, a glycopeptide antibiotic naturally synthesized by *Streptoalloteichus hindustanus*. In combination with etoposide and cisplatin, bleomycin contributed substantially to improved treatment outcomes in testicular cancer. It is also used against squamous cell carcinoma, melanoma, sarcoma, ovarian cancer, and Hodgkin and non-Hodgkin lymphomas (4).

Amongst the anthracycline polyketides produced by Streptomyces spp. via polyketide synthase pathways are daunorubicin, epirubicin, and doxorubicin. Daunorubicin and doxorubicin were introduced into clinical oncology in the 1960s. Daunorubicin is primarily used to treat hematologic malignancies, and doxorubicin has a broader therapeutic range, such as the treatment of breast cancer, pediatric solid tumors, soft tissue sarcomas, and other lymphomas (20).

Other microbial natural products with significant antiproliferative properties include rapamycin, wortmannin, and geldanamycin. The antibiotic drug, rapamycin, produced by Streptomyces rapamycinicus, has anticancer, anti-inflammatory, antifungal, and immunosuppressive properties, and is able to inhibit tumor growth and tumour-induced angiogenesis. Penicillium funiculosum produces a furanosteroid metabolite called Wortmannin that has primary antitumor activity through the inhibition of the PI3K/Akt signaling pathway (21).

Geldanamycin is a benzoquinone ansamycin metabolite isolated from Streptomyces hygroscopicus, which acts mainly through heat-shock proteins, disrupting protein stability and activity of several proteins that have roles in oncogenic signalling pathways. Derivatives of geldanamycin have been shown to be active against multiple myeloma, breast and prostate cancers. The epothilones, made by Sorangium cellulosum, are microtubule stabilizers and cell-cycle inhibitors. Furthermore, dolastatin-related compounds from cyanobacteria, including Symploca and Lyngbya, have been found to have considerable anticancer activity (22).

Table 3. Microbial-Derived Anticancer Agents and Their Major Therapeutic Applications

No.	Anticancer agent and microbial source	Major therapeutic application	Ref.
1	**Bleomycin** — derived from *Streptomyces verticillus* and related actinomycetes	Used primarily in the treatment of squamous cell carcinomas, Hodgkin lymphoma, and testicular tumors	(4)
2	**Daunorubicin** — produced by *Streptomyces peucetius* and closely related strains	Mainly employed in the treatment of acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML)	

5- Immunosuppressive Agents

Two naturally occurring microbial metabolites, rapamycin (also called sirolimus) and FK506 (tacrolimus), are known to have strong immunosuppressive effects. Rapamycin inhibits cell proliferation mediated by multiple signaling factors, including interleukin-2 (IL-2), interleukin-3 (IL-3), platelet-derived growth factor (PDGF), epidermal growth factor (EGF), and insulin. When administered with other immunosuppressive agents, it can reduce acute renal allograft rejection. In addition to its immunosuppressive effects, rapamycin exhibits anticancer, neuroprotective, neuroregenerative, and antineoplastic activities and has also been associated with lifespan extension (23).

FK506 was originally isolated from *Streptomyces tsukubaensis*. It promotes immunosuppression and reduces transplant rejection primarily by inhibiting calcineurin-dependent T-cell activation. Tacrolimus has been widely applied in heart, liver, and kidney transplantation because of its strong immunosuppressive activity. Similar to rapamycin, FK506 also exhibits antifungal, anti-inflammatory, neuroprotective, and neuroregenerative properties (24).

6- Anti-inflammatory Agents

Several microbial natural products exhibit notable anti-inflammatory properties. FK506 has demonstrated therapeutic activity in refractory rheumatoid arthritis, while rapamycin may reduce secondary spinal cord injury and exert neuroprotective effects by suppressing inflammatory cell activation, proliferation, and cytokine production (27).

Strepsesquitriol, a bioactive metabolite isolated from *Streptomyces* sp. SCSIO 10355, has demonstrated anti-inflammatory properties by suppressing tumor necrosis factor (TNF) production in macrophages stimulated with lipopolysaccharide (LPS). In addition, salinamides A and B derived from *Streptomyces* sp. CNB-091 have demonstrated potent topical anti-inflammatory effects. Seven peptides obtained from the supernatant of *Faecalibacterium prausnitzii* were also reported to possess anti-inflammatory activity in experimental models of colitis (28).

7- Biofilm Inhibitory Agents

Biofilm formation occurs when microorganisms adhere to surfaces and develop a structured extracellular matrix, which can enhance antimicrobial tolerance and contribute to persistent infections. Several compounds derived from marine natural sources have demonstrated significant antibiofilm activity, including inhibition and disruption of MRSA biofilms. Aminoimidazole triazoles have also been reported to suppress biofilm development in *Acinetobacter baumannii* and MRSA (29).

Cahuitamycins A–C, isolated from *Streptomyces gandocaensis*, represent another group of promising antibiofilm compounds. Cahuitamycin C exhibited

inhibitory activity against *A. baumannii* biofilms, while modified cahuitamycins D and E showed enhanced activity. Actinomycin D can also be used as an inhibitor for biofilms in methicillin-resistant and methicillin-sensitive Staphylococcus aureus (MRSA and MSSA). Additionally, biosurfactants derived from *Lactobacillus* species have demonstrated the ability to inhibit biofilm development by various pathogenic microorganisms, including *Candida albicans*, *Listeria monocytogenes*, *Salmonella arizonae*, *Escherichia coli*, and *Staphylococcus aureus* (30).

Table 4. Microbial-Derived Immunosuppressive Agents and Their Reported Biological Activities

No.	Immunosuppressive/Anti-inflammatory agent and microbial source	Reported biological activities	Ref.
1	**Rapamycin (Sirolimus)** — produced by *Streptomyces rapamycinicus* (formerly *Streptomyces hygroscopicus* ATCC 29253); related rapamycin-type metabolites have also been reported from *Streptomyces iranensis* and *Actinoplanes* sp. N902-109	Exhibits potent immunosuppressive activity together with antifungal, antitumor, neuroprotective, and neuroregenerative properties. Rapamycin has also been associated with lifespan extension in experimental models and inhibition of the growth of several fungal species.	(25)
2	**FK506 (Tacrolimus)** — originally isolated from *Streptomyces tsukubaensis*, with related production reported among other *Streptomyces* species	Displays strong immunosuppressive and anti-inflammatory effects, in addition to antifungal, neuroprotective, and neuroregenerative activities. Tacrolimus also has important therapeutic applications in immune-mediated conditions.	(26)

Table 6. Microbial-Derived Biofilm-Inhibitory Agents and Their Biological Activities

Biofilm-Inhibitory Agents		Biological activity	Ref.
Cahuitamycins	*Streptomyces gandocaensis*	Inhibitors of *Acinetobacter baumannii* biofilms	(30)

8- Others

A variety of natural products derived from microorganisms exhibit significant antiparasitic and insecticidal properties. Avermectins and their derivative ivermectin have been widely used against parasitic diseases, particularly onchocerciasis and lymphatic filariasis. Other microbial metabolites, such as spinosad and milbemycins, exhibit potent insecticidal activity. Spinosad is a naturally derived insecticidal compound composed predominantly of spinosyn A and spinosyn D, which are produced by *Saccharopolyspora spinosa*. It exhibits substantial activity against a variety of ectoparasites affecting livestock (31).

Milbemycins exhibit insecticidal and acaricidal properties by interfering with inhibitory neurotransmission in arthropods and mites. Another microbial natural product, mollemycin A, is a glycol-hexadepsipeptide–polyketide metabolite obtained from *Streptomyces* sp. that has demonstrated both antibacterial effects and antimalarial activity against drug-sensitive as well as multidrug-resistant strains of *Plasmodium falciparum*. In addition to these activities, microbial-derived metabolites can serve as inhibitors of various enzymes. Lipstatin, produced by *Streptomyces toxytricini*, inhibits pancreatic lipase through its β-lactone moiety and has provided an important natural-product scaffold for the development of anti-obesity therapeutics (32).

Table 7. Other Microbial-Derived Bioactive Compounds and Their Therapeutic Activities

No.	Bioactive compound and microbial source	Biological/Therapeutic activity	Ref.
1	*Avermectins originated from Streptomyces avermitilis*	Onchocerciasis and lymphatic filariasis	(33)
2	*Mollemycin A 20 originated from Streptomyces* sp. (CMB-M0244)	Gram-positive and Gram-negative bacteria, antimalarial activity	(34)
3	*Lipstatin originated from Streptomyces toxytricini*	Pancreatic lipase inhibitor for obesity and diabetes	(35)

9- History of antibiotics:

Antibiotics are naturally occurring chemicals produced by bacteria or fungi that can impede the growth of other microorganisms and kill their cells. Apoptosis occurs when a microbe's growth is inhibited by a natural, semi-synthetic, or synthetic chemical (3).

Before antibiotics, the male was virtually always infected. Pneumonia, meningitis, and tuberculosis were treated poorly or not at all. Major epidemics were feared by mankind. Infections killed many people in fields like surgery, pediatrics, and hematology. For many years, medicine has evolved. Without the stress of infection, doctors might widen and enhance their studies. Surgical and hematological specialties thrived. Moreover, significant pandemics (e.g., plague, syphilis) and diseases like tuberculosis have been effectively treated for decades. Antibiotics were slowly accepted as a medical salvation by the general public. It is clearly proven that the current armament provides comprehensive protection against practically all infections. Antimicrobials are now widely employed in agriculture, cattle, and fish

farming, as growth promoters or growth inhibitors. Antibiotics are chemotherapeutic agents of biological origin that specifically inhibit or eliminate bacteria, whereas antimicrobial agents encompass a broader range of substances active against various microorganisms (36).

Antibiotic discovery, development, and use have changed human and veterinary medicine. Antibiotics have proven essential in the prevention and treatment of disease since their discovery in 1928. A modest concentration of antibiotics inhibits bacterial development. Antibacterial, antifungal, antiparasitic, and antiviral medications are all antimicrobials. Chemicals that kill or inhibit the growth of bacteria are classified as antimicrobial agents. This review will use the term antibiotic or antimicrobial interchangeably (37).

Alexander Fleming discovered penicillin in 1928 from a Petri dish containing a Staphylococcus culture infected with a Penicillium mold spore. At the same time, Gerhard Domagk developed the first synthetic sulfa medication, sulfonamide chrysoidine (Prontosil). Resistance to both Penicillin and Prontosil appeared soon after their release. Resistance has been identified with every new antimicrobial agent. Antibiotic resistance is the ability of a microorganism to proliferate in the presence of a medicine intended to kill or inhibit it. Antibiotic resistance is a natural phenomenon caused by selective pressures from antibiotic use (38).

Antimicrobial resistance is a global health threat. A post-antibiotic era of untreatable infections is a serious possibility as new antimicrobial medicines are developed less frequently. As a result of lengthier hospital stays, additional diagnostic tests, and more comprehensive therapies, antimicrobial resistance increases patient mortality and expenses. The annual economic impact from rising health care expenses is estimated at $20 billion in the US and €1.5 billion in Europe. Annually, the CDC estimates that antibiotic-resistant microbes cause about 2 million illnesses and 23,000 deaths. Multidrug-resistant bacterial infections are thought to be responsible for 33,000 deaths in Europe each year. That number might rise to 10 million by 2050, according to a 2014 analysis commissioned by the British Prime Minister (39).

Before the beginning of the twentieth century, treatments for infectious diseases were largely based on traditional practices and empirical knowledge. Historical evidence indicates that antimicrobial preparations had been used for more than 2,000 years, with ancient civilizations such as the Egyptians and Greeks employing medicinal plants and molds to manage infections. Interestingly, analyses of Nubian mummies conducted in the 1990s detected traces of tetracycline, which were suggested to originate from fermented beverages consumed at that time. Later, the development of synthetic antibacterial compounds derived from dyes marked an important transition toward modern antimicrobial chemotherapy (40).

Synthetic antibiotics derived from dyes

In the late nineteenth century, Paul Ehrlich pioneered the concept of synthetic antimicrobial chemotherapy. His observations that certain dyes selectively stained microbial cells led to the idea of developing compounds capable of targeting pathogens without damaging host cells. This concept ultimately contributed to the discovery of Salvarsan (arsphenamine), an organoarsenic compound introduced in the early twentieth century as one of the first synthetic antimicrobial agents (41).

In 1907, Alfred Bertheim and Paul Ehrlich investigated a series of synthetic arsenic-based compounds as potential antimicrobial agents. Their early studies explored dye-derived chemicals against trypanosomes in mice and spirochetes in rabbits, although several initial candidates showed considerable toxicity. Working with the Japanese bacteriologist Sahachiro Hata, Ehrlich later identified compound 606 as a promising agent against syphilis. The compound was presented at the Wiesbaden Congress of Internal Medicine in 1910

and subsequently marketed as Salvarsan (arsphenamine), becoming an important early treatment for syphilis. Ehrlich received the 1908 Nobel Prize in Physiology or Medicine for his contributions to immunology (42).

Prontosil, the first sulfonamide with effective systemic antibacterial activity, was developed in the early 1930s by a research group led by Gerhard Domagk at Bayer Laboratories in Germany. Its active component, sulfanilamide, had previously been used in the dye industry and therefore could not be patented. Prontosil showed notable activity against Gram-positive cocci but limited effectiveness against enteric Gram-negative bacteria. Its therapeutic success stimulated extensive research into antimicrobial compounds and marked an important milestone in the beginning of the modern antibacterial era (43).

- Penicillin and other natural antibiotics

Since the late nineteenth century, scientists have observed that certain microorganisms can suppress the growth of others, a phenomenon known as microbial antibiosis. These observations provided an important foundation for the discovery of naturally derived antibacterial agents. Louis Pasteur recognized that microbial antagonism could potentially be exploited for therapeutic purposes (44).

- In 1874, Sir William Roberts observed that cultures of *Penicillium glaucum* remained largely free from bacterial contamination. John Tyndall later reported related observations concerning the inhibitory effects of molds on bacteria, further supporting the concept of microbial antagonism (45).
- "Antibacterial efficacy of mold extracts" was published in 1895 by Italian physician Vincenzo Tiberio (46).
- In 1897, Ernest Duchesne submitted his doctoral thesis on the competition between molds and bacteria. His experiments suggested that the molds have therapeutic potential and that Penicillium glaucum could inhibit the growth of bacteria. But the development of his work at the time wasn't continued. It took several decades for Alexander Fleming's observations to finally lead to the recognition of penicillin as an important antibacterial agent (47).
- In 1928, Fleming noticed a Penicillium mold growing on a culture of bacteria, and observed that it inhibited the growth of bacteria around it. He called this antibacterial substance penicillin and saw its potential to be used medicinally. Further research, however, by other scientists was needed to purify and develop penicillin into a clinically useful drug.
- Later, penicillin G became easily produced and purified in large quantities and was widely available during the 1940s. Norman Heatley made important contributions to penicillin recovery and purification, and its chemical structure was studied by Ernst Chain and Edward Abraham and later confirmed by Dorothy Crowfoot Hodgkin. Purified penicillin was found to be very active against bacteria but moderately toxic to animals. Fleming, Chain, and Howard Florey shared the 1945 Nobel Prize in Physiology or Medicine for the discovery and therapeutic development of the antibiotic penicillin.
- Other antibacterial compounds were also discovered in the course of the systematic study of microbial metabolites. Tyrothricin, which is made up primarily of tyrocidine and gramicidin, was isolated in 1939 by René Dubos and his colleagues from Bacillus brevis. This discovery provided yet another proof of the capacity of microorganisms for the production of antimicrobial products.
- Tyrothricin became one of the early commercially produced antibiotics and was primarily used for topical treatment of wounds and ulcers. However, the systemic toxicity of gramicidin and tyrocidine restricted their clinical application. These early discoveries nevertheless contributed substantially to the subsequent expansion of antibiotic research and development (48).

Late 20th century

The number of novel antibiotic compounds for medical application expanded dramatically in the mid-20th century. The classes expanded from 1935 to 1968. After that, just two additional classes were added between 1969 and 2003 (49).

The Chinese utilized antibiotics for the first time 2,500 years ago. Moldy soybeans were used to treat furuncles, carbuncles, and other ailments. Antibiotic chemicals were used by the Egyptians and Greeks to heal ailments. That was before antibiotics (50).

Robert Hooke, the first scientist to use a rudimentary microscope, spotted microorganisms and fungi in 1665. Hooke observed a thin slice of cork and stated that the smallest units of life were termed cells. He saw individual cells using a composite microscope with two lenses. Hooke's finding ushered in cell theory, the idea that all living things are made up of cells. In 1674, Antonie van Leeuwenhoek used his improved high-magnification microscopes to observe microorganisms, including protozoa and bacteria, providing some of the earliest direct descriptions of microbial life. He was the first to see live germs with several of his 400 microscopes. The huge lens micro-organisms were living, he contended to the Royal Society of London in 1676. Van Leeuwenhoek produced precise plans of these little critters living in the water, faces, and mouth. These were the earliest bacterium and protozoa designs. As a result, it took two hundred years for Luis Pasteur and Robert Koch to successfully link bacteria to illnesses (51).

For example, Pasteur defined microbiology in 1859, Koch established that carbon illness is caused by bacilli in 1876, and tuberculosis was related to the bacillus mycobacteria in 1882. It was discovered in the late 1890s by two German researchers, Rudolph Emmerich and Oscar Löw, who used it to treat cholera and typhus patients. For the treatment of syphilis, Paul Ehrlich developed the arsenic-based medication Salvarsan in 1909. This discovery paved the way for future antibacterial agent research. But it was Alexander Fleming's 1928 discovery of penicillin that changed the course of antimicrobial medication research. In 1897, the French researcher Ernest Duchesne was among the first to document the antibacterial activity associated with *Penicillium* species. Alexander Fleming's discovery of penicillin changed the scientific community. To test its efficacy against major bacterial illnesses, Gerhard Domagk discovered the first sulphonamide, prothosyl, in 1932 with Bayer's research team. A fungus called Penicillium produced penicillin, which was first made available to doctors in 1946. Because it was developed during WWII, it is a "war child." Infections caused by staphylococci and streptococci were treated with penicillin, a modern miracle. We can all feel relieved after learning that these two viruses are the most common cause of infection known (52).

Streptomycin and tetracycline were developed in the late 1940s and early 1950s, and were well tolerated in clinical practice. These medicines worked against Bacillus tuberculosis and other pathogens. In the 1970s, scientists were interested in pharmaceuticals and hormones in the environment for the first time. In the 1980s, hormones lost favor, and studies focused on environmental contaminants such as heavy metals, polycyclic aromatic hydrocarbons, chlorinated dioxins, pesticides, and detergents. Analgesics, anti-rheumatic medicines, and antibiotics have all been added to the research lists since the mid-1990s (49).

Cost of antibiotics from 2017-2028:

The global antibiotics market was worth USD 40.7 billion in 2020 and is predicted to increase at a CAGR of 4.5% from 2021 to 2028. Infectious illness outbreaks and supportive government laws are important market drivers. Antibiotic resistance infections owing to misuse or overuse will shift prescription patterns to innovative medicines to treat bacterial infections. The CDC estimates that over 2.8 million Americans have antibiotic-resistant illnesses. Pathogens such as Enterobacteriaceae, P. aeruginosa, and K. pneumoniae have a 40 percent resistance rate in developed countries.

Limitations and Challenges

Despite the remarkable success of microbial natural products in pharmaceutical development, several limitations continue to hinder their discovery, optimization, and commercialization. One of the primary challenges is the low natural abundance of many bioactive metabolites, which often results in insufficient yields for large-scale production and clinical development. In addition, many microorganisms are hard to grow and/or take a long time to grow in industrial laboratories, which means that some potentially valuable compounds made by microorganisms that are difficult to grow in the lab are not accessible.

Rediscovery of known metabolites in screening programs is another major drawback, as it hampers natural product discovery pipelines. Many microbial metabolites, however, are also highly complex, which makes purification, characterization, chemical modification, and industrial-scale production difficult. Additionally, there are numerous compounds with promising therapeutic potential that suffer from suboptimal pharmacokinetics, such as low bioavailability, poor solubility, instability, or an unfavorable toxicity profile, and thus might not be able to be used in therapy.

The issue of antimicrobial resistance further restricts the clinical use of the existing microbe-derived antibiotics. Pathogens evolve resistance mechanisms that reduce the efficacy of current drugs, and a need for new antimicrobial scaffolds and therapeutic approaches is of critical importance. At the same time, economic factors have encouraged many pharmaceutical firms to limit their R&D efforts in finding new antibiotics, due to the lower financial returns compared to other therapeutic fields.

Despite breakthroughs in the field of genomics, metagenomics, synthetic biology, and metabolic engineering, many microbial biosynthetic gene clusters are not expressed in the lab or are silenced. The activation of such cryptic pathways and generating clinically relevant products from genomic information are key scientific challenges. Further, the regulatory challenges, development timelines, and expensive research costs still continue to hold back the path of commercializing promising microbial metabolites from the bench to approval.

Integration of multi-omics technology, artificial intelligence (AI) in drug discovery, genome mining, and advanced microbial engineering approaches will be important for future progress. All of this can help to address current limitations and optimize production, enable the discovery of novel bioactive molecules, and play a role in the design of new therapeutic approaches to tackle antimicrobial resistance and other emerging global health issues.

Conclusion

Microbial natural products are one of the most significant sources of clinically useful therapeutic products and have contributed greatly to the development of modern medicine. Microorganisms have been used to produce structurally diverse compounds with antibacterial, antifungal, anticancer, immunosuppressive, anti-inflammatory, anti-parasitic, and antibiofilm properties, from the discovery of penicillin to the development of advanced biopharmaceuticals. These natural metabolites have been safely applied to human health through the effective treatment of infectious disease, cancer, immune disorders, and other complex medical conditions.

With the rise of antimicrobial resistance, new infections, and restrictions in conventional therapeutics, microbial biodiversity has once again gained importance as a reservoir of novel bioactive molecules. All recent developments in genomics and metagenomics, in synthetic biology and metabolic engineering, and in recombinant expression technologies have helped to discover, optimize, and scale up production of microbial compounds and biologics. These innovations have given rise to more than just antibiotics and led to the creation of

targeted therapeutics and next-generation biologics that deliver greater efficacy and improved safety.

While considerable advances have been made, there are many challenges to address, such as rediscovery of known metabolites, low production yields, complicated biosynthetic pathways, and the quick emergence of drug-resistant pathogens. Interdisciplinary solutions that combine microbiology, biotechnology, bioinformatics, medicinal chemistry, and systems biology will be needed to tackle these challenges. In the future, new microbial ecosystems will be investigated, novel biosynthetic gene clusters will be reactivated, and artificial intelligence (AI) supported drug discovery platforms will be used to discover new therapeutic molecules. In general, microbial natural products and biologics are valuable tools in the pharmaceutical research toolbox and are expected to provide solutions to future global challenges for effective and sustainable therapeutic strategies.

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