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Biodiversity in Production of Antibiotics and Other Bioactive Compounds

Girish Mahajan and Lakshmi Balachandran

Abstract Microbes continue to play a highly considerable role in the drug discovery and development process. Nevertheless, the number of new chemical entities (NCEs) of microbial origin that has been approved by the Food and Drug Administration (FDA) has been reduced in the past decade. This scarcity can be partly attributed to the redundancy in the discovered molecules from microbial isolates, which are isolated from common terrestrial ecological units. However, this situation can be partly overcome by exploring rarely exploited ecological niches as the source of microbes, which reduces the chances of isolating compounds similar to existing ones. The use of modern and advanced isolation techniques, modification of the existing fermentation methods, genetic modifications to induce expression of silent genes, analytical tools for the detection and identification of new chemical entities, use of polymers in fermentation to enhance yield of fermented compounds, and so on, have all aided in enhancing the frequency of acquiring novel compounds. These compounds are representative of numerous classes of diverse compounds. Thus, compounds of microbial origin and their analogues undergoing clinical trials continue to demonstrate the importance of compounds from microbial sources in modern drug discovery.

Keywords Actinomycetes · Fungi · Myxobacteria · Biodiversity · Antibiotics · Antitumor · Anticancer

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1 General Introduction

Natural product compounds (NPCs), especially those mined from microbes (bacteria and lower eukaryotes) are established resources for a variety of remedial agents. Such drugs of microbial origin have been classified as (i) original microbial products, (ii) products derived or chemically synthesized from microbial products, or (iii) synthetic products based on microbial product structures [1]. Early scientific observations on the antagonism among soil microflora led scientists to speculate on the existence of some compound that held the key to their survival [1, 2]. The soil, despite teeming with billions of microbes, enables only some of them to endure the struggle for existence. In recent times, many compounds used in the treatment and management of cancer, infections due to drug-resistant microbes (bacteria, fungi, and viruses), and immunosuppressive disorders, have been derived from microbial sources.

Investigations and observations gave way to the concept of the term "antibiosis" (against life). The renowned Nobel Laureate, Selman Abraham Waksman, coined the word "antibiotic". The discovery and launch of microbial antibiotics such as penicillin and streptomycin, were early evidence that microbes could be further explored for novel bioactive compounds for human use. The pharmaceutical industry owes an immense amount of its early success to the development of antibacterial drugs, and as an upshot the market is abundant with old drug scaffolds. Essentially the scaffold of a molecule is taken to be its framework, defined as all its ring systems and all the linkers that connect them [3]. For the past seven decades, the need for new antibiotics has relied largely upon semisynthetic tailoring of natural product scaffolds, discovered in the middle of the twentieth century. During the past decade, however, advances in technology such as high-throughput screening facility, the launch of high-resolution NMR facilities, upgraded separation systems, and, moreover, recent molecular techniques for the investigation of marine metagenomes have revealed a large number of new

phylogenetic lines of groups of bacteria and archaea [4, 5], which has sparked a resurgence in the discovery of natural product antibiotics from microbial sources.

Microbial metabolites are among the most important chemotherapeutic agents in oncology. This aspect of microbes was identified as early as 1940 with the discovery of actinomycin from *Streptomyces* [2]. Since then, many compounds with anticancer properties have been isolated from microorganisms. More than 60 % of the current compounds with antineoplasic activity have been originally isolated as natural products or are their derivatives. Among the approved products deserving special attention are actinomycin D, anthracyclines (daunorubicin, doxorubicin, epirubicin, pirirubicin, and valrubicin), bleomycin, mitomycin C, anthracenones (mithramycin, streptozotocin, and pentostatin), enediynes (calcheamycin), taxol, and epothilones [2]. Several of these compounds were discovered by (i) understanding the genetics of secondary metabolism in Actinomycetes, myxobacteria, other eubacteria, fungi, and slime molds (ii) exploring the marine environment, and (iii) applying modern screening technologies. In quite a few cases, the discovery of a novel natural derived product has been reported to be used as a tool to better understand compound targets and new pathways in the disease process [6].

This review describes the current role of biodiversity in drug discovery and pharmaceuticals from microbial sources, and aims to take the reader through a journey of recent advances in the role of biodiversity in the synthesis of novel scaffolds, having an unreported framework of chemical rings. We have focused essentially on those bioactive compounds from microorganisms, which are reported and being used as antibiotic and other bioactive compounds without any further chemical modifications.

1.1 Biodiversity

For researchers involved in the discovery of novel bioactive microbial products, microbial diversity is a key factor for the novelty of the molecules. Although wide diversity is observed among the microbes with reference to their habitat, metabolism, and extremity tolerance, microbes with an established record of synthesis of novel pharmaceutically important lead compounds are very limited. Actinomycetes, fungi, and myxobacteria are the leaders among these microbes.

Prior to the discovery of antibiotics in the nineteenth and twentieth centuries, natural remedies and herbal treatments were used for the treatment of most infectious diseases (or medical conditions). The serendipitous discovery of penicillin (from *Penicillium rubens*), followed by streptomycin (from *Streptomyces griseus*) transformed the lives of millions of people. Since then, natural habitats have been continuously explored for new antibiotics and other bioactive compounds in order to combat the onslaught of new infections and other diseases.

Different communities of microbes coexist in extreme terrestrial regions and oceans, and they constitute an untapped source of bioactive compounds. Advances in basic research have enabled scientists to understand the course of disease and the

way a drug works at the molecular level. Continuous improvements in isolation techniques for screening, separation, and isolation have aided the identification of over one million natural compounds, of which 50–60 % are of plant origin and over 5 % are of microbial origin [2]. Around 25 % of these compounds are reported to be biologically active, of which 10 % are derived from microbial sources [2]. There have been approximately 22,500 biologically active compounds [2] obtained thus far from microbes. Of these, 45 % are produced by Actinomycetes, 38 % by fungi, and 17 % by unicellular bacteria [2, 7, 8]. This highlights the immense contribution of these microbes in the production of antibiotics.

Natural habitats, especially the soil—and plant-associated environments, are teeming with microbes that produce bioactive metabolites that shield them against extreme environmental conditions. Such bioactive entities presumably confer an ecological advantage to the producer, by prolonging their survival in an environment challenged by predators and competitors. Secondary metabolites at subinhibitory concentrations also influence developmental changes in the producer. Critical processes such as nutrient supply, developmental changes, survival rate under stressful conditions, and complex interactions are presumably affected by these metabolites [9].

The euphoria over the discovery of a new drug is often short-lived due to the development of resistance in microbes or the tumor cells in addition to the drug's toxicity. This results in limiting the optimum use of a drug. Hence, there is a compelling need for discovering new drugs with newer mechanisms to tackle the menace of drug resistance. Identification of new molecules for disease management mandates the exploration of diverse ecosystems [2].

The marine ecosystem houses most of the animals from the 28 major animal phyla, thus comprising nearly half of the total biodiversity for the discovery of useful therapeutic agents [10]. Soils from the Antarctic regions, extreme cold deserts, playa regions, geothermal vents, hot spring outlets, high pH lakes, acidic water bodies, metal mining areas, sugarcane bagasse, marine sediment soils, and soil from the areas of radionuclear (heavy metal) waste depositions, among others are some of the unique regions for isolation of diverse microbes.

In terms of microbial diversity, not all the microbial phyla have been cultivated, and among the cultivated microbes, not all of them produce secondary metabolites. In this scenario, targeting bacterial phyla, renowned for antibiotic production seems to be a viable option. Hence, Actinomycetales and fungi are attractive targets, inasmuch as they produce most of the antibiotics currently in use [11].

2 Actinomycete-Derived Compounds

Actinomycetes are prokaryotes whose growth (prothallus) consists of branching threads, and rods, and occasionally give rise to a typical mycelium, which is unicellular, during the early stages of growth. The hyphae, which are generally nonseptate, have a tendency to turn septate under special conditions, such as while growing in solid culture media for a long time [12]. Actinomycetes with prostate

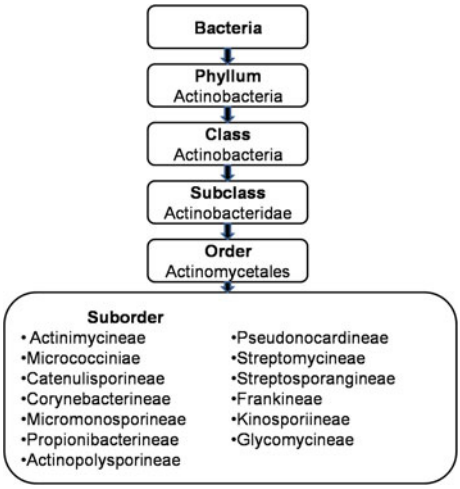


Fig. 1 Systemic classification of Actinomycetes

mycelium grow on the substrate, and those with aerial mycelium grow above the vegetative growth [13]. Currently, Actinomycetes are classified as actinobacteria and include Gram-positive bacteria with their DNA high in guanine-plus-cytosine content (69–73 mol %); and extensive branching substrates and aerial mycelia [14, 15]. The complete taxonomy of Actinomycetes (Fig. 1) and details of each genus can be observed elsewhere [1, 16, 17].

The historical discovery of streptomycin in 1945 was preceded by decades of research on the slender filamentous bacteria, the Actinomycetes. The pioneering work of Selman Waksman inspired many researchers to pursue research on Actinomycetes, which was a new microbe then, hovering for an identity between fungi and bacteria. The most notable feature of these bacteria was the production of secondary metabolites, most of which possessed antimicrobial properties. Many antibacterial compounds including tetracyclines, cephalosporins, aminoglycosides, and macrolides were derived, which addressed concerns regarding disease management in the early twentieth century [18, 19]. A representative list of the different classes of antibiotics produced by Actinomycetes is presented in Table 1.

2.1 Streptomyces: A Sustained Gold Mine of Bioactive Compounds

Streptomyces, a well-explored genus of Gram-positive bacteria, is included in the phylum Actinobacteria. These prokaryotes present a strikingly similar lifestyle to that of filamentous fungi and, as do fungi, most Streptomycetes live as saprophytes in the soil [53]. In fact, almost half of all known natural products (NPs) are produced by Actinomycetes (mainly *Streptomyces*) [19, 53]. Nearly two thirds of

Table 1 Antibacterial agents from Actinomycetes

Class	Mechanism of action	Actinomycetes	Antibiotic	Reference
Aminoglycoside	Inhibition of protein synthesis and increase in translation errors	*Streptomyces kanamyceticus*	Bekanamycin	[20]
	Inhibition of protein synthesis and increase in translation errors	*Streptomyces kanamyceticus*	Kanamycin	[21]
	Inhibits protein synthesis by binding to L6 protein of 50S ribosomal subunit	*Micromonospora purpurea*	Gentamicin	[22]
	Binds to 30S and in some cases the 50S subunit causing miscoding; inhibits initiation and elongation during protein synthesis	*Streptomyces fradiae*	Neomycin	[23]
	Inhibits bacterial protein synthesis	*Streptomyces griseus*	Streptocin	[24]
	Inhibits protein synthesis by binding to S12 protein of 30S ribosomal subunit, causing miscoding or inhibiting initiation	*Streptomyces griseus*	Streptomycin	[25]
Acetamide	Inhibits protein biosynthesis by impairing translation on the 50S ribosomal subunit	*Streptomyces venezuelae*	Chloramphencol	[26]
Aminocoumarin	Inhibits DNA synthesis by inhibiting the DNA polymerization	*Streptomyces niveus*/ *S. spheroids*	Novobiocin	[27]
Aminocyclitol	Disrupts bacterial protein synthesis	*Streptomyces spectabilis*	Spectinomycin	[28]
Cyclic hexapeptide	Inhibits seryl-t-RNA synthetase and impairs protein biosynthesis	*Streptomyces griseus*	Grisein0 (albomycin)	[29]
Cyclic oligopeptide	Impairment of the coupling of the 30-S initiation complex to the 50-S ribosomal subunit	*Streptomyces azureus* and *Streptomyces laurentii*	Thiostrepton	[30]
Galactoocto-pyranoside	Inhibits bacterial protein synthesis	*Streptomyces lincolnensis*	Lincomycin	[31]
Galactoocto-pyranoside	Inhibits bacterial protein synthesis	*Streptomyces sp*	Clindamycin	[32]
Glycolipo-depsipeptide	Inhibits transglycosylation in peptidoglycan synthesis	*Streptomyces azureus* and *Streptomyces laurentii*	Thiostrepton	[33]
Glycolipo-depsipeptide	Inhibits transglycosylation in peptidoglycan synthesis	*Actinoplanes sp* ATCC 33706	Ramoplanin (INN)	[34]

(continued)

Table 1 (continued)

Class	Mechanism of action	Actinomycetes	Antibiotic	Reference
Glycopeptide	Inhibits cell wall synthesis	*Amycolatopsis orientalis*	Vancomycin	[35]
Glycopeptide	Binds to D-ALA-D-ALA terminal end of peptidoglycan precursors and inhibits cell-wall synthesis	*Actinoplanin teichomyceticus*	Teicoplanin	[36]
Imidazo pyridine-4-one	Inhibits polypeptide synthesis via interaction with the ribosome	*Streptomyces lavendulae, Streptomyces noursei*	Streptothricin	[37]
Lipopeptide	Bactericidal activity by disrupting plasma membrane function without penetrating into the cytoplasm	*Streptomyces roseosporus*	Daptomycin	[38]
Macrolide	Inhibits bacterial protein synthesis	*Streptomyces halstedii*	Carbomycin	[39]
Macrolide	Inhibits elongation at transpeptidation step of protein biosynthesis	*Saccharopolyspora erythrea*	Erythromycin	[40]
Macrolide	Inhibits bacterial protein synthesis	*Streptomyces antibioticus*	Oleandomycin	[41]
Macrolide	Inhibits protein biosynthesis by rapid breakdown of polyribosome's by binding 50S unit	*Streptomyces ambofaciens*	Spiramycin	[42]
Natural polycyclicpolyketide	PABA pathway inhibitor	*Verrucosispora AB-18-032*	Abyssomicins	[43]
Naphthalene (ansamycins subclass)	Inhibits bacterial DNA-dependent RNA-polymerase	*Amycolatopsis rifamycinica*	Rifamycin	[44]
Peptide	Inhibits bacterial protein synthesis	*Streptomyces pyridomyceticus*	Pyridomycin	[45]
Thiopeptide	Inhibits bacterial protein synthesis	*Kocuria sp*	PM181104	[45, 46]
Polyketide-Streptogramin	Inhibits protein biosynthesis by binding to 50S ribosome unit	*Streptomyces virginiae*	Streptogramin A	[47]
Polyene lactam macrolides antibiotic	Inhibits bacterial protein synthesis	*Micromonospora sp*	Micromonosporin	[48]

(continued)

Table 1 (continued)

Class	Mechanism of action	Actinomycetes	Antibiotic	Reference
Tetracyclines	Inhibits protein synthesis (elongation) by preventing binding of aminoacyl-tRNA to the 30S subunit	*Streptomyces aureofaciens*	Chlortetracycline	[49]
Tetracycline	Inhibits protein synthesis (elongation) by preventing binding of aminoacyl-tRNA to the 30S subunit	*Streptomyces rimosus*	Oxy tetracycline	[50]
Thiolactone	Inhibition of fatty acid synthesis	*Nocardia sp*	Thiolactomycin	[51]
Unknown	–	*Streptomyces sp*	Bonactin	[52]

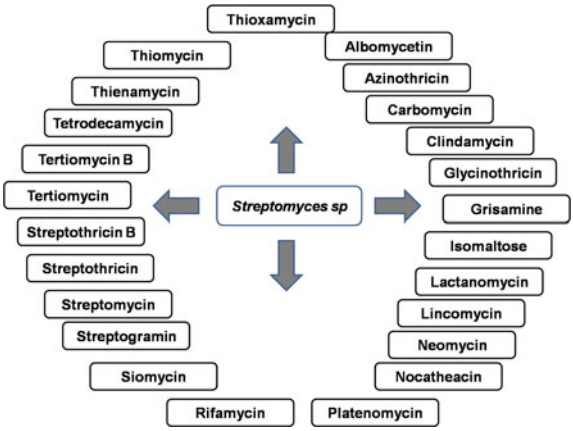


Fig. 2 Representative metabolites by *Streptomyces sp*

Table 2 Recently discovered bioactive compounds from *Streptomyces* sp

Antibiotic	Actinomycetes	Potential use	Reference
BE43472A	*Streptomyces* strain (N1-78-1)	Antibacterial	[55]
Citreamicin delta	*Streptomyces vinaceus*	Antitumor	[56]
Dynemicin	*Micromonospora chersina*	Anticancer	[57]
Lenticulone	*Streptomyces sp* JP 95	Antibacterial	[58]
Lucensimycin D	*Streptomyces lucencis* MA 7349	Antibacterial	[59]
Mediomycin B	*Streptomyces mediocidicus*	Antifungal	[60]
Rapamycin	*Streptomyces hygroscopicus*	Immunosuppressant	[61]
Sansanmycin A	*Streptomyces sp SS*	Antibacterial	[62]

all known antibiotics are produced by these Actinomycetes. The secondary metabolites expressed by *Streptomyces* also find application in the treatment of cancer and autoimmune diseases [19, 53, 54] (Fig. 2). Currently it is reported that there are more than 2,400 different secondary metabolites produced by *Streptomyces* sp. [53]. Scientists and researchers believe that there could be many more such metabolites with therapeutic potential to be discovered and explored [54].

Some of the recently discovered antibiotics from *Streptomyces* are listed in Table 2.

2.2 Rare Actinomycetes: Future Gold Mine of Bioactive Compounds

Streptomyces and other common Actinomycetes have since been exploited so often that the prospects of a new strain often seem remote. Very similar strains most often produce the same or similar compounds, thus hampering the rationale for discovery of new antibiotics. In the quest for new strains and products, marine Actinomycetes home to novel genera and have resulted in some new leads.

Table 3 List of representative bioactive compounds from rare actinomycetes

Antibiotic	Actinomycetes	Potential use	Reference
EHA–2	*Actinomadura spadix*	Antimicrobial	[64]
Teichoplanin	*Actinoplanes teichomyceticus*	Antibiotic	[65]
Vancomycin	*Amycolatopsis orientalis*	Antibiotic	[66]
Pyridomycin	*Dactylosporangium falvum*	Antibiotic	[67]
Aridicins A, B and C	*Kibdelosporangium aridum*	Antimicrobial	[68]

The rare Actinomycetes are usually regarded as strains of Actinomycetes whose frequency of isolation by conventional methods is lower than that of Streptomycete strains and usually comprises those genera other than *Streptomyces*. Notable producers of secondary bioactive metabolites from this class of Actinomycetes are from genera such as *Actinomadura*, *Actinoplanes, Amycolatopsis, Dactylosporangium, Kibdelosporangium, Kitasatospora, Microbiospora, Planomonospora, Planobispora, Salinispora, Streptosporangium, and Verrucosispora* (Table 3) [63].

Marinospora, affiliated with the *Streptomycetaceae* family has yielded some secondary metabolites named marinimycins, with potential antibacterial and cytotoxic activity [69]. Novel compounds of the napyradiomycin class have also been identified from the "MAR4" lineage [70].

Among the terrestrial sources, *Ktedenobacteria, Actinospica,* and *Catenulispora* also appear to possess the ability to produce secondary metabolites.

3 Myxobacteria-Derived Compounds

Myxobacteria, the gliding, Gram-negative bacteria, produce highly colored macroscopic fruiting bodies on decomposed wood and other substrates. Myxobacteria are unique, with a lifestyle differing from all other prokaryotes. They are capable of excreting hydrolytic enzymes and decomposing various and complex biopolymers but can also lyse and destroy other prokaryotes, and even eukaryotic cells [71]. It has been reported that myxobacteria form a phylogenetically coherent group and constitute the order Myxococcales in the class Deltaproteobacteria. They are subdivided into the three suborders Cystobacterineae, Sorangiineae, and Nannocystineae [71, 72]. They produce a large number of unusual secondary metabolites, with potential antibiotic activity [73]. Myxobacteria have been regarded as "microbe factories" for active secondary metabolites because they have great potential as producers of new drugs [72]. They move by an axonal cellular motion (i.e., gliding) and form fruiting bodies when resources are scarce. Individual cells of myxobacteria organize themselves as waves during cooperative feeding. As the cells collide, they aggregate in mounds that grow in size, forming fruiting bodies that can harbor up to 10^5 individuals. Cells within these structures become myxospores, which germinate to new swarms when nutrients are available. Diverse proteins and metabolites mediate these signaling processes [73, 74]. Their secondary metabolites are unusual hybrids

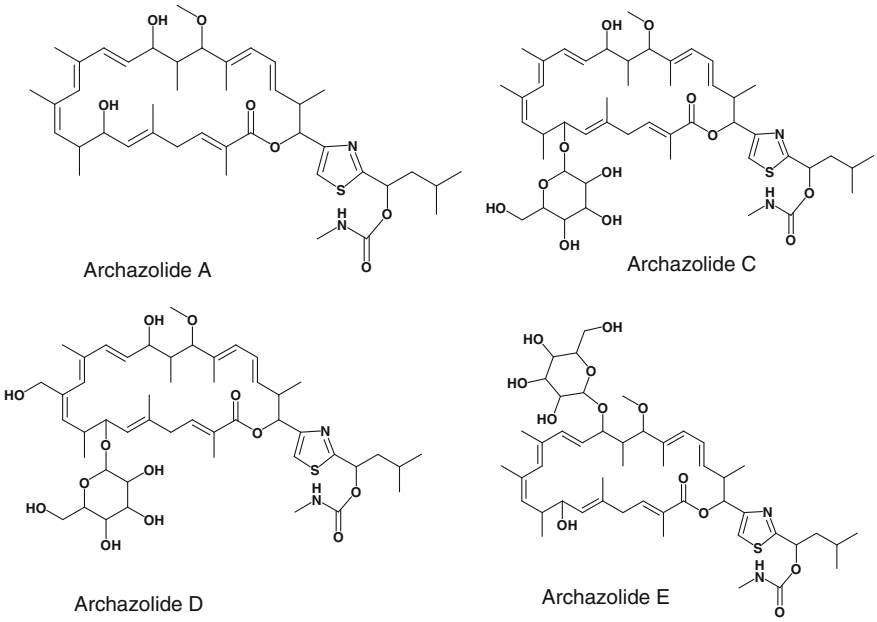


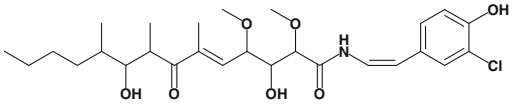
Fig. 3 Chemical structure of Archazolides

of polyketides and nonribosomal-made polypeptides. Unlike metabolites from Actinomycetes, Myxobacterial metabolites are not glycosylated, and their target areas are not the same as other microbial products [74]. They are found mostly in the soil as opposed to marine environments, and are prolific producers of secondary metabolites, which aid their role as predators. Also fascinating is the fact that these bacteria possess the ability to assault their prey in a "pack" or as a single bacterium with cell-to-cell contact [75]. The majority of myxobacteria have been isolated from the soil, a habitat rich in both organic matter and microbial life, including fungi and Actinomycetes. Compound production rates are typically highest during the exponential phase of growth. This behavior is unlike that of the Actinomycetes, in which secondary metabolism correlates with the onset of the stationary phase [76]. Recently, secondary metabolites from myxobacteria have been well reviewed by Weissman and coworkers [77].

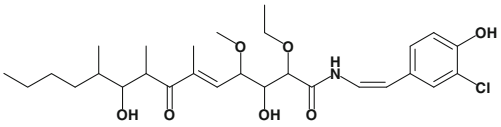
Some of the recent scaffolds reported from the myxobacteria class of microbes are as follows.

Archazolides (Fig. 3)
Three compounds, Archazolide C (MW: 901.169), Archazolide D (MW: 917.168), and Archazolide E (901.169) have been reported from the *Cystobacter violaceus* Cb vi105 strain [78]. An amorphous solid, Archazolide D, was reported to have vacuolar-type H+–ATPase (V-ATPase) inhibitor activity, whereas the parent compound Archazolide A (MW: 739.027) was examined and confirmed for its V-ATPase inhibition, antifungal, and antineoplastic activity [79].

Fig. 4 Chemical structure of Chondrochloren

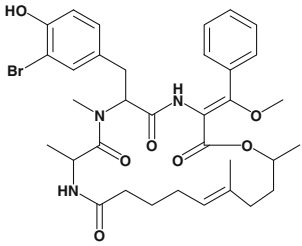


Chondrochloren A



Chondrochloren B

Fig. 5 Chemical structure of Miuraenamide A



Chondrochloren (Fig. 4)
Chondrochloren A (MW: 526.068), an antibacterial compound, was reported from *Chondromyces crocatus* strain Cm c5 in 2003. The attempts of unusual chemistry in the biosynthesis of the antibiotic Chondrochloren A and B had been well documented in 2009 [80].

Miuraenamide (Fig. 5)
A series of potent antifungal compounds, Miuraenamide A–F were reported from the slightly halophilic myxobacterium *Paraliomyxa miuraensis* strain SMH-27-4 [81, 82].

Pedein (Fig. 6)
Chondromyces pediculatus strain Cm p3 has been reported to produce the antifungal compounds Pedein A (MW: 925.390) and Pedein B (MW: 890.945) [83].

Myxobacteria, with their variety of secondary metabolites, unique structures, and new modes of action, are emerging as a highly valuable source of natural products. Myxobacteria are also known to produce different metabolite compounds from different structural classes. Steroid synthesis is extremely rare in bacteria, but both cholesterols and lanosterols have been isolated from myxobacterial extracts [84]. Iron transport metabolites, nannochelins, and myxochelins A and B are produced by myxobacteria. With genome sequencing and metabolic profiling of

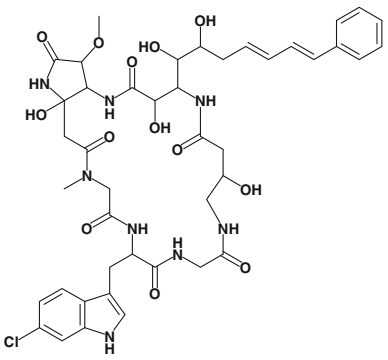


Fig. 6 Chemical structure of Pedein A

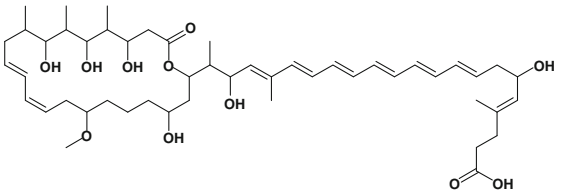


Fig. 7 Chemical structure of Etnangien

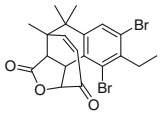


Fig. 8 Chemical structure of Salimabromide

myxobacteria, new strains may be unveiled leading to more promising metabolites with antibiotic potential [85].

Etnangien (Fig. 7)
It is a macrolide antibiotic isolated from the myxobacterium *Sorangium cellulosum*, strains So ce750 and So ce1045. Initial studies have indicated that bacterial and viral nucleic acid polymerases are inhibited by etnangien [86].

Recently, a novel analogue, comparable to that of etnangien has been obtained from the fermentation broths of *Sorangium cellulosum* [87].

Salimabromide (Fig. 8)
Salimabromide is the first natural product from the marine myxobacteria *Plesiocystis/Enhygromyxa* and has revealed antibiotic activity against *Arthrobacter cristallopoietes* [76].

4 Eubacteria-Derived Compounds

In this section we dwell on those prokaryotes under the subcategory of true bacteria or "Eubacteria". In the past decade, within the Eubacteria phyla, many microorganisms have been identified as a sources of bioactive compounds. For instance, marine bacteria have often been reported to produce antibacterial and anticancer compounds, allowing the (i) ecological steadiness of manifold marine ecosystems (ii) interrelations between epiphytic microorganism ambiences, and (iii) inhibition of rival organisms and pathogenic microbes [88]. The sharing or competition mechanisms that are known between these microorganisms are varied, such as antibiotic production, bacteriocins, siderophores, and even pH alteration through the production of organic acids [89]. In the past five years many more bioactive compounds have been reported, however, very few have progressed beyond the discovery or preclinical stage. Moreover, in recent years, research has to a large extent focused on altering existing, naturally occurring antibiotics. These have paved the way for a new class of antibiotics called lantibiotics.

Lantibiotics are peptides with lanthionine and/or methyllanthionine residues produced by Gram-positive bacteria. Modified amino acids such as dehydroalanine and dehydrobutyrine may be also components of the lantibiotics. More recently, they have been the focus of much attention as a consequence of the increasing understanding of their biosynthesis and mode of action, and their high specific activity against multidrug-resistant bacteria [90].

5 Fungal-Derived Compounds

The identification of antibiotics was heralded by the discovery of penicillin from a fungus, the *Penicillin notatum*. Since then, several genera of fungi have been extensively screened for bioactive compounds. However, publications and reviews until now attribute only 5 % of the fungi as producers [91, 92], and the rest await their turn to be tapped for human benefit. This indicates a huge cache of potentially useful fungi that can be tapped with modern techniques of cultivation and identification. Techniques used until now include media optimization, coculturing, chemical induction, epigenetic modulation, and metabolite remodeling, coupled with the fermentation technology for scale-up [93]. These techniques will thus enable their extensive cultivation for the mass production of natural products, both known and novel [93], along with bioprospecting of fungi from every possible source including extreme environments such as marine sediments, geothermal vents, cold deserts, and antarctic and arctic regions.

In recent times, endophytic fungi associated with plants have been viewed as a new source of these pharmacologically active natural products. It is evident that in some cases these associated fungi might be involved in the biosynthesis of compounds that had been previously isolated from plants and might by themselves be the producers of a multitude of new metabolites. However, it is only recently that

Table 4 List of compounds sourced from fungi

Antibiotic	Fungus	Potential use	Reference
FR (KARST)	*Ganoderma lucidum*	Antimicrobial	[94]
Ganodermycin	*Ganoderma applanatum*	Anti-inflammtory	[95]
Aspergiolide	*Aspergillus glaucus*	Antitumor	[96]
Bioxanthracenes	*Cordyceps pseudomilitaris*	Antimalarial	[97]
Chaetominine	*Chaetomium sp*	Anticancer	[98]
Communesins	*Penicillium expansum*	Cytotoxic	[99]
Dolastatin	*Marine mollusks*	Antineoplastic	[100]
Gliocladins	Gliocladium roseum	Antinematode	[101]
Spirolaxine	*Sporotrichum laxum*	Antiproliferative	[102]
Topopyrones A, B, C	*Phoma sp*	Antibacterial	[103]
Variecolorquinines	*Aspergillus variecolor*	Cytotoxic	[104]
Variecolortides	*Aspergillus variecolor*	Cytotoxic	[105]

their capacity for producing biologically active compounds has been explored. Examples are taxol from *Taxomyces andreanae*, podophyllum from *Phialocephala fortinii*, camptothecin from the endophytic fungus of *Camptotheca acuminata*, and hypericin from *Chaetomium globosum*.

Some recently derived compounds from fungi, in various stages of development, are tabulated in Table 4.

Several of these marine-fungal–derived compounds have been well reviewed by Abdessamad et al. [106].

5.1 Slime-Molds–Derived Compounds

Slime molds is a general term used to describe organisms that reproduce by spores. The Myxomycetes (true slime molds) are an unusual group of organisms that may be assigned to one of the lowest classes of eukaryotes. As their fruiting bodies are very small and it is very difficult to collect an adequate quantity of slime molds, few studies have been conducted on the chemistry of Myxomycetes. In a certain stage of their life cycle, they form jellylike plasmodia that feed on bacteria and are able to move by a synchronized perpendicular flow of their protoplasm. Later, the plasmodium transforms in a few hours into small fruiting bodies. These bodies (peridia) often exhibit delicate structures and colors. They release spores from which protozoa like amoeba originate that mate and finally aggregate again to the plasmodia stage. Initially classified under fungi, they are now a separate group as they are quite unrelated to fungi. Among fungi, the number of bioactive compounds reported from slime molds have been less compared to imperfect fungi, the Ascomycetes, and several other filamentous and endophytic fungal species [107]. Approximate 60 bioactive metabolites have been reported from slime molds [107]. The three main groups include *Physarum*, cellular slime molds, and *Labyrinthulomycota*. Of these,

Physarum gyrosum has been shown to express metabolites with antibacterial activity [108]. Masami reported new antimicrobial naphthoquinone pigments, tyrosine–kinase inhibitory bisindole alkaloids, a cytotoxic triterpenoid aldehyde lactone with a reversal effect of drug resistance, a cycloanthranilylproline with sensitizing effect of TRAIL-induced apoptosis through activation of COX2, a dibenzofuran glycoside, and, moreover, sterols with a 2,6-dioxabicyclo[2.2.2] octan-3-one ring system were also isolated from field-collected fruit bodies of Myxomycetes [109]. Secondary metabolites of slime molds were well reviewed in 2005 by Dembitskya et al. [110]. The review included several well-defined and characterized bioactive compounds. In the past few years there have been very sparse reports on significant bioactive compounds from this class of microbes. Nevertheless recently aquatic Myxomycetes have been thoroughly reviewed by Mitsunori and Harold in a 2013 review article [111].

6 Pipeline of Microbial Bioactive Compounds

Numerous companies worldwide are involved in bioprospecting, drug discovery, and drug development programs. However, the past 10–12 years have witnessed major progress in relying on innovation-driven natural products as the sole source of new compounds.

Recent advances in screening, analytical methods in isolating minor compounds, and genomic mining approaches have propelled natural products research to the next stage in the pharmaceutical business. Marine microbes, hitherto not readily accessible as compared to microbes from other sources, have been a source of unique compounds, leading to an increase in the number of drugs entering the drug development phase [112].

In the last decade, 13 new antibiotics have been approved by the FDA, of which just three—Linezolid, Daptomycin, and Retapamulin—have novel action mechanisms [113]. Recently, Fidaxomicin (Dificid, by Optimer Pharmaceuticals), a new scaffold from an Actinomycetes genera (*Dactylosporangium auranticum)* and an anti-*Clostridium difficile* antibiotic have been approved by the FDA and launched to the market in May 2011. Dificid (fidaxomicin) is a narrow-spectrum macrocyclic antibiotic. Dificid is specifically indicated in adults for treatment of *C. difficile*-associated diarrhea [114]. To reduce the development of drug-resistant bacteria and maintain the effectiveness of Dificid, it should be used only to treat infections that are proven or strongly suspected to be caused by *C. difficile*. Dificid is supplied as a tablet designed for oral administration. It is reported that Fidaxomicin is bactericidal against *C. difficile* in vitro, inhibiting RNA synthesis by RNA polymerases [114].

The pharmaceutical industry's main markets are under serious performance pressure. Higher R&D costs, a relatively dry pipeline for new drugs, the increasing demands from payers and providers for reduced healthcare costs, and a host of other factors are putting pressure on global pharmaceutical companies [115].

Cancer is the most important cause of global fatality, with 7.6 million deaths (around 13.6 % of all deaths) in 2008 [116]. Half of the deaths can be attributed to lung, stomach, liver, colorectal, and female breast cancers. About 47 % of cancer cases and 55 % of the cancer deaths occur in less-developed regions of the world. One of the recent reports predicts that the world market for anticancer agents will reach $116.5 billion in 2017, and expand further to 2023 [117]. Ten anticancer drugs have been approved by the FDA in 2013 [118], although none are from microbial resources. However, 86 anticancer compounds from natural products are reported to be under development, of which nine compounds are undergoing Phase III trials [119].

Despite a slowdown of the discovery programs of many pharmaceutical companies, at present there are numerous promising drug candidates in the current development pipeline. Interestingly, many of these promising candidates are of microbial origin. Scientific and practical shortcomings associated with microbial product research are being minimized, and better prospects are envisaged with the exploration of microbial compounds expressed by microbes in ecosystems that were not accessible before. Extrapolating the current situation, it will not be long until the second golden era of microbial compounds will be unveiled.

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