Insights into bioactive microbial natural products and drug discovery

Ahmed A. Hamed[a], Mosad A. Ghareeb[b], Nariman R. Soliman[c], Boulanouar Bakchiche[d], Sanaa K. Bardaweel[e]

[a]Microbial Chemistry Department, National Research Centre, [b]Medicinal Chemistry Department, Theodor Bilharz Research Institute, Kornish El-Nile, Warrak El-Hadar Imbaba (P.O. 30), Giza 12411, Egypt, [c]Dairy Science Department, National Research Centre, 33 El-Buhouth Street, Dokki, Giza, Egypt, [d]Laboratory of Biological and Agricultural Sciences, Amar Telidji University, Laghouat, Algeria, [e]Department of Pharmaceutical Sciences, School of Pharmacy, University of Jordan, Amman, Jordan

Correspondence to Sanaa Bardaweel, PhD, Department of Pharmaceutical Sciences, School of Pharmacy, University of Jordan, Amman 11942, Jordan. Tel: +20201012346834; fax: 00962-6-5300240; e-mail: s.bardaweel@ju.edu.jo

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Recently, natural products have attracted much attention as a valuable source for the discovery of new and potential lead compounds with widely diverse biological activities. Among all-natural product sources, microorganisms emerged as a potential pipeline for new drug leads and new chemical entities with promising biomedical applications. Since the discovery of the first bioactive microbial product, penicillin, the exploitation of microorganisms has led to the production of a variety of natural products ranging from alcohol to antibiotics with multiple applications, including inhibition of infectious diseases such as (antifungal, antibacterial, and antiviral) and noninfectious diseases like obesity, some kinds of diarrhea, cancer, anemia, atopic dermatitis, and diabetes. In this review, we aim to highlight the current literature describing the bioactive microbial natural products, produced by bacteria, fungi, and algae, which have distinct chemical structures that may serve as a robust platform for drug discovery inspiration.

Keywords:
algae, *Bacillus subtilis*, fungus sp, microbial sources, secondary metabolites, *Streptomyces* sp

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Introduction

Nature has always been a 'treasure trove of natural products' with a tremendous biodiversity including millions of species of animals, marine organisms, plants, and microorganisms [1]. This magnificent biodiversity has led to the creation of remarkable chemical assortments [2]. Throughout history, nature has inspired humans to meet their basic needs and prepare their medicines [2]. The first records for using natural products as medications were found written on clay tablets in cuneiform from Mesopotamia dated ca. 2600 before the common era (BCE) [3]. Another ancient record back to the ancient Egyptian civilization (2900 BCE), in the Ebers Papyrus that documented more than 700 plant-based drugs for the treatment of many diseases (2900 BCE) [4,5]. Additional pioneers in using natural products were the Chinese, while Chinese Materia Medica (1100 BCE), an excellent documentation for using natural products to treat diseases (Wu Shi Er Bing Fang with 52 prescriptions) [6].

The scientist and peripatetic philosopher, Theophrastus (~300 BCE), dealt with the herbs as medicines, whilst the Greek physician, Dioscorides 'The Father of Pharmacognosy', (100 A.D.) recorded the use of medicinal herbs [7]. In the eight century, the Arabs were the first to establish pharmacies, and Avicenna, a talented Persian pharmacist, significantly contributed to the sciences of medicine and pharmacy through his works such as the *Canon* Medicine [6].

Furthermore, the use of natural products for the treatment of diseases has been described in the form of traditional medicines, while many of these bioactive natural products still being unidentified [7]. These traditional medicinal practices have created the basic knowledge for drug discovery through extensive chemical, pharmacological and clinical studies [8].

Since then, scientists started searching for natural products (NPs) with new structures and potential applications such as pharmaceuticals, agrochemicals, cosmetics, and nutraceuticals. Despite there are several sources that could be used for natural products

production including microbes, plants, insects, or other animals [1], plants, and marine invertebrates are considered vital suppliers of bioactive chemical components for the development of pharmaceutical products with significant antimicrobial, antiviral, and anticancer properties [9]. Natural products from microbial origins are also well-known for their chemical diversity, and their myriad range of biological properties [10].

Microorganisms as a prolific source of natural products

By the early 19th century, about 80% of all medicines were obtained from plants [11,12]. The discovery of penicillin antibiotics by Alexander Fleming in 1928, has led to a remarkable shift from plants and other sources to microbes as natural product sources [13]. Since then, natural products from microbes have served as a potential source for new chemical entities and new drug leads [14].

Over time, microorganisms remained an attractive source for a variety of lead compounds with a wide range of applications including agrochemicals, immunosuppressants, antibiotics, anticancer and antiparasitic agents [15]. Out of approximately one million already known natural products, 250 000 are biologically active, and large numbers of these biologically active compounds are derived from microorganisms [16]. Microorganisms have been recognized to be one of the optimal systems to produce natural products due to their biosynthetic pathways that can be easily predicted, characterized, and manipulated. Additionally, microorganisms are also known for their high productivity in a very short incubation period. One microbe can produce many secondary metabolites [15]. About 50 secondary metabolites have been isolated from *Micromonospora,* a gentamicin-producing strain, and 38 different epothilones were obtained from the gram-negative *Myxococcus xanthus* [17,18], 16 compounds by *Aspergillus ochraceus* and 19 compounds by the fungus, *Sphaeropsideles* sp., F-240707. These large numbers of natural products were obtained by optimizing physical parameters, nutritional conditions, and/or modifying the chemical environment [19].

Bacteria as a source of bioactive natural products

Production of natural products from bacteria has always been one of the optimal systems for the generation of bioactive materials due to the easy manipulation of bacterial genetic DNA and the high productivity [20,21]. Moreover, several gram-positive and gram-negative bacteria have been studied for their ability to produce numerous bioactive compounds including bacteriocins [22], peptides/glycopeptides [23], tetracyclines [24], phenazines [25], anthraquinones [26], anthracyclines [27], and beta-lactams [28].

Bacillus subtilis

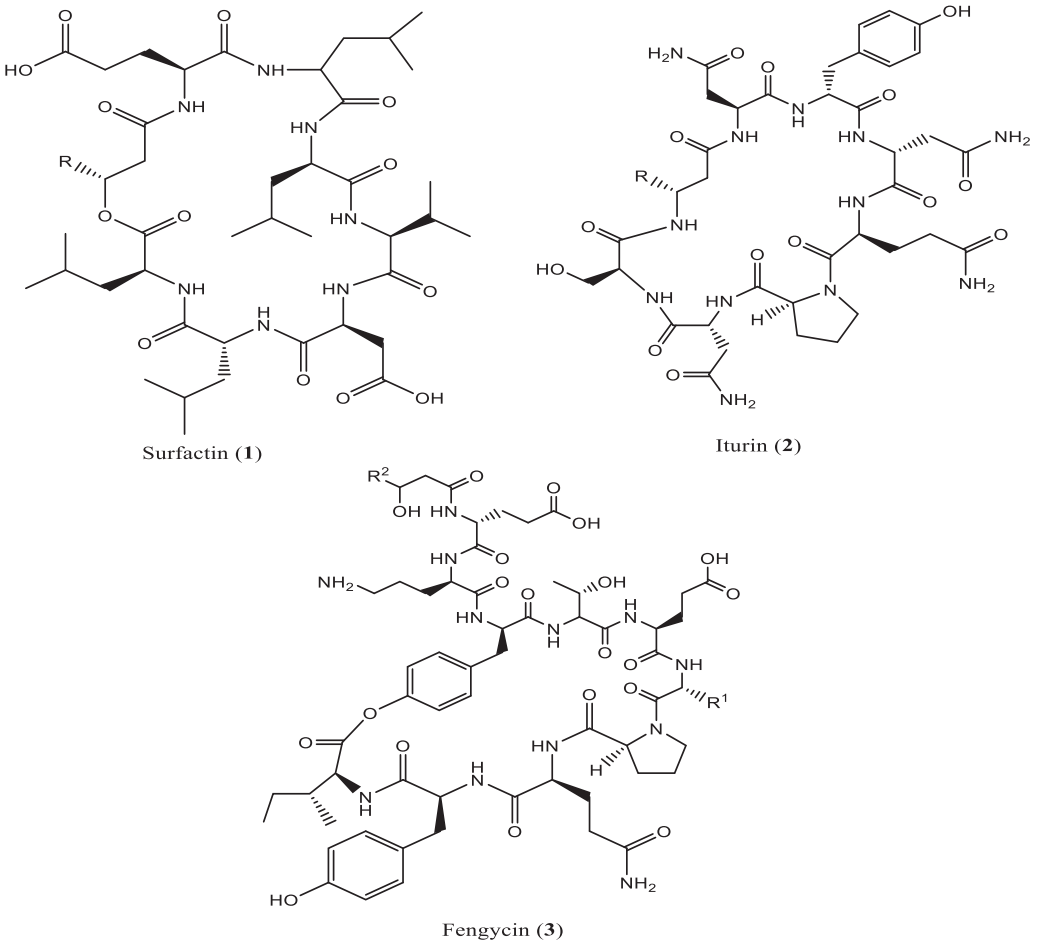
Bacillus species are gram-positive, aerobic, or facultatively anaerobic with rod-shaped structures [29]. *Bacillus* species belong to phylum *Firmicutes,* which includes 266 termed species [30,31]. To protect themselves, *Bacillus* species, under harsh conditions, can form and surround themselves with oval endospores to keep them safe in a dormant state for years. Some species could survive in the dormant state over 420°C [32]. For many years, *Bacillus* species were one of the most important sources of enzymes. Approximately, 50% of all enzymes in the market originate from *Bacillus* species [33]. Over 200 *Bacillus* species have been classified as pathogenic; however, *Bacillus subtilis* is a nonpathogenic strain that can grow in different habitats due to its unusual genetic adaptability [34]. Moreover, the effortless genetic manipulation of *Bacillus subtilis* attributed to natural competence, absence of outer membrane, high secretory capacity, and well-known expression systems, make it a suitable organism for a wide range of studies [35]. All these features make *Bacillus subtilis* a distinguished candidate as a laboratory model strain [36]. Biotechnologically, *Bacillus subtilis* is a well-established candidate for the synthesis of many valuable products ranging from small molecules to vital NPs including enzymes such as stable alkaline cellulase, alkaline protease, and alkaline a-amylase as well as chemicals like (Bacillomycins D-L and bacitracin) which act as antibiotics [35,37].

From the biological control point of view, *Bacillus subtilis* has gained great attention from researchers in the agriculture field due to its ability to kill and control plant pathogens [38]. In the same context, many reports demonstrated that *Bacillus subtilis* also plays a vital role in promoting plant growth [38]. In addition to its application in the bioproduction of cyclic lipopeptides, several wild-type strains from different sources have displayed a powerful inherent biosynthetic potential. These biosynthetic pathways are dedicated natural products such as complex cyclic lipopeptides, including fengycins iturins, and surfactins with several

biotechnological and pharmaceutical applications as biosurfactants and antibiotics [34,39,40]. The first documented natural products obtained from *Bacillus subtilis* were cyclic lipopeptides [34]. Their potent activity and unique chemical structures made them a very attractive group of metabolites as candidates with surfactant and antibiotic activity [34]. In general, the cyclic lipopeptides produced by *B. subtilis* are grouped into three families namely surfactin (1), iturin (2), and fengycin (3) (Fig. 1) [41]. The iturin family comprises a class of lipoheptapeptides with antimicrobial activity against several bacterial and fungal strains [42]. Iturin A (2) is an example of the iturin family produced by *Bacillus subtilis*, which showed antimicrobial activity through its ability to permeate the cell membrane by insertion into the cytoplasmic membrane [43–45]. Even though iturin A (2) antibacterial activity is limited to certain gram-positive bacteria, it possesses a remarkable antifungal activity against a wide range of fungi [46].

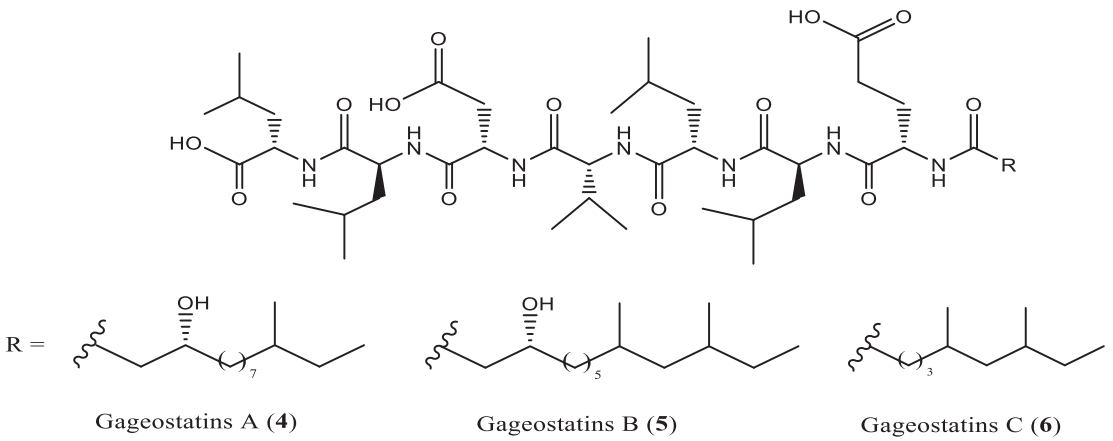
Another lipopeptide produced by *Bacillus subtilis* is Surfactin (1) [47,48]. It is considered one of the strongest biosurfactants due to its remarkable surfactant activity. Interestingly, the amphiphilic structure of Surfactin (1) makes it suitable for a broad range of pharmaceutical applications, ranging from antibiotic and cancer therapy [49]. Fengycins A (1) are fungicidal decapeptides also produced by *Bacillus subtilis*. Their ring structure is formed via macro-lactonization between the acyl moiety of the isoleucine (Ile) and tyrosine hydroxylase (TyrOH). Fengycins are less toxic to plants while displaying a selective antifungal activity against some pathogenic filamentous fungi, such as *Paecilomyces varioti* and *Rhizoctonia solani* Loeffler and colleagues, [50–52]. Gageostatins A-C (4–6) (Fig. 2) were reported as the first example of the linear lipopeptides from *B. subtilis* 109GGC020 [53–55]. Gageostatins A-B (4-5) displayed potent antifungal activity against destructive pathogenic fungi such as *R. solani*, *C. acutatum*, and *B.*

Figure 1



Cyclic lipopeptides obtained from *Bacillus subtilis.*

Figure 2

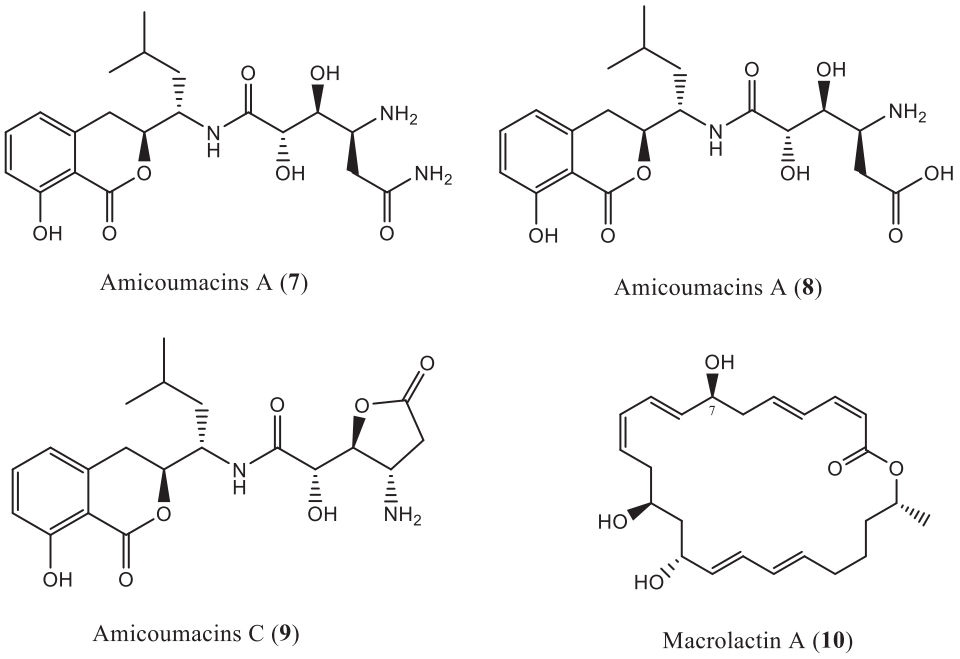


Linear lipopeptides obtained from *Bacillus subtilis*.

cinereal. While gageostatin C (6) displayed only weak antimicrobial activity. Interestingly, gageostatins A (4) and B (5) synergistically act against fungi, gram-positive, and gramf-negative bacteria, as a mixture of both components is strikingly more potent than the individual compounds [34].

Another interesting group of metabolites is the isocoumarins, which also have been reported from *B. subtilis*. The first reported dihydroisocoumarins from *Bacillus* were amicoumacins A-C (7-9) (Fig. 3). Notably, compounds 7-9 exhibited potent anti-inflammatory and antibacterial activities, which highlight such a group of compounds as attractive lead structures for drug development. Additionally, due to the strong antibacterial activity of amicoumacin A (7) against *S. aureus*, it has gained great attention [56,57]. Moreover, macrolides are bioactive metabolites produced by *B. subtilis*. It is reported that most of the macrolides are biosynthetic derivatives of macrolactin A (10) (Fig. 3). The macrolactins have attracted attention due to their potent bioactivities as antimicrobial and cytotoxic agents. It was shown that they have inhibitory

Figure 3



Isocoumarins and macrolactin A obtained from *Bacillus subtilis*.

activity against *S. aureus*, murine tumor cells, *Herpes simplex* type I and II, and several fungi [58–60].

Streptomyces species

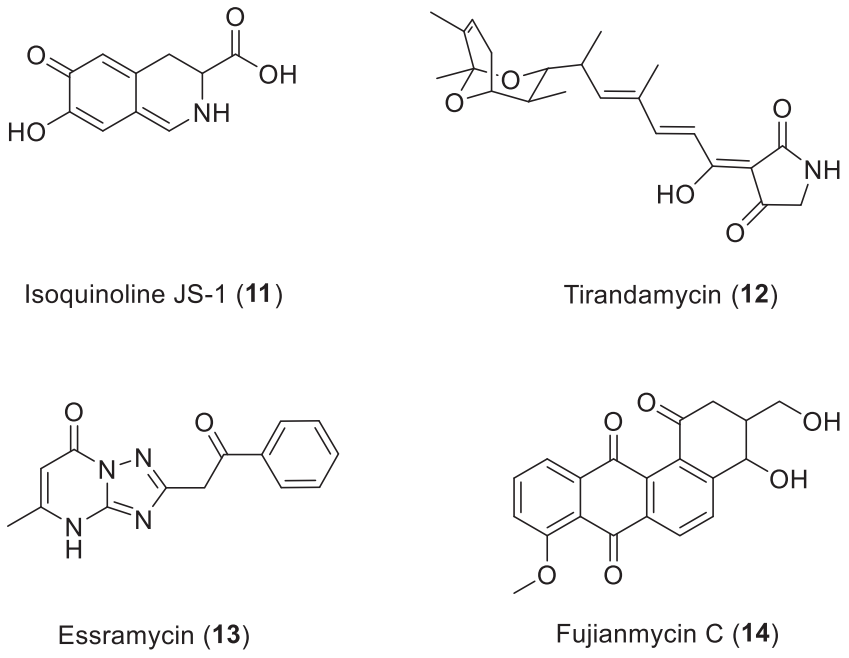
The genus *Streptomyces* is a gram-positive bacteria that grow in different environments of air, water, and soil. *Streptomyces* has been shown as a promising source of bioactive pharmaceutical agents as antibacterial, antifungals, antivirals, antitumors, immunosuppressants, antihypertensives, and antibiotics. *Streptomyces* species grow in different environments ranging from normal to extreme habitats [61]. The classification of *Streptomyces* is based on the morphology involving the formation of hyphae with a chain of spores [62,63]. For more than 70 years, *Streptomyces* has proven to be a promising manufacturer of unique structurally bioactive natural products producing about 70-80% of the natural bioactive substances pipelined for pharmaceutical applications [64]. Loads of new metabolites with completely different biological activities are isolated from *Streptomyces* strains [65]. Approximately, more than 60% of antibiotics such as chloramphenicol and neomycin originated from *Streptomyces* sp [66]. Several studies have reported other bioactive metabolites of the same class such as nystatin by (*Streptomyces noursei*) [67], natamycin by (*Streptomyces natalensis*) [68], and amphotericin B by (*Streptomyces nodosus*) [69]. Additional groups of bioactive metabolites have been isolated from *Streptomyces* sp. and displayed antibacterial activity, such as aminoglycosides, which include neomycin by (*Streptomyces fradiae*) [70], streptomycin by (*Streptomyces griseus*) [71], erythromycin by (*Streptomyces erythraea*) [72], kanamycin by (*Streptomyces kanamyceticus*) [73], vancomycin by (*Streptomyces orientalis*) [74], chloramphenicol by (*Streptomyces venezuelae*) [75] and thienamycin by (*Streptomyces cattleya*) [76]. Besides antibiotic uses, nowadays, cytotoxic studies for Streptomyces-derived bioactive products have gained great attention as possible candidates as chemotherapeutic drugs including plicamycin (*Streptomyces plicatus*) and bleomycin (*Streptomyces verticillus*) [77].

Up to 60% of antibiotics produced *Streptomyces* genus showed great applications in the agricultural industry [78] and medicinal applications. The reason relates to its wide applications and different functions [79], such as antibacterial [80], antiviral [81], antifouling [82], antiparasitic [83], anti-inflammatory, antitumor, insecticidal [83], enzyme inhibitors [84], and insecticidal [83]. Historically, the origins of the biggest number of new antibiotic drugs were obtained from *Streptomycetes* when compared with bacteria and fungi [85]. Today, *Streptomyces* species are approximately responsible for more than 75% of both commercial and medical antibiotics. It has also been shown that the optimization of nutritional and cultural conditions may provide control over how *Streptomyces* produce their antibiotics [86].

Several bioactive secondary metabolites have been isolated and/ or identified from *Streptomyces*. These compounds belong to different chemical families including meroterpenoids, pyrrolosesquiterpenes, sesquiterpenes, polyketides, peptides, quinones, and macrolides. It is worth noting that such compounds showed a broad spectrum of biological activities. For instance, glaciapyrroles A, B, and C, SBR-22, salinamides A and B, tetracenomycin D, resistoflavine, himalomycins A and B, and bonactin exhibited antibacterial activities. While daryamides, piperazimycins, piericidins C7 and C8, tetracenomycin D, resistoflavine, chinikomycins A and B, trioxacarcins, and streptokordin demonstrated anticancer activities, other compounds like cyclomarin A, resistomycin, and komodoquinone A showed anti-inflammatory, antiviral, and neuritogenic activities, respectively [80–85].

Streptogramins are bioactive natural products produced by *Streptomyces* that showed antibacterial activity through the inhibition of bacterial ribosomal protein synthesis. Etamycin and streptogramin antibiotics were produced by *S. griseus* in the 1960s [87], Etamycin displayed a strong activity against methicillin-resistant *S. aureus*, including hospital-acquired type (HA-MRSA) (MIC=8-16 μg/ml) and community-acquired type (CA-MRSA) (MIC=1-2 μg/ml). Etamycin also showed antibacterial activity toward *Streptococcus pyogenes* (*S. pyogenes*) and *S. agalactiae* (MIC=8 μg/ml) strains [88]. *S. virginiae* produces two streptogramin antibiotics, virginiamycin S (VS) and virginiamycin and both compounds show strong synergetic co-activity [89]. Isoquinoline JS-1 (11) (Fig. 4) is a bioactive isoquinoline derivative; it was produced by *Streptomyces* sp. 8812. It exhibited antibacterial activity through inhibition of DD-carboxypeptidases/ transpeptidases enzymes involved in bacterial cell wall biosynthesis. Isoquinoline JS-1 (11) showed inhibition activity toward MRSA and *Bordetella bronchiseptica.* Moreover, compound 11 does not have any genotoxic or hemolytic properties, so its antibacterial activity can be increased by potential modifications [90].

Figure 4

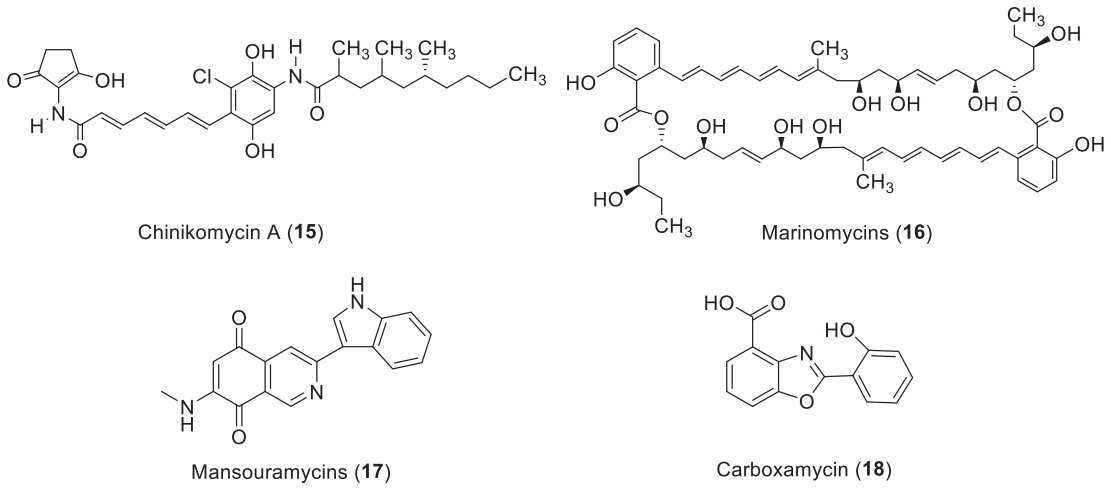


Isoquinoline JS-1, tirandamycin, essramycin, and fujianmycin C obtained from *Streptomyces* sp.

Tirandamycin (12) (Fig. 4) was produced by *Streptomyces* sp. 307-9 and showed a potent inhibition activity against vancomycin-resistant *Enterococcus faecalis* [91]. Tirandamycin weakens the transcription process through the inhibition of ribonucleic acid polymerase in the bacteria [92]. Additionally, essramycin (13) (Fig. 4), is a triazolopyrimidine derivative, obtained from *Streptomyces* sp. Merv8102. It showed a strong broad-spectrum antibacterial activity against *P. aeruginosa, E. coli, S. aureus, B. subtilis,* and *M. luteus* [93]. Fujianmycin C (14) (Fig. 4), a bioactive compound and a member of the angucyclinone family, was produced by *Streptomyces* sp. B6219 [94]. Fujianmycin A and B were isolated alongside fujiamycin C (14), which were known previously. Previous reports revealed that fujianmycin C (14) showed antibacterial activity against *S. aureus B. subtilis*, and *E. coli* [95]. Tigecycline, a derivative of minocycline, was produced by *Streptomyces aureofaciens* and demonstrated antibacterial activity [91].

Amphotericin B was isolated from *S. nodosus*, a macrolide polyene antibiotic is an antifungal compound with a broad-spectrum activity [96]. The mechanism of inhibition includes the inhibition of fungal chitin synthase: nikkomycins and polyoxins [97]. Polyoxins produced by *S. cacaoi* var. *asoensis* showed antifungal activity against phytopathogenic fungi (e.g., *Pricularia oryzae, Alternaria kikuchiana*) [97]. Nikkomycins (nikkomycin Z) are more active against *Candida albicans* than polyoxins. Nikkomycins have been isolated from *S. tendae* and *S. ansochromogenes*, which showed inhibition activity against *Botrytis cinerea* and *Rhizopus carcinans* [97]. Another compound produced by *Streptomyces hygroscopicus* was everolimus, which showed an immunosuppressive activity [92]. *Streptomyces* also have proven to be a potential candidate for the production of several antitumor metabolites. One example of these antitumor natural products is brostallicin, which is produced by *Streptomyces distallicus* and showed anticancer activity [93]. Chinikomycin A (15) (Fig. 5) obtained from *Streptomyces* sp. exhibited antitumor activity towards different human cancer cell lines. Marinomycins (16) (Fig. 5) were produced by *S. peuceticus*, which showed anticancer activity [98]. Epirubicin is an anthracycline compound, which was approved by the FDA in 1999 due to its potential therapeutic profile with less-adverse effects than doxorubicin [99]. It is used in the treatment of different forms of carcinomas including ovarian cancer, lung cancer, breast cancer, and leukemia. Bleomycin is an antitumor compound produced by *S. verticillus*, which was approved for clinical treatment by the FDA in 1973 [100]. Other

Figure 5



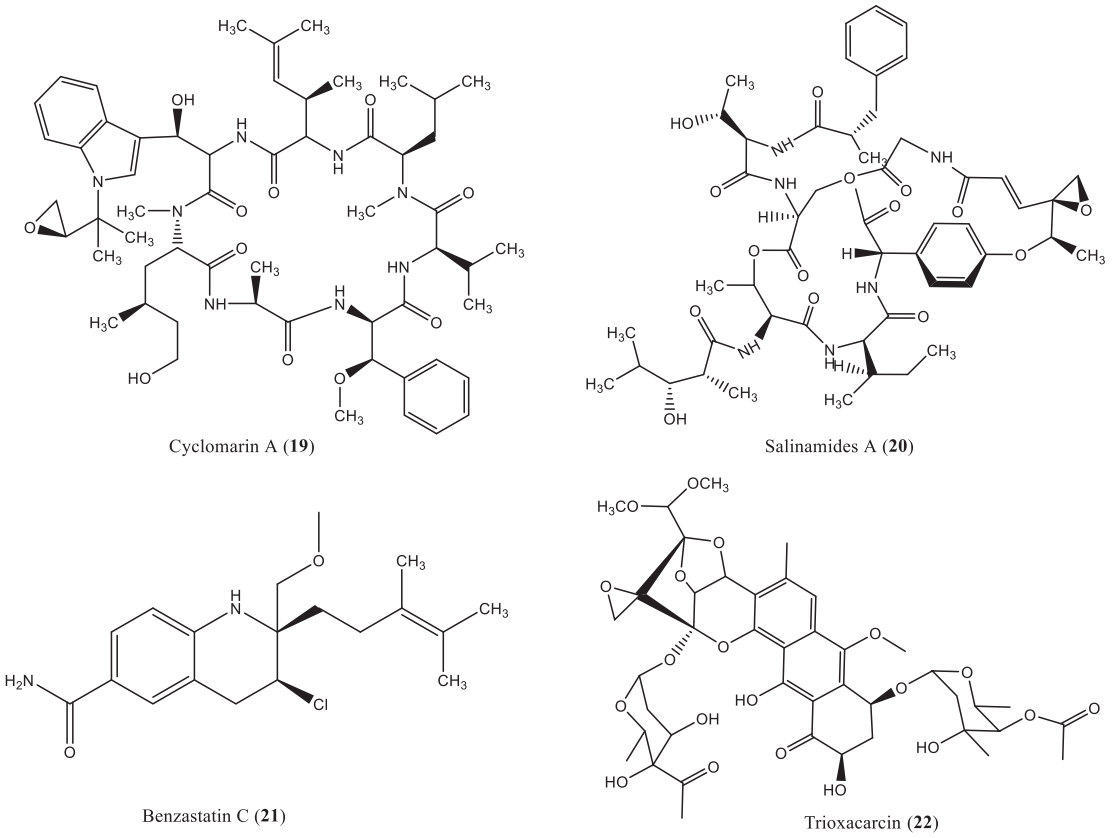
Chinikomycin A, marinomycins, mansouramycins, and carboxamycin obtained from *Streptomyces* sp.

metabolites produced by *S. caesptitosus* are mitomycins, which demonstrated high antitumor activity. Mitomycins exhibited limited uses due to their toxicity [101]. Streptozotocin, also obtained from *S. achromogenes*, revealed selective toxicity toward pancreatic β cells. It was approved by the FDA in 1982 as a pancreatic islet cell antitumor drug [102]. Mansouramycins (17) (Fig. 5) are isoquinoline quinones metabolites produced by marine-derived *Streptomyces* sp. These metabolites showed antitumor activity toward breast cancer, melanoma, lung cancer, and prostate cancer cells [103]. Tartrolons are a distinct group of bioactive compounds obtained originally from *Actinomycetes*. Tartrolon D was obtained from *Streptomyces* sp. MDG-04-17-069. It showed cytotoxicity against human tumor cell lines: colon (HT29), lung (A549), and breast (MDA-MB-231) [104]. Carboxamycin (18) (Fig. 5) was produced by *Streptomyces* sp. NTK 937 isolated from sediments of the Canary Basin. It showed antitumor activity against hepatocellular carcinoma (HepG2), gastric adenocarcinoma cell lines (AGS), and breast carcinoma (MCF7) [105].

Besides their ability to produce antibiotic metabolites, *streptomyces* have proven to be a powerful candidate for the production of metabolites with anti-inflammatory activities. *S. arenicola* produces the anti-inflammatory metabolites cyclomarin A and C. Moreover, it was reported that cyclomarin A has antituberculosis and antimalaria activities [106]. Cyclomarin A (19) (Fig. 6) produced by *Streptomyces* sp., is a cyclic heptapeptides metabolite, which displayed potent anti-inflammatory activity in both *in vivo* and *in vitro* assays [107]. Salinamides A (20) (Fig. 6) obtained from *Streptomyces* sp. CNB-091, derived from jelly fish *Cassiopeia xamachana*. These metabolites are considered potential anti-inflammatory and antibiotic agents [108]. Complestatins, known as peptides, are obtained from *Streptomyces lavendulae*. These peptides did not display any inhibitory activity against HIV enzymes. Where they act by interacting with target cells' surface molecules and inhibiting the adsorption of human immunodeficiency virus type 1 (HIV-1) to cells [109]. Benzastatin C (21) (Figs 6), 3-chloro-tetrahydroquinolone alkaloid, produced by *Streptomyces nitrosporeus* displayed antiviral activity against *herpes simplex* virus type 1 and 2 (HSV-1, 2) and vesicular stomatitis virus (VSV) [110].

Anti-parasitics drugs are a class of medications that are indicated for the treatment of parasitic diseases. Nanchangmycin is a polyether metabolite that showed activity against chicken coccidial parasites, and meilingmycin, which demonstrated antiparasitic activities against arthropod parasites of domestic animals. The two compounds were isolated from *S. anthogenesis* and reported to be active against harmful insects and nematodes [110]. While Pimentel-Elardo and colleagues [83] isolated valinomycin, staurosporine, and butenolide from a marine sponge-derived *Streptomyces* sp., and by studying their antiinfective activities, he reported their anti-parasitic activities against *Leishmania major* and

Figure 6



Cyclomarin A, salinamides A, benzastatin C, and trioxacarcins obtained from *Streptomyces* sp.

Trypanosoma brucei. Trioxacarcins (22) (Fig. 6) is a complex metabolite with higher antimalarial activity against malarial pathogens. Trioxacarcin A, B, and C were produced by marine *Streptomyces ochraceus* [111]. Some of these compounds showed high antiplasmodial activity when compared with artemisinin, the most active antimalarial drug.

Fungi as a source of natural products

Statistically, ~38% of the 22 000 microbial natural bioactive metabolites were derived from fungi, and as estimated, only 5% of the world's fungal taxa have been identified and studied [112,113]. Recently, fungi presented tremendous importance for the discovery of novel bioactive metabolites. After the discovery of the first class of antibiotics, penicillins, fungal natural products, and their effects have gained researchers' major interest. Since then, fungi have served as a source for many interesting bioactive metabolites with a wide range of applications such as peptidic terpenoids and polyketides. Currently, the continuous increase of antimicrobial resistance is a major global challenge, and an urgent need to discover new bioactive secondary metabolites to combat this global health risk [114].

Several therapeutic leads, such as mycophenolic acid, cyclosporine, griseofulvin, fusidic acid, and other novel semisynthetic antifungal drugs, such as caspafungin and anidulafungin, have been obtained from fungal natural products [8]. Another product derived from fungal cyclosporine is Debio 025 which was clinically approved as an antiviral agent [115]. Statin's derivatives are important drugs for the treatment of cardiovascular diseases, including lovastatin obtained by *Aspergillus terreus* and mevastatin obtained from *Penicillium citrinum* [116–118]. Another fungal metabolite also used for plant protection, strobilurins which were isolated from *Strobilurus* species, led to the production of synthetic fungicides such as trifloxystrobin [119]. Fungal endophytes are a group of fungi with rich chemistry and biodiversity, found naturally in every plant species. It is noteworthy that all

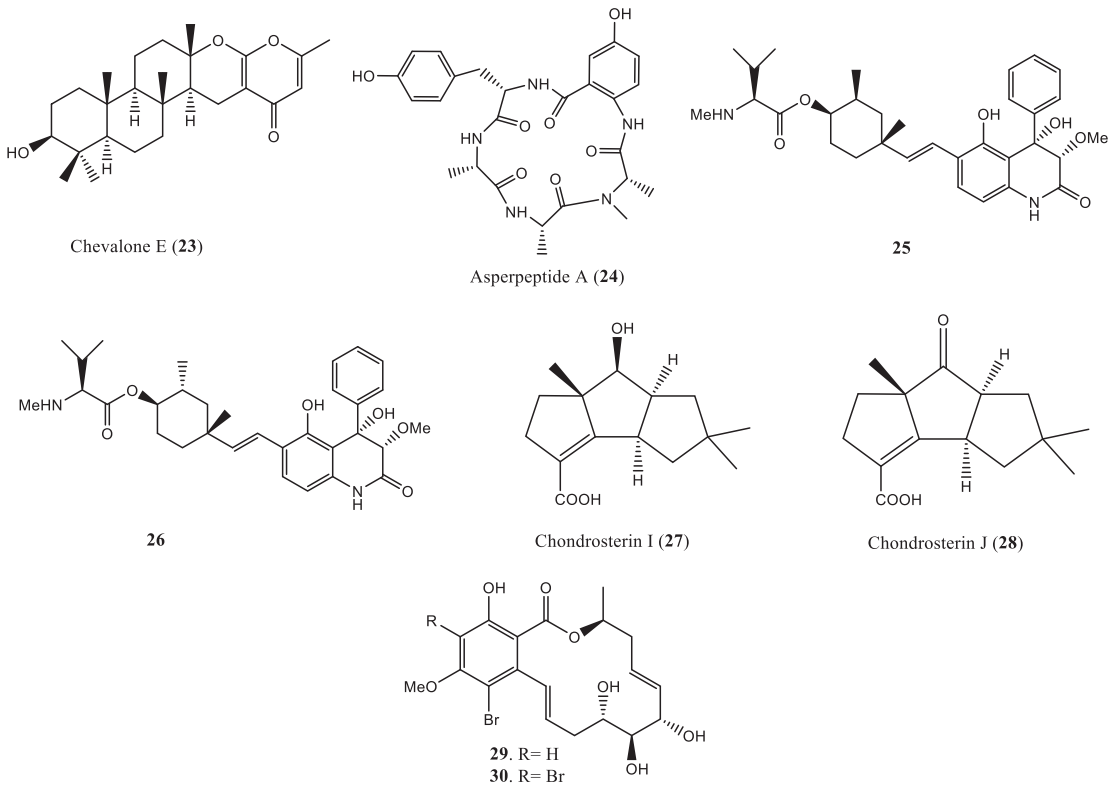
300 000 plant species found on the earth host at least one endophyte [120]. Several natural products including alkaloids, mycotoxins, terpenoids, fatty acids, steroids, flavonoids, etc reported for their wide range of applications [120–135]. Specifically, some of these products have been identified or isolated from fungal species like *Rhinocladiella* sp. (alcytochalasins) [120], *Aspergillus fumigatus* (stearic acid, α-linolenic acid, and physcion) [121], *Penicillium* sp. (n-trcosanyl-n-octaced-9-enoate, and 7α, 9β, 15β-triacetoxy-3-β-hydroxy jatropha-5E, 11E-diene) [124], *Emericella* sp. (emericellamides A and B) [130], and *Aspergillus terreus* (butyrolactone I) [130].

Between 2000 and 2006, 140 new bioactive secondary metabolites were isolated from endophytic fungi [136]. Cryptocin, a potent antifungal compound that is isolated from endophytic fungus *Cryptosporiopsis quercina* and *Tripterigeum wilfordii*, has displayed strong activity against plant pests, *Pyricularia oryzae*, and other plant pathogenic fungi [137]. Another interesting group is the fungi-derived marine invertebrates, which are known for their pioneer ability to produce unique structures. *Aspergillus similanensis* isolated from a sponge yielded a deacetyl analog of chevalone E (23) (Fig. 7). Chevalone E (23) displayed a synergetic effect with the ampicillin and oxacillin antibiotics against MRSA [138]. Asperpeptide A (24) (Fig. 7) is an acyclic pentapeptide, which was yielded from the Gorgonian *Aspergillus* sp [139]. The two prenylated hydroquinone derivatives (25) and (26) (Fig. 7) were also obtained from a Gorgonian-derived *Aspergillus* sp., while (26) exhibited potent activity toward respiratory syncytial virus (RSV) [140].

Two sesquiterpenes chondrosterin I (27) and J (28) were obtained from *Chondrostereum* sp. soft coral derived from fungus (Fig. 7). Chondrosterin J (28) showed strong activity against HTCLs [141]. Epigenetic modification treatment of *Cochliobolus lunatus* using histone deacetylase (HDAC) led to the isolation of two brominated 14-membered resorcylic acid lactones (29) and (30) (Fig. 7).

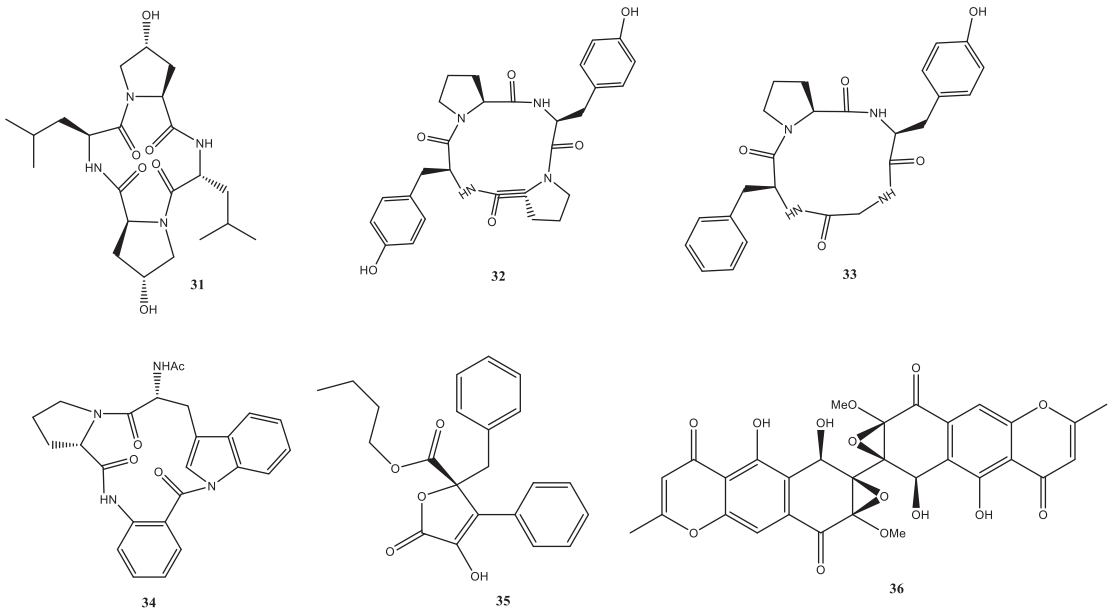
On the other hand, fungi from mangroves have been also recognized for their ability to produce very important lead compounds. In 2014, up to 108 new compounds have been identified. The co-culturing of *Alternaria* with *Phomopsis* species resulted in the

Figure 7



Chevalone E, Asperpeptide A, chondrosterin I, J, and prenylated hydroquinone derivatives obtained from fungi.

Figure 8



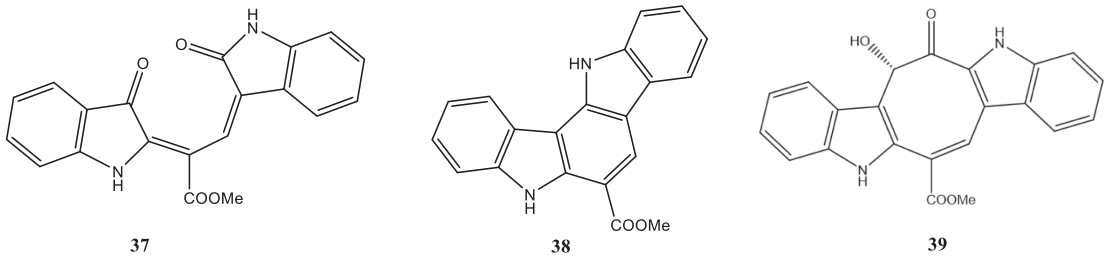
Cyclic peptides, butyrolactones, and polyketides obtained from fungi.

production of three cyclic peptides (31-33) (Fig. 8). They displayed strong inhibition activity towards many plants pathogenic fungi [142,143] while co-culturing of two *Aspergillus* species isolated from brown alga (*Sargassum*) produced a cyclic peptide, psychrophilin E (34) (Fig. 8) [144]. Aromatic butyrolactone flavipesin A (35) (Fig. 8) was obtained from *Aspergillus flavipes*. Flavipesin A (35) showed moderate to good antibacterial activity. Unlike penicillin, it was able to penetrate the biofilm matrix to kill live bacteria inside mature *Staphylococcus aureus* biofilm [145]. Endophytic fungus *Diaporthe sp.* was found to produce diaporine (36) (Fig. 8), a polyketide that induces the conversion of tumor-associated macrophages from the M2 to the M1 phenotype in both cellular and animal models [146,147]

Algae as a source of natural products

Algae are a diverse group of aquatic organisms that play an important role in the supply of oxygen to the atmosphere through photosynthesis [148]. Approximately 30 000 algal species could be served as a very good nutritional source for fish and humans, also, in medicine and fertilizers. Several groups of secondary metabolites are obtained by algae which including terpenoids, phenazine derivatives, brominated derivatives, amino acids, guanidine

Figure 9



Bisindole alkaloids obtained from Algae.

derivatives, oxygen, and nitrogen heterocycles. The racemosines A-C (37-39) (Fig. 9), bisindole alkaloids produced by *Caulerpa racemose* [149,150], caulerpin, also from a *Caulerpa* sp [151]. Caulerpin is featured in studies of antinociception mechanisms [152] and the antituberculosis activities of caulerpin and synthetic analogs [153].

Conclusion

Microorganisms represent one of the biggest and the most diverse eco-systems on earth. Since the discovery of the antibiotic penicillin, microbial natural products have been earth emerged as powerful and renewable sources of pharmacologically active metabolites. Since the 2000s, up to 77% of the approved antibiotics by the FDA are natural products, originating from microbes [154]. Several reports and reviews on microbial natural products show the importance of microbes and their secondary natural products for health and medicine [155,156]. Each day, there is increasing evidence that microbial natural products and their chemical diversity will be the key to the successful improvement of the drug discovery future [156]. Moreover, microbial natural compounds are expected to form a great achievement in the global drug market, with estimation to reach by 2025 upto 400 billion USD [157]. At the same time, the spreading of infectious and noninfectious diseases creates an urgent need for novel drug discovery with efficient bioactivity including antimicrobial, antitumor, and immunosuppressant, along with other pharmacological activities [158,159]. At present, several successful microbial-based natural products have been approved for the treatment of many diseases. This implies the distinguished participation of microbial natural products in drug manufacturing, and this recently motivates scientists to apply recent biotechnology such as recombinant DNA, genetic engineering, and epigenetic strategies to produce novel therapeutic entities that can have a huge commitment to the cure of humanity. Additionally, the continuous improvement of analytical techniques for chemical skeleton interpretation, overall chemical synthesis, biosynthesis, and genetic engineering are all critical for the success of microbial natural products as drug leads [160]. Overall, microbial bioactive compounds will continue to broaden their diverse and integral role in human life.

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Conflicts of interest

The authors declare there are no conflicts of interest.

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