Review

A Review on Microorganisms-Derived Products as Potential Antimicrobial Agents

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Simple Summary: The current manuscript reviewed the microbial metabolites, including growth hormones, pigments, antibiotics, etc., that have become significant sources for life-saving drugs to combat the issues of multi-drug resistance by activating particular target sites. Thereby, they can be an attentive source for biotechnological applications, specifically for pharmaceuticals and nutraceuticals. Apart from plants, we briefly highlighted the various microorganisms, including bacteria, actinomycete, fungi, mushroom, microalgae, etc., as a well-acknowledged source to produce extensive biocontrol metabolites that are generally regarded as safe (GRAS). Such antimicrobial agents are actively used in the food, feed, agriculture, cosmetics, and pharmaceutical industries.

Abstract: Microorganisms including actinomycetes, archaea, bacteria, fungi, yeast, and micro algae are the auspicious source of vital bioactive compounds. In this review, the existing state of the art regarding antimicrobial molecules from microorganisms has been summarized. The potential antimicrobial compounds from actinomycetes, particularly *Streptomyces* sp.; archaea; fungi including endophytic and marine-derived fungi, mushroom; yeast, and microalgae were briefly described. Furthermore, this review briefly summarized the activity and mode of action of bacteriocins, a ribosomally synthesized antimicrobial peptides product of *Eurotium* sp., *Streptomyces parvulus*, *S. thermophiles*, *Lactococcus lactis*, etc. Bacteriocins have inherent properties such as targeting multiple-drug resistant pathogens, which allows them to be considered next-generation antibiotics. Similarly, *Glarea lozoyensis* derived antifungal lipohexpeptides i.e., pneumocandins, inhibits 1,3-β-glucan synthase of the fungal cell wall and acts as a precursor for the synthesis of caspofungin, is also elaborated. In conclusion, this review highlights the possibility of using microorganisms as an antimicrobial resource for biotechnological, nutraceutical, and pharmaceutical applications. However, more investigations are still required to separate, purify, and characterize these bioactive compounds and transfer these primary drugs into clinically approved antibiotics.

Keywords: Antimicrobial; bacteriocins; halocin; Chlorellin; killer yeast.

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1. Introduction

For the last few decades, antibiotics have saved millions of lives but the prevalence of multidrug resistance (MDR) microbial strains, nullifying the effects of antibiotics are the expected consequences of antibiotics abuse. The emergence and prevalence of antibiotic-resistant microbial strains remain one of the major health issues of the 21st century, creating selective pressure on natural microbiota. The ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species) are one of the greatest challenges in medical practices as most of them are multidrug-resistant isolates [1]. The US Centres for Disease Control and Prevention (CDC) classified the most concerning antimicrobial resistance (AMR) threats, cataloging carbapenem-resistant *P. aeruginosa, Clostridium difficile*, and *A. baumannii*; MDR *Neisseria gonorrhoeae* and carbapenem- and cephalosporin-resistant *Enterobacteriaceae* as "urgent" threats [2], requiring urgent measures to cope up the situation. Pendleton et al. [3] provide a contemporary summary and clinically relevant information on the ESKAPE pathogens. In contrast, the detailed description regarding the antimicrobial resistance mechanisms of ESKAPE pathogens was illustrated by Santajit and Indrawattana [1], which can be used as a tool and applied to emerging MDR pathogens. Mulani et al. [4] highlight the use of therapies, including the combination of antibiotics, bacteriophages, antimicrobial peptides, nanomedicines, and photodynamic light therapy to overcome the limitations of individual therapy. These advanced and combinatorial therapies could be used as an alternate solution to combat AMR.

Due to increased consumption of livestock products in middle-income countries, antimicrobial consumption will increase up to 67%, and up to two-fold in India, Brazil, China, Russia, and South Africa, by 2030 [5]. However, the approval of antibacterial agents decreased by 56 % from 1998 to 2002 as compared to the period from 1983 to 1987, and out of total 225 new molecular entities, only 3% of antimicrobial agents were approved by the United States Food and Drug Administration (FDA) from 1983 to 2002. FDA approved 6 novel antibacterial drugs, including the 3rd generation cephalosporin and β-lactamase inhibitor combination ceftazidime/avibactam, in 2015 [6], whereas in 2018 and 2020, not a single antimicrobial drug had been approved by FDA [7].

The current review summarizes the microbial metabolites, including growth hormones, pigments, antibiotics, etc., that have become significant sources for life-saving drugs. Many of these microbial metabolites hold specific antimicrobial potential and act at particular target sites (Figure 1); thereby, they can be an attentive source for biotechnological applications, specifically for pharmaceuticals and nutraceuticals [8]. During the late 1980s, a shift from chemical synthesis of drug discovery from nature to the laboratory bench has taken place, resulting in the discovery of approximately 50 % natural drugs from 1981 to 2010 [9]. Prodigiosin, an antimicrobial pigment produced by the marine bacterium *Vibrio ruber*, induces autolytic activity in the *Bacillus subtilis.* Similarly, Lantibiotics from Gram-positive bacteria were bioengineered to increase their effectiveness against a wide range of bacterial strains and improve their stability while transmitting through the gastrointestinal (GI) tract making them protease-resistant [10].

Biofilms formed by bacteria are ubiquitous and are a part of their survival mechanisms. Biofilms have been involved in many clinical infections such as atherosclerosis, pharyngitis, laryngitis, pertussis, bacterial vaginosis, etc. [11]. Apart from causing deadly infections and diseases, bacterial antimicrobial compounds are reported as antifungal, antiviral, etc., as described in this review. We briefly highlighted the bacteriocins from lactic acid bacteria (LAB) and their mode of action. Most antimicrobials disrupt the cell membrane integrity or inhibit cell wall synthesis, protein, and nucleic acid synthesis. A recent study by Ting et al. [12] updated the epidemiology of the infectious keratitis (IK), the leading cause of corneal blindness; its causative microorganisms including bacteria, virus, fungi, parasites, and polymicrobial infections; major risk factors associated with IK and the impact of AMR on the treatment of IK. Antimicrobial compounds such as vinaceuline, bafilomycin, antimycin, and other anti-methicillin-resistant *S. aureus* (MRSA) compounds

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synthesized by *Streptomyces* sp., having antagonistic activity against different microbial strains are discussed in the present review. We also elaborated on the halocins and sulfolobicin from archaea. Further, the antimicrobials reported from endophytic and marine-derived fungi along with mushrooms, yeasts, and microalgae are summarized. Microalgae act as a potential source of antimicrobial substances due to the synthesis of indoles, acetogenins, terpenes, phenols, and volatile halogenated hydrocarbons, which have also been discussed. Hence this review documented the potential antimicrobial compounds discovered from the all-possible microbial resources, including microbes inhabiting extreme habitats.

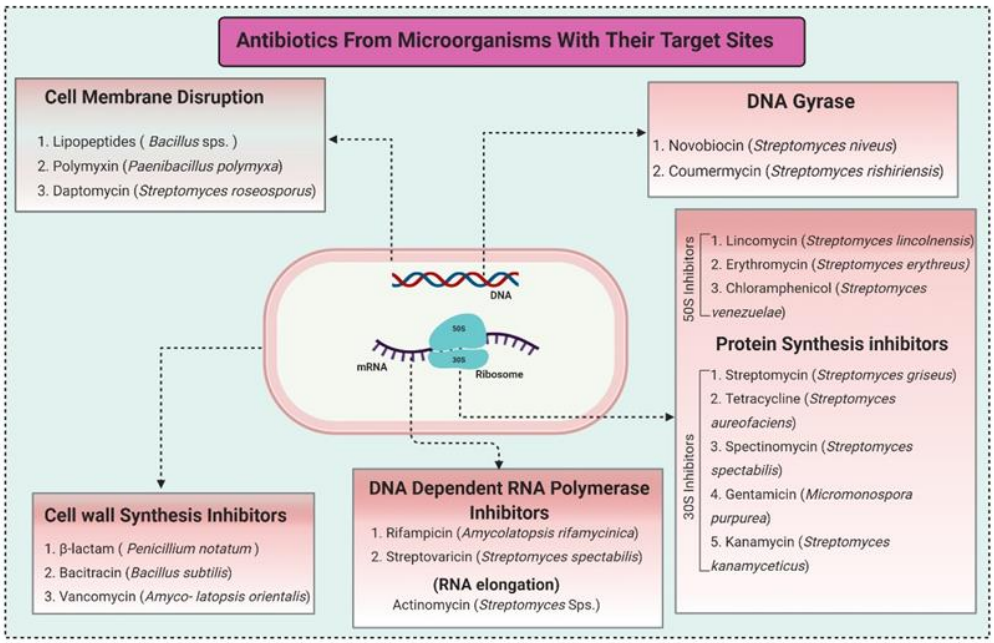

Figure 1. Antibiotics reported from different microorganisms with their target sites.

2. Bacteria

Bacterial antimicrobial compounds have been used traditionally for numerous reasons, including delaying the spoilage of food material or crops by plant pathogens in agriculture and extending the shelf life of products in the food industry [13]. *Bacillus* strains are well-acknowledged to produce extensive biocontrol metabolites, which include the ribosomally synthesized antimicrobial peptides (bacteriocins) [14], as well as non-ribosomally synthesized peptides (NRPs) and polyketides (PKs) [15].

2.1 Ribosomally synthesized antimicrobial peptides (bacteriocins) and bacteriocin-like inhibitory substances (BLIS):

Bacteriocins are antimicrobial ribosomal peptides reported from all major lineages of bacteria and some members of archaea. Gram-negative bacteria *Escherichia coli* produces colicins that are bacteriocidal protein, which is larger than 20 kDa and prevents the growth of closely related strains [16]. Bacteriocins have attracted more attention because of their impending use as a usual food preservative and therapeutic antibiotic. Another reason is that they have a rapid-acting mechanism by forming pores in the membrane of target bacterial cells, even at very low concentrations (Figure 2). The recently reported bacteriocins along with their characteristics are presented in Table 1. Bacteriocins from lactic acid bacteria (LAB) have gained significant attention due to their food-grade quality and industrial significance. LAB and its by-products are generally regarded as safe (GRAS) as a human food component by the U.S. Food and Drug Administration (FDA). Hence it is safer to use LAB bacteriocin to constrain the growth of pathogenic/undesirable bacteria [17]. Lozo et al. [18] isolated the strain *Lactobacillus paracasei* from customarily homemade

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white-pickled cheese and reported that it produces bacteriocin 217 (Bac217), exhibiting antimicrobial activity against *Pseudomonas aeruginosa, Bacillus cereus, Salmonella* sp., and *S. aureus*.

A study by Drissi et al. [19] suggests that bacteriocins are widespread across the human GI tract, with 317 microbial genomes encoding maximum bacteriocins of classes I (44%) as compared to class II (38.6%) and III (17.3%). Further, they elaborated the bacteriocins produced by gut microbiota, i.e., Class I bacteriocins display low antimicrobial activity. Whereas maximum class II bacteriocins were reported from bacteria not occurring in the gut. Similarly, Leite et al. [20] described BLIS produced by *Bacillus cereus* LFB-FIOCRUZ 1640, with activity against *Listeria monocytoges* and other *Bacillus* species in pineapple pulp and can be used as a potential food bio preservative. Also, Choeisoongnern et al. [21] reported that BLIS produced by *Pediococcus pentosaceus*, and *Enterococcus faecium* from fermented food inhibits the growth of *Carnobacterium maltraromaticum*, *Candida albicans*, *Listeria ivanovii*, *Listeria innocula*, *Pseudomonasc aeruginosa*, *Streptococcus mutans*, and *S. aureus.* More recently, Pircalabioru et al. [22] comprehensively reviewed bacteriocins' potential as an antimicrobial agent against infections mainly due to resistant pathogens i.e., MRSA. In contrast, Jawan et al. [23] suggest that BLIS from *Lactococcus lactis* Gh1 inhibits the growth of *Listeria monocytogenes* and can be used in the food industries as functional foods for the preparation of starter culture and probiotic products. In addition, BLIS from *B. subtilis* BSC35 inhibits *Clostridium perfringens*; therefore, it can be used to control *C. perfringens* in fermented foods [24].

Unfortunately, many factors cause a reduction in BLIS antimicrobial activity affecting the efficacy of bacteriocins. Such factors include the advent of bacteriocin-resistant strains, conditions that were destabilizing its biological activities such as oxidation processes, poor solubility, proteases or inactivation by other additives, and pH or temperature. Therefore, it is necessary to develop such a system that minimizes these drawbacks and maximizes bacteriocins' bioprotective potential.

Table 1. List of recently reported Bacteriocins (ND: not determined).

Type	Characteristics	Example	Producer	Mode of action	References
Bacteriocin type I	Lantibiotics, very small (<5 kDa) peptides containing lanthionine and β-methyllanthionine	Nisin Z and Q, Enterocin W Nukacin ISK-1	*Lactococcus lactis*	Membrane permeabilization forming pore	[25]
Bacteriocin type II	Small (<10 kDa), non-lanthionine-containing peptides				
	IIa heat-stable peptides synthesized as a precursor and processed after two glycine residues, antilisterial, bear consensus sequence YGNGV-C at the N-terminal	Enterocin NKR-5-3C, Enterocin A, Leucocin A, Munditicin	*Pediococcus pentosaceus, P. Acidilactici* and *L. sakei*	Membrane permeabilization forming pore	[26]
	IIb Two-component systems: two different peptides work together and generate an active poration complex	Lactococcin Q, Enterocin NKR-5-3AZ, Enterocin X	*L. lactis sub* sp. *cremoris, L. plantarum*	Membrane permeabilization forming pore	[22, 27]
	IIc N- and C- termini are covalently linked, generating a circular bacteriocin	Lactocyclicin Q, Leucocyclicin Q	*L. gasseri, Enterococcus faecalis, L. garvieae*	Membrane permeabilization forming pore	[28]
	IId Other class II bacteriocins, including unmodified, *sec*-dependent bacteriocins and leaderless, non-pediocin-like bacteriocins	Lacticin Q and Z, Weissellicin Y and M, Leucocin Q and N, Bactofencin A, LsbB	*L. salivarius, L. lactis Sub* sp. *Lactis*	ND	[22, 29]
Bacteriocin type III	Large peptides, sensitive to heat		*L. crispatus, L. helveticus, E. faecalis*		[30]

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IIIa	27 kDa, heat-labile protein	Lysostaphin and enterolysin A	*S. simulans* biovar Staphylolyticus, *Enterococcus faecalis*	Cell-wall degradation	[31]
IIIb	-	Helveticin J	*Lactobacillus helveticus*	Disrupt membrane potential, which causes ATP efflux	[32]

Nisin belongs to type I bacteriocin and is the first antimicrobial peptide from *Lactococcus* and *Streptococcus* sp. and has been regarded as GRAS by both FDA and WHO [33]. Nisin has been used to inhibit microbial growth in beef, ground beef, sausages, liquid whole eggs, and poultry. It was reported that when nisin was cross-linked to chitosan, minimum inhibitory concentration (MIC) decreased from 48 μg/ml to 40 μg/ml for *Staphylococcus aureus* ATCC6538. Antimicrobial activity of nisin was increased after crosslinking with a lesser concentration of chitosan i.e., the ratio of 200:1, thereby allowing better penetration into the lipid membrane [34]. The antibacterial constancy of nisin was successfully enhanced after its conjugation with gellan. The gellan–nisin conjugate was able to tolerate a broad range of pH and temperature, and also its antibacterial duration against *Staphylococcus epidermidis* was improved from 48 h to 144 h under alkaline environments and from 96 h to 216 h under acidic conditions. Therefore this conjugate can be an encouraging biomaterial for wound dressings and transplant coatings [35]. Heunis et al. [36] stated that the application of nisin-coated wound dressing *prevented S. aureus'* colonization and quickened the healing procedure. A study revealed the proficiency of nisin in combination with polymyxin in combating *P. aeruginosa* biofilms and reduced the dose of polymyxin required to interrupt *P. aeruginosa* biofilms [37]. Possibly polymyxin might facilitate the transfer of nisin to its target. Along with nisin's synergistic action with polymyxin and clarithromycin against *P. aeruginosa* and other non–*β*-lactam antibiotics against MRSA [38] and strains of vancomycin-resistant enterococci [39] was also reported. Webber et al. [40] embedded 0.89 μg cm^{-2}, positively charged nisin Z within polyelectrolyte multilayers (PEMs) i.e., 9 layers of carrageenan (CAR) and chitosan (CS), forming a 4.5 bilayer film with antimicrobial activity against *S. aureus* and MRSA. Therefore, the antimicrobial potential of CAR/CS multilayers helps in realizing its applicability within food, pharmaceutical, and biomedical industries [40]. Apart from bacteria, nisin also inhibits fungal growth (i.e., *Candida albicans*). Though nisin has a broad range of biomedical applications and is used in food bio preservation yet further justification of nisin's practicality and evaluation of its efficacy in biomedical fields will require *in vivo* and *in vitro* studies.

Bacteriocins in Gram-positive bacteria follow two possible mechanisms, as shown in Figure 2.

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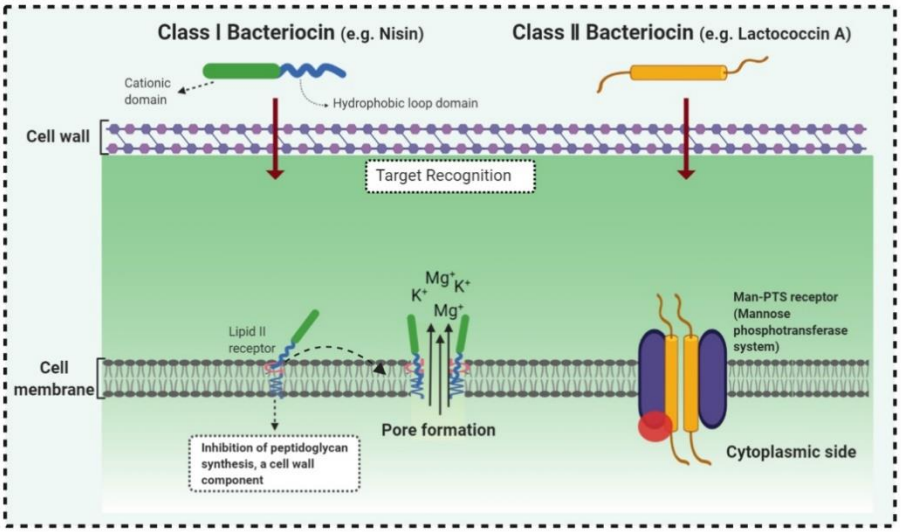

Figure 2. Mode of action of bacteriocins via the dual mechanism. (a) inhibition of cell wall synthesis: Class II bacteriocins (e.g., lactococcin), cross the cell wall and bind with the pore-forming receptor in the mannose-phosphotransferase (man-PTS), resulting in the pore formation in the cell membrane. (b) pore formation: Class I bacteriocins, (e.g., nisin) can follow both mechanisms. Nisin generated pores in the cell membrane resulting in the efflux of ions (K^+ and Mg^{2+}), amino acids (glutamic acid, lysin), generating proton motive force dissipation and ultimately cause cell death.

Class I bacteriocins are cationic lantibiotic (e.g., nisin) that electrostatically binds with the negatively charged membrane phospholipids II, allowing further interaction of bacteriocin's hydrophobic domain with the target cytoplasmic membrane (lipid II), thereby preventing the biosynthesis of peptidoglycan [22, 41-42].

2.2 Non-ribosomal synthesized peptides (NRPs) and polyketides (PKs):

NRPs and PKs include a range of cyclic, linear, and branched compounds, synthesized by composite enzymes viz. non-ribosomal peptide synthetases (NRPS), polyketide synthetases (PKS), and hybrid of NRPS/PKS, respectively [15, 43]. Lipopeptides (LPs) are NRPs produced by Bacillales, have significant antimicrobial activity [44]. LAB is considered the primary producer of ribosomally synthesized antimicrobial peptides, as reviewed by Alvarez-Sieiro et al. [45] and Pircalabioru et al. [22]. However, the classification scheme for antimicrobial compounds produced by *Bacillus* is not explored as compared to LAB. Caulier et al. [15] reviewed and updated the antimicrobial metabolites classification from the *B. subtilis* group based on the biosynthetic pathway and chemical nature. Zhao et al. [14] acknowledged 31 types of PKs, NRPs, and NRPS/PKS hybrid synthesized antimicrobials using antiSMASH.

2.3 Lipopeptides (LPs):

LPs occur naturally and are of bacterial origin, contain a hydrophobic long alkyl chain that associates with a hydrophilic polypeptide, and forms a cyclic or linear structure [46]. Traditional LPs including the iturins, surfactins, and fengycins (Table 2) produced from *Bacillus* species and are homologs that differ in length, branching pattern, and saturation of their acyl chain. LPs comprise anionic (e.g., surfactin and daptomycin) or cationic (e.g., colistin and polymixin B) peptide motif, dictating the range of its activity. As demonstrated by Perez et al. [47] *Bacillus* sp. P5 synthesize LPs iturin A, bacteriocin subtilosin A and surfactin exhibiting antimicrobial activity against *Listeria monocytogenes* and *Bacillus cereus*, along with the antifungal activity. A study by Kourmentza et al. [48] reported that a mixture of mycosubtilin and mycosubtilin/surfactin LPs inhibits the growth of

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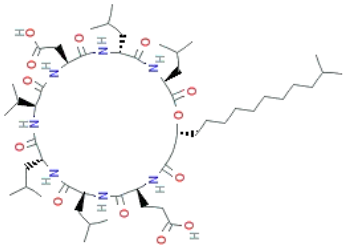
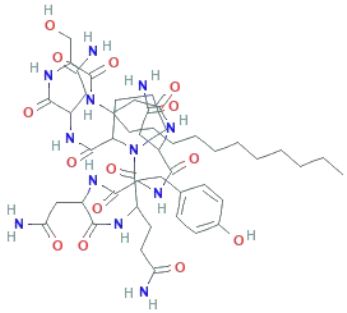
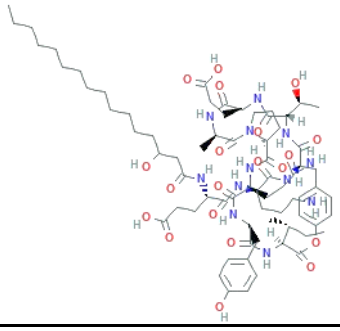
filamentous fungi *Byssochlamys fulva* and *Paecilomyces variotti*, with MICs of 1–16 mg/L and *Candida krusei* with MIC of 16–64 mg/L.

Table 2: Various types of LPs with their characteristics.

Type	Characteristics features	Molecular weight	Chemical structure	Producer	Applicability	References
Surfactin	Cyclic heptapeptide is an antibiotic with seven amino acids i.e., Glu-Leu-Leu-Val-Asp-LeuLeu (ELLVDLL). A, B, and C types varying according to their amino acid sequences.	~1.03 kDa		*B. subtilis* MSH1 and *B. amyloliquefaciens* ES-2	Antimicrobial, antifungal, insecticidal, antimycoplasma, hemolysis, and formation of ion channels in lipid membranes.	[49]
Iturin	Contains two major parts: a peptide part composed of 7 amino acid residues (Asn-Tyr-Asn-Gln-Pro-Asn-Ser) and 11-12 carbons hydrophobic tail. Example Iturin A, Bacillomycin D, Bacillomycin L, Mycosubtilin	~1.04 kDa		*B. subtilis*, *B. amyloliquefaciens* B128 and *B. amyloliquefaciens* BUZ-14	Antimicrobial and antifungal activities. Disrupt the membrane of yeast cells by increasing the electrical conductance of bimolecular lipid membranes.	[50]
Fengycin	An array of 10 amino acids with a lactone ring and a ß-hydroxy fatty acid linked to the N-terminus of a decapeptide. Example Plipastatin A and B	1463.7 g/mol		*B. subtilis*	Act as bioagents showing hypocholesterolemic activities, immuno-modulators; antibiotics, antiviral, and antitumor agents; toxins; and enzyme inhibitors	[51]

Surfactins, a cyclic heptapeptide that formulates a lactone bridge with *ß*-hydroxy fatty acids, are the most potent biosurfactant. It displays an array of activities including hemolytic, antiviral, anti-mycoplasma, and antibacterial [52]. Surfactin WH1 fungin from *Bacillus amyloliquefaciens* WH1 is an antifungal inhibiting glucan synthase that reduces the synthesis of callose on the fungal cell wall and binds to ATPase on the mitochondrial membrane ultimately inducing apoptotic markers to stimulate the extracellular apoptotic pathway [53]. Many researchers claim that after inserting into the lipid bilayers, surfactin acts by forming voltage-independent channels in biofilms, distorting the membrane integrity and permeability of ions, i.e., K^+ and Ca^{2+}, causing membrane disruption [54].

Iturins comprises A, C, D, and E isoforms, bacillomycin D, F and L, and mycosubtilin that inhibit bacterial growth in the same manner as Class I and Class II bacteriocins [55], whereas mycosubtilin modifies the plasma membrane permeability, thereby liberating nucleotides, proteins, and lipids from the cell [56]. A marine-derived *Bacillus velezensis* 11-5 produced a cyclic lipopeptide (CLP) iturin A, considered an antagonist against *Magnaporthe oryzae*, a rice pathogen [57].

Fengycin, an anti-fungal lipopeptide, isolated from *Bacillus* sp. *is* also called plipastatin. Its isoforms fengycin A and fengycin B vary in the single amino acid at the sixth position (D-alanine and D-valine, respectively) [58]. Both iturins and fengycins act as

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biocontrol agents preventing plant diseases and inhibiting the progression of a wide variety of plant fungal pathogens including *Aspergillus flavus*, *Rhizoctonia solani*, *Fusarium graminearum*, *Botritis cinerea,* and *Penicillium expansum* [59].

Kurstakins are cyclic heptalipopeptides [60], whereas cerexins are linear LPs [61], and both are isolated from *Bacillus thuringiensis* and *Bacillus cereus* respectively. Cerexins are active against *S. aureus* and *Streptococcus pneumoniae* [62]. Octapeptins, cationic peptides produced by *Bacillus* sp. and *Paenibacillus* sp., have antimicrobial activity, inhibiting filamentous fungi, yeasts, and protozoa along with some Gram-positive and Gram-negative bacteria by disrupting the cytoplasmic membrane [63].

However, no doubt LPs are a novel class of antibiotics exhibiting a wide range of activities. Therefore, detailed structural and functional knowledge is required to exploit these LPs as antibiotics, anti-tumor agents, antimicrobials, feed additives, and drug delivery systems.

3. Actinomycetes

The actinomycetes are Gram-positive, aerobic, filamentous, and spore-forming bacteria, with a foremost reputation for producing chemically different metabolites bearing a broad spectrum of biological activities, including antifungal, antibacterial, and insecticidal activities. Approximately 75% of the known industrial antibiotics and economically important compounds were obtained from the *Streptomyce*s species [64]. Actinobacteria can synthesize antifungal, antiviral, antitumor, anti-inflammatory, antioxidants, immunosuppressive, plant-growth-promoting, and herbicidal compounds [65]. Among actinobacteria, *Streptomyces* is the utmost and dominant because of a broad range of bioactive metabolites. The genus *Streptomyces* alone contributes approximately 7500 compounds among the 10,000 known compounds from actinobacteria, whereas the other genera including *Actinomadura, Micromonospora, Nocardia, Saccharopolyspora, Actinoplanes* and *Streptosporangium* contributes approximately 2500 compounds [66]. Marine or terrestrial actinobacteria utilize enzymes polyketide synthases (PKS) or non-ribosomal peptide synthetases (NRPS) for the synthesis of metabolic bioactive compounds [67].

Widowati et al. [68] reported a new strain of marine actinomycetes, NPS12745 associated with marine sediment from the coast of San Diego, California, and after using 16S rRNA gene sequencing, NPS12745 was confirmed as an innovative strain of genus *Marinispora,* which produced ample new chlorinated bisindole pyrroles and their derivatives including chromopyrrolic acid, which was earlier isolated from *Chromobacterium violaceum*. The first halogenated bisindole derivative was lynamicins A–E, having activity against several Gram-positive and Gram-negative bacteria, i.e., MSSA (methicillin-susceptible *Staphylococcus aureus*), MRSA, *S. epidermidis,* and *Enterococcus faecalis*, signifying possible cure of nosocomial infections [69]. Siddharth and Vittal (2018) isolated *Streptomyces* sp. S2A from marine sediment from the Gulf of Mannar, with persuasive antagonistic activity against bacterial (*Micrococcus luteus, S. epidermidis, Klebsiella pneumoniae, Bacillus cereus,* and *S. aureus*) and fungal (*Fusarium moniliforme* and *Bipolaris maydis)* pathogens [66]. Igarashi et al. [70] reported Maklamicin, a novel spirotetronate of class polyketide from an endophytic actinomycete *Micromonospora* sp. GMKU326, inhibiting *Micrococcus luteus, B. subtilis, S. aureus, B. cereus,* and *Enterococcus faecalis*, Gram-positive bacteria with minimum inhibitory concentrations (MICs) of 0.2, 1.7, 13, 6.5, and 13 μg/ml respectively. A unique prenylated-indole derivative known as 3-acetonylidene-7- prenylindolin-2-one, hybrid isoprenoids, 3-cyanomethyl-6-prenylindole, 7-isoprenylindole-3-carboxylic acid, and 6-isoprenylindole-3-carboxylic acid were extracted from the *Streptomyces* sp. neau-D50. These antifungal compounds prevent the growth of phytopathogenic fungi *Corynespora cassiicola, Phytophthora capsica, Colletotrichum orbiculare,* and *Fusarium oxysporum* [71]. Djinni et al. [72] described *Streptomyces sundarbansensis* WR1L1S8, an endophyte sequestered from brown algae yields an innovative anti-MRSA compound, [2-hydroxy-5-((6-hydroxy-4-oxo-4H-pyran-2-yl)methyl)-2-ropylchroman-4-one] beside three

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already reported polyketides namely phaeochromycin B, C, and E which are active against Gram-positive pathogenic MRSA.

Yang et al. [73] isolate vinaceuline, a cyclopeptide, activity against bacteria, from the broth culture of endophytic *Streptomyces* sp. YIM64018 allied with *Paraboea sinensis*. The same team isolated a new benzamide, 2-amino-3, 4-dihydroxy-5-methoxybenzamide in 2015, from *Streptomyces* YIM67086 that attacks *E. coli* and *Candida albicans* (MICs of 64 and 32 μg/ml, respectively). Ding et al. [74] reported 7, 3′-di-(c,c dimethylallyloxy)-5-hydroxy-40-methoxyflavone, a novel antifungal compound, from the broth culture of *Streptomyces* sp. MA-12 obstructs the growth of plant pathogens *Penicillium citrinum, Gibberella zeae*, and *Colletotrichum musae*.

Lee et al. [75] isolated 87 actinobacterial species including a novel species *Streptomyces pluripotens* MUSC135T, that inhibit MRSA. This antibacterial metabolite-producing ability was confirmed by PKS (polyketide synthetase) and NRPS (non ribosomal polyketide synthetase) gene detection process. *Streptomyces* sp. colonizing on root tissues produce ample antifungal and antibacterial compounds i.e., antimycin A18, phaeochromycin B, C and E, diastaphenazine, 3-acetonylidene-7-prenylindolin-2-one, and staurosporine, some of them are represented in Table 3. The unique properties of rhizospheric actinomycetes to produce a diverse range of bioactive metabolites with antagonistic outcomes toward pathogens have led them to be a potent agent ensuring plant health.

Cycloserin, an antibiotic produced by *Streptomyces orchidaceus*, block protein synthesis and is used to treat tuberculosis in conjugation with other drugs [84]. Robertsen and Musiol-Kroll, [85] reviewed the actinomycetes-derived polyketide drugs such as erythromycin A, tetracyclines, rifamycin, tylosin, monensin A, amphotericin B, etc. with antimicrobial activity, including the source of the compounds, their structure, the biosynthetic mechanisms, and mode of action. However, the increasing rate of MDR requires the rediscovery of compounds from potential producers. However, many organisms require special cultivation conditions, so many strategies need to be developed to overcome such barriers. Hug et al. [86] described the strategies and innovative methods such as advanced cultivation methods, genomics, metabolomics, and metagenomics-based approaches to explore the new reservoir of actinomycetes and improve the efficacy of antimicrobial compounds.

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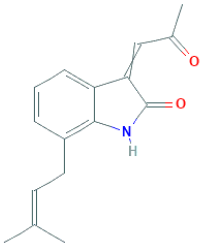
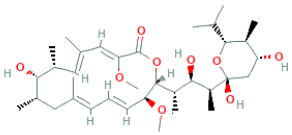
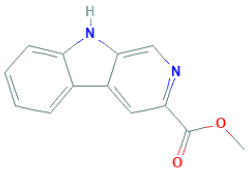
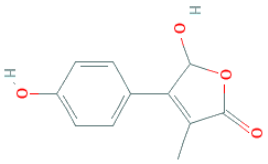
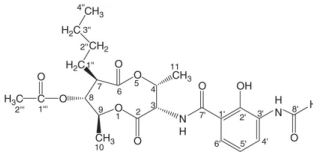
Table 3. Bioactive compounds from endophytic actinomycetes.

Endophytic Actinomycetes	Host	Bioactive compounds	Structure	Bioactivity	Reference
Streptomyces sp. YIM64018	*Paraboea sinensis*	Vinaceuline	-	Antibacterial activity	[76]
Streptomyces sp. neau-D50	*Glycine max*	3-acetonylidene-7-prenylindolin-2-one, 7-isoprenylindole-3-carboxylic acid		Cytotoxic and antifungal activities	[71]
Streptomyces sp. YIM56209	*Drymaria cordata*	Bafilomycin D, B1, B2, C1, C2, C1 amide and C2 amide		Antibacterial, antifungal, insecticidal, antihelmintic and cytotoxic activity	[87]
Streptomyces diastaticus Sub sp. *ardesiacus*	*Artemisia annua*	Diastaphenazine	-	Antibacterial and antifungal activity	[78]
Streptomyces sp. YIM67086	*Dysophylla stellata*	4-hydroxy-3-methoxybenzoic acid, p-hydroxytruxinic acid	-	Antifungal activity	[73]
Microbispora sp. LGMB259	*Vochysia divergens*	β-carboline or 1-vinyl-β-carboline-3-carboxylic acid		Antibacterial, antifungal and anticancer activity	[79]
Streptomyces sp. YIM66017	*Alpinia oxyphylla*	Yangjinhualine A and 2,6-dimethoxy terephthalic acid		Radical scavenging activity	[80]
Streptomyces albidoflavus 07A-01824	*Bruguiera gymnorrhiza*	Antimycin A18		Antifungal activity	[81]
Streptomyces sp. VITMK1	mangrove soil	Pyrrolopyrazines	-	Antimicrobial	[82]
Streptomyces sp.		Diketopiperzines	-	Anti-H1N1 activity	[83]

4. Archaea

Archaeocins, is a proteinaceous antibiotic produced from archaea and mark the chronicled beginning in the series of antimicrobial compounds. The term "archaeocin" was used to differentiate the archaeal peptide and protein-based antibiotics from those produced by bacteria [88]. Only two phylogenetic groups have produced Archaeocins (Table 4); one is euryarchaeal producing "halocins" whereas the other group is crenarchaeal genus Sulfolobus producing "sulfolobicin" [89]. Valera et al. [90] reported halocins, the first proteinaceous antimicrobial compound from halophilic members of the archaeal domain. Archaeal protein VLL-28, from *Sulfolobus islandicus*, is the first archaeal antimicrobial peptide, possessing a broad-spectrum antibacterial and antifungal activity [91]. Until now, very few reports were available on the characterization of antimicrobial compounds from archaea. Besse et al. [92] and his team comprehensively reviewed the

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archaeocins and sulfolobicins antimicrobial peptides ribosomally-synthesized by archaea belonging to the order Halobacteriales and Sulfolobales, respectively. However, till now halocin A4, G1, R1, H1 [93]; H2 [29]; H3, H5 [90]; H4 [94]; H6 [95]; C8 [96]; S8 [97]; HalR1 [98]; and Sech7a [99] have been considered up to their molecular level, still their mode of action is not clearly understood [100]. Only some workers reported that halocins kill the indicator organisms by altering the cell permeability at membrane level followed by cell lysis. However, to date, only the mode of action mechanism of halocin H6/H7 produced by *Haloferax gibbonsii* was characterized. HalH6 specifically inhibits Na^+/H^+ antiporter and proton flux ultimately causing cell lysis and death [101].

H1 and H4 are proteinaceous halocins of roughly 30-40 kDa [102], whereas C8, H6, H7, R1, U1, and S8 are microhalocins of size smaller than 10kDa. Microhalocins are more vigorous than proteinaceous halocins since they are resistant to flexibility in temperature, salinity, exposure to organic solvents, acids, and bases [102]. Halocins have a wide-ranging activity against haloarchaea and members of the family Halobacteriaceae [103]. Mainly halocin production is prompted during the progression between exponential and stationary phases, with H1 being an exception, produced during the exponential phase of the growth cycle [104]. Recently, Sahli et al. [105] screened 81 halophilic strains collected from solar salterns of Algeria's northern coast for the production of antimicrobial compounds. Through partial 16S rRNA gene sequencing, these strains were recognized to belong to the *Haloferax* (*Hfx*) sp.

Table 4. Archaeocins reported from halobacteria (ND: not determined).

Halocin	Producers	Size (kDa)	Origin	Active against	Mode of action	Reference
HalH1	*Haloferax mediterranei* Xia3	31	Solar salterns, Alicante, Spain	Members of the Halobacteriales	Alter membrane permeability	[92]
HalH4	*Hfx. mediterranei* R4	34.9	Solar salterns, Tunisia	Members of the Halobacteriales, Strains of *Sulfolobus* sp.	Alter macromolecular synthesis, cell wall conformation, and Na + /H+ antiport inhibitor	[106]
HalH6	*Hfx. gibbonsii* Ma2.39	32	Solar salterns, Alicante, Spain	Members of the Halobacteriales	Alter intracellular osmotic balance, Na + /H+ antiport inhibitor	[92]
HalS8	Haloarchaeal strain S8a, *Halobacterium salinarum* strain ETD5	3.58	Great Salt Lake, (Utah, United States)	*Halobacterium salinarum* NRC817, *Hbt*. sp. strain GRB and *Hfx. gibbonsii*	ND	[97, 107]
HalC8	*Natrinema* sp. AS7092	7.4	Chaidan Salt Lake in Qinghai province, China		ND	[104, 108]
HalR1	*Hbt. salinarum* GN101	3.8	Guerrero Negro, Mexico	Members of the Halobacteriales, Strains of *Sulfolobus* sp., *Methanosarcina thermophile*	ND	[29, 92]
Sulfolobicins	*Sulfolobus Islandicus* HEN2/2	33.9 (proprotein), 3.6 (mature)	Solfataric fields, Iceland	Strains of *Sulfolobus* sp.	ND	[109]

Note: ND: Note Detected or Not Reported.

Roscetto et al. [110] reported that VLL-28 damages the cell wall of *Candida albicans* and *C. parapsilosis* by binding to their cell surface. Kumar and Tiwari [111] purified halocin HA1 from *Haloferax larsenii* HA1 and HA3 from *H. larsenii* HA3; both were halocidal against *H. larsenii* HA10, instigating cellular distortion, releasing cell contents, and finally causing cell death. Because of these properties, it can be used for the preservation of leather hides and salted foods in the leather and food industries. Ghanmi et al. [107] isolated *Halobacterium salinarum* ETD5, *H. salinarum* ETD8, and *Haloterrigena thermotolerans* SS1R12 of the order Halobacteriales and reported that their antimicrobial activity is due to the production of a halocin, HalS8, a hydrophobic peptide. Quadri et al. [112] isolated

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archeal strain *Natrinema gari,* the common producer of antimicrobial compounds, which after partial purification and characterization resembles the microhalocin HalC8. Besse et al. [108] confirmed that *Natrinema* sp. synthesizes Halocin C8, a 7.4 kDa peptide involving the genes *halC8*.

Although many studies characterized the synthesis of halocins however the research concerning their structure and mode of action is still far behind compared to the antibiotics produced by other domains. Nowadays, when archaea gain more attention, it becomes necessary to explore their metabolites' biosynthesis, including haloarcheocins and sulfolobicins, using the latest available technology and interdisciplinarity.

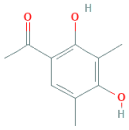
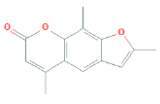
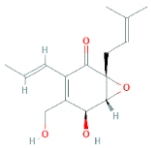
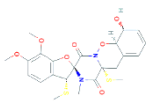
5. Fungi

In 1929, Alexander Fleming discovered that mold juice 'Penicillin' from *Penicillium notatum* fungus with an antibacterial activity [113]. Afterwards, several researchers started to find out for a better strain to attained higher yield in easier growth conditions. After the extensive research *Penicillium chrysogenum* strains considered for commercial production of *Penicillium* [114]. Revilla reported in 1986 that the formation of the intermediate isopenicillin N in the course of penicillin G production in *P. chrysogenum* cultures [115], while thereafter the formation of isopenicillin N/penicillin N and its late transformation to cephalosporin C in *Acremonium chrysogenum* [116]. Cephalosporins, a known antimicrobial agent were purified from a marine fungus, *Cephalosporium acremonium* [117]. Recently, Li et al [118] reported that pneumocandins, a lipohexapeptides of the echinocandin family, were produced by wild-type fungi *Glarea lozoyensis* and *Pezicula* (*Cryptosporiopsis*) species. Pneumocandins non-competitively bind to a catalytic unit of *β*-1,3-glucan synthase resulting in osmotic uncertainty and cell lysis.

5.1 Endophytic fungi

Huang et al. [119] discovered ten membered lactones from endophytic fungus *Phomopsis* sp. YM 311483, with antifungal activity against *Aspergillus niger*, *Fusarium,* and *Botrytis cinere*. Endophytic *Fusarium* sp. from *Selaginella pollescens* collected from the Guanacaste conservation area of Costa Rica inhibit *Candida albicans* [120]. The number of antimicrobial compounds was reported from the endophytic fungi, some of which are listed in Table 5.

Table 5. Antimicrobial compounds extracted from endophytic fungi.

Compound	Chemical structure	Producer	Active against	Host	Reference
e 1, 4-naphthoquinone derivatives	-	*Talaromyces* sp. *SK-S009*	*Pseudomonas* sp.	*Kandelia obovata*	[121]
Clavatol		*Aspergillus clavatonanicus, Aspergillus elegans KUFA0015*	*Botrytiscinerea, Didymella bryoniae, Fusarium oxysporum f.* sp. *cucumerinum, Rhizoctonia solani,* and *Pythium ultimum*	*Taxus mairei, Monanchora unguiculate* (Marine sponge)	[122]
Lactones		*Phomopsis* sp. YM 311483	*A. niger, Botrytis cinere,* and *Fusarium*	*Azadirachta indica*	[123]
Jesterone		*Pestalotiopsis jesteri*	*Pythium ultimum, Phytophthora citrophthora, Rhizoctonia solani* and *Sclerotinia sclerotiorum*	*Fragraea bodenii*	[124]
Peniciadametizine A		*Penicillium adametzioides* AS-53, *Penicillium janthinellum strain HDN13-309*	*Alternaria brassica*	Sponge collected at the Hainan Island of China, roots of *Sonneratia caseolaris*	[125]

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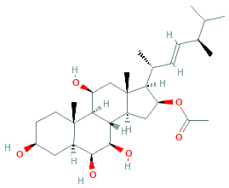
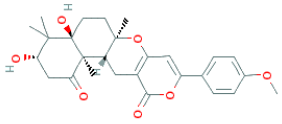
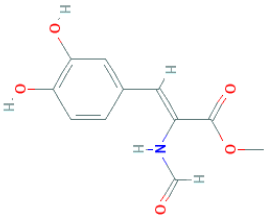
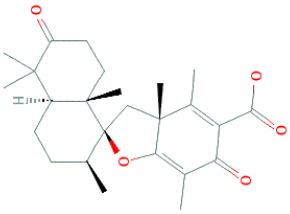
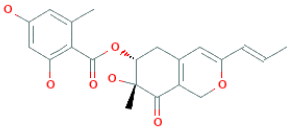
5.2 Marine-derived fungi

Meng et al. [126] in 2015 discovered pyranonigrin F from fungus *Penicillium brocae* MA-231 allied with the *Avicennia marina,* a marine mangrove plant. Pyranonigrin F inhibits *S. aureus* (Gram-positive), *Vibrio harveyi,* and *Vibrio parahemolyticus* (Gram-negative bacteria), with considerably lower MIC values as compared to the positive control (chloromycetin). Likewise, it is active against plant fungal pathogens *Alternaria brassicae* and *Colletotrichum gloeosprioides*, with improved MIC values compared to the positive control (bleomycin). Wu et al. [127] discovered Lindgomycin from *Lindgomyces* strains LF327 and KF970, reported from a sponge in the Baltic Sea, Germany, and Antarctica, respectively. Lindgomycin displayed antimicrobial activity against *S. aureus, S. epidermidis,* and methicillin-resistant *S. epidermidis* (MRSE). However, the inhibiting potential was two times lesser as compared to the positive control chloramphenicol. It also constrains plant pathogenic bacterium *Xanthomonas campestris.* There is a never-ending list of antimicrobial compounds from marine fungi; a few of them are listed in Table 6, mentioning their host, producer species, and bioactivity.

Table 6. Antimicrobial compounds extracted from marine fungi.

Compounds	Structure	Producer	Active against	Environment source	Reference
Penicisteroid A		*Penicillium chrysogenum* QEN-24S	*Aspergillus niger* and *Alternaria brassicae*	Marine algae associated *Penicillium* sp.	[128]
Arisugacin K		*P. echinulatum*	*E. coli*	Marine alga *Chondrus ocellatus.*	[129]
Methyl (Z)-3-(3, 4-dihydroxy-phenyl)-2-Formamidoacrylate		*P. oxalicum* EN-290	*S. aureus*	Marine algae associated *Penicillium*	[130]
Chermesins A and B		*P. chermesinum* EN-480,	*C. albicans, E. coli, M. luteus,* and *V. alginolyticus*	Marine algae associated *Penicillium*	[131]
Comazaphilones C (C–E)		*P. commune* QSD-17	*Antibacterial*	*Penicillium* sp. from marine sediments	[132]
Penicibilaenes A	-	*P. bilaiae* MA-267	*Colletotrichum gloeosporioides*	Rhizospheric soil of *Lumnitzera racemosa*	[133]

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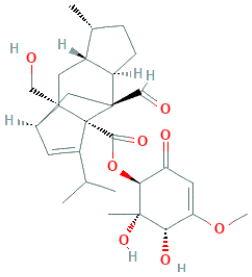
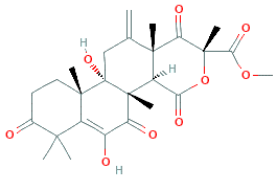
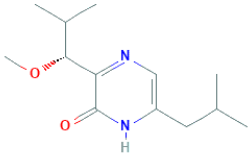
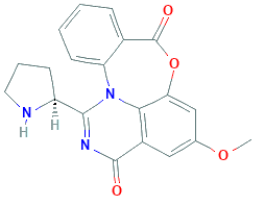
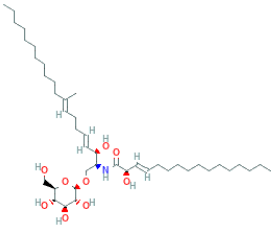
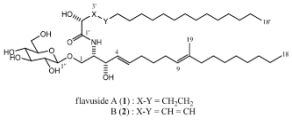
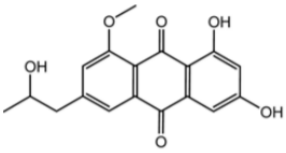
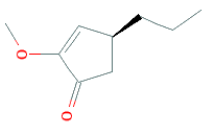
Xylarinonericin D and E		*Penicillium* sp. H1	*Fusarium oxysporum f.* sp. *Cubense* (antifungal)	Beibu Gulf nearby Guangxi	[129]
Terretonin G		*Aspergillus* sp. *OPMF00272*	*S. aureus* FDA209P, *Bacillus subtillis* PCI219 and *Micrococus luteus* (ATCC9341)	Ishigaki island	[134]
Schevalone E	-	*A. similanensis* sp. *nov.*	MRSA	Sponge *Rhabdermia* sp. from the coral reef of the Similan Island	[135]
Asperitaconic acids A–C	-	*A. niger* LS11	*S. aureus*	Sponges-associated *Aspergillus* sp.	[136]
Ochramide B		*A. ochraceus* LCJ11-102	*Enterobacter aerogenes*	Marine sponge *Dichotella gemmacea*	[137]
Spiculisporic acids F and G	-	*A. candidus* HDf2	*P. solanacearum* and *S. aureus*	Marine animals associated *Aspergillus* sp.	[138]
Aspergicin		*Aspergillus* sp. FSY-01 and *Aspergillus* sp. FSW-02	*S. aureus, S. epidermidis, B. subtilis, B. dysenteriae, B. proteus* and *E. coli,*	Mangrove *Avicennia marina* in Guangdong.	[139]
Asperamide		*A. niger* EN-13	*C. albicans*	Marine algae associated *Aspergillus* sp.	[140]
Flavusides A and B		*A. flavus*	*S. aureus* and MRSA	Marine algae associated *Aspergillus* sp.	[141]
Isorhodoptilometrin-1-methyl ether		*A. versicolor*	*B. subtilis, B. cereus* and *S. aureus*	Marine algae associated *Aspergillus* sp.	[142]
Asperterrein		*Paecilomyces lilacinus* EN-531 and *A. terreus* EN-539	*Alternaria brassicae, E. coli, Edwardsiella tarda, Physalospora piricola,* and *S. aureus*	Marine algae associated *Aspergillus* sp.	[143]

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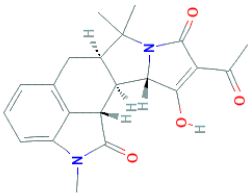
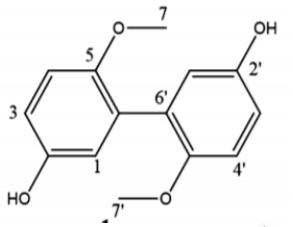
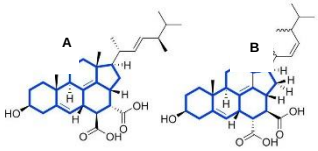
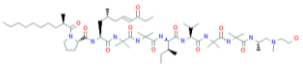
Speradine A		*A. tamarii* M143	*Mycrococcus luteus*	driftwood in Okinawa	[144]
Versiperol A		*A. versicolor* MCCC 3A00080	*S. aureus*	seawater-associated *Aspergillus* sp.	[145]
Ergosterdiacids A and B		*Aspergillus* sp.	*M. tuberculosis*	Marine sediments associated *Aspergillus* sp.	[146]
Heptapeptide RHM1	-	*Acremonium* sp. HM1	*S. epidermidis*	Marine sponges-associated fungi	
Trichoderins A		*Trichoderma* sp. 05FI48	*M. smegmatis*	Marine sponges-associated fungi	[147]
Botryorhodines I and J	-	*Setosphaeria* sp. SCSIO 41009	*Colletotrichum asianum*	Marine sponge *Callyspongia* sp.	[148]

Peniciadametizine A and Peniciadametizine B derivative of thiolated diketopiperazine was isolated from a sponges-associated *Penicillium* sp. viz. *Penicillium adametzioides* AS-53 and *Penicillium* sp. LS54 respectively. Both derivative inhibits *Alternaria brassicae* (pathogenic fungus) with a MIC of 4.0 µg/mL and 32.0 µg/mL respectively [131]. Communol A, G, and F extracted from *P. commune* 518 displayed antibacterial activities against *E. coli* with MIC values of 4.1, 23.8, and 6.4µM, respectively, and also against *E. aerogenes* [129]. Pyrrospirones were produced by marine-derived fungus *Penicillium* sp. ZZ380, isolated from *Pachygrapsus crassipes* which is a wild crab found on the seaside rocks of Putuo Mountain (Zhoushan, China). Pyrrospirones C-F, H, and I inhibit MRSA and *E. coli* having MIC values of 2.0–19.0 µg/mL [149]. Song et al. [150], following the previous lead, separated penicipyrrodiether A from a cultured marine fungal strain *Penicillium* sp. ZZ380 inhibits *E. coli* and *S. aureus* with MIC of 34.0 and 5.0 µg/mL, respectively. These laboratory studies need to be directed toward enlightening the efficiency and effectiveness of isolated compounds that could benefit society in the long-run.

5.3 Mushroom

Mushrooms are colonizing fungi belonging to division Eumycota and subdivision Basidiomycetes, characterized by the formation of basidiospores. Most of these macrofungi are edible, with culinary, nutritional, and medicinal characteristics, but many of them are not palatable or poisonous [151]. Besides the nutritional and culinary properties, their antimicrobial activities attracted people seeking natural solutions to cope with the urgent requirement for food safety. Mushrooms have been publicly consumed for thousands of years due to their medicinal and nutritional properties. Secondary metabolites and extracts from mushrooms have recently attained considerable attention due to their anti-cancer, antioxidant, anti-inflammatory, antimicrobial, antidiabetic, and immunomodulatory activities. Approximately 1069 mushroom species have been consumed by people [152]. Till today, numerous antimicrobial peptides have been acknowledged from mushrooms. Plectasin (endogenous peptide antibiotics), an antibacterial peptide, was extracted from *Pseudoplectania nigrella*. Mygind et al. [153] demonstrated the potent activity

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of recombinant plectasin against some Gram-positive *Streptococcus pneumoniae*. Wong et al. [154] described an antifungal peptide, cordymin isolated from medicinal mushroom *Cordyceps militaris,* which repressed mycelial growth of *Bipolaris maydis, Mycosphaerella arachidicola, Candida albicans,* and *Rhizoctonia solani* with IC_{50} values of 50 µM, 10 µM, 0.75 mM, and 80 µM respectively. They also reported the remarkable pH stability (pH 6–13), thermostability (100 °C), and metal ion stability (10 mM Mg^{2+} and 10 mM Zn^{2+}) of cordymin. An investigation by Gebreyohannes et al. [155] revealed that **c**hloroform, ethanol, and hot water extract of *Auricularia* and *Termitomyces* sp. promisingly inhibited *E. coli, K. pneumoniae, C. parapsilosis*, and *S. aureus.* Poompouang and Suksomtip, [156] isolated an antifungal compound of 17 kDa from fruiting bodies of edible mushroom *Lentinus squarrosulus,* inhibiting *Trichophyton mentagrophytes* and *T. rubrum,* a human fungal pathogen. More recently, Irshad et al. [157] comprehensively reviewed the synthesis and action mechanism of polysaccharides silver nanoparticles (NPs) from *Pleurotus* mushroom. They characterized the NPs through ultraviolet-visible (UV–Vis), Fourier transformation infrared spectroscopy (FT-IR), scanning electron microscopy (SEM), energy dispersive spectroscopy (EDS), transmission electron microscopy (TEM), etc. and disclosed their promising antimicrobial efficiency. However, further studies are required to fortify and test these extracts and NPs against human and plant pathogenic microbes coupled with the purification and characterization of the compounds from mushroom.

Hamamoto et al. [158] screened the volatile compound, 3,4-dichloro-4-methoxy benzaldehyde (DCMB) from mycelia of *Porostereum spadiceum.* It remarkably inhibited the plant-pathogenic bacteria (*Clavibacter michiganensis* and *Ralstonia solanacearum*) and inhibit the conidial germination of plant-pathogenic fungi (*Alternaria brassicicola* and *Colletotrichum orbiculare*). However, further studies are essential to investigate its effects on plant-pathogens *in vivo*. Subrata et al. [159] reported that edible wild mushrooms' methanolic extracts exhibited different levels of antimicrobial activities. A recent work by Sevindi [160] analysed the phenolic content of the wild edible mushroom *Melanoleuca melaleuca* (Pers.) Murrill had antimicrobial activities inhibiting Gram-negative *E. coli, Pseudomonas aeruginosa,* and *Acinetobacter baumannii*.

6. Yeast

Yeasts mainly occur in milk, meat, food, and products such as fruit, yogurt, jams, sausage, and cheeses. Generally, antimicrobial compounds produced from yeasts inhibit the evolution/growth of pathogenic organisms (bacteria or molds) in food products. Some classes of yeasts secrete toxins, thereby naming them killer yeasts. Killer yeasts naturally occur in rotten vegetables and fruits and constrain the growth of other yeast strains and also inhibit microbial growth [161]. *Saccharomyces cerevisiae* (Baker's yeast), unicellular yeast, is the most widely studied microorganisms involved in many biotechnological practices because of its good fermentation capacity [162]. The inhibitory mechanism of *S. cerevisiae* killer strains was discovered in 1963 by Bevan and co-worker's, and the phenomenon is related to the secretion of a protein toxin, k1, and k28 from the host that kills sensitive target pathogenic cells in a receptor-mediated approach without direct cell-to-cell contact [163]. Other genera producing killer toxins include *Cryptococcus, Candida, Kluyveromyces, Williopsis, Pichia, Debaromyces,* and *Zygosaccharomyces* [164]. The anti-bacterial capability of *S. cerevisiae* is attributed to:

a) Secretion of inhibitory proteins
b) Production of extracellular protease
c) Stimulation of immunoglobulin A
d) Procurement and eradication of secreted toxins
e) Killer toxins, sulfur dioxide, etc.

Sequential re-pitching of *Saccharomyces* biomass is a common process during brewing. Therefore, yeast is reused many times before its final dumping [165]. Hence, yeast develops an adaptive response against oxidative stress like that of human cells, leading to the accumulation of vitamins (B6 and B12) and minerals (enzyme co-factors including

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zinc, manganese, and copper) in the yeast cell. Phenolic compounds are also adsorbed by *Saccharomyces* from the exterior medium, which increases the phenolic content and antioxidant activity within yeast cells [166]. Efficient means are required to disrupt yeast cell walls and separate the products of interest, which are further used for food applications. However, increasing consumers' fears regarding the toxicity of killer yeast strains present in food, and milk products, constituting a direct risk to public health.

7. Microalgae

The antimicrobial activity of microalgae is due to the presence of phytochemicals, including indoles, acetogenins, terpenes, fatty acids, phenols, and volatile halogenated hydrocarbons (Table 7) [167]. Moreno et al. [168] reported that *Chaetoceros muelleri* extracts' antimicrobial activity is due to their lipid configuration, whereas *Dunaliella salina* is attributed to the presence of β-cyclocitral, α and β-ionone, phytol, and neophytadiene. In natural environmental conditions, microalgal cells release fatty acids against predators and pathogenic bacteria. It is elucidated that these fatty acids act on bacterial cell membranes causing cell seepage, a decline in nutrient intake, and reduced cellular respiration, ultimately resulting in cell death [169].

Table 7. Selected antimicrobial extracts from microalgae.

Microalga	Target microorganism	Active extract	References
Scenedesmus quadricauda	*S. aureus* and *P. aeruginosa*	Methanolic extract	[170]
Tetraselmis sp.	*E. coli, P. aeruginosa,* and *S. aureus*	Ethanolic extract	[171]
Phaeodactylum tricornutum	*Listonella anguillarum, Lactococcus garvieae,Vibrio* spp. and MRSA	Eicosapentaenoic acid	[169]
C. vulgaris	*Steinernema feltiae*	Hydrophilic extracts	[172]
Skeletonema costatum	*Listeria monocytogenes*	Extra-metabolites	
S. costatum	*Vibrio* spp., *Pseudomonas* sp. and *Listeria monocytogenes*	Unsaturated, saturated long-chain fatty acids	[173]
Haematococcus pluvialis	*E. coli, S. aureus, Candida albicans*	Short-chain fatty acids (butanoic acid and methyl lactate), Astaxanthin	[174]
Amphidinium sp.	*A. niger*, *Trichomonas foetus*	Karatungiols	[175]
Chlamydomonas reinhardtii	*A. niger, A. fumigatus, C. albicans, S. aureus* and *E. coli*	Methanolic extracts	[176]

Chlorellin, the first antibacterial compound from a microalga *Chlorella* is composed of a mixture of fatty acid was isolated by Pratt et al. [177] reported to inhibit the activity of both Gram-positive and Gram-negative bacteria. *Arthrospira platensis*, commercially known as *Spirulina* had MIC of 0.20% for *L. innocua* and *P. fluorescens* and 0.25% for *Serratia,* whereas minimal bactericidal concentration (MBC) value was 0.30% for all these species [178]. HPTLC screening and GC–MS analyses were done to detect and screen the macroalgae's antimicrobial compounds. Peptides namely AQ-1756, AQ-1757, and AQ-1766 identified from *Tetraselmis suecica* exhibited an antibacterial activity resulting in decreasing cell viability (human embryonic kidney cells) (HEK293) up to 75% after 24 h of

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treatment. AQ-1766 was more active against Gram-positive than Gram-negative bacteria, with MBC values between 40 and 50 μM [179]. Mendiola et al. [180] demonstrated that lipid fractions obtained from *Chaetoceros muelleri* by the supercritical CO_2 method have antibacterial activity against *Staphyloccocus aureus* and *E. coli*. In contrast, extraction via classic methods using hexane, dichloromethane, and methanol solvent did not possess any activity against *E. coli*. However, these studies were unable to elaborate on these bioactive compounds' antibacterial activity's exact mode of action.

Axenic microalgae co-culture can produce compounds with potent activity against pathogenic bacteria. Kokou et al. [181] reported that axenic cultures of *Tetraselmis chui, Chlorella minutissima*, *Isochrysis* sp. and *Nannochloropsis* sp. inhibit *Vibrio harveyi* . The potent activity of microalgal compounds against microbes requires further development in the search for drugs and food preservatives. Therefore, the exploitation in medicine deserves to be further investigated.

8. Discussion and Future prospect

One of the major challenges healthcare services face worldwide is the excessive use of antibiotics as medicine and in food production leading to microbiome disruption. With the burst of antimicrobial resistance strains, there is a continuous decline in the antimicrobial drug pipeline, and it has become mandatory to discover and develop new agents/metabolites to tackle antibiotic resistance. The microbial metabolites were used as antibiotics with the discovery of penicillin and are easy to isolate, culture, and engineered compared to plants. After discovering penicillin, many drug discoveries from microbial sources had been reported, and the advancement of techniques such as genetic engineering during the 1970s, which later on opened the door to the ignored source, i.e., microbial metabolites [182].

Microbial products are vital constituents of new drug molecules, and ample research is being carried out to search for novel antimicrobial agents from biological sources that include bacteria, actinomycetes, fungi, yeast, etc. LAB producing bacteriocins, antimicrobial ribosomal peptides, is a promising advancement for the food and feed industry by extending their shelf life and safeguarding consumers' health. *Actinomycetes*, particularly *Streptomyces*, exhibited effective antagonistic activity and played a significant role in drug discovery and development. The bioactive compounds obtained so far from actinomycetes include streptomycin, antimycin, vinaceuline, bafilomycin, diastaphenazine, etc. However, not all of them have achieved commercial success. This might be due to the low potency of drugs, their pharmacological properties, related safety issues, or the rapid advent of resistant strains.

In the ongoing search for novel antibiotics, archaeocins have generally been overlooked. Halocins are extensively reviewed and halocin H6 has been revealed to inhibit the Na+/H+ antiporter causing cell lysis and death of pathogens. Further studies on purifications and characterizations to the archaeocins and sulfolobicins are in progress, resulting in the economical production of bioactive compounds for pharmaceutical applications. It becomes desirable to expand our understanding of the effectiveness and use of other naturally occurring ribosomally-synthesized peptide antimicrobials to understand their implantation and survival strategies and quantitatively estimate their efficacy for future applications pharmaceutical and health care sectors.

Many achievements have been made regarding fungal antibiotics starting from penicillin. Fungi synthesized small quantities of bioactive compounds in response to explicit environmental conditions, which cannot be reproduced easily in the laboratory. Therefore, effective methods of strain improvement are required to increase the ability of a fungus to produce bioactive metabolites in large amounts consistently. Also, to develop novel antimicrobial drugs from these fungal metabolites, commercial-scale synthesis must be accomplished, potentially through strain improvement, optimizing growth conditions, and incorporating techniques, such as metabolomics, genomics, and pathway engineering.

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Endophytic and marine-derived fungi offer a suitable substitute against toxic, ineffective, and expensive antimicrobial drugs because they act as a warehouse filled with novel bioactive compounds with never-ending potentials for biological properties. Apart from other fungal species, mushrooms are continued to be consumed in their natural forms since time immemorial.

Antimicrobials, isolated from mushrooms, are important as potential substitutes to synthetic drugs and preservatives, whose protection and influence on the health of humans, animals, and food are still uncertain. This review demonstrates that edible mushrooms are a potent source of countless bioactive substances with antimicrobial activity. Hence, they must not be considered only as a culinary delicacy but also taken as therapeutic agents. However, we are still required to develop methods for isolation, purification, identification, and characterization of antimicrobial compounds to develop antibiotics.

Microalgae are a promising source of high-value products, and large-scale screening programs have been conducted to discover the antimicrobial potential of microalgal extracts against pathogenic and foodborne organisms. However, major antibacterial and antifungal activity reports were predominantly from the *chlorella* sp. and *Chlamydomonas* sp. Still, many hurdles exist in developing the marine product, including resource supply issues, large-scale production, production cost, determination of the efficacy target [183]. These obstacles must be bypassed by optimizing mass culturing conditions, utilizing biotechnological techniques, etc. Along with these measures, extensive clinical trials will be needed to determine the *in-vivo* fortune of antimicrobials from microbial extracts on mammalian cells. A consolidated bio-refinery approach must be accepted to expand the utility of microalgae biomass [167]. Systematic research should be carried to evaluate the microalgae potential as a promising biotechnology tool.

Although killer yeasts strain secret toxins, many yeasts have antimicrobial activities inhibiting other yeast strains, molds, and bacteria. Regardless of this, preliminary research has been conducted on the bioactive compounds from *S. cerevisiae*; the widely studied yeast has been involved in many biotechnological processes because of its good fermentation capacity, probiotics, and health benefits. Therefore, developing and using robust screening and high-throughput methods will be essential to study yeast antimicrobial activity, thereby increasing the chances of discovering and identifying novel antibiotic molecules. To achieve this goal, the experimental design must include all possible variables, including recovering both intra- and extracellular extracts produced by microbes under variable growth conditions, utilizing potential inducers of antimicrobial activity, and testing these compounds against a more significant number of targets.

The detailed functional and structural knowledge would explain the mode of action and performance at cellular and molecular levels.

9. Conclusions

In the present review, it could be concluded that the promising novelty of microorganisms brought them under the focus of intensive research. Microbes' applications in human foods, animal feeds, agriculture, and increased market demand are motivating to continue the research and development of novel antibiotics and preservatives. Furthermore, the molecular docking and structural analysis approach can better design pathogen-specific antimicrobial agents that exhibit lesser toxicity, higher selectivity, and biodegradability. Therefore, exploiting microbial biodiversity and biotechnological potential to determine new pipelines for bioactive compounds discovery is approached to treat life-threatening diseases and safeguard human health.

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References

1. Santajit, S.; Indrawattana, N., Mechanisms of antimicrobial resistance in ESKAPE pathogens. *BioMed research international* **2016,** *2016*.
2. Centers for Disease Control and Prevention 2019. Antibiotic resistance threats in the United States. https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pd (accessed 29 January 2021).
3. Pendleton, J. N.; Gorman, S. P.; Gilmore, B. F., Clinical relevance of the ESKAPE pathogens. *Expert review of anti-infective therapy* **2013,** *11* (3), 297-308.
4. Mulani, M. S.; Kamble, E. E.; Kumkar, S. N.; Tawre, M. S.; Pardesi, K. R., Emerging Strategies to Combat ESKAPE Pathogens in the Era of Antimicrobial Resistance: A Review. *Frontiers in Microbiology* **2019,** *10* (539).
5. Van Boeckel, T. P.; Brower, C.; Gilbert, M.; Grenfell, B. T.; Levin, S. A.; Robinson, T. P.; Teillant, A.; Laxminarayan, R., Global trends in antimicrobial use in food animals. *Proceedings of the National Academy of Sciences* **2015,** *112* (18), 5649-5654.
6. Andrei, S.; Valeanu, L.; Chirvasuta, R.; Stefan, M.-G., New FDA approved antibacterial drugs: 2015-2017. *Discoveries (Craiova)* **2018,** *6* (1), e81-e81.
7. FDA Drugs@FDA: FDA-Approved Drugs. https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2020 (accessed 12 March, 2021).
8. Rani, A.; Saini, K. C.; Bast, F.; Mehariya, S.; Bhatia, S. K.; Lavecchia, R.; Zuorro, A., Microorganisms: A Potential Source of Bioactive Molecules for Antioxidant Applications. *Molecules* **2021,** *26* (4), 1142.
9. Newman, D. J.; Cragg, G. M., Natural products as sources of new drugs over the 30 years from 1981 to 2010. *Journal of natural products* **2012,** *75* (3), 311-335.
10. Mazzoli, R.; Riedel, K.; Pessione, E., Editorial: Bioactive Compounds from Microbes. *Frontiers in microbiology* **2017,** *8*, 392-392.
11. Vestby, L. K.; Grønseth, T.; Simm, R.; Nesse, L. L., Bacterial Biofilm and its Role in the Pathogenesis of Disease. *Antibiotics (Basel)* **2020,** *9* (2), 59.
12. Ting, D. S. J.; Ho, C. S.; Deshmukh, R.; Said, D. G.; Dua, H. S., Infectious keratitis: an update on epidemiology, causative microorganisms, risk factors, and antimicrobial resistance. *Eye* **2021**.
13. Sumi, C. D.; Yang, B. W.; Yeo, I.-C.; Hahm, Y. T., Antimicrobial peptides of the genus *Bacillus*: a new era for antibiotics. *Canadian journal of microbiology* **2015,** *61* (2), 93-103.
14. Zhao, X.; Kuipers, O. P., Identification and classification of known and putative antimicrobial compounds produced by a wide variety of *Bacillales* species. *BMC Genomics* **2016,** *17* (1), 882.
15. Caulier, S.; Nannan, C.; Gillis, A.; Licciardi, F.; Bragard, C.; Mahillon, J., Overview of the antimicrobial compounds produced by members of the *Bacillus subtilis* group. *Frontiers in microbiology* **2019,** *10*, 302.
16. Praptiwi; Fathoni, A.; Putri, A. L.; Wulansari, D.; Agusta, A. In *Assessment of actinomycetes isolated from soils on Simeuleu Island as antibacterial and antioxidant*, AIP Conference Proceedings, AIP Publishing LLC: 2019; p 080011.
17. Register, F., Nisin preparation: affirmation of GRAS status as a direct human food ingredient. *Federal Register* **1988,** *53*, 11247-11251.

18. Lozo, J.; Vukasinovic, M.; Strahinic, I.; Topisirovic, L., Characterization and antimicrobial activity of bacteriocin 217 produced by natural isolate *Lactobacillus paracasei* subsp. paracasei BGBUK2-16. *Journal of food protection* **2004,** *67* (12), 2727-2734.

19. Drissi, F.; Buffet, S.; Raoult, D.; Merhej, V., Common occurrence of antibacterial agents in human intestinal microbiota. *Frontiers in Microbiology* **2015,** *6* (441).

20. Leite, J. A.; Tulini, F. L.; Reis-Teixeira, F. B. d.; Rabinovitch, L.; Chaves, J. Q.; Rosa, N. G.; Cabral, H.; De Martinis, E. C. P., Bacteriocin-like inhibitory substances (BLIS) produced by *Bacillus cereus*: Preliminary characterization and application of partially purified extract containing BLIS for inhibiting *Listeria monocytogenes* in pineapple pulp. *LWT - Food Science and Technology* **2016,** *72*, 261-266.

21. Choeisoongnern, T., Sivamaruthi, B. S., Sirilun S., ; Sartjin P., Y. C., Hanitra R.,Thomas H. and Chaiyavat C., Screening and identification of bacteriocin-like inhibitory substances producing lactic acid bacteria from fermented products. *Food Science and Technology* **2019,** (AHEAD).

22. Gradisteanu Pircalabioru, G.; Popa, L. I.; Marutescu, L.; Gheorghe, I.; Popa, M.; Czobor Barbu, I.; Cristescu, R.; Chifiriuc, M.-C., Bacteriocins in the Era of Antibiotic Resistance: Rising to the Challenge. *Pharmaceutics* **2021,** *13* (2), 196.

23. Jawan, R.; Abbasiliasi, S.; Mustafa, S.; Kapri, M. R.; Halim, M.; Ariff, A. B., In Vitro Evaluation of Potential Probiotic Strain *Lactococcus lactis* Gh1 and Its Bacteriocin-Like Inhibitory Substances for Potential Use in the Food Industry. *Probiotics and Antimicrobial Proteins* **2020**.

24. Hyun, W. B.; Kang, H. S.; Lee, J. W.; Abraha, H. B.; Kim, K.-P., A newly-isolated *Bacillus subtilis* BSC35 produces bacteriocin-like inhibitory substance with high potential to control *Clostridium perfringens* in food. *LWT* **2021,** *138*, 110625.

25. Garsa, A. K.; Choudhury, P. K.; Puniya, A. K.; Dhewa, T.; Malik, R. K.; Tomar, S. K., Bovicins: the bacteriocins of *streptococci* and their potential in methane mitigation. *Probiotics and antimicrobial proteins* **2019,** *11* (4), 1403-1413.

26. Meade, E.; Slattery, M. A.; Garvey, M., Bacteriocins, potent antimicrobial peptides and the fight against multi drug resistant species: resistance is futile? *Antibiotics* **2020,** *9* (1), 32.

27. Shand, R. F.; Leyva, K. J., Peptide and Protein Antibiotics from the Domain Archaea: Halocins and Sulfolobicins. In *Bacteriocins: Ecology and Evolution*, Riley, M. A.; Chavan, M. A., Eds. Springer Berlin Heidelberg: Berlin, Heidelberg, 2007; pp 93-109.

28. Ibrahim, O. O., Classification of antimicrobial peptides bacteriocins, and the nature of some bacteriocins with potential applications in food safety and bio-pharmaceuticals. *EC Microbiol* **2019,** *15*, 591-608.

29. O'connor, E.; Shand, R., Halocins and sulfolobicins: the emerging story of archaeal protein and peptide antibiotics. *Journal of Industrial Microbiology and Biotechnology* **2002,** *28* (1), 23-31.

30. Garcia-Gutierrez, E.; Mayer, M. J.; Cotter, P. D.; Narbad, A., Gut microbiota as a source of novel antimicrobials. *Gut Microbes* **2019,** *10* (1), 1-21.

31. Newstead, L. L.; Varjonen, K.; Nuttall, T.; Paterson, G. K., Staphylococcal-Produced Bacteriocins and Antimicrobial Peptides: Their Potential as Alternative Treatments for *Staphylococcus aureus* Infections. *Antibiotics* **2020,** *9* (2), 40.

32. Negash, A. W.; Tsehai, B. A., Current Applications of Bacteriocin. *International Journal of Microbiology* **2020,** *2020*, 4374891.

33. Małaczewska, J.; Kaczorek-Łukowska, E., Nisin—A lantibiotic with immunomodulatory properties: A review. *Peptides* **2021,** *137*, 170479.

34. Yu, X.; Lu, N.; Wang, J.; Chen, Z.; Chen, C.; Mac Regenstein, J.; Zhou, P., Effect of N-terminal modification on the antimicrobial activity of nisin. *Food Control* **2020**, 107227.

35. Peng, X.; Zhu, L.; Wang, Z.; Zhan, X., Enhanced stability of the bactericidal activity of nisin through conjugation with gellan gum. *International Journal of Biological Macromolecules* **2020,** *148*, 525-532.
36. Heunis, T. D.; Smith, C.; Dicks, L. M., Evaluation of a nisin-eluting nanofiber scaffold to treat *Staphylococcus aureus*-induced skin infections in mice. *Antimicrobial agents and chemotherapy* **2013,** *57* (8), 3928-3935.
37. Field, D.; Seisling, N.; Cotter, P. D.; Ross, R. P.; Hill, C., Synergistic Nisin-Polymyxin Combinations for the Control of *Pseudomonas* Biofilm Formation. *Frontiers in Microbiology* **2016,** *7* (1713).
38. Alves, F. C. B.; Albano, M.; Andrade, B. F. M. T.; Chechi, J. L.; Pereira, A. F. M.; Furlanetto, A.; Rall, V. L. M.; Fernandes, A. A. H.; Dos Santos, L. D.; Barbosa, L. N., Comparative proteomics of methicillin-resistant *Staphylococcus aureus* subjected to synergistic effects of the lantibiotic nisin and oxacillin. *Microbial Drug Resistance* **2020,** *26* (3), 179-189.
39. El-Kazzaz, S. S.; Abou El-Khier, N. T., Effect of the lantibiotic nisin on inhibitory and bactericidal activities of antibiotics used against vancomycin-resistant enterococci. *Journal of global antimicrobial resistance* **2020,** *22*, 263-269.
40. Webber, J. L.; Namivandi-Zangeneh, R.; Drozdek, S.; Wilk, K. A.; Boyer, C.; Wong, E. H. H.; Bradshaw-Hajek, B. H.; Krasowska, M.; Beattie, D. A., Incorporation and antimicrobial activity of nisin Z within carrageenan/chitosan multilayers. *Scientific Reports* **2021,** *11* (1), 1690.
41. Shindo, K.; Takenaka, A.; Noguchi, T.; Hayakawa, Y.; Seto, H., Thiazostatin A and thiazostatin B, new antioxidants produced by *Streptomyces tolurosus*. *The Journal of antibiotics* **1989,** *42* (10), 1526-1529.
42. Perez, R. H.; Perez, M. T. M.; Elegado, F. B., Bacteriocins from lactic acid bacteria: a review of biosynthesis, mode of action, fermentative production, uses, and prospects. *International Journal of Philippine Science and Technology* **2015,** *8* (2), 61-67.
43. Wang, H.; Fewer, D. P.; Holm, L.; Rouhiainen, L.; Sivonen, K., Atlas of nonribosomal peptide and polyketide biosynthetic pathways reveals common occurrence of nonmodular enzymes. *Proceedings of the National Academy of Sciences* **2014,** *111* (25), 9259-9264.
44. Aleti, G.; Sessitsch, A.; Brader, G., Genome mining: prediction of lipopeptides and polyketides from *Bacillus* and related Firmicutes. *Computational and Structural Biotechnology Journal* **2015,** *13*, 192-203.
45. Alvarez-Sieiro, P.; Montalbán-López, M.; Mu, D.; Kuipers, O. P., Bacteriocins of lactic acid bacteria: extending the family. *Applied microbiology and biotechnology* **2016,** *100* (7), 2939-2951.
46. Baltz, R. H., Combinatorial biosynthesis of cyclic lipopeptide antibiotics: a model for synthetic biology to accelerate the evolution of secondary metabolite biosynthetic pathways. *ACS synthetic biology* **2014,** *3* (10), 748-758.
47. Perez, K. J.; Viana, J. d. S.; Lopes, F. C.; Pereira, J. Q.; dos Santos, D. M.; Oliveira, J. S.; Velho, R. V.; Crispim, S. M.; Nicoli, J. R.; Brandelli, A.; Nardi, R. M. D., *Bacillus* spp. Isolated from Puba as a Source of Biosurfactants and Antimicrobial Lipopeptides. *Frontiers in Microbiology* **2017,** *8* (61).
48. Kourmentza, K.; Gromada, X.; Michael, N.; Degraeve, C.; Vanier, G.; Ravallec, R.; Coutte, F.; Karatzas, K. A.; Jauregi, P., Antimicrobial Activity of Lipopeptide Biosurfactants Against Foodborne Pathogen and Food Spoilage Microorganisms and Their Cytotoxicity. *Frontiers in Microbiology* **2021,** *11* (3398).
49. Isa, M. H. M.; Shannaq, M. A.-H. F.; Mohamed, N.; Hassan, A. R.; Al-Shorgani, N. K. N.; Hamid, A. A., Antibacterial activity of surfactin produced by *Bacillus subtilis* MSH1. *Transactions on Science and Technology* **2017,** *4* (3-3), 402-407.
50. Calvo, H.; Mendiara, I.; Arias, E.; Blanco, D.; Venturini, M., The role of iturin A from *B. amyloliquefaciens* BUZ-14 in the inhibition of the most common postharvest fruit rots. *Food microbiology* **2019,** *82*, 62-69.
51. Sur, S.; Romo, T. D.; Grossfield, A., Selectivity and mechanism of fengycin, an antimicrobial lipopeptide, from molecular dynamics. *The Journal of Physical Chemistry B* **2018,** *122* (8), 2219-2226.

52. Meena, K.; Sharma, A.; Kanwar, S., Microbial lipopeptides and their medical applications. *Ann Pharmacol Pharm. 2017; 2 (24)* **2017,** *1126*.
53. Qi, G.; Zhu, F.; Du, P.; Yang, X.; Qiu, D.; Yu, Z.; Chen, J.; Zhao, X., Lipopeptide induces apoptosis in fungal cells by a mitochondria-dependent pathway. *Peptides* **2010,** *31* (11), 1978-1986.
54. Inès, M.; Dhouha, G., Lipopeptide surfactants: production, recovery and pore forming capacity. *Peptides* **2015,** *71*, 100-112.
55. Straus, S. K.; Hancock, R. E., Mode of action of the new antibiotic for Gram-positive pathogens daptomycin: comparison with cationic antimicrobial peptides and lipopeptides. *Biochimica et Biophysica Acta (BBA)-Biomembranes* **2006,** *1758* (9), 1215-1223.
56. Nasir, M. N.; Besson, F., Interactions of the antifungal mycosubtilin with ergosterol-containing interfacial monolayers. *Biochimica et Biophysica Acta (BBA)-Biomembranes* **2012,** *1818* (5), 1302-1308.
57. Ma, Z.; Zhang, S.; Sun, K.; Hu, J., Identification and characterization of a cyclic lipopeptide iturin A from a marine-derived *Bacillus velezensis* 11-5 as a fungicidal agent to *Magnaporthe oryzae* in rice. *Journal of Plant Diseases and Protection* **2020,** *127* (1), 15-24.
58. Malfanova, N.; Franzil, L.; Lugtenberg, B.; Chebotar, V.; Ongena, M., Cyclic lipopeptide profile of the plant-beneficial endophytic bacterium *Bacillus subtilis* HC8. *Archives of microbiology* **2012,** *194* (11), 893-899.
59. Touré, Y.; Ongena, M.; Jacques, P.; Guiro, A.; Thonart, P., Role of lipopeptides produced by *Bacillus subtilis* GA1 in the reduction of grey mould disease caused by *Botrytis cinerea* on apple. *Journal of applied microbiology* **2004,** *96* (5), 1151-1160.
60. Gélis-Jeanvoine, S.; Canette, A.; Gohar, M.; Caradec, T.; Lemy, C.; Gominet, M.; Jacques, P.; Lereclus, D.; Slamti, L., Genetic and functional analyses of krs, a locus encoding kurstakin, a lipopeptide produced by *Bacillus thuringiensis. Research in microbiology* **2017,** *168* (4), 356-368.
61. Das, P. K.; Das, S.; Sahoo, D.; Dalei, J.; Rao, V. M.; Nayak, S.; Palo, S., Comparative Evaluation of Purification Methods for Production of Polypeptide Antibiotics–"Polymyxin B" and "Cerexin A" from *Bacillus* Species. *Pharma News* **2021**.
62. Hathout, Y.; Ho, Y.-P.; Ryzhov, V.; Demirev, P.; Fenselau, C., Kurstakins: a new class of Lipopeptides isolated from *Bacillus thuringiensis*. *Journal of natural products* **2000,** *63* (11), 1492-1496.
63. Velkov, T.; Gallardo-Godoy, A.; Swarbrick, J. D.; Blaskovich, M. A.; Elliott, A. G.; Han, M.; Thompson, P. E.; Roberts, K. D.; Huang, J. X.; Becker, B., Structure, function, and biosynthetic origin of octapeptin antibiotics active against extensively drug-resistant Gram-negative bacteria. *Cell chemical biology* **2018,** *25* (4), 380-391. e5.
64. Solecka, J.; Zajko, J.; Postek, M.; Rajnisz, A., Biologically active secondary metabolites from Actinomycetes. *Open Life Sciences* **2012,** *7* (3), 373-390.
65. Dholakiya, R. N.; Kumar, R.; Mishra, A.; Mody, K. H.; Jha, B., Antibacterial and antioxidant activities of novel actinobacteria strain isolated from Gulf of Khambhat, Gujarat. *Frontiers in microbiology* **2017,** *8*, 2420.
66. Siddharth, S.; Vittal, R. R., Evaluation of antimicrobial, enzyme inhibitory, antioxidant and cytotoxic activities of partially purified volatile metabolites of marine *Streptomyces* sp. S2A. *Microorganisms* **2018,** *6* (3), 72.
67. Dhakal, D.; Sohng, J. K.; Pandey, R. P., Engineering actinomycetes for biosynthesis of macrolactone polyketides. *Microbial Cell Factories* **2019,** *18* (1), 137.
68. Widowati, I.; Zainuri, M.; Kusumaningrum, H. P.; Susilowati, R.; Hardivillier, Y.; Leignel, V.; Bourgougnon, N.; Mouget, J.-L. In *Antioxidant activity of three microalgae Dunaliella salina, Tetraselmis chuii and Isochrysis galbana clone Tahiti*, IOP Conference Series: Earth and Environmental Science, IOP Publishing: 2017; p 012067.

69. McArthur, K. A.; Mitchell, S. S.; Tsueng, G.; Rheingold, A.; White, D. J.; Grodberg, J.; Lam, K. S.; Potts, B. C., Lynamicins a− e, chlorinated bisindole pyrrole antibiotics from a novel marine actinomycete. *Journal of Natural Products* **2008,** *71* (10), 1732-1737.
70. Igarashi, Y.; Ogura, H.; Furihata, K.; Oku, N.; Indananda, C.; Thamchaipenet, A., Maklamicin, an antibacterial polyketide from an endophytic *Micromonospora* sp. *Journal of natural products* **2011,** *74* (4), 670-674.
71. Zhang, J.; Wang, J.-D.; Liu, C.-X.; Yuan, J.-H.; Wang, X.-J.; Xiang, W.-S., A new prenylated indole derivative from endophytic actinobacteria *Streptomyces* sp. neau-D50. *Natural Product Research* **2014,** *28* (7), 431-437.
72. Djinni, I.; Defant, A.; Kecha, M.; Mancini, I., Metabolite profile of marine-derived endophytic *Streptomyces sundarbansensis* WR 1 L 1 S 8 by liquid chromatography–mass spectrometry and evaluation of culture conditions on antibacterial activity and mycelial growth. *Journal of applied microbiology* **2014,** *116* (1), 39-50.
73. Yang, X.; Peng, T.; Yang, Y.; Li, W.; Xiong, J.; Zhao, L.; Ding, Z., Antimicrobial and antioxidant activities of a new benzamide from endophytic *Streptomyces* sp. YIM 67086. *Natural product research* **2015,** *29* (4), 331-335.
74. Ding, W.-J.; Zhang, S.-Q.; Wang, J.-H.; Lin, Y.-X.; Liang, Q.-X.; Zhao, W.-J.; Li, C.-Y., A new di-O-prenylated flavone from an actinomycete *Streptomyces* sp. MA-12. *Journal of asian natural products research* **2013,** *15* (2), 209-214.
75. Lee, L.-H.; Zainal, N.; Azman, A.-S.; Eng, S.-K.; Goh, B.-H.; Yin, W.-F.; Ab Mutalib, N.-S.; Chan, K.-G., Diversity and antimicrobial activities of actinobacteria isolated from tropical mangrove sediments in Malaysia. *The scientific world journal* **2014,** *2014*.
76. Yang, X.; Yang, Y.; Peng, T.; Yang, F.; Zhou, H.; Zhao, L.; Xu, L.; Ding, Z., A new cyclopeptide from endophytic *Streptomyces* sp. YIM 64018. *Natural product communications* **2013,** *8* (12), 1934578X1300801225.
77. Koller, M.; Muhr, A.; Braunegg, G., Microalgae as versatile cellular factories for valued products. *Algal research* **2014,** *6*, 52-63.
78. Li, Y.; Han, L.; Rong, H.; Li, L.; Zhao, L.; Wu, L.; Xu, L.; Jiang, Y.; Huang, X., Diastaphenazine, a new dimeric phenazine from an endophytic *Streptomyces diastaticus* subsp. ardesiacus. *The Journal of Antibiotics* **2015,** *68* (3), 210-212.
79. Savi, D. C.; Shaaban, K. A.; Vargas, N.; Ponomareva, L. V.; Possiede, Y. M.; Thorson, J. S.; Glienke, C.; Rohr, J., *Microbispora* sp. LGMB259 endophytic actinomycete isolated from *Vochysia divergens* (Pantanal, Brazil) producing β-carbolines and indoles with biological activity. *Current microbiology* **2015,** *70* (3), 345-354.
80. Zhou, H.; Yang, Y.; Peng, T.; Li, W.; Zhao, L.; Xu, L.; Ding, Z., Metabolites of *Streptomyces* sp., an endophytic actinomycete from Alpinia oxyphylla. *Natural Product Research* **2014,** *28* (4), 265-267.
81. Yan, L.-L.; Han, N.-N.; Zhang, Y.-Q.; Yu, L.-Y.; Chen, J.; Wei, Y.-Z.; Li, Q.-P.; Tao, L.; Zheng, G.-H.; Yang, S.-E., Antimycin A 18 produced by an endophytic *Streptomyces albidoflavus* isolated from a mangrove plant. *The Journal of Antibiotics* **2010,** *63* (5), 259-261.
82. Manimaran, M.; Gopal, J. V.; Kannabiran, K., Antibacterial Activity of *Streptomyces* sp. VITMK1 Isolated from Mangrove Soil of Pichavaram, Tamil Nadu, India. *Proceedings of the National Academy of Sciences, India Section B: Biological Sciences* **2017,** *87* (2), 499-506.
83. Wang, P.; Xi, L.; Liu, P.; Wang, Y.; Wang, W.; Huang, Y.; Zhu, W., Diketopiperazine derivatives from the marine-derived actinomycete *Streptomyces* sp. FXJ7.328. *Mar Drugs* **2013,** *11* (4), 1035-49.
84. Kang, H.-K.; Hyun, C.-G., Anti-inflammatory effect of d-(+)-cycloserine through inhibition of NF-κB and MAPK signaling pathways in LPS-induced RAW 264.7 macrophages. *Natural Product Communications* **2020,** *15* (4), 1934578X20920481.
85. Robertsen, H. L.; Musiol-Kroll, E. M., Actinomycete-derived polyketides as a source of antibiotics and lead structures for the development of new antimicrobial drugs. *Antibiotics* **2019,** *8* (4), 157.
86. Hug, J. J.; Bader, C. D.; Remškar, M.; Cirnski, K.; Müller, R., Concepts and methods to access novel antibiotics from actinomycetes. *Antibiotics* **2018,** *7* (2), 44.

87. Yu, Z.; Zhao, L.-X.; Jiang, C.-L.; Duan, Y.; Wong, L.; Carver, K. C.; Schuler, L. A.; Shen, B., Bafilomycins produced by an endophytic actinomycete *Streptomyces* sp. YIM56209. *The Journal of antibiotics* **2011,** *64* (1), 159-162.
88. Bulut, N.; Kocyigit, U. M.; Gecibesler, I. H.; Dastan, T.; Karci, H.; Taslimi, P.; Durna Dastan, S.; Gulcin, I.; Cetin, A., Synthesis of some novel pyridine compounds containing bis-1, 2, 4-triazole/thiosemicarbazide moiety and investigation of their antioxidant properties, carbonic anhydrase, and acetylcholinesterase enzymes inhibition profiles. *Journal of biochemical and molecular toxicology* **2018,** *32* (1), e22006.
89. Gulcin, İ., Antioxidants and antioxidant methods: an updated overview. *Archives of Toxicology* **2020,** *94* (3), 651-715.
90. Rodriguez-Valera, F.; Juez, G.; Kushner, D., Halocins: salt-dependent bacteriocins produced by extremely halophilic rods. *Canadian Journal of Microbiology* **1982,** *28* (1), 151-154.
91. Gaglione, R.; Pirone, L.; Farina, B.; Fusco, S.; Smaldone, G.; Aulitto, M.; Dell'Olmo, E.; Roscetto, E.; Del Gatto, A.; Fattorusso, R.; Notomista, E.; Zaccaro, L.; Arciello, A.; Pedone, E.; Contursi, P., Insights into the anticancer properties of the first antimicrobial peptide from Archaea. *Biochimica et Biophysica Acta (BBA) - General Subjects* **2017,** *1861* (9), 2155-2164.
92. Besse, A.; Peduzzi, J.; Rebuffat, S.; Carré-Mlouka, A., Antimicrobial peptides and proteins in the face of extremes: Lessons from archaeocins. *Biochimie* **2015,** *118*, 344-355.
93. Platas, G.; Meseguer, I.; Amils, R., Purification and biological characterization of halocin H1 from *Haloferax mediterranei* M2a. *International Microbiology* **2002,** *5* (1), 15-19.
94. Meseguer, I.; Rodriguez-Valera, F., Production and purification of halocin H4. *FEMS microbiology letters* **1985,** *28* (2), 177-182.
95. Torreblanca, M.; Meseguer, I.; Rodríguez-Valera, F., Halocin H6, a bacteriocin from *Haloferax gibbonsii*. *Microbiology* **1989,** *135* (10), 2655-2661.
96. Li, Y.; Xiang, H.; Liu, J.; Zhou, M.; Tan, H., Purification and biological characterization of halocin C8, a novel peptide antibiotic from *Halobacterium* strain AS7092. *Extremophiles* **2003,** *7* (5), 401-407.
97. Price, L. B.; Shand, R. F., Halocin S8: a 36-amino-acid microhalocin from the haloarchaeal strain S8a. *Journal of bacteriology* **2000,** *182* (17), 4951-4958.
98. Ebert, K.; Goebel, W.; Rdest, U.; Surek, B., Genes and genome structures in the archaebacteria. *Syst Appl Microbiol* **1986,** *7*, 30-35.
99. Pašić, L.; Velikonja, B. H.; Ulrih, N. P., Optimization of the culture conditions for the production of a bacteriocin from halophilic archaeon Sech7a. *Preparative biochemistry & biotechnology* **2008,** *38* (3), 229-245.
100. Shand, R. F.; Leyva, K. J., Peptide and protein antibiotics from the domain Archaea: halocins and sulfolobicins. In *Bacteriocins*, Springer: 2007; pp 93-109.
101. Karthikeyan, P.; Bhat, S. G.; Chandrasekaran, M., Halocin SH10 production by an extreme haloarchaeon *Natrinema* sp. BTSH10 isolated from salt pans of South India. *Saudi journal of biological sciences* **2013,** *20* (2), 205-212.
102. Wali, A. F.; Al Dhaheri, Y.; Ramakrishna Pillai, J.; Mushtaq, A.; Rao, P. G.; Rabbani, S. A.; Firdous, A.; Elshikh, M. S.; Farraj, D. A. A., Lc-ms phytochemical screening, in vitro antioxidant, antimicrobial and anticancer activity of microalgae *Nannochloropsis oculata* extract. *Separations* **2020,** *7* (4), 54.
103. Tan, L. T.-H.; Chan, K.-G.; Khan, T. M.; Bukhari, S. I.; Saokaew, S.; Duangjai, A.; Pusparajah, P.; Lee, L.-H.; Goh, B.-H., *Streptomyces* sp. MUM212 as a Source of Antioxidants with Radical Scavenging and Metal Chelating Properties. *Frontiers in Pharmacology* **2017,** *8* (276).
104. de Castro, I.; Mendo, S.; Caetano, T., Antibiotics from Haloarchaea: What Can We Learn from Comparative Genomics? *Marine Biotechnology* **2020,** *22* (2), 308-316.

105. Sahli, K.; Gomri, M. A.; Esclapez, J.; Gómez-Villegas, P.; Ghennai, O.; Bonete, M. J.; León, R.; Kharroub, K., Bioprospecting and characterization of pigmented halophilic archaeal strains from Algerian hypersaline environments with analysis of carotenoids produced by *Halorubrum* sp. BS2. *Journal of Basic Microbiology* **2020**.
106. Ghanmi, F.; Carré-Mlouka, A.; Vandervennet, M.; Boujelben, I.; Frikha, D.; Ayadi, H.; Peduzzi, J.; Rebuffat, S.; Maalej, S., Antagonistic interactions and production of halocin antimicrobial peptides among extremely halophilic prokaryotes isolated from the solar saltern of Sfax, Tunisia. *Extremophiles* **2016,** *20* (3), 363-374.
107. Ghanmi, F.; Carré-Mlouka, A.; Zarai, Z.; Mejdoub, H.; Peduzzi, J.; Maalej, S.; Rebuffat, S., The extremely halophilic archaeon *Halobacterium salinarum* ETD5 from the solar saltern of Sfax (Tunisia) produces multiple halocins. *Research in Microbiology* **2020,** *171* (2), 80-90.
108. Besse, A.; Vandervennet, M.; Goulard, C.; Peduzzi, J.; Isaac, S.; Rebuffat, S.; Carré-Mlouka, A., Halocin C8: an antimicrobial peptide distributed among four halophilic archaeal genera: *Natrinema, Haloterrigena, Haloferax,* and *Halobacterium*. *Extremophiles* **2017,** *21* (3), 623-638.
109. Quehenberger, J.; Shen, L.; Albers, S.-V.; Siebers, B.; Spadiut, O., Sulfolobus – A Potential Key Organism in Future Biotechnology. *Frontiers in Microbiology* **2017,** *8* (2474).
110. Roscetto, E.; Contursi, P.; Vollaro, A.; Fusco, S.; Notomista, E.; Catania, M. R., Antifungal and anti-biofilm activity of the first cryptic antimicrobial peptide from an archaeal protein against *Candida* spp. clinical isolates. *Scientific Reports* **2018,** *8* (1), 17570.
111. Kumar, V.; Tiwari, S. K., Activity-guided separation and characterization of new halocin HA3 from fermented broth of *Haloferax larsenii* HA3. *Extremophiles* **2017,** *21* (3), 609-621.
112. Quadri, I.; Hassani, I. I.; l'Haridon, S.; Chalopin, M.; Hacène, H.; Jebbar, M., Characterization and antimicrobial potential of extremely halophilic archaea isolated from hypersaline environments of the Algerian Sahara. *Microbiological Research* **2016,** *186-187*, 119-131.
113. Photolo, M. M.; Mavumengwana, V.; Sitole, L.; Tlou, M. G., Antimicrobial and Antioxidant Properties of a Bacterial Endophyte, *Methylobacterium radiotolerans* MAMP 4754, Isolated from *Combretum erythrophyllum* Seeds. *International Journal of Microbiology* **2020,** *2020*, 9483670.
114. Ayyanna, R.; Ankaiah, D.; Arul, V., Anti-inflammatory and Antioxidant Properties of Probiotic Bacterium *Lactobacillus mucosae* AN1 and *Lactobacillus fermentum* SNR1 in Wistar Albino Rats. *Frontiers in Microbiology* **2018,** *9* (3063).
115. Revilla, G.; Ramos, F.; López-Nieto, M.; Alvarez, E.; Martin, J., Glucose represses formation of delta-(L-alpha-aminoadipyl)-L-cysteinyl-D-valine and isopenicillin N synthase but not penicillin acyltransferase in *Penicillium chrysogenum*. *Journal of bacteriology* **1986,** *168* (2), 947-952.
116. Zanca, D. M.; Martin, J. F., Carbon catabolite regulation of the conversion of penicillin N into cephalosporin C. *The Journal of antibiotics* **1983,** *36* (6), 700-708.
117. Malve, H., Exploring the ocean for new drug developments: Marine pharmacology. *Journal of pharmacy & bioallied sciences* **2016,** *8* (2), 83.
118. Li, Y.; Lan, N.; Xu, L.; Yue, Q., Biosynthesis of pneumocandin lipopeptides and perspectives for its production and related echinocandins. *Applied Microbiology and Biotechnology* **2018,** *102* (23), 9881-9891.
119. Huang, Z.; Cai, X.; Shao, C.; She, Z.; Xia, X.; Chen, Y.; Yang, J.; Zhou, S.; Lin, Y., Chemistry and weak antimicrobial activities of phomopsins produced by mangrove endophytic fungus *Phomopsis* sp. ZSU-H76. *Phytochemistry* **2008,** *69* (7), 1604-1608.
120. Strobel, G.; Daisy, B., Bioprospecting for microbial endophytes and their natural products. *Microbiology and molecular biology reviews* **2003,** *67* (4), 491-502.

121. Liu, H.; Yan, C.; Li, C.; You, T.; She, Z., Naphthoquinone derivatives with anti-inflammatory activity from mangrove-derived endophytic fungus *Talaromyces* sp. SK-S009. *Molecules* **2020,** *25* (3), 576.
122. Zhang, C.-L.; Zheng, B.-Q.; Lao, J.-P.; Mao, L.-J.; Chen, S.-Y.; Kubicek, C. P.; Lin, F.-C., Clavatol and patulin formation as the antagonistic principle of *Aspergillus clavatonanicus*, an endophytic fungus of *Taxus mairei*. *Applied microbiology and biotechnology* **2008,** *78* (5), 833-840.
123. Wu, S.-H.; Chen, Y.-W.; Shao, S.-C.; Wang, L.-D.; Li, Z.-Y.; Yang, L.-Y.; Li, S.-L.; Huang, R., Ten-membered lactones from *Phomopsis* sp., an endophytic fungus of *Azadirachta indica*. *Journal of natural products* **2008,** *71* (4), 731-734.
124. Toghueo, R. M. K.; Sahal, D.; Boyom, F. F., Recent advances in inducing endophytic fungal specialized metabolites using small molecule elicitors including epigenetic modifiers. *Phytochemistry* **2020,** *174*, 112338.
125. Liu, Y.; Mándi, A.; Li, X.-M.; Meng, L.-H.; Kurtán, T.; Wang, B.-G., Peniciadametizine a, a dithiodiketopiperazine with a unique spiro [furan-2, 7'-pyrazino [1, 2-b][1, 2] oxazine] skeleton, and a related analogue, peniciadametizine B, from the marine sponge-derived fungus *Penicillium adametzioides*. *Marine drugs* **2015,** *13* (6), 3640-3652.
126. Meng, L.-H.; Zhang, P.; Li, X.-M.; Wang, B.-G., Penicibrocazines A–E, five new sulfide diketopiperazines from the marine-derived endophytic fungus *Penicillium brocae*. *Marine drugs* **2015,** *13* (1), 276-287.
127. Wu, B.; Wiese, J.; Labes, A.; Kramer, A.; Schmaljohann, R.; Imhoff, J. F., Lindgomycin, an unusual antibiotic polyketide from a marine fungus of the Lindgomycetaceae. *Marine drugs* **2015,** *13* (8), 4617-4632.
128. Gao, S.-S.; Li, X.-M.; Du, F.-Y.; Li, C.-S.; Proksch, P.; Wang, B.-G., Secondary metabolites from a marine-derived endophytic fungus *Penicillium chrysogenum* QEN-24S. *Marine drugs* **2011,** *9* (1), 59-70.
129. Wang, C.; Tang, S.; Cao, S., Antimicrobial compounds from marine fungi. *Phytochemistry Reviews* **2020**, 1-33.
130. Li, X.; Li, X.-M.; Zhang, P.; Wang, B.-G., A new phenolic enamide and a new meroterpenoid from marine alga-derived endophytic fungus *Penicillium oxalicum* EN-290. *Journal of Asian Natural Products Research* **2015,** *17* (12), 1204-1212.
131. Liu, H.; Li, X.-M.; Liu, Y.; Zhang, P.; Wang, J.-N.; Wang, B.-G., Chermesins A–D: Meroterpenoids with a drimane-type spirosesquiterpene skeleton from the marine algal-derived endophytic fungus *Penicillium chermesinum* EN-480. *Journal of natural products* **2016,** *79* (4), 806-811.
132. Gao, S.-S.; Li, X.-M.; Zhang, Y.; Li, C.-S.; Cui, C.-M.; Wang, B.-G., Comazaphilones A− F, azaphilone derivatives from the marine sediment-derived fungus *Penicillium commune* QSD-17. *Journal of natural products* **2011,** *74* (2), 256-261.
133. Meng, L.-H.; Li, X.-M.; Liu, Y.; Wang, B.-G., Penicibilaenes A and B, sesquiterpenes with a tricyclo [6.3. 1.01, 5] dodecane skeleton from the marine isolate of *Penicillium bilaiae* MA-267. *Organic letters* **2014,** *16* (23), 6052-6055.
134. Fukuda, T.; Kurihara, Y.; Kanamoto, A.; Tomoda, H., Terretonin G, a new sesterterpenoid antibiotic from marine-derived *Aspergillus* sp. OPMF00272. *The Journal of Antibiotics* **2014,** *67* (8), 593-595.
135. Prompanya, C.; Dethoup, T.; Bessa, L. J.; Pinto, M. M.; Gales, L.; Costa, P. M.; Silva, A.; Kijjoa, A., New isocoumarin derivatives and meroterpenoids from the marine sponge-associated fungus *Aspergillus similanensis* sp. nov. KUFA 0013. *Marine drugs* **2014,** *12* (10), 5160-5173.
136. Ding, L.; Li, T.; Liao, X.; He, S.; Xu, S., Asperitaconic acids A–C, antibacterial itaconic acid derivatives produced by a marine-derived fungus of the genus *Aspergillus*. *The Journal of antibiotics* **2018,** *71* (10), 902-904.
137. Peng, X.; Wang, Y.; Zhu, T.; Zhu, W., Pyrazinone derivatives from the coral-derived *Aspergillus ochraceus* LCJ11-102 under high iodide salt. *Archives of Pharmacal Research* **2018,** *41* (2), 184-191.
138. Wang, R.; Guo, Z. K.; Li, X. M.; Chen, F. X.; Zhan, X. F.; Shen, M. H., Spiculisporic acid analogues of the marine-derived fungus, *Aspergillus candidus* strain HDf2, and their antibacterial activity. *Antonie van Leeuwenhoek* **2015,** *108* (1), 215-219.
139. Zhu, F.; Chen, G.; Chen, X.; Huang, M.; Wan, X., Aspergicin, a new antibacterial alkaloid produced by mixed fermentation of two marine-derived mangrove epiphytic fungi. *Chemistry of Natural Compounds* **2011,** *47* (5), 767-769.

140. Zhang, Y.; Wang, S.; Li, X.-M.; Cui, C.-M.; Feng, C.; Wang, B.-G., New sphingolipids with a previously unreported 9-methyl-C 20-sphingosine moiety from a marine algous endophytic fungus *Aspergillus niger* EN-13. *Lipids* **2007,** *42* (8), 759-764.
141. Yang, G.; Sandjo, L.; Yun, K.; Leutou, A. S.; Kim, G.-D.; Choi, H. D.; Kang, J. S.; Hong, J.; Son, B. W., Flavusides A and B, antibacterial cerebrosides from the marine-derived fungus *Aspergillus flavus*. *Chemical and Pharmaceutical Bulletin* **2011,** *59* (9), 1174-1177.
142. Hawas, U. W.; El-Beih, A. A.; El-Halawany, A. M., Bioactive anthraquinones from endophytic fungus *Aspergillus versicolor* isolated from red sea algae. *Archives of pharmacal research* **2012,** *35* (10), 1749-1756.
143. Li, H.-L.; Li, X.-M.; Yang, S.-Q.; Cao, J.; Li, Y.-H.; Wang, B.-G., Induced terreins production from marine red algal-derived endophytic fungus *Aspergillus terreus* EN-539 co-cultured with symbiotic fungus *Paecilomyces lilacinus* EN-531. *The Journal of antibiotics* **2020,** *73* (2), 108.
144. Cao, C. W. S. T. S., Antimicrobial compounds from marine fungi. *Phytochem Reviews* **2020**.
145. Zhu, A.; Yang, M.-Y.; Zhang, Y.-H.; Shao, C.-L.; Wang, C.-Y.; Hu, L.-D.; Cao, F.; Zhu, H.-J., Absolute configurations of 14, 15-hydroxylated prenylxanthones from a marine-derived *Aspergillus* sp. fungus by chiroptical methods. *Scientific reports* **2018,** *8* (1), 1-10.
146. Liu, Z.; Dong, Z.; Qiu, P.; Wang, Q.; Yan, J.; Lu, Y.; Wasu, P.-a.; Hong, K.; She, Z., Two new bioactive steroids from a mangrove-derived fungus *Aspergillus* sp. *Steroids* **2018,** *140*, 32-38.
147. Pruksakorn, P.; Arai, M.; Kotoku, N.; Vilchèze, C.; Baughn, A. D.; Moodley, P.; Jacobs Jr, W. R.; Kobayashi, M., Trichoderins, novel aminolipopeptides from a marine sponge-derived *Trichoderma* sp., are active against dormant mycobacteria. *Bioorganic & medicinal chemistry letters* **2010,** *20* (12), 3658-3663.
148. Pang, X.; Lin, X.; Yang, J.; Zhou, X.; Yang, B.; Wang, J.; Liu, Y., Spiro-phthalides and isocoumarins isolated from the marine-sponge-derived fungus *Setosphaeria* sp. SCSIO41009. *Journal of natural products* **2018,** *81* (8), 1860-1868.
149. Song, T.; Chen, M.; Chai, W.; Zhang, Z.; Lian, X.-Y., New bioactive pyrrospirones C− I from a marine-derived fungus *Penicillium* sp. ZZ380. *Tetrahedron* **2018,** *74* (8), 884-891.
150. Song, T.; Chen, M.; Ge, Z.-W.; Chai, W.; Li, X.-C.; Zhang, Z.; Lian, X.-Y., Bioactive penicipyrrodiether A, an adduct of GKK1032 analogue and phenol A derivative, from a marine-sourced fungus *Penicillium* sp. ZZ380. *The Journal of organic chemistry* **2018,** *83* (21), 13395-13401.
151. Shen, H.-S.; Shao, S.; Chen, J.-C.; Zhou, T., Antimicrobials from Mushrooms for Assuring Food Safety. *Comprehensive Reviews in Food Science and Food Safety* **2017,** *16* (2), 316-329.
152. Thu, Z. M.; Myo, K. K.; Aung, H. T.; Clericuzio, M.; Armijos, C.; Vidari, G., Bioactive Phytochemical Constituents of Wild Edible Mushrooms from Southeast Asia. *Molecules* **2020,** *25* (8), 1972.
153. Mygind, P. H.; Fischer, R. L.; Schnorr, K. M.; Hansen, M. T.; Sönksen, C. P.; Ludvigsen, S.; Raventós, D.; Buskov, S.; Christensen, B.; De Maria, L.; Taboureau, O.; Yaver, D.; Elvig-Jørgensen, S. G.; Sørensen, M. V.; Christensen, B. E.; Kjærulff, S.; Frimodt-Moller, N.; Lehrer, R. I.; Zasloff, M.; Kristensen, H.-H., Plectasin is a peptide antibiotic with therapeutic potential from a saprophytic fungus. *Nature* **2005,** *437* (7061), 975-980.
154. Wong, J. H.; Ng, T. B.; Wang, H.; Sze, S. C. W.; Zhang, K. Y.; Li, Q.; Lu, X., Cordymin, an antifungal peptide from the medicinal fungus *Cordyceps militaris*. *Phytomedicine* **2011,** *18* (5), 387-392.
155. Gebreyohannes, G.; Nyerere, A.; Bii, C.; Sbhatu, D. B., Investigation of antioxidant and antimicrobial activities of different extracts of *Auricularia* and *Termitomyces* species of mushrooms. *The Scientific World Journal* **2019,** *2019*.
156. Poompouang, S.; Suksomtip, M., Isolation and characterization of an antifungal peptide from fruiting bodies of edible mushroom *Lentinus squarrosulus* Mont. *Malaysian Journal of Microbiology* **2016,** *12* (1), 43-49.

157. Irshad, A.; Sarwar, N.; Sadia, H.; Malik, K.; Javed, I.; Irshad, A.; Afzal, M.; Abbas, M.; Rizvi, H., Comprehensive facts on dynamic antimicrobial properties of polysaccharides and biomolecules-silver nanoparticle conjugate. *International Journal of Biological Macromolecules* **2020,** *145*, 189-196.
158. Hamamoto, E.; Kimura, N.; Nishino, S.; Ishihara, A.; Otani, H.; Osaki-Oka, K., Antimicrobial activity of the volatile compound 3,5-dichloro-4-methoxybenzaldehyde, produced by the mushroom *Porostereum spadiceum*, against plant-pathogenic bacteria and fungi. *Journal of Applied Microbiology n/a* (n/a).
159. Subrata, G.; Gunjan, B.; Prakash, P.; Mandal, S. C.; Krishnendu, A., Antimicrobial activities of basidiocarps of wild edible mushrooms of West Bengal, India. *International Journal of PharmTech Research* **2012,** *4* (4), 1554-1560.
160. Sevindi, M., Phenolic content, antioxidant and antimicrobial potential of *Melanoleuca melaleuca* edible mushroom. *The Journal of Animal & Plant Sciences,* **2021,** *31* (3), 824-830.
161. Endo, H.; Niioka, M.; Kobayashi, N.; Tanaka, M.; Watanabe, T., Butyrate-producing probiotics reduce nonalcoholic fatty liver disease progression in rats: new insight into the probiotics for the gut-liver axis. *PloS one* **2013,** *8* (5), e63388.
162. Fakruddin, M.; Hossain, M. N.; Ahmed, M. M., Antimicrobial and antioxidant activities of *Saccharomyces cerevisiae* IFST062013, a potential probiotic. *BMC Complementary and Alternative Medicine* **2017,** *17* (1), 64.
163. Breinig, F.; Sendzik, T.; Eisfeld, K.; Schmitt, M. J., Dissecting toxin immunity in virus-infected killer yeast uncovers an intrinsic strategy of self-protection. *Proceedings of the National Academy of Sciences* **2006,** *103* (10), 3810-3815.
164. Muccilli, S.; Wemhoff, S.; Restuccia, C.; Meinhardt, F., Exoglucanase-encoding genes from three *Wickerhamomyces* anomalus killer strains isolated from olive brine. *Yeast* **2013,** *30* (1), 33-43.
165. Gao, D.; Gao, Z.; Zhu, G., Antioxidant effects of *Lactobacillus plantarum* via activation of transcription factor Nrf2. *Food & function* **2013,** *4* (6), 982-989.
166. Diao, Y.; Xin, Y.; Zhou, Y.; Li, N.; Pan, X.; Qi, S.; Qi, Z.; Xu, Y.; Luo, L.; Wan, H., Extracellular polysaccharide from *Bacillus* sp. strain LBP32 prevents LPS-induced inflammation in RAW 264.7 macrophages by inhibiting NF-κB and MAPKs activation and ROS production. *International immunopharmacology* **2014,** *18* (1), 12-19.
167. Molino, A.; Iovine, A.; Casella, P.; Mehariya, S., Microalgae Characterization for Consolidated and New Application in Human Food, Animal Feed and Nutraceuticals. *International Journal of Environmental Research and Public Health* **2018,** *15* (11).
168. Moreno-Garcia, L.; Adjallé, K.; Barnabé, S.; Raghavan, G., Microalgae biomass production for a biorefinery system: recent advances and the way towards sustainability. *Renewable and Sustainable Energy Reviews* **2017,** *76*, 493-506.
169. Desbois, A. P.; Mearns-Spragg, A.; Smith, V. J., A fatty acid from the diatom *Phaeodactylum tricornutum* is antibacterial against diverse bacteria including multi-resistant *Staphylococcus aureus* (MRSA). *Marine Biotechnology* **2009,** *11* (1), 45-52.
170. Arguelles, E., Proximate analysis, antibacterial activity, total phenolic content and antioxidant capacity of a green microalga *Scenedesmus quadricauda* (Turpin) Brébisson. *Asian Journal of Microbiology, Biotechnology and Environmental Sciences* **2018,** *20*, 150-158.
171. Maadane, A.; Merghoub, N.; Mernissi, N. E.; Ainane, T.; Amzazi, S.; Bakri, I. W., Antimicrobial activity of marine microalgae isolated from Moroccan coastlines. *Journal of Microbiology, Biotechnology and Food Sciences* **2020,** *9* (5), 1257-1260.
172. Zielinski, D.; Fraczyk, J.; Debowski, M.; Zielinski, M.; Kaminski, Z. J.; Kregiel, D.; Jacob, C.; Kolesinska, B., Biological activity of hydrophilic extract of *Chlorella vulgaris* grown on post-fermentation leachate from a biogas plant supplied with stillage and maize silage. *Molecules* **2020,** *25* (8), 1790.

173. Alsenani, F.; Tupally, K. R.; Chua, E. T.; Eltanahy, E.; Alsufyani, H.; Parekh, H. S.; Schenk, P. M., Evaluation of microalgae and cyanobacteria as potential sources of antimicrobial compounds. *Saudi Pharmaceutical Journal* **2020,** *28* (12), 1834-1841.

174. Maadane, A.; Merghoub, N.; Mernissi, N. E.; Ainane, T.; Amzazi, S.; Bakri, I. W., Antimicrobial activity of marine microalgae isolated from Moroccan coastlines. *Journal of Microbiology, Biotechnology and Food Sciences* **2021,** *2021*, 1257-1260.

175. Washida, K.; Koyama, T.; Yamada, K.; Kita, M.; Uemura, D., Karatungiols A and B, two novel antimicrobial polyol compounds, from the symbiotic marine dinoflagellate *Amphidinium* sp. *Tetrahedron letters* **2006,** *47* (15), 2521-2525.

176. Ghaidaa, H.; Neihaya, H.; Nada, Z. M.; Amna, M., The Biofilm Inhibitory Potential of Compound Produced from *Chlamydomonas reinhardtii* Against Pathogenic Microorganisms. *Baghdad Science Journal* **2020,** *17* (1).

177. Pratt, R.; Daniels, T.; Eiler, J. J.; Gunnison, J.; Kumler, W.; Oneto, J. F.; Strait, L. A.; Spoehr, H.; Hardin, G.; Milner, H., Chlorellin, an antibacterial substance from *Chlorella*. *Science (Washington)* **1944**, 351-2.

178. Bancalari, E.; Martelli, F.; Bernini, V.; Neviani, E.; Gatti, M., Bacteriostatic or bactericidal? Impedometric measurements to test the antimicrobial activity of *Arthrospira platensis* extract. *Food Control* **2020,** *118*, 107380.

179. Guzmán, F.; Wong, G.; Román, T.; Cárdenas, C.; Alvárez, C.; Schmitt, P.; Albericio, F.; Rojas, V., Identification of antimicrobial peptides from the microalgae *Tetraselmis suecica* (Kylin) Butcher and bactericidal activity improvement. *Marine drugs* **2019,** *17* (8), 453.

180. Mendiola, J. A.; Torres, C. F.; Toré, A.; Martín-Álvarez, P. J.; Santoyo, S.; Arredondo, B. O.; Señoráns, F. J.; Cifuentes, A.; Ibáñez, E., Use of supercritical CO 2 to obtain extracts with antimicrobial activity from *Chaetoceros muelleri* microalga. A correlation with their lipidic content. *European Food Research and Technology* **2007,** *224* (4), 505-510.

181. Kokou, F.; Makridis, P.; Kentouri, M.; Divanach, P., Antibacterial activity in microalgae cultures. *Aquaculture Research* **2012,** *43* (10), 1520-1527.

182. Blunt, J. W.; Copp, B. R.; Keyzers, R. A.; Munro, M. H.; Prinsep, M. R., Marine natural products. *Natural Product Reports* **2015,** *32* (2), 116-211.

183. Sanzo, G. D.; Mehariya, S.; Martino, M.; Larocca, V.; Casella, P.; Chianese, S.; Musmarra, D.; Balducchi, R.; Molino, A., Supercritical carbon dioxide extraction of astaxanthin, lutein, and fatty acids from Haematococcus pluvialis microalgae. *Marine drugs* **2018,** *16* (9), 334.