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Review

Microorganisms: A Potential Source of Bioactive molecules for Antioxidants and Antimicrobial Applications

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Abstract: Oxidative stress is an elevated intracellular level of free oxygen radicals that cause lipid peroxidation, protein denaturation, DNA hydroxylation, and apoptosis, ultimately negotiating cells viability. Antioxidants can scavenge such free radicals, thus reducing the oxidative stress and eventually prevent cellular damage. Medicinal plants, fruits, and spices remain the prioritized sources of antioxidants and antimicrobial properties since the time immemorial, but in contrast to plants, microorganisms can be grown at a faster rate under controlled conditions. They are non-toxic, non-carcinogenic, and biodegradable as compared to synthetic antioxidants. Microorganisms including actinomycetes, archaea, bacteria, protozoa, yeast, and fungi are auspicious source of vital bioactive compounds. The list comprises ample of bioactive components from microorganisms. One of them is bacteriocins, which are ribosomally synthesized antimicrobial peptides product of *Eurotium* sp., *Streptomyces parvulus, S. thermophiles, Lactococcus lactis, etc.* It has a great potential as next-generation antibiotics targeting the multiple-drug resistant pathogens. Pneumocandins are antifungal lipohexapeptides derived from the fungus *Glarea lozoyensis,* and inhibit 1,3-β-glucan synthase of the fungal cell wall and act as a precursor for the synthesis of caspofungin. It is widely used against invasive fungal infections and has been recently approved by the FDA. Taxol (paclitaxel), a chemotherapeutic drug derived from the bark of *Taxus brevifolia* can also be produced by endophytic fungi *Taxomyces andreanae* and *Nodulisporium sylviforme.* It is known to inhibit several fungi such as *Pythium, Aphanomyces and Phytophthora*. Hispidin and its derivate isolated from *P. hispidus*, reduce inducible nitric oxide synthase (iNOS) expression, obstruct the transcriptional activity of NF-κB, and also decrease the production of reactive oxygen species (ROS) in macrophages. Astaxanthin, known as an "aquatic" carotenoid produced by *H. pluvialis,* also has excellent ROS quenching activity. This study mainly focuses on fascinating antioxidant and antimicrobial compounds that have been scarcely investigated in microorganisms and discuss the promise and challenges of microorganisms as providers of health benefits.

Keywords: Astaxanthin, natural antioxidant, bacteriocins, hispidin, oxidative stress.

1. Introduction

Microorganisms are a heterogeneous group of diverse living things that are too small to be viewed with naked eyes. The major clusters of microorganisms include archaea, bacteria, fungi, protozoa, algae, and viruses. Microbial diversity produces a massive pool of inimitable chemicals, which nowadays become a treasured source for innovative biotechnology. About 23,000 secondary metabolites from microorganisms are known, out of which approximately 42% are exclusively produced by actinomycetes, whereas fungi form almost parallel amount (42%), and remaining 16% is produced by eubacteria [1].

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Microbial secondary metabolites, including growth hormones, pigments, antibiotics, antitumor agents, etc. are not utilised for their growth and development, yet they have revealed an excellent prospective for human health. These bioactive compounds have become significant sources for life saving drugs, which include penicillin, amphotericin, streptomycin, erythromycins, tetracycline, vancomycin, etc. (Figure 1) [2]. Antibiotics testified from different microorganism act at particular target sites (Figure 1). These secondary metabolites are chiefly produced due to the initiation of some cryptic gene clusters, which are generally inactive under normal conditions; hence their expression would be significant in exploiting the chemical diversity of microorganisms. Many of these secondary metabolites hold specific antioxidant and antimicrobial potential. Such bioactive molecules are the attentive source for biotechnological applications, specifically for pharmaceuticals, nutraceuticals, and cosmetics.

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

As estimated by the Business Communication Company (BCC), in 2014, the total world-wide market for microbial products was assessed at approximately $143.5 billion and was expected to increase up to $306 billion from 2015 to 2020, at a compound annual growth rate (CAGR) of nearly 14.6%. Advancement in new technologies and economical advantages are substituting the synthetic products and production processes with the microbial products. The major end-user market for microbes and microbial products is healthcare sector, which was about $100.4 billion in 2014, approximately $111.5 billion in 2015, and is expected to increases upto $187.8 billion by 2020 [3, 4]. According to Boeckel *et al.* (2015), by 2030 the antimicrobial consumption will increase upto 67%, and increase upto two fold in India, Brazil, China, Russia, and South Africa, due to increased consumption of livestock products in middle-income countries [5]. However, the approval of antibacterial agents decreased by 56 % during the period of 1983 to 1987 and only 3% of antimicrobial agents were approved by the United States Food and Drug Administration (FDA). Gemifloxacin and daptomycin were approved on 7 April and 12 September of 2003, whereas in 2018, no antibacterial drug was approved. Besides, in 2015 FDA approved 6 novel antibacterial drugs including the 3rd generation cephalosporin and β-lactamase inhibitor combination ceftazidime/avibactam [6].

Antioxidants scavange free radicals to avoid cellular damage caused due to oxidative stress. Microorganisms produce many bioactive compounds bearing antioxidant properties. For example astaxanthin produced by *Haematococcus pulvialis* (microalgae), *Xanthophyllomyces dendrorhous* (yeast) and *Paracoccus sp.* (bacteria) [7], has antioxidant activities and health benefits to humans and animals. Astaxanthin was primarily discovered in 1938 and was initially used as a colorant for aquaculture besides being approved as a colouring agent for food supplement since 1991. Due to emerging health benefits, demand for astaxanthin has increased rapidly in medicine, food industries and cosmetics, etc. Its market share was USD 512.8 million in 2016, which increases in 2017 at a CAGR of 6.73% and is expected to reach up to USD 814.1 million by 2022 and $2.57 billion by 2025 worldwide [7, 8]. Same is the case with carotenoid, whose market demand was 1.24 billion USD (B$) in 2015 and is expected to raise to 1.6 B$ by 2023 with a CAGR of 3.5%. The demand for lutein in market in 2015 was 135 M$, which may rise up to 200 M$ in 2024, with a CAGR of 5.3 %. This hike is due to the increasing demand of lutein-rich dietary supplements [9].

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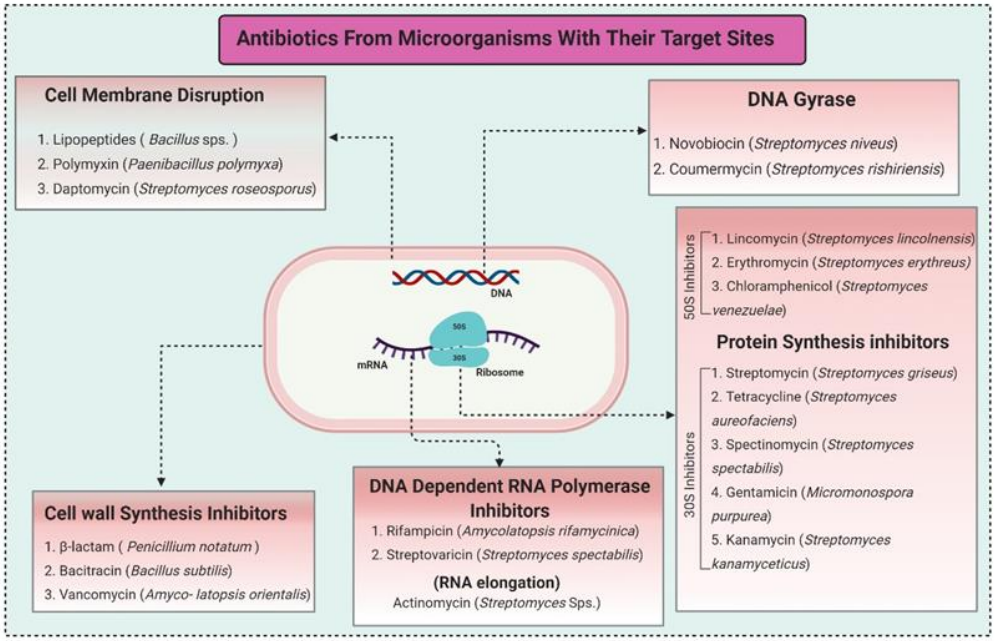

Figure 1. Antibiotics reported from different microorganism with their target sites.

2. Concept of ROS (Reactive Oxygen Species) and antioxidants

Life on Earth cannot be possible without oxygen; however, it can be harmful to life by instigating oxidative stress in cells and tissues due to the formation of ROS (reactive oxygen species). Exceptionally high levels of ROS, reactive nitrogen species (RNS), and reactive sulfur species (RSS) cause metabolic malfunctioning, destruction to cellular proteins, nucleic acids (RNA and DNA), lipids and ultimately cell death. Several sources and mechanisms have been advocated, which contribute to the generation of these ROS. Antioxidants are ROS scavengers can shield, scavenge, and repair oxidative damage, thereby defending target assemblies or molecules from oxidative damages. According to the mode of action antioxidants are either primary or secondary antioxidants. Primary antioxidants nullify free radicals by two mechanism, one is by donating an H-atom known as hydrogen atom transfer (HAT), other is through a single electron transfer (SET) mechanism. These antioxidants are required in lesser amount to neutralize a huge sum of free radicals. For example phenolic antioxidants have high catalytic properties and can be easily regenerated [10]. The secondary antioxidants neutralize the ROS through prooxidant catalysts mechanism such as β-carotene, which neutralize ROS like singlet oxygen by quenching free radical and are thus certainly exhausted. Both primary antioxidants and secondary antioxidants can be either synthetic or natural [10]. Synthetic antioxidants, such as butylated hydroxytoluene (BHT), tertbutyl hydroquinone (TBHQ), butylated hydroxyanisole (BHA), and propyl gallate (PG) have been used to prevent lipid peroxidation (LPO), in food products. However, these synthetic antioxidants are cheap and stable at extreme ranges of environmental conditions, but they negatively impact the health causing toxicity that endorses DNA damage (Figure 2). To cope up with such side effects, microorganisms were preferred and since early 1980s, antioxidants from microorganisms were identified and used in healthcare, and agriculture due to their valuable therapeutic efficacy and accessibility [11]. Antioxidants not only protect against ROS but also enhance human physiological functions, consequently assisting to sustain a healthy state and defend against ailments. Living organisms have different antioxidant mechanisms, including enzymatic and non-enzymatic for inactivating ROS. Enzymes, including catalase, glutathione peroxidase and superoxide dismutase are the endogenous antioxidants that control the damage of ROS, whereas carotenes, flavonoids, reduced glutathione, bilirubin, coenzyme Q, and vitamin C, are the sources of exogenous antioxidants.

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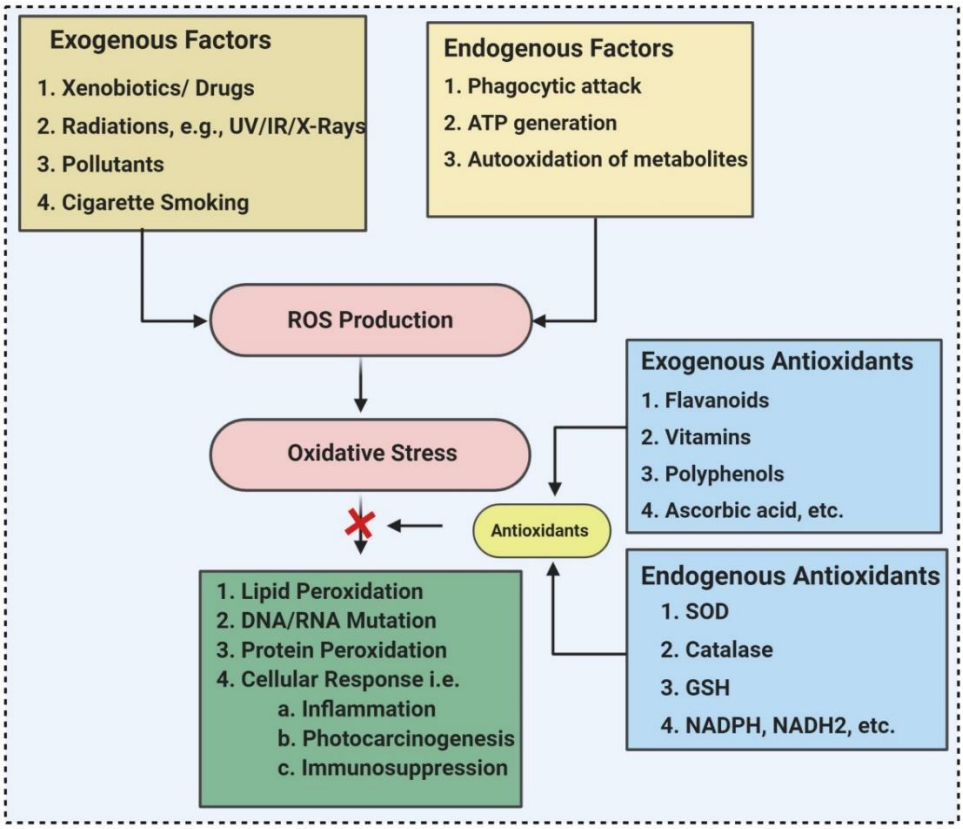

Figure 2. Various sources of oxidative stress and antioxidants.

After exposure to a maximum concentration of ROS, sometimes the endogenous antioxidant system is conceded and unable to assure thorough security of the organism, to reimburse this scarcity of antioxidant; exogenous antioxidants are supplied through food or nutritional supplements. Antioxidants not only play a key role in inhibiting oxidative damages but also aid in the prevention of diseases like degenerative neuropathies, cardiovascular diseases, and cancer, as well as exerting anti-inflammatory, antiviral and anti-aging activities.

Many microorganisms have been identified as a natural source of antioxidants including both $Gram^-$ and $Gram^+$ bacteria. Antioxidant fraction extracted from marine bacteria, *Kocuria marina* CDMP 10, from the Gulf of Mannar, Bay of Bengal, India contains the short hydrophobic peptide Ser–Ser–Gln, which is demonstrated as a potent free radical scavenger in Hepatocellular carcinoma cell lines, signifying its potential as a potent pharmaceutical candidate with antioxidant activity [12].

3. Microorganisms as a Source of Antioxidant and Antimicrobial Compounds

3.1 Actinomycetes

The actinomycetes are gram-positive, aerobic, filamentous and spore-forming bacteria, with a foremost reputation in producing chemically different metabolites bearing a broad spectrum of biological activities, including antifungal, antibacterial and insecticidal activities. Mycothiol (MSH), a principal 'sugar' thiol present in the cell wall of actinomycetes that serves as the glutathione (GSH) analog. Actinomycetes lack the enzymes for GSH biosynthesis, but as a substitute, they utilize alternative low molecular weight thiols (LMW), such as bacillithiol (BSH) and MSH, ergothioneine (ESH) [13]. MSH maintains the intracellular redox homeostasis, allowing the appropriate working of many biological processes, counting enzyme activation, DNA synthesis, and cell-cycle regulation. MSH acts as an electron donor/acceptor and also assists as a cofactor in detoxifying free radicals, xenobiotics and alkylating agents. Unlike GSH, MSH has two sugar component viz N-

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glucosamine and inositol along with cysteine component as an alternative of the two amino acids, glycine, and glutamic acid [13].

3.1.1 Actinomycetes as a source for antioxidants

3.1.1.1 Biosynthesis of MSH

MSH biosynthesis involves five enzymes and the substrates *myo*-inositol-1-phosphate (Ins-P), UDP-*N*-acetyl glucosamine (UDP-GlcNAc) and Cysteine (Cys), represented in Figure 3. Firstly Ins-P is conjugated with UDP-GlcNAc to yield *N*-acetyl glucosamine *myo*-inositol-1-phosphate (GlcNAc-Ins-P) via enzyme glycosyltransferase MshA. The MSH phosphatase MshA2 dephosphorylated GlcNAc-Ins-P, which is further deacetylated by the metal-dependent deacetylase MshB generating glucosamine inositol [1-O-(2-amino-1-deoxy-a-Dglucopyranosyl)-D-myo-inositol]. The Cys ligase MshC inserted Cys to yield Cys-GlcN-Ins. Finally, the Cys amino group is acetylated by the MSH acetyltransferase MshD to produce MSH [14] .

3.1.1.2 Catalytic action of the mycothiol disulfide reductase (Mtr):

When there is an oxidative stress, MSH get oxidized to mycothiol disulfide (MSSM), which further get reduced by the NADPH-dependent Mtr. Mtr is the key enzyme involved in retaining MSH levels, which reduces the oxidized MSH disulfide. Mtr is a homodimeric flavoprotein disulfide isomerase which requires a cofactor viz. FAD (flavin adenine dinucleotide). The oxidized Mtr (Mtrox) comprises of a disulfide bridge between Cys39-Cys44, which is further reduced by accepting electrons from NADPH through FAD cofactor to produce reduced Mtr, as depicted in Figure 3. MSSM is confronted via the swapping of Cys39, resulting in the generation of Cys39-SSM and discharge of first MSH moiety. Consequently the disulfide bond in Cys39-SSM is condemned by the thiolate present at Cys44 forming Mtrox [15] and [16].

3.1.1.3 Mycothiol-dependent detoxification of electrophiles:

MSH *S*-transferases (Mst) conjugate with MSH electrophiles (RX), creating MS-electrophiles (MSR), MSH *S*-conjugate amidase (Mca) cleave an amide bond of MSR to form a glucosaminylinositol (GlcN-Ins) and mercapturic acid (AcCys-R). AcCys-R or MSH-S-associates of antibiotics or toxins are expelled from cells via ABC transporters, whereas GlcN-Ins is salvaged back to mycothiol (Figure 3) [17, 18].

3.1.2 *Detoxification of NO:*

Detoxification of NO requires the MSH-dependent detoxification enzyme nitrosothiol reductase (MscR) that exhibits S-nitrosomycothiol (MSNO) reductase action generating MSH sulfonamide (MSO_2H) [19]. Both MSH-dependent formaldehyde dehydrogenase AdhE and MscR oxidize formaldehyde to formate. In the case of *Corynebacterium glutamicum*, maleylpyruvate that is a ring fission output of gentisic acid and is converted to fumarylpyruvate through gentisate pathway by the MSH-dependent maleylpyruvate isomerase (Figure 3) [15, 18].

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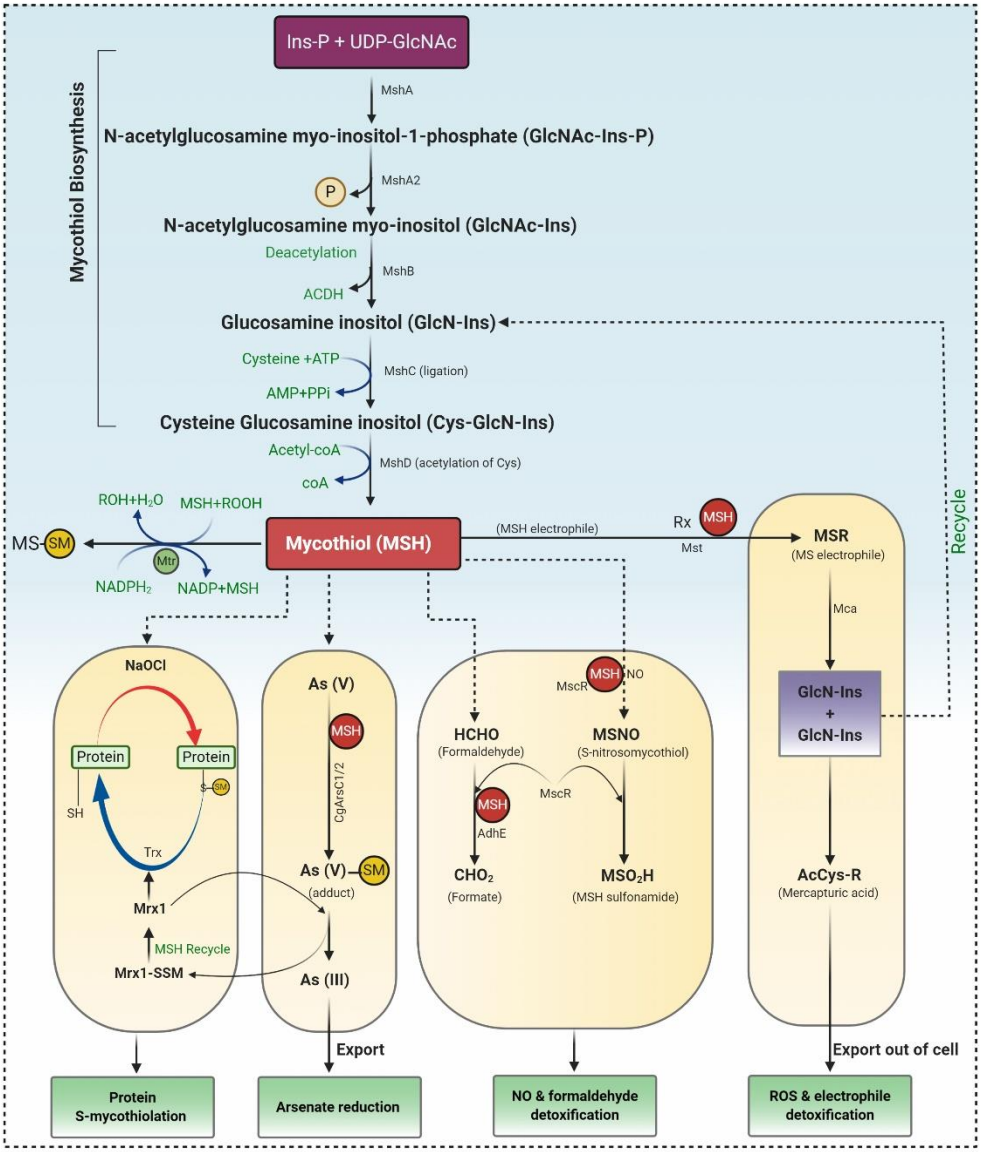

Figure 3. MSH biosynthesis and regulation in actinomycetes. Synthesis of MSH is catalyzed by five enzymes, including MshA, MshA2, MshB, MshC and MshD. 1) Under ROS, MSH is oxidized to MSSM which is further reduced by Mtr. 2) *S*-mycothiolation and protein regeneration occur via Mrx1/MSH/Mtr and Trx/TrxR pathway. 3) Arsenate reductases CgArsC1/CgArsC2 along with MSH and Mrx1 reduced As (V) to As (III), which is exported through ABC transporter. 4) MSH acts as thiol cofactor for alcohol dehydrogenase MscR and formaldehyde dehydrogenase AdhE and are involved in the detoxification of NO and formaldehyde. 5) Mycothiol amidase (Mca) and mycothiol-S-tranferases are involved in the ROS and xenobiotic detoxification.

3.1.3 *Detoxification of arsenate:*

Arsenate detoxification is catalysed by the arsenate reductases (CgArsC1/CgArsC2), which associate arsenate As (V) to MSH, generating As(V)-SM adduct, that is later on reduced by mycoredoxin-1 (Mrx1), forming Mrx1-SSM intermediate and As (III). As (III) is disseminated from the cells using two arsenite permeases of the Acr3 family (Figure 3). Mrx1-SSM depend on MSH for the regenerating Mrx1 [17] and[13].

3.1.4 *Protein S-mycothiolation under NaClO and H_2O_2 stress:*

Proteins are *S*-mycothiolated and recreated by the Mrx1/MSH/Mtr and Trx/TrxR pathways during NaOCl and H_2O_2 stress. These proteins control the activity of Mpx, Tpx and MsrA *in vitro* [17]. Mpx and MsrA result in the formation of intramolecular disulfides and *S*-mycothiolations and involve both the Trx and Mrx1 pathways for reformation [20].

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The Mrx1/Mtr/MSH pathways are likewise involved in the reduction of the peroxiredoxin AhpE in *Mycobacterium tuberculosis* (Figure 3) [21].

3.1.5 Antimicrobial applications of Actinomycetes:

Approximately 75% of the known industrial antibiotics and abundant economically important compounds were attained from the *Streptomyces*'s [22]. *Actinobacteria* have the capability to synthesize antifungal, antiviral, antitumor, anti-inflammatory, antioxidants, immunosuppressive, plant growth-promoting and herbicidal compounds [23]. Among actinobacteria, *Streptomyces* is the utmost and dominant cause of bioactive metabolites with a broad range of bioactivity. 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 approx. 2500 compounds [24]. Marine or terrestrial Actinobacteria utilize enzymes polyketide synthases (PKS) or non-ribosomal peptide synthetases (NRPS) for the synthesis of metabolic bioactive compounds [25]. Marine sediment sampled off the coast of San Diego, California, has a new marine *actinomycete*, NPS12745, associated with it. After 16S rRNA sequences, it is confirmed that NPS12745 is a innovative strain of genus *Marinispora,* which produced ample of new chlorinated bisindole pyrroles and lynamicins A-E. The bisindole pyrrole derivatives include chromopyrrolic acid, earlier isolated from *Chromobacterium violaceum* [26]. The first halogenated bisindole derivative was Lynamicins A–E, having antibacterial activity against a panel of $Gram^+$ and $Gram^-$ bacteria, i.e., MSSA, MRSA: methicillin-resistant *S. aureus*, *Staphylococcus epidermidis* and *Enterococcus faecalis*, signifying possible cure of nosocomial infections [27].

Siddharth & Vittal (2018) isolated *Streptomyces sp.*S2A from marine sediment from Gulf of Mannar, that was reported to bear persuasive antagonistic activity against bacterial (*Micrococcus luteus, Staphylococcus epidermidis, Klebsiella pneumoniae, Bacillus cereus* and *Staphylococcus aureus*) and fungal (*Fusarium moniliforme* and *Bipolaris maydis)* pathogens [24]. Igarashi *et al.,* in 2011, isolated Maklamicin, a novel spirotetronate of class polyketide from an endophytic actinomycete *Micromonospora sp.* GMKU326. The Maklamicin bears antimicrobial activity against *Micrococcus luteus, Bacillus subtilis, Staphylococcus aureus, Bacillus cereus,* and *Enterococcus faecalis*, $Gram^+$ bacteria with MIC values of 0.2, 1.7, 13, 6.5, and 13 μg/ml respectively [28]. A unique prenylated-indole derivative known as 3-acetonylidene-7- prenylindolin-2-one was extracted from endophytic actinomycete *Streptomyces sp.* neau-D50. Other compounds isolated from *Streptomyces sp.* neau-D50 were hybrid isoprenoids, 3-cyanomethyl-6- prenylindole, 7-isoprenylindole-3-carboxylic acid and 6-isoprenylindole-3-carboxylic acid. These compounds display antifungal activity against phytopathogenic fungi *Corynespora cassiicola, Phytophthora capsici Colletotrichum orbiculare* and *Fusarium oxysporum* [29]. *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 reported polyketides namely phaeochromycin B, C, and E which are $Gram^+$ pathogenic MRSA MIC value of 6 μM [30]. Vinaceuline, a cyclopeptide active against bacteria, was extracted from the broth culture of endophytic *Streptomyces sp*. YIM64018 allied with *Paraboea sinensis*. Yang *et al*. (2015) isolated a new benzamide, 2-amino-3, 4-dihydroxy-5-methoxybenzamide from endophytic *Streptomyces*YIM67086 attacks *Escherichia coli* and *Candida albicans* (MICs of 64 and 32 μg/ml, respectively) [31]. Ding *et al.* (2013) reported the production of a novel antifungal compound, 7, 3'-di-(c,cdimethylallyloxy)-5-hydroxy-40-methoxyflavone from the broth culture of endophytic actinomycete *Streptomyces sp.* MA-12 identified from the root of the *Myoporum bontioides* A. Gray, an associated mangrove and it inhibits the growth of plant pathogens *Penicillium citrinum, Gibberella zeae* (Schweinitz) Petch and *Colletotrichum musae* [32]. Table 1 represents the list of bioactive compounds reported from some endophytic actinomycetes.

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Table 1. Bioactive compounds from endophytic actinomycetes

Endophytic Actinomycetes	Host	Bioactive compounds	Bioactivity	Reference
Streptomyces sp. YIM64018	*Paraboea sinensis*	Vinaceuline	Antibacterial activity	[33]
Streptomyces sp. neau-D50	*Glycine max*	3-acetonylidene-7-prenylindolin-2-one, 7-isoprenylindole-3-carboxylic acid	Cytotoxic and antifungal activities	[29]
Streptomyces sp. YIM56209	*Drymaria cordata*	Bafilomycin D, B1, B2, C1, C2, C1 amide and C2 amide	Antibacterial, antifungal, insecticidal, antihelmintic and cytotoxic activity	[34, 35]
Streptomyces diastaticus subsp. *ardesiacus*	*Artemisia annua*	Diastaphenazine	Antibacterial and antifungal activity	[36, 37]
Streptomyces sp. YIM67086	*Dysophylla stellata*	4-hydroxy-3-methoxybenzoic acid, p-hydroxytruxinic acid	Antifungal activity	[31, 38]
Microbispora sp. LGMB259	*Vochysia divergens*	1-vinyl-b-carboline-3-carboxylic acid	Antibacterial, antifungal and anticancer activity	[39]
Streptomyces sp. YIM66017	*Alpinia oxyphylla*	Yangjinhualine A and 2,6-dimethoxy terephthalic acid	Radical scavenging activity	[40]
Streptomyces sp. YIM65408	*Tripterygium wilfordii*	1”-O-methyl-8-hydroxymethyl-daidzein	Radical scavenging activity	[33, 38]
Streptomyces albidoflavus	*Bruguiera gymnorrhiza*	Antimycin A18	Antifungal activity	[41, 42]

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3.2 Archaea

3.2.1 Antioxidant activity

Finding list about carotenoids reported from extremophile microorganisms are limited in comparison to knowledge existing about carotenoids from non-extremophile microorganisms. Halophilic archaea are a promising candidate for generating carotenoids, thereby show red and orange coloured colonies. A universal purpose of carotenoids their antioxidant activity leading to the protection of cells against oxidative stress, thus benefiting human health. Most haloarchaea biosynthesized bacterioruberin (BR), a C50 carotenoid, and its precursors bis-anhydrobacterioruberin (BABR), 2-isopentenyl-3,4-dehydrorhodopin (IDR), and mono-anhydrobacterioruberin (MABR) represented in Table 2 [43]. Bacterioruberin (BR) present in the cell membrane assist haloarchaeal cells to acclimatize to hypersaline environments, resulting in stabilization of the cell membrane under such stress. BR acts as a ''rivet'' and affects membrane fluidity by imitating as a water barricade and permitting

Table 2. Characterization of bacterioruberin, and its most abundant derivatives.

Common name	Molecular formulae	Scientific name	Producers	Mode of action	References
Bacterioruberin (BR)	$C_{50}H_{76}O_4$	2,2′ - bis (3- hydroxy- 3- methylbutyl)- 3,4,3′ ,4′ - tetradehydro- 1,2,1′ ,2′ - tetrahydro- γ,γ- carotene- 1,1′ - diol	*Haloarcula japonica*, *Halobacterium salinarum*, *Halorubrum sodomense* and *Haloarcula vallimortis* and *Halorubrum* sp. TBZ126	Protection against oxidative stress by arachidonic acid and H2O2	[43, 44]
Mono-anhydro-bacterioruberin (MABR)	$C_{50}H_{74}O_3$	30- (2- hydroxypropan- 2- yl)- 2,6,10,14,19,23,27,33- octamethyl3- (3- methylbut- 2- en- 1- yl) tetratriaconta4,6,8,10,12,14, 16,18,20,22,24,26,28- tridecaene- 2,33- diol	*Haloferax volcanii*	Scavenging activity	[44]; [43]
Bis-anhydro-bacterioruberin (BABR)	$C_{50}H_{72}O_2$	2,6,10,14,19,23,27,31- octamethyl3,30- bis (3- methylbut- 2- en- 1- yl) dotriaconta4,6,8,10,12,14, 16,18,20,22,24,26,28- tridecaene- 2,31- diol	*Haloferax volcanii*	Scavenging activity	[44]

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permeability to oxygen and other molecules [45]. In BR 13 pairs of conjugated double bonds are present as compared to the nine pairs of conjugated double bonds present in β-carotene. This transformation makes BR a better ROS scavenger as compared to β -carotene [46]. This offers resistant to gamma irradiation, intense light, and DNA damage caused due to UV irradiation, radiography, and H_2O_2 exposure [47]. Carotenoids from *Halorubrum* sp. BS2 reported having extraordinary antioxidant capacity than that of the ascorbic acid, a standard antioxidant [48]. The antioxidant capabilities of carotenoids produced by *Haloterrigena turkmenica, Haloferax volcanii, Halococcus morrhuae, Halogranum rubrum,* and *Halobacterium salinarum* were significantly higher than the standards β-carotene [43].

3.2.2 Antimicrobial activity of Archaea

The use of antibiotics in the last few decades leads to the rise of multi-drug resistant bacteria (MDR), which reduces and nullifies the effect of antibiotics. So, there is a vital requirement to discover novel and effective antimicrobial therapies by exploiting all possible natural and sustainable resources, including extreme environments. Archaeocins are protein antibiotics produced from archaea, and it marks the chronicled beginning in the series of antimicrobial compounds. The term "archaeocin" was used to differentiate the peptide and protein based antibiotics generated from Archaea than those produced by Bacteria [49]. Till date archaeocins (Table 3) have been produced by only two phylogenetic groups, one is euryarchaeal, that are extreme halophiles (haloarchaea) producing "halocins" whereas the other group producing "sulfolobicin" is crenarchaeal genus Sulfolobus that are aerobic hyperthermophile [50]. Valera *et al* in 1982 reported the first proteinaceous antimicrobial compounds i.e., halocins, from halophilic members of the Archaeal domain [51]. Peptide antibiotics are generally synthesized in two distinguished ways, one is ribosomally using transcripts (gene-encoded) and other is stepwise synthesis hiring either multienzyme complexes or sequential enzyme reactions. H1 and H4 are protein halocins of roughly 30-40 kDa [52], whereas C8, H6, H7, R1, U1 and S8 and are microhalocins of size smaller than 10kDa. Microhalocins are more vigorous than protein halocins since they are resistant to flexibility in temperature, salinity, exposure to organic solvents, acids and bases [52]. Halocins have a wide ranging of activity against Haloarchaea and members of family Halobacteriaceae [53] . Mostly halocin production is prompted during the progression between exponential and stationary phases, with H1 being an exception, which is produced during the exponential phase of the growth cycle [54]. Many workers reported the mode of action of halocins that they alter the cell permiability at membrane level and inhibit Na^+/H^+ antiporter and proton flux ultimately causing cell lysis and death [55]. Still till today only the mechanism of halocin H6/H7, produced by *Haloferax gibbonsii* Ma2.39 was explored. H6/H7 halocin kills delicate cells by inhibiting Na^+/H^+ antiporter resulting in cell lysis [53]. In 2020, Sahil *et al* screened 81 halophilic strains collected from solar salterns of the northern coast of Algeria for the production of antimicrobial compounds. Through partial 16S rRNA sequencing, these strains were recognized to belong to *Haloferax* (*Hfx*) sp. [48].

Table 3. Archaeocins reported from halobacteria.

Halocin	Producers	Size (kDa)	Origin	Active against	Mode of action	Reference
HalH1	*Hfx. mediterranei* Xia3	31	Solar salterns, Alicante, Spain	Members of the Halobacteriales	Alter membrane permeability	[13]
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	[56]

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HalH 6	*Hfx. gibbonsii* Ma2.39	32	Solar salterns, Alicante, Spain	Members of the Halobacteriales	Alter intracellular osmotic balance, Na + /H+ antiport inhibitor	[9]
HalS 8	Haloarchaeal strain S8a, *Halobacterium salinarum* strain ETD5	3.58	Great Salt Lake, UT	*Hbt. salinarum* NRC817, *Halobacterium* sp. strain GRB and *Hfx. gibbonsii*	ND	[57, 58]
HalC 8	*Natrinema* sp. AS7092	7.4	Chaidan Salt Lake in Qinghai province, China		ND	[1, 59]
HalR 1	*Hbt. salinarum* GN101	3.8	Guerrero Negro, Mexico	Members of the Halobacteriales, Strains of *Sulfolobus* sp., *Methanosarcina thermophile*	ND	[9, 60]
Sulfolobicins	*Sulfolobus Islandicus* HEN2/2	33.9 proprotein), 3.6 (mature)	Solfataric fields, Iceland	Strains of *Sulfolobus* sp.	ND	[61]

3.3 Bacteria

3.3.1 Antioxidant activities of bacteria

Carotenoids, a yellow-red precursor of vitamin A and fat-soluble pigment that is associated with plants, animals, and microorganisms. They represent a valuable group of molecules associated with chemical, pharmaceutical, food, and feed industries for their coloring and antioxidant activities. Ingestion of carotenoids might decrease the threat of diseases linked with oxidative stress. The carotenoids are proficient scavenger of ROS, RNS, singlet oxygen species ($^1O_2$), and non-biological radicals [62] . In the case of bacteria, carotenoids are produced by the extremophiles, including *Thermus filiformis, Halococcus morrhuae,* and *Halobacterium salinarium.* Halophilic microorganisms produce carotenoids viz. bacterioruberin, trisanhydrobacterioruberin, bisanhydrobacterioruberin, and their derivatives, whereas thermophilic bacterium produces all-*trans*-zeaxanthin, zeaxanthin monoglucoside, thermobiszeaxanthins, and thermozeaxanthins [63].

The biosynthesis of carotenoids is characteristic of the genus *Rhodotorula [64].* Correa *et al* (2012) analyzed that when Antarctica bacteria belonging to the *Pedobacter* genus were exposed to cold temperatures and high UV radiation, they had developed an important antioxidant system and produce variety of pigments that belongs to the carotenoids group and are capable of preventing oxidative damage. The antioxidant capacity of a mix of pigments viz. yelcho2, β-Carotene, and α-Tocopherol, was analysed by three different meth-

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ods viz. 1,1-diphenyl-2-picrylhydrazyl, ROS detection, and oxygen electrode [65]. In December 1988, the Marine Biotechnology Institute Co., Ltd. (MBI, Kamaishi, Japan) was established and began the isolation of novel or rare marine bacteria, many among them have been revealed to yield dicyclic or monocyclic C40 carotenoids, along with several acyclic C30 carotenoids [66]. MBI reported that *Paracoccus* sp. strain N81106 [67], *Brevundimonas* sp. strain SD212 [68] and *Flavobacterium* sp. PC-6 [69] produce astaxanthin glucoside, 2-hydroxyastaxanthin and 4-ketonostoxanthin 3'-sulfate, respectively. These are novel dicyclic C40 carotenoids with β-carotene (β, β-carotene) skeleton. The carotenoid biosynthesis gene cluster that is responsible for the manufacturing of astaxanthin was reported from the marine bacterium *Agrobacterium aurantiacum [70].* This carotenoid gene cluster consists of five carotenogenic genes viz. crtB, crtW, crtZ, crtY and crtI with the same orientation. Mishra *et al* (2013) investigated the capabilities of a semiquinone glucoside derivative (SQGD) reported from a *Bacillus* sp. INM-1 toward SOD, Catalase, GSH, GST antioxidant enzymes. There were a significant increase in SOD (35%) activity and GST level (0.46 ± 0.03 μmol/min/mg of protein) in the kidney of mice after SQGD treatment as compared to untreated control mice within 12–72 h [71]. Sy *et al* in 2015 demonstrated that (gastrointestinal) GI tract sometimes undergoes considerable oxidative stress in postprandial circumstances when dietary iron is exceedingly existing in food in the form both as heme or free form [72]. Excessive iron accumulation results in lipid peroxidation, specifically in acidic conditions. Sy *et al* (2015) isolated *Bacillus indicus* HU36, producing carotenoids from human fecal and assessed the stability (sensitivity to iron-induced autoxidation) and antioxidant activity (inhibition of iron-induced lipid peroxidation) [72]. The most notable initiators in lipid oxidation are ROS, especially HO· The common mechanism of heme-induced lipid peroxidation include the lipid hydroperoxide (LOOH) cleavage by hemeFeIII forming hemeFeIV and causing oxidization of linoleic acid (LH) in the medium.

3.3.2 Antimicrobial compounds from bacterial strains

Bacterial antimicrobial compounds have been used traditionally for numerous reasons, which include delaying the spoilage of food material or crops by plant pathogens in agriculture and extending the shelf life of products in the food industry [73]. *Bacillus* strains are well acknowledged to produce extensive biocontrol metabolites, which include the ribosomally synthesized antimicrobial peptides (bacteriocins) [74], as well as non-ribosomally synthesized peptides (NRPs) and polyketides (PKs) [75].

3.3.2.1 Bacteriocins and bacteriocin-like inhibitory substances (BLIS):

Bacteriocins are antimicrobial ribosomal peptides reported from all major lineages of bacteria and also from some members of Archaea. Gram- bacteria *Escherichia coli* produces colicins that is bacteriocidal protein, larger than 20 kDa, and prevent the growth of closely related strains [76]. Bacteriocins have attracted more attention because of their impending use both as a usual food preservative and as therapeutic antibiotics. 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. The recently reported bacteriocins along with their characteristics are presented in Table 4. LAB bacteriocins have gained significant attention due to its food-grade quality and industrial significance of these bacteria. 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 [77]. Lozo *et al* (2004) isolated the strain *LactoBacillus paracasei* subsp. *paracasei* BGBUK2-16, from customarily homemade white-pickled cheese, and reported that this species produced bacteriocin 217 (Bac217) having molecular weight of approximately 7 kDa. Bac217 displayed antimicrobial activity against a few pathogenic bacteria, including *Pseudomonas aeruginosa* ATCC27853, *Bacillus cereus, Salmonella sp.,* and *Staphylococcus aureus* [78].

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Table 4. 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	*L. lactis*	Membrane permeabilization forming pore	[79]
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	*P. pentosaceus, P. Acidilactici* and *LactoBacillus sakei*	Membrane permeabilization forming pore	[56]
	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 subsp. cremoris, Lb. plantarum*	Membrane permeabilization forming pore	[80]
	IIc N- and C- termini are covalently linked, generating a circular bacteriocin	Lactocyclicin Q, Leucocyclicin Q	*L. gasseri, E. faecalis, L. garvieae*	Membrane permeabilization forming pore	[56, 81]
	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 subsp. Lactis*	ND	[82]
Bacteriocin type III	Large peptides, sensitive to heat	Helveticin M, helveticin J and enterolysin A	*Lb. crispatus, L. helveticus, E. faecalis*	ND	[61]

Nisin is the first antimicrobial peptide that has been regarded as GRAS status from both FDA and WHO. 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. Nisin antimicrobial activity 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 [83]. The antibacterial constancy of nisin was successfully enhanced after conjugating it with gellan. The gellan–nisin conjugate was able to tolerate broad range of pH and temperature and also its antibacterial duration n against *Staphylococcus epidermidis was* improved from 48 h to 144 h under alkaline environments and from

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96 h to 216 h under acidic environments. Therefore this conjugate can be an encouraging biomaterial for wound dressings and transplant coatings [84]. Heunis *et al* (2013) stated that the application of nisin-coated wound dressing prevented the bacterial colonization of *Staphylococcus aureus* and quickened the healing procedure [85].

3.3.2.2 Mode of action of Bacteriocins:

Bacteriocins in Gram-positive bacteria follow two possible mechanisms as shown in the Figure 4. 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). Bacteriocins cross the cell wall and bind with lipid II present in the cell membrane, thereby preventing the biosynthesis of peptidoglycan (a cell wall component) [86].

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. Several Class I bacteriocins, for example, nisin, can follow both mechanisms. Nisin generated pores in cell membrane result in the submissive efflux of ions (K^+ and Mg^{2+}), amino acids (glutamic acid, lysin), generating proton motive force dissipation, and ultimately cause cell death [87].

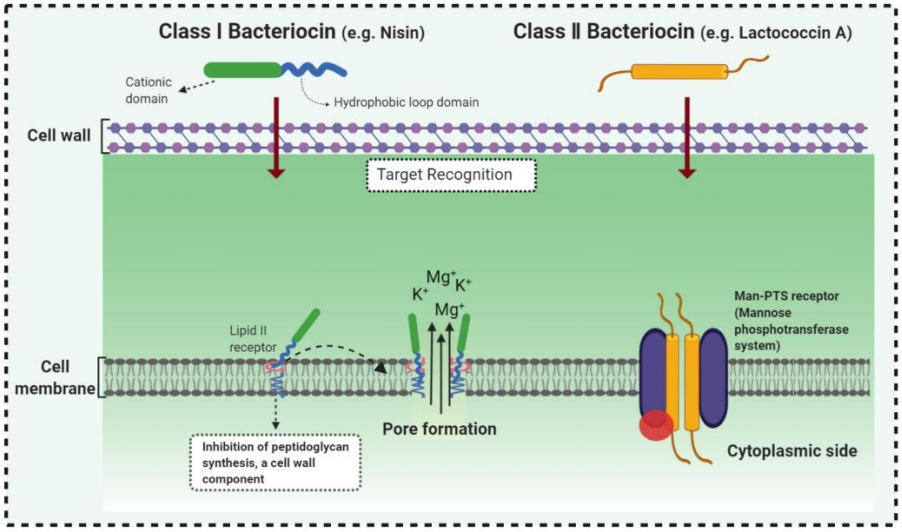

Figure 4. Mode of action of bacteriocins via dual mechanism (a) inhibition of cell wall synthesis and (b) pore formation. Adapted from: [87, 88].

3.3.3 **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 [89]. Lipopeptides (LPs), which bears significant antimicrobial activity is a NRPs produced by Bacillales [90].

3.3.4 *Lipopeptides (LPs):*

LPs occur naturally and are of bacterial origin, contain a hydrophobic long alkyl chain which associat with a hydrophilic polypeptide and form a cyclic or linear structure [91]. Traditional LPs including the iturins, surfactins and fengycins produced from *Bacillus* and are homologues which differ in length, branching pattern, and saturation of their acyl chain.

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3.3.5 *Surfactins:*

They comprise of a cyclic heptapeptide that formulate a lactone bridge with ß hydroxy fatty acids (92) and is the most potent biosurfactants. Surfactins are considered for their extraordinary foaming, emulsifying, anti-mycoplasma and antiviral activities (93); however, these peptides are not fungi toxic but they still exhibit some synergistic effects on the antifungal activity of iturin A. Iturin group comprises of A, C, D and E isoforms, bacillomycin D, F and L and mycosubtilin. Iturin A, mycosubtilin and bacillomycins also inhibit bacterial growth in the same manner as Class I and Class II bacteriocins, i.e. by pores formation in the cell membrane (94), whereas mycosubtilin modifies the plasma membrane permeability, thereby liberating nucleotides, proteins, and lipids from the cell (95). a marine-derived *Bacillus* velezensis 11-5 produced a cyclic lipopeptide (CLP) iturin A, which has been considered as an antagonist against Magnaporthe oryzae, a rice pathogen (96).

Fengycin consists of a ß-hydroxy fatty acid linked to the N-terminus of a decapeptide. Its isoforms fengycin A and fengycin B vary in a single amino acid at the sixth position (D-alanine and D-valine, respectively) (97). Both iturins and fengycins are used as a biocontrol to prevent plant diseases and inhibit the progression of an extensive variety of plant fungal pathogens (*Aspergillus* flavus, Rhizoctonia solani, *Fusarium* graminearum, Botritis cinerea and *Penicillium* expansum) (98). Kurstakins is a cyclic heptalipopeptides, whereas Cerexins are linear LPs, and both are isolated from B. thuringiensis and B. cereus strains, respectively (99). Cerexins is active against S. aureus and Streptococcus pneumoniae (100).

3.4 Fungi

Whenever there is a discussion about fungal metabolites, the story of penicillin has been told many times. Alexander Fleming, in 1929 discovered that mold juice' from *Penicillium notatum* had antibacterial action and named this biological activity 'Penicillin' [92]. A decade later, researchers instigated to look for a higher yielding strain that could be grown quickly in submerged culture. Later on, *Penicillium chrysogenum* was selected for large-scale production of *Penicillium* [93]. Revilla *et al* in 1986 reported the formation of the intermediate isopenicillin N in the course of penicillin G production in *P. chrysogenum* cultures [94] and the formation of isopenicillin N/penicillin N and its late transformation to cephalosporin C in *Acremonium chrysogenum* [95].

3.4.1 Antioxidant compounds produced by endophytic fungi

Endophytic fungi are those living internally healthy and asymptomatic hosts. De Bary, in 1866 introduced the term "Endophyte" [96]. Recently, many studies had guided the way towards the discovery of significant plant secondary metabolites from endophytic fungi, thereby educating the viewpoint of consuming endophytic fungi as substitute of such metabolites. From 1987 to 2000, around 140 new natural products were extracted from endophytic fungi [97]. 5% fungal species had been characterized to produce bioactive metabolites [98].

A wide range of natural products including antioxidants, anti-cancerous, anti-viral, antiinsecticidal, immunosuppressant, anti-mycobacterial, anti-microbial and anti-malarial, has been considered from endophytic fungi [99]. The discovery of antioxidant compounds from *Pestalotiopsis microspore,* an endophytic fungus which was isolated from *Terminalia morobensis*, has directed the way towards the exploration for endophytic fungi with such potential [100]. Zeng *et al.* (2011) explored 49 endophytic fungi, which were isolated from the liverwort *Scapania verrucosa* for in-vitro antioxidant activities. These isolates of endophytic fungi have its place in one family, Xylariaceae and seven genera including

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Penicillium, Hypocrea, Tolypocladium, Chaetomium, Nemania, Xylaria, and Creosphaeria. Among them, endophytic fungi from *S. verrucosa* were reported as a budding and novel source of natural antioxidants [101]. Pestacin and Isopestacin were isolated from *Pestalotiopsis microspora* from plant *Terminalia morobensis*, a native of the Papua New Guinea [102]. Prihantini *et al.* (2017) isolated seven fungal strains of the genus *Pestalotiopsis* from the leaves and stems of *Elaeocarpus sylvestris*. *Pestalotiopsis sp*. EST 02 and *Pseudocercospora sp*. ESL 02 were reported to have antioxidant activity. The team isolated terreic acid and 6-methylsalicylic acid from *Pseudocercospora sp. ESL 02* [103]. Nuraini *et al.* in 2019 isolated *Aspergillus minisclerotigens* AKF1 and *Aspergillus* oryzae from an endemic plant from South Kalimantan named *Mangifera casturi* Kosterm. AKF1 and DK7 exhibited antioxidant ability with an IC50 of 142.96µg/mL and 145.01µg/mL respectively. GC-MS analysis confirmed that the most dynamic compound isolated from AKF1 and DK7 was dihydropyran and 4H-Pyran-4-one,5-hydroxy-2-(hydroxymethyl-(CAS) Kojic acid, respectively [104]. *Fusarium oxysporum* was isolated by Caicedo *et al.* (2019) from the leaves of *Otoba gracilipes* which is a medicinal tree found in a tropical rainforest of Colombia [105]. Jaszek *et al.* (2013) extracted three bioactive portions viz. crude endopolysaccharides (c-EPL), a low molecular subfraction of secondary metabolites (ex-LMS) and extracellular laccase (ex-LAC) exhibiting scavenging abilities, from the idiophasic cultures of *Cerrena unicolor,* a white rot fungus. These fractions have antibacterial activity against *S. aureus* and *E. coli* [106]. Methanol extracts from *M. purpureus*, OYRM1, *P*. 32783, *P. salmoneo-stramineus* and *T. versicolor* inhibit linoleic acid oxidation by at least 53% [107]. Total 42 fungal endophyte strains related to a medicinal plant, *Nerium oleander L.* (Apocynaceae) were isolated and screened for antioxidant and antimicrobial capacity. Out of these 42 isolated only *Chaetomium sp.* inhibit xanthine oxidase activity with an IC50 of 109.8 lg/mL, had antioxidant activity with highest level of phenolics [108].

3.4.2 Antioxidants from mushrooms

Many fungal species are edible, which include mushrooms that are both cultivated and harvested wild. Now a day's cultivated mushrooms are more common and readily available in the market as compared to wild mushrooms. Porcini (*Boletus edulis*) is cultivated on a small scale and is one of the most common palatable mycorrhizal mushrooms in China also called "white bolete" in Yunnan [109]. Edible mushrooms are a substantial source of vitamins (B_1, B_2, B_{12}, C, D and E), PUFA, etc. Mushrooms are used as a vital source of home remedies against several ailments stimulated by oxidative stress in Asia [110] . The investigation of the methanolic extract of *Cantharellus cibarius* by Kozarski *et al.* (2015) exhibited that the major antioxidant components were phenols followed by flavonoids. Polysaccharides ((1→6)-β-d-glucans) obtained from *Aspergillus brasiliensis* after pronase deproteinization had maximum antioxidant activity against $^{\bullet}OH$ and $^{\bullet}O_2^-$ radicals [111]. β-glycan is a major contributor of the antioxidant effects of mushroom, which can be directly taken up by M cells of Peyer's patches or dendritic cells activating systemic response in organisms [112] and [113]. Chen *et al*. (2012) reported the presence of ergothioneine (ET) from the fruiting bodies of palatable species, *P. ostreatus*, *P. citrinopileatus*, *P. salmoneostramineus* and *P. ostreatus* ET play a part in guarding mitochondrial apparatuses from oxidative damage caused by the mitochondrial generation of $^{\bullet}O_2^-$ [114].

3.4.3 Antimicrobial activity of Endophytes

Huang *et al.* (2008) discovered ten membered lactones from endophytic fungus *Phomopsis sp*. YM 311483, which displays antifungal activity against *Aspergillus niger*, *Fusarium*, and *Botrytis cinere* [115]. Endophytic *Fusarium sp.* isolated from *Selaginella pollescens* collected from the Guanacaste conservation area of Costa Rica displays potent inhibitory activity against *Candida albicans* [116]. Ample of antimicrobial compounds were reported from the endophytic fungi, some of which are listed in Table 5.

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Table 5. Antimicrobial compounds extracted from endophytic fungi.

Compound	Producer	Active against	Host	Reference
e 1, 4-naphthoquinone derivatives	*Talaromyces sp. SK-S009*	*Pseudomonas sp.*	*Kandelia obovata*	**[117]**
Clavatol	*Aspergillus clavatonanicus, Aspergillus elegans KUFA0015*	*Botrytis cinerea, Didymella bryoniae, Fusarium oxysporum f. sp. cucumerinum, Rhizoctonia solani,* and *Pythium ultimum*	*Taxus mairei, Monanchora unguiculate* (Marine sponge)	**[118, 119]**
Lactones	*Phomopsis sp.* YM 311483	*A. niger, Botrytis cinere,* and *Fusarium*	*Azadirachta indica*	**[120, 121]**
Jesterone	*Pestalotiopsis jesteri*	*Pythium ultimum, Phytophthora citrophthora, Rhizoctonia solani and Sclerotinia sclerotiorum*	*Fragraea bodenii*	**[122]**
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*	**[123, 124]**

3.4.4 Antimicrobial activity of marine-derived fungi:

Meng *et al.* in 2015 discovered Pyranonigrin F from fungus *Penicillium brocae* MA-231 allied with the *Avicennia marina,* a marine mangrove plant and have inhibitory action against *S. aureus* (Gram^{+}) and *Vibrio harveyi* and *Vibrio parahemolyticus* (Gram^{-} bacteria), with considerably lower MIC values as compared to the positive control (chloromycetin). It is likewise active against plant fungal pathogens *Alternaria brassicae* and *Colletotrichum gloeosprioides*, with improved MIC values as compared to the positive control (bleomycin) [125]. Wu *et al.* (2015) discovered Lindgomycin from *Lindgomyces* strains LF327 and KF970, reported from a sponge in the Baltic Sea, Germany, and the Antarctic, respectively. Lindgomycin displayed antimicrobial activity against *S. aureus, Staphylococcus 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* [126]. There is a never-ending list of antimicrobial compounds from marine associated fungi; few of them are listed in Table 6, mentioning their host, producer species and bioactivity.

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Table 6. Antimicrobial compounds extracted from marine fungi.

Compounds	Producer	Active against	Environment source	Reference
Penicisteroid A	*Penicillium chrysogenum* QEN-24S	*A. niger* and *Alternaria brassicae*	Marine algae-associated *Penicillium sp.*	[127, 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*	[123].
Comazaphilones C–E	*P. commune* QSD-17	*antibacterial*	*Penicillium* sp. from marine sediments	[131, 132]
Penicibilaenes A	*P. bilaiae* MA-267	*Colletotrichum gloeosporioides*	Rhizospheric soil of *Lumnitzera racemosa*	[133]
Xylarinonericin D and E	*Penicillium sp.* H1	*Fusarium oxysporum f. sp. cubense*, *F. oxysporum f. sp. cubense* (antifungal)	Beibu Gulf nearby Guangxi	[134]
Terretonin G	*Aspergillus sp. OPMF00272*	*S. aureus* FDA209P, *Bacillus subtillis* PCI219 *and Micrococus luteus* (ATCC9341)	Ishigaki island	[135]
Schevalone E	*A. similanensis sp. nov.*	MRSA	Sponge *Rhabdermia sp.* from the coral reef of the Similan Island	[136]
Asperitaconic acids A–C	*A. niger* LS11	*S. aureus*	Sponges-associated *Aspergillus* sp.	[137]
Ochramide B and ochralate A	*A. ochraceus* LCJ11-102	*Enterobacter aerogenes*	Marine sponge *Dichotella gemmacea*	[84]
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.*	*S. aureus*, *S. epidermidis*, *B. subtilis*, *B. dysenteriae*, *B.*	Mangrove *Avicennia marina* in Guangdong.	[139, 140]

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	FSW-02	*proteus* and *E. coli,*		
Asperamide and nigerasperone C	*A. niger* EN-13	*C. albicans*	Marine algae associated *Aspergillus* sp.	[141, 142]
Flavusides A and B	*A. flavus*	*S. aureus* and MRSA	Marine algae associated *Aspergillus* sp.	[143, 144]
Isorhodoptilometrin-1-methyl ether	*A. versicolor*	*B. subtilis, B. cereus* and *S. aureus*	Marine algae associated *Aspergillus* sp.	[145, 146]
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.	[147]
Speradine A	*A. tamarii* M143	*Mycrococcus luteus*	driftwood in Okinawa	[148]
Versiperol A	*A. versicolor* MCCC 3A00080	*S. aureus*	seawater-associated *Aspergillus sp.*	[149]
Ergosterdiacids A and B	*Aspergillus sp.*	*M. tuberculosis*	Marine sediments associated *Aspergillus sp.*	[150]
Heptapeptide RHM1	*Acremonium sp.* HM1	*S. epidermidis*	Marine sponges-associated fungi	
Trichoderins A	*Trichoderma sp.* 05FI48	*M. smegmatis*	Marine sponges-associated fungi	[151, 152]
Botryorhodines I and J	*Setosphaeria sp.* SCSIO 41009	*Colletotrichum asianum*	Marine sponge *Callyspongia sp.*	[153]

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. Peniciadametizine A and Peniciadametizine B both inhibits *Alternaria brassicae* (pathogenic fungus) with an MIC value of 4.0 lg/mL and 32.0 lg/mL (Liu *et al*. 2015a respectively [154]. Communol A, communol G, and communol F extracted from *P. commune* 518 displayed antibacterial activities against *E. coli* with MIC values of 4.1, 6.4 and 23.8 lM, respectively and also against *E. aerogenes* [134]. 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 both MRSA (methicillin-resistant *Staphylococcus aureus*) and *E. coli* having MIC values of 2.0–19.0 lg/mL [155]. Song *et al*. (2018), following the previous lead, separated penicipyrrodiether A from a cultured marine fungal strain *Penicillium sp*. ZZ380, which inhibits *E. coli* and *S. aureus* with MIC values of 34.0 and 5.0 lg/mL, respectively [156].

3.5 Microalgae

More than 28,000 potential compounds are reported from microalgae, including hundreds of new compounds discovered every year [157]. Most of them have been reported from *Chordata* (including ascidians) and *Porifera* (sponges), but they are hard to cultivate, and to attain a sustainable supply of the compounds of interest is problematic. In recent times,

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high interest is paid in analysing the biotechnological potential of microalgae as they have short generation time, easier to cultivate, and signify an eco-friendly approach but a less explored resource for drug discovery. Microalgae are photosynthetic eukaryotes comprising one of the key members of freshwater and marine phytoplankton and are exceptional cradles of pigments, carotenoids, ω-3 fatty acids, lipids and other fine chemicals [158]. More than 7000 species are enlisted as "Green microalgae" and they all grow in a diversity of habitats. Among the, *Haematococcus pluvialis* is most important microalgae commercially and is also the richest source of natural astaxanthin which is regarded as "super anti-oxidant." [159].

3.5.1 Antioxidants from microalgae:

L-Ascorbic acid (vitamin C), present both in cytosol and chloroplast, reduce many ROS and act as a scavenger for hydroxyl radicals, superoxide, and lipid hydroperoxides. Maximum concentration of vitamin C was reported from *Chlorella* sp. [160] and *Dunaliella* sp. [161], *Skeletonema costatum* and *Chaetoceros calcitrans*. Glutathione (GSH), a tripeptide (Glu-Cys-Gly), acts as a sequence breaker of ROS reactions and regeneration of ascorbate. α-tocopherol is the most active antioxidant synthesized in the chloroplasts of microalgae *Dunaliella tertiolecta* and *Tetraselmis suecica*. The lipophilic carotenoids, synthesized in diatoms and dinoflagellates (Figure 5) allow quenching of singlet oxygen [162], leading to the formation of a carotenoid triplet state (equation 1).

$$^1O_2{}^* + CAR \longrightarrow {}^3O_2 + {}^3CAR^* \qquad (1)$$

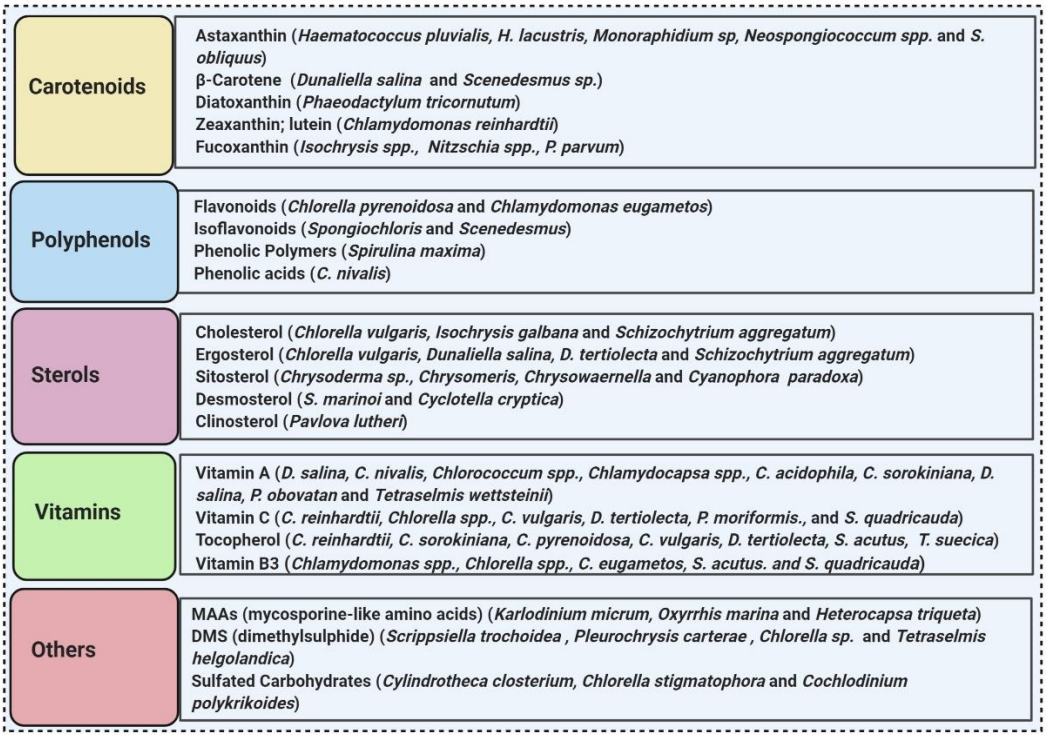

Figure 5. Some antioxidant compounds reported from microalgae.

Lutein is a xanthophyll and can defend long-chain polyunsaturated fatty acids. A microalgae *Muriellopsis* sp. accumulate high levels of lutein, whereas, in *Scenedesmus*, lutein production and β-carotene production is accelerated by increasing both the pH and temperature throughout the cultivation [163]. The commercial source of lutein is Chlorophyte *Muriellopsis sp*. The secondary carotenoid astaxanthin, an "aquatic" carotenoid, is produced by *Haematococcus pluvialis* via non-mevalonate (MEP) pathway, and sold as an antioxidant. It is a secondary metabolite belonging to family lutein, and is present in many

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seafood including trout, salmon, shrimp, fish eggs and lobster, etc. Its antioxidant activity is 65 times stronger than vitamin C and 54 times more powerful than β-carotene. An annual worldwide market of astaxanthin is estimated to be US$ 200 million. Approximately 95% astaxanthin is synthetically synthesized, whereas only 1.5-3.0% is naturally derived from *H. pluvialis* [164].

Recently, AIgatechnologies, Mera Pharmaceuticals Inc, Cyanotech Corporation, Fuji Chemical Industry Co. Ltd etc. are involved in commercial production of *H. pluvialis* and astaxanthin, which is approved in several European countries, USA, and Japan as a color additive and as a dietry-supplement for human consumption [165]. The UK Food standards Agency (FSA) approved CO_2 extracts from *H. pluvialis* as a "novel food" and US FDA (Food and Drug Administration) approved it as a "GRAS" (Generally Recognised as Safe) for human consumption [164]. The European Food Safety Authority (EFSA) recommended the use of 0.034 mg/kg of body weight of astaxanthin. Spiller and Dewell (2003) reported that 2-4 mg of a daily dose of astaxanthin is safe whereas not toxicity was repoted upto 6mg/day consumption [166]. β-carotene, isolated from the halophile *Dunaliella salina*, is commercially produced for its antioxidant properties. Marennine is isolated from the marine diatom *Haslea ostrearia* also have antioxidant and antimicrobial activities [167]. Apart from diatoms, additional microalgae, including flagellates, dinoflagellates and green algae have also been scrutinized for potential biotechnological applications [168]. Carotenoid fucoxanthin reported from brown seaweeds and some diatom species also have antioxidant, antidiabetic, antiangiogenic, anti-inflammatory, anticancer, and antimalarial activities. Methanolic extract of microlgae, *Spirulina maxima* exhibit antioxidant properties with the IC_{50} of 0.18 mg/ml [169]. The methanol extract from *Chlorococcum minutum* NIOF17/002, isolated from the Delta region of Egypt, revealed the maximum reducing activity and total antioxidant activity of 3.92 and 9.83 mg of ascorbic acid equivalents g^{-1}, respectively [170].

3.5.2 Antimicrobial activity of microalgae:

The antimicrobial activity of microalgae is due to the presence of phytochemicals (table 8), including indoles, acetogenins, terpenes, fatty acids, phenols, and volatile halogenated hydrocarbons in them (Table 7) [171] . The antimicrobial activity of *Chaetoceros muelleri* extracts is due to its lipid configuration, whereas the antimicrobial activity of *Dunaliella salina* is attributed to the presence of β-cyclocitral, α and β-ionone, phytol and neophytadiene [172]. In natural environmental conditions microalgal cells releases fatty acids against predators and pathogenic bacteria. It is elucidated that these fatty acids act on bacterial cellular membrane causing a cell seepage, a decline in nutrient intake and a reduces cellular respiration, ultimately resulting in cell death [173].

Table 7. Selected antimicrobial extracts from microalgae.

Microalga	Target microorganism	Active extract	References
Scenedesmus quadricauda	*Staphylococcus aureus* and *Pseudomonas aeruginosa*	Methanolic extract	[174]
Tetraselmis sp.	*Escherichia coli, Pseudomonas aeruginosa* and *Staphylococcus aureus*	Ethanolic extract	[175]
Phaeodactylum tricornutum	*Listonella anguillarum, Lactococcus garvieae,Vibrio* spp. and MRSA	Eicosapentaenoic acid	[173, 176]

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C. vulgaris	*Steinernema feltiae*	Hydrophilic extracts	[177]
Skeletonema costatum	*Listeria monocytogenes*	Extra-metabolites	
Skeletonema costatum	*Vibrio* spp., *Pseudomonas* sp. and *Listeria monocytogenes*	Unsaturated, saturated long chain fatty acids	[178]
Haematococcus pluvialis	*Escherichia coli, Staphylococcus aureus, Candida albicans*	Short-chain fatty acids (butanoic acid and methyl lactate), Astaxanthin	[178]
Amphidinium sp.	*A. niger*, *Trichomonas foetus*	Karatungiols	[179]
Chlamydomonas reinhardtii	*Aspergillus niger, Aspergillus fumigatus, Candida albicans, S. aureus and E. coli*	Methanolic extracts	[180]

Chlorellin, the first antibacterial compound from a microalga, *Chlorella* is composed of a mixture of fatty acid and it was isolated by Pratt *et al.* in 1994 and also inhibit the activity of both $Gram^+$ and $Gram^-$ bacteria [181]. *Arthrospira platensis*, commercially known as *Spirulina* had MIC values 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 the species [182]. HPTLC screening and GC–MS analyses is done to detect and screen the antimicrobial compounds present in macroalgae. 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) upto 75% after 24 h of treatment. AQ-1766 was more active against $Gram^+$ than $Gram^-$ bacteria, with MBC values between 40 and 50 μM [183].

3.6 Yeast

Yeasts are mostly occurred in milk, processed milk, raw materials, meat, and food products such as fruit yogurt, sausage and cheeses. Yeasts usually produce antimicrobial compounds that inhibit growth of harmful bacteria or mold. Some classes of yeasts secrete toxins thereby naming them killer yeasts. Killer yeasts naturally occur in rotten vegetables and fruits and constrain growth of other yeast strains and also inhibit microbial growth [184]. *Saccharomyces cerevisiae* (Baker's yeast), unicellular yeast, is most widely studied microorganisms that are involved in many biotechnological practices because of its good fermentation capacity [185]. Inhibitory mechanism of *S. cerevisiae* killer strains were discovered in 1963 by Bevan and his team and the phenomenon is related with the secretion of a protein toxin, k1 and k28 from host that kills sensitive target pathogenic cells in a receptor-mediated approach without direct cell-to-cell contact [186]. Other strains producing killer toxins include *Cryptococcus*, *Candida*, *Kluyveromyces*, *Williopsis*, *Pichia*, *Debaromyces*, and *Zygosaccharomyces* [187]. Anti-bacterial capability of S. cerevisiae is attributed to:

a) Secretion of inhibitory proteins

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b) Production of extracellular protease

c) Stimulation of immunoglobulin A

d) Procurement and eradication of secreted toxins

e) Killer toxins, sulfur dioxide etc.

Sequential repitching of *Saccharomyces* biomass is a common process during brewing. Therefore, yeast is reused many times before its final dumping [188]. Hence yeast develops an adaptive response against oxidative stress alike to that of human cells, leading to the accumulation of vitamins (B6 and B12) and minerals (enzyme co-factors including zinc, manganese, and copper) in yeast cell. Phenolic compounds are also adsorbed by *Saccharomyces* from the exterior medium, which increases the phenolic content and antioxidant activity within yeast cells [189]. Efficient means are required of disrupting yeast cell walls and separating the products of interest which are further used for food applications.

The antioxidant property of yeast is due to the high content of polysaccharides, β-D-glucans, and α-D-mannans existing in the yeast cell wall. These two cell wall polysaccharides were isolated from the industrial yeast strains, *Saccharomyces cerevisiae,* and *Candida utilis.* β-D-glucans and α-D-mannans exhibited a protective effect of water-soluble carboxymethylated yeast (1→3)-β-D-glucan (CMG) alongside lipid peroxidation in phosphatidylcholine liposomes, which act as a cell membrane model. CMG is also cable of inhibiting peroxidation persuaded by ultraviolet radiation (UVA), which causes the production of singlet oxygen. The use of *Saccharomyces* β-glucans had already been approved by the European Food Safety Authority (EFSA). *Saccharomyces* β-glucans, denoted as "yeast beta-glucans," is used as a latest food ingredient [190].

Peroxiredoxins (Prxs) are discovered as an abundant proteins' family of antioxidant enzymes, expressed ubiquitously, and act as peroxidases which reduce H_2O_2 and alkyl hydroperoxides into water or alcohol, respectively. The Prx superfamily comprises of two subgroups, 1-Cys Prx and 2-Cys Prx, based on the occurrence of one or two preserved cysteine residues (Figure 6) [191]. Prx had first discovered in *Saccharomyces cerevisiae* as a protein that could prevent the reactivation of glutamine synthetase via thiol/Fe (III)/oxygen oxidation system. The genome of *S. cerevisiae* encompasses a sequence (ORF YBL064C), which codes for a protein corresponding to human 1-Cys Prx [192].

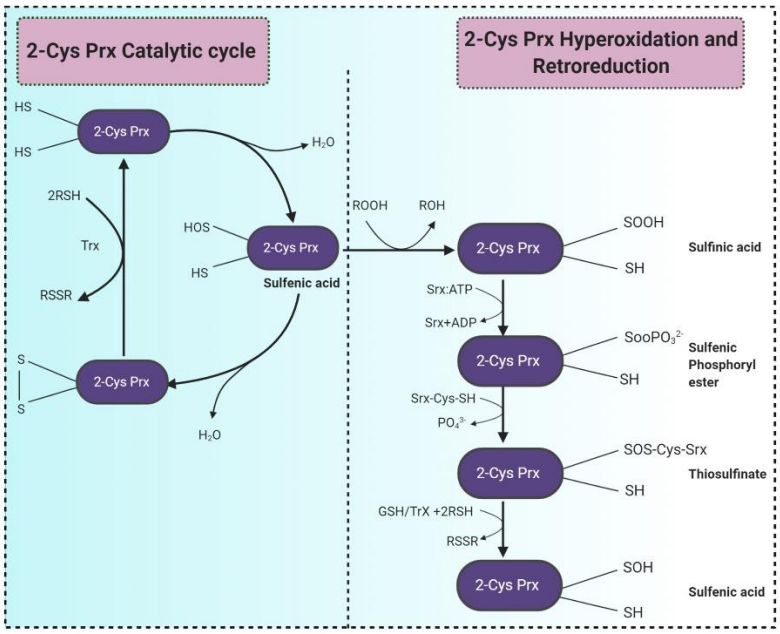

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Figure 6. Two-step catalytic mechanism of 2-Cys Prx. The sulfhydryl group at the 2-Cys Prxs is oxidized to sulfenic acid (–SOH) which condenses with the –SH group at the cysteine from the other subunit forming an inter-subunit disulfide bond. This bond if further reduced by thioredoxin (Trx) or another reductase. Continuous peroxide signalling lead tversible hyperoxidation and formation of sulfinic acid (–SOOH) at the peroxidatic cysteine. Sulfinic 2-Cys Prx is reduced by sulfiredoxin (Srx) with the consumption of an ATP and generates a sulfinic phosphoryl ester intermediate. Cys 99 present in Srx react with this intermediate to form thiosulfinate that can be attacked by RSH to generate sulfenic acid. (RSH signifies a thiol equivalent such as glutathione, dithiothreitol, or thioredoxin). Adapted from [193].

3.7 Protozoa

Protozoa are regarded as first and simplest organisms of the animal kingdom discovered by Anton van Leeuwenhoek using simple lens microscopes, he constructed. Most protozoan species are unicellular, free-living, motile and microscopic in size whereas some species are mutualistic and parasitic in nature. More than 10,000 protozoan species are described as parasitic [194]. Protozoan diseases are either very mild or life-threatening. *Toxoplasma gondii* is a very usual protozoan parasite which causes a slight preliminary illness which is followed by a long-lasting latent infection. *Entamoeba histolytica, Trypanosoma, Giardia, Leishmania, Trichomonads* and *Plasmodium* are usually anaerobic but sometimes found to be microaerobic or microaerophilic and produce H_20_2 as a product of metabolism. Some intracellular protozoans are manifest to the toxic oxygen metabolites produced by the host's effector immune cells. Protozoa lack or are deficient in antioxidant enzyme systems i.e. catalase, GSH and SOD, which are necessary for the detoxification of H_20_2. However, they have alternative detoxification mechanisms. Higher concentration of NADH dependent oxidase and lower concentration of NADH dependent peroxidase activities were perceived to accomplish this task. *Entamoeba histolytica, Trichomonas vaginalis* and *Tritrichomonas foetus* were reported to encompass NADH oxidase activity. Since protozoa are known to be parasitic, very few reports are available regarding their antimicrobial activity. Pant *et al.* in 1997 reported the production of photosensitive red pigment, blepharismin (BLR) from a ciliated protozoan *Blepharisma japonicum*. BLR prevents the growth of Gram positive methicillin resistant *Staphylococcus aureus* (MRSA) which is resistant to arbekacin (ABK) [195]. Another report is of climacostol (5-[(2Z)-non-2-en-1-yl] benzene-1, 3-diol) from Buonanno *et al.* (2020) which is a toxic secondary metabolite reported from ciliate *Climacostomum virens* and are used for defence against predators. Climacostol was analyzed to be cytotoxic against *Blepharisma japonicum*, *Dileptus margaritifer*, *Didinium nasutum*, *Spirostomum ambiguum*, *Euplotes aediculatus*, *Paramecium tetraurelia*, *Stentor coeruleus*, *Spirostomum teres* and *Stentor niger*. Alkyl and alkynyl derivatives of climacostol also inhibits the fungus *Candida albicans*, some Gram positive and Gram negative pathogen bacteria [196]. Yet a lot is remained to be explored about the protozoan.

4. Future prospectus

Bioactive pigments producing microorganisms are relatively common in nature. Hence research on antioxidants and antimicrobial agents is a real and major challenge of this century, predominantly due to cumulative resistance of microorganisms to synthetic antibiotics. Antimicrobial resistance to an extensive range of contagious agents is a severe global threat to public health and arose a major concern to various countries and multiple sectors. Microorganisms are presently considered as a significant source of therapeutic bioactive compounds that might lead to the advancement towards the novel drugs. Maximum bioactive compounds from microbial sources include phenolics and flavonoids that exhibit positive impact on health and wellbeing. Nowadays about 60% of drugs available in the market are from natural sources. Microorganisms produce nearly 23,000 known secondary metabolites including 42% entirely produced by actinomycetes and fungi, and approximately 16% is formed by eubacteria. Increased level of ROS, RNS, and RSS results in metabolic malfunctioning, aberrations in cellular proteins, RNA and DNA, lipids and ultimately cell death. Antioxidant, including catalase, glutathione peroxidase, SOD, carotenes, flavonoids, reduced glutathione, bilirubin, coenzyme Q, and vitamin C control the damage caused by ROS. MSH present in the cell wall of actinomycetes is an analogue of

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GSH that detoxify electrophiles, NO, arsenate, NaClO and H_2O_2 stress. Same as MSH, BR is manufactured by archaea, which is equivalent to carotenoids and offers resistant against gamma irradiation and DNA damage same as bacterial carotenoid. From 1987 to 2000, around 140 new natural products were mined from endophytic fungi and mushroom, which are utilized as a cure for various ailments caused due to oxidative stress. Ample of research were conducted to testify the antioxidant activity of various extracts from the microbes. The methanolic extract of *Cantharellus cibarius* had antioxidant components that are phenols and flavonoids. Astaxanthin produced by *H. pluvialis* is sold as an antioxidant and *H. pluvialis* is approved by FSA and US FDA as a "GRAS" (Generally Recognised as Safe) for human consumption. Likewise, yeast cell wall contains polysaccharides, β-D-glucans, and α-D-mannans which act as a cell membrane model.

Apart from antioxidant activity, microorganisms also have antimicrobial activities. The discovery of Penicillin by Alexander Fleming was the beginning of a marvellous trend of using microorganisms for the human welfare. Marine or terrestrial Actinobacteria utilize enzymes PKS or NRPS to synthesize bioactive compounds having antibacterial activity against a panel of $Gram^+$ and $Gram^-$ bacteria. Whereas, archaea produce archaeocins including halocins and sulfolobicins marking the beginning of the series of antimicrobial compounds. Bacteriocins are antimicrobial ribosomal peptides described from all major bacterial lineages. Bacteriocins from LAB are considered GRAS by FDA, preventing the biosynthesis of peptidoglycan by binding with lipid II. Colicins, a bacteriocidal protein, synthesized by $Gram^-$ bacteria *Escherichia coli*. Nisin is the first antimicrobial peptide and is also considered as GRAS by both FDA and WHO. Similarly, chlorellin is the first antibacterial compound isolated from a microalga, *Chlorella*, inhibiting the activity of both $Gram^+$ and $Gram^-$ bacteria. Overall, there are auspicious signs for antioxidant and antimicrobial compound discovery, but extensive research is required to interpret scientific progresses into clinically accepted components.

5. Conclusions

The present review highlights the potential of microorganisms to produces antioxidant and antimicrobial compounds and their importance as innovative sources of natural bioactive molecules. Microorganisms are easily cultivable and deliver quicker production of natural antioxidants as compared to higher plants and are non-mutagenic and non-cytotoxic over synthetic antioxidants. Microorganisms, due to its potential activity against several pathogenic microbial strains, can act as a potential source of many drugs to cure patients infected with pathogenic microbial strains. There is a vast diversity of microorganisms, but only a minor section of microbes has been cultured and examined for secondary metabolite production. A deeper inspection of known microbial bioactive compounds might lead to the development of new drugs. The factors significant for the discovery of novel compounds of the future are our capability to exploit nature's biodiversity.

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