SCIENCE LETTERS

ISSN: 1675-7785
eISSN: 2682-8626

Available online at
https://scilett-fsg.uitm.edu.my/

Science Letters 19(1) 2025, 60 – 74.

Science Letters

Microalgae as Antimicrobial and Antibiofilm Agents: A Review

Syaza Syasya Lakman[1], Nurul Aili Zakaria[1] and Mohd Taufiq Mat Jalil[1,2*]

[1]*Faculty of Applied Sciences, Universiti Teknologi MARA, 40450 Shah Alam, Selangor, Malaysia*
[2]*Molecular Microbial Pathogenicity Research Group, Pharmaceutical and Life Sciences CoRe, Universiti Teknologi MARA, 40450, Shah Alam, Selangor, Malaysia.*

ARTICLE INFO

Article history:
Received 8 August 2024
Revised 6 October 2024
Accepted 10 October 2024
Published 30 January 2025

Keywords:
Microalgae
Antibacterial
Antifungal
Antiviral
Antibiofilm
Cyanobacteria

ABSTRACT

Bacterial biofilms produce the majority of medical infections, and biofilm formation is also associated with 60–70% of nosocomial infections. It has become a huge public health concern as antibiotics' effectiveness is dwindling at an alarming rate due to the emergence of antibiotic-resistant microbes. Microalgae, both eukaryotic and prokaryotic, have been found to produce intracellular and extracellular metabolites with a variety of biological activities such as antibacterial, antifungal, antiviral, and antibiofilm activity by microalgae and cyanobacteria species. Several compounds have been reported to possess antimicrobial and antibiofilm activity, including phenol, hexadecanoic acid, phycocyanin, phycobiliproteins, hassallidin, parsinguine, gambierdic acids, tannins, terpenoids, and flavonoids. This review outlines the uses of microalgae as a renewable and underexploited resource for antimicrobial and antibiofilm agents and its prospects.

* Corresponding author. *E-mail address*: taufiqjalil@uitm.edu.my

INTRODUCTION

According to the World Health Organization (WHO), the emergence of multidrug-resistant strains is a major public health concern. Medical devices, including urinary catheters, prostheses, and prosthetic heart valves, provide an ideal surface for biofilm formation. Once a biofilm has formed, antimicrobials and immune responses are ineffective in eradicating infection. Shahid et al. (2021) reported that antibiotics such as vancomycin or silver are commonly used to coat medical devices. However, antibiotic usage can lead to the selection of antibiotic-resistant bacteria and even the development of biofilms. This provides a clear and urgent need for new drugs to treat disease, particularly for new classes of antibiotics to tackle the growing problem of antibiotic resistance in many bacterial infections.

To seek new bioactive compounds as antimicrobial and antibiofilm agents, the pharmaceutical industry has shifted its attention to alternate sources, such as marine life, which offers a wide range of valuable compounds. Many microalgae strains produce diverse biologically active compounds such as

toxins, algaecides, plant growth regulators, and, most importantly, those compounds used in the pharmaceutical industries. Microalgae are photosynthetic species classified as unicellular organisms with a size of 0.2 um. Besides, they have an effective biological system that enables them to make organic compounds from sunlight. They can grow alone or in symbiosis with other species in various environmental conditions, including reservoirs and deserts with varying temperatures, salinities, and pH values, as well as under varying light intensities. Martínez-Francés & Escudero-Oñate, (2018) demonstrated that manipulating the growth conditions of microalgae or cyanobacteria, for example, by applying various forms of stress to the cells, could promote the production of biomass containing valuable secondary metabolites, some of which have pharmaceutical or industrial value. The secondary metabolites from microalgae are called "High-Value Molecules (HMV)". Moreover, a study by López & Soto (2019) described compounds produced by microalgae and cyanobacteria species with antimicrobial, antibiofilm, anticancer, anti-inflammatory, antifungal, antibiotics, and other pharmaceutical activity. Antimicrobial agents discovered in the marine environment have been studied to combat current antimicrobial resistance issues.

Multidrug-resistant (MDR) strains are becoming more prevalent at both community and hospital levels, resulting in antibiotic treatment failure, increased mortality and morbidity, and a significant impact on the cost of medical treatment and prevention of bacterial infectious diseases. Microorganism resistance to available antimicrobials is rising, as is the toxic nature of some currently available drugs, which restricts their use. This seriously threatens effective preventive care for various infections caused by microorganisms such as bacteria, viruses, and fungi. Horizontal gene transfer causes increased antimicrobial resistance since plasmids and transposable elements usually carry resistance determinants for multiple antimicrobial classes. For instance, the main routes of colistin resistance in Gram-negative bacteria are structural modifications of bacterial lipopolysaccharides. Following chromosomal mutations in genes encoding the two-component systems PhoPQ and PmrAB, or in mgrB, a PhoPQ negative regulator, these modifications include the addition of 4-amino-4-deoxy-l-arabinose or phosphoethanolamine (Zafer et al., 2019). Besides, antimicrobial therapy for enterococcal infections is difficult due to their inherent susceptibility to several commonly used antimicrobial agents, including clindamycin, aminoglycosides, cephalosporins, and trimethoprim. Vancomycin-resistant enterococci (VRE) is a major cause of hospital-acquired infections in intensive care unit (ICU) patients.

Other than that, fungal infections have increased dramatically worldwide due to antifungal resistance and the limited number of available treatments. Antifungal therapy is complicated in clinical settings by frequent diagnostic uncertainty, difficulties assessing therapeutic response, antifungal drug toxicity, drug-drug interactions, and uncertainty about the appropriate duration of therapy. As a result, these widespread infections caused by MDR yeasts and molds are difficult to treat because of the rising threat of antifungal drug resistance. Nweze et al. (2020) reported that other serious drug-resistant pathogens include MDR *Mycobacterium tuberculosis*, *Plasmodium falciparum*, MDR Candida species (resistant to fluconazole, echinocandin, and amphotericin B). One distinguishing feature of these emerging fungal pathogens is their high resistance to antifungal drugs.

Biofilm

The rise in antimicrobial resistance among microorganisms (bacteria, fungi, and viruses) is one of today's most important health problems worldwide. According to the National Institutes of Health (NIH), biofilm formation accounts for 65% of microbial infections and 80% of chronic diseases. The biofilm mode of growth is another less common mechanism of resistance observed in *P. aeruginosa* strains that infect individuals with CF. Enterococci have a strong biofilm-forming potential, complicating the therapy of enterococcal infections and impeding antibiotic penetration. Fallah et al. (2017) revealed that biofilm producers had higher resistance to various antimicrobial agents (such as penicillin G, ampicillin, vancomycin, ciprofloxacin, chloramphenicol, and nitrofurantoin) than biofilm non-producers.

Biofilm formation

Biofilm formation consists of several major steps, which are (i) attachment, (ii) microcolony formation on the surface, followed by (iii) maturation and architecture, and lastly (iv) the detachment or dispersion of biofilm, as shown in Figure 1 below. The first step is the attachment of microorganisms to the surface. In this step of biofilm formation, microbial cells attach to the surface using a variety of mechanisms, including their appendages (such as pili and flagella) and physical factors (such as van der Waal's forces, electrostatic interactions, steric interactions, protein adhesion). Moreover, hydrophobicity may also play a role in strengthening microbe attachment because it reduces the repulsion force between bacteria and the surface. This stage is known as reversible attachment because the initial interaction between the bacteria and the surface can be transient and reversible due to weak interactions between the bacteria and the surface. The ability of bacterial adhesion on an implant surface is determined by the material's composition and the surface properties of the bacterial cell.

Next, after the attachment of microorganisms to a biotic or abiotic surface is established and this attachment becomes stable, a process of microbial cell multiplication and division begins, triggered by specific chemical signaling within the extracellular polymeric substance (EPS). This results in the formation of micro-colonies. When the attractive forces outweigh the repulsion forces, some reversibly attached cells become immobilized and irreversibly attached, followed by specific and strong adhesion and monolayer formation. The next step in biofilm formation is the maturation and architecture of microorganisms. Adherent cells grow and mature during this phase by interacting with one another and producing autoinducer signal molecules such as N-acylated homoserine lactone (AHL), which causes the expression of biofilm-specific genes (Khatoon et al., 2018). These auto-inducers aid quorum sensing. EPS production is part of the biofilm maturation process, in which the biofilm matrix gradually builds up, and larger bacterial aggregates known as towers form. At this point, the bacterial cells begin secreting more EPS that encloses them, stabilizing the biofilm network and guarding themselves against antimicrobial agents. These microcolonies then mature into macrocolonies, encased in the EPS, where inter-cellular signaling and quorum sensing occur. Arciola et al. (2018) reported that the β -subclass of phenol-soluble modulins (PSMs) in *S. epidermidis* contributes to biofilm structuring and forms characteristic water channels seen in mature biofilms.

The next step involved in biofilm formation is detachment or dispersion of microorganisms. During this phase, microbial cells stimulate the expression of proteins involved in flagella formation, helping them in motility and allowing bacteria to move to a new location. Microbial cell detachment and transfer to a new location help spread infections. Resources become scarce as biofilm matures, and toxic by-products may accumulate. As a result, the cells disperse to other parts of the host's body or the medical implant to expand, obtain nutrition, and eliminate stress-inducing conditions and waste. The dispersion of cells is triggered by nutrition starvation, and this starvation activates small molecules such as the fatty acid DSF (cis-11-methyl-2-dodecenoic acid), which causes autophosphorylation and the modulation of c-di-GMP phosphodiesterase, which degrades c-di-GMP. A decrease in c-di-GMP levels inhibits the production of biofilm matrix components and causes biofilm bacteria to disperse into the planktonic mode of life. Other than that, N-acetyl-heparosan lyase is produced by *E. coli*, alginate lyase by *P. aeruginosa* and hyaluronidase by *S. equi* for EPS matrix breakdown and subsequent detachment. Arciola et al. (2018) stated that phenol-soluble modulins (PSMs) are important in dispersal, particularly implant-associated biofilm infections. PSMs disrupt the non-covalent forces that strengthen the biofilm matrix, promoting the formation of channels for nutrient delivery to deeper biofilm layers and aiding in the dispersal and dissemination of biofilm clusters to distal sites. In short, dispersal is aided by the inhibition of matrix production and the enzymatic degradation of EPS and surfactant molecules.

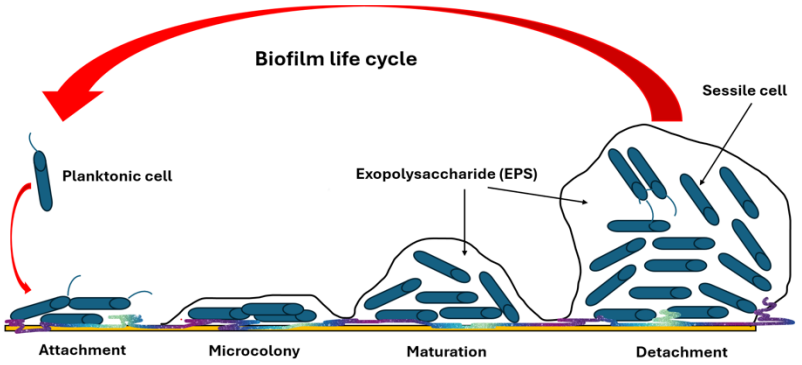

Figure 1: Diagram showing the different stages of biofilm formation: (i) attachment, (ii) microcolony formation, (iii) maturation and architecture of microorganisms, and (iv) detachment or dispersion. Abbreviations: EPS, extracellular polymeric substance. This figure is adapted from Bai et al. (2021).

Microalgae

Due to the emergence of MDR strains and their ability to form a biofilm, there is an urge to search for novel antimicrobial and antibiofilm agents with a broad spectrum to combat this phenomenon. Hence, this review has highlighted the potential of microalgae as a source of bioactive compounds with pharmaceutical properties since they have been found to produce microalgal extracts extracellularly or intracellularly that have proven to exhibit antibacterial, antifungal, antiprotozoal, and antiplasmodial activities. Microalgae are photosynthetic microorganisms in freshwater, sea, and soil environments worldwide. For the microalgae to be noticeable, they must be present in large numbers in water bodies. Four divisions of lentic habitats were discovered, which are Chlorophyta, Cyanophyta, Baccilariophyta, and Euglenophyta, with species such as *Chlorella* sp., *Oscillatoria* sp., *Gloecapsa* sp., *Oedogonium* sp., *Scenedesmus* sp., and *Microspora* sp.

Furthermore, cell division in microalgae occurs one to two times per day. In contrast, cyanobacteria divide into one or more consecutive planes at perfect angles or irregular planes, so cells may appear single or aggregates of different sizes. Besides, Deviram et al. (2020) reported that microalgae are regarded as the most productive plants in the modern world because they grow faster than terrestrial plants. Microalgae do not require external organic compounds for growth and reproduction. In contrast to heterotrophic microorganisms, which require a variety of organic compounds to grow, unicellular photosynthetic organisms generate biomass from inorganic substances and mineral elements due to the light energy converted during photosynthesis. Even though they are predominantly photoautotrophic organisms, some strains can utilize organic carbon without light, thus classifying their metabolism as photoautotrophic, heterotrophic, or mixotrophic. Demirel et al. (2018) revealed that microalgae can adapt to various conditions and temperatures in their cultivation.

Their evolutionary adaptations have enabled them to colonize various low-temperature habitats, frequently characterized by significant seasonal fluctuations in environmental factors such as light and osmotic stress. For instance, McConville (2018) reported that microalgae have been found colonizing within the ice or on the bottom surface of the ice in the Arctic and Antarctic. Moreover, algae are critical in maintaining environmental balance because they are carbon fillers and biomass generators. Several advantages of microalgae biomass production technology include that it is non-polluting, utilizes carbon dioxide while producing oxygen, requires little water, and may occupy land unsuitable for agricultural crop cultivation. Furthermore, the ease with which microalgae and cyanobacteria can be obtained makes them viable candidates for several biotechnological applications such as food, feed, and fuel. However, many microalgae strains remain unexplored to this day. Deviram et al. (2018) reported that more than 50,000

microalgae species have been estimated to exist based on biodiversity studies, but only 30,000 have been examined and documented. The lack of strain robustness or low productivity under outdoor conditions is usually the reason these strains have not been studied and have not yet achieved commercial-scale production.

Green microalgae

These characteristics describe the group known as Chlorophyta, or green algae: cells with chlorophyll-A and B as pigments, thylakoids, true starch, cellulosic walls, and membrane-bound chloroplast but with no external endoplasmic reticulum. Green algae can be found worldwide in fresh, salty, brackish water bodies. *Koliella antarctica*, a psychrophilic species microalga, has recently piqued the interest of researchers not only for its ability to produce important nutritional essential compounds (EPA, DHA, astaxanthin, and lutein) but also its ability to grow at temperatures below 10◦C. Moreover, Cuaresma et al. (2011) found that *Chlamydomonas acidophila* can be found in a mining area in an acidic river that ranges in pH from 1.7 to 3.1. Besides, at pH 2.5, *C. acidophila* can grow mixotrophically without carbon dioxide and CO_2 by utilizing different carbon sources, particularly starch, glucose, and glycerol. These adaptations to extreme environmental conditions may be advantageous in industrial cultivation systems, where microalgae are frequently subjected to fluctuations in low temperatures and pH, as well as variable salinity, which can impact productivity.

Red microalgae

Rhodophyta, also known as red algae, is distinguished by chloroplasts with no external endoplasmic reticulum, unstacked thylakoids, floridean starch, and the absence of flagella. Phycoerythrin is a major phycobiliprotein accessory light-harvesting pigment that gives microalgae its characteristic red colour. Moreover, two additional phycobiliproteins found in red microalgae are phycocyanin and allophycocyanin. Among the industrially exploited microalgae, red microalgae are gaining popularity as a rich source of compounds such as extracellular polysaccharides and long-chain PUFAs. *Galdieria sulphuraria* is a fascinating species of red microalgae that has been discovered to have extreme growth properties. *G. sulphuraria* can survive in highly acidic environments, with a pH as low as 1.8. Additionally, *G. sulphuraria* exhibits thermophilic growth behaviour up to a temperature of 56◦C (Selvaratnam et al., 2014).

Diatoms

Bacillariophyceae, also known as diatoms, are recognized by certain characteristics, such as four-membraned chloroplasts, stacked thylakoids, and chrysolaminarin as the photosynthetic reserve product. Ambati et al. (2018) reported that diatoms play a significant role in the ocean's biogeochemical cycling of silicon (Si). Their external siliceous cell wall structures create distinctive morphologies that serve as taxonomic keys. According to Artamonova et al. (2017), there are approximately 20,000 different species of diatoms, each with a unique arrangement of pores in a rigid walled nanoarchitecture. In addition, fucoxanthin, a pigment molecule from the carotenoids class that is abundant in diatoms, gives the microalgae its distinctive golden-brown colour. They come in various shapes and sizes ranging from 2-200 μm and are classified morphologically and molecularly. Besides, they are ubiquitous, photosynthetic organisms that fix approximately 25% of atmospheric CO_2 and produce a variety of biomolecules such as proteins and lipids. Moreover, three common northern cold water (7°C) diatoms, *Coscinodiscus concinnus*, *Porosira glacialis*, and *Chaetoceros socialis*, were analyzed by Artamonova et al. (2017) for phospholipids and neutral lipids.

Dinoflagellates

Dinoflagellates, or Pyrrhophyta, are classified by the presence of true starch, a theca covering, a posterior flagellum, stacked thylakoids, and chloroplasts with three surrounding membranes. These dinoflagellates can be identified by their golden-brown plastids (peridinin), distinctive swimming patterns, and large nuclei containing visible chromosomes under the light microscope. Based on genomics analysis, dinoflagellate DNA is associated with histone-like proteins (HLPs), like bacterial DNA binding proteins. This type of microalgae can be found in a wide range of aquatic habitats, including oceans, brackish waters, and freshwaters, and they play an important role in the cycling of aquatic carbon and nutrients.

Durán-Riveroll et al. (2019) reported that some species of benthic dinoflagellates thrive in low-light conditions so that they can be found in tropical waters with higher transparency and withstand high irradiance and salinity. Unlike other planktonic organisms such as chlorophytes, haptophytes, and diatoms, dinoflagellates are less efficient at absorbing nutrients and grow slower. Furthermore, instead of "blooms" in the water column, they form dense aggregations or colonies of attached cells. Dinoflagellates are known to contain a high concentration of DHA. However, some species of dinoflagellate in the Gambierdiscus and Fukuyoa genera produce neurotoxins (ciguatoxins and maitotoxins) that can contaminate marine food chains and cause ciguatera fish poisoning (CFP).

Cyanobacteria

Cyanobacteria, also known as blue-green algae, are prokaryotes with the following features: cells with no membrane-bound organelles, such as chloroplasts, unstacked thylakoids, phycobiliprotein pigments, cyanophycean starch, and peptidoglycan walls. They are characterized by filamentous cells that are occasionally large enough to be visible to the naked eye, especially during blooms. Cyanobacteria are the only prokaryotic organisms capable of oxygenic photosynthesis and are thought to be the first life forms responsible for oxygenating the atmosphere and oceans. They possess diverse cellular strategies, physiological abilities, and adaptations that enable them to colonize various microenvironments worldwide. As a sequence, cyanobacteria can thrive in various environments, including the ocean, land, freshwater, and hot springs, and reside in nearly every terrestrial and aquatic. Moreover, cyanobacteria cells are an excellent source of biotechnology because they do not require arable land for growth and can rapidly grow on residual nutrients.

Besides, Kozak et al. (2019) stated that cyanobacteria are integral to numerous biological monitoring programs used to determine drinking water quality. Demay et al. (2019) reported over 90 cyanobacteria genera with potentially beneficial compounds, most classified as *Oscillatoriales, Nostocales, Chroococcales*, and *Synechococcales*. Meanwhile, other cyanobacterial orders' molecular diversity and relative bioactivity (*Pleurocapsales, Chroococcidiopsale*s, and Gloeobacterales) have been poorly studied. Alkaloids, depsipeptides, lactones, peptides, terpenes, lipids, polyketides, portoamides, hierridin-B, bartolosides, and sphaerocyclamides are among the cyanobacterial secondary metabolites with biotechnological applications. On the other hand, some secondary metabolites may harm other organisms, including humans.

Antibacterial activity of microalgae

Antibacterial activity of green microalgae

Dunaliella sp. is a well-known green microalgae species for its use in recovering valuable compounds or as whole cells in various biotechnological processes. For instance, methanolic extracts of *D. primolecta* exhibited significant activity against MRSA (Dewi et al., 2018). Moreover, supercritical carbon dioxide (CO_2) extraction of *D. salina* was found to have antibacterial properties against *E. coli* and *S. aureus* (Jafari et al., 2018). Furthermore, when silver is available in the nanometer range, its contact surface area increases, increasing efficiency. Thus, the silver nanoparticles are highlighted, and biomass from

microalgae such as *Chlorella vulgaris* (both live and dried) can be used to biosynthesize silver nanoparticles (AGNPs). In addition, the extract of *Tetraselmis* sp. exhibited the highest antibacterial activity, with a minimum inhibitory concentration (MIC) of 2.6 to 3.0 mg/mL extract culture for the three species of bacteria studied, which are *E. coli*, *P. aeruginosa*, and *S. aureus*. Antibacterial activity against gram-positive and gram-negative bacteria was observed by Navarro et al. (2017) in fatty acids extracts from *Coccomyxa onubensis*, with the lowest MIC of 305 and 106 µg/mL against *E. coli* and *Proteus mirabilis*, respectively. In addition, methanol extracts from the biomass of a local microalgae, namely *Chlorella* sp. (UKM8), were screened by Shaima et al. (2021) for their antibacterial bioactive compounds and the extract showed excellent activity against MRSA, *S. epidermidis*, *S. aureus*, *Bacillus thuringiensis*, *P. aeruginosa*, *E. coli*, and *B. subtilis*.

Antibacterial activity of red microalgae

Bioactive compounds from red microalgae *Dixoniella grisea* and *P. aerugineum* were used to develop hydrogels with promising antimicrobial properties in the study by Netanel Liberman et al. (2021). The highest level of inhibition was observed against the gram-positive bacterium, *B. subtilis,* resulting in the presence of the largest clear zone. Another study discovered that when zinc ions are combined with a sulfated polysaccharide extracted from the red microalga *Porphyridium* sp., the resulting hydrogels exhibit antibacterial activity against *E. coli* and *B. subtilis* (Netanel Liberman et al., 2021). Moreover, antimicrobial effects have been attributed to phycobiliproteins, the light-harvesting proteins found in microalgae, responsible for the microalgae's ability to absorb light. For instance, the Gram-positive bacterium *S. aureus* has been reported to be inhibited by 7 µg/mL of phycobiliproteins (MIC level) compound extracted from the *P. aerugineum*. In addition, phycobiliproteins of *Porphyridium cruentum* were found to be active against *S. aureus*, and extracellular sulfated polysaccharides (1%) were found to be active against *E. coli* and *S. aureus* (Dewi et al., 2018). Moreover, antibacterial activity against *S. aureus*, *Streptococcus pyogenes*, *B. cereus*, and *Salmonella typhimurium* was observed *in vitro* using exopolysaccharides from the red microalga *Rhodella reticulata*.

Antibacterial activity of diatoms

Diatoms have been reported to possess antibacterial activity against pathogenic bacteria. For instance, Dewi et al. (2018) revealed that the n-hexane extracts of *Chaetoceros calcitrans* can inhibit *S. aureus*, *B. subtilis*, and *E. coli* with a MIC level of 250 µg/mL. Moreover, antibacterial activity was evaluated by comparing the antibacterial properties of diatom organic extracts against various pathogenic bacteria such as *Proteus* sp., *Salmonella* sp., *Staphylococcus* sp., and *Vibrio* sp. The results indicated that methanol extracts of *Skeletonema costatum* were the most effective against all bacteria tested. In contrast, water extracts did not affect any of the bacteria tested, and ethanol extracts had a minimal impact on *P. mirabilis* and *Salmonella Paratyphi* B. Other than that, according to the study by Al-Jbory & Al-Mayaly (2019), the methanolic extract of *Navicula* sp. exhibited remarkable antibacterial activity against *Enterococcus faecalis*, *S. aureus*, *B. cereus*, and *Klebsiella pneumoniae* with MIC values ranging from 2000 to 10000 µg/ml. Mishra et al. (2020) discovered three marine diatoms to synthesize AgNPs: *Chaetoceros* sp., *Skeletonema* sp., and *Thalassiosira* sp. Diatom-based AgNPs are an excellent bactericidal agent against gram-negative bacteria, including *Aeromonas* sp. and *E. coli,* or gram-positive bacteria, such as *B. subtilis* or *S. pneumonia*.

Antibacterial activity of Cyanobacteria

Nanoparticles (NP) incorporated with bioactive compounds from microalgae are gaining recognition as versatile materials because they have a higher surface-to-volume ratio, which is critical for antimicrobial activity. Patel et al. (2015) reported that *Anabaena* sp., *Cylindrospermopsis* sp., *Lyngbya* sp., *Limnothrix* sp., *Synechococcus* sp., and *Synechocystis* sp. were the six strains of cyanobacteria that were

evaluated for their ability to biosynthesize AgNPs. These nanoparticles were evaluated against harmful bacteria such as *Bacillus megaterium*, *Micrococcus luteus*, *B. subtilis*, *S. aureus*, *E. coli*, and *P. aeruginosa*. However, out of six strains tested, it was discovered that only one strain, *Limnothrix* sp., which synthesized the larger nanoparticles, lacked antibacterial activity. Moreover, Karthika and Muruganandam (2019) reported that *Stigonema* sp. extracts (100 µl) showed a significant inhibition zone when tested against some bacteria species such as *B. cereus*, *K. pneumoniae*, *Proteus vulgaris*, *P. aeruginosa*, *S. aureus*. The n-hexane extracts of *Oscillatoria redekeii* successfully inhibited the pathogenic bacterium, *S. aureus*, with a MIC of less than 100g/mL. Additionally, the antibacterial metabolites determined from the methanolic extract of *Oscillatoria* sp. are fatty acids, triazine derivatives, pyridine derivatives, and acridine derivatives. A total of 411 cyanobacteria strains from Brazil were evaluated in vitro against various pathogenic bacteria in a large screening study by Silva-Stenico et al. (2013).

Intracellular extracts of *Phormidium autumnale*, *Myxosarcina* sp., *Gloeotrchia* sp., *Cyanobium* sp., and *Cyanobacterium* sp. were highlighted for their significant antibacterial activity. According to mass spectrometry analysis, these cyanobacteria secreted compounds such as cyanopeptolin, microcystin, aeruginosin, and cyanopeptolin that are responsible for preventing the growth of gram-negative and gram-positive pathogenic bacteria by 49% and 35%, respectively. However, stability studies on these naturally occurring antimicrobial compounds produced by microalgae are scarce. Furthermore, among three cyanobacterial species, *Anabaena oryzae*, *Oscillatoria* sp., and *Stigonema ocellatum*, the acetone extract of *A. oryzae* was found to show a maximum antimicrobial activity against tested human pathogenic bacterial strains, *Serratia marcescens*. *Anabaena circinalis* buffer extract was most effective against *Listeria monocytogenes* ATCC 7644, while *Nostoc entophytum* buffer extract was most effective against pathogenic *E. coli* O 157:H7 in terms of antimicrobial activity. Antibacterial properties of *Nostoc commune* and *Lyngbya majuscula* against pharmaceutically important microorganisms have been tested by Chauhan et al. (2020), and their ethanolic extract has been tested using UV-HPLC and HPTLC analysis. Table 2 summarizes the antibacterial compounds of microalgae and cyanobacteria from previous studies.

Antifungal activity of microalgae

Antifungal activity of green and red microalgae

Green and Red microalgae have been reported to exhibit antifungal activity against pathogenic fungi. For instance, benzene extracts of *Chlorococcum humicola* displayed the best antifungal activity against *Candida albicans*, *Aspergillus niger*, and *A. flavus*. Moreover, the antifungal activity of *P. aerugineum* and *P. cruentum* against *C. albicans had* MIC values of 2.1 and 7.0mg/mL, respectively (Najdenski et al., 2013). Compared to other groups, only a few studies have been conducted on red microalgae, perhaps because of the limited number of species available. Only two microalgae strains, *Heterochlorella luteoviridis* and *Porphyridium purpureum,* out of 88 microalgal strains showed antifungal activity against *C. albicans* in a large screening study conducted by Mudimu et al. (2014). The Chlorella genus of green microalgae has been extensively studied to produce bioactive compounds with promising antimicrobial activity. For instance, Vehapi et al. (2018) reported that *Chlorella vulgaris* and *C. minutissima* extracts have a powerful antifungal effect against *A. niger* and *Fusarium oxysporum* when cultivated in Iroko tree extract water and culture supernatants from *C. vulgaris* and *C. ellipsoidea* were found to be fungicidal against *Candida kefyr*, *A. fumigatus*, and *A. niger*.

Table 2: Antibacterial compounds of microalgae and cyanobacteria

Microalgae	Compounds	Target bacteria	Reference

Dunaliella primolecta	γ-linolenic acid	MRSA	(Dewi et al., 2018)
Tetraselmis sp.	Palmitic acid, oleic acid and linoleic acid	*E. coli, P. aeruginosa, and S. aureus*	(Maadane et al., 2017)
Coccomyxa onubensis	Palmitic acid (C16:0), oleic acid (C18:1), linoleic acid (C18:2) and (C18:3)	*E. coli and P. mirabilis*	(Navarro et al., 2017)
Chlorella sp. UKM8	Phenol and hexadecanoic acid	*S. epidermidis*	(Shaima et al., 2021)
Dixoniella grisea and Porphyridium aerugineum	Sulfated polysaccharides	*B. subtilis*	(Netanel Liberman et al., 2021)
Porphyridium aerugineum	Phycocyanin	*S. aureus*	(Dewi et al., 2018)
Stigonema sp.	Anthraquinones, amino acids, carbohydrates, flavonoids, phenols, proteins, steroid hormones, saponin, tannin, and terpenoids	*B. cereus, K. pnemoniae, P. vulgaris, P. aeroginosa, and S. aureus*	(Karthika & Muruganandam, 2019)
Anabaena oryzae	Diacetone alcohol, acetic acid butyl ester, mesityl oxide, and heptadecane	*Serratia marcescens*	(Seddek et al., 2019)

Antifungal activity of diatoms and dinoflagellates

The in vitro antifungal tests were carried out by Dewi et al. (2018) using various organic extracts of 11 diatom species. *Thalassiothrix frauenfeldii* was the most effective antifungal agent against *A. niger* and *Candida neoformans*. There are dinoflagellates in the genera Gambierdiscus and Fukuyoa that are known to produce toxic metabolites, but some of these toxins have been shown to have antimicrobial properties. Moreover, supercritical CO_2 extracts from the marine diatom *Chaetoceros muelleri* are effective against *C. albicans* (Mendiola et al., 2007). In addition, polysaccharides derived from *Asterionella glaciallis*, *Chaetoceros lauderi,* and *C. diadema* were discovered to possess antifungal activity against a variety of species, including *Trichophyton rubrum*, *Fusarium fuhum*, and *Colletotrichum acutatum*. Additionally, toxicology studies on these microalgae-secreted antimicrobial compounds are lacking. Therefore, toxicity testing is required, as it is critical to screening newly developed drugs before their use on living organisms.

Antifungal activity of Cyanobacteria

According to recent studies, Cyanobacteria, the blue-green algae, may contain bioactive compounds with antifungal properties. For instance, Shishido et al. (2015) reported the antifungal activity of methanolic extracts from 11 cyanobacterial strains belonging to the genera Nostoc sp., Anabaena sp., *Scytonema* sp., and *Fischerella* sp. (originating in brackish, freshwater, and terrestrial environments). Cyclic glycosylated lipopeptides produced by cyanobacteria are antifungal agents and have been identified in several cyanobacteria strains from the genera *Anabaena, Nostoc, Aphanizomenon,* and *Tolypothrix*. Cyanobacterial cyclic antifungal lipopeptide classes include hassallidin, pauwainaphycins, laxaphycins, and anabaenolysins. Anabaena and Nostoc species produced the antifungal bioactive compound

glycolipopeptide, inhibiting *C. albicans* and *A. flavus* growth. Another subtype of hassallidins, hassallidin D, demonstrated significant antifungal activity against *C. krusei*, with MIC values of less than 2.8g/mL.

Another study found that cyclic antifungal lipopeptides isolated from the epilithic cyanobacterium *Hassallia* sp. were effective against opportunistic human pathogens. However, Vestola et al. (2014) reported that hassallidin D is ineffective against Aspergillus strains. The mechanism by which antifungal cyclic lipopeptides from cyanobacteria work is mainly described by membrane disruption. Moreover, *Fischerella ambigua* methanol extracts contained the antifungal compound with a MIC value of 20 μg/mL and inhibited the growth of *C. krusei*. Acetone extract of three microalgae isolates, *Gloeocapsa*, *Fischrella*, and *Chlorella*, yielded beta-carotene pigment. It was determined that Beta-carotene pigment was effective in inhibiting the pathogenic fungi *C. albicans* and *Fusarium solani* (Al-taie and Al-katib, 2020).

Moreover, toxins commonly produced by *Desmonostoc muscorum* have been shown to have remarkable inhibitory effects against plant pathogens. Seddek et al. (2019) revealed that *A. oryzae* acetone extract was found to be the most effective against the tested fungus out of three cyanobacterial species (*A. oryzae*, *Oscillatoria* sp., and *S. ocellatum*) when tested for antimicrobial activity against pathogenic microorganisms. Further, a gas Chromatography-mas spectrophotometer (GC–MS) analysis of the acetone extracts was used to determine major compounds responsible for antifungal activities in cyanobacterial species. Table 3 summarizes the antifungal compounds of microalgae and cyanobacteria based on the pieces of literature.

Antibiofilm activity

Antibiofilm activity of microalgae and Cyanobacteria

Microalgae and cyanobacteria extracts have been reported to show an inhibitory effect against the biofilm formation of various fungi and bacteria strains. It was found that the extracts from methanol and ethyl acetate were the most capable of killing the microorganisms studied. In the case of the cyanobacterium *Sphaerospermopsis* sp. (LEGE00249), the antibiofilm subfraction inhibited biofilm formation by 61%–70% for Coagulase-negative Staphylococcus (CoNS) strains. The compound lysophosphatidylcholine (C16:0 LPC) was found to have antibiofilm activity against *K. pneumoniae*, *E. coli*, *S. epidermidis*, and *C. parapsilosis*. In contrast, fatty acids had no antibiofilm activity against the tested microorganisms. The study by Gayatri et al. (2019) aimed to examine the anti-biofilm properties of Chlorella lyophilized extracts. Based on MTT assay results, the lyophilized ethanolic extract of Chlorella inhibited biofilm formation by as much as 85%. A paper by Lauritano et al. (2016) analyzed microalgae, including diatoms, dinoflagellates, and flagellates, to determine if they possessed any biological activity. There was no cytotoxicity in previous antibacterial tests, and the diatoms *Leptocylindrus danicus* and *L. aporus* genus showed strong antibiofilm activity, preventing 90 percent bacterial growth in microalgae cultivated under nitrogen stress. Moreover, López & Soto (2019) reported that at a concentration of 4 mg/mL, an extract of *C. vulgaris* demonstrated antibiofilm activity, and analysis of the extracts indicated that tannins, terpenoids, and flavonoids are responsible for the extract's antimicrobial properties.

A concentration of 2 mg/mL of *D. salina* extract was required to inhibit biofilm growth, and extract analysis revealed that compounds such as n-hexadecane, PUFAs, 3,3,5-trimethylheptane, neophytadiene, and β-ionone from *D. salina* extract played a role to the antimicrobial properties. Moreover, glucosyltransferases (GTF) secreted by *C. vulgaris* and *D. salina* have suppressive activity and are responsible for their antibiofilm activity. Adebayo-Tayo et al. (2019) used silver nanoparticles (OsSNPs) containing a methanol extract of the green microalgae Oscillatoria sp to identify novel bioactive compounds with antibiofilm activity. The findings of this study indicated that biosynthesized silver nanoparticles (OsSNPs) were the most effective antibiofilm against *P. aeruginosa* ATCC 27853, while Citrobacter was the least inhibited. Unlike traditional antimicrobial agents, silver nanoparticles require low doses to treat

disease. When silver nanoparticles encounter microorganisms, silver ions are released. Silver ions can kill microbial cells by deactivating enzymes within the cell and disrupting the cell membrane, resulting in apoptosis. Another important area of research is oral health. Because of their biofilm-forming activities, *S. mutans* and *Lactobacillus* sp. are the most common bacteria linked to tooth decay and other oral diseases. Ethanolic extracts of the green microalgae *C. vulgaris* and *D. salina* may facilitate reducing biofilm formation. Scanning electron microscopy revealed that antibiofilm compounds reduced microcolony formation and structural changes in exopolysaccharides, limiting growth and virulence properties in *S. mutans*. Various antibiofilm compounds were identified from microalgae. However, additional research on the modes of action of these compounds is required.

Table 3: Antifungal compounds of microalgae and cyanobacteria

Microalgae	Compounds	Target fungi	Reference
Porphyridium aerugineum and P. cruentum	Phycobiliproteins	*C. albicans*	(Najdenski et al., 2013)
Gambierdiscus toxicus	Gambierdic acids	*A. niger*	(Morohashi et al., 2000)
Hassallia sp.	Hassallidins (A and B)	*A. fumigatus, C. albicans*	(Neuhof et al., 2005)
Anabaena sp, and *Nostoc sp.*	Hassallidin	*C. albicans and A. flavus*	(Shishido et al., 2015)
Fischerella ambigua	Parsinguine	*C. krusei*	(Dewi et al., 2018)
Anabaena oryzae	Diacetone alcohol, acetic acid butyl ester mesityl oxide, and heptadecane	*C. albicans*	(Seddek et al., 2019)

CONCLUSION AND FUTURE PROSPECTS

Indeed, microalgae and cyanobacteria are excellent candidates for discovering significant antimicrobial and antibiofilm compounds that will combat various multi-drug resistance strains to currently existing antimicrobial drugs. As a result of the findings, several gaps in the research on microalgae bioactive compounds have been identified that have not been adequately addressed. Future work should search for more industrially robust microalgae strains capable of successfully manufacturing lucrative bioproducts. Besides, methods for enhancing microbial yield to satisfy industrial needs must be developed. Current biomolecular tools, such as CRISP-Cas9, are one strategy for increasing yield without requiring many reagents or a lengthy process, thereby lowering the cost of this production. Moreover, future researchers should conduct additional research on antibiofilm activity, emphasizing the mechanisms of action. Furthermore, toxicity studies on antimicrobial compounds produced by microalgae are required because toxicity testing aims to determine how safe a test substance is and to characterize the potential toxic effects it may produce. In addition, a stability test on these antimicrobial compounds produced by microalgae is required to ascertain how a pharmaceutical substance's quality is affected by several environmental factors. Finally, in vivo studies are recommended in the future because they provide researchers with a better understanding of the experiment's effects on the entire living organism.

ACKNOWLEDGMENTS

We want to acknowledge that this work was conducted without external funding. We appreciate the collaborative effort of all authors in compiling this review. Their dedication and expertise contributed to the completion of this work.

AUTHOR'S CONTRIBUTION

Syaza Syasya Lakman contributed to this review. She was involved in the literature review, data synthesis, and manuscript drafting. Nurul Aili Zakaria and Mohd Taufiq Mat Jalil guided throughout the review process, critically reviewed the manuscript, and contributed to its finalization.

CONFLICT OF INTEREST STATEMENT

The authors affirm that there are no competing interests regarding the publication of this paper.

REFERENCES

Adebayo-Tayo, B., Salaam, A., & Ajibade, A. (2019). Green synthesis of silver nanoparticle using *Oscillatoria* sp. extract, its antibacterial, antibiofilm potential, and cytotoxicity activity. *Heliyon*, *5*, e02502. https://doi.org/10.1016/j.heliyon.2019.e02502

Al-Jbory, M. J., & Al-Mayaly, I. K. (2019). Evaluation of the activity of the diatom *Navicula incerta* cultivated in different environments against several species of pathogenic bacteria. *Iraqi Journal of Science*, *60*(3), 486–493. https://doi.org/10.24996/ijs.2019.60.3.8

Al-taie, M. F., & Al-katib, M. A. (2020). Beta-Carotene Extraction from Some Microalgae, Cyanobacteria and Chlorophyta with Its Antibacterial and Antifungal Activity. *Plant Archives*, *20*(2), 8085–8097.

Ambati, D. R. R., Gogisetty, D., Gokare, R., Ravi, S., Narasimharao, B., Bo, L., & Yuepeng, S. (2018). Industrial potential of carotenoid pigments from microalgae: Current trends and future prospects. *Critical Reviews in Food Science and Nutrition*, *59*(12), 1880–1902. https://doi.org/10.1080/10408398.2018.1432561

Arciola, C. R., Campoccia, D., & Montanaro, L. (2018). Implant infections: adhesion, biofilm formation and immune evasion. *Nature Reviews Microbiology*, *16*(7), 397–409. https://doi.org/10.1038/s41579-018-0019-y

Artamonova, E. Y., Svenning, J. B., Vasskog, T., Hansen, E., & Eilertsen, H. C. (2017). Analysis of phospholipids and neutral lipids in three common northern cold-water diatoms: *Coscinodiscus concinnus*, *Porosira glacialis*, and *Chaetoceros socialis*, by ultra-high performance liquid chromatography-mass spectrometry. *Journal of Applied Phycology*, *29*(3), 1241–1249. https://doi.org/10.1007/s10811-017-1055-0

Bai, X., Nakatsu, C. H., & Bhunia, A. K. (2021). Bacterial Biofilms and Their Implications in Pathogenesis and Food Safety. *Foods* (Basel, Switzerland), *10*(9), 2117. https://doi.org/10.3390/foods10092117

Chauhan, A., Chauhan, R., Basniwal, R. K., & Narwadiya, S. C. (2020). Cyanobacteria: an emerging source for antibacterial, antimycobacterial and antifungal properties. *Science Archives*, *01*(01), 35–41. https://doi.org/10.47587/sa.2020.1104

Cuaresma, M., Casal, C., Forján, E., & Vílchez, C. (2011). Productivity and selective accumulation of carotenoids of the novel extremophile microalga *Chlamydomonas acidophila* grown with different carbon sources in batch systems. *Journal of Industrial Microbiology & Biotechnology*, *38*(1), 167–177. https://doi.org/10.1007/s10295-010-0841-3

Demay, J., Bernard, C., Reinhardt, A., & Marie, B. (2019). Natural Products from Cyanobacteria: Focus on Beneficial Activities. *Marine drugs*, *17*(6), 320. https://doi.org/10.3390/md17060320

Demirel, Z., Yilmaz, F., Ozdemir, G., & Dalay, M.C. (2018). Influence of Media and Temperature on the Growth and the Biological Activities of *Desmodesmus protuberans* (F.E. Fritsch & M.F. Rich) E. Hegewald. *Turkish Journal of Fisheries and Aquatic Sciences*, *18*, 1195-1203.

Deviram, G., Mathimani, T., Anto, S., Ahamed, T. S., Ananth, D. A., & Pugazhendhi, A. (2020). Applications of microalgal and cyanobacterial biomass on a way to safe, cleaner and a sustainable environment. *Journal of Cleaner Production*, *253*, 119770. https://doi.org/https://doi.org/10.1016/j.jclepro.2019.119770

Dewi, I. C., Falaise, C., Hellio, C., Bourgougnon, N., & Mouget, J.-L. (2018). Chapter 12 - Anticancer, Antiviral, Antibacterial, and Antifungal Properties in Microalgae. In *Microalgae in Health and Disease Prevention*, (pp: 235–261). Academic Press. https://doi.org/https://doi.org/10.1016/B978-0-12-811405-6.00012-8

Durán-Riveroll, L. M., Cembella, A. D., & Okolodkov, Y. B. (2019). A Review on the Biodiversity and Biogeography of Toxigenic Benthic Marine Dinoflagellates of the Coasts of Latin America. *Frontiers in Marine Science*, *6*, 148. https://www.frontiersin.org/article/10.3389/fmars.2019.00148

Fallah, F., Yousefi, M., Pourmand, M. R., Hashemi, A., Nazari Alam, A., & Afshar, D. (2017). Phenotypic and genotypic study of biofilm formation in Enterococci isolated from urinary tract infections. *Microbial Pathogenesis*, *108*, 85–90. https://doi.org/10.1016/j.micpath.2017.05.014

Gayatri, K. V., Soundhari, C., & Pavithra, B. P. (2019). Biofilm Inhibitory Effect of Chlorella Extracts on *Pseudomonas aeruginosa*. *International Journal of Pharmaceutical Sciences and Research*, *10*(4), 1966–1971. https://doi.org/10.13040/IJPSR.0975-8232.10(4).1966-71

Jafari, S., Mobasher, M. A., Najafipour, S., Ghasemi, Y., Mohkam, M., Ebrahimi, M. A., & Mobasher, N. (2018). Antibacterial Potential of *Chlorella vulgaris* and *Dunaliella salina* Extracts Against *Streptococcus mutans*. *Jundishapur Journal of Natural Pharmaceutical Products*, *13*(2), e13226. https://doi.org/10.5812/jjnpp.13226

Karthika & Muruganandam, A. (2019). Bioactive Compounds and Antimicrobial Activity of Cyanobacteria from Southeast Coast of India. *International Journal of Current Research in Life Sciences*, *08*(01), 3027–3030.

Kozak, A., Celewicz-Gołdyn, S., & Kuczyńska-Kippen, N. (2019). Cyanobacteria in small water bodies: The effect of habitat and catchment area conditions. *Science of The Total Environment*, *646*, 1578–1587. https://doi.org/https://doi.org/10.1016/j.scitotenv.2018.07.330

Khatoon, Z., McTiernan, C. D., Suuronen, E. J., Mah, T.-F., & Alarcon, E. I. (2018). Bacterial biofilm formation on implantable devices and approaches to its treatment and prevention. *Heliyon*, *4*(12), e01067. https://doi.org/https://doi.org/10.1016/j.heliyon.2018.e01067

Lauritano, C., Andersen, J., Hansen, E., Albrigtsen, M., Escalera, L., Esposito, F., Helland, K., Hanssen, K., Romano, G., & Ianora, A. (2016). Bioactivity Screening of Microalgae for Antioxidant, Anti-Inflammatory, Anticancer, Anti-Diabetes, and Antibacterial Activities. *Frontiers in Marine Science*, *3*. https://doi.org/10.3389/fmars.2016.00068

López, Y., & Soto, S. M. (2019). The Usefulness of Microalgae Compounds for Preventing Biofilm Infections. *Antibiotics* (Basel, Switzerland), *9*(1), 9. https://doi.org/10.3390/antibiotics9010009

Maadane, A., Merghoub, N., El Mernissi, N., Ainane, T., Amzazi, S., Wahby, I., & Bakri, Y. (2017). Antimicrobial activity of marine microalgae isolated from Moroccan coastlines. *Journal of Microbiology, Biotechnology and Food Sciences*, *6*(6), 1257–1260. https://doi.org/10.15414/jmbfs.2017.6.6.1257-1260

Martínez-Francés, E., & Escudero-Oñate, C. (2018). Cyanobacteria and Microalgae in the Production of Valuable Bioactive Compounds. *InTech*. doi: 10.5772/intechopen.74043

McConville, M. (2018). Chemical Composition and Biochemistry of Sea Ice Microalgae. (pp. 105–129). https://doi.org/10.1201/9781351076548-4

Mendiola, J., Torres, C., Toré, A., Martín-Álvarez, P., Santoyo, S., Arredondo, B., Señoráns, F., Cifuentes, A., & Ibáñez, E. (2007). 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*, *224*, 505–510. https://doi.org/10.1007/s00217-006-0353-6

Mishra, B., Saxena, A., & Tiwari, A. (2020). Biosynthesis of silver nanoparticles from marine diatoms *Chaetoceros* sp., *Skeletonema* sp., *Thalassiosira* sp., and their antibacterial study. *Biotechnology Reports*, *28*, e00571. https://doi.org/https://doi.org/10.1016/j.btre.2020.e00571

Morohashi, A., Satake, M., Nagai, H., Oshima, Y., & Yasumoto, T. (2000). The Absolute Configuration of Gambieric Acids A–D, Potent Antifungal Polyethers, Isolated from the Marine Dinoflagellate *Gambierdiscus toxicus*. *Tetrahedron*, *56*, 8995–9001. https://doi.org/10.1016/S0040-4020(00)00753-5

Mudimu, O., Rybalka, N., Bauersachs, T., Born, J., Friedl, T., & Schulz, R. (2014). Biotechnological Screening of Microalgal and Cyanobacterial Strains for Biogas Production and Antibacterial and Antifungal Effects. *Metabolites*, *4*, 373–393. https://doi.org/10.3390/metabo4020373

Najdenski, H. M., Gigova, L. G., Iliev, I. I., Pilarski, P. S., Lukavský, J., Tsvetkova, I. V, Ninova, M. S., & Kussovski, V. K. (2013). Antibacterial and antifungal activities of selected microalgae and cyanobacteria. *International Journal of Food Science & Technology*, *48*(7), 1533–1540. https://doi.org/https://doi.org/10.1111/ijfs.12122

Navarro, F., Forján, E., Vázquez, M., Toimil, A., Montero, Z., Ruiz-Domínguez, M. del C., Garbayo, I., Castaño, M. Á., Vílchez, C., & Vega, J. M. (2017). Antimicrobial activity of the acidophilic eukaryotic microalga *Coccomyxa onubensis*. *Phycological Research*, *65*(1), 38–43. https://doi.org/https://doi.org/10.1111/pre.12158

Netanel Liberman, G., Ochbaum, G., Bitton, R., & Malis Arad, S. (2021). Antimicrobial hydrogels composed of chitosan and sulfated polysaccharides of red microalgae. *Polymer*, *215*, 123353.

Neuhof, T., Schmieder, P., Preussel, K., Dieckmann, R., Pham, H., Bartl, F., & Döhren, H. (2005). Hassallidin A, a Glycosylated Lipopeptide with Antifungal Activity from the *Cyanobacterium hassallia* sp. *Journal of Natural Products*, *68*, 695–700. https://doi.org/10.1021/np049671r

Nweze, J. A., Mbaoji, F. N., Huang, G., Li, Y., Yang, L., Zhang, Y., Huang, S., Pan, L., & Yang, D. (2020). Antibiotics development and the potential of marine-derived compounds to stem the tide of multidrug-resistant pathogenic bacteria, fungi, and protozoa. *Marine Drugs*, *18*(3). https://doi.org/10.3390/md18030145

Patel, V., Berthold, D., Puranik, P., & Gantar, M. (2015). Screening of cyanobacteria and microalgae for their ability to synthesize silver nanoparticles with antibacterial activity. *Biotechnology Reports*, *5*, 112–119. https://doi.org/https://doi.org/10.1016/j.btre.2014.12.00

Seddek, N., Fawzy, M., El-Said, W., & Ahmed, M. (2019). Evaluation of antimicrobial, Antioxidant and Cytotoxic activities and characterization of bioactive substances from freshwater blue-green algae. *Global Nest Journal*, *21*, 328–336.

Selvaratnam, T., Pegallapati, A. K., Montelya, F., Rodriguez, G., Nirmalakhandan, N., Van Voorhies, W., & Lammers, P. J. (2014). Evaluation of a thermo-tolerant acidophilic alga, *Galdieria sulphuraria*, for nutrient removal from urban wastewaters. *Bioresource Technology*, *156*, 395–399. https://doi.org/10.1016/j.biortech.2014.01.075

Shahid, Aqsa, Aslam, B., Muzammil, S., Aslam, N., Shahid, M., Almatroudi, A., Allemailem, K. S., Saqalein, M., Nisar, M. A., Rasool, M. H., & Khurshid, M. (2021). The prospects of antimicrobial coated medical implants. *Journal of Applied Biomaterials & Functional Materials*, *19*, 22808000211040304. https://doi.org/10.1177/22808000211040304

Shaima, A. F., Mohd Yasin, N. H., Ibrahim, N., Takriff, M. S., Gunasekaran, D., & Ismaeel, M. Y. Y. (2021). Unveiling antimicrobial activity of microalgae *Chlorella sorokiniana* (UKM2), *Chlorella* sp. (UKM8) and *Scenedesmus* sp. (UKM9). *Saudi Journal of Biological Sciences*. *29*(2), 1043-1052. https://doi.org/https://doi.org/10.1016/j.sjbs.2021.09.069

Shishido, T. K., Humisto, A., Jokela, J., Liu, L., Wahlsten, M., Tamrakar, A., Fewer, D. P., Permi, P., Andreote, A. P., Fiore, M. F., & Sivonen, K. (2015). Antifungal compounds from cyanobacteria. *Marine drugs*, *13*(4), 2124–2140. https://doi.org/10.3390/md13042124

Silva-Stenico, M. E., Kaneno, R., Zambuzi, F. A., Vaz, M. G. M. V, Alvarenga, D. O., & Fiore, M. F. (2013). Natural products from cyanobacteria with antimicrobial and antitumor activity. *Current*

Pharmaceutical Biotechnology, *14*(9), 820–828. https://doi.org/10.2174/138920101466613122711484 6

Vehapi, M., Yilmaz, A., & Özçimen, D. (2018). Antifungal Activities of *Chlorella vulgaris* and *Chlorella minutissima* Microalgae Cultivated in Bold Basal Medium, Wastewater and Tree Extract Water Against *Aspergillus niger* and *Fusarium oxysporum*. *Romanian Biotechnological Letters, 1.*

Vestola, J., Shishido, T. K., Jokela, J., Fewer, D. P., Aitio, O., Permi, P., Wahlsten, M., Wang, H., Rouhiainen, L., & Sivonen, K. (2014). Hassallidins, antifungal glycolipopeptides, are widespread among cyanobacteria and are the end-product of a nonribosomal pathway. *Proceedings of the National Academy of Sciences of the United States of America*, *111*(18), E1909-17. https://doi.org/10.1073/pnas.1320913111

Zafer, M. M., El-Mahallawy, H. A., Abdulhak, A., Amin, M. A., Al-Agamy, M. H., & Radwan, H. H. (2019). Emergence of colistin resistance in multidrug-resistant *Klebsiella pneumoniae* and *Escherichia coli* strains isolated from cancer patients. *Annals of Clinical Microbiology and Antimicrobials*, *18*(1), 40. https://doi.org/10.1186/s12941-019-0339-4