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Microalgae as a source of antimicrobial compounds: A review of bioactive metabolites and their therapeutic potentials

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Abstract: Microalgae, a varied collection of photosynthetic microorganisms, have become a promising source of bioactive compounds known for their antimicrobial properties. These organisms can transform inorganic carbon-di-oxide (CO2) into biomass while producing an extensive range of primary and secondary metabolites, such as proteins, polysaccharides, lipids, pigments, and polyphenols, that demonstrate antibacterial, antiviral, antifungal, and antiprotozoal effects. As antibiotic-resistant microbes are on the rise, there is an urgent need to explore new treatment options. Microalgae, which have been largely overlooked, could be a promising source of novel antimicrobial compounds. Here, we review microalgae-derived substances that fight off various pathogens, including Gram-positive and Gram- negative bacteria, fungi, viruses, and protozoa. Early findings are promising, but more research is needed to fully understand these compounds, improve their production, and confirm their safety and efficacy in real-world medical use. The review highlights the potential of microalgae as a key tool in fighting infections and calls for continued research into their bioactive properties.

Keywords: Microalgae; Antimicrobial Compounds; Bioactive Metabolites; Antibiotic Resistance; Therapeutic Potential

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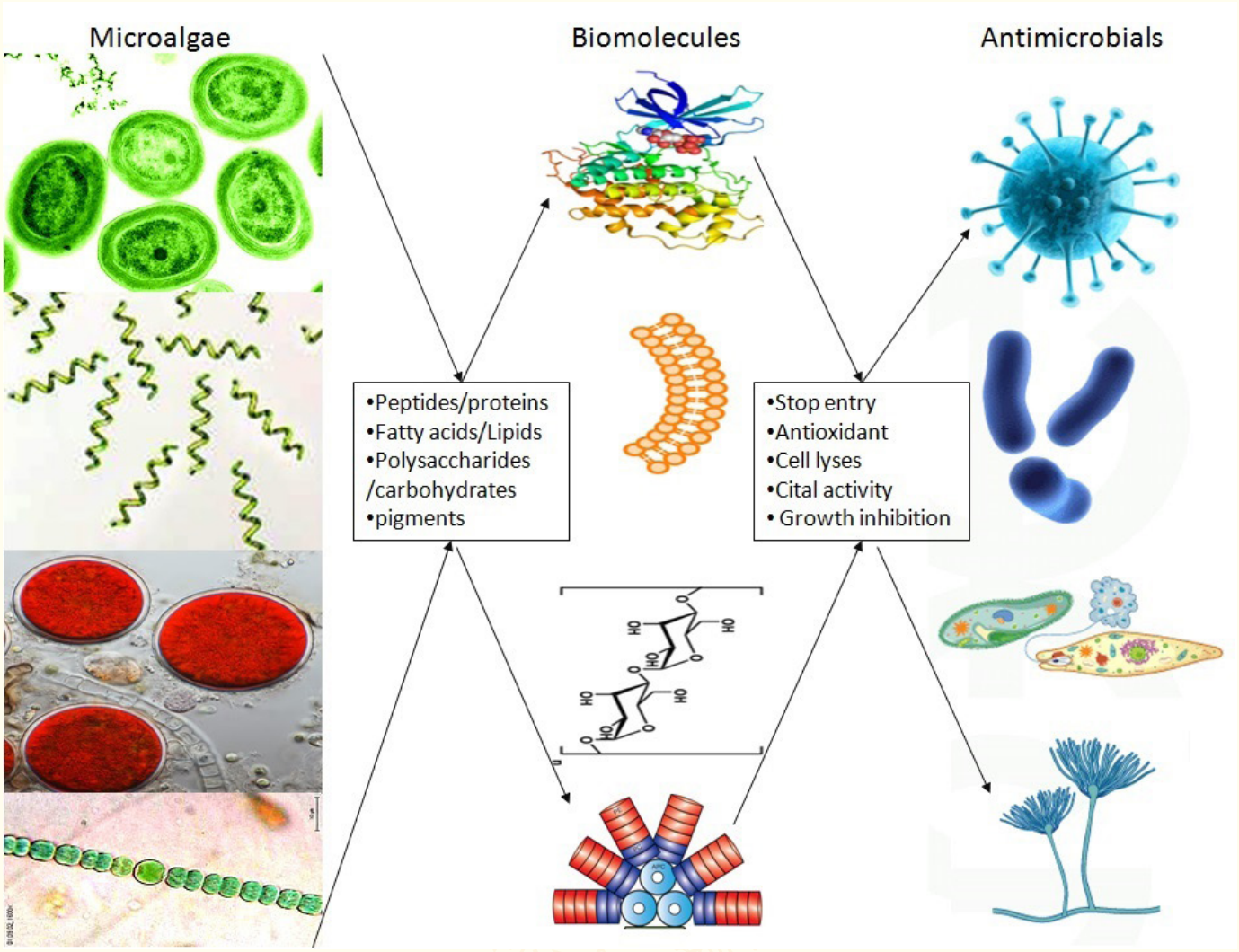
Graphical Abstract



1. Introduction

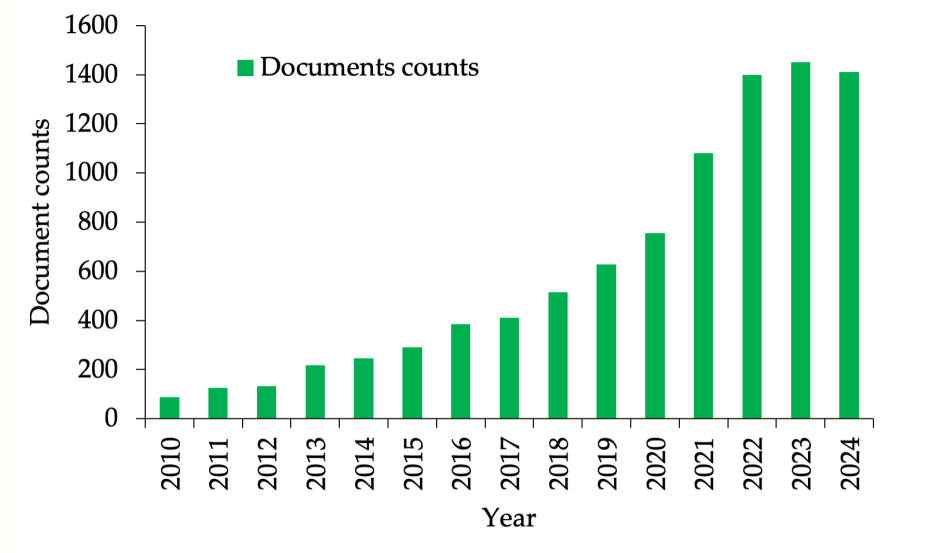
Microalgae, a varied collection of microscopic tiny (1-100µm) phytoplankton, are photosynthetic entities that can transform inorganic carbon dioxide into biomass utilizing water and light energy, thereby playing an essential role in the global carbon cycle[1]. Microalgae play a crucial role in ecosystems and are a goldmine of bioactive compounds with huge medical and pharmaceutical potential[2]. Their biomass is packed with proteins, polysaccharides, lipids, healthy fats, fibers, pigments, vitamins, and minerals making them useful across many industries[3]. They also produce powerful secondary metabolites like sterols, lectins, polyphenols, terpenes, and peptides, which have wide-ranging biological effects[4]. Compounds from microalgae show real promise in fighting bacteria, viruses, fungi, and parasites[5,6]. For instance, some microalgae-derived molecules have proven effective against antibiotic-resistant bacteria[7], viruses, fungi[8], and even protozoan infections[9], making them exciting candidates for new treatments.

With antibiotic resistance on the rise and few new drugs in the pipeline, the hunt for alternative antimicrobials has put microalgae in the spotlight. These tiny organisms are among Earth's oldest life forms, and humans have used them for millennia. Historical records show the Chinese relied on microalgae as a famine food over 2000 years ago, while the Aztecs included them in their diet, as noted by Spanish chroniclers[10,11]. Today,

we know microalgae are incredibly diverse with roughly ~1 million species, including both cyanobacteria and eukaryotic varieties. More than 50,000 species have been identified to date in oceans, lakes, and rivers[12]. Despite this diversity and their advantages over other microbes, the potential of microalgae as a source of bioactive compounds remains largely untapped. In the last decade, there has been a significant surge in interest, with a 3.5-fold increase in research publications focusing on the antimicrobial properties of microalgae (Figure 1).

This review offers an overview of the germ-fighting abilities of microalgae. It brings together recent breakthroughs in their use against hard-to-treat bugs, including ESKAPE bacteria and new fungal threats like mucormycosis. Unlike other reviews which focused on specific types of compounds or single pathogens, our work covers a wide range of microalgal products (peptides, fatty acids, polysaccharides, phenolics, and pigments) and the way they work against bacteria, fungi, viruses, and protozoa. This review also tackles cutting-edge topics such as gene tweaking and improving production processes giving a forward-looking view on how to turn microalgal research into real-world medical and farming uses. This big-picture approach highlights the untapped potential of microalgae as a lasting source of new germ-fighters in the face of worldwide antibiotic resistance

Figure 1. Number of documents counts on "Microalgae" and "Antimicrobials" for the period of 2010-2025 from the Google scholar database using custom range, accessed 12th March 2025 (https://scholar.google.com/).



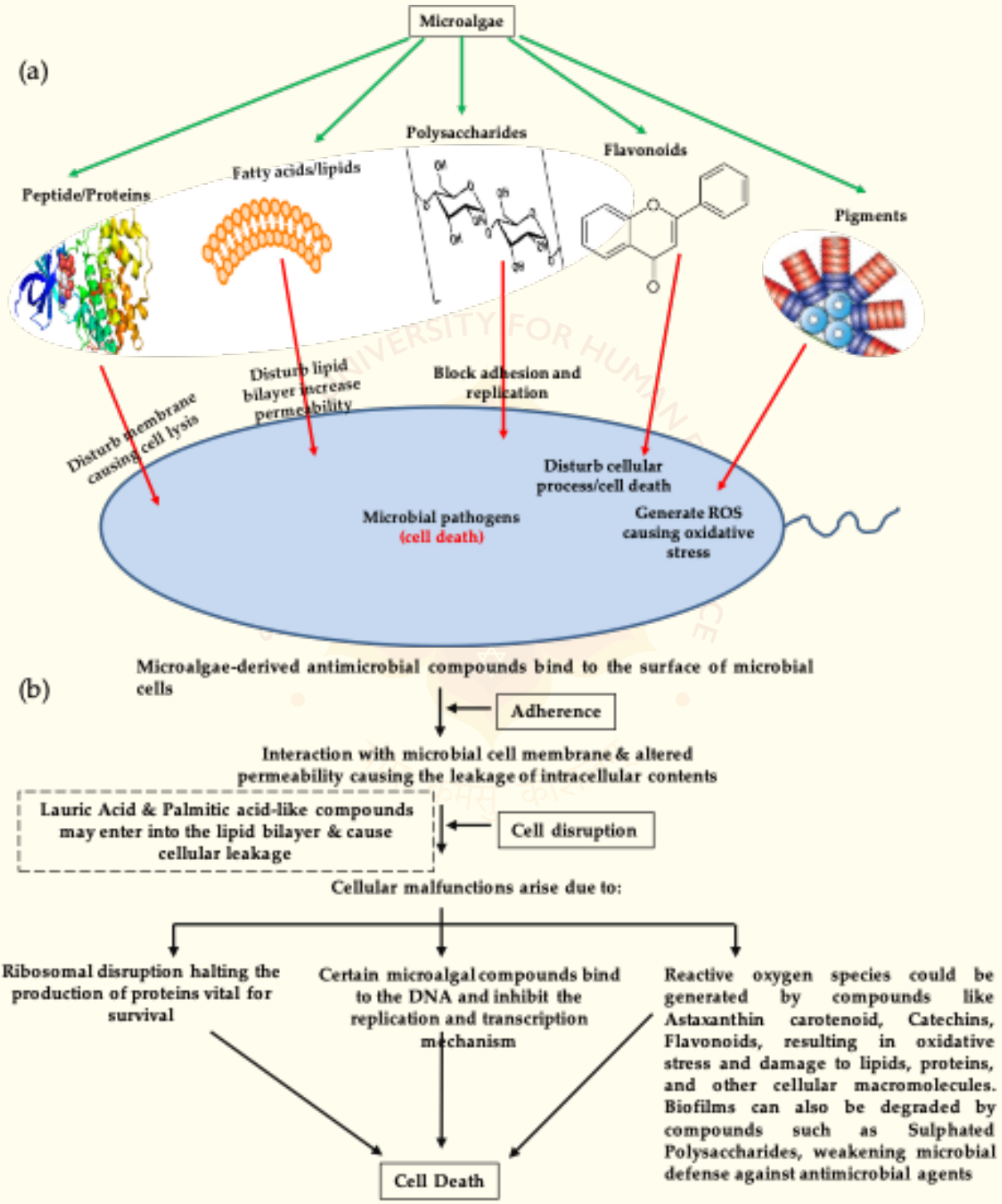
2. Microalgal Antimicrobial Compounds and Mode of Action

The rising incidence of antibiotic-resistant pathogens has prompted the exploration of new antimicrobial agents, with microalgae emerging as a largely underutilized source of such compounds. Their capacity to flourish in a variety of often harsh environments has led to the development of distinctive biochemical pathways, which in turn produce defensive compounds (both primary and secondary metabolites) that exhibit significant antimicrobial properties[13,14,15]. These metabolites, including peptides, fatty acids, polysaccharides, phenolic compounds, and pigments, have different modes of action (Table 1 and Figure 2), and demonstrate efficacy against a wide range of pathogens, encompassing bacteria, fungi, parasites, and viruses[15,16].

Table 1. Antimicrobial compounds produced by microalgae and their modes of action

Compound Type	Biomolecules/ Microalgae	Mode of Action	Pathogens Targeted	Reference
Peptides and Proteins	Nostocyclopeptides, AMPs from *Tetraselmis suecica*	Disrupt cell membranes, leading to cell lysis and de ath	Gram-positive and Gram-negative bacteria	[17,20]
Fatty Acids	EPA, DHA from *Chlorella, Spirulina, Phaeodactylum tricornutum*	Disrupt lipid bilayers, increasing membrane permeability	*Staphylococcus aureus, Escherichia coli,* MRSA	[21]
Polysaccharides	Sulfated polysaccharides from *Porphyridium, Dunaliella*	Inhibit bacterial and viral adhesion and replication; block viral entry	HSV, HIV, *Bacillus subtilis, Pseudomonas aeruginosa*	[24,25]
Phenolic Compounds	Flavonoids, phenolic acids, tannins from *Haematococcus pluvialis*	Neutralize ROS, disrupt cellular processes	*Candida albicans,* drug-resistant food-borne pathogens	[15,27]
Pigments	Phycobiliproteins, chlorophylls, carotenoids from *Chlorococcum humicola*	Generate ROS, cause oxidative stress, disrupt cell membranes	*B. subtilis, S. aureus, E. coli*	[28,29]

Figure 2. Microalgal antimicrobial compounds (a, b) and their mode of action



2.1 Peptides and Proteins

Microalgae are recognized for their ability to synthesize antimicrobial peptides (AMPs), which are small, positively charged molecules essential to the innate immune defense of these organisms. AMPs generally exert their antimicrobial properties by disrupting the cell membranes of pathogens, resulting in cell lysis and subsequent death[17,18]. For instance, the cyanobacterium *Nostoc* produces nostocyclopeptides, a category of cyclic peptides that have shown significant antibacterial efficacy against various Gram-positive and Gram-negative bacteria. Additionally, research by Guzman et al.[20] revealed that AMPs extracted from the microalga *Tetraselmis suecica* also demonstrated antibacterial properties.

2.2 Fatty Acids

Polyunsaturated fatty acids (PUFAs) derived from microalgae, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have demonstrated notable antimicrobial effects. These fatty acids compromise the integrity of microbial cell membranes by disrupting lipid bilayers, which results in increased permeability and subsequent cell death. For example, microalgae such as *Chlorella* and *Spirulina* are recognized for their substantial production of PUFAs, which have been effective in inhibiting the proliferation of various bacterial pathogens, including *Staphylococcus aureus* and *Escherichia coli*[21]. Additionally, EPA and DHA sourced from *Phaeodactylum tricornutum* have exhibited antimicrobial properties against methicillin-resistant strains of Gram-positive *S. aureus*[22]. Furthermore, fatty acid extracts from *Coccomyxa onubensis* have shown inhibitory effects against a diverse array of Gram-positive and Gram- negative bacteria as well as fungi, with the lowest minimum inhibitory concentration (MIC) recorded at 305 and 106 µg/mL against *E. coli* and *Proteus mirabilis,* respectively[23]. The significance of the antimicrobial properties of these fatty acids is underscored by their dual functionality as both nutritional and therapeutic agents.

2.3 Polysaccharides

Sulfated polysaccharides extracted from microalgae, particularly those produced by *Porphyridium* and *Dunaliella*, have attracted significant interest due to their extensive antimicrobial properties. These polysaccharides impede the proliferation of bacteria and viruses by disrupting their adhesion and replication mechanisms. For instance, sulfated polysaccharides derived from *Porphyridium cruentum* have demonstrated the ability to inhibit the replication of herpes simplex virus (HSV) and human immunodeficiency virus (HIV)[24]. The antiviral efficacy of these compounds is linked to their capacity to prevent viral entry into host cells, positioning them as promising candidates for antiviral therapy development. Recently, Pointcheval et al.[25] examined the antimicrobial characteristics of exopolysaccharide-rich extracts from five microalgal species, which exhibited growth inhibition against both Gram- positive (*Bacillus subtilis*) and Gram-negative bacteria (*Pseudomonas aeruginosa*), as well as fungi (*Cladosporium cladosporioides*). The diverse bioactive properties of these extracts vary according to the specific microalgal species involved.

2.4 Phenolic Compounds

Microalgae, particularly *Haematococcus pluvialis*, are known to synthesize phenolic compounds, which encompass flavonoids, phenolic acids, and tannins. These compounds possess significant antioxidant and antimicrobial properties. They effectively neutralize reactive oxygen species (ROS) and impede the proliferation of pathogenic microorganisms by interfering with their cellular mechanisms. For instance, phenolic compounds derived from *H. pluvialis* have demonstrated the ability to inhibit the growth of *Candida albicans*, a prevalent fungal pathogen[15]. The combined antioxidant and antimicrobial functions of these compounds render them especially advantageous in the formulation of multifunctional therapeutic agents[26]. Research conducted by Alshuniaber et al.[27], revealed that fraction B of the methanol extract from Spirulina is rich in polyphenols, which exhibit a broad spectrum of antimicrobial activity against drug-resistant foodborne bacterial pathogens. Additionally,

various potential secondary metabolites, including benzophenone, dihydro-methyl-phenylacridine, carbanilic acid, dinitrobenzoate, propanediamine, isoquinoline, piperidine, oxazolidine, and pyrrolidine, have shown efficacy against both Gram-positive and Gram-negative pathogens.

2.5 Pigments

Microalgae serve as abundant reservoirs of pigments, including phycobiliproteins, chlorophylls, and carotenoids, which have been recognized for their antimicrobial properties[28]. For example, the green alga *Chlorococcum humicola* synthesizes pigments that exhibit efficacy against various bacterial pathogens, such as *B. subtilis, S. aureus,* and *E. coli*[29]. The antimicrobial effects of these pigments are believed to arise from their capacity to produce ROS within microbial cells, resulting in oxidative stress and subsequent cell death. Additionally, these pigments can compromise bacterial cell membranes by interacting with their lipid components, leading to cell leakage and ultimately cell lysis. Microalgae thus represent a significant and largely underexplored source of antimicrobial agents. Ongoing research and advancements in microalgal biotechnology will be essential for fully harnessing the potential of these extraordinary organisms.

3. Microalgae as a Source of Antibacterial Activity

Microalgae have emerged as a promising source of bioactive compounds with antimicrobial properties, driven by the increasing burden of antibiotic resistance in humans[30.] These compounds have demonstrated significant potential in inhibiting a wide range of pathogenic bacteria, both Gram-positive and Gram-negative (Table 2). The first milestone in microalgal antibacterial research came with *Chlorella vulgaris*, from which bactericidal compounds were initially isolated, demonstrating effective inhibition against *P. aeruginosa, S. aureus, Streptococcus pyogenes,* and *B. subtilis*[31]. Further studies confirmed its broad-spectrum activity, with methanol extracts showing effectiveness against *S. aureus, E. coli*, *B. subtilis*, and *B. cereus*[32,33]. Notably, Chlorella sp. UKM8's methanol extract exhibited broad-spectrum activity against both Gram-positive and Gram-negative bacteria, attributed to compounds such as phenol (18.5%), hexadecanoic acid (18.25%), phytol (14.43%), and octadecadienoic acid (13.69%)[34]. Methanol extracts of *Scenedesmus obliquus* demonstrated activity against *E. coli, B. cereus*, and *S. aureus,* producing inhibition zones of 9-9.7 mm[35]. Additionally, whole-cell applications of *Scenedesmus spp.* cells eliminated *Salmonella enterica* growth within 48 hours, though the mechanism remained unclear[36]. Extracts from *Dunaliella tertiolecta* inhibited *S. aureus* and *P. aeruginosa*[37], while *D. salina* extracts, attributed to fatty acids like α-linolenic, palmitic, and oleic acid, showed activity against *E. coli,* and *S. aureus*[38]. The microalga *Isochrysis galbana* synthesized antibacterial fatty acids that notably limited the growth of pathogenic Vibrio species such as *V. alginolyticus*, *V. campbellii,* and *V. harveyi,* except *V. parahaemolyticus*[39].

Alsenani et al.,[40] found strong antibacterial activity against Gram-positive bacteria than Gram-negative bacteria from the microalgae extracts of *Isochrysis galbana, Scenedesmus sp.* and *Chlorella sp*., and identified and purified the fatty acids of linoleic acid, oleic acid, docosahexaenoicacid (DHA) and eicosapentaenoic acid (EPA) from the extract (Figure 3). Similarly, *Phaeodactylum tricornutum* extracts, particularly hexadecatrienoic acid (HTA), were active against *S. aureus,* including multidrug-resistant strains (MRSA)[41]. *T. suecica* extracts, containing fatty acids like methyl caprate and palmitic acid, elicited growth inhibition on *Streptococcus pyogenes*[42]. Short-chain fatty acids from *H. pluvialis* ethanolic extract also showed antimicrobial activity against Gram-negative *E. coli*[43]. *C. vulgaris* peptides inhibited *P. aeruginosa* growth[15,] while *Dunaliella tertiolecta* extracts also demonstrated activity against this pathogen[37]. *Nannochloropsis oceanica*, *Isochrysis* sp., and *Thalassiosira weissflogii* also showed promising results against *V. harveyi*[44].

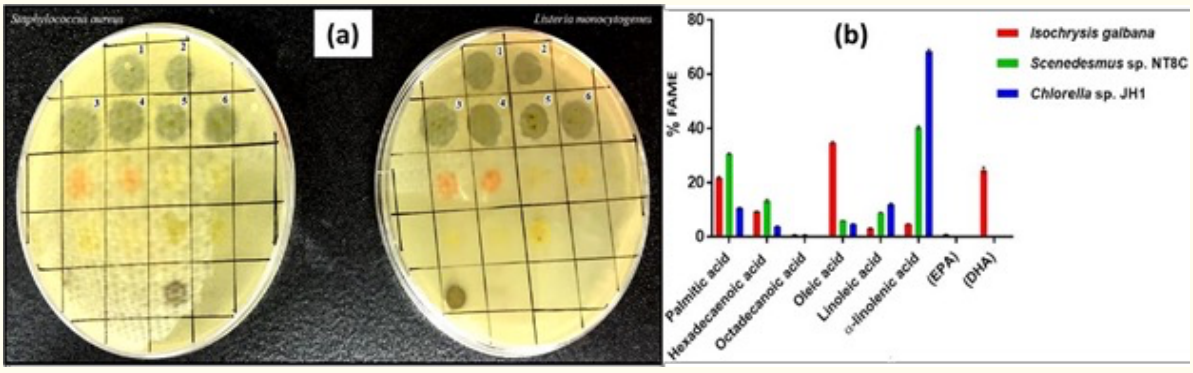
Ali and Doumandji[45] found methanol extract from Spirulina exhibited widespread spectrum of antimicrobial activities against Gram-positive bacteria (43 ± 4.24 mm) and minimum inhibitory concentrations (MIC) 128

± 0.71 µg/mL. Organic extracts from *Chlorella* excreted a broad spectrum of antimicrobial substances against Gram-negative bacteria. Recently, Ilieva et al.,[46] discussed *Arthrospira platensis* with very potent antibacterial activity and minimum inhibitory concentrations (MICs) as low as 2-15 µg/mL against bacterial fish pathogens including *Bacillus* and *Vibrio* spp., also demonstrated an inhibition zone (IZ) of 50 mm against *S. aureus*. *D. salina* exhibited MIC values lower than 300 µg/mL and an IZ value of 25.4 mm on different bacteria, while *D. tertiolecta* showed MIC values of 25 and 50 µg/mL against some Staphylococcus spp. These values fulfill the criteria for significant antibacterial activity and sometimes are comparable or exceed the activity of the control antibiotics. Fusiform morphotypes of *P. tricornutum* expressed higher antibacterial activity than oval morphotypes, attributed to high levels of palmitoleic acid and other bioactive fatty acids[22]. Interestingly, polysaccharides from *Chlamydomonas reinhardtii* showed promising anti- biofilm potential by preventing biofilm formation and dissolving existing biofilms[47].

Influence of methanol extraction has proven effective for isolating antimicrobial components from microalgae[48]. For example, *Chlorella* methanolic extracts showed antimicrobial activity against various bacteria with MIC values ranging from 2.6 to 5 mg/mL[49]. Short-chain fatty acids from *H. pluvialis* ethanolic extract showed antimicrobial activity against *E. coli* and *S. aureus*[43]. Mixed solvents (methanol:acetone:diethyl ether mixture) extracts of desert-sourced *C. vulgaris* and *D. salina* demonstrated broad-spectrum antibacterial activity[50]. Environmental conditions may influence antibacterial properties, as demonstrated by *Cosmarium* sp., from hot springs showing significant activity against various bacteria[51], while *Cosmarium laeve* from non-extreme environments showed minimal activity. This indicates that stressed microalgae produce secondary metabolites with bioactive molecules, particularly with antimicrobial activities[52].

Further research has shown the efficacy of microalgal compounds against drug-resistant ESKAPE germs. For example, methanol extracts from *Chlorella vulgaris* stopped the growth of drug-resistant *Klebsiella pneumoniae*. The lowest amount needed to inhibit growth was 3.2 mg/mL[33]. Also fatty acid (palmitoleic acid) extracts from *Phaeodactylum tricornutum* were effective against methicillin-resistant *Staphylococcus aureus* (MRSA) and *Acinetobacter baumannii*. The lowest amounts needed ranged from 50-100 µg/mL[41]. Furthermore, *Scenedesmus obliquus* extracts, which have phenolic compounds and fatty acids, showed good results (inhibition) against *Pseudomonas aeruginosa*[35]. These results show that microalgal compounds could be new treatments for ESKAPE germs, and warrant continued investigations on their mechanism of action and for clinical use.

Figure 3. Reproduced with permission from Alsenani et al., (2020)[40], (a), Inhibition zones of *Staphylococcus aureus* and *Listeria monocytogenes* growth. 1: *Isochrysis galbana* crude extract; 2: I. galbana n-hexane fraction; 3: *Scenedesmus* sp. crude extract; 4: *Scenedesmus* sp. n-hexane fraction; 5: *Chlorella* sp. crude extract; 6: *Chlorella* sp. n-hexane fraction. (b), Percentage of individual fatty acid methyl esters (FAME) detected in each microalgal species.



3.1 Microalgal Compounds Against Biofilm Infections

Microalgal compounds have shown promise to fight biofilm infections, which resist antibiotics. Polysaccharides from C. *reinhardtii* have an impact on anti-biofilm activity. They stop biofilm formation and break up existing *P. aeruginosa* biofilms. At 100 µg/mL, they cut biofilm biomass by 60%[47]. Also methanolic extracts from *Scenedesmus obliquus* full of phenolic compounds, prevent *S. aureus* from forming biofilms. They reduce biofilm sticking by 70%[35]. These compounds likely alter or interfere with quorum sensing and the strength of the extracellular matrix, which are key to biofilm stability. This area also encourages continued research on mechanistic aspects and for their effective use in hospitals for long-lasting infections linked to medical devices.

Table 2. Antibacterial activity of microalgae, their active compounds, and the targeted bacterial pathogens

Microalgae Species	Active Compounds	Pathogens Targeted	Key Findings	Reference
C. vulgaris	Phenol, hexadecanoic acid, phytol, octadecadienoic acid	Pseudomonas aeruginosa, Staphylococcus aureus, Streptococcus pyogenes, Bacillus subtilis	Broad-spectrum activity, effective against Gram-positive and Gram-negative bacteria	[31,34]
Scenedesmus obliquus	Methanolic extracts	E. coli, B. cereus, S. aureus	Inhibition zones of 9-9.7 mm	[35]
Dunaliella tertiolecta	Fatty acids	S. aureus, P. aeruginosa	Inhibited growth of pathogens	[37]
Dunaliella salina	α-linolenic, palmitic, oleic acid	E. coli, S. aureus	MIC values lower than 300 µg/mL, IZ of 25.4 mm	[38]
Isochrysis galbana	Fatty acids	Vibrio alginolyticus, V. campbellii, V. harveyi,	Strong activity against Vibrio species	[39]
I. galbana, Scenedesmus sp. Chlorella sp.	*Fatty acids (linoleic acid, oleic acid, DHA and EPA*	S. aureus, Listeria monocytogenes	Strong activity against Gram-positive	[40]

4. Microalgal Antifungal Activity

Fungal diseases are among the deadliest contagious diseases, causing approximately 1.5 million deaths annually[53]. Recent outbreaks, such as mucormycosis (black fungus), have highlighted the urgent need for effective antifungal treatments[54]. Despite the potential of microalgae as a source of antifungal agents, only a limited number of studies have explored this area, even though over 400 fungal species are known to act as opportunistic human pathogens[55]. The detrimental effects of fungal infections, such as black gill infections, allergic reactions, and asthmatic diseases, underscore the need for more comprehensive screening of microalgal species to identify potential antifungal compounds[55].

Microalgae have shown promising antifungal properties against a range of fungal species (Table 3). For instance, fatty acids derived from *Nannochloropsis oculata* have been shown to inhibit the growth of *C. albicans*[56]. Similarly,

liquid extracts of *C. vulgaris* and *Chlorella ellipsoidea* exhibited antifungal activity against *Aspergillus niger* and *Aspergillus fumigatus*[57,58]. Ethanol extracts of *H. pluvialis*, containing methyl lactate and butanoic acid, also demonstrated antifungal properties against *A. niger*[43]. Several strains of microalgae isolated from freshwater lakes in Turkey have shown antifungal activity against *Saccharomyces cerevisiae, C. albicans, Candida tropicalis,* and *Chlorococcus* sp.[59]. Additionally, liquid extracts of *Chlorococcum humicola* and supercritical CO_2 extracts from *D. salina* have shown antifungal activity against *A. niger* and *C. albicans*[29]. Furthermore, liquid extracts of *Heterochlorella luteoviridis* and *Porphyridium purpureum* have been effective against *C. albicans*[60]. Karatungiols, a novel antimicrobial polyol compounds, were isolated from the cultivated symbiotic marine dinoflagellate *Amphidinium* sp., exhibited antifungal activity against *A. niger* at 12 µg/disc[61]. Aqueous extracts from microalgal species such as *Spirulina, Chlorella, Nannochloropsis, Scenedesmus,* and *P. tricornutum* have shown antagonistic activity against fungal pathogens like *Alternaria alternata, Sclerotium rolfsii,* and *Rhizoctonia solani* in vitro. Among these, *Scenedesmus obliquus* exhibited the highest inhibition against *S. rolfsii* (32.01 ± 4.82%), while *Nannochloropsis* sp. and *P. tricornutum* suppressed the growth of *S. rolfsii* and *R. solani* by up to18.35 ± 3.45%62. These results suggest that microalgae could serve as sustainable alternatives to chemical fungicides in agriculture.

Table 3. Antifungal activity of microalgae, their active compounds, and the targeted fungal pathogens

Microalgae Species	Active Compounds	Pathogens Targeted	Key Findings	Reference
Nannochloropsis oculata	Fatty acids	*Candida albicans*	Growth inhibition	[56]
Chlorella vulgaris	Liquid extracts	*Aspergillus niger, Aspergillus fumigatus*	Antifungal activity observed	[57]
Chlorella ellipsoidea	Liquid extracts	*A. niger, Aspergillus fumigatus*	Antifungal activity observed	[58]
Haematococcus pluvialis	Methyl lactate, butanoic acid	*A. niger*	Ethanol extracts showed antifungal properties	[43]
Chlorococcum humicola	Liquid extracts	*A. niger, C. albicans*	Antifungal activity observed	[29]
Dunaliella salina	Supercritical CO2 extracts	*A. niger, C. albicans*	Antifungal activity observed	
Heterochlorella luteoviridis	Liquid extracts	*C. albicans*	Effective against C. albicans	[60]
Porphyridium purpureum	Liquid extracts	*C. albicans*	Effective against C. albicans	
Amphidinium sp.	Karatungiols (polyol compounds)	*A. niger*	Antifungal activity at 12 µg/disc	[61]
Scenedesmus obliquus	Aqueous extracts	*Sclerotium rolfsii*	Highest inhibition (32.01 ± 4.82%) against S. rolfsii	[62]
Nannochloropsis sp.	Aqueous extracts	*S. rolfsii, Rhizoctonia solani*	Suppressed growth by up to 18.35 ± 3.45%	
Phaeodactylum tricornutum	Aqueous extracts	*S. rolfsii, R. solani*	Suppressed growth of fungal pathogens	
Spirulina	Aqueous extracts	*Alternaria alternata, S. rolfsii, R. solani*	Antagonistic activity against fungal pathogens	
Chlorella	Aqueous extracts	*A. alternata, S. rolfsii, R. solani*	Antagonistic activity against fungal pathogens	

5. Microalgal Antiviral Activity

Microalgae-derived compounds have demonstrated significant antiviral activity against a range of viruses, including herpes simplex virus (HSV), human immunodeficiency virus (HIV), influenza virus, and SARS-CoV-2 (Table 4) and shown potential development of antiviral therapies and vaccines. Sulfated polysaccharides from *Porphyridium cruentum* have shown antiviral activity against HSV and HIV[63]. Similarly, Spirulina extracts have been reported to inhibit the replication of influenza virus[64]. China's first anti-AIDS drug, a heparin-like sulfated polysaccharide (sulfated polymannuroguluronate, SPMG) extracted from the brown macroalga Saccharina japonica, has entered Phase II clinical trials. This compound inhibits HIV replication and interferes with HIV entry into host T lymphocytes[16]. The inhibitory effects of microalgae-based bioactive metabolites are often due to their interaction with the positive charge on the virus's cell surface, preventing penetration into the host cell. Alternatively, these compounds may inhibit viral genome transcription or obstruct the formation of new virus particles[65-67]. *Spirulina* pigments C-phycocyanin (PC) has demonstrated unique antiviral properties against HIV-1 by inhibiting reverse transcriptase and protease enzymes. A concentration of 0.356 mg/mL of PC was found to inhibit HIV-1 replication by 80% while remaining safe for normal cells[68]. Ethanol extracts from *H. pluvialis* have demonstrated strong inhibition of herpes simplex virus type 1 (HSV-1) infection. The antiviral activity is attributed to short-chain fatty acids such as propanoic, lactic, and butanoic acids, as well as palmitic acid, hexadecatrienoic acid, and α-linolenic acid[69]. Microalgal species such as *H. pluvialis* and *D. salina* have also shown antiherpetic activity[69]. Extracts from *A. maxima* demonstrated greater antiviral activity compared to the commercial antiviral ribavirin. The study involved culturing four microalgae strains and testing their antiviral effects in vitro, revealing all strains had anti-Mayaro activity[70]. Compounds such as α- and β-ionone, neophytadiene, β-cyclocitral, and phytol extracted from microalgae have demonstrated antiviral properties[71]. These compounds further underscore the potential of microalgae as a source of bioactive metabolites for antiviral applications. Algae-derived vaccines are being explored for their potential in treating viral infections. For example, *D. salina* has been used to express a surface antigen for hepatitis B treatment[72], and *Chlamydomonas* has been engineered to produce malaria vaccine antigens[73]. *Spirulina*- enriched diets have shown antiviral effects against HIV, improved insulin sensitivity, and regulated IL-6 and lipoprotein lipase activity. Immulina, a Spirulina extract, enhances immunological functions by activating toll-like receptors[74]. *H. pluvialis,* enriched with astaxanthin, has shown potential in reducing acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). This suggests probable actions against cytokine storms caused by SARS-CoV-2 by increasing lymphocytes and reducing oxidative damage or decreasing IL-6 activity[75.76].

Table 4. Antiviral activity of microalgae, their active compounds, and the viral targets

Microalgae Species	Active Compounds	Pathogens Targeted	Key Findings	Reference
Porphyridium cruentum	Sulfated polysaccharides	HSV, HIV	Inhibited viral replication and entry	[63]
Spirulina	C-phycocyanin (PC)	Influenza virus, HIV-1	Inhibited viral replication; PC inhibited HIV-1 reverse transcriptase and protease	[64, 68]
Saccharina japonica	Sulfated polymannuroguluronate (SPMG)	HIV	Inhibited HIV replication; entered Phase II clinical trials	[16]
Haematococcus pluvialis	Short-chain fatty acids (propanoic, lactic, butanoic acids), astaxanthin	HSV-1, SARS-CoV-2	Inhibited HSV-1; potential against cytokine storms in SARS-CoV-2	[69, 75]
Dunaliella salina	Extracts	HSV	Antiherpetic activity observed	[69]
A. maxima	Extracts	Mayaro virus	Greater antiviral activity compared to ribavirin	[70]
D. salina	Surface antigen	Hepatitis B	Expressed hepatitis B surface antigen	[72]

6. Microalgal Antiprotozoan Activity

Microalgae have demonstrated significant antiprotozoan activity against neglected tropical diseases (NTDs) such as leishmaniasis, Chagas disease, and human African trypanosomiasis (HAT). These diseases are caused by protozoan parasites, including *Leishmania* spp., *Trypanosoma cruzi*, and *Trypanosoma brucei*[77]. The bioactive compounds derived from microalgae show promise as potential treatments for these diseases (Table 5), addressing the urgent need for effective and safe therapies.

Microalgal extracts have shown significant trypanocidal activity against *T. cruzi*, the causative agent of Chagas disease. Methanol extracts of *S. obliquus* and *T. suecica*, as well as ethanol extracts of *C. reinhardtii* and *T. suecica*, demonstrated trypanocidal activity against both extracellular trypomastigotes and intracellular amastigotes, with IC_{50} values ranging from 60 to 70 µg/mL[9]. The ethanol extract of *C. reinhardtii* was found to enhance the efficacy of the conventional antichagasic drug nifurtimox, suggesting a potential synergistic effect[9]. Additionally, *C. vulgaris* and *Tetradesmus obliquus* have shown significant trypanocidal activity against *T. cruzi*. *C. vulgaris*, in particular, demonstrated a high selectivity index (SI > 18) and no cytotoxic effects on Vero cells, making it a promising candidate for drug development[78]. Microalgae have also demonstrated antileishmanial activity against *Leishmania* spp., the causative agents of leishmaniasis. For instance, *D. salina* showed moderate antileishmanial activity, which may be attributed to its high β-carotene content[77]. Gharbi et al.[79] identified *Dunaliella* sp. from Tunisian water bodies, highlighting its promising antileishmanial activity against *L. infantum* and *L. major* (IC_{50}=151 and 284 µg/mL, respectively). Similarly, *D. tertiolecta* and *A. platensis* extracts demonstrated a selectivity index (SI) of 4.7 and 3.8 against *L. infantum,* outperforming meglumine antimoniate (SI=2.1), respectively[80]. Cyanobacteria have also been a source of antileishmanial compounds. Palstimolide A, a complex polyhydroxy macrolide isolated from *Leptolyngbya* sp., showed significant antileishmanial activity with an IC_{50} of 4.67 µM[81]. Coibacin A, derived from *Oscillatoria* sp., also demonstrated antileishmanial properties[82]. Viridamide A, isolated from *Oscillatoria nigro-viridis*, showed antitrypanosomal activity with an IC_{50} of 1.1 µM[83]. Additionally, peptides such as almiramides, dragonamides, and herbamide, biosynthesized by Lyngbya majuscula, exhibited activity against *T. brucei* at micromolar concentrations[77]. Microalgal extracts have also shown antiplasmodial activity against *Plasmodium falciparum*, the causative agent of malaria. The chloroform extract of *Skeletonema costatum* demonstrated the highest inhibitory activity (91% inhibition) with an IC_{50} of 0.043 µg/mL, while the ethanol extract of *S. platensis* showed 91.9% inhibition with an IC_{50} of 5.25 µg/mL[84]. Despite the promising results, no natural microalgae products or their derivatives have entered clinical testing for antiprotozoan activity. Further research is needed to isolate and characterize bioactive compounds from microalgae and cyanobacteria, evaluate their safety and efficacy, and explore their potential as novel treatments for NTDs.

Tabel 5. Antiprotozoan activity of microalgae, their active compounds, and the protozoan parasite targets

Microalgae Species	Active Compounds	Pathogens Targeted	Key Findings	Reference
Scenedesmus obliquus	Methanolic extracts	Trypanosoma cruzi (Chagas disease)	IC50 values of 60-70 µg/mL against trypomastigotes and amastigotes	[9]
Tetraselmis suecica	Methanolic and ethanolic extracts	T. cruzi	IC50 values of 60-70 µg/mL; synergistic effect with nifurtimox	
Chlamydomonas reinhardtii	Ethanolic extracts	T. cruzi	Enhanced efficacy of nifurtimox; IC50 values of 60-70 µg/mL	
Chlorella vulgaris	Extracts	T. cruzi	High selectivity index (SI > 18); no cytotoxicity on Vero cells	[78]
Dunaliella salina	β-carotene	Leishmania infantum, L. major	Moderate antileishmanial activity; IC50 = 151 and 284 µg/mL SI of 4.7	[77,79]
Dunaliella tertiolecta	Extracts	Leishmania infantum	SI of 4.7	[80]
Arthrospira platensis	Extracts	L. infantum	SI of 3.8	
Leptolyngbya sp.	Palstimolide A (polyhydroxy macrolide)	Leishmania spp.	IC50 of 4.67 µM	[81]
Oscillatoria sp.	Coibacin A, Viridamide A	Leishmania spp., Trypanosoma brucei	IC50 of 1.1 µM for Viridamide A	[82,83]
Lyngbya majuscula	Almiramides, dragonamides, herbamide	T. brucei (HAT)	Activity at micromolar concentrations	[77]
Skeletonema costatum	Chloroform extracts	Plasmodium falciparum (malaria)	91% inhibition; IC50 of 0.043 µg/mL	[84]
Spirulina platensis	Ethanol extracts	P. falciparum (malaria)	91.9% inhibition; IC50 of 5.25 µg/mL	

7. Challenges and Future Directions

Microalgae show real promise as antimicrobial powerhouses, yet there are hurdles before their potential is fully harnessed. There is a need to fine-tune their growth conditions to maximize the yield of bioactive compound production, develop better extraction and purification methods, and establish rigor in testing their safety and efficacy. Another challenge is that many microalgae derived compounds have complex structures that make large-scale production tricky. The good news is that breakthroughs in genetic engineering and synthetic biology could be game-changers. Imagine tweaking microalgae DNA to pump out more antimicrobial compounds or even engineer entirely new ones, which could dramatically boost both yields and variety. Pairing microalgae farming with bio-refinery techniques might also offer a cost-effective, eco-friendly way to scale up production. Interestingly, research into antifungal resistance has trailed behind antibacterial studies, partly because fungal

infections weren't seen as major threats until recently. But the stakes are high for example, deaths from candidiasis have surged due to modern medical practices like use of immunosuppressive therapies and broad-spectrum antibiotics[85]. Ability of microalgae to produce diverse bioactive molecules makes them exciting candidates for next-gen antifungals and other antimicrobials. However, there is imminent need for extensive research to unlock their full potential both for fighting human infections and protecting crops; and to develop sustainable solutions that actually work in the real world.

7.1 Bioprocesses and Bioreactor Design for Antimicrobial Production

Producing antimicrobial compounds from microalgae needs custom bioprocesses and bioreactor designs to boost yield and cut costs. Photobioreactors built to improve light penetration and CO_2 delivery, play a key role in growing microalgae. These systems must keep ideal conditions like light intensity (100-200 µmol photons m^{-2} s^{-1}), pH (7-9), and temperature (20-30°C) to boost biomass and metabolite production14. Unlike bacterial fermenters, photobioreactors don't need organic carbon sources, which might lower running costs. But, issues like high energy costs for mixing and lighting, plus the need for good harvesting and extraction methods, increase financial implications. Current studies focus on using bio-refinery approaches where they extract many products (e.g., biofuels, pigments, and antimicrobials) from microalgal biomass to improve cost-effectiveness[11]. To scale up production, better bioreactor designs and process improvements to make microalgal antimicrobials compete with synthetic options emerge as the need of the hour.

7.2 Safety and Efficacy of Microalgal Compounds

The potential of microalgae-derived antimicrobial compounds to treat diseases faces challenges due to the lack of thorough safety and efficacy studies. Lab tests show these compounds can fight various germs, but research on living organisms or in clinical settings is limited. Sulfated polysaccharides from *Porphyridium cruentum* which can combat HSV and HIV viruses without harming cells[24] is a good example. However, not enough is known about how they move through and might affect the human body. In the same way, peptides from Chlorella vulgaris can kill bacteria, but if they trigger immune responses or cause harm throughout the body needs to be established[20]. Rules set by agencies like the Food and Drug Administration (FDA) require a lot of testing prior to and during clinical trials to ensure these compounds are safe. This includes looking at short-term and long-term toxic effects, allergic reactions, and unintended impacts. Moving forward, researchers should focus on running standard toxicity tests and clinical trials to establish how safe these compounds are, which will help bring them into regular medical use.

7.3 Genetic Engineering for Enhanced Antimicrobial Production

Researchers explore new ways to use genetic engineering and synthetic biology to get microalgae to produce more and different types of antimicrobial compounds. They apply novel genome editing tools like CRISPR-Cas9, RNAi, ZNFs, TALENs and synthetic biology to adjust microalgal genomes. This allows them to improve processes inside the cells that create useful substances. Researchers enhanced genes linked to enzymes, lipid synthesis and pigment production[86,87]. Nuclear engineering allows protein secretion and post-translational modifications, such as glycosylation, while chloroplast engineering ensures high-level, stable expression without these modifications[88]. *Chlamydomonas reinhardtii* has emerged as a key model, producing therapeutic proteins like endolysins at ~1% of total soluble protein. Diatoms, such as Thalassiosira pseudonana, have been engineered to produce vaccines, with yields enhanced by conditions like silicon limitation. Techniques like codon optimization and synthetic promoters have boosted expression levels, and companies like Triton Health and Nutrition are advancing commercial production[88]. While these advancements are promising, challenges remain. Complicated microalgal genomes and fears of unintended genetic effects add to the difficulty. GMO regulations also create obstacles. Using techniques such as high-throughput screening and metabolic modeling may help make engineered microalgae more practical to produce antimicrobial compounds on a large scale.

7.4 Potential for Resistance to Microalgal Compounds

The rise of resistance to antimicrobial compounds from microalgae also poses a serious problem, but research is still limited as the field is new. Conventional antibiotics target one specific pathway, while microalgal compounds like antimicrobial peptides (AMPs) and fatty acids work in several ways. They disrupt membranes and cause oxidative stress, which might make resistance harder to develop[18]. AMPs from *Nostoc* species, for instance, break down bacterial membranes in a broad non-specific way making it tough for bacteria to build resistance[19]. Still long-term exposure might push bacteria to adapt, like by activating efflux pumps or changing their membrane structure. The need to study resistance patterns, test combination treatments, and perform detailed investigations to reduce this risk and keep microalgal compounds effective for the future remains high.

8. Conclusion

Microalgae constitute a large, mostly underutilized source of bioactive substances with considerable antimicrobial capabilities. Their capacity to generate a varied range of metabolites such as peptides, fatty acids, polysaccharides, phenolic compounds, and pigments makes them a valuable alternative in combating antibiotic-resistant pathogens. Nevertheless, issues like enhancing their cultivation conditions, refining extraction techniques, and guaranteeing the safety and efficacy of these compounds need to be tackled to completely leverage their therapeutic capabilities. Developments in genetic engineering and synthetic biology present exciting prospects for improving the production and variety of these bioactive metabolites. Intense research especially in vivo studies with interdisciplinary collaboration will be crucial to realize the complete potential of microalgae, leading to sustainable and effective antimicrobial treatments in the future.

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