

The Potential of Microalgae in the Era of Antibiotic Resistance

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Abstract: A major global health issue is antimicrobial resistance. Antibiotic resistance is caused by bacteria gradually developing resistance to antibiotics. This resistance allows bacteria to survive conventional therapeutic doses of antibiotics, leading to persistent infections and making treatment more difficult. The emergence of antibiotic resistance in microalgae is a complicated biological process that is connected to a number of variables, such as bacterial-microalgae interactions, environmental pollution, and antibiotic use. This study reviews the antibacterial mechanisms of microalgae and their role in antibiotic elimination, such as the ability of microalgae to produce substances with broad-spectrum antimicrobial activity, the synergistic effect of microalgae and antibiotics to enhance the antibacterial effect of antibiotics, and the potential of microalgae to degrade antibiotics due to their impact on antibiotic antimicrobial activity. In addition, this paper discusses the limiting factors and future research directions of the application of microalgae impact products, and the analysis shows that microalgae, as a natural material, has good potential application value in antimicrobial and antibiotic removal, and provides new ideas and solutions to address the problem of antibiotic resistance.

Keywords: Microalgae, Antibiotic resistance, Antibacterial, Antibiotic

1. Introduction

A class of medications known as antibiotics is used to treat bacterial illnesses by preventing the development, reproduction, or death of bacteria. Macrolides, cephalosporins, and penicillins are examples of common antibiotics. Antibiotics' discovery has been crucial to preventing and managing infectious illnesses in humans, preventing and treating them [1]. Antimicrobial resistance (AMR) is the ability of bacteria to survive in the presence of antimicrobial drugs [2]. Under selective pressure, bacteria have evolved resistance mechanisms to various antibiotics. Among them, antibiotic resistance genes (ARGs) are the root cause of bacterial resistance and the spread of resistance. Vertical gene transfer (VGT) and horizontal gene transfer (HGT) are the primary ways that ARGs are dispersed across the environment [3]. Since the resistant strains die, the DNA produced by them that carries antibiotic-resistance genes will remain in the environment for a long time because deoxyribonucleic acid protects it. Antibiotics are the cornerstone of antibacterial agents in medicine, agriculture, and animal husbandry, and their overuse will intensify [4]. The contamination of resistant

genes and the residual toxicity of antibiotics caused by misuse have sparked widespread attention from scholars worldwide.

Microalgae is a general term for a group of microplankton with a wide variety of uses. Their ability to convert solar energy into chemical energy and produce substantial biomass is crucial for producing biofuels and animal feed [5, 6]. Lipids, proteins, polysaccharides, alkaloids, and pigments with antioxidant, cytotoxic, and antimicrobial activities found in microalgae are highly valuable bioactive compounds with antioxidant and cytotoxic effects [7, 8]. Many studies have used microalgae as an antibiotic substitute to study its antimicrobial activity. Compared with traditional antibiotics, disinfectants, and food preservatives, microalgae not only have potential biopesticide value but also have lower toxicity to humans and fewer side effects, which can reduce the problem of drug resistance [9]. Microalgae can eliminate antibiotics in water through biodegradation due to their antibiotic resistance. The elimination of antibiotics in water can be achieved through biodegradation, bioabsorption, and bioaccumulation, which have certain detoxification characteristics [10]. This review introduces the antimicrobial ability and antibiotic clearance effect of microalgae. It discusses the limiting factors and application potential of microalgae products in antibiotic substitution and removal, aiming to provide a scientific basis for developing antibiotic resistance and pollution control in the ecological environment.

2. The Potential of Microalgae to Replace Antibiotics

2.1. Antimicrobial Substances Produced by Microalgae

The bioactive compounds produced by microalgae are highly diverse and can be used for various purposes, making them highly diverse photosynthetic microorganisms. Many algae have primary and secondary metabolites that have antimicrobial properties. The antimicrobial activity of microalgae was first discovered by Pratt et al., who isolated an antimicrobial compound called *Chlorella vulgaris* from *Chlorella vulgaris*. The inhibition effect of fatty acid mixtures was defined by its ability to inhibit both Gram-negative and Gram-positive bacteria. New drugs such as antimicrobial, anti-inflammatory, and anticancer agents can be developed with the help of secondary metabolites [11]. Stephen and colleagues screened culture supernatants, methanol, and hexane extracts of 132 marine microalgae. The antimicrobial activity of 28 organic solvent extracts, tested in vitro, was the most effective against *Staphylococcus aureus* [12]. The prokaryotic algae *Nodularia* spp., *Nostoc* spp. and *Nostoc insulare* produce 4,4'-dihydroxy biphenyl, Norhalman and diterpenes with antimicrobial activity against *Escherichia coli*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Bacillus cereus* and *Staphylococcus epidermidis* [13]. Cyanobacteria produce enzymes that degrade fungal cell walls, such as chitosanase, β -1,4-glucanase, β -1,3-glucanase and benzoic acid, which inhibit the growth of *Fusarium*, *Penicillium* and *Candida* [14]. Among eukaryotic algae, Sedighi et al. extracted a 62 KDa peptide from *Chlorella vulgaris* and found that the peptide had antimicrobial activity and inhibited cell wall synthesis in an *E. coli* strain [15]. Six cyclic phosphoric acid tannins were extracted from *Eisenia bicyclis*, among which fucofuroeckol-A (FFA) showed that with an MIC of 16-32 μ g/ml, it exhibits strong antimicrobial activity against *Listeria monocytogenes* [16].

2.2. Antimicrobial Mechanisms of Microalgae

Microalgae's antimicrobial mechanism is mainly achieved by creating broad-spectrum antimicrobial substances, working with antibiotics to improve their antibacterial effects, and depleting and degrading antibiotics to degrade their concentrations in the environment. Additionally, microalgae can generate reactive oxygen molecules through photosynthesis in the water environment, which can harm bacteria cells [17].

2.2.1. Photooxidative Damage

The damage to bacterial cells caused by photooxidative damage to microalgae is not directly related, but the photooxidative damage of microalgae may indirectly affect bacteria. Photooxidative damage occurs because microalgae photosynthesize under strong light, which produces a large amount of reactive oxygen species (ROS) in the process, such as superoxide ions (O_2^-), hydrogen peroxide (H_2O_2) and hydroxyl radicals ($\cdot OH$) and so on. These ROS can damage the cellular structure of microalgae, including the photosynthetic system and other biomolecules, leading to photooxidative damage. At the same time, light intensity, light quality, temperature and other chemicals in the water are all important factors affecting the photooxidative damage of microalgae. For example, high-intensity exposure and specific light quality can exacerbate ROS production, increasing the risk of photooxidative damage.

2.2.2. Algal Metabolites with Antimicrobial Activity

Algae metabolites showed significant antimicrobial activity, which provided the possibility for the development of new antimicrobial drugs. Some algal metabolites with antimicrobial activity include cyanobacterial metabolites, carrageenan from red algae and fucoidan from brown algae. Among these, metabolites produced by cyanobacteria, such as *cyanovirulence*, *certovirulence* and *microvirulence*, are compounds that are effective against various viruses. At the same time, the extraction of carrageenan from red algae has antiviral and antibacterial properties that can prevent the replication of different viruses, such as HIV, hepatitis A virus, and human papillomavirus. Moreover, fucoidan is obtained from the brown seaweed cell wall, and it has L-fucoidan and sulfate compounds. These compounds show a variety of therapeutic activity, including effectiveness against influenza viruses and coronaviruses. Algae metabolites showed significant antimicrobial activity, which provided the possibility for the development of new antimicrobial drugs.

3. The Potential of Microalgae to Remove Antibiotic Contamination

Common antibiotic removal methods include activated sludge treatment, membrane bioreactors and adsorption, membrane filtration, and ionic resin treatment are all biological methods and chemical methods such as strong oxidant oxidation and advanced oxidation [18]. Due to the antimicrobial properties of antibiotics, biological treatments that use bacteria as the main component are often not effective in removing antibiotics [19]. Despite its high removal rate for some antibiotics, it cannot completely break down antibiotics, which can result in secondary pollution and require further advanced treatment [20]. Chemical processes require large quantities of expensive chemicals or catalysts and may also produce secondary pollutants [21]. In the past few years, microalgae have been widely used in the treatment of urban, domestic and industrial wastewater [21]. Microalgae are highly resistant to stress and can survive in a variety of extreme environments. Most antibiotics' semi-maximum effective concentration (EC50) has an order of magnitude greater than that of wastewater or surface/groundwater, suggesting that antibiotic resistance is generally high in microalgae [22]. Microalgae are capable of synthesizing a wide range of primary and secondary metabolites, including extracellular polymers (EPS), which are key to microalgae's role as antibiotic removers [23]. For example, *Dictyosphaerium* sp. has a large amount of EPS and a high content of polysaccharides, which facilitates the elimination of antibiotics and can be achieved through adsorption, accumulation, or degradation. Microalgae's enhanced photosynthesis can result in a rise in dissolved oxygen and pH when exposed to strong light, thereby inducing the production of reactive oxygen species and enhancing the removal of tetracycline [24]. It has been proven that microalgae are capable of effectively removing pharmaceutical and personal care products (PPCPs), such as antibiotics, from wastewater [25]. For example, the high-velocity algae pond (HRAP) system, dominated by

Coelastrum sp., removed 64 PPCPs, including 33 antibiotics (at an average concentration of 223 mg/L), from municipal wastewater over six months, with a 5-50% higher ability to remove antibiotics than the traditional activated sludge method [26]. Microalgae biotechnology has been engineered to efficiently and environmentally friendly treatment of contaminated water sources containing antibiotics.

3.1. Bioadsorption

The primary mechanism for microalgae to absorb antibiotics is through hydrogen bonding, charge attraction, void filling, partitioning, and functions on the cell wall surface or extracellular polymers (EPS) (similar to cellulose, hemicellulose, and proteins) that are hydrophobic interact with functional groups. Due to the hydrophilicity, function, and structure of specific antibiotics and microalgae, adsorption performance can vary greatly. In general, biosorption of antibiotics is more likely to occur when their hydrophobicity is higher, and their voltage is opposite to the microalgae. In most cases, biosorption has little effect on antibiotic removal [27]. Nevertheless, it is still very important for the biodegradation of antibiotics. The adsorption of antibiotics on microalgae can allow them to enter cells through cell walls, which is the first step in the process of biosorption, where they bioaccumulate and biodegrade [28].

3.2. Bioaccumulation

Bioaccumulation removes contaminants from inside cells, a process that takes place in living cells. Bioaccumulation is a metabolic activity that requires energy and absorbs substrates, which store antibiotics inside the cell and do not degrade them. Bioaccumulation typically occurs in 2 situations, i.e., the amount of enzymes within the microalgae that degrade the antibiotic is limited, or the ability of intracellular enzymes to degrade the antibiotic is insufficient. Biodegradation comes after accumulation, and the two processes working together inside algal cells greatly facilitate the absorption of certain antibiotics. The build-up of antibiotics triggers the formation of reactive oxygen species, which at normal concentrations are essential for the control of cellular metabolism but, in excess, can lead to severe cellular damage or eventual death [29].

3.3. Biodegradation

Biodegradation is the primary mechanism by which antibiotics are removed from lysoles. The biodegradation of antibiotics by microalgae is mainly divided into three stages: the first step involves using oxidation, reduction, or hydrolysis reactions to change lipophilic exogenous substances into more hydrophilic compounds. The second stage is when enzymes in microalgae, such as glutathione-S-transferase (GST), catalyze the degradation of antibiotics to produce smaller, less toxic molecules. The third stage is to sort the exogenous material in the vacuole or cell wall to exclude it from the body [30]. By metabolizing and co-metabolizing organic substrates, microalgae get rid of antibiotics. The term "co-metabolism" describes the metabolism of non-specific enzymes and cofactors in microorganisms, which necessitates the simultaneous forced degradation and transformation of two substances, the presence of which is necessary for the degradation and transformation of the second substance (non-growth substrate). The initial antibiotic dose significantly influences algae degradation, and at minimal levels, it fails to initiate biodegradation via algae detoxification reactions. The introduction of extra organic substrates not only supports the production of biomass but also serves as a non-growing substrate, functioning as an electron donor for co-metabolism, thereby enhancing the breakdown of contaminants. Sodium acetate as a synergistically metabolized organic substrate promotes a positive effect on the removal of ciprofloxacin (CIP) by *Chlamydomonas mexicana*, with a 3-fold increase in removal rate [31].

3.4. Photodegradation

Antibiotic photodegradation is thought to be a very effective and environmentally friendly approach. There are two types of photodegradation: direct and indirect. Direct photodegradation is the removal of antibiotics by direct photolysis by light in the absence of algae, and the antibiotics directly absorb sunlight energy, resulting in the breaking or rearrangement of chemical bonds. Indirect photodegradation is the production of oxidizing active substances such as hydroxyl radicals($\cdot\text{OH}$), hydrogen peroxide(H_2O_2), etc., which react with antibiotics to degrade them [32]. Algae can produce reactive oxygen species under laser (650 nm) [33]. Enhance indirect photodegradation of antibiotics. Compared with direct photodegradation, indirect photodegradation is the main way to degrade residual antibiotics in natural water.

3.5. Hydrolysis of Algae

Moreover, hydrolysis and volatilization are commonly used to extract antibiotics from algae. Antibiotics that have relatively high Henry's Law Constant (H) values can be removed via volatilization, but they are sensitive to the system's temperature and pressure and can only transfer contaminants from the liquid phase to the atmosphere; they cannot decompose. Hydrolysis can also break down some antibiotics. Metabolites produced by algae, including those resulting from enzyme-driven hydrolysis reactions, can certainly be regarded as part of biodegradation processes. The proliferation of algae has the potential to modify the pH of the culture. For instance, the photosynthetic activity of microalgae can elevate the pH levels, thereby significantly influencing the hydrolysis of antibiotics that are sensitive to pH changes. The hydrolysis reaction enhances the antibiotic's polarity and hydrophilicity, thereby promoting the adsorption and subsequent biodegradation of the microalgae.

3.6. Microalgae Work in Synergy with Other Microorganisms to Remove Antibiotics

By conjugating with bacteria and fungi, microalgae can increase their efficacy in eliminating antibiotics. Many strains can remove antibiotics. Algal antibiotic degradation products may be more easily broken down by bacteria, and vice versa. A major factor in improving the effectiveness of antibiotic removal may be the synergistic degradation capabilities of different microorganisms as well as the possibility of bacteria and algae exchanging antibiotic breakdown products. Much of the research on bacterial antibiotic degradation has focused on aerobic degradation, and microalgae, as photosynthetic organisms, can provide oxygen to their metabolic processes [34]. Bacteria can also use microalgae as a protective habitat to promote their growth. Some studies have found that microalgae EPS can change the microbial community structure of water bodies. After adding EPS to lake water contaminated by enrofloxacin (ENR), the number of ENR-decomposing special functional bacteria increased significantly. Among these, the EPS of *Spiraxellaceae* increased the abundance of *Moraxellaceae* and *Spirosomaceae*, while the EPS of *Chlorella vulgaris* increased the abundance of *Sphingomonadaceae* and *Microbacteraceae*. The maximal ENR clearance rates under the synergistic effect were 28.9% for *Reticulum colloidis* and 24.2% for *Chlorella* [35].

4. Challenges and Opportunities in the Application of Microalgae Products

Microalgae have the characteristics of low toxicity, certain antibacterial, and degradation of some antibiotics, which are the biological prerequisites for their application in the field of antibiotic substitution and antibiotic clearance. The antibacterial activity and antibiotic removal ability of microalgae are affected by various factors such as algae species selection and nutritional environment. The cooperative breakdown capabilities of different microorganisms, coupled with the potential for

algae and bacteria to share the byproducts of antibiotic decomposition, contribute significantly to improving the effectiveness of antibiotic elimination. Although the antimicrobial application of microalgae is promising, there are still some technical challenges, such as the screening of high-efficiency microalgae varieties, the large-scale production and purification of antimicrobial substances, and the safety evaluation. The utilization of microalgae as a biomaterial to create products that replace and eliminate antibiotics has both benefits and drawbacks. With the development of biotechnology, more and more biotechnological tools can be applied to develop microalgae to replace and remove antibiotic products. Microalgae demonstrate impressive evolutionary adaptability, allowing them to thrive in diverse environmental conditions. This remarkable versatility contributes to their extensive genetic diversity, making it possible to selectively cultivate strains that are notably productive and efficient [36]. In commercial manufacturing, a variety of physical and chemical mutagens are commonly used for random mutagenesis, followed by screening techniques [37]. The best approach, however, incorporates metabolic and genetic engineering, and this is uncertain and time-consuming. By performing single, double, and triple conversions of *Brown Finger Triangularis* using one, two, and three carotenoid biosynthetic genes, Manfellotto et al. discovered that the threefold transformation boosted the fucoxanthin content by four times [38]. Multi-omics technologies, including genomics technology, can help the microalgae sector grow by identifying the target sequence for study and modifying the corresponding genetic sequences to create a wide range of desired products. Sequences can be compared using transcriptome analysis to identify transcription factors and the degrees of their expression. Advanced methods like GC-MS can be utilized in proteomics to determine whether a post-translational protein of interest is generated. Accurate separation and differentiation of secondary metabolites can be achieved through metabolic profiling using liquid chromatography-mass spectrometry (LC-MS) [40]. Bioengineering problems, such as culture, harvesting, extraction, and purification, are linked to biology as well as the limitations of low-cost and effective product creation. Products made from microalgae may be made easier with the advancement of bioengineering technology.

5. Conclusion

In this review, the antimicrobial mechanisms of microalgae and their role in antibiotic removal. In addition, this paper discusses the constraints and future research directions for the application of microalgae products, and the analysis shows that microalgae, as a natural material, has a good potential application value in antimicrobial and antibiotic removal, which provides new ideas and solutions to deal with the problem of antibiotic resistance.

Microalgae can produce substances with broad-spectrum antimicrobial activity. However, a number of environmental factors may have an impact on the actual antimicrobial effect, including temperature, pH, and nutrient availability. In addition, microalgae and antibiotics can have a synergistic effect that enhances the antibacterial effect of antibiotics; however, the complexity and condition-restricted nature of this synergistic effect requires further research to optimize the effectiveness of its use. Meanwhile, in response to the effect of microalgae on antibiotic antimicrobial properties, some microalgae can have a degrading effect on antibiotics. Therefore, these potential interactions need to be considered when using combinations of microalgae and antibiotics.

Large-scale production and purification of antimicrobial compounds, as well as more screening of effective microalgae species, are necessary for future research. In addition, the production of antimicrobial substances from microalgae should be optimized using genetic and metabolic engineering, while a systematic safety assessment should be carried out to ensure the safety of their application.

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