

Microalgal Metabolites: Nature's Blueprint for Novel Bioactive Compounds

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Abstract

Microalgae represent a vast reservoir of chemically diverse metabolites that play critical roles in marine ecosystems. As primary producers, they not only sustain oceanic food webs but also generate unique bioactive compounds through biosynthetic pathways distinct from those of terrestrial organisms. Secondary metabolites from microalgae exhibit remarkable structural diversity, ranging from polyketides to polycyclic ethers (saxitoxin, domoic acid, okadaic acid, maitotoxin, lyngbyatoxin, and kahalalide F) many of which hold ecological, pharmacological, and biotechnological significance. Recent advances in molecular biology have illuminated the genetic basis of metabolite biosynthesis, including the identification of gene clusters linked to toxin production and novel polyketide backbone formation. Taxonomic and phylogenetic perspectives further reveal the evolutionary underpinnings of metabolite distribution across algal groups. Beyond their ecological roles, these compounds have spurred interest due to their potential applications in drug discovery, bioenergy, and environmental monitoring. By integrating insights from biosynthetic mechanisms, genetic regulation and evolutionary context, microalgal metabolites can be viewed not only as chemical curiosities but also as key drivers of marine chemical ecology and promising resources for biotechnology.

Keywords

Bioactive compounds, Cyanobacteria, Marine drug discovery, Microalgae, Secondary metabolites

Introduction

Microalgae are a highly diverse assemblage of microscopic, photosynthetic organisms including eukaryotic algae and cyanobacteria that form the foundation of aquatic food webs. They drive global carbon fixation and oxygen production, contributing nearly half of Earth's primary productivity and atmospheric oxygen generation (Hoque et al., 2025; Siddhnath et al., 2024; Ibrahim et al., 2023; Prasad et al., 2021). Occupying marine, freshwater, and moist terrestrial niches, microalgae rapidly convert solar energy and inorganic nutrients into biomass, thereby

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sustaining trophic interactions, biogeochemical cycling, and overall ecological balance (Gamal et al., 2024; Chen et al., 2023; Dolganyuk et al., 2020; Mutanda et al., 2020).

Microalgae encompass both prokaryotic cyanobacteria and diverse eukaryotic lineages, including chlorophytes, diatoms, dinoflagellates, haptophytes, and cryptophytes. Their simple cellular architecture and fast metabolic rates enable rapid growth, often allowing biomass to double within hours under optimal cultivation conditions. These traits make microalgae promising platforms for environmentally sustainable bioenergy generation and emerging biotechnological production systems (Gupta et al., 2024; Ashour et al., 2024; Wang et al., 2024).

Beyond essential metabolic products such as carbohydrates, lipids, and proteins, many microalgae synthesize structurally complex and bioactive secondary metabolites. These compounds spanning polyketides, non-ribosomal peptides, alkaloids, terpenoids, and pigments play pivotal ecological roles in defense, signaling, and competition while presenting significant prospects for pharmaceutical, nutraceutical, and industrial innovation (Li et al., 2023; Martínez-Ruiz et al., 2022; Sathasivam & Ki, 2019; Sasso et al., 2012;). This review examines microalgal secondary metabolites from a holistic perspective, focusing on their structural diversity, biosynthetic pathways, genetic regulation, phylogenetic distribution, ecological relevance, and current and emerging biotechnological applications.

Diversity of Microalgal Secondary Metabolites

Microalgal secondary metabolites exhibit remarkable structural diversity with key classes of metabolites including polyketides, non-ribosomal peptides, alkaloids, and hybrid peptide–polyketide compounds. The dinoflagellates produce large polyether toxins such as brevetoxins, maitotoxin, okadaic acid, ciguatoxins and guanidinium alkaloids like saxitoxin, while cyanobacteria produce cyclic peptides such as microcystins, nodularins and lipophilic lipopeptides dolastatins in symbionts (Bouyahya et al., 2024; Li et al., 2023; Assunção et al., 2017). Table 1 summarizes microalgal metabolites and their sources. Many microalgal metabolites are toxins that can accumulate through food webs which include saxitoxin produced by certain dinoflagellates and by freshwater cyanobacteria. Saxitoxin binds voltage-gated sodium channels, blocking nerve transmission and causing paralytic shellfish poisoning (PSP) in humans and marine animals (Li et al., 2023; Pradhan et al., 2022). Domoic acid is another potent toxin, a tricarboxylic acid with a glutamate-like structure. It is produced by marine diatoms like pseudo-nitzschia spp. and some red algae. Domoic acid acts as a strong agonist of ionotropic glutamate receptors in the brain, causing neuronal excitotoxicity (Brunson et al., 2018).

Okadaic acid is a potent inhibitor of protein phosphatases PP2A and PP1, causing diarrhetic shellfish poisoning (DSP) when contaminated shellfish are ingested (Bui et al., 2024; Assunção et al., 2017). Like brevetoxins and ciguatoxins, the polycyclic ether scaffold of okadaic acid suggests biosynthesis via a highly modified polyketide pathway. These toxins frequently accumulate along trophic chains, affecting shellfish, fish, birds, and marine mammals (Bouyahya et al., 2024; Pradhan et al., 2022). Maitotoxin is an extraordinarily large polyether toxin produced by the benthic dinoflagellate *Gambierdiscus toxicus*. It is among the most potent natural toxins known, inducing massive calcium influx in cells and disrupting ion homeostasis (Bui et al., 2024; Assunção et al., 2017). Maitotoxin is also thought to originate via a polyketide synthase pathway, although its gene cluster remains unknown due to the extreme size and complexity of

dinoflagellate genomes. Some microalgal metabolites have pharmacological potential. Kahalalide F is a cyclic depsipeptide originally isolated from the sea slug *Elysia rufescens*, which sequesters it from its diet. Kahalalide F exhibits anticancer activity through mechanisms that include membrane disruption and lysosomal permeabilization and has been evaluated in clinical trials for solid tumors (García-Rocha et al., 1996). Likewise, other cyanobacterial peptides such as apratoxins and symplostatins show antitumor, antiviral, or antifungal activity and are considered promising leads for drug discovery (Bouyahya et al., 2024; Li et al., 2023; Pradhan et al., 2022).

Carotenoid pigments from microalgae are potent antioxidants and have nutraceutical value, with species such as *Haematococcus pluvialis* and *Dunaliella salina* widely exploited for commercial pigment production (Bouyahya et al., 2024; Pradhan et al., 2022). To summarize, microalgal secondary metabolites span diverse chemical types such as alkaloids, polyethers, peptides, terpenoids, etc. Many with potent bioactivities affection channels, enzymes, or receptors in animals. These natural products have ecological functions in defense and competition, and emerging applications in medicine and industry.

Table 1. Illustrates various microalgal secondary metabolites, their sources, and bioactivities

Metabolite Class	Metabolites	Producing Organisms	Bioactivity	References
Polyketides (polyethers)	Brevetoxins, Okadaic acid, Maitotoxin, Ciguatoxins	Dinoflagellates (e.g., <i>Karenia</i> , <i>Dinophysis</i> , <i>Gambierdiscus</i>), Haptophytes	Neurotoxicity and ion-channel modulation; Diarrhetic toxins	Siddhnath et al., 2024; Beedessee et al., 2018
Non-ribosomal peptides	Microcystins, Nodularins, Lyngbyatoxin, Kahalalide-F	Cyanobacteria (<i>Microcystis</i> , <i>Anabaena</i> , <i>Lyngbya</i>); Marine algal symbionts (Bryopsis)	Hepatotoxicity, tumor promotion, anticancer activity	Li et al., 2023; Wyer et al., 2022
Alkaloids (guanidines)	Saxitoxin, Gonyautoxins	Dinoflagellates (<i>Alexandrium</i> , <i>Gymnodinium</i>), Cyanobacteria	Paralytic Shellfish Poisoning via sodium-channel blockade	Li et al., 2023
Amino-acid analogues	Domoic acid	Diatoms (<i>Pseudo-nitzschia</i>), Red algae	Amnesic Shellfish Poisoning via glutamate-receptor agonism	Siddhnath et al., 2024
Carotenoids & pigments	β -Carotene, Astaxanthin, Phycocyanin	Green algae (<i>Dunaliella</i>), Cyanobacteria (<i>Arthrospira</i>)	Antioxidant, anti-inflammatory, nutraceutical applications	Yu et al., 2024

Biosynthetic Mechanisms and Pathways

Microalgal metabolites often arise from PKS and NRPS pathways, as well as mixed or unique routes. Compared to terrestrial organisms, microalgae especially dinoflagellates exhibit unusual biosynthetic genetics (Beedessee et al., 2018; Sasso et al., 2012). Cyanobacteria, though prokaryotic, deploy typical bacterial PKS/NRPS gene clusters. The microcystin peptide is made by a large NRPS–PKS hybrid cluster in *Microcystis* and *Anabaena* (Li et al., 2023; Sathasivam &

Ki, 2019). Similarly, the saxitoxin sxt genes in cyanobacteria encode a novel PKS-like assembly line (Bui et al., 2024; Li et al., 2023).

In contrast, many eukaryotic microalgae have complex genomic architectures. Dinoflagellates have enormous genomes with many gene copies and trans-splicing; as a result, intact biosynthetic clusters are hard to identify by standard genome assembly (Bouyahya et al., 2024; Beedessee et al., 2018). Nevertheless, studies suggest that dinoflagellate toxins are also polyketide derived. For instance, isotope feeding experiments with ^{13}C -acetate showed that okadaic acid, brevetoxins, and ciguatoxins incorporate acetate units, implying a PKS origin (Assunção et al., 2017).

However, these compounds do not always follow the “head-to-tail” acetate assembly rule; some dinoflagellate polyketides have truncated backbones or non-colinear structures, suggesting unusual enzymatic steps or rearrangements. A new proposal for such truncated polyketide formation has been suggested, indicating novel PKS enzymology in these algae (Bouyahya et al., 2024). Recent advances in genomics and transcriptomics have begun to illuminate these pathways. For domoic acid, a cluster of four genes (dabA–D) was discovered in *Pseudo-nitzschia*, revealing a multi-enzyme pathway that constructs the amino-acid geranyl scaffold (Brunson et al., 2018). In the case of saxitoxin, feeding and biochemical studies in cyanobacteria showed that SxtA initiates the pathway by linking an arginine-derived fragment into a larger scaffold (Li et al., 2023).

Additional enzymes introduce hydroxylations and sulfo-groups to yield diverse saxitoxin analogs (Bui et al., 2024). Although complete dinoflagellate biosynthetic pathways are still elusive, homologous genes to sxt have been found in *Alexandrium* transcriptomes, indicating similar chemistry (Beedessee et al., 2018). Furthermore, microalgae sometimes use hybrid biosynthetic strategies. Some toxins incorporate amino acids via NRPS modules or unusual precursors. Lyngbyatoxin A is a cyclic dipeptide that originates from a tryptophan–valine dipeptide and undergoes prenylation, a process resembling fungal indole alkaloid biosynthesis (Assunção et al., 2017). The kahalalide F peptide likely derives from ribosomal peptides of the algal host or its symbiont, followed by tailoring steps (Király et al., 2013).

Overall, microalgal biosynthesis combines bacterial-like modular enzymes and unique algal variations. This yields novel metabolic routes: e.g., prenylated amino acids, mixed PKS/NRPS toxins (microcystins), and giant polyether metabolites. Continued genome sequencing is beginning to reveal PKS and NRPS gene families (Beedessee et al., 2018). Notably, recent large-scale genome studies have identified hundreds of PKS/NRPS genes in dinoflagellates, indicating an extensive repertoire of secondary-metabolite enzymes (Li et al., 2023; Sasso et al., 2012).

Molecular Biology and Genetic Regulation

Control of metabolite biosynthesis in microalgae involves regulation at multiple levels. Transcription of toxin genes is often upregulated under stress or specific conditions. *Pseudo-nitzschia* increases domoic acid gene expression under phosphate stress (Brunson et al., 2018). In cyanobacteria, microcystin production is regulated by nitrogen status, and light mcys operon expression is modulated by global regulators (Pradhan et al., 2022; Sathasivam & Ki, 2019). In dinoflagellates, transcripts for PKS/NRPS appear as multiple transcript isoforms; environmental

cues can alter toxin profiles, though the regulatory networks are poorly defined (Bouyahya et al., 2024; Beedessee et al., 2018).

At the genomic level, many biosynthetic genes are organized in clusters. The *sxt* cluster in cyanobacteria is contiguous, and the *dab* cluster in diatoms is co localized (Li et al., 2023; Brunson et al., 2018). Dinoflagellates may employ trans-splicing for secondary-metabolism genes, as seen in some ribosomal and peridinin genes (Beedessee et al., 2018). Chromatin structure and epigenetics might also influence metabolite genes in large dinoflagellate genomes (Bouyahya et al., 2024; Assunção et al., 2017). Genetic engineering of microalgae is still in early stages, but advances are beginning to allow pathway manipulation. Heterologous expression of dinoflagellate PKS modules in bacteria has provided partial products (Király et al., 2013; Sasso et al., 2012).

Pharmacological and Drug Discovery Applications

The potent bioactivities of microalgal metabolites have attracted interest in drug discovery and biotechnology. Several compounds or analogs are in pharmaceutical pipelines. Saxitoxin derivatives have been studied for use as local anesthetics and as tools in neurobiology (Király et al., 2013; Zhang et al., 2020). Okadaic acid is used in research to study cell signaling. Brevetoxin analogs have been investigated for treating cystic fibrosis by modulating chloride channels. Notably, many cyanobacterial peptides are anticancer leads. Curacin A is a potent antimetabolic agent; bryostatins are being trialed in cancer and Alzheimer's therapy (Robles-Banuelos et al., 2023). Kahalalide F has reached clinical trials for solid tumors (Wyer et al., 2022; Pardo et al., 2008). Algal pigments and fatty acids are marketed as nutraceuticals like astaxanthin and β -carotene are sold as antioxidant supplements (Siddhath et al., 2024; Higuera-Ciupara et al., 2006). Omega-3 fatty acids (EPA, DHA) are commercially produced by microalgae as sustainable alternatives to fish oil (Kunj et al., 2020; Sprague et al., 2017).

Marine bioprospecting continues high-throughput screening of algal extracts has revealed antibacterial, antiviral, anti-inflammatory, and antifouling compounds (Hernández-Urcera et al., 2023). Halogenated monoterpenes from red algae have antitubercular activity, and cyclopeptides from green algae show immunosuppressive effects. Many microalgal compounds target human disease pathways: their unique structures often interact with protein-protein interactions or ion channels in ways drugs rarely do. Calcium-channel modulators from algae could lead to new painkillers, and novel scaffolds provide templates for synthetic chemistry (Robles-Banuelos et al., 2023). In drug discovery, microalgal metabolites bridge marine chemical ecology and medicine. The challenges are supply and synthesis: many toxins are produced in tiny amounts, and their complex structures make total synthesis difficult (Lee et al., 2025). Advances in fermentation of algae and chemoenzymatic synthesis are mitigating these issues (Gupta et al., 2024; Li et al., 2023). Microalgae can be cultured in bioreactors to produce desired metabolites; genetic engineering may soon allow overproduction of pharmaceutically relevant compounds in algal hosts (Ashour et al., 2024; Sathasivam and Ki, 2019). Table 2 describes the difference in metabolite from microalgae and plants.

Table 2 Comparative features of microalgal metabolites and plant metabolites.

Feature	Microalgal Metabolites	Plant Metabolites	Reference
Diversity	Extremely high; many unique scaffolds (polyethers, peptides)	High diversity (alkaloids, phenolics) but many shared scaffolds (terpenoids)	Assunção et al., 2017
Biosynthetic Genes	Often large, multi-domain PKS/NRPS clusters; some in plastid genome	Commonly gene clusters (e.g. alkaloids) or distributed enzymes	Beedessee et al., 2018; Sathasivam & Ki, 2019
Examples of Compounds	Saxitoxin, Domoic acid, Okadaic acid, Microcystin	Morphine, Aspirin (salicylic acid), Artemisinin	Li et al., 2023; Brunson et al., 2018
Ecological Roles	Chemical defense in aquatic food web (fish toxins)	Defense against herbivores/pathogens	Reguera & Blanco, 2019; Berdalet et al., 2016; Turner & Tester, 1997
Commercial Products	Biofuels (algal oil), Astaxanthin, Nutraceuticals	Spices, drugs (e.g. taxol), edible oils	Kunj et al., 2020; Higuera-Ciapara et al., 2006; Sprague et al., 2017
Cultivation	Aquatic bioreactors possible (non-arable land)	Agricultural land needed	Gupta et al., 2024; Chew et al., 2017; Turner & Tester, 1997
Regulatory Status	Emerging (few approved algal drugs)	Many approved (traditional herbal medicines)	Reguera & Blanco, 2019

Future Directions and Challenges

Despite remarkable advances in microalgal biotechnology, several scientific and technological challenges continue to limit the full exploitation of microalgal metabolites. Many algae produce their valuable compounds in low quantities or under very specific conditions, which makes growing them on a large scale expensive and time consuming. Their genomes can also be extremely complex, especially in dinoflagellates which baffle scientists to locate the exact genes responsible for making these useful chemicals. We need better sequencing tools and easier ways to genetically engineer these organisms. Nevertheless, the vast majority of microalgal biodiversity remains unexplored, representing an immense reservoir of potentially novel bioactive compounds. Emerging technologies, including metabolomics, artificial intelligence-assisted natural product discovery, genome mining, and innovative cultivation approaches, are rapidly transforming the pace of metabolite identification and characterization. By addressing current limitations through interdisciplinary research and technological innovation, microalgae have the potential to become one of the most sustainable and versatile sources of next-generation pharmaceuticals, functional biomaterials, nutraceuticals, and other high-value bio-based products.

Conclusion

Microalgal metabolites represent one of the most promising frontiers in natural product research, offering an unparalleled diversity of structurally unique and biologically active compounds with significant pharmaceutical, biotechnological, and ecological value. The remarkable biosynthetic capabilities of cyanobacteria, diatoms, green microalgae, and dinoflagellates have led to the discovery of numerous metabolites exhibiting anticancer, antimicrobial, antiviral, anti-inflammatory, antioxidant, and neuroprotective activities. Beyond their therapeutic potential, these compounds also provide valuable insights into ecological interactions, chemical defense mechanisms, and cellular signaling pathways, highlighting the multifaceted roles of microalgae in aquatic ecosystems.

Recent advances in genomics, transcriptomics, metabolomics, synthetic biology, and bioinformatics have substantially accelerated the discovery and characterization of novel microalgal metabolites while enabling the identification of previously inaccessible biosynthetic gene clusters and metabolic pathways. In parallel, innovations in metabolic engineering, heterologous expression systems, and sustainable cultivation technologies are overcoming limitations associated with low metabolite yields, slow growth rates, and large-scale production, thereby facilitating the translation of promising natural products into commercially viable pharmaceuticals and industrial bioproducts. Despite these advances, significant challenges remain, including incomplete characterization of microalgal biodiversity, difficulties in metabolite isolation and structural elucidation, and the need for scalable and cost-effective production platforms. Addressing these challenges will require interdisciplinary collaboration integrating phycology, molecular biology, analytical chemistry, systems biology, biotechnology, and pharmaceutical sciences.

In conclusion, microalgae should be regarded not merely as primary producers within aquatic ecosystems but as sophisticated biological factories capable of generating an extraordinary repertoire of high-value natural products. Continued integration of advanced omics technologies, artificial intelligence-assisted metabolite discovery, genome engineering, and sustainable bioprocess development will unlock their full biosynthetic potential, paving the way for the discovery of next-generation therapeutics, nutraceuticals, cosmeceuticals, and environmentally sustainable bio-based products. As research continues to reveal the remarkable chemical diversity encoded within microalgal genomes, these microscopic organisms are poised to play an increasingly central role in future innovations spanning medicine, biotechnology, and environmental sustainability.

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