Received: 13-06-2025; Accepted: 25-09-2025

https://doi.org/10.56024/ispm.75.3ampersand4.2025/143-161

PHYTOMORPHOLOGY

Algal Omics - A Systems Biology Approach to Microalgal Research and Applications

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Abstract

Microalgae are used extensively today to produce carotenoids for commercial purposes and serve as an excellent model for research on the metabolism of the carotenogenesis pathway in plants. Recently, with the emergence of high-throughput omics technologies, such as genomics, transcriptomics, and metabolomics, information about microalgal metabolism has led to the use of microorganisms from diverse lineages in producing bio-based feedstock and many bioactive compounds. The evolution of omics technologies has enabled systems biology to develop a comprehensive global metabolic network, allowing researchers to generate and analyze vast amounts of data on microalgal metabolism. It has significantly enhanced our understanding of cellular physiology and regulatory mechanisms. However, microalgal strain improvement necessitates appropriate engineering methods that enable the complete biotechnological potential of microalgae to be realized. This review paper describes the crucial role of algomics studies in enhancing microalgal production and its various byproducts, thereby facilitating the commercial production of these organisms.

Keywords: Microalgae, Carotenoid accumulation, Carotenogenesis, Functional annotation, Algal omics, Genomics, Proteomics

Introduction

The current impetus of microalgal research rests extensively on tapping the potential of multi-omics methodologies for various commercially viable byproducts. More recently, comprehensive studies of multiomics in microalgae have emerged from the biofuel perspective (Rai et al., 2016). Microalgal genomics and transcriptomics have provided crucial insights and a basic understanding of lipid biosynthesis, complemented by proteomics and metabolomics, which together complement algal omics and provide precise functional insights into static and dynamic physiological contexts. The strategic data from these integrated platforms can offer a comprehensive, system-wide overview. To fully exploit the potential of microalgae as commercial green hosts, the scientific community

https://doi.org/10.56024/ispm.75.3ampersand4.2025/143-161

is now moving towards a better understanding of these microorganisms from a systems biology perspective. Algal omics, therefore, warrants closer attention from a future perspective, due to its economic, technical and societal impacts that are projected in the current postgenomic era.

Insights into Algal Omics and their potential role in augmenting carotenoid accumulation

Exploiting the potential of multi-omics techniques in relation to diverse commercially viable byproducts is a major driving force behind current microalgal research. From the perspective of biofuels,

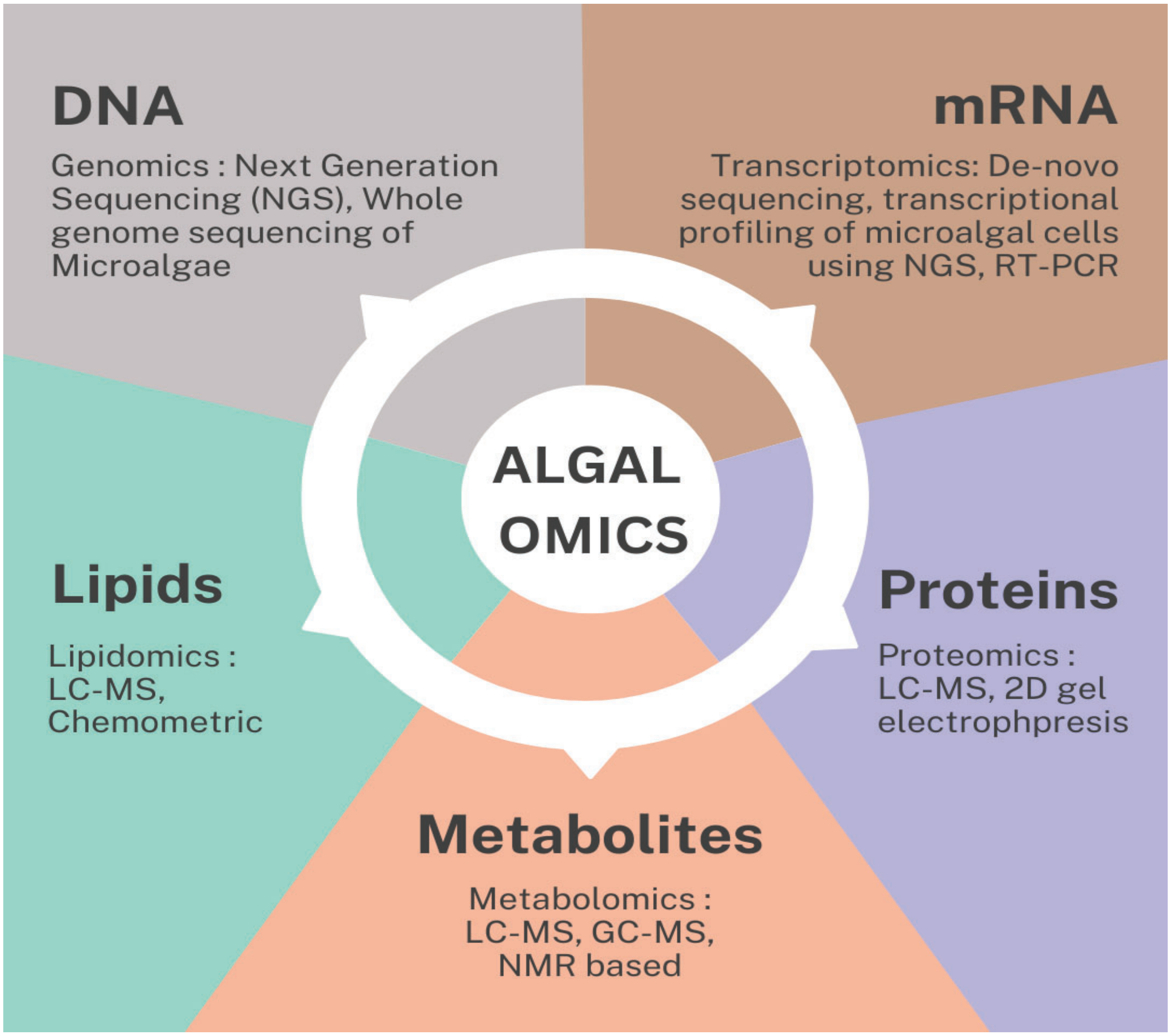

Figure 1. Various approaches of Algal-Omics used in the metabolic pathway's regulation (Source: modified from Rawat et al., 2021)

comprehensive investigations of multi-omics in microalgae have emerged only recently (Rai et al., 2016). Proteomics and metabolomics, which complement algal omics, provide precise functional insights into static and dynamic physiological contexts and have contributed to gaining decisive leads and a fundamental understanding of lipid biosynthesis. A thorough system-wide overview can thus be enabled by a few multi-omics technologies and the strategic data from these platforms (Fig. 1).

Genomics approaches

Genomic techniques encompass a range of approaches, including nucleotide sequencing, next-generation sequencing, pyrosequencing, expressed sequence tags (ESTs), recombinant cDNAs, full-length cDNAs, and real-time sequencing. Different studies have identified numerous genes associated with various functions. Traller et al. (2016) revealed genetic flexibility of the oleaginous diatom *C. cryptica* towards a high lipid phenotype by studying its genome and methylome. Similarly, diversification of secondary metabolite biosynthetic pathways has been studied using comparative genomics by Beedessee et al. (2018). The knowledge obtained from genome sequences can be used to generate beneficial traits, develop genetically modified microalgae for improved productivity and yield. Genomics has proven helpful in understanding the dynamic role of microalgae in metabolic responses and the mechanisms involved in bioremediation and environmental toxicity (Pandey et al., 2019).

Functional genomics encompasses genome, gene, protein expression, and transcriptomic analysis. The majority of previous genetic modification studies on microalgae have been particularly focused on *Chlamydomonas*, and little to no information is available for other algal species (Merchant et al., 2011). However, as of now, according to the available data (ncbi.nlm.nih.gov), approximately 62 algal genomes and nearly 30,000 bacterial genomes have been sequenced (Nelson et al., 2021). This includes some potential biofuel feedstock strains, such as *Chlorella* sp., *Nannochloropsis* sp., *P. tricornutum, Coccomyxa* sp., *Micromonas* sp., *O. lucimarinus, V. carteri*, and *T. pseudonana*, which are available in the public domain (Singh et al., 2016). Genomic information of these sequences, along with EST data, could open new avenues for improved carotenoid engineering studies in microalgae (Reijnders et al., 2014; Misra et al., 2013).

The genome sequence of the cyanobacterium *Synechocystis* was a driving force behind the accumulation of a vast gene repertoire in public databases (Nakamura et al., 1998). The data of all microalgal species from around the world are hosted at the algal culture collection centres at the Centre for Algae Research at the University of Texas, Austin (UTEX; utex.org) and the National Centre for Algae and Microbiota (NCMA; ncma.bigelow.org), among others. The genomes of various microalgae are available in different databases, providing information about the sequences of these genomes that can be used for research purposes (Table 1). A repository of the *Synechocystis* sp. database is CyanoBase, located at the Kazusa Institute in Japan, which provides genetic context, gene lists, functions, and classifications, along with protein domains (Nakao et al., 2010). The entire nuclear genome of *C. reinhardtii*, a model organism for photosynthesis, was sequenced in 2007 (Merchant et al., 2007). This marked the

Table 1. Different genomic databases with algal genome information

Database	Link
Pico-Plaza	https://bioinformatics.psb.ugent.be/plaza/versions/pico-plaza/
Joint Genome Institute (JGI)	https://genome.jgi.doe.gov/algae/algae.info.html
Genome Portal for Algae	https://protists.ensembl.org/species.html
Ensembl Protists	https://protists.ensembl.org/species.html
BioCyc	https://protists.ensembl.org/species.html
PlaNet	https://biocyc.org/
DiatomCyc	http://www.gene2function.de/

Source: Modified from Lauritano et al. (2019)

basis for the future analysis of the whole genome of eukaryotic microalgae. Other microalgal genomes sequenced by whole-genome shotgun sequencing include *C. subellipsoidea, O. tauri, O. lucimarinus, M. pusilla*, and *P. tricornutum* (Blanc et al., 2012).

Moreover, metagenomics is also being used to understand different metabolic pathways of microalgae (Table 2). Genomic approaches have been utilized in pharmaceuticals, therapeutics, nutraceuticals, and cosmeceuticals, and are expected to hold greater future value. The Marine Microbial Eukaryote Transcriptome Sequencing Project (MMETSP) was one of the major projects for transcriptome sequencing (van Vlierberghe et al., 2021). Close to 700 microbial algal transcriptomes have been sequenced, which signify a valuable resource for phylogenomic analysis, ecological roles, and evolutionary relevance in the tree of microeukaryotes (http://marinemicroeukaryotes.org/) (Table 3). The Tara Oceans expedition (http://oceans.taraexpeditions.org) was one of the most significant sequencing projects

Table 2. Various metagenomic databases with algal genome information

Database	Link
iMicrobe	www.imicrobe.us
Ocean Gene Atlas	http://tara-oceans.mio.osupytheas.fr/ocean-gene-atlas/
JGI Integrated Microbial Genomes	http://tara-oceans.mio.osupytheas.fr/ocean-gene-atlas/
GOLD	https://img.jgi.doe.gov/cgi-bin/m/main.cgi/

Source: Modified from Lauritano et al. (2019)

Table 3. Some of the marine microalgae with complete genomes

Genomes of species	Description	Genomes of species	Description
Aureococcus anophagefferens	Ochrophyta	*Fistulifera solaris*	Bacillariophyta
Bathycoccus prasinos	Chlorophyta	*Fragilariopsis cylindrus*	Bacillariophyta
Chlorella vulgaris UTEX395	Chlorophyta	*Phaeodactylum tricornutum*	Bacillariophyta
Coccomyxa sp. C-169	Chlorophyta	*Skeletonema costatum*	Bacillariophyta
Dunaliella salina	Chlorophyta	*Thalassiosira oceanica*	Bacillariophyta
Micromonas pusilla (CCMP1545)	Chlorophyta	*Thalassiosira pseudonana*	Bacillariophyta
Micromonas pusilla (NOUM17)	Chlorophyta	*Guillardia theta*	Cryptophyta
Micromonas sp. RCC299	Chlorophyta	*Nannochloropsis gaditana* CCMP1894	Eustigmatophyte
Ostreococcus lucimarinus	Chlorophyta	*Nannochloropsis gaditana*	Eustigmatophyte
Picochlorum costavermella	Chlorophyta	*Symbiodinium kawagutii*	Dinoflagellata
Emiliania huxleyi	Haptophyta	*Symbiodinium microadriaticum*	Dinoflagellata

Source: Modified from Lauritano et al. (2019)

undertaken for the in-depth analysis of microbial genes in marine organisms (Karsenti et al., 2011). It established a reference database for ecologically and phylogenetically relevant photosynthetic protists (Flora & Bowler, 2022).

The initial microalgal genome sequenced included the diatom *Thalassiosira psuedonana* in the year 2004, which was followed by green algae *C. reinhardtii* in the year 2007, then in the year 2008 another diatom species, *P. tricornutum* (Fu et al., 2019), followed by the *C. variabilis* genome sequenced in the year 2010 (Blanc et al., 2012). The genome sequencing of *C. reinhardtii* has revealed the evolution of many plant and animal functions (Merchant et al., 2007). Chen et al. (2022) have shown a significant expansion of different metabolic genes into the biosynthesis pathways of fucoxanthin in *I. galbana*. Similarly, studies have been conducted to understand the production of biofuels in *C. reinhardtii* (Aucoin et al., 2016). Complete or partial genome sequencing of many other microalgae has provided information relevant for biofuel production (Mishra et al., 2019). Genomes of several organelles, including mitochondria and plastids, have also been sequenced in microalgae (Salama et al., 2019). Genomic studies have revealed that differentially expressed genes in *P. minimum* are associated with ribosomes, amino acid biosynthesis, spliceosomes, and cellular processes under stress conditions induced by polychlorinated biphenyls (PCBs) (Wang et al., 2018).

To improve the biological properties of microalgae, enhancing their lipid and carotenoid content, various studies have been conducted, indicating that molecular evolution and adaptive changes are effective means of improvement. Both marine and freshwater microalgae have been explored for biofuel production and enhanced carotenoid content. The key aspects required for a high yield of carotenoids include the selection of a particular strain, optimization of growth conditions, and genetic manipulations that induce various stress conditions, such as nutritional and other abiotic stresses, which channel metabolic fluxes into the biosynthesis of lipids. Lipid production can be enhanced in microalgae. To enhance carotenoid accumulation and identify the rate-limiting steps in the carotenoid biosynthesis pathway, genetic engineering and metabolic tools are utilized, targeting the enzymes involved in the metabolic pathways. For biotechnological interventions, the introduction of foreign genetic material into host cells after DNA synthesis is significant (Chen et al., 2022). These methods of DNA delivery result in either stable chromosomal integration or extrachromosomal plasmid replication of the foreign transgenic expression elements (Wannathong et al., 2016). One of the first examples of manipulating the carotenogenic pathway in eukaryotic microalgae was the genetically engineered *Chlamydomonas reinhardtii*, which was engineered to insert the carotene ketolase cDNA, bkt1 gene from *Haematococcus pluvialis* (Le'on et al., 2007). This gene is involved in the synthesis of astaxanthin, which leads to the production of ketocarotenoids in the transgenic strain of *C. reinhardtii* (Perozeni et al., 2020). Another example of heterologous expression is the overexpression of the Or gene from the plant *Brassica oleracea* in the microalgae *C. reinhardtii* (Kumari et al., 2020). This gene plays a significant role in enhancing carotenoids in the tissues of several plant species.

Transcriptomics approaches

Transcriptomics provides insight into gene function through the analysis of RNA transcripts. It involves de novo sequencing, next-generation sequencing, microarrays, and RNA sequencing, among others. Several transcriptomes have been annotated to understand different transcriptional mechanisms in microalgae. These sequences have been deposited in various databases, such as GenBank, and are also available on web-based databases (Table 4).

Many transcriptomic studies have also been conducted to understand the biosynthesis and genetics of polyketides in marine microalgae (Kellmann et al., 2010). Different polyketides with anticancer, antifungal properties, and other beneficial effects have also been identified through transcriptomic studies. Zhang et al. (2017) conducted a whole-transcriptome analysis of *A. catenella*, revealing the molecular mechanisms underlying toxin production in dinoflagellates. De novo transcriptome studies on *Amphidinium carterae,*

Table 4. Different transcriptomic databases with algal genome information

Database	**Link**
MMETSP	https://www.imicrobe.us/#/projects/104
AlgaePath	https://www.imicrobe.us/#/projects/104
Alganaut	http://algaepath.itps.ncku.edu.tw/

Source: Modified from Lauritano et al. (2019)

Azadinium spinosum, and *Karenia brevis* revealed the presence of enzymes with biotechnological importance (Lauritano et al., 2019). Guarnieri et al. (2011) showed an upregulation of fatty acid and triacylglycerol biosynthetic machinery in *C. vulgaris* under oil-accumulating conditions. Similarly, Rismani-Yazdi et al. (2012) showed a five-fold increase in the production of triglycerides in *Neochloris oleoabundan*. Genes related to the triacyl glyceride synthesis pathway have also been identified in *C. reinhardtii* (Légeret et al., 2016).

Transcriptomic analysis of *Chlamydomonas* sp. revealed that many genes encoding enzymes for polyunsaturated fatty acid (PUFA) synthesis, molecular chaperones, and transport proteins exhibit high similarity to those from Antarctic bacteria (Liu et al., 2016). Furthermore, transcriptomic analyses of *I. zhangjiangensis* revealed that the genes involved in the folate biosynthesis pathway were upregulated under nitrogen deficiency (Wu et al., 2016). Transcriptomic studies have also shown that *Chlorella* sp. under UVR stress exhibits downregulation of genes in several metabolic pathways, including those involved in conserving energy, reallocating carbon resources, and counteracting oxidative damage (Guarnieri et al., 2011). Transcriptome analysis has revealed the impact of carbon sources (glycerol and glucose) on genetic regulation and metabolism in *Schizochytrium* sp. S056 (Chen et al., 2022). Furthermore, numerous studies have been conducted to investigate the potential of microalgae as a source of biofuels, utilizing transcriptomic analyses to elucidate the mechanisms within algae that make them suitable for biofuel production (Guarnieri et al., 2011).

Numerous studies have examined changes in the expression of genes involved in carotenoid biosynthesis, with findings indicating that intense light (Römer & Fraser, 2005) or simultaneous exposure to light reduction and nitrogen deprivation (Grünewald et al., 2001) upregulate these genes. Increased transcription of the isopentenyl pyrophosphate (IPI), phytoene synthase (PSY), phytoene desaturase (PDS), and ß-carotene ketolase (BKT) genes was seen in conjunction with gibberellin's role in astaxanthin accumulation (Gao et al., 2013).

Furthermore, through genome modification, such as genetic engineering, the overexpression or deletion of a gene in various microalgal strains with high potential for lipid and biofuel production has been achieved (Bajhaiya et al., 2017). For example, in a transcriptome study of the microalgae *C. reinhardtii*, lipid accumulation was accompanied by a considerable upregulation of Lysophosphatidic acid acyltransferase and Glycerol-3-phosphate dehydrogenase, indicating a positive correlation between cellular lipid accumulation and the transcription of these genes (Lv et al., 2013). Furthermore, studies in C. *reinhardtii, Chlorella* sp., *Monoraphidium neglectum*, and *Nannochloropsis* sp. have been conducted, which analyzed the correlation between transcriptome patterns and the accumulation of stored compounds, and identified possible metabolic nodes and transcription factors that suggest an exchange of lipids and starch, as well as metabolism (Chen et al., 2022).

In another study, the transcriptional regulators involved in regulating astaxanthin accumulation were identified for the first time (Cristina et al., 2021). In this study, *Haematococcus* vegetative cells were grown under different nitrogen levels of abundance and constraint. A comprehensive transcriptomic and metabolic profiling revealed that cells obtained under N constraint exhibited transcriptional activation of essential enzymes, which function as precursors for the synthesis of carotenoids. The gene IPI1/2, which encodes isopentenyl pyrophosphate isomerase (IPI), was found to be activated in these cells, along with the genes for phytoene synthase (PSY), phytoene desaturase (PDS), and zeta-carotene desaturase (ZDS).

Furthermore, transcription factors were identified as the genes responsible for the biosynthesis of astaxanthin, which were coregulated transcriptionally. The bHLH transcription factors were found to antagonistically regulate the synthesis of carotenoids, while the bZIP transcription factor activated the biosynthesis.

In a similar study, the expression pattern of certain genes, such as the phytoene desaturase (PDS), ß-ring hydroxylase (LUT5), beta-carotene hydroxylase (crtZ), carotenoid cleavage dioxygenase 8 (CCD8), carotene epsilon-monooxygenase (LUT1), lycopene ß-cyclase (lcyB), lycopene epsilon-cyclase(lcyE), prolycopene isomerase (crtISO), zeaxanthin epoxidase (ZEP) involved in the carotenoid biosynthesis, was observed to vary under different conditions of acetate and Fe_2^+ under high light conditions. Acetate enhanced the gene expression of the carotenoid biosynthesis pathway, whereas the presence of Fe_2^+ enhanced the gene expression of photosynthetic genes (He et al., 2018).

In a recent study, Hu and his research team (Hu et al., 2025) utilized 96 RNA samples from *Haematococcus pluvialis*, collected from two distinct stages: the vegetative development stage and the astaxanthin accumulation stage. The research identified 39 modules, each with varying numbers of genes, based on the time variables and the exogenous treatment. Further, the gene expression and functions were analysed. The gene ß-carotene ketolase (BKT3), which is a rate-limiting gene in the biosynthesis of carotenoid asthaxanthin, was found to be significantly enriched in one of the modules. Thus, this transcriptome dataset provides a detailed account of *H. pluvialis* gene expression in diverse growth conditions. Additionally, it serves as a useful instrument for investigating the regulatory processes involved in astaxanthin accumulation and cell proliferation. These data can further allow for commercial astaxanthin production in *Haematococcus* using systems metabolic engineering.

Proteomics approaches

Proteomics provides data on proteins, post-translational modifications, subcellular localisation, and numerous protein-protein interactions, and investigates several mechanisms that may be engaged in various biological processes and network functions. *C. reinhardtii* has been used as the model organism in microalgae for various proteomic studies. Similarly, many other species have also been used in proteomic studies, such as *P. tricornutum, C. vulgaris*, and *Fistulifera solaris*, for the production of biofuels and other bioproducts (Lauritano et al., 2019). Davidi et al. (2015) demonstrated the deposition of different types of lipids, including ß-carotene-rich (ßC) plastoglobuli and cytoplasmic lipid droplets (CLD), in *D. bardawil* and *D. salina* through proteomic studies. Similarly, proteome response during lipid accumulation was studied in *P. tricornutum* in nitrogen-depleted

Table 5. Different proteomic databases used for algal information

Database	Link
Alga-PrAS	http://alga-pras.riken.jp/
Uniprot	http://alga-pras.riken.jp/
Protein Data Bank archive (PDB)	https://www.uniprot.org/

Source: Modified from Lauritano et al. (2019)

conditions by Longworth et al. (2016). Several proteomic databases are available for use in algal research (Table 5).

Various data analysis tools, including Mascot, Sequest, Swiss-Prot, Skyline, Tandem, UniNovo, and SWPepNovo, are available for identifying peptides and proteins (Amer & Baidoo, 2021). Additionally, several bioinformatics tools, including CRONOS, COVAIN, SIGNOR, STRING, and KEGG, are utilised for proteomic research. Liu et al. (2015) studied the effects of ammonium on the biotransformation efficiency of *C. vulgaris* and identified the mechanisms by nitrogen isotope fractionation and proteome approaches. They showed a differential expression of glutamine synthetase associated with ammonium assimilation. Furthermore, proteomic studies in *N. oculate* revealed that organic carbon and nitrogen from the breakdown of proteins and pigments were primarily utilised in fatty acid synthesis under depleted nitrogen conditions (Tran et al., 2016).

Similarly, other studies revealed the effect of dark stress on lipid biosynthesis in *P. tricornutum* (Bai et al., 2016). Many recent studies, such as array-based proteomics, oligonucleotide chips, and imaging, deal with the structure and analysis of proteins, including their three-dimensional shape, localisation, and physiological and metabolic parameters, which have helped in understanding the various biotechnological applications of microalgae. Proteomics plays a complementary role, providing information alongside genomics and transcriptomics, to understand the complex biochemical processes at the molecular level.

Proteomic analysis conducted in *Haematococcus lacustris* revealed the regulatory mechanism of proteins involved in the carotenoid biosynthesis pathway (Tran et al., 2009). In the experiments conducted, certain proteins were found to be upregulated under stress conditions of high irradiance and nitrogen depletion. Signal transduction proteins, such as the translocase of the outer mitochondrial membrane (spot 8), along with CBL-interacting protein kinase 10 (spot 34), showed significantly increased expression. Furthermore, proteins involved in the hydrolysis of fatty acids also exhibited enhanced expression, which is required for the esterification of the carotenoid astaxanthin.

The comprehensive proteome characterisation of the microalagal species *Chlorella* (*Chlorella vulgaris*) and *Spirulina* (*Arthrospira platensis*) has paved the way for the identification of bioactive peptides with functional significance in the pharmaceutical and food industries (Guadalupi et al., 2025). Notable proteins identified in *Chlorella* have been found to play a significant role in photosynthesis and also have therapeutic potential. These include chlorophyll a-b binding proteins, glycoproteins, and water-soluble antitumor proteins, among others. In *Spirulina*, the study identified several key proteins integral to the photosynthesis process, including the photosystem proteins and the phycobiliproteins. Certain ATPases, ribosomal proteins, DNA repair and modification proteins, and chaperone proteins were also recognised. The complete repertoire of the proteins of *Chlorella* and *Spirulina* reflects the potential for further biotechnological applications.

In another study on the microalgae, proteomic analysis revealed a novel understanding of the effect of various selenite concentrations on *Dunaliella salina* (Jiang et al., 2023). It was observed that proteins such as Glutathione peroxidase (GPX7), ascorbate peroxidase (APX8), and chlorophyll a-b binding proteins (LHCB), which are required for antistress and redox functions, as well as energy metabolism in the cell, were upregulated. However, certain proteins, including proteasome subunit beta type, ring box protein, E3 ubiquitin protein ligase, and cullin-3, as well as pre-mRNA-processing factor 19, involved in the ubiquitin-proteasome pathway, were downregulated. In addition to providing insights into the responses of a microalga as a biological carrier of selenium to selenite, this study offers new insights useful for the industrial production of *D. salina* strains rich in selenium.

Metabolomics approaches

The comprehensive analysis of metabolites, along with an understanding of their properties and biosynthesis, is known as metabolomics. Marine organisms exhibit diverse expressions of metabolites due to their unique environment, which involves changing patterns of light, nutrients, salinity, pressure, and temperature. Measurement of small molecule substrates, intermediaries, and/or end products of cellular metabolism (metabolites) may be part of metabolomics. This technique offers an instantaneous and dynamic response to environmental and/or genetic perturbations in a biological system. In fact, several secondary metabolites from marine algae are High-Value Molecules (HMVs) (Bule et al., 2018).

Different types of secondary

Table 6. Various metabolomic databases used for algal information

Database	**Link**
ChEBI	www.ebi.ac.uk/chebi/
DrugBank	ww.drugbank.ca/
PubChem	http://pubchem.ncbi.nlm.nih.gov/
KEGG Compound	http://pubchem.ncbi.nlm.nih.gov/
MetaCyc	https://www.genome.jp/kegg/compound//
MMCD	http://mmcd.nmrfam.wisc.edu/
MetaboLights	https://www.ebi.ac.uk/metabolights/

Source: Modified from Lauritano et al. (2019)

metabolites, such as carotenoids, PUFAs, polysaccharides, and glycolipids, have been identified in several microalgae (Liu et al., 2015; Ambati et al., 2019). Different techniques, such as nuclear magnetic resonance (NMR) and mass spectrometry, are used for metabolic studies. However, few studies have been conducted, and as a result, no extensive database dedicated to metabolomics is currently available. Some of the publicly assessed databases used for metabolomic studies are shown in Table 6.

Crnkovic et al. (2018) conducted metabolomic studies on three filamentous freshwater cyanobacterial strains: cf. *Oscillatoria* sp. UIC 10045, *Scytonema* sp. UIC 10036, and *Nostoc* sp. UIC 10110. He studied the effects of nitrate and phosphate on biomass production and metabolomic profiles. Metabolomic studies have also been conducted to understand the impact of metal toxicity on microalgae, such as *Chlorella* sp., and their interactions using NMR techniques (Zhang et al., 2017). Metabolomic analysis of *Aurantiochytrium* sp. revealed a 43.6% increase in lipid production under the influence of phytohormones gibberellin and an increase in glucose utilization rate and other metabolites in the fatty acid biosynthesis pathway (Yu et al., 2016). Popko et al. (2016) showed that under nitrogen-depleted conditions, betaine lipids of *P. tricornutum* act as a key source for triglyceride formation, and there is the accumulation of sedoheptulose. The metabolic responses of *C. reinhardtii* to sublethal concentrations of inorganic and methylmercury were studied by Slaveykova et al. (2021), revealing changes in the algae in response to these toxic compounds. Microalgal metabolomics studies are diversified to include secondary metabolites of economic value in the nutraceutical, pharmaceutical, and biofuel industries, as well as the microalgal response to different environmental stimuli.

Acutodesmus sp. HLGY was studied using a multi-omics strategy to analyze the factors leading to carotenoid leutin accumulation (Zhao et al., 2025). In the study, the N-hexanoyl-DL-homoserine lactone (C6-HSL), a quorum-sensing molecule, was investigated through metabolomic analysis. Results revealed that C6-HSL was significantly involved in enhancing the rate of metabolic cycles, such as the tricarboxylic acid (TCA) cycle, gluconeogenesis, and tryptophan (Trp) metabolism, along with leutin accumulation in the cells. This study presents a potential framework for utilising a metabolomics approach to enhance carotenoid accumulation. In another study, metabolomics analysis was performed to gain insight into the chemical composition of commercially marketed microalgae, including *Spirulina, Chlorella*, and *Amphora* species (Hegazi et al., 2024). The analysis using various metabolomics technologies revealed differences in the large molecular weight metabolome, including phospholipids, glycolipids, free fatty acids, nitrogenous lipids, and pigments, in each of the species. Glycolipids were abundant in *Spirulina*, while *Chlorella* was enriched in phospholipids. *Amphora* species, due to its potential use as a food supplement and biofuel, is rich in fatty acids, supporting its commercialisation.

Glycomics and lipidomics approaches

Glycomics is related to the identification, characterization and quantification of carbohydrates and their conjugates, including proteoglycans, sulfoglycans, aminosugars and glycolipids. Glycome studies can identify essential carbohydrate molecules involved in various pathways and interactions with pathogens. It elucidates the interactions of drugs with target molecules in organisms and can be further used for polysaccharide characterisation for various biotechnological and industrial applications. Ahmadi et al. (2015) have discussed the potential of various algal polysaccharides derived from different marine resources, including the antiviral activities of Carrageenan, Galactan, Alginate, Fucan, Laminaran, Naviculan, Calcium spirulan, Nostaflan, etc., derived from various algae. *Arthrospira* sp. produces many carbohydrate derivatives with therapeutic properties, including immunomodulatory, anticancer, anti-inflammatory and antibacterial properties. Further, major carbohydrate databases include Glycosciences.de (GS) and the Bacterial Carbohydrate Structure Database (BCSDB).

Microalgae are potential sources of various fatty acids, which exhibit multiple bioactivities. The microalgal PUFAs are essential components of glycolipids, phospholipids, and betaines. Several lipids such as Sulfoquinovosyldiacyl glycerol (SQDG), Sulfoquinovosylmonoacyl glycerol (SQMG), Gamma-linoleic acid, α-linoleic acid, etc., are derived from *Spirulina* sp., *Chlorella* sp., *Pavlova lutheri* and have antiviral, immunomodulatory and neurological properties (Ahmadi et al., 2015). Other microalgae, such as diatoms, flagellates, and dinoflagellates, have also been reported to produce bioactive lipid molecules. In a study to determine the fatty acid composition of various glycolipids, a mass-spectrometry-based lipidomic approach was employed for several microalgal species (Da Costa et al., 2016). Monogalactosyldiacyl glycerolipid (MGDG) was observed to be the most abundant glycolipid, and more than 20 of these MGDGs were identified. Furthermore, glycolipids included 35 sulfoquinovosyl diacylglycerolipids and 20 digalactosyl diacylglycerolipids molecular species, which account for about 0.1-40% and 0.02-50% of the total lipids. The glycolipid content and composition vary according to growth conditions and parameters, including temperature, salinity, light, and nutrient availability. These glycolipids are taxonomically significant and can serve as markers for various metabolic pathways in microalgae. A comparison of different omics techniques, which can also be utilised to study microalgae, is summarised in Table 7, as discussed by Amer & Baidoo (2021).

Challenges and prospects of algal carotenoid production

The ability of microalgae to photosynthesize natural chemicals with biomedical and industrial implications has made them scientifically more studied organisms. Carotenoids and other bioproducts produced from a potentially sustainable platform of microalgae have gained increased attention owing to their unique properties and promising future. These bioproducts, such as feed, fuels, medications, among others, obtained from microalgae are sustainable, cost-effective and efficient food sources. Several commercially viable algal-derived chemicals have been targeted for low-cost synthesis in conjunction with the co-production of algal biomass, due to algae's rapid growth, inherent genetic diversity, and capacity to utilise resources efficiently. The presence of vitamins, lipids, and biomass in microalgae makes them a natural source of recombinant proteins, which are used in synthetic biology.

Table 7. A comparative depicting different Omics techniques which can be used for studying microalgae

Omics technology	**Definition and description**	**Benefits**	**Redundancies**	**Ease of use**	**Tools used**	**Acquisition tools**	**Reproducibility**
Genomics	Genome (the complete set of genes) Genomic sequencing Gene functionality and interactions Metagenomics	Evaluate genome modification in engineered and natural systems	Cannot solely provide complete description of complex biological system	Easiest	EBI GEO ArrayExpress GenBank	NGS PCR RFLP-PCR	High
Transcript omics	Transcriptome (the complete set of RNA transcripts) Gene transcription (gene expression) Metatranscriptomics via 16S rRNA	Evaluate gene function through mRNA 16S rRNA sequencing for constructing phylogenies	Cannot solely provide complete description of complex biological system Cross contamination and cross hybridization	Easy	DESeq2 DEXseq	RNA seq	Good
Proteomics	Proteome (the complete set of proteins) Protein translation (gene expression) Post-translational modification of proteins Metaproteomics	Evaluate gene function Evaluate protein translation and PTM and identify diagnostic biomarkers Gives phenotypic information	Difficult protein/ peptide quantification Inaccurate analysis of labile PTM Difficult to cover whole proteome due to large number of proteins	Difficult	Mascot Sequest Tandem Skyline Uni-prot Swiss-prot	LC-MS MALDI	Moderate
Metabolomics	Metabolome (the complete set of metabolites) Metabolites (substrates, intermediates and end products of cellular metabolism) Pathway flux (concentration and/or metabolic flux analysis)	Identify metabolic pathway bottlenecks and identify diagnostic biomarkers Evaluate protein functionality	Metabolites can have short half-lives due to instability and/or bio-transformations -Low abundance metabolites are difficult to analyze	Difficult	R and Matlab based tools SIMCA WebSpecimine, SIRIUS 4 MetaboAnalyst 4.0, SECIM COLMAR, MzMine	LC-MS GC-MS CE-MS NMR	Low to moderate
Multi-omics	Integration of all the above	Identify diagnostic biomarkers with high accuracy and provides a comprehensive knowledge and understanding of biological systems	very expensive Requires good/ rigorous experimental design accounting for all parameters pertaining to individual and combined omics technologies	Most difficult	ECMDB 2.0 YMDB 2.0 GenBank	Combination of multi omics tools	Depends on omics technology used

Source: Modified from Amer & Baidoo (2021)

However, scaling up the production of microalgae to an industrial level still presents several challenges.

The low microalgal yield, coupled with high production and energy costs, restricts the commercial potential of these microorganisms. To achieve high output of target products, genetic toolkits to modify strains must be established, along with optimising the microalgal strains. Metabolic engineering, combined with genetic modification of microalgal species, enables the production of extremely stress-tolerant strains with enhanced algal lipid and carotenoid levels, as well as improved bioproduct properties. With multiple benefits of carotenoids in various fields, such as nutrition and health, it is imperative to cultivate and enhance microalgal carotenoids as a viable alternative to meet the increasing demand for these valuable compounds. Even as considerable advancements have been made in the field of omics technologies, the major hurdles that remain pose several crucial questions that need to be addressed.

The carotenoids produced by different microalgal strains vary, and the enzymes involved in each of these carotenoid biosynthesis pathways have not been fully characterized. Despite various improvements in proteomic techniques over the past decade, limitations associated with the complete coverage of proteins remain to be addressed. However, the methods are limited to only a few of the microalgal strains, as the genome sequences of many microalgal species remain unexplored. To fully understand carotenoid biosynthesis and its enhancement, it is essential to have a comprehensive understanding of the enzymes involved in the carotenoid pathway. A key question that arises is how to utilise bioinformatics and metagenomics to identify novel enzymes and their role in the associated pathways. The possible expansion of yet-to-be-identified microalgal carotenoids using mining pathways and carotenoid accumulation in cells, which determines the microbial host manipulation needs, needs to be validated.

Though data from the individual omics platforms is available it requires integration and analysis from a systems biology perspective to achieve the desired results. We need to determine what computational framework, along with analytical tools, would be required to build models of microalagal cell factories with potential for enhanced carotenoid content. The algal biomass must be co-productized to produce an economically viable algae-derived harvest. This inherent genetic potential can further limit carotenoid production, as genetically modified strains of microalgae may pose environmental risks. This raises a challenge for synthetic biology in how to engineer genetically stable strains for commercial production that are both highly productive and safe. Furthermore, the finite and intricate genetic potential of microalgae limits their ability to produce carotenoid pigments, posing a critical constraint to their large-scale, viable exploitation. The transition from lab to the industrial scale continues to pose a significant hurdle. This raises a question about which metabolic engineering technique and bioreactor design can best utilise omics insights to optimise production efficiency and overcome the high costs of cultivation and extraction.

These challenging issues require efforts for enhanced industrial carotenoid production. Hence, emerging synthetic biology and systems biology are the future tools for harnessing microalgal cell factory development, which is needed for enhanced carotenoid production.

Acknowledgements

We would like to thank Sri Guru Tegh Bahadur Khalsa College, University of Delhi for providing us with the resources for the completion of this work. Also, would like to thank Prof. Vishakha Raina, and Dr. Namrata Misra, School of Biotechnology, KIIT University, Bhubaneshvar for providing their valuable input.

Author's contributions: PKN, MY and SG conceptualized the review and wrote the initial draft. PKN assisted in the literature search while MY and SG revised the manuscript. All authors read and approved the final manuscript.

Conflict of interests: The authors declare no conflict of interest.

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