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Challenges and Opportunities in the Present Era of Marine Algal Applications

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Abstract

Marine algae are of high importance in their natural habitats and even more now in the world of green technology. The sprouting interest of the scientific community and industries in these organisms is driven by the fast-growing world of modern biotechnology. Genomics, transcriptomics, proteomics, metabolomics and their integration collectively termed here as 'marine algal-omics' have broadened the research horizon in view of enhancing human's life by addressing environmental problems and encouraging novelty in the field of pharmaceuticals among so many more. Their use in the human society dates back to 500 B. C. in China and later across the globe; they are still being used for similar purposes and more today. There is a hiking interest in marine algae and their derivatives—from phycoremediation, food supplements, pharmaceuticals to dyes. Marine algae are currently considered as an emerging panacea for the society. They are being studied in a multitude of arenas. The multi-use of marine algae is enticing and promises to be a boon for industrial applications. Yet, most marine algae face challenges that might variably constrain their commercialisation. This chapter gives an overview of marine algae including all the 'omics' technologies involved in studying marine algae and it explores their multitude applications. It also draws the various successful industries budded around them and presents some of the challenges and opportunities along with future directions.

Keywords: applications, challenges, marine algae, 'marine algal-omics', opportunities

1. Introduction

Algae can be generally categorised into two large sub-groups, namely, microalgae (microscopic) and macroalgae (macroscopic). Although both groups have common traits such as the ability to carry out photosynthesis, they differ in various ways from their size to their phylogeny. Yet, they are of common interest to scientists and industries around the globe as part of biotechnological development and the exploitation of their metabolites of high economic values. Their use as food dates back to 500 B.C. in China and the ninth century A.D. in Chad [1]. Eventually, the purpose of their exploitation has expanded to other avenues. Since the nineteenth century or so, several marine macroalgae have been used as a natural fertiliser in several countries, for instance, *Ascophyllum* spp. in Scotland and *Sargassum* spp. in the Philippines among others [2]. In the late twentieth century, around 1980, the natural blue dye phycocyanin from the microalga *Spirulina* sp. was mainly used as a colourant for ice creams and cosmetics [3]. Over the years, several industries have experienced a spike in the use of marine algae owing to the 'omics' technologies [4]. Akin to other organisms and cellular omics studies, omics studies of marine algae—termed 'marine algal-omics' in this chapter—essentially include genomics, transcriptomics, proteomics, metabolomics and system biology tagged along with miscellaneous ones (e.g., fluxomics) which furthers the understanding of marine algae as a whole system [4].

At the very beginning of the twenty-first century, genomics marked the dawn of a different epoch of biological research providing a blueprint for genetic engineering for the optimisation of productivity of marine algae, reassembling the puzzle of evolution and the discovery of genes of interest coding for biological compounds of high significance. For instance, Stephenson et al. [5] provided an insight of several genes that have the potential to improve the solar conversion efficiency in mass culture of marine algae for biofuel production. Although genomics provide a static view of the capacity of a marine algal cell, the integration of transcriptomics, proteomics, metabolomics and system biology allows the study of its gene expression in response to environmental stresses [6–8], evolution among others. Examples range from the upregulation of gene coding for proteins of several pathways of the microalga *Ostreococcus tauri* in response to the effect of nitrogen deprivation and chemical defence activation in the macroalga *Caulerpa taxifolia* to cell damage [9] to the phylogenetic relationships of bacterial and the macroalgal *Laminaria digitata* enzymes—mannuronan C-5-epimerases in the alginate biosynthesis [10]. The advent of the 'omics' technologies has allowed for the discovery of a consortium of novel molecules that are guiding the nascent industries such as pharmaceuticals, biodiesel and papermaking to promote instances of international interest under the blue economy umbrella.

The Economist Intelligence Unit Limited [11] acknowledges the emergence of several ocean industries including marine biotechnology, e.g., the commercial production of β -carotene from the microalga *Dunaliella salina* [12]. Alongside the sustainability aspect of the industries, the blue annotation to the ocean economy is now gaining momentum worldwide. However, further research is needed to test the potential of the different aspects of this sector including the marine algae component. In such a quest, there are multiple challenges and opportunities

that need to be addressed. The marine algal large-scale production and its pounding monetary implications of the cost of production represent the major challenges to date [13]. However, as per literature, marine macroalgae are presently more appealing for industrial applications as they are readily accessible, easy to harvest compared to microalgae [2] have lower cost of production [14] and biosynthesise commercially important molecules such as the phycocolloids while remediating environmental stresses [15]. On the other hand, marine microalgae are also stirring interest in other fields such as biodiesel production that could cut several costs if symbiotic microalgae such as *Symbiodinium* spp. are used [16]. The choice of the most appropriate marine algal strain is an option which could be coupled with genetic engineering and commercialisation of by-products to enhance the economic value of marine algal production processes [17].

This chapter describes the taxonomic classification of marine macroalgae and microalgae as well as gives a brief description of their characteristics. It also discusses the phycoremediation technology using marine algae and the study of the metabolites of interest using the 'omics' technologies for their subsequent commercial/industrial applications. In addition, it points out the main challenges that their associated industries are facing and discusses future directions in both the research and commercialisation/industrialisation arenas.

2. Description of marine algae: morphological and genetic characterisation

More than 71% of the world's surface is covered by oceans that serve as habitats to a diversity of marine organisms including marine algal species [18, 19]. Ecologically, marine algae are at the base of most aquatic food chains and are important in biogeochemical cycling and, in addition, serve as habitats for many organisms in aquatic ecosystems [20–22]. Marine algae can be prokaryotic or eukaryotic. They usually inhabit shallow waters and belong to two main sub-groups (**Figure 1**), namely, macroalgae (also commonly known as seaweeds) and microalgae. The macroalgae are macroscopic and consist of three main groups: Chlorophyta (green macroalgae), Rhodophyta (red macroalgae) and Phaeophyta (brown macroalgae) [25]. They are thallophytes (non-vascular plants). They constitute of leaf-like structures known as blades, stem-like structures known as stipe and root-like structures such as rhizoids and holdfasts. In contrast, microalgae are microscopic and are grouped as follows: Cyanophyta (blue-green algae), Pyrrophyta (dinoflagellates), Chrysophyta (diatoms and golden-brown algae) and Chlorophyta (green algae) [23, 24, 26]. Marine algae are taxonomically classified using diverse methods including analyses of their morphological key features and molecular characteristics – pigments (phycocyanin, phycobilins, β -carotene and chlorophyll) [27], genetic molecules, fatty acids distribution, secondary metabolites distribution [28, 29], and diffraction, light scatter and fluorescence parameters (through flow cytometry)[30]. The choice of use or the extent of the use of the different methods is dependent upon the level of difficulty in identifying a particular species.

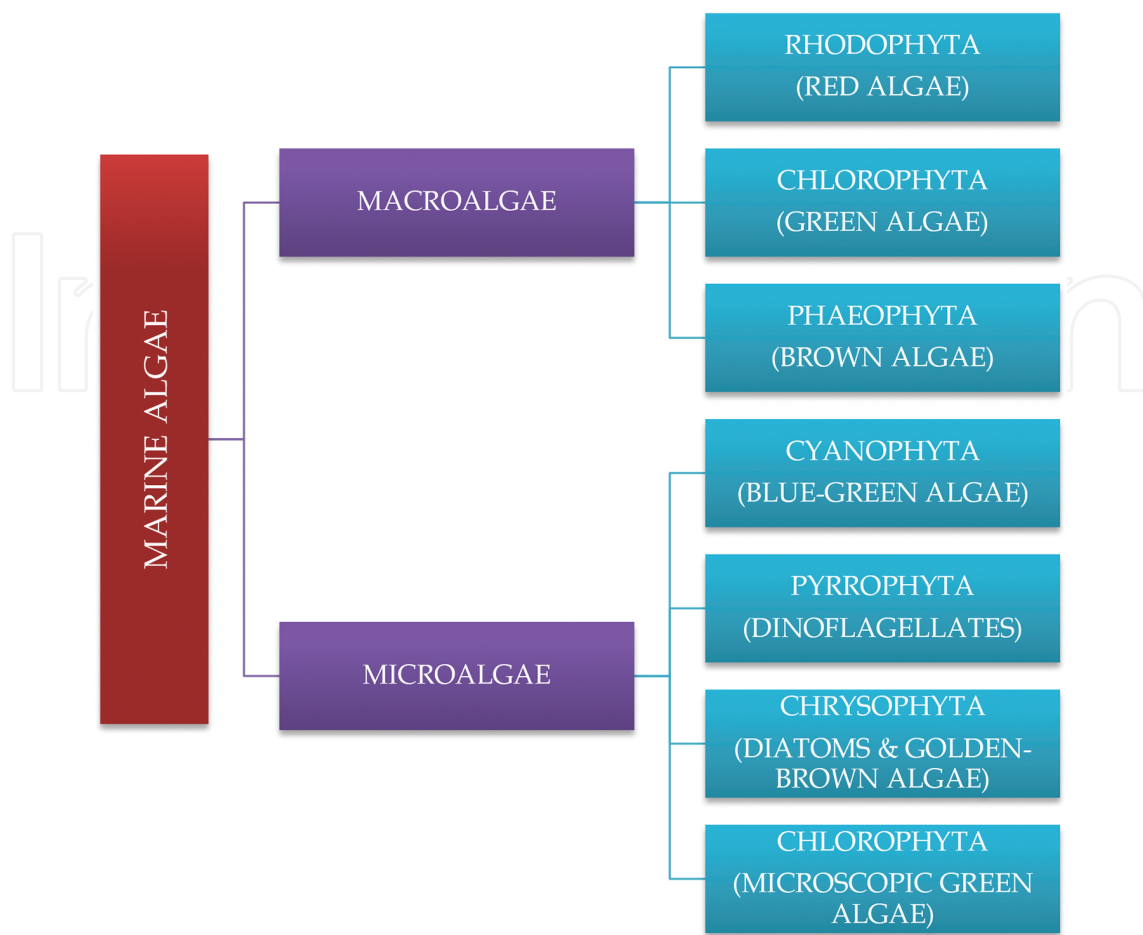


Figure 1. Classification of marine algae—adapted from Richmond and Radesandratana [23] & Oliveira et al. [24].

3. Applying biotechnology tools to explore the hidden properties of marine algae

The ‘omics’ technologies have revamped biological research and have led the twenty-first century into the post-genomic era that goes beyond the static state of genomics. Organisms being subjected to such high-throughput technologies include marine algae and hence the expression: ‘marine algal-omics.’ Analogous to other organisms and cellular omics studies, ‘marine algal-omics’ include essentially genomics, transcriptomics, proteomics, metabolomics and system biology tagged along with miscellaneous ones (e.g., fluxomics) which deepen our understanding of the respective organisms [4]. In this chapter, we use the expression ‘marine algal-omics’ to illustrate the advanced technologies involved in the study of marine algae.

Marine algae have built up their profiles exponentially in the omics world: their significance as primary producers of the blue planet, their impacts on global productivity as well as biogeochemical cycling are acknowledged [31]. ‘Marine algal-omics’ provide better understanding of biological system as well as commercially important molecules for marine

macroalgae and microalgae alike [1, 32–34]. Hitherto, the marine algae had to satisfy a set of criteria before being considered as potential candidates for such endeavours [31], but with the advent of meta-omics, the possibilities now seem endless.

3.1. Genomics

Genomics, the first of the ‘omics’ technologies, defines an organism’s native biosynthetic and metabolic capacities as a potential microbial cell factory, and provides a blueprint for engineering and optimising productivity. Although during the early genomics era studies were focused mainly on bacterial and mammalian organisms for biomedical applications and subsequent improvement to the human health sector, genomics has been a key technology involving several steps (**Figure 2**) in unlocking the biocatalytic potential of marine algae.

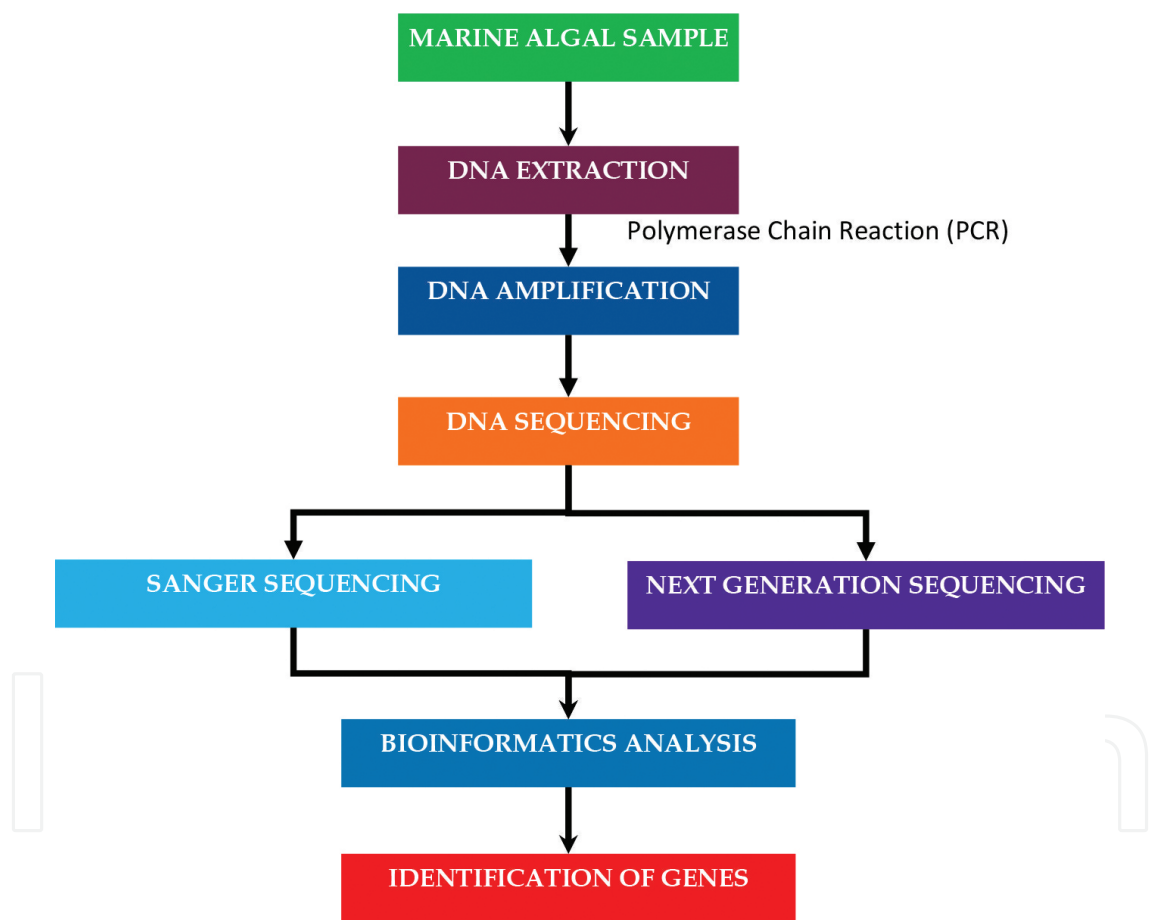


Figure 2. Methodology for genomics analysis—adaptation from Li et al. [35].

The advent of the next-generation sequencing technologies such as sequencing by ligation, pyrosequencing and real-time sequencing has revolutionised the field of genomics [36]. It has helped in the rapid, reliable and accurate sequencing of a number of marine algal species at a comparative cost [31, 37]. Successively, after more than a decade following the human genome project, scientists around the world have sequenced many different organisms including

marine algae [4]. About 8000 organisms' genomes from different kingdoms have been completely sequenced and published with thousands more in the pipeline [Genome OnLine Database (GOLD)]. The first marine alga to be sequenced is *Guillardia theta* that was followed by other marine algae including *Thalassiosira pseudonana*, *Phaeodactylum tricornutum*, *Aureococcus anophagefferens*, *Emiliania huxleyi*, *Ostreococcus tauri*, *O. lucimarinus*, *Micromonas pusilla* strain NOUM17 and *M. pusilla* strain CCMP1545 [37].

Genome sequencing provides a sequence of nucleotides which should be assembled and analysed for gene annotation. It indicates genes encoding proteins and functional RNAs available to the cell along with their associated regulatory elements [38]. Gene sequencing of the microalga *O. tauri* has exposed its very condensed genomes boiling down to a very low number of non-functional genes and allowed the identification of 8166 protein-coding genes in the nuclear genome. The same study also provided an understanding of the metabolic pathways of the pigment biosynthesis and photosynthesis. The absence of the gene coding for the light-harvesting complex proteins associated with photosystem II depicted the difference between *O. tauri* and terrestrial plants as well as other algae [39]. Grossman [31] discussed the importance of the genomic studies of the microalgae (diatoms) *T. pseudonana* and *P. tricornutum* with respect to its biology and nanotechnology related to the biogenesis and organisation of the highly patterned silicified diatom cell wall. The analysis of the genome of *T. pseudonana* unravelled the presence of five genes encoding the silaffin polypeptides most likely associated with the cell wall of the diatom. Stephenson et al. [5] summarised several genes that could be overexpressed or modified in targeted marine algae to improve their solar conversion efficiency in mass culture for biofuel production—some targeted genes are the *psaA*, *psaB*, *psbA*, sedoheptulose-1-7-bisphosphatase (SBP) and transketolase (TK).

Evolution study is another prime element of genomics providing a description of the phylogenetic relationship of all organisms on Earth. The comparative genomics analysis of the genome sequence of the filamentous brown marine macroalga *Ectocarpus siliculosus* and others has allowed the understanding of evolutionary hypothesis of the carbon storage and cell wall biosynthesis metabolic processes [32, 40, 41]. Furthermore, DNA barcoding is one of the most important aspects of taxonomic investigation and the economics of the marine algae because it allows the identification of strains of interest for the study of evolution as well as commercial/industrial applications [42, 43]. DNA barcoding uses molecular markers for characterisation of the marine algae of interest. Other technologies include DNA–DNA hybridisation, restriction fragment length polymorphism (RFLP), amplified fragment length polymorphism (AFLP) and random amplified polymorphic DNA (RAPD) among others [42]. Examples include the application of AFLP technique to 16 strains of *Alexandrium tamarense* in a phylogenetic analysis [44]; RFLP analysis of 18S ribosomal RNA for identification of five species of marine *Dunaliella* resulting in identification of three species, namely, *D. salina*, *D. parva* and *D. bardawil* [45]; and RAPD technique for the phylogenetic analysis of the marine macroalga *Porphyra* spp., *Ulva*, *Sargassum*, *Ceramium*, *Hizikia*, *Chara* and *Gracilaria* [46].

In addition, marine algal genomics encourages the understanding of algae allowing them to serve as model organisms [32]. Subsequently, studies have used several marine algae as model

organisms such as the microalga *O. tauri* and the macroalga *E. siliculosus* to study cellular and developmental processes, respectively [32, 47, 48].

3.2. Transcriptomics

The term ‘transcriptomics’ refers to the study of transcriptome, the whole set of transcribed RNAs, at a certain period of development as well as under a specific biological condition. Transcriptomics gives insights into genome expression that lends a view on gene structure, gene expression regulation, gene product function and the dynamics of the genome. Over the years techniques used for transcriptome analysis have evolved from the initial expression sequencing tag (EST) strategy to gene chips, and now the RNA-seq and bioinformatics analysis (Figure 3) [50]. Dong and Chen [50] and Morozova et al. [51] provide an in-depth review of transcriptomics techniques.

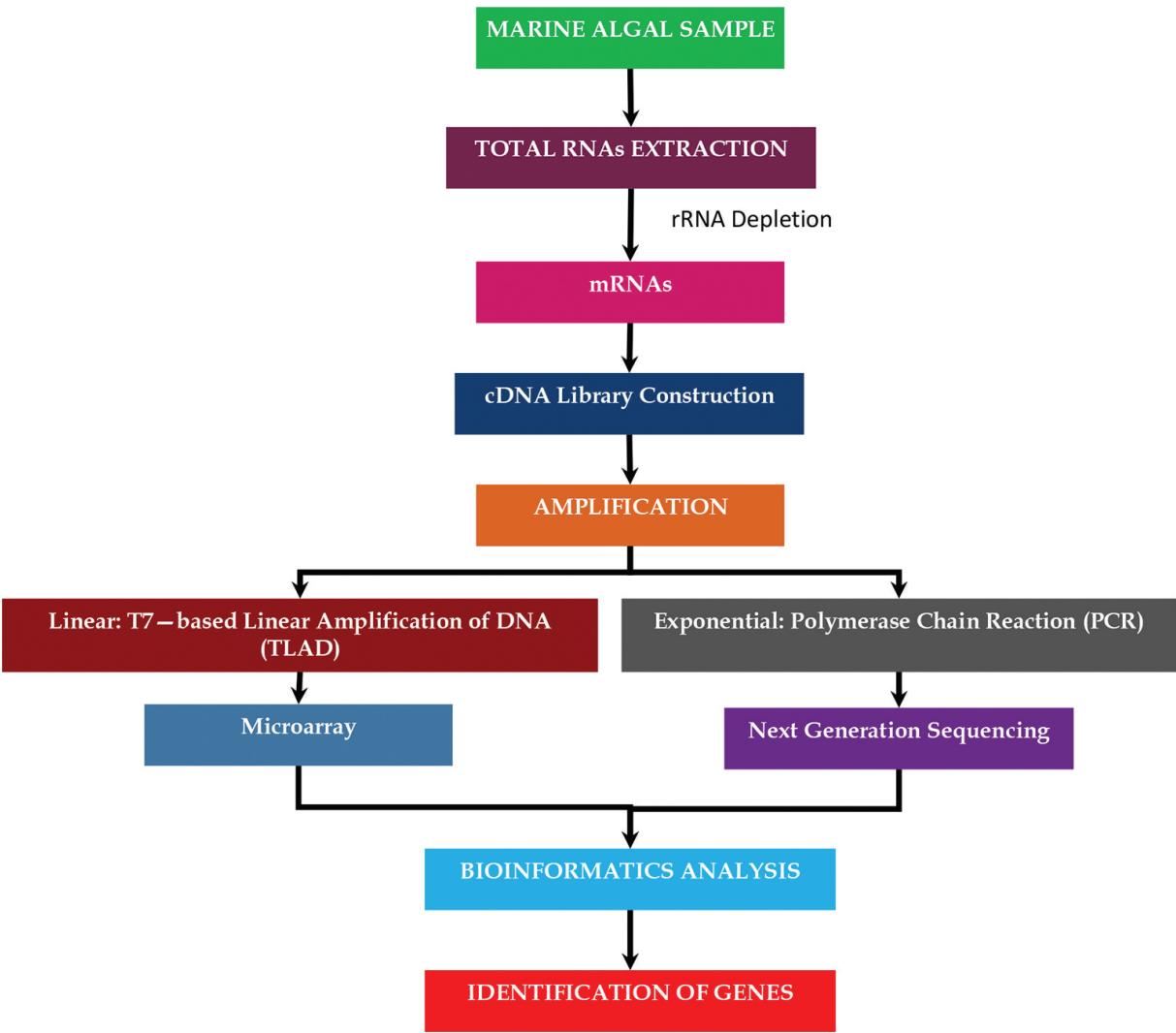


Figure 3. Methodology for transcriptomics analysis—adaptation from Tang et al. [49].

The integration of transcriptomic studies in 'marine algal-omics' assists the elucidation of gene expression in response to environmental stresses [6, 7], evolution [52], biochemical pathways [53] and the characterisation of genes of those biochemical pathways [10]. The relevance of transcriptomics exemplified by the studies herein mentioned ranges from the understanding of overexpression of respective enzymes in a particular biochemical pathway for pertinent applications to that of carbon capture.

The ability of marine algae to produce secondary metabolites in response to an environmental change is well understood. Radical changes are observed at the first gene expression level (i.e., transcription level). Transcriptomics studies on the response to environmental variability include *E. siliculosus*' response to saline environment as well as heavy metal concentrations [6, 54] and *Saccharina japonica*'s (macroalga) response to blue light induction [55] along with the response of microalgae *E. huxleyi* to nitrogen and phosphorus starvation [7] and *P. tricornutum* to iron starvation [56].

E. siliculosus subjected to hyposaline, hypersaline and oxidative stress conditions study revealed consequential alterations at transcription level which further impacted translation, amino acid metabolism, protein turnover, photosynthesis, and protein and nutrient recycling. Many unprecedented reactions such as the upregulation of many unknown genes along with a number of gene coding for chlorophyll *a* and *c* binding proteins were also observed [6]. In response to high copper contaminations, *E. siliculosus* exhibited several changes at transcriptomic level [54]. Ritter et al. [54] reported novel genes specific to brown macroalgae along with the downregulation of gene coding for enzymes related to nitrogen assimilation but an increase in free fatty acids content. A comparative analysis of the gene expression of *S. japonica* under blue light induction revealed a transcriptome reprogramming that resulted in the upregulation of 7808 and the downregulation of 3852 unigenes. The study also provided important points of information for other functional genes identification in kelp [55]. On the other hand, the long serial analysis of gene expression of the marine coccolithophore *E. huxleyi* suggests a strong transcriptomic response to both nitrogen and phosphorus starvation with an upregulation of the respective metabolism [7]. The transcriptomic analysis of *P. tricornutum* under iron starvation indicated the downregulation of photosynthesis, mitochondrial electron transport and nitrate assimilation [56].

Furthermore, the transcriptome analysis of marine macroalgae of economic importance in China covering two groups Rhodophyta and Phaeophyta—3 classes, 11 orders and 19 families—helped to decipher the proteins involved in the ability of these macroalgae to cope with extreme environmental variabilities [57]. The study reported three types of phycobiliproteins in *Gracilaria* spp. and all studied red algal species. Moreover, the study also helped to annotate the whole set of macroalgal C4-pathway genes including genes encoding pyruvate kinase, phosphoenolpyruvate carboxylase and others [57]. Nyvall et al. [10] carried out the first characterisation of a gene involved in the synthesis of alginate in the brown algae,

L. digitata, by means of northern-blot analysis and reverse transcriptase-polymerase chain reaction. The same study established the phylogenetic relationships of the bacterial and brown algal enzymes—mannuronan C-5-epimerases in the alginate biosynthesis.

3.3. Proteomics

In a broad sense, the term ‘proteomics’ can be defined as the study of proteins coupled with transcriptomics and genomics for they are complementary [58]. A cell’s Proteome – the whole cell protein – is dynamic: proteins extracted and studied at a particular point in time and under certain physiological condition(s) represent the cell’s immediate response to its environment, transcriptome alike. While there is a fine line of distinction between the classical and contemporary proteomics, the aim remains the global study of a cell’s proteome – protein–protein interaction, protein modifications, protein function and location of proteins among others. Proteomics involves different separation techniques to multiple analyses and different identification tools (**Figure 4**). Graves and Haystead [58] provide an in-depth review of proteomics techniques.

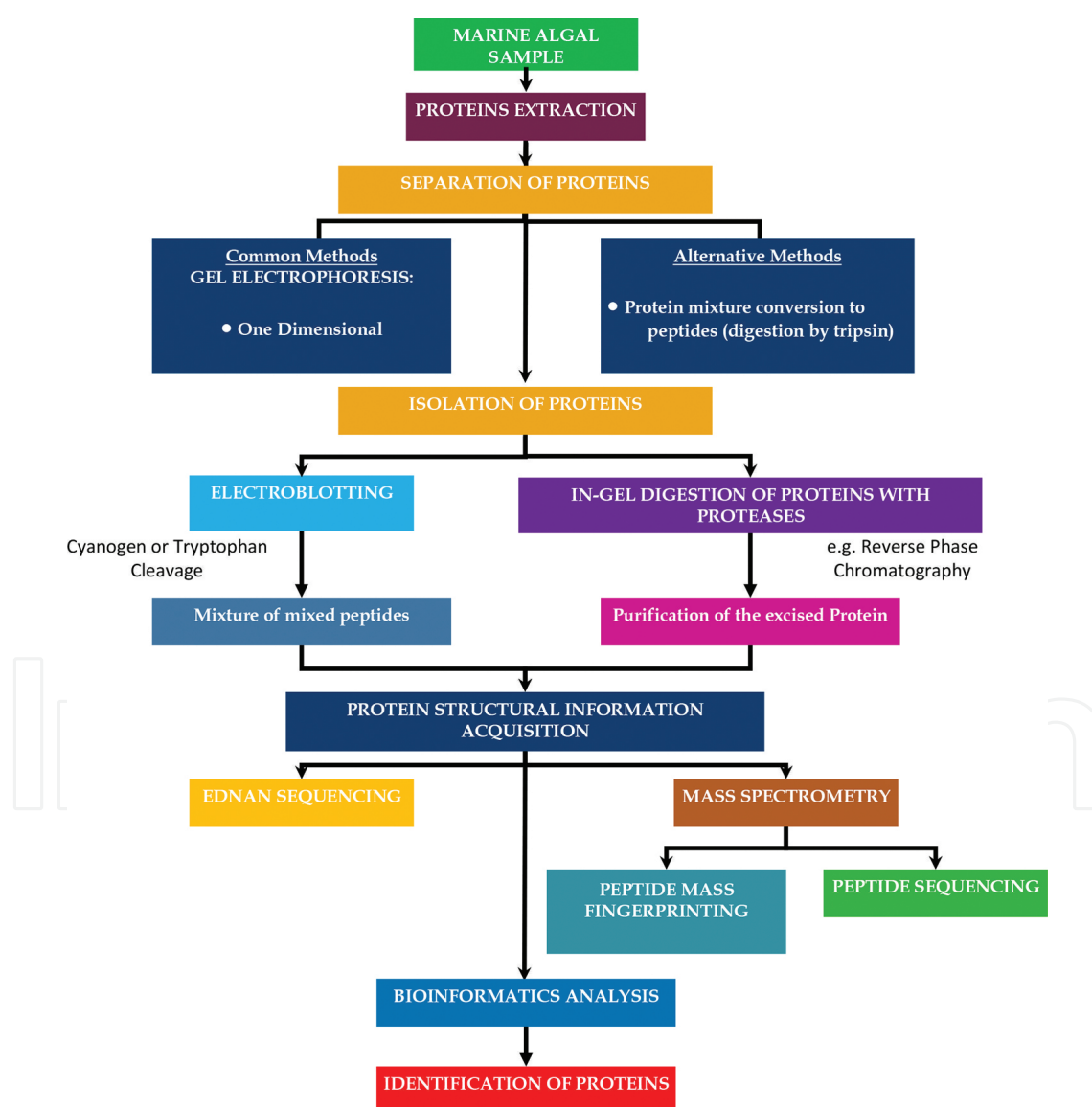


Figure 4. Methodology for proteomics—modified from Graves and Haystead [58].

For the past decade or so, several novel marine algal proteins have been identified by two-dimensional electrophoresis (DE) and mass spectrometry (MS) including proteins from the macroalga *Gracilaria changii* [59], and the microalgae *Dunaliella bardawil* [60] and *Nannochloropsis oculata* [61]. Nevertheless, proteomics does not end with the identification of a particular protein, it also helps to uncover the underlying function of the latter including its role in evolution as well as taxonomic studies and biochemical pathways [8, 61, 62].

Proteomic studies on algae are still relatively limited compared to higher plants. So far, it is the freshwater Microalga – *Chlamydomonas reinhardtii* – that has been thoroughly studied from various omics-angle. *O. tauri* is now being considered as a research model [63].

O. tauri being particularly small with a compact genome of around 13 Mbp makes it a perfect candidate to be used as a model organism to better understand the multiple metabolic pathways involved in a marine microalgae. Nonetheless, there are other marine algae that have been studied for several biochemical pathways such as the urea cycle [62], glycolysis [8] and Calvin-Benson cycle [64] among others.

The shotgun proteomics technique is being profusely applied to the study of marine algal proteome. The first shotgun proteomics analysis of *T. pseudonana* revealed 1928 proteins expressed under optimal growth conditions—out of which 70% were found to be involved in cellular metabolism and 11% in transport of molecules while all the participatory proteins in the urea cycle were unveiled [62].

Le Bihan et al. [8] investigated the effect of nitrogen deprivation on the biosynthetic pathways of *O. tauri* which led to the upregulation of proteins of several pathways including that of glycolysis, carbon storage and phosphate transport while proteins related to nitrogen assimilation in its plastid experienced downregulation. Liska et al. [64] examined the effect of high salinity concentration on the photosynthetic pathway of the halotolerant organism *D. salina* using nanoelectrospray MS combined with MS BLAST and MultiTag. The study revealed the upregulation of gene coding for several enzymes including plasma membrane carbonic anhydrases, Rubisco and other fundamental enzymes of the Calvin-Benson cycle, enzymes for adenosine triphosphate (ATP) and redox energy, glucose-6-phosphate dehydrogenase and 6-phosphogluconate dehydrogenase, and enzymes in amino acids biosynthesis [64]. High copper concentrations also affect the metabolism of marine algae. Although copper is an essential micronutrient to macroalgae, it can be toxic at high concentrations. Nonetheless, it has been reported that the brown macroalgae *Scytosiphon* spp. are tolerant to high concentration of copper leading to bioaccumulation. In order to decipher this particular genus' tolerance, a proteomic analysis was carried out by Contreras et al. [65] on *S. gracilis*. Twenty-nine proteins were identified including 19 overexpressed and hypothetically involved in copper tolerance.

It is noteworthy that marine macroalgal proteomic studies are relatively uncommon and studies of those under stress are further limited but there are some whose expressed proteome in response to an environmental stress has been explored and these include *Pyropia orbicularis* and *S. gracilis*. López-Cristoffanini et al. [66] probed into the proteome of *P. orbicularis*, a desiccation-tolerant red macroalga, by means of 2-DE and liquid chromatography (LC)–MS/MS analyses. A decline in photosynthetic activity but an increase in the antioxidant activity

by the upregulation of gene coding for phycobiliproteins and production of proteins such as superoxide dismutase were observed. On the other hand, *S. gracilis* in response to high copper concentration using peptide *de novo* sequencing revealed overexpression of proteins including cytosolic phosphomannomutase and glyceraldehyde-3-phosphate, a chloroplast peroxiredoxin among others [65].

Additionally, proteomic studies are also being carried out to investigate the biosynthesis mechanism of harmful marine algae particularly in relation to human health and safety [67]. Saxitoxin, for instance, is associated with paralytic shellfish poisoning. For a long time, little was known of the biosynthetic pathway of saxitoxin synthesis but studies are now revealing the enzymes implicated [68]. Marine algal toxins are being considered for potential commercial applications such as the use of saxitoxin and tetrodotoxin as an anaesthetic [69] and insights of their production would be an advantage for the industry.

3.4. Metabolomics

Owing to the relationship between genes and proteins, proteomics became the main focus of the post-genomic era. However, being of subordinate relevance to the evaluation of phenotypic responses of organisms, proteomics gradually took the backseat while metabolomics was brought in the limelight [70]. Akin to the definition of the other ‘omics’ terms, ‘metabolomics’ refers to the study of the metabolome that is the complete set of metabolites of an organism. The metabolites of an organism can be categorised as primary (fundamental for cell develop-

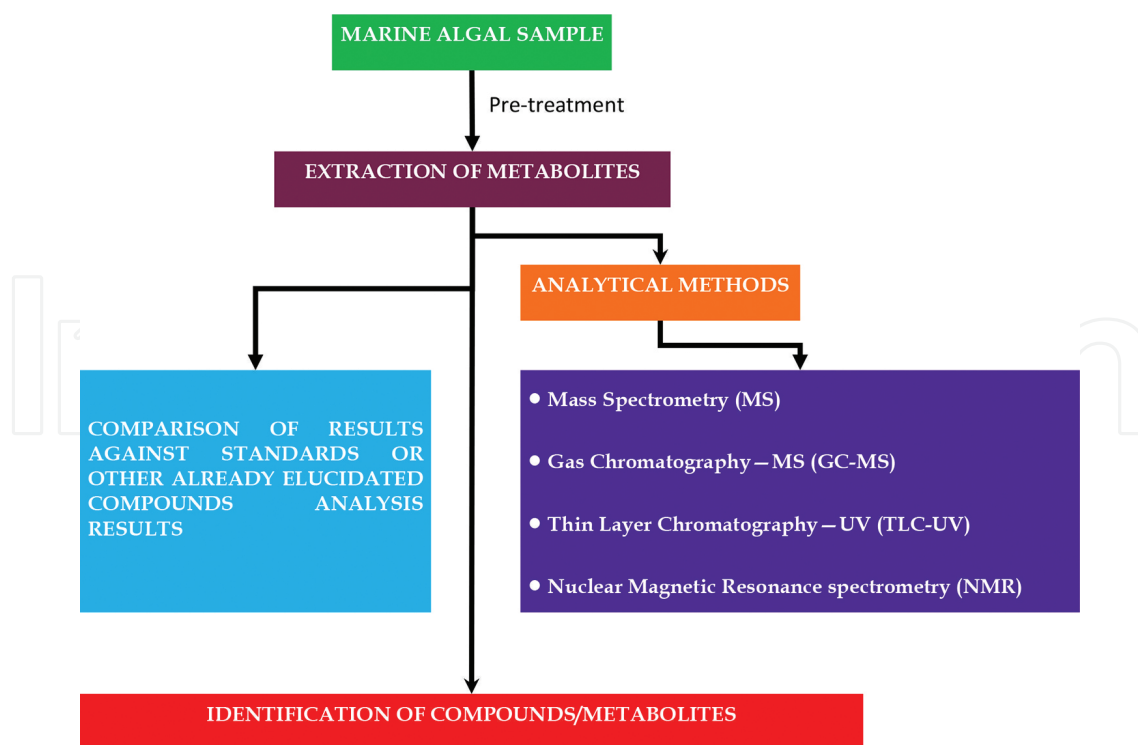


Figure 5. Methodology for metabolomics—adaptation from Verpoorte et al. [70].

ment and are continually produced, e.g., amino acids and polysaccharides) or secondary (produced in response to a stimulus such as an environmental distress, e.g., sterols). Secondary metabolites of marine algae are of major interest but not all can be expressed at all times. Their synthesis must be triggered by a stimulus—mostly physiological and/or environmental. Verpoorte et al. [70] advocated that the prime goal of metabolomics is the qualitative and quantitative analysis of all the metabolites present in an organism. They mentioned five major approaches including high-performance liquid chromatography/thin layer chromatography–ultraviolet (HPLC/TLC–UV), gas chromatography–MS (GC–MS), LC–MS, MS and nuclear magnetic resonance (NMR) spectrometry. Roessner and Bowne [71] summarised metabolomics approaches as follows: target analysis, metabolite profiling, metabolomics and metabolic fingerprinting (**Figure 5**).

As metabolomics depicts the physiological states of any organism including marine algae, the research database of this omics surpasses that of proteomics as well as transcriptomics in the functional genomics arena. The exometabolome and endometabolome of both marine microalgae and macroalgae have been thoroughly studied for multiple purposes including ecology [72], physiological states [73] and applications in multiple sectors such as health [34, 74] and energy [16].

Barofsky et al. [72] explored the exometabolomes of the marine microalgae (diatoms) *Skeletonema marinoi* and *T. pseudonana* to understand the dynamic nature of their ecology and the function of the metabolites they exuded. It was observed that some of the metabolites exuded acted as info-chemicals for the microalgal ecology very much like quorum sensing by bacteria. Furthermore, Vidoudez and Pohnert [73] untangled the general patterns of the metabolism of *S. marinoi* during the different growth (exponential, stationary and declining phase) by analysing its metabolome. Sugar and amino acids metabolisms were reported to be the highest in the exponential phase and accumulating in the night, whereas glucose and glutamate exhibited other different characteristics. The declining phase was characterised by the catabolism-related metabolites and the increase in terpenes as well as putrescine. The studies indicate that investigations dealing with both ecological and physiological aspects of diatoms need to consider the dynamic changing nature of their metabolism.

Barre et al. [75] depicted several analytical methods used to study the marine macroalgal metabolites including coupling MS with GC, coupling MS with HPLC and NMR spectroscopy. Several applications of those analytical methods for the understanding of species like the macroalga *Delisea pulchra* whose level of compounds have been quantified using GC–MS along with the characterisation of the variation in levels of furanones were reviewed. On the other hand, LC/APCI–MS provided opportunities to study the response of the macroalga *C. taxifolia* to cell damage revealing subsequent chemical defence activation [9]. NMR has also been used in metabolic profiling of macroalgae such as *L. digitata* and *Gracilaria conferta* among others [9, 75].

The understanding of metabolisms (e.g., fatty acids) and identification of respective metabolites go beyond the mere comprehension of the marine algal world. Its application as a panacea for the benefits of the society is what is mostly driving the marine algal metabolomics. A concrete example is the quest for cancer remedy. Cancer is the gangrening scourge of the

modern world and is on the forefront in the research arenas of several organisms including marine algae. Studies on the red macroalga *Callophycus serratus* by Lin et al. [34] and Kubanek et al. [74] provide ounces of hope for such festering health problems. The metabolites of *C. serratus* were explored by 1-dimensional (1D) and 2D NMR along with mass spectroscopic analyses resulting in the identification of four bromophycolides. The bromophycolides presented cytotoxicity towards selected human cancer cell lines. It is noteworthy that one of the bromophycolides exhibited submicromolar activity against human malaria parasite *Plasmodium falciparum* [34]. The *C. serratus* also revealed a bromophycolide that presents cytotoxicity against several human tumour cell lines via specific apoptotic cell death [74]. The plausible applications of marine algal metabolites are ever expanding. Gupta et al. [76] carried out NMR-based metabolome analysis on marine macroalgae—*Ulva lactuca*, *Gracilaria dura* and *Sargassum tenerrimum*. The metabolic level regulations of choline containing lipids of marine macroalgae, presence of acetate and lactate for all the macroalgal species indicating the existence of fermentative regulatory switching and identification of non-proteinogenic cysteine-oxoforms such as hypotaurine in *U. lactuca*, isethionic acid in *G. dura* and cysteine-sulfinic acid in *S. tenerrimum* were noted. The hypotaurine looks very promising for non-communicable diseases and can be an anti-hypertensive and a hypocholesterolemic agent. It is noteworthy that a limited number of studies have been carried out on the exometabolomes for pertinent application such as therapeutic ones. Kumari et al. [77] investigated the quantitative profiles of targeted hydroxy-oxylipins from 40 macroalgal taxa. The oxylipins extracted from the medium were analysed using HPLC. Even if the study indicated low hydroxyl-oxylipin content, the compound being similar to those of mammalian oxylipins could serve as substitute for the treatment of inflammatory diseases, cancer and atherosclerosis among others.

The metabolome composition is affected by mutations and endogenous as well as exogenous stimuli. There are some metabolites that can even induce perturbations at the transcriptional level and, consequently, modify the proteins' activities. Goulitquer et al. [78] reported on a broad spectrum identification of several metabolites using GC-MS of marine microalgae including *Cocconeis scutellum* and *S. marinoi* as well as targeted studies on diatom metabolism such as fatty acids profiling of *Cylindrotheca closterium* and *Seminavis robusta*.

As is the case with proteomics, the nature and concentration of metabolites vary with respect to environmental stress conditions. An inexhaustive list of such metabolomic studies includes defence response of the macroalga *Gracilaria vermiculophylla* [79] and others. Chen et al. [80], Lee et al. [81], Ye et al. [82] and Satoh et al. [83] provide for more details on metabolomics.

3.5. System biology

System biology is a multidisciplinary field of study with the integration of the 'omics' promoting the holistic approach and condemning the reductionist one [38]. The integration of the 'omics' results is imperative for the appreciation of an organism at the system level. The aim of system biology is to establish a profound understanding of the behaviour of and the interaction between the individual components of the organisms [4]. The basic principle of

system biology is modelling, which unveils the dynamics of the organisms. To date, studies on marine macroalgal and microalgal system biology are very limited.

E. siliculosus has been considered as a system biology model detailing its acclimatisation to environmental variability [84]. One of the issues highlighted in the study was the importance of non-coding RNAs in the regulation of the abiotic stress response mechanisms. Furthermore, proteomics and transcriptomics complement each other as do metabolomics and transcriptomics. Allen et al. [56] described the amalgamation of non-targeted metabolomics and transcriptomic analyses to explore the biochemical pathways of *P. tricornutum* under iron starvation. The study revealed several issues including the downregulation of photosynthesis, mitochondrial electron transport and nitrate intake, but there was a compensation of nitrogen and carbon from protein and carbohydrate breakdown, and adaptations to the biosynthesis of chlorophyll and the metabolism of pigment.

System biology is unravelling the novelty of metabolic capabilities and potential bioproducts of marine algae. Genomics, transcriptomics, proteomics and metabolomics are leading to the discovery of innumerable novel molecules, which are proving to be crucial resources and assets in emerging industries such as nutraceuticals, biofuels, pharmaceuticals and cosmeceuticals based on marine algae.

In this section, we have attempted to address the majority of 'marine algal-omics' research that has been conducted to date. However, it is far from being an exhaustive review. 'Marine algal-omics' have the potential to further develop a whole range of relevant industrial products including commodity and specialty chemicals and enzymes, biopolymers and pigments as well as application to the examination of marine algal bioremediation.

4. Existing and potential applications of marine algae

The array of marine algae and their derivatives are gaining increasing recognition worldwide. In addition to the panoply of ecosystem services that marine microalgae and macroalgae provide, the extensive range of biotechnological exploitation and the subsequent industrial applications of these organisms as biological factories are thoroughly documented. Marine algae are being widely used (**Figure 6**)—both at the molecular and organismal levels—as food [85, 86] and nutraceuticals [87], animal and fish feed [86, 88], biofertiliser [89], bioplastics [90], pharmaceuticals [91], cosmeceuticals [91–93], fluorophores [94], food colourants and textile dyes [95, 96], and biofuels [16] as well as for phycoremediation [97–99] (**Table 1**).

4.1. Phycoremediation

Phycoremediation is the use of algae to destroy or biotransform pollutants to innocuous level [107]. Marine algae are being considered for their multiple advantages. Marine algae can remediate heavy metal contamination [97, 98, 108], contribute to wastewater treatment [99], lower the atmospheric carbon dioxide [14, 15] via photosynthesis [109] and produce biomass for industrial applications [15, 108].

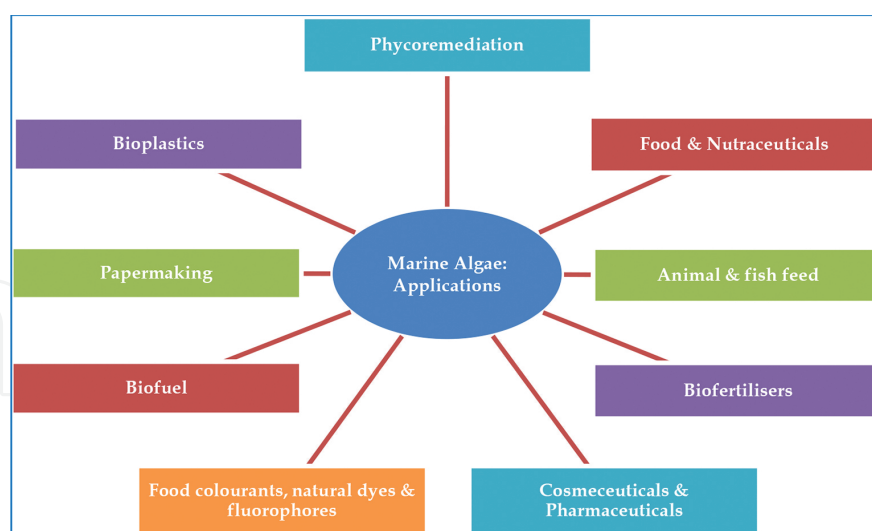


Figure 6. Applications of marine algae.

Carsky and Mbhele [108], Lawton et al. [110] and Imani et al. [98] investigated the potential of several marine algae to be considered for heavy metal contamination remediation. *Sargassum* spp. were found to have good copper biosorption capacity making it a good candidate for effluent treatment processes for copper pollution control purposes. On the other hand, six *Ulva* spp. found in Eastern Australia were studied for bioremediation of land-based aquaculture activities. *Ulva ohnoi* was found to be the most appropriate one as it had high growth rates, tolerance to extreme environment and good ability to use multiple sources of nitrogen [110]. Imani et al. [98] tested the tolerance of *Dunaliella* to mercury, cadmium and lead contamination revealing the ability of *Dunaliella* as a useful biological tool for the elimination of heavy metals in the environment.

Increasing atmospheric carbon dioxide concentration is another major environmental threat affecting the balance of nature. Brennan and Owende [111] enumerated three sources of CO₂, namely, the atmosphere, industrial power plants and soluble carbonate. The desirable traits of microalgae, we assume which applies to algae in general, were considered to be the high growth rates, high metabolism of CO₂, high tolerance to SO_x and NO_x, biosynthesis of economically viable products, non-tedious harvesting methods, and tolerance to extreme environmental conditions.

Sydney et al. [112] reported that the freshwater microalga *Botryococcus braunii* had the highest CO₂ fixation rate than the marine *Spirulina platensis* and *Dunaliella tertiolecta*. Nonetheless, a high lipid accumulation was also noted in *D. tertiolecta*—a characteristic coveted in the biodiesel industry [16]. In addition, Moheimani et al. [113] stated that the coccolithophorid microalgae are of prime interest for CO₂ bioremediation as they form CaCO₃ scales along with photosynthetic carbon fixation. It was also noted that CO₂ is one of the photosynthetic rate limiting factor for marine phytoplankton. However, they cited studies which have shown that many of the phytoplankton species have evolved a CO₂ concentrating mechanism that allows them to use either CO₂ and/or HCO₃⁻ such as *E. huxleyi*. Chiu et al. [114] stated that *Chlorella*

sp. is a potential candidate for lipid and biomass productivity. The study also showed that *Chlorella* sp. underwent rapid growth in a high-density culture with CO₂.

Chung et al. [14] mentioned that over half a million tonnes of carbon is removed from the sea yearly within commercially harvested macroalgae (seaweeds). They stated that large-scale seaweed cultivation is attractive owing to their decades-proven, low-cost technologies and the panoply uses of their products. They provided an overview of the Korean Coastal CO₂ Removal Belt which promotes the removal of atmospheric CO₂ via marine forests—approximately 10 tonnes of CO₂ per hectare yearly for the brown macroalga *Ecklonia*.

Kaladharan et al. [15] investigated the carbon sequestration ability of the following marine algae: *G. corticata*, *S. polycystum*, *U. lactuca*, *N. salina* and *Isochrysis galbana*. It was found that *U. lactuca* is more efficient in carbon utilisation than its fellow counterparts. They advocated that large scale mariculture of commercially significant macroalgae can help mitigate the atmospheric CO₂ concentration and, subsequently, provide a consequent amount of biomass to be used as raw material for the phycocolloid industry.

The phycoremediation through marine algae is still at an infancy stage and it is unclear whether marine macroalgae or microalgae will monopolise this sector. So far, taking into consideration the literature cited, it is of opinion that marine macroalgae will be the first monopoly of this sector as it has been for the other sectors since the advent of marine algal industrialisation.

4.2. Food and nutraceuticals

The consumption of marine algae originates from countries such as Japan, China and the Republic of Korea [2, 89] where several genera of marine macroalgae, such as *Porphyra*, *Laminaria*, *Saccharina* and *Undaria*, have been used as staple food since prehistoric times [115]. The marine algal metabolites such as carotenoids, fatty acids, polysaccharides, minerals, vitamins and antioxidants have enabled synergistic benefits to humans via direct consumption [86]. The concept of 'nutraceutical' encompasses nutrition and pharmaceutical whereby food products comprise supplementary aforementioned chemical compounds that are beneficial to the human society, especially in the health sector [87, 116]. In quest for a healthy lifestyle, consumers are showing an ever-growing interest in products with health-enhancement capabilities [117]. Consequently, the demand for marine algae as food products and nutraceuticals has increased [2].

The high nutritional value and rich source of phycocolloids of several genera of marine macroalgae have been reported to be used as food. In this chapter, the term 'phycocolloid' refers to three commercially important high molecular weight polysaccharides, namely, alginate, carrageenan and agar. Sulphated galactans—agar and carrageenan—are extracted from Rhodophytes [118], whereas alginate (composed of mannuronic acid and guluronic acid [119]) is extracted from Phaeophytes. They are vastly used in the food industry as cost-effective gelling, viscosifying or thickening agents in ice creams and jellies [85]. The global value of these phycocolloids approximates to US\$1 billion [13]. Other economically important phycocolloids extracted from macroalgae are ulvans and fucoidans [101].

Marine microalgae have also been reported to contain proteins, carbohydrates and lipids in substantial amounts [85], which have been widely utilised as nutritional supplements and health food. *Dunaliella* spp. (Chlorophyceae) have been a rich source of β -carotene [120] that is a red–orange pigment acting as an antioxidant to protect against cancer [119, 121]. Chidambara et al. [122] reported on the significant restoration in antioxidant activities of enzymes such as catalase, superoxide dismutase and peroxidase in rats when treated with *D. salina* powder. Thereupon, *D. salina* has been widely exploited in the nutraceutical industry by companies such as Nature's Plus® and Carlson® for soft gelatine capsules of β -carotene for instance [117].

Polyunsaturated fatty acids (PUFAs) such as omega-3 eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [85] and omega-6 arachidonic acid (ARA) [89] are sourced from marine microalgae. Presently, focus is being laid on *Nannochloropsis oceanic* *N. oculata*, and *N. gaditana* for the commercial extraction of EPA and DHA, as tablets and freeze-dried powder by Eco Mundo®. High levels of EPA and DHA in diets have also been linked to reduced occurrence of cardiovascular diseases, rheumatoid arthritis, psoriasis, dementia, depression and Alzheimer's disease [123, 124]. The omega-6 ARA commercially extracted from the marine microalga *Porphyridium* [102] taken as supplement has been reported to enhance cognitive response [125] and coronary flow velocity reserve [126] in elderly persons.

4.3. Animal and fish feed

Strains of marine microalgae with high EPA/DHA levels used as a component of aquaculture and livestock feed [127] have been observed to augment its nutritional value [85, 128], increase the digestion capability, and induce positive growth and reproductive results to a certain extent [128]. Shifting from the conventional use of fish meal, a protein-rich product made from processing remainder fish after human consumption, fish bones and offal, microalgae are now progressively being used as constituents of animal feed. Furthermore, farmed carnivorous fish species fed by a marine microalgae-based diet obtain ample amount carotenoids, lipids, vitamins, proteins and energy for enhanced growth and reproduction [129]. Among cyanobacteria (blue-green algae), species of the genus *Arthrospira*, such as *A. platensis* and *A. maxima*, are mainly used in aquaculture to feed larvae and zooplankton (*Arthrospira* dietary supplement is known as *Spirulina*) [129, 130]. *Arthrospira* spp. also help to protect cultured organisms against pathogens, thereby, reducing the costs associated with the use of antibiotics in aquaculture [131].

The marine microalgae *I. galbana* and *Pavlova lutheri*, rich in DHA, are used as live feed for aquaculture [128, 129], whereas *Dunaliella* spp. are used in the dried form [102]. A mixed diet of marine microalgae *I. galbana*, *P. lutheri* and *Chaetoceros calcitrans* is commonly favoured to feed the larval, early juvenile and broodstock stages of bivalve molluscs [129]. *I. galbana* and *Diacronema vlkianum* have been obtaining a lot of attention due to their ability to produce long chain PUFAs (DHA and EPA). A diet composed of an amalgam of species is preferred to a diet consisting of a single species for it provides a more balanced nutrition and improves growth rates [130]. Another vital nutritional component for the growth of aquacultured organisms is sterols. The ability to carry out *de novo* synthesis of sterols is usually low or entirely absent in bivalves [119]. In order to overcome this inefficiency, phytosterols such as ergosterol and 7-

dehydroporiferasterol in *Dunaliella* spp. [132], obtained from a mixed diet of microalgae act as supplements in the diet of cultured bivalves. Countries such as Norway, Iceland and United Kingdom have been using the marine macroalgae *Ascophyllum* spp., growing in the eulittoral, zone as seaweed meal to feed animals in coastal areas, while France as well as Iceland have been using *Laminaria* spp.. "Seaweed meal consists of dried seaweed powder containing useful amounts of potassium, magnesium, sodium, phosphorus, calcium, chloride and sulphur, vitamins and trace elements." On the other hand, fresh brown and red macroalgae, such as *Macrocystis pyrifera* and *Gracilaria edulis* respectively, have been used as feed for abalone in Australia, whereas in South Africa the macroalga *Porphyra* has a huge market for abalone feed [2].

4.4. Biofertilisers

Marine macroalgae have long been used as a natural fertiliser on the shore and nearby land: *Ascophyllum* spp. in Scotland, brown algae in certain places in United Kingdom and France, *Sargassum* spp. in the Philippines and green algae in certain parts of Argentina among others [2]. These marine algae were buried into the sand on the beach or nearby land and allowed to rot and form a useful organic fertiliser. Brown algae, namely, species of *Ascophyllum*, *Ecklonia* and *Fucus*, are commonly used to produce organic compost. This compost is produced by drying and milling the macroalgae, and is sold as soil additives that function both as a biofertiliser and a soil conditioner. Compared to conventional composts, marine macroalgae-based composts provide the following advantages: high nitrogen, high potassium and low phosphorus content, good moisture retention properties, and improvement of soil structure and aeration. Examples include commercially available dried macroalgae Afrikelp® from brown algae *Ecklonia maxima*, *Ascophyllum* used as soil conditioner [133] and commercially available fertiliser Maerl® derived from red algae *Phymatolithon calcareum* and *Lithothamnion corallioides* [2].

4.5. Cosmeceuticals and pharmaceuticals

The bioprospecting of marine algae has gained momentum in the development of products for cosmeceuticals and pharmaceuticals. Significant marine algal compounds of the cosmeceutical industry include phlorotannins (also used in the food industry), sulphated polysaccharides, tyrosinase inhibitors and suppressors of matrix metalloproteinase (MMP). The marine algal extracts have recently received bouncy attention especially for their antimicrobial properties and in the treatment of the skin related issues (skin anti-aging, skin whitening and pigmentation reduction) [93]. Examples of such extracts from marine algae include *Arthrospira* (microalga) extract that prevents early skin aging by exerting a tightening effect [93]; *Alaria esculenta* (macroalga) extract that induces a significant decline in the amount of progerin that triggers cellular senescence in skin [134]; the macroalgae *Fucus vesiculosus* and *Turbinaria conoides* that contain polysaccharides such as laminaran, fucoidan and alginate having antioxidative properties [135] as well as properties for skin care and cutaneous disorders either as nutritional supplements or for topical application. *Porphyra umbilicalis* also contains large amounts of Mycosporine-like amino acids (MAAs) that can absorb UV light; therefore, it acts

as sunscreen [136] in cosmetics. *Sargassum horneri* extract, containing Sargachromanol E., inhibits lipid peroxidation and, thus, has great potential to prevent photo-aging of the skin if applied in cosmetics [93]. It has been reported that some marine macroalgae extracts have the potential to suppress the production of MMP in skin which normally cause the degradation of collagens and elastic fibres, and induce loss of skin elasticity. For instance, phlorotannins (dieckol and eckol) is isolated from *E. stolonifera* and *Corallina pilulifera* methanol extract [92, 137]. Additionally, the marine algae-derived antioxidants can help to maintain the organoleptic properties of cosmetic products by inhibiting lipid oxidation, thus, avoiding changes in appearance, odour and flavour of the cosmetic products [93].

Furthermore, marine algae are the most abundant source of natural polysaccharides—fucoidans, Carrageenans and ulvans. Those polysaccharides are used in some cosmetics as moisturising and thickening agents, rheology modifiers, suspending agents, and hair conditioners among others [93, 138]. Polysaccharides extracted from the macroalgae *S. japonica* and *Chondrus crispus* performed as a better moisturising agent in cosmetics as compared to hydroxy acid (HA) in conventional cosmetics. They also have hydrating, therapeutic as well as moisturising effects whereas *Codium tomentosum* regulates water distribution in the skin; hence, protects the skin from dryness. Marine algal pigments such as carotenoids are also used as natural pigmenting agents in pharmaceutical and cosmetic products [93].

4.6. Food colourants, natural dyes and fluorophores

Marine microalgae have also been explored for and used as a renewable source of natural food colourants and dyes. The bright red pigmentation exhibited by the carotenoids of *Dunaliella* is used as natural food colourants [102, 120]. Betatene® (natural mixed carotenoids), a natural colourant extracted from *D. salina*, has been approved and affirmed safe as a natural food colour for use in various food products and beverages by the United States Food and Drug Administration [120, 139]. Another important carotenoid of the microalgae species *Dunaliella* – which is incorporated in animal feed (poultry) and fish meals as a colour enhancer to allow pigmentation of the flesh, egg yolk and shell of the farmed organisms (fish and prawns) and ornamental fish – is lutein [140].

Microalgae are also sources of phycobiliproteins (phycoerythrin and phycocyanin and allophycocyanin) and chlorophylls that are used as natural dyes in various industries and as food colourants [94, 102]. These proteins are brightly coloured and fluorescent constituents of cyanobacteria and red macroalgae (*Hypnea*, *Acanthophora*, *Porteria* and *Sarconema*). Phycoerythrin, extracted from the microalga *Porphyridium cruentum*, is gaining momentum for its application in the food industry as a red pigment [96, 141]. In addition, the natural blue dye phycocyanin, extracted from the microalga *Spirulina* sp., has been used as a food colourant and an edible dye for ice creams since 1980 under the brand 'Lina Blue-A' marketed by the Daipon Ink & Chemicals, Inc. [3]. Owing to the increasing demand for a healthier food additive to enhance colour in the food industry, mass cultivation of the microalgae *Porphyridium*, *Rhodella* and *Rhodospirillum rubrum* is practiced for phycobiliprotein extraction [96]. Furthermore, on account of their spectroscopic properties, phycobiliproteins are also used as fluorescent probes with numerous applications in fluorescent immunoassays, flow cytometry, fluorescence

microscopy, fluorescence activated cell sorting and immunodiagnostics to name a few [94, 141, 142].

4.7. Biofuels

Both sub-groups of marine algae have the potential to contribute towards the world's future energy security, at the same time helping to reduce CO₂ emissions and mitigate global climate change impacts as compared to conventional fuels. The biomolecules for the biofuel industry are carbohydrates and lipids for the production of bioethanol and biodiesel respectively. Several strains of marine algae which produce carbohydrates and lipids via photosynthesis have the potential to be exploited as biofuel feedstock [143]. The choice of marine algae as biofuel feedstock is dictated by a number of advantages: relatively rapid growth rate and high productivity compared with other conventional oil crops, high photosynthetic efficiency, great potential for CO₂ fixation, low percentage of lignin and a high content in carbohydrates and lipids (20–50%) [143–147]. Microalgae can provide several types of renewable biofuels, for example, methane — produced by the anaerobic digestion of the algal biomass; biodiesel — derived from microalgal oil; and biohydrogen — produced by photobiologically [16, 144]. Several studies have focused mostly on eukaryotic species such as *Nannocloropsis* sp. because of their relatively higher lipid content [148] and cyanobacteria because of their fast growth rate and higher lipid content [16, 149]. According to Chu [102], microalgae appear to be a promising potential for biodiesel production. The study carried out by Beetul et al. [16] corroborated that argument; the cyanobacterial mats and the symbiotic microalga *Symbiodinium* clade C were found to contain relatively significant amounts of lipids making them good candidates for biodiesel feedstock.

4.8. Papermaking

Delving into the potential applications of marine macroalgae, many authors have reported the use of algae-sourced cellulose in papermaking, a field of application still at an infancy stage. In general, wood-based pulp utilised in the papermaking industry has to undergo a lignin removal process to liberate the cellulose, which is the desired component for producing high quality bleached paper. Lignin is a polymer intercalated between the cellulose fibres in cell walls. Lignified pulp is normally used for low-quality papermaking, for instance, newsprints. Owing to the lack or substantially low amount of lignin in the cell walls of algae [150, 151], the lignin removal process is omitted when using algae [152], making them potential candidates for sustainable and profitable papermaking as long as cultivation methods are cost effective. This can be achieved by mass cultivation of raw material for a fully established algae-based papermaking industry. Seo et al. [150] attempted to use lignin-free red macroalgae *Gelidium corneum* and *G. amansii* to produce printing grade paper. The wild Rhodophytes yielded 8–11% pulp with a brightness of over 80%. The smoothness and opacity of the red macroalgae handsheet, characteristics critical for good quality paper, were high compared to commercial high-quality paper manufactured from wood pulp [150]. Other patented methods to extract cellulose from marine macroalgae for papermaking have also been described by Sakai et al. [152] and You and Park [153].

4.9. Bioplastics

Bioplastics have been derivative from organic sources such as potatoes, corn, vegetable oil, and most recently from marine algae. Polysaccharides from macroalgae – carrageenan, agar and alginate – can be used to make bioplastics [90]. Marine algae-based bioplastics have the following advantages: no competition with food resources, ease of growth in a wide range of environments, high yield/biomass, cost-effectiveness, address the issue of excessive CO₂ emissions and is environment-friendly [2, 154]. The various types of plastics that are derived from marine algal feedstock include the following: *hybrid plastics*—which are made by adding denatured algal biomass (for example, the filamentous macroalga *Cladophora*) to petroleum-based plastics (like polyurethane and polyethylene) as filler to increase their biodegradability; *cellulose-based plastics*—which are made from cellulose component of the algal biomass left after the extraction of algal oil (about 30% of the total algal biomass); *Poly-lactic acid (PLA)*—which is produced by the bacterial fermentation of algal biomass; and *bio-polyethylene*—which can be derived from the bacterial digestion of algal biomass [2]. Other examples of bioplastics sources include the red macroalga *Eucheuma cottonii* [103] and the microalga *Spirulina dregs* [154]. However, these marine algae cannot be easily harvested [104]. Marine algae-based bioplastics are used in the packaging and automobile industries, as catering, gardening and medical products [154].

Macroalgae			
Product	Level of exploitation	Applications	Genus
Biomass	Organism	Food	<i>Porphyra</i> , <i>Laminaria</i> , <i>Saccharina</i> , <i>Undaria</i>
		Biofertiliser, organic compost, soil conditioner	<i>Ascophyllum</i> , <i>Sargassum</i> , <i>Ecklonia</i> , <i>Fucus</i> , <i>Phymatolithon</i> , <i>Lithothamnion</i>
Vitamins, minerals and trace elements	Organism	Feed	<i>Ascophyllum</i> , <i>Laminaria</i> , <i>Macrocystis</i> , <i>Gracilaria</i> , <i>Porphyra</i>
Phycocolloids—alginate	Extract/molecule	Stabilisers and thickeners in food industry, wound dressing, prosthetic devices, matrices to encapsulate and/or release cells and medicine, medical sutures	<i>Undaria</i> , <i>Laminaria</i> , <i>Ascophyllum</i> , <i>Durvillaea</i> , <i>Ecklonia</i> , <i>Lessonia</i> , <i>Macrocystis</i> , <i>Sargassum</i>
Phycocolloids—agar	Extract/molecule	Gelling agent in food industry, food gums, thickener in ice creams, excipient in pills, growth media for bacteria culture, biotechnological applications	<i>Gracilaria</i> , <i>Gracilariopsis</i> , <i>Gelidium</i> , <i>Pterocladia</i> , <i>Ahnfeltia</i> , <i>Gelidiopsis</i> , <i>Hypnea</i> , <i>Gelidium</i> , <i>Gigartina</i>
Phycocolloids—carrageenan	Extract/molecule/ algal biomass (for bioplastics)	Food industry, gel formation and coatings in the meat and dairy industries, stabilisers and thickeners in cosmetics, binders in toothpaste	<i>Chondrus</i> , <i>Eucheuma</i> , <i>Gigartina</i> , <i>Sarcothalia</i> ,

Macroalgae			
Product	Level of exploitation	Applications	Genus
		and tablets, smoothers in feed, paint industry, bioplastic	<i>Mazzaella</i> , <i>Iridaea</i> , <i>Hypnea</i> , <i>Mastocarpus</i> , <i>Kappaphycus</i>
Phycobiliproteins	Molecule	Natural dyes in cosmetics, natural food colourants, fluorophores in immunodiagnostics	<i>Hypnea</i> , <i>Acanthophora</i> , <i>Porteria</i> , <i>Sarconema</i> , <i>Gracilaria</i>
Cellulose	Extract	Papermaking	<i>Gelidium</i>
Carotenoids - β -carotene	Organism/ molecule	Health food, food supplement, feed, natural food colourant	<i>Dunaliella</i>
Carotenoids—phytosterols	Organism	Feed	<i>Dunaliella</i>
Carotenoids—lutein	Organism/ molecule	Natural colour enhancer in aquaculture	<i>Dunaliella</i>
Fatty acids	Organism/ molecule	Health food, food supplement, cosmetics, prevention of disease	<i>Nannochloropsis</i> , <i>Porphyridium</i> , <i>Odontella</i> , <i>Isochrysis</i> , <i>Phaedactylum</i>
	Organism	Live feed, mixed algal diets	<i>Arthrospira</i> , <i>Pavlova</i> , <i>Chaetoceros</i> , <i>Diacronema</i>
Polysaccharides	Molecule/extract	Pharmaceuticals, cosmetics, nutrition	<i>Porphyridium</i>
Phycobiliproteins	Molecule	Natural dyes in cosmetics, natural food colourants, fluorophores in immunodiagnostics	<i>Porphyridium</i> , <i>Arthrospira</i> , <i>Rhodella</i> , <i>Rhodosorus</i>
Lipids	Organism	Biofuels	<i>Botryococcus</i> , <i>Chlamydomonas</i> , <i>Nannocloropsis</i>
	Organism/ molecule	Nanotechnology, optical systems, semiconductor, nanolithography, drug delivery, medical	<i>Spirulina</i>

Table 1. Application areas of selected marine macro and microalgal species and derivative compounds (data from: [2, 13, 87, 89, 100–102, 90, 100, 103–106]).

5. Challenges and opportunities in biotechnological applications of marine algae

‘In the end, the objective of microalgal biotechnology is to make money by selling a product for a higher price than it costs to produce.’ —Olaizola [155]

'Marine algal-omics' studies have given rise to new opportunities and subsequent industrial applications. While the prospects of those organisms are huge, there are multiple challenges that this sector has been facing since its foundation. Olaizola [155] presented one of the major issues that the field of marine algal biotechnology faces and why many marine algal applications have not yet reached the commercial and industrial scale. As a whole, for this chapter's scope, the challenges and prospects are discussed under the following umbrellas: marine algae taxonomic classification, 'marine algal-omics' and applications of marine algae.

5.1. Marine algae taxonomic classification

The taxonomic classification of marine algae has been tedious for the past decades. Morphological identification (using both microscopic and macroscopic features) of algae engenders various limitations such as change in morphology due to environmental factors [156], presence of similar morphotypes, complex cellular structure [157], lack of characteristic morphological features of the organisms as well as time-consuming and expertise-requiring in this field [158]. The ambiguities of identification using morphological keys have been found in most microalgal genera following phylogenetic analyses of ribosomal genes (SSU and ITS rDNA sequences) [159].

Identification of marine algae is highly problematic. In this view, taxonomic classification of marine algae is being reviewed through phylogenetic studies supported by analyses of cell division processes, physiological products (pigments and oils produced) and genetic characterisation [27]. For example, the taxonomy of the *Sargassum* spp. of the Mascarene Islands was revised as the available list of species was often biased using morphological identifications. Using morphological features, specimens previously identified as *S. polycystum* and *S. gaudichaudii* were recommended to be considered superfluous and synonyms of *S. polycystum* [160]. As for marine microalgae, the morphological misidentifications with respect to the genus *Dunaliella* have been spelled out in the past. The taxonomic revision following phylogenetic analyses allowed a better taxonomic classification of the *Dunaliella* spp. [161, 162].

As aforementioned, phylogenetic analyses help in categorising species which are difficult to identify. However, from a taxonomic point of view, DNA sequence information without other corroborating evidence can never be used by itself as an indicator for species delimitation [163]. In conjunction, molecular phylogenetic studies often address such issues. Nonetheless, it is still unclear whether the detected sequence differences may be used for delimitation of different species. This is explained by the progress of lineage sorting [164]. The use of different tools as well as sorting out of all lineages of algae is imperative for the identification of marine algae and further enhances their taxonomic exploration.

5.2. Marine algal-omics

'Marine algal-omics' are subjected to pretty much the same challenges that other microbial 'omics' agonise over. Graves and Haystead [58] put forward that the foremost challenge of proteomic studies is the analysis of low-abundance proteins and further deplored the archaic methods used to study proteins including the dearth of bioinformatics tools for data interpre-

tation. They also advocated that there is an urgency for new algorithms and that the mundane technologies should retreat while other technologies involving large-scale analyses need to be conceived.

On the other hand, transcriptomics experiences challenges of both worlds—genomics and proteomics. Dong and Yan [165] summarised the challenges as being experimental, technological and at the level of data interpretation to address issues like unveiling the regulating targets for each non-protein coding RNA and to decipher the complexity of the transcriptome. Bioinformatics is the resonance factor in all the ‘omics’. The advancement in high-throughput technologies of metabolomics is gaining momentum. Nevertheless, there is still an echo of data interpretation difficulties: identification of a panoply of unknown metabolites and transformative agents of metabolism, and data mining [166].

We are certainly past the genomics era; however, it is only recently that marine algal genomics took off. It has multiple challenges with an echo of bioinformatics especially in the context of the acquisition of growing amounts of data. It is further to be noted that significant advances in algal bioinformatics tool development, such as the Algal Functional Annotation Tool [167] and GreenCut2 [168], are therefore unequivocally important drivers in the study of ‘omics’ in marine algae. ‘Marine algal-omics’ also represents a major challenge at organismal level for a set of criteria, such as *in vitro* culture, and must be satisfied before being considered for ‘omics’ studies [31]. Algae, inclusive of marine species, have a failure record in terms of culturing and cultivation. This might be also part of the reasons why development in marine algal genomics is lagging behind in the genomics arena. Interestingly, with the advent of ‘meta-omics’, such challenges may be circumvented to some degree. The National Human Genome Research Institute [169] defines meta-genomics as being ‘*the study of a collection of genetic material (genomes) from a mixed community of organisms*’. Meta-genomics can be applied to marine algae that are hard to culture or to isolate from a microbial community. The significance of this technique is tremendous, for instance, meta-genomics could provide a sequence that could be of importance to several industries or even to our understanding of evolution among others. In this context, ‘meta-omics’ is being considered to study the proteome, transcriptome and metabolome of the marine algae that are hard to be isolated from their microbial community or cultured *in vitro*.

In addition, ‘marine algal-omics’ encounters pronounced issues with respect to macroalgae and microalgae. Contreras-Porcia and Lopez-Cristoffanini [170] underlined that protein extraction of algae follows no common protocol and pointed out that it is particularly difficult to extract proteins from macroalgae due to their low concentration and the co-extraction of contaminants. In the years to come, the proteomics studies of marine algae are expected to increase by multiple folds taking into account their commercial/industrial implication and the will of many countries to develop their blue economy. Such ‘omics’ studies are also opening a plethora of opportunities for several algal species in multiple fields such as *D. salina* for carbon capture to address climate change. As mentioned earlier, the marine microalga yields glucose-6-phosphate dehydrogenase and 6-phosphogluconate dehydrogenase. Those are of prime importance as they boost the pentose phosphate pathway which is crucial for carbohy-

drate metabolism that includes the provision of precursors for the biosynthesis of Lipids and sugar derivatives among others [64].

The 'omics' technologies detailed in this review are the most commonly used in 'marine algal-omics.' Conversely, earlier on, we deplored the static nature of the results that they provide. We also brought the perspective of other avenues (e.g., fluxomics) to the attention of the readers for a dynamic distinction in this arena. Many metabolomics studies provide a snapshot of the targeted or untargeted metabolome at a specific time and can be altered at any given time in response to stimuli or different life stages and growth conditions [78]. Metabolomics allows scientists to catch a glimpse of such a dynamic nature which in fact makes the static picture a limitation in itself. The curiosity even more importantly the urgency to discover the function of several metabolic pathways is now taking over the post-genomic era leading to the field of fluxomics, which is the study of metabolites fluxes. Fluxomics is still in its infancy stage and demands more research in this area for an understanding of how the system works.

5.3. Applications of marine algae

As a consequence, only a few species have been able to reach the industrial and commercial level while many marine algae still remain largely untapped as an asset due to an apparent lack of utility as a primary active ingredient [93]. While some advocate for the industrial application of marine macroalgae, others favour the marine microalgae. However, literature shows that both the marine macroalgae and microalgae can be useful to different industries. Nonetheless, marine macroalgae are currently more appealing for industrial application as they are readily accessible and easy to harvest compared to microalgae [2] but also have lower cost of production [14] and biosynthesise commercially important molecules such as the phycocolloids [15]. Marine microalgae, on the other hand, are attracting more attention as a feedstock for biodiesel production and other products such as β -carotene. However, as listed in **Table 2**, marine algal applications face many challenges that need to be addressed prior to commercialisation.

Aspects hindering commercialisation of marine algae	Challenges	References
Biomass production	High cost of production due to significant cost implication with respect to resource supply: water, carbon dioxide and nutrients	[17]
In-sea cultivation	Alterations to biosynthesis of molecules of interest due to spatial and seasonal variations, location and depth	[172]
Biomass harvest	Energy intensive process: centrifugation*	[16, 17, 173]
Oil extraction	Use of petroleum derivatives	[16, 17, 173]

Aspects hindering commercialisation of marine algae	Challenges	References
Algal strain	In-breeding leads to negative alteration of trait of economic importance such as decline in yield and quality	[17, 172, 173]
Algal diseases	Affect the candidature of strain to be considered as a feedstock	[172]
External factors affecting production	Impact of microbial interactions with marine algae on bioactivity	[172]
Land use	Non-arable land hosting marine algal mass production increases proportionately with increase in demand	[147, 173]
Carbon dioxide input	Contribute to high cost of production due to purchased carbon dioxide	[17]
Nutrient supply (especially nitrogen and phosphorus)	Limited nutrient supply limits algal mass production	[17]
Dehydration	Energy intensive	[17, 128]
Water use	Limited by freshwater	[17, 173]
Light	Optimal production limited by shading as well as photo inhibition	[17]

*Applicable to marine microalgae only.

Table 2. Challenges of industrial applications of marine algae.

As a whole, the numerous challenges mentioned (Table 2) can be addressed by genetically enhancing the algal strains, improving the production of high-value products and lowering its cost. Hybridisation of marine macroalgae [172] and genetic engineering [17] of both macroalgae and microalgae are promising tools assuring expression of important traits such as disease resistance and overproduction of specific compounds of interest. The compounds of interest may be targeted molecules as well as by-products. Furthermore, the in-sea culture exercise should be carried out along a standard for cultivation to circumvent issues such as inconsistent depth, environmental changes and others which may impact the production of bioactive compounds and composition [172]. In view of lowering the cost of production of marine algae, the by-products of macroalgae biomass production such as protein, alginates and phenolic compounds should be considered as an integral part of commercialisation to enhance the economic value of marine algal biofuel production process. The nutrients can be recycled while wastewater can also be used to some extent [17].

The last few decades have witnessed several developments in biotechnological applications of marine algae on three scales: research, commercial and industrial. However, the inexhaustive list of challenges mentioned here has hindered the Full-fledged application of marine algae. The challenges are being progressively addressed and opportunities are being generated. It is with confidence that we advocate the determinant role ‘marine algal omics’ will play in the marine algal economy.

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