



“Recent Advances in Algal Biotechnology: Toward the Development of a Sustainable, Algae-Based Bioeconomy”

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Abstract. Land plants have long been valued by mankind as sustainable supplies of food, medicine, and building materials. Agriculture has undergone constant development throughout human history to adapt to the changing demands of civilization. As a result of today's rapidly expanding population, current industrial and agricultural methods have major environmental implications and practical restrictions that must be addressed. Microalgae are a diverse collection of unicellular photosynthetic organisms that have the ability to meet critical demands in industry and agriculture. They are emerging as next-generation resources. Algae's rich biological diversity can be used to generate a variety of useful bioproducts, either naturally or by genetic engineering. Additionally, microalgae have a number of inherent benefits, such as low production costs, the ability to grow quickly in both scalable, fully contained photo bioreactors and large-scale outdoor systems without the need for arable land. In order to show how algae could offer high-tech, reasonably priced, and environmentally friendly solutions to many of our society's current and future requirements, we will now discuss technological developments, fresh fields of application, and products in the field of algal biotechnology. We discuss how cutting-edge technologies can advance our understanding of algal biology and, ultimately, help establish an algal-based bioeconomy. These technologies include synthetic biology, high-throughput phenomics, and internet of things (IoT) automation applied to algal manufacturing technology.

Keywords: microalgae, synthetic biology, phenomics, bioproducts, food, bioremediation, feedstock

1. Introduction

The world population is predicted to reach over 10 billion people by 2050. (United Nations, 2019). The majority of fertile land has already been used for agriculture, and factors like climate change and urbanisation present significant hurdles for the industry's future (Foley et al., 2011). Future demands cannot be met by simply intensifying current agricultural, forestry, fisheries, and fossil fuel extraction practises. In order to reduce environmental impact through sustainable sourcing of commodities like food, bioproducts, and bulk chemicals, current agrotechnology must undergo significant changes due to rising global temperatures, extreme weather, changing climatic patterns, and loss of cultivable land (Wurtzel et al., 2019). The productivity, cost-effectiveness, and environmental impact of agricultural crops including soy, corn, wheat, and rice have been significantly improved via the application of high-tech engineering and molecular genetics methodologies, in the forms of phenomics and genetic engineering (Mir et al., 2019). Likewise, products made from plants such as polymers are being created to replace products made from petroleum, such as meat and dairy (Zhu et al., 2016). Every ecosystem on Earth has been colonised by photosynthetic microalgae, which contain a staggering amount of biological diversity—more than 200,000 species, according to Guiry (2012)—reflecting a wide range of ecological adaptations. Phototrophic algae have the benefit of using sunlight to fix atmospheric carbon, which lessens their dependency on sugars for fermentation. This is in contrast to other microbes frequently used for bio-based manufacturing, such as yeast and bacteria. As a result, algae frequently outperform plants in terms of photosynthetic efficiency (Bhola et al., 2014), which increases their ability to produce biomass (Benedetti et al., 2018). Microalgae can be cultivated on non-arable soil with little freshwater consumption, or even grow in seawater or wastewater, and are more water-efficient than crop plants when produced on a large scale in a pond or photobioreactor (Demirbas, 2009). Thus, it is possible to effectively grow algae on a big scale even in many locations that are not ideal or adequately productive for crop production. Numerous algae species are naturally effective producers of a variety of commercial secondary metabolites that are currently derived from traditional agriculture, including lipids, proteins, pigments, and carbohydrates (Koyande et al., 2019). Currently, only a few industrial applications involving algae are used. The shift in emphasis from algae-based bioenergy to high-value bioproducts and the paradigm of algae-based biorefineries have been extensively discussed in recent studies (Laurens et al., 2017). In this analysis, we discuss how significant recent developments have illustrated the unrealized commercial potential of applications based on algae. We specifically describe how, in the upcoming years, cutting-edge technological advancements like automation, synthetic biology, and phenomics might harness the microalgae's already inherently promising characteristics. We define the future growth of microalgae as next-generation, low-cost, sustainable, scalable, and high productivity crop system by emphasising recent important successes and unresolved knowledge gaps in the field - both in terms of technological breakthroughs and applications. We anticipate that this will help create a bioeconomy based on algae, which will help find solutions to the impending problems brought on by our expanding civilization.

2. Technology Development

All current microalgal species are essentially environmental isolates, in contrast to crop plants that have been cultivated and selected over millennia to isolate certain features and produce highly productive strains. It is essential to improve the organism and environment that enable microalgae growth in order to enhance productivity and expand its industrial potential. We explain how this can be done using the most recent technological advancements in algae cultivation and harvesting, automation, phenotyping, and synthetic biology in the sections that follow.

Algal Cultivation: The ability of many algae species to produce significant amounts of biomass more quickly and cheaply than plants is one of their most alluring inherent characteristics (Brennan and Owende, 2010). Microalgae can grow to high biomass concentrations in eutrophic environments in nature, yet even these concentrations are insufficient for mass culture. A significant amount of research has been done over the last ten years with the goal of maximising the circumstances that encourage algal growth rates or stimulate increased production of a particular product in artificial growth environments. However, developing a system for production that is cost-effective is one of the main obstacles to algae mass culture. Accordingly, a wide variety of algal cultivation methods can provide varying degrees of control over the rate of growth and product production, as well as varying levels of capital and operating expense. In mass culture, a number of parameters, such as the availability of light, temperature, pH, and the concentration and ratio of the three main nutrients, carbon, nitrogen, and phosphorus, might inhibit the growth of microalgae (Sutherland *et al.*, 2015). The most affordable alternative to stagnant ponds for large-scale microalgal production is a shallow open pond raceway design with minimal mixing. Additionally, they may be constructed on a wide scale, consume less energy, and have lower capital and operational expenses than other photobioreactor (PBR) designs (Brennan and Owende, 2010; Borowitzka and Vonshak, 2017). Bioreactors for attached growth, including algal turf scrubbers (ATS) or motorised wheels with biofilm growth, are another advancement in outdoor open cultivation (Wang and Lan, 2018). Recent years have witnessed an upsurge in research into novel biofilm-based algae growth, in part because of the lower harvesting costs associated with higher recovered solid content (10–20% compared to 0.02% for suspended systems). While biofilm growth has been studied for wastewater remediation (Gross *et al.*, 2015) (section "Algal Biodegradation of Emerging Contaminants"), it has not been found to be suitable for all algal species and can result in complex mixed algae-bacterial communities (and therefore less suited for high-value, single products). While closed suspended growth PBRs, including flat-plate, tubular, or bag reactors, are appropriate for genetically modified organisms and have improved operating control, better mixing, and lower risk of contamination than open systems, they also have much greater capital and operating expenses (Gupta *et al.*, 2015). Artificial light can be used in closed systems to boost productivity (at an increased expense). Artificial light can be customised for the particular algae (Schulze *et al.*, 2014; Glemser *et al.*, 2016). Additionally, genetically modified organisms (GMOs) may be subject to regulatory restrictions that prevent them from developing in natural environments before being released into the wild. As a result, closed systems might be used more frequently in the future. Despite these benefits, most current production of products like biofuels, animal feed, and nutraceuticals is done in open pond systems (on the order of thousands of tonnes per year), whereas closed systems (hundreds of tonnes per year) are predominantly employed for high-value products (Posten, 2009; Borowitzka and Vonshak, 2017). Many times, the finished goods can be used with already-in-use industrial processes, such as transesterification for biofuels and the extraction of highly valuable compounds (Greenwell *et al.*, 2010; Khanra *et al.*, 2018). In addition, studies are being conducted to find ways to improve the extraction of algal products, such as by using supercritical extraction, pressure or microwave assisted extraction, ionic liquids, novel (less toxic) solvents, enzyme assisted extraction, or aqueous biphasic systems (Kadam *et al.*, 2013; Kumar *et al.*, 2015, 2017; T Lam *et al.*, 2018; Khanra *et al.*).

Phenomics: "The acquisition of high-dimensional phenotypic data on an organism-wide scale" is the definition of phenomics (Houle *et al.*, 2010). Although algal phenomics is still in its infancy, it has enormous potential for microalgal agriculture, biopolymers, bioplastics, and bulk chemicals, food and nutraceuticals, feedstocks, high-value products, biopolymers, bioplastics, and carbon sequestration, as well as bioremediation (section "Algal Biodegradation of Emerging Contaminants," section "Food and Nutraceuticals," and "Food and Nutraceuticals"). Researchers can screen natural and artificial diversity for the combination of gene alleles that will combine necessary characteristics, such as rapid growth and high product production, by building a database of GxE = P interactions for a given algae species. The potential influence of phenomics methods and technology in microalgae has recently come to light thanks to developments in the field of plant phenomics. The absence of searchable phenomics databases is a significant barrier to modern microalgal phenomics. Researchers studying plants and yeast, for instance, can plan or even carry out *in silico* experiments using the databases PROPHECY (Fernandez-Ricaud *et al.*, 2005; Fernandez-Ricaud *et al.*, 2016) and The Arabidopsis Information Resource (TAIR) (Lamesch *et al.*, 2011). Such instruments speed up research by demonstrating how various genes might be associated by a common phenotype (Ohyama *et al.*, 2008), or even by differentiating the activities of gene copies that appear to be redundant (Yadav *et al.*, 2007). An extensive phenotypic database will need to be built in order to apply this capacity to the field of algae study.

Synthetic Biology: In synthetic biology, the logical design of living things is based on engineering concepts. A biological system is seen in this field of study as a collection of defined genetic components that can be altered and reassembled to create new functionalities in different host species or change existing ones. In order to create optimum metabolic configurations for biotechnological applications, genetic designs are modified through iterations of a design-build-test-learn cycle (Khalil and Collins, 2010; Nielsen and Keasling, 2016). This potent new strategy will be combined with the advantages of a

photosynthetic microbial host in synthetic biology applied to microalgae to create unique production strains tailored to future environmental issues. The number of designs that genetic engineers can now assemble and test is constrained. The rising use of automation and computational design in biology, however, is expected to quickly change this paradigm. The optimization of terpenoid production in cyanobacteria serves as an example of how computational modelling can be used to predict counterintuitive methods to maximise metabolic flux through heterologous pathways (Lin et al., 2017). The development of innovative, new-to-nature molecules with possible new functions and uses will be an interesting area of synthetic biology (Moses et al., 2014; Arendt et al., 2016; Luo et al., 2019). The culture of microalgae can also benefit from synthetic biology, which can be used to optimise photosynthetic efficiency and increase carbon consumption (Gimpel et al., 2013.).

3. Applications

Food and Nutraceuticals: Research is being done to expand the ability of microalgae to serve as a source of nutrients, minerals, trace elements, and other bioactive components. This work sets a precedent for the creation of novel health products (Plaza et al., 2008; Lordan et al., 2011; Wells et al., 2017; Barkia et al., 2019). With an estimated \$1 to \$1.5 billion global net worth, the microalgal industry has not yet reached its full potential (Pulz and Gross, 2004). The United States Food and Drug Administration (FDA) has designated the cyanobacteria *Spirulina* sp., green algae *Chlorella* sp., and *C. reinhardtii* as "generally regarded as safe" (GRAS) due to a history of safe production and consumption (FDA, 2019). Green algal species like *Haematococcus* sp. and *Dunaliella* sp. are also GRAS-certified (FDA, 2019). Ingredients and goods made from microalgal biomass can be found in a wide range of commercial food markets. For instance, bulk lipids, carbs, and protein can be found in microalgal biomass (Koyande et al., 2019). A particularly promising path forward for agriculture based on sustainability is microalgal protein. Currently, higher plants are responsible for the majority of the world's protein consumption (Billen et al., 2014; Henchion et al., 2017; Caporgno and Mathys, 2018). However, plants require a lot of water, arable land, and the application of herbicides and fungicides (Dahman et al., 2019). Due to its increased protein content and favourable amino acid profile, algal-sourced protein can be a sustainable alternative to soy-based protein, making it a high-quality protein for human nutrition (Spolaore et al., 2006; Kent et al., 2015). Recent research on enhanced physico-chemical and nutritional qualities of *Spirulina* protein blends has produced encouraging results (Grahl et al., 2018; Palanisamy et al., 2019). Microalgae are therefore expected as a promising future agricultural crop to meet the rising demands of future human and animal nutrition or other high-value ingredients, thanks to efforts being made in new technologies such as phenomics and bioprocessing.

Feedstocks: Algae have the potential to be the next generation of biological resources, yet their use as a feedstock is already common in some well-established industrial sectors. For decades, the aquaculture sector has used algae to produce "aquafeed" out of them (Hemaiswarya et al., 2011). Aquaculture production facilities frequently use microalgae, either directly as live feed or indirectly as algal meal, which is the leftover biomass after lipid extraction, because to their quick growth rates and balanced nutritional content (Borowitzka, 1999). The recent increase in customer demand for more environmentally friendly food products is the key factor driving the market for algal meal. Currently, a significant component of conventional agriculture and aquaculture uses fishmeal, a crude flour made from fish parts that has been cooked, dried, and ground. Fishmeal has a high protein and PUFA content and is produced at a very moderate cost (\$1,500 per tonne, source1). Historically, fishmeal has been used as a fertiliser, a feed for pigs, poultry, and farmed seafood (Hardy and Tacon, 2002). However, fishmeal is now widely acknowledged as being unsustainable because it is mostly produced via by-catch, which causes ecosystems to be depleted and local fisheries to fail. As a result, additional environmentally friendly materials are being examined as substitutes for fishmeal, such as soybean meal, cottonseed meal, insects meal, legumes, and algae (Alvarez et al., 2007). (Hardy and Tacon, 2002).

High-Value Products: In addition to being naturally created by algae, high-value goods that are now derived from higher plants can also be made by algae via genetic engineering and synthetic biology. Microalgae are incredibly diverse, and as a result, they naturally produce a huge variety of natural compounds that could be beneficial for human consumption and use. According to the sections "Algal Cultivation," "Phenomics," and "Synthetic Biology," some products are already efficiently synthesised, while the yields of others can be increased to suit industrial needs by integrating advanced strain and bioprocess engineering. Currently, only a tiny portion of all algal species—mostly model species—have their biochemical characteristics characterised (Sasso et al., 2012). Plastics can be made from the starch, carbohydrates, and lipids found in microalgal biomass (Noreen et al., 2016). There are currently three primary ways to make bioplastics from microalgae: (i) using microalgae directly as bioplastics; (ii) combining microalgae with already-existing bioplastics or plastics derived from petroleum; and (iii) genetically engineering microalgae to produce bioplastic polymer precursors. In the first method, Zeller et al. (2013) reported making thermoplastic blends and bioplastics from *S. platensis* and *C. vulgaris*, whereas Wang et al. (2016) detailed making thermoplastics by mixing a variety of planktonic algae.

Algal Biodegradation of Emerging Contaminants: Synthetic organic compounds including medicines, herbicides, pesticides, and flame retardants make up the majority of emerging contaminants (EC), and when they are present in the environment at levels that are relevant to the environment, they pose a risk to ecosystems and human health (Petrie et al., 2015; Tran et al., 2018; Sutherland and Ralph, 2019). The occurrence of ECs in agricultural water and landscapes is causing growing concern. Accumulating ECs brought on by intensifying agriculture and greater water reuse could have unanticipated long-term effects on people and the environment due to climate change and growing populations (Martinez-Piernas et al., 2018).

Improved on-farm best management practises can manage direct application, but indirect application depends on wastewater treatment advancements that would lower, transform, or get rid of ECs. Microalgae-based wastewater treatment is a well-established technology that is more effective than conventional wastewater treatment systems and has lower capital and operating expenses (Benemann, 2008; Craggs et al., 2012). Despite their potential to detoxify both organic and inorganic contaminants, there have only been a limited number of researches on the use of microalgae for bioremediation of ECs. Combining the removal of nutrients and EC by microalgae may result in wastewater treatment that is more economical, effective, and protective of both human and environmental health (Sutherland and Ralph, 2019). Although it has been shown that microalgae may biodegrade ECs related to agricultural practices, more research is required to fully use micro algal biodegradation through improved enzyme expression and growth conditions. Micro algal treatment of EC can be a financially viable alternative for reducing pollutant contamination in rivers when combined with nutrient removal, such as HRAPs (Sutherland and Ralph, 2019).

4. Conclusion

One of humankind's oldest traditions, agriculture has always been crucial to civilization. Human society and agriculture have coevolved, mutually affecting one another. Humans have isolated, bred, and created new species over millennia to meet demands that have been constantly growing in number and diversity. Thanks to advancements in cultivation technology, genetics, and phenomics, agriculture technology has witnessed notable increases in productivity, efficiency, and product differentiation in the contemporary era. Although there have always been uses for algae in human history, using these organisms as industrial resources is a relatively new goal. All present industrial algal strains are comparatively uncharacterized, and algae-based techniques constitute a very recent application field in comparison to traditional agricultural crops. To speed up the utilisation of algae in biotechnology, decades of fundamental research on the biochemistry and physiology of algae (not reviewed here) may be used (Hildebrand et al., 2013). The relatively few algae species that are now used in commercial applications, however, primarily consist of natural isolates with little to no selection, breeding, or genetic engineering (if any) done to increase their performance in industrial settings or for higher yields. Despite this, algae already find uses in numerous industrial industries and sectors, as seen by the accomplishments described in this review, frequently with the clear potential to replace more energy-, money-, and environmentally costly alternatives. When considering the trajectory of future advancements in this subject, it is important to take into account how amazing and inspiring the current advancement and achievement of algal biotechnology and industry are. The industrialization of algae will proceed much more quickly because to the developing technologies we discussed, which will also give people the knowledge and resources they need to meet a variety of societal requirements with solutions based on algae that are extremely productive. This entails a greater comprehension of the biology, genetics, and biochemical properties of algae, which will be used to optimise both the organisms and the environment in which they are grown. This will make it possible to develop novel, highly productive strains in the near future, either as genetically modified or novel natural isolates, as well as effective growing techniques with little negative influence on the environment. As a result, we believe that the development of algae biotechnology will have a disruptive impact on the industrial landscape currently in place and will lead to the emergence of an efficient, scalable, and sustainable bio-economy based on algae, which will be essential to overcoming the obstacles and constraints that conventional agriculture will face in the years to come.

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