Chapter

Industrial Applications of Cyanobacteria

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Abstract

Cyanobacteria also known as blue-green algae are oxygenic photoautotrophs, which evolved ca. 3.5 billion years ago. Because cyanobacteria are rich sources of bioactive compounds, they have diverse industrial applications such as algaecides, antibacterial, antiviral and antifungal agents, hence, their wide use in the agricultural and health sectors. Cyanobacterial secondary metabolites are also important sources of enzymes, toxins, vitamins, and other pharmaceuticals. Polyhydroxy-alkanoates (PHA) which accumulate intracellularly in some cyanobacteria species can be used in the production of bioplastics that have properties comparable to polypropylene and polyethylene. Some cyanobacteria are also employed in bio-remediation as they are capable of oxidizing oil components and other complex organic compounds. There are many more possible industrial applications of cyanobacteria such as biofuel, biofertilizer, food, nutraceuticals, and pharmaceuticals. Additionally, the metabolic pathways that lead to the production of important cyanobacterial bioactive compounds are outlined in the chapter along with commercial products currently available on the market.

Keywords: agricultural applications, bioactive compounds, biofuels, bioplastics, cosmetics, cyanobacteria, environmental remediation, pharmaceuticals

1. Introduction

Cyanobacteria are one of the oldest organisms on earth, based on the evidence of 3.5 million year-old fossilized records [1]. These ancient organisms are ubiquitous photoautotrophic microorganisms found in fresh, brackish, marine or wastewater [2]. They are able to adapt to a wide range of conditions (salinities, temperatures, pH factors, light intensities, and so on). Oxygenic photosynthesis is believed to have started with these microbes, making them a big contributor to the oxygen-rich atmosphere we enjoy today. Cyanobacteria are by far, the only known prokaryotes that perform oxygen-evolving photosynthesis [3] and the concentration of CO₂ in the atmosphere would be twice as high had it not been for cyanobacteria [4]. Thus, cyanobacteria have helped to shape the evolutionary trajectory of the earth. It has been suggested that the oil-producing gene in plant chloroplasts originated from cyanobacteria. According to [5] a primordial plant cell “engulfed” a cyanobacterium about a billion years ago. The bacterium lived in the cell and supplied it with photosynthetic products. Thus, implying that the oil synthesis enzyme (acyltranferase) of
the chloroplasts originated from cyanobacteria. Similarly, according to [6] ethylene production existed before land plants colonized the earth as evidenced by unambiguously homologous ethylene-signaling pathways in \textit{Spirogyra} and \textit{Arabidopsis}; implying that cell elongation was possibly an ancestral ethylene production response.

Nearly 2,700 species of cyanobacteria have been described, however, prediction models suggest that between 2,000 and 8,000 cyanobacteria species exist in nature [7]. Some of the described species have been studied and known to have potential applications in agriculture, energy, food and pharmaceutical industries because of their ability to produce oil, fix atmospheric nitrogen, and also have high vitamin, mineral and protein contents among others [8].

Eutrophic water bodies facilitate the proliferation of cyanobacteria cells into blooms. Some of the blooms consist of cyanotoxin-producing species. The cyanotoxins are poisonous to humankind, animals and aquatic life. This has led to the closure of recreational centres and caused huge economic losses [9]. It is, therefore, imperative to understand the actions of these metabolites, their biosynthesis and possible applications in industry. This review will discuss the mechanisms involved in the cellular production of important metabolites and address the far-reaching industrial applications of these cyanobacteria compounds. Commercial products and companies producing cyanobacteria products are highlighted.

2. Biology of cyanobacteria

The composition of the earth’s earlier environment may have influenced the evolution of the metal resistance features and the metal-utilizing proteins in cyanobacteria during a period when the atmosphere was limited in oxygen. Thus, some cyanobacteria still thrive in low oxygen conditions and some strains are highly tolerant to free sulfide [10]. Additionally, cyanobacteria have a high tolerance to ultraviolet-B and -C radiations along with high temperature tolerance, as high as 73°C [10]. Their tolerance to radiation is likely to have been crucial in the early evolution of the cyanobacteria.

Morphologically, cyanobacteria cells are coccoid, filamentous (filamentous non-heterocyst forming, and heterocyst forming) forms [10, 11]. Cyanobacterial cells have an outermost peptidoglycan layer composed mainly of proteins and lipopolysaccharides. Other minor components of the peptidoglycan cell wall include carotenoids and lipids that enhance permeability, mechanical stability and resistance toward chemical substances [12]. Despite their overall gram-negative structure, the peptidoglycan layer in cyanobacteria is significantly thicker than that of most gram-negative bacteria [12]. Outside the cell wall is a carbohydrate-rich gycocalyx with varying proportion of three distinct layers; a closely associated sheath, a well-defined capsule, and loosely attached slime [13]. These three layers protect cyanobacteria cells from desiccation and possibly from predators and phages, making their applications in biotechnology more feasible due to their robust nature.

Cyanobacteria cells divide by fission (binary or multiple), fragmentation or spore-formation processes. The doubling time of cells can occur between 2.1 hours and 72 hours under optimal conditions and as long as 10,000 years under stress conditions such as \textit{Chroococcidiopsis} in dry deserts of Antarctica [10]. Their presence in such dry conditions confirms their ability to tolerate desiccation and water stress, allowing their use in biological processes under arid conditions. The fast doubling time of cyanobacteria cells leads to rapid growth rate which makes their application in industry economically sustainable.
In addition to their fast growth rate, cyanobacteria possess superior photosynthetic capabilities that enables them to convert about 10% of the solar energy received, into biomass which is relative to the 1% conversion done by traditional energy crops like sugarcane or corn, grown for biofuel production [14]. Some cyanobacteria cells possess gas-filled cavities that allow them to float on water surfaces, enhancing light capture for better photosynthetic efficiency. Internal thylakoid membranes are the site of photosynthetic reactions in cyanobacteria. The presence of chlorophyll and phycobilins increase the capture and conversion of light energy during photosynthesis. Other pigments including xanthophylls, carotenes, c-phycoerythrin and c-phycocyanin are present in cyanobacteria. C-phycoerythrin and c-phycocyanin are unique to blue-green algae.

Circadian rhythms are very important in cyanobacteria. These rhythms are fundamental adaptations to the earth's daily light and temperature fluctuations that lead to proper metabolic activity [15]. For example, nitrogen fixation is common in many species of cyanobacteria. However, oxygenic photosynthesis and nitrogen fixation are discordant processes because the nitrogenase enzyme is inactivated by oxygen. Two mechanisms are used to separate these activities. First, a biological circadian clock separates them temporally and cellular differentiation separates them spatially. For instance, a unicellular species such as *Cyananae* strain ATCC 51142 stores glycogen at daytime and fixes nitrogen at night [15], whereas the filamentous strain, *Trichodesmium erythraeum* IMS101 fixes nitrogen during the day in groups of specialized cells known as heterocysts [16]. Based on this, heterocyst-forming cyanobacteria are able to differentiate highly specialized cells to provide fixed nitrogen to the vegetative cells in a filament. This property allows cyanobacteria to be used as bio-fertilizers in agriculture because of their ability to fix atmospheric nitrogen [14].

Fluctuation in environmental conditions causes oxidative stress to cells which inevitably lead to increased reactive oxygen species (ROS) production. As a form of defense, photosynthetic microorganisms including cyanobacteria have developed several mechanisms to evade the negative effects of ROS. Antioxidants and polyunsaturated fatty acids (PUFAs) are known to provide protection to the cell against oxidative stress by stabilizing free radicals [17]. Among the many fatty acids, PUFAs are of great interest due to their numerous health benefits and increasing global demand [18]. Additionally, they help regulate various cellular processes such as oxygen and electron transport, membrane fluidity, and heat adaptation [19]. Cyanobacteria lack organelles such as endoplasmic reticulum, mitochondria, chloroplasts and Golgi apparatus typically found in eukaryotic cells. However, ribonucleic acid (RNA)-containing organelles known as ribosomes are widespread in cyanobacterial cells. Ribosomes are responsible for protein synthesis that enables cells to perform efficient metabolic activities.

3. Metabolic activities and the production of bioactive compounds

Cellular metabolic processes lead to the production of valuable primary and secondary metabolites. Photosynthesis and carotenogenesis are examples of metabolic processes that lead to the production of primary metabolites like lipids (e.g., PUFAs), antioxidants (e.g., carotenoids) and some proteins (e.g., primary proteins). Primary metabolites are directly involved in normal developmental processes such as cell division, growth and reproduction [20]; and can also be transformed into products such as bio-fertilizers, bio-plastics, nutrient supplements, and dyes. These are beneficial in industrial applications (Figure 1). Secondary
metabolites, on the other hand, are not utilized by the cells for their primary needs. These include hormonal compounds and antibiotics, or toxins [21].

Cyanobacteria possess a relatively simple genome [14], making it easy for gene modification and manipulations for the exploration of novel metabolites. From a nutritional perspective, microbes can alter their cellular metabolism naturally through stress response such as nutrient deficiency [22]. Growth conditions can be manipulated to promote the production of biomass rich in valuable secondary metabolites of economic value. This is usually achieved through a two-stage culture technique where in the first step the cells are grown under optimal conditions to maximize biomass production. The second step involves the introduction of stress factors, such as nutrient deprivation or high light intensity, to induce the production of valuable secondary metabolites. Although a deficiency in nitrogen is known to inhibit cell cycle processes and the production of several cellular components, surprisingly, lipid and biopolymer (PHB) syntheses rather increase under these conditions [23]. This leads to the accumulation of oil droplets and starch granules in starved cells [22, 24]. These adaptive responses help to ensure the cell’s survival during stressful conditions. Both metabolites (lipids and starch granules) serve as energy stores coupled with the special role of the starch granules in osmotic balance, heat, freezing, and ultraviolet (UV) rays [22, 23].

The methylerythritol 4-phosphate (MEP) pathway, known to occur in algae, bacteria, and plants, is a classic example of a metabolic pathway that is exploited for drug discoveries. In cyanobacteria, the MEP pathway leads to chlorophyll and hormone production [17]. It is observed that secondary metabolite production is species-specific and environmental conditions can influence their production. For instance, microalgae growing under stress conditions are more likely to produce secondary metabolites with antibacterial activity. In cyanobacteria, fatty acid synthesis (FAS) is performed by a type II fatty acid synthase complex and these
fatty acids have anticarcinogenic, antibiotic, antifungal, and antiviral [25] properties that facilitates their use in pharmaceutical applications.

The shikimate pathway has been proposed to be responsible for mycosporine-like amino acids (MAAs) and scytonemin biosynthesis [26, 27]. These compounds have the potential to be used as natural UV blockers in product formulations such as cosmetic creams or paints, and varnishes (Figure 1).

4. Industrial applications of bioactive compounds

4.1 Bio-plastics

Cyanobacteria, have the potential to produce renewable biopolymers from natural resources such as, solar energy, water and CO$_2$, reducing the need for fertile soils, fertilizers, herbicides and potable water for crop production. Biodegradable polymers such as PHAs are produced as inclusion bodies within cells via the beta-oxidation pathway [28]. Arthrospira (Spirulina), Synechococcus, and Synechocystis, are examples of cyanobacteria species widely employed in biopolymer production [23, 29]. Currently majority of commercial bioplastics produced from biologically-derived polymers are sourced from first generation feedstock through fermentation processes. Companies like Tianjin GreenBio (China), Metabolix (USA), Biocyte (Brazil) and Polyferm (Canada) produce biopolymers from sugars and vegetable oils. Some biopolymers are also produced by microorganisms like methanotrophs as in the case of Mango Materials (USA). Although the potential for biopolymer production from cyanobacteria exists, commercialization on an industrial scale is yet to be achieved. Research is currently geared towards optimization of cultivation and genetic modification approaches for enhanced biopolymer production [23, 30, 31].

4.2 Agricultural applications and environmental remediation

Cyanobacteria are known to play a key role in maintaining the stability of the surface crusts of dry lands. Thus, to combat desertification, cyanobacteria can be used in conjunction with bacteria, algae, mosses, lichens, or fungi, which form the biological soil crusts in unique geographical regions [32]. These biological soil crusts help primary succession in arid regions by improving the nutrient and moisture contents [32]. Cyanobacteria help to form a complex of heavy metals and xenobiotics to limit their mobility and transport in plants. Additionally, they offer protection to plants from disease-carrying insects, act as bio-control agents as well as enhance the mineralization of simpler organic molecules for easy assimilation. Additionally, cyanobacteria have been extensively applied in the area of environmental bioremediation through wastewater treatment processes [33, 34].

Arthrospira maxima and A. platensis, generically referred to as Spirulina are widely used as dietary supplements in feed for the poultry and aquaculture industries for their nutritional benefits due to their protein, vitamin and fatty acid content. Species such as Anabaena, Aulosira, Calothrix, Nostoc, and Plectonema are also used for agricultural purposes because of their nitrogen-fixing capabilities. They are able to fix atmospheric nitrogen (N$_2$) by the conversion of nitrogen to ammonia (N$_2$ + 3H$_2$ → 2NH$_3$) also reducing soil salinity and controlling weed growth [35, 36]. Additionally, they increase soil phosphates [32] by converting insoluble phosphorus in the soil to phytoavailable forms [37], making them an excellent choice as bio-fertilizers. Studies have shown that endophytic cyanobacteria strains such as Nostoc strains have the ability to produce phytohormones,
indole-3-acetic acid and cytokinins in root cells of both rice and wheat for their growth and development [38]. In Asian regions for instance, *Azolla* is either mixed into soil prior to rice planting or grown as a mixed crop along with rice in rice fields due to the presence of a cyanobacterium endosymbiont, *Anabaena azollae*, which fixes nitrogen [39].

Cyanobacteria also have other agriculture potential. Some cyanotoxins demonstrate biocidal activity. These biocides inhibit the growth of microorganisms such as viruses, bacteria and fungi; they also affect invertebrates including crustaceans, bivalves and vertebrates such as fish, birds, and mammals [40–44]. Thus, cyanobacteria toxins could be developed into active biological compounds and applied in crop fields as algaecides, fungicides, herbicides and insecticides because of their allelopathic effects [17, 43, 44]. Biocides have low environmental risks and are thus preferable to synthetic pesticides negatively affect the environment [17].

### 4.3 Biofuels

Our reliance on petroleum products has resulted in polluting the environment. Aside the release of toxic fumes including green-house gasses, into the atmosphere, the process of obtaining the fuel in itself presents potential environmental hazards. Cyanobacteria hold great promise as sources of renewable by-products (biodiesel) especially for the energy sector [45]. Cyanobacteria cells can be engineered to convert CO$_2$ and water into biofuels through photosynthesis. In a study [46] four modules were optimized to achieve high titer values (4.8 g/L$^{-1}$) of a petroleum substitute, 1-butanol. Firstly, 1-butanol biosynthesis was introduced and re-cast by systematic screening of genes and pathways. Module 2 involved the optimization of the 5’-regions of expression units to tune protein expression levels. Module 3 rewired carbon flux by editing acetate metabolism. In module 4, photosynthetic central carbon metabolism was rewritten by installing a phosphoketolase (PK) pathway. Several other biofuels have been produced from engineered cyanobacteria e.g., acetone, 2,3-butanediol ethanol, ethylene, isobutanol, 2-methyl-1-butanol from *Synechocystis* sp. [47]. *Algenol*, and *JouleUnlimited* are USA-based companies that use genetically modified cyanobacteria capable of growing in brackish or saltwater to produce a range of biofuels such as ethanol, biodiesel, gasoline and jet fuel in addition to other valuable chemicals [48–50]. Their ability to grow in salt-water makes their industrial application more economically and environmentally sustainable as it reduces the burden of using limited freshwater resources for their cultivation.

### 4.4 Cosmetics

Numerous cyanobacteria species have been used in the cosmetics industry for many decades because of their anti-inflammatory, antioxidant, and detoxifying properties [15, 17]. The cosmetic industry has evolved from just topical skin products to a more invasive approach of beautifying from within. This booming industry seeks to address skin-related issues by resolving internal problems at the cellular level. Skin aging, wrinkling, drying and other skin conditions occur as a result of loss of elasticity to the skin. In the cosmetic industry, for instance, a novel extract, extracellular polysaccharide (EPS), extracted from *Pseudomonas fluorescens* PGM37 has been found to have higher moisturizing retention ability and has the potential to be used in cosmetics and medicinal products [46]. Similarly, sacran a known cyanobacteria gel extracted from *Aphanathece sacrum* can be used as a moisturizing and anti-inflammatory agent [51, 52].
Again, microalgae strains with high amino acid content are great for improving skin texture and elasticity. Other strains rich in lipids help soothe and moisturize skin tissues, while antioxidant-rich algae with chlorophyll are ideal for detoxifying. Many Spirulina-infused cosmetic products are already on the market in the form of tablets, lotions and facial masks. Skin perfection has garnered so much attention in recent years. For instance, skin whitening has become a common practice world-wide, with a booming market in Asia and Africa [47]. Tyrosinase inhibition is the most common approach to achieving skin hypo-pigmentation as this enzyme catalyzes the rate-limiting step of pigmentation. Tyrosinase inhibitors have been isolated from numerous marine macroalgae species such as *Ecklonia cava*, *Laminaria japonica* and *Sargassum silquastrum* [47]. Oscillapeptin G, is an example of a tyrosinase inhibitor isolated from toxic cyanobacteria, *Oscillatoria agardhii* [48]. There is a huge potential for commercialization of cyanobacteria since their cells grow faster than that of marine macroalgae and thus would be more economically efficient at industrial scale.

### 4.5 Food

Food supplements, animal feed, food additives, and colorants produced from cyanobacterial carotenoids such as canthaxanthin, beta-carotene, nostoxanthin, and zeaxanthin are on the rise. *Spirulina* is a cyanobacterial specie rich in riboflavin, thiamine, beta-carotene, and vitamin B$_{12}$. These supplements are sold as capsules, granules and tablets on the market. A carotenoid such as the ketocarotenoid, astaxanthin is known to be a more powerful antioxidant than vitamin C and A or other carotenoids which play a vital role in preventing damage in human cells through photooxidation [17]. Astaxanthin obtained from *Haematococcus pluvialis* contains protease inhibitors that may be used to treat diseases, such as HIV [17]. These food supplements are usually made from cyanobacterial biomass and consumed whole unlike extracts used in the production of pharmaceuticals [53].

### 4.6 Pharmaceuticals

Natural products have become important contributing sources of semi-synthetic and synthetic drugs in all major disease fields; predominantly in antibiotic therapies, immunoregulation and oncology [54–56]. Most of these bio-medical natural products or metabolites have been derived from cyanobacteria. These cyanobacterial metabolites have exhibited both interesting and exciting biological activities including antibacterial, anticancer, antifungal, antimicrobial, and antiviral activities. Others are anticoagulant, anti-HIV, anti-inflammatory, anti-malarial, antiprotozoal, antituberculosis, antitumor, and immunosuppressant activities [54, 55]. Some of these bioactive compounds are Borophycin from *Nostoc* sp. against human carcinoma, Calothrix from *Calothrix* sp. against human HELa cancer cells and inhibition of growth of chloroquine-resistant strain of malaria parasite *Plasmodium falciparum* [8, 54]. Extracts from *Lyngbya lagerhaimanni* has anti-HIV activity, whilst *Lyngbyatoxin* A from toxic strains of *Lyngbya majuscula* is highly inflammatory [56, 57].

### 4.7 Bio-pigments

Phycobilisomes are phycobiliproteins accumulated by cyanobacteria and these include phycocyanin (blue), phycoerythrin (red), and allophycocyanin (blue-gray). They are major light-harvesting complexes in cyanobacteria [58, 59]. These compounds are used as bio-pigments in industrial applications. Linablue®
Chlorophylls for instance have been used as a textile dye with antimicrobial properties and also as a biomordant to enhance dyeing processes in textile production [8].

### 4.8 Research and development

Other applications of cyanobacterial extracts include their use in scientific research experiments. For instance, phycobiliproteins have fluorescent properties that can be used in flow cytometry and in immunoassay techniques [61]. Among these numerous bioactive compounds are terpenoids such as terpenes, diterpenes, and others.

| Company/Country (founding year) | Focus area | Industrial applications | Reference |
|---------------------------------|------------|-------------------------|-----------|
| LG Sonic/Netherlands (1999)     | Algal blooms | Effective ultrasonic frequencies for algae control on large water surface areas | [62] |
| Cyano Biotech/Germany (2004)    | Development of novel cyanobacteria products | Discovery and development of novel structures based on cyanobacterial natural products | [63] |
| Photanol/Netherlands (2008)     | Genetic modification of cyanobacteria | Produces broad range of biochemicals from cyanobacteria | [64] |
| Algae Biotechnologia/Brazil (2009) | Technological development of microalgae and cyanobacteria cultivation systems | Treatment of liquid and gaseous agro-industrial effluents. Production of ingredients and additives for animal nutrition. Production of human food supplements and production of biofuels. | [65] |
| Algenuity/United Kingdom (2009) | Synthetic biotechnology | Produces lab scale photobioreactor for algae and cyanobacteria research and also harness specific microalgal strains for synthetic biology applications | [66] |
| Living Ink Technology/USA (2013) | Production of ecofriendly ink products | Develops a variety of ink products and colors, including digital ink | [67] |
| Spira Inc./USA (2016)           | Incorporation of algae-based ingredients into everyday products | Extract high-value compounds from algae. | [68] |

Table 1. Major industrial companies involved in the production of cyanobacterial metabolites.
and sesquiterpenes. These organic compounds are widely found in cyanobacteria and are used as natural ingredients in flavors and perfumes. Such applications are recently gaining grounds in therapeutic and pesticide industries [17]. Terpenoid type compounds such as carotenoids and phytols are crucial for chlorophyll and hormone biosynthesis through the mevalonate pathway of MEP (mevalonate) pathway in cyanobacteria that was discussed in Section 3.

The rapid development of molecular tools for whole genome sequences promotes the use of omics technology i.e. transcriptomics, proteomics, and systems biology approaches to manipulate metabolic pathways for producing valuable products [8].

Experimental approaches that require fluorescent probes such as fluorescence microscopy for diagnostics and biomedical research utilizes the autofluorescent properties of cyanobacteria pigments such as phycobiliproteins. Among these, the most widely exploited fluorescent probe is phycoerythrin utilized in biomedical research [8].

5. Conclusions

Bioactive compounds synthesized by cyanobacteria are innumerable coupled with their vast industrial applications. More of these natural compounds are being discovered on a regular basis through research and development. There also exists an untapped pool of bioactive compounds that genetic engineering techniques can unfold. Current process engineering strategies in cyanobacteria research is centered on the regulation of metabolic pathways for the production of bioactive compounds. Such exploitations are feasible due to the small and simple genome of cyanobacteria species. Considering the fact that cyanobacteria are a promising feedstock for a circular economy, it is important to develop robust strains suitable for industrial applications.

The possibility of producing novel biopolymer blends, biofuel components, and pharmaceutical compounds that are capable of meeting the demands of a biotechnologically-driven society is vast. Thus, cyanobacteria will continue to play crucial roles in terms of health, energy, food, and many other aspects of our lives.

To achieve great strides in the cyanobacteria production sector, a synergistic approach should be adopted by cyanobacteria-related companies. Collaboratively, companies dealing in products such as biofuels, and bioplastics that involve extraction of compounds from cyanobacteria cell biomass, could supply their waste biomass to other companies that require the waste biomass as raw materials for production, such as algae ink or biochar for wastewater treatment. Thus, forming a biorefinery supply chain network that will essentially benefit both the producers and consumers from an economic and environmental point of view. Cyanobacteria industrial harmonization will ensure the valorization of production processes.

Conflict of interest

The authors declare no conflict of interest.
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