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Review

The other way around: Using eco-cyanomolecules for human welfare

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Abstract: Cyanobacteria constitute a group of photooxybacteria. It is difficult to provide an estimate of their diversity due to the ongoing debate on the usefulness of various species concepts and methodologies used to delineate them. They occupy, thrive, and proliferate in diverse habitats, exhibiting unparalleled physiological plasticity and adaptations, potentiated by diverse mechanisms and the production of a range of novel molecules. Human use of cyanobacteria (and also other microalgae) and products thereof is not new, with reports from before 2700 BC. In recent times, some ecologically relevant molecules, such as cyanotoxins to deter grazers and osmoprotectants for survival in saline environments, have found multiple human uses, from feeding products to therapeutics and energy. Technological advancements have allowed precise identification and a better mechanistic understanding of their production on a commercial scale. Here, we discussed some of these commercially useful molecules and their production mechanisms, scaling-up possibilities, cost-effectiveness, and challenges and opportunities associated with future research.

Keywords: cyanomolecules; cyanotoxins; metabolic engineering, economics; halophiles; osmolytes

1. Introduction

Cyanobacteria, as a taxon, include a heterogeneous assemblage of photooxybacteria, with well-known evolutionary, agronomic, and other economic significance [1]. Traits such as minimal external resource requirements and photosynthetic ability enable them to survive, proliferate, evolve, and diversify in diverse and extreme environments (e.g., saline and haline environments). They produce a wide range of secondary metabolites and compounds such as peptides and lipopeptides, depsipeptides, polyketides, alkaloids [including indole alkaloids (bauerines, nostocarboline, hapalindole, welwitindolinone, ambiguine, etc.)], terpenes, macrolides/lactones, polysaccharides, lipids, iron chelators (siderophores, e.g., schizokinen, synechobactin, anachelin), trypsin/chymotrypsin protease inhibitors (e.g., cyanopeptolins, micropeptin, oscillapeptin), and conjugated carbohydrates (e.g., proteoglycans, aminosugars, sulfoglycans, glycolipids). Such metabolites allow them to remain metabolically active and confer protection in stressful environments (from both biotic and abiotic factors). Many of these bioactive compounds exhibit potential applications in medicine (e.g., as antibiotics, immunosuppressants, anticancer, antiviral, anti-inflammatory, antidiabetic, anti-aging, anti-HIV, proteinase inhibitors, and ion channel activators) [2], agriculture (herbicides and insecticides), food and nutraceuticals [3], cosmetics industry (mycosporine-like amino acids and scytonemin), and water treatments (i.e., algicidal activities) [4,5]. For instance, as a shield against ultraviolet (UV) radiation, cyanobacteria produce UV-absorbing/screening compounds, such as mycosporine-like amino acids (MAAs) and scytonemin, which are natural photoprotectants exploited by the cosmetic industry [6]. It is estimated that by 2026, the global algal product market will reach 6.09 billion USD, with a compound annual growth rate (CAGR) of 6.7% [4].

Cyanobacteria employ four different biosynthetic pathways (except peptides and polyketides), namely shikimate, malonate, mevalonate, and methylerythritol-phosphate (MEP) pathways, to produce different secondary metabolites [7]. Verma et al. [4] summarized the different secondary metabolite production pathways in cyanobacteria (refer to their Figure 2). Peptides and polyketides are primarily formed through non-ribosomal peptide synthetase (NRPS), polyketide synthase (PKS), and mixed NRPS–PKS enzymatic systems [8]. Cyanobacteria dedicate nearly 5% of their genome to the NRPS and PKS pathways [9]. Further, more than 70% of the cyanobacterial genome contains these pathways [9]. A survey of 452 PKS/NRPS gene clusters from 89 cyanobacterial genomes revealed that 80% of these gene clusters could not be assigned to any known natural product [10]. Thus, a majority of cyanobacterial secondary metabolite (CSM) production is yet to be discovered [4]. Moreover, most of these products have been reported only from a handful of genera [2]. Marine cyanobacteria are a comparatively better source of bioactive metabolites than freshwater forms [11]. A bulk of the known CSMs are produced by genera such as *Lyngbya* (especially *L. majuscula*), *Nostoc*, *Anabaena*, *Oscillatoria,* and *Microcystis*. Demay and colleagues [2] reported that the members of the order Oscillatoriales produce the maximum number of CSMs, followed by Nostocales. The use of synthetic biology and a variety of omics approaches will improve the production of CSMs.

Thus, cyanobacteria are a sustainable and promising source for many commercially useful molecules [2,5]. However, providing such a detailed account is not the aim of this article. Many updated reviews on their nature, production mechanism, and associated constraints are already available [12–14]. The present article focuses on their biosynthesis as approaches that can be used to

enhance the yield, available constraints, and potential use scenarios of certain CSMs produced under salt stress and as a defensive deterrent (e.g., cyanotoxins), vis-à-vis their biotechnological and industrial exploitations.

2. Salt-adapted life

Salt is vital for life, but its abundance and scarcity have serious consequences for organisms. Increasing salt concentration in soils has been a major factor causing a decline in modern agricultural productivity. Historically, increased salinization of soils had decreased agricultural yield, leading to the fall of many great civilizations [15–17]. Technically, a medium with an electrical conductivity (EC) value > 4 dS/m (EC equal to approximately 80 mM NaCl at saturation) is referred to as saline. Based on the amount of salt present, water bodies are classified as fresh water (<0.05%), brackish water (0.05%–3%), saline water (3%–5%), and brine (>5%). Earth's surface mainly contains saline waters, with oceans holding a bulk of it (96.5%). The rest is present in saline groundwater, inland seas, or saltwater lakes [18]. Environments with total salt concentrations greater than 3.5% are designated as hypersaline systems. Likewise, due to the presence of halides, the salinity of ocean water is often referred to as "halinity". Low rainfall and high temperature have resulted in several evaporite deposits across the globe, which contain hypersaline waters within and between their salt crystals. Globally, nearly 6% of the total land and 20% of the total irrigated land area are salt-affected [19]; this area continues to rise due to intensive agricultural practices, climate change, and land clearance. The productivity of more than one-third of global arable land is affected by soil salinity [16].

Many microbes thrive and proliferate under high salt concentrations. They are grouped as halotolerant (i.e., salt-tolerant, preferring an ambient environment but able to survive and grow in high-salt environments) and halophilic (i.e., salt-loving, essentially requiring a particular concentration of salt for optimal growth). For halotolerant organisms, a fine regulation of cellular salt concentration against the external medium is essential. High external salt concentration reduces growth by changing the water and ionic status of the cells (i.e., hyperosmotic stress). It reduces water uptake with a concomitant decrease in micronutrient availability to the cells. Hyperosmotic stress resulting from ionic imbalance and chaotropic effects causes turgor imbalance and other secondary stresses, such as nutritional disorder and oxidative stress [20]. Salt, ionic, and osmotic stresses are sensed separately. The exact response depends on the specific ions/osmoticum used. Salt stress causes desaturation of membrane lipids (i.e., membrane fluidity) and exposes hydrophobic surfaces, leading to protein aggregation and, ultimately, cell death (i.e., stability of proteins). [17]. Chaotropic solutes (e.g., urea) weaken the electrostatic interactions of the constituting molecules, which destabilize the biological macromolecules, whereas kosmotropes (e.g., most compatible solutes) strengthen electrostatic interactions, thereby stabilizing macromolecules and protecting cells from osmotic stress [18].

Excess salt concentration imposes constraints on life, which becomes energetically expensive. Organisms inhabiting these environments require additional energy to adapt (i.e., energetic constraints). To counter such high external salt concentration, organisms use the "salt in" (e.g., maintain high intracellular K^+ ion concentration) and "salt out" strategies (e.g., accumulating compatible solutes). The choice of strategy adopted by an organism depends on the energetic cost of the process. In the "salt out" strategy, microbes either de novo synthesize or accumulate organic

compatible solutes (known as osmolytes and osmoprotectants) from the external medium, if available. The energetic cost of de novo synthesis of compatible solutes is higher compared to that of accumulating from the external medium [21].

Osmoprotectants are low-molecular-weight uncharged organic solutes and include glycerols (polyols), sucrose and trehalose (sugars), glycine betaine, ectoine, N-acetylated diamino acids, and N-derivative carboxamides of glutamine (amino acid derivatives). They have no adverse effect on the enzymatic activity of the organisms [22–24]. To maintain osmotic equilibrium, the molar concentration of intracellular solutes should equal the ionic concentration of the surrounding medium. With an increase in turgor pressure, the mechano-sensitive channels (e.g., MscL) in the membranes are activated to excrete the extra osmolytes non-selectively from cells to regulate cell volume [25].

2.1. Cyanobacterial osmolytes

Cyanobacteria occupy a diverse habitat [26], including high-salt-containing environments [17], using a range of strategies to survive, grow, and multiply in such environments. This includes cellular and molecular events such as efficient salt sensing and signal transduction systems, changes in membrane composition, expression of a variety of salt-stress-responsive genes, the exclusion of Na^+ and the accumulation of K^+ in cells, synthesis of different organic solutes, and subtle shifts in metabolism [17,20]. Molecular and genetic studies have broadened our understanding and elucidated the mechanisms adopted by halotolerant and halophilic cyanobacteria to overcome salt stress. It is widely believed that land plants inherited a substantial fraction of the stress-responsive pathways from their streptophyte algal ancestors, with subsequent refinements [27]. The dominant compatible solute may vary from species to species. Based on their ability to withstand salt concentration, cyanobacteria are categorized as low (<1.5 M), moderate (1.5–3.0 M), and extreme halophiles [>3.5 M to the salt saturation point; for NaCl, the saturation level is 300 g/L (i.e., 5 M)]. Freshwater and marine cyanobacteria synthesize sucrose and trehalose as major organic solutes [28]. The intermediate halotolerant forms synthesize heteroside glucosylglycerol, while relatively high salt-tolerant and halophilic cyanobacteria synthesize the quaternary ammonium compounds glycine betaine and glutamate betaine [29]. Certain forms also accumulate additional organic solutes depending upon growth temperature, ambient salinity, and duration of salt stress [30]. Following the application of salt stress, regardless of the final compatible solute, sucrose is nearly always synthesized in a pulse of ~30 min. Metabolic engineering pathways have been elucidated to enhance the accumulation of these osmoprotectants in different organisms, including plants [31]. Hereunder, we describe the pathways used by cyanobacteria and other microbes to synthesize commercially useful osmolytes and biotechnological interventions to scale up their production.

2.1.1. Sucrose

Sucrose (α-D-glucopyranosyl β-D-fructofuranoside) is a disaccharide, mainly synthesized by microalgae and cyanobacteria [32]. Its synthesis involves the enzyme sucrose-phosphate synthase (SPS) that catalyzes the conversion of UDP-glucose and fructose-6-phosphate to sucrose-6-phosphate and sucrose-phosphate phosphatase (SPP) that converts sucrose-6-phosphate into sucrose [33] (**Figure 1**). The SPS enzymes isolated from different sources differ in substrate specificity, effect of divalent cations, native molecular mass, and oligomeric composition [34]. A sucrose synthase gene (*susA*)

isolated from a filamentous N_2-fixing cyanobacterium has been shown to encode a protein similar to those of plants [35].

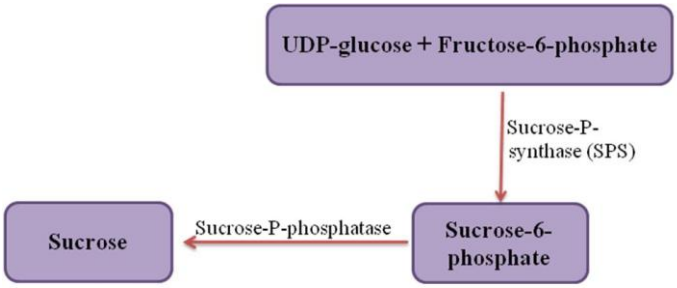

Figure 1. Schematic diagram of the sucrose biosynthetic pathway: the enzyme sucrose-phosphate synthase (SPS) catalyzes the conversion of UDP-glucose and fructose-6-phosphate to sucrose-6-phosphate, and sucrose-phosphate phosphatase (SPP) converts sucrose-6-phosphate into sucrose.

2.1.2. Trehalose

Trehalose is a non-reducing disaccharide consisting of two subunits of glucose bound by an α: 1-1 linkage (α-D-glucopyranosyl-1, 1-α-D-glucopyranoside). It shows properties such as high hydrophilicity, chemical stability, and no internal hydrogen bond formation. It forms amorphous, non-hygroscopic crystals, which are stable at high temperatures, and allows trehalose to form a vitreous state to continually interact for longer times at extreme temperatures than any other sugar. The flexible glycosidic linkage between the two D-glucose residues allows trehalose to interact with other irregular polar groups of different macromolecules [36].

The best-elucidated trehalose biosynthesis pathway involves the enzyme trehalose-6-phosphate synthase (TPS), which catalyzes the transfer of glucose, using UDP-glucose, to glucose-6-phosphate, resulting in trehalose-6-phosphate phosphatase (TPP). Subsequently, TPP catalyzes the hydrolysis of the phosphate group from the intermediate disaccharide to generate trehalose [37]. Analysis of TPS and TPP domains showed that these genes are clustered in eubacteria, while fused in eukaryotes [38]. Another pathway of trehalose biosynthesis is from maltose, catalyzed by the enzyme trehalose synthase (TS) (**Figure 2**). TS isomerizes the α1-α4 bond of maltose to an α1-α1 bond, which forms trehalose [39,40].

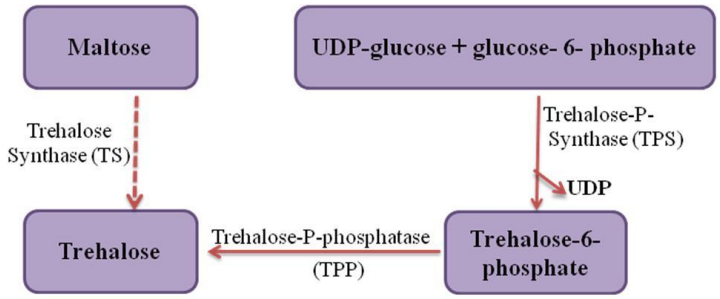

Figure 2. Different pathways of trehalose biosynthesis: the solid line indicates the pathway involving enzymes trehalose-6-phosphate synthase (TPS) and trehalose-6-phosphate (T6P), and the dotted line shows another pathway that involves enzyme trehalose synthase (TS).

2.1.3. Glycine betaine

Glycine betaine (a glycine derivative, GB) is one of the most extensively studied compatible solutes reported from many microbes [29,41]. It is a primary metabolite in halophilic archaeal methanogens [42]. There are two known pathways of GB biosynthesis. First, the choline oxidation pathway is a two-step process: (1) choline → betaine, and (2) aldehyde → betaine (Figure 3). The enzyme involved in the conversion of choline to betaine aldehyde, in plants, is a novel Rieske-type iron-sulfur enzyme, choline monooxygenase (CMO); in animals and bacteria, it is the membrane-bound choline dehydrogenase (CDH), and in other bacteria, it is the choline oxidase (COD). However, the second step (betaine aldehyde → GB) is catalyzed by the NAD^+-dependent betaine aldehyde dehydrogenase (BADH), which is similar in all organisms [43]. Microbes and plants containing CMO, CDH, or COD transgenes show increased tolerance to salt. *Synechococcus* sp. PCC 7942, a freshwater cyanobacterium, transformed with *Escherichia coli bet* gene cluster (*betABIT*), exhibited increased salt tolerance [44].

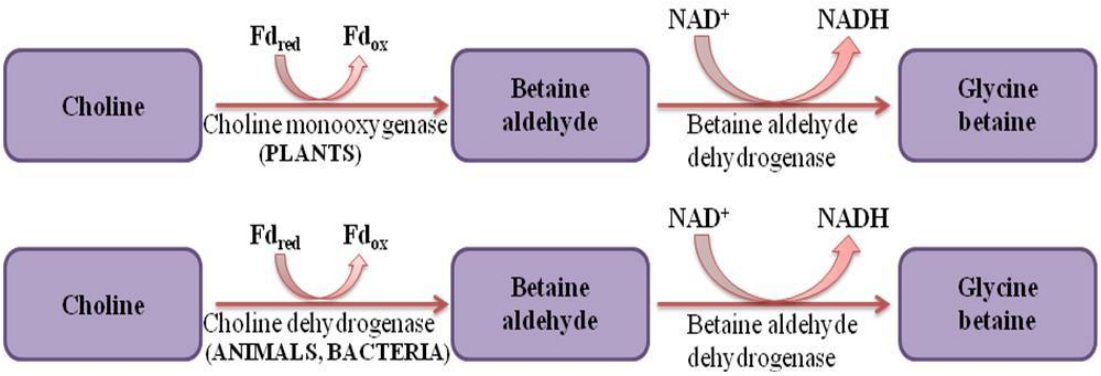

Figure 3. Glycine betaine biosynthesis via choline oxidation. The pathway involves the enzyme choline monooxygenase (CMO) in plants, membrane-bound choline dehydrogenase (CDH) in animals and bacteria, and choline oxidase (COD) in other bacteria.

In a moderately halophilic bacterium, *Halobacillus halophilus*, GB is synthesized from choline, involving choline dehydrogenase (*gbsB*) and glycine betaine aldehyde dehydrogenase (*gbsA*) genes, which together constitute an operon. Choline oxidation is induced by salinity and suppressed by exogenous GB [45]. In the bacterium *Ectothiorhodospira halochloris,* GB is synthesized via methylation of glycine (Figure 4). This pathway involves the enzyme EcGSMT (glycine sarcosine methyltransferase), which catalyzes the methylation of glycine and sarcosine to sarcosine and dimethylglycine. The other enzyme, EcSDMT (sarcosine dimethylglycine methyltransferase), catalyzes the methylation of sarcosine and dimethylglycine to dimethylglycine and GB [46,47]. Waditee and co-workers [48] characterized the N-methyltransferase genes *ApGSMT* and *ApDMT* in the halophilic cyanobacterium *Aphanothece halophytica (Ap. halophytica)*. Subsequent transformation of filamentous nitrogen-fixing *Anabaena* species with GSMT-DMT genes from *Ap. halophytica* resulted in an increase in de novo synthesis of GB, conferring enhanced salt tolerance to the transformants [49,50]. GB is a relatively more effective compatible solute than dimethylglycine and glycine [51].

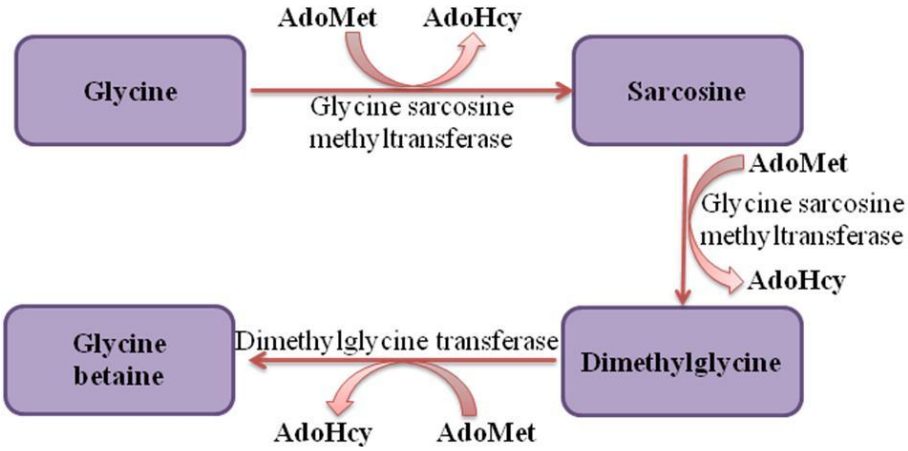

Figure 4. Glycine betaine biosynthesis via three-step glycine methylation: the enzyme GSMT (glycine sarcosine methyltransferase) catalyzes the methylation of glycine and sarcosine to sarcosine and dimethylglycine, and the enzyme SDMT (sarcosine dimethyl glycine methyltransferase) catalyzes the methylation of sarcosine and dimethylglycine to dimethylglycine and betaine (e.g., *Aphanothece halophytica*).

GB enhances tolerance to various types of abiotic stresses by (1) stabilizing the highly ordered structures of certain complex proteins to prevent denaturation, (2) inducing the expression of specific genes encoding ROS-scavenging enzymes and subsequent depression of levels of ROS in cells, and (3) preventing the accumulation of excess ROS, protecting the photosynthetic machinery from the combined effects of light and other stresses, as well as maintaining ion-channel proteins and the integrity of cell membranes [51].

Organisms using the choline oxidation pathway for GB synthesis require an exogenous supply of choline from the medium [44], which may be limiting in natural saline environments. Because of the de novo synthesis of glycine (GB) in cells, transformation with *GSMT* and *DMT* genes (i.e., the glycine methylation pathway) to produce salt-tolerant plants is a better option than the choline oxidation pathway [51].

2.1.4. Alanine, glutamine, and proline

Alanine, glutamine, and proline are the principal compatible solutes present in many microbes. Glutamine is present in the form of α-glutamine and the β-isomer of glutamine. Certain gram-positive bacteria accumulate low levels of alanine and glutamine but high concentrations of proline [52]. Proline accumulation has been reported in halophilic and non-halophilic *Bacillus* species and halophilic members of the Bacillariophyceae family. Proline levels may reach molar concentrations, up to 20% of the dry weight of organisms [53]. The moderately halophilic bacterium *Halobacillus halophilus* synthesizes glutamate and glutamine at 1.0 M NaCl but switches over to proline at 2.0–3.0 M NaCl concentrations [54,55]. Maximal proline accumulation occurs during early exponential phases, which is downregulated during the late exponential phase and then overtaken by ectoine accumulation [56,57].

Proline biosynthesis is encoded by a cluster of three genes (*proH*, *proJ*, and *proA*) organized in an operon. The corresponding enzymes encoded by these genes are pyrroline-5-carboxylate reductase (ProH), glutamate 5-kinase (ProJ), and glutamate 5-semialdehyde dehydrogenase (ProA) (Figure 5). External medium salinity upregulates the expression of the operon, with a maximum at 2.5 M NaCl. The transcript (highest at >1.5 h of the upshock) and related enzyme levels (highest after 6 h) increase with increasing salinity. Glutamate enhances the accumulation of proline. A minimal concentration of 0.2 M glutamate is sufficient to stimulate *pro* gene transcription [56]. NaCl not only triggers the production of proline but also increases the internal concentration of glutamate, which enhances proline biosynthesis. Thus, glutamate acts as a secondary messenger to salt-induced proline accumulation [57]. However, proline is degraded by the enzymes proline dehydrogenase (ProDH) and D1-pyrroline-5-carboxylate dehydrogenase (P5CDH), together forming the *put* operon. This operon is upregulated by increasing salinity levels [58].

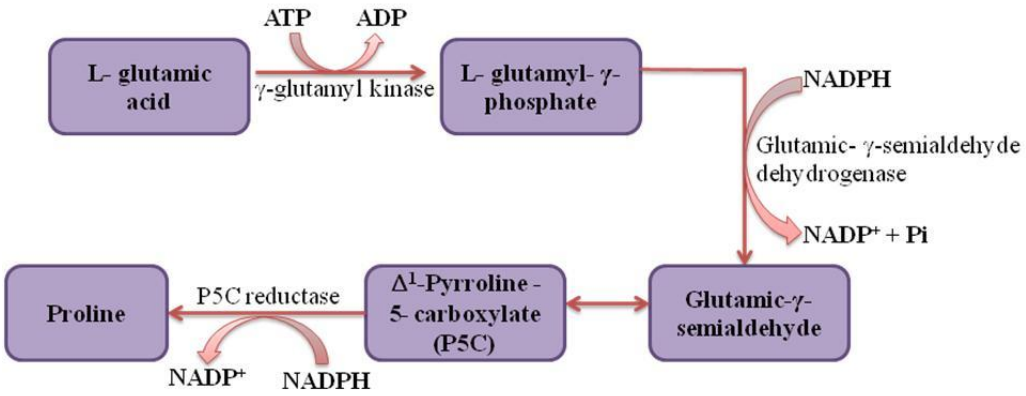

Figure 5. Proline biosynthesis pathway: Glutarate acts as a substrate and is enzymatically converted into proline using ATP and NADPH as reductants.

Proline acts as an effective compatible solute in halotolerant and moderately halophilic organisms, but not in organisms living at extreme salt concentrations. It functions as a molecular chaperone, helping in stabilizing the proteins, buffering the cytosolic pH, and balancing the redox status of the cells [59]. Further, it exerts its stabilizing properties through the formation of polymeric aggregates of proline monomers in the solvent. In *proHJA*-mutant *Halobacillus halophilus,* proline

was produced but with a loss of its osmoprotective function. However, this loss was compensated by an increase in the production of glutamate, glutamine, and ectoine [60].

A comparative study of halophilic and non-halophilic bacteria showed that under salt stress, there is a significant change in the composition of non-hydrophobic surface amino acids (e.g., aspartic acid and glutamic acid), with little variation in the composition of other amino acids [61]. The relatively small pK_a value (log measure of acid dissociation constant) allows aspartic acid to increase at high salt concentrations compared to that of glutamic acid [62]. Further, a nuclear magnetic resonance (NMR) study of halophile proteins confirmed that it is the size of the amino acids' side chains that is mainly involved in conferring salt tolerance capacity [63]. Reduction in the size of the side chains improved the salt tolerance limit, while charges on the side chains had little effect [64].

2.1.5. Ectoine and hydroxyectoine

Ectoine [(S)-2-methyl-1,4,5,6-tetrahydropyrimidine-4-carboxylic acid] and its derivative hydroxyectoine [(S,S)-2-methyl-5-hydroxy-1,4,5,6-tetrahydropyrimidine-4-carboxylic acid] were first reported in the phototrophic sulfur bacterium *Ectothiorhodospira halochloris*. In *Halobacillus halochloris,* at high salinities, ectoine is synthesized together with proline. The ratio of ectoine to proline increases sharply during the late stationary phase [55].

Ectoine biosynthesis is encoded by the *ectABC* gene operon that shows salinity-dependent expression (maximal at 3.0 M NaCl) (Figure 6**)**. The enzyme diaminobutyrate aminotransferase (encoded by the *ectB* gene) catalyzes the conversion of L-aspartate semialdehyde to L-2,4-diaminobutaonate, which is acted upon by the enzyme L-2,4-diaminobutyrate acetyltransferase (encoded by the *ectA gene*) to produce N-acetyl L-2,4-diaminobutaonate. Finally, the enzyme ectoine synthase (encoded by the *ectC* gene) acts on N-acetyl L-2,4-diaminobutaonate to produce ectoine [65,66]. Transcript abundance as well as ectoine concentration remains low at low salinity (0.4–1.5 M NaCl) and increases with salt concentrations (2.0–3.0 M NaCl). The expression of *ectABC* genes precedes the expression of glutamine, glutamate, and proline biosynthesis genes. This suggests that ectoine accumulation is a delayed response compared to that of proline accumulation. The methyl group of ectoine plays a major role in the stabilization of proteins against various stresses (e.g., salt, low and high temperature, UV radiation) [67,68]. The entire ectoine metabolic pathway of *Halomonas elongata* has been elucidated [69]. The *doeAB* genes are responsible for the degradation of ectoine in non-halophiles; the two-step process involves hydrolysis of ectoine (DoeA) to N-α-acetyl-L-2,4-diaminobutyric acid and its subsequent deacetylation to diaminobutyric acid (DoeB) [69].

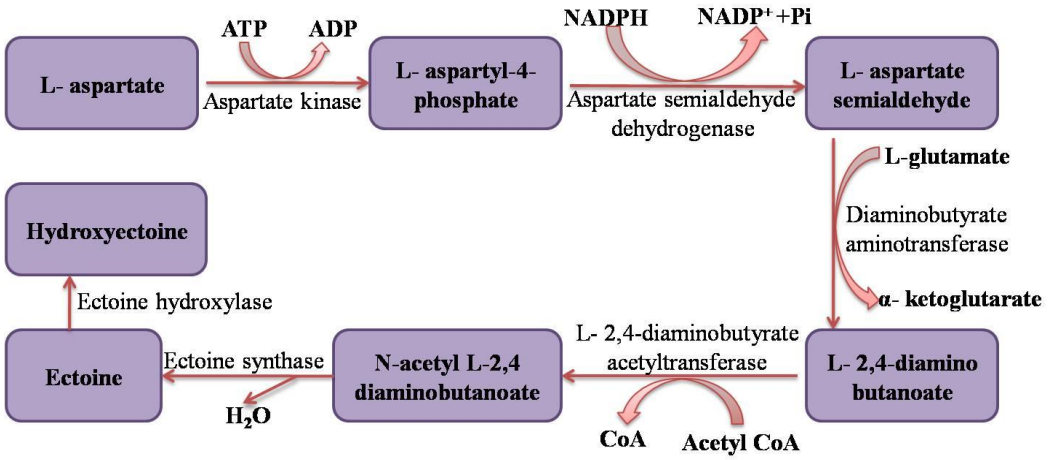

Figure 6. Biosynthetic pathways of ectoine and hydroxyectoine. The enzyme diaminobutyrate aminotransferase converts L-aspartate semialdehyde to L-2,4-diaminobutaonate, which is acted upon by the enzyme L-2,4-diaminobutyrate acetyltransferase to produce N-acetyl L-2,4-diaminobutaonate and ultimately to ectoine by the enzyme ectoine synthase. The enzyme ectoine hydroxylase converts ectoine to hydroxyectoine.

Abiotic stresses such as high salinity, high temperature, and desiccation cause hydroxylation of ectoine [70]. The resulting hydroxyectoine (5-hydroxyectoine) is produced by the action of the enzyme ectoine hydroxylase (encoded by the *EctD* gene) on ectoine [70]. The enzyme has been reported in *Streptomyces chrysomallus, Streptomyces coelicolor, Chromohalobacter salexigens*, and *Halomonas ventosae* DL7 [70–73]. The OH group of the hydroxyectoine increases the stability of the protein's native structure compared to ectoine [74]. The bacterium *Halomonas ventosae* DL7 produced identical levels of ectoine and hydroxyectoine (1 mM) at high salt concentrations (2–2.7 M NaCl). However, an increase in temperature (about 42°C) increased the level of hydroxyectoine, suggesting enhanced synthesis of ectoine hydroxylase at high temperature [73]. An X-ray structure of the EctD protein from the moderately halophilic *Virgibacillus salexigens* has revealed the double-stranded β-β-helix structure of its active site and the binding position of the co-substrate (2 2-oxoglutarate) [75].

2.2. Human uses of cyanobacterial osmolytes

Osmolytes help the organism to survive under stressful conditions. Freshwater cyanobacteria produce commercially valuable biomolecules when challenged with high salt concentrations, and halophilic cyanobacteria are an important natural source of many of these compatible solutes (acting as biomolecule stabilizers or stress protective agents) and stable enzymes that allow them to function under high salt concentrations [76]. However, to date, only the alga *Dunaliella salina* (for carotenoid production), the halophilic bacterium *Halomonas elongata* (for ectoine production), and the cyanobacterium *Spirulina platensis* (for glucosylglycerol production) have achieved some industrial success. Carotenoids (carotenes and xanthophylls) are hydrophobic compounds with a C40 hydrocarbon backbone. They show strong antioxidative, immune-boosting, antitumor, and anti-aging

properties and are extensively used as natural dyes and functional ingredients in food and cosmetic products. They are also used as enhancers of in vitro antibody production [77].

Sucrose is an important source for bioethanol production. Salt-treated freshwater species or moderately salt-tolerant species produce sugar, which may be milked out from the cells after hypoosmotic shock. Alternatively, cyanobacteria may be genetically engineered to produce the desired product using CO_2, light, and basic nutrients. Accordingly, the genetically engineered photosynthetic ability of a cyanobacterium is coupled with chemotrophy so that metabolic intermediates are directly converted into a biofuel through the addition of a heterologous fermentative metabolic pathway [78]. Other desired products may also be produced using this approach [79–82]. A start-up named Photanol was founded in 2008 as a spin-off of the University of Amsterdam by Professors Klaas Hellingwerf and Joost Texeira de Mattos to exploit this very idea. In the USA, Alganol is doing the same work for biofuel production. The pyruvate decarboxylase (*pdc*) and alcohol dehydrogenase II (*adh*) genes from *Zymomonas mobilis* (a prolific ethanol producer) were transferred into *Synechocystis* sp. PCC 6803 using a light-driven psbA2 promoter to produce bioethanol [83]. Due to its high stability and protective properties, trehalose is used as a stabilizer, humectant, and cryoprotectant in food, pharmaceuticals, cosmetics, and medical sectors.

Glycine betaine has important agricultural, therapeutic, and other industrial uses. It acts as a crop biostimulant, increases crop yield, improves stress tolerance, and reduces water use (i.e., agronomic importance) [84]. Besides, it improves digestion and nutrient utilization as an animal feed. It helps in dairy waste treatment, biofuel production, and in the food industry as a stabilizer and humectant. Betaine prevents both alcohol-induced and metabolic-associated liver diseases, is neuroprotective, preserves myocardial function, and prevents pancreatic steatosis. It also mitigates oxidative stress, endoplasmic reticulum stress, inflammation, and cancer development [85]. Similarly, alanine and glutamine also have wide applications in the food, pharmaceutical, cosmetic, and agricultural sectors.

Proline has multiple applications in the pharma industry, from drug designing to drug development. It stabilizes peptide bonds and ensures proper protein folding (induces turns and kinks in polypeptide chains) and enhances the bioavailability, stability, and efficacy of pharmaceutical compounds. The presence of proline in collagen assists tissue regeneration and skin repair. It helps in improving the taste and nutritional content of food products, stabilizes formulations, and enhances product shelf life. Its structural properties make it useful in the development of biodegradable bioplastics, medical devices, and coatings. Furthermore, proline plays a pivotal role in agriculture, particularly in plant biology. In the agriculture sector, proline-rich biostimulants and fertilizers enhance crops' resilience and yield [86].

Ectoine and hydroxyectoine stabilize proteins and protect membranes from desiccation; they are used in skin care products [74,87]. Hydroxyectoine lessens the side effects of immunotoxins; hence, it is helpful in cancer therapy [88]. Ectoine may be released in the medium through the milking process [89]. Mutant strains excreting ectoine have been developed [69,90]. Besides osmolytes, halophilic microbes are a rich source of various hydrolytic enzymes (i.e., hydrolases, lipases, esterases, proteases, nucleases), with potential industrial applications [76]. The global cosmetic-grade ectoin market was valued at approximately USD 23–49 million in 2024 and is projected to reach USD 45–70.5 million by 2031.

2.3. Strategies to enhance cyanobacterial osmolyte production

Cyanobacteria directly convert solar energy and CO_2 into various products, a process known as photosynthetic biomanufacturing (PBM), which combines carbon sequestration and clean production (net zero CO_2 emission) of desired metabolites. Several strategies can be used for a successful PBM. First, screening of cyanobacteria and their industrially relevant high-value metabolites (i.e., screening to find). Second, co-culturing (biotic stress) or modification of normal culture conditions and media (abiotic stress) may induce silent metabolic pathways and functional modules to produce high-value chemicals (i.e., stressing to activate). Third, the use of different synthetic biological tools and metabolic engineering for artificial designing and rational engineering, to force cyanobacteria to direct carbon flow toward tailored metabolites (i.e., engineering to modify). Two or more of these strategies may be used to improve the performance and productivity of cyanobacteria. A genetically engineered strain may be cultured and optimized under stressful conditions to increase the accumulation of the target molecule. These strategies may also increase strain or species fitness under stress and redirect carbon and energy flow toward specific osmolyte production [91].

Cyanobacterial osmolyte production can be enhanced using various genetic engineering tools, genome editing, and systems biology. Synthetic biology tools and strategies can be applied for converting cyanobacteria into a cell factory, for example, by introducing heterologous genes and remodeling the endogenous synthesis pathway, exhibiting strong expansibility for target chemicals production. The genetic manipulation protocols for cyanobacteria are relatively well-established (refer to [91] for details), allowing precise remodeling of the photosynthetic metabolism networks, manipulation of related metabolic pathways, increased antioxidant enzyme expression, or optimization of carbon partitioning. Metabolic pathway engineering includes modifying specific enzymes and pathways involved in the synthesis and regulation of a particular osmolyte. Likewise, stress response engineering may enhance cyanobacterial ability to respond to different abiotic stresses. Overexpression of genes responsible for sucrose, glycine betaine, and ectione and other antioxidant enzymes like superoxidase dismutase (SOD) and catalases may help cyanobacteria manage stress and ROS, along with osmolyte production. The modulation of the sucrose synthesis pathway by co-expressing *CscB, sps,* and *spp* genes resulted in high sucrose productivity (i.e., enhancing the efficiency of pathway enzymes) [92,93]. Glycogen is a significant carbon sink; modifying this pathway can alter the way carbon is stored and utilized, potentially diverting it to the production of other osmolytes instead of glycogen. Cyanobacterial circadian clock can also be engineered to control the temporal partitioning of carbon flow, directing it toward osmolyte synthesis during specific periods (i.e., redirecting carbon flux through overflow metabolism). Acetyl-CoA is a key node in cellular metabolism and a precursor of a variety of high-value chemicals (i.e., enhancing specific nodal points like acetyl-CoA to improve production). Its production can be enhanced using various strategies [94,95]. Studies have shown that the loss of the flavodiiron (Flv) protein and Pgr5 can improve the biosynthesis of reducing capacity-dependent molecules (i.e., engineering the electron transport chain) [91]. The expression of an insect trehalose transporter 1 (TRET1) in the PCC 7942 strain allowed the secretion of intracellular trehalose (97%) into the medium (i.e., improving the excretion of end products) [96]. Furthermore, arresting growth may improve carbon partitioning and the productivity of desired chemicals (i.e., decoupling growth from product synthesis) [97]. Co-culturing of photosynthetic microorganisms (producers) and other heterotrophic microbes (converters) may be used for in situ conversion of the products into useful products. The

co-culture of the sucrose-producing strain UTEX 2973 and the 3-HP-producing strain *E. coli* resulted in the conversion of sucrose derived from the cyanobacterium to fuels and chemicals under photoautotrophic conditions [98].

The systems biology approach uses computational tools and a deep understanding of cellular networks to design and construct engineered biological systems. It helps in creating optimized cyanobacterial cell factories with desirable traits. Further, gene editing and plasmid-based modifications can be used for targeted changes to the cyanobacterial genome. However, their effectiveness depends on the amenability of cyanobacteria to undergo genetic modification. Such modifications must be carefully balanced to maintain the overall cellular health and metabolic robustness of the cyanobacteria. Disturbed metabolic pathways may negatively impact their growth and productivity. Moreover, managing the competition for carbon and energy between osmolyte production, biomass synthesis, and other metabolic processes is a significant challenge that requires careful temporal and metabolic control.

2.3.1. Using stress for the synthesis of the desired osmolyte

In recent times, stress activation strategies, characterized by their strong controllability and the absence of transgenic risks, have gained significant attention. They boost the production of targeted molecules; wherein cyanobacterial native metabolic networks are reprogrammed to redirect photosynthetic flux toward targeted biosynthesis pathways while maintaining cellular viability [99]. Various stresses (physical, chemical, and biological) can be used to activate the production of high-value molecules. Under normal conditions, genes responsible for their production either remain silent or are expressed in low amounts. Co-culturing (with other organisms to cause biotic stress) or modifying culture media (or exposing to different abiotic stresses, e.g., light intensity, pH, salinity, UV irradiation, oxidative stress, nitrogen and phosphorus limitation, chemical and nanomaterial disturbances) may activate the production of the desired molecules. In combination with omics analyses, this approach will effectively expand the utilization of the metabolic network of cyanobacteria for large-scale metabolite production. Yun et al. [100] found that under high-light conditions, in high-cell-density cultures of the PCC 7942 strain expressing *cscB/sps* genes, there was an increased sucrose yield (3.8 g/L of sucrose). The glucosylglycerol (GG) production by PCC 6803 mutants with an inactivated GG uptake system and ggpS transcriptional repressor GgpR) was 982 mg/L under salt stress [101]. However, issues such as growth rate, low yield of target products, biocontamination, and biosafety remain major concerns for using genetically modified cyanobacteria for commercial-scale production. Spirulina can be used to produce GG outdoors under high-salinity conditions [102].

The production of metabolites under different stress conditions has a complex regulation [103], involving the activation of gene expression by transcriptional regulation, activation of key enzyme activity by biochemical regulation, and ROS mediation [91]. For example, the transcriptional regulation of the sucrose-phosphate synthase (Sps) is largely unknown. In transduction mutants (Synpcc7942_1125 and Synpcc7942_1404 inactivated), the transduction protein does not regulate salt-induced sucrose synthesis by directly regulating the expression of *sps*; as a result, under salt stress, sucrose production increased, but the growth and expression of *sps* were not affected [104]. Under salt stress, increased ion concentration allowed rapid accumulation of sucrose in *Synechococcus* PCC 7942, directly activating the SPS while inhibiting the sucrose-degrading enzyme

invertase [105], but not in PCC 6803, suggesting that the biochemical mechanism of sucrose synthesis is not conserved [106].

3. Making the most of cyanotoxins

As a defense deterrent, cyanobacteria produce a wide range of toxic secondary metabolites, referred to as cyanotoxins, which are variously classified depending on the organs affected (e.g., hepatotoxins, neurotoxins, dermatotoxins, and cyanotoxins), their chemical features (peptides, alkaloids, and lipopolysaccharides), and molecular structures, biosynthesis, and modes of action (alkaloids, non-ribosomal peptides, polyketides, non-protein amino acids, indole alkaloids, organophosphates, lipopeptides, lipoglycans, etc.) (Table 1) [107].

Table 1. A List of cyanotoxins with biotechnological applications (adopted from Ricciardelli et al. [91], with due permission from the authors, and the article is freely available under the terms of the Creative Commons CC-BY).

Class	Common name	Mode of action	Bioactivity
Alkaloids	Anatoxins (ATXs)	Agonists of the muscular and neuronal nicotinic acetylcholine receptor (nAChR); neurotoxic.	Larvicide
	Cylindrospermopsins (CYNs)	Protein synthesis inhibitors, glutathione synthesis inhibitors, cause DNA damage, induction of oxidative stress; cytotoxic	Larvicide
	Saxitoxins (STXs)	Block the voltage-gated Na^+ channels (VGSCs) in neuronal cells, inhibiting propagation of an action potential along neuronal axons, or reduce or eliminate the transmission of a nerve impulse; neurotoxic	Local anesthetic
Indole alkaloids	Ambiguines	NF-kB pathway blockers	Antimicrobial, anticancer
	Fischerindoles	Bacterial RNA polymerase inhibitors	Antimicrobial, anticancer
	Hapalindoles (HIs)	Bacterial RNA polymerase inhibitors	Antimicrobial,anticancer, algaecide, insecticide
	Lyngbyatoxins (LTXs)	Protein kinase C activators	Grazing deterrent
	Welwitindolinones	Tubulin polymerization inhibitors	Antimicrobial, anticancer, insecticide
Non-protein amino acids	β-N-methylamino-L-alanine (BMAA)	Glutamate receptor agonists, protein misfunction, misfolding and/or aggregation; neurotoxic	
Lipoglycans	Lipopolysaccharides (LPS)	TLR4 antagonists	immunomodulatory

Continued on next page

Class	Common name	Mode of action	Bioactivity
Lipopeptides & non-ribosomal peptides	Curacins	Microtubule assembly inhibitors	Anticancer activity against breast, colon, and renal cells
	Aeruginosins	Proteases inhibitors	Antithrombotic
	Apratoxins	Cotranslational translocation inhibitors	Anticancer
	Antillatoxins (ANTXs)	Sodium channel activators	Neuroplasticity promoter
	Anabaenolysins (ABLs)	Biological membrane disruption	Antimicrobial
	Cryptophycins	Microtubule assembly inhibitors	Anticancer
	Dolastatins	Microtubule assembly inhibitors	Anticancer
	Lagunamides	Mitochondria-mediated apoptosis	Anticancer
	Microcystins (MCYSTs)	1) Inhibitors of the serine/threonine protein phosphatase families PP1 and PP2A, leading to hyperphosphorylation of functional and cytoskeletal proteins, followed by cell process alterations (cell-cell adhesion, actin filaments structuring, MAPKs signaling) and finally apoptosis 2) Pro-oxidants with the potency to induce cell-damaging oxidative stress through the generation of reactive oxygen species (ROS), with subsequent genotoxic effects such as DNA fragmentation, chromosomal aberrations, or base substitution mutations	Algaecide, larvicide, herbicide
	Nodularins (NODLNs)	Protein phosphatase inhibition similar to the MCYSTs	Larvicide
	Anabaenopeptins (APs)	Carboxypeptidases, phosphatases and proteases inhibitors	Antithrombotic
	Lyngbyabellins (LYBs)	Actin microfilaments depolymerization; inhibits cytokinesis, inducing alterations in cell morphology	Anticancer, antimicrobial, antifouling
Organophosphates	Guanitoxin (GNT)	Irreversible inhibition of acetylcholinesterase	Insecticide
Polyketides	Aplysiatoxins (APTXs)	Protein kinase C activators; Potassium channel blocker; Dermatotoxins	Anticancer
	Scytophycins	Actin microfilaments depolymerization	Antimicrobial

The exact role of cyanotoxins is still a matter of speculation [108]. It is believed that they provide an advantage in competitive habitats or assist in physiological functions, such as maintenance of homeostasis, iron scavenging, or cell–cell signaling [109]. However, nothing could be clearly said about their ecophysiological role. On the other hand, over the years, their structures, toxicity, primary mechanisms of action, and preventive measures, as well as responsible organisms, have been extensively studied and reviewed. In recent times, with limited success [14], attention has shifted to their medicinal (e.g., as anticancer, antimicrobial, local anesthetics, antithrombotics, neuroplasticity promoters, and immunomodulating agents) and other industrial applications (biocidal and antifouling agents). The cytotoxicity of compounds like microcystins, saxitoxins, or anatoxins has raised severe concerns about deterring their use in the pharmaceutical and food industries [110].

Mynderse et al. [111] provided the first evidence that cyanobacteria produce compounds that show anticancer activity (i.e., antileukemia activity of members of the family Oscillatoriaceae). Thereafter, many studies have confirmed cyanotoxins as an attractive source of pharmacologically active compounds exhibiting a range of beneficial activities such as antibiotics, immunosuppressants, anticancer, antiviral, anti-inflammatory, and proteinase inhibitors [2,107,112]. A few highly promising cyanotoxins for potential drugs are those that inhibit different proteases, since their deregulation is vital in curing inflammation, atherosclerosis, coagulation abnormalities, and pulmonary, neuronal, or immunological disorders [113]. Anabaenopeptins (APs) and aeruginosins have been useful for the prevention and treatment of thrombotic diseases [114–116]. Antillatoxins increase intracellular Ca^{2+}, which activates the downstream Ca2+-dependent CaMKK pathway, responsible for the induction of neurite outgrowth [117], and also promotes neuronal plasticity through the NMDAR-BDNF-TrkB mechanism [118]. The saxitoxin-loaded liposomes extend the duration of the anesthetic effect and minimize myotoxicity, neurotoxicity, inflammation, and systemic toxicity [119]. Cyanobacterial LPSs are important anti-inflammatory and immunomodulatory agents. For example, Cyp, a lipopolysaccharide from *Planktothrix* sp. FP, acts as a selective TLR4-MD-2 receptor antagonist against *Neisseria meningitidis* lipopolysaccharide. It also inhibits cytokine production in septicemia [120,121].

Besides the above-mentioned possibilities, none of these compounds has reached commercial-scale production; their clinical success is still unknown. Reasons for that include the limited knowledge of the synthesis of cyano-metabolites; the functions and regulation of the enzymes involved in the cellular pathways and biosynthetic processes are partially known, complicating the use of genetic engineering techniques to produce more metabolites. Also, more information on the exact mechanism of the bioactive compounds is needed to make them feasible for pharmaceutical use. The stability and bioavailability of bioactive compounds also remain unclear (e.g., cyanobacterial peptides are highly unstable and require different stabilizing strategies like replacing amino acids with other amino acids more resistant to hydrolysis, structural restriction, cyclization or stapling) [14]. Nonetheless, cyanobacteria could clearly be used as a biofactory to produce such compounds [122].

4. Other promising CSMs

Cyanobacteria produce and secrete many secondary metabolites showing allelochemical and algicidal/biocidal properties to limit the growth of sympatric algal species, potential competitors, and grazers present in their environments [123,124]. Species of *Nostoc* produce algicidal compounds

such as nostocyclamide, nostocine A, and nostocarboline [125]. β-ionone produced by *Tyconema bourrellyi* CHAB663 showed strong inhibitory effects against toxigenic *Microcystis* [126]. Likewise, compounds such as hassallidins (produced by *Anabaena, Cylindrospermopsis*, *Nostoc*, *Aphanizomenon*, and *Tolypothrix* spp.), laxaphycins (by *Anabaena* spp.), tolytoxin (by *Scytonema* spp.), calophycin, tolybyssidin, schizotrin A, abiguine isonitrile, carriebowlinol, and scytoscalarol have shown excellent antifungal activities, with promising future applications [14].

Many cyanotoxins are potent allelochemicals and could be used as algaecides, herbicides, and insecticides. However, a lack of knowledge about their exact mode of action, de novo testing efforts, and their potential ecological impact is one of the challenges preventing their use as algaecides, herbicides, and insecticides. Guanitoxin, a natural analogue of the banned pesticides and insecticides (Sarin and Tabun), has never been tested for its potential application as a pesticide. Moreover, a better biocide should be target-specific. Hapalindole A and other indole alkaloids isolated from Nostocales and Stigonematales show algicidal activities, specifically inhibiting photosystem II in algae and other photosynthetic organisms [127], and are a comparatively better choice. However, in this case, all photosynthetic plants shall invariably be affected. Therefore, we need to find better-defined target molecules.

5. Concluding remarks and future possibilities

As an ancient group of organisms, cyanobacteria have witnessed profound ecological changes throughout their evolutionary history. They exhibit incredible metabolic plasticity and produce a range of metabolites that facilitate their survival, growth, and proliferation in challenging environments (i.e., eco-cyanomolecules). They offer immense economic possibilities and have emerged as a prime feedstock with multiple potential applications in agriculture, energy, and industry sectors [122]. Refined identification approaches, cutting-edge genetic manipulation tools, and innovations in mass cultivation facilities can be used to ensure commercial-level production of CSMs for the greater benefit of human beings.

Cyanobacteria are relatively easy to manipulate. Recent advances in metabolic engineering, an increasing number of whole genome and proteome sequences, the availability of standardized broad-range vectors, and genetic components have opened new ways to the large-scale production of many cyanobacterial value-added compounds. Integration of system biology with omics data (genomics, transcriptomics, proteomics, and metabolomics) allows a better understanding of various metabolic pathways and regulatory networks, which are helpful in strain improvement and optimization of metabolite production (refer to [4,91,99] for details). Genome-scale models (GSM) can provide details of all biochemical and metabolic transformations occurring inside a cell for a gene or enzyme [128].

Suitable promoters (both inducible and constitutive) may be used to increase the CSM yields. Native transcriptional regulation networks may be disrupted through promoter engineering, activating silent biosynthetic genes [129]. Gene expression could also be manipulated through modifying ribosome binding sites (RBS, affecting translational efficiency) [130]. RBS optimization improves downstream processing, and several synthetic RBSs have been developed for different cyanobacteria. Likewise, riboswitch design facilitates gene expression through secondary structure manipulation, and the aptamer sequence in the riboswitch can influence translational efficiency from the transcript [131]. Genome editing and transcriptional regulation (e.g., CRISPR/Cas9, transcription

activator-like effector nucleases [TALEN], zinc-finger nucleases [ZFN], and meganucleases [MNs]), with a certain degree of challenges, are other approaches to insert exogenous homologous DNA into the target locus. Besides, metabolomics and fluxomics (i.e., the rate of in vivo metabolic reactions) could be used to enhance metabolite production. For example, enhancing carbon fixation rates (thus, the total carbon flux) by optimizing metabolic pathways may also improve the product biosynthesis [132].

In recent times, there has been a substantial improvement in photobioreactor technology, capacity, and efficiency, easing the way for large-scale cyanobacterial culture [4]. Applications of synthetic biology have made it possible to engineer up- and downstream production pathways and design new metabolic pathways [133,134]. Industry 5.0 is based on the use of smart sensors, artificial intelligence (AI) [135], and the internet of things (IoT) [136], enabling real-time monitoring, data-driven optimization, and automated control of cultivation parameters. Similarly, the use of other suitable economic substrates, such as food waste, has gained popularity for the sustainable cultivation of microalgae [137]. This reduces the dependency on freshwater for cultivation, but it is in its infancy and poses numerous challenges [138]. However, up until now, only a handful of microbes (e.g., *Dunaliella salina* for carotenoid production, *Halomonas elongata* for ectoine production, and *Spirulina platensis* for GG production) have been used for commercial-level molecule production. At present, no estimates are available about the cost-effectiveness of using cyanobacteria for large-scale production of these molecules. Therefore, providing direct unit cost comparisons between chemical synthesis and cyanobacterial production is not possible. However, the chemical synthesis of glycine betaine has a high carbon footprint and potential environmental issues, whereas cyanobacterial fermentation offers a more sustainable, low-cost approach due to factors like low energy consumption, potential waste recycling, and the use of readily available resources. The cost-effectiveness of cyanobacterial products will increase as technology matures.

Author contributions

NKS, SS, AS, and AKR were involved in the ideation and writing of the manuscript. GA and AKR did the final editing. All authors have read and approved the final manuscript.

Use of Generative-AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

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Conflict of interest

The authors declare no conflict of interest in this paper.

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