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Adaptation and synthetic biology of the model cyanobacterium *Synechococcus elongatus* for sustainable development: a review

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Synechococcus elongatus is a model cyanobacterium with remarkable adaptability to diverse environmental stresses, making it a promising candidate for the photoautotrophic conversion of carbon dioxide into valuable chemicals. This review explores the adaptive mechanisms that allow *S. elongatus* to survive under various abiotic stresses, such as changes in CO_2 levels, heavy metals, and light conditions. We also highlight recent advancements in synthetic biology that have enabled the engineering of *S. elongatus* to produce biofuels and other value-added compounds, including fatty acids, alcohols, and carotenoids. Additionally, we discuss the applications of modern omics techniques to elucidate the genetic basis of stress tolerance and metabolic regulation. Despite the promising potential of *S. elongatus* for industrial applications, challenges remain in scaling up production, enhancing genetic stability, and optimizing bioreactor systems. Finally, we provide insights into future directions, including the integration of genome engineering, system-level modeling, and co-culture strategies, to improve the efficiency of cyanobacterial cell factories for sustainable biotechnology applications.

KEYWORDS

***Synechococcus elongatus*, cyanobacteria, synthetic biology, cell factory, stress tolerance**

1 Introduction

Cyanobacteria, also known as blue-green algae, are gram-negative bacteria. *Synechococcus elongatus*, a model species of cyanobacteria, has been widely studied for its fast photoautotrophic growth (Zouni et al., 2001). Bibliometrics analysis indicates a rising trend of global research interest in *S. elongatus* as relevant publications have increased significantly over the last three decades (Supplementary Figure 1).

The cyanobacterium *S. elongatus* possessed strong adaptability, endowing their outstanding survival ability in ocean and freshwater environments (Lai et al., 2024). It has an efficient photosynthesis system, rapid reproduction (Table 1), strong carbon sequestration capacity, and good tolerance to extreme environments. Moreover, *S. elongatus* has a smaller genome (Table 1), with efficient molecular biology tools for gene editing and genetic engineering (Yu et al., 2015). Physiological studies could provide a theoretical basis for cultivating different stress-resistant varieties, and several subspecies of *S. elongatus* have been used as model strains for various applications (Ungerer et al., 2018a). However, the subspecies' growth characteristics vary, so it is essential to make selections before conducting specific experiments (Yu et al., 2015; Jaiswal et al., 2020). Compared with other typical microbial cell factories, the growth rate of *S. elongatus* is slower than that of *Escherichia coli* (Table 2). However, *S. elongatus* has a significant advantage among photosynthetic autotrophic cells, with its fastest doubling time being only 1.9 hours (Table 2). Towards a sustainable society, *S. elongatus* can produce renewable products such as biochemicals and fuels (Table 2).

Metabolic engineering, developed in the late 20th century, employs genetic modifications (e.g., gene knockout, promoter engineering) to optimize metabolic networks for enhanced product synthesis (Hong and Nielsen, 2012; Keasling, 2012). Emerging in the 21st century, synthetic biology utilizes standardized biological parts (e.g., gene circuits, clustered regularly interspaced short palindromic repeats (CRISPR) technology) to construct novel biological systems (Stephanopoulos, 2012; Baltes and Voytas, 2015). These disciplines synergistically advance microbial cell factories: synthetic biology designs new pathways while metabolic engineering refines their efficiency (Lin et al., 2015; Jarboe et al., 2010).

In this review, we delve into the intricate physiological and biochemical responses exhibited by *S. elongatus* when subjected to diverse environmental stresses. The aim is to provide a nuanced understanding of the adaptive mechanisms employed by this model cyanobacterium to cope with adverse conditions. To this end, we review the latest research on how *S. elongatus* responds to various stressors such as CO_2 levels, pollutants, and high-light conditions (Figure 1).

TABLE 1 Physiological characteristics of different subspecies of *S. elongatus*.

Subspecies	Genome information	Doubling time	Characteristics
PCC 7942	2.7 Mb (Holtman et al., 2005).	7–10 h (Yu et al., 2013)	The first cyanobacterial strain to be reliably transformed by exogenous DNA (Shestakov and Khyen, 1970); a model organism for studying the circadian rhythm of cyanobacteria (Holtman et al., 2005).
PCC 6301	The homology to PCC 7942 was 99.86% (Sugita et al., 2007).	3.4 h (Binder and Chisholm, 1990)	The genes for two-component signal transduction systems are only 37 genes (Sugita et al., 2007).
PCC 11801	The homology to PCC 7942 was 83% (Jaiswal et al., 2018).	2.3 h (Jaiswal et al., 2018)	A high growth rate (Jaiswal et al., 2018).
PCC 11802	The homology to PCC 11801 was 97% (Jaiswal et al., 2020).	2.8 h (Jaiswal et al., 2020)	Key enzymes of the Calvin cycle are not repressed under elevated CO_2 (Jaiswal et al., 2020).
UTEX 2973	There is a difference of 53 SNPs, a 7.5-kb deletion, and a 188-kb inversion compared with PCC 7942 (Yu et al., 2015).	1.9 h (Yu et al., 2015)	With high light resistance and photosynthetic rate, the biomass productivity was three times that of PCC 7942 (Ungerer et al., 2018b).
BDU 130911	Not available	Not available	High efficacy of uranium adsorption (Rashmi et al., 2013).

TABLE 2 Comparison of microbial cell factories.

Species	Doubling time (h)	Common medium	Cell size (μm)	Representative product
Escherichia coli	0.3 ~1 (Cooper and Helmstetter, 1968)	Luria-Bertani (LB)	0.5 ~ 3	Insulin (Baeshen et al., 2014)
Saccharomyces cerevisiae	1.5 (Kaeberlein et al., 2005)	Yeast extract peptone dextrose	3 ~ 6	Fuels, chemicals, pharmaceuticals (Hong and Nielsen, 2012)
Chlamydomonas reinhardtii	2.5 (Lien and Knutsen, 1979)	Tris-acetate-phosphate (TAP)	7 ~ 10	High quality mammalian proteins (León-Bañares et al., 2004)
Synechocystis PCC6803	4.3 (Van et al., 2018)	BG-11	NA	Renewable biofuels and chemicals (Liu et al., 2012)
Synechococcus elongatus	1.9 (Yu et al., 2015)	BG-11	2	Renewable chemicals and fuels (Vayenos et al., 2020)

NA, not available.

Furthermore, we explore the biosynthetic capabilities of *S. elongatus*, focusing on both naturally occurring and heterologous bioactive compounds. We summarize the potential applications of *S. elongatus* in synthetic biology, discussing how its unique characteristics can be harnessed to design novel cell factories to produce high-value chemicals and materials. A timeline of the progress in physiological adaptations and synthetic biology of *S. elongatus* is shown in Figure 2. We also acknowledge the challenges encountered during the industrialization of *S. elongatus*, such as scalability, stability, and economic feasibility. By discussing the bottlenecks in algal engineering development, we aim to provide insights that can inform the design of photosynthetic cell factories and promote the practical applications of cyanobacteria.

2 Different environmental factors, related abiotic stresses, and adaptive strategies for *S. elongatus* survival

Advances in omics technologies such as genomics, transcriptomics, and proteomics enable scientists to conduct in-depth research on the molecular mechanisms and genetic basis of environmental resistance in *S. elongatus*. It is possible to discover a series of genes and proteins related to environmental resistance with crucial roles in cellular stress response, metabolic regulation, and cell repair. Systematic analysis of *S. elongatus*' transcriptional regulatory network (TRN) was conducted through machine learning methods, revealing its gene regulatory mechanisms in key biological processes such as photosynthesis, carbon fixation, and nitrogen metabolism (Yuan et al., 2024). Studies on the environmental resistance of *S. elongatus* have deepened the understanding of the survival strategies of aquatic organisms and also provided novel insights into bioengineering and biotechnology development of microalgae, which could pave the way to produce valuable bioproducts under harsh conditions.

2.1 CO_2 levels

CO_2, the greatest greenhouse gas, is a critical environmental factor and also the major carbon source that affects microalgal growth. It was reported that *S. elongatus* PCC 7942 achieved optimal growth when supplied with 5% CO_2 (Kuan et al., 2015). However, an excessively elevated CO_2 concentration reduced the pH value dramatically and inhibited the growth of cyanobacteria (Mortezaeikia et al., 2016). For *S. elongatus*, the CO_2 concentration influences biomass productivity and reduces its ability to absorb CO_2 (Hashemi et al., 2020). The CO_2 response mainly depended on the autoregulation of the cmpR gene (encoding the DNA-binding transcription factor) in *S. elongatus* PCC 7942, as the transcription factor CmpR activates the *cmpABCD* operon under low CO_2 conditions while repressing its promoter (Pan et al., 2016). The *cmpABCD* operon encodes subunits of an ABC-type high-affinity HCO_3^- transporter, which is activated under low CO_2 conditions and repressed under high CO_2 conditions (Pan et al., 2016). Since atmospheric CO_2 levels are insufficient to saturate Rubisco

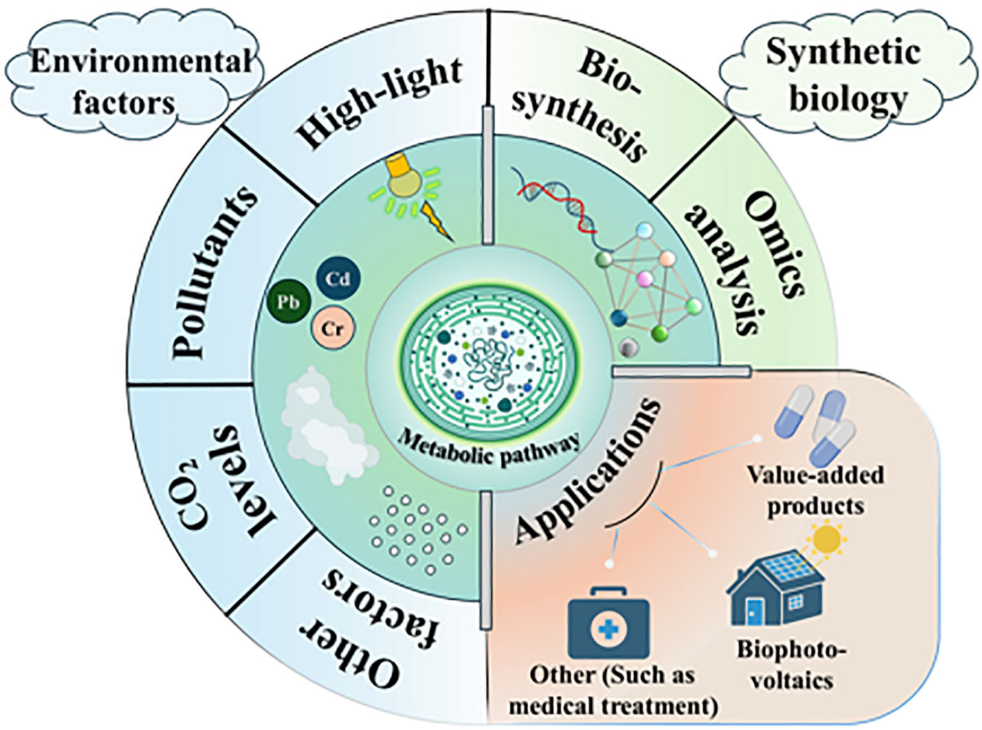

FIGURE 1
A diagram showing the concepts and applications of cyanobacterial cell factories.

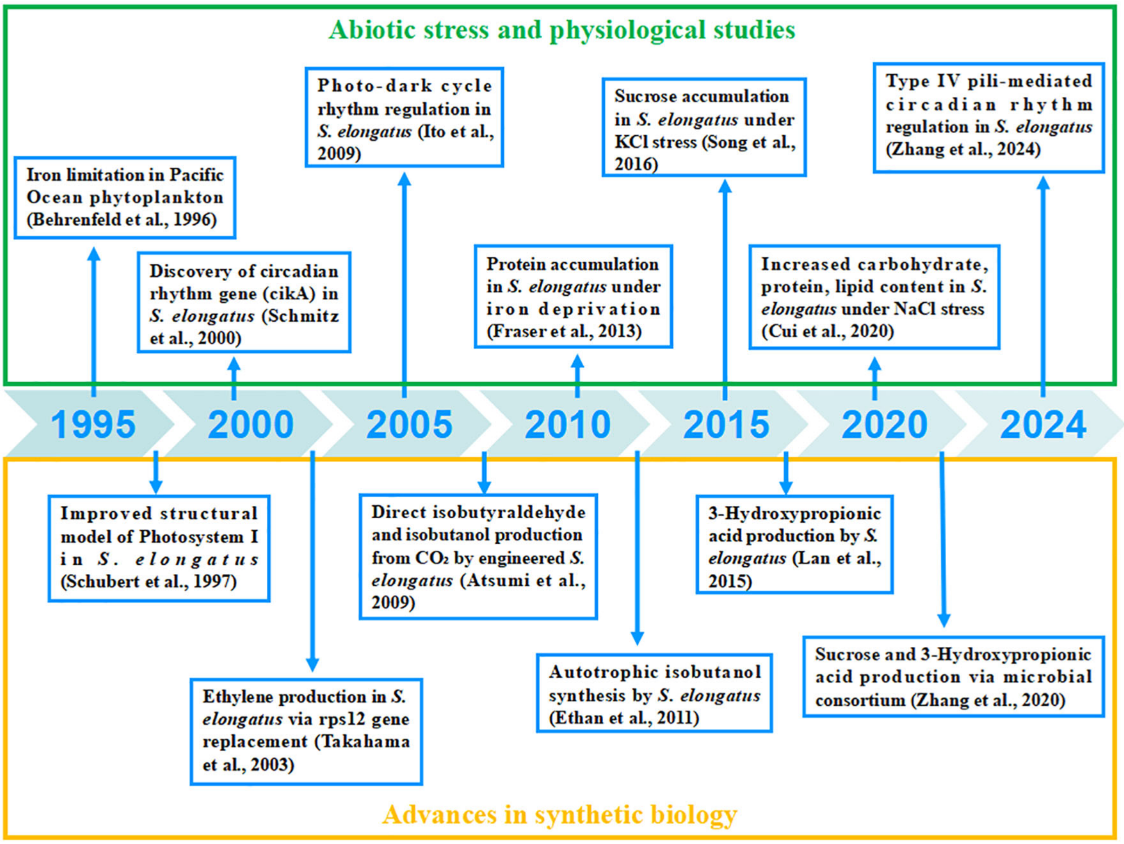

FIGURE 2
Advances in physiological adaptation and synthetic biology of *S. elongatus*. References cited: Atsumi et al. (2009), Behrenfeld and Bale (1996), Ito et al. (2009), Schmitz (2000), Schubert et al. (1997), Song et al. (2016), Takahama et al. (2003), Zhang et al. (2024), Fraser et al. (2013) and Cui et al. (2020).

(ribulose-1,5-bisphosphate carboxylase/oxygenase), O_2 competes as an alternative substrate for Rubisco, impairing carboxylation reaction. Cyanobacteria mitigate this issue through CO_2 concentrating mechanisms (CCMs), with the *cmpABCD* operon playing a key role in enhancing photosynthetic efficiency and environmental adaptation (Pan et al., 2016). Proteomic data revealed that elevated CO_2 conditions in *S. elongatus* PCC 11801 led to the downregulation of photoprotection and redox-related genes while shifting from TCA cycle-dependence to a photosynthesis-dominated NADPH/ATP supply mode (Mehta et al., 2019). These studies suggest that the CO_2 stress response in *S. elongatus* is a complex physiological process.

2.2 Pollutants

Pollutants such as nitrogen and phosphorus are major factors that cause frequent algal blooms. Under eutrophication conditions, *S. elongatus* has shown potential in water treatment, with its phosphorus and nitrogen removal rates reaching 85.1% and 87.4% respectively (Pishbin et al., 2020). *S. elongatus* has been used to treat wastewater from dairy and other industries (Ruiz-Güereca and Sánchez-Saavedra, 2016; Samiotis et al., 2021; Usai et al., 2024). In addition, *S. elongatus* PCC 7492 showed the capability to remove nitrogen from wastewater under different salinities (Samiotis et al., 2022).

Sulfur is a common pollutant in the environment and also an essential element for algae growth, and the use of *S. elongatus* to treat sulfur-containing wastewater is widely studied (Yang et al., 2015). Recently, the pollution of heavy metals is becoming a serious environmental issue. The survival of cyanobacteria could be affected by heavy metal stress. The heavy metal stress of Cd^{2+} or Ni^{2+} prevented *S. elongatus* PCC 7942 cells from properly entering the chlorosis process under nitrogen starvation (Selim and Haffner, 2020). As a potential carcinogenic pollutant, 2,4-dinitrotoluene is classified as "possibly carcinogenic to humans" (Group 2B) by the International Agency for Research on Cancer with environmental persistence and health risks (Oh et al., 2011). Compared to physical adsorption and chemical oxidation, bioremediation shows potential in degrading 2,4-dinitrotoluene. For example, *S. elongatus* PCC 7942 could degrade the nitro groups of 2,4-dinitrotoluene, demonstrating its application potential in biological treatment (Fedeson et al., 2020).

2.3 High-light stress

Light is the primary energy to support cyanobacterial growth and development, which affects the physiology of cyanobacteria through light intensity and composition. High-density culture could be achieved through high-light conditions (Moronta-Barrios et al., 2012). *S. elongatus* UTEX 2973, the fastest-growing cyanobacterial strain, was studied under high-light conditions, and comparative genomics analysis revealed that *hltA* is a key factor for high-light tolerance as HltA senses environmental signals under high-light conditions and activates stress pathways, thereby helping cyanobacteria avoid photoinhibition and oxidative damage (Walker and Pakrasi, 2022). High-light stress can rapidly decrease the ratio of phosphorylated RpaB to non-phosphorylated RpaB, indicating that RpaB plays a crucial role in high-light signal transduction (Moronta-Barrios et al., 2012). Furthermore, high-light conditions mitigate the growth inhibition caused by salt stress in *S. elongatus*, which is more severe under low-light conditions. This alleviation likely occurs because high light counteracts the salt-induced suppression of photosynthetic pigment accumulation (Kumar et al., 2021).

2.4 Other environmental factors

There are a large number of emerging environmental pollutants due to human activities. In recent years, there have been many studies on the effects of other emerging environmental stresses on *S. elongatus*. For example, the discharge of aquaculture wastewater is an essential cause of the anti-growth surge in the water environment. Low-concentration kanamycin enhances the biofilm formation of *S. elongatus* by upregulating photosynthesis and carbonic anhydrase genes (Tan et al., 2016). The toxic effects of Micro- and nano-sized polystyrene particles on *S. elongatus* have been demonstrated, resulting in damage to the integrity of the cell membrane (Feng et al., 2019). The zinc oxide used in sunscreen enters domestic wastewater through washing, and improper treatment may lead to water pollution. Zinc oxide could induce oxidative stress, leading to lipid peroxidation and DNA damage in *S. elongatus*, and genes involved in the photosynthetic system, oxidative phosphorylation, and transcription/translation were down-regulated (Vicente et al., 2019). Due to improper agricultural application, glyphosate can accumulate significantly in soil. Through surface runoff and rainwater erosion, it can enter water bodies, easily causing water pollution. Glyphosate may exert an inhibitory effect on *S. elongatus*, leading to a notable reduction in its growth rate (Moraes et al., 2021). In summary, emerging environmental pollutants markedly influence the physiology of S. elongatus, which demonstrates strong potential as a candidate for industrial wastewater treatment.

3 Synthetic biology and biotechnology applications

As a photosynthetic microbial cell factory, *S. elongatus* exhibits remarkable competitiveness in the fields of synthetic biology and biomanufacturing. Beyond its rapid growth rate (Table 2), *S. elongatus* holds promise for sustainable bioeconomies due to its photoautotrophic metabolism, genetic tractability, and robust metabolic plasticity. Moreover, its inherent capacity to synthesize diverse natural products—such as glycogen, pigments, and lipids—provides essential precursors for metabolic engineering. These attributes have facilitated numerous successful heterologous expression cases (Figure 3), underscoring its potential for high-value compound production.

3.1 Synthetic biology for improved biomass production and carbon fixation

Biomass as a renewable resource, has huge potential for developing sustainable feedstock. Due to the increase in global population and the shortage of resource supply, increasing biomass production has become a challenge that needs to be addressed. Knocking out two glucokinase genes caused glucose accumulation and a spontaneous mutation in the genome of *S. elongatus* PCC 7942, which resulted in direct glucose secretion (Zhang et al., 2023). Genetically engineering *S. elongatus* PCC 7942 for expressing heterologous hexose transporter gene to perform mixotrophy under natural light is also a scheme to increase biomass yield and productivity (Sarnaik et al., 2017). In addition, heterotrophic partners have a significant growth promotion effect on cyanobacteria, resulting in an 80% increase in growth rate and enhanced photosynthetic capacity (Kratzl et al., 2024). These findings could provide new insights into improving biomass production and carbon sequestration in the future.

3.2 Synthetic biology for value-added products in *S. elongatus*

3.2.1 Bioenergy sources

Bioenergy is fuel derived from biological sources, also known as biofuels (Voshol, 2015). Currently, there are still some limitations in bioenergy development and applications, such as higher manufacturing costs and lower energy content than fossil fuels. However, bioenergy does have distinct advantages, such as being the only alternative energy source that could replace vehicle fuel without major modifications to vehicle engines and being renewable and relatively simple to process (Kaygusuz, 2009). Different types of bioenergy are summarized below.

3.2.1.1 Fatty acids

Cyanobacteria obtain energy from sunlight and convert carbon dioxide into free fatty acids (FFAs) through photosynthesis. FFAs can be utilized as feedstock and precursors for renewable biodiesel production, and therefore, the production of FFA has attracted much attention (Wijffels et al., 2013). There is rapid progress in the biosynthesis of FFA. For instance, *S. elongatus* PCC 7942 was engineered to produce free FFAs via gene knockout of the FFA-recycling acyl-ACP synthetase gene and expression of a thioesterase for FFA release, which provided the basis for large-scale FFA production (Ruffing A et al., 2012). However, the final FFA

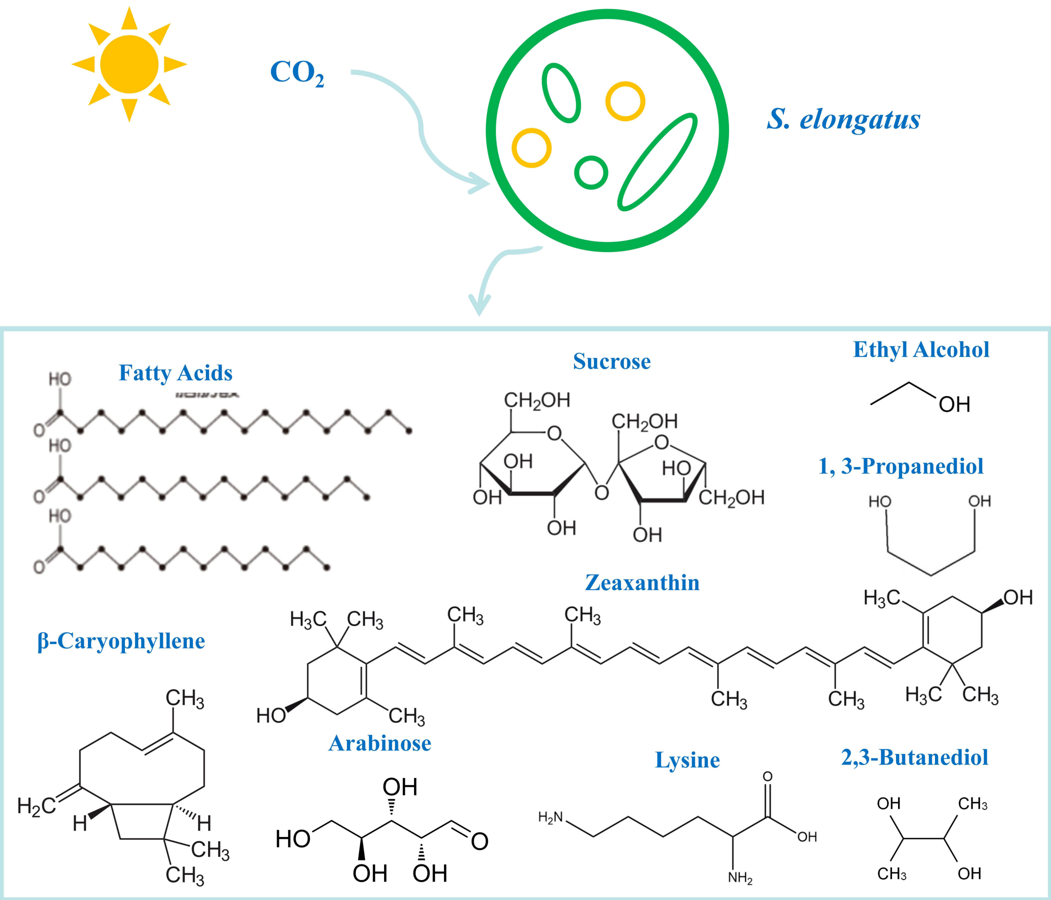

FIGURE 3
Cell factories of *S. elongatus* to produce biochemicals such as fatty acids and ethyl alcohol.

concentration in *S. elongatus* PCC 7942 was lower compared with other algal strains (Liu et al., 2011). To address this issue, an engineered *S. elongatus* strain achieved similar FFA secretion rates as other productive cyanobacterial species by modulating the expression level of the acyl-acyl carrier protein thioesterase and increasing the light intensity during cultivation (Kato et al., 2016). To remove FFAs from the medium during cultivation, an aqueous-organic two-phase culture system was developed that provides a basis for *S. elongatus* to produce FFA industrially (Kato et al., 2017). By covering the aqueous medium with isopropyl myristate (IM), FFA is effectively extracted from the medium into the organic phase, thereby reducing the accumulation of intracellular FFA and avoiding cell death due to FFA toxicity (Kato et al., 2017).

3.2.1.2 Alcohols

Alcohols produced from cyanobacteria have great potential as sustainable biofuels. Recently, a high-yielding strain of 1-butanol was constructed through metabolomics-assisted strain engineering (Fathima et al., 2020). 1-Butanol has the advantage of high energy density, with a heat value close to that of gasoline and superior to ethanol. The development of genetic modifications has increased the production of ethanol and butanediol from *S. elongatus* (Velmurugan and Incharoensakdi, 2020; Oliver et al., 2013). The synthesis of isopropanol has been the focus of research on biofuels, and *S. elongatus* has also shown great potential in this direction. Through the construction of synthetic pathways, genetic modification (Hirokawa et al., 2017), and growth optimization (Chandra and Mallick, 2022), it is feasible to increase productivity with reduced costs.

3.2.1.3 Other energy materials

Sugar represents a promising renewable feedstock for biofuel production, with sucrose being the most commonly utilized substrate. *S. elongatus* has demonstrated efficacy in sucrose synthesis (Ducat et al., 2012). Notably, genetic modifications in *S. elongatus* PCC 7942 enhanced intracellular sucrose accumulation, significantly improving yield (Vayenos et al., 2020). To further reduce production costs, co-culture fermentation systems have been employed. For instance, a synthetic microbial consortium comprising *E. coli* and *S. elongatus* UTEX 2973 was developed to directly convert CO_2 into sucrose (Zhang et al., 2020). Additionally, the introduction of the L-arabinose metabolic pathway into *S. elongatus* boosted biomass productivity under phototrophic conditions (Cao et al., 2017).

In addition to sugars, cyanobacteria can synthesize energy-dense hydrocarbons such as alkanes. For example, the CRISPR-

Cpf1 system (derived from Prevotella and Francisella 1) was employed to engineer *S. elongatus* PCC 11801, enabling regulated expression of ethylene-forming enzyme and high-efficiency ethylene production (Sengupta et al., 2020). Heterologous expression of cyanobacterial genes in fungal hosts has also facilitated the production of pentacene and heptadecane alkenes (Sinha et al., 2017). Moreover, pathway engineering and synthase optimization in *S. elongatus* UTEX 2973 achieved the highest reported β-caryophyllene yield in a cyanobacterial chassis (Li et al., 2020).

3.2.2 Feed additive

Carotenoids are industrially significant fine chemicals commonly used in the food, pharmaceutical, and healthcare industries (Maoka, 2011). Common carotenoids in the market include β-carotene, astaxanthin, and zeaxanthin, among others (Saini et al., 2018). The CrtR (β-carotene oxygenase) gene was cloned from *S. elongatus* PCC 7002 by homologous recombination, and then PCC 7942 was genetically modified to enhance β-carotene flux towards zeaxanthin synthesis (Sarnaik et al., 2018).

Cyanobacteria can also synthesize key amino acids for bioplastic production. For instance, engineered *S. elongatus* UTEX 2973 overproduces lysine, enabling concurrent cadaverine and glutamate biosynthesis for bioplastic production (Dookeran and Nielsen, 2021). Specifically, cadaverine can be used to synthesize biopolyamides (such as polynylon-5,10), while glutamate can be used to synthesize polyesters and other biobased plastics.

3.2.3 Other value-added products

3-Hydroxypropionic acid (3-HP) is a valuable chemical product used to synthesize polymers and other chemicals such as acrylic acid. However, cyanobacteria do not have a native pathway to synthesize 3-HP. By constructing an alternative pathway in *S. elongatus* PCC 7942, 3-HP could be synthesized (Lan et al., 2015). However, the yield remains insufficient for industrial production purposes. A microbial complex composed of *S. elongatus* UTEX 2973 and *E. coli* was constructed to convert CO_2 into sucrose from *S. elongatus* UTEX 2973, and then sucrose was used as raw material for the production of 3-HP by *E. coli* (Zhang et al., 2020). The artificial co-culture system could significantly increase the yield of 3-HP and does not require foreign carbon sources (Matson and Atsumi, 2018). Further, the xylose utilization pathway from *E. coli* was introduced into *S. elongatus* UTEX 2973 through genetic engineering, which reconstituted the natural glycolytic pathway to transfer more carbon flux from xylose to acetyl-CoA, thereby increasing 3-HP biosynthesis by approximately 4.1-fold (Yao et al., 2022). The genetic engineering method also has great potential for the production of other value-added chemicals that require acetyl-CoA as a precursor.

3.3 Biophotovoltaic platforms

Cyanobacteria have been studied for biopower generation. In photosynthesis, only a small part of the absorbed solar energy is converted into chemical energy, while the rest of the energy is wasted as heat and fluorescence (Yagishita et al., 1997). Therefore, it is doable to harvest solar energy through a biophotovoltaic (BPV) platform to generate electricity. Cyanobacteria exhibit light-dependent electrogenic characteristics in photo-bioelectrochemical cells that generate substantial photocurrents, but the current densities are lower than their photovoltaic counterparts (Logan, 2009). However, by studying the algal biofilms formed on indium tin oxide anodes that were used in the algal biophotovoltaic platforms, it was found that several strains of cyanobacteria had high photosynthetic performance, and their biofilm and power generation capacity had application potential in the BPV platform (Ng et al., 2014). In a cyanobacterium called *Nostoc* sp. (NOS), it was found that the power generation capacity of NOS could be significantly increased by adding 1, 4-benzoquinone as a redox medium (Sekar et al., 2014). Inspired by the study on NOS, *S. elongatus* PCC 7942 was genetically modified to express a non-natural redox protein, which significantly improved the bioelectricity production capacity of the cyanobacterium (Sekar et al., 2016). Reduced graphene oxide-based BPV devices were found to produce reduced bioelectricity under dark conditions (Ng et al., 2018). An initial cross-comparison of *S. elongatus* PCC 7942 with other exoelectrogenic cultures showed a hindered exoelectrogenic capacity (McCormick et al., 2011).

3.4 Other applications

S. elongatus has been studied for medical purposes such as the photosynthetic therapies that protect ischemic tissues and ensure the aerobic metabolism of tissue cells (Williams et al., 2020; Zhu and Woo, 2022). *S. elongatus* PCC 7942 has shown potential as a new treatment for burn wounds (Yin et al., 2019). However, these applications are still in their experimental stage before clinical practice.

4 Concluding remarks and future perspectives

In this review, we explored the physiological and biochemical responses of *S. elongatus* to various environmental stresses and its potential applications in synthetic biology and biotechnology. *S. elongatus* is a highly adaptable organism that can thrive under diverse conditions, making it a promising candidate for industrial-scale applications in renewable energy, wastewater treatment, and bio-based manufacturing. Its rapid growth rate and metabolic versatility position it as an ideal model for advancing cyanobacterial biotechnology.

However, several challenges still impede the industrial application of *S. elongatus*. Although *S. elongatus* has good genetic operability, its gene editing tools and expression systems are not as mature as model organisms such as *E. coli*. Furthermore, light availability remains a critical bottleneck for high-density cultures, and scalability issues make it difficult to translate laboratory success into large-scale production. To address these challenges, advancements in genome editing tools, such as CRISPR-Cas systems specifically tailored for *S. elongatus*, will enable more precise genetic modifications. Additionally, genome-scale reconstruction and modeling through collaborative research could accelerate metabolic pathway optimization.

On the bioprocess front, optimizing photobioreactor designs is crucial to enhancing light utilization. Strategies such as incorporating light-harvesting technologies, like optical fibers or adjustable light emission strategies, could increase the efficiency of photosynthesis and boost biomass productivity. Furthermore, engineering *S. elongatus* to enhance carbon fixation, for example, by introducing high-affinity Rubisco variants or optimizing bicarbonate transport, could improve CO_2 utilization, especially under suboptimal conditions.

Co-culture systems, where *S. elongatus* is paired with heterotrophic microorganisms, may also provide solutions for improving overall productivity. These systems can facilitate nutrient recycling and create stable growth environments, helping to reduce costs and improve efficiency in large-scale applications. For instance, it was demonstrated that co-culturing *S. elongatus* with *E. coli* can enhance the production of biofuels by leveraging complementary metabolic pathways. However, due to the metabolic byproducts generated during co-cultivation, the complexity of downstream processing is increased.

Downstream processing, including cell harvesting and product extraction, also presents a significant barrier. Current methods are often energy-intensive and costly, particularly for low-value products like biofuels. Advances in cell lysis techniques, such as enzymatic or mechanical disruption, and improved separation technologies, such as membrane filtration or chromatography, are needed to enhance efficiency and reduce costs.

Looking ahead, the integration of genetic engineering, bioreactor optimization, and system-level modeling will be essential to overcoming current challenges. For example, the use of artificial intelligence and machine learning to predict optimal metabolic pathways and cultivation conditions could significantly accelerate the transition from lab-scale to industrial-scale production. Furthermore, policy support, such as government subsidies or tax incentives for sustainable biotechnologies, will play a crucial role in fostering commercialization.

In conclusion, while *S. elongatus* holds immense potential for industrial applications, realizing this potential will require interdisciplinary innovations and collaborative efforts across academia, industry, and government. By addressing the technical, economic, and policy-related challenges, *S. elongatus* can be positioned as a key player in sustainable biotechnology, contributing to global efforts to address environmental and energy challenges.

Author contributions

WM: Visualization, Writing – original draft, Writing – review & editing. MX: Writing – review & editing. JH: Writing – original draft. CW: Writing – original draft. CQ: Writing – review & editing. MZ: Writing – review & editing. WF: Conceptualization, Funding acquisition, Resources, Supervision, Writing – review & editing.

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Conflict of interest

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The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmars.2025.1542670/full#supplementary-material

SUPPLEMENTARY FIGURE 1
The annual publication of *S. elongatus*-related article based on Google Scholar (https://scholar.google.com) using the keyword "*Synechococcus elongatus*". The literature search was completed on December 1st, 2024.

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