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Review

Cyanobacteria-Mediated Light-Driven Biotransformation: The Current Status and Perspectives

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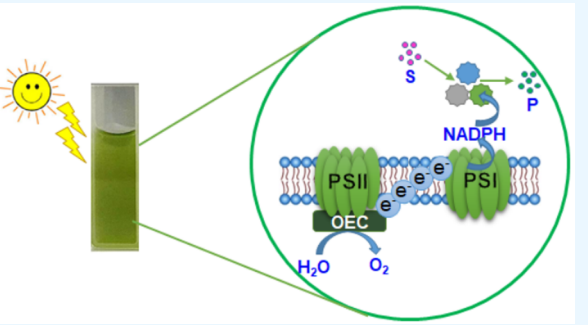
ABSTRACT: Most chemicals are manufactured by traditional chemical processes but at the expense of toxic catalyst use, high energy consumption, and waste generation. Biotransformation is a green, sustainable, and cost-effective process. As cyanobacteria can use light as the energy source to power the synthesis of NADPH and ATP, using cyanobacteria as the chassis organisms to design and develop light-driven biotransformation platforms for chemical synthesis has been gaining attention, since it can provide a theoretical and practical basis for the sustainable and green production of chemicals. Meanwhile, metabolic engineering and genome editing techniques have tremendous prospects for further engineering and optimizing chassis cells to achieve efficient light-driven systems for synthesizing various chemicals. Here, we display the potential of cyanobacteria as a promising light-driven biotransformation platform for the efficient synthesis of green chemicals and current achievements of light-driven biotransformation processes in wild-type or genetically modified cyanobacteria. Meanwhile, future perspectives of one-pot enzymatic cascade biotransformation from biobased materials in cyanobacteria have been proposed, which could provide additional research insights for green biotransformation and accelerate the advancement of biomanufacturing industries.



1. INTRODUCTION

Most chemicals are currently manufactured using petroleum-derived feedstocks through traditional chemical processes, and chemical catalysts have been used to achieve the conversion of substrate molecules and product molecules under harsh conditions such as high temperature, high pressure, strong acids, and strong bases. Although chemical products produced from fossil materials have greatly improved our living standards over the last two centuries, a series of problems have arisen and created increasing pressure, including resource waste, greenhouse gas emissions, and environmental pollution, posing a challenge and threat to human health.[1−3] Along with the rising global energy demands and pressing environmental issues, efforts are intensifying to bridge the gap between fossil carbon consumption and renewable supply.[4] An increasing number of scientific researchers are committed to developing sustainable production processes of the same chemical products with renewable feedstocks as the raw materials to render the production of chemical products more cost-effective, reduce energy consumption, and limit the emission of harmful gases.[5] Consequently, more attention has converged toward such green types of chemical synthesis in recent years, which has stimulated extensive research on several biomasses to support renewable chemical synthesis.[5−13]

Enzymes have been widely used as biocatalysts in organic synthesis due to their substrate specificity and high catalytic activity, especially for the introduction of several enantiomeric or regioselective functional groups. Enzymatic catalysis has the advantages of convenient reaction protocols, mild reaction conditions, excellent stereoselectivity, broad substrate scope, and short reaction time and may help avoid various problems in chemical synthesis, including isomerization or racemization. Photobiocatalysis, a light-mediated enzymatic catalysis, has achieved significant progress due to the capacity to use light for organic synthesis, which has provided versatile protocols and approaches to synthesis various natural or non-natural products.[14] Since then, different applicable tools in photobiocatalysis, such as photoenzymes, enzyme−photocatalyst-coupled systems (EPCSs), and light-driven biotransformation, have been well documented, and the current status of photoenzymes and EPCS have been reported in previous

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reviews.[15−18] Light-driven biotransformation conforms to the principle of "green chemistry" and has been also accessible in a mature technology. With this emphasis, this paper focuses on the advances and challenges of cyanobacteria-mediated light-driven biotransformation toward the efficient synthesis of green chemicals. In particular, we display the potential of cyanobacteria as a promising light-driven biotransformation platform for the efficient synthesis of green chemicals and current achievements of light-driven biotransformation processes in wild-type cyanobacteria or recombinant cyanobacteria. Meanwhile, future perspectives of one-pot enzymatic cascade biotransformation from biobased materials in cyanobacteria have been proposed, which could provide additional research insights for green biotransformation and accelerate the advancement of biomanufacturing industries.

2. COFACTOR IN SITU REGENERATION: THE PROMISING STRATEGY IN THE WHOLE-CELL BIOTRANSFORMATION SYSTEM

Biotransformation refers to the process of converting precursor substrate molecules into targeted products through a specific reaction or a series of reactions using isolated enzymes or the whole cell as the catalytic mediator, which could obtain target products through fewer enzymatic reactions compared with de novo biosynthesis.[19] Unlike chemical catalysis, biotransformation often has some unique advantages, for instance: (1) the reactions involved in biotransformation are usually performed under low temperature and low pressure conditions; (2) higher chemical selectivity, regioselectivity, and stereoselectivity; and (3) allowing for environmentally friendly catalytic processes.[20−22] As a result, biotransformation is increasingly applied to replace traditional catalysis and has been widely used in the green and sustainable production of chiral compounds. Biotransformation includes whole-cell biotransformation and enzyme catalysis, and the difference is that the catalytic mediator of the former is the whole cells or resting cells, while the latter employs cell-free extracts or purified enzymes as the catalytic mediator.[23] Whole-cell biotransformation is usually more convenient and stable than purified enzymes because it lacks expensive purification processes and the addition of exogenous coenzymes, although cell-free extracts or purified enzymes could also be used as biocatalysts. Besides, enzymes are considered powerful catalytic tools, but the number of commercial free or immobilized enzymes on the market remains limited. Consequently, the whole-cell catalytic system is usually the best choice for biotransformation.

The whole-cell biotransformation system could be significantly affected by multiple factors. On the one hand, most enzymatic reactions should be performed in an aqueous medium, and the solubility of organic molecules is always a problem when the reaction is performed under aqueous conditions. Using insoluble or slightly soluble organic compounds as substrate molecules will affect the efficiency of the whole-cell biotransformation system to some extent.[24] On the other hand, although the cells can regenerate cofactors required for reductions during the whole-cell biotransformation process when adding organic carbon (such as glucose) to the culture medium, the efficiency of cofactor regeneration is also a limiting factor for whole-cell biotransformation, resulting in the limited supply of cofactors and the imbalance of reducing power. The efficiency of cofactor regeneration plays an important role in reducing process costs and promoting the orderly progress of target reactions.[25]

As far as the enzymes used in the whole-cell biotransformation system are concerned, oxidoreductases are widely used in the biotransformation process because they can catalyze various complex reactions, among which nicotinamide coenzymes are the most widely used cofactors, including NADH and NADPH.[26−30] However, adding exogenous NAD(P)H to industrial production has proved to be a daunting choice due to its high price and large consumption.[31−33] Furthermore, thermodynamically unfavorable chemical reactions could be achieved in the direction of the target product synthesis through the appropriate cofactor regeneration reaction. Therefore, it is necessary to develop an effective cofactor in situ regeneration system to meet the needs of the large-scale application process. An ideal cofactor in situ regeneration system should meet the following requirements. First, the cost of the cofactor in situ regeneration system should be low and the system should be stable. Second, there should be no cross-reaction between the sacrificial substrate molecules used in the cofactor regeneration system and the target product synthesis pathway. Third, the influence of nontargeted product formation on cofactors could be ignored without affecting the downstream separation of targeted products.

Up to now, several approaches to NAD(P)H regeneration were explored in previous studies,[34,35] among which the introduction of oxidoreductases to achieve NAD(P)H regeneration was found to be the most common method; formate dehydrogenase and glucose dehydrogenase were the most commonly used oxidoreductases. Specifically, formate dehydrogenase catalyzes the oxidation of formic acid to CO_2, accompanied by the conversion of NAD^+ to NADH. The cofactor regeneration system based on formate dehydrogenase has the following advantages.[36,37] First, formic acid, the sacrificial substrate molecule, is a cheap and nontoxic compound harmless to most enzymes. Second, the reaction catalyzed by formate dehydrogenase is irreversible, which is conducive to the efficient accumulation of NADH. Third, the nontargeted product (CO_2) is easy to remove. For instance, the overexpression of formate dehydrogenase in *Klebsiella pneumonia* enables an efficient synthesis of 1,3-propanediol by increasing the amount of NADH available in cells.[38] Additionally, glucose dehydrogenase is an effective catalyst for converting β-D-glucose to D-glucono-1,5-lactone, whereby the lactone is converted into its corresponding acids, accompanied by the regeneration of NADPH.[39] For instance, NADPH is regenerated via the overexpression of glucose dehydrogenase from *Bacillus subtilis*, promoting the conversion of vanillic acid to vanillin.[40]

3. CYANOBACTERIA: PROMISING LIGHT-DRIVEN BIOTRANSFORMATION SYSTEMS TOWARD THE EFFICIENT SYNTHESIS OF GREEN CHEMICALS

Although biotransformation has several advantages, selecting proper biocatalysts for particular reactions is essential for further application.[41] To date, many microorganisms or enzymes, such as bacteria,[42,43] yeast,[44] fungi,[45] plant tissues,[46] cell extracts,[47] and several isolated enzymes,[48,49] have been proven to be versatile biocatalysts to synthesize a host of natural products or unnatural chemicals. However, plant-derived fermentable sugars should be used to obtain abundant precursor and cofactor pools in heterotrophic microorganisms, resulting in competition with food production.[50] Furthermore, NAD(P)H regeneration based on an enzymatic reaction often requires the participation of sacrificial substrate molecules, resulting in the formation of nontargeted products that increase the separation difficulty of

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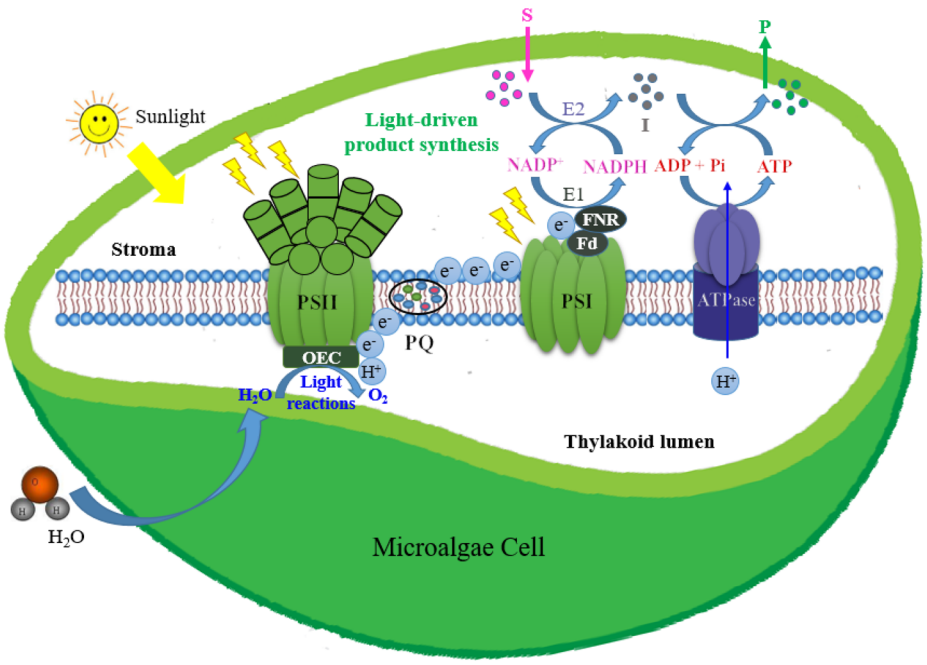

Figure 1. Using cyanobacteria as the chassis organisms to design and develop light-driven biocatalysis platforms for chemical synthesis. Photosynthesis is a powerful enzymatic redox process in which light-driven oxidation stimulates the photosynthetic electron transport chain. Meanwhile, photosynthesis has also been identified as a source of ATP and NADPH, the only reducing agents used in the whole-cell catalysis system. Abbreviations are as follows: S, substrate; P, product; E, enzyme; PQ, plastoquinone; PSII, photosystem II; and PSI, photosystem I.

downstream targeted products and industrial production costs. These shortcomings restrict the accumulation of intracellular products and the application value of the whole-cell biotransformation system in producing high-value pharmaceutical intermediates, fragrances and flavors, fine chemicals, and natural products. Consequently, it is a wise choice to unearth a cheap and easily available cofactor regeneration strategy in which electron donor and cofactor regeneration could be achieved in a pot without an additional supply of organic compounds, and using a photoautotrophic organism as the whole-cell biotransformation platform seems to be the best option to solve the above problems.

Recently, photosynthetic microorganisms have served as important model organisms for studying photosynthesis and are of considerable interest for applications in light-driven biotechnological applications. These versatile and resilient microbes harness light energy to oxidize organic matter, inorganic matter, or water molecules to generate electrons, which then enter into the photosynthetic electron transport chain to power the synthesis of NADPH and ATP and can be used to drive the sustainable production of high-value chemical products in genetically modified strains. Consequently, photosynthetic microbes have emerged as promising cell factories for producing high-value chemicals. Among the various photosynthetic microorganisms, cyanobacteria are the ancient photoautotrophic prokaryotes considered to be the ancestors of chloroplasts in higher plants.[51] They are distributed in different environmental niches and could survive in any aqueous environment.[52] These microbes are inventors of photosynthesis, and their activity led to an increase in oxygen in the atmosphere, providing the possibility for the evolution of life forms on Earth.[53] Over the past 150 years, the concentration of carbon dioxide (CO_2) in the atmosphere has increased by nearly 25%, leading to serious climate problems such as global warming and ocean acidification.[4,54] Cyanobacteria play an essential role in the global carbon cycle and use sunlight and CO_2 as energy and carbon sources, respectively to convert inorganic carbon into organic carbon through photosynthesis and the Calvin cycle. As reported, the biomass derived from cyanobacteria accounts for about one-quarter and two-thirds of the Earth's global primary productivity and the open ocean's primary productivity, respectively.[55,56]

Recently, many de novo synthesis metabolic pathways have been explored to synthesize different kinds of valuable chemical products in model freshwater cyanobacteria, with the drawback of lower yields.[57,58] Although strategies based on dynamic metabolic regulation have been explored to redirect the carbon flux to low-flux pathways,[59,60] the complex and lengthy synthetic routes in de novo synthesis often require a coordinated supply of precursors, energy, and reducing power to maintain both cell metabolism and product synthesis, reducing the effective resources for the synthesis of targeted products.[61,62] In addition, substrates entering the metabolic network have different energetic and redox statuses, and shortening the enzymatic reaction required for synthesizing targeted products may help reduce the burden of intracellular proteins.[61] Consequently, providing appropriate and effective substrate molecules for engineering strains can avoid metabolic constraints and provide sufficient degrees of freedom for cells to efficiently synthesize chemical products. Solar energy is increasingly being used due to its abundant resources and ease of access.[63,64] Photosynthesis is a powerful enzymatic redox process, whereby light-driven oxidation is used to initiate the photosynthetic electron transport chain. Meanwhile, photosynthesis has also been identified as a source of ATP and NADPH, the only reducing agents used in the whole-cell catalysis system. To sum up, a cyanobacterium-mediated light-driven whole-cell biotransformation system represents a promising strategy for the synthesis of targeted products from the perspective of green chemistry, which could combine two of the most research-intensive fields of

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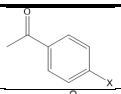
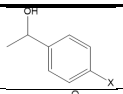
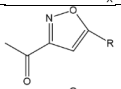
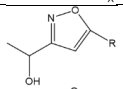
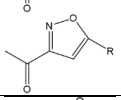
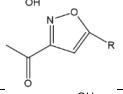
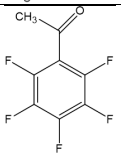
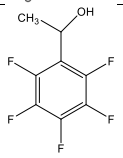
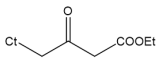
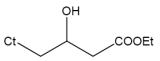
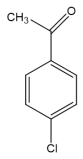
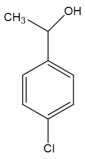
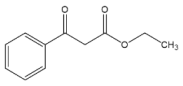
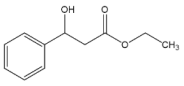
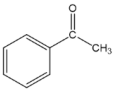
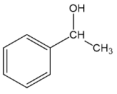
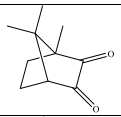
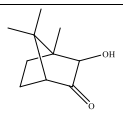
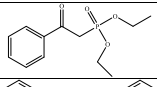
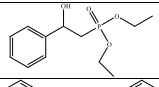
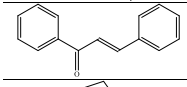
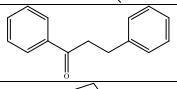
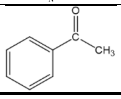
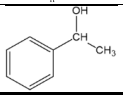
Table 1. Examples of Reductive Biotransformation Processes in Several Wild-Type Cyanobacteria or Recombinant Cyanobacteria

Substrate	Product	Biocatalysts	Yield	Excellent enantiomeric excess	References
		PCC7942	> 45.00 mg/L	> 99.0%	41
		PCC7942	105-285 mg/L	91.0–96.0%	72
		PCC6803	100-265 mg/L	91.0–95.0%	
		*Anabaena variabilis*	5.03 mM	> 99.8%	
		PCC7942	8.78 mM	96.8%	
		*Nostoc muscorum*	2.08 mM	91.0%	70
		*Anabaena variabilis*	2.27 mM	99.0%	
		*Spirulina platensis*	2.25 mM	97.0%	76
		PCC7942	0.344 mg/mL	/	73
		*Nodularia sphaerocarpa*	0.99 mM	93.0%	77
		*Merismopedia glauca*	18.40 mg/L	/	81
		Recombinant PCC6803 with heterologous *ene-reductase* from *Bacillus subtilis*	14.85 mM	/	91
		Recombinant PCC6803 with heterologous imine reductases from *Streptomyces* sp. GF3587	4.15 mM	/	93
		Recombinant PCC7942 with heterologous alcohol dehydrogenase from *Lactobacillus kefir*	19.80 mM	/	92

catalysis (photocatalysis and biocatalysis) to form enzymatic catalysis systems based on cofactor in situ regeneration to realize clean and efficient chemical synthesis (Figure 1).

4. THE CURRENT ACHIEVEMENTS OF LIGHT-DRIVEN BIOTRANSFORMATION PROCESSES IN WILD-TYPE CYANOBACTERIA OR RECOMBINANT CYANOBACTERIA

Wild-type cyanobacteria have been widely used to achieve a series of biotransformations via endogenous highly selective oxidoreductases. Optically active alcohols possess unique structural properties and are the most important chiral structural units that can be used for the organic synthesis of chemical catalysts, agricultural chemicals, and drugs.[26,48,65−67] To date, there are many reports on the biosynthesis of optically active alcohols using biological catalysts that focus on the non-photosynthetic heterotrophic microorganisms or isolated enzymes.[21,68,69] Meanwhile, from the perspective of green chemistry, using cyanobacteria as light-driven biotransformation platforms is a promising alternative to traditional chemical processes for synthesizing optically active alcohols.

Up until now, wild-type cyanobacteria have been intensively studied as biotransformation hosts to the asymmetric reduction of prochiral ketones (Table 1). Several aryl methyl ketones have

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first been reduced to corresponding alcohols. Specifically, *Synechococcus* sp. PCC 7942 (PCC7942) reduced 2′-3′-4′-5′-6′-pentafluoroacetophenone asymmetrically to the corresponding alcohols with a conversion efficiency and enantiomeric excess of 90% and 99%, respectively.[41] Subsequently, the rapid reduction process of 2′,3′,4′,5′,6′-pentafluoroacetophenone has been reported by Havel et al., in which 4.1 mM 2′,3′,4′,5′,6′-pentafluoroacetophenone was reduced within 48 h with 82.00% conversion in PCC7942.[70] Furthermore, PCC7942 produced 0.385 mM of the corresponding (*R*)-alcohol from 0.500 mM *α*,*α*-difluoroacetophenone with an enantiomeric excess of 66% when the cell density was 1 g/L.[71] Subsequently, the biocatalytic asymmetric reduction of 3-acetylisoxazole derivatives to the corresponding alcohols with high enantioselectivities has been performed in PCC7942 and *Synechocystis* sp. PCC6803 (PCC6803).[72] The reduction of monoterpenes with moderate selectivity via endogenous alcohol dehydrogenases in PCC7942 and PCC6803 has also been recorded.[73] Specifically, (+)-camphorquinone was reduced into *α*-keto alcohols with 92.00% conversion over 48 h in both PCC7942 and PCC6803; however, 91.00% conversion of *α*-keto alcohols was obtained at a cell density of 1 g/L within 144 h when (−)-camphorquinon was used.[73] Moreover, reduction of cinnamaldehyde to cinnamyl alcohol was catalyzed by PCC6803, and cinnamyl alcohol production reached 0.049 mg/mL from 0.050 mg/mL cinnamaldehyde with 98.00% conversion.[74] In addition, relevant attempts were made with other cyanobacteria. For example, the previous study compared three representative cyanobacteria, PCC7942, *Anabaena variabilis*, and *Nostoc muscorum*, as biocatalysts for the asymmetric reduction of prochiral ketone.[70] Meanwhile, the reduction of several aldehydes and ketones has also been attempted in *Synechococcus* sp. PCC6911, *Synechococcus* sp. PCC6716, and *Anabaena oscillarioides*,[75] and *Spirulina platensis* and *Anabaena flosaquae* have also been used for the asymmetric reduction of acetophenone and ethyl acetoacetate.[76] Three cyanobacterial strains have been used to transform xenobiotic oxophosphonates to *β*-hydroxyalkylphosphonates, and *Nodularia sphaerocarpa* displayed excellent enantioselectivity and high specific activity for the substrate 2-oxo-2-phenylethylphosphonate.[77] Meanwhile, novel reductases and efficient biocatalysts have also been further developed. For instance, Holsch et al. identified a novel NADPH-dependent 3-ketoacyl-[acyl-carrier-protein] reductase in PCC7942 for the asymmetric synthesis of chiral alcohols, and this enzyme displayed excellent enantioselectivities and high specific activity for ethyl 4-chloroacetoacetate and 2′,3′,4′,5′,6′-pentafluoroacetophenone.[78] To discover new and efficient biocatalysts, a comparative study of 3-ketoacyl-[acyl-carrier-protein] reductases from 16 cyanobacteria was conducted for the asymmetric reduction of prochiral ketone.[79] Except for endogenous highly selective oxidoreductases, ene-reductase activity has also been discovered in a few cyanobacterial strains, which could be used to reduce cyclic enones or cinnamaldehyde with the help of oxidoreductases in PCC7942.[74,80] Additionally, reduction of chalcones and their substituted derivatives has been observed for several cyanobacterial strains.[24,81,82] Meanwhile, Tanaka et al. investigated the asymmetric reduction of *β*-keto esters to the corresponding (*R*)-*β*-hydroxy esters employing PCC6803, and the *R*-selectivity increased with decreasing substrate concentrations.[83]

Furthermore, studying the mechanism of light-driven biotransformation could further improve the application of cyanobacteria in the asymmetric reduction of prochiral ketones. Considering that the growth of algal cells and the asymmetric reduction of prochiral ketones require light, it is necessary to study the effects of light on the reductive reaction. Nakamura et al. studied the light-mediated regulation of asymmetric reduction and reported that light is conducive to improving the conversion efficiency and enantioselectivity of the reduction process of prochiral ketones,[71,84] which may be related to the phenomenon that the NADPH/NADH ratio in cyanobacteria cells is higher under light conditions than under dark conditions.[85] Yamanaka et al. investigated the mechanism of light-enhanced ketone reduction and observed a positive correlation between the reduction of ketones and light intensity within a certain range.[50] Besides, previous literature reported the effects of different light wavelengths on the asymmetric reduction of 2′-3′-4′-5′-6′-pentafluoroacetophenone using PCC6803 as the biocatalyst, showing that orange light and red light were more conducive to the reduction of ketones.[86]

Moreover, ketone reduction in cyanobacteria depends on NADPH from photosynthesis,[50,78,79] and the asymmetric reduction of prochiral ketones is promoted when the content of NADPH available in cells increases. To accelerate the regeneration rate of NADPH, the plastoquinone reduction process and ferredoxin NADP reductase activity in the photosynthetic electron transport chain seem to be the best regulatory targets. Luo et al. increased the level of intracellular NADPH by lowering the Calvin cycle activity or accelerating the photosynthesis activity and found that it increased the efficiency of the asymmetric reduction of prochiral ketones.[87] Additionally, the reduction efficiency of *α*, *α*, *α*-trifluoroacetophenone in PCC7942 could be improved by 1.5× by adding inhibitors of related enzymes in the carboxylation and regeneration processes of the Calvin cycle.[50] Meanwhile, NADPH is involved in converting 1,3-diphosphoglycerate to 3-phosphoglyceraldehyde in the Calvin cycle, and the intracellular NADPH content could be increased by inhibiting the activity of glyceraldehyde 3-phosphate dehydrogenase and adding some sulfhydryl reagents. For instance, Luo et al. increased the amount of NADPH in *Spirulina platensis* FACHB-834 by 80% and 96% by adding iodoacetic acid and Angeli's salt, which increased the efficiency of asymmetric reduction by 12.9% and 63.3%, respectively.[87] In addition, Fan et al. investigated the effects of temperature, light, substrate, and cell concentration on substrate conversions and increased the NADPH content by 20% and 25% by adding $Na_2S_2O_3$ and Angeli's salt.[88] Previous literature has also confirmed that the availability of reduced redox cofactors is a limiting element for chemical synthesis, which would be exacerbated at moderate to high cell densities due to the further reduction in photosynthetic activity, and the removal of natural electron sinks appears to be a promising strategy to overcome the above challenge.[89] Furthermore, the specific activity and initial reaction rate of redox enzymes in cyanobacteria would be improved by the rational design of electron transfer pathways, and a light-driven C═C reduction rate has been significantly improved by deleting several natural electron switches.[90] It is worth noting that the strategy mentioned above could also prevent the over-reduction of the electron transport chain by removing electrons from the photosynthetic electron transport chain. To sum up, light and NADPH pools play an important role in the asymmetric reduction of prochiral ketones, and selecting appropriate light conditions and improving the regeneration efficiency of NADPH is an effective strategy to improve the asymmetric reduction of prochiral ketones.

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Although significant progress has been achieved in the light-driven biotransformation in nonmodified cyanobacterial strains, the involved enzymes are difficult to optimize through genetic engineering. Consequently, the development of highly active recombinant cyanobacteria is needed to allow for efficient light-driven biotransformation. Asymmetric reduction of C=C double bonds has been performed in recombinant cyanobacterium PCC6803 by heterologous expression of the ene-reductase from *Bacillus subtilis* with a maximum specific activity of 123 U/gCDW.[91] Additionally, biotransformation approaches have been applied for the synthesis of chiral 1-phenylethanols and chiral amines by heterologous alcohol dehydrogenase in recombinant PCC7942 and imine reductase in recombinant PCC6803, respectively.[92,93] Moreover, cyanobacteria produce oxygen via photosynthetic water oxidation, which represents an ideal oxidant for oxidative catalysis. For instance, cytochrome P450 monooxygenase (CYP1A1) has been heterologously expressed in *Synechococcus* sp. PCC7002 to perform the O-de-ethylation of 7-ethoxyresorufin,[94] and a novel method to optimize photosynthesis-driven cytochrome P450 activity has been reported by the previous study, which indicated that the flavodoxin-like carrier provides appreciable reducing power.[95] Additionally, P450 monooxygenase from *Acidovorax* sp. CHX100 catalyzes the transformation of cyclohexane into cyclohexanone in PCC6803, and the production of 2.6 g of cyclohexanol has been reported in 3 L stirred-tank photobioreactors via the biphasic system.[96] Cyclohexanone monooxygenase (CHMO) has also been proven to catalyze Baeyer−Villiger oxidation, and the recombinant PCC6803 strain could catalyze the formation of lactones from a series of cyclic ketone substrates.[97] Tüllinghoff et al. reported the heterologous expression of an NADPH-dependent Baeyer−Villiger monooxygenase gene from *Acidovorax* sp. CHX100 IN in PCC6803, and P*nrsB*-(Ni^{2+})-controlled expression based on a replicative plasmid yielded the highest intracellular enzyme concentration.[98] Tüllinghoff et al. also described the first artificial light-driven redox cascade in PCC6803 to convert cyclohexanone to 6-hydroxyhexanoic acid by coexpressing Baeyer−Villiger monooxygenase and lactonase from *Acidovorax* sp. CHX100.[99] However, native alcohol dehydrogenases in cyanobacteria will reduce the conversion efficiency of the Baeyer−van der Milliger oxidation reaction, and alcohol dehydrogenases seem to be key nodes that restricts the consumption of ketone substrates in the reduction process to improve the output of targeted products during the Baeyer−van der Milliger oxidation process. Meanwhile, screening of several novel enzymes has also been an effective approach to improve the conversion efficiency of the Baeyer−Villiger oxidation reaction. Specifically, a Baeyer−Villiger monooxygenase from *Burkholderia xenovorans* exhibited higher reaction rates in the reduction of cyclohexanone to lactone compared to *Acinetobacter* sp. and almost completely suppressed the unwanted side reaction, such as cyclohexanol formation.[100] Moreover, it is worth noting that electrons derived from photosynthesis are used for biotransformation reactions, and the ATP surplus would hinder cell activity. Consequently, photosynthetic performance should be improved by several engineered metabolic pathways, which could correct the source/sink imbalances.[101] Regardless, these proof-of-concept studies demonstrate that photosynthesis is sufficient to supply the cofactor used in the whole-cell catalysis system, which will accelerate the applicability of light-driven biotransformation in cyanobacteria.

5. CONCLUSIONS AND FUTURE PERSPECTIVE

Traditional chemical synthesis has the disadvantages of hazardous catalysis, high energy consumption, and waste-generating chemical processes. In comparison, biotransformation is a green, sustainable, and cost-effective process. Cyanobacteria, important members of the photoautotrophic organism class, have attracted extensive attention due to their tremendous potential for the sustainable production of green chemicals. As cyanobacteria use light as the energy source to power the synthesis of NADPH and ATP, using cyanobacteria as the chassis organisms to design and develop light-driven biotransformation platforms for chemical synthesis provides a theoretical and practical basis for the sustainable and green biotechnology production of chemicals.

Notwithstanding several proof-of-concept studies demonstrating the applicability of light-driven biotransformation in cyanobacteria, the applicability of cyanobacteria-mediated biotransformation has received relatively little attention due to the poor biotransformation performance, which is not good enough to meet industrial needs. To exploit the potential of cyanobacterial biotransformation, an assessment of cyanobacteria as hosts for light-driven biotransformation is still missing. As is known to all, the titer of chemicals by the biotransformation method is usually low in wild-type cyanobacterial strains, and biotransformations with recombinant cyanobacteria strains contribute significantly to the industrial scale. Moreover, engineered cyanobacteria have greater potential in the formation of new products by artificial cascades of enzymatic reactions,[102,103] and enzymes involved in related metabolic pathways should be manipulated to achieve highly selective activity,[104] which could also avoid the possible side reactions.[105] However, there is limited literature on the exploration of engineered cyanobacteria for one-pot enzymatic cascade biotransformation by artificial multienzyme complexes in the production of green chemicals. Consequently, synthetic biology and genome editing techniques should be used to further engineer and optimize cells of cyanobacteria to achieve efficient light-driven systems for synthesizing various chemicals, as these could provide additional research insights for green biotransformation and accelerate the advancement of biomanufacturing industries.

Currently, synthesis of the green chemicals in cyanobacteria is mainly focused on introducing heterologous synthetic pathways to drive the utilization of intermediate metabolites; however, genetic engineering of cyanobacteria faces numerous challenges. The first challenge is that it is difficult for cyanobacteria to reach the theoretical yield due to the deficiency of genetic manipulation tools, and novel promoters or ribosome binding sites for precise gene expression control should be further investigated. The next challenge is that although the genome editing of cyanobacteria is simple, the cycle is relatively slow. The traditional homologous recombination-mediated approach should integrate heterologous expression modules into chromosomes or endogenous plasmids but has the challenge of being time-consuming, and the use of a broad-host-range vector faces the problem of compatibility.[106] Further, developing stable shuttle expression vectors in cyanobacteria will accelerate the construction of recombinant cyanobacteria.[107]

Moreover, the industrial application of cyanobacteria-mediated light-driven biotransformation is limited due to scale-up difficulties, and the illumination efficiency and light availability were the main limiting factors.[108] Consequently,

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novel photobioreactors should be developed to allow a short light path between the light source and the reaction medium. Taken together, the development of stable shuttle expression vectors and novel photobioreactors would provide us with better research capabilities in cyanobacteria-mediated light-driven biotransformation.

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J.C. and K.Z. conceived and designed the project. C.Z., W.X., Y.H., J.X., and Y.S. had constructive discussions and interpreted the significance of this study. J.C. and K.Z. prepared the draft and finalized the manuscript. J.L. and C.X. had constructive discussions during the revision process of this manuscript and revised the manuscript. K.Z. supervised the project and critically reviewed the manuscript. All authors read and approved the final version of the manuscript.

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Notes

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