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Using different cultivation strategies and methods for the production of microalgal biomass as a raw material for the generation of bioproducts

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ABSTRACT

Microalgal biomass and its fine chemical production from microalgae have pioneered algal bioprocess technology with few limitations such as lab-to-industry. However, laboratory-scale transitions and industrial applications are hindered by a plethora of limitations comprising expensive in culturing methods. Therefore, to emphasize the profitable benefits, the algal culturing techniques appropriately employed for large-scale microalgal biomass yield necessitates intricate assessment to emphasize the profitable benefits. The present review holistically compiles the culturing strategies for improving microalgal biomass production based on appropriate factors like designing better bioreactor designs. On the other hand, synthetic biology approaches for abridging the effective industrial transition success explored recently. Prospects in synthetic biology for enhanced microalgal biomass production based on cultivation strategies and various mechanistic modes approach to enrich cost-effective and viable output are discussed. The State-of-the-art culturing techniques encompassing enhancement of photosynthetic activity, designing bioreactor design, and potential augmenting protocols for biomass yield employing indoor cultivation in both (Open and or/closed) methods are enumerated. Further, limitations hindering the microalgal bioproducts development are critically evaluated for improving culturing techniques for microalgal cell factories, subsequently escalating the cost-benefit ratio in bioproducts synthesis from microalgae. The comprehensive analysis could provide a rational and deeper detailed insight for microalgal entrepreneurs through alternative culturing technology viz., synthetic biology and genome engineering in an Industrial perspective arena.

1. Introduction

Microalgae is a ubiquitous class of oxygenic photosynthetic organisms having wide range of industrial applications with biological significance. The cultivation of photoautotrophic microalgae is a hopeful reservoir for blue biotechnology better than other photoheterotrophic, mixotrophic and heterotrophic species (Lau et al., 2015; Rumin et al., 2020). As a matter of fact, microalgae merely utilizes light and CO_2, and also numerous advantages as hosts for employing genetic manipulation protocols (Pal et al., 2019). Significantly, microalgae cultivation is simple and do not require any harmful chemicals, a massive amount of water and fertile land compared to the other land-based crops (Tan et al., 2020). The microalgae are a group of prospective resources cultivated in fresh, brackish, seawater, wastewater, and soil habitats. Microalgal cultivation can facilitate the rising sustainable application through biomass production used in the pharmaceuticals, nutraceuticals, biofertilizers, bioplastics, biofuels, cosmetics and feeds for aquaculture and poultry (Baldev et al., 2013; MubarakAli et al., 2018; Deepika and MubarakAli, 2020). On the other hand, it can extensively reduce atmospheric CO_2 and consequently control environmental pollution (Pathak et al., 2018). Interestingly, the excessive nutrients present in the waste and polluted water could be a suitable medium for

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microalgal cultivation that corresponds to the efficient removal of N, P and heavy metals (Singh et al., 2019). Microalgal cultivation requires a high level of nutrients such as Fe, K, S, P, N, C for sustainable biomass production. Using nutrient recycling, wastewater, and synthetic nutrient resources is an important aspect of reducing nutrient supplies, and eventually, it's cost-effective (Markou et al., 2014). The land utilized for microalgal cultivation and biomass production includes land under wastewater treatment or adjacent to high-temperature heating plants and other industrial facilities that produce organic compounds and nutritional constituents emitting escalated carbon dioxide levels surpassing agriculture purposes (Dębowski et al., 2020). It is to understand that the allelopathic interactions are believed to play a crucial role in controlling the contaminants resulting in the consistent productivity of microalgal cultivation. Plenty of microalgal species have been documented to synthesize allelopathic compounds inhibiting the growth of biological contaminants, thereby increasing biodiesel production (Dias et al., 2017). Biological contamination remains a severe challenge for outdoor mass production of microalgae, leading to the reduction of product synthesis or cell growth by blooming effects. The controlling strategies preventing biological contamination using novel potent evolutionary methodologies and metabolic engineering have focused on mitigating biological contamination's deleterious consequences (Zhu et al., 2020). The microalgal microbiome corroborates in addressing the crucial part regulated by cyanobacteria as a holobiont in modulating cyanobacterial diversity in natural environments. Coexisting microbiome with cyanobacterial farming are recommended for favourable downstream, growth enhancement and broad-spectrum control of cyanobacterial pathogens (Lian et al., 2018). Green algal, *Navicula* sp., *Scenedesmus* sp., and *Chlorella* sp. contamination was reduced in the open cultivation of desert cyanobacterium, *Microcoleus vaginatus* under high light intensity. The biomass productivity was attained was 41.3 mg L^{-1} d^{-1} (Lan et al., 2015). Fortunately, microalgae are primarily the attractive agents for large-scale production for their uses in health and nutraceuticals, amino acid biosynthesis, bioplastics production, bioremediation protocols, antibiotic production, biodiesel, edible oils and several useful byproducts for sustainable industrial and social benefits (Fig. 1). This review article aims to outline cultivation strategies as a potential resource for future biomass production and industrial profits. A brief outline of the biomass production from microalgal natural strains cultivated in the laboratory conditions used for bioproducts production, developing bioreactors for cultivation, cultivation system for biomass production, and increased chemical production of microalgae using synthetic biology are investigated (Fig. 2). A handful study reported the holistic compilation of the intricate molecular mechanism of synthetic biology and genetic engineering modalities to enhance bioproducts for wide outreach applications. However, the inherent culturing conditions, medium optimization and variability patterns that envisage the primary and key regulation of the OMICS of the bioproducts has not been reported earlier. The present validations provide clues for culturing by modifications of media, conditions, bioreactor design, cost-effectiveness, and escalated cost-benefit ratio in microalgal-derived bioproducts.

2. Prologue on rationale utilities based on microalgae culturing techniques and conditions

It is believed that cultivation conditions and media are vitally controlling the synthesis of the essential compounds in the microalgae (Encarnação et al., 2015). A semi-continuous mode of cultivation of *Cyanobacterium aponinum* was attributed for higher biomass productivity in commercially developed urea-phosphoric acid medium (5.3 g L^{-1} d^{-1}) than that of blue-green medium (4.7 g L^{-1} d^{-1}). Therefore, the appropriate and cost-effective medium for mass cultivation poses a critical control phenomenon (Rajvanshi et al., 2019). The dodecane used as an *in-situ* extractant for commercial lab-scale and high-density cultivation of *Synechocystis* sp. PCC 6803 for sesquiterpenoid biosynthesis has proved as an effective protocol. Synthesis of (E)-α-bisabolene of about 179.4 $\pm$ 20.7 mg L^{-1} was found high in a two-step semi-batch mode for eight days than the cyanobacterial strains reported previously (Dienst et al., 2020). Mixed cultivation of *Synechococcus elongatus* cscB and *Pseudomonas putida* cscAB with the nitrogen-limited procedure enhances the production of polyhydroxyalkanoates (PHA) of about 23.8 mg L d^{-1} and a maximal titer of 156 mg L^{-1} (Löwe et al., 2017). Freshwater unicellular cyanobacterium, *Synechocystis* sp. PCC 6803 was cultivated in a HEPES buffer and seawater-based medium supplemented with phosphorus and nitrogen sources in augmenting amino acid biosynthesis. Primary metabolism was ameliorated by changing the cultivation medium that highly up-regulated a plethora of amino acids (Lysine, Ornithine, Proline, Glycine, Glutamine, and Aspartate) biosynthesis (Iijima et al., 2015). *Dunaliella salina* cultivated in a treated vinasse medium comprising rice vinasse using immobilized *Synechococcus pevalekii* in alginate beads were proved 175% of cell replication was increased when *D. salina* cultivation in treated vinasse medium confirms that reducing cost spends for natural seawater using culture medium improved the industrial context (Colusse et al., 2021).

Microalgae contribute to the copious synthesis of novel and innovative bioactive compounds and fine chemicals with industrial prominences, such as pigments and lipids. Microalgae resultant chemicals and biofuels (biohydrogen, bioethanol, biodiesel, and biogas) are not competitive with fossil-derived fuels because of the latter's high production cost, emphasizing alternative energy resources. Minimizing the expenditure of microalgal culturing and other cultivation strategies would play an essential function in reducing the cost of the fuels and chemicals generated from them (Johnson et al., 2018). The nitrogen source, light quality, light intensity, and photobioreactors (PBR) (closed or open) contribute to enhance the cultivation setups for increasing the production of biomass and biocompatible compounds (Furmaniak et al., 2017). The regulating assembly of FtsZ belongs to tubulin-like protein families playing an essential role in the *S. elongatus* PCC 7942 division plane controlled by altering Min system proteins' levels. Varying the expression of FtsZ-regulatory protein increases the 20% length of cells than the wild type. The cells were elongated by morphology engineering to improve by gravity-assisted settling or the sedimentation under low centrifugal forces (Jordan et al., 2017). Minimizing greenhouse gases (CH_4), nitrous oxide, emissions from crop fields can be efficiently combated by cultivating microalgae. Microalgal biomass is also promising candidates for bio-fertilizer application as they enhance water-holding capacity, augment soil fertility and aid in atmospheric N_2 fixation and mineral nutrient status of the degraded land soils (Singh et al., 2016). Increased plastic utilization necessitates bioplastics production, which correlates to the alternative synthesis of conventional petrochemical plastics with PHA to contend with fossil fuel plastics in diminishing recycling costs and reuse. Sustainable production of PHA based bioplastics from cyanobacteria promotes bioremediation, mitigates CO_2 waste reuse and reduces production costs for optimal environmental benefits (Gradíssimo et al., 2020). The microalgal potential was also confirmed by preventing oral cancer, chronic periodontitis, and controls oral disease-causing microbes, *Herpes labialis*, *Streptococcus mutans* and *Candida albicans* and acts as a good supplement for the co-adjuvant treatment and prevention of diverse oral illnesses (Ferrazzano et al., 2020). Although culturing conditions for microalgal bioproducts production has been comprehendingly successful, lab-scale output and transition to upscaled industrial production necessitate concrete evidence.

3. Lab-scale bioproducts production from naturally occurring microalgal strains in different cultivation conditions

Microalgal strains are usually present in the environment and obtained in an uni-algal culture state, cultivated in laboratory conditions screened for bioproducts production. The strains isolated from the natural environments are well adapted to the local needs would be the best

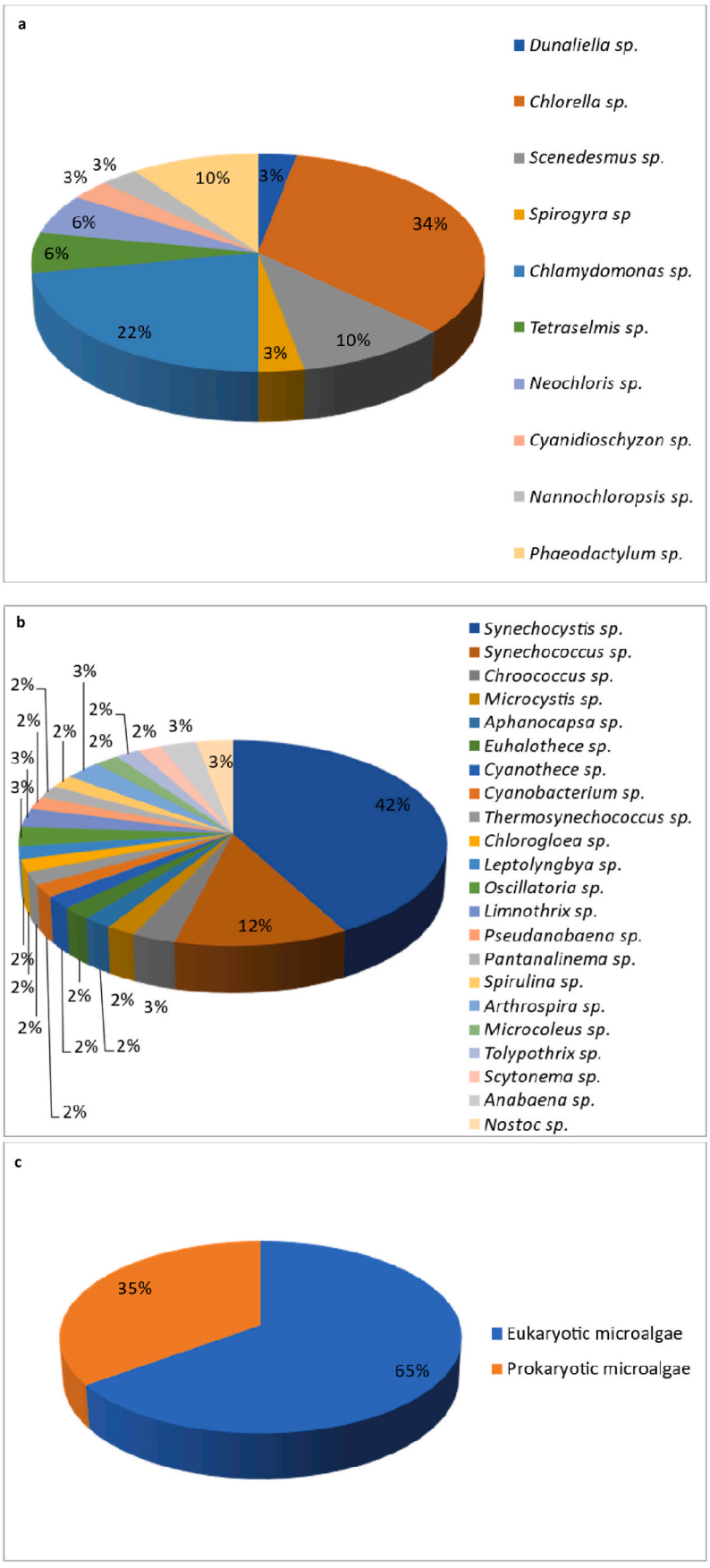

Fig. 1. Revealing the percentage distribution of a) Eukaryotic microalgal species rich in bioproducts production (*Chlorella* sp.) b) Prokaryotic microalgal distribution (*Synechocystis* sp) c) Comparison between prokaryotic and eukaryotic microalgal bioproduct distribution patterns showing high levels in prokaryotic microalgae.

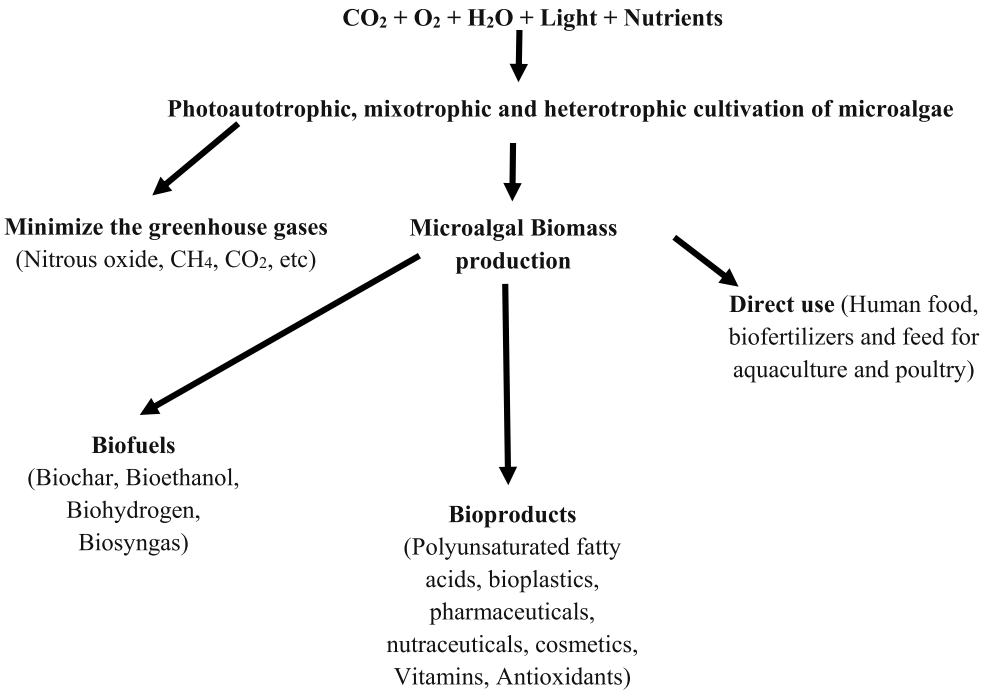

Fig. 2. Schematic overview of different uses and bioproducts of microalgae revealing cultivation modes for enhanced biomass yielding value added bioproducts.

for large-scale cultivation to industrial production. Miao et al. (2018) proved that cultivation setups widely influence the display of isobutanol in *Synechocystis* PCC 6803. Cyanobacteria cultivated at 50 μmol photons m^{-2} s^{-1} and pH 7–8 proved the maximum production of isobutanol with in-flask titer of 194 mg L^{-1} after ten days and 435 mg L^{-1} at 40 days. This matches an increasing isobutanol production of 911 mg L^{-1} after 46 days, with the highest production rate of 43.6 mg L^{-1} d^{-1} was noted between days 4 and 6. Marine form of *Synechococcus* sp. VDW were grown under optimal conditions (inoculum size 0.17 (OD_{730}), ammonium concentration 10.5 mg L^{-1}) and pH 7.4), maximal removed ammonium (34 mg L^{-1} d^{-1}), and given biomass productivity about 95% later seven days of culturing. The fatty acid methyl ester (FAME) analysis exhibited neutral lipid and total lipid maximum than control. These results are pointing out that *Synechococcus* sp. VDW can be used for simultaneous water treatment, and biomass production applied to large palmitic acid production (Srimongkol et al., 2019). Mode of growth (biofilm or planktonic) is significant for attaining a high level of bioactive metabolite, EPS and chlorophyll-*a* production from *Chroococcus* sp. (AP3U), *Leptolyngbya* sp. (AP3b) and *Oscillatoria* sp. (AP17) (Veerabadhran et al., 2018). The bloom-forming cyanobacterium, *Microcystis*, efficiently removes the nitrogen and reaches a maximum intracellular C/N ratio to cultivate under limited nitrogen conditions. A significant increase of the specific NO_X-N removal rate was observed at 14.2 times greater than that of the control in the anoxic system with a sediment-water interface. This learning initial recommends that cultivation in nitrogen-limited media can provoke a high C/N ratio, carbohydrate and organic accumulation in cyanobacteria. These can act as a hopeful carbon source for denitrification (Huang et al., 2018). *Pantanalinema rosaneae* CACIAM18 *Synechocystis* sp. CACIAM05 and *Limnothrix* sp. CACIAM25 produced a high lipid content at a low level of $NaNO_3$ concentration (1 g L^{-1}) and a high level of light intensity (100 µmol photons m^{-2} s^{-1}). Simultaneously, the *M. aeruginosa* CACIAM08 was given an elevated level of lipid production at high levels of both variables (luminous intensity equivalent to 100 µmol photons m^{-2} s^{-1} and $NaNO_3$ concentration at 2 g L^{-1}). The CACIAM25 and CACIAM05 attained improved biodiesel quality parameters with low nitrogen concentration and light intensity, whereas CACIAM18and CACIAM08 obtained better parameters with high luminous intensity and low nitrogen concentrations (Aboim et al., 2019). Glycogen production by marine cyanobacterium NKBG15041c was examined under different culturing environments and produced up to 399 μg mL^{-1} OD_{730}^{-1} glycogen. At the same time, cells were grown for 168 h in a nitrogen-depleted seawater medium following medium replacement. Cultivation under nitrogen ambient (3 mM NaNO3) conditions also gave a higher yield of glycogen (404 μg mL culture^{-1} OD_{730}^{-1}) in 23% of dry cell weight (DCW) of NKBG15041c cells after 288 h of cultivation. The significant results characterize the highest glycogen generation reached in marine cyanobacteria, indicating the potential of NKBG15041c in prominent applications for carbohydrate production (Badary et al., 2018). *Cyanidioschyzon merolae* 10D wild-type 40 was cultivated under continuous white light (50 μmol m^{-2} s^{-1}) in liquid MA2 medium 41 (2% CO_2) at 40 °C and nitrogen-depleted conditions for starch accumulation. The cyanobacterial biomass treating with various homogeneous catalysts, led to the fastidious generation of successful development of new carbon resources such as methyl lactate or methyl levulinate holds good as a solution for the depletion of fossil fuels and the raw materials for the manufacture of lacquers, dopes, spices, pharmaceuticals, plasticizers, adhesives and coatings (Yamaguchi et al., 2017 Apr 12**)**. Demonstration of increased lipid accumulation potential of *Stigeoclonium* sp., Kutz. BUM11007 under nitrogen starved regime studied and found a new source of lipids for biodiesel production (Praveenkumar et al., 2012). The *Synechocystis* sp. PCC 6803 wild-type (with S-layer and non-motile) and respective tolC-deletion mutant was cultivated in BG-11 medium and added with kanamycin (100 μg mL^{-1}) for the tolC-mutant, at 30 °C, under a 12 h dark/12 h light (25 μmol photons m^{-2} s^{-1}) of photoperiod. The lipid composition changes of tolC-mutant strain and wild-type strain were observed similar when cultivated in fast-growth or slow-growth (Hewelt-Belka et al., 2020). *Synechocystis* sp. PCC 6803 were cultivated in standard BG11 medium supplemented with 5 mM $NaHCO_3$ under continuous shaking at 120 rpm and constant illumination of ~50 μE m^{-2} s^{-1} at 28 °C. PHB content per cell-dry-weight was increased in shaking culture in a 12 h light/dark regime (Koch et al., 2020a). Based on the informative criteria, the enhancement of value-added bioproducts can yield deeper insights.

4. Cultivation methods and cost-effective media for high-value natural products production

Microalgae grow either planktonic and or forming a biofilm. It is known that cultivation is an essential step for biomass production and easy harvesting is an economically feasible way, suggestively affects the growth pattern and metabolism of microalgae and regulates the quantity and quality of bioproducts (Table 1). Conversely, harvesting from large scale microalgal cultivation systems requires high-energy input for commercial products production. Significantly, energy expenditure for the mixing and dewatering/harvesting process was reduced when cultivating the biofilm mode of microalgae growth. By the way, the biomass was scraped from the surface, and carbon dioxide and light utilization much improved in the biofilm mode of cultivation (Heimann, 2016). By this method, nitrogen-fixing *Tolypothrix* sp was cultivated in outdoor condition using simulated ash dam wastewater in 500 L modified algal-turf scrubbers. The biofilm cultivation method was aerated with 15% CO_2, resulted in ~40 increased c-phycocyanin, c-phycoerythrin contents and 1.25-fold increased biomass production (Velu et al., 2020). Similarly, high-density cultivation of *Nostoc punctiforme* PCC 73102 for filamentous cyanobacterial rapidly produces biomass density up to 400 g (wet weight) L^{-1}. The two-tier vessel cultivation process increased the high-value natural products and biomass production (Guljamow et al., 2017). Mixotrophic biofilm cultivation of two microalgal species, *Scenedesmus dimorphus* and *Chlorella vulgaris*, improves biofuel feedstock production and showed 2 and 3-time increased biomass productivity, biomass accumulation in 9 days. It is 2- to 10-times increased lipid production than autotrophic cultivation comparatively (Roostaei et al., 2018). A green alga, *Chlorella*, is cultured in waste water as a medium for biomass production and biofuel feedstock (Baldev et al., 2021a) and paves the way for developing a biorefinery from microalgae (Rohitha Thangam et al., 2021).

An immobilized *Scenedesmus vacuolatus* cultivated in a novel twin-layer system porous substrate PBR. The microalgal biomass was high at 29 g m^{-2} d^{-1}. By the way, microalgal productivity and biomass density were increased (Carbone et al., 2017). A cyanobacterium, *Chlorogloea fritschii* TISTR 8527 cultivated initially under normal photoautotrophic condition for biomass. After expanding, the biomass was recultivated using a single substrate under heterotrophic cultivation. The two-stage cultivation of *Chlorogloea* increased the efficiency of converting acetate substrate to PHB of about 51 ± 7% (Monshupanee et al., 2016). The dual (solid and liquid)-phase cultivation system (DuPHA) represents a new hybrid cultivation system encompassed easy collection and concurrent microalgal growth in liquid and solid phases and recovered for adequate biomass production. Continuous circular cultivation of typical filamentous cyanobacteria *Limnothrix* sp. SK1-2-1 and *Pseudoanabaena* sp. ABRG 5–3 yield biomass production of approximately 8–27 g m^{-2} d^{-1} DCW floor under indoor opened or indoor closed setups (Aoki et al., 2018). A novel-designed photobioreactor (NPBR) was used to cultivate *Chlorella sorokiniana* CY-1 in palm oil mill effluent. NPBR was designed with thin and transparent flat panels with a high surface area for easy biomass harvesting. Biomass, and lipid production (2.3–2.9 folds) and nutrient removal efficiencies of total phosphorus (TP), total nitrogen (TN) and chemical oxygen demand (COD) is 96.0 (), 98.6 (and 93.7%) respectively were high in NPBR (Cheah et al., 2020).

Usually, cost-effective harvesting methods done by bio-flocculation of microalgae by co-cultivation with filamentous fungi rely largely on an ideal process. The different microalgal strains, *Anabaena spiroides Nitzschia palea*, *Selenastrum capricornutum*, *Scenedesmus obliquus*, and *C. vulgaris* were co-cultured with activated sludge or fungi or different ratio of mixed LED light wavelengths for biogas slurry nutrient removal and improvement in biogas production. The mixed LED light wavelengths, and co-cultivation increased the COD (85.82 ± 5.37%), TN (83.31 ± 4.72%), and TP (84.26 ± 5.58%) removal efficiency and CH_4 production (90%) (Wang et al., 2017). Co-cultivation of microalgae with fungus, *Aspergillus fumigatus* increased the harvesting efficiency, enhanced biomass production, and wastewater treatment. Co-cultivation was used to optimize the lipids' fatty acid composition without genetic modification (Wrede et al., 2014). A microalga, *C. sorokiniana*, was co-cultivated with blastospore of *Isaria fumosorosea* under strict autotrophic condition and pH 7–8. The stable pellets were formed, and biomass was easily harvested for hydrothermal gasification (Mackay et al., 2015). Recently, hydroxyapatite used as nanoflocculant for harvesting of *Chlorella* sp. (MubarakAli, 2019)

Commencing seawater into media ensured *Spirulina subsalsa* found restricting bacterial infections during growth and obtained high lipid productivity about 120 mg $^{-1}$ L^{-1} d^{-1}. Besides, the production of phytols, carotenoids and protein were also enhanced in seawater mixed with monosodium glutamate residue (MSGR). This medium also helps to produce *S. subsalsa* with high lipid (92 mg L^{-1} d^{-1}) and biomass (253 mg L^{-1} d^{-1}) productivity (Jiang et al., 2019). A dessert crust constructing cyanobacterium, Scytonema javanicum, cultivated in various diluted artificial synthetic wastewater found growing well. After continuous cultivation, the S. javanicum gradually removed nitrogen and phosphorus from synthetic water. A biomass harvest range of 3.91 mg Chl-a L^{-1} in the synthetic wastewater and nutrient transferring from wastewater to dessert confirms the above-said phenomenon (Wu et al., 2018). Dominant species of cyanobacteria were cultivated through the composition of urban digestate and secondary effluent and worked in semi-continuous mode. Nevertheless, a cyanobacterial consortium comprising of cf. *Oscillatoria* sp., *Aphanocapsa* sp. and *Chroococcus* sp. revealed a high proportion with limitation of low phosphorus content and carbon conditions in the culture, resulting in high biomass yield

Table 1
Method of cultivation for enhanced the bioproducts production in chronological order.

Microalgae	Method of cultivation	Products	Reference
Chlamydomonas reinhardtii	Phytohormones supplemented media	Significantly increases growth	Park et al. (2013)
Chlorella protothecoides	Dual-mode (heterotrophically and autotrophically) cultivation	Improved lipid quality	Santos et al. (2014)
Synechocystis sp. PCC 6803	Anaerobic digestion effluents used cultivation	D-lactate production	Hollinshead et al. (2014)
C. vulgaris (UTEX #236)	Rotating algal biofilm system	Improved biomass productivity (70–100%)	Michael et al. (2015)
C. sacchrarophila, *C. pyrenoidosa* and *C. reinhardtii*	Co-cultivation with *Cellvibrio pealriver*	Effectively enhance the biomass production	Xie et al. (2016)
Arthrospira platensis	Hydrothermal carbonization-algal cultivation	Enhanced nitrogen utilization	Yao et al. (2016)
Tetraselmis chuii	Co-cultivate with *Muricauda* sp.	Higher cell density (21.37–31.18 and 65.42–83.47%) production	Han et al. (2016)
C. vulgaris	Attached biofilm mode cultivation	30.4% higher biomass production	Huang et al. (2016a)
Indigenous microalgae	Co-cultivate with bacteria	Enhance microalgal biomass and lipid productivities	Cho et al. (2017)
Diatoms, green algae, and cyanobacteria	Communities of microalgae	Increase the stability and biomass quality	Olofsson et al., 2019
C. reinhardtii	High cell density cultivation	Cadaverine increased yields 10-fold	Freudenberg et al. (2021)

(Arias et al., 2017). A green alga, *C. vulgaris* OW-01 were cultivated in orange peel extract (OPE) as an organic and inorganic nutrient source for growth exhibited 4.5 times more FAMEs and 3.4 times high biomass production than cells cultivated in BG11 medium with glucose supplementation (Park et al., 2014). Apart from culturing medium and conditions, significant production could be accounted for by the appropriate bioreactors used. Table 1 indicates the cultivation methods enhancing bioproducts production. However, determining large-scale production envisages the appropriate bioreactor usage to augment microalgal growth patterns and, subsequently, biomass production. Bioreactor design coupled with cultivation method enhancing the biosynthesis of bioproducts.

5. Open and closed bioreactors for microalgal cultivation

Large-scale cyanobacteria cultivation was done using prominent natural locations, open raceway pond systems and a sophisticated, closed production system: PBR for biomass production (Kamravamanesh et al., 2018). Competent and economically feasible photosynthetic bioreactors require growth abundance resulting in highest productivity in large-scale cyanobacterial cultivation with the least operation costs. Broad research has been conducted to cultivate diverse cyanobacteria through various cultivation methods covering closely controlled laboratory methods to less predictable outdoor tanks. Usually, industries prefer natural setups for cultivation, viz., open ponds or seawater, to decrease infrastructure expenses (Parmar et al., 2011). PBR are playing essential roles in cultivating the photosynthetic microalgae for making required and eco-friendly products. Advantages of using PBR corresponds to a precisely controlled environment, water loss prevention caused by evaporation, low contamination, higher photosynthetic efficiency, higher concentrations, and area dependant productivities (Huang et al., 2017). Cultivation of microalgae in the tubular bioreactor is the main advantage as a large available surface area for illumination. The highest possible area-to-volume ratio is favourable for high photosynthetic activity and mixing pattern. The tubular system was most beneficial to cultivate the unicellular forms (*Synechocystis* sp.). It is unsuitable for filamentous ciliate microalgae due to cause shear stress of the pump and culture crashes. The major disadvantage of using the tubular bioreactor was heating sterilization was not possible, and photo limitation frequently occurs in outdoor cultivations (Troschl et al., 2017). Fig. 3 represents the various bioreactors and their design showing the feasibility in production and application settings. Studies regarding the comparative efficacies of different bioreactors require further investigations.

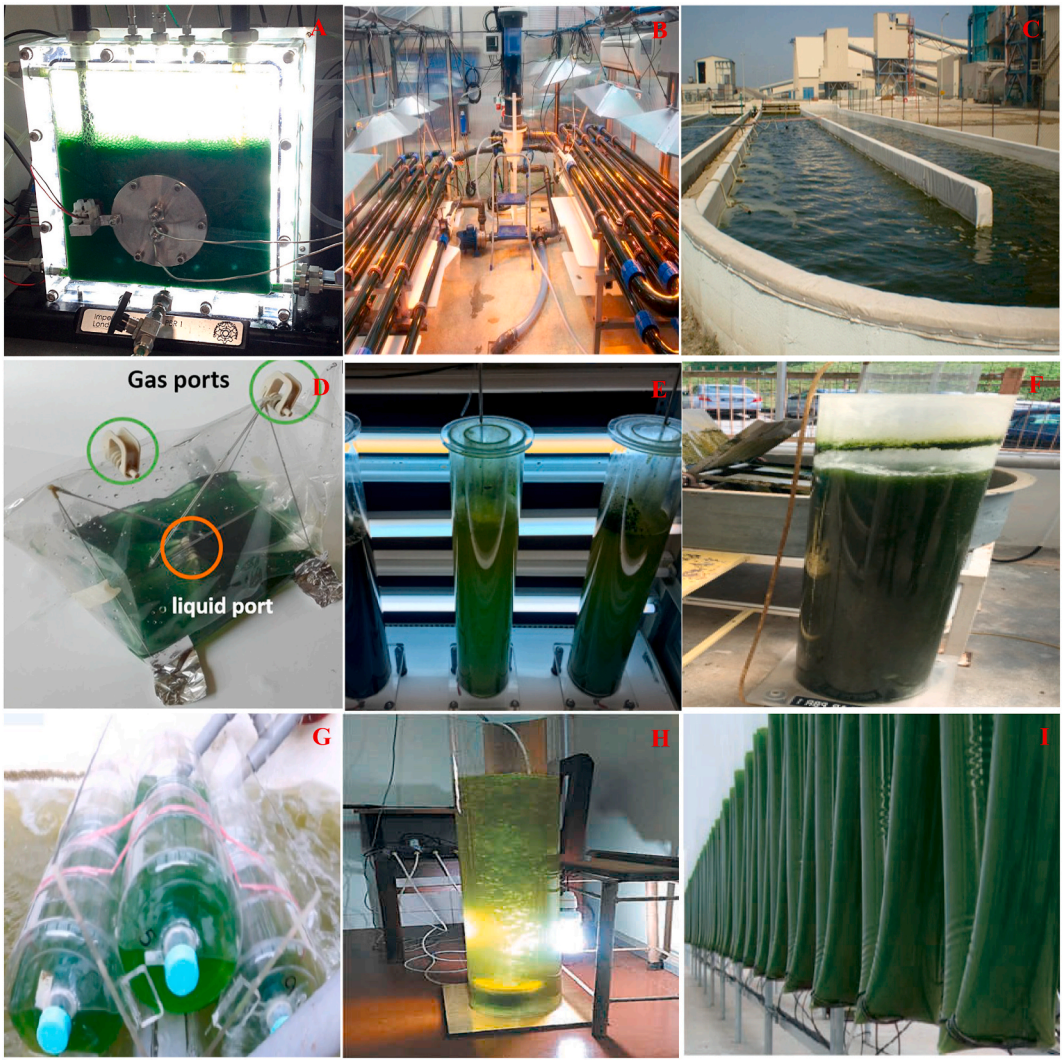

Fig. 3. Photobioreactors used for microalgal cultivation (**A**) Flat-plate panel; (**B**) Tubular; (**C**) open pond; (**D**) Single bag with culture; (**E**) indoor annular column; (**F**) Open annular; (**G**) rotating floating; **(H)** Bubble column; **(I)** plastic bag (Zhang et al., 2015; Troschl et al., 2017; Shastik et al., 2020: Bacellar Mendes and Vermelho, 2013; Balasubramaniam et al., 2021; Huang et al., 2016b; Huang et al., 2017; Mubarak et al., 2019).

5.1. Cultivation in raceway, open ponds and plastic bag

Investment cost and operation cost was significantly less for the classical open (raceway and pond) air cultivation system. The advantages are easy operation, high longevity of nearly 50 years and ready to access the sunlight at ease (Grubišić et al., 2019). Open pond cultivation of marine cyanobacterium, *Anabaena* sp. ATCC 33047 cultivated in the semi-continuous regime for biomass production and the quality achieved of 9 g ((dry weight (DW)) m^{-2} d^{-1} (winter) to over 20 g m^{-2} d^{-1} (summer). The exopolysaccharide (35 g m^{-2} d^{-1}) and high-value phycobiliproteins were rich in the cyanobacterial biomass (Moreno et al., 2003). Red luminescent solar concentrators (LSCs) in raceway ponds were proved to enhance c-phycocyanin productivity (8.5 mg L^{-1} d^{-1}), and biomass (12.2 g m^{-2} d^{-1}) of *Arthrospira platensis* increased growth and biomass of 44% and 26%, respectively. Consequently, 44% less cultivation area required to produce c-phycocyanin using red LSCs. This could be straight to a significant cost-effective production of c-phycocyanin (Raeisossadati et al., 2019). *Scenedesmus* sp. cultivated in an airlift-driven raceway reactor for energy-efficient biomass yield, similarly enhancing efficient utilization of CO_2 and exhibited the productivity of 0.19 ± 0.003 dry g L^{-1} d^{-1} at 1% CO_2 under continuous culturing conditions. The maximum CO_2 utilization efficacy of 33% was noted under batch culturing at a 0.25% CO_2-to-air ratio (Ketheesan and Nirmalakhandan, 2012). *Chlorella* sp cultivated in an open raceway pond system about 35.000 L working volume and found biomass productivity was doubled when the culture exposed to the pulsed magnetic field (Baldev et al. 2018, 2021b). In the open cultivation system, drawbacks hindering cultivation owes to contamination (airborne microorganisms, fungi, other species of algae, viruses, and protozoa) risk, CO_2 losses, evaporation and harvesting costs are very high. An **a**lkalihalophilic cyanobacterium, *Euhalothece* sp. ZM001 was cultivated in a horizontal plastic bag bioreactor on a rocking platform for biomass production. A novel bioreactor's feasibility increased the biomass concentration of 1.88 g L^{-1} and accessible to scaling-up. The low-cost plastic bag alternative for horizontal PBR was evidenced probability of an innovative PBR operating by nature force, in addition to easy scaling-up and low cost of manufacturing (Zhu et al., 2017). A cyanobacterium, *Anabaena* sp. PCC 7120 ΔHup mutant cells were cultivated in transparent plastic bags with a gas barrier layer for hydrogen (H_2) production. The H_2 production rate was 20.6 mL d^{-1} L^{-1} of culture, with an accumulation of 33.2 mL L^{-1} during 5 days and final H_2 content of 1.1% (v/v). It was the first report on *Anabaena* sp. PCC 7120 ΔHup were cultivated in the outdoor region using a feasible cheap bioreactor. However, H_2 production found low than the previous experiments due to contamination, unsuitable culture conditions and suboptimal weather conditions (Shastik et al., 2020).

5.2. Cultivation using flat panels

The flat-panel PBRs system has a large illumination surface-area-to-volume ratio. The culture media in this bioreactor by aeration were given by low input energy materials such as air tube. A cyanobacterium, *Cyanothece* sp. ATCC 51142 corresponds to a low-chlorophyll mutant cultivated in different configurations of PBRs. Lower incident light intensity and double exposure surfaces conditions enhance biomass and H_2 production than the natural strain (Zhang et al., 2015). Similarly, *Synechocystis* sp. PCC 6803 was cultivated in a flat PBR panel under various conditions (light-inhibited growth, light-saturated and light-limited). A downregulation of light-harvesting components and the upregulation of the translational machinery with increasing growth rate and light intensity were noticed (Zavřel et al., 2019). The phosphate regulator lack *Synechocystis* sp. PCC 6803 (ΔSphU) were cultivated using shrimp wastewater in a flat-plate PBR. The ΔSphU exhibited the highest nutrients removal of 98.07% ammonium, 67.90% nitrite, 80.10% nitrate, and 96.99% phosphate) and phosphate uptake rate of 20.16 mg g dw^{-1} d^{-1}. In the shrimp wastewater, nitrogen assimilation could induce the maximum PHB (32.48% (w/w) DW, with the highest PHB production of 12.73 mg L^{-1} d^{-1}) accumulation in DSphU (Krasaesueb et al., 2019). The wild-type of *Synechocystis* sp. PCC 6803 were grown in turbidostat-controlled lab-scale flat panel PBR with a wide range of 50–1460 μE m^{-2} s^{-1} intensities. The *Synechocystis* PSII activity, cell size and growth rate were altered by resistance to high light stress conditions (800 μE m^{-2} s^{-1}) and light intensity (Cordara et al., 2018). A thermophilic cyanobacterium, *Thermosynechococcus* CL-1, was grown in Su and Chu's medium in the flat plate PBR in the 1.5 cm light path under 2000 μE m^{-2} s^{-1} illumination. The strain was adopted in the new cultivation medium to increase the CO_2 fixation rate, biomass and glycogen productivity and found 221.5, 138.7 and 75.9 mg L^{-1} h^{-1} (respectively (Su et al., 2017). The material cost for the production is very high; fouling formed inside the material and gas hold-up are disadvantages of using this PBR system.

5.3. Flat-panel airlift PBR, airlift PBR, bubble column PBR, rotating floating PBR and prototype floating PBR

A green filamentous freshwater microalga, *Spirogyra* sp the cultivated in flat-panel airlift PBR and found good growth. During the cultivation, the average productivity of 0.78 g DW L^{-1} d^{-1} and the highest productivity of 1.15 g DW L^{-1} d^{-1} were obtained in the last cultivation (Vogel and Bergmann, 2018). Use a vertical semi-closed airlift PBR to cultivate nitrogen-fixing cyanobacteria (*Nostoc muscorum* UTEX 2209S, *Anabaena* sp. UTEX 2576) and later affirmed the efficiency of biofertilizers in rice plant growth. The vertical semi-closed system PBR cultivation process was demonstrated as an easy and efficient method for cultivating at a medium scale that can open the future prospectus of microalgal biofertilizers' rice production (Jochum et al., 2018). Prototype floating PBRs used to cultivate *Tetraselmis* sp. KCTC12236BP in the sea and the fatty acid and biomass productivity in the PBRs were raised up to 44% and 50% due to the enhanced mixing efficiency and mass transfer (Kim et al., 2016). Similarly, *Chlorella pyrenoidosa* was cultivated in 20 L of bubble column photobioreactor for biomass and lipid production exhibited 19.04% DW and 1.18 g L^{-1}, correspondingly, at the end of the cultivation. In the bubble column photoreactors, the light penetration sufficiently transfers to the materials; the bubbles are produced from the bottom giving efficient removal of O_2, sufficient supply of CO_2, and good mixing. The main drawback in using this system is the large angle relative to sunlight, which causes a high fraction of incident energy to be reflected back and thus lost in terms of biomass growth purposes (Mubarak et al., 2019). *Dunaliella tertiolecta* was cultivated in a rotating floating photobioreactor (RPF) for biomass production. The RFP might be drive by tidal waves, river and natural flowing stream in which no equipment required for agitation of the cultures in maintaining the cell suspension. RFP is considered via the subject temperature control properties and energy-saving and further regular light supply in the culture as related to conventional raceway pond culture systems (Huang et al., 2016b). Bioreactor design and intricate mechanisms for augmenting the biomass yield are categorically summarized along with key factors accounting for limitations in culturing maximization.

6. Enhancement of production of the fine chemicals in cyanobacteria applying synthetic biology protocols

Bioproducts concentration and production were increased in engineered microalgae for industrial application. Genetic and metabolically engineering was more effective to get the desired products when cultivated in suitable culturing systems. In recent decades, synthetic biology tools and advancements are illustrated and genetic regulatory phenomenon and strategies in microalgal cell factories' growth (Wang et al., 2020a). Systems metabolic engineering facilitates the improvement of microbial cell factories able to capably synthesize numerous compounds and substances and polymers, fine and bulk chemicals, biofuels, natural

Table 2
Enhanced chemical production in the genetically engineered microalgae by overexpressing or inactivating the genes.

Species	Gene's manipulation	Products	Reference
Synechocystis	Fumarase and zwf (catalyzes the first reaction in the oxidative pentose phosphate pathway) gene deletion	Excreted significant amounts of fumarate	Du et al. (2019)
Synechocystis sp. PCC 6803	Inactivating the glutamate decarboxylase gene	Enhanced the bioaccumulation of pyruvate and PHB	Monshupanee et al. (2019)
Neochloris oleoabundans	Overexpression of plastidial lysophosphatidic acid acyltransferase	Increased triacylglycerol production	Chungjatupornchai et al. (2019)
Nannochloropsis salina	Overexpressing a basic helix-loop-helix transcription factor	Improved growth and lipid production	Kang et al. (2019)
Phaeodactylum tricornutum	Overexpressed the glucose-6-phosphate dehydrogenase gene	Higher of both lipid content and growth	Wu et al. (2019)
C. reinhardtii	Introduction of labdane-type diterpene (LD) cyclase, copal-8-ol diphosphate synthase	Production of labdane-type diterpenes	Papaefthimiou et al. (2019)
N. oleoabundans	Single Expression of *Lysophosphatidic Acid Acyltransferase, Glycerol-3-Phosphate Acyltransferase*, and *Diacylglycerol Acyltransferase*	Higher lipid production	Muñoz et al., 2019
P. tricornutum	Expression of oxidosqualene cyclase and cytochrome P450 along with its native reductase	High-value plant triterpenoid production	D'Adamo et al. (2019)
Synechocystis sp. PCC 6803	Calvin–Benson– Bassham (CBB) cycle including rbcLXS and glpD and free fatty acid recycling including aas encoding acyl-ACP synthetase	Highest contents of both intracellular lipids and extracellular free fatty acids of about 35.9 and 9.6% w/DCW	Eungrasamee et al. (2020)
S. elongatus PCC 7942	Introduce phosphite oxidoreductase (PtxD) gene	Control biological contaminants during cultivation	González-Morales et al. (2020)
Synechocystis sp. PCC 6803	Expressing the inositol-1-phosphate synthase and myo-inositol-1-monophosphatase genes	Myo-inositol production	Wang et al. (2020b)
Synechocystis sp. PCC 6803	Expression of bisabolene synthase and co-expression of farnesyl pyrophosphate synthase	Increased bisabolene production	Sebesta and Peebles (2020)
Synechocystis sp. PCC 6803	Deletion of PII-interacting regulator gene of carbon metabolism	Accumulate more than 80% of PHB	Koch et al. (2020b)
S. elongatus PCC 7942	Inducer-free gene expression of 1-deoxy-D-xylulose-5-phosphate synthase gene, isopentenyl diphosphate isomerase gene, farnesyl diphosphate synthase gene and squalene synthase gene	Squalene production	Choi et al. (2020)
C. pyrenoidosa	Expression of glucose-6-phosphate dehydrogenase	Increase of neutral lipid content	Xue et al. (2020)
P. tricornutum	Over-expressing the genes Violaxanthin de-epoxidase (Vde), Vde-related (Vdr) and Zeaxanthin epoxidase 3 (Zep3)	Accumulation of carotenoids, with an increase in the fucoxanthin	Manfellotto et al. (2020)
C. reinhardtii	Overexpression of CrtYB (phytoene-β-carotene synthase - PBS) gene	Enhanced β-Carotene and Lutein	Rathod et al. (2020)
C. reinhardtii	Highly expressed phosphite oxidoreductase gene	Crop-protection tool	Changko et al. (2020)
Tetraselmis sp.	Knockout of ADP-glucose pyrophosphorylase gene	Enhanced lipid productivity	Chang et al. (2020)
Nostoc PCC 7120	Overexpression of fv3B gene	Enhances the photobiological hydrogen production	Roumezi et al. (2020)
C. reinhardtii CC-400	Expression of pyridoxal kinase gene	Carbon dioxide assimilation to enhance the biomass	Lin et al. (2021)
Synechocystis sp. PCC 6803	Expressed α-ketoisocaproate dioxygenase	Isobutene production	Mustila et al. (2021)
Synechocystis sp. PCC 6803	Expressing the gene L-proline-4-hydroxylase	*Trans*-4-hydroxy-L-proline production	Brandenburg et al. (2021)
Synechocystis sp. PCC 6803	Expression of the bisabolene synthase, 1-deoxy-D-xylulose-5-phosphate synthase and IPP/DMAPP isomerase	Increase the production of bisabolene	Rodrigues and Lindberg, 2020

products, drugs and amino acids (Ko et al., 2020). In modern days, the existing strategy and devices for altering cyanobacteria have been growing and progress in marker less selection systems, modular vector systems, reporter proteins, riboswitches, ribosome binding sites, and genetic promoters. Since these novel techniques, microalgae have been effectively engineered to express heterologous pathways to produce a broad diversity of bioproduction potential (Santos-Merino et al., 2019). Significant developments in increasing and establishing new and competent genetic tools, for instance, clustered regularly interspaced short palindromic repeats (CRISPR)-associated nuclease (CRISPR/Cas9) systems, metabolic flux analysis, synthetic or system biology tools, high throughput OMICS analyses and genome-scale modelling have been built for engineering microalgal strains (Khan et al., 2019). The CRISPR application results in site-directed mutagenesis, multiple gene targeting without off-target mutants for precise genome engineering. These underlying molecular mechanisms were utilized for condensing the lengthy and too long engineering procedure rooted by cyanobacteria's polyploidy genome feature for enhanced bioproducts synthesis (Jeong et al., 2020) were tabulated (Table 2). On the contrary, CRISPR/Cas 9 approaches in improving bioproducts production from microalgae have been reported elsewhere. However, culturing conditions and an intensive molecular background using the CRISPR system could result in efficient microalgal application and augmented industrial bioproducts synthesis. A tuned feeding strategy in mutants of *Synechocystis* sp. PCC 6714 (MT_a24) were gained, exhibiting improved PHB (1.16 g L^{-1}) and glycogen (2.6 g L^{-1}) content in controlled PBR in DW of 30 ± 4% and 76.2%, correspondingly. In outline, the effort demonstrates as feedstock for the production of energy and value-added compounds, such as PHB and the potential of glycogen enriched MT_a24 for bio-refinery (Kamravamanesh et al., 2019). The activity was maximum for the aldehyde-deformylating oxygenase (ADO) from *S. elongatus* PCC 7942 (7942ADO). Hydrocarbon-producing activities of 10 representative ADOs were evaluated and confirmed that 7942ADO had the maximum activity. These results may help produce combinatory mutants of ADO that improve action and maximum yields of the soluble protein *in vivo*, thus deciphering the high production of hydrocarbons (Kudo et al., 2019). Increased lipid content was prominent in all the engineered strains contrasted to WT cells. Above all, in *aas* (encoding acyl–acyl carrier protein synthetase)-overexpressing strain, high content and synthesis rate of 34.5% w DW^{-1} and 41.4 mg L^{-1} d^{-1}, correspondingly after 4 days cultivation was reported. These findings correlate to metabolic engineering of a variety of genes concerned in the recycling of free fatty acid, alkane synthesis, phospholipid hydrolysis, and fatty acid synthesis in *Synechocystis* sp PCC 6803 which designated a rise in acetyl Co-A fux towards common ways of PHB synthesis and lipid as noticeable via, their amplified contents (Eungrasamee et al., 2019). The negative

regulation of *ntcA* and the modified tricarboxylic acid cycle (MH043) were made in *Synechocystis* through global transcription machinery engineering. The ethylene production rate of 2463 ± 219 μL L^{-1} h^{-1} OD_{730}^{-1} reached multi-copy ethylene forming enzyme (*efe*) recombinants, a notable improvement in ethylene production by microalgae (Mo et al., 2017).

The outcomes recommended that facilitates the supply of NADPH and ATP were amplified considerably. Moreover, the precursor acetyl-CoA and malonyl-CoA could be added after 3-hydroxypropionic acid (3-HP) production at a maximum level in *Synechocystis*. The over-expression of three transporter genes involved in phosphate, manganese and cobalt/nickel and transporting (i.e., sll0679, sll1598 and sll0385) might show an enhanced 3-HP synthesis in *Synechocystis* (Wang et al., 2016). Using the microbial consortium contains the *Escherichia coli* and fast-growing cyanobacterium *S. elongatus* UTEX 2973 to make the platform chemical 3-HP from CO_2 then sucrose afterwards under photoautotrophic culture setups. The efficient sucrose secretion was obtained in *S. elongatus* UTEX 2973 by overexpressing the sucrose permease-coding gene *cscB* in the strong promoter *Pcpc560* (Zhang et al., 2020). In the existence of $CaCl_2$ and lysozyme, productivity, yield, and ethanol titer enhanced to 1.0 g L^{-1} h^{-1}, 93% of theoretical yield and 48 g L^{-1}, and from *A. platensis*, comparable to 90 g L^{-1} of glycogen (Aikawa et al., 2018). Genetic stability of *Synechocystis* sp. PCC6803 was tested through value to their mannitol production, with and without salt stress, through prolonged turbidostat cultivations. The acquired outcomes demonstrate that mannitol synthesis under salt stress environments in the *Synechocystis* sp PCC6803 replaces the endogenous compatible solutes' synthesis. Control groups lost mannitol synthesis due to the multiple types of mutation in the DNA (Wu et al., 2020). The recombinant strain *S. elongatus* PCC 11801 produced 1044.18 and 338.26 μmol g DW^{-1} h^{-1} for succinate and ethylene, correspondingly in the photoautotrophic conditions. This was attained through introducing a single copy of the *efe* under the inducer-free super-strong promoter of phycocyanin β subunit, the control of *PcpcB* (Sengupta et al., 2020a). Succinic acid production was 2.2-fold high (0.93 g L^{-1}) in the engineered (two genes knocked out and genes overexpressed) novel cyanobacterium *S. elongatus* PCC 11801. They can produce succinate higher than the previously reported engineering of the model cyanobacterium *S. elongatus* PCC 7942 of about 0.43 g L^{-1} in 8 days (Sengupta et al., 2020b). The *efe* substrate 2-oxoglutarate increased in glycogen knockout *Synechocystis* sp PCC 6803 under nitrogen limiting setup increases ethylene formation. Subsequently, the ethylene production rate was twofold increasing through ribosome-binding site screening, RSF1010-based broad-host self-replicating plasmid, using multiple tandem promoters and single gene copy of *efe* (Veetil et al., 2017). Enzyme limonene synthases from the plant's *Citrus limon* and *Mentha spicata* were introduced in *Synechocystis* sp. PCC 6803 for limonene synthesis. Genetic engineering (ribose 5-phosphate isomerase and ribulose 5-phosphate 3-epimerase) in the geranyl diphosphate synthase from the plant *Abies grandis* was expressed pentose phosphate pathway was overexpressed to optimize the limonene biosynthetic pathway. The engineered strain produced a 2.3-fold enhancement (6.7 mg L^{-1}) in limonene yield (Lin et al., 2017). This way, synthetic biology systems provide a possible escalated approach in combining the altered culture conditions, cultivation medium, appropriate bioreactor and site-specific genome engineering for enhanced bioproducts production with cost-effective mechanisms for improved financial profits.

7. Limitations of the present study

The review assessment enumerates the culturing conditions, cultivation medium, type of bioreactors for enhancing biochemicals and bioproducts production. Several synthetic biology approaches regarding larger applications in the industrial sector are understudied. Moreover, profit in the markets and the methodology used by the industries for enhancing the production scales remain concealed. By patent laws, data protection and trade secret management render the appropriate technology for ample use in markets and upgraded technological innovations. Profit margin scale assessment was not feasible as the datasets pertaining to variability patterns signifying cost-effective strategies for medium and large-scale industries remain a significant drawback. However, lab-scale achievements in synthesis are adequately reported than at the industrial and cost-benefit ratios for bioproducts production statistics are not harnessed at ease.

8. Concluding remarks and future perspectives

The review analyzed the present status of bioproducts synthesis through microalgae cultivation from basics and advancement. Microalgal market strategy for overwhelmed commercial and industrial applications with high profits and less investment confers algal-based entrepreneurs in utilizing scientific approaches in improving bioproducts production. However, algal biorefineries are no longer a postulated concept that will sooner reinstate explicit advancements in commercial and cost-effective bioproducts. Cyanobacteria are smart photosynthetic host organisms for the eco-friendly generation of fuels and other value-added fine chemicals. Though, cost-effective approaches and advanced achievement of proficient and sustainable cultivation schemes are essential. Lab–to-industry upheaval in bioprocess technology could have probable commercial consequences based on the present review.

The significant obstacles in bioproducts production employing microalgae might be concluded as.

(i) Development of the low-cost cultivation system for mass-scale production of biomass
(ii) Maintenance of the axenic culture in outer cultivation
(iii) Total productivity and Yield enhancement
(iv) Economically feasible downstream processing and reuse of residuary through biorefinery approach.

Genetically engineered microalgae result in the production of a low quantity of desired molecules on a laboratory scale. Using the different experimental conditions and cultivation techniques and synthetic biology insights, and appropriate bioreactors could increase production and cost-effective production with high profits in the microalgal based bioproducts industry.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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