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REVIEW

Media Optimization Techniques for Microalgae Through Technological Advancements: A Mini Review

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ABSTRACT

Microalgae have been classified as the most primitive plant species and the ability to grow rapidly makes it very suitable for biomass cultivation by using different technologies over the past years. Microalgal biomass can be used for various productions such as biofuels, food, supplements, and more as it is categorized as environmentally friendly throughout the cultivation process. Nutrients play one of the most important roles in cultivating microalgae besides other factors such as temperature, pH, salinity, inorganic carbon, oxygen, light intensity, and carbon dioxide availability. The technology has become much more advanced in cultivating microalgae for maximizing lipid or biomass production. In this paper, we reviewed the technologies used for media optimization of microalgae growth along with the advancement in technology, starting from traditional techniques to more advanced techniques employing statistical or mathematical analysis. The traditional media optimization technique is known as the classical one-factor-at-a-time (OFAT) technique which is sub-grouped into three types of experiments—removal experiment, supplement experiment, and replacement experiment. The advanced technique for the optimization of medium components concentration discussed in this paper includes Response Surface Methodology (RSM), Artificial Neural Network (ANN) and Genetic Algorithm (GA).

Keywords: Advanced technique, ANN, Biomass, GA, Optimization, Media technology advancement, Microalgae, Nutrient, Traditional technique, RSM

1. Introduction

Microalgae has recently captured worldwide interest due to its substantial application in pharmaceuticals, nutraceutical, bioremediation, and agricultural industries as well as a new alternative for renewable energy sources [1, 2]. The rapid growth of the world's population has continuously driven the demand for energy resources such as fossil fuels and food supplies from agricultural activities [3]. The extensive utilization of land and fossil fuels has contributed to the increment of atmospheric greenhouse gases which is the predominant cause of global climate changes. This overexploitation can be mitigated by the creation of biofuels and bioproducts from microalgae [4, 5]. As well as Microalgae have manifested various potential as a protein source to satisfy the population's dietary requirement for a more sustainable food supply. These promising protein sources can be cultivated in a relatively shorter time with less environmental impact. However, a vast amount of microalgae biomass is required to fulfil the demands with the prospect of cost-saving as the main objective. This mass production can be accomplished with the

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application of advanced technique in culture media optimization [6, 7].

The choice of technology used in media optimization plays a crucial role in determining the effectiveness of yielding microalgae. Algae may be cultured through various methods, starting from technologically advanced solutions where the process is thoroughly monitored and controlled and end in less predictable techniques based on the use of open tanks. The technological and economic effectiveness of the process is significantly affected by the source of nutrients [8]. Subramanian et al. [9] and Sun et al. [10] also mentioned that the microalgae are adapting to the culturing environment by evolving their systems and metabolic pathways to produce biomass with less conversion efficiency. As a substitution, genetic and metabolic engineering technologies of microalgae are considered to create pathways for efficient microalgae production platforms such as Calvin-Benson-Bassham (CBB) cycle, Embden-Meyerhof Pathway (EMP), Pentose Phosphate (PP) pathway, and Tricarboxylic Acid (TCA) cycle [11, 12].

Before the 1970s, media optimization was carried out by using classical methods, which were expensive, time-consuming, and involved multiple experiments with compromised accuracy. Nevertheless, the emergence of modern mathematical and statistical techniques has led to media optimization approaches that are more vibrant, effective, efficient, economical, and robust in giving the results [13]. Multiple strategies can be adopted during the creation of the optimization model. The strategies include the traditional one-factor-at-a-time (OFAT) techniques and advanced techniques. Advanced techniques which consist of statistical or mathematical-based optimization, involve screening of significant components through Taguchi and Plakett Burman Design (PBD). Apart from that, the advanced technology also optimizes component concentration through Response Surface Methodology (RSM), Artificial Neural Network (ANN), and Genetic Algorithm (GA) [14]. This review focuses on a selection of sophisticated strategies that may be used to optimize the medium for microalgae cultivation. To enhance the understanding, the significance of microalgae, delve into the nutritional needs for microalgae cultivation, and give a thorough description of sophisticated optimization approaches based on mathematics were discussed.

1.1. Microalgae

Microalgae are photosynthetic organisms that are considered the most ancient form of plants due to their single-cell structure and the ability to carry out photosynthesis using the same mechanism as higher plants [15]. The nature of microalgae's simple cellular structure has appointed this organism as one of the best solar converters [16]. They have a broad tolerance range for various environmental factors such as temperatures, salinities, pH values and light intensity [17]. Microalgae thrive within water bodies such as lakes, ponds, rivers, and wastewater. The nature of this habitat allows microalgae to have better access to water, carbon dioxide and other required nutrients [18]. During their peak growth phase, microalgae biomass doubles up every 24 h, and even as quickly as every 3.5 h as reported by [19].

Microalgae have been receiving attention for their various direct and indirect uses that are beneficial in multiple fields. Microalgae biomass can either be directly incorporated into human food, animal fodder and food supplements or be manipulated to produce biofuels and bioproducts as shown in Fig. 1 [20]. These organisms are very efficient in sequestration of atmospheric carbon dioxide (CO_2) and nutrient utilization besides having a rich source of lipids within their cell structure that can be used as biofuel feedstock [2]. As compared to terrestrial oilseed crops, greater quantities of oil per unit area can be generated from microalgae. Microalgae fuel can be one of the alternatives for producing sufficient automotive fuel to replace the current demand for petrol and diesel. Other than biofuels, microalgae also provide a wide range of bioproducts such as poly unsaturated fatty acids, antioxidants, proteins, and pigments for the biotechnology industry [21].

1.2. Nutrient requirement for microalgae

The growth of microalgae is influenced by several environmental conditions, including temperature, pH, salinity, inorganic carbon, oxygen, light intensity, carbon dioxide, and nutrient availability. The specific requirements for each species may differ. Every individual microalgae species has a specialized nutritional need that is necessary for its optimal growth and development [22]. Microalgae growth development requires macronutrients such as nitrogen, phosphorus, sodium, magnesium, calcium, and potassium, as well as micronutrients including molybdenum, manganese, boron, copper, iron, and zinc, along with trace elements [23]. Despite having different nutritional needs, the backbone of all microalgae species is made up of carbon, nitrogen, and phosphorus. Carbon is an important macronutrient in the culture medium of microalgae as it provides energy for microorganisms [24]. According to Prasad et al. [25], carbon is required for the photosynthesis process, therefore it has a significant role in

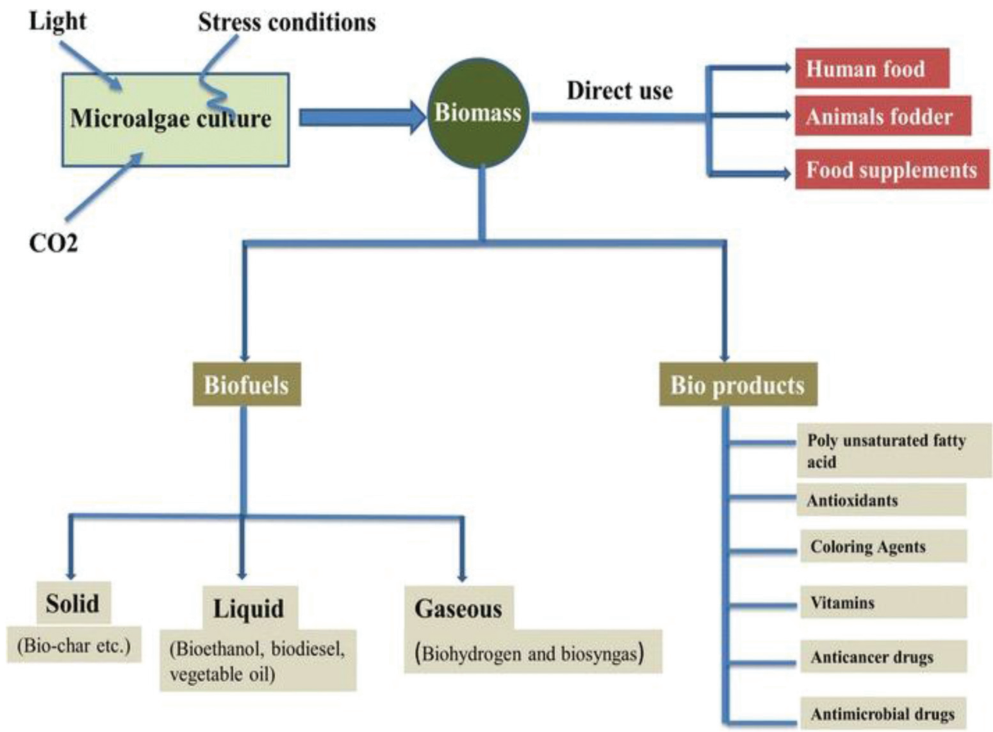

Fig. 1. The various utilization of microalgae biomass [20].

microalgal growth and reproduction. Singh et al. [26] added that carbon is also essential to produce metabolites. This macronutrient is utilized in different forms depending on the type of microalgal growth. Autotrophic growth uses inorganic carbons such as carbon dioxide (CO_2), carbonate, and bicarbonate while heterotrophic growth makes use of carbon in its organic form, for example, glycerol, acetate, and glucose.

Nitrogen, like carbon, plays a crucial role in the development of microalgae, biomass productivity, and the generation of metabolites. Because of its fundamental function as a constituent in proteins and nucleic acids, the lack of nitrogen in the culture medium of microalgae suppresses the protein synthesis required for activities that contribute to biomass production such as cellular division [27]. Ragaza et al. [28] stated that these microorganisms utilize nitrogen in their inorganic form such as nitrates. Also, that urea is an alternative nitrogen source that is much cheaper and suitable to use for microalgal cultivation. Besides carbon and nitrogen, phosphorus is another important medium component for microalgae culture. Phosphorus is one of the vital elements for nucleic acid production as it makes up the backbone of DNA and RNA. Additionally, it plays a crucial role in ATP, which is a vital component of energy-supplying molecules. Furthermore, phosphorus is present in microbial cell membranes as an essential constituent of phospholipids. Microalgae absorb inorganic phosphorus, namely phosphates.

Nitrogen and phosphorus are the two components of culture media for microalgae that are closely linked together in previous studies. According to Yaakob et al. [29], the growth and metabolism of algal cells are heavily dependent on nitrogen and phosphate, whereby these two important macronutrients make up about 10 to 20% of microalgae biomass. A lack of these two nutrients in the culture medium would lead to a decrease in the development of microalgae, while simultaneously lead to the accumulation of lipids [30]. Valenzuela et al. [31] and Wang et al. [32] stated in their studies on *Phaeodactylum tricornutum* and *Chlamydomonas reinhardtii* respectively. Another study explained the decline in the growth of *Chlorella vulgaris* and *Pseudochoricystis ellipsoidea* was noted during nitrogen and phosphorus decreased. In the same context [33] reported that when the concentration of nitrogen and phosphorus are insufficient, the metabolism of lipids would shift to lipid storage from the synthesis of membrane lipids.

Other than macronutrients, micronutrients are also important as one of the medium components for microalgae culture. According to Khan et al. [34], the small amount of these required micronutrients is able to alter the enzymatic activities in algal cells, hence

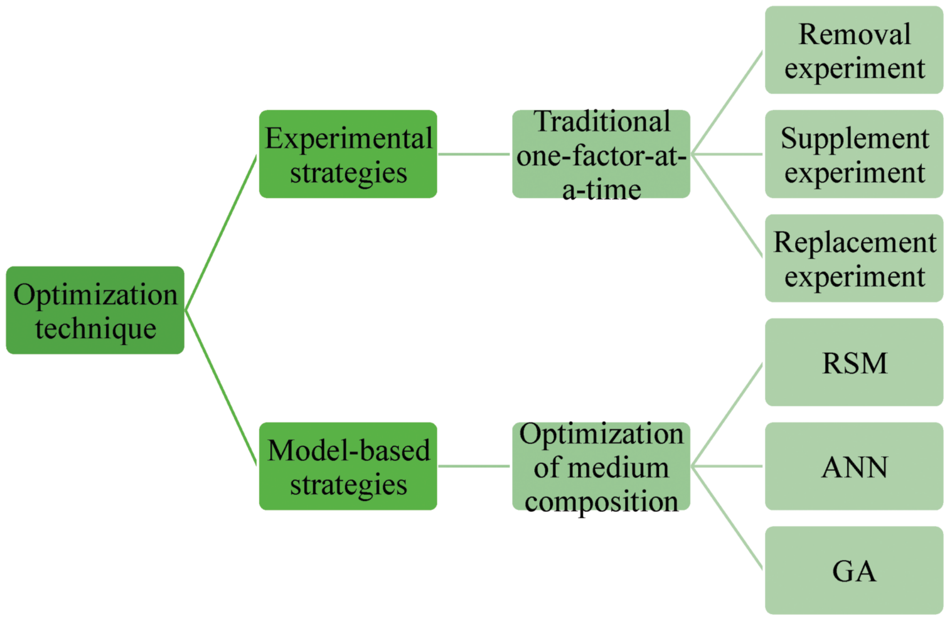

Fig. 2. The approaches used in media optimization [38].

affecting the growth of the microalgae. Maltsev et al. [35] stated that there are six essential trace metals responsible for various metabolic functions in algae which are iron, manganese, cobalt, zinc, copper, and nickel. The limited supply of these trace metals will suppress microalgae growth while the excess metal concentration in culture media may prevent growth, reduce antioxidants, disturb the photosynthesis process, and impair the cell membrane. Iron deficiency resulted in the downregulation of enzymes such as β-carbonic anhydrase and ribulose-1,5-bisphosphate carboxylase (RuBisCO) [36].

1.3. Media optimization techniques

Media optimization techniques have evolved from the traditional experimental techniques to a more advanced statistical approach in order to enhance microalgae biomass or metabolites production [37]. Fig. 2 lists the traditional and advanced techniques that are discussed in this paper [38].

1.4. Traditional techniques

The conventional method for optimizing media is referred to as the one-factor-at-a-time (OFAT) experiment. In this experiment, a single element or variable is manipulated at a time while the other components are held constant. According to Singh et al. [26], OFAT can be classified into three sub-groups removal experiment, supplementation experiment, and replacement experiment. These experiments differ in how they are being conducted but the purpose of these experiments is the same, which is to evaluate the effects of medium components on the production of metabolites or specific products of interest. In removal experiments, the medium components are taken out from the composition one by one. The effect of the removal on either the secondary metabolite production or the product of interest will be observed after a period of incubation. The supplement experiment is performed by introducing various types of carbon and nitrogen supplements into the culture media. As for the replacement experiment, it is continuous to the supplement experiment, whereby the supplement that results in the desired effects will be focused as the main source of carbon or nitrogen.

This traditional approach is preferred by many for medium composition as it is easy to practice. The simplicity of experiments enables the analysis of results without employing high-end statistical analysis or programs [39]. Although it is convenient to practice, these classical OFAT experiments have their own drawbacks. OFAT experiments would be time-consuming and burdensome for experiments with many components that need to be optimized. It is also difficult to estimate the interaction between multiple components of the media when these components are varied and independent of each other [40].

1.5. Advanced techniques

1.5.1. Response surface methodology (RSM)

Response surface methodology (RSM) is a mathematical approach that consists of statistical experimental design and multiple regression analysis. RSM employs factorial designs for the optimization of the process that leads to metabolites production. The general purpose of RSM is to determine the best formulation under a group of constrained equations [41, 42]. In addition, this advanced technique is also utilized for the optimization of the media formulation and fermentation process. RSM is not only a simple, efficient, and time-saving model, but this technique also has the ability to estimate the enhancement of processes linked to the production of metabolites [43]. Pereira et al. [44] added that the employment of RSM in the medium optimization process has removed the disadvantages faced by depending on the traditional single factor optimization process. There are three phases or basic steps that take place when RSM is being conducted, beginning with the screening of factors that exert significant response, conducting suitable experiments to determine the optimum operating condition and ending with optimization of quadratic regression model using canonical regression analysis method [45]. The study by Radzun et al. [6] employed an automated nutrient screening system that is able to determine the optimum nutrient conditions for a broad range of microalgae species. This study consists of an automated two-phase screening process whereby the optimization of nitrogen and phosphorus was done as the first step followed by the optimization of all other components. After the screening process, the highest growth rate was determined by an incomplete factorial *Box-Behnken* analysis. Each microalgae strain in this study was analysed for a total of 246 trials. Other study by [46] proved that RSM can optimize the medium composition for green microalgae, *Tetraselmis suecica*. In this study, the types of carbon and nitrogen source that heavily influence the growth of the microalgae were determined and optimizes using the RSM technique. The optimal medium for the cultivation of *T. suecica* is made up of 5.78 g/L of glucose, 9 g/L of peptone, 4.48 g/L of yeast extract, and 3.01 g/L of meat extract. It is also reported that the cell yield from this optimized medium was about three times greater than the yield obtained from the non-optimized medium. Skorupskaite et al. [47] also reported that the optimization of *Chlorella* sp. biomass using RSM was able to harvest 2.41 g/L biomass concentration in the media containing 0.114 g/L nitrogen and 2.70 g/L technical glycerol.

1.5.2. Artificial neural network (ANN)

An Artificial Neural Network (ANN) is a computational model, drawing inspiration from the structure and operation of biological neural networks. Frequently employed for forecasting multiple future steps across various tasks, neural networks can also serve as controllers themselves or adjust parameters for conventional controllers [48]. ANNs can be described as a mathematical understanding of the neurological functioning of the human brain. They emulate the brain's learning process by arithmetically modelling the network structure of interconnected nerve cells. In most cases, ANN represents an adaptive system that changes its structure according to external or internal information that flows through the network during the learning phase [49]. They are simply "trained" using a data set and then applied to predict new data points. Prior knowledge of equations is not essential for this training as the network and system remain as a black box to the user. The phrase "black box" is used to describe the lack of transparency and interpretability of the underlying mechanisms of ANNs. Although the network is capable of making precise forecasts, comprehending the precise process by which it reached a particular prediction is sometimes difficult [74].

ANN is well suited for medium design, as it generates a large amount of data that often contains the hidden pattern [50]. The architecture of the ANN consists of three layers of information known as neurons: a layer of "input" units is connected to a layer of "hidden" units, which is further connected to a layer of "output" units. The "learning conditions" of neural networks are classified into three groups as supervised (associative), where the neural network is trained by giving it input and output experimental data. Unsupervised (self-organization) in which the output unit is trained to respond against clusters of patterns within the input. Different from the supervised, there is no prior set of groups into which the patterns are to be classified; rather the system must develop its own representation of the input stimuli. Reinforcement where learning may be considered as an intermediate form of the above two classes of learning. The learning system categorized its action as good or bad based on the environmental response and accordingly adjusts its parameters. Generally, the parameter adjustment is continued until the attainment of an equilibrium state [51].

ANNs have been widely applied with great success for system designing, modelling, optimization, and control mainly due to their capacity to learn filter noisy signals and generalize information through a systematic training procedure [52]. ANN modelling has been applied to maximize lipid from *Chlorella vulgaris* [53], optimize *Euglena sp.* growth [54] and increase *Spirulina platensis* productivity [55]. Morowvat and Ghasemi [53] proved that amounts of lipid and biomass in the ANN-optimized culture condition were improved up to 2.59 and 1.71 folds, as compared to its initial values in the basic cultivation conditions. Extra experimental study in assessing the validity of the provided model has resulted in 98.48% and 98.33% similarity with the predicted values. Susanna et al. [55] stated that moderate culture density between 0.16 and 0.32 g/L of *Spirulina platensis* has resulted in about 14% more productivity than maintaining the cell density between 0.16 and 0.53 g/L or 48% more than by daily harvest above 0.16 g/L.

A neural network can perform on problems that have non-linear programs or relationships. Although an element of the neural network fails, it can continue working without any problem by their parallel nature [56]. Neural networks, either supervised or unsupervised have emerged as an important tool in various engineering applications, especially for modelling of non-linear systems [57]. On basis of supplied training data, the network learns the hidden relationship between the process input and output. The trained network then undergoes simulation to predict the output for unknown inputs. Reinforcement learning allows the ANN agents to automatically determine the ideal behaviour within a specific environment. Thus, ANN learns its behaviour based on the feedback from the environment. A reward feedback or reinforcement signal is required for the network to learn. If the problem is appropriately modelled, the reinforcement learning algorithms can converge to the global optimum [58].

1.5.3. Genetic algorithm (GA)

Genetic algorithm (GA) is a mathematical technique for solving a variety of optimization problems that is based on Charles Darwin's natural selection theory "survival of the fittest", where the fittest individuals are selected for reproduction to produce offspring of the next generation [59]. Firstly, the individuals are evaluated and ranked based on fitness value and this process is accomplished through repeated applications of three main genetic operators, which are selection, crossover, and mutation [60]. As illustrated in Fig. 3, the individuals (treatments or media compositions) with better fitness have a higher probability to being selected and will be combined through crossover operator to produce new generations. These new generations will be evolving towards an optimal solution, for instance, in tissue culture, the purpose of achieving optimal media composition is to increase biomass yield of cultured cells [61]. After several generations, the diversity of population may decline, as the fittest individuals possessed the highest probability of being selected causing the solutions to be similar across the generations. During this period, mutation mechanism is implied to induce diversity into the population and avoid stagnation [62].

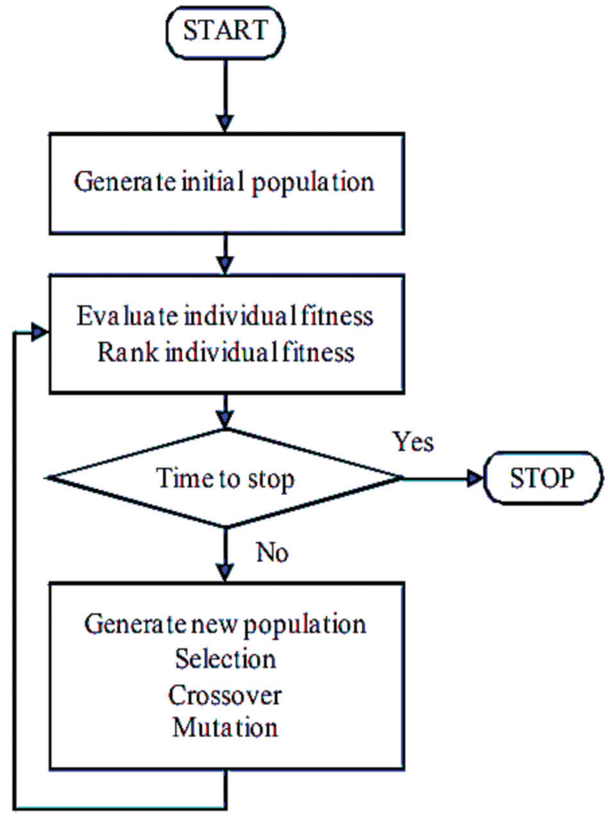

Fig. 3. Flowchart of genetic algorithm (GA) [61].

GA has also been utilized to optimize the growth of microalgae *Nannochloropsis gaditana* [63] and dinoflagellate microalgae *Karlodinium veneficum* [64]. Camacho-Rodríguez et al. [63] study was focusing on optimizing the medium formulation for *N. gaditana* growth with the prospect of maximizing both biomass and eicosapentaenoic acid (EPA) productivities while reducing the culture medium cost. The highest biomass yield was obtained by formulated medium (G8) by GA and the recorded reading for EPA production by G8 was 33 percent higher than the EPA production obtained using a commercial formulation of ALGAL [64]. The study also highlighted on optimization of culture conditions for the dinoflagellate microalga *K. veneficum*. These microalgae were grown in a bubble column photobioreactor using the GA-based experimental optimization with biomass productivity as a primary objective. The best growth condition for this dinoflagellate microalgae was found at gas flow rates of less than 0.26 L min^{-1}, culture heights of more than 1.25 meter and a nozzle diameter of 1.5 millimetre.

Other findings by Kumar et al. [65] has adopted five-level-five-factor central composite design (CCD)

Table 1. Microalgae culture with its respective optimization technique.

Species	Technique	References
Nannochloropsis gaditana	GA	[63]
Karlodinium veneficum	GA	[64]
Dunaliella tertiolecta	GA, RSM	[65]
Tetraselmis suecica	RSM	[46]
Chlorella sp.	RSM	[66]
Chlorella vulgaris	ANN	[53]
Spirulina platensis	ANN	[55]
Euglena sp.	ANN	[54]

assisted response surface methodology (RSM) to achieve optimal cultivation of *Dunaliella tertiolecta.* Results obtained from this technique were compared with simple non-dominated sorting GA as to select the best variables in maximizing both biomass and lipid production. A significant improvement in biomass productivity and lipid accumulation were obtained with simple GA over RSM oriented optimization technique. The increments were recorded by 4.4% and 1.8% for biomass productivity and lipid accumulation respectively. Hence, GA technique is advantageous as it provides a simplified method that suitable for optimization of a relatively large number of medium components for non-model organisms with unknown nutrient requirements. GA approach in medium optimization can also be implied for other species cell cultures and may be useful in the future prospect to increase productivity of both biomass and bioactive compounds of interest. Table 1 shows some studies that used different media optimization techniques for enhancement microalgae culture.

1.6. Problem and future prospects in media optimization

Advanced technology in medium optimization has proven evidence about its capability to enhance both biomass yield and desired secondary metabolites accumulation from microalgae and other diversity. The efficiency of this technique in selecting the best nutrient combination will greatly reduce both fermentation production cost and time [66]. However, every technique responsible for medium optimization is constrained by some limitations. For instance, GA technique does not always result in a global optimum all the time specifically when the overall so [67], where GA are heuristic algorithms that provide satisfactory results but may not always achieve the optimal solution. This attribute stems from their dependence on probabilistic mechanisms and the difficulty of achieving a balance between exploration and exploitation. There are many techniques that may be used to improve the performance of GAs. However, due to the fundamental structure of the algorithm, there will always be some level of uncertainty in finding the best possible solution [75].

In ANN, the quality of the input data for training decides the quality of the output data, thus, proper training is necessary in order to operate the system efficiently [68]. The purpose of culturing a specific microorganism is primarily to obtain its biomass and secondary metabolite production [69]. Hence, researchers have applied a variety of alternatives to accomplishing this target. Nonetheless, every microorganism has their own limitation at both genetic and enzymatic levels [70]. Altering the micronutrient and culture condition may increase the productivity of metabolites but it will reach a certain saturation point where further alteration will result in no positive impact [71]. Thus, genetic manipulation can be one of the alternatives to increase the productivity of the organism [72]. In fact, more study is needed to elucidate the complete pathways of stress perception and signal transduction in specific species of microalgae as to allow an efficient optimization of culture conditions [73]. Future research should swift the purpose of cultivating microalgae from anthropocentric to ecocentric. If major microalgae culture project is mainly focusing on carbon sequestration and shifting the utilization of fossil fuels to biofuels, the probability for climate changes and global warming to be reduced is promising.

2. Conclusion

The culture's media play crucial role in microalgae growth. Therefore, it's important to make deep vision about the different techniques that can improve the culture media. The different optimisation techniques for microalgae culture presented in this review and the comparison between the traditional and modern has been explained, where can this technique used to increase the yield of biomass as well as save time to get maximum quantities within short time. The limitations of OFAT experiments which are time-consuming, burdensome for some experiments with large number of components that need to be optimized, and the difficulty to estimate the interaction between multiple components of the media, resulting the researchers to opt out to a much more advanced techniques like RSM, ANN and GA that gives much better result in cultivating microalgae and easier to work with. Based on the review, we can conclude that there is a technology advancement in cultivating microalgae biomass based on the traditional OFAT technique and advanced techniques.

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