[Frontiers In Bioscience, Landmark, 23, 1487-1504, March 1, 2018]

Interactions of microalgae and other microorganisms for enhanced production of high-value compounds

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1. ABSTRACT

The cultivation of microalgae for the production of biomass and associated valuable compounds has gained increasing interest not only within the scientific community but also at the industrial level. Microalgae cells are capable of producing high-value compounds that are widely used in food, feed, pharmaceutical, medical, nutraceutical, cosmeceutical, and aquaculture industries. For example, lipids produced by algae can be converted to biodiesel, other fuels and bio-products. Hence, high oil content algal biomass has been regarded as a potential alternative feedstock to replace terrestrial crops for sustainable production of bio-products. It has been reported that the interaction of microalgae and other microorganisms greatly enhances the efficiency of microalgal biomass production and its chemical composition. Microalgae-bacteria interaction with an emphasis on the nature of symbiotic relationship in mutualisitc and parasitic consortia has been extensively studied. For instance, it is well documented that production of vitamins or growth promoting factors by bacteria enhances the growth of microalgae. Little attention has been paid to the consortia formed by microalgae and other microorganisms such as other microalgae strains, cyanobacteria, fungi, and yeasts. Hence, the aim of this review is to investigate the impact of the microalgae-other microorganism interactions on the production of high value compounds.

2. INTRODUCTION

Autotrophic microalgae are ubiquitous microscopic unicellular organisms that are capable of converting solar energy to chemical energy via the well-known process of photosynthesis. Algae can fix atmospheric carbon dioxide (CO_2) and use water to produce hydrocarbons as biomass that can be harnessed for commercial use. The bioactive compounds and metabolites that microalgae are capable of producing include but are not limited to proteins, lipids, carbohydrates, carotenoids, polysaccharides and vitamins (1-3). These compounds can be utilized in health, food, feed, pharmaceutical, cosmetic, and aquaculture industries (4, 5). In addition, microalgae can uptake various organic and inorganic contaminants, heavy metals and radioactive compounds from water making them ideal candidates for the wastewater remediation. The ability of these microorganisms to treat wastewater from a wide range of sources has been studied extensively (6-10). Sequestration of CO_2 emitted by industrial production plants, i.e. power plants, and production of feedstock (algal lipids and/or biomass) that can be converted to bio-products have gained great interest. The concerns about the sustainability of the current fossil fuel reservoirs to meet the future worldwide demand for oil and gas and the growing apprehension of the increasing CO_2 levels in the atmosphere leading to global warming and climate change are the main

driving forces behind the interest in renewable fuels (11-13). The economic viability of microalgae derived products depends on the properties of the selected strain selected for cultivation. Robustness, adaptation to a wide range of growth conditions and high content of the desired products (lipids, bioactive compounds) are some of the factors that need to be considered while selecting an algae strain for commercial cultivation (14). Many researchers have investigated how growth parameters and culture conditions can be controlled and manipulated to enhance cell growth and metabolite production. Culture pH, light intensity, temperature, carbon source, aeration rate, nutrient concentrations, and genetic manipulation are some of the parameters that have significant effect on cell growth kinetics and metabolite production (15, 16).

Co-cultivation of microalgae with other microorganisms (naturally present in their growth medium or added) is an approach that could promote cell division and production of a wide range of metabolites with high economic value. Algae-bacteria consortia, which were believed to be detrimental for algae growth, have been investigated extensively (17). Recent studies have established that in some cases, the presence of bacteria in algae cultures may actually play a positive role in algal cell growth (18, 19). Symbiosis between algae and other microorganisms (i.e. bacteria) was first reported during the early 1950s as a method to improve oxygen (O_2) supply to the oxidation ponds at wastewater treatment plants (20). The symbiotic relationship established between microalgae and other microorganisms includes all possible interactions known in nature: mutualism, commensalism and parasitism. The line that delineates symbiosis and adverse effects is very thin and mostly depends on environmental factors (17). There are studies highlighting how nutrient availability, N:P ratio and light intensity can cause a shift from mutualism to parasitism and vice versa via commensalism (21). Some of these interactions can be found amongst different species of organisms while others are strictly species specific (17). This review will focus on the beneficial interactions of microalgae with other microorganisms and the potential of these interactions for high value product development. A good understanding of the biotrophic interactions between algae and other organisms is crucial for exploring the commercial value of algae as a food source and other biotechnological applications.

3. MUTUALISM

Mutualism is defined as a biologic interaction in which two or more partners belonging to different species live in close proximity and benefit each other in terms of nutrient supply, protection, habitat or transport (17, 22, 23). During the interaction both organisms alter and influence their metabolism to meet their respective needs. Obligate mutualism refers to the conditions that neither organism involved in the mutualistic interaction can survive without the other. On the other hand, facultative mutualistic organisms can survive independently but additional benefits may be gained if they remain together (17). In this section, examples of mutualism between microalgae and other microorganisms are reviewed (Table 1).

3.1. Algae-bacteria

The most well-known and documented example of mutualism in an algae-bacteria consortium occurs when micro- and macronutrients needed for cell growth are exchanged (24, 25). A good example involves vitamin B12 and fixed carbon exchange between microalgae and bacteria. Like most plants, algae cannot produce vitamin B12 and, consequently, does not have an active mechanism to store it. Nevertheless, vitamin B12 is required for growth and algae cells are rich in enzymes that can metabolize vitamin B12 since it is required for their growth. Croft and coworkers (24) have shown that a source of vitamin B12 for microalgae is through a direct interaction with bacteria. This symbiotic interaction is classified as mutualism, with algae supplying photosynthetically fixed carbon to bacteria in return for vitamin B12. A survey of 326 algal species indicated that 171 of the algae examined were cobalminauxotrophic, meaning that they require exogenous vitamin B12 as a cofactor for vitamin B12-dependent methionine synthesis needed for cell growth (24). An example of facultative mutualism was reported regardless the microalga *Chlamidomonas reinhardtii* and an heterotrophic bacterium able to produce and deliver the vitamin B12 to the alga (25). *Chlamidomonas* can encode both vitamin B12-dependent and -independent methionine synthases gene and is able to activate or deactivate it based on the presence of bacteria in the growth environment. In the presence of vitamin B12 producing bacteria the algae cells repress the expression of vitamin B12-indipendent gene, allowing the opportunistic production of the enzyme required to assimilate the vitamin delivered by the bacteria. In exchange, *Chlamidomonas* provides fixed carbon even if it might not be taken up by bacteria. The reason for this type of relationship is not clear yet. In another study carried out by the same team, vitamin B12-dependent green alga, *Lobomonas rostrata,* was cultivated in a medium having the bacterium *Mesorhizobium* sp. It was found out that this bacterium was able to support the growth of the microalga in return for fixed carbon. These two organisms were able to form and maintain a stable cell equilibrium in a semi-continuous culture over many generations. However, addition of either vitamin B12 for the alga or a carbon source to the medium resulted in a perturbation of the equilibrium, revealing a mutualistic and facultative nature of the symbiosis (25).

Table 1. Overview of the most important symbiosis partners of microalgae in biotechnology

Microorganisms	Partners	Symbiosis	Bio-products - Potential application	References
Microalgae/ bacteria	*Botryococcus braunii/Rhizobium* sp.	Mutualism	Hydrocarbons for biofuels	51
	Lobomonas rostrata/Mesorhizobium loti	Mutualism	Model algae for interaction assays	25
	Chlamidomonas reinardtii/heterotrophic bacterium	Mutualism	Model algae for interaction assays	25
	Thalassiosira psudonana/*Reugeria pomeroyi*	Mutualism	Model algae for interaction assays	26
	Scrippsiella trochoidea/*Roseobacter-Marinobacter*	Mutualism	Model algae for interaction assays	28
	Chlorella vulgaris/Rhizobium-Flavobacterium-Hypomonas-Sphingomonas	Mutualism	Model algae for interaction assays	18
	Chlorella sp./*Azospirillum brasiliense*	Mutualism	Model algae for interaction assays	35, 36
	Amphinidium opercolatum/*Halomonas* sp.	Mutualism	Model algae for interaction assays	24
	Chlorella sorokiniana/*A. brasiliense*	Mutualism	Starch production	48
	C. reinardtii/M. loti	Commensalism	model algae for interaction assays	25
	Neochloris oleabundas /Azotobacter vinelandii	Commensalism	CO_2 fixation without fertilizer added	
	Scenedesmus sp. */ A. vinelandii*	Commensalism	CO_2 fixation without fertilizer added	96
Microalgae/ cyanobacteria	*Chlorella vulgaris / Leptolyngbya* sp.	Commensalism	Lipids for biodiesel	60
Microalgae/yeasts	Spirulina platensis / Rhodotorula glutinis	Mutualism	Lipids for biodiesel	82
	C. vulgaris/R. glutinis	Mutualism	Lipids for biodiesel	80
	Chlorella sp. KKU-S2/ *Thorulaspora globosa* YU5/2	Mutualism	Lipids for biodiesel	83
	Chlorella sp. KKU-S2/ *T. malee* YU5/2	Mutualism	Lipids for biodiesel	83
	Chlorella sp. KKU-S2/ *T. globosa* YU5/2	Commensalism	Lipids for biodiesel	103
	Chlorella sp. KKU-S2/ *T. malee* YU5/2	Commensalism	Lipids for biodiesel	103
	Isochrysis galbana / *Ambrosiozyma cicatricosa*	Mutualism	Aquaculture feed	79
	Haematococcus pluvialis/*Phaffia rodzyma*	Mutualism	Astaxanthin production	78
	C. vulgaris/Candida utilis	Mutualism	Model of micro-ecosystem	113
	Chlorella prototechoides/ Rhodosproridium turoloides	Commensalism	Lipids for biodiesel, carotenoids	103
Microalgae/fungi	lichens	Mutualism	Medicine, perfume, dying, brewery, food industry	70, 74
	Chorella vulgaris / *Aspergillus niger*	Commensalism	Biofilm formation to enhance microalgae harvest	82
	C. vulgaris/Mucor sp.	Commensalism	Biofilm formation to enhance microalgae harvest	82, 83
Microalgae/ microalgae	*Chorella prototechoides* heterotrophy / *C. prototechoides* autotroph	Commensalism	Lipids for biodiesel, lutein for food	102
	Chlorella prototechoides autotroph / *C. prototechoides* heterotroph	Commensalism	Lipids for biodiesel, lutein for food	102
	Chlorella sorokiniana / Auxenochlorella	Commensalism	Lipid for biodiesel, wastewater treatment	92

Some microalgae can produce complex chemicals such as sulphonates in which a sulphur atom is covalently linked to a carbon atom. This compound can serve as carbon and sulphur sources for many bacteria. A study on the mutualistic interaction between the diatom *Thalassiosira pseudonana* and the Roseobacterium *Reugeria pomeroyi* by Durham *et al*. (26) demonstrated that *R. pomeroyi* supplies vitamin B12 to the diatom which, in turn, excretes 2,3 dihydroxypropane-1-sulphonate used as a carbon source for the bacterium to use. Interestingly, *T. pseudonana* was able to modulate the activation of its

gene expression based on the presence or absence of the bacterium in the medium, suggesting a direct influence of *R. pomeroyi* on the diatom metabolism. Since *T. pseudonana* is an auxotrophic strain for vitamin B12, as expected, the algal growth was found to be slower without any source of vitamin B12 in the medium. However, when the alga was co-cultured with *R. pomeroyi* its growth was found to be similar to that in the absence of Roseobacterium but supplemented with vitamin B12. The latter finding suggests that the presence of vitamin B12 in the medium produced by *R. pomeroyi* might have a positive effect on the growth of *T. pseudonana*. The role that ecologically engineered bacteria consortium play in enhancing microalgal biomass and lipid productivities through carbon exchange has recently been reported (18). The green algae *Chlorella vulgaris* was co-cultured with four growth promoting bacterial strains (*Flavobacterium, Hypomonas, Rhizobium, Sphingomonas*) in an artificial microalgae-bacteria consortium (AMBC) for 24 days. The final biomass concentration when cultivated in the presence of these bacteria was 3.31 g L^{-1} compared to the control (1.3 g L^{-1}) revealing a growth enhancing effect of co-culturing on algae cells. Also, a mild increase in the lipid content from 22% to 28% and for the triacylglycerols (TGA) content (20%) was reported. Fatty acids methyl esters (FAME) analysis of the biomass obtained from algae-bacteria co-culture showed a significant shift towards oleic (C18:1) and palmitic (C16:0) acids from the FAME composition obtained during the axenic cultivation of *C. vulgaris*, which was dominated by hexadecatrienoic (C16:2) and linoleic (C18:2) acids. Studies on carbon exchange revealed that bacteria in the AMBC might utilize fixed organic carbon released by microalgae, and in return, supply inorganic and low molecular weight organic carbon influencing algal growth and metabolism. Undoubtedly, such exchanges have enormous significance in carbon cycle and can be exploited in microalgal biotechnology industry. Another role of bacterial communities is to provide microalgae with inorganic micronutrients that otherwise would not be available to them. An example of this type of mutualism has been reported for microalgae *Scrippsiella trochoidea* and proteobacteria *Roseobacter* and *Marinobacter*. This microalgae uses proteobacterial siderophore vibrioferrin, which can bind Fe (III), making it available for photosynthetic processes that fix inorganic carbon (27). A portion of photo synthetically fixed carbon is later released back to the medium as dissolved organic matter, and used for bacterial growth sustaining further production of siderophores (28).

Also, macronutrients such as nitrogen, phosphorous, potassium, sulphur and sodium, are essential chemical elements required to generate organic matter during the photosynthetic fixation of inorganic carbon. Low concentrations of these elements in the growth environment lead to a decrease in algal cell growth. Some of these elements are found in nature in a chemical form that cannot be absorbed by algae cells. Bacteria are capable of fixing atmospheric nitrogen, solubilizing phosphorus and iron and producing plant hormones (auxins, gibberelins, cytokinins), ethylene, nitrite and nitric oxide. Hence, these macronutrients can be metabolized by microalgae, especially in an oligotrophic environment. The exchange of macronutrients between microalgae and bacteria *Mesorhizobium*, *Azospirillum, Roseobacter, Rhizobium* and *Bacillus* has been documented in nature (29-32). A well-studied example of mutualistic relationship based on nutrients exchange involves *Chlorella* sp. and the rhizosphere-dwelling growth promoting bacterium *Azospirillum brasiliense*. The research group headed by de-Bashan and Bashan and their coworkers (33-47) studied how the cell growth enhancement and significant changes in physiological, morphological and biochemical pathways occur in the microalgae during a mutualisitc relationship. It has been shown that symbiosis takes place both in nature and in laboratory through experiments with co-immobilized cells on alginate beads. During a mutualistic interaction *Azospirillum* can increase accumulation of cell components (pigments, lipids and fatty acids), activity of the nitrogen assimilation enzymes, and total carbohydrate and starch contents in *Chlorella*. Over ten years of research (35, 36, 44, 45) revealed that the beneficial effect of *Azospirillum* is hormonal, mainly due to the production of indole-3-acetic acid (IAA).

The bacteria belonging to this genus show three different metabolic pathways to produce IAA in abundance, using amino acid tryptophan as a precursor. It has been proven that IAA can increase metabolism and change cell physiology and biochemistry in microalgae cells. Under autotrophic and heterotrophic aerobic growth conditions, *Chlorella* is able to accumulate large quantities of starch and this feature can be exploited for several industrial applications such as production of bioethanol, thickeners and sweeteners for food applications. Recently, the enhanced production of starch by *Chlorella sorokiniana* as a result of an increased activity of the starch synthesis regulatory enzyme ADP-glucose pyrophosphorylase (AGPase) was reported by Palacios *et al*. (48). *C. sorokiniana* was co-immobilized with both wild-type and mutant *A. brasiliense* on alginate beads. *Chlorella-Azospirillum* consortium was cultivated under dark, heterotrophic and aerobic growth conditions in nitrogen-replete and nitrogen-starved media. Under all incubation conditions examined, *C. sorokiniana* produced amino acid tryptophan, as well as thiamine, but not *A. brasilense*. A positive correlation between IAA-production by *A. brasilense* and starch accumulation in *C. sorokiniana* was found (48). More specifically, the highest AGPase activity, starch content and glucose uptake were found

when microalgae were co-immobilized with the wild type strain of *A. brasiliense*. The production of starch was strongly depressed when the microalgae were grown without bacteria, while supplementation with synthetic IAA enhanced the above parameters, but only transiently. Beside the *Chlorella-Azospirillum* consortium reported by many authors (33-47), there is another example of mutualistic relationship that occurs between *Chlorella vulgaris* and *Bacillus pumilis*, a plant growth-promoting bacterium. Hernandez and co-workers (31) demonstrated that *B. pumilis* enhanced *C. vulgaris* growth when co-cultured in a synthetic medium deprived of nitrogen, but not in a medium with nitrogen. *B. plumilis* was able to fix nitrogen in N-free synthetic medium and its growth resulted in accumulation of ammonium in the medium. In the presence of nitrogen in the medium there was no apparent enhancement of algae growth by *B. plumilis*. It was speculated that inability of this bacterium to produce IAA, probably due to the absence of tryptophan in the synthetic medium, was the reason for the lack of beneficial algae growth. However, when another source of nitrogen was not available, this species was capable of accumulating sufficient ammonium in the medium that could enhance microalgae growth and biomass production. Therefore, the most likely mechanism by which *B. pumilus* promotes the growth of *C. vulgaris* is nitrogen fixation under severe nitrogen starvation conditions.

The microalgae *Botryococcus braunii* is regarded as a potential source of renewable fuel due to its high lipid (up to 75%) and hydrocarbon contents (49, 50). This strain is characterized by a low growth rate, therefore, improvement of biomass production in large-scale cultures is of great interest and still under investigation. A recent report describes mass cultivation of *B. braunii* in association with planktonic bacteria (free in the water column) and with bacteria adhering to microalgae and forming a biofilm on cell surfaces (51). Eight different species of bacteria were isolated in the biofilms. *Pseudomonas* sp. and *Rhizobium* sp., were not detected at all in the water column but present in the bacterial biofilm associated with the microalgae. In particular, *Rhizobium* sp. served as a probiotic providing growth factors needed by *B. braunii*. Overall, all these studies demonstrate the crucial role bacteria play in mutualistic relationships with algae, especially in aquatic ecosystems, in cycling of carbon (18, 52, 53), nitrogen (54), sulphur (26, 55), and phosphorus cycling in aquatic ecosystems (56, 57).

Another practical application of algae-bacteria consortia that has been receiving considerable attention is the wastewater remediation. Integration of wastewater treatment systems with microalgae cultivation is promising for microalgae-based biofuel production (58). Mixed cultivation of algae and bacteria can be a useful tool for wastewater remediation and enhancing contaminant removal by microalgae cells. Zhao *et al*. (59) evaluated the role of a microalgae-bacteria consortium cultivated in landfill leachate for carbon fixation and lipid production. The leachate was spiked with a municipal wastewater at 0%, 5%, 10%, 15%, and 20% level. The test results demonstrated that the algae-bacteria consortium was effective in treating landfill leachate with up to 95% removal of ammonia nitrogen and phosphorous when the leachate was spiked with 10% wastewater. Under these conditions a maximum value of 24.07 mg L^{-1} d^{-1} for the lipid productivity in *C. vulgaris* cells was obtained.

3.2. Algae-cyanobacteria

Similar to bacteria, cyanobacteria can form symbiotic association with microalgae. There are studies indicating that microalgae-cyanobacteria consortium can result in higher microalgal growth rate, production of metabolites with high biotechnological application potential and improved nutrient and pollutants uptake (19, 60). So far, the exact metabolic mechanism involved in this interaction is unclear, but the benefits of this growth strategy could potentially be exploited in different biotechnology fields, such as biofuel production, especially if microalgae cells are known to possess a high lipid content. An example of mutualism was reported for the Louisiana native co-culture of a microalgae (*Chlorella vulgaris*) and a cyanobacterium (*Leptolyngbya* sp.) (61). In the latter study, dextrose and sodium acetate were provided at different C:N ratios (15:1 and 30:1) under heterotrophic (dark) and mixotrophic (400 µmol m^{-2} s^{-1}) regimes and algae growth rates were compared with those under autotrophic conditions. The carbon source and C:N ratio were found to impact both growth rate and biomass productivity. Mixotrophic cultures with sodium acetate (C:N 15:1) resulted in the highest mean biomass productivity (134 g m^{-3} d^{-1}) and neutral lipid productivity (24.07 g m^{-3} d^{-1}) compared to the autotrophic growth (66 g m^{-3} d^{-1} and 8.2 g m^{-3} d^{-1}, respectively). The Louisiana co-culture lipid content was also significantly higher for mixotrophic growth with sodium acetate addition (18.2%) compared to autotrophic growth (8.7.%). Thus, based on this experiment, mixotrophic growth with sodium acette (C:N 15:1) was found to be the preferred cultivation condition to improve biomass and lipid production by the Louisiana co-culture. The latter findings suggest that other symbiotic relationships between microalgae and cyanobacteria could be potentially exploited to improve cultivation efficiencies.

3.3. Algae-fungi and Algae-yeasts

The Kingdom of fungi includes fungi (or mushroom correct in the strictest sense of the word), molds and yeasts. The most common feature, that separates fungi from the other eukaryotic plants and animals, is the presence of chitin in their cell walls (62).

Probably the most well-known example of mutualistic relationship involving algae and fungi in nature is represented by lichens, which are widely found on rocks and trees as green crusts. Lichens are formed of fungi and photosynthetic algae or cyanobacteria (63). Fungi-algae association is named depending on the phyla of algae in the relationship. Lichens refer to the formations resulting from cyanobacteria or green algae and fungi association, while the name mycophycobioses is used when fungi are linked to Chromophyta or red algae (23). The resulting algae-fungi formation is a unique vegetative body called thallus which is completely different in size and shape from the two organisms, alga (called photobiont or phytobiont) and fungus (called mycobiont), associated with this new formation resembling a moss or small plant. It has been estimated that more than one-fifth of all existent fungal species are known to be lichenized (64). Within an algae-fungi association, fungi meet their requirement for organic carbon utilizing carbon produced by algal photosynthesis. The benefits of this association for microalgae/cyanobacteria are that fungal filaments provide moisture, nutrients, protection and anchor to algal cells. Few examples of artificial lichens constructed under controlled laboratory conditions are also available (65). One of the most interesting characteristic of lichens is their tolerance to extreme environments and sensitivity to pollution. The importance of lichens in terms of ecology, biodiversity and global environment well-being cannot be overstated and has been well investigated (66). Lichens can colonize at sites where nothing else can grow. Lichens are found on or inside rocks (epilithic or endolithic, respectively), bark of woody plants such as epiphytes, wood, barren soil, mosses, leaves of vascular plants and on other lichens. They can also live on manmade substrates such as concrete, glass, metals and plastic. Lichens contribute to the soil enrichment by trapping water, dust and silt. When lichens die they release organic matter improving soil fertility and allowing other plants to grow there. Thanks to their association with algae, lichens fix nitrogen in the air into nitrates. The conversion of atmospheric nitrogen has a great impact on the ecosystem, because when it rains, nitrates are leached from lichens for use by nearby plants. Sensitivity of lichens to air pollution is well known. Dying of lichens in a specific site is an early warning sign of pollution. For this reason, some scientists use them to assess the air pollution coming from industrial plants and urban areas. Since lichens can absorb from the air CO_2 and heavy metals, scientists can determine the level of air pollution in a given area by the extraction of toxic compounds from lichens (63, 67). From a metabolic point of view lichens are known for the production of important secondary metabolites that have found application in medicine, perfume, brewing, dying, and food industries (63, 68). It is estimated that 8000 tonnes of two species of lichens (*Usnea barbata* and *Evernia prunastri*) are harvested annually and used as an ingredient to enhance the persistence of a fragrance on the skin (69).

There are also examples of mutualistic associations involving three different kingdoms. One of the most studied associations is that of the lung lichen, *Lobaria pulmonaria*, formed by an algal photobiont (*Dictyochloropsis reticulata*) and an ascomycete fungus living together with a cyanobacterium (*Nostoc*). In this symbiosis cyanobacteria cells support algae by supplying vitamin B12, nutrients, growth hormones and conferring resistance to pathogens (70). Metabolites produced by *L. pulmonaria* find application in pharmaceutical industry as antiseptic (71), antioxidant (72), anti-inflammatory (73), aemostatic (74), and in cosmetic and brewery industry as well (75).

One of the main bottleneck associated with the cultivation of microalgae is the cost for their harvest, especially at large scale. Typically, microalgae cells are small and grow suspended in water. Harvesting these cells is difficult and contributes to 20–30% to the total cost of biomass production. While current approaches have limitations for efficient and cost-effective microalgal production, new economic, environmentally sustainable, and ecologically stable processes are needed. In this light, two new processes emphasizing the co-culture of *C. vulgaris* with fungi for easier algal biomass harvest have been reported in literature. The first study, examined co-culture of filamentous fungal spores from *Aspergillus niger* and mixotrophic green algae *C. vulguris* to stimulate pellets formation for easier cells harvest. It was found that pellets clearly formed within two days of culture. Microalgae cells, aggregated together with fungal cells, were immobilized in the pellets (76). This new process can be applied to microalgae cultures in both autotrophic and heterotrophic conditions to allow microalgae cell flocculation. The cell pellets, due to their large size, can be harvested by sieving of filtering which is much more effective than trying to harvest the cells suspended in the growth medium. This method has the potential to significantly decrease the processing cost for generating microalgal biofuel or other bio-products. This co-culture can be regarded as a form of commensalism since the benefit of the mixed culture can be exploited at commercial level. In a second study, Rajendran *et al*. (77) developed a novel biofilm platform technology using filamentous fungi and microalgae to form a lichen type “mycoalgae” biofilm on a supporting polymer matrix. The fungus *Mucor* sp. was used to produce a mycoalgae biofilm on a polymer-cotton composite matrix with 99% algae attachment efficiency. Co-culture *Mucor* sp. and *Chlorella* sp. produced higher amount of biomass than the axenic cultures of fungi and algae under the similar test conditions test. These results showed that algae can be grown on a bio-augmenting fungal surface, biofilm, with high attachment efficiency. This

technique would allow harvesting biomass readily as a biofilm for product extraction. This research is the first example that demonstrates development of an artificial lichen type "mycoalgae" biofilm with high solid matrix attachment efficiency in liquid cultures. This new finding can stimulate new applications for bioremediation and bio-products manufacturing.

The interest in microalgae co-cultivation with other microorganisms has also been extended to yeasts due to the known ability of these single-cell eukaryotic organisms to produce a wide range molecules that promote microalgal growth and productivity. It has been demonstrated that yeast-microalgae co-culturing improved yield of high value products, and resulted in high growth rate and biomass concentration (79-80). The benefits of mutualistic algae-yeast interaction include CO_2 production by yeast that is used by algae for photosynthesis and the utilization of O_2 produced by algae for heterotrophic metabolism of yeast. A well-studied symbiosis involves the oleaginous yeast *Rhodotorula glutinis* which is able to use a vast variety of organic materials for accumulating high amount of lipids in the cells (up to 72% of dry weight) (81). *R. glutinis* and the microalgae *Chlorella vulgaris* were co-cultured in industrial wastewater to enhance lipid production in both algae and yeast (80). When the yeast was cultivated in monoculture, it grew slower and the lipid production was lower than when cultivated with the alga. The growth of *Chlorella* in monoculture was also slower than that in co-culture. In the co-culture, *C. vulgaris* acted as an O_2 generator for the yeast to utilize while *R. glutinis* produced CO_2 needed for the alga growth resulting in an overall enhanced lipid production in both algae and yeast cells. Synergic use of CO_2 (released by the yeast and taken up by the alga) and O_2 (released by the alga and taken up by the yeast) averted the accumulation of higher concentration of both gases that can become deleterious for the two organisms. The same mechanism was responsible for the enhanced accumulation of total biomass and total lipid yield when *R. glutinis* was co-cultured with the microalga *Spirulina platensis* (82). Similar to the results obtained in the previous study, when the oleaginous yeasts *Torulaspora malee* Y30 and *T. globosa* YU5/2 were co-cultured with *Chlorella* sp. KKUS2, using sugarcane juice as source of organic carbon, the balanced O_2 and CO_2 uptake and release lead to 96% increase in total lipid yield (83). Cai *et al*. evaluated the mixed culture of the alga *Isochrysis galbana* and the yeast *Ambrosiozyma cicatricosa* for cell growth performance and biochemical composition (79). Significantly higher specific growth rates were achieved in the mixed culture as compared to the monocultures during the same growth phases. The final biomass concentration in the mixed culture was significantly higher than those obtained in monocultures. Overall, the latter study demonstrated improved growth performance and similar biochemical compositions in mixed culture as compared to monocultures.

The use of yeast in aquaculture as feed for rotifers is limited due to the unsaturated fatty acids (UFA) deficiency in yeast biomass. This aspect negatively impacts the nutritional value of yeast. Microalgae are excellent sources of food for rotifers, but their cultivation in sufficient quantities it is a time and space consuming task. Co-cultures of microalgae and yeast can be exploited to reduce costs of aquatic food production. James *et al*. (84) investigated the co-culture of microalgae *C. vulgaris* with the marine yeast *Candida* sp. and the beakers' yeast *Saccharomyces cerevisiae* for mass culture of rotifer *Brachionus plicatilis*. The culture density of marine yeast fed rotifers was significantly higher than that of rotifers fed bakers' yeast. Rotifer production was significantly higher and the doubling time was lower for marine yeast fed rotifers than for bakers' yeast fed ones. It appeared that the addition of marine yeast to the feed enhanced the birth rate and overall production of rotifers. It was found that nutritive by-products released by decomposition of yeast cells enhanced microalgae growth.

The microalgae *Haematococcus pluvialis* and the red yeast *Phaffia rhodozyma* are the two main known natural producers of natural astaxanthin. *H. pluvialis* is a ubiquitous unicellular green alga that utilizes CO_2 and produce O_2 via photosynthesis, and it is able to accumulate astaxanthin in response to environmental stress such as high irradiance and temperature, and nitrogen and phosphate starvation (3). *P. rhdozyma* is a red yeast that can use different organic materials as substrates to direct its metabolism towards the formation of astaxanthin during fermentation (85). These two astaxanthin over-producing microorganisms were co-cultured in the same medium in order to fix CO_2 generated by the microbial fermentation (78). During the mutualistic symbiosis, CO_2 produced by *P. rhodozyma* during fermentation was simultaneously fixed by *H. pluvialis* in the process of photosynthesis, while O_2 produced by microalgae during the photosynthesis stimulated astaxanthin formation in *P. rhodozyma*. Experimental results suggested that the balance between CO_2 production and uptake is directly correlated with the microorganisms inoculums/volume ratio. As a result, in the mixed cultures both concentrations of biomass and astaxanthin increased significantly compared to the pure culture of the two species. The latter study represents one of the first examples of improved yields of higher valued bio-products with *in situ* CO_2 fixation. It can be inferred from the studies discussed in this section that lipid productivity in the mixed cultures is generally higher than that of yeast in monoculture. The advantage of symbiosis in mixed culture is the balanced CO_2 production and uptake within the system which

is correlated with to the inoculums/volume ratio and specific growth rate that determine the performance of the culture (79, 80, 82, 83).

4. COMMENSALISM

Commensalism refers to a relationship in which only one of the associated partners obtains food or other benefits from the other without harming or benefiting the latter (17). Since the commensalism entails a relationship in which only one partner benefits, commensals could be considered as non-interacting partners. In this section, the most commonly studied examples of commensalism between microalgae and other microorganism are reviewed (Table 1). One of the first cases of commensalism between algae and bacteria was reported by Guerrini *et al*. (86). The latter study investigated how the presence of marine bacteria influenced the growth and polysaccharide production during the cultivation of the diatom *Cylindrotheca fusiformis* in phosphate limited batch cultures. It was found out that the diatom growth was inhibited under low inorganic phosphate concentrations (36.3 µM), corresponding to an increased N/P ratio, and higher amounts of polysaccharides were extruded to the medium, especially during the stationary growth phase of diatoms. The presence of bacteria reduced the diatom cell density only when phosphate was added to the medium at the concentration corresponding to 1/6 of the initial phosphate amount present in the growth medium. Under the same initial phosphate concentration, the presence of bacteria stimulated a higher amount of polysaccharide production, even when there was no improvement in the diatom cell growth. There has been a recent surge in research and development efforts to develop diatoms as a source of bioactive compounds to be used in the food and cosmetic industries (87). Therefore, diatoms-bacteria interactions are worthy of further investigation due to the potential applications of algal biomass as feedstock in aquaculture, human health and food supplements (88).

As reported in the previous section on mutualism, commensalism can also take place in the form of vitamin B12 and organic carbon exchange between two commensals. Green alga *Chlamydomonas reinhardtii* benefits from vitamin B12 produced by the heterotrophic bacterium *Mesorhizobium loti*, although bacterium does not use organic carbon released by the alga (25). Due to the long established role of *C. reinhardtii* in the field of strain development research for commercial application, the investigation of commensalism symbiosis appears to be a good approach to maximize biofuel and bio-product yields at commercial scale.

Another example of commensalism between algae and bacteria involves relationship between *Dunaliella* sp. and *Alteromona*s sp. as reported by Le Chevanton *et al*. (54, 89). Microalgae *Dunaliella* is considered as the best strain for the algal production of β-carotene and it is well exploited at commercial level (90). The role of bacterial contamination on algae growth during commercial algae cultivation in open ponds could be significant. Nitrogen and phosphorous are the main macronutrients required for microalgae growth. When *Dunaliella* sp. and the bacterial strain *Alteromonas* sp. SY007 were co-cultivated in batch cultures, green alga biomass increased significantly, probably due to higher nitrogen incorporation into algal cells (89). In the presence of bacteria the mineralization of organic nitrogen in microalgae cells is well documented (91). It is hypotized that the remineralization of organic nitrogen released by *Dunaliella* sp. occurred in the presence of *Alteromonas* sp. SY007. Bacterial remineralization of extracellular organic matter, originating from algal cells death or algal organic excretion, could provide ammonium and delay nitrogen starvation for *Dunaliella* sp. Co-cultivation of *Dunaliella-Alteromonas* in batch culture can be classified as mutualism. However, co-cultivation of the same microorganisms in chemostats limited by nitrogen produced contradictory results, revealing a competition for nitrogen during continuous production (54). Axenic and mixed continuous cultures were cultivated in chemostat for 85 days at two successive dilution rates (low dilution rate at 0.005 d^{-1} from day 1 to 35 and high dilution rate at 0.3 d^{-1} from day 35 to 79) to evaluate the impact of nitrogen limitation on algae-bacteria interactions. These dilution rates corresponded to conditions that allow 15% and 90% of the experimental maximal growth rate of *Dunaliella* sp., previously measured by Le Chevanton *et al*. (89). Addition of *Alteromonas* to the growth medium resulted in increased cell size of *Dunaliella* as well as in decreased carbon incorporation, which was exacerbated by high nitrogen limitation. Biochemical analyses for the different components in the co-culture (microalgae, bacteria, non-living particulate matter), suggested that bacteria take carbon-rich particulate matter released by microalgae up. Dissolved organic nitrogen released by microalgae was apparently not taken up by bacteria, which casts doubt on the remineralization of dissolved organic nitrogen by *Alteromons* sp. in chemostats. *Dunaliella* sp. utilized ammonium-nitrogen more efficiently at low nitrogen concentration in the medium. Overall, this study revealed competition between microalgae and bacteria for ammonium when it was supplied in continuous but limited amount. Competition for nitrogen increased with decreasing nitrogen concentration. In conclusion, Le Chevanton *et al*. (54) showed that microalgae and heterotrophic bacteria coexisted in a complex win-win relationship in stable cultures at equilibrium. The latter interaction was driven by the need of bacteria to utilize carbon released by microalgae. The relationship can shift from competitive to mutualistic depending on the

nitrogen availability in the medium. It was suggested that competitive or mutualistic relationships between microalgae and bacteria largely depend on the ecophysiological status of the two microorganisms. Due to the primary role bacteria play on the metabolism of *Dunaliella* cells in mixed cultures, a better understanding of biochemical pathways involved in this symbiotic relationship is essential to increase the productivity of β-carotene by microalgae.

Higgings *et al*. co-cultured green-algae *Auxenochlorella protothecoides* (formerly known as *Chlorella minutissima*) with bacterium *Escherichia coli* to investigate cofactor symbiosis for enhancing the effectiveness of algal biofuel production and wastewater treatment (92). Under mixotrophic conditions, a 2–6 fold increase in algal growth, doubling of neutral lipid content, and elevated nutrient removal rates were achieved compared to axenic growth (93, 94). *E. coli* provided *A. prototechoides* with thiamine derivatives and degradation products such as 4-amino-5-hydroxymethyl-2-methylpyrimidine (HMP) to algae. It was hypothesized that upon cell lysis, *E. coli* released thiamine and other metabolites (TMP, TPP) into the medium. These molecules further degrade into HMP and other products which are taken up by algae cells. These compounds promote microalgae growth, lipid accumulation, and glucose uptake by dramatically improving substrate utilization efficiency. *Auxenochlorella* cells were able to absorb thiamine precursors suggesting the presence of a HMP salvage pathway, as reported for other thiamine auxotrophs (95). Higgins *et al*. suggested that, both under autotrophic and mixotrophic conditions, a robust bacterial population is required to produce a sufficient amount of cofactors needed for improved algal growth. The latter study also reported that when *A. protothecoides* was cultivated in a medium where *Chlorella sorokiniana* was grown earlier, a 8.5 fold increase in *A. protothecoides* growth was achieved, suggesting that *C. sorokiniana* was capable of synthesizing thiamine (92). Commensalism can be exploited at commercial level as an inexpensive method to increase algal growth rates and lipid accumulation and for wastewater treatment.

Another example of microalgae-bacteria commensalism is that involving fixation of inorganic nitrogen under aerobic conditions by nitrogen-fixing bacteria. This process may supply inorganic nitrogen to sustain microalgae growth. Villa *et al*. (96) co-cultured microalgae *Neochloris oleoabundans* and *Scenedesmus* sp. with a free-living diazotroph *Azotobacter vinelandii*. This bacterium can fix nitrogen in the presence of reduced carbon sources such as sucrose or glycerol and is also known to produce siderophores (azotobactin) to scavenge different metals from the environment. Microalgae were co-cultivated with both a *A. vinelandi* wild-type and a mutant which was created by substituting a single gene involved in azotobactin production. Microalgae grown with the mutant bacteria exhibited limited growth. In the presence of the wild-type bacterium microalgal growth was enhanced. These results supported the hypotesis that azotobactin provides the nitrogen required to sustain growth in the media.

N. oleabundans and *Scenedesmus* sp. are two microalgae species largely exploited at commercial level for their high lipid content, accounting up to 50% (97) and 30% (98) of their dry biomass weight, respectively. *A. vinelandi* was also found to promote the growth of three microalgae strains, *Chlorella sorokiniana*, *Pseukirchneriella* sp., and *Scenedesmus obliquus* (99). In the latter study, Ortiz-Marquez *et al*. evaluated the possibility of nitrogen biofertilization by diazotrophic bacteria to produce microalgal biomass as feedstock for biofuel production. An *A. vinelandii* mutant strain that accumulates ammonium in the culture medium several times more than that produced by wild-type strain. Both wild-type bacterium and microalgae were separately cultivated in agar medium with and without the presence of the ammonium-excreting *A. vinelandi*. Neither the wild-type bacterium nor the three oleaginous eukaryotic microalgae were able to grow on solid medium with no ammonium unless they were streaked in proximity to the mutant bacterium strain. This provided evidence that the ammonium excreted by the mutant strain was bioavailable to promote the growth of nondiazotrophic microalgae. Moreover, this synthetic symbiosis was able to produce an oil-rich microalgal biomass using both carbon and nitrogen from the air. Since nitrogen is one of the macronutrients that greatly impact the economics of mass algae cultivation, the interaction between algae and bacteria could be exploited to reduce the costs of algal biomass production. Hence, artificial symbiosis should be considered an alternative strategy to lower nitrogen use for cultivation of microalgae.

Very few examples of commensalism between microalgae and yeast are known. Puangbut and Leesing reported the first commensalism example involving microalgae *Chlorella* sp. and the yeast *Thorulaspora malee* (100). The objective of the latter study was to investigate the microbial lipid production by photosynthetic microalgae and oleaginous yeast using CO_2 emissions from yeast fermentation. When CO_2 from air was used for *Chlorella* sp. KKU-S2 cultivation, maximum specific growth rate of 0.28 d^{-1}, and maximum lipid yields of 1.34 g L^{-1} and 0.97 g L^{-1} were obtained after 5 and 6 days of cultivation, respectively. On the other hands, when CO_2 in ambient air supplemented with CO_2 emissions from yeast fermentation, volumetric lipid and production cell mass production rates were 0.22 g L^{-1} d^{-1} and 1.15 g L^{-1} d^{-1}, respectively. Overall lipid yield of 8.3 g L^{-1} (1.34 g L^{-1} from *Chlorella* sp. KKU-S2 and 7.06 g L^{-1} from *T. maleeae* Y30) was obtained with integrated cultivation

while a low lipid yield of 0.97 g L^{-1} was found using non-integrated cultivation technique.

The first observation of commensalism among fungus, bacteria, and green algae was reported by Watanabe *et al*. (30) in a consortium where fungus and bacteria cells adhered directly to the algae cells. Four bacteria (*Ralstonia pickettii*, *Sphingomonas* sp. DD38, *Microbacterium trichotecenolyticum*, and *Micrococcus luteus*), a fungal strain (*Acremonium* sp.) and green algae *Chlorella sorokiniana* formed the consortium. Under photoautotrophic conditions, the growth of *C. sorokiniana* was not significantly affected by the addition of *Ralstonia pickettii* and *Sphingomonas* sp. DD38. However, in mixed cultures of *M. trichotecenolyticum* and *Acremonium* sp. growth rate of *C. sorokiniana* significantly increased after 7 days of cultivation. These results demonstrated commensalism among that *C. sorokiniana, Ralstonia pickettii* and *Sphingomonas* sp. DD38 meaning that bacteria received carbon needed for their heterotrophic growth from the microalgae without affecting algal cell growth. On the other hands, *M. trichotecenolyticum* and *Acremonium* sp. exhibited mutualism, receiving nutrients from the microalgae for enhancing growth. When the growth medium for the mixed co-culture *C. sorokiniana-Acremonium* sp. was supplemented with 1% of glucose fungal growth was enhanced while microalgae growth was significantly inhibited. These findings demonstrated the importance of nutritional balance of the medium for the formation of a microalgae-fungus consortium. Interaction between *C. sorokiniana* and *Acremonium* sp. was not symbiotic but competitive under eutrophic conditions. The interest in *C. sorokiniana* related consortia is due to its very high growth rate, high lipid content and tolerance to temperatures as high as 42°C. All the latter parameters are advantageous for algal biomass production for biofuels in large-scale production photobioreactors (101).

Symbiosis between microorganisms can also be created by growing heterotrophic microorganisms in a fermenter while culturing photoautotrophic microorganisms in a separate photobioreactor. In such a case, gas exchange can be controlled to maintain the conditions favoring both organisms or just one, but not damaging the other (102, 103). When a *Chlorella protothecoides* culture was aerated with the off-gas from the fermentation of yeast *Rhodosporidium toruloides*, biomass (0.015 g L^{-1} h^{-1}) and lipid productivity (2.2 mg L^{-1} h^{-1}) increased 87% and 83%, respectively, compared with the same culture aerated with air and no gas exchange between the reactors (103).

5. PARASITISM

Parasitism refers to a relationship in which only one of the two species involved in the interaction benefits at the expense of the other and exerts a negative and even if some cases leading to the death of the host organism. Usually, the parasite is smaller in size and needs the host to be survive. This relationship, unlike mutualisms and commensalism, is relatively well studied between bacteria and algae (22). Since the parasitism causes damage to algal symbiont, it is a negative relationship. Only a few examples of parasitism with a positive effect on microalgae are known. The first form of bacterial parasitism on algae (that can be also between bacteria and fungi) is the actual lysis of algae cells and the use of intracellular compounds as nutrients by bacteria. Normally, this takes place with the release of glucosidase, chitinases, cellulases and other enzymes by bacteria (104). However, there is a second form of bacterial parasitism that leads to a competition for existing nutrients and resulting in slower algae growth rates without killing the host (17). A third version of parasitism and competition is referred to as altruism, in which an organism (algae) acts for the exclusive benefit of another organism (bacteria). This act is either self-driven or driven by the beneficiary (105). A particular case of an initial mutualism shifting to a fatal parasitism in the end has been reported between Roseobacteria, *Phaeobacter inhibens* (55) and *Phaeobacter gallaeciensis* (106), and algae, the Coccolithophore *Emiliana huxleyi*. In the first case, a controlled laboratory experiment was carried out to demonstrate that *P. inhibens* lives by attaching itself on an algal host to obtain nutrients oozing out of the algal cells. Amazingly, not only the presence of this bacterium greatly enhanced *E. huxleyi* growth but also bacteria use a molecule released by algae to produce a small hormone-like molecule (belonging to the family of troponoids) that further enhances algal growth. This rare case of apparent or incident altruism results from being driven by the beneficiary itself. However, when this produced molecule reaches high concentration, it becomes detrimental for the algal cells, thereby killing them. The behavior of these bacteria suggests that initially they promote alga growth to boost their supply of nutrients and, when algal cells become older, they use algal host for a final harvest of nutrients before swimming away from it and attaching themselves on younger algal cells (55). It has been proposed that a similar mechanism could be the basis of algal bloom collapse in water environment where algae and bacteria live intimately connected. Negative bacterial parasitism has been proposed as an efficient tool to control microalgal and cyanobacterial bloom (107, 108). It has been reported that an algal senescence signal produced by *E. huxleyi* elicited the production of troponoids from the bacterial symbiont *P. gallaeciensis.* Chemical analysis of this hormone-like molecule clarified that it is formed of aromatic amino acids (106). These studies support a model where algal senescence converts a mutualistic bacterial symbiont into an opportunistic parasite of its hosts. *E. huxleyi* is of great interest in biotechnology for the synthesis of polyketides, a group

of secondary metabolites. These compounds have been shown to possess pharmacologically important properties, including antimicrobial, antifungal, antiparasitic, antitumor and agrochemical properties (106). Controlling mutualistic bacterial symbionts and preventing a shift to opportunistic parasitism could lead to a more stable and enhanced algal growth and polyketides production. This concept can also be extended to other forms of known parasitism between algae and bacteria. In general parasites have wide-ranging applications pharmaceutical, food, brewering, wine, textile, pulp and paper industries for producing cellulases, hemicellulases, pectinases, and chitinolytic enzymes, among others (110, 111). Finally, it is worth mentioning that algae are not only victims of parasitism but sometimes they can also be parasitic towards other algae species, as it has been reported for about 10% of known red algae (112).

6. CONCLUSIONS

Recently, interest in microalgae has increased tremendously due to the interest in biofuels as well as bio-products, including food supplements, supplements of animal feed, pigments, and cosmetics derived from algal biomass. Both economic and technical optimization of algal growth are the keys for the success of commercial cultivation of microalgae. Traditionally these goals have been achieved by optimizing the growth conditions these goals, such as pH, temperature, irradiance level, carbon source, aeration, and concentrations of specific nutrients for monocultures of the target organism. A new attractive trend is the use of mixed cultures. The interaction between microalgae and microorganisms involves different mechanisms, including the production of growth stimulatory or inhibitory compounds, availability of macro- and micronutrients, gas exchange mechanisms, cross-signaling, and environmental protection. In order to get the most benefits out of the interactions among microorganisms, it is important to select the best consortia and thoroughly investigate the different aspects involved. Different combinations of microalgae and their symbionts could exhibit different activities. Recent developments in the understanding of these interactions have driven the attention to specific biotechnological applications in the fields of pharmacy and energy generation. Emerging applications of microbial symbiosis are receiving attention also in other fields of environmental remediations (nutrient removal, wastewater treatment, bioremediation, bloom control) and biorefineries (cultivation systems, microalgal biomass harvesting, sustainable aquaculture systems). In summary, as described in this chapter, a variety of interactions between algae and other microorganisms can range from beneficial to detrimental for algal growth. Controlling some of these interactions may serve as a very useful tool to stimulate algal growth, produce high-value bio-products and biofuels, and even for easier harvesting of algal biomass at a low cost.

7. ACKNOWLEDGMENT

We would to thank the anonymous reviewers for their critical comments that greatly improves the manuscript.

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Key Words: Microalgae-Bacteria Interaction, Microalgae-Cyanobacteria Interaction, Microalgae-Fungi Interaction, Microalgae-Yeasts Interaction, High-Value Compounds, Review

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