Bioproducts from the Microalgae-Bacteria Interaction

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In nature, interactions between bacteria and microalgae play an indispensable role in maintaining the integrity of the aquatic ecosystem through networks of interactions such as competition and mutualism. In fact, in the wild, the growth of algae is consistently associated with the growth of other microorganisms, especially bacteria. Axenic culture systems and sterilization of culture media in large-scale production of microalga are not economically feasible. Therefore, the characterization of associated heterotrophs in algae culture systems is an important step since bacteria may use compounds excreted by algae, increasing the availability of trace elements and solubility of nutrients, making them more bioavailable for microalgae. In addition, they can help to reduce the saturation of dissolved O_2. In microalgae cultivation, it is well known that dissolved O_2 can attain inhibitory levels.

Keywords: microalgae ; bacteria ; bioproducts

1. Microalgae-Bacteria Interaction

1.1. Microbial Interactions through Quorum Sensing

Quorum sensing (QS) is a phenomenon of communication between microorganisms through the release and detection of small signaling molecules that accumulate in their surroundings as a function of cell-density [1]. Cell-to-cell communication system is used by bacteria in order to assimilate environmental cues and to monitor microbial population density, ultimately affecting gene expression and microbial group behavior responses [2].

There are several QS communication systems, and the most well-known mechanisms are described in bacteria. QS is usually based on the production, secretion and detection of low molecular weight signaling biomolecules commonly referred to as autoinducers (AI). Quorum sensing plays essential roles in regulating gene expression and modulating complex processes such as virulence, symbiosis, production of bacteriocins, sporulation, conjugation, bioluminescence, motility, and biofilm formation, among others [3].

Signaling molecules vary according to each bacterial group. In Proteobacteria, AI molecules belong to the group of acylated homoserine lactones (AHLs), initially known as autoinducer-1 (AI-1). AHL molecules vary in size and substitutions in the carbon chain, creating specificity in the communication within the species level. However, it is known that AHL molecules from one species can be detected by homologous signaling receptors present across different bacterial species [4]. Autoinducer peptides (AIP) are used by Gram-positives as QS mediators, presenting significant structural variations among different organisms. A molecule known as autoinducer 2 (AI-2), derived from 4,5-Dihydroxy-2,3-pentanedione (DPD), is produced universally and has been associated with interspecific bacterial communication. Additionally, many other small signaling molecules belonging to different chemical classes, mediate cell-to-cell communication within different microbial groups, including bacteria, yeast, and fungi. Quorum sensing signaling is prevalent in the microbial world with a diverse signaling repertoire and a range of cell-density population responses [3].

Microbial communication through signaling molecules has been intensively investigated, and two-way interactions between bacteria and other organisms have been reported across different fields of study. For instance, Kim and collaborators (2020) described a type of interkingdom communication between *Escherichia coli* and humans through the host-derived adrenergic signals norepinephrine and epinephrine that activate bacterial responses, meanwhile, the bacterial signaling molecules collectively known as autoinducer 3 (AI-3) have been shown to exert immunological effects in human tissues [5]. Studies concerning interactions of microorganisms in the rhizosphere (the zone surrounding the roots of plants) have revealed that plant species may respond to bacterial autoinducers by secreting phenolic compounds that act as inhibiting contaminants, in addition to interfering in their signaling pathways [6]. Similarly, phytoplankton-bacteria interactions have also been investigated, and studies have shown that besides the exchange of nutrients, chemical signals are also important players in the phycosphere, which is the region close to the microalgal cell where bacteria may thrive [7][8]. Some microalgae can synthesize quorum sensing mimics that can affect bacterial communication and behavior [9].

Quorum sensing molecules (QSMs) extracted from wastewater microbial consortiums increased the production of lipid content by the microalgae *Chlorophyta* sp. by 86%, but algal biomass was slightly reduced [10]. The scholars hypothesized that QSMs triggered an environmental pressure on the microalgae, having a positive effect on microalgae biofuel production. In another study, when adding bacterial QSMs extracted from anaerobic bacterial sludge of a microbial fuel cell to a photobioreactor containing the microalgae *Chlorella sorokiniana*, there was an improvement in algae biomass productivity by 2.25 times, as well as significant increases in the lipid and protein content, as well as in the harvest efficiency [11]. The supposedly QSMs present in the extract included several N-acyl homoserine lactones, bacterial siderophores, oligopeptides, and vitamin B12. Thus, it seems that besides true QS signaling molecules represented by the AHLs detected in the extracts, cross-feeding may also be involved in this bacterial-algal interaction.

Microalgae can produce amino acids such as tryptophan, a precursor for auxin biosynthesis in bacteria, promoting mutualistic interactions [12][13].

1.2. Oxygen and Carbon Dioxide Exchanges

The co-cultures of bacterium and algae may be effective in detoxifying inorganic and organic pollutants and removing nutrients from wastewater if compared to the activity of these microorganisms individually. Photosynthesis by cyanobacteria and eukaryotic algae provides oxygen, an essential factor for heterotrophic bacteria that degrade pollutants. Sequentially, the bacteria help the photoautotrophic growth of the collaborators, furnishing carbon dioxide and stimulating factors [14] and decreasing the oxygen concentration in the culture medium [15].

This relationship is interesting because microalgae can be part of a circular economy, since it allows the use of CO_2 coming from industrial processes, like distilleries (CO_2 from alcoholic fermentation and sugarcane bagasse burning), cement industry (CO_2 from burning of energy source and $CaCO_3$ decomposition), energy industry (CO_2 from burning of energy source) as well as from aerobic and anaerobic treatment of wastewaters, as a carbon source to produce microalgae biomass. Simultaneously, the oxygen produced by phytoplankton may support the necessity of aerobic processes in these industries. The oxygen produced by microalgae could be used in an integrated process involving aerobic depuration of wastewaters, with a production of bacteria which could be used in different applications, like agricultural inoculants, among others, depending on the species of microorganism cultivated [16].

2. Effects of Interactions

2.1. Inhibitory Effect by Metabolites on Algae and Bacteria

Although several species of bacteria have a beneficial effect on algae growth, some bacterial species may also inhibit microalgae by producing extracellular algaecide compounds [17]. This inhibitory effect helps to control the proliferation of harmful algae in bodies of water [15].

Some bacteria can induce the lysis of microalgal cells. For instance, the *Kordia algicida* secretes an algaecide protease that hinders the growth of several diatomaceous marine species [18]. Bacteria can compete with microalgae for limiting nutrients, such as nitrogen and phosphorus, when they grow together in an organic carbon source. Due to the higher growth rate of bacteria than microalgae in this condition, their propagation would consume more nutrients, limiting the growth of eukaryotic photosynthetic microorganisms due to a lack of nutrients [19]. For instance, when *Acinetobacter* sp. was inoculated in the exponential phase, a substantial drop in the growth of *Botryococcus braunii* was observed. This bacterium, which presented a negative interaction with *B. braunii*, produces AHL signaling molecules involved in bacterial quorum sensing, which were found in the non-axenic culture of microalgae [20].

From these considerations, it is important to evaluate the environmental conditions of the processes where the presence of undesirable bacteria is minimized and preferentially suppressed to maximize the microalgal growth. Otherwise, favoring beneficial bacteria within an appropriate threshold is also a determinant for optimizing microalgae growth.

2.2. Bacteria That Promote the Growth of Microalgae

Normally, non-pathogenic bacteria from several species have been found in microalgae cultivations with beneficial effects on their growth.

It has been shown that bacteria may modify the growth of phytoplankton, accumulating biomass and increasing cell productivity, which is of particular interest for industrial production. The bacteria of the genera *Alteromonas* and *Muricauda* allowed the most significant accumulation of *Dunaliella* biomass due to the increase in the availability of nitrogen for microalgae. However, more research is needed to understand the mechanisms behind these interactions [21].

In the cultivation of *Chlorella prototecoides* in synthetic wastewater media in co-culture with *Brevundimonas diminuta* with light intensities of 75 and 130 μmol photons $m^{-2}s^{-1}$, the μ values in non-axenic conditions were at least five times higher than in cultivations without co-culture. Thus, under these conditions, the addition of *Brevundimonas diminuta* was able to provide higher growth rates of *C. protothecoides* with more efficient nutrient removal [22].

A substantial promotion in the growth of phytoplankton has been described because the bacterium produces indole-3-acetic acid (IAA) [15]. The *Achromobacter* sp. produces IAA, which promotes the growth of *Haematococcus pluvialis*, with an increase in chlorophyll and cell concentrations [23]. In fact, the bacterial population in low concentrations can improve the microalgae metabolism by releasing factors that promote growth or reduce the concentration of O_2 in the medium, preventing this gas from reaching an inhibitory concentration. As a consequence of higher microalgae growth in co-culture with bacteria, there is a higher removal of nutrients from the cultivation medium, which is particularly important in the tertiary treatment of wastewater since nitrogen and phosphorus are constituents of the microalgae biomass. In a study using synthetic wastewater with a semi-continuous process, the immobilized consortium of *Chlorella vulgaris* and *Azospirillum brasilense* led to an increase in the uptake of ammonium by culture [24]. Thiamine and tryptophan released by *C. sorokiniana* are signaling molecules that may be used by *A. brasilense* to synthesize and secrete another signaling molecule, indole-3-acetic acid, which promotes microalgae growth. The occurrence of signaling compounds, such as thiamine and tryptophan in the exudates of *Chlorella sorokiniana*, supports the mutualistic interaction of this photosynthetic microorganism with *A. brasilense* [25].

2.3. Supply of Nutrients

Microalgae may increase bacterial activity by secreting extracellular molecules such as lipids, proteins, and nucleic acids that serve as nutrients for bacterial growth. In this sense, dead microalgae cells can also provide nutrients for the growth of bacterial cells [15].

Croft et al. (2005) showed that vitamin B12 is an important molecule in algae metabolism, the main cofactor for methionine synthase, which depends on vitamin B12. They also observed that cobalamin auxotrophy had appeared numerous times throughout evolution processes, probably related to the presence or absence of vitamin B12-dependent enzymes. An example of this symbiosis is the case of bacteria of the genus *Halomonas*, that supply cobalamin for the microalgae *Amphidinium operculatum* [26]. *Pseudomonas* sp., on the other hand, produced a glycoprotein that performed as a growth factor for *Asterionella glacialis* [27]. In another research, the growth of *Chlorella* sp was shown to be improved due to the release of riboflavin by *E. coli* [28].

2.4. Modification of the Composition of Microalgae in Co-Culture

The association of *Rhizobium sp*. KB10 with *B. braunii* increased algae growth by nine times and improved the oleate content, used to produce biodiesel [29]. Inoculation of the bacterial strain *Rhizobium* 10II in the cultivation of *Ankistrodesmus* sp. strain SP2-15 increased by 30% the chlorophyll content in the microalgae biomass, and the lipid productivity was up to 112 $g.m^{-2}d^{-1}$ on the sixth day of cultivation [30]. The co-cultivation of *Chlamydomonas reinhardtii* with *Bradyrhizobium japonicum* improved the growth of the microalgae by 3.9 times, reaching lipid contents 26% higher and increasing Fe-hydrogenase activity and H_2 production [31].

2.5. Flocculant Activity by Bacteria

The activity of bio-flocculant depends on the growth phase of the bacteria, being enzymatic activities related to the formation of bio-flocculants observed during the stationary growth phase. Although the production of bacterial bio-flocculant is beneficial for improving the formation of large flakes of microalgae and bacteria, the additional cost related to the carbon source required for the growth of these bacteria still remains a challenge [32], which evidence that organic by-products could be used to produce such bacteria, thus diminishing the cost of the process [33].

Exopolysaccharides and pyruvic and uronic acids are important for cell adhesion. In addition, factors such as the sources of nitrogen and carbon and the ratio between these two elements influence the production of bio-flocculants. The bio-flocculant produced by the *Paenibacillus polymyxa* exhibited high efficiency for the flocculation of *C. vulgaris* and *Scenedesmus* sp. [32].

Bacteria such as *Flavobacterium, Terrimonas,* and *Sphingobacterium* and their extracellular polymeric substances may help to increase the flocculating activity of algae such as *C. vulgaris*, resulting in sedimentable flakes [34].

2.6. Microalgae Co-Immobilization by Bacteria

Microalgae are part of the organisms attached to filters in wastewater treatment plants, where the wastewater percolates during the treatment process. In these filters, enzymes or whole cells may be immobilized, including microalgae cells, which serve to obtain more biomass and for removing macronutrients since the production of oxygen by the algae improves the aerobic degradation of these substances. Moreover, the consumption of CO_2 and the production of exopolysaccharides by microalgae can increase the bacterial growth rate, as CO_2 and the production of growth-promoting substances by bacteria can improve microalgae growth. However, bacteria and microalgae may produce substances that hinder the growth of the other co-immobilized organism. Besides, the increase in pH and oxygen concentration in the medium, due to photosynthetic activity, can reduce bacterial growth in the system with the co-immobilization of bacteria and algae [35].

3. Microalgae as Potential Raw Material for Bioproducts

Considering the information on the interaction of microalgae and bacteria, besides the high potential of using microalgal biomass as a source of carbohydrates or fatty acids for energy production, food, cosmetic, and pharmaceutical industries, one could develop products in which microalgae, or their components could be used to confer special properties to them (**Figure 1**).

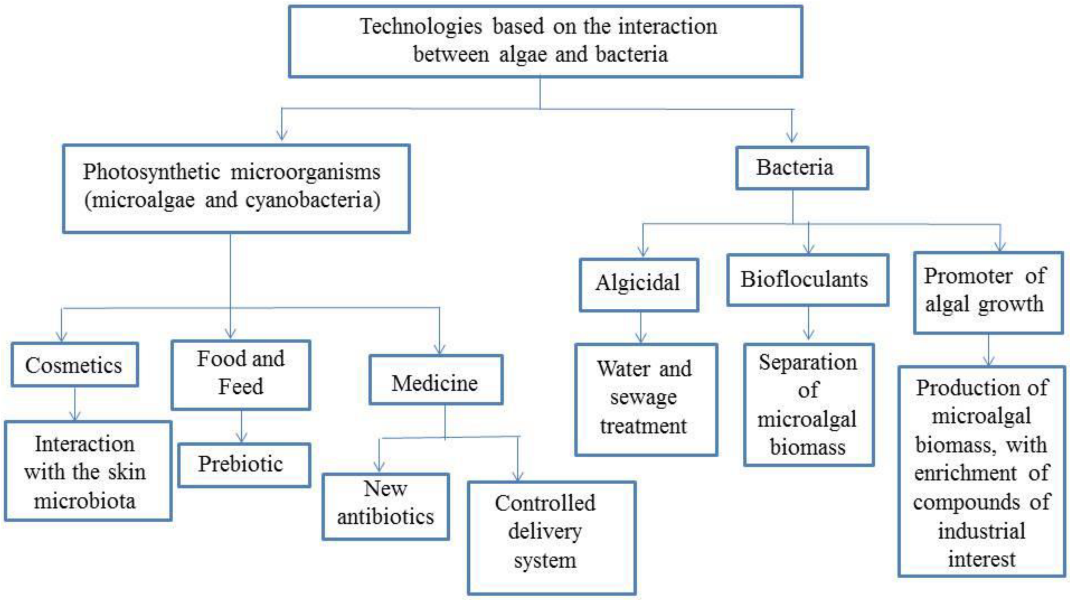

Figure 1. Diagram about how the study of microalgae-bacteria interactions can result in bioproducts.

3.1. Extracts for Microbial Growth

Considering that bacteria and microalgae are rich in valuable organic compounds, and considering the related well-succeeded co-culture between these organisms, their extract could improve their growth. In this approach, Carvalho et al. (2021) developed a bacterial extract to promote the cultivation of microalgae, providing important nutrients for their growth. This extract allows greater growth in axenic and non-axenic strains of *Dunaliella salina* and non-axenic strains of *Chlorella vulgaris* [33].

3.2. Bioproducts

3.2.1. Microalgae for Developing Prebiotic Products

It is possible to develop foods based on the interactions between microalgae and bacteria, such as those that are not digestible, to beneficially affect the host by stimulating proliferation or activity of populations of beneficial bacteria in the intestine. There was a positive effect of *Arthrospira* on bacteria in the intestine, increasing the growth rate of *Lactobacillus*, thus supporting the function of the digestive tract and being used as a prebiotic [36].

3.2.2. Animal Diet

Cerezuela et al. (2012) carried out in vivo studies of experimental diets with *Tetraselmis chuii* (T), *Phaeodactylum tricornutum* (P) and *Bacillus subtilis* (B), simple or combined, showing morphological changes and significant signs of intestinal damage. The diets applied to fish led to a decrease in the bacterial diversity in the intestinal microbiota. Only diets containing *Bacillus subtilis* resulted in a significant reduction in the height of the microvilli. Moreover, fish fed with experimental diets showed different signs of edema and inflammation, and the scholars concluded that such effects could compromise fish body homeostasis [37]. These findings highlight the necessity of evaluating, case by case, the benefits and risks of including any microorganism in animal and human diets.

3.3. Cosmetics

The growing need for obtaining safe products by bioprocesses has made microalgae a sustainable source for new products. Currently, microbial sources are the best available on the market to replace implemented entities [38].

Several secondary metabolites produced by algae are known to benefit the skin. Algae cells are naturally exposed to oxidative stress, which makes them develop efficient protection systems against radicals and reactive oxygen species, producing biomolecules that may act in cosmetics against the damaging effects of UV radiation, promoting the same action of inorganic filters and organic agents currently commercialized. There is an increase in the production of carotenoids and chlorophyll by *Chlorella vulgaris, Arthrospira,* and *Nostoc* when growing in the presence of radiation. These biomolecules can help to protect against the oxidative process of oil in formulations, especially in emulsions with a large quantity of oily phase, as they have antioxidant activities [39]. Such properties of microalgae can be used for the development of sunscreens, being associated with the formulation or the skin.

Due to the fact that biofilm is related to infections, particularly due to the low susceptibility of microorganisms to traditional antimicrobial agents, microalgae may be explored seeking an innovation to solve this problem. The antibiofilm activity of *Arthrospira platensis* extracts, which are abundant in free fatty acids, was verified. The nanocarriers based on copper alginate loaded with extract, were able to inhibit the formation of biofilms from one and two species of *Cutibacterium acnes*, but did not inhibit preformed biofilms. Nanovectorized extracts reduced the growth of *Candida albicans* biofilms, as well as preformed biofilms [40].

3.4. Pharmaceuticals

Currently, resistant strains are gaining attention in the treatment of bacterial infections [41]. Therefore, a new strategy is oriented, using a chemically modified *Chlamydomonas reinhardtii* as a drug delivery system. These modified microalgae masked vancomycin thanks to an insertion of a photocleavable binder on the cell surface, and the antibiotic was released in a controlled way, under exposure to ultraviolet light (340–400 nm). This technique was tested on *Bacillus subtilis*, successfully resulting in growth inhibition of this bacterium [42]. Microalgae, as earlier commented, can produce compounds that lead to the inhibition of bacteria, which can be extended to other microorganisms and even viruses [43].

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