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Review

Insights into Co-Cultivation of Photosynthetic Microorganisms for Novel Molecule Discovery and Enhanced Production of Specialized Metabolites

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Abstract: Meso- and extremophilic microalgae and cyanobacteria have a wide range of biotechnological applications. However, the industrial demand for bioactive molecules and the redundancy of these molecules has resulted in a need for new methodologies for enhanced production and the discovery of specialized metabolites. Co-cultivation has been established as a promising approach to addressing these challenges. In this context, this work aimed to describe the state of the art of the co-cultivation method involving meso- and extremophilic photosynthetic microorganisms, as well as discuss the advantages, challenges, and limitations of this approach. Co-culture is defined as an ecology-driven method in which various symbiotic interactions involving cyanobacteria and microalgae can be used to explore new compounds and enhanced production. Promising results regarding new bioactive metabolite expression and increased production through co-cultivation-based research support that idea. Also, the metabolic diversity and evolutionary adaptations of photosynthetic microorganisms to thrive in extreme environments could improve the efficiency of co-cultivation by allowing the implementation of these microorganisms. However, the complexity of ecological interactions and lack of standardization for co-cultivation protocols are obstacles to its success and scientific validation. Further research in symbiotic interplays using -omics and genetic engineering, and predictive experimental designs for co-cultures are needed to overcome these limitations.

Keywords: bioactive metabolites; ecological interactions; co-culture; new bioprospecting; algae

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1. Introduction

Mesophilic and extremophilic microalgae, including both eukaryotic and cyanobacteria, are valuable microorganisms to produce high-value compounds, including vitamins, pigments, lipids, bioactive peptides, and alternative energy sources, among others [1–3]. This wide range of industrial applications has made them a significant object of study. However, there are limitations to implementing these microorganisms in large-scale production systems. Maintaining axenic cultures is expensive and labor-intensive due to high risk of contamination, and meeting the insatiable demand for their products is infeasible with their natural abilities alone [4].

To overcome these issues, new culture methodologies have emerged. One promising approach is co-culturing, a cultivation system incubating two or more species in a solid or liquid medium to promote interactions between microorganisms [5]. This aligns with a new perspective: considering exogenous microorganisms as a resource capable of providing

added value [6]. Additionally, the growth conditions of extremophilic species help to prevent contamination by other undesirable microbes [3].

In this sense, co-cultivation has been shown to improve the production of metabolites and play relevant roles in industry and other research areas [4]. For example, the co-culture of yeast and microalgae has increased biomass and total lipid content, and benefited the natural cell lysis for down-stream processing [7]. Additionally, discovering new natural products has shown improvements with co-cultivation techniques, allowing access to new bioactivate metabolites [8,9] and helping overcome the metabolic redundancy of molecules with antimicrobial properties [10].

As photosynthetic microorganisms are proposed as a new scope for bioprospecting [11,12], this review summarizes the findings from research on the co-cultivation of photosynthetic microorganisms to: (i) highlight the advantages of the co-cultivation technique for microorganism bioproduction, (ii) expose the potential of using co-cultures of mesophilic and extremophilic photosynthetic microorganisms for the discovery and enhanced production of bioactive compounds, and (iii) explore the challenges and limitations of this methodology.

2. Ecological Interactions of Photosynthetic Microorganisms Related with the Production of Specialized Metabolism

Microorganisms, such as cyanobacteria, were the first photosynthetic oxygen-producing organisms to evolve, with evidence tracking back to ~3.0 billion years ago [13]. This long history on the planet has conferred upon them an ecological adaptability to various environments, allowing colonization of a wide range of niches on Earth and, hence, the development of a diverse secondary metabolism for environmental adaptations [14]. This, in turn, has resulted in a multitude of ecological interactions where photosynthetic microorganisms play a crucial role. Some examples of these interactions are discussed in this review and summarized in Figure 1.

Cyanobacteria can form associations with heterotrophic bacteria and other eukaryotic organisms. Nitrogen-fixing cyanobacteria provide bioavailable nitrogenic compounds to diatoms and marine environments, influencing their growth and impacting the biogeochemical nitrogen and carbon cycle [15]. A clearer example of symbiosis is found in cyanosponges, which involves a close relationship between photosynthetic bacteria and sponges. Here, the cyanobacteria provide photosynthates (e.g., glycerol, organic phosphates) that cover part of the energy and carbon requirements of the associated organism, while the sponge primarily serves as a suitable environment to grow with higher levels of ammonium and phosphorus, protected from some predators [16]. Photosynthetic microbes are also the photobiont on the metaorganisms known as lichens, partnering with fungi and bacteria. Due to this interaction, lichens manage to survive in virtually every terrestrial ecosystem [17]. In this symbiosis, each partner can produce unique secondary metabolites, exclusively synthesized when in partnership with particular photosynthetic organisms; hence, different partners influence the ecology of the symbiosis and the molecular responses to environmental stressors [18]. In some cases, relations with N-fixing bacteria or diazotrophic bacteria have also been reported for cyanosponges and lichens. A recent review comprehensively summarizes numerous examples of interactions between microalgae and nitrogen-fixing bacteria with significant biotechnological potential [19]. Here, the authors emphasize that most photosynthetic microbes have undergone prolonged coevolution and persistent interactions, making them challenging to culture axenically in laboratory conditions. Consequently, the potential of co-cultivating these microorganisms with nitrogen-fixing bacteria holds promise for advancing a range of biotechnological applications, as evidenced by examples of improved biomass production, lipid accumulation, hydrogen generation, and wastewater treatment [19].

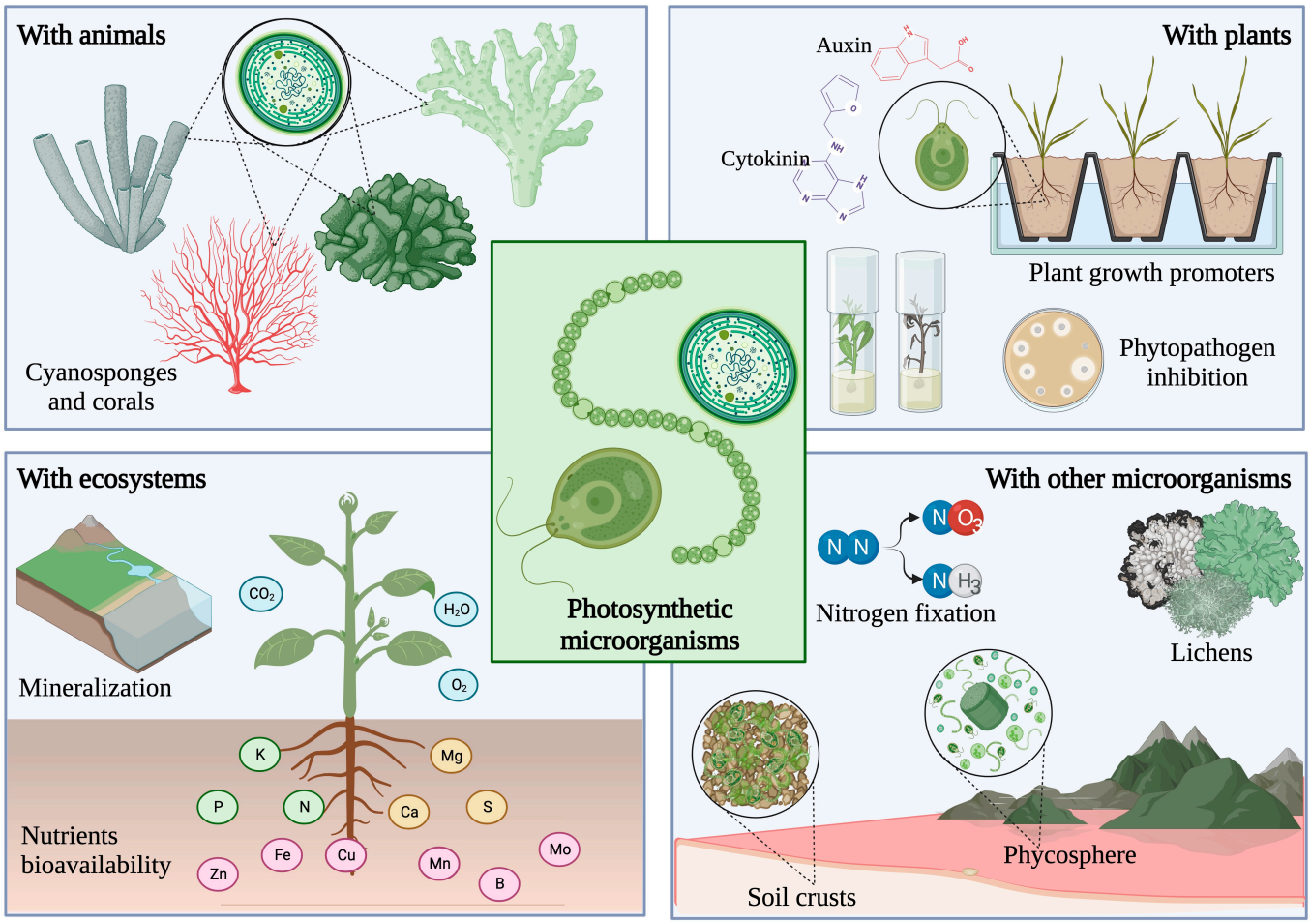

Figure 1. Examples of ecological interactions involving photosynthetic microorganisms with animals (mutualistic interaction with cyanosponges and corals), plants (secretion of phytohormones, exopolysaccharides, and antimicrobial compounds), other microorganisms (nitrogen-fixing cyanobacteria, production of allelochemicals, and soil crust and phycosphere microbiome), and biogeochemical modeling (increasing nutrient bioavailability, soil regeneration, and mineralization processes). Created with BioRender (https://www.biorender.com, accessed on 24 October 2023).

Moreover, as primary producers, cyanobacteria play a significant role in biogeochemical modeling, facilitating the colonization and development of heterotrophic microorganisms in harsh environments. Van Goethem et al. (2017) summarize some of the contributions of photoautotrophs in the transfer of nutrients to those heterotrophic microbes, participating in the mineralization and transformation of organic matter, thereby increasing soil fertility [20]. The authors also establish by 16S rRNA transcript analysis that cyanobacteria are one of the most active member of the microbial communities and may be central to biogeochemical cycling in desert niches [20]. Eukaryotic microalgae, which are also considered as photosynthetic microorganisms, engage in similar ecological relationships to cyanobacteria [21,22]. For example, dinoflagellate symbionts from the *Cladocopium* species have been identified in a mutualistic relationship with reef-building *Pocillopora* corals showing long-range dispersal capabilities, genetically connected across the tropical and subtropical Pacific Ocean [21]. Also, microalgae and bacteria consortia from desertic environments have been proposed to improve soil fertility, water preservation, primary production, pollutant removal, and maintaining soil stability due to their multiple functional and beneficial interactions [22].

As a consequence, cyanobacteria and microalgae are known to play a relevant role in soil maintenance by fixing carbon dioxide and nitrogen, stimulating mineralization

processes, and promoting oxygenation [23]. Their ecological relationship has extended the usage of these microorganisms for soil regeneration, where previous results have suggested improved C and N content, and increased microbial activity and water drop penetration by the application of microalgae in different soil types [23]. Additionally, several photosynthetic microorganisms engage in symbiotic relationships with major organisms like plants, producing compounds such as exopolysaccharides (EPSs) that helps with soil aggregation, organic content accumulation, and increased water holding capacity of the soil [24]. They have also been proved to produce bioactive metabolites and extracellular products that act as plant biostimulants comparable with commercial phytohormones in hydroponic co-cultivation with microalgae or cyanobacteria [24,25].

In this context, the ecological relevance of photoautotroph microorganisms suggests that they can be used as biofertilizers and biostimulants in sustainable agriculture, products which vaguely imply the co-culture of photosynthetic microorganisms [26]. Previous studies have shown promising results, reinforcing the advantage of these microbes in co-culture approaches. For example, a mixed algal consortium and tomato plant (*Solanum lycopersicum*) co-culture resulted in a symbiotic interaction in a hydroponic system [27], with an increase in dissolved oxygen, and the uptake of N, P, and K macroelements by up to 85% more efficiently [27]. Similarly, the co-culture of *Chlorella vulgaris* and mint plants (*Mentha* × *piperita*) evidenced a significant weight gain and leaf quality improvement compared to control treatments [28]. The microalgae did not affect the chlorophyll content of mint leaves, and no contamination occurred in inoculated plants [28]. In this case, it was evidenced that the microalgae co-culture protected the plants from the contamination of the hydroponic system. Therefore, this interaction suggests that co-cultivation could help to prevent industrial processes of undesired contamination.

On the other hand, microalgae and cyanobacteria can be involved in antagonist interactions partially due to the production of antimicrobial compounds [29,30]. Many cyanobacteria and eukaryotic microalgae have been reported to produce allelochemicals, such as cyanobacterin or chlorellin, that can inhibit the growth of other microbes [31,32]. This phenomenon is known as allelopathy, caused by 'blooms' (a rapid and exponential proliferation of these photoautotrophs) [31]. Cyanobacterial and microalgae blooms are caused by the eutrophication of the aquatic systems, a process enhanced by climate change, resulting in more frequent and intense events [33]. In response, affected individuals (e.g., zooplankton, bacteria) have evolved to coexist with cyanobacteria/microalgae, rather than eliminating them, by developing high-tolerance strains and phenotypes related to stress response [34,35]. For example, cyanolytic bacteria in the presence of cyanobacteria increase the expression of genes associated with protection from radiation and oxidative stress such as catalase and hydroperoxide reductase [36]. Studies have revealed a change in transcriptomic and metabolomic profiles in co-cultures simulating a cyanobacterial bloom, possibly due to cell-to-cell contact and disturbance interactions [36]. Therefore, it is thought that these microbes are even responsible for the Earth's biosphere as we know it today [13].

Secondary metabolism allows these microorganisms to produce a wide variety of molecules that help them to thrive in a particular ecological niche [37], participate in many symbiotic interplays, and communicate with other individuals [38,39]. In nature, the stimuli needed to up-regulate gene expression are triggered by biochemical activity of other species [40,41]. Different methods of interspecies communication in the environment have been described, including the elicitation of signaling molecules in the vicinity, the diffusion of small molecules into a neighboring microorganism, cell-to-cell interactions based on enzymes facilitating biosynthetic routes, and even electrical signaling related to ion channels [42–45]. Although the molecular mechanisms for gene expression are largely unknown, some molecules have been shown to interact as transcriptional or epigenetic modifiers [46,47]. In this sense, specific bacteria exploit the vicinity of microalgae, known as the "phycosphere", establishing mutualistic relationship that requires an enormous metabolic activity linked to a complex signaling network [48]. These bacteria benefit from the high concentrations of fixed organic carbon, displaying functions such as complex polysaccha-

ride degradation and competition prevention [48]. Signaling in this microenvironment modulates microbial colonization, mutualism and competition establishment, and marine biogeochemical cycles. A recent review provides the state of the art regarding the quorum sensing communications and bioactive compound involved in the phycosphere [49]. For example, the diatom *Asterionellopsis glacialis* promotes the attachment of beneficial bacteria by secreting rosmarinic acid and azelaic acid [50], and, during *Emiliania huxleyi* bloom, normally silent biosynthesis pathways are activated in *P. gallaeciensis* to produce tropodithietic acid that helps algae resist harmful bacteria, while as the bloom fades it produces the algaecide molecule roseobacticide [49,51]. It has also been reported that photosynthates released by photosynthetic microorganisms influence the production of cryptic molecules in marine actinobacteria [52]. While the production of interesting specialized metabolites naturally occurs in many ecosystems, replicating these interactions can be challenging and, in some cases, impossible under monoculture laboratory conditions.

The ancestry of photosynthetic microorganisms has been well-established. Given their extensive presence throughout Earth's history, these microbes have established multiple intimate interactions with other organisms. While some of these interactions have been extensively studied, it is likely that most are still awaiting thorough exploration and comprehension. It will be beyond the scope of this review to provide specific details about the interplays of the known interactions; however, it offers a concise summary of illustrative examples. These examples shed light on the ecological context that underpins the rationale for the enhanced bioprospecting outcomes expected from co-cultivating cyanobacteria and microalgae. The co-cultivation method recreates the naturally occurring interplay in nature and, therefore, it is considered an ecology-driven strategy [53]. The explored ecological findings of photosynthetic microbes suggest that they are an advantageous and promising underexploited source for this approach. Co-cultivation studies involving these microorganisms are described in Section 3.

3. Recent Status of Co-Cultivation of Photosynthetic Microorganisms

As previously discussed, photosynthetic microorganisms can be involved in symbiotic interactions developing genuine ecological relationships and incurring two-way compound interchanges [54]. This foundation has paved the way for a wide array of artificial co-cultivation studies involving photosynthetic microorganisms alongside other organisms from diverse kingdoms, including microalgae, cyanobacteria, bacteria, fungi, and even phytoplankton (animal). In most reports, the available evidence demonstrates that co-culturing enhances productivity, whether in terms of biomass or the synthesis of specific compounds like lipids, starch, or antimicrobials (Table 1). Recent reports on this topic are summarized here, and the limitations and perspectives of this strategy are discussed in the following sections (Figure 2).

Given that microalgae need to be cultured and marketed as a large-scale product, most available co-cultivation studies are focused on increasing the production of algae biomass. Light-to-biomass conversion efficiency represents a major constraint to finally fill the gap between theoretical and industrial productivity [55]. Co-cultivation is now recognized for its ability to boost biomass production [56], a feature of paramount importance in well-established microalgae industrial applications, such as bioenergy production, as comprehensively reviewed by Ray et al. (2022) [57], and in wastewater treatment. It is not surprising that most of the recent reports on co-cultures involving photosynthetic organisms align with this focus. For example, the co-culture of *Botryococcus braunni* and *Nostoc muscorum* resulted in a 27% increased total lipid content compared to the *B. braunii* monoculture, a valuable molecule for the biofuels industry [58]. Remarkably, co-culture also resulted in the expression of novel molecules with antimicrobial properties, which were not observed in monocultures such as such as triacontanol (phytohormone) [58]. Similarly, Rashid et al. (2019) co-cultured the microalgae *Ettlia* sp. and *Chlorella* sp. for biomass and lipid production. They concluded that co-cultivation is more favorable than monoculture to obtain high biomass productivity and stable biomass composition

for biodiesel production [59]. Previous authors proposed two possible mechanisms for enhanced biomass and lipid production in the co-culture system, nutrient exchange between species (e.g., oxygen and nitrogen) and synergistic effects of metabolites such as cyclohexane (plant promoter growth), that may have resulted in the enhancement of the growth rate of green algae [58].

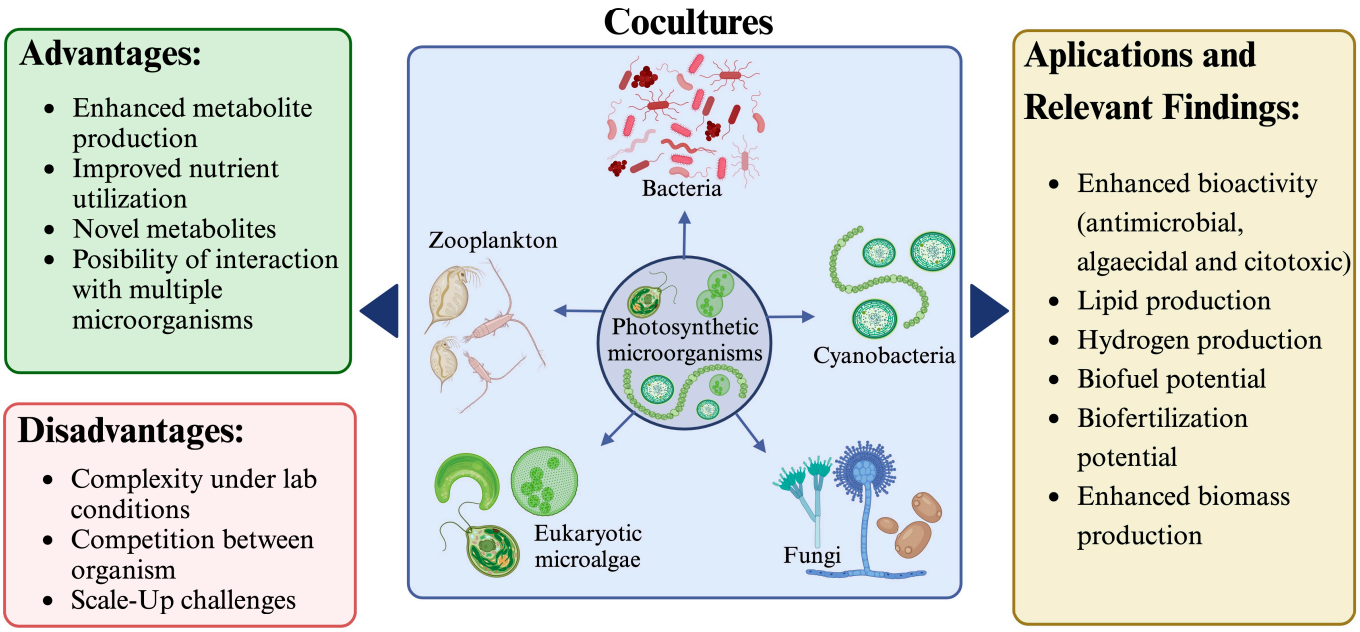

Figure 2. Graphical summary of findings on photosynthetic microorganism co-cultures for specialized metabolite production. The central image displays various types of co-cultures that have been reported and included in this review. These co-cultures involve photosynthetic microorganisms cultivated with cyanobacteria, microalgae, bacteria, fungi, and phytoplankton species. The main findings obtained from these co-cultures are listed, along with the advantages and disadvantages of this approach, based on the analysis of current works in this area. One advantage is that co-cultures often result in increased metabolite production due to cross-talk and synergy between different organisms. This can lead to higher yields of valuable compounds, including those that are usually cryptic. In co-cultures, one microorganism's waste can serve as a nutrient source for another, improving nutrient utilization and offering more energy sources. This leads to higher biomass yields, especially beneficial for industrial applications. Moreover, photosynthetic microorganisms, due to their ecological context, interact with a variety of micro- and macroorganisms from different kingdoms. These interactions offer potential opportunities for optimizing suitable co-cultures in the future. On the other hand, managing and studying co-culture systems can be complex, as our molecular understanding of these interactions is limited. Understanding and controlling interactions among multiple organisms is challenging and may be difficult to optimize; therefore, competition can lead to reduced productivity. Finally, achieving reproducible results for scaling up can be challenging, primarily due to the fine-tuning of molecular signaling and the different microbial responses in co-culture systems. Created with BioRender (https://www.biorender.com, accessed on 24 October 2023).

Novel applications of co-cultures involving photosynthetic organisms in bioenergy encompass the production of bioelectricity and hydrogen. In both instances, co-cultures have demonstrated the capacity to enhance the generation of energy molecules when compared to monoculture approaches [60,61]. Nonetheless, it is important to note that these studies are still in their early experimental phases but the prospects are promising. On the other hand, a broader spectrum of co-cultures involving photosynthetic organisms has been directed towards wastewater treatment, with a particular emphasis on augmenting the sequestration of specific chemicals or assisting in the growth of biomass to enhance

nutrient removal [62,63]. In addition to chemical removal, certain co-cultures, particularly those involving algae and fungus, demonstrated the ability to form aggregated structures that facilitated easier settling and removal from wastewater, streamlining the wastewater treatment process [64].

Beyond these industrial applications, co-cultivation studies are beginning to yield promising results for the discovery and enhancement of various bioactive molecules. Increased biomass and heightened bioactivity of molecules are commonly observed in co-cultivation approaches. For instance, *Chaetoceros calcitrans*, a marine diatom, exhibited antimicrobial activity against the pathogenic bacteria *Vibrio parahaemolyticus* strain MO904 when co-cultured at its logarithmic growth phase [65]. The observed enhancement in bioactivity is believed to stem from the cell-to-cell interactions between the associated microorganisms facilitated by co-cultivation. As mentioned before, some ecological interplays are impossible to achieve under monoculture conditions. *C. vulgaris* MACC-1 and *Scenedesmus acutus* MACC-677 exhibited high antimicrobial activity against the crop pathogens *Clavibacter michiganensis* and *Pythium ultimum*, exclusively through co-cultivation [66]. This finding highlights the importance of co-cultivation for exploring novel biological activities in photosynthetic microorganisms.

Co-culture-exclusive bioactivity from photosynthetic microorganisms is not uncommon but studies are still in early stages. For example, the co-culture of *Porosira glacialis*, a marine photosynthetic diatom, with zooplankton resulted in a fivefold increase in more than a third of its metabolic profile [67]. The increase in metabolic profile led to the extraction of a bioactive organic extract that was effective against human melanoma and normal lung fibroblasts [67]. In addition, a nonpolar extract of *Nostoc* sp. co-cultured in an algal-assisted microbial fuel cell system with *Enterobacter aerogenes* showed novel antimicrobial activity against pathogenic species *Citrobacter freundii*, *Vibrio alginolyticus*, *Streptococcus iniae*, and *Escherichia coli* [60]. Other studies have revealed that co-cultivation of microalgae and bacteria can produce algicidal compounds. Unlike biomass enhancement, these compounds are aimed at controlling algae blooms in aquaculture [68,69]. As mentioned earlier, while there has been limited research dedicated solely to co-culturing photosynthetic organisms to produce bioactive metabolites or the discovery of new molecules, the experience gained from various co-cultivation applications and the reported bioactivities indicate a highly positive outlook. This suggests that future research can exclusively focus on studying, producing, and characterizing metabolite production using this technique.

Table 1. Photosynthetic microorganisms' co-cultivation advances in recent years.

Co-Culture Type	Organism	Product/Application	Co-Culture Condition	Main Findings	Compounds Discovery with Biological Activity	Reference
Microalgae/cyanobacteria	*Botryococcus braunii*/*Nostoc muscorum*	Biofuels	Bioreactor	50% enhancement in nitrogen fixation. 27% enhancement in lipid content. 38% enhancement in biomass content.	Triacontanol (phytohormone)	[58]
Microalgae/bacteria	*Chaetoceros calcitrans*, *Tetraselmis suecica*, *Nannochloropsis* sp., and *Thalassiosira weissflogii*/*Vibrio parahaemolyticus*	Antimicrobial compound production	-	*V. parahaemolyticus* was significantly inhibited in co-culture.	Hydrophilic compounds of *C. calcitrans* with antibiotic activities	[65]
Microalgae/microalgae	*Chlorella vulgaris*/*Scenedesmus acutus*	Biomass production and nutrient removal efficiencies	Thin-layer cascade (TLC) and thin-layer raceway pond	Better nutrient removal efficiencies. Maximum biomass densities of 1.3 and 2.1 g DWL^{-1}.	Antifungal compounds against Pythium *ultimum*	[66]
Microalgae/animalia	*Porosira glacialis*/zooplankton	Changes in bioactivity and metabolome	Outdoor 6000 L glass fiber vertical column open photobioreactor	Induced the production of compounds with cytotoxic activity towards normal lung fibroblasts.	Production of novels carotenoids in *P. glacialis*	[67]
Cyanobacteria/bacteria	*Nostoc* sp./*Enterobacter aerogenes*	Bioelectricity, bioactive compound production, wastewater treatment	Two-chambered microbial fuel cell (MFC) with the algae in the cathode chamber and the bacteria in the anode chamber	MFC generated a maximum power density of 168 W/m^2 and removed 84% of the chemical oxygen demand from the wastewater.	FTIR analysis of the extract confirmed the presence of bioactive compounds	[60]
Microalgae/microalgae	*Ettlia* sp./*Chlorella* sp.	Biomass productivity and biodiesel production	Photobioreactor	Higher biomass productivity in coculture than in the monoculture of either *Ettlia* or *Chlorella*.	-	[59]
Microalgae/bacteria	*Chlorella pyrenoidosa*/*Rhodobacter capsulatus*	Wastewater treatment, biomass production, lipid production	Batch culture (250 mL flasks)	The co-culture produced more biomass and lipids than either monoculture.	-	[62]

Table 1. *Cont.*

Co-Culture Type	Organism	Product/Application	Co-Culture Condition	Main Findings	Compounds Discovery with Biological Activity	Reference
Cyanobacteria/microalgae	Leptolyngbya tenuis/*Chlorella ellipsoidea*	Biodiesel production, carbon sequestration, cadmium accumulation	Batch culture (250 mL flasks)	The co-culture produced more biomass and lipids than either monoculture. It was also more effective at sequestering carbon and accumulating cadmium.	-	[70]
Microalgae/fungi	*Chlorella sorokiniana*/*Rhodotorula glutinis* *C. vulgaris*/*Aspergillus* sp.	Biofuel production and bioremediation	-	Enhanced phosphate removal efficiencies. Enhanced ammonium–nitrogen removal. Enhanced biomass and oil production.	-	[71,72]
Cyanobacteria/cyanobacteria	*Anabaena cylindrica*/*Nostoc* sp.	Polysaccharides, extracellular proteins, nitrogen fixation, biofertilizer	400 mL bubble column photobioreactor	The co-culture produced more biomass, polysaccharides, extracellular proteins, and it had higher nitrogenase and photosynthetic activity than either monoculture.	-	[73]
Microalgae/fungi/bacteria	*Chlorella vulgaris/Aspergillus niger/Enterobacter aerogenes*	Wastewater treatment	Photobioreactor (16.8 L)	The co-culture was more effective at removing organic matter and nutrients from wastewater than either monoculture.	-	[63]
Microalgae/bacteria	*Chlamydomonas reinhardtii/Escherichia coli*, *Pseudomonas stutzeri* and *Pseudomonas putida/unknown bacterial consortium*	Hydrogen production	Bioreactors (100 mL)	*Chlamydomonas* could grow properly in presence of bacterial consortium and hydrogen evolution improved up to 56% in these co-cultures.	-	[61]
Microalgae/bacteria	*Chaetoceros muelleri/Vibrio parahaemolyticus*	Algicidal activity (algal bloom control)	Batch culture (250 mL flasks)	Algicidal activity against *Chaetoceros muelleri* due to extracellular metabolites produced by the bacteria.	-	[69]

Table 1. *Cont.*

Co-Culture Type	Organism	Product/Application	Co-Culture Condition	Main Findings	Compounds Discovery with Biological Activity	Reference
Microalgae/bacteria	*Streptomyces rosealbus/Chlorella vulgaris*	Biodiesel production, bioflocculation formation	Batch culture (1 L flasks)	Co-culture produced more biomass and lipids, and better bioflocculation properties.	-	[74]
Microalgae/bacteria	*Chlamydomonas reinhardtii/Escherichia coli*	Biomass production, starch production	Batch culture (250 mL flasks)	The co-culture produced more biomass and starch than either monoculture.	-	[75]
Microalgae/fungi	*Chlamydomonas reinhardtii/Saccharomyces cerevisiae*	Biomass production	Batch culture (250 mL flasks)	The co-culture produced more biomass. Gene expression levels of 363 green algae and 815 yeast genes were altered through co-cultivation.	-	[76]
Microalgae/bacteria	Free-living *Symbiodinium/Alteromonas abrolhosensis*	Algal bloom control	-	Algicidal activity against free-living *Symbiodinium*, attributed to the production of extracellular metabolites by the bacteria. The metabolites produced oxidative stress and photosynthetic system damage in the algae.	-	[68]
Microalgae/fungi	*Chlorella vulgaris/Aspergillus niger*	Swine wastewater treatment	Batch culture (250 mL flasks)	The co-culture was able to form aggregated structures, which were mediated by extracellular polymeric substances (EPSs), simplifying the wastewater treatment.	-	[64]

Extreme-Tolerant and Extremophilic Photosynthetic Microorganisms in Co-Cultivation Studies

Under the co-culture approach, a new bioprospecting scope for microorganisms with biotechnological applications has been proposed, focusing on exploring non-traditional environments for rare and uncommon species of microorganisms [77]. This group includes extremophilic microorganisms that have previously shown promise in producing relevant compounds and having potential industrial applications [78]. Extremophiles are constantly exposed to harsh ecological conditions, such as heavy metal and chemical contamination, low/high temperature, freeze–thaw cycles, and high salinity. Only individuals with the ability to cope with these extreme conditions can survive and grow [79–81]. Moreover, these specific growth conditions are thought to be another method to avoid undesirable contamination in industrial processes [3].

Although extremophiles have been less studied than popular biosynthetic strains, the metabolic adaptation of extremophilic photosynthetic microorganisms increases the chances of finding biotechnological applications [82,83]. In addition, these extremophiles are known to be a promising source of new antimicrobial molecules [84], which is relevant to the bioprospecting effort to fight against the global antibiotic resistance crisis [12]. Therefore, we consider that extremophiles must be a focus of research for the scientific community to find natural products and biotechnological potential, employing the co-cultivation approach.

Extremophilic environments are defined as those characterized by one or a combination of extreme abiotic variables [82], such as deserts, sediments, permafrost soil, volcanoes, hot springs, and the Arctic and Antarctic regions. As mentioned before, photosynthetic microorganisms were among the first to colonize the harsh conditions of primordial Earth. They play a crucial role in the primary colonization of ecosystems, which requires a very specialized metabolism that has been impacted by an increased genetic diversity due to anthropogenic activities [85–88].

As stated, the plasticity of extreme photosynthetic microorganisms, their evolution history, and the selective pressure they face to adapt to a wide range of environments make them a hot spot for discovering microorganisms with relevant biotechnological applications [84]. For example, extremophilic cyanobacteria *Aliinostoc alkaliphilum* are considered promising for new antimicrobial discovery, as they have been shown to be active against the pathogens *Staphylococcus aureus*, *Bacillus cereus*, *Aspergillus flavus*, and *Mucor* sp. [89]. Other cold-tolerant microalgae have also showed antibacterial activity against pathogenic Gram-positive (*S. aureus*, *Streptococcus epidermis*, and *B. subtilis*) and Gram-negative (*Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*) species [90]. Finally, the halophilic species *Cystoseira foeniculacea* inhibited the growth of some *Vibrio* spp. strains [91].

Remarkably, the extremophilic microalgae, *Isochrysis galbana*, have been the subject of extensive research for their potential to produce lipids and biomass [92,93]. They have also been shown to be a food enrichment ingredient [94], degrade phenol, promote environmental restoration [95], and produce antioxidant compounds [96] and other molecules of pharmaceutical interest [97,98]. Additionally, promising antimicrobial activity has been shown by the secondary metabolites of *I. galbana* against pathogenic bacteria such as *Listeria monocytogenes*, *S. aureus*, *B. subtilis*, *E. coli*, *S. epidermidis*, *Enterococcus faecalis*, *P. aeruginosa*, and fungi from the *Candida* genus [99,100].

In this sense, extremophilic photosynthetic microbes might be promising targets for co-culture studies, as this approach could extend their biotechnological potential. Notably, *I. galbana* have shown promising results in the literature which increases our interest in this microalgae species. In co-culture, *I. galbana* have been shown to inhibit the growth of antibiotic-resistant *Vibrio vulnificus* strains, a feature that has not been previously reported in monoculture [101]. An enhanced production of docosahexaenoic acid (DHA), a lipid with antimicrobial properties, was also observed when *I. galbana* were co-cultured with *Marinobacter* species [102].

The co-culture of photosynthetic extremophilic microorganisms isolated from extreme environments opens up new possibilities for applied research, especially in industry-related applications. Here, costly effective strategies have demonstrated enhanced production yields and a reduction in contamination risks, which can prove economically advantageous [103]. To our knowledge, few studies have focused on the analysis of silent genes or chemical characterization of unknown molecules through co-cultures of extremophilic microorganisms, including the promising *I. galbana*. However, due to the recent studies on this species and its complete genome publicly available, *I. galbana* could be a suitable model microorganism to establish and understand co-culture methods for expanding the biotechnological applications of extremophiles.

4. Limitations on the Understanding of Ecological Interactions and Available Methodologies for Co-Cultivation

The challenges of co-cultivations are rooted in the complexity of microbial interactions and the many outcomes that have been observed in nature. Previous studies have shown that ecological coexistence is delicate, as one strain can be excluded over the other at slightly changed temperature conditions, or different types of interactions and excreted substances can develop under the same cultivation parameters [104,105].

The use of co-cultivation medium is also a challenge. Co-cultivation can be achieved in a solid or liquid medium (also called 'mixed fermentation'), and there are some notable differences between the two. The solid medium can stimulate the production of new metabolites, by reducing the growing competition between strains but it also restricts the exchange of metabolites between strains. In contrast, the liquid medium allows for direct exchange of metabolites, which facilitates communication between strains. However, the growth competition is severe and appropriately controlled co-culture conditions are needed [5].

Additionally, direct co-cultivation (with cell-to-cell interaction) can negatively affect the exchange of different metabolites but it may be necessary to evaluate the growth inhibition [106]. Also, the physiological and metabolic responses cannot be easily studied. On the other hand, indirect co-cultivation (without cell-to-cell interaction) is another common approach. It is achieved by separating microorganisms with a protein-based or synthetic membrane (e.g., hydrophilic polyvinylidene fluoride filter) [107,108]. This method facilitates studying the induction for new molecule biosynthesis but it is challenging to quantify the concentration of the molecules due to a dilution factor [108]. Therefore, more efficient methodologies are needed that allow the interaction and interchange of chemicals while avoiding other unwanted competitions [109].

In this sense, the wide diversity of ecological interspecies interactions and methodologies applied make co-cultivation method difficult to reproduce. However, the possible outcomes can be normally observed in preliminary experiments to standardize an effective co-culture protocol [110]. Subsequently, the challenge is to find a pair of microorganisms suitable for the bioprocess goal.

As mentioned in Sections 1 and 2, all the interspecies interactions are directly and indirectly related to the ecological niche of the individuals. A study showed that the production of L-(+)-lactic acid by *Lactobacillus* sp. was increased in the presence of *L. amylovorus* DSM 20,531 [111], similarly to the co-culture of *L. delbrueckii* and *L. plantarum* [112]. However, in the latter case, the biomass was lower compared to monoculture due to the toxicity of lactic acid [112]. The different outputs regarding toxicity remark the sensibility of the co-culture techniques to the ecological niche of the species and the importance of understanding the individual's needs to achieve the objective for each co-culture [113].

The co-culture method is not yet fully understood or standardized, and the high number of possible results makes the methodology very exploratory [110]. In this sense, understanding and controlling the factors that affect co-cultures must be prioritized in experiment design [110]. This guarantees the reproducibility of the assays, as well as the accuracy and reliability of the obtained results.

5. -Omics-Based Research and Standardized Methodologies as Future Directions of Co-Cultivation Methods

Recent methods have been developed to overcome the complications related to the complexity of ecological niches. A high throughput assay for co-culture and microbiome research has been proposed by Temkin et al. (2019) [114] using a simple and inexpensive methodology. This consists of a 3D-printed polycarbonate inoculation stamp that allows for faster and more precise inoculation of the producer and partner strains on 12-well bioassays plates [114]. The incubated plates are later qualitatively scored from 0 to 2 with 0 indicating 'no inhibition', 1 indicating 'weak inhibition', and 2 indicating 'strong inhibition'. This helps to explore a greater number of microorganisms in a shorter time. In addition, the development of -omics-based techniques such as metagenomics analysis has been shown to be useful for preliminary screening for bioactive compounds in environmental samples and the current microbial profile, facilitating the bioprospecting of promising metabolites [115,116]. Sonowal et al. (2022) employed a genomic approach for annotation of secondary metabolites in endophytic bacteria associated with the endangered Himalayan medicinal plant *Paris polyphylla*, revealing the presence of siderophores and antimicrobial lipopeptides encoding genes which are considered relevant against pathogen attack [117]. This also led to the identification of several bioactive compounds evidenced by the occurrence of nonribosomal peptides (NRPS) and polyketide synthases (PKS). Based on this genomics context the authors evaluate the co-culture of these endophytes with the microalgae *Micractinium* sp. GA001, showing a positive modulation of the microalgal photosynthesis and an increased accumulation of lipids [117]. To our knowledge, neither high throughput assays nor culture independent -omics screenings have been used for microalgae co-cultures directly, yet they represent promising techniques to preliminary studies regarding microorganisms' compatibility for co-cultivation.

Also, understanding symbiotic interactions for gene expression induction is considered relevant and functional for improving the co-cultivation methodology, as an ecologically driven method, for a specific research or production goal [118]. In this sense, identifying transcriptomics, metabolomics, and proteomics profiles in microorganisms involved in ecological interactions is an important approach for understanding their molecular basis [119,120]. Recent studies have employed metabolomics and genomics approaches. Perera et al. (2022) used a flowing proton nuclear magnetic resonance spectroscopy to identify the over-expressed metabolites in a microalga (*Tetradesmus obliquus* IS2 or *Coelastrella* sp. IS3)–bacteria co-culture (*Variovorax paradoxus* IS1) [121]. This revealed the presence of riboflavin, lumichrome, and thiamine which promoted the growth and supported the cross-feeding of carbon and nitrogen sources, and was therefore considered responsible for the mutualistic interaction of the companion strain [121]. Also, a greater metabolic activation, of both primary and secondary metabolites, was evidenced in the co-culture of the microalga *Galdieria sulphuraria* and the fungus *Penicillium citrinum* by GC–MS-based metabolomics [122]. Moreover, genome engineering techniques, such as in vivo expression technology, can be used to identifying genetic elements related to symbiosis and activation of specialized metabolites [50]. We believe that, coupled with other -omics approaches, genetic engineering could provide new insights about the molecular pathways to induce gene expression of target secondary metabolism in co-cultivation systems. Although this combined approach had been previously applied to other bacterial co-cultures [123], only a few studies used multi-omics co-cultivation assays involving microalgae and/or cyanobacteria responses [124,125]. Ma et al. used integrated transcriptomic, proteomic, and metabolomic analyses to evaluate the interactions that can be achieved from cross-feeding co-culture between a phototroph (cyanobacterium *Synechococcus*) and a prokaryotic heterotroph (*Escherichia coli*) [125]. Meanwhile, Kawai et al. conducted a metatranscriptomic analysis and metabolic study in situ of the thermophilic photosynthetic bacterium *Chloroflexus aggregans* in microbial mats dominated by cyanobacteria [124].

The experimental methodology of co-culture is still under development. Boruta (2021) discusses key aspects of co-cultivation experimental design, including the initiation

approach, experimental setup, medium, and process conditions, using *Streptomyces* genus as a model microorganism [110]. Expanding these experimental designs and assays to be applicable to a more diverse range of microbes, including promising photosynthetic microorganisms, is a required research area to standardize the co-culture strategies [113].

6. Conclusions

The physiological flexibility and diverse ecological interactions of photosynthetic microorganisms are favorable when included in ecology-driven methodologies like co-cultivation. Several co-culture studies have shown promising results, such as enhanced production and discovery of novel bioactive compounds, especially antimicrobial, when cyanobacteria and microalgae are used as the producer or associated strain. In this co-cultivation approach, we promote the idea of bioprospecting promising photosynthetic extremophiles, such as *I. galbana*, to increase the chances of expanding the biotechnological applications of these species. Although the results are promising, challenges remain due to the complexity of microbial interactions and research methods, which limit the application of co-cultivation to a wide range of microorganisms. Developing efficient methodologies to study ecological interactions and their connection to the genetic elements that produce secondary metabolites is a research area that could help solve the challenges regarding co-cultivation techniques and expand their understanding and applicability.

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