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The Postbiotic Potential of Microalgae

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ABSTRACT

The International Scientific Association for Probiotics and Prebiotics (ISAPP) has defined postbiotics as “preparations of inanimate microorganisms and/or their components that confer a health benefit on the host.” Considering that microalgae are prepared and used as inactivated powders in foods and food supplements due to their rich composition of nutrients and bioactive compounds known to positively influence human health, this opinion review aims to evaluate whether they may be classified as postbiotics. To this scope, nutritional aspects of microalgae and cyanobacteria and their use in foods and food supplements are reported, highlighting their potential postbiotic activity within the framework of the concept and definition of postbiotic. Despite the growing body of evidence on the health benefits of microalgae, unlocking the full potential of microalgae as postbiotics would offer promising opportunities for advancing health and nutrition.

1 | Introduction

Many studies aimed at identifying food sources that enhance consumers’ health have been published, and research in this area continues to grow. In recent years, the use of microorganisms and bioactive compounds derived from their metabolism has gained considerable attention, revealing the beneficial potential of various “biotics,” like probiotics, prebiotics, and synbiotics (Gibson et al. 2017; Hill et al. 2014; Swanson et al. 2020). More recently, the International Scientific Association for Probiotics and Prebiotics (ISAPP) has issued a consensus statement defining postbiotics (Salminen et al. 2021b). This refers to non-living microbes and their derivatives, providing a beneficial effect when used, thereby broadening the range of bioactive compounds available to support human health. Most common postbiotics, besides parts of the cells, such as wall fragments and lipopolysaccharides (LPS), include components such as short-chain fatty acids (SCFAs), enzymes, and proteins present within microbial cells, which exert beneficial effects on humans (Salminen et al. 2021b).

Among those microorganisms that are increasingly recognized as valuable food supplements, microalgae and cyanobacteria are well recognized mainly due to their rich nutritional composition. Typically sold as powders of whole, inactivated cells, microalgal cells are rich in bioactive compounds, including antioxidants, fatty acids, and polysaccharides, which may offer promising postbiotic benefits. Evidence suggests that microalgae could support wellness beyond the traditional scope of live probiotics. Therefore, considering the available literature on microalgae’s beneficial effects, the way they are prepared as food or food supplements, and the current regulatory framework, this review aims to explore the potential for including microalgal

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cells and their bioactive compounds within the definition of postbiotics.

2 | Postbiotics Concept and Definition

The definition of postbiotics given by ISAPP in 2021 indicates that they are a "preparation of inanimate microorganisms and/or their components that confers a health benefit on the host" (Salminen et al. 2021b). As inferable from the name postbiotic (post- meaning "after" and -biotic meaning "living organisms"), eating food or food supplements containing postbiotics does not imply the consumption of metabolically active microorganisms. Postbiotics are dead cells, microbial cell components, fragments, or structures that may or may not include metabolites or other products released during metabolism. Thus, contrary to probiotics, which, as per their definition, must be alive when administered (Hill et al. 2014), postbiotics must be inactivated cells still providing health benefits via cell components. Inactivation of cells can be performed in several ways, such as applying traditional thermal processing (pasteurization, tyndallization, and sterilization) or spray drying, freeze-drying, electric fields, ultrasonication, high pressure, x-rays, ionizing radiation, high-voltage electrical discharge, pulsed light, magnetic field heating, moderate magnetic fields, and plasma technology (Salminen et al. 2021b). Regardless of the method of cells inactivation the postbiotic preparation must include dead cells or their components, such as peptidoglycans, teichoic acids, and lipids included in microbial cell walls and membranes (Collado et al. 2019). It is important to underline that any microbial metabolite deriving from the microorganisms before inactivation loses the status of postbiotic, regardless of its potential health benefits, when extracted from inactivated cells in a way that leaves no cell biomass or components behind. Any microorganism can be used to produce a postbiotic if it is: (i) considered safe by the competent authority; (ii) identified at the strain level; (iii) has a detailed preparation process; and (iv) demonstrates safety and efficacy through appropriate studies in the intended host through well designed clinical trials (Vinderola, Sanders, et al. 2024). Furthermore, understanding the mechanism of action is not required to define a product as a postbiotic, nor is it necessary to determine which specific postbiotic components confer health benefits to the host (Vinderola, Sanders, et al. 2024). Moreover, since it is unnecessary to keep the microorganisms alive, a significant advantage of postbiotics, compared to probiotics, is that they do not require technology or environmental conditions to maintain cell viability during transportation and storage (Mishra et al. 2024). Consequently, postbiotics have a longer shelf life and can be easily marketed in countries where it is not possible to store or maintain the cold chain. From a food security perspective, these advantages are crucial, given postbiotics' health benefits. The increasing market demand for postbiotic products, as reflected in studies on humans and animals (Heniedy et al. 2024), has spurred commercialization efforts. ISAPP's definition of postbiotic does not specify particular health benefits, finished products, target populations, or regulatory statuses, thereby allowing it to encompass a wide range of traditional and innovative products, including foods, food supplements, and medicinal products (Vinderola, Druart, et al. 2023). In this context, fermented foods have also been considered for their capacity to deliver postbiotics. However, this is strictly dependent on the microbiological and chemical level of characterization, the reproducibility of the technological process used to produce the fermented foods, the evidence for health benefits conferred by the postbiotic, as well as the type and amount of testing carried out to prove the potential postbiotic role of the fermented food (Vinderola, Cotter, et al. 2023). It is critical to emphasize that, similar to probiotics, postbiotic status is not associated with the microbial species as a whole but rather represents a strain-specific attribute. Accordingly, rigorous characterization and documentation of the bioactivities attributed to individual inactivated strains are essential to define a microorganism as postbiotic (Salminen et al. 2021b). While the academic and scientific communities are still debating the proper meaning of the term postbiotics (Aguilar-Toalá et al. 2021; Salminen et al. 2021a; Vinderola, Sanders, et al. 2024), the concept of postbiotics as defined by ISAPP is gaining consensus in the regulatory context (Vinderola 2024). The use of the term postbiotic, as per the definition given by ISAPP, is gaining ground also across academic environments, as suggested by the constantly increasing number of reviews published on this topic (Stelmach et al. 2024).

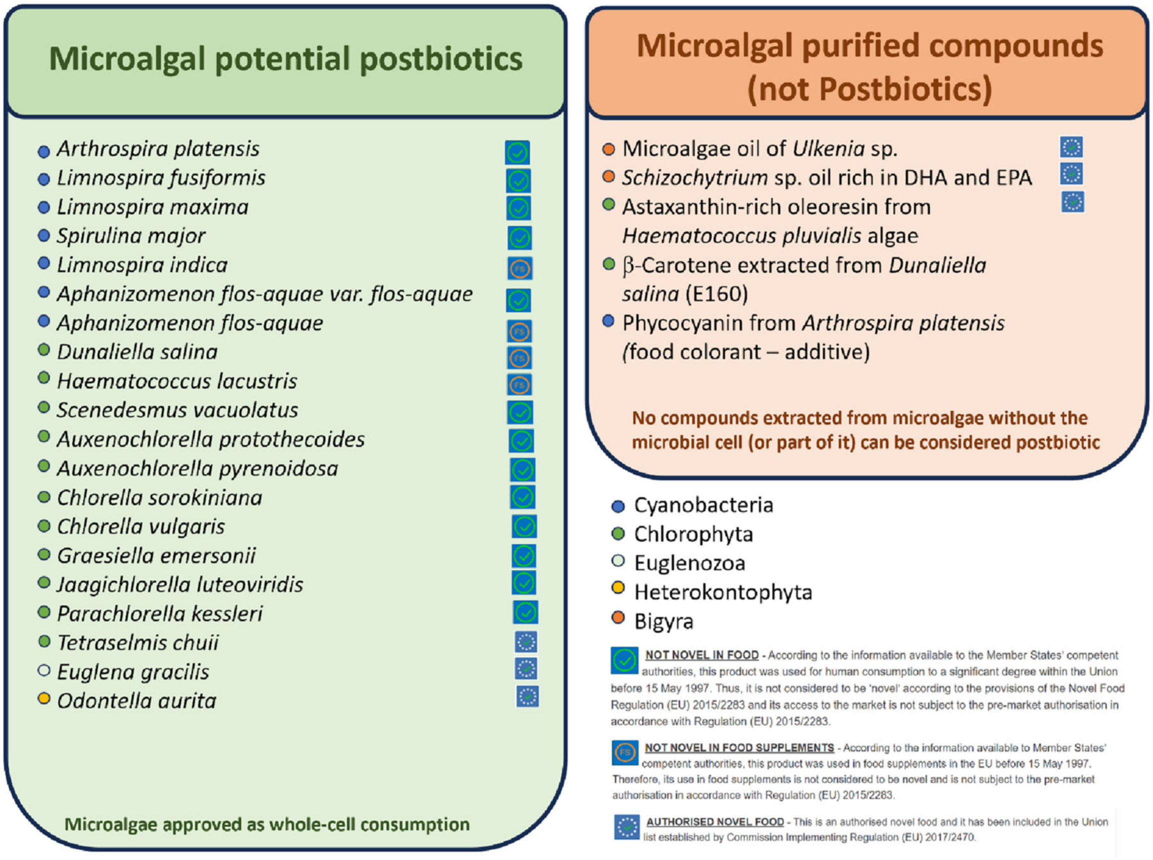
3 | Microalgae and Cyanobacteria Nutritional Aspects and Use in Foods and Food Supplements

Existing food systems are experiencing a crisis due to the challenge of meeting increasing nutrient and protein demand alongside population growth (Rockström et al. 2020). In this context, microorganisms are gaining attention as a new food source due to their valuable protein and nutrient composition, lower carbon footprint compared to traditional food sources, no need for arable land, lower water usage, and independence from seasonal variations (Graham and Ledesma-Amaro 2023). Microalgae and cyanobacteria are among the most promising and extensively studied microbial food sources (Janssen et al. 2022). Their use as food ingredients or food supplements has already been authorized by the European Food Safety Authority (EFSA) and Food and Drug Administration (FDA), and the list of microalgae and cyanobacteria with the QPS (Qualified Presumption of Safety) status is growing. For practical reasons, in this paper, the term microalgae refers to both prokaryotic (cyanobacteria) and eukaryotic microorganisms, including some protists (e.g., *Euglenozoa* and *Bigyra*). They share the ability to perform photosynthesis, converting light energy and carbon dioxide (CO_2) into biomass and O_2 (Hu et al. 2023). Unlike traditional crops, microalgae also show higher productivity in terms of biomass (Kornienko et al. 2018). What makes them particularly promising for future food security is their composition of nutrients. Overall, microalgae contain high levels of dietary fiber, polyunsaturated fatty acids (PUFA), vitamins (A, C, D, E, K, and group B vitamins), and essential minerals like iron, calcium, magnesium, and potassium (Barkia et al. 2019). Microalgae, like *Arthrospira platensis, Limnospira maxima*, *Chlorella vulgaris*, and *Auxenochlorella pyrenoidosa*, are rich in protein, with 50%–70% of protein per dry weight, including essential amino acids (EAA) (J. Y. Wu et al. 2023). The EAA composition in some microalgae meets the Food and Agriculture Organization (FAO) nutritional guidelines and is comparable to conventional protein sources like soybeans and eggs (FAO 2013), suggesting their usage as valuable protein sources on the same level as those obtained from animals (Andrade et al.

2018). The second most abundant component of microalgae is carbohydrates, including polysaccharides like cellulose, starch, and glycogen. The abundance of dietary fibers in microalgae (Wells et al. 2017) is reported to increase satiety, aid peristalsis, slow gastric emptying, and support a healthy gut microbiome (J. Y. Wu et al. 2023). Microalgal species such as *C. vulgaris, A. platensis, Euglena gracilis*, and *Dunaliella salina* are also rich in polysaccharides with potential prebiotic activities such as sulfated polysaccharides, oligosaccharides, glucans (β-glucan), and exopolysaccharides (de Jesus Raposo et al. 2016; Hyrslova et al. 2021; Lv et al. 2022; Patel et al. 2021). These compounds are known for their potential prebiotic activities. However, given the most recent recommendations, more studies should be conducted to classify microalgal compounds as prebiotics (Hutkins et al. 2024). Another important component of microalgae cells is lipids, which are essential for maintaining cellular structure and acting as an energy source (Fernandes and Cordeiro 2021). The lipid content of microalgae is variable, and it can reach 40% in some species. Several species of microalgae are composed of PUFA, frequently commercialized for nutraceutical and pharmaceutical applications, such as omega-3 (ω-3) α-linolenic (ALA, C18: 3), eicosapentaenoic (EPA, C20: 5), and docosahexaenoic (DHA, C22: 6) acids and omega-6 (ω-6), including linoleic (LA, C18: 2), γ-linolenic (GLA, C18: 3), and arachidonic (ARA, C20: 4) acids (Koller et al. 2014). Of great importance is also the high quantity of pigments such as chlorophylls, carotenoids, and phycobilins included in microalgae. As stated before, microalgae represent a phylogenetically diverse group of organisms, encompassing both prokaryotic and eukaryotic and spanning multiple taxonomic kingdoms. The composition of their biomass is highly variable across broad taxonomic levels, and this variability persists down to the species and strain levels. Therefore, greater emphasis should be placed on specifying the exact strain used in cultivation, as strain-level differences could significantly influence the biochemical and functional properties of the biomass. In addition to genetic differences, environmental factors such as cultivation conditions and downstream processing steps play a critical role in shaping the biochemical profile and concentration of bioactive compounds. Microalgal cells are cultivated using two main systems: raceway ponds and photobioreactors (PBR) (Janssen et al. 2022). Raceway ponds are the most used and cost-effective and can be placed in greenhouses for better containment and product control. However, the inability to constantly control cultivation parameters can lead to lower product quality and potential contamination of the biomass by undesirable bacteria (Alinovi et al. 2021; Martelli et al. 2021). Tubular photobioreactor units are closed systems that allow cultivation in controlled conditions, allowing the obtaining of biomasses of higher quality and without any type of undesired contamination (Janssen et al. 2022). Due to their composition, most microalgae are produced to be used as nutraceuticals or food supplements and are sold in powder, tablets, or other dehydrated forms, composed of collected and desiccated biomasses (García et al. 2017). Drying and inactivation of algal biomass are meant to ensure stability, and effective methods are used to preserve microalgae's delicate structure and quality by minimizing thermal and structural degradation (Show et al. 2013). Common techniques include rotary drying, spray drying, drum drying, solar drying, and vacuum or freeze drying. Each method has distinct trade-offs in terms of energy requirements, cost, scalability, and product quality (Loke Show 2022). Alternative approaches to biomass inactivation and treatment have been explored with promising results in preserving the biochemical composition of microalgal biomass. For instance, high-pressure processing applied to *A. platensis* biomass demonstrated no significant impact on pigment composition, total phenolic content, or antioxidant capacity (Alinovi et al. 2021). Similarly, the application of pulsed electric fields to *C. vulgaris* has been shown to effectively induce high cell disruption, leading to enhanced digestibility and bioavailability of its bioactive compounds (Van Nerom et al. 2024). After drying, microalgae can be sold as whole cells or as extracts rich in specific compounds. However, many species of microalgae are also consumed as food ingredients. For example, some microalgal species have been employed in food formulations to obtain or enhance functional and technological properties of cheese, yogurt, soft drink beverages, bread, cookies, and pasta, underlining the efforts of the food industry and scientists to implement the use of these microorganisms in food formulations (Çelekli et al. 2024; Martelli, Alinovi, et al. 2020). Despite their potential as a sustainable source of nutrients and bioactives, the large-scale adoption of microalgae in food systems faces several economic and technological challenges. A primary obstacle in using microalgae as a food ingredient is their strong, often fishy flavor, which limits consumer acceptance and hampers the development of appealing food products (Martelli, Cirlini, et al. 2020). The most significant barrier, however, remains the high production cost of microalgal biomass. Cost analyses, particularly for spirulina, the most widely cultivated microalga, indicate that its price is considerably higher than traditional protein sources (Ciani et al. 2021). Production costs vary significantly with cultivation method: PBRs are more expensive, ranging from €18.71 to €75.29/kg, while open pond systems are more economical, costing between €3.86 and €9.59/kg (Delrue et al. 2017). Although these costs are higher than those for protein crops like soy, advancements in cultivation technology and optimized production strategies are expected to lower costs, enhancing the viability of microalgae as a competitive food ingredient (Barbosa et al. 2023; Lu et al. 2023). Despite these limitations, the global market for microalgal food supplements is expanding rapidly and is anticipated to continue growing in the coming years (Loke Show 2022).

4 | Which Microalgae and Cyanobacteria Can Be Considered Postbiotics?

As previously mentioned, the consumption of several microalgae species as food or food supplements is approved in Europe. Some species have been designated by EFSA as "Novel Food." According to Regulation (EC) No 258/97, subsequently abrogated by (EC) No 2283/2015, a novel food is any product with no significant history of consumption before May 15, 1997, and which is entirely new to the European population (Regulation (EU) 2015/2283 of the European Parliament and of the Council of November 25, 2015, on Novel Foods, Amending Regulation (EU) No 1169/2011 of the European Parliament and of the Council and Repealing Regulation (EC) No 258/97 of the European Parliament and of the Council and Commission Regulation (EC) No 1852/2001 (Text with EEA Relevance), EUR-Lex 2015, 1997). Most microalgal species marketed in Europe were already significantly consumed before that date and are therefore classified as "Not Novel in Food" or "Not Novel in Food Supplement." Examples



✓ **NOT NOVEL IN FOOD** - According to the information available to the Member States' competent authorities, this product was used for human consumption to a significant degree within the Union before 15 May 1997. Thus, it is not considered to be 'novel' according to the provisions of the Novel Food Regulation (EU) 2015/2283 and its access to the market is not subject to the pre-market authorisation in accordance with Regulation (EU) 2015/2283.

FS **NOT NOVEL IN FOOD SUPPLEMENTS** - According to the information available to Member States' competent authorities, this product was used in food supplements in the EU before 15 May 1997. Therefore, its use in food supplements is not considered to be novel and is not subject to the pre-market authorisation in accordance with Regulation (EU) 2015/2283.

AUTHORISED NOVEL FOOD - This is an authorised novel food and it has been included in the Union list established by Commission Implementing Regulation (EU) 2017/2470.

FIGURE 1 | Legal framework of microalgae as postbiotics in the EU; in the green box: microalgae whose consumption as whole cells is approved by EFSA; in the red box: food supplements based on compounds extracted from microalgae. The colored dots indicate the phyla of each microalgal species.

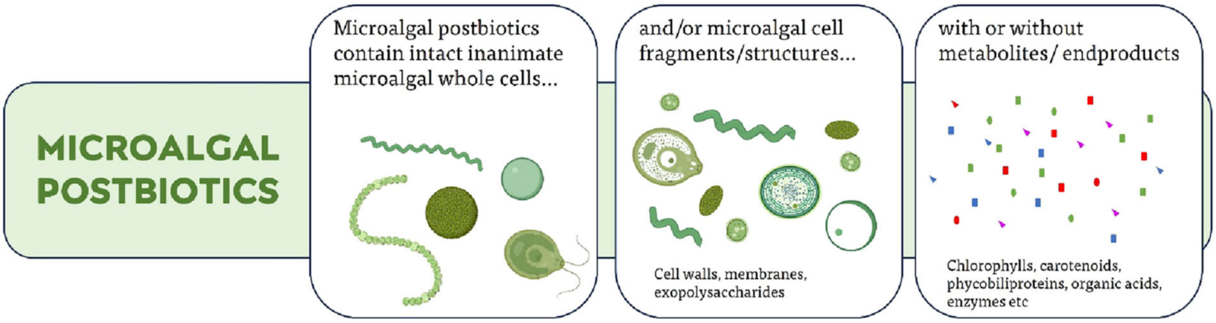


FIGURE 2 | Adaptation of "Microalgal postbiotics" as per the consensus representation of "Postbiotics" given by ISAPP (Salminen et al. 2021b) (Icons produced with BioRender).

are *A. platensis, C. vulgaris*, and *Aphanizomenon flosaquae*. A comprehensive list of microalgae approved as food, and whether they are considered "Novel foods" or not, is presented in Figure 1. EFSA has issued positive safety evaluations for 20 different species of microalgae that can be marketed as whole cells. Of these, most (13 species) are classified as "Not Novel in Food," four are considered as "Not Novel in Food Supplements," and three are categorized as "Novel Foods."

Considering ISAPP's definition of postbiotics, only these 20 species of microalgae could potentially qualify for this designation when sold as inactivated whole cells or broken cells and their components (Figure 2). On the other hand, despite several purified compounds or extracts from microalgae, such as oils from *Ulkenia* spp. and *Schizochytrium* spp., and astaxanthin-rich oleoresin from *Haematococcus pluvialis*, which have been approved as novel foods and demonstrated notable bioactivities, they cannot be classified as postbiotics (Table 1). Bioactive compounds in microalgal biomass provide strong incentives for cultivating these organisms. Numerous studies have indeed explored the bioactivity of microalgal and cyanobacterial components through in vitro analyses, with very promising results across a variety of species. However, despite growing demand for the approval of microalgal species as "Novel Foods," new species are not always successfully approved; for instance, *Phaeodactylum tricornutum*, *Galdieria sulphuraria*, and *Nannochloropsis oculata* were recently

TABLE 1 | Main conclusions of the consensus panel regarding postbiotics published by ISAPP and analysis about why microalgae can be defined as postbiotics.

Conclusion of the consensus panel on postbiotics	Fits for algae?
A postbiotic is defined as a "preparation of inanimate microorganisms and/or their components that confers a health benefit on the host."	Yes, this definition could fit all microalgal biomasses that can be sold as whole cells and have proven bioactivity.
Postbiotics are deliberately inactivated microbial cells with or without metabolites or cell components that contribute to demonstrated health benefits.	Generally, all the whole-cell microalgal food supplements are sold in dehydrated powder, and no live microalgal cells are present in the biomass. Also, the cells are generally broken during the process, giving more access to the cell components (pigments, exopolysaccharides, etc.).
Purified microbial metabolites and vaccines are not postbiotics.	For that reason, only whole-cell microalgae are proposed as postbiotics. No purified supplements of phycobiliproteins (phycocyanin, phycoerythrin), carotenoids (*H. pluvialis* astaxanthin, *D. salina* β carotene), or algal oils (*Ulkenia* or *Schizochytrium*) can be defined as postbiotics.
A postbiotic does not have to be derived from a probiotic for the inactivated version to be accepted as a postbiotic.	There are no microalgae known as probiotic.
The beneficial effects of a postbiotic on health must be confirmed in the target host (species and subpopulation).	The beneficial effect of microalgal biomass and its components is well known and discussed in the literature (Table 2).
The host can include humans, companion animals, livestock, and other targets.	Microalgae are also used for companion animals (dogs and cats) and livestock (fish, chickens, and cows).
The site of action for postbiotics is not limited to the gut. Postbiotics must be administered at a host surface, such as the oral cavity, gut, skin, urogenital tract, or nasopharynx. Injections are outside the scope of postbiotics.	Many bioactivities have been attributed to the consumption of microalgal biomass (Table 2).
Implicit in the definition of a postbiotic is the requirement that the postbiotic is safe for the intended use.	All the microalgae that are described in Figure 1 are considered safe by EFSA and can be consumed in Europe.

denied approval for classification as "Novel Foods" or for QPS (EFSA Panel on Biological Hazards (BIOHAZ) et al. 2020, 2023; EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA) et al. 2023). Regulatory approval of additional microalgal species as food sources could further stimulate growth in the food supplement sector. Additionally, in alignment with ISAPP's guidelines for postbiotics, thorough characterization of these microorganisms and well-documented health benefits through robust clinical trials will be essential for classifying microalgae as postbiotics.

5 | Microalgal-Postbiotics Activity

The bioactivity of microalgae is well documented in scientific literature, with various microalgal components demonstrating notable bioactive properties (Anbarasan et al. 2011; Bancalari et al. 2020; Martelli et al. 2024; Pagarete et al. 2021). However, as previously mentioned, to classify a microorganism as a postbiotic, its bioactivity must be validated through rigorous clinical studies. Table 2 summarizes the health-promoting activities of microalgal whole-cell consumption proven in clinical trials.

Currently, clinical trials involving the consumption of "whole-cell" microalgal food supplements are available for only a subset of the 22 microalgae species approved as food in the EU. *A. platensis*, commercially known as spirulina, is the microalgal species with the highest number of clinical studies. Spirulina is the most widely cultivated and consumed microalgae (cyanobacteria) due to its high protein content (60%–65% dry weight) with a rich profile of EAA (such as leucine, isoleucine, and valine). In 2019, 18,000 tons of this cyanobacteria were produced on a global scale (Janssen et al. 2022). Numerous health-promoting activities have been associated with the consumption of this microorganism. In a randomized, double-blind, placebo-controlled trial involving 52 obese participants, daily intake of 2 g of spirulina combined with a calorie-restricted diet for 12 weeks led to reductions in body weight, waist circumference, body fat, BMI, and triglyceride (TG) levels compared to a calorie-restricted placebo group (Yousefi et al. 2018). Another clinical trial showed similar positive effects on 62 obese subjects after administering 1 g/day of spirulina for 12 weeks, resulting in reduced appetite, BMI, body weight, and total cholesterol (TC) while increasing high-density lipoprotein-cholesterol (HDL-C) (Zeinalian et al. 2017). Proposed mechanisms include reduction in macrophage infiltration into visceral fat, inhibition of hepatic fat buildup, oxidative stress reduction, improved insulin sensitivity, and enhanced satiety (DiNicolantonio et al. 2020). These mechanisms could be linked to chlorophyll derivatives, as well as specific fatty acids and fatty amides present in *A. platensis* and other cyanobacteria biomass, as proved in model studies using *Danio rerio* (Bellver et al. 2021; Freitas et al. 2019; Martelli et al. 2024). Additional

TABLE 2 | List of bioactivities assessed with well-designed clinical trials involving the use of "whole cells" microalgae consumption.

Whole-cell microalgal species consumed with documented health benefits in clinical trials	Reported bioactivities
Arthrospira platensis	Lipid profile improvement (Deng and Chow 2010; H. J. Park et al. 2008; Rahnama et al. 2023; Serban et al. 2016; Zeinalian et al. 2017); antioxidant (Q. Wu, Liu, et al. 2016); immunomodulatory effect (Ge et al. 2019; Masuda and Chitundu 2019a; H. J. Park et al. 2008); antiviral (Ngo-Matip et al. 2015); reduction of myelosuppression (Ge et al. 2019); faster motor development in children (Masuda and Chitundu 2019a, 2019b); reduction of systolic and diastolic blood pressure (Ghaem Far et al. 2021); improvement of Type 2 diabetes (E. H. Lee et al. 2008); improvement of oral submucous fibrosis (Shetty et al. 2013); reduced sleep disturbances (Moradi et al. 2021); weight loss (Yousefi et al. 2018; Zarezadeh et al. 2021; Zeinalian et al. 2017); hypoglycemic activity (Mani et al. 2000)
Limnospira fusiformis	Lipid profile improvement (Ramamoorthy and Premakumari 1996)
Limnospira maxima	Lipid profile improvement (Hernández-Lepe et al. 2019; Szulinska et al. 2017); BMI reduction (Szulinska et al. 2017); improvement of insulin sensitivity (Szulinska et al. 2017); improved total antioxidant status (Szulinska et al. 2017); improvements in blood pressure and endothelial function (Miczke et al. 2016); antihypertensive and antioxidant effects (Martínez-Sámano et al. 2018);
Dunaliella salina	Beneficial activity against psoriasis (Greenberger et al. 2012); improvement of retinitis pigmentosa (Rotenstreich et al. 2013)
Auxenochlorella pyrenoidosa	Defecation quality improvement (Fujishima et al. 2017); reduced risk of pregnancy-associated anemia, proteinuria, and edema (Nakano et al. 2010); stability of the immunity system during intensive training (Chidley and Davison 2018); anti-inflammatory (Chiu et al. 2021); antioxidant (Chiu et al. 2021); reduction of glucose levels (Mizoguchi et al. 2008); lipid profile improvement (Mizoguchi et al. 2008)
Chlorella vulgaris	Improvement of NAFLD (Aliashrafi et al. 2014; Ebrahimi-Mameghani et al. 2014, 2017; Talebi Pour et al. 2015); antioxidant activity on smokers (S. H. Lee et al. 2010; Panahi et al. 2013); decrease in ALT liver enzyme levels (Azocar and Diaz 2013); reduction of fatigue (Noguchi et al. 2014); help to prevent the development of senile dementia (Miyazawa et al. 2013); improvement of dry skin (Noguchi et al. 2014); lipid profile improvement (Kim et al. 2016; Panahi et al. 2015); hypoglycemic activity (Ebrahimi-Mameghani et al. 2017; Panahi et al. 2015); dysmenorrhea reduction (Haidari et al. 2018)
Euglena gracilis	Reduction and prevention of upper respiratory tract infection symptoms (Evans et al. 2019); improved immunological function (S. Park et al. 2023); improvement of digestive health and defecation (Nakashima et al. 2021)

studies highlighted *A. platensis*'s positive effects on lipid profiles, immune function, and antioxidant capacity. For instance, a randomized, double-blind, placebo-controlled study of 78 healthy participants aged 60–87 demonstrated that ingestion of 8 g/day of *A. platensis* for 16 weeks led to improvements in these health parameters (H. J. Park et al. 2008).

When using rats as a model, *A. platensis* supplementation has demonstrated an improvement of gut health by reducing intestinal inflammation, modulating gut microbiota composition, and enhancing gut barrier integrity, thereby counteracting high-fat diet-induced gut dysbiosis and permeability issues (Yu et al. 2020). Comparable benefits were observed when *Limnospira fusiformis* was used (Ramamoorthy and Premakumari 1996). Another cyanophyta, *L. maxima*, has exerted positive effects in clinical trials. Among 50 hypertensive, obese patients on antihypertensive treatment, supplementation with 2 g/day of *L. maxima* for 90 days resulted in significant improvements in body mass index (BMI), waist circumference, LDL-cholesterol (LDL-C), interleukin-6 levels, total antioxidant status, and insulin sensitivity compared to placebo (Szulinska et al. 2017). Furthermore, a trial involving 40 hypertensive patients without evidence of cardiovascular disease showed that 2 g/day of *L. maxima* over 90 days significantly reduced weight, BMI, systolic blood pressure, and arterial stiffness index. These results suggest beneficial cardiovascular effects with short-term, low-dose supplementation

(Miczke et al. 2016). These cyanobacteria contain a range of valuable antioxidant compounds, including vitamin B12, β-carotene, sulfated polysaccharides, tocopherol, various carotenoids, and the phycobiliprotein, phycocyanin (Q. Wu, Liu, et al. 2016). Scientific studies have proven that these components help to neutralize free radicals, reduce oxidative stress, and support cellular health. Phycocyanin is noted for its anti-inflammatory and immune-boosting properties, making cyanobacteria highly valued ingredients in health supplements aimed at enhancing antioxidant defense (H.-L. Wu, Wang, et al. 2016).

Another microalga deeply studied for its ability to accumulate highly efficient antioxidants such as chlorophyll, PUFA, lutein, and zeaxanthin is *Dunaliella*. This Chlorophyta is widely cultivated because it is the most efficient source of β-carotene (Duan et al. 2024), a pigment frequently used as a component in cosmetics or food supplements. Being a potential source of a wide range of nutritionally important compounds, the consumption of *Dunaliella* sp. biomass or its extracts has been studied for the positive effect on the treatment of cardiovascular diseases and cancer, together with immunomodulatory and anti-inflammatory properties (Bansal and Jaswal 2009; Jayappriyan et al. 2013; da Silva et al. 2021; Singh et al. 2016). The beneficial effects related to the consumption of this microalga were also assessed by means of clinical trials. The consumption of capsules of *Dunaliella bardawil* (synonym for *D. salina*) for 12 weeks has significantly positively influenced the Psoriasis Area and Severity Index (PASI) in adult patients with mild, chronic, plaque-type psoriasis during a monocentric, prospective, randomized, double-blinded pilot study (Greenberger et al. 2012). This activity has been attributed to the 9-cis β-carotene naturally present in this microalgal biomass. This compound was linked to the bioactivity of *D. bardawil* also in a randomized, double-masked, placebo-controlled, crossover clinical trial, where 34 patients with retinitis pigmentosa (RP) consumed capsules containing 300 mg of 9-*cis* β-carotene-rich *D. bardawil* daily for 90 days, resulting in increased retinal function (Rotenstreich et al. 2013). β-carotene extracted from *Dunaliella*, has also been indicated to have a positive consequence in alleviating aging and age-related diseases (Duan et al. 2024). *D. salina* is also a very interesting source of PUFA with a content that can range from 7%–60%, depending on the cultivation method and harvesting phase (de Souza Celente et al. 2022). The lipid profile of *D. salina* has been fully characterized, revealing significant in vitro anti-inflammatory, antioxidant, and antidiabetic potential (inhibition of α-glucosidase) of its lipid components (Pais et al. 2024). These findings suggest *D. salina* has a strong potential for use as a food supplement, but clinical studies are needed to confirm its bioactivities also in vivo.

A further genus within Chlorophyta, which is known for its diverse bioactivities demonstrated in both in vitro and in vivo studies, is *Chlorella* (Barkia et al. 2019). As many species within this genus, namely *Auxenochlorella protothecoides, A. pyrenoidosa, Chlorella sorokiniana, C. vulgaris, and Graesiella emersonii*, have been consumed in the EU before May 1997, they are not considered as "Novel Foods." For some of these species, health-related aspects have been investigated. *A. pyrenoidosa* has been studied for its potential to prevent pregnancy anemia and pregnancy-induced hypertension (PIH), given its richness in folate, vitamin B-12, and iron (Nakano et al. 2010). To verify this, 70 pregnant women were involved in a clinical trial, where the test group was supplemented daily, from 12 to 18 weeks of gestation until delivery, with 6 g of *Auxenochlorella* supplement. Findings proved that compared to control group, the group supplemented with *Chlorella* showed a significantly reduced risk of pregnancy-associated anemia, proteinuria, and edema (Nakano et al. 2010). *A. pyrenoidosa* was also proved to improve defecation frequency and conditions (Fujishima et al. 2017) in a randomized, placebo-controlled, double-blind, crossover study conducted on 40 constipated adult women over 4 weeks. Furthermore, depending on the cultivation method, *A. pyrenoidosa* can be considered a valuable source of proteins (65%) (Safafar et al. 2016). Its bioactive peptides show significant health benefits, including antioxidant, antihypertensive effects, anti-inflammatory, cholesterol-lowering, and immunomodulatory properties (Ko et al. 2012; Soto-Sierra et al. 2018). *C. vulgaris* is the second most cultivated microalgae, with 9500 tons produced in 2019 (Janssen et al. 2022). Supplementation of *C. vulgaris* has been investigated as a complementary treatment to limit the effect of non-alcoholic fatty liver disease (NAFLD). In a double-blind randomized placebo-controlled clinical trial on 60 NAFLD patients, participants were given 400 mg/day of vitamin E plus four 300 mg/day of *C. vulgaris* tablets for 8 weeks. The results have demonstrated a significant improvement in fasting blood sugar (FBS) and lipid profiles, supporting the use of this microalga as an effective complementary beneficial adjunct treatment in NAFLD (Ebrahimi-Mameghani et al. 2014). PUFAs, notably long-chain ω-3 and ω-6, are abundant in *Chlorella* and beneficial for cardiovascular, cancer prevention, and neurological health, particularly in early development (Barta et al. 2021). Another study suggested that the numerous nutrients, including antioxidants, present in *C. vulgaris* may provide important antioxidative benefits by scavenging free radicals in smokers. In a randomized, double-blind, placebo-controlled trial, 52 smokers aged 20–65 received a daily supplementation of 6.3 g of *C. vulgaris* for 6 weeks. This supplementation helped maintain plasma antioxidant nutrient levels and improved erythrocyte antioxidant enzyme activity. The supplementation of this microalga resulted in the conservation of plasma antioxidant nutrient status and improvement in erythrocyte antioxidant enzyme activities in patients (S. H. Lee et al. 2010). *Chlorella* is also rich in chlorophyll and carotenoids, pigments critical for photosynthesis and cellular protection from oxidative damage (Ali et al. 2021). Carotenoids, including lutein, have documented roles in antioxidant activity and cardiovascular health, as well as in preventing conditions such as age-related macular degeneration (L. Ma et al. 2012). The anti-inflammatory and analgesic properties of *Chlorella* have also been widely suggested. To assess these effects in vivo, a double-blind, randomized, placebo-controlled clinical trial examined the impact of *C. vulgaris* supplementation (1.5 g/day for 8 weeks) on menstrual pain in 44 young women with primary dysmenorrhea. Among participants receiving *Chlorella*, the severity and duration of the systemic symptoms of dysmenorrhea (fatigue, headache, nausea, vomiting, and lack of energy) decreased significantly (Haidari et al. 2018). Supplementation of *C. vulgaris* has also proved the increase of propionate-producing bacteria in in vitro human gut fermentation. An increase in propionate generation and presence has been reported to be effective in weight loss and inhibition of pathogen infection (Jin et al. 2020). Furthermore, while using zebrafish as a model organism, the supplementation of *C. sorokiniana*, *A. platensis*, and *D. salina* improved zebrafish growth performance, enhanced immune status by reducing pro-inflammatory cytokine expression, and promoted gut health

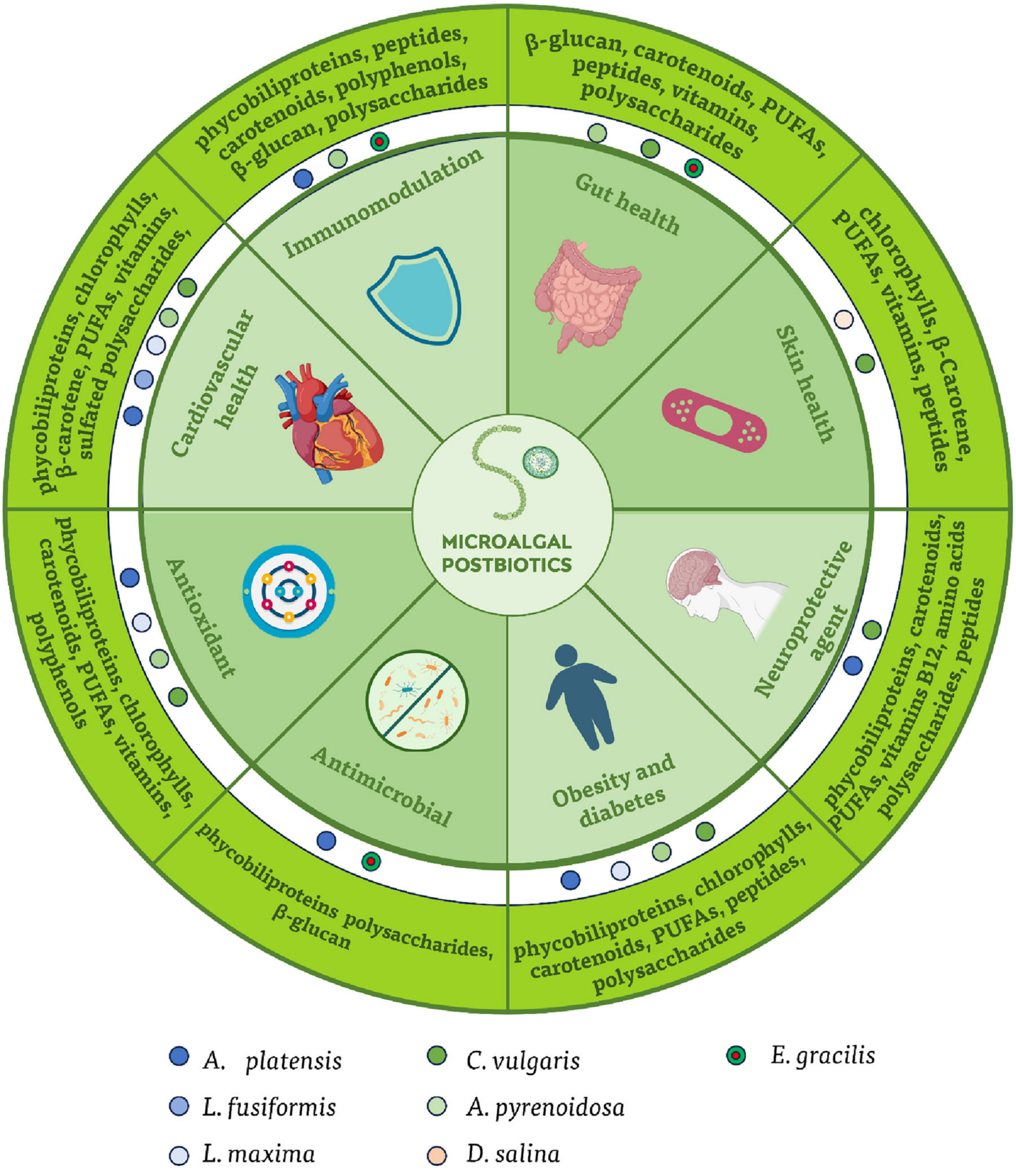


FIGURE 3 | Schematic representation of the main health-promoting activities associated with microalgal whole-cell consumption, as demonstrated in clinical trials, along with the putative bioactive compounds responsible for these effects. Colored dots indicate the microalgal species evaluated in clinical settings and shown to exert the indicated bioactivities. (Icons produced with BioRender).

by modulating the gut microbiota, increasing beneficial bacteria (K. Ma et al. 2022).

A further species of potentially beneficial algae is *E. gracilis*, one of the few microalgae (Protist) approved by EFSA as a "Novel food" (EFSA Panel on Nutrition, Novel Foods, and Food Allergens (NDA) et al. 2020). In its safety evaluation, EFSA recognized *E. gracilis* as an ingredient with a not disadvantageous nutritional profile, rich in vitamins (C, E, D2, D3, and K), minerals, fatty acids, carotenoids, and amino acids, and containing a high content of β-1,3-glucan (at least 50%) (EFSA Panel on Nutrition, Novel Foods, and Food Allergens (NDA) et al. 2020). β-glucan plays an important role in regulating metabolic disturbances linked to metabolic syndrome (El Khoury et al. 2012). The benefits of β-glucan stem from its structural characteristics, enabling it to form viscous solutions in the upper gastrointestinal tract and undergo fermentation in the colon, working as one of the most studied prebiotics (Gibson et al. 2017; Hutkins et al. 2024). β-1,3-glucan from *E. gracilis* was also linked to immunomodulatory effects upon consumption. In one clinical trial, researchers investigated the impact of β-1,3-glucan-rich *E. gracilis* (over 50% content) on immune function and the prevention of upper respiratory tract infection symptoms. A total of 34 healthy, endurance-trained participants were randomized to receive either 367 mg of *E. gracilis* supplement or a placebo for 90 days. The group receiving *Euglena* supplementation reported significantly fewer sick days, reduced upper respiratory infection symptoms, and shorter duration and intensity of symptoms compared to the placebo group (Evans et al. 2019). The immune-boosting effects of *β*-1,3-glucan in *E. gracilis* were further evaluated in another clinical trial involving 100 healthy male and female volunteers. These were 20–70 years old, showed white blood cell counts ranging from 4×10^3 to 10×10^3/μL, had a history of at least two upper respiratory infections in the past, and had a "severe" stress rating. Participants received 700 mg/day of *E. gracilis* powder for 8 weeks, showing a significant increase in NK cell activity, thus an improved immune function. The authors concluded that *Euglena* consumption has promising potential for supporting immune function in healthy individuals (S. Park et al. 2023). The potential role of *β*-1,3-glucan from *E. gracilis* as an immunomodulatory agent has also been studied in animals (de Carvalho et al. 2023; de Souza Theodoro et al. 2024; Yamamoto et al. 2018). However, the effects of *E. gracilis* on immune function have been defined as only partially attributable to the content of the *β*-glucan, suggesting the need to deepen the knowledge of mechanisms regulating additional cellular responses (Phillips et al. 2019). Figure 3 illustrates the main health-promoting activities of microalgal whole-cell consumption demonstrated in clinical trials, along with the putative compounds responsible for these bioactivities.

6 | Conclusions

The reported number of studies showing that the consumption of certain microalgal species, as inactivated whole cells or derived products, can positively impact health suggests the possibility to classifying these microorganisms as postbiotics. While much of the existing research and evidence focuses on *A. platensis* and *C. vulgaris*, findings on other microalgal extracts indicate promising avenues for discovering new bioactive properties of microalgae. These properties, pending validation through in vivo clinical trials, could further expand the scope of microalgae with postbiotic potential. As more studies emerge to clinically validate the health effects of consuming these species in whole-cell form, the list of microalgae qualifying as postbiotics is expected to grow. Several other species of microalgae and cyanobacteria have already been approved as food sources worldwide. For instance, the FDA has approved *Chlamydomonas reinhardtii*, *Prototheca moriformis*, and *Schizochytrium sp*. (Ferreira De Oliveira and Bragotto 2022); similarly, in China and Japan, *Nostoc commune*, *Aphanothece sacrum*, and *Nostoc flagelliforme* have a long history of safe consumption (Gao and Ye 2003). Expanding the catalog of microalgae recognized as "Novel Foods" also in Europe could pave the way for new microalgal-derived postbiotics and food supplements with beneficial effects. Unlike traditional postbiotics, which are typically derived from *Lactobacillaceae*, *Bifidobacteria*, and other well-known chemoorganotrophic microorganisms, microalgae and cyanobacteria are photosynthetic organisms rich in pigments such as chlorophylls, carotenoids, and phycobiliproteins. These pigments remain in the biomass even after cell inactivation and represent a distinctive source of bioactive compounds. The wide variety of functional compounds associated with different microalgal species suggests the possibility of addressing their cultivation to obtain postbiotics. However, both biomass yield and bioactive compound content are significantly influenced by specific strain as well as by growth factors such as light, temperature, and nutrient medium (Ebrahimi-Mameghani et al. 2014). To support the effective selection and application of microalgal postbiotics, it is essential for the scientific community and algae producers to specify the strains used and document cultivation conditions. This level of detail will enable a more precise correlation between bioactivities and the specific strains under the chosen cultivation conditions.

A recent call to action, published in the paper called "Microbial solutions must be deployed against climate catastrophe," highlights the critical role that microorganisms play in addressing the impending climate crisis (Peixoto et al. 2024). Among the microbial strategies to mitigate the catastrophic impact on human health, developing "microbial therapies" using probiotics, postbiotics, and prebiotics stands out as a promising solution. Recent studies highlight the significant therapeutic potential of postbiotics as functional food components in managing cancer, diabetes, and inflammatory diseases, underlining their value in future medical and nutritional applications (Gurunathan et al. 2024). Consequently, research focused on innovative postbiotics and the recognition of microalgae as a valuable health-boosting resource is becoming increasingly essential.

Author Contributions

F.M., C.N., and B.B. wrote the main manuscript text, and F.M. prepared Figures 1 and 2 and Tables 1 and 2. All authors reviewed the manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

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