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The microalgal sector in Europe: Towards a sustainable bioeconomy

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ABSTRACT

Microalgae are a diverse group of photosynthetic microorganisms that can be exploited to produce sustainable food and feed products, alleviate environmental pollution, or sequester CO_2 to mitigate climate change, among other uses. To optimize resource use and integrate industrial waste streams, it is essential to consider factors such as the biology and cultivation parameters of the microalgal strains, as well as the cultivation system and processing technologies employed. This paper reviews the main commercial applications of microalgae (including cyanobacteria) and examines the biological and biotechnological aspects critical to the sustainable processing of microalgal biomass and its derived compounds. We also provide an up-to-date overview of the microalgal sector in Europe considering the strain, cultivation system and commercial application. We have identified 146 different microalgal-derived products from 66 European microalgae producers, and 49 additional companies that provide services and technologies, such as optimization and scalability of the microalgal production. The most widely cultivated microalga is 'spirulina' (*Limnospira* spp.), followed by *Chlorella* spp. and *Nannochloropsis* spp., mainly for human consumption and cosmetics. The preferred cultivation system in Europe is the photobioreactor. Finally, we discuss the logistic and regulatory challenges of producing microalgae at industrial scale, particularly in the European Union, and explore the potential of new genomic techniques and bioprocessing to foster a sustainable bioeconomy in the microalgal sector.

1. Introduction

The rapid deterioration of natural resources and high CO_2 emissions from non-renewable fuels, mainly from industrial activities, are causing a high impact on climate. Bioeconomy is recognized as a realistic solution for achieving sustainable development and contributing to the United Nations' Sustainable Development Goals (SDGs) [1]. The circular bioeconomy model has gained attention for its emphasis on a sustainable production, the utilization of renewable resources, and their conversion into value-added products [2]. Microalgae biotechnology is seen as a promising approach to save natural resources, reduce CO_2 emissions, and produce compounds and molecules sustainably, as shown by the growing literature in the last decade [3]. Cultivation of microalgae to sequester CO_2, removal of macronutrients from other industries, and generation of biomass for different purposes are part of the strategies implemented by the EU to reach zero pollution, circularity and protection of our ecosystems [4]. The cultivation of microalgae for biomass production has numerous advantages over terrestrial crops, supporting the principles of a sustainable bioeconomy: (i) Due to their short generation times (~24 hours), microalgae can produce relatively large amounts of biomass without the need of arable soils; (ii) the nutrient uptake rate in microalgae is very efficient, contributing to minimize nutrient pollution in the environment [5]; (iii) the high efficiency to fix CO_2 has positive implications in the context of global climate change [6]. Within the microalgal sector, economic sustainability can be achieved through the different production steps, ranging from the optimization of resource use (water, nutrients) in the upstream production to the valorization of waste and/or side-streams in the downstream processing (bioprocessing) [7].

Here, we review the main current applications of microalgae biomass for commercial use to obtain products (bioenergy, biomaterials, biofertilizers, proteins for food and feed, high-value products) and environmental benefits (carbon sequestration, bioremediation), and we examine the biological and biotechnological aspects critical to the

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sustainable processing of microalgae biomass and its derivatives. We also provide an up-to-date overview of the most common strains, cultivation systems and biotechnological applications, and we show potential market trends in Europe, in comparison with other continents. Finally, we discuss the logistic and regulatory challenges of producing microalgae in Europe, and identify new perspectives to foster a sustainable bioeconomy in the microalgal sector.

2. Biology of microalgae

2.1. Characteristics of microalgae

Microalgae are microscopic photosynthetic organisms that play an important role in the global carbon cycle [8], as they convert CO_2 into biomass with different industrial applications*e.g.,* biofuels, food, feed, and high-value products [9]. The diversity of these microorganisms at various levels (phylogenetic, morphological, physiological) is also reflected at the taxonomic level, with two main groups: eukaryotic microalgae (mainly kingdom Chromista, *sensu* [10]) and prokaryotic cyanobacteria (kingdom Bacteria), colloquially considered as microalgae due to similar cultivation processes and biotechnological applications as eukaryotic microalgae [5]. Most microalgae are unicellular, with a morphology that varies largely from species to species, and reproduce asexually, but some species may reproduce sexually under stress, *e.g.*, *Chlamydomonas* spp. [11].

The number of microalgal species is currently uncertain, but numerous efforts to estimate global diversity have been made. Guiry [12] reported estimates of 21,000 different species of the two most common microalgal groups (*i.e.*, 8000 cyanobacteria and 13,000 eukaryotic green microalgae). According to AlgaeBase, the largest online dataset of microalgae and seaweeds, the recorded species number of the two major microalgal groups is around 14,000 (6000 cyanobacteria and 8000 green microalgae) [13]. These figures are in contrast to the low number of species (less than 30) that are currently exploited in Europe for biotechnological applications [14].

In nature, most microalgae grow autotrophically and synthetize biomolecules by using light and inorganic compounds (water, CO_2) via photosynthesis. Some microalgae can grow heterotrophically, using organic compounds as a substrate, but strict heterotrophy is not common unless it is induced and maintained over time under controlled conditions (*e.g.*, [15–17]). Only few microalgae are capable of combining both heterotrophic and autotrophic nutrition modes (mixotrophy), and shift to heterotrophy when resources are limiting in nature, *e.g.*, *Ochromonas* spp. [16].

Two microalgae dominate the industrial production of microalgal biomass globally [18]: *Chlorella* spp. (eukaryotic) and the cyanobacterium *Limnospira* spp. (formerly known as *Arthrospira* spp. [19], and commonly referred to as ‘spirulina’). Both microalgae have been commercially cultivated for several decades, with a long history of safe use, and are regarded as some of the most promising systems for the bioeconomy [18]. Table 1 summarizes the main properties of both microalgae.

2.2. Microalgal biocompounds of interest and applications

Microalgal cultivation conditions usually differ from strain to strain and will depend on the targeted compound of interest. Once the optimal conditions are reached, microalgae can produce a wide variety of compounds. Common uses include either untransformed biomass for food or feed or, after some processing, high-value products with applications in bioenergy, cosmetics, pharmaceutical, or food industries, as well as bioremediation technologies [42–44]. Examples of compounds that are currently commercialized include pigments (*e.g.*, chlorophylls, phycoerythrin, phycocyanin and carotenoids, including astaxanthin and lutein), polyunsaturated fatty acids (PUFAs), exopolysaccharides (EPS), and mycosporine-like amino acids (MAAs) [45]. See Table 2 for a

Table 1

List of biological, ecological and cultivation-processing characteristics of the two most commonly cultivated microalgae, *Chlorella* spp. and *Limnospira* spp. (commercially known as ‘spirulina’). References in the first column are common references to the second and third columns. Abbreviations: HABs = Harmful Algal Blooms, HGT = Horizontal Gene Transfer, PBRs = Photobioreactors.

Characteristics	*Chlorella* spp.	*Limnospira* spp. (’spirulina’)
General organism classification	Eukaryotic	Prokaryotic
Total species number	> 100 [20,21]	> 20 [19]
Species of commercial interest	6	3
Average composition (dry weight, [18])	60 % proteins, 10–15 % polysaccharides, 12–15 % lipids, pigments (chlorophylls, lutein), B vitamins	70 % proteins, 15–25 % polysaccharides, 3–9 % lipids, pigments (phycocyanin), B vitamins, iron, manganese
Cultured since [22]	1975	1965 [23]
Processed products obtained since [22]	1994	1985
Annual production (estimation, fresh weight, [24])	4000 T	10000 T
Producing countries	Japan, China, Taiwan, Germany, etc [25]	> 22 countries, with China as the main producer [23, 24]
Toxin-producing and/or harmful species (*sensu* [26])	No [27]	Only *A. fusiformis* has shown harmful effect [26]
Habitat	Freshwater, terrestrial, marine	Mainly freshwater (3 marine species)
Reproduction	Autospores (asexual); fast growing	Fragmentation (asexual); bloom forming
Morphology	Coccoid	Straight or spirally coiled filaments
Cultivation system [22]	Open ponds, PBRs, fermenters	Natural locations, open ponds (raceway), semi-open ponds (enclosed), PBRs
Main mode of cultivation (energy source)	Photoautotrophic, mixotrophic, heterotrophic	Photoautotrophic
Cultivation parameters	Thermal tolerance, N starvation to increase lipid content [28]	High pH (8.5–10.5); high salinity (20–70 mg/L); high light conditions (tropics) [23]
Biocompounds of interest	Proteins, lipids, lutein, astaxanthin (one species), Chlorella Growth Factor (CGF)	Proteins and amino acids, phycocyanin, phytohormones
Improved traits (without NGTs)	Higher lipid yield (biofuels) [29]; higher lutein production (human visual function) [30]; higher protein levels (food, feed) and lower chlorophyll levels (higher palatability) [31]	Higher protein levels (food, feed); higher C-phycocyanin levels (nutraceuticals, cosmetics, food colorants) [32]
Required processing steps	Monitoring (contamination), drying, break cell wall (high cellulose content, not digestible by humans)	Monitoring (contamination and photoinhibition, if cultivated outdoor), drying
Applications [18]	Food supplement, food emulsion, food colorant, bioremediation (wastewater), cell factory (biomedicine)	Food supplement, protein supplement (poultry and livestock feeds, aquaculture); colorant (food, feed); fertilizer and/or biostimulant; bioremediation (heavy metals) [23]; anti-cancer [33]
Commercial applications available on the market	Food supplement (powder, tables, capsules); cosmetics (moisturizing, antioxidant properties); feed supplement (aquaculture, poultry)	Food supplement (powder, tables, capsules), feed supplement and additive, biostimulant

(*continued on next page*)

Table 1 (*continued*)

Characteristics	*Chlorella* spp.	*Limnospira* spp. ('spirulina')
Potential risks to the environment	Outcompete endemic and/or rare phytoplankton species (medium)	HGT (high), HABs (rare)
GRAS status (Generally Recognized As Safe) [34]	Yes, *C. sorokiniana* [35]	Yes, *L. platensis* [36]
Novel Food status [37]	*C. protothecoides, C. pyrenoidosa, C. sorokiniana, C. vulgaris, C. luteoviridis, C. kessleri* do not fall under the scope of Novel Food Regulation (consumed in EU countries before 1997) [38, 39]	*L. platensis* do not fall under the scope of the Novel Food Regulation (consumed in EU countries before 1997)
Animal feed status [40]	No species registered as animal feed or ingredients for animal feed	*L. platensis and L. maxima* are registered as animal feed or ingredients for animal feed
Biostimulant status [41]	Allowed	Not allowed

selection of compounds obtained from microalgae and their applications.

A simple way of classifying the biocompounds is to make a distinction between primary metabolites, directly involved in the general metabolism of microalgae (lipids, proteins and carbohydrates); and secondary metabolites, which are not directly involved in the survival of the microalga (pigments, alkaloids, isoprenoids, sterols, MAAs, etc.). Table 2 shows the different microalgal metabolites according to this classification.

2.2.1. *Current applications of microalgae*

Current applications of microalgae include, but are not limited to:

1) **Nutritional supplements (nutraceuticals)**: Spirulina and *Chlorella* spp. have high protein content, vitamins, minerals, essential amino acids and fatty acids, and are allowed as food/feed supplements [35, 36] (Tables 1 and 2). Also, food supplements containing microalgal pigments are commercialized for their health benefits; for example, lutein and β-carotene have anti-inflammatory properties and positive effects on eye health [42,54,68](Table 2).

   Functional ingredients in food and beverages include microalgal oils, rich in DHA and EPA, as a plant-based alternative to fish oil supplements rich in omega-3 fatty acids.

   Most microalgal pigments (chlorophylls, β-carotene, astaxanthin, lutein, phycocyanin, phycoerythrin) are used in the food and beverage industry as food colorant [54].

   Supplementary information Table SI 1 shows examples of microalgae-based food supplements, functional ingredients and colorants produced and commercialized in Europe.
2) **Aquaculture (aquafeed) and animal feed**: Microalgal biomass is used as a protein-rich ingredient for aquaculture (fish, shrimps, bivalves), livestock industries (poultry, pig, cattle) and animal feed for pets. Both marine and freshwater microalgal species are cultivated for animal feed. We identified at least eight companies in Europe with specialization in aquafeed and hatcheries using microalgae, and seven companies producing products for pet feed and animal feed (see Supplementary Information Table SI 1).
3) **Agricultural applications**: Microalgal by-products can be used as biostimulants, due to their high levels of primary nutrients (N, P, K) and micronutrients (Mg, Cu, Zn) [73]. The application of live cyanobacteria as biofertilizers can improve crop yields, since some species fix atmospheric N_2 and convert it to ammonia (which can be assimilated by plants).

   Some microalgal extracts have shown phytostimulant activity due to their production of phytohormones [74]. In Europe, several companies produce biostimulants rich in amino acids from microalgae [75–77]. Interestingly, none of them provide the microalgal composition in the technical factsheets. This could be part of a strategy to gain trust of farmers, as a recent study showed that farmers have low knowledge of microalgae and low levels of acceptance of using microalgae as biofertilizers [78].
4) **Cosmetics and personal care**: Specific microalgal compounds, algal extracts and algal oils are commonly used in cosmetics. Examples of specific compounds are astaxanthin and lutein (powerful antioxidants used as an anti-aging agents), MAAs (with photoprotector properties, used in sunscreens, anti-photoaging agents and wound-healing agents), and EPS (with moisturizing and hydrating properties, Table 2) [79]. Algal extracts and oils are purified extracts from one or more microalgal strains, with a high concentration of fatty acids, in the case of algal oils. We identified at least 13 companies in Europe that develop microalgae-based active ingredients for the cosmetic industry , five of them in France (Supplementary Information Table SI 1).
5) **Pharmaceuticals**: Regulations on pharmaceutical products are stricter than those on nutraceuticals and cosmetics, and Good Manufacturing Practices (GMP) are mandatory. The main applications of microalgae in the pharmaceutical and medical industries include compounds with antimicrobial, anti-inflammatory and antitumor properties, recombinant proteins, and drug delivery systems [42,68]. Microalgae have demonstrated antimicrobial activity against different microorganisms (virus, bacteria, fungi) and structures (biofilms) [68].

   To date, a variety of recombinant proteins have been produced experimentally from the nuclear or chloroplast genome of microalgae. These include monoclonal antibodies, vaccines, hormones, pharmaceutical proteins, and industrial enzymes, amongst others. *Chlamydomonas reinhardtii* is generally recognized as a safe host for the production of high-value recombinant products, and has been successfully employed as a green cell factory ([80] and references therein).

   A recent review on microalgae-made vaccines shows six prototypes against animal infectious diseases, and twelve cases of microalgae-made vaccines against human infectious diseases [81]. Preclinical trials have been carried out in most cases, but further research is needed [81].

   Microalgae used as drug delivery carriers include the nanocarriers from the diatom shells. The porous silica nanoparticles (SiO_2) from diatoms have low toxicity and high biocompatibility, compared to synthetic materials [68,69]. Siliceous shells from diatoms can be also used as an excipient in pharmaceutical formulations (*e.g.,* patent WO2011148209A2 from Egis Pharmaceuticals PLC, Budapest, Hungary). The use of other microalgae as drug excipients due to their emulsifying and foaming properties is still in early stage [42].
6) **Wastewater treatment and bioremediation**: Microalgae are used in (tertiary) wastewater treatment plants to remove pollutants and excess macronutrients (N, P) from industrial and urban effluents [82]. Microalgae can be also used for bioremediation and purification of polluted or damaged aquatic systems to remove organic matter, nutrients, heavy metals and/or specific pollutants [83–85]. Spirulina, *Chlorella* spp., *Scenedesmus* spp., *Picochlorum* sp. and *Tetraselmis* sp. are common microalgal genera used in wastewater treatment and can be valorized for biofuel and other applications [86]. We identified several companies in Europe that either use residual effluents from the industry to produce microalgal biomass for animal feed, or use microalgae in tertiary wastewater treatments as a Nature-based Solution (NbS) (Supplementary Information Table SI 2).
7) **Carbon sequestration**: Microalgae are known as the most efficient biological sequesters of CO_2. Recently, they have been exploited to

Table 2

List of the most relevant microalgae-derived compounds, their main properties and commercial applications. Asterisks denote prospective uses or applications that are not available on the market. Abbreviations: PUFA = Polyunsaturated fatty acids; DHA = Docosahexaenoic acid; EPA = Eicosapentaenoic acid; ARA = Arachidonic acid.

Compound name	Properties	Applications	Microalgae	References
Carbohydrates				
Exopolysaccharides (EPS) *e.g.*, β-glucan	Adhesion of biofilms, antiviral activity, antitumor action, sorption of compounds	Food industry (thickeners, preservatives), medical use, wastewater treatment, soil health	*Chlorella* spp., *Chaetoceros* spp., *Euglena gracilis*	[44,46,47]
Sulfated polysaccharides *e.g.*, Spirulan	Anti-inflammatory, antiviral activity, anti-adhesive action	Medical use (treatment of herpes simplex, preventing adhesion of tumor cells and bacteria)	*Limnospira platensis, Porphyridium* spp. (sulfated EPS), *Cylindrotheca closterium* (sulfated EPS)	[44,48,49]
Lipids and fatty acids				
Omega−3 PUFAs *e.g.*, DHA, EPA, ARA	Cardioprotective properties, immuno-modulatory	Human functional foods (omega−3 supplement); animal feed (aquaculture, livestock)	*Chlorella* spp., *Nannochloropsis* spp., *Schizochytrium* spp., *Phaeodactylum tricornutum, Porphiridium cruentum*	[44,50,51]
Phytosterols *e.g.*, ergosterol, cholesterol, campesterol	Cholesterol-lowering activity, anti-inflammatory	Functional foods, pharmaceutics	*Pavlova lutheri, Scenedesmus quadricauda, Isochrysis galbana, Nannochloropsis* sp., *Dictyosphareium* sp.	[52,53]
Pigments				
Chlorophylls *e.g.*, chlorophyll *a*, chlorophyll *b*	Coloring effect, tissue growth stimulation, antioxidant	Food and beverage colorant (green pigmentation); odor masking (personal care products); ulcer treatment, cosmetics	*Chlorella* spp., *Scenedesmus* spp., *Selenastrum* spp. (*Monoraphidium* spp.), *L. platensis*	[44,49,54,55]
Astaxanthin (carotenoid)	Coloring effect, lipid-lowering activity, potent antioxidant	Food and beverage colorant (red pigmentation), aquafeed colorant (salmonids), food supplement, sports nutrition, animal nutrition, pharmaceutics, cosmetics	*Haematococcus pluvialis, Chlorella zofingiensis*	[44,56]
β-carotene (pro-vitamin A)	Antioxidant, anti-tumor, eye health	Food supplement, food colorant, cosmetics, animal feed	*Dunaliella salina*	[44]
Fucoxanthin	Anti-inflammatory, antioxidant and oxidative stress prevention, anti-microbial, skin protection against UVR	Nutraceutical, cosmetics (UV-blocking, anti-aging)	*Isochrysis galbana, P. tricornutum, Odontella aurita*	[42,44,57,58]
Lutein (carotenoid)	Skin protection against UVR, antioxidant, eye protection	Food supplement, colorant (feathers, egg yolk), cosmetics	*Tetraselmis* sp., *Scenedesmus* sp., *Chlorella* spp., *Muriellopsis* sp., *Chlamydomonas* sp.	[42,44,59–62]
Lycopene	Antioxidant, skin protection against UVR	Food colorant, cosmetics (antiaging, sunscreens)	*Anabaena vaginicola*	[44,63]
Polyphenolic compounds ***e.g.*, phenolic acids, flavonoids**	Antioxidant, anti-inflammatory, anti-microbial	Nutraceuticals	*Chlorella pyrenoidosa, C. minutissima, D. salina, L. platensis*	[49,60]
Proteins, peptides, amino acids				
Mycosporine-like Amino Acids (MAAs) *e.g.*, Shinorine, palythine, mycosporine-glycine	Skin protection against UVR, anti-desiccant, anti-cancer, antioxidant, anti-photoaging, wound healing agent	Cosmetics (sunscreens, antioxidants); pharmaceuticals (fibroblast growth promoter), additives to protect materials against UV radiation	*Anabaena* spp., *C. vulgaris, D. salina, Scytonema* sp., *L. platensis, Glenodinium foliaceum*	[42,45,64–66]
Phycobiliproteins (PBP) *e.g.*, phycoerythrin (PE), phycocyanin (PC)	Antioxidant, hepato-protective, anti-inflammatory, immuno-modulatory, anti-cancer	Food, cosmetic and textile colorant, fluorescent probes, pharmaceuticals	Cyanobacteria *(L. platensis, Aphanizomenon flos-aquae,* etc.), *P. cruentum, P. aerugineum*	[49,63,67]
Silica ***e.g.*, silica nanoparticles, diatomite**	Filtering properties, natural particles of nanoscale size	Biosensing, water filtration / purification, medical (drug delivery, excipients)	Diatoms	[42,68,69]
Toxins				
Cyanotoxins *e.g.*, microcystins, anatoxins, saxitoxins	Allelochemical properties	Biocides	Cyanobacteria (*Microcystis* spp, *Anabaena* spp, *Aphanizomenon* spp., *Lyngbya* spp., etc.), dinoflagellates (*Alexandrium* spp., *Gymnodinium* spp., *Pyrodinium* spp., etc.)	[70]
Vitamins ***e.g.*, vitamins B_1, B_2, B_3, B_6, B_9, B_{12}, C, E.**	Antioxidant	Food supplement (including vegan population), cosmetics, animal feed	Most microalgae *(Tetraselmis suecica, Dunaliella tertiolecta, Skeletonema marinoi*, etc.)	[42,44,61]
Minerals and trace elements				
Macrominerals *e.g.*, calcium, nitrogen, magnesium, phosphorous, potassium, sodium, sulfur	Essential nutrients for metabolism	Macronutrients (food and feed industry), biostimulants	Most microalgae *(Phaeodactylum* sp., *Thalassioria* sp., *Amphora* sp., *Achnanthes* sp., etc.*)*	[42,44,61,71]
Microminerals *e.g.*, cobalt, copper, iodine, iron, manganese, molybdenum, selenium, zinc	Physiological functions (as enzyme cofactors and hormone components)	Food supplement, cosmetics, biostimulants	Most microalgae (*Tetraselmis chuii, Phaeodactylum* sp., *Aphanothece* sp., *Navicula* sp., *Thalassiosira* sp., etc.)	[42,44,61,71]
Enzymes ***e.g.*, cellulases, amylases, galactosidases, proteases, lipases, antioxidant enzymes, carbon accumulation enzymes**	Degradation, hydrolysis or catalysis of carbohydrates, proteins, lipids, phenolic compounds, antioxidant activity, carbon fixation	Food and feed industry, bioremediation (macronutrients, heavy metals, antibiotics, phenol, colorants), medical use, biofuels*	*Chlamydomonas reinhardtii, Chlorella ellipsoidea*, cyanobacteria (*Synechococcus* sp., *Anabaena* spp., *A. platensis*), *P. cruentum, D. tertiolecta, Nannochloropsis oceanica*	[72]

enhance air quality by decreasing CO_2 levels and toxic chemicals from the air and increasing oxygen (O_2) concentrations, as a mechanism of air purification [87].

The intrinsic property of CO_2 fixation of microalgae is nowadays gaining more interest due to the high value of microalgae in the Voluntary Carbon Markets (VCM). VCM give companies, nonprofits, governments and individuals the opportunity to buy and sell carbon offset credits, in form of a certain amount of CO_2 or GHG emissions that will be reduced.

In the context of climate change, microalgae can be advantageous to positively impact on the rumen microbiome of cattle and reduce the enteric emission of methane [88,89].

We identified eleven companies in Europe that are currently offering biosolutions for Carbon Capture and Utilization (CCU), and three companies in Europe that are improving microalgae and/or cyanobacteria that increase the capture of CO_2 and transform it into green chemicals (Supplementary Information Table SI 2).

8) **Biofuels**: Microalgae and cyanobacteria have been used to produce third-generation biofuels since early 2000s because they produce 20–300 times more oils than conventional crops [90]. The various forms of biofuels generated from microalgae (biodiesel, bioethanol, biomethane, biohydrogen) are considered as an alternative energy source for fossil fuels without GHG emissions. As biomass for biofuels from crop plants (maize, corn, soybean) have negative impacts on food markets, water supply and arable land; microalgae are being used as feedstock for third-generation biofuels [91]. However, third-generation biofuel production is not economically (not environmentally) viable at industrial-scale [90], since high levels of energy, nutrients and water are needed to scale-up, increasing costs enormously. To address these challenges, genetically modified (GM) algae are currently used to enhance biofuel production by improving photosynthetic efficiency, increasing light penetration, and/or reducing photoinhibition [92]. However, legislation issues and environmental risks related to the production of GM microalgal biomass are two important topics that need further attention [90,92,93].
9) **Biopolymers**: Novel applications in industry include the use of microalgal compounds to produce biopolymers, such as polyhydroxyalkanoates (PHAs), microalgal starch and microalgal cellulose [94]. In all cases, these biopolymers are composites and blends

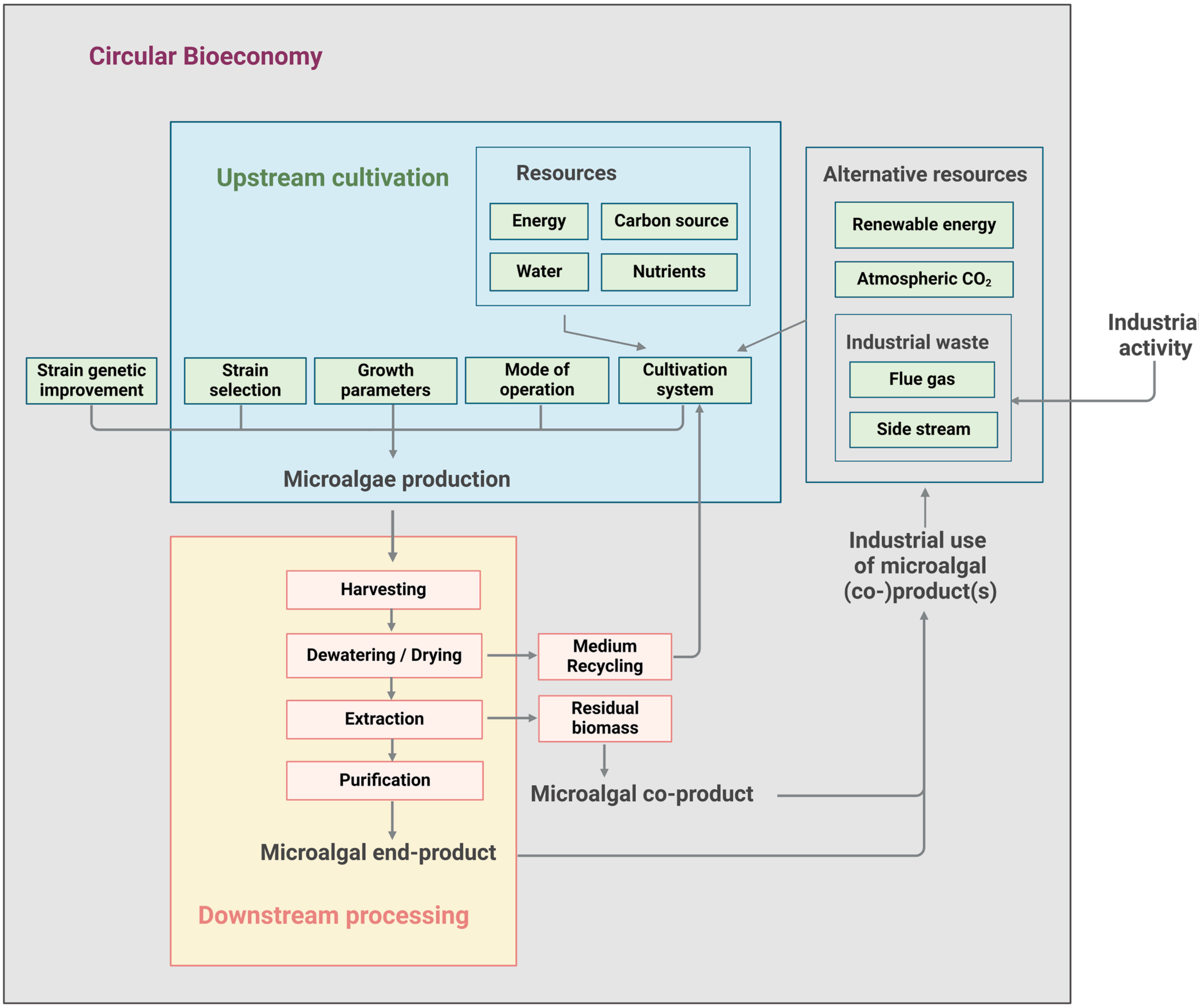

Fig. 1. Workflow of microalgae production following the conventional upstream cultivation and downstream processing for microalgae production (blue and yellow boxes, respectively). The circular bioeconomy approach (grey box) incorporates genetically improved strains to increase productivity and optimize resource use, alternative resources for microalgae cultivation (either renewable resources or side streams and/or waste from the industrial activity), and valorization of the culture medium and residual biomass, once the main microalgal end-product is obtained.

of polymers, with a relatively small percentage of microalgal biomass [94]. Biopolymers can have various applications, for example as coatings in some cosmetic formulations (Supplementary Information Table SI 1).

3. Microalgae production

Generally, when microalgal whole-biomass is not used directly, production has two stages: Upstream cultivation and downstream processing to obtain the final end product with commercial applications. Innovative technologies to optimize resource consumption and reduce waste can be applied in both stages. Circularity and sustainability can be incorporated in both stages of microalgae production (Fig. 1). For instance, using genetically improved strains with enhanced nutrient uptake and/or light efficiency, and the valorization of industrial side-streams to grow microalgae will have a positive impact on the upstream cultivation because the consumption of resources is reduced (Fig. 1). Downstream processing can also benefit from circularity, if the culture medium from dewatering is recirculated into the main cultivation system [95]. The residual biomass after extraction of high-valuable compounds from microalgae can be valorized for other commercial applications, such as biofertilizers, biostimulants or animal feed (Fig. 1).

3.1. Upstream process: Cultivation

Apart from the intrinsic properties of the strain(s) selected, microalgal production depends on three main factors: the cultivation parameters that enhance biomass production or the biocompounds of interest, the mode of operation and the cultivation system.

Selecting the microalga strain with potential production of the compound(s) of interest is the initial step. Strains can be either isolated from their natural habitats, or be purchased from a culture collection, or ‘algae biobanks’. In Europe, a total of 32 Algae Culture Collections have been identified throughout fifteen countries [96]. Culture collections not only provide strains, but may also offer detailed data on specific culture conditions, biochemistry, genomics and ecology for each strain.

3.1.1. Cultivation parameters

Several parameters regulate the microalgal cell metabolism and thus influence its growth. Parameters such as pH, temperature, gas exchange (supply of CO_2 and removal of O_2), agitation, irradiance and nutrients must be controlled (in closed systems), or at least monitored (in open systems) [97–99]. Photoautotrophic cultivation of microalgae will use sunlight to capture CO_2 and to produce molecules such as lipids, proteins and carbohydrates. This is the most conventional and sustainable method to grow microalgae, as the energy and carbon sources are renewable [99]. Heterotrophic production of microalgae on the contrary, does not require light, but a source of organic carbon that has to be added to the medium (sugars, glycerol, acetic acid, etc.), which increases costs. Using wastewater as a source of organic carbon increases sustainability, but producing high-value biocompounds for pharmaceutical use with wastewater raises biosafety concerns [100] and therefore, the final application should be matched with the quality of the biomass. Only few microalgae can grow heterotrophically, *e.g.*, *Chlorella* spp.

In most cases, culture parameters (light-dark cycle, temperature, agitation, etc.) will require some ‘inducers’ to enhance microalgal growth, lipid yield production and/or production of other biocompounds, by 1) imposing nutrient-starvation conditions, 2) adding acids to the culture medium (fulvic acid, indole acetic acid, or gibberellic acid [101], or 3) inducing salinity stress [97].

3.1.2. Mode of operation

Microalgae can be grown under different modes of operation. Batch cultures are the simplest way to grow algae. A single inoculation of algae into a closed container will be followed by a growing period of days. No culture medium is added (thus, nutrients concentration decay over time) or removed (CO_2 and any products produced by the microalgae increase over time). Microalgae are harvested or transferred when they reach a defined maximum density. Batch cultures are generally used to start growing a strain, and to upscale from a test tube (lab-conditions) to a tank (pilot and industrial scales). Generally, it is desirable to have continuous cultures at larger scales, with a constant nutrient supply added into the microalgal container, and the excess of culture medium washed out at a constant rate. This allows the culture to maintain growth close to its maximum growth rate.

3.1.3. Cultivation system

Cultivation systems can be classified into two different types: Closed and open systems. Closed systems are reactors frequently used to generate high-value biocompounds, which require controlled conditions to enhance the concentration of such compounds[7,99]. Photobioreactors and fermenters are the most common closed systems. Photobioreactors (PBRs) are closed, transparent culture vessels designed to optimize light penetration and to facilitate photosynthesis by autotrophic microalgae. The PBR design includes several types of bioreactors: tubular PBRs (which can be placed vertically, helically, or horizontally), column PBRs, annular PBRs, flat panel (plate) PBRs, plastic bags and stirred tank PBRs [102]. Fermenters are mainly used to cultivate microalgae under heterotrophic and/or mixotrophic conditions (*e.g.*, *Auxenochlorella protothecoides*). The microalgae require an organic substrate (usually glucose), which increases production costs, but the upscaling process is accelerated. For example, *Chlorella vulgaris* requires 5 weeks to grow autotrophically (1000 L), but less than 5 days if it is cultivated under heterotrophic conditions [103]. New fermentation technologies, such as Dark Fermentation (DF), combine the use of bacteria that generate acetic and butyric acids, which are the source of carbon microalgae will use to grow [104]. The advantage of using fermenters over PBRs is that the scale-up is faster, with fewer steps and consequently, a lower risk of contamination [103].

Generally, using closed systems is advantageous because the environmental factors and parameters to enhance biomass productivity are efficiently controlled [105]. They also provide high illumination surface areas, improved gas solubility, high productivity and a lower risk of contamination, (when compared to open systems). However, these cultivation systems have high costs and energy requirements, which is not ideal for a bioeconomy-based setup. Using flue gases rich in CO_2 and waste water / side streams from other activities (industry, urban) rich in nitrogen and/or phosphorous enhance circularity and may reduce economic costs up to 80 % [7].

Open-culture systems are shallow ponds or tanks that usually allow mixing the culture with a stirrer, or by aeration. This type of cultivation system includes natural locations of production (*e.g.*, lake Texcoco in Mexico), unstirred ponds (the simplest but most inefficient system), circular ponds (widely used in Asia) and raceway ponds (the most widely used systems consisting of parallel channels with a paddle wheel to promote microalgae circulation) [102]. The first natural locations where microalgae were collected and used as food supplement are located in Mexico (Aztecs already ate spirulina) and in Central Africa (lakes Chad and Niger), where strong sunshine, high temperatures and alkaline conditions favor the growth of spirulina [23,106]. Over the years, these natural locations started to be commercially exploited and their high irradiance and temperature conditions were emulated in ponds, in equatorial and tropical regions (*e.g.*, Thailand, Taiwan, India, Vietnam, Brazil, Ecuador, Senegal, Togo) [23]. In Europe, open pond systems for microalgae production are mostly found in Mediterranean countries (Spain, Portugal, Italy, Greece) due to the abundant sunshine, which provides ideal conditions for microalgal growth [105].

Microalgal cultivation in open systems have numerous advantages: it requires much lower investment in terms of energy, construction and operational costs, and it is relatively easy to scale up to generate very high volumes of biomass. The drawbacks of using open systems are the high risk of contamination, the low control of the environmental conditions and the higher water requirements. For these reasons, open systems are commonly used to generate low-value compounds and/or for biomass production.

Recent research studies show that two-stage cultivation systems (hybrid systems) increase production while reducing contamination and grazing [91,107]. These systems combine exponential biomass production in a PBR with a nutrient-depletion phase in open raceway ponds.

Sometimes, the terms ‘photobioreactor’ (PBR), ‘bioreactor’, or ‘reactor’ refer to both open and closed cultivation vessels. Although they should be exclusively reserved for closed reactors systems, some authors claim that open raceway ponds fulfill all three criteria included in the term ‘photobioreactor’: it is used for cultivation of living matter, employs light as an energy source, and consists of a vessel in which growth-related reactions are performed [25].

3.2. *Downstream processing*

3.2.1. *Harvesting, transportation and drying*

Harvesting is one of the main stages of microalgal processing, with estimated costs of ∼ 25 % of the total production costs [108]. Culture media must be removed to facilitate processing and microalgae can be then harvested using different methods such as sedimentation, flocculation, flotation, filtration or centrifugation [108]. Sedimentation with ozonation pre-treatment is proven to be highly effective to simultaneously harvest and rupture the microalgae cell wall for the release of the content [109].

Transportation of the wet algal biomass over great distances is uneconomic. To minimize costs, it is recommended to concentrate the microalgal biomass on-site. Flocculation and settling during the harvesting facilitate transportation too. Wet biomass can be then pumped into containers for drying or further downstream processing. In any case, sterilization of any material used in transportation is recommended after use.

Drying removes most of water content inside the microalgal cells to achieve 5 % of total water content, either to produce and store whole-algal biomass that can be utilized directly, or to facilitate further transformations to obtain the bioproduct(s) of interest. This step is critical to stabilize the microalgal biomass and minimize its decomposition. Solar drying, spray drying and freeze drying (lyophilization) are the most common drying techniques [110]. Whilst lyophilization is the gentlest technique because it sublimates the water from the frozen biomass with vacuum, spray drying is the most common method at industrial scale. However, both methods require a high energy demand and high costs, reaching up to 60 % of the total costs for biofuel production [110]. Solar drying is the most cost-effective drying method, with an approximate cost of 1.16 €/kg biomass, whilst costs of conventional spray dryer systems are estimated at 2.37 €/kg [111]. Another techno-economic analysis reveals that spray drying is slightly more economically viable (7.03 % reduction of biomass cost) than freeze drying [112].

3.2.2. *Extraction of bioproducts*

Disruption of the cells is an important step, since some species have tough cell walls. Conventional extraction methods include mechanical extraction and chemical extraction (with solvents) to extract the intracellular compounds [108]. Ionic liquids (molten organic salts) may be toxic and pose environmental risks if they are not treated properly before discharge [108]. Deep Eutectic Solvents (DES) are a new subclass of the ionic liquids used in a more cost-effective and bio-friendly (biodegradable and non-toxic) approach [113]. If the origin of its components is natural, they are referred as Natural DES (NaDES) [114].

3.2.3. *Water recycling and disposal*

Water from the harvesting and drying processes can be recirculated to minimize the water footprint and reduce the economic costs for water consumption [95].

If the cultivated microalgal species is potentially invasive, residual water must be ‘deactivated’ before disposal. Common methods include UV treatment, pasteurization, dilution, filtration, chemical deactivation, and heat deactivation [92].

At lab scale, microalgal waste can be treated as any microbiological waste, following the SOP established at each lab. Liquid waste can be treated with autoclave at 121°C for at least 30 min, or with chemical disinfectants such as 10 % hypochlorite. Solid material can also be sterilized with autoclave, or UV-radiation.

In scale-up processes, waters with microalgal waste are usually treated with chemical disinfectants (hypochlorite, copper salts) because of the large volume to be treated and the non-expensiveness of such disinfectants. UV-radiation is also a common method to deactivate microalgal DNA, as it is very cost-effective and only requires a recirculation system for a couple of hours. Ozonation is an efficient -but costly- alternative to conventional disinfectants. It is important to highlight that there is no single solution to address microalgal disposal, and it is highly recommended to combine two (or more) of the above-mentioned methods. For example, batch ozonation combined with peroxymonosulfate is a common and effective treatment to inactivate microalgae [115].

Open ponds and PBRs can be cleaned mechanically and with the same disinfectant agents mentioned. There are also PBRs with patented cleaning systems incorporated [116].

4. State of the art in the microalgal sector

4.1. *State of the art in EU*

Official data on microalgae production are difficult to obtain, and information is scattered and difficult to access [105]. Also, data available from FAO or Eurostat are limited and fragmented. A recent review paper identified more than 79,000 scientific publications on microalgae produced in Europe since the 1960 s [117]. The most recent studies and reports at the EU level show a production of 182 tons dry weight (DW) of eukaryotic microalgae and 142 tons (DW) of spirulina. These values must be taken with caution, as most data reported are production estimates, and some recent companies might have not been included in these estimations [105].

After thorough research on the internet and consulting updated information on European microalgal producers publicly available at the website of the European Algal Biomass Association (EABA, www.eaba-association.org), we identified at least 66 European companies that currently produce 146 different microalgae-derived products, and 49 companies that offer consultant services and provide biotechnological solutions for microalgae production. We excluded manufacturers that do not cultivate microalgae. Most companies producing microalgae were created after 2005 in Europe (74 %) and have been fully operative (into business) less than fifteen years. The first European microalgae cultivation plant at industrial scale was launched in 2000 in Germany. The plant produces *Chlorella* spp. and consists of a closed system with glass tubular photobioreactors enclosed in a glasshouse, with a total surface of 1.2 ha. The biomass produced goes entirely to the nutritional sector, as *Chlorella* spp. is a food supplement widely consumed.

4.1.1. *Type of cultivation and species produced in Europe*

The type of cultivation is dependent on the species (strain), the biocompound(s) of interest and the environmental conditions in the production location. In general, photobioreactors (PBRs) are the preferred cultivation methods for microalgae within the EU [105], but the use of fermenters for microalgae production has increased worldwide (and presumably in Europe too), over the last decade [118]. We observed that 47 % of the microalgae producers we identified in Europe use freshwater culture media, whereas 41 % of the producers cultivate their microalgal strains in marine water (Fig. 2a). Moreover, 48 % of the

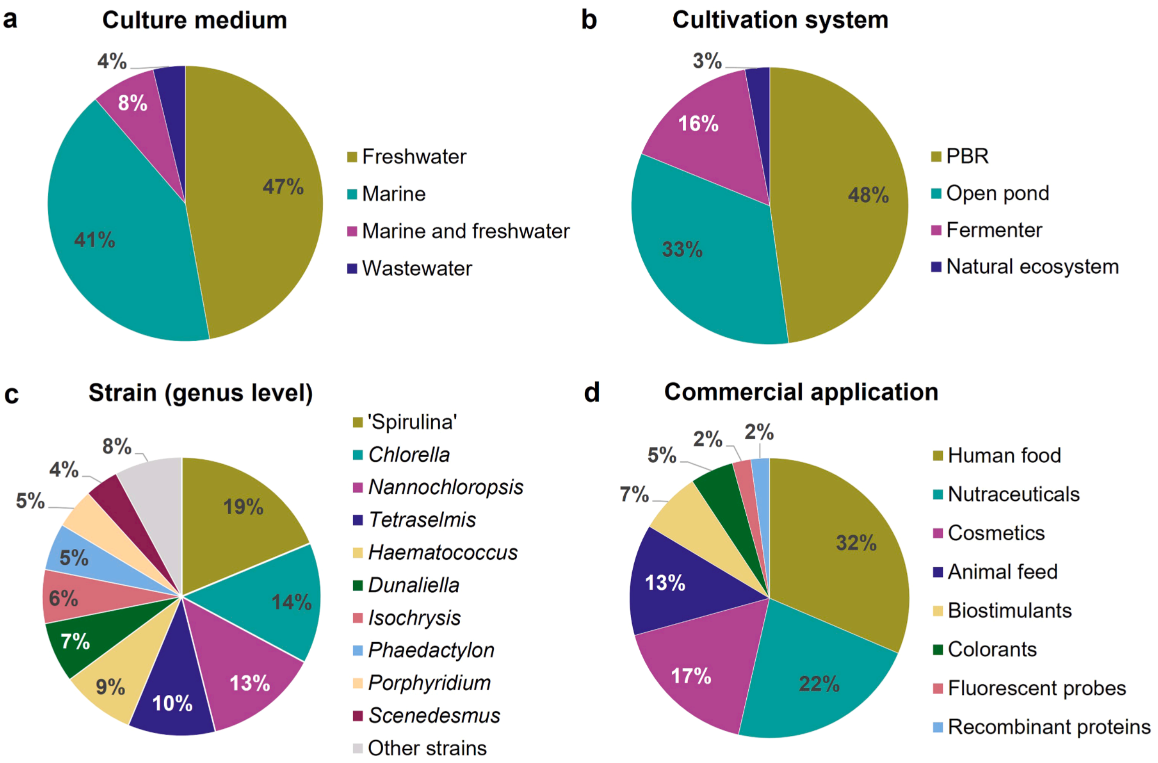

Fig. 2. Microalgae production in Europe, according to a) the culture medium used (n = 66), b) the type of cultivation system (n = 69), c) the microalgal strain produced (n = 117), shown at genus level, and d) the application of the microalgae-derived compound(s) produced (n = 140). .

European companies we identified use PBRs, 33 % of them are cultivating microalgae in ponds, and 16 % of the companies use fermenters. Only 3 % of microalgal producers in Europe exploit natural ecosystems (Fig. 2b). This is in line with previous data showing that most European producers of eukaryotic microalgae use closed systems (71 % of producers use PBR and 10 % use fermenters) and only 19 % use open systems (ponds) [105]. In the case of cyanobacteria, cultivation is mainly produced in open systems (83 %) [105].

The eukaryotic species that are mostly cultivated in Europe include *Chlorella* spp. (30 European enterprises produce 82 tons of algae per year, dry weight), followed by *Nannochloropsis* spp. (25 companies that produce 21 tons/year), and *Haematococcus pluvialis* (17 companies that produce 66 tons/year) (Fig. 2c) [105]. The main cyanobacteria produced in Europe is spirulina, with 222 companies that generate approx. 142 tones/year dry weight (Fig. 2c) [105].

Our results show that 19 countries produce microalgae and cyanobacteria at medium- or large-scale. In our up-to-date compilation, we show that France has recently registrered several microalgae biotech companies and is the European country with the highest number of microalgae companies and microalgae-derived products already available on the market (Fig. 3). In 2021, Germany and Spain were the main producers of eukaryotic microalgae (19 and 16 enterprises, respectively), followed by Italy, Portugal, The Netherlands and France, with seven to nine companies each [105]. In all cases, the predominant cultivation was closed system with PBRs, and Spain had the highest number of companies with open systems (ponds), (six companies) [105]. Fermenters are less common than PBRs and open ponds, as they are used to cultivate microalgae under heterotrophic conditions, but they are increasing since 2021 (Fig. 2b). France, United Kingdom, The Netherlands and Spain have microalgae production plants with fermenters [105].

For prokaryotic cyanobacteria, the vast majority of companies are based in France (129 companies), followed by Italy (22 companies) and Spain (18 companies) [119]. Most of the French companies producing

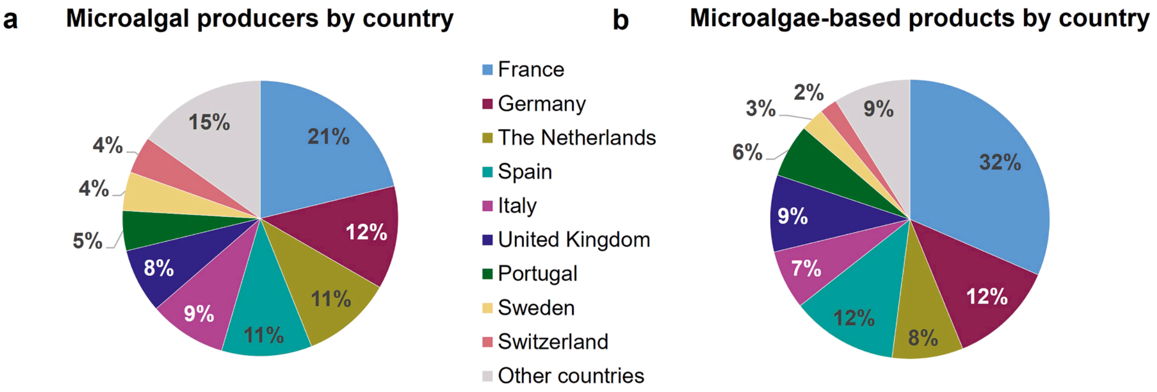

Fig. 3. Distribution (percentage) of microalgal producers in Europe by country, as indicated by a) the number of microalgae-producing companies (n = 66), and b) the number of microalgae-based products available on the market (n = 146).

spirulina are microfarms, *i.e.,* small-scale open ponds [120].

4.1.2. Bioproducts of interest produced in Europe

Our investigations revealed the main applications of microalgae produced in Europe are human food and supplements, nutraceuticals, and cosmetics, which represent 71 % of all the microalgae-based products cultivated in Europe (Fig. 2d). Spirulina is mainly consumed as human food (47 %) and food supplements (29 %) (see also Fig. 4).

Other applications using microalgae and/or spirulina include agricultural and pharmaceutical applications. The percentage of companies is similar in both sectors (≤ 7 %) (Figs. 2d, 4). Although biorefinery and biofuel production have been developed for decades and are nowadays very promising (particularly in the context of sustainability and bioeconomy), further technological developments are needed to upscale the production and reduce costs. A previous study on the algal sector in Europe shows that less than 3 % of the European microalgal companies work on biofuels [105]. Recently, the biorefinery approach has gained attention in Europe due to the optimization of by-products from other industries [7,105]. Environmental sustainability can be more easily achieved if the excess of nutrients from industrial activity is used to grow microalgae. Bioremediation (or phycoremediation) is used to treat wastewater and/or residual industrial waters rich in N and P, and flue gases from industries containing CO_2 can be utilized for Carbon Capture and Utilization (CCU). At least eleven European companies provide decarbonization and CCU solutions with microalgae (Supplementary Information Table SI 2). Interestingly, six companies are already working with gene-edited microalgae, either for CCU or to maximize the production of high-value biocompounds (Supplementary Information Table SI 2).

4.2. State of the art in the microalgal sector outside EU

Data Bridge Market Research analyses show interesting trends and predictions on the microalgae-based market [121]. In Europe, the market is growing with a CAGR (compound annual growth rate) of 5.8 %. These predictions are, however, lower than those for Asia (with a CAGR of 7.4 % in the forecast period of 2023–2030, reaching USD 279.79 million by 2030, from USD 159.65 million in 2022) [121]. Predictions are similar for other continents: The North America microalgae market is expected to grow with a CAGR of 6.6 % in the forecast period of 2023–2030 and might reach USD 670.58 million by 2030. The Middle East and Africa microalgae market is also expected to grow in the same forecast period (2023–2030) with a CAGR of 4.6 % and might reach USD 36.80 million by 2030 [121].

Data and statistics on the microalgal sector in other continents are difficult to obtain. The Asia-Pacific region, with a long tradition of microalgae cultivation and consumption, had more than 110 commercial producers of microalgae by the end of the 20th century [122]. *Chlorella* spp. and spirulina were the most cultivated algae, with an annual production that ranged from 3 to 500 tons [122]. Over the last 15 years, China has become one of the major producers of microalgal biomass, mainly for spirulina, and, to a lesser extent, *Chlorella* spp. The Chinese microalgae industry focuses on bulk biomass production for human consumption and aquafeed, but also high-value products are produced [123]. Interestingly, China has recently taken over Japan as the major worldwide producer of *Chlorella* spp. In Japan and India, the microalgal production has pivoted towards the biofuel market, in an effort to provide an alternative to fossil fuels [123].

North America is expected to lead the global microalgae market due to higher awareness among consumers about the health benefits of microalgae products, but also because of the development of innovative biotechnology and products [121]. North America (mainly U.S.) has the largest algal biofuel market, with 30 % of the global share, a very high number of start-ups, and the largest share of nutraceutical market [124]. These figures are in line with the 'Patent Landscape Report' for microalgae-related technologies, where the U.S. ranks as the second country in patent filing (only after China), particularly in bioengineering processes [125].

5. Challenges and prospects in the microalgal sector in Europe

The microalgae sector is aiming to emulate the consolidated production systems in agriculture and aquaculture. However, some bottlenecks that are interconnected, have been identified and need to be addressed: 1) The logistics are quite challenging, as operation units at different scales need to be developed and professionals must be trained to overcome technical challenges, *e.g.*, controlling contamination. Moreover, the high production costs (mostly associated with the scale-up and downstream processing) negatively impact the market demand and return of investment [126]. 2) The regulatory framework for microalgae and the absence of economic incentives may limit the innovative pathway of the microalgal industry [126,127].

5.1. Logistic challenges

Despite the high microalgae growth rates, scalable cultivation is a major techno-economic bottleneck, as production costs can increase dramatically. During the scale-up phase, water and energy consumption are high, complex infrastructure is necessary, and microalgal growth conditions (temperature, pH, aeration, nutrients, light) must be controlled and monitored frequently to avoid the collapse of the culture. Also, microbial contamination caused by pathogens (bacteria, fungi, viruses) and predators (protozoa, rotifers, cladocera) must be minimized by adopting specific management practices, such as the application of control agents [128]. While open production systems are more cost-effective than closed systems (2–10 € / kg biomass and >20 €/ kg

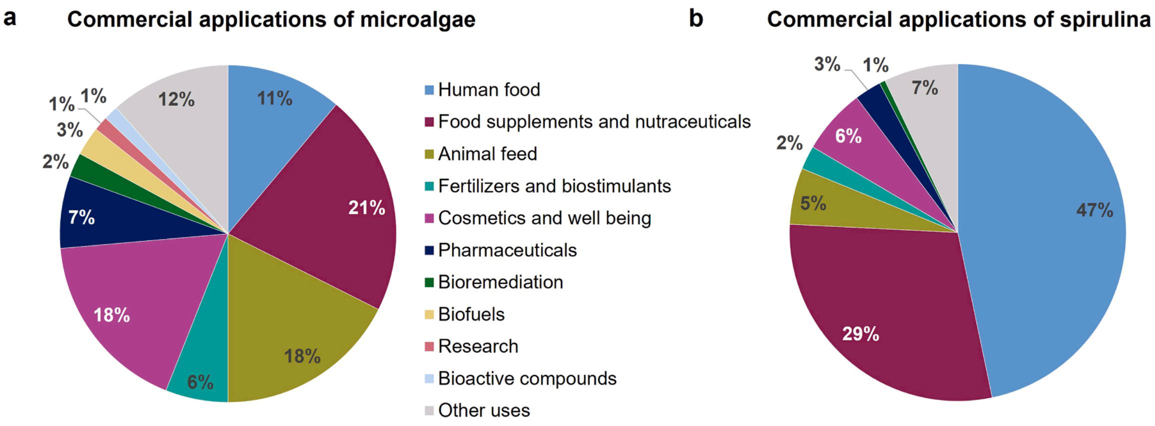

Fig. 4. Commercial applications of a) microalgae and b) spirulina production companies (n = 300). Data were extracted from the total algal production in EU [150].

biomass respectively) [7], contamination risk is higher in such systems [129].

Downstream operations and bioprocessing are by far the most expensive steps in microalgae production, being normally unprofitable when only one single microalgal product is exploited. The biorefinery approach offers a solution to this challenge, as it focuses on co-exploitation of different microalgal components and minimizing waste, or performing an end low-value application that leads to zero-waste [130]. Useful tools such as life cycle assessment (LCA) and techno-economic analysis (TEA) will contribute to define a sustainable and economically feasible strategy of co-production, particularly if the compounds are medium- to low-value [130].

5.2. Regulatory challenges

EU-specific and international regulations pose a challenge for the use of novel microalgal strains or species, in particular for strains improved with genetic engineering methods, including new genomic / breeding techniques (NGTs) [131,132].

The heterogeneous and complex regulatory landscape covering microalgae and their products, as well as a lack of harmonization to regulate different aspects of microalgae use, are present in the European Union. For example, the EU Regulation 2019/1009 excludes the use of any cyanobacteria (including spirulina) as a fertilizing product [133]. Paradoxically, *L. platensis* (spirulina) is recognized as ‘safe use for human consumption’ according to the EU Novel Food Regulation 258/97 [134]. Other regulations, *e.g.*, the EU Regulation for food supplements (which includes microalgae-based products), are based on the ‘precautionary principle’ (Novel Food Regulation 2015) [37]. This is seen as a commercialization barrier for microalgal producers in Europe, as imported microalgal products are authorized without passing the same controls and authorization processes [127].

A relevant international treaty is the Nagoya Protocol on Access and Benefit-Sharing (ABS) that regulates access to genetic resources and the fair and equitable sharing of benefits arising from their utilization [135]. In practice, the implementation of this regulation limits the use of microalgae that are regarded as ‘non-domestic’ and the exchange of microalga species or strains across borders [132]. In the EU, specific legislation has been developed including the ABS Regulation (EU) 511/2014 [136] to harmonize the application of the Nagoya Protocol. The regulation contains obligations for users of genetic resources and associated traditional knowledge in the EU and for governments of EU Member States. Member States may have additional ABS legislation. Overall, the high diversity of existing regulations and competent authorities dealing with the Nagoya Protocol and ABS matters at regional, national and international levels makes the due diligence process heavy and difficult [131].

Additional regulations apply when microalgae are genetically engineered (GE). GE microalgae used for food or feed production under containment are regulated by the Directive 2009/41/CE [137] aiming to limit their possible negative consequences for human health and the environment, to prevent accidents and control waste. An environmental risk assessment needs to be conducted to ensure safety in the event of a significant and unintended release. GE microalgae produced in open systems for food or feed (or used to produce food or feed) would fall within the Directive 2001/18/CE of GMOs for deliberate release into the environment (amended by Directive 2008/27/EC) [138,139]. In those cases, a full and laborious environmental risk assessment is required [140]. Currently, more than fourteen EU countries have banned GMO production [141].

New genomic/breeding techniques including targeted mutagenesis such as CRISPR-Cas, are expected to significantly improve and expand the use of microalgae [132]. As of today, these organisms would be regulated as GE microalgae, but there is some uncertainty on how to assess the environmental impacts of such microalgae [142].

In addition to the fragmented regulation, microalgal producers emphasize the scarce incentives and funding for R&D in biotechnology, which results in an under-exploitation of microalgae as a source of valuable compounds, and brings the bioprocessing industry into a stalemate [123]. In Europe, frustration is evident amongst microalgae producers, as research projects are funded by EU institutions to boost the development of the microalgal sector but simultaneously EU regulations constrain the market opportunities of microalgae-based products [143].

5.3. Prospects in the microalgal sector: bioprocessing and new technologies

To ensure economic feasibility and increase the production of microalgal biomass and/or the hyperaccumulation of valuable compounds, innovative techniques must be incorporated during the different bioprocessing stages. Mixotrophic cultivation systems may reduce energy consumption by 40 %, when compared with autotrophic systems, and pilot scale-up has been already successful [144]. Electro-technologies (based on the direct application of an external electric field through a semiconductor) are also cost-effective and sustainable, and can be applied either during the upstream, *e.g.*, to inactivate contaminants or improve growth kinetics, and the down-stream processing, *e.g.*, harvesting and extraction methods [145].

The development of new molecular biology tools has great potential to advance in the microalgal sector. Innovation has mainly focused on four main aspects: 1) improving microalgal strains (genetic engineering, targeted mutagenesis); 2) discovering metabolic pathways to understand biosynthesis processes (genomics, metabolomics, proteomics); 3) increasing the efficiency of different cultivation systems (production technology), and 4) developing new products [146].

During the last decade, the application of new genomic/breeding techniques (NGTs) based on gene editing tools (including targeted mutagenesis) have been extended, as they hold the greatest potential for strain improvement and for a more sustainable economy [147]. Amongst these, the CRISPR-Cas systems are considered more accurate, target-specific, easy to use and multi-potential, compared to previous tools [148]. However, organisms developed using new genomic/-breeding techniques are considered GMOs under the current regulation and thus their use is prevented or greatly hindered in the EU. As a consequence, much innovation on gene-edited microalgae comes from research groups based in the EU, but the commercial applications of these technologies occur outside of the EU due to the regulatory conditions [123].

Whole-genome sequencing and transcriptome have fast-forwarded the detection of mechanisms regulating resource uptake or adaptation to stress, which is essential to boost microalgal growth. Mutant libraries and high-throughput screening methodologies go hand in hand with the improvement of techniques used in each step of the genome transformation, from gene transfer to gene expression and production of the desired metabolic derivates [149].

The advancement of production technologies is currently undergoing significant development, spanning from the design of new bioreactors to the optimization of new cultivations modes, like mixotrophy [144]. Microalgae are key players in the new paradigm of bioeconomy, and incorporating side-streams and residues from downstream processes will not only benefit a circular economy model, but will also contribute to the feasibility of the microalgal production system [7].

6. Conclusion

Within the microalgal sector, economic sustainability can be achieved through the different production steps, ranging from the optimization of resource use (water, nutrients) in the upstream production to the valorization of waste and/or side-streams in the downstream processing (bioprocessing). A microalgae-based circular bioeconomy that includes side-streams, renewable energies and recirculation of effluents do not only reduce economic costs and resource utilization, but also contributes to more sustainable production system. The microalgal sector in Europe is highly innovative, and the incorporation of the latest biotechnological advances, such as the novel genomic techniques to improve industrially relevant microalgae, and the bioprocessing technologies to increase the concentration of microalgal high-value compounds, has a great potential to advance and to position the European microalgae-based sector in the global market.

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CRediT authorship contribution statement

Elke Vereecke: Writing – review & editing, Conceptualization. **Johan Robbens:** Writing – review & editing, Conceptualization. **Joerg Romeis:** Writing – review & editing, Writing – original draft, Investigation, Funding acquisition, Conceptualization. **Jakob Skov Pedersen:** Writing – review & editing, Conceptualization. **Nikola Medic:** Writing – review & editing, Conceptualization. **Praveen Kumar Ramasamy:** Writing – review & editing, Conceptualization. **Irene Gallego:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.nbt.2025.01.002.

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