From the sea to aquafeed

A perspective overview

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REVIEW

REVIEWS IN Aquaculture

From the sea to aquafeed: A perspective overview

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Abstract

Aquaculture has been one of the fastest-growing food production systems sectors for over three decades. With its growth, the demand for alternative, cheaper and high-quality feed ingredients is also increasing. Innovation investments on providing new functional feed alternatives have yielded several viable alternative raw materials. Considering all the current feed ingredients, their circular adaption in the aquafeed manufacturing industry is clearly of the utmost importance to achieve sustainable aquaculture in the near future. The use of terrestrial plant materials and animal by-products predominantly used in aquafeed ingredients puts a heavily reliance on terrestrial agroecosystems, which also has its own sustainability concerns. Therefore, the aquafeed industry needs to progress with functional and sustainable alternative raw materials for feed that must be more resilient and consistent, considering a circular perspective. In this review, we assess the current trends in using various marine organisms, ranging from microorganisms (including fungi, thraustochytrids, microalgae and bacteria) to macroalgae and macroinvertebrates as viable biological feed resources. This review focuses on the trend of circular use of resources and the development of new value chains. In this, we present a perspective of promoting novel circular economy value chains that promote the re-use of biological resources as valuable feed ingredients. Thus, we highlight some potentially important marine-derived resources that deserve further investigations for improving or addressing circular aquaculture.

KEYWORDS
alternative protein, aquafeed, circular aquaculture, fatty acid, lipids, single cell protein

For affiliation refer to page 19

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1 | INTRODUCTION

The predicted increase in the world population, combined with enhanced well-being and life quality demands, will require a significant increase in food production and a reduction in food waste. Overpopulation, climate change, ethical production and responsible consumption of food and health are each intricately intertwined; higher population growth requires more food production, which generally generates more waste and emissions and produces greater vulnerability to climate-related and human health impacts if we are not adjusting our lifestyle. To meet the Sustainable Developmental Goals (SDGs) and the main initiatives for the protection and restoration of marine environment, new production concepts are required to address this growing demand and provide sufficient quantities of high-quality food in the future.[1,2] Aquaculture is currently one of the fastest-growing food-producing industries in the world. According to newly released SOFIA 2022, by 2050, aquaculture production is projected to reach 140 million tonnes under business-as-usual scenarios, compared with 2030 (previously projected to 109 million tonnes) as a result of technological improvements.[1] However, that growth is dependent on sustainable supplies of protein feedstuff to feed aquaculture animals.[3] Proteins and lipids are fundamental macronutrients in aquaculture.[4] Traditionally, feeds were reliant on the use of marine ingredient resources (proteins and oils, mainly from fisheries—Aquafeed v1.0). However, recognition of the constraints to the supply of those resources led to significant progress in the development of alternative feed resources for aquaculture mainly deriving from terrestrial-animal or plant-based sources (Aquafeed v2.0).[5] More recently, the efforts are focused on developing of circular and regenerative ingredient resources (Aquafeed v3.0) that valorise by-products from other sectors or even remediate nutrient discharges, for example, macroalgal and microbial protein sources.[6–8]

Aquaculture heavily relies on marine-derived resources such as fish meal (FM) and fish oil (FO). These are strategic ingredients in aquafeed as their supply is cannot match the demand.[6,9] Although considerable progress has been made in replacing them, many cultured species have identified various challenges.[6,10–12] Numerous feedstuffs have been intensively tested and adopted to remove or substantially reduce FM and FO inclusion in aquafeed without affecting the growth and health of the cultured fish. For instance, to reduce the use of wild catch fish as feed in salmon aquaculture, aquafeed manufacturers substitute the fishmeal with soy protein to reduce the marine origin of ingredients to approximately 30%[13] and soy protein has become an important ingredient, replacing up to half of the fishmeal used in aquaculture.[14] Plant-based feed is considered to have a lower environmental impact than fishmeal-based feed.[15] However, the soy production for fish feed ingredients is recognised to cause significant ecosystem losses,[16] increased degradations of the vulnerable habitat.[17]

The global use of proteins and oils, of terrestrial origin, for livestock, including aquatic animals, significantly contributes to the negative impact of livestock production on the environment and climate change.[11] Additionally, increasing pressure on freshwater resources for the production of terrestrial feed ingredients is an additional drawback to the use of many alternative feedstuffs in aquaculture, as most available alternative feed resources are also fed to terrestrial animal production systems such as pigs and poultry, thereby accentuating pressure on the resources supply to the feed-food-chain.[12] Aquaculture competes for crop resources with livestock, the energy industry and direct human consumption, raising concerns about the impact of aquatic farming on global food resilience, albeit representing only a small fraction of resources compared to other animal food production systems.[18] Hence, there is still a need to find appropriate, economic and sustainable protein and lipid sources to underpin the increasing demands for aquafeed based on sustainably sourced ingredients.

In addition to macro-nutrients, many feed ingredients contain certain bioactive compounds (natural products including secondary metabolites) that influence the growth and the overall health of animals.[19,20] Such nutrients often act in a preventative or responsive manner to animal health issues and have colloquially been termed nutraceuticals. In an animal production system, where medicinal antibiotics are increasingly subject to regulations, nutraceuticals have been eagerly embraced as a 'natural' way to address animal health issues. The variety of bioactive compounds that have purported nutraceutical benefits is growing and frequently seen as the 'point-of-difference' among the range of feed ingredients used. Ingredients such as yeasts are known for their β-glucan as a prebiotic and nucleotide content and their protein value.[7] On the other hand, probiotics, that is, live microorganisms providing health benefits in aquacultural settings are gaining increasing attention. Probiotics do not only stimulate the immune system of the cultured fish and ameliorate the effects of stress, but also improve the growth and feed conversion, thereby reducing the use of FM to support a more sustainable aquaculture.[21,22]

The European Union considers blue bioeconomy as any economic activity associated with the use of renewable aquatic biological resources to make products.[23] This involves all activities that are involved in growing, extraction, processing and transformation of raw materials.[23] The contribution of aquaculture to blue bioeconomy is fully embedded into Aquafeed v3.0, either by selecting novel feed resources from aquatic organisms, or by valorising by-catch or discards from fisheries and aquaculture that accumulate during capture and processing. Indeed, around 130 million tonnes of fish waste are produced each year by fisheries and aquaculture and its disposal is connected to economic losses and environmental impact.[24] However, their valorisation represents an opportunity to increase production, while enhancing sustainability.[25] Moreover, these high-potential new value chains can create additional jobs, thus contributing to economic prosperity. The valorisation of discards can be done through biorefinery, a process that collects, valorises and reutilises biomass for the production of value-added bio-based products and processes through additional value chains.[26] Such circularity of bioresources, minimises and repurposes waste and can lead to stress-resilient fisheries and aquaculture.[27] This way, circular aquaculture drives sustainability.[28] Considering the sustainable production of the abovementioned nutrients and certain bioactive compound, circular aquaculture has clear relevance to sustainability. Indeed, it aims to produce biological resources, facilitating conversion of these resources and waste streams into value added products, such as feed, food, biobased products and compounds. However, it is important to keep in mind that, when developing alternative/circular feed and aquaculture strategies, evaluation of these should be assessed through environmental, economic, social, legislative, technical and business criteria.[28] Such assessment is necessary to evaluate the new products in relation to existing products and concepts and provides producers with relevant data and evaluation that can finalise the development of novel circular strategies.

This review, therefore, aims to establish a broad overview and provide a preliminary analysis of some of the potential marine resources that can be applied to the sustainable nutrient demand challenge by embracing the circular aquaculture bio-economy framework. In this regard, we examine a wide range of potential organisms and their use in novel aquafeeds, their potential mode of use and benefits, not only as alternative nutrient sources, but also as promoters of growth and health. We also offer a novel view on the circular aquaculture potential, and assess its two levels: the direct one, through valorisation of waste and the indirect one, through integrated multitrophic aquaculture (IMTA), emerging as a sustainable and circular alternative to traditional monoculture of aquatic species.

2 | MICROORGANISMS AS SINGLE-CELL INGREDIENTS

Microorganisms such as microalgae, yeasts, bacterial and fungal-like protests, represent sustainable and renewable protein-enriched ingredients of single-cell ingredients (SCI) with a wide array of use in the aquaculture sector. These organisms can environmentally utilise nutrients derived from different waste streams and other industrial by-products and turn-over time is short and therefore shows high productivity.[8] Thus, this microbial-based feedstock can be produced more sustainably and circularly. On one hand, such broad class of SCI can be dried and/or processed and used as a source of protein (SCP), lipids and specific nutritional components in aquaculture feed, or to enhance the survival and immune response and, on the other hand, when microorganisms remain viable, they can be used as probiotics.[7,29,30]

2.1 | Microalgae resources

An increased awareness of circular bio-economy affected the intensive utilisation of microalgae as alternative feed source for sustainable aquaculture. Microalgal resources are considered sustainable sources of nutrient and high-value-added compounds such as phycobiliproteins/phycobilins, fatty acids, carotenoids and antioxidants.[31,32] Microalgal production provides the base for circular aquaculture industry by cultivating on non-arable land, minimising water demand, recovering and converting nutrients into high-quality feed ingredients.[33] Along with these beneficial effects, microalgae cultivation offers the possibility of CO_2-uptake (i.e. 1 tonne of microalgae corresponds to 1.47 tonnes CO_2) and is of interest to advance the objective of a circular bio-economy.[34] Integrating algal production system into aquaculture industry also underpin several UN Sustainable Development goals (SDG), specifically no. SDG1, SDG2, SDG12 and SDG14, which considers no poverty, zero hunger, reasonable consumption and production and life below water, respectively. This concept of bio-economy reveals major opportunities for microalgae to take a part in reducing environmental footprint, water pollution and deleterious ecological effects, but creating renewable and healthy diets for the aquaculture and people in the end, thus providing eco-friendly value chain.[33] In this part of the review, we will mainly focus on microalgal resources as essential nutrients, pigments and antioxidants, along with their biocircular effects in aquafeed.

Microalgae are currently being researched for their usefulness in remediating nutrients in organic waste, and a source of different nutrients, that is, fatty acids, amino acids, vitamins and carotenoids in feed. Despite the high nutrient content of essential polyunsaturated fatty acids (PUFAs) and amino acids in many species of microalgae (i.e. genera *Nannochloropsis*, *Dunaliella*, *Chlorella*), the data on the substitution of FM or FO with microalgal biomass suggests that there is an upper limit to how large a fraction of the fish feed can be composed of microalgal biomass derivatives. The recent review by Shah et al.[35] Glencross et al.[8] summarises recent studies on applications of microalgae biomass as feed for aquaculture. The effect of microalgae varies among microalgae species, type of aquaculture species and % of FM replaced and/or % dietary inclusion level. All studies where microalgae replaced less than 30% of the fish meal demonstrated either positive impact or there were no effects observed. The benefits of including microalgae in the diet of aquaculture species were increased growth and survival rate, improved pigmentation, enhanced immunological response and overall health of the organisms.[35–37] Besides protein content, new microalgal resources have attracted much attention due to their long-chain polyunsaturated fatty acids content. It was possible to achieve eicosapentaenoic acid (EPA, 20:5$n-3$) yields of up to 133 mg/L of culture under optimum conditions (21.5–23.0°C and pH 7.6) for the diatom *Phaeodactylum tricornutum*. In this case, EPA constituted 30%–40% of the total fatty acid.[38] Similarly, the marine *Nannochloropsis* sp., contains a large quantity of EPA and under optimum conditions EPA production can be maximised, reaching 0.1–0.4 pg cell^{-1}.[39] Other examples for a heterotrophic marine microalga, *Crypthecodinium cohnii* was identified as a good producer of docosahexaenoic acid (DHA, 22:6$n-3$). This strain can accumulate lipids in more than 20% of its biomass dry weight, with DHA representing 30% of the total lipids content.[40]

There are several marine microorganisms capable of producing arachidonic acid (ARA, 20:4$n-6$). The cyanobacterium *Phormidium pseudopristleyi* can produce between 24% and 32% of ARA of the total fatty acids.[41] Besides the reported cyanobacterium, Su et al.[42] described that unicellular red alga, *Porphyridium purpureum* showed significant ARA production under stress conditions, reaching up to 36% of the total fatty acids. *Cylindrotheca gryllotalpa* is another marine microalga that presents the ability to produce essential metabolites, such as fatty acids like ARA. Similarly, *C. closterium* produced significant amounts of ARA when it was first grown in a photobioreactor at 20°C. It was then suddenly stressed by decreasing the temperature at the stationary growth phase. In this way, the alga could produce 502 mg of ARA per 100 g of biomass.[43] The production of ARA was also reported in a comparison study of microalgae where *Chlorella vulgaris*, *Haematococcus pluvialis* and *Isochrysis galbana* were identified as ARA producers. In this case, these strains could produce 12 mg of ARA, 292 mg and 69 mg (100 g^{-1} of biomass), respectively.[44]

The algae, *Isochrysis galbana* can produce 9.0% of linoleic acid (LA, 18:2$n-6$) and 10.9% alpha-linolenic acid (ALA, 18:3$n-3$) in total fatty acids, which correspond to 2245 mg (100 g^{-1} wet weight) and 2557 mg (100 g^{-1} wet weight), respectively.[45] In another study, the lipid content and fatty acid profiles were analysed in 10 microalgae species, where *Chlorella vulgaris*, a freshwater microalga, produced 7.44% of LA and 22.17% of ALA, showing in this study the highest levels of linoleic and linolenic acids, followed by the marine specie *Tetraselmis chuii* that could produce 6.2% of LA and 17.67% of ALA.[46] On the other hand, oleic acid was produced in low quantity (0.2%–1.3%) by *Crinoidea* sp.[47] *Nocardioides* isolate MSL-01^T produced 4.3% of linolelaidic acid.[48] Four actinobacteria strains, belonging to *Salinispora* genus, were capable of producing stearic acid. *S. tropica* (3.7%), *S. vitiensis* (3.2%), *S. mooreana* (2.1) and *S. fenicalii* (2.9%) managed to produce stearic acid.[49] Different microorganisms were identified as fatty acid producers, in a study performed by Ratledge,[50] *Candida diddensiae*, *Cryptococcus albidus*, *C. curvatus*, *Lipomyces starkeyi*, *Rhodotorula glutinis*, *Rhodosporidium toruloides*, *Waltomyces lipofer* and *Yarrowia lipolytica* producing steric acid ranged from 1% to 15%. The same strains also produced different percentages of oleic acid between 28% to 66%. Furthermore, *C. diddensiae*, *C. albidus*, *C. curvatus*, *L. starkeyi*, *R. glutinis*, *W. lipofer* and *Y. lipolytica* produced between 3% and 51% of linoleic/linolelaidic acid.[50]

Pigments are another important microalgae-generated compound class. The most important pigments extracted from microalgae for use in aquaculture are no doubt astaxanthin and β-carotene. Astaxanthin is a red pigment of huge commercial interest as a food and flesh colourant, such as a fish feed additive. It is especially important to give the flesh of farmed Atlantic salmon (*Salmo salar*) and rainbow trout (*Oncorhynchus mykiss*) its desired colour by consumers.[51] Wild catch of salmon and rainbow trout has this colour from their natural diet, the pink pigment originally deriving from the microalgal base of the feed chain. Astaxanthin is the only pigment that can be incorporated into fish flesh.[52] It may be obtained from various sources, including chemical synthesis, but the increasing demand for astaxanthin is making biological sources for this pigment increasingly important, the most important microalgal sources being *Haematococcus pluvialis*, *Chlorella zofingiensis* and *Chlorococcum* spp.[53] In addition to its role as a flesh colourant, astaxanthin may serve as a vitamin A precursor in some fish.[54] This is especially important in fish unable to absorb β-carotene, which is the most important precursor for vitamin A in fish and in other organisms. β-carotene is found in high concentrations in many species of microalgae, especially in species of the Chlorophyte *Dunaliella*.[55]

Many microalgal pigments and phycobiliproteins have also been shown to have antioxidant properties. These include β-carotene and astaxanthin.[56] Other microalgal pigments and phenolic substances from microalgae have been shown to have antioxidant properties.[57,58] The most important microalgal species in terms of substances with anti-oxidant properties are *Tetraselmis suecica*, *Botryococcus braunii*, *Neochloris oleoabundans*, *Chlorella vulgaris*, *Phaeodactylum tricornutum* and *Isochrysis* spp.[57] Various antioxidant properties are thus widespread across various taxa of microalgae. Besides carotenoids, microalgae contain other types of powerful antioxidants including polyphenols (e.g. phenols and flavonoids), sterols, vitamins (e.g. vitamin A and E) and other compounds (e.g. butylated hydroxyanisole and butylated hydroxytoluene). The antioxidant power of compounds produced by microalgae is well documented and, in some cases superior to that of plants or fruits.[59]

Besides providing essential nutritional requirements, the research focus on novel aquaculture feed can be widened to include additional benefits and innovations, specifically additional nutraceutical value, disease prevention and improved sustainability and circular economy. As described above, microalgae are rich in protein and valuable oils, pigments and antioxidants; however, microalgal biomass contains other beneficial compounds such as vitamins and a variety of bioactive compounds. These bioactive compounds are central to innovative aquaculture research because of their immune-stimulating properties and even anti-parasitic effects. For example, the immune response of freshwater prawn *Macrobrachium rosenbergii* increased after replacing 8% of fishmeal with *Chlorella vulgaris*. The positive immune response was demonstrated by higher total haemocyte count and phenol oxidase activity, which enhanced the resistance of prawns to *Aeromonas hydrophila* infection.[60] Similarly, consumption of chlorophyte *Dunaliella salina* enhanced the immune response (superoxide dismutase and catalase) in shrimp *Penaeus monodon* making the shrimp more resistant to white spot syndrome.[61]

2.2 | Fungi and thraustochytrids

2.2.1 | Fungi (filamentous and yeast) as a source of antimicrobial compounds for aquaculture

Fungal biomass has increasingly been regarded as a potential feed source given its nutritional content including protein, essential amino acids, PUFAs, fibres, minerals and vitamins.[62] The utilisation of fungi as an alternative protein source in feed is not new concept. In most cases, data refers to fungi of terrestrial origin, which, however, from a nutritional point of view, do not present significant differences compared to those of marine origin. This is partly due to the fact that there is a consolidated tradition in using of fungi as effective biorefineries to valorise agricultural by-products, while there are still few applications in aquaculture. The increasing availability of fungal strains of marine origin, and the development of new production chains in the blue bio-economy will soon fill this gap.

Numerous papers report the efficacy of by-products of mushroom production as an FM replacer.[63,64] Fungal biomasses or their derivatives have been used as prebiotics, with beneficial effects demonstrated in several fish and shrimp species.[65,66] Dadi et al.[67] reported that the cell-free supernatants of two marine fungi endophytes can be used as feed supplements to protect shrimps (*P. vannamei*) against hepatopancreatic necrosis disease caused by *Vibrio* spp. Moreover, several publications recently demonstrated that marine fungi are a source of antimicrobial compounds for use in aquaculture against fish pathogens. Fungi from sponges have been screened for the production of antimicrobial compounds active against different fish pathogens, that is, *Lactococcus garvieae*, *Vibrio anguillarum*, *Vibrio harveyi*, *Yersinia ruckeri* and *Vagococcus salmoninarum*.[68–71] Since bacterial pathogens are a serious threat in aquaculture and the antimicrobial resistance in cultured aquatic animals is at concerning levels,[72] there is an increasing need for new tools and approaches to manage aquaculture sustainably. New antimicrobial agents from marine fungi have received considerable attention to overcome difficulties and limitations related to widespread multidrug-resistant bacteria. Hence, further research is needed on the lead compounds generated by these fungal strains that have the potential for use as feed additives as an alternative to antibiotics.

Fungal bioactive molecules display various biological properties, such as antioxidant, anti-cancer, anti-microbial and immunostimulation; indeed, they can activate the innate immune system in either of two ways, by direct stimulation of the immune cells and by improving the growth of intestinal microbiota.[66] The intestinal tracts of animals host a wide diversity of microbiota, which form a complicated gut microbiome with numerous roles in physiological processes, including, but not limited to, the inhibition of pathogenic bacteria and maturation of the immune system and metabolism.[73,74] Fungal ingredients can stimulate growth and enhance immune responses and defence mechanisms against pathogenic microbes and abiotic stressors. Fungal polysaccharides and crude polysaccharides mainly produced from processing waste from mushrooms intended for human consumption act as prebiotic substances and are deemed as a nutritional component for regulating growth and health conditions.[65] Such immune enhancers can improve the health of aquatic animals, including sea cucumbers, by modifying the host intestinal microbiota structure.[75–79]

Recent papers highlight the environmental sustainability of mycoproteins with respect to animal- or plant-based proteins as demonstrated by life cycle assessment analysis.[80,81] The benefit of mycoprotein production for sustainable feed production lies in their capability to grow in bioreactors with high metabolic rates using different by-products such as C and N sources.[81–84] Fungal biomasses rich in proteins, can be produced both in submerged[68–72] and in solid-state fermentation[85,86] of agro-industrial residues according to circularity assessment criteria that have been outlined in the introduction. This approach has two important advantages: (i) it reduces the production costs; (ii) valorises processing by-products otherwise treated as waste. To date, most of the works refer to the conversion of agricultural by-products. Still, recent studies have demonstrated the feasibility of converting fish processing wastewater into feed ingredients through the submerged cultivation of filamentous fungi.[87,88] The studies revealed the adaptability provided by the integration of fungal cultivation to fish processing industries, and demonstrated a range of economic and environmental advantages (significant chemical oxygen demand [COD], total solids and nitrogen decrease). Fungi produce a wide range of enzymes that enable them to biotransform various substrates into biomasses rich in proteins and in additional bioactive molecules (e.g. essential amino acids, $n-3$ long-chain [LC PUFAs] and polysaccharides with immunostimulant activity). Moreover, they perform better in reducing COD levels compared to unicellular microorganisms (e.g. bacteria and microalgae) that typically entail costly biomass recovery processes.[87] Therefore, mycoproteins obtained through a circular economy approach have increasingly been studied as an alternative ingredient for animal feed production.

Furthermore, fungi could shortly be used to limit the environmental effects of aquaculture (i.e. nutrient and effluent build-ups and release of antibiotics). Recently, some marine fungi isolated from salmon farming areas in the south of Chile have been reported to degrade antibiotics such as oxytetracycline that are routinely administered in the diet, both in the freshwater smolt phase and in marine farms.[89] These vast quantities of antibiotics cause severe detrimental effects to the environment where they are disseminated and remain active for months, thus favouring the development of antimicrobial resistance.[90] It is essential that the aquaculture industry incorporates biotechnological innovations to mitigate its negative environment impact. For example, existing chemical and physical strategies to degrade organic pollutants from the fish farming industry are costly and produce waste that needs to be quenched after treatment, thus unlikely to be realistically implemented in aquaculture facilities.[91] Moreover, potential alternatives could be based on microorganisms or enzymes able to degrade harmful organic pollutants efficiently. Using bio-based approaches to tackle environmental issues associated with aquaculture represents a sustainable, green and cost-efficient strategy that should be strongly considered. Mycoremediation approaches have proven to be effective for treating contaminated water with antibiotics[92,93] and hopefully, they will also be applied in circular aquaculture in the near future.

2.2.2 | Thraustochytrids

Thraustochytrids are heterotrophic eukaryotic protists, with a wide geographic distribution from polar regions to the tropics, ubiquitously distributed in all shallow and deep waters habitats as saprophytes, detritivores, parasites, pathogens (including edible invertebrates[94]) and bacterivores.[94–106] For more than four decades, the research on

Thraustochytrids focused on the producing of valuable nutrition sources. Yet recently, more research efforts revealed the importance of these unicellular organisms in circular economies.[33,107] Just an example is the employment of waste Thraustochytrids biomass following lipid extraction as an efficient adsorbent for triphenylmethane dye in aquaculture.[108]

Within the Thraustochytrids, the genus *Schizochytrium* is the most commonly used in aquaculture.[109] Several *Schizochytrium* products containing high DHA concentrations have been developed commercially. Further, the dried *Schizochytrium* product is highly effective when included in the diets of channel catfish, *Ictalurus punctatus*,[110] and Asian seabass, *Lates calcarifer*[111] and has been employed as a replacement for FO in the diets of various species.[112,113] The global research community attention has shifted to Thraustochytrids only in the last two decades, primarily due to their high lipid contents, particularly EPA and DHA. Consequently, the research on mass cultivation of Thraustochytrids targeting the potential production of valuable bioactive compounds (such as $n-3$ LC PUFAs, DHA, squalene, carotenoids and more) has been attracting significant scientific and commercial interest.[114,115] With their high levels of saturated fatty acids, the Thraustochytrids have been further explored in industrial biotechnology as source materials for biofuels and lipid biofactories,[116] supplying numerous nutraceuticals, food additives, squalene, carotenoids and other products of economic significance[115,117,118] and contribute to the essentials of marine biotechnology.[119]

Since dietary DHA is an essential nutrient for optimal growth and development of many fish species, Thraustochytrids have been considered a novel alternative source of $n-3$ LC PUFAs. *Thraustochytrium striatum* can produce a high content of DHA, ranging from 5.18 to 83.63 mg g^{-1} biomass, when monosaccharides, like glucose, D-fructose, D-xylose, among others, are used as carbon sources.[120] Moreover, the thraustochytrid *Schizochytrium limacinum*, isolated from the coastal seawater in the west of Pacific Ocean, produced DHA content between 36.9% and 37.6%, at a temperature of 16–30°C and salinity at 0.9%–3.6%.[121] Until recently, most of the DHA supply for aquafeed originated from FO obtained from wild harvested fish. As an alternative strategy, the literature has reported three avenues for using this group of unicellular eukaryotic organisms as aquaculture feed. The first avenue is the direct use of Thraustochytrids (spray dried or freeze dried) and their derived oils for aquafeeds.[98,122] An increasing number of species have been fed such Thraustochytrids, including invertebrates such as shrimp and molluscs (geoduck clam, abalone) and a wide range of fish, including Nile tilapia, rainbow trout (*Oncorhynchus mykiss*) and Atlantic salmon (*Salmo salar*).[113,123–126] The second avenue deals with replacing yeasts and algal cells supplemented with rotifers and *Artemia* nauplii, which are employed as larval fish feed in marine aquaculture.[127] A third feeding avenue deals with newly formulated fishmeal formulations that include thraustochytrid-derived oil (not the cells with the other materials included), an approach already extensively worked-out with various fish species, including salmon parr, channel catfish (*Ictalurus punctatus*), Atlantic salmon post-smolt, giant grouper (*Epinephelus lanceolatus*) and longfin yellowtail (*Seriola rivoliana*).[98]

2.3 | Marine bacteria as a source of ingredients for aquaculture feeds and probiotics

In aquaculture, SCP sources, such as bacteria, have been gathering interest as they represent an effective approach to managing production expenses, not only by maintaining feed performance, but also by benefiting the health of aquaculture fish.[29] Besides vitamins, phospholipids and other functional compounds, bacteria can produce high values of crude protein, essential amino acids and bioactive secondary metabolites. A wide range of inexpensive and waste-based feedstocks that various microorganisms can utilise—methane, methanol, synthetic gas, H_2, CO_2 and sugars—as carbon and energy source to grow and enhance biomass production has also inspired deeper exploration of bacteria as SCP.[127–129] Bacterial SCP-based products can be used as effective growth promoters,[130–135] as an alternative protein source with no adverse effects, to replace FM,[136–140] or even as a boost to improve immune response and survival,[133,140,141] with applicability across a wide range of aquaculture relevant species such as salmonids and shrimps.

Bacteria can be useful at different levels in aquaculture systems: they can feed different taxonomic groups of zooplankton used as live food to larvae in aquaculture hatcheries, or directly included in the diet of various groups of organisms, such as fish, bivalves and crustaceans. In the early stages of production, larvae of aquaculture organisms require essential nutrients such as $n-3$ long-chain PUFAs (such as EPA and DHA), so live food organisms, as such as rotifers, nematodes or *Artemia*, must be enriched prior to larval feeding, using, for instance, marine bacteria or marine bacteria-sourced products.[142] As an example, marine cyanobacterium *Synechococcus elongatus* is used as food for *Artemia franciscana*.[143] Other examples can be mentioned, as the use of heterotrophic marine bacteria to improve the survival, population growth and nauplii production of the copepod *Apocyclops dengizicus*, using a low-cost waste-based diet[144]; and the incorporation of the marine bacterium *Rhodovulum sulfidophilum* in the rotifer *Brachionus rotundiformis* diet to increase protein and fatty-acids yields.[145] Marine bacteria can moreover be relevant in digestibility, another major milestone in aquaculture feed. Several *Bacillus* strains isolated from marine sediments produced beneficial enzymes such as proteases, carbohydrolases and lipases.[146]

Apart from the beneficial role that marine bacteria-sourced products can have on aquaculture diets, marine bacteria can also be a key to improve animal health within aquaculture systems. In addition to traditional nutrients, quality functional food must contain components able to add immune or physiological gains.[147] In this regard, live microorganisms with probiotic effects can positively affect the host performance by improving food degradation, enhancing their nutritional value or upgrading the quality of the environmental parameters[148] and are currently gaining increasing attention by the research sector and the aquaculture industry. Some successful examples of the applications of bacteria as probiotics in aquaculture with antimicrobial activity against several microorganisms responsible for diseases in economically important aquaculture fish species are reported (i) the marine sponge symbiont *Pseudovibrio denitrificans*, effectively used to control pathogenic *Vibrio* sp. in aquaculture shrimps[149]; (ii) marine-derived Actinobacteria of the family Bifidobacteriaceae, which produced bacteriocins[150]; (iii) marine *Phaeobacter* sp. strain, isolated from a mollusc, with protective effect against shellfish and fish pathogens[151]; (iv) *Methylococcus capsulatus* that prevented the development of enteritis in salmon when incorporated in the diet as SCP[140]; (v) marine-derived *Bacillus* and *Aeromonas* strains, isolated from *Artemia* cultures that protect *Artemia* against different pathogens[152]; (vi) several marine-derived *Streptomyces* strains, recovered from sediment samples, which when used as food supplement decreased mortality in nauplii and adult *Artemia* cultures[153]; and (vii) various deep-sea bacteria associated with the haemolymph of marine bivalves that proved to be important to bivalve protection, conferring a health benefit to the host.[154]

An emerging and very logical trend is the use of fish gut-associated microbiota in aquaculture. As the gut microbiota is crucial for health and plays an essential role in the growth, reproductive performance, digestion and mucosal tolerance of the fish,[155] it offers versatile and multifaceted support for sustainable aquaculture. The first layer uses indigenous gut microbiota as probiotics, that is, as living microbial food additives. Most commercial probiotics originate from terrestrial organisms or products (e.g., milk, cheese).[21,156] Growing evidence indicates that the indigenous microflora, particularly bacteria, of the fish digestive tract (also called as host associated or intrinsic bacteria) confer greater probiotic effect and higher performance.[157] The finfish alone have provided many beneficial lactic acid bacteria (LAB) belonging to genera of, for example, *Lactococcus*, *Lactobacillus*, *Leuconostoc* and *Carnobacterium* with well-known probiotic effects.[155] LAB and other host-associated probiotics (HAP) adapt easily to the colonic environment. They are more beneficial to the host on specific parameters, including growth performance, nutrient digestibility, immune system response and better persistence in the host gut after removal of the probiotic.[158] A recent study compared the efficacy of HAP *Enterecoccus faecium* derived from the intestine of adult Caspian roach and the commercial probiotic strain (*Pediococcus acidilactici*). Indigenous *E. faecium* was more effective in promoting growth, feeding efficiency, secretion of digestive enzymes and enhancing the mucosal and systemic immune systems than the commercial probiotic in roach fingerlings. Commercial probiotics suppressed some immune parameters such as lysozyme or complement activity, indicating potential antagonistic effects on the native roach microbiota.[156] These results suggest that bacteria derived from the gut environment of the fish host are more suitable sources of probiotics for the aquaculture sector. Besides Gram-positive host-associated bacteria, several members of Gram-negative bacterial genera, such as *Vibrio*, *Pseudomonas* or *Roseobacter* have also been proposed as probiotics.[21,159] Additionally, many probiotics also have antimicrobial activities on other microbial populations. They produce ribosomal peptides (such as bacteriocins, as mentioned above), siderophores, quorum quenching compounds or hydrogen peroxide, thus preventing the growth of opportunistic pathogens.[160] Some LAB obtained from fish guts have been shown to inhibit the growth of fish pathogens, for example, *Aeromonas salmonicida*, *Vibrio anguillarium*, *V. harveyi* and *V. splendidus*, thereby decreasing the incidence of fish diseases and increasing larval survival.[21,160,161] Fish gut-associated microorganisms may also provide long-chain PUFAs. Several EPA-producing *Vibrio* or *Shewanella* strains have been isolated and characterised from various freshwater fish species.[162,163] Hence, the microbiota of marine fish with all types of microbial components (bacteria, fungi and yeast) should be studied more intensively to untap their full potential for feed and other multiple health beneficial effects on cultured fish.

Overall, marine microorganisms represent an untapped and realistic potential for their use in a circular aquaculture setup. They can be used in bioremediation to improve aquaculture water quality, as converters of waste and as underexploited alternatives to land-based nutrient resources. However, alternative ingredients must meet environmental sustainability and economic viability criteria.[164] Hence, to guarantee the sustainability of circular use of microorganisms in aquaculture, more effort is needed to optimise the processes and reduce costs of growing, handling, processing and extraction processes.[165]

3 | MACROORGANISMS AS AQUACULTURE FEEDS

3.1 | Macroalgae

Macroalgae as aquafeed were recently reviewed by Moreira et al.[166] Besides their nutritional value (mostly protein source), seaweeds contain several compounds and secondary metabolites that could benefit farmed fish. In particular, various seaweed extracts exhibit properties that indicate they could be used as prophylactic and/or therapeutic agents in aquaculture.[167]

In recent years, several investigations were made to evaluate the potential of seaweed as a source of fish feed protein. With current technology, producing protein for fish feed using seaweed biomass is neither economical nor environmentally sustainable without key technical innovations to overcome several existing bottlenecks (available volume of seaweed biomass, protein content and biomass conservation technology).[168–170] Nonetheless, in some countries, such as Norway, the seaweed industry, the technology suppliers and food and feed manufacturers are showing strong interest in participating or supporting the needed step to increase the seaweed volume produced locally.[171] Furthermore, the fermentation process was recognised for improving the nutritional quality of plant protein sources.[172] It has been recently explored to improve the nutrient efficiency and nutritional quality of the seaweed proteins.

Further, all groups of seaweeds exhibit significant antimicrobial properties against many infectious agents of fish and shrimp. Still, the genera exhibiting a broader range of antibacterial properties are *Asparagopsis* spp. (red seaweed) and *Sargassum* spp. (brown seaweed).[167] This bioactivity can, however, be affected by many factors. The extraction method is one of the most important steps to consider when extracting these compounds: organic solvents appear more efficient. When the antimicrobial properties are studied in vivo, the seaweed extracts are either incorporated directly into the feeds (dry or live) or added into the water in which the fish and shrimp are reared. Incorporating the extracts into the feeds appears to be an effective delivery method for preventing and treating different infectious diseases. To the best of our knowledge, there have been no complete studies reported on the pharmacodynamics and pharmacokinetics of seaweed extracts in fish or shrimp. Besides antimicrobial activity, seaweeds also demonstrate anti-inflammatory activities and immune modulation properties in fish.[173,174] Another issue that has not been examined yet is the increased technology readiness level to use these bioactive extracts on a commercial scale. Hence, further research is needed to assess the full potential of seaweed ingredients in aquafeed.

3.2 | Invertebrates

Many commercially important fish species, produced in aquaculture, are unable to grow if fed exclusively with formulated inert feed during their early developmental stages. However, there have been some encouraging results on sing of fish meals with species of fish that were considered to demand live feed exclusively.[175,176] Nonetheless, many finfish larvae still rely on live feed for the first few weeks of their life. This type of production demands trained personnel and infrastructure investments to maintain hatcheries or optimise the supply chains to guarantee the steadiness of live feed provision when obtained from external producers.

The two main reasons for fish depending on live feed are (i) small size of larval mouths, and underdevelopment of their gut at the time of the first feeding. This necessitates feeding on the live feed, supplying exoenzymes to the fish and helping to digest the prey.[175] (ii) Additionally, moving prey attracts the fish more than inert particles.[177] This is of the utmost importance to some altricial fish larvae that may need to feed within short time spans after hatching due to the rapid depletion of their energy reserves, which may occur within a few hours for some species.[178]

Most hatcheries are using brine shrimps (*Artemia* spp.) as live feed due to the easy use of these organisms. However, many of these hatcheries suffer from high mortality among the first developmental stages of the fish larvae despite using these live feeds. This is due to the unfavourable biochemical composition of *Artemia*, requiring their enrichment before using them as first feeds.[179,180] In addition, the size of *Artemia* is too large for early feeding in many fish larvae with very small mouths. Furthermore, *Artemia* is harvested in the wild (in salt lakes) and its availability is subject to variation due to climatic factors and other parameters, leading to varying or, even worse, increasing prices of this feed item.[181] Together with *Artemia*, rotifers have great potential for live feed in aquaculture, particularly marine hatcheries. The two main species used are *Brachionus plicatilis* and *B. rotundiformis*. Rotifers are parthenogenetic, reproducing at high rates and achieving high densities in cultures.[182] The availability of rotifers as live prey has contributed to successful hatchery production of several marine finfish and crustacean species.[182] However, just as for *Artemia*, the biochemical composition of rotifers is poor, and they need enrichment to be used as live feed.

Copepods are not often used in aquaculture, even though it is well accepted that they are valuable feed sources for fish larvae. Compared to *Artemia* or rotifers, their favourable biochemical composition indicates that they should become more frequently used in the future,[183,184] which will also significantly raise the number of fish species that can be successfully produced in aquaculture. Both cultured and wild-harvested copepods possess biochemical characteristics that make them attractive as live prey in fish larvae rearing.[178] Compared to both *Artemia* and rotifers, copepods have a higher content of PUFAs and they especially have more favourable content of the two important PUFAs, DHA and EPA represent two highly bioactive and physiologically important fatty acids within the $n-3$ series.[183] Their DHA/EPA, ratios and DHA + EPA/total fatty acids, ratios are closer to those needed by fish than those of alternative feed organisms, which make them more easily digestible for fish larvae and with a higher nutritional value for fish than either rotifers and *Artemia*.[183] Copepods also have higher contents of essential amino acids than both rotifers and *Artemia*.[183] Further, copepods experience a slower gut passage in fish larvae than alternative live feed items, leading to a complete digestion and more efficient nutrient uptake in the fish larvae.[185] It has been argued that this is due to a higher digestive enzyme content in copepods, used by the fish larvae as exoenzymes.[186] Copepods are part of the natural fish feed present in aquaculture ponds, and good results from sustainable intensive cultures have been achieved.[184,187] Copepods are used at a semi-intensive scale in some form of aquaculture,[188,189] and several attempts have been made to scale up copepod production and use to a full, intensive, industrial-scale.[183,190] More than 60 species of copepods have been cultivated in the laboratory, but the copepod industry is still not fully developed due to a certain lack of knowledge dissemination of large-scale cultivation of copepods, especially regarding recent developments in the field.[191,192] This lack of dissemination of knowledge has led to a situation, where copepod cultivation is generally perceived as overly complicated within the aquaculture industry. One of the factors limiting the use of copepods in industrial-scale aquaculture is that large-scale production of copepods also necessitates a large-scale production of microalgae as feed for the copepods,[193] which is expensive. New results indicate that some species of copepods are in fact capable of synthesising essential $n-3$ PUFAs such as DHA, EPA and ALAon their own, something that has previously been assumed only to take place in lower organisms, such as microalgae.[194] This means that these species of copepods can be fed low-quality feed such as baker's yeast and do not need to be fed with microalgae.[195] This will contribute greatly to making the production of copepods for aquaculture easier, cheaper and biocircular. It is easier and cheaper as baker's yeast can be acquired from outside the aquaculture industry, with no need for an integrated production of the feed, as is the case with microalgae. It will also contribute to a more circular bioeconomy in the aquaculture sector, as baker's yeast is a waste product from bread and beer production, so the utilisation of baker's yeast in aquaculture production will serve as an example of a waste product from one sector being a resource for another sector. Hence, future investigations are needed to optimise and promote the use of copepods as an aquaculture feed.

The use of meal rendered from macroinvertebrates as a potential alternative to marine-origin FM have been reported as a promising approach.[196,197] Different worms have been particularly studied as potential sources of live feeds for marine fish larvae as a potential food source for aquaculture hatcheries.[198] Macroinvertebrates, especially amphipods are a significant part of benthic communities[199] and an important food for many fish and invertebrate species as natural live prey in aquaculture feed. Amphipods are usually rich in proteins, representing the main biochemical class of organic compounds, approximately 40% of dry weight.[200] Many crustacean species can be cultivated in laboratory cultures. Still, there is a dearth of research on the potential of marine gammarids as a novel aquatic crop to be produced in commercial-scale feed systems[201] and missing knowledge about the use of live organisms as feed-grade ingredients that can be sustainably produced.[202] Overall, marine amphipods have shown advantages and disadvantages with their use as natural live aquaculture feed. For example, lipid content in marine amphipods was more suitable for aquaculture than freshwater species.[196] Caprellid amphipods have been identified as possible candidates for exploitation as a live aquaculture feed.[198] They can be either field collected, or cultured. Indeed, laboratory culturing methods have been successfully performed.[203] The *Monoporeia affinis* which is highly abundant in the Baltic Sea, is tolerant to low oxygen concentrations and certain chemicals.[204–206] Such tolerant species could be suitable for cultivating as aquafeed. However, *M. affinis* females give birth to only 20–80 juveniles, which happens only once during 2–4 years.[204,206] Although this species can live in laboratory cultures and give birth to the next generation, the quality of most eggs is not satisfactory (Strode E. pers. obs., unpublished results). Moreover, pilot research showed that protein concentration decreased in *M. affinis* with longer cultivation time. *M. affinis* usually live in deep water sediments (>20 m) with decreased oxygen concentration. Hypoxia could lead to physiological changes in organisms, such as increased ventilation frequency, decreased protein synthesis, further retarded individual and population growth and increased mortalities.[207,208] In general, amphipods have adequate nutritional values for applications in aquaculture, but cultivation processes lead to low survival rates or species reproduction.[201] Overall, the optimal cultivation conditions for these organisms are still not defined and more research efforts should be put to optimise the cultivation techniques, taking into consideration the available knowledge on organism ecology, biology, feeding and reproduction becomes important.

Among Cnidaria, a few scyphozoan pelagic jellyfish species could be exploited for developing aquafeed supplements due to their high content of proteins, phenols, essential $n-3$ long-chain PUFAs (EPA and DHA), essential ω-6 fatty acids as linoleic acid, essential minerals (Na, Mg, K and Ca) and trace elements (Fe, Zn, Cu, Mn and Se), as reported for the Mediterranean pelagic jellyfish, a mauve stinger *Pelagia noctiluca*.[209] Some others, such as *Aurelia aurita* and *Chrysaora pacifica*, with also peculiar metal profiles, have already shown to support the growth and survival of farmed lobster *Ibacus novemdentatus* phyllosomas.[210]

Among macroinvertebrates, amphipods constitute a significant part of benthic communities[199] as an important feed for many fish and invertebrate species and are utilised as natural live prey in aquaculture feed. Amphipods are often rich in proteins (estimated at 40% of their dry weight) and contain less than 10% of carbohydrates and lipids.[200] They also show well-balanced fatty acid composition, with high levels of favourable PUFAs such as DHA and EPA. Although many crustacean species can be cultivated under laboratory conditions, sustainable technologies are still lacking to enable a commercial scale production of such a novel aquatic crop[201] and manufacturing a feed-grade ingredient out of amphipods.[202] Marine amphipods may have more suitable lipid content than their freshwater counterparts.[196] Amphipods are already reported as valuable feed for farmed and exploited populations of fish. *Melita palmata* may be attractive as a food resource for aquaculture mainly due to its high phospholipid and ω-3 PUFA levels. Similarly, *Microdeutopus gryllotalpa* and *Monocorophium acherusicum* have high lipid and DHA concentrations. These two amphipods' size is notably smaller (<0.5 cm) than other amphipods species, meaning a higher number of specimens are necessary to obtain the proper amount of biomass for fish feeding.[200] The Caprellid amphipods have also been identified as a possible candidate for exploitation as a live aquaculture feed.[198] Some amphipod species such as *Corophium volutator*, *Gammarus locusta* and *Monoporeia affinis* have been extensively used in bioassays.[203–206] As they often tolerate a wide range of environmental conditions, including oxygen concentration and chemicals and have high productivity, they may be good candidates for aquafeed species. Among these species *M. affinis* is known to have high lipid levels.[211] However, some cultivation trials with *M. affinis* showed a low reproduction success and a declined protein concentration along with cultivation time. Here, hypoxia could have profound physiological changes in organisms, such as increased ventilation frequency, oxygen affinity to decreased protein synthesis, and further retarded individual and population growth and increased mortalities.[207,208] Similarly, many other gammarid amphipods have shown rewarding nutritional value for applications in aquaculture, but poor cultivation performance under laboratory conditions.[201,206]

Mollusc meat is another promising source of essential nutrients for shrimps and also possesses excellent chemo-attractant properties for fish.[212] Importantly, farming and harvesting mussel species can be a promising internal measure for eutrophication control in many estuarine ecosystems and regional seas.[213] In the Baltic Sea, due to low salinity, mussels are small and making it difficult to process them into a meal. To overcome this limitation, black soldier fly larvae were first fed a paste made of blue mussels, spiking the larvae with ω-3 fatty acids from mussels. The larvae were then dried and turned into a meal, rich in protein but also valuable fatty acids.

The sea urchin *Diadema setosum* has been reported as alternative fish food for the African cichlid fish, *Oreochromis niloticus* during growth,[214] but also a chemoattractant for juveniles of barramundi, *Lates calcarifer* which makes this echinoderm species a potential candidate for aquafeed.[215] Free-living nematodes have a great potential for use as live food in the early stages of life of several species in marine aquaculture. Still, data on cultivating of marine nematode species suitable for fish/shrimps aquafeed are scarce. Thus, nematodes of the genus *Panagrellus* have long been used in larviculture of a numerous fish[216] and shrimp species[217,218] as well as a liquid culture of free-living nematodes *Panagrolaimus sp*.[219] While freshwater oligochaetes were widely used, cultured as a supplement or fish/crustacean food,[220] only a few species of marine oligochaetes have been introduced for cultured purposes. Maheswarudu and Vineetha[221] described a protocol for culturing the littoral oligochaete *Pontodrilus bermudensis* in sand vermibed enriched with various organic amendments for use as a supplementary diet for maturation and spawning of broodstock of penaeid prawns (*Fenneropenaeus indicus*, *P. monodon*, *P. semisulcatus*) and portunid mud crab *Scylla tranquebarica*.

In the last decade, several studies have focused on polychaetes of the family Nereididae and their potential applications in aquafeed: (i) as an alternative feed source that could replace FM and FO or used as a dietary supplement in artificial fish diets[222,223]; (ii) as a stimulator of gonad development and prawn/ shrimp spawning, due to particular lipid content[224]; (iii) as chemoattractants for many species of fish and shrimp trough increasing food palatability (mostly due to glutamic acid, arginine and glycine content)[222,225]; (iv) as a source of glycosaminoglycans (GAGs) for supplement in farmed cartilaginous fish[225]; and (v) as a bioremediator in integrated multitrophic aquaculture system (IMTA).[226] Besides *Hediste diversicolor* (=*Nereis diversicolor*), an excellent biopotential was reported for *Sabella spallanzanii* through a gross protein content of almost 55% of dry matter, which is significantly higher than that of the bivalve *Mytilus galloprovincialis* (8%), the anemone *Anemonia viridis* (11%) and the lobster *Nephrops norvegicus* (19%–20%), essential amino acid composition and a low ω-3 and ω-6 fatty acids ratio (1.7),[225] but also its bioremediation role in an IMTA, with the macroalga *Chaetomorpha linum*.[216]

Among the invertebrates mentioned above, non-indigenous species (NIS) can also be considered under certain conditions as natural resource in aquaculture nutrition regarding their protein content. To date, the dispersal of NIS by human activities, such as aquaculture, shipping and creation of artificial canals, is redefining the biogeography of the oceans and seas.[227] The consequences of the introduction of NIS span from detrimental environmental effects to a complete reorganisation of ecosystems, threats to human health and severe impacts on human wellbeing and different economies such as tourism and fishing.[228–231] The latter might have substantial social, economic and cultural consequences.[232,233] The Global Assessment Report on Biodiversity and Ecosystem Services, prepared by the Intergovernmental Science-Policy Platform on Biodiversity and Ecosystem Services (IPBES)[234] identified NIS as one of the five top direct drivers of biodiversity loss, pointing to one of the most significant threats for humanity in the next decade.[234]

The significantly negative consequences of NIS on marine ecosystems and relevant industries triggered the establishment of novel NIS mitigation strategies that are defined as 8R—Recognise, Reduce, Replace, Reuse, Recycle, Recover/Restore, Remove and Regulate[235] and the Regulation (EU) No. 1143/2014 on the prevention and management of the introduction and spread of NIS. This Regulation sets out rules to prevent, minimise and mitigate the adverse impact on the biodiversity of the introduction and spread of NIS both intentional and unintentional, within the Union. The management measures consider lethal or non-lethal physical, chemical or biological actions aimed at restricting, restricting or controlling a population of NIS. Although eradicating of marine NIS is unfeasible, this regulation allows the commercial use of already established NIS as a part of management measures directed toward their elimination, control or prevention of their spread, if there is a justifiable reason for it. In such a context, the exploitation of NIS as a food for fish may become an important contributor to circularity and sustainable aquaculture systems. Although NIS may contribute to highly nutritious and valuable organic aquaculture feed, they primarily represent an unexploited natural protein resource in aquaculture nutrition. Besides the published evidence there are many other local or regional initiatives to exploit the potential of NIS in fish feed, such as round goby *Neogobius melanostomus* in the Baltic Sea region.

Another potential candidate of NIS to exploit for aquafeed is the veined rapa whelk (*Rapana venosa*) which have invaded the Indo-Pacific region to Black, Red and Adriatic Seas, the south-eastern coasts of South America. *R. venosa* has a high protein level (72%) and rewarding amino acid composition. Despite that its nutritional profile may greatly vary depending on the environmental conditions and season, the species has relatively constant nutritional value throughout the year.[236] Edible tissues of the whelk contain high levels of ω-3 fatty acids, especially EPA and DHA.[237] Hemocyanin and its functional units isolated from veined rapa whelk exhibited antimicrobial activity, antiviral activity and phenol oxidase activity.[236] Since veined rapa whelk is widely spread throughout the world waters and has beneficial nutritional value, it could be a good protein source in aquafeed.

The zebra mussel (*Dreissena polymorpha*) could also serve as an alternative feed supplement for fish. To date, there is no evidence of the use of zebra mussels in aquafeed. On the other hand, zebra mussels were documented to be a palatable feed ingredient for chicken.[238] The literature suggests that zebra mussels have a protein content of up to 70%.[239] In contrast, according to McLaughlan et al.,[238] zebra mussels contain lower protein and energy levels because mussel meal consists of meat and shell. The shell contains a small amount of protein, which is scleroprotein, while flesh has considerable protein content. For zebra mussels to be utilised as a sustainable and long-term feedstuff for fish, flesh should be secluded from the shells economically.

Starfish (*Asterias rubens*) is a natural predator of mussels and if occurring at high densities they may deplete natural and commercially grown mussels. The species is native to the northern Atlantic Ocean but was recently introduced to the Black Sea.[240] Starfish are another underutilised natural source of protein and collagen. Hence, they have a huge potential to be successfully valorised into aquafeed. It was estimated that 10,000 tons of starfish catch can turn into approximately 2500 tons of starfish meal. Starfish meal has high nutritional value as it may contain up to 70% proteins, which surpasses the protein content of seaweed and mussels.[241] The quality of protein fraction in starfish meal is comparable to FM.[242] It was documented that the protein-containing liquid part of starfish should be collected and drained rapidly to obtain a high protein level in the starfish meal. Furthermore, starfish meal is interestingly characterised by a better amino acid profile than other plant alternatives. The biochemical composition of starfish is variable and depends significantly on the season, environmental factors, size and freshness.[242] According to Sørensen and Nørgaard,[242] starfish meal has comparable fat content to FM but higher ash and calcium content. Numerous chemical components with antimicrobial, antifungal or antiviral activities found in starfish meal make this alternative feed ingredient suitable for general animal nutrition.[242]

Overall, the growth conditions for these NIS are still not defined and more research efforts to increase knowledge on ecology, biology, feeding and reproduction. The collection methods should be optimised and mitigation measures developed to control their invasions should at the same time to make use of their collected biomass in aquafeed.

4 | MARINE SIDE STREAMS (FROM INDUSTRY/DISCARD): A CIRCULAR AQUACULTURE PERSPECTIVE

In recent years, a shift in the global bio-economy is becoming apparent with a transition from linear models (produce-use-dispose as waste) to the development of the circular models (produce-use-valorise side streams in other industries). Regarding alternative aquaculture sources, two circularity levels have emerged: (i) indirect and (ii) direct. Concerning the 'indirect' circularity level, aquaculture generates significant amounts of waste, these become investigated as potential sustainable sources of biomolecules in various industries, such as cosmetics, pharmaceuticals, food packaging, energy, aquaculture or cattle feed ingredients.[243,244] Indeed, alternative use as feed for several fishery by-products is obvious. Since the fisheries discard ban and landing obligation in the frame of the Common Fisheries Policy (https://ec.europa.eu/oceans-and-fisheries/fisheries/rules/discarding-fisheries_en), undersized fish need to be landed, however, they cannot be used for human food.[245] The same goes for side streams from the fish processing industry. Producing fish silage is an excellent way to valorise these byproducts as feed in aquaculture and agriculture, particularly relevant for countries with small-scale fisheries. Nutritional quality depends on the freshness and composition of the raw material.[246] Alternatively, enzymatic hydrolysis and microbial conversion could also be used to valorise such sidestreams for FM and other applications.[247] Regarding second circularity levels—'direct', the concept of integrated multi-trophic aquaculture and the acronym IMTA was proposed almost two decades ago,[248] making a revolutionary contribution to aquaculture sustainability. This combined cultivation of fed species (finfish or shrimps) with extractive species, which utilise the inorganic (e.g. seaweeds) and organic (e.g. suspension- and/or deposit-feeders) nutrients from fed aquaculture for their growth, showed a more sustainable solution than monoculture. Created as a bio-mitigation strategy that aims to reduce the adverse effects of aquafarming pollutants (i.e. depletion of oxygen in water, algal blooms and dead zones) on the marine ecosystem, through the co-cultivation of complementary species, IMTA also finds the best practices for 'by-products' reuse. As a new generation of aquaculture, IMTA provides engineering systems for environmental sustainability, economic stability and diversification of commercial production, as well as societal acceptability due to better management practices.[249] Conceived from the beginning as 'a concept, not a formula', IMTA implies a multidisciplinary approach and dynamic system that is subject to change in response to local/global challenges (environmental, climatic, social, political, etc.), as well as new scientific knowledge.[250] To significantly improve bio-mitigation efficiency and economic farm production, designing the best locally suited IMTA (and marine IMTA, i.e. MIMTA) demands creating a comprehensive database of individual-based sub-models for IMTA candidate organisms as recently suggested.[251]

Thus, besides the need for aquafeed, marine macroinvertebrates may contribute to water quality close to aquafarms, in integrated mariculture composed of filter/deposit-feeding animals such as sponges and echinoderms.[252] For the sea cucumber *Holothuria tubulosa* as one of the most commercially exploited echinoderms, the ability of organic waste consumption from fish farms was recently described, making it a strong candidate for the potential development of IMTA in the Mediterranean region.[253,254] Marine sponges are sessile filter feeders that can act as biofilters and bioremediators[255] as already demonstrated for *Hymeniacidon perlevis*, capable of bioremediating bacterial pollution in the intensive aquaculture water system of turbot *Scophthalmus maximus*[256] or in co-culture with mussel *Mytilus galloprovincialis*.[257] In addition, their ability to survive in eutrophic conditions supports their potential role as a 'biofilter' in MIMTA, while the resistance of the sponge-associated microbial communities to opportunistic infections even in polluted water suggests the bioactive compound synthesis, as demonstrated by *Gelliodes obtuse*.[258]

Most sponges use dissolved organic matter (DOM; 0.2–0.7 μm[259]) in their organic diet, which is not bioavailable to most other heterotrophic organisms. In contrast, particulate organic matter (POM) represents a minor proportion of their total organic intake. Their ability to turn a DOM into a POM through a pathway called 'the sponge loop', in which resources stored in the DOM efficiently return to the benthic food chain,[260] making them an important participant in IMTA. The preferred sponge candidates for mariculture applications and IMTA are those with beneficial bioactive compounds, such as the common Mediterranean demosponges, *Chondrosia reniformis*, due to its collagen-rich cortex with great biomedical potential,[261] *Sarcotragus spinosulus*[262] and *Aplysina aerophoba*, a gold-mine of various biomaterials with biomimetic and pharmacologic potential.[263] Moreover, Giangrade et al.[264] recently listed a set of macrobenthic filter-feeding invertebrates, such as sabellid polychaetes, sponges and mussels, coupled with macroalgae, which act as bioremediators in inshore marine fish farms. Further challenges of this complex, innovative MIMTA necessitate serious valorisation of the biomass obtained as value-added by-products.[264] The cultivation of polychaetes on waste products from finfish and crustacean aquaculture, using their coprophagous feeding behaviour, represents a promising practice example in the waste handling challenges of the aquaculture industry. A few studies have highlighted the importance of intensive farming of polychaete *Hediste diversicolor* (=*Nereis diversicolor*), rich in PUFAs, cultivated on waste streams from freshwater aquaculture with great sturgeon, *Huso huso*[265] and marine finfish aquaculture with European bass, *Dicentrarchus labrax* and gilthead sea bream, *Sparus aurata*, wastes.[266] Moreover, the cultivation of *Hediste diversicolor* on salmon smolt waste, converted by polychaetes to high valuable compounds as protein and lipids, should be considered as an alternative aquafeed source with excellent potential in sustainable aquaculture production.[267]

5 | ADDED VALUE ACTIVITIES FOR NOVEL AQUAFEED

Besides the direct contribution to circularity in aquaculture, the use of novel aquafeeds from the marine environment offers additional benefits to the cultured species. They are important to highlight when evaluating the circularity criteria to incentivise researchers, producers and consumers about secondary added values of proposing Aquaculture v3.0 products.

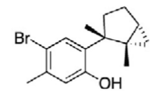
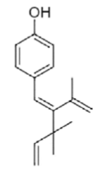
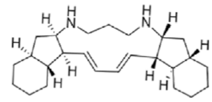
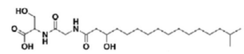
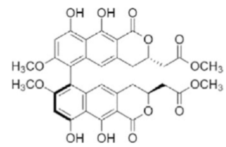
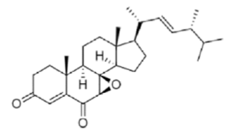
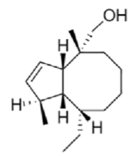
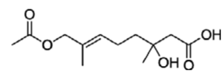
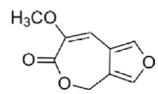
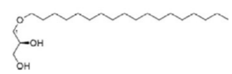
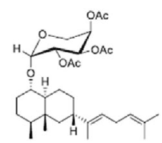
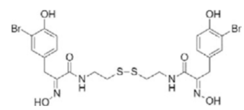
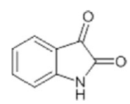
At least 22 bacterial genera have been reported in the literature as pathogenic to fish, including Gram-positive bacteria *Mycobacterium*, *Streptococcus*, *Lactococcus*, *Aerococcus*, *Renibacterium*, *Nocardia*, *Clostridium* and *Enterobacterium*[268] and gram-negative bacteria *Vibrio*, *Aliivibrio*, *Moritella*, *Photobacterium*, *Aeromonas*, *Edwardsiella*, *Pseudomonas*, *Flavobacterium*, *Tenacibaculum*, *Piscirickettsia*, *Heptobacter*, *Francisella*, *Chlamydia* and *Yersinia*. Hence, despite the global increase in the aquaculture sector, it still faces numerous challenges connected to the frequent use of antibiotics, their persistence in the environment and the spread of antimicrobial resistance.[269,270]

For many years, traditional antibiotics used in human medicine such as oxytetracycline and amoxicillin, have also been used to treat fish diseases in the aquaculture industry. However, antibiotic-resistant bacteria associated with fish diseases are increasing, mainly due to the absence of safer and more effective use of antibiotics. It is becoming necessary to search for alternative compounds to mitigate this problem. Using natural products from marine organisms can be a possible alternative for inspiring veterinary drug discovery for prevent and treatfish infectious diseases. Marine natural products are formed by natural selection through the high selectivity and efficient interaction with cellular targets, tailored to avoid resistance.[271–275] Natural products isolated from marine-derived micro and macroorganisms with biological activity against the pathogenic bacteria associated with fish diseases have been comprehensively reviewed and are summarised in Table 1, these natural products are suggested for drug lead development of antibiotics for fish treatment. In detail, *Laurencia johnstonii*, a marine alga, produces several bioactive compounds, including laurinterol, which has an antimycobacterial effect against *Mycobacterium fortuitum*.[272] Nodosol, a natural product produced by the marine angiosperm *Cymodocea nodosa*, showed strong activity against *M. fortuitum*. Nodosol has a simple meroterpenoid structure, and this characteristic makes it a feasible target for its chemical modification and synthesis, which can optimise of its antibacterial activity.[276] Furthermore, *Mycobacterium marinum* was inhibited by (−)-papuamine, isolated from the crude organic extract of the marine sponge *Haliclona sp.* 10.[277]

The pathogens that cause streptococcosis disease can be tackled with several marine natural products. Bacteria from the genus *Algibacter*, isolated from the Barents Sea, produced lipid 430, with activity against *Streptococcus agalactiae*.[278] *S. agalactiae* was also inhibited by rhamnolipids produced by the Arctic marine bacterium *Pseudomonas fluorescens*.[279] *S. iniae* and *S. parauberis* were both suppressed by viriditoxin, a natural product isolated from the jellyfish (*Nemopilema nomurai*)-derived fungus *Paecilomyces variotii*. Interestingly, viriditoxin was 10 times more potent against these drug-resistant fish pathogens than oxytetracycline (a traditionally used antibiotic in aquaculture).[280] Rhizome crude extracts obtained from *Juncus maritimus*, an extremophile plant, showed potent activity against *S. dysgalactiae*, another pathogenic bacterium responsible for streptococcosis disease in fish.[281] Besides *Streptococcus* sp., *Aerococcus viridans* and *Lactococcus garvieae* are also fish pathogenic bacteria that cause streptococcosis disease. Several extracts from Caribbean gorgonian corals inhibited *A. viridans*. However, the overall studies suggested that the inhibition of bacterial growth is not the primary ecological function of secondary metabolites of gorgonian corals.[282] Moreover, two antimicrobial peptides (AMP), *arasin-likeSp* and *GRPSp*, were obtained from the mud crab, *Scylla paramamosain*. These AMPs showed antibacterial activity against *A. viridans*, suggesting their involvement in the immune responses of this mud crab and possible future use to combat these bacteria.[283] *Lactococcus garvieae* was efficiently inhibited by an ethyl acetate extract obtained from a marine sponge associated with marine fungus *Aspergillus iizukae*.[69] *Arthrobacter davidanieli*, a non-pathogenic actinobacterium, is used and licensed in Canada as an effective live vaccine against *Renibacterium salmoninarum*.[284] To date, no marine natural products have been reported for *R. salmoninarum*, *Clostridium botulinum* and *Enterobacterium catenabacterium* inhibition. Nevertheless, natural compounds are considered potent inhibitors against *C. botulinum*, such as nitrophenyl psoralen, a small natural product extracted from Indian plants.[285]

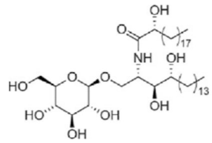
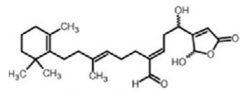
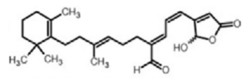
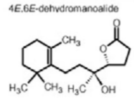
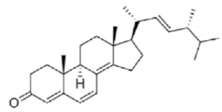
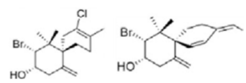
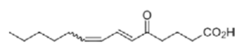
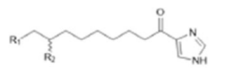
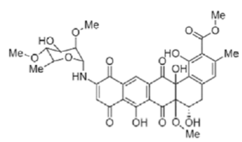
Recently, the steroid 7β,8 β-epoxy-(22*E*,24*R*)-24-methylcholesta-4,22-diene-3,6-dione, isolated from the deep sea-derived fungus, *Aspergillus penicillioides* showed antimicrobial activity against *Vibrio anguillarum*.[286] The strain *Vibrio parahaemolyticus* was inhibited by a guaiane sesquiterpene derivative, guai-2-en-10α-methanol, isolated from the abundant green seaweed *Ulva fasciata*.[287] Furthermore, a new monoterpenoid, penicimonoterpene(+), was isolated and identified from the marine-derived endophytic fungus *Penicillium chrysogenum*. From this compound, derivatives with antimicrobial potential were synthesised. Five penicimonoterpene derivatives presented strong inhibition against *V. anguillarum* and *V. parahaemolyticus*.[288] Moreover, from the crude extract of a sponge-derived fungus, *Penicillium* sp. LS54, a novel seven-membered lactone derivative, penicillilactone A, exhibited inhibition activity against *V. harveyi*.[289] In addition, a lipidic compound, batyl alcohol, isolated from the Colombian Caribbean Sea soft coral *Eunicea* sp. and a terpenoid, fuscoside *E. peracetate*, isolated from *E. fusca* showed biofilm inhibition

TABLE 1 Fish pathogenic bacteria, associated diseases and marine natural products with antimicrobial activity against the corresponding bacteria pathogen

Bacteria type	Pathogenic bacteria	Disease	Antimicrobial natural product name/ natural product source	Chemical structure	References
gram+	*Mycobacterium fortuitum*	Mycobacteriosis	Laurinterol *Laurencia johnstonii* (red alga)		272
			Nodosol *Cymodocea nodosa* (seagrass)		276
	Mycobacterium marinum		(−)-papuamine *Haliclona sp.* (sponge)		277
	Streptococcus agalactiae	Streptococcosis	Lipid 430 *Algibacter sp.* (bacteria)		278
	Streptococcus iniae		Viriditoxin *Paecilomyces variotii* (fungus)		280
	Streptococcus parauberis				
	Aerococcus viridans		Peptides arasin-likeSp and GRPSp *Scylla paramamosain* (crab)	NA	283
gram-	*Vibrio anguillarum*	Vibriosis	7β,8β-epoxy-(22*E*,24*R*)-24-methylcholesta-4,22-diene-3,6-dione *Aspergillus penicillioides* (fungus)		286
	Vibrio parahaemolyticus		Guai-2-en-10α-methanol *Ulva fasciata* (green alga)		287
			Penicimonoterpene-derivatives *Penicillium chrysogenum* (fungus)		288
	Vibrio harveyi		Penicillilactone A *Penicillium* sp. LS54 (bacteria)		289
			Batyl alcohol[a] *Eunicea* sp. (soft coral)		290
			Fuscoside E peracetatate[a] *Eunicea fusca* (soft coral)		290
	Vibrio vulnificus		Psammaplin A *Poecillastra* sp., *Jaspis* sp. and *Poecillastra wondoensis* (sponges)		293
			Sulphated polysaccharides *Spirulina platensis* (microalga)	NA	294
	Aeromonas salmonicida	Aeromoniasis/ furunculosis	Isatin *Alteromonas* sp. (bacteria)		295

(Continues)

TABLE 1 (Continued)

Bacteria type	Pathogenic bacteria	Disease	Antimicrobial natural product name/ natural product source	Chemical structure	References
			Cerebroside *Axinella donnani* (sponge)		296
	A. salmonicida and *A. hydrophila*		Combination of secomanoalide, dehydromanoalide and cavernosine *Fasciospongia cavernosa* (sponge)	 Secomanoalide  4E,6E-dehydromanoalide  Cavernosine	296
	Edwardsiella tarda	Edwardsiellosis	Ergosta-4,6,8(14),22-tetraene-3-one *Aspergillus penicillioides SD-311* (fungus)		286
	Pseudomonas anguilliseptica	Pseudomonasis	Chamigrene-derived sesquiterpenes *Laurencia chondrioides* (seaweed)		298
	Tenacibaculum maritinum	Flavobacteriosis	(6E,8Z)-5-oxo-6,8-tetradecadienoic acid *Micrococcus* sp. C5–9 (actinobacteria)		301
			Bulbimidazoles A–C *Microbulbifer* sp. (bacteria)	 bulbimidazole A $R_1 = R_2 = Me$ (R:S = 9:91); bulbimidazole B $R_1 = Me, R_2 = H$; bulbimidazole C $R_1 = H, R_2 = Me$	302
	Chlamydia sp.	Infection with Intracellular Bacteria	Naphthacene glycoside SF2446A2 *Streptomyces* sp. strain RV15 (actinobacteria)		303

Abbreviation: NA, not available in the cited reference.
[a]Antibiofilm activity.

against *V. harveyi*.[290] Antibiofilm natural products hold great promise as effective agents to overcome bacterial resistance to antibiotics, which makes them suitable resources for future controlling agents of aquatic pathogens.[291,292] Psammaplin A, a natural product isolated from the marine sponges *Poecillastra* sp., *Jaspis* sp. and *Psammaplysilla* sp., exerted a strong inhibitory activity against *V. vulnificus*.[293] Moreover, sulphated polysaccharide, isolated from *Spirulina platensis*, exhibited potent antibacterial activity against *V. vulnificus*. In fact, *Spirulina* is one of the most commercialised microalgae, due to its bioactive properties and nutritional value.[294] Isatin is a biologically active secondary metabolite produced by *Alteromonas* sp., a synthetically modified isatin derivative was reported to have potent inhibitory activity against *A. salmonicida*, responsible foraeromoniasis and furunculosis disease.[295]

Several marine natural products have been isolated and identified against *A. sobria*, *A. hydrophila* and *A. salmonicida*. The most promising antimicrobial activity against *A. salmonicida* was exhibited by the metabolite cerebroside, produced by the sponge *Axinella donnani*. Additionally, when combined, three metabolites, secomanoalide, dehydromanoalide and cavernosine, isolated from the sponge *Fasciospongia cavernosa*, had a synergistic antimicrobial effect against *A. salmonicida* and *A. hydrophila*.[296] Furthermore, a novel natural protein, siganus oramin L-amino acid oxidase, isolated from the serum of the rabbitfish *Siganus oramin*, showed antibacterial activity against the fish pathogenic bacteria *A. sobria*. Although this protein was isolated from a marine organism, the protein was produced using the yeast eukaryotic expression system, by genetic engineering tools. The recombinant crude protein showed strong antimicrobial activity against *A. sobria*.[297]

The natural product ergosta-4,6,8(14),22-tetraene-3-one obtained from deep sea-derived fungi *Aspergillus penicillioides* showed strong inhibitory activity against the pathogenic bacteria *Edwardsiella tarda*.[286] The fungus *Penicillium canescens*, isolated from the marine sponge *Cacospongia* sp., collected from the Aegean Sea Coast of Turkey, revealed activity against *Yersinia ruckeri*, however, the bioactive compounds were not isolated nor identified.[69] Two chamigrene derived sesquiterpenoids isolated from the red seaweed *Laurencia chondrioides*, demonstrated antimicrobial bioactivity against *Pseudomonas anguilliseptica*.[298] Furthermore, studies described the antibacterial capacity of the crude extracts of two marine sponges, *Neopetrosia exigua* and *Iotrochota birotulata* against *P. fluorescens*.[299] Actinobacteria *Streptomyces* sp. (described as phylotype 44) associated with the bryozoan *Membranipora membranacea*, collected from the Baltic Sea, also revealed activity against *P. fluorescens*.[300]

Marine-derived actinobacteria from the genus *Micrococcus*, isolated from the stony coral *Cataphylia* sp., produced two new unsaturated keto fatty acids, (6E,8Z)-5-oxo-6,8-tetradecadienoic acid and (6E,8E)-5-oxo-6,8-tetradecadienoic acid (Table 1) that were effective in inhibiting the pathogenic bacteria *Tenacibaculum maritimum*.[301] In addition, three new alkanoyl imidazoles, bulbimidazoles A-C, isolated from the gammaproteobacterium *Microbulbifer* sp., demonstrated antimicrobial activity against *T. maritimum*. *Microbulbifer* sp. was also isolated from a stony coral belonging to *Tubastraea* genus.[302]

There are several reports of microorganisms capable of inhibiting *Piscirickettsia salmonis*. A live vaccine using the actinobacteria species *Arthrobacter davidanieli*, is used under field conditions in Chile. This live vaccine led to a significant reduction in the incidence of these pathogenic bacteria in coho salmon.[302] Moreover, the inhibitory activity of naphthacene glycoside SF2446A2 was reported against *Chlamydia* pathogenic bacteria (*C. trachomatis* considered a 'traditional' *Chlamydia* bacteria), a natural product isolated from *Streptomyces* sp. symbiont of the marine sponge *Dysidea tupha*, collected off Croatia.[303] All the above-mentioned antimicrobial compounds can be suggested as leads developing and producing of aquaculture drugs or for prebiotics and probiotics applications for disease control.

It needs to be stated that secondary metabolites produced by microorganisms are particularly promising, as their production can be scaled-up through optimisation of fermentation conditions and/or heterologous expression of the secondary metabolites producing genes by recombinant microbes.[275] Microorganisms are a sustainable and renewable resource that can be industrially cultured, rather than harvested from nature, facilitating future industrial compound scaling-up and circumventing raw material supply. Using microorganisms to improve aquaculture specie's health and wellbeing and in turn using aquaculture waste as carbon source for producing antimicrobial natural products or other biobased products for aquaculture purposes and needs are examples of circular bioeconomy approaches that can be developed.

6 | RISK ASSESSMENT OF THE USE OF POTENTIAL MARINE ORGANISMS FROM SEA-TO-AQUAFEED

Like all ingredients, any novel ingredients derived from marine origin also present the potential for introducing a range of risks. Managing these risks requires adopting a series of risk assessment strategies for which there are a systematic series of policies, procedures and practices can be applied.[9] Risk assessment on scientific-based processes is generally represented as four stages: (i) hazard identification, (ii) hazard characterisation, (iii) exposure assessment and finally (iv) risk characterisation. From this process, it can be noted that fundamental to the risk analysis process is the communication of the issues, and establishment of the risk context, followed by the identification, analysis, evaluation, treatment, monitoring and review of the identified risks (Figure 1). Based on this series of approaches, the risk can be more clearly considered and assumptions and uncertainties about those risks can be evaluated in Codex Alimentarius Commission (CAC, http://www.fao.org/fao-who-codexalimentarius/home/it/). For further details on each stage of this risk assessment process.[9]

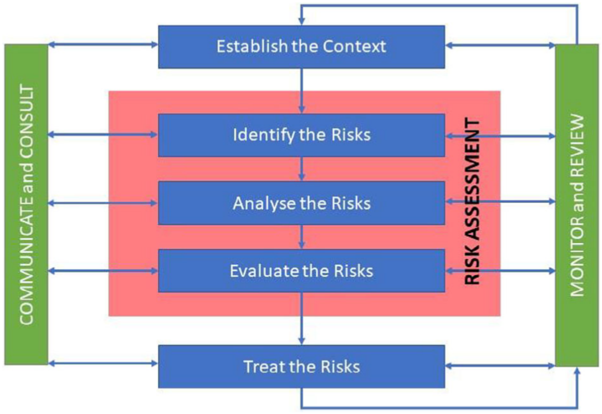


FIGURE 1 A standard risk analysis pathway map adapted from Colombo and Turchini[8]

6.1 | Logistical risks

Applying any ingredient to feed brings with it a suite of production, safety and logistical risks. In feed production, different elements are associated with those risks that need to be considered. Feed production is a manufacturing process, there are always risks associated with producing a product to the required specifications. The ability to formulate and produce feed based on data of any specific batch of ingredients and have the final composition of the combination of various ingredients meet the planned expectations have varying degrees of probability subject to the number of ingredients used, the confidence around safety and performance the parameters being assessed and the fidelity of any analytical method used. Additionally, in this process of combining raw materials, there is also potential for those raw materials to bring in contaminants and pathogens.

Other critical logistical risks include the supply and price of the ingredients being considered. It is important to note that most feed production facilities have limited capacity for the number of (bulk) ingredients they can use. Because of this, there is a preference to use ingredients that can be reliably obtained at large volumes and consistent supply. The ability to obtain ingredients on such a basis

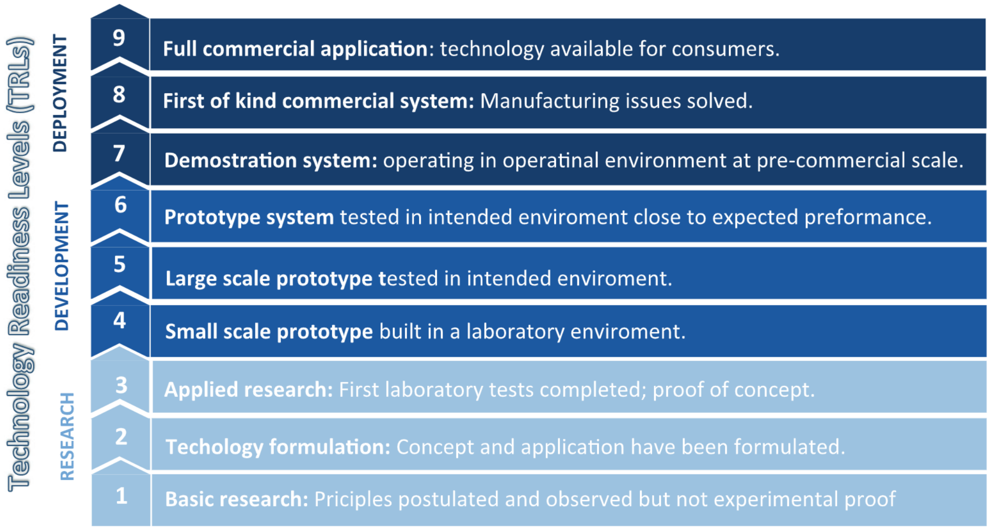


FIGURE 2 Standard technology readiness levels as defined by the European Commission.

significantly decreases the risk associated with the reliable production of feeds. However, this does not preclude the use of low volume and/or novel ingredients. Still, there is a critical need to scale through various technology readiness levels (TRLs in Figure 2) to meet this requirement and reduce logistical risk when introducing new ingredients. In addition, the logistical risks are accompanied by the price. Various economic factors influence the price of any ingredient and its utility in the feed sector. While it may be possible to produce an ingredient from arguably anything, this does not necessarily mean it can be done in the most cost-competitive manner. The cost efficiency includes a range of considerations: the cost of production, the qualities the ingredient contributes (e.g. compositional, sensory and structure) and the perceived value of the product by the buyer, the willingness to pay and the fact that the price will be consistently iterated to respond to market forces and competition. Therefore, the risk associated with cost viability may also change over time.

6.2 | Biological risks

Regarding biological risks, the primary ones likely to be encountered in the application of different marine ingredients include issues with the variability in nutrient supply, the potential for the presence of contaminants and the presence of anti-nutritional factors.[9] Several groups of ANF have a potentially harmful compound and it is thus important to have sufficient information about the presence of ANFs in new aquafeed sources. These ANFs should be reduced or removed using appropriate physical or chemical methods.[304–306] This way the biological risk to animal health, welfare, growth performance and safety of the final product is guaranteed.[307] The ability to ascribe values to various compositional parameters and the variability in their nutritional effects is critical to determine the nutritional value of any ingredient. As such this process must commence with a characterisation of the ingredient (e.g. what is it and what is its composition) followed by an assessment of its palatability and digestibility.[308,309] Once an ingredient has been characterised and its palatability and digestibility constraints defined, its appropriate application in a diet formulation can be considered in any subsequent growth study. When any of these foundational steps are omitted, there can be a critical feed failure due to poor intake and/or incorrect nutrient supply, both of which can be effectively managed if known prior. Problems with variability in nutrient supply can be managed through the processes of characterisation of the ingredient followed by both palatability and digestibility assessment.[308,309] However, in practice, the palatability and digestibility of each batch of ingredients are seldom appropriately assessed, although it is common practice in the feed industry to undertake the characterisation step of the ingredient for each batch based on an assessment of the composition, usually using modern near-infrared spectroscopy (NIR) techniques.[310] In contrast, it is more common to apply 'trade knowledge' to the palatability information requirement, and 'book values' or database values (e.g. https://www.iaffd.com/) to the digestibility information requirement. However, there is increasing capability being shown by the industry to adapt NIR to predict nutrient digestibility in both feeds and ingredients.[311,312]

Contaminants present a significant risk in using of marine ingredients as many persistent pollutants accumulate in marine ecosystems from terrestrial run-offs. Various contaminants are known to exist but usually, there are either certain heavy metals or persistent organic pollutants (POPs). For a comprehensive review of the various potential contaminants affecting aquafeeds see Glencross et al.[9] Notably, feed ingredients can also be contaminated during the production and processing stages. However, such contamination of an ingredient presents a significant risk to the animal to which it is being fed, and to the ultimate consumer of that animal that was fed. Most management of contaminant risk of feed ingredients is undertaken by maximum residue levels (MRLs) for each contaminant in the material of concern and monitoring materials considered risky. Globally, this is regulated by the United Nations (UN) through the World Health Organization

(WHO) and the Food and Agriculture Organisation (FAO) through the CAC. Additionally, most developed economies worldwide also have governmental authorities regulating this process (e.g. European Food Safety Authority).

7 | BOTTLENECKS AND OPPORTUNITIES OF SEA-TO-AQUAFEED

There is an increasing need to invest in research and development that will provide effective alternatives and new supply chains to replace FM and FO. However, before any successful and scalable market introduction of novel feed formulations, several challenges need to be addressed by the industry to achieve sustainable and responsible practices. Collaboration and investment: The blue growth initiative, proposed in 2013 by FAO, aims to build resilience of coastal communities, and restore the productive potential of the ocean by promoting the sustainable management of aquatic resources.[313] To improve and boost the development of a sustainable aquaculture, there is a need for international and transdisciplinary research and innovation collaborations. These collaborations are supported through investment by national and international funding agencies to transfer the developed technologies to the industry.[314,315] The European Union provides many strategies and funding mechanisms that can boost and stimulate innovations within marine biotechnology and improve the aquaculture sector. A detailed presentation of the EU's strategy and funding opportunities for marine biotechnology is presented in the review by Rotter et al.[119] To promote the development and commercialisation of novel aquafeeds, a cross-sectorial and transnational collaboration is needed to create more efficient and financially supported networks along the new value and supply chains of seafood and aquaculture sectors.[316,317] These involve research and develop experts to cover the lower TRLs and develop/test the efficiency of extraction/small scale production of novel aquafeeds, as well as representatives from the industry (e.g., commercial farms) for testing novel aquafeeds in an operational

	Potential organisms	Nutritional content †	Scientific Knowledge	Bio-circularity	Practical application	Feasibility /Cost
Micro-organisms	*Microalgae Resources*	+	+	+	+	−
Micro-organisms	*Fungi and Thraustochytrids*	+	+	+	−	−
Micro-organisms	*Marine bacteria*	+	+	+	−	−
Macro-organisms	*Macroalgae*	+	+	+	+	−
Macro-organisms	*Invertebrates*	+	+	+	−	−
Marine side streams		+	+	+	+	+

FIGURE 3 A qualitative assessment of potential organisms considered circular aquaculture along with nutritional content, scientific knowledge, practical application (large-scale production and commercially applicable in aquafeed) and feasibility/cost of production. Positive (+) represents an alternative protein source with high potential while negative (–) represents that has still need some development according to allocated criteria. †Nutritional content of the potential organisms was subjective and reported based on a comparison with FM in Figure S1.

environment. Importantly, as the prototyping of novel aquafeeds advances through the technology readiness, other expertise is necessary, such as legal, market research supply chain and potential customer feedback/market acceptance.

7.1 | Sustainability

Research on the sustainability of alternative feed production should be tackled on four levels: (i) supply sustainability, (ii) environmental sustainability, (iii) economic sustainability and (iv) social sustainability. Supply chains must be examined to determine the network of entities and activities from primary alternative feed providers to feed producers, suppliers, distributors and finally to final users—aquafeed marketers and fish farmers.[317,318] Strengths and weaknesses of each link have to be identified to propose management and mitigation strategies.[317] Environmental sustainability is essential as aquaculture is markedly impacted by climate change effects,[319] especially water shortage, and resource declines that impact the use of terrestrial feed ingredients.[320] Moreover, alternative feedstuffs are needed to counterbalance the unsustainable feed ingredients. Although some alternative feedstuffs hold a great promise to maintain the environmental sustainability of aquaculture, they still need to consider the release of waste by the fed organisms, the resultant nutrient loading in surrounding waters as a result of uneaten feed, bad feeding strategies or poor feed quality.[321] Economic sustainability is needed that links innovation, market trends, consumer demand and consumer acceptance balanced with cost calculations.[313]

Finally, social responsibility involves the responsibility from all stakeholders involved in the industry for application of good practices. These include the sharing of resources, knowledge, education, promoting the health and environmental benefits (especially as a result of a circular approach). It is important, however, to highlight the need of assessment of circularity through environmental, economic, social, legislative, technical and business criteria[28] and provide indicators to monitor the implementation and success of implemented novel aquafeeds as contributors to sustainable bioeconomy practices.[322] These can produce indicators and impacts that can be used by all stakeholders, including the policy makers and the final consumers, to make decisions on further supporting the development and implementation of these circular practices.

7.2 | Legal requirements

As one of the fastest growing industries within global food production sectors, an increasing attention to legal requirements especially in developing new technologies and applications has been placed on the aquaculture sector. In the early 1990s, the United Nations provided The Convention on Biological Diversity, which represented a framework for countries to structure regulations and legislation on the access, use, exchange and benefit of genetic resources. Access and benefit sharing (ABS) is a legal framework for regulating access and use of genetic resources that controlled by the provider, as well as sharing benefits resulting from research and commercial use of the provider.[323] Three other international agreements also frame national legislations on exchanging aquaculture genetic material: Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from Their Utilisation to the Convention on Biological Diversity, Agreement on trade-related aspects of intellectual property rights and, United Nations Convention on the Law of the Sea. A recent study demonstrated the low levels of awareness and application of some of these regulatory frameworks in the blue biotechnology sector and consequently, proposed a series of recommendations to close the breach at the European, national and organisational levels.[324] Recent reviews[323,325] also show that those international agreements are insufficient for sustainable aquaculture, where the aim is to provide nature conservation, food and health security. Finally, they have examined the ABS of aquaculture genetic resources, emphasising that most aquaculture products are provided by developing countries (mostly from Asia) that use over 580 species. It is suggested that international and national ABS legislations on aquaculture genetic resources should be restructured and tailor-made (species-specific, geographically specific) after an in-depth analysis of the global status of ABS within the aquaculture industry. In the European Union, the pursue to find novel feed ingredients to build new sustainable food systems and the creation of alternative sustainable businesses and jobs is strategically included in the guidelines to build a more sustainable and competitive aquaculture by the year 2030.[316] In the context of circular aquaculture, there is hence an increasing need to reinforce the dialogue between the policy makers and aquaculture specialists. This can, for example, incentivise a broader adoption of circular fish feed in countries that still do not legally authorise the adoption of alternative proteins for the aquaculture industry.[316]

8 | FINAL REMARKS AND FUTURE PERSPECTIVES

As in other industries, aquaculture is transitioning from linear to circular models, involving the valorisation of a wide range of resources from the marine environment. These biological resources can be used as whole (either as a live feed or their biomass) or through the valorisation of their bioactive compounds, including as effective alternative feedstuffs. However, more research is needed to understand the production of bioactive compounds in organisms and their impact on target aquaculture species. It is also important to bear in mind that the greatest challenges to alternative protein sources derived from the marine sources in aquafeed include varied protein content (Figure S1), scientific knowledge, practical application in the industry, feasibility along with the biocircularity of these resources (Figure 3). Given these challenges, like all alternative ingredients, some of these potential organisms have critical scalability and cost points at where they compete. Thus, more effort should be put into transitioning to innovative aquaculture approaches using the same producer organisms that can economically complement the traditional fish sources for FM and FO as a source of additional advantages. Putting further efforts into better understanding these micro and macro organisms, namely their contribution as value-added products and their capacity to improve animal performance, nutrient availability, food palatability and digestibility, could be part of the route to successfully integrating them as vital resources in aquaculture feeds. Broader systems and sustainability values of various resources should be investigated in addition to the nutritional benefits associated with the consumption of marine organisms. An example is provided by the use of macroalgae and bacteria that are also effective at treating wastewater generated by aquaculture production, hence providing a win–win service for the aquaculture industry. As many of these alternative feed resources are still under development but critically needed in the growing aquaculture sector, now is the right time for additional investment into collaborations that will drive the development of market-ready products with validated value to entire supply chains. In addition, close collaborations need to be maintained with the local, national and international legislation to design novel waste management strategies, invest in necessary infrastructures and raise awareness among the end users of products that have been developed respecting the circularity design principles.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest on this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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