REVIEW ARTICLE

Marine Bioactive Peptides in Supplements and Functional Foods – A Commercial Perspective

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Abstract: Many bioactive peptides have been described from marine sources and much marine biomass is still not explored or utilized in products. Marine peptides can be developed into a variety of products, and there is a significant interest in the use of bioactive peptides from marine sources for nutraceuticals or functional foods. We present here a mini-review collecting the knowledge about the value chain of bioactive peptides from marine sources used in nutraceuticals and functional foods. Many reports describe bioactive peptides from marine sources, but in order to make these available to the consumers in commercial products, it is important to connect the bioactivities associated with these peptides to commercial opportunities and possibilities. In this mini-review, we present challenges and opportunities for the commercial use of bioactive peptides in nutraceuticals and functional food products. We start the paper by introducing approaches for isolation and identification of bioactive peptides and candidates for functional foods. We further discuss market-driven innovation targeted to ensure that isolated peptides and suggested products are marketable and acceptable by targeted consumers. To increase the commercial potential and ensure the sustainability of the identified bioactive peptides and products, we discuss scalability, regulatory frameworks, production possibilities and the shift towards greener technologies. Finally, we discuss some commercial products from marine peptides within the functional food market. We discuss the placement of these products in the larger picture of the commercial sphere of functional food products from bioactive peptides.

1. INTRODUCTION

The marine space is known to be a potential source of new chemistry and bioactive components, and much of the marine space is currently unexplored. Many bioactive substances from marine sources are reported in the literature [1-19], and the compounds can be used in many different products, including food, feed, pharmaceuticals, cosmetics, agriculture and other applications. The value of the product and the degree of processing varies from very low to very high [5, 6, 14, 20-22] and this is connected to the resources needed in development, as well as the availability of the resources [20]. In general, there are two ways of utilizing identified active compounds. The compounds can either be used directly in the form they are in when isolated from a marine source, or they can be used as templates for further developments using synthetic methods to achieve more active compounds [5, 10, 12]. The first type of isolation is mostly used in food, feed, cosmetics or other applications [11-13, 20, 22]. The latter, where synthetic replication is involved, is more applicable to drug, medical devices, or in very high-end products [10, 11, 23]. The focus in this mini-review is placed on bioactive marine peptides that are used in functional foods or nutraceuticals, mainly derived from side streams from fisheries and aquaculture or from new and unusual biomasses. In functional foods, the peptides used are typically isolated from specific biomass and then formulated in a certain way to yield a functional food product. There are many types of products like meals, shakes, bars, powders and supplements within the functional food or nutraceutical category [3, 12-14]. Here, we want to look at the coupling between identified bioactivities, market possibilities and how the isolation of bioactive peptides can be achieved at the industrial scale. Moreover, how production can be made cost-competitive, and how to ensure that the products meet regulatory and safety requirements, are touched upon. The aim is to illustrate the use of bioactive marine peptides within a sustainable framework, commenting on the challenges and opportunities the bioactive compounds present.

2. BIOACTIVE PEPTIDES FROM MARINE SOURCES

2.1. Identification of Bioactive Candidate Compounds

Bioactive compounds in functional foods can have a variety of desired activities. The most common activities are anti-inflammatory, anti-hypertensive, anti-oxidant, anti-bacterial and anti-diabetic/-concerning metabolic syndrome [7, 13, 16, 17, 24]. Bioactive compounds have been identified in many different marine species, including plants [18, 25], marine bacteria and fungi [4, 9, 21], microalgae [13-15], shellfish [24], wild and farmed fish [1-3, 11, 20]. There is much interest in the use of side streams or left-over biomass from the marine industry and methods to transform these into more valuable products [16, 26, 27]. In addition, a number of new biomasses have been introduced to the market in later years, including micro and macroalgae, and lower trophic species like copepods and mesopelagic fish [8, 28, 29]. All of these biomasses are potential sources of bioactive peptides that can be suitable for use in nutraceuticals or functional food products. In order to determine whether biomass is a suitable source for bioactive peptides for this purpose, there are several aspects that need to be considered; these are described in more detail below. The biomass must meet the regulatory requirements such as being handled and approved for humans consumption [30] and in some cases, Novel Food approval is required [31]. The bioactive peptides are made into products that are intended for a specific identified market, and thus the biomass must be available in the right amount to meet those needs [3, 19]. Many bioactive compounds are demonstrated in a laboratory scale with good effect [7, 9, 13, 14, 17, 21, 32]; however, scale-up of many of the processes is not straight forward, and the infrastructure needed to demonstrate these processes in the industrial scale can be difficult to access [3, 33, 34]. While there has been much interest

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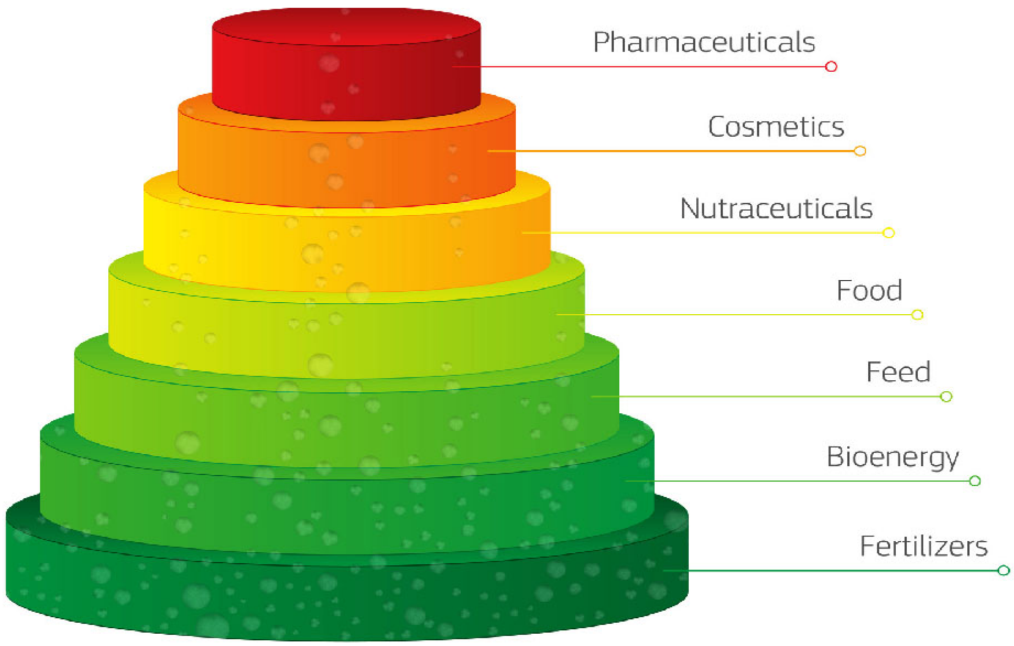

Products	Time to market (years)	Product development costs	Resource availability	Need for documentation	Potential market value	Skills and competencies
Pharmaceutical	10-15 +	Very high	Limited	Very high	Very high	Extensive medica and market
Cosmetic	3-5 +	Low to high	Fair	Medium	High	Toxicology and effects
Nutraceutical	3-5 +	Medium to high	Fair	Medium to high	High	Nutrition and medicine
Food	2-5 +	Low to medium	Good	Medium	Medium to high	Nutrition, food science
feed	2-5 +	Low to medium	Very good	Medium	Medium to high	Nutrition, animal science
Bioenergy	2-5 +	Low to medium	Very good	Low to medium	Moderate	Energy
Fertilizers	1-2	Low	Very good	Low to medium	Moderate	Agriculture, agronomy

Fig. (1). The traditional value pyramid for marine biomass demonstrates higher value from the products used towards nutraceutical and functional food markets, however, before venturing into the development of new products in these sections, it is important to understand the underlaying requirements for academic and industrial research and leadership. Some of these are discussed in this article. Figure from Roadmap for the Blue Bioeconomy by European Blue Bioeconomy Forum [20]. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

in the increased utilization of marine bioactive peptides, the market is still developing, therefore the strategies for production and market entry can be difficult to identify [22, 35-37]. Many marine compounds have undesirable or unusual organoleptic properties, and it can de difficult to know how to place a product in the market and how to fit in with existing products [22, 35, 36].

2.2. Identification of Marine Peptides for Functional Foods

As mentioned above, there are several ways of identifying active peptides from marine sources, and many have been reported and are well described in the literature. The process of bioactivity screening from the marine biomasses is also well documented [38, 39]. Bioactivity from marine sources can be applicable to many areas, such as agriculture, biofuel, feed, food, nutraceuticals, cosmeceuticals and pharmaceutical products [3, 5, 7, 17, 19, 20]. The amount of development and processing needed in order to reach the different markets is illustrated in Fig. (**1**). From the figure, it can be seen that the need for processing generally increases as the value of the product increases. This is often referred to as proceeding upwards in the value chain. When moving from one product to another, in addition to increased processing requirements, it is important to be aware of the additional need for increasing translational knowledge, regulatory documentation, logistics and time to market [20].

The two main methods of exploiting bioactive chemistry in marine biomasses are either bioprospecting and replication using synthetic methods, or direct use after extraction and isolation without further modifications. In the first instance, a marine organism is used as the basis for discovering new chemistry. The chemical structures are identified through further studies such as structure-activity relationship (SAR) studies, which are typically synthesized in some way for the market. In these cases, very little biomass is needed for the identification and initial testing of the compounds, however, the optimization and synthesis can be lengthy and therefore, such marine bioactives are more applicable for pharmaceutical or very high-end activities and products [5, 10, 40-42]. For functional foods, a different approach is usually taken, where biomass that is accessible in suitable amounts is used to isolate an identified active compound. Traditional bioactivity screening can often be costly and time-consuming. In traditional bioactivity screening, the knowledge about what type of bioactive effect is expected from the processed biomass can be limited, and one can therefore be searching for the desired bioactivity without knowing the likelihood (if any) that it will occur. As the focus on the identification of bioactive compounds has increased, several new methods have been used in order to increase the likelihood of identifying thedesired bioactivity. Methods like multivariate analysis and in-silico prediction are being used more extensively. Bioinformatics and in-silico analysis combine biological and chemical information with mathematics and statistics to predict functional or sensory attributes. For example, chemical fingerprinting of the biomass can be combined with predictive modelling in order to predict possible bioactivities. Fingerprinting has been performed using both Fourier Transform Infra-Red (FTIR) spectroscopy and mass spectrometry to predict bioactivity, functional properties and bitter taste [43, 44]. Another tool in the prediction of bioactivity is the use of accessible databases, which will likely be used increasingly in the future development of bioactive peptide products [45, 46]. A number of databases are available that describe bioactivity in various peptides, allowing for the prediction of bioactivity of newly isolated peptides. Bechaux *et al.* [46], discuss available databases and the use of these, and Table **1** points the several resources that are available. In--silico prediction can also be used to predict the formation of hydrolysates by using various enzymes, allergenicity and theoretical bioactive profiles [47-49]. Predicted activities still have to be confirmed, but employing more predictive methods in order to shorten the screening and identification time for new bioactive peptides in foods, is expected to be very beneficial for the functional food section. In principle, by having access to in-depth chemical characterization of bioactive peptides and mixtures of peptides, products exhibiting similar bioactivities as an already existing product can be developed from other marine sources if replacement of one's marine species in the product is desired. This can increase the use and allow for the utilization of a larger variety of marine sources. Marine peptides as candidates for functional food should demonstrate bioactivity in the form they are in when extracted and isolated from the biomass and not require significant (if any) chemical alterations. Bioactive peptides for functional foods are commonly short amino-acid sequences, with bioactivity and about 2 to 20 amino acids long [11] or longer at ingestion [22]. Longer peptides typically further digest in the body. For bioactive peptides, activity retention during digestion can be evaluated in-vitro [1] and, if needed, *in vivo* [12]. The most common bioactivities that are used in functional foods are anti-inflammatory, anti-hypertensive, anti-oxidant, anti-bacterial and anti-diabetic activities [7, 13, 16, 17, 24]; however a wide range of activities have been reported [10, 13, 14]. Upon identifying bioactivity, further choices towards commercialization include processing and production methods at scale for isolation of bioactive peptides and how to meet challenges in producing a product that is acceptable for the market and meet all regulatory requirements.

Table 1. Overview of databases that are available to perform *in silico* prediction of bioactivity of peptides. Adapted from Bechaux *et al.* [45].

Database	Description of Function of Database	Refs.
APD3	Antimicrobial peptide database	[93]
BioPep	Evaluate proteins as possible precursors for bioactive peptides	[94]
$CAMP_{R3}$	Anti-microbial peptides collection	[95]
PepBank	Peptide database for available sequences	[96]
Pep Fold	Predict peptide structures from amino acid sequences	[97]
Peptide cutter	Predicts protease cleavage sites, based on the protein sequence	[98]
Peptide locator	Identify bioactive peptides based on the protein sequence	[99]
Peptide ranker	Prediction of bioactive peptides with probability scoring	[100]
Peptigram	Visualization of peptides detected by MS/MS for rapid comparison of samples	[101]
ProtParam	Computation of a range of physical and chemical parameters from a given sequenced protein	[98]
ToxinPred	*In silico* method to predict and design toxic/non-toxic peptides	[102]
UniProtKB	UniProt is an open-access resource of functional parameters and protein sequence	[103]

2.3. Market-driven Innovation in Functional Food

There is an increased need for reduction in food waste and achieving total utilization of all biomasses, and for this purpose, new and more circular value chains will have to be created [50, 51]. In addition, an increasing focus on sustainability is observed in the society, in general [52]. The emphasis is shifting towards maximizing value creation in all parts of the food supply chain to ensure a sustainable and profitable industry, with a focus on keeping components at their highest value at all times, while reducing waste to a minimum [51]. The role of the oceans in the future is important, and many reports explicitly state that total utilization and increased valorization of marine resources are key strategies [13, 20, 53]. In communication with the marine industry, we see great interest in increasing the value of the side streams or "left-over" biomass from fish and shellfish. In addition, new marine biomasses are being introduced to the market, including mesopelagic fish, Calanus and algae. In addition, the accessibility of some biomasses changes due to climate changes [8]. Many of these marine sources can, as mentioned, be candidates for bioactive peptides, both for functional foods and towards improving health while reducing hunger; thus they can be exploited at a high value [51].

The functional food and nutraceutical market is growing. The Functional food market is expected to pass 92 billion dollars in 2021, while the dietary supplement market is expected to reach 87 billion dollars with an average CAGR for these to product groups at about 7%. In addition, the market for bioactive peptides is also expected to grow at a similar CAGR for the next 7 years [54, 55].

While these facts point towards great opportunities for marine peptides, it can be challenging to know where to place marine peptides in these new markets. In addition to the volume, regulatory and production challenges described below, a significant insight into consumer behavior and how the side streams and new biomasses are received in the different consumer groups is critical [6, 35]. There has been a clear trend of increased consumer awareness and reduction in consumer skepticism towards new foods, and there is a general expectation that producers have a focus on sustainability [56]. There might not be an established market or alternative product that producers can compare marine-based functional foods with. In developing new functional foods, it will be important to identify consumer attitudes and willingness to pay for new ingredients as well as assess how to describe the ingredients, *e.g.* as environmentally friendly/sustainable or as contributing to the reduction of food waste [35, 50]. Consumers often rely on trusted sources of information as well as ingredients, in order to evaluate and purchase new products, thus the reputation of the science, technology and the biomass being used is expected to affect decisions [3, 35]. Demographics has also proven to affect how nutritional labeling on products is used, and thus can also be utilized towards targeted consumer groups [57]. By combining this knowledge with the possible available volumes, regulatory production and manufactural possibilities, a better business plan for the product can be made [20, 22]. We do not know how the corona pandemic will change the market and consumer focus; therefore new products must be adaptable to these changes.

2.4. Biomass Suitability and Regulatory Approval

For biomass to be approved for human consumption, it must be handled as food at all times, following the same rules for food safety as conventional marine products [30]. This means that at the start of the development of a new product, the entire value chain must be considered in order to ensure that the product being made can be brought to market. Before the biomass is further developed into functional food, it must be demonstrated that it is suitable for human consumption, and further, when the peptide process is carried out, it must meet the requirements for approved product and marketing. In the case of side-streams from marine industries, the biomass is divided into either appropriate for human use, or as a by-product that is further divided into different classifications [30]. It is important to consider that if biomass is classified as a by-product under this regulation, it can not be processed back to being suitable for human consumption. In addition to this, local regulation regarding hygiene, cooling, microbial monitoring, toxin levels and safety must also be adhered to. In the EU, an application in the form of a dossier is provided to the commission, and the European Food Safety Authority (EFSA) is responsible for scientific risk assessment and provides a scientific evaluation of the application as described below. For products with international strategies, it is important to consider that different countries follow different processes. The process has been described by Chalamaia *et al.* [58], and is illustrated in Fig. (**2**).

Predictive microbiology modeling can be an effective way to assist in the early development and ensuring that new products can meet the regulatory framework. Predictive microbiology modelling, with applications in HACCP, risk assessment, and process/product design, allows anticipating the impact of technological and food intrinsic/extrinsic factors on product safety and spoilage. Predictive modelling can pave the way for user-friendly decision-support interfaces in relation to microbial risk management by food business operators (EFSA BIOHAZ Panel, 2017).

A major bottleneck for high-value applications of marine peptides in functional foods on human nutrition markets is the new Novel Food Regulation (EU) 2015/2283 (as of 1st January 2018), which extends to any food product not subject to significant human consumption in the EU before 1997. If the eligible product does not fall within the Union list of authorized novel foods, food business operators must submit an application for authorization to the EC, in compliance with the EC implementing rules and the EFSA guidance on safety assessment, before placing the novel food on the market. Likewise, application dossiers for pre-market approval of feed additives are enforced by the Regulation (EC) 429/2008. On the other hand, the eligibility of specific products under the novel food regulation raises significant uncertainty among food business operators. For instance, the application of enzymatic hydrolysis does not require novel food authorization, however, hydrolyzed products still could fall under the novel food definition, *e.g.* foods without a conventional counterpart, and thus require pre-market approval. Such a regulatory framework may drastically impact the time-to-market [18 months for approval] and return on investment [≈ 30%, 4 M€/product] for those applications subject to novel food evidence, whereas the applicant-specific (5-year) data protection may eventually hinder open innovation [59, 60]

Upon meeting regulatory requirements for production and marketing of a new product, a producer must also adhere to rules regarding labelling, presentation and advertising food Regulation (EC) N 1924/2006, and for functional foods claiming any health claims, these must be approved by a scientific evaluation conducted by the EFSA [61].

3.. DEVELOPMENT OF PROCESSES

3.1. Isolation of Bioactive Peptides

Isolation of bioactive peptides from marine biomasses is realized and tested in the laboratory scale and significant efforts are made into identifying and concentrating the active fractions from the marine biomass [4, 10, 12-14]. For functional food, the bioactive active fraction must be available for isolation from the biomass using a sustainable and scalable process. At the same time, the characteristics of the ingredients in terms of organoleptic properties, safety, allergenicity, color, solubility and functional properties like foaming and emulsification must be considered, as well as the reproducibility of the processes [3, 14, 22].

Many processes to isolate bioactive peptides from the biomass are reported in the literature [3, 14, 22]. Protein hydrolysis is a very common process used to liberate peptides from the remaining biomass. The proteins can be hydrolyzed using both acids, bases, endogenous and exogenous enzymes [3, 19, 22]. For functional foods, in order to ensure the reproducibility of the ingredient produced, exogenous enzymes are commonly employed. These are commercially available enzymes approved for food production. Different enzymes cleave proteins at specific amino acid sites. This cleavage will expose specific amino acids, and these amino acids dictate the type of functionality or bioactivity that the peptides initiate [2, 3, 62]. In addition to employing specific enzymes enhancing the desired bioactivity, conditions during hydrolysis such as pH, temperature and time are vital for control over the process. Specific enzymes will, in addition to enhancing bioactivity, also affect sensory properties, for example, taste, where exposure of hydrophobic peptides is known to increase the bitter taste [62, 63], and exposure of charged or ionizable groups will affect the water solubility, foaming and emulsifying properties of the peptides. All these factors influence the type of possible products that can be produced [62, 64].

Hydrolysis can be performed both in batch and continuous fashion. The first type is performed in large reactors, while the second is performed in tubular modules based on heat exchanger designs [65, 66]. The progress of break down in the biomass can be monitored by changes in viscosity, while the process of hydrolysis is monitored by measuring the degree of hydrolysis (% DH) [3, 19, 62, 64, 66]. %DH describes the percentage of peptide bonds that have been broken. Conventional methods to determine %DH are optical methods, including TNBS and OPA and a titration method called pH-stat measuring the release of protons. A drawback of these methods is that they are time-consuming and not amenable to real-time monitoring [67, 68]. Real-time spectroscopic methods are described in the literature for better process monitoring, scaling and steering, and these methods are addressed in chapter 4.1 [2, 69].

Upon hydrolysis, post-processing commonly includes separation of the water-soluble active peptides from other phases in the

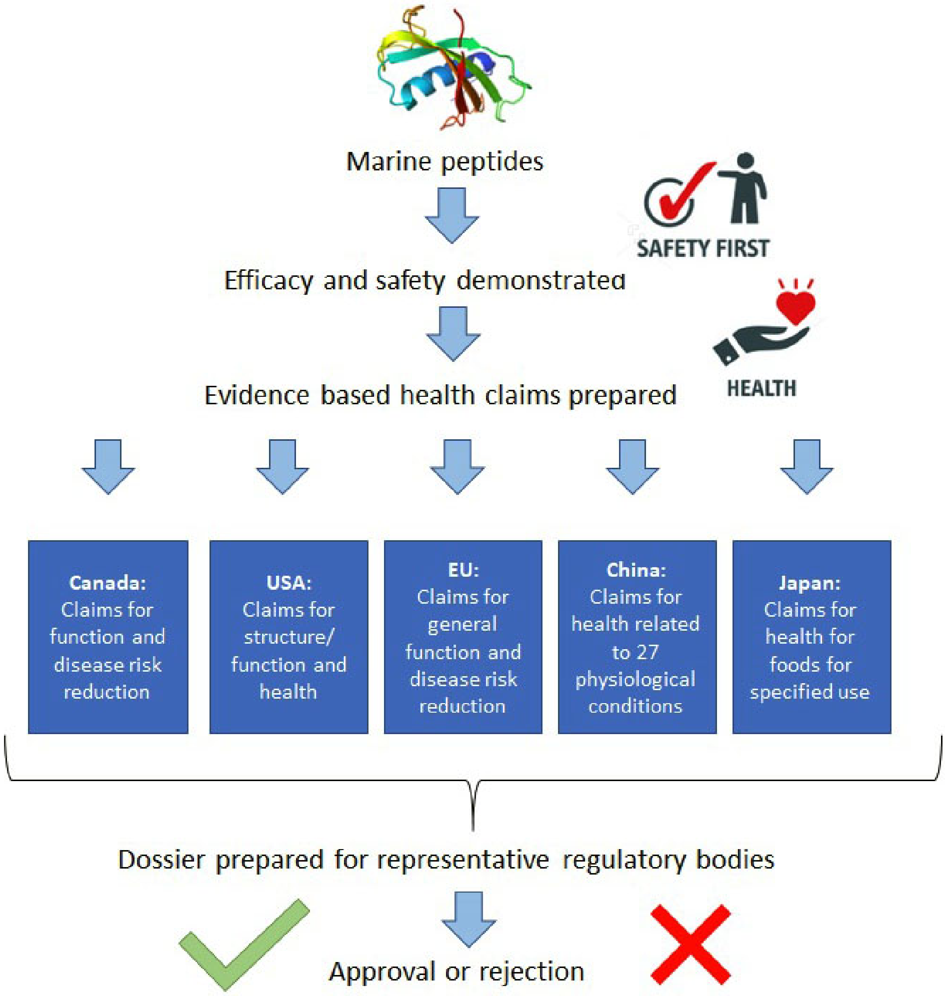

Fig. (2). Regulatory processes for approval of products for both nutraceutical and functional food markets vary between countries and regions, and this can be a challenge in both getting on the market as well as expending internationally. Adapted from [53]. (*A higher resolution/-colour version of this figure is available in the electronic copy of the article*).

biomass, *e.g*. lipids and solids, in a centrifuge or de-/tri-canter. After separation, the hydrolysates are commonly filtered to remove unwanted fractions. The choice of filtration methods and types of filters significantly affect the product, and the process and scalability must always be considered in the development [3, 19, 34]. The bioactive peptide is further concentrated in an evaporation step, and the ingredient is then used in a concentrated or dried form. The drying process is often energy and time consuming and can be costly. Furthermore, the transportation of dried versus concentrated matter can impact the cost of production as the dried product exhibits lower weight and volume. Thus all aspects of water removal must be evaluated at an early stage of process development and in connection with new technologies as described below [3, 34].

3.2. Shifting Towards Greener Technologies and Solutions

While hydrolysis has often been described as the main method for isolating bioactive compounds, an increased focus is placed on developing new technologies for pre-and post-processing in connection with hydrolysis and isolation of bioactive compounds. These alternative techniques can be used in order to enhance mass transfer, yield and reduce energy costs. An alternative to thermal treatment can be a desirable approach. Thermal treatment is extensively used in stabilization/processing of marine side streams, including bioactive peptides, despite its environmental footprint and the fact that the treatment can result in undesirable effects on food nutritional and sensory attributes, including taste, smell and color. Alternatively, non-thermal processing and advanced volumetric heating (*e.g*. high pressure, ultrasound, plasma, microwave, electric pulse field) have gained significant attention in the last decade due to enhanced product safety and quality, production efficiency and green shift [36, 70, 71].

Furthermore, the promising potential of such emerging strategies towards the extraction of bioactive peptides has recently been demonstrated with regard to increased recovery yield and enhanced techno-functionality and bioactivity of end products, and thus high market value [72]. Such forefront technologies can contribute to enhanced stability of food residuals with regard to microbial and enzymatic degradation (*e.g*. formation of biogenic amines), and process cost-efficiency (*e.g*. recovery yield, hydrolysis time, enzyme/substrate ratio), by facilitating the access to cleavage sites through biomatrix/protein restructuration [73]. Moreover, replacement of post-hydrolysis thermal enzyme inactivation (95℃ for 10-15 min) with innovative processing would lead to game-changing energy savings and have a minimum impact on nutritional and functional properties [74-76].

Upon food processing, protein conformational changes could affect linear and conformational epitopes (protein sites eliciting immune responses) and antibody biding ability and thus, mitigating protein allergenicity. Besides well-established industrial strategies (*e.g.* enzymatic hydrolysis, heating, fermentation) towards hypoallergenic foods, emerging technologies (*e.g.* high pressure, ultrasound, plasma, pulsed electric field) have gained increasing attention in recent years [77, 78].

Another important factor to consider when developing functional food products from marine biomass, is the site of generation and volumes that are generated at the same site. This will be an important factor in developing products for the right market, as well as in designing sustainable value chains that are adjusted to volume and location [79]. This means that if the volumes are small and very spread out, their collection is to be given due importance, and it should be analysed if some sort of water removal or stabilization step should be performed locally to reduce the amount of water that is transported to ensure stability of the active fraction. Another consideration to be made is whether processing should be done locally or semi-locally at smaller facilities or collection is to be carried out in one large facility.

Techno-economic and environmental sustainability of bioactive peptide extraction from marine biomass, typically targeting specific individual components, still remains a challenge. Thus, zero-waste cascading biorefinery concepts have emerged as a cost-effective niche and opportunity of full biomass valorisation into multiple added-value streams with a combination of commercially sound applications. Macroalgal biomass is of particular interest in this context due to its high market value constituents (*e.g.* proteins, bioactive peptides, pigments) and suitability for microbial/enzymatic bioconversion into platform chemicals, energy and feed [28]

4. SCALE-UP OF PROCESSES AND COMMERCIALIZATION

4.1. Process Scale-Up

In the scaling-up of processes for isolation of bioactive peptides, processes can proceed very differently at small-scale and large-scale. Therefore, the processes should be scaled up step-wise in order to ensure that the desired outcome is the same as observed in the laboratory scale. As mentioned above, enzymatic hydrolysis is often used in order to break down proteinaceous structures in the biomass and further create and isolate bioactive peptides. These processes are controlled through the use of specific enzymes, as well as controlled temperature, pH and time. It is known that heat transfer and mixing at laboratory scale will be different from large scale reactors [62, 80, 81], thus, the temperature and enzyme accessibility in the biomass will not be different. This will cause changes in enzyme activity and protein accessibility, which will affect the formation of the bioactive peptides. Different enzymes exhibit different activities over a range of pH, and while pH adjustments can be performed with relative ease in the laboratory scale, these can be very challenging at large-scale due to changes in mass transfer and buffering capacity of marine biomasses [82, 83]. Another challenge that has been seen in large-scale hydrolysis for marine biomasses is sequential hydrolysis. In these processes, enzymes are utilized sequentially in the biomasses in order to target production of specific bioactive peptides. In traditional batch hydrolysis, enzymes are inactivated before the addition of a second enzyme. In the large scale, this will require the heating of a large volume of biomass to a temperature of about 95 degrees Celsius before the biomass is cooled down to an appropriate temperature, which will be time and energy consuming. As described above, new technologies are being employed for developments in order to implement other techniques to replace thermal treatments, and these are candidates for future production of marine bioactive peptides [36, 70]. In addition, it has been observed that the coupling of the processes is very different in small and large-scale for marine biomass processing, and that in shifting a process from laboratory to industrial scale, biomass losses and changes can occur between infrastructures.

Biomasses from sources like fisheries side streams are commonly complex and can vary between batches and seasons. It is, therefore important to be able to predict changes to the process as well as adjust the process between batch to batch such that the result is the same for each process. Progress monitoring has been done using %DH; however, as mentioned, marine side streams can be heterogeneous and vary from batch to batch. Therefore there is a need for continuous process monitoring in order to ensure reproducibility.

Recent publications described average molecular weight (AMW) where the average size combination in the processed biomass is used to characterize the progress of the process [2, 69]. This is performed using rapid and non-invasive FTIR spectroscopy, a technique that can also be used as an on-line or near real--time technique. This AMW monitoring presents that possibility to adapt the process rapidly in scale-up processes, thus significantly improving the end result [2, 69, 84]. With biomass variation between batches or over time, the hydrolysis process can be stopped at the desired molecular weight, which might not be at the same time for each batch.

Removing water from the biomass is an energy-demanding process, and it is common in large scale that water removal is performed in several steps by filtration, followed by evaporation up to about 50% dryness and then further dried to dryness. The filtration is combined with the removal of unwanted particles that are selected in a certain size fraction of the peptides, thus concentrating the active ingredient. Evaporation can be performed using various different evaporator systems, including evaporators like falling film, rising film, and plate evaporators, where the liquid is passed over a hot surface and water is evaporated at reduced pressure [34, 85, 86]. It has been observed that some peptides can be sensitive to the commonly used evaporators, including darkening of the color, foaming and loss of activity. Less harsh drying techniques including vacuum flash drying, infrared thermal drying and low-temperature refractive index drying have been described in the literature [85-87]. Upon evaporation, the biomass can be further dried, and in large scale, spray drying and drum or mill drying are the most common ones [34]. For peptides, spray drying is an applicable technique due to small components. Freeze drying is a very common laboratory drying technique, however, freeze-drying in large scale is considered more difficult and is costly, time, and energy demanding [88]. Therefore, it is less common and rarely cost-competitive to freeze dry products at a large scale. In developing processes, it is important to understand the differences found between marine peptides when they are freeze-dried and spray-dried. These differences include solubility, sensory properties and bio-activity; thus this needs to be taken into account if freeze-drying is used on a laboratory scale.

4.2. Demonstration Plants in the Commercialization of Research

The differences between laboratory and large-scale processes of isolation of marine bioactive peptides can be difficult to predict,

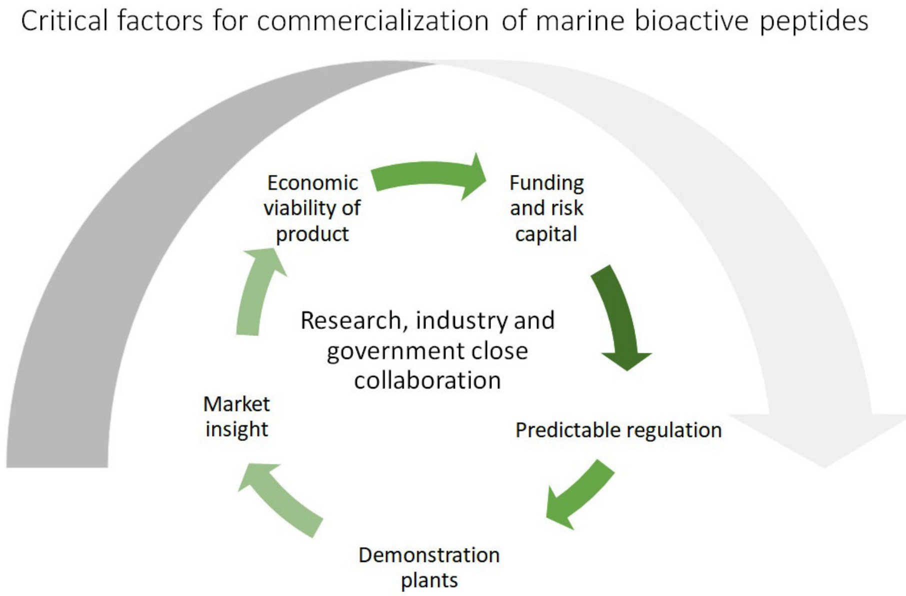

Fig. (3). The figure illustrates stakeholders and challenges and the need for interplay between stakeholders when developing commercial products from marine resources, also bioactive peptides. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

thus process scaling and demonstration of large scale benefits obtained greatly from testing on demonstration plants before investments in a scaled infrastructure are carried out [3, 33]. Demonstration plants are, in many cases, publicly financed and usually designed to bridge the gap between generating basic and technological knowledge with market innovation and commercialization. The access to risk capital in demonstrating and market testing a new ingredient or product is also difficult to attain; thus the demonstration plants can play a role in reducing the risk when new developments are translated from the laboratory to commercialization. The use of demonstration plants allows for testing the scaling of the developed process and ensuring that the desirable peptides that are isolated from the marine biomass have the same properties as the one identified in the laboratory scale. These properties include the identified bioactivity, in addition to the observed sensory and physiochemical properties. This is important to demonstrate that the peptides produced at scale can still be incorporated in the same products as those identified in the early screening phase and market studies. Demonstration plants can, in a commercialization phase, provide a product prototype that can be tested in the market or potential specific customers. Market feedback can then be taken into account and adjustments can be made according to the feedback [3, 33, 89]. Demonstration plants will thus allow for a new product to be tested in the market before infrastructure investments are made, significantly reducing the risk for a new producer. In addition, information on what is the best infrastructure, as well as a tested scaled process can be the result of testing in a demonstration plant. By knowing the infrastructure needs, the necessary investments for production, CAPEX, can be estimated, and based in time and consumption in chemicals and energy, operational costs, OPEX can be estimated. With a per unit cost estimate, a market evaluation, the risk of market entry is lowered [3, 33, 89].

Several demonstration plats are available for use in Europe; for example, Pilots4U [90] provides a database for available demonstration plants in Europe. Both public and private plants are listed here; it can be a helpful tool in a commercialization phase for new producers. In addition to reducing the risk of commercialization, demonstration plants also play the role of creating a collaborative space and connections within academia and industry as well as having the possibility to deliver information that can be used in policy-making and funding schemes [2, 3, 19, 22, 33].

The possibilities to demonstrate a process as well as to test a product in the market is in our experience vital in order to commercialize marine products, at the same time, knowing how the consumer will respond to new products and how to place a product in the market will improve the chances to receive higher prices and market share [20, 51]. In our experience, the close collaboration between all stakeholders is vital. Lack of access to infrastructure, cost of development and lack of investments, lack of access to trained personnel can be hurdles in commercialization. Fig. (**3**) illustrates the important stakeholders in the commercialization of marine products, including marine peptides, and illustrates the importance of collaboration between stakeholders.

4.3. Commercial Examples for Functional Foods with Bioactive Marine Peptides

Marine peptides are sold in many different products as health-promoting, stating a variety of benefits and health-promoting effects. These effects include improved skin and joint health, improved digestibility, improvement of metabolic syndrome and glucose metabolism, and immune-modulatory to mention a few [91]. One group of marine peptide products that have gained a lot of commercial interest in later years is marine collagen peptides. Collagen peptides from marine sources are available as powders, tablets, capsules bars, shakes and other supplements and are well established in the market. Collagen and collagen peptides from marine sources have been made commercially available in later years, but traditionally collagen has been derived from terrestrial sources. The marine collagen market is expected to grow significantly in the next years [54]. Other marine peptides are also present on the market as commercial products; these include hydrolyzed

Table 2. Overview of commercial marine peptides with functional claims. Adapted from Hayes *et al.* [29], and added from [86].

Product Name	Claim	Producer	Product Type	Source	Refs.
PeptACE™	Antihypertensive	Natural Factors Nutritional Products Ltd., Canada	Capsules	Bonito	[104]
Vasotensin®	Antihypertensive	Metagenics, USA	Tablet	Bonito	[104]
Levenorm®	Antihypertensive	Ocean Nutrition Canada Ltd., Canada	Tablet	Bonito	[104]
Peptide ACE 3000	Antihypertensive	Nippon Supplement Inc., Japan	Capsules	Bonito	[104]
Peptide Tea	Antihypertensive	Nippon Supplement Inc., Japan	Powder	Bonito	[105]
Lapis Support	Antihypertensive	Tokiwa Yakuhin Co., Ltd., Japan	Beverage	Sardine	[105]
Valtyron®	Antihypertensive	Senmi Ekisu Co., Ltd., Japan	Ingredient	Sardine	[105]
Precardix®	Antihypertensive	Marealis Health Inc., Norway	Capsules	Shrimp peel	[92, 106]
Wakame Jelly	Antihypertensive	Riken Vitamin, Japan	Jelly	Seaweed	[107]
Peptide Nori S	Antihypertensive	Riken Vitamin, Japan	Beverage	Seaweed	[29]
Mainichi Kaisai Nori	Antihypertensive	Shirako Co., Ltd., Japan	Powder	Seaweed	[29]
Stabilium® 200	Stress relief	Yalacta, France	Capsules	Mixed fish	[108]
AntiStress 24	Stress relief	Forte Pharma Laboratories, France	Capsules	Fish	[108]
Protizzen®	Stress relief	Copalis Sea Solutions, France	Powder	Fish	[108]
Collagen HM	Joint health	Copalis Sea Solutions, France	Powder	Fish Collagen	[109]
Glycollagen®	Joint health	Copalis Sea Solutions, France	Powder	Skate Collagen	[109]
PeptiBal™	Immune modulatory	InnoVactiv Inc., Canada	Capsules	Shark	[110]
Seacure®	Gastrointestinal health	Proper Nutrition, USA	Capsules	Fish	[110]
Marine Collagen	Joint and skin health	Seagarden Norway	Powder	Various wild-caught fish	[111]
ProGo®	Weight management, anti-inflammatory	Hofseth Biocare Norway	Tablet	salmon	[112]
CollaGo®	Joint and skin health Anti-inflammatory	Hofseth Biocare Norway	Powder	salmon	[113]
CalGo®	Bone health	Hofseth Biocare Norway	Powder	salmon	[114]

proteins from wild and farmed fish as well as from shellfish. Some marine peptides are marketed with claims, and as mentioned above, these claims must be approved by the respective regulatory bodies where the product is sold. According to the regulations, a functional food must demonstrate both safety as well as efficacy and effects beyond conventional nutrition. Table **2** provides an overview of commercial marine peptide-based functional foods and products [29, 92]. From the table, it can be seen that many of the products are anti-hypertensive or anti-stress. In addition, the products claim to improve bone, skin and joint health. Other products claim anti-inflammatory and anti-obesity effects when ingested. Some products are promoted as providing a combination of bioactivities. The market entry of these products can be seen as a successful commercial venture of these products. In section 2.3, we discuss that the commercialization of marine peptides is a fairly new market that is still being developed. Bioactive peptides have been available as commercial products for a long time from plant and meat-based sources and in later years, both marine sources and other new sources from plants and animals have been introduced to the market. The market for bioactive peptides from all the mentioned sources is predicted to keep increasing in the coming years [55] and the sports and the elderly market is predicted to take a large share of this growth [55]. Compared to bioactive peptides from plants and meat, the relative share of marine bioactive peptides is less than 5% [55], thus a relatively small part of the global bioactive peptide products. While the market for bioactive peptides in itself is predicted to grow for the next years [55], the product communication around marine-based products is more uncertain [35]. In addition, it is not certain whether the marine products should be marketed as an alternative to the already established bioactive peptide products on the market, for example, whey or casein products, or if the products should be communicated to a different or a new consumer group. The choice of products where the bioactive peptides are included, will also depend on how the consumers evaluate the use of marine sources of bioactive peptides. Consumers' attitudes to marine-derived sources can be both positive and negative in comparison to traditional products with terrestrial sources of bioactive peptides [35].

5. CONCLUSION

There are many possibilities for commercial innovation towards the use of marine bioactive peptides in products intended for human consumption and improved health. Some of the opportunities and challenges have been discussed here. The gap from the scientific demonstration of bioactivity in marine biomasses to the commercial product can be large, therefore the coupling between academic research and commercial production is important and we have investigated this coupling here. While the bioactivity demonstration, safety and efficacy demonstrations are vital in order to get to the market, we have also discussed the need for market-based innovation with consumers' involvement in order to create products that can be both attractive and competitive. In addition, we have described practical challenges with respect to the scaling of processes, both with regard to process and investments. Development of new and greener technologies processes and analyses that can aid in the development and commercial production of new ingredients and products are of increasing interest and new methods are being frequently documented. Green and sustainable methods will be vital in the future, both in a sustainability framework and in a market pull. As many new and emerging technologies are being developed, these technologies need to be implemented in commercial production. The use of accessible demonstration plants can be a valuable opportunity and a key player in the testing and implementation of new technologies. In conclusion, the use of marine peptides will be part of future nutrition, both as conventional healthy food and as a functional food, and there is a need for close collaboration between academia, industry, regulatory, funding bodies and investments, as well as an in-depth understanding of the consumer expectations and desires in order to fully realize the potential of marine bioactive peptides.

LIST OF ABBREVIATIONS

CAGR	=	Compound Annual Growth Rate
CAPEX	=	Capital Expenditure
OPA	=	o-Phthaldialdehyde
OPEX	=	Operating Expense
TNBS	=	Trinitrobenzene Sulfonic Acid

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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