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Protein hydrolysates from animal processing by-products as a source of bioactive molecules with interest in animal feeding: A review☆

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ABSTRACT

Industrial processing of livestock, poultry and fish produces a large amount of waste in a solid or liquid form that can either be destroyed or be used to make compost, biogas or other low-added value products. However, the by-products from animal processing industries have a potential for conversion into useful products of higher value, such as protein hydrolysates, with interesting applications in animal feed. Low amounts of animal protein hydrolysates included in aqua-feeds may enhance growth rate and feed conversion of farmed fish and crustacean. Animal protein hydrolysates may also be incorporated in diets to enhance the nonspecific immunity of fish. As well, these hydrolysates can be used as a good source of amino acids for newly weaned animals. Protein hydrolysates from animal by-products including antimicrobials, antioxidants, opioid-like and/or other interesting bioactive molecules have promising and interesting applications on companion and production animals. By-products from animal processing industries are therefore a promising source of bioactive peptides of considerable interest for animal care, always within the framework of the existing legislation. Possible drawbacks and future trends of the use of animal by-products and/or production of protein hydrolysates from those materials are also discussed.

1. Introduction

Industrial processing of livestock and poultry generates significant amounts of waste including viscera, meat, fat or lard, skin, feet, abdominal and intestinal contents, bone, feather and blood. Data on the amount of waste are relatively sparse and vary from around 33% to around 43% (w/w) of the live weight (Hamilton, 2004). The by-products derived from slaughter and processing of cattle, pigs and broilers may represent about 49, 44 and 37% of the total live weight, respectively (Meeker, 2009). In the specific case of chickens, blood represents about 2–6% of the total bird weight, and feathers could be up to 10% (Jamdar & Harikumar, 2005; Lasekan, Abu Bakar, & Hashim, 2013).

Fish processing industries also generate large amounts of waste that can represent as much as 57% (w/w) of the weight of the total catch after filleting (Meeker, 2009). This waste is mainly composed of muscle-trimmings (15–20%), skin and fins (1–3%), bones (9–15%), heads (9–12%), viscera (12–18%) and scales (5%) (Rustad, Storrø, & Slizyte, 2011; Torres, Chen, Rodrigo-García, & Jaczynski, 2007). In the particular case of cephalopods, waste resulting from processing may amount to as much as 60% of the total live weight of the animal.

In general terms, the current volume of animal by-products generated from the industry is nearly 54 billion pounds annually (Meeker, 2009). Non-utilization or underutilization of animal by-products not only leads to loss of potential revenues but also leads to increasing cost of disposal of these products. For that reason, industry has begun to develop various technologies to make use of this waste, mainly in the form of low value-added products, at the same time reducing the costs derived from its disposal. In global terms, the rendering industry processes approximately 60 million tonnes per year of animal by-products (Hamilton, 2004), from which 25 million tonnes are processed in North America and 15 million tonnes in European Union. Argentina, Australia, Brazil and New Zealand collectively process another 10 million tonnes of animal by-products per year. However, the reality is that considerable amounts of animal by-products are hardly recovered in most of countries, and in many cases it comes up against limitations imposed by existing legislation. In this regard, the outbreak of Bovine Spongiform Encephalopathy (BSE) in Europe during the 1990s led to ban the use of slaughterhouse waste material as a fodder ingredient as being a probable transmission pathway. Although BSE has been almost eradicated worldwide, the reality is that the use of animal by-products is nowadays restricted and they are mainly used as either animal feed ingredients or fertilizers, or mostly disposed of. In Europe, only those by-products belonging to the third category (EC Regulation No. 1069/2009) can be

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used, after technological processing, for the production of low value-added products (animal feeds, silages, fertilizers, etc.), or derived products of greater added value (cosmetic, sanitary or veterinary medicinal products), as expressed in the Article 33. Legislation in the United States is also restrictive regarding the use of animal by-products for various purposes (Liu, 2002).

The animal by-products are mostly rich in high-quality protein than can be hydrolysed by proteases to obtain bioactive peptides with promising therapeutic, functional and/or nutritional applications, as has been mainly reported in dairy hydrolysates (Choi, Sabikhi, Hassan, & Anand, 2012). Protein from feathers, bristles, horns, beaks or wool can be only enzymatically hydrolysed after destruction of the keratin structure, either by acid or base treatment, by the use of specific microorganisms or enzymes, by thermochemical pre-treatment, or else by steam flash explosion (Eslahi, Dadashian, & Nejad, 2013; Lasekan et al., 2013; Mokrejs, Svoboda, Hrncirik, Janacova, & Vasek, 2011; Zhang, Yang, & Zhao, 2014).

The protein hydrolysates derived from animal by-products have potential applications in food technology as flavourings, functional ingredients, or else as a good source of amino acids (Cho, Baik, Choi, Hahm, & Kim, 2010; Guérard et al., 2010; Kumar, Nazeer, & Ganesh, 2012; Qiao, Tong, Zhou, & Zhu, 2011; Zhang et al., 2013). In addition, animal by-products hydrolysates include peptides that are claimed to be potential health enhancing nutraceuticals for food and pharmaceutical preparations (Khan et al., 2011; Lasekan et al., 2013; Rustad et al., 2011; Senevirathne & Kim, 2012; Toldrá, Aristoy, Mora, & Reig, 2012). All these properties make animal protein hydrolysates of interest for manufacture of products for human or animal feed. In the specific case of pets and production animals, the objectives of the use of animal by-products hydrolysates should be focused on strategies to optimize animal welfare and/or food production (e.g. increasing milk production in dairy cows, increasing survival rates in aquaculture species, or increasing weight gain in post weaning pigs). However, the functional and/or nutritional applications of those hydrolysates for pets or production animals have not been widely studied.

The present review focuses on the current and potential applications of bioactive protein hydrolysates from animal processing by-products for aquaculture species, farm animals and pets. Furthermore, possible drawbacks and future perspectives of the use of these hydrolysates in animal feeding will be discussed.

2. Application of animal protein hydrolysates in aquaculture

2.1. Application of seafood protein hydrolysates in aquaculture

The worlds' harvest of seafood has increased considerably in recent years, reaching about 158 million tonnes in 2012, of which 66.6 million (42.1% of the total) came from aquaculture (FAO, 2014). This increase is mainly due to a gradual increment in aquaculture output and for the coming decades it is expected that this production will be decisive to compensate for the stagnation of fishing catches and to satisfy the growing demand for seafood and fresh-water fish. The satisfaction of future demand for fish farming will largely depend on the availability of cheap and good quality feed in the sufficient quantities. Soybean meal is currently used as a protein source in aqua-feeds to reduce costs (Uran et al., 2009), although it contains antinutritional substances as phytic acid or lectins that affect growth and feed efficiency. In contrast, fishmeal does not contain antinutritional factors and is a much more appropriate protein source than soybean meal in aqua-feeds. In fact, aqua-feeds use to contain a minimum level of fishmeal in order to ensure an optimal content of amino acids and other nutrients needed for fish growth and flesh quality. However, the variations in the catches of wild pelagic fish (mainly anchovy) and the growing demand for fishmeal has pushed prices up during the last years (FAO, 2014; Tacon, Hasan, & Metian, 2011). This fact, and also the running costs and the thermal damage induced by the drying process on protein quality and overall protein digestibility, have increased the interest in fish silage, protein hydrolysates and fermented products as alternatives of fishmeal in aqua-feeds. Fish silage has been used particularly in the feeding of fish farming (De Arruda, Borghesi, & Oetterer, 2007). However, production of silage requires the use of acids that might potentially destroy essential amino acids, particularly tryptophan, and reduce the nutritional value of the silage (Plascencia-Jatomea, Olvera-Novoa, Arredondo-Figueroa, Hall, & Shirai, 2002). Protein hydrolysates are produced with proteases under mild conditions and could be much more suitable than silage as a source of good quality protein in aqua-feeds (Santos et al., 2013).

2.1.1. Effect of seafood protein hydrolysates on fish growth

The enhancement of growth rate is a particularly important economic parameter, as it can significantly reduce the time required to produce market-size fish. To increase growth rate, researchers have primarily used transgenic fish species that overexpress growth hormones, and have also experimentally treated fish with recombinant growth hormones. The administration of these hormones as a food supplement is known to be a viable method to enhance growth rates and feed conversion in cultured fish. However, the production and use of hormones is expensive and difficult, and there is concern over the safety of hormone-fed fish destined for human consumption. In this context, some aqua-feeds supplemented with seafood protein hydrolysates stimulate fish growth and are a cheap and natural alternative to growth hormones. This growth promoting effect can be largely attributed to the flavouring characteristics of diets including protein hydrolysates, which promotes a higher feed intake (Carvalho, Sá, Oliva-Teles, & Bergot, 2004; Chotikachinda, Tantikitti, Benjakul, Rustad, & Kumarnsit, 2013; Grey, Forster, Dominy, Ako, & Giesen, 2009; Ho, Li-Chan, Skura, Higgs, & Dosanjh, 2014; Kotzamanis, Gisbert, Gatesoupe, Zambonino Infante, & Cahu, 2007; Refstie, Olli, & Standal, 2004). As well, it is important to note that these diets are highly digestible and that facilitates the fast passing and absorption of peptides and amino acids through intestinal membrane (Aksnes, Hope, Høstmark, & Albrektsen, 2006; Wilson & Castro, 2010; Zheng, Liang, Yao, Wang, & Chang, 2012). Aksnes, Hope, Jönsson, Björnsson, and Albrektsen (2006) suggested that diets supplemented with seafood protein hydrolysates may contain low molecular weight compounds beneficial for growth and feed performance. Other theories suggest that protein hydrolysates contain molecules with ability to stimulate production of insulin-like growth factors (IGF-I and IGF-II) which may enhance fish growth. In this field, incorporation of fish protein hydrolysates in fish feed has been related to increments in growth performance, plasma IGF-I levels and liver IGF-I mRNA expression, whereas partial or total replacement of fish meal by plant-protein sources has been associated with low growth performance, low feed intake and low plasma IGF-I levels (Aksnes, Hope, Jönsson, Björnsson, & Albrektsen, 2006; Gómez-Requeni et al., 2004; Zheng, Liang, Yao, Wang, & Chang, 2013). These differences ascribed to the protein source result in changes in the plasma levels of the essential amino acids Lys and Met, nucleotides, anserine and taurine, and lead to significant differences in IGF-I and Growth Hormone (GH) regulation (Espe, Hevrøy, Liaset, Lemme, & El-Mowafi, 2008; Hevroy et al., 2007).

During the last decades, extensive efforts have been focused on the use of microdiets as first feeds for most marine fish larvae, in such a way to completely or partially substitute live food organisms which production is costly and time consuming (Kolkovski, 2001). Microdiets represent a considerable saving in production costs and infrastructure, as well as offering nutritional consistency and off-the-shelf convenience. The formulation and manufacturing of microdiets have been improved during the last years and several commercial microdiets can be found in the market. However, marine fish larvae fed microdiets have not, at this stage, matched the growth and survival performances demonstrated by larvae fed live feeds such as rotifers and *Artemia* *nauplii*. The use of microdiets has numerous limitations, since larvae are unable to digest and assimilate nutrients efficiently. During the first month after hatching, the stomach is not yet fully developed and the digestive enzyme activity of the pancreas is low compared with adult fish. As microdiets contain proteins, they are difficult for larvae to digest compared with live feed. As a result, poor growth is associated with low digestion and assimilation of microdiets. The partial substitution of marine protein for protein hydrolysates in microdiets is an alternative for overcoming the limited digestive capacity of fish larvae. The inclusion of hydrolysates as partial protein replacements increases the ingestion rates, induces changes in the activity of the main digestive proteases of fish larvae, and also promotes an earlier intestinal maturation (Kotzamanis et al., 2007; Ovissipour, Abedian Kenari, Nazari, Motamedzadegan, & Rasco, 2014; Santos et al., 2013; Zambonino Infante, Cahu, & Peres, 1997). Nowadays, several commercial microdiets include a moderate level of marine protein hydrolysates in their formulations (Gisbert et al., 2012). However, the level of the inclusion should be monitored carefully, as higher inclusion rates of hydrolysate can result in a negative effect on larval performances. It is well stablished that the incorporation of protein hydrolysates in microdiets at moderate levels (lower than 10-15%) promote growth performance and feed utilization of fish larvae (Table 1), while levels higher than 25–30% are linked to low growth and survival of larvae. The negative effect of high inclusion levels of hdrolysed protein in microdiets for fish larvae may be the result of several conditions. Peptides in the hydrolysates may confer bitter taste and unpleasant odour to feeds and it may negatively affect ingestion. Moreover, the presence of high levels of free amino acids in microdiets depresses the maturation process of pancreatic cells in fish larvae and therefore does not facilitate the onset of the adult mode of digestion in developing fish (Cahu, Zambonino Infante, Quazuguel, & Le Gall, 1999). It is also worth mentioning that ingestion of microdiets with high inclusion levels of protein hydrolysate may saturate the intestinal peptide transport mechanism (Cahu et al., 1999; Carvalho et al., 2004; Gisbert et al., 2012; Kotzamanis et al., 2007) and reduce performance of fish larvae.

The benefits of fish protein hydrolysates on feed intake and/or growth have also been reported in juvenile fish (Table 1). However, the benefits on the incorporation of hydrolysates in juvenile diets are lower than in fish larvae because of the higher ability of juvenile fish to digest dietary protein (Kolkovski, 2001). As previously described in fish larvae, the concentration of seafood protein hydrolysate in aquafeeds seems to be important to promote juvenile fish growth, and the best growth rates are obtained with feeds containing low concentrations of hydrolysate.

2.1.2. Effect of seafood protein hydrolysates on growth of crustacean and molluscs

Crustaceans are primary chemosensory feeders, so chemoattractants and feeding stimulants (feeding effectors) are important components of their prey or feed. Certain amino acids (taurine, glycine, arginine, glutamic acid, and alanine) have been identified as feeding enhancers, and would be the main responsible of the positive effect of feeds supplemented with seafood protein hydrolysates on shrimp growth (Table 2). Only moderate inclusion levels of hydrolysed protein in the diet are necessary to promote shrimp growth, probably because high quantities of free amino acids in feed can change the rate of absorption in the gastrointestinal tract, which induces a premature absorption of certain free essential amino acids in relation to the absorption of amino acids that are present in polypeptide chains. The incorporation of seafood protein hydrolysates in shrimp diets will be especially important for feeds with high protein plant meal and low fishmeal content, as it will improve its attractiveness and will induce adequate feed consumption levels by shrimp (Grey et al., 2009). The ability of moderate amounts of seafood protein hydrolysates to increase feed intake is now well recognised. However, a minimal amount of hydrolysate in feeds (1–2%) is necessary to elicit a positive effect on shrimp feeding.

The effect of feeds containing seafood protein hydrolysate on growth of molluscs is not well described, and the threshold where dietary inclusion levels of hydrolysed fish proteins affect growth positively or negatively has not yet been reported. Improved immunity in molluscs could have benefits to producers, as a good immune response is critically important in ensuring good disease resistance. In a recent paper, Goosen, de Wet, Goergens, and Görgens (2014) demonstrated that low inclusion levels (0.6 and 1.8 %) of the commercial fish protein hydrolysate Actipal® (Aquativ, France) in abalone diets significantly improved daily weight increase after approximately 5 months of feeding trial. The incorporation of high amounts of protein hydrolysate in feeds is therefore not necessary to increase growth of abalone, as also observed in fish and shrimp feeds.

2.1.3. Effect of seafood protein hydrolysates on survival of aquaculture species

The commercial development of aquaculture and the increasing demand for fish lead to intensive fish culture, where the fish is at high risk of infectious disease caused by pathogens. The use of antibiotics to control these diseases can result in the development of drug-resistant bacteria, environmental pollution and residues in fish, and the search of some alternative strategies is of interest to reduce the use of these chemicals. In this sense, several studies have shown that some protein hydrolysates enhance the nonspecific immunity in fish and are an

Table 1
Positive effects of animal protein hydrolysates on aquaculture fish. Stage: larvae (l), juvenile (j). N.S.: Not specified. Optimum concentration in diets was expressed as g/100 g of dried weight.

Hydrolysate	Enzyme	Parameters positively affected	Concentration	Fish specie (stage)	Reference
Tuna viscera	Alcalase	Feeding, growth	1–4	Asian Sea bass (j)	Chotikachinda et al. (2013)
Pacific hake	Alcalase	Feeding, growth	2	Chinook salmon (j)	Ho et al. (2014)
Pollok heads	Alcalase + Flavourzyme	Growth, feed efficiency, antioxidant activity	3.7	Turbot (j)	Zheng et al. (2013)
Tuna viscera	*Alcalase*	Growth, feeding, intestinal development	4.5, 18.7	Persian sturgeon (l)	Ovissipour et al. (2014)
Krill	N.S.	Growth, feed utilization, protein digestibility	4%	Red Sea bream (j)	Bui et al. (2014)
Shrimp heads	N.S.	Growth, feed utilization, protein digestibility	4.8%		
Sardine	N.S.	Weight, length	4	Iguacu catfish (j)	Lewandowski et al. (2013)
Tilapia carcass	N.S.	Weight, feed efficiency	6		
Swine liver	N.S.	Weight, length, feed efficiency	6		
Pollock	Alcalase + Flavourzyme	Growth, feed efficiency	8	Japanese flounder(j)	Zheng et al. (2012)
N.S.	N.S.	Growth, intestinal development	10	European Sea bass (l)	Kotzamanis et al. (2007)
Pollock	Protamex	Feeding, growth	10	Atlantic Salmon (j)	Refstie et al. (2004)
Fish (N.S.)	N.S.	Feeding	10	Senegalese sole (j)	Barroso, Rodiles, Vizcaino, Martínez, and Alarcón (2013)
Cod + Squid (9:1)	Pepsin	Growth	10	Atlantic halibut (l)	Kvåle et al. (2002)
Pollock	Acid protease	Growth	15	Sea bass (j)	Liang et al. (2006)
Herring	Alcalase	Feeding	18–24	Atlantic Salmon (j)	HevrØy et al. (2005)

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Table 2
Positive effects of animal protein hydrolysates on crustaceans. Stage: larvae (l), juvenile (j), adult (a). N.S.: Not specified. Optimum concentration in diets was expressed as g/100 g of dried weight.

Hydrolysate	Enzyme/Microbial	Parameters positively affected	Concentration	Specie (stage)	Reference
Commercial (specie N.S.)	N.S.	Cellular immunity and growth	0.6–1.8	Abalone (a)	Goosen et al. (2014)
Golden thread-fin bream	Alcalase	Growth	2	Pacific white shrimp (l)	(Niu et al. (2014)
Tuna	*L. plantarum*	Growth	5	Pacific white shrimp (j)	(Hernández, Olvera-Novoa, Smith, Hardy, and Gonzalez-Rodriguez (2011)
Salmon heads and frames	Papain	Feeding	5, 11.89	Pacific white shrimp (j)	(Grey et al. (2009)
Tuna	Protamex	Survival, feeding and growth	15	White shrimp (a)	(Nguyen et al. (2012)

interesting alternative to antibiotics for controlling the propagation of infectious disease (Table 3). The effect of protein hydrolysates on fish immunity was firstly observed *in vitro* by Bøgwald, Dalmo, Leifson, Stenberg, and Gildberg (1996) and Gildberg, Bogwald, Johansen, and Stenberg (1996). Thus, Bøgwald et al. (1996) reported that intraperitoneal injection of cod muscle hydrolysate (molecular weight ranged 500–3000 Da) in Atlantic salmon stimulated production of reactive oxygen metabolites in head kidney leucocytes. Gildberg et al. (1996) found an increment in the respiratory burst activity of Atlantic salmon kidney leucocytes exposed to small amounts of cod stomachs hydrolysate in culture media.

The *in vitro* stimulatory effect of some protein hydrolysates on fish leucocytes suggests that their inclusion in aqua feeds could be effective in reducing disease-related losses among farmed fish. However, these immune-modulatory effects have been barely translated into a significantly greater survival (Table 3). Bui, Khosravi, Fournier, Herault, and Lee (2014) observed that superoxide dismutase activity was significantly increased in juvenile red sea bream fed feeds containing 4% Antarctic krill hydrolysate compared to the control diet. They also reported that survival rate and total immunoglobulin level were significantly elevated in fish fed diets containing approximately 4–5% of hydrolysates from whole Antarctic krill, white shrimp or tilapia. As well, they found that dietary inclusion of krill or tilapia hydrolysate increased resistance of fish against *Edwardsiella tarda*. Liang, Wang, Chang, and Mai (2006) showed that 15% of Pollock hydrolysate in juvenile Sea bass diets enhanced the lysozyme activity after feeding for 30 or 60 days, and complemented the haemolytic (CH50) activity after feeding for 60 days. Moreover, Hermannsdottir et al. (2009) reported that the incorporation of Pollock hydrolysate into diets enhanced lysozyme activity and the complement C3 component in first feeding Atlantic halibut larvae.

Several experiments have shown a significant and positive effect of feeds supplemented with moderate amounts of seafood protein hydrolysate (lower than 15%) on survival rates of fish but any effect on fish immunity (Table 3). In contrast to these studies, Lian, Lee, and Bengtson (2008) achieved best survival of summer flounder larvae fed diets including high doses of seafood protein hydrolysates (about 73%). As well, Day, Howell, and Jones (1997) observed a positive correlation between the amount of fish protein hydrolysate in juvenile Dover sole diets (26–80%) and survival over a period of 22 days, although mortality was lower in fish fed a control diet containing polychaete and mollusc meal. The results obtained by different authors in this field thus appear contradictory. However, the differences observed can be attributed to differences in the hydrolysates and diets tested. Moreover, the experiments were conducted on different species with some variation in age and digestive physiology. In spite of the variations in the results, it seems that lower levels of fish protein hydrolysate in feeds support fish survival better than higher levels. This fact can be largely explained by the leaching of water-soluble protein from feeds that contain a high proportion of soluble hydrolysate. Leaching results in a less nutritious diet. Moreover, in some cases leaching can be very rapid and the feed particles remain suspended for a long time before they are consumed, stimulating proliferation of deadly species such as *Vibrio* spp. and increasing mortality of fish larvae (Kotzamanis et al., 2007; Kvåle, Harboe, Espe, Næss, & Hamre, 2002). The immunostimulatory effect of feeds containing fish protein hydrolysates on crustaceans and molluscs has been scarcely reported. Improved immunity in shrimp or abalone could have benefits to producers, as a good immune response is critically important in ensuring good disease resistance. However, continuous feeding of dietary immune stimulants could be counterproductive and increase production costs, as is known in finfish where continual feeding of immune stimulants over an extended period of time can lead to decreased efficacy of immune stimulants (Goosen et al., 2014). Recently, Nguyen, Perez-Galvez, and Berge (2012) showed the ability of a diet including 20% of tuna head hydrolysate to improve growth and survival rates of Pacific white shrimp in a 6-week feeding trial. As well, Goosen et al. (2014) reported that low levels of commercial fish protein hydrolysate (Actipal®, 0.6%) in abalone feeds significantly increased the cellular immunity through increasing the phagocytic activity of haemocytes by 18% compared to the control diet.

2.2. Application of protein hydrolysates from livestock and poultry by-products in aquaculture

By-products derived from livestock processing industry are also used in the manufacture of aqua-feeds, although to a lesser extent because of the limitations imposed to prevent the possibility of transmission of prion diseases via consumption of farmed fish (Friedland, Petersen, & Rubenstein, 2009). In this regard, it is important to emphasize that

Table 3
Effects of animal protein hydrolysates on survival of aquaculture fish. * Concentration in culture media (μg/ml). ** Effect *in vivo* after intraperitoneal injection (mg/kg of fish). *** The peptide hydrolysate (g/1000 ml) was added to the fatty acid enrichment medium of *Artemia*.

Hydrolysate	Enzyme	Parameters positively affected	Concentration	Fish specie (stage)	Reference
Cod muscle	Neutrase	Stimulation of leucocytes (in vitro, in vivo)	100–1000 *, 100 **	Atlantic salmon (a)	Bøgwald et al. (1996)
Pollock fillets	Alcalase + Protamex	Innate immunity	N.S.***	Atlantic Halibut (l)	Hermannsdottir et al. (2009)
Cod stomachs	N.S.	Stimulation of leucocytes (in vitro)	1, 5 *	Atlantic salmon (a)	Gildberg et al. (1996)
Krill	N.S.	Survival, innate immunity, disease resistance	4	Red Sea bream (j)	Bui et al. (2014)
Shrimp heads	N.S.	Survival, innate immunity, disease resistance	4.8	Red Sea bream (j)	
Tilapia	N.S.	Survival, innate immunity, disease resistance	4.2.	Red Sea bream (j)	
Cod + Squid (9:1)	Pepsin	Survival rate	10	Atlantic halibut (l)	Kvåle et al. (2002)
N.S.	N.S.	Survival rate	10	European Sea bass (l)	Kotzamanis et al. (2007)
Pollock	Acid protease	Innate immunity	15	Japanese Sea bass (j)	Liang et al. (2006)
Squid	Endogenous enzymes	Survival rate	73.3	Summer flounder (l)	Lian et al. (2008)

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European legislation does permit the use of hydrolysed protein from ruminant hides/skin and also of gelatine, collagen and hydrolysed protein from non-ruminants for the preparation of feed. Nonetheless, the use of non-marine animal proteins in aquaculture feeds is expected to grow, especially as competition and prices for fishmeal increase.

Rendered animal by-product meals such as meat meal, blood meal and feather meal have been used for decades in salmonid feeds and are currently applied in many commercial aqua-feeds. In contrast, protein hydrolysates from by-products of livestock or poultry have been rarely incorporated in aqua-feeds. Fries et al. (2011) found that the incorporation of 3% of hydrolysates from poultry viscera or pig liver into goldfish feeds did not affect the productive performance or the attractiveness of the diet. Similar results, as well as a lower incidence of skeletal deformities, were reported by Gisbert et al. (2012) in Gilthead sea bream larvae fed microdiets containing 12% of commercial pig blood hydrolysate. More recently, Lewandowski et al. (2013) found that incorporation of 6% of swine liver hydrolysate in diets improved weight, weight gain, length and feed conversion of catfish and did not affect the blood biochemical parameters.

3. Application of animal protein hydrolysates on production and companion animals

The protein used in diets for production and companion animals originates from a variety of sources including forage, grains, legumes, animal meal and various by-products. Soybean meal is the main protein source used in animal feeds (FAO, 2004); however, it contains both anti-nutritional factors (anti-trypsin) and several allergenic proteins (glycinin and β-conglycinin) that make recommendable its replacement by alternative protein sources in feedstuffs, mainly for newly weaned animals (Kim & Easter, 2001). In this regard, animal protein hydrolysates derived from industrial wastes are interesting alternatives to soybean meal. Protein hydrolysates do not use to include aggregated protein, do not contain anti-nutritional factors, present high solubility over a wide range of pH and ionic strength and may show suitable amino acid profile. However, it is important to note that some wastes derived from industrial processing of ruminants cannot be used for production of ruminant feeds because of the risk of transmission of BSE (EC 1069/2009 and Title 21, CFR 589.2000, for Europe and the USA, respectively).

The positive effect of protein hydrolysates from animal by-products on animal performance has been reported and the principles behind how they work are well established. First, the hydrolysates contain short peptides and certain amino acids (taurine, glycine, arginine, glutamic acid, and alanine) that are feeding stimulants and palatability enhancers and increase the acceptance of artificial diets. Second, the small peptides and amino acids are readily absorbed in the small intestine without previous gastrointestinal digestion and potentially enhance animal growth and development (Gilbert, Wong, & Webb, 2008; McCalla, Waugh, Lohry, Pasupuleti, & Demain, 2010). Third, absorption of labile and insoluble amino acids such as cysteine, glutamine or tyrosine in a small peptide form increases availability of these amino acids to the body. Fourth, specific hormone-like peptides obtained by protein hydrolysis might modulate gastrointestinal motility, endocrine metabolism and intake and affect positively the animal performance (Martínez-Alvarez, 2013).

3.1. Applications of seafood protein hydrolysates in animal feeding

The young animals have immature digestive and immune systems and must rely on maternal milk to provide antibodies to achieve passive immunity for protection from disease and efficient early growth performance. The diet for post-weaning animals should attempt to continue this trend and include easily digestible sources of protein to stimulate feed intake and meet requirements, not only for growth but also for maintaining a normal immune response. In this regard, seafood protein hydrolysates are rich in peptides and free amino acids and are a good source of protein for newly weaned animals, as reported by several authors. Nørgaard, Blaabjerg, and Poulsen (2012) found that weaning pigs' diets containing 12.3% of salmon protein hydrolysate resulted on greater feed intake than those containing soy proteins, although non-significant differences in gain or feed utilization of weaning pigs were found. Tucker, Naranjo, Bidner, and Southern (2011) reported that the inclusion of up to 3% of salmon protein hydrolysate in diets does not affect the growth performance of weaning pigs. Similarly, Sun, Ma, Li, and Ji (2009) observed that the partial substitution of spray-dried porcine protein and fish meal by 2% of shrimp protein hydrolysate does not show any adverse effect on growth performance, nutrient digestibility and serum biochemical parameters in weaned piglets. In the past, other authors successfully used fish protein hydrolysates in the formulation of milk replacers for early weaned calves (Diaz-Castañeda & Brisson, 1987, 1989). However, and despite the promising result obtained by those authors, investigations in this research area have been sparse.

Another way of using fish hydrolysates in animal feeds is in the form of fish silage. However, the disagreeable odour of fish silage limits its use in a high proportion in feed formulations. The feed applications of fish silage are primarily limited to young animals owing to the extensive hydrolysis of the protein, even though fish silage has also been used in commercial concentrate mixtures for growing-finishing pigs and broilers. The nutritional value of fish silage has been evaluated in pigs (Thuy, Lindberg, & Ogle, 2011), broilers (Al-Marzooqi, Al-Farsi, Kadim, Mahgoub, & Goddard, 2010; Santana-Delgado, Avila, & Sotelo, 2008), and quails (Ramirez et al., 2013). Although lactic fermentation provides fat stability in fish silage and improves its acceptability (Enes Dapkevicius, Nout, Rombouts, & Houben, 2007), lipid oxidation after incorporation in feeds may confer undesirable fishy and rancid off-flavours and affect animal performance (Rose, Anderson, & White, 1994). Possible alternatives to improve performance include the incorporation of antioxidants in feeds, or the use of preheating treatment to deactivate lipases and other enzymes (Santana-Delgado et al., 2008). Finally, it is worth noting that fat remaining in silage may increase PUFA content, modifying the pig's and chicken's requirements for vitamin E and other antioxidants, and negatively affecting the sensory quality of meat (Kjos, Herstad, Overland, & Skrede, 2000; Kjos, Herstad, Skrede, & Overland, 2001; Kjos, Skrede, & Overland, 1999).

Seafood protein hydrolysates could be used as a source of essential and non-essential amino acids and palatability-enhancing agents in pet food formulations (Folador et al., 2006). Nevertheless, this potential use has only been studied to a limited extent (Folador et al., 2006; Zinn et al., 2009).

3.2. Applications of protein hydrolysates from livestock and poultry by-products in animal feeding

Protein hydrolysis of livestock and poultry by-products yields easily absorbable hydrolysates of interest for feeding weaning animals. Recent *in vivo* experiments have demonstrated that hydrolysates from porcine intestinal mucosa can positively replace other protein sources commonly used in weaning pig diets, such as blood plasma (Corassa, Lopes, Pena,, Freitas, & Pena, 2007), soybean meal (Scandolera et al., 2008) or fish meal (Sulabo et al., 2012). Protein hydrolysates from poultry or sheep by-products obtained by autolysis could also be used in animal nutrition (Jamdar & Harikumar, 2008; Lasekan et al., 2013). Hydrolysed feather meal is also an attractive source of amino acids for pigs (Divakala et al., 2009). However, cleaned feathers must be previously processed to modify the keratin structure prior to hydrolysis, and it may promote destruction of some heat-labile amino acids and racemization of amino acids. Feather hydrolysates produced via these methods need to be supplemented with certain amino acids, such as lysine, methionine or histidine before using in animal feeds (Lasekan et al., 2013). Alternatively, feathers could be digested by using microorganisms

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under anaerobic conditions and improve amino acid digestibility and consequently the growth response (Gousterova et al., 2011; Lasekan et al., 2013).

The incorporation of protein hydrolysates derived from livestock and poultry by-products in animal feeds may be limited by their palatability. This is especially important in stages in which feed intake may be compromised, such as weaning, or after changes in feed composition. Solà-Oriol, Roura, and Torrallardona (2011) conducted an experiment to evaluate the effect of fifteen different animal and vegetable protein sources on feed preferences in young pigs. They showed that, in general, feeds with 5–10% of fish meal or 5% of dried porcine hydrolysed protein were preferred to the reference feed with soybean meal. However, values of dried porcine hydrolysed protein higher than 5% reduced the feed preference, probably because of the high mineral content of the feed.

Meat protein hydrolysates have also been used to improve the palatability of kibbles produced from low ash poultry meal (Nchienzia, Morawicki, & Gadang, 2010). Although most protein hydrolysates produced by endoproteases contain hydrophobic peptide fractions that confer bitter taste, the use of exoproteases as Flavourzyme helps to cleave most of the hydrophobic amino acids from the peptide fractions thus making kibbles more appealing to pets.

3.3. Bioactive properties of animal protein hydrolysates. Possible applications as nutraceuticals for animals

Advances in pet nutrition and veterinary care have resulted in increased life expectancy of companion animals and in a higher risk for development of chronic diseases. It has increased the research and use of nutraceuticals (or therapeutic supplements) for the pet industry. In this context, the market for companion animal health products has grown by around 2.5% per annum in nominal terms since 1992. The companion animal market is mainly concentrated in the USA and Europe, where five (France, Germany, Italy, Spain, and the United Kingdom) of the top ten world markets are located (Horspool, 2013).

The pet food industry uses protein hydrolysates in food formulations to ensure that the products are hypoallergenic and also to improve palatability. The protein hydrolysates are also promising nutraceuticals with interest for the animals health market. The development of animal protein hydrolysates and peptides as functional ingredients in animal food has gained in popularity because of the array of potential bioactive properties associated with them, including antioxidative, antihypertensive, immune-modulatory or hormone-regulating properties (Thorkelsson et al., 2008). In fact, a variety of peptide-based products can currently be found in the market, although there is some debate over their efficacy, mainly because of the scarce *in vivo* trials performed. Protein hydrolysates provide a rich source of protein which is useful in situations where excess protein is needed, such as during inflammation and infections. Some protein hydrolysates may perform a useful immune-stimulant function, as has been observed in aquaculture fish. Hydrolysates including epidermal growth factor (EGF)-like molecules could provide a novel and inexpensive approach for prevention and treatment of the harmful effects of non-steroidal anti-inflammatory drugs on the bowels of farm animals or pets, where therapy is nowadays suboptimal (Fitzgerald et al., 2005; Marchbank, Elia, & Playford, 2009). Gelatine hydrolysates could be useful for the treatment of osteoarthritis in dogs, cats and horses (Beynen et al., 2010; Weide, 2004). More than 90% of dogs over 5 years of age are affected by osteoarthritis. Osteoarthritis cannot be cured and management aims at the relief of pain through reduction of inflammatory reactions and further breakdown of cartilage. Current treatment involves the use of non-steroidal anti-inflammatory drugs to decrease inflammation and consequently pain, but side effects such as vomiting and diarrhoea may occur. There are various nutraceuticals on the market that are promoted as safe, effective compounds to manage canine osteoarthritis. However, their efficacy of is questioned. Preclinical and clinical studies in humans have shown that orally administered gelatine hydrolysate is absorbed by the intestine, accumulated in joint cartilage and provide symptomatic relief of pain (Bello & Oesser, 2006). In experiments performed with dogs, Beynen et al. (2010) observed that a dose of about 2.5% of gelatine hydrolysate in a dry food significantly improved vitally and significantly reduced stiffness and lameness in dogs. However, the efficacy of collagen hydrolysates on osteoarthritis in animals is controversial because of the few published and rigorous controlled trials.

Antibiotics are important tools for the prevention and treatment of bacterial diseases in animals. Appropriate selection and responsible usage of antimicrobial medicines for use in veterinary settings is vital to maintain the efficacy of these treatments in animals and to minimise antibiotic resistance that can seriously compromise animal health and welfare and can have negative implications for public health. Many veterinary associations have developed prudent use guidelines promoting appropriate and selective use of antibiotics in animals. However, there may be restrictions on the use of some antibiotics in veterinary medicine and the search for new antimicrobial agents or new compounds able to potentiate the antimicrobial activity of old antibiotics against resistant microorganisms has become an important area of research. Some animal protein hydrolysates have shown antimicrobial effect against pathogenic species (Adje et al., 2011; Anal, Noomhorm, & Vongsawasdi, 2013; Catiau et al., 2011; Gómez Guillén et al., 2010; Hedhili et al., 2014; Najafian & Babji, 2012; Toldrá et al., 2012) and could be interesting antimicrobials or antibiotic adjuvants for treatment of animal diseases. Antimicrobial peptides have been found in bovine haemoglobin hydrolysates (Adje et al., 2011; Catiau et al., 2011; Hedhili et al., 2014; Lafarga & Hayes, 2014; Toldrá et al., 2012), in beef sarcoplasmic protein hydrolysates (Jang, Jo, Kang, & Lee, 2008), in seafood skin hydrolysates (Anal et al., 2013; Gómez Guillén et al., 2010), and also in a barbell muscle hydrolysate (Sila et al., 2014). Although there are many antibiotics on the market that have a more powerful effect than these antimicrobial peptides, the advantage of peptides is their fast bactericidal effect and their wide spectrum of activity. Nonetheless, it is worth noting that the bactericidal and/or bacteriostatic effect of animal protein hydrolysates has not yet been demonstrated *in vivo*.

Animals continually produce free radicals through normal cellular activity and from various stressors. These radicals can overwhelm an animal's defence system, resulting in diseases and may aggravate genetically predisposed conditions such as canine hip dysplasia (CHD), chronic obstructive pulmonary disorder or arthritis. The incorporation of antioxidants in diets could play an important role in animal health by inactivating harmful free radicals, as it has been reported in dogs (Dowling & Head, 2012; Nippak, Mendelson, Muggenburg, & Milgram, 2007). In this regard, powerful antioxidants as vitamin E, vitamin C, carotenoids and/or vitamin A are incorporated into pet foods to counteract the effect of free radicals, thereby reducing oxidative stress. Protein hydrolysates derived from animal by-products including antioxidative peptides (Chalamaiah, Dinesh Kumar, Hemalatha, & Jyothirmayi, 2012; Lafarga & Hayes, 2014; Najafian & Babji, 2012) could also be used to boost the antioxidant content of the diet.

Animal protein hydrolysates may also include opioid-like peptides with interesting applications in animals as anti-stress or satiety agents (Bernet, Montel, Noël, & Dupouy, 2000; Cudennec, Fouchereau-Peron, Ferry, Duclos, & Ravallec, 2012). The occurrence of these peptides in protein hydrolysate has been demonstrated *in vitro*. However, to date there are no rigorous studies that prove anti-stress or satiety effects of protein hydrolysates on companion animals. Opioid-like peptides exert their effects on the nervous system, especially on the control of pain, sleep and behaviour. As well, they have the ability to regulate the functions of digestion and ingestion of food (Wada & Lönnerdal, 2014) and can have important effects against pet obesity. The opioid-like effect of these peptides is mainly due to their ability to mimic the effect of opioid hormones by interacting with specific opioid receptors in the nervous, endocrine and immune systems, as well as in the intestinal tract of mammalians. Opioid-like peptides have been generated

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from different food sources (mainly bovine haemoglobin and fish) but to date there has been no report on the generation of opioid peptides from meat muscle proteins (Martínez-Alvarez, 2013; Toldrá et al., 2012).

4. Drawbacks

Despite the important and promising applications of protein hydrolysates derived from animal by-products in animal feeding, some drawbacks associated with the raw material used must be taken into account (Jayathilakan, Sultana, Radhakrishna, & Bawa, 2012). Thus, animal processing by-products varies highly in its physical nature and proximate composition. These organic materials are also highly perishable and laden with microorganisms, many of which are pathogenic to both humans and animals. As well, by-products with high fat content are susceptible to oxidation that leads to the release of foul smelling fatty acids. Another great limitation derives from the important restrictions imposed to safeguard against BSE. Other drawback is the possible accumulation of pesticides, drug residues and toxic heavy metals in animal by-products, which may limit their use in animal feeds (Liu, 2002).

Other important drawbacks are associated with the production of bioactive protein hydrolysates. The production of bioactive peptides is often an expensive process due to up-scaling problems and the need to use expensive isolation, purification and characterization technologies in large-scale. It is also worth mentioning that the high moisture content of protein hydrolysates may make handling difficult and favour microbial contamination. Mechanical removal of water through use of a press can lead to further problems with waste disposal due to the high levels of organic matter in the water, and drying can lead to important microbial growth. Also, protein hydrolysates should be thermally processed to inactivate proteases before their incorporation into feeds and it may promote destruction and racemization of amino acids (Meister, 2012). Finally, it is important to note that the majority of the beneficial bioactivities described for animal-derived peptides have been assessed only *in vitro*. It is therefore necessary to evaluate the activity of those peptides in animals after digestion to assess their efficacy, dose response and safety before use as a functional ingredient.

5. Conclusions and future research

The knowledge of the biological effect of protein hydrolysates on animals has increased enormously during the past few decades, but there are still many gaps that require further research. Thus, it is necessary to improve the knowledge on the best levels of protein hydrolysates from animal processing in microdiets that will lead to the fastest growth and development of fish larvae. This will permit the development of optimal species-specific feed formulations. As well, it is necessary to minimise the risk of leaching of peptides and free amino acids due to the solubility and small surface to volume ratio, and improve the knowledge on the effect of co-feeding live food and microdiets-including protein hydrolysates on larval performance.

The *in vitro* stimulatory effect of some protein hydrolysates on fish immunity suggests that their inclusion in aqua feeds could be effective in reducing disease-related losses among farmed fish. Nonetheless, very little is known on the effect of protein hydrolysates, mainly those from livestock processing by-products, on fish survival. This knowledge will contribute to the design of stage-specific diets for individual species.

Another issue that needs attention is the determination of the threshold where dietary inclusion levels of protein hydrolysates negatively affect growth and immunity of molluscs and crustaceans. For aquaculture producers, it will also be important to determine appropriate inclusion levels to prevent negative impacts on feed water stability and production performance.

In spite of numerous studies on the biological effect of animal protein hydrolysates on aquaculture fish, the knowledge of their effect on farm animals is limited. In fact, the use of nutraceuticals is a relatively recent practice in veterinary medicine. The incorporation of animal protein hydrolysates in diets for post-weaning animals (e.g. pigs or calves) would be of interest for producers as it might stimulate feed intake and/or improve health.

Although the nutraceutical effect of animal protein hydrolysates on companion animals has been scarcely reported, some of these hydrolysates (mainly those derived from collagen) could promptly be used mainly to treat the pain and swelling of osteoarthritis-affected joints. However, nowadays it is difficult to reach a conclusion about the efficacy of collagen hydrolysates in osteoarthritis of cats, dog or horses because there are few published rigorous randomised controlled trials. Future research must clarify if dietary chondroprotective supplements including collagen hydrolysates can help to mitigate the loss of cartilage and relief osteoarthritis pain in animals.

Moreover, *in vivo* trials must be performed to demonstrate that protein hydrolysates including antibacterial peptides can be used as antimicrobials or antibiotic adjuvants for treatment of animal diseases. Furthermore, it is important to note that the nutraceutical effect of animal protein hydrolysates on exotic pets (exotic mammals, reptiles, etc.) has not been investigated.

Animal protein hydrolysates including bioactive components are used to improve palatability of kibbles, but more efforts must be done to identify the compounds that contribute to savoury flavour and also to maximize the production of these flavour chemicals. Understanding the kinetics of these reactions will be helpful to activate only the relevant pathways that would generate the desired flavours without the release of undesirable flavours, also generating and/or maintaining the bioactivity of the hydrolysates.

Furthermore, the knowledge of the molecular structures of the peptidic chains of the protein hydrolysates must improve. As well, broader and deeper knowledge of the occurrence of hormone-like peptides in the hydrolysates is necessary to understand the effect of feeds containing hydrolysates on the growth and health of animals.

In summary, scientific data suggest that animal by-products hydrolysates have promising applications in animal feeding, either as a source of essential amino acids or nitrogen, or else as a source of molecules with bioactive potential. The great amount of waste generated in slaughterhouses and in the seafood industry makes necessary to carry out a deeper exploration of new applications of this waste, in view of the environmental problems caused by its disposal and the economic importance that would result from converting this low-value waste into high value-added products.

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