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Production of Fish-Bioactive Peptides by Conventional & Emerging Technologies: A Review

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ABSTRACT

Fish is a type of food that is perishable. High production and perishable characteristics cause fish commodities to be immediately given storage or processing treatment so that they do not decrease in quality. The processing of fishery commodities has focused on producing foods with health effects for humans, such as functional foods, functional ingredients, and nutraceuticals. The health effects are caused by the content of bioactive compounds, one of which is bioactive peptides. Bioactive peptides are fragments from hydrolysis and have several biological functionalities such as antioxidant, anti-inflammatory, antihypertensive, anti-obesity, antimicrobial, and immunomodulatory properties. Generally, bioactive peptides can be produced from substrates such as foods with high protein content using enzymatic hydrolysis, chemical hydrolysis, and microbial fermentation technologies. However, these methods result in low peptide yields. Several emerging technologies have been applied in producing bioactive peptides, such as Ultrasound-Assisted Processing, Microwave-Assisted Processing, High Hydrostatic Pressure Processing, and Pulsed-Electric Field Processing. The application of emerging technologies is expected to produce peptides with high yield, fast, and low cost.

Keywords: Corruption crimes, return of state financial losses

Introduction

Indonesia is the largest archipelago in the world, with abundant fisheries resources. The Indonesian Ministry of Maritime Affairs and Fisheries reported that the production of capture fisheries and aquaculture in Indonesia in 2022 amounted to 24.84 million tons. This fisheries production has increased by 13.63% from 2021 of 21.87 million tons (KKP 2022). Fish is a type of food that is perishable or easily damaged (Prabhakar et al., 2020; Xu et al., 2018). The damage is caused by the high water content, and the content of various nutrients in fish that can support a variety of spoilage microorganisms to grow (Chan et al., 2023; Zang et al., 2020). High production and perishable characteristics cause fish commodities to be immediately given storage or processing treatment so that they do not decrease in quality (Ježek & Buchtová, 2007; Tavares et al., 2021).

Currently, processing various fishery commodities such as fish is not only intended for basic consumption needs. However, the processing of fishery commodities has now focused on producing foods with health effects for humans, such as functional foods, functional ingredients, and nutraceuticals (Murtaza et al., 2022). The health effects are caused by the content of bioactive compounds that are naturally present in food types or formed during the processing process (Kurnianto et al., 2023). One of the bioactive compounds that has received much attention today is bioactive peptides (Kurnianto, Syahbanu, et al., 2023; Kurnianto et al., 2023).

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Bioactive peptides are fragments resulting from hydrolysis of low molecular weight proteins (<6 kDa), composed of 2 - 20 amino acids, and have certain biological activities that are beneficial for human health (Abdel-Hamid et al., 2017; Kurnianto et al., 2023). Bioactive peptides offer several biological functionalities such as antioxidant, anti-inflammatory, antihypertensive, anti-obesity, antimicrobial, and immunomodulatory properties (Aluko, 2015; Ulug et al., 2021). Generally, bioactive peptides can be produced from substrates such as foods with high protein content using technologies such as enzymatic hydrolysis, chemical hydrolysis, and microbial fermentation (Ulug et al., 2021). However, despite being widely used, these methods result in low peptide yields (Murtaza et al., 2022; Raveschot et al., 2018). Currently, various emerging technologies are developing and can be combined with conventional methods to produce peptides with high yield, fast, and low cost (Murtaza et al., 2022).

Several emerging technologies have been applied in producing bioactive peptides, such as Ultrasound-Assisted Processing, Microwave-Assisted Processing, High Hydrostatic Pressure Processing, and Pulsed-Electric Field Processing (Ulug et al., 2021). Most of these emerging technologies are applied as pre-treatment and are proven to enhance the bioactivity of bioactive peptides (Murtaza et al., 2022; Ulug et al., 2021). This review will focus on the potential utilization, use cases, and advantages of emerging technologies in producing bioactive peptides sourced from food substrates.

Discussion

Fish: Source of bioactive peptides

Fish and fish products are regularly consumed foods as a reliable source of nutrients. They are good sources of polyunsaturated fatty acids such as omega-3, proteins, vitamin D, and selenium, which can contribute to a healthy diet (Tørris et al., 2018). According to FAO data, global fish production increased from 20 million tons in 1950 to 184.6 million tons in 2022; this is also linear with consumption levels. Numerous studies have found a beneficial association between fish product consumption and human health. One component that has attracted attention due to its positive effects is bioactive peptide (BP). *Bioactive peptides* are fragments resulting from hydrolysis of low molecular weight proteins (<6 kDa), composed of 2 - 20 amino acids, and have certain biological activities that are beneficial for human health (Abdel-Hamid et al., 2017; Kurnianto et al., 2023). More than 4,032 BP sequences have been identified and stored in the BIOPEP-UWM database (Minkiewicz et al., 2019). These various BP sequences have been identified as having various biological activities such as antibacterial, antidiabetic, antioxidant, cholesterol-lowering, antidiabetic, ACE inhibitor, and immunomodulatory (Akbarian et al., 2022; de Castro & Sato, 2015; Kurnianto et al., 2023). Several BP from fish can be obtained from body parts such as muscle protein, skin collagen and gelatin, fish bones, and other body parts such as internal organs (Senevirathne & Kim, 2012). Several studies have shown the potential of bioactive peptides from fish, such as the APGHPVPA, GVAAPGHP, and LVVAIPAALGHA sequences with antioxidant activity from catfish (*Pangasius* sp.) (Najafian & Babji, 2014), MLVFAV and DLDLRKDLYA sequences with ACE inhibitor activity and antioxidant activity from skipjack fish (*Katsuwonus pelamis*) (Intarasirisawat et al., 2013), GAAEKGVPLF and GVDNPGHPF sequences with antioxidant activity from salmon (*Salmo salar*) (Dinh et al., 2018), and LDDFKL and GTEDELDKY sequences with antithrombotic activity from sardine fish (Jemil et al., 2016).

The biological activity of BP from fish is influenced by several factors, such as the composition of the constituent amino acids and structural properties of the peptide, such as sequence, length, molecular weight, charge, and position of the amino acid (-N or -C terminal) (Karami & Akbari-adergani, 2019). Several types of BP bioactivity have distinctive characteristic markers, such as BP with antioxidant activity having a high hydrophobicity value because the peptide must interact strongly with targets that are also hydrophobic on the cell membrane (Himaya et al., 2012; Zou et al., 2016). In BPs with antimicrobial activity, bioactivity depends on molecular weight, hydrophobicity, and cationic charge. These three are related to antimicrobial mechanisms that target the integrity of negatively charged bacterial membranes (Kurnianto et al., 2022). Meanwhile, in BP with ACE inhibitor activity, peptides with short sequences (dipeptides and tripeptides) and small molecular weight are more effective because they can quickly pass through intestinal epithelial cells to prevent gastrointestinal digestion (Roberts et al., 1999).

Conventional methods for bioactive peptide production

Currently, most bioactive peptides are produced using conventional methods such as enzymatic hydrolysis, fermentation using microorganisms, and chemical hydrolysis.

Enzymatic hydrolysis

Enzymatic hydrolysis is the most common method used to produce bioactive peptides because it is reliable, efficient, has high specificity and has a low content of organic solvent residues or toxic chemicals (Zambrowicz et al., 2013). In general, the principle of peptide formation through this process is breaking peptide bonds, which are facilitated by proteolytic enzymes that produce peptide fragments with certain biological activities (Adebiyi et al., 2008; Marciniak et al., 2018). The proteolysis process can be done with a single enzyme or a combination of several enzymes to produce smaller peptide fragments (Singh et al., 2014). This enzymatic hydrolysis process must occur under controlled parameters, including pH, temperature, substrate concentration, and enzyme activity. This relates to the optimal enzyme conditions used (Boschin et al., 2014). The yield of bioactive peptide production using enzymatic hydrolysis largely depends on two factors: the primary structure of the parent substrate protein and the specificity of the enzyme used (Otte et al., 2007). Several enzymes produced by animals, plants, or microbes such as neutrase, thermolysin, ficin, pronase, flavourzyme, papain, trypsin, pepsin, and chymotrypsin have been used in the process of hydrolysis of protein substrates into peptides with a molecular weight of 500 - 1800 kDa or 2 - 20 unit of amino acids (Abdul Salam, 2015; Luo et al., 2014).

Microbial fermentation

Fermentation is an ancient method that is widely used to preserve food. This is the most efficient and economical technique for producing peptides (Daliri et al., 2017). In principle, fermentation is a hydrolysis method that utilizes proteolytic enzymes produced by microorganisms (Chakrabarti et al., 2018; Girgih et al., 2014). The fermentation process can use proteolytic microorganisms (single or in combination), such as bacteria, moulds, and yeasts, under natural or controlled conditions (Castro & Sato, 2014). Each microorganism produces different proteolytic enzymes, so their use during fermentation significantly influences the formation of organoleptic properties of bioactive peptides and their bioactivity (Otte et al., 2007). Lactic acid bacteria are generally microorganisms widely used in fermented food products (Kurnianto et al., 2023). The fermentation process with LAB causes a decrease in pH, which can inhibit the growth of pathogenic microorganisms. It also indirectly affects protein degradation by increasing muscle protease activity. Polypeptides produced by endogenous meat proteases are further degraded by bacterial enzymes during fermentation, which release potential bioactive peptides in meat products (Murtaza et al., 2022). Several types of typical Indonesian fermented products are reported to have potential bioactivity such as rusip (Kurnianto et al., 2023), bekasam (Retno Wikandari et al., 2011; Wikandari & Yuanita, 2016), shrimp paste (Kleekayai et al., 2015), joruk (Anggrahini et al., 2020) and budu (Najafian & Babji, 2019).

Chemical hydrolysis

This process utilizes chemical compounds that are either acidic or alkaline to break the peptide bonds in the parent proteins, turning them into peptides or free amino acids (Wang et al., 2017). Chemical hydrolysis is a widely used method due to its simplicity and cost-effectiveness. However, this method is not favored, especially in the production of bioactive peptides, because it has several drawbacks such as a difficult-to-control process leading to variable chemical compositions, which can compromise nutritional quality and result in low functionality (Ulug et al., 2021). In general, chemical hydrolysis processes are commonly used to produce meat flavor enhancers. In the case of fish, this method has been employed for the production of fish protein hydrolysates. Nevertheless, Wisuthiphaet et al., (2016) reported that acid hydrolysis produces lower functional properties compared to those obtained by enzymatic hydrolysis. Additionally, alkaline hydrolysis leads to the undesirable formation of lisoalanine amino acids in food products (Ulug et al., 2021).

Emerging technology for bioactive peptide production

The advancement of science and technology has led to the development of the production processes for bioactive peptides. Various emerging methods have been explored to enhance the degree of hydrolysis in the production of these bioactive compounds (Bamdad et al., 2017). Some reported emerging methods include ultrasound, high hydrostatic pressure, pulsed electric field, microwave, and ohmic heating.

Ultrasound-assisted processing

Ultrasound-assisted processing is one of the emerging non-thermal technologies that utilizes high-frequency acoustic waves or ultrasonic waves with frequencies above 20 KHz for peptide production (Cárcel et al., 2012; Ulug et al., 2021). During ultrasound treatment, several phenomena occur when ultrasound waves pass through a medium, including acoustic cavitation, acoustic streaming, and mechanical vibrations. Acoustic streaming can facilitate and enhance mass transfer through a medium, which can alter the size and structure of solid particles (Tho et al., 2007). Generally, ultrasound treatment must be combined with other methods to increase the production of bioactive peptides because ultrasound treatment alone is not sufficient to break peptide bonds (Ulug et al., 2021). Wu et al. (2018) reported that ultrasound pre-treatment enhances the release of bioactive peptides from substrate proteins by increasing the accessibility of enzymes to peptide bonds and causing changes in conformation with increased formation of β-sheet and β-turn. Several studies have demonstrated the use of ultrasound in hydrolyzing food-source substrate proteins to produce bioactive peptides, including whey protein (Wu et al., 2018), milk protein concentrate (Uluko et al., 2015), rapeseed protein (Wali et al., 2017), corn protein (Liang et al., 2017), cheddar cheese (Munir et al., 2020), and fresh milk (Cui et al., 2020). Wu et al., (2018) reported a significant increase in ACE inhibition activity and immunomodulator activity in whey protein hydrolysate when enzymatic hydrolysis was assisted by ultrasound pre-treatment. Ultrasound treatment also significantly enhanced ACE inhibitor activity in rapeseed protein hydrolysate (Wali et al., 2017). In this study, it was reported that ultrasound pre-treatment could promote the production of small-sized peptides (200 - 3000 Da).

Microwave-assisted processing

Microwave-assisted processing is an emerging method that utilizes electromagnetic radiation from 300 MHz to 300 GHz (Barba et al., 2016). In food, microwave treatment is conducted in food processing ovens that generate microwave waves with a frequency of 2.54 GHz and a wavelength of less than 1 cm (Murtaza et al., 2022). Microwave-assisted processing is commonly combined with enzymatic hydrolysis because this combination offers advantages such as faster hydrolysis processes and the production of a greater quantity of short-chain peptide sequences (Zhong et al., 2005). Microwave-assisted processing for protein hydrolysis has been applied to dairy proteins in cheddar cheese, dairy protein concentrates, and bovine whey protein concentrates (Chen et al., 2014; El Mecherfi et al., 2019). Several studies have utilized this combination, including the production of bioactive peptides from crickets (Hall & Liceaga, 2020), chia seeds (Urbizo-Reyes et al., 2019), trout (Ketnawa et al., 2018), sea cucumber collagen (Li et al., 2019), bovine serum albumin (Chen et al., 2014), and bighead carp (Yang et al., 2016). This combination has been shown to enhance the bioactivity of bioactive peptides compared to thermal processing by improving proteolysis processes and forming low-molecular-weight peptides. Urbizo-Reyes et al. (2019) reported that enzymatic treatment (single: alcalase 93.13% or sequential: alcalase + flavourzyme; 94.76%) combined with microwaves significantly (87.54%) increased antioxidant activity compared to conventionally hydrolyzed products using thermal treatment. Similar improvements in activity were also observed in the hydrolysis of trout and fish proteins (Ketnawa et al., 2018).

High hydrostatic pressure processing

High-pressure processing (HHP) is a non-thermal technology that utilizes isostatic pressure ranging from 100 to 1000 MPa using water as its transmission medium (Naderi et al., 2017). This method has attracted attention because it can minimize damage to bioactive compounds, which are often susceptible to degradation in conventional methods due to moderate or high temperatures (Ulug et al., 2021). However, this method has the drawback of a very high initial investment cost (Yamamoto, 2017). In the production of bioactive peptides, HHP has been used to hydrolyze various food source proteins, including legume-based ones such as soybean, flaxseed (Perreault et al., 2017), kidney bean (Al-Ruwaih et al., 2019), and Pinto bean (Garcia-Mora et al., 2016), as well as dairy-based proteins like cheddar cheese (Munir et al., 2020), whey protein concentrate (Landim et al., 2021), and bovine whey protein (Peñas et al., 2006). Based on several studies, HHP is generally combined with enzymatic hydrolysis because HHP can induce the opening of protein structures, making enzyme cleavage sites more visible, and this can accelerate the proteolysis process (Ulug et al., 2021). Ulug et al. (2021) also reported that HPP has limitations in breaking covalent bonds, so it needs to be combined with enzymatic hydrolysis to denature proteins and enhance access to enzyme cleavage sites. Al-Ruwaih et al. (2019) reported that HPP treatment (300, 400, and 500 MPa) for 15 minutes as a pre-treatment, followed by enzymatic hydrolysis with alkalase, significantly increased the antioxidant activity of kidney bean protein hydrolysate. Pre-treatment with HPP at pressures of 400-600 MPa for 10 minutes before enzymatic hydrolysis with trypsin beta-lactoglobulin was also reported to increase the production of bioactive peptides from 26.7% to 38.64% (Boukil et al., 2018). Short peptides were produced with a higher yield after HHP treatment at 100 MPa compared to air conditions (Bamdad et al., 2017).

Pulsed-electric field processing

Another promising emerging method for producing bioactive peptides is the pulsed electric field (PEF). PEF is a novel non-thermal processing technology that utilizes the principle of a short-pulsed electric field with high intensity, typically ranging from 10 to 80 kV/cm in a short period (Mohammed, & Eiss, 2012). PEF can be applied to liquid or semi-liquid foods placed between electrodes capable of transmitting high-voltage pulses to the food. According to Lin et al. (2013), parameters that can influence proteins include the strength of the electric field, the number of pulses, treatment time, and pulse shape. Based on these parameters, PEF can enhance the production of bioactive peptides through processes such as unfolding, denaturation, and gelling, inducing molecular polarization in proteins. PEF is also known to disrupt non-covalent bonds, such as hydrogen bonds and hydrophobic interactions, and release sulfhydryl groups, as well as covalent bonds (disulfide bonds), depending on the duration of application (Ulug et al., 2021). This method offers several advantages, including a short processing time, low energy consumption, and the ability to inactivate microorganisms (Lin et al., 2013). PEF has been used to hydrolyze various food proteins, such as egg white (Lin et al., 2013) and soybean protein (Lin et al., 2016). Lin et al. (2013) reported that PEF can break down large peptides into smaller peptide fragments with increased antioxidant activity during a 4-hour treatment. This research also indicates that PEF can unfold and release sulfhydryl groups and alter the secondary protein structure based on treatment intensity and processing time.

Conclusion

Various emerging technologies can produce bioactive peptides, such as Ultrasound-Assisted Processing, Microwave-Assisted Processing, High Hydrostatic Pressure Processing, and Pulsed-Electric Field Processing. Most emerging technology methods are used simultaneously or combined with conventional methods (enzymatic hydrolysis, chemical hydrolysis, and fermentation) as pre-treatment. Several research results show that pre-treatment using emerging technology methods followed by conventional methods can significantly increase biological activity and bioactive peptide yield. These results show great potential for using emerging technology methods in producing bioactive peptides.

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