A Review On Bioactive Peptides Derived From Various Sources Of Meat And Meat By-Products

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Abstract: Bioactive peptides are short polymers from proteins that have a positive impact functionally for human health. This paper provides a review of bioactive peptides derived from various sources of meat and the generation of bioactive peptides. Bioactive peptides can be produced from a variety of animal species, such as bovine, poultry, and porcine. They can be obtained by hydrolysis from their parent protein sequence to release bioactive peptides. Some of the methods are enzymatic hydrolysis using enzymes from animals, commercial proteinase, or enzymes from plants. In addition, microorganism fermentation with starter lactic acid bacteria may also be used. Some of the functions of bioactive peptides that are beneficial for humans include antimicrobials, antithrombotic drugs such as the prevention of blood clots and strokes, antioxidants that counteract free radicals, and antihypertensive drugs that can lower blood pressure.

Index Terms: Bioactive peptide, meat, protein, hydrolysis, animal

1. INTRODUCTION
Meat is edible parts that are separated from the body of an animal or carcass, both from livestock and wild animals [1]. Meat is a valuable source of nutrients such as vitamins, fiber, antioxidants, and especially proteins [2]. Due to their high digestibility and balanced composition in essential amino acids, especially in sulfated ones, meat proteins are known to be high-quality proteins [3], [4]. Recently, meat has been found to be a good source of bioactive peptides such as protein-derived peptides, creatine, carnosine, L-carnitine, glutathione, conjugated linoleic acid, and taurine [5]. Bioactive peptides are short polymers consisting of about 2-20 amino acids and have a relatively low molecular weight compared to proteins [1]. The lower the molecular weight of bioactive peptides, the greater the likelihood of the peptide being absorbed into the small intestine and exert its biological effects [6]. These bioactive peptides are present in raw materials or can be generated using hydrolysis, cooking, or fermentation. These peptides are not bioactive when in their natural protein chains, but after they are released, they turn active and have functional properties that are good for health. These bioactive properties can be triggered by fermentation, enzymatic hydrolysis, and digestion in the gastrointestinal (GI) [7], [8]. The behavior of this bioactive peptide depends on its structure and sequence of amino acids, such as N- and C-terminal form of amino acid, the weight and length of the peptide chain, hydrophobic/hydrophilic properties, spatial structure, and charge character of amino acid [4], [9]. Meat-derived bioactive peptides have a lot of potentials that can benefit humans’ health. Several studies have shown that bioactive peptides also have antioxidant, antimicrobial, antihypertensive, antithrombotic, anticancerogenic activities; improve satiety, immunomodulatory system, improve the immune system, blood circulation, and digestion [10]. Protein-derived peptides can inhibit angiotensin-converting enzymes (ACE) and dipeptidyl peptidase-IV (DPP-IV) that can lower the blood tension increasing the lifetime of incretins which is useful in the management of type 2 diabetes respectively, carnosine and anserine have antioxidant properties, creatine can be used for improved muscle performance, taurine can modulate lipid metabolism and stimulate energy expenditure to decrease the risk of obesity, and so on [11]–[13]. Moreover, based on its structural properties, these bioactive peptides exert multifunctional properties in many bioactive peptides, which provide more application in functional food production [8]. This is a good breakthrough because the meat was always linked with negative images due to its fat content and increased risk of cancer, especially in colorectal cancer, obesity, and other chronic lifestyle-related diseases (CLSRDs) [4], [14]. Different meat sources contain different bioactive peptides [12]. Even bioactive peptides from the same type of meat can have different contents. This is mainly related to metabolic differentiation and energy requirements required in its activities [15]. Some bioactive peptides content is also dependent on the production system, feed composition, and the feeding regime [16]. The meat processing industry produces many by-products and is largely wasted. This makes the potential use of these byproducts attractive as an inexpensive raw material for manufacturing bioactive peptides [1]. In this review, we provide the current understanding of meat-derived bioactive peptides from various sources of meat with emphasis on their generation and functionality for human health.

2 MEAT SOURCES
Meat consist of water, protein, lipids, minerals, carbohydrates, vitamins, and other bioactive compounds, in which protein is the most important component [1]. Different animals will have specific meat characteristics, especially in the composition of the components and their degradation once it is consumed. Bovine, swine, poultry, and sheep have a different skeletal muscle protein in their isoelectric point or molecular weight [17]. Martini et al. [3] found that there is a difference in protein digestibility between beef, pork, turkey, and chicken, especially in the amount of peptides that can be released after pancreatic digestion. Peptide release from beef is higher than from pork and turkey. But not every peptide released from its parent protein chains is bioactive because not every peptide has a physiological, hormone-like effect on humans in addition to its nutritional value contribution [18].
2.1 Bovine

Because of its constituent amino acids, beef meat is a significant source of high-quality dietary proteins for humans. The bioactive contents of beef meat depend largely on the composition of the fiber and the muscle function [15]. Muscles that have a high aerobic metabolism contain more coenzyme Q10 and taurine, while carnosine and creatine content is less [16]. Moreover, the peptides produced during the human digestion process have been shown to have established biological functions and potential-promoting functions [19]. Kęska, Wójciak, and Stadnik [18] found using LC-MS/MS chromatography that there were 452 peptides presented in semimembranosus muscle of Limousine cattle with 62 peptides that consist of 7 to 21 amino acids, have the bioactivity index greater than 0.5, meaning that these 62 peptides are potentially bioactive with the highest potential activity was determined for the octapeptide FPMNPPKFK (myosin-1, Uniprot ID: Q9BE40, bioactive score 0.97) and the nonapeptide FPMNPPKFD (myosin-2, Uniprot ID: Q9BE41, bioactive score 0.87). Jang & Lee [20] reported an ACE inhibitor hexapeptide VLAGYK from the beef rump.

2.2 Poultry

The level of bioactive peptides in chicken meat is greatly affected by the breed of chicken, the type of meat, and the method of cooking chicken meat. Carnosine, anserine, carnitine, and betaine are some of the bioactive compounds in chicken meat. Jayasena et al. [12] found that the amount of carnosine and anserine is 2-3 times higher in breast meat than those of leg meat. This is because breast muscle requires endogenous compounds such as anserin and carnosine in higher amounts as a buffering potential. Carnosine and anserine are soluble in water, so once the chicken has been cooked, the amount of these biopeptides will be depleted due to the release of the cooking juices [21].

2.3 Porcine

Many bioactive peptides are derived from pork sources, either directly from pork meat or pork products [22]. Some bioactive peptides have been successfully taken from porcine sarcoplasmic proteins, myofibrillar proteins, longissimus lumbarum muscles, their by-products Like blood, collagen, bone, and pig products like dry-cured ham [23], [24]. Research on pig red blood cell fraction hydrolysates using FP400, FPH, or bromelain showed higher DPPH radical scavenging activity compared to sheep, deer, and cattle red blood cell fractions hydrolyzed with the same method [25]. Saiga et al. [23] successfully isolated peptides with DSGVT, IAEAEG, DAQKLE, EELDNALN, and VPSIDDQEELM sequences from porcine myofibrillar proteins that have excellent DPPH radical scavenging activity and chelating activity to the metal ions.

3 GENERATION OF BIOACTIVE PEPTIDES

Protein integrity and activity will undergo various breakdown/transformation, which are different due to the influence of environmental factors, both exogenous and endogenous, such as biochemical and enzymatic reactions [1]. During digestion in the digestive tract, bioactive peptides are produced through protein hydrolysis, which is controlled by digestive enzymes such as pepsin, chymotrypsin, or trypsin [20]. Generally, bioactive peptides produced from animal products like meat are often using general enzymatic or microbial hydrolysis and depending on the method used [26]. Meat is one of the most researched food sources associated with the isolation of novel bioactive peptides [27]. Some mechanisms that can be used for meat and meat products to generate bioactive peptides are enzymatic hydrolysis, microbial fermentation, acid and alkaline hydrolysis, and several non-conventional methods of extraction such as sub-critical hydrolysis of water and isoelectric solubilization [22]. The ultimate objective of these different mechanisms is to destructurized proteins in order to release bioactive peptides from their parent proteins [28]. Some of the bioactive peptides have been isolated and produced from meat using digestive enzymes in animals such as trypsin and chymotrypsin, pepsin; commercial proteinase such as flavourzyme®, protamex®, alcalase®, neuramidase and proteinase K, or enzymes from plant such as ficin, bromelain, and papain [29], [30]. Bioactive peptides are commonly known to occur naturally in mammal’s gastrointestinal tract during the metabolism of dietary meat proteins [27]. Meat-derived protein that has been eaten by humans during gastrointestinal proteolysis is hydrolyzed by enzymes that are secreted by the stomach and small intestine. Therefore, the gastrointestinal digestive system has begun to simulated for the production of peptides with the same physiological properties as in the digestion process using the enzymes mentioned above [31]. Jang et al. [32] utilized seven types of enzymes, named trypsin, pepsin, tyrosinase, thermolysin + proteinase A, proteinase K, papain, and protease to hydrolyze beef sarcoplasmic proteins to separate peptides with antihypertensive and antimicrobial activity. Bioactive peptides can be produced economically, mainly through microbial fermentation [33]. Microorganisms release proteases into large peptides, small peptides, and free amino acids as a result of hydrolyzed extracellular proteins because they need proteins as a source of nitrogen [34]. One way to generate bioactive peptides by controlled protein hydrolysis is by using lactic acid bacteria (LAB) as a proteolytic enzyme source [35]. Most bioactive peptides are derived from meat by-products, but there is hardly any literature on bioactive peptides isolated from muscle proteins, possibly due to the poor proteolytic activity of Lactobacillus [22]. Castellano et al. [36] were able to generate bioactive peptides with antihypertensive activity from porcine sarcoplasmic protein fermentation by using lactic acid bacteria (L. sakei CRL1862 and L. curvatus CRL705), but peptides that have been produced from myofibrillar proteins do not have any bioactivity. A similar result was also found after testing the antioxidant activity of porcine sarcoplasmic peptides and myofibrillar proteins using mixed starters Staphylococcus simulans NJ201 and Lactobacillus plantarum CD101 [37]. Bioactive peptide generation using acid and alkaline hydrolysis is a method that has been used for a long time but is becoming obsolete because this approach is generally not compatible with food manufacturing strategies [38]. Protein hydrolysis methods using acids are usually performed using HCL or other sulphonic acids. Meanwhile, for the alkaline hydrolysis method, it usually uses NaOH or KOH, Where the peptide bonds are cleaved and form potassium and sodium salts of free amino acids using the alkaline hydrolysis process [22]. Sub-critical water hydrolysis and isoelectric solubilization/precipitation are some non-conventional hydrolysis methods that can be used to extract bioactive peptides [39], [40]. Subcritical water hydrolysis is the hydrolysis method using water as a solvent, which is maintained in a liquid state at temperatures above the boiling...
conventional antibiotics, where that has a isoelectric protein level (pH 5.5) so that the membrane phospholipids. The latter is called, of 70 mg/kg that has the significant antimicrobial activity [48]. Some bioactive peptides bioactive peptide derived directly from meat t and amphiphilic acid is known to have antimicrobial activity. Ionic/electrostatic interactions, leading to cellular membrane carpet mechanisms, where the peptides are deposited on b the toroid pores are created by combining the polar peptides one is called the toroid pores or wormhole mechanisms, where they have three different antimicrobial peptide action mechanisms as compared to conventional antibiotics, where they have three different antimicrobial peptide action mechanisms. The first mechanism is called the barrel-stave mechanism, where peptides are bound across the membrane to form a pore. In this case, the peptide’s hydrophobic segments interact with the membrane’s aliphatic chains while its hydrophilic segments form the pore’s interior. The second one is called the toroid pores or wormhole mechanisms, where the toroid pores are created by combining the polar peptides with the bilayer membrane phospholipids. The latter is called the carpet mechanisms, where the peptides are deposited on the bilayer surface in a carpet-like fashion, primarily by ionic/electrostatic interactions, leading to cellular membrane destabilization and membrane destruction [47]. The peptide with a relatively short chain, positively charged, and amphiphilic acid is known to have antimicrobial activity. Unfortunately, there is a little known article that proves a bioactive peptide derived directly from meat that has a significant antimicrobial activity [48]. Some bioactive peptides that are antimicrobials are usually derived from meat by-products. Jang et al. [32] found several peptides derived from beef sarcoplasmic proteins that have antimicrobial activity, including peptide GLSDGEWQ on B. cereus, S. typhimurium, E. coli, and L. monocytogenes, peptide GFHI on E. coli and P. aeruginosa, and peptide FHG and GFHI on P. aeruginosa. Keska & Stadnik [49] found out that there was no evidence of growth inhibitory properties of peptides isolated from the pig (Sus scrofa) and cow (Bov Taurus) proteins against E. coli K12 ATCC 10798 and S. aureus ATCC 25923.

3.2 Antithrombotic
Thrombosis is a condition in which blood flows weaken because of the formation of clots in the blood vessels [50]. This process of clot formation involves a complex interaction of vascular endothelium, platelets and coagulation factors, which eventually develop into venous thromboembolism (VTE) or acute coronary syndrome [51]. This VTE condition usually happened in arteries, which lead to myocardial localized necrosis and stroke [52]. This condition is an illness that can cause disability in many people over the age of 50 until death, where this condition can affect 1 in 100 people annually [50]. Several peptides are known to be able to inhibit blood platelet aggregation and binding of fibrinogen γ-chain to the receptors of platelet fibrinogen, but peptides from animals with antithrombotic activity are quite uncommon [48], [52]. Morimatsu et al. [53] reported that porcine peptides hydrolysis with the papain enzyme had hypocholesterolemic activity associated with the antithrombotic activity. Shimizu et al. [52] reported that purified pork peptide had an antithrombotic activity in vivo at oral administration of 70 mg/kg that has the same effect as the activity of aspirin. In comparison to pork meat, which has no general antithrombotic function, this papain-hydrolyzed pork peptide has greater content of isoleucine, leucine, and phenylalanine, which could be indicated why it has an antithrombotic activity.

3.3 Antioxidant
Reactive oxygen species (ROS) are compounds that are produced during cell metabolism to protect the body against pathogenic attacks and act as cell signaling systems. Free radicals can attack neighboring molecules, even key biological molecules like DNA, by subtracting electrons and initiating chain reactions when it is generated in excess and when it cannot be eradicated after formation [6], [54]. This excessive free radical activity can negatively impact human health, such as cancer, heart disease, inflammatory disease, and so on [55]. The antioxidant activity of peptides is determined by a number of factors, including the position of peptides in the protein structure, protein isolation methods, degree of hydrolysis, hydrophobicity, enzymes used, peptide concentrations, and its most basic constituent amino acids [4]. Some of the amino acids known to have antioxidant activity include histidine, phenylalanine, tyrosine, glycine, leucine, and alanine [56]. Peptides may have antioxidant activity if they contain hydrophobic amino acid and one or more residues of histidine (H), proline (P), cysteine (C), tyrosine (Y), tryptophan (W), phenylalanine (F), or methionine (M) in their sequence. Peptides containing histidine may act as radical scavengers by chelating metal ions, scavenging hydroxyl radicals, and acting as an active-oxygen quencher [6]. There are two main mechanisms that can deactivate free radicals by peptides with antioxidant activity, namely hydrogen atom transfer (HAT) and

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single electron transfer (SET) [57]. Both of these mechanisms would generate an identical final product, although the mechanism varies. In the HAT mechanism, one H atom of antioxidant peptides was transferred to free radicals to form radical antioxidant peptides, while in the SET mechanism, peptides would provide free radicals with electrons to convert into radical cations. SET Tyrosine-containing peptides generally act as antioxidants through the HAT mechanism, while cysteine, histidine, and tryptophan-containing peptides are usually working through the SET mechanism [57]. There are many peptides derived from meat sources that have antioxidant activity [4]. Di Bernardini et al. [58] was able to identify the antioxidant activity from 3-kDa and 10-kDa peptic fractions from bovine brisket muscle sarcoplasmic proteins that contain alanine and leucine in their sequences using FRAP, DPPH, and Fe2+ chelating ability assays. Escudero et al. [6] managed to identify some peptides that have antioxidant activity using reducing power analysis and DPPH radical-scavenging assay, where SAGPNP peptides show the strongest radical-scavenging activity, and GLAGA peptides show higher reducing power than other bioactive peptides.

3.4 Antihypertensive
Angiotensin I-converting enzyme (ACE) peptide inhibitors are bioactive peptides, mainly from meat protein derivatives, which have the ability to prevent hypertension [36]. Angiotensin I-converting enzyme (EC 3.4.15.1) is a carboxyl-terminal dipeptidyl, exopeptidase that converts an inactive form of angiotensin I (decapetide) to a potent vasoconstrictor angiotensin II (octapeptide) and inactivates a vasodilatory peptide known as bradykinin [59]. Some of the meat-derived bioactive peptides are capable of inactivating this enzyme’s function and would have the opposite effect, such as reducing blood pressure. There has been some report that peptides rich in hydrophobic amino acids and had aromatic (Phe or Tyr) or imino acid (Pro) at the C-terminal [60]. There are a lot of ACE-inhibitory peptides that have been found in enzymatic hydrolysates of meat proteins. These peptides inhibitory potency is evaluated in vitro and measured by the IC50 value, the peptide concentration that inhibits 50% of ACE activity [4]. Peptides with the same sequence and have an ACE inhibitory activity can be found in many different species of animals. Tetrapeptide FQPS is an ACE inhibitory peptide with an IC50 of 27.0 μg/mL that was found in Kangac goat, wild swine, chum salmon, silkworm, and pacific oyster [30]. Jang & Lee (2005) reported that, with a sequence of VLAQYK, hexapeptide derived from beef rump sarcoplasmic proteins has an ACE inhibitory activity of 30% with an IC50 value of 23.11 μg/mL. Castellano et al. [36] found that there are more than 50 peptides from pork sarcoplasmic proteins showed a prevalence of hydrophobic such as aliphatic (V, I, and A), basic (R) and aromatic (Y and F) residues and neutral residues such as proline (P), aromatic (W, Y, and F), and aliphatic (I, A, L, and M) in the penultimate and ultimate C-terminal position that are often found in ACE inhibitory peptides, with one peptide sequence (FISHNAY) showed 54% ACE inhibition activity. DI Bernardini et al. [58] stated that two peptides from bovine brisket muscle with the sequence of INDPIFLHYM and RGDGIPEAKVF might be having ACE-I inhibitory activity because of their hydrophobic amino acids (methionine and phenylalanine) at their C-terminus. The hydrophobic amino acid residues at the three C-terminal positions are responsible for the ACE-inhibitory activity because of an interaction between the hydrophobic amino acid residues with the tree hydrophobic subunits at the active site [61].

4 CONCLUSION
Meat and its by-products are a valuable source of bioactive peptides that can be used in a variety of ways, including antimicrobial, antithrombotic, antioxidant and antihypertensive. Many animal types of meat and its by-products like bovine, poultry, and porcine can be used as a source of bioactive peptides. These peptides must be isolated from their parent protein bonds to acquire the bioactive peptides. Some methods that can be used to generate these bioactive peptides include enzyme hydrolysis, microbial fermentation, acid-base hydrolysis, and non-conventional hydrolysis such as sub-critical water hydrolysis and isoelectric solubilization/precipitation.

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