Food Chemistry: X 13 (2022) 100181

Contents lists available at ScienceDirect

Food Chemistry: X

journal homepage: www.sciencedirect.com/journal/food-chemistry-x

Bioactivity of peptides obtained from poultry by-products: A review

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ARTICLE INFO

Keywords:
Poultry
By-products
Proteins
Peptides
Bioactive

ABSTRACT

The production and consumption of poultry products (chicken, duck, and turkey) are continually growing throughout the world, leading to the generation of thousands of tons of organic by-products, which may be important sources of bioactive peptides. The bioactive peptides isolated from poultry by-products have biological properties that can be useful in the prevention of different metabolic diseases and hence, their consumption could be beneficial for human health. Such peptides can be used as nutraceuticals, and their inclusion as active components of functional food products is increasingly gaining attention. The aim of this review was to present the investigations of the biological effect of the peptides obtained from different poultry by-products and the possible mechanisms of action underlying these effects.

1. Introduction

Notwithstanding the perceived high impact of peptides, there are only a few reviews addressing poultry by-products; therefore, this work is of utmost importance by providing a current overview of bioactive peptides derived from poultry by-products, the possible mechanisms of action underlying their beneficial effects, as well as the amino acids related to this biological activity. The poultry meat industry generates large volumes of by-products, such as blood, bones, meat scraps, skin, fatty tissues, feet, skulls and, viscera, among others, and the ecological cost of their treatment and disposal is high (Lafarga, Álvarez, & Hayes, 2017; Toldrá et al., 2016). Commonly, poultry by-products are used for livestock feed and as organic fertilizers, however, it was determined that they contain a large number of proteins, fats, carbohydrates, minerals, vitamins and other nutrients (Moutinho et al., 2017), making them a viable option for obtaining new compounds and functional ingredients (Pateiro et al., 2019) and provide the opportunity to take advantage of existing protein resources in the diet (Zou et al., 2021). In this regard, a large number of studies have focused on the extraction, isolation and use of biomolecules such as bioactive peptides (Lasekan et al., 2013). Proteins present in poultry by-products are reduced to peptides by hydrolysis, and these peptides can have positive effects on human health (Onuh & Aluko, 2019). However, bitterness of protein hydrolysate is an important undesirable aspect for various applications, hence, for the removal of bitterness from protein hydrolysates, exopeptidase treatment, Maillard reaction, plastein reaction and encapsulation are being worked on (Fu et al., 2019), this would potentiate the acceptance of peptides by consumers. Hydrolysis, and in particular enzymatic hydrolysis allows obtaining hydrolysates with a high degree of hydrolysis which in turn results in a high yield (Gajanan et al., 2016) with a higher release of small peptides favoring their functional properties such as their solubility, emulsification and foam formation (Zou et al., 2021), at this point it should be noted that poultry by-products have presented yield values between 46% and 65% with production of peptides with biological activity (Romero-Garay et al., 2020).

Bioactive peptides, are short sequences of 2–30 amino acids (AA) (Toldrá et al., 2016; Lafarga et al., 2017) and a molecular weight of 400–2000 Da (Maestri et al., 2018), however, their bioactivity and bioavailability depend on the composition and sequence of AA in the peptide (Lafarga et al., 2017). Bioactive peptides derived from animal protein are recognized for their biological activity and positive effects on human health, especially for their antihypertensive, antioxidant, antidiabetic, antimicrobial and anti-inflammatory properties (Bravo et al., 2019; Xing et al., 2019a). They have also been proposed as antioxidant

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https://doi.org/10.1016/j.fochx.2021.100181
Received 3 August 2021; Received in revised form 2 December 2021; Accepted 3 December 2021
Available online 9 December 2021

and antimicrobial ingredients for food preservation (Tkaczewska, 2020). They are currently used by pharmaceutical companies for health promotion (Lafarga et al., 2017), in the cosmetology and beauty industry (Phipps et al., 2020); they also show promise in the food industry as nutraceuticals and therapeutics (Udenigwe & Fogliano, 2017; Schwartz et al., 2019; Phipps et al, 2020).

2. Biological activities of peptides obtained from poultry by-products

There is a strong link between nutrition and health, and various compounds such as bioactive peptides could play a key role in improving health. It has been proven that they are capable of interacting with other substances to generate an effect in living organisms, tissues, and cells over a wide spectrum of biological functions that can help reduce different health risk factors involved in metabolic disorders such as coagulation, obesity, lipoprotein metabolism, peroxidation, intestinal and neurologic functions, immunity, cancer, dental health, and mineral metabolism (Daliri et al., 2017; Mas-Capdevila, et al., 2018 ; Mas-Capdevila et al., 2019a,b).

The proteins present in poultry by-products (Fig. 1) have proven to be a good source for the production of hydrolysates and bioactive peptides important in the area of health and evaluation of their biological activity *in vitro* and *in vivo* is a useful tool to determine their effectiveness and relevance in the promotion of human health and prevention of diseases (Bouglé & Bouhallab, 2017; Bravo et al., 2019).

Physiologically, the bioactivity generated from peptides is mainly related to their bioaccessibility and bioavailability. They must cross different barriers such as digestive enzymes, absorption through the gastrointestinal tract, and hydrolysis by blood proteases, which can either inactivate peptide fragments or generate peptides with greater biological activity (Segura-Campos et al., 2010). It is well known that peptides are ligands that bind to physiologic targets to carry out various signaling processes, which may have regulatory functions that can lead to beneficial health effects, as demonstrated mainly through *in vitro* analysis, cell culture and animal studies. This wide range of biological effects is due to multiple factors, such as molecular size, hydrophobicity, charge, and spatial conformation, offered by the variability of AAs in their structure, which leads to a diversity of peptides (Udenigwe & Fogliano, 2017). However, it is difficult to establish a direct relationship between the possible *in vitro* and *in vivo* biological activity of peptides, hence the importance of our studies (Segura-campos et al., 2010).

It has been shown that the physiologic activities of the peptides derived from poultry by-products include antioxidant and antihypertensive effects, lipid regulation, and effects on the liver, primarily demonstrated through *in vitro* analysis, culture cell, and animal studies (Table 1).

In addition, Table 2 describes both the biological effect of dipeptides and AA present in the C-terminal and *N*-terminal chains of hydrolysates and bioactive peptides obtained from poultry by-products, as well as the possible chemical structure and functional groups associated with their biological activities.

2.1. Antioxidant activity

The biological effect of hydrolysates and peptides isolated from poultry by-products is mainly related to the structure and nature of the component AAs (Table 2). For example, antioxidant capacity is attributed mainly to the presence of aromatic AAs (tyrosine, tryptophan, and phenylalanine) in the terminal chains, because they can efficiently neutralize free radicals, acting as electron/hydrogen donors due to the presence of phenolic, indole, and imidazole groups; in the same way, they can reduce Fe^{3+} ions to Fe^{2+} and chelate Fe^{2+} as well as Cu^{2+} ions (Duan et al., 2014; Zheng et al., 2016).

Peptides < 10,000 Da obtained from different sources of poultry by-products from different hydrolysis processes (autolytic digestion, enzymatic hydrolysis, and fermentation) have been shown to exert an antioxidant effect (Table 1). Evaluating the antioxidant capacity of peptides denotes the possible biological effect that they can generate, and for this, it is necessary to understand the mechanisms that may be involved in exerting their effect. When an oxidative stress environment is generated, overproduction of reactive oxygen species (ROS) is obtained, mainly in the form of H_2O_2, which denotes damage to lipids, proteins, DNA, and consequent cell death (apoptosis) (Sanches et al., 2015).

Peptides < 3000 Da derived from duck by-products (gizzard) have shown to have antioxidant capacity *in vitro* by protecting DNA from oxidative damage induced by free radicals (Su et al., 2016). It has also been determined that the peptide Trp-Tyr-Pro-Ala-Ala-Pro (693.90 Da) generates a protective effect in human liver cells (Chang cells, ATCC CCL-13) against oxidative stress induced by *tert*-butyl hydroperoxide (Lee et al., 2013), leading to the suggestion that the peptide participates in the positive regulation of the expression of Bcl-2, a gene that encodes the 26-kDa protein that blocks programmed cell death without affecting cell proliferation. In addition, negative regulation of the Bax protein, which belongs to the Bcl-2 family that promotes apoptosis, generates a protective effect on the liver.

Peptides in chicken liver hydrolysates (cLH) < 10,000 Da with high content of Glu (62.62 mg/g), Asp (44.15 mg/g), Cys (8.24 mg/g), Ser (20.48 mg/g), Gly (23.19 mg/g), Thr (20.70 mg/g), Arg (32.44 mg/g), Ala (29.46 mg/g), Leu (37.25 mg/g), Lys (37.71 mg/g), and Tau (1.55 mg/g) have shown an antioxidant effect in murine models with induction of oxidative stress, favoring an increase in endogenous antioxidant activity in mice treated with D-galactose, increasing the activities of superoxide dismutase (SOD), glutathione (GSH), and glutathione

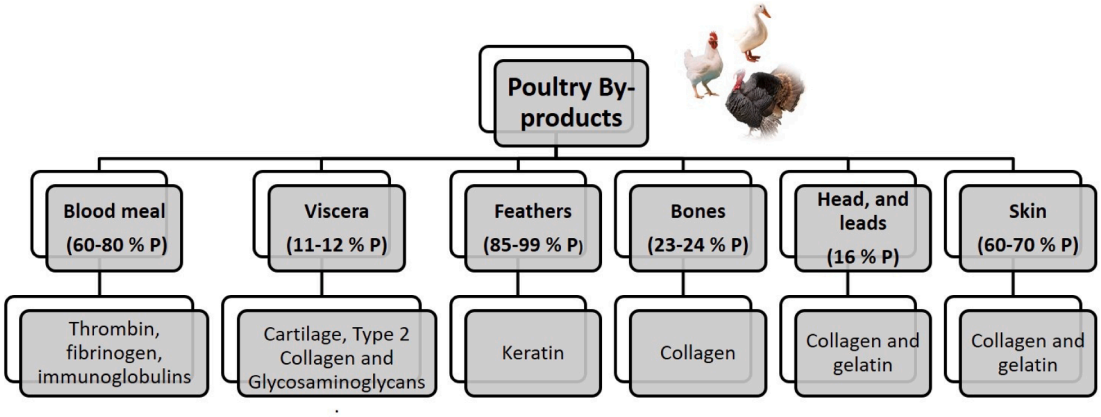


Fig. 1. Poultry by-products, crude protein content (% P) and their main structural proteins.

Table 1
Biological activity of hydrolysates and peptides obtained from different sources of poultry by-products.

Biological Activity	Type of assay	Source	Process	Hydrolysate/ Sequence/MW (Da)	Reference
Antioxidant Antihypertensive	*In vitro*	Poultry viscera	Autolytic digestion	F1 (>10 000 Da) F2 (3 000 Da to 10 000 Da) F3 (<3 000 Da)	Jamdar et al., 2012
Antioxidant	*In vitro* and culture cell	Duck skin	Synthesis of solid phase peptides using ASP48S (Peptron Inc.)	Trp-Tyr-Pro-Ala-Ala-Pro (693.90 Da)	Lee et al., 2013
Antioxidant Antihypertensive Antidiabetic	*In vitro* and animal study	Chicken Feathers	Fermented by *Chryseobacterium* sp. kr6	< 10 000 Da	Fontoura et al., 2014
Antioxidant	Animal study	Chicken liver	Hydrolysis with Pepsin	< 10 000 Da	Chou et al., 2014
Lipid Regulatory Antioxidant	Animal study	Chicken liver	Hydrolysis with Pepsin	Taurine (350 mg/100 g) Carnosine (194 mg/100 g) Anserine (18.9 mg/100 g)	Yang et al., 2014
Lipid Regulatory Anti-inflammatory	*In vitro*	Turkey Heads	Multienzyme hydrolysis (alcalase / flavorzyme / trypsin)	555.26 Da to 2 093.74 Da	Khiari et al., 2014
Antioxidant	*In vitro*	Chicken skin	Hydrolysis with alcalase and pepsine/ pancreatin	< 1 000 Da	Onuh et al, 2014)
Antihypertensive	Animal study	Chicken skin	Hydrolysis with alcalase and pepsine/ pancreatin	< 1 000 Da	Onuh et al., 2015
Antioxidant Antibacterial	*In vitro*	Chicken liver	Fermented by *Pediococcus acidilactici*	Protein content (55.85 % y 61.34 %)	Chakka et al., 2015
Antihypertensive	Animal study	Chicken skin	Hydrolysis with alcalase and pepsine/ pancreatin	Cys-Gly-Lys-Pro Ser-Gly-Arg Cys-Thr-Ser-His Val-Tyr-Lys-Lys Lys-Lys-Phe-Thr Ile-Pro-Ala-Lys-Phe-Leu-Gln-Gly-Leu	Onuh et al., 2016
Antioxidant Protective effect against oxidative DNA damage	*In vitro*	Duck gizzard	Hydrolysis with papain	<3 000 Da	Su et al., 2016
Antioxidant	*In vitro*	Chicken feathers	Fermented by *Bacillus subtilis*	Ser-Asn-Leu-Cys-Arg-Pro-Cys-Gly (848.8 Da)	Wan et al., 2016
Antioxidant	*In vitro*	Chicken neck	Multienzyme hydrolysis: Alcalase, Neutrase, Flavourzyme, Protamex	48 % (<3 000 Da) 42 % (3 000 Da to 10 000 Da)	Nikolaev et al., 2016
Antihypertensive	*In vitro*	Chicken skin	Hydrolysis with Elastase and Alcalase	≤3 000 Da	Yusop et al., 2016
Antihypertensive	*In vitro*	Poultry viscera	Autolytic digestion	Ala-Arg-Ile-Tyr-His Leu-Arg-Lys-Gly-Asn-Leu-Glu Arg-Val-Trp-Cys-Pro	Mane & Jamdar, 2017
Antioxidant	*In vitro*	Chicken bones	Multienzyme hydrolysis (Papain, neutral Proteases and Trypsin)	3 000 Da to 10 000 Da	Nie et al., 2017
Hepatoprotective effect	Animal study	Chicken liver	Hydrolysis with pepsin	Taurine (365.57 mg/100 g) Carnosine (14.03 mg/100 g) Anserine (151.58 mg/100 g)	Chen et al., 2017
Hepatoprotective effect	Animal study	Chicken liver	Hydrolysis with pepsin	Taurine (440.07 mg/100 g) Carnosine (16.94 mg/100 g) Anserine (207.16 mg/100 g)	Lin et al., 2017
Antihypertensive	Animal study	Chicken legs	Hydrolysis with Protamex	Total protein (0.67 %) Moisture (98.63 %) Ashes (0.17 %)	Mas-Capdevila et al., 2018
Antihypertensive	Animal study	Chicken legs	Hydrolysis with Protamex	Isoleucine (28.18 mg/g) Proline (22.2 mg/g) Leucine (41.07 mg/g)	Mas-Capdevila et al., 2019a
Antihypertensive	Animal study	Chicken legs	Hydrolysis with Protamex	Ala-Val-Phe-Gln-His-Asn-Cys-Gln-Glu	Mas-Capdevila et al., 2019b
Antihypertensive	*In vitro*	Chicken legs	Hydrolysis with Protamex	Ala-Val-Phe-Gln-His-Asn-Cys-Gln-Glu Gln-Gly-Pro-Leu-Ile-Gly-Arg-Tyr-Arg-Cys-Gly	Bravo et al., 2019
Antihypertensive	Animal study	Chicken legs	Synthesized by CASLO Aps.	Ala-Val-Phe-Gln-His-Asn-Cys-Gln-Glu	(Mas-Capdevila et al., 2020)
Cardiac protection	Animal study	Chicken liver	Hydrolysis with Pepsin	Taurine (308.10 mg/100 g) Anserine (126.02 mg/100 g)	(Y. H. S. Wu et al., 2020)

The amino acid content is reported in mg/100 mg hydrolyzed

peroxidase (GPx) mainly in the liver and kidney (Chou et al., 2014). It has been found that GSH is derived from three types of AAs (Cys, Glu and Gly), and is the main endogenous antioxidant (Yuan & Kaplowitz, 2009). The increase in endogenous antioxidant activity is mainly attributed to the content of Cys, Glu, and Gly. GSH regulates cell and redox signaling. It protects cells against oxidative damage by reducing H_2O_2 and eliminating reactive oxygen and nitrogen radicals (Yuan & Kaplowitz, 2009). Therefore, it is suggested that peptides derived from poultry by-products may be suitable ingredients for the formulation of functional and nutraceutical foods that can potentially be used to prevent or control diseases associated with oxidative stress.

2.2. *Antihypertensive activity*

Antihypertensive activity has been associated with the ability of these peptides to inhibit angiotensin-converting enzyme (ACE), which

Table 2
Biological effect of dipeptides and amino acids present in the C-terminal and *N*-Terminal chains of hydrolysates and bioactive peptides obtained from poultry by-products.

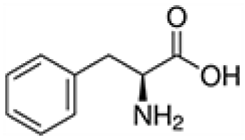
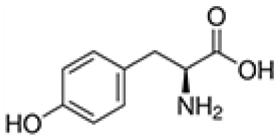
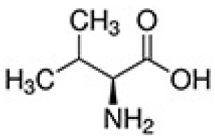
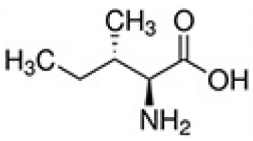
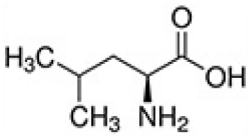
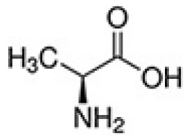
Aminoacid	Functional group/ types	Biological Activity	Reference
 **Phenylalanine, Phe, F** Phenylalanine, Phe, F	Benzene Aromatic Hydrophobic	Antioxidant Antihypertensive	Zheng et al., 2016Kapel et al., 2006
 **Tyrosine, Tyr, Y** Tyrosine, Tyr, Y	Phenol Aromatic polar	Antioxidant Antihypertensive	Zheng et al., 2016Kapel et al., 2006
 **Valine, Val, V** Valine, Val, V	Ibutane Hydrophobic	Antioxidant Antihypertensive Lipid regulatory	Wu et al., 2020Bravo et al., 2019
 **Isoleucine, Ile, I** Isoleucine, Ile, I	Ibutane Hydrophobic	Antioxidant Antihypertensive Lipid regulatory	Wu et al., 2020Bravo et al., 2019
 **Leucine, Leu, L** Leucine, Leu, L	Ibutane Hydrophobic	Antioxidant Lipid regulatory Cardioprotective effect	Chou et al., 2014Ren et al., 2008Wu et al., 2020
 **Alanine, Ala, A** Alanine, Ala, A	Ibutane Hydrophobic	Lipid regulatory Antihypertensive Cardioprotective effect	Khiari et al., 2014Soladoye, 2014Wu et al., 2020
	Hydrophobic		Bravo et al., 2019Khiari et al., 2014

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Table 2 (*continued*)

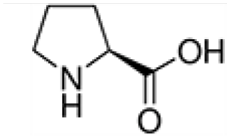
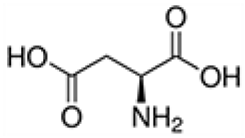
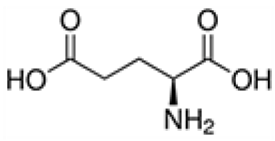
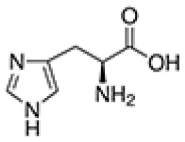
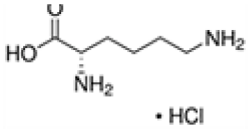
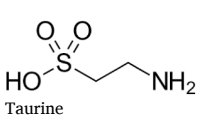
Aminoacid	Functional group/ types	Biological Activity	Reference
 **Proline, Pro, P** Proline, Pro, P		Antihypertensive Lipid regulatory	
 **Aspartic acid, Asp, D** Aspartic acid, Asp, D	Acetate ion Charged (-)	Antioxidant Lipid regulatory Cardioprotective effect	Wu et al., 2020Ren et al., 2008Wu et al., 2020
 **Glutamic acid, Glu, E** Glutamic acid, Glu, E	Acetate ion Charged (-)	Antioxidant Lipid regulatory Cardioprotective effect	Yuan & Kaplowitz, 2009Ren et al., 2008Wu et al., 2020
 **Histidine, His, H** Histidine, His, H	Imidazole Aromatic polar	Antioxidant Cardioprotective effect Hepatoprotective effect	Chou et al., 2014Wu et al., 2020Lin et al., 2017
 **Lysine, Lys, K** Lysine, Lys, K	Metylammonium Charged (+)	Lipid regulatory	Khiari et al., 2014
 Taurine	-acidic sulfonic group (R-SO3H) - alkaline amino group (NH2)	Antioxidant Lipid regulatory Cardioprotective effect Hepatoprotective effect	Chou et al., 2014Yang et al., 2014Wu et al., 2020Lin et al., 2017
	Imidazole Aromatic polar	Antioxidant Lipid regulatory Hepatoprotective effect	Chou et al., 2014Yang et al., 2014Chen et al., 2017

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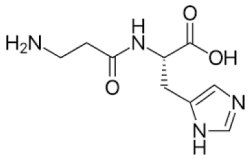
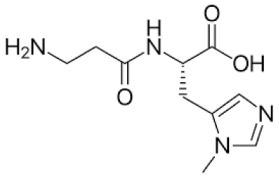
Table 2 (*continued*)

Aminoacid	Functional group/ types	Biological Activity	Reference
 **Carnosine** Carnosine	Imidazole Aromatic polar	Antioxidant Lipid regulatory Cardioprotective effect Hepatoprotective effect	Chou et al., 2014Yang et al., 2014Wu et al., 2020Lin et al., 2017
 **Anserine** Anserine			

plays an important role in the regulation of blood pressure, and is the main mechanism of the proposed action. In general, drugs indiscriminately block ACE and interfere with its activity, and ACE inhibitor peptides competitively block the binding of angiotensin I to ACE, thus inhibiting the formation of angiotensin II, a potent vasoconstrictor (Mas-Capdevila et al., 2018).

The action of these peptides is attributed to the presence of some aromatic and aliphatic AAs, such as Pro, Phe, or Tyr, in the C-terminal position and Val or Ile in the *N*-terminal position (Kapel et al., 2006), Hydrophobic AAs, such as Pro or Ala (Soladoye, 2014; Wada & Lönnerdal, 2014), can interact hydrophobically in the subsites (S1, S′1, and S′2) of the active site of ACE, thus inhibiting its activity, acting as an antihypertensive agent and regulator of blood pressure.

For most studies, the antihypertensive activity of the peptides is generally investigated as the half-maximal inhibitory concentration (IC_{50}) in animal models for the control of blood pressure (Xing et al., 2019a). The peptides Ala-Arg-Ile-Tyr-His, Leu-Arg-Lys-Gly-Asn-Leu-Glu, and Arg-Val-Trp-Cys-Pro ace inhibitors were isolated from hydrolysates of poultry viscera proteins with IC_{50} values of 0.009, 0.009, and 0.005 mg/ml, respectively (Mane & Jamdar, 2017); peptides < 3000 Da from chicken and hen skin showed ACE inhibitory activities of 88.21% and 86.46%, respectively (Yusop et al., 2016), and peptides < 1000 Da derived from chicken skin generated an antihypertensive effect by inhibiting ACE with an IC_{50} values of 0.36 mg/ml (Onuh et al., 2015) (Table 1).

In a study of antihypertensive activity in murine models, it was determined that peptides < 1000 Da derived from chicken skin with high hydrophobic AA content reduced systolic blood pressure in spontaneously hypertensive rats (SHRs) with an oral dose of 100 mg of peptides/kg of body weight (Onuh et al.,2015). Likewise, the antihypertensive effect was determined using hydrolyzed chicken legs (Hpp11) at different concentrations to correlate the effective amount in the short and long term and to establish possible mechanisms of action (Bravo et al., 2019; Mas-Capdevila et al., 2018). Administration of HP11 at a dose of 55 mg/kg caused a decrease in systolic blood pressure with a peak at 6 h post administration in SHRs, a behavior similar to that of captopril (50 mg/kg), and a 21% reduction in plasma ACE activity was observed (Mas-Capdevila et al., 2018).

Metabolic profiles have been determined in plasma and urine of SHRs treated with chicken skin protein hydrolysates to establish possible biomarkers of blood pressure regulation (Onuh et al., 2016). Metabolites presented as symmetric dimethylarginine, N_2-acetyl-L-ornithine, buthionine sulfoximine, uric acid, α-tocopherol succinate, L-isoleucine, creatinine, and phospholipids play key roles within the physiologic and metabolic pathways *in vivo* and are implicated as biomarkers of NO (nitric oxide) availability, various cardiovascular diseases, hypertension, endothelial dysfunction, and kidney function (Hsu, Huang, Lau, Lin, & Tain, 2012; Onuh & Aluko, 2019).

Peptides can also influence blood pressure through mechanisms other than ACE inhibition, which are related to the expression of genes involved in the alteration of endothelial function that stimulates the production of vasoconstrictors and pro-inflammatory agents in an oxidative stress environment (Yanai et al., 2008). It has been reported that carnosine can regulate the production of factors derived from the endothelium by reducing oxidative stress, which leads to a decrease in blood pressure (Chakrabarti & Wu, 2016).

Based on the above, it was determined that the oral administration of Hpp11 peptides at 55 mg/kg in hypertensive rats on a cafeteria diet, decreased the gene expression of ET-1 (endothelin-1), one of the strongest vasoconstrictors known, and induced the positive regulation of NOX4 (NADPH oxidase-4) and NO enhancers of Sirt-1 (Sirtuin-1), which promotes inhibition of the activity of NADPH oxidase (NOX), which is known to be a producer of ROS, which suggests a vasoprotective effect; in addition, it increased levels of hepatic GSH (Mas-Capdevila et al., 2019a). On the other hand, to demonstrate the participation of NO in the antihypertensive effect, oral administration of the peptide Ala-Val-Phe-Gln-His-Asn-Cys-Gln-Glu derived from Hpp11 at doses of 10 mg/kg in rats negatively regulated the expression of the aortic gene of the vasoconstrictor factor ET-1 and the main endothelial producer of NOX4 free radicals (Mas-Capdevila et al., 2019b). In addition, it was determined that the Ala-Val-Phe-Gln-His-Asn-Cys-Gln-Glu peptide requires absorption to have an effect on blood pressure, demonstrating that its antihypertensive effect is mediated by NO through its interaction with opioid receptors (Mas-Capdevila et al., 2020). Some bioactive peptides could mediate their physiologic effects through binding to receptors present in the intestinal wall (Hernández-Ledesma et al., 2011). It has been shown that some opioid peptides are not absorbed and can produce their biological effects through interaction with opioid receptors (μ, δ, and κ), which have been described in several tissues, including the gastrointestinal tract; this implies that their absorption is not required (Holzer, 2009; Miner-Williams et al., 2014). Therefore, it is suggested that peptides from poultry by-products could be used as ingredients in the

development of nutraceuticals and functional foods for the management of hypertension.

2.3. Lipid regulatory activity

The lipid regulatory activity is mainly attributed to the profile of AAs (Asp and Glu) and the hydrophobic (Ile, Leu, Val) AA profile, which show high antioxidant capacities (Ren et al., 2008; Saiga et al., 2008); the content of taurine, carnosine, and anserine in peptides has an inhibitory effect on lipase activity and a high binding capacity with bile acids due to its hydrophobic nature (Yang et al., 2014). cLHs that present high concentrations of taurine (350 mg/100 g), carnosine (194 mg/100 g), and anserine (18.9 mg/100 g) (Yang et al., 2014) and peptides from 555.26 Da to 2 093.74 Da obtained from turkey heads (Khiari et al., 2014) showed lipid regulatory activity *in vitro* by inhibiting the lipase enzyme and its binding capacity with bile acid. Pancreatic lipase is a key enzyme in the absorption of triacylglycerol in the diet because it hydrolyzes triacylglycerols to 2-monoacylglycerol and fatty acids; therefore, inhibition of lipase activity is often discussed in anti-obesity studies (Yang et al., 2014). On the other hand, it is argued that peptides with high binding capacity with bile acid block the reabsorption of bile acid and, therefore, lower the level of cholesterol in the blood (Iwami et al., 1986). The binding of bile acid is mainly due to the hydrophobic interactions of the AAs present in the terminal chains and their binding capacity (Kern et al., 1978). The *in vivo* biological effect of cLH has been evaluated in hamsters on a high-fat diet, which was shown to have a regulatory effect on the genes involved in lipid metabolism, as well as a protective effect. (Yang et al., 2014).

Peptides < 10,000 Da derived from Chicken liver hydrolysates (generated negative regulation of the genes involved in lipogenesis such as acetyl-CoA carboxylase (ACC), fatty acid synthase (FAS), 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMG-CoA reductase), sterol regulatory element-binding protein-1c (SREBP-1c), and sterol regulatory element-binding protein-2 (SREBP-2), as well as positive regulation of genes involved in energy metabolism such as peroxisome proliferator-activated receptors (PPARα), peroxisome proliferator-activated receptors (RXRα), carnitine palmitoyltransferase 1 (CPT1) and uncoupling protein 2 (UCP2) and LDL receptor (LDLR), cholesterol 7 alpha-hydroxylase (CYP7A1), genes involved in cholesterol metabolism, resulting in increased serum cholesterol clearance/catabolism and energy expenditure (Chang et al., 2011). SREBP1c is the transcription factor for lipogenesis, and the expression of SREBP2 and HMG-CoA reductase is related to cholesterol biosynthesis and CYP7A1 to catabolism (Yang et al., 2014); increase in the expression of the genes PPAR-α, RXRα, UCP2 results in greater oxidation of fatty acids in the liver (Seo et al., 2008); RXRα is a transcription factor and can form a heterodimer with PPAR-α, thus promoting the expression of the target gene PPAR-α, involved in the oxidation and activation of genes related to the catabolism of fatty acids (Sandoval et al., 2009). In the same way, a protective effect is related to the increase in endogenous antioxidant activity (SOD, CAT, GPx, GSH), reduction of total cholesterol and triglycerides, reduction of oxidizing substances (TBARS) and inflammatory cytokines, tumor necrosis factor-α (TNF-α), and interleukin-1 β (IL-1β).

On the other hand, alteration of lipid homeostasis induced by a high-fat diet can lead to the generation of cardiorenal syndrome (Nishi et al., 2019; Ren & Xu, 2015), a pathologic process related to a signaling cascade that promotes the autophagy-lysosomal pathway. cLH was shown to exert a cardioprotective effect by blocking the autophagy pathway at an early stage, which could lead to normal cardiac regulation in mice. This effect is attributed to a combination of its hepatic lipid-lowering effect and systemic antioxidation, mainly associated with the content of different bioactive substances such as anserine, taurine, glutamic acid, aspartic acid, branched chain AAs, α-alanine and histidine, and the presence of antioxidant minerals (*e.g.*, Mn, Zn, and Se) in the hydrolysates (Wu et al., 2020).

2.4. Hepatoprotective effect

The liver is the main organ affected when there are metabolic changes generated by different factors such as central obesity, type II diabetes mellitus, hypertension, hyperglycemia, and hyperlipidemia (Sanches et al., 2015), These changes trigger an imbalance in the biochemical reactions that occur in the liver, affecting other metabolisms (lipids, glucose, etc.), which leads to the development of chronic degenerative diseases. The hepatoprotective effect of chicken by-product peptides was determined in murine models induced with liver fibrosis (Chen et al., 2017) and alcoholic fatty liver (Lin et al., 2017). The main mechanisms of action involve (1) regulation of lipid homeostasis through the regulation of genes that participate in the β-oxidation of fatty acids and lipogenesis, (2) decrease in lipid peroxidation through the improvement in antioxidant enzymatic activities (SOD and CAT), (3) improvement in the expression of genes related to the pathologies evaluated, and (4) decrease in hepatic inflammatory responses (IL-1β and TNF-α). It was determined that cLH generate a regulatory effect of genes involved in liver fibrosis through the transforming growth factor-beta (TGF-β) pathway with negative expression of genes such as a member of the SMAD 4 (SMAD4) family, connective tissue growth factor (CTGF), collagen type I alpha (Col1α), and smooth muscle actin alpha (αSMA). CTGF is a protein secreted by human endothelial cells; the relationship between CTGF and some organ fibrogenesis, such as liver, lung, and kidney, has been demonstrated. Protein expression of αSMA is associated with decreased activation of hepatic stellate cells (HSCs). HSCs favor the expression of αSMA, which regulates the production of type I collagen through the expression of Col1α (Friedman, 2008).

The protective effect of cLH on liver damage was attributed to regulation of the inflammatory response and decreased collagen accumulation, referring to the modulation of genes that are expressed in liver fibrosis (Chen et al., 2017). Similarly, cLH favors the positive regulation of genes involved in the β-oxidation of fatty acids (PPAR-α, CPT1b, CPT2, and UCP2). The negative expression of genes (SREBP1-c, ACC1, FAS, and SCD1) related to lipogenesis and genes involved in the development of alcoholic fatty liver generated an increase in the enzymatic activity of aldehyde dehydrogenase (ALDH), which plays an important role in the conversion of ethanol to acetic acid, after being metabolized into acetaldehyde by the enzyme alcohol dehydrogenase (ADH) in the liver (Lieber, 1993; Lin et al., 2017).

cLHs with a hepatoprotective effect are characterized by high concentrations of taurine (365.57 mg/100 g and 440.07 mg/100 g), carnosine 14.03 mg/100 g and 16.94 mg/100 g) and anserine (151.58 mg/100 g and 207.16 mg/100 g) (Chen et al., 2017; Lin et al., 2017). The presence of taurine (Tau) could be directly related to the hepatoprotective effect of hydrolyzed chicken by-products. It has been determined that the consumption of Tau generates a preventive effect on the development of hepatic steatosis induced by a high-fat/cholesterol diet in a hamster model by regulating the expression of PPAR-α and UCP2 (Chang et al., 2011). The protective effect of hydrolysates is also related to the content of carnosine and anserine, natural dipeptides that contain His, derived from meat and that have strong antioxidant and lipid-lowering capacity (Mong et al., 2011). The lipid-lowering effect of Tau and carnosine has been demonstrated through a decrease in the expression of SREBP-1c, ACC, and FAS in murine models fed a high-fat diet. In addition, the consumption of His and carnosine showed a therapeutic effect on hepatic steatosis in mice fed a diet high in saturated fat through the negative regulation of FAS, SREBP1c, and SREBP-2 (Mong et al., 2011).

2.5. Bioaccessibility/bioavailability of bioactive peptides from poultry and by-products

Implementation of a peptides' potential biological effect depends largely on its ability to remain intact until it reaches the target organ (Segura-campos et al., 2010; Segura-Campos et al., 2011). The structural

integrity of peptides must be maintained during digestion and transport (Udenigwe & Fogliano, 2017). During digestion, proteolytic gastrointestinal enzymes release peptides and AA sequences that were inactive in the core of the source protein but can exhibit special properties once released (Segura-Campos et al., 2011). The activity of the ACE inhibitory peptide (<3 kDa) obtained from duck meat increased significantly by 9.08% after *in vitro* digestion. The peptides were cleaved into smaller fragments after digestion and led to greater exposure of hydrophobic residues, which can favor their biological activity (Shi et al., 2019). High permeability of the ACE inhibitor peptide (Lys-Pro-Leu-Leu) obtained from cooked chicken breast was determined by *in vitro* gastrointestinal digestion using the Caco-2 cell model system (Sangsawad et al., 2018). In a related work, it was determined that cooking process does not affect the bioactivity of the peptides extracted from chicken breast muscle; however, the antioxidant activity increased when simulated gastrointestinal digestion was performed (Xiao et al., 2020a). They also determined that the muscle hydrolyzes of the chicken breast have high stability against physicochemical treatments and the simulation of gastrointestinal digestion, which allowed obtaining a functional ingredient that allows the activation of dehydrogenase alcohol (ADH) and the improvement of the hepatic injury induced by alcohol (Xiao et al., 2020b).

The peptides have remarkably low oral bioavailability (Segura-campos et al., 2010; Udenigwe & Fogliano, 2017). However, there is concrete evidence that supports the transport of orally consumed food peptides to the bloodstream in animals and humans (Caira et al., 2016; Sánchez-Rivera et al., 2014). Carnosine (β-alanyl-L-histidine), which is a highly concentrated dipeptide in the skeletal muscles of poultry and its by-products, has presented high bioavailability capable of reaching the blood in intact form by absorption through the gastrointestinal tract (Xing et al., 2019b). Regarding its bioaccessibility, Marcolini et al. (2015) determined that carnosine is easily released from the food matrix after digestion within the gastrointestinal tract, favoring its bioavailability and optimal absorption. Thus, carnosine absorption is mediated mainly through peptide transporters coupled to protons PepT1 in the small intestine (Son et al., 2004).

2.6. Possible applications of bioactive peptides in the food, pharmaceutical, and cosmetic industries

Bioactive peptides in the food industry are considered promising ingredients or additives for incorporation into novel foods (Lafarga et al., 2017), due to the different biological functions that they can perform at a systematic level, in addition to the fact that they have been found to favor human health. These compounds can be used to obtain functional foods (Neyra, 2017) and nutraceutical products (Sandoval-Peraza et al., 2017). The most recent research involves oral administration of hydrolyzed cartilage extract in the prevention of osteoarthritis (Ma et al., 2021). Studies have also shown effects in the prevention of cardiovascular diseases (Wu et al., 2020) and chronic liver diseases (Chen et al., 2017; Lin et al., 2017; Wu et al., 2021), in antihypertensive treatments (Bravo et al., 2019; Mas-Capdevila et al., 2020), in the regulation of lipid metabolism as alternative treatments for obesity (Yang et al., 2014) and to obtain antioxidant agents (Chou et al., 2014).

Bioactive peptides are currently used by pharmaceutical companies for health promotion (Lafarga et al., 2017). There are more than 60 medicines on the market that incorporate hydrolysates of other by-products of animal origin as well as nutraceutical products such as Valtyron (a patent-protected peptide extract made from the hydrolyzed protein found in sardine muscle), which contains dipeptides Val-Tyr, and Calpis sour milk containing tripeptides Ile-Pro-Pro and Val-Prol-Prol, which lowers blood pressure after oral administration in hypertensive patients (Fosgerau & Hoffmann, 2015).

Another approach regarding the use of hydrolysates and peptides is directed to the area of cosmetology and beauty. Oral administration of a hydrolyzed chicken sternal cartilage extract (BioCell Collagen) was recently shown to reduce UVB-induced photoaging in mice (Phipps et al., 2020). Topical anti-aging products have been obtained from low molecular weight keratins from poultry feathers (Yeo et al., 2018). Other products include a mild shampoo and a conditioner by adding peptides (800 to 1079 kDa) of chicken feather keratin, which have been shown to be highly effective on the hydration of hair fibers leading to a significant increase in shine and softness (Villa et al., 2013). In general, there has been great interest in the use of poultry by-products as promising sources of bioactive peptides and their application in various areas. However, there is a lack of studies related to the bioavailability and bioavailability of peptides obtained from shrimp by-products, four models are used to evaluate the bioavailability: *in vitro* (simulated gastrointestinal digestion using intestinal epithelial Caco-2 cell cultures); *ex vivo* (gastrointestinal organs or organoids in laboratory conditions); *in situ* (intestinal perfusion in animals) and *in vivo* (animal studies and human studies), (Pateiro et al., 2020). Therefore, future studies should focus in new perspectives on bioavailability and biodestibility studies.

3. Conclusions

Existing research on the peptides obtained from different poultry by-products and their biological activity shows the feasibility of taking advantage of these by-products and application of these molecules of interest as functional ingredients in the food industry and as health protective agents in the pharmaceutical industry. However, the *in vivo* mechanisms of action of peptides derived from poultry by-products are not yet clearly established, so it is imperative to continue evaluating the possible mechanisms of action involved, as well as the specific structural characteristics of peptides that promote gastric stability, intestinal absorption, cellular uptake, distribution, as well as the biological half-life of bioactive peptides in target tissues and cells after oral ingestion.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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