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Chicken slaughterhouse by-products: A source of protein hydrolysates to manage non-communicable diseases

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ABSTRACT

Background: The poultry industry is a growing livestock sector, which generates large volumes of by-products with negative environmental impacts that must be revalorized. Modern lifestyles have contributed to a significant increase in the incidence of non-communicable diseases worldwide. Thus, many efforts have been made to identify novel agents with biological activities. In this regard, chicken slaughterhouse by-products are interesting materials because of their protein content, which can be subjected to proteolytic procedures to obtain bioactive peptides.

Scope and approach: This review focuses on the valorization of chicken slaughterhouse by-products as a source of functional protein hydrolysates and peptides; specifically, it reviews the potential of these compounds to manage non-communicable diseases and the mechanisms involved.

Key findings and conclusions: Hydrolysates obtained from chicken slaughterhouse by-products have antioxidant, antidiabetic, anti-inflammatory, anti-coagulant, anti-anaemic, cardioprotective, hepatoprotective, and neuroprotective properties, as well as the ability to manage body weight and lipid metabolism. Antioxidant and antihypertensive effects were the activities most studied in both *in vitro* and *in vivo*; however, only a chicken leg-derived hydrolysate was tested in humans, demonstrating its blood pressure-lowering effects. The obtained results are promising enough to encourage further research to explore the versatility of chicken by-products as a source of bioactive peptides.

1. Introduction

The incidence of chronic diseases has increased worldwide during the last decades, and this growing trend is projected to be maintained during the forthcoming years. These non-communicable conditions are strongly correlated with risk factors, such as hypertension, oxidative stress, and inflammatory processes (Hajat & Stein, 2018). Therefore, there is a huge interest in the development of novel strategies, which could help prevent or ameliorate the onset or progression of these diseases. In this context, there is strong evidence that different compounds present in food or natural sources could exert these desired effects, overcoming some side or adverse effects of existing therapeutic treatments (Rezvankhah, Yarmand, Ghanbarzadeh, & Mirzaee, 2021). In this regard, bioactive peptides, a relevant group of dietary-derived compounds, are promising candidates.

Bioactive peptides are specific protein fragments of small length (2–20 amino acid residues) that, when released from the native protein by intentional methods including fermentation and hydrolysis (enzymatic or chemical), as well as by unintentional methods, such as gastrointestinal digestion or food technological processes, exert

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interesting biological activities (Korhonen & Pihlanto, 2006; Nikhita & Sachindra, 2021). Food of animal origin is rich in proteins and is considered an excellent source of bioactive peptides (Borrajo et al., 2019; Mora, Gallego, & Toldrá, 2018). A recent peptidomic study revealed that *in vitro* gastrointestinal digestion of meat proteins from different sources generated a high number of peptides capable of inhibiting dipeptidyl peptidase IV (DPP-IV) and angiotensin-converting enzyme (ACE), which are crucial for the management of diabetes and hypertension, respectively (Martini, Conte, & Tagliazucchi, 2019). According to this aforementioned study, chicken meat seems to be a better potential protein source for antioxidant peptides than pork meat, and is a source of ACE inhibitory (ACEi) peptides that are more active than the peptides released from turkey and pork meat. Other studies have also obtained peptides with *in vitro* antioxidant, ACEi, alcohol dehydrogenase-activating, bile acid-binding or anti-inflammatory activities from chicken breast muscle or spent hen muscle subjected to different hydrolysis conditions (Hamzeh, Sangsawad, Noisa, Choowongkomon, & Yongsawatdigul, 2022; Saiga et al., 2003; Wu, Lin, et al., 2020; Xiao et al., 2020; Sun et al., 2012; Yu, Field, & Wu, 2018). Moreover, chicken protein hydrolysates showed beneficial effects in different animal models, including the reduction of high blood pressure (BP), decreased oxidative stress, stimulation of interleukin (IL) 1, amelioration of acute alcohol-induced liver injury, and reduction of serum total cholesterol (TC) (Fan et al., 2022; Fu, Therkildsen, Aluko, & Lametsch, 2019; Udenigwe et al., 2017; Wu, Lin, et al., 2020; Xiao, Zhou, Zhao, Su, & Sun, 2018).

In addition, agro-food industry by-products have emerged as an important source of bioactive peptides (Le Gouic, Harnedy, & FitzGerald, 2018). Their use for this purpose provides an excellent opportunity to valorize them, generating value-added products within the principles of a circular economy. In this sense, the meat industry is a relevant sector, the by-products of which have a significant impact, and their management must be improved to ameliorate this growing problem (Li, Arulnathan, Heidari, & Pelletier, 2022). For instance, chicken meat industry, which represented the 36% of global meat production in 2020, generates approximately 25–30% of the live chicken weight in by-products, being the chicken meat production of over 80.2 million metric tons in 2021 (Food and Agriculture Organization of the United Nations, 2013; 2022). Chicken slaughterhouse by-products are rich in proteins, including collagen, and keratin (Bravo et al., 2023). Different studies have confirmed that collagen is an excellent source of peptides with a wide range of bioactivities including lipid-lowering, metal--chelating, antioxidant, antidiabetic, immune modulation, and ACEi (Fu et al., 2019).

Given the importance of reducing the incidence of non-communicable diseases and valorizing food industry by-products, which are rich in proteins containing bioactive peptides, this review focuses on collecting the existing evidence regarding the functional properties of the hydrolysates related to non-communicable diseases and peptides obtained from chicken slaughterhouse wastes.

2. Poultry industry and chicken slaughterhouse by-products

Poultry farming is one of the most potent livestock sectors, because avian foodstuffs constitute a key source of high-quality protein for the human diet. Environmentalist, vegan, and vegetarian currents are being consolidated during the last decades, as well as plant-based diets; however, the global production and consumption of poultry meat are still steadily growing. In fact, more than 100,000 tons of chicken meat and 70 million tons of eggs are annually produced worldwide, followed by an upward trend during recent years, and is projected as the livestock segment with the highest growth rate until 2050 (Kanani, Heidari, Gilroyed, & Pelletier, 2020; Laca, Laca, & Diaz, 2021; Li et al., 2022). Thus, the impact of poultry waste on the environment is growing along with the soaring production numbers and, although in a lower amount than other livestock species, it generates greenhouse gases in form of respiratory CO_2, manure CH_4 and N_2O emissions, being produced 61, 0.97 and 0.57 million metric tons per year, respectively (Seidavi, Zaker-Esteghamati, & Scanes, 2019). In addition to chicken excreta and focusing on chicken meat production, diverse slaughterhouse by-products are released during the production of broiler meat. Thus, reutilization strategies to revalorize these materials have been proposed, developed, and encouraged, because compensation is offered to poultry farmers that implement sustainable activities in several countries (Tao & Wang, 2020).

The principles of a circular economy lead to reduce waste accumulation and pollution, and create value-added products. Normally, the most widespread approaches are related to the reuse of poultry by-products (from farms, slaughterhouses, industrial facilities, etc.) as fertilizers or compost because of their interesting carbon and amino acid contents, but with the disadvantage of high nitrogen concentration, although they can be easily treated and processed to design biostimulators that have proven their efficacy on plants (Chiarelotto, Restrepo, Lorin, & Damaceno, 2021; Izydorczyk et al., 2022). Furthermore, in line with the adoption of renewable energy sources, chicken slaughterhouse leftovers have been subjected to specific operations (including hydrolysis, acidogenesis, acetogenesis, and methanogenesis) to produce biogas, and therefore, electricity (Arshad et al., 2018; Siddiki et al., 2021). Even the textile industry has taken advantage of recycled poultry materials because chicken feather wastes can be processed to produce keratin filaments with enhanced properties such as higher ductility, compared to natural feathers (Mi et al., 2020). Moreover, different poultry by-products, such as blood or bones, are usually used for animal feed, as mentioned in Section 3. In addition, other studies have focused on the valorization of these by-products into high-value products. These by-products are rich in proteins, with the collagen being one of the major proteins in some of these by-products (Bravo et al., 2023). Given the beneficial effects of collagen, some studies have focused on developing methods to extract collagen from chicken feet, bones, skin, and sternal cartilage (Akram & Zhang, 2020; Cao & Xu, 2008; Cliche, Amiot, Avezard, & Gariepy, 2003; Matinong, Chisti, Pickering, & Haverkamp, 2022; Munasinghe, Schwarz, & Nyame, 2014; Potti & Fahad, 2017). Finally, it is worth mentioning that they have been widely used for the production of bioactive peptides (explained in Section 4.2) that could be used in animal feed and human nutrition to prevent non-communicable diseases (Bravo et al., 2023), which could be useful for valorizing these by-products.

3. Chicken slaughterhouse by-products

Diverse slaughterhouse by-products are released during the production of broiler meat, including blood, feathers, bones, legs (feet), blood, crests, beaks, skin, and viscera. Fig. 1 summarizes the main characteristics of these by-products. In this review, egg-derived by-products and spent egg-laying hens were not considered, since they are not directly generated in slaughterhouses (Fan & Wu, 2022; Quina et al., 2014).

3.1. Blood

Chicken blood represents approximately 6–7.5% of the live animal weight (Kelly & Alworth, 2013). Despite its high protein content (80–90% in dried whole blood, with high amounts of Arg, Thr, Tyr, and Ile), it is mostly converted to animal feed or inexpensive food products as 'blood cubes' particularly in Asian countries as a source not only of protein but also iron (Sorapukdee & Narunatsopanon, 2017; Wongngam, Mitani, Katayama, Nakamura, & Yongsawatdigul, 2020). Other minor components are fat (7–8%) and carbohydrates (7–8%) (Huang & Liu, 2010).

By-product	Blood	Bones	Feathers	Feet	Skin	Viscera
% of animal (w/w)	6-7.5	-	10	-	8-20	30
% Protein	80-90	25	90	75	8-12	90
Main protein	Hemoglobin	Collagen	Keratin	Collagen	Collagen	-

Fig. 1. Schematic representation of the main characteristics of chicken slaughterhouse by-products.

3.2. Bones and cartilages

Chicken bones are complex materials that are mainly formed by collagen surrounded by 'bone minerals' (modified forms of calcium apatite or hydroxyapatite) and fat. The organic part of the bone is mostly protein (70% of the organic part and up to 35% of the bone), with mostly collagen (approximately 90%, rich in Pro and Gly) (Cansu & Boran, 2015). Poultry components with higher bone share include carcasses, backs, necks, legs, and wings, among others. Normally, bone residues can be used for animal feed as well as for human diet and are traditionally added to soups and broths (Cansu & Boran, 2015; Polyanskikh, Danyliv, Dubrovina, Ozherelyeva, & Vasilenko, 2020).

Besides bones and related to them, cartilages are interesting as they contain high amounts of type-2 collagen, which could be used for cartilage engineering approaches (Wu, Korntner, Mullen, & Zeugolis, 2021). Thus, different studies have been carried out to extract this collagen from chicken sternal cartilage using a multi-step process, which combines protein hydrolysis with other steps, such as precipitation and purification or ultrasound treatment (Akram & Zhang, 2020; Cao & Xu, 2008). Moreover, they contain bioactive compounds, highlighting glycosaminoglycans, such as hyaluronic acid or sulfated glycosaminoglycans such as chondroitin sulfate (Narayanaswamy, Kanagesan, Pandurangan, & Padmanabhan, 2016; Stiborova et al., 2020). The potent immunomodulatory effects of these molecules have directed research towards many functionalities, including anti-atherosclerosis, anti-osteoarthritis, and anti-aging (Stiborova et al., 2020). In chickens, an interesting cartilage type is the trachea. It contains approximately 70% protein and 16% fat (Pramualkijja, Pirak, & Euston, 2021) and is part of the solid waste from slaughterhouses, although it has a lower impact in terms of volume and weight than other chicken by-products.

3.3. Crest

Although chicken crests are usually consumed and can be found in numerous and varied recipes around the world, they are often discarded on many occasions, especially those from female animals that do not contain a significant amount of edible meat. Therefore, several studies have been conducted to provide additional value to these parts, targeting hyaluronic acid as a target molecule (Rosa et al., 2007; Severo da Rosa, Hoelzel, Viera, Barreto, & Beirão, 2008). This molecule has a potent antioxidant effect and good physicochemical properties which allow its biomedical applications in plastic, ocular, and osteoarthritis surgeries, as well as in tissue engineering (Sudha & Rose, 2014).

3.4. Feathers

Approximately 5 million tons of feathers are generated annually worldwide. Thus, there is a great interest in searching for new methods to valorize this by-product as an alternative to landfilling or incineration (Callegaro, Brandelli, & Daroit, 2019). Feathers represent up to 10% of the chicken's total weight and are composed of over 85–90% protein, with keratin as the major component (Fakhfakh et al., 2011; Taskin & Kurbanoglu, 2011). This structural protein is rich in Gly, Ala, Ser, Cys, Leu, Val, Arg, Ile, Phe and contains smaller proportions of Lys, Met, His and Trp. Due to its interesting protein and amino acidic composition, feather meal is used as feed supplement for animals (Adler, Slizyte, Honkapää, & Løes, 2018).

3.5. Legs and feet

Although they are used in some countries as part of traditional cuisine, in many others, they are discarded and considered as by-products (Potti & Fahad, 2017). The major constituents of this by-product are proteins (>75%), especially collagen (>50%), and fat (approx. 15%). Special attention has been devoted to collagen in terms of its technological and functional properties (Araújo, Lima, Pereira, & Madruga, 2019).

3.6. Skin

One of the chicken slaughterhouse by-products with the highest impact is chicken skin, which represents between 8 and 20% of chicken carcass weight (Heydarpour et al., 2006). It is usually underutilized despite its composition, containing 30–40% fat with high concentrations of n-3 and n-6 fatty acids, and 8–12% protein, which makes it a good source of collagen. Normally, this skin is easily and rapidly defatted, obtaining a protein content over 60% with abundance of hydrophobic amino acids (Fallah-Delavar & Farmani, 2018; Onuh, Girgih, Aluko, & Aliani, 2013). Several studies have focused on developing methods for extracting this collagen from this by-product (Cliche et al., 2003; Matinong et al., 2022; Munasinghe et al., 2014).

3.7. Viscera

More than 30% of poultry by-products are referred to as chicken viscera, which are the internal organs and materials that are not usually commercialized and are therefore discarded along the production chain. Although hearts, livers, and gizzards can be found in offal shops in some countries (Spain, Italy, and some African and Asian regions) (Babicz, Kropiwiec-Domańska, Skrzypczak, Szyndler-Nędza, & Szulc, 2020), they are less frequent and have a great impact on waste. Nevertheless, these chicken parts contain a relevant amount of high-value protein with a balanced amino acid profile and low carbohydrate content. Because of this composition, they have been widely used for animal feeding, particularly in aquaculture, to replace fish flour. Interestingly, after processing and defatting viscera, the meal contains more than 90% protein and 22% lipids (Giri, Sahoo, & Mohanty, 2010; Oké, Olaniran Odountan, Abou, & Odountan, 2016).

4. Production and bioactivity of chicken slaughterhouse by-products

4.1. Production of chicken slaughterhouse by-products

Chicken slaughterhouse by-products, such as blood, bone, cartilage, comb, feather, feet, gizzard, liver, residues from mechanical chicken

deboning, skin, trachea, viscera, and wattle, were used as sources of bioactive peptides (Alahyaribeik, Nazarpour, Tabandeh, Honarbakhsh, & Sharifi, 2022; Bezerra et al., 2020; Chen et al., 2017; Gonçalves dos Santos Aguilar, Santos de Souza, & Soares de Castro, 2020; Lima et al., 2019; Mas-Capdevila, Pons, Aleixandre, Bravo, & Muguerza, 2018; Nie, Xu, Zhao, & Meng, 2017; Onuh et al., 2013; Yang et al., 2019; Zheng, Si, Ahmad, Li, & Zhang, 2018). These peptides were intentionally released from proteins contained in chicken by-products, mainly via enzymatic hydrolysis. Chemical hydrolysis using hydrochloric or sulfuric acid was also used for blood red cells and feathers, respectively (Ben Hamad Bouhamed, Krichen, & Kechaou, 2020; Nikhita & Sachindra, 2021).

Regarding the enzymatic process, different steps compromised the production of these bioactive peptides, which are contained in the elaborated protein hydrolysates (Fig. 2). Initially, chicken by-products were usually milled or ground to facilitate protein solubilization (Alahyaribeik et al., 2022; Mas-Capdevila et al., 2018; Yang, Lin, Liu, & Chen, 2014). Moreover, some were subjected to a lipid removal process using organic solvents (Alahyaribeik & Ullah, 2020; Onuh, Girgih, Aluko, & Aliani, 2014). Regarding blood, it was used directly to elaborate protein hydrolysates or subjected to centrifugation to obtain corpuscle and plasma fractions (Carrera-Alvarado, Toldrá, & Mora, 2022; Cheng, Lai, Lin, & Sakata, 2016). The next step was protein solubilization, which was performed by mixing the chicken by-products with water, and the resultant solution was heated or boiled (Carrera-Alvarado et al., 2022; Mas-Capdevila et al., 2018; Xiong et al., 2020). In this step, a particular by-product was the feather, as its proteins (mainly keratin) are difficult to solubilize. Thus, feathers were subjected to steam or temperature-pressure processes (Adler et al., 2018; Qin et al., 2022) or heated in a solution containing hydroxymethyl aminomethane, urea, ethylene diamine tetraacetic acid, and sodium sulfite to increase keratin solubility (Alahyaribeik et al., 2022; Alahyaribeik & Ullah, 2020). Finally, these protein solutions, with or without non-soluble residues, were hydrolyzed to obtain bioactive peptides. The most common method was using commercial enzymes, although some studies isolated proteases from feathers (Fakhfakh et al., 2011; Fontoura et al., 2014) and different *Bromelia* species (Romero-Garay et al., 2020). The most common enzymes used for this issue and in a variable concentration enzyme/substrate were Alcalase® and pepsin (Bjørndal et al., 2020; Chakka, Ramanatikara, Zituji, Pedda, & Narayan, 2021; Pramualkijja et al., 2021; Safar Razavizadeh, Farmani, & Motamedzadegan, 2022b; Yang et al., 2014), although enzymes such as trypsin, papain, Flavourzyme®, Protamex®, neutral Protease, Neutrase®, elastase, and collagenase, among others, were also used alone or in combination (Casanova-Martí et al., 2019; Mas-Capdevila et al., 2018; Nadalian, Kamaruzaman, Yusop, Babji, & Yusop, 2019; J. Yang et al., 2019; Zheng et al., 2018). The hydrolysis time varied between 30 min and 24 h (Casanova-Martí et al., 2019; Romero-Garay, Becerra-Verdín, Soto-Domínguez, Montalvo-González, & García-Magaña, 2022), with shorter times (1 and 2 h) being the most used (Aloysius et al., 2018; Bjørndal et al., 2020; Mas-Capdevila et al., 2018; K. T. Yang et al., 2014). In addition, fermentation using bacteria species, such as *Pedobacter* sp. *3.14.7, Bacillus pumilus strain A1,* or *Chryseobacteriumsp.kr6,* was the most used method for generating protein hydrolysates from feathers (Bezus et al., 2021; Fakhfakh et al., 2011; Fontoura et al., 2014). This is because these bacteria contain alkaline keratinases that allow the hydrolysis of feather keratin. However, this process appeared to be slower than hydrolysis with commercial enzymes, as it required hydrolysis times of 48 h (Alahyaribeik et al., 2022; Fontoura et al., 2014). Temperature and pH (less common) were mainly adjusted based on the manufacturer's description using the conditions in which enzymes are the most active or optimal bacterial growth conditions. For ending the hydrolysis/fermentative step, enzymes or bacteria were heat-inactivated at temperatures between 80 °C and 95 °C for 15–30 min. Finally, it is common to include a filtering or centrifugation step to remove the insoluble solids or bacteria (Mas-Capdevila et al., 2018). In some cases, an ultracentrifugation step is also included to obtain the 3–10 KDa fraction to purify and concentrate the bioactive peptides, obtaining peptide solutions with improved bioactivity compared to the initial hydrolysate ((Alahyaribeik et al., 2022; Inkanuwat et al., 2019; Zhang, Kouguchi, Shimizu, Ohmori, et al., 2010).

Once obtained, bioactivities of the hydrolysates were usually assessed *in vitro* and/or *in vivo* in its liquid format *or* by its resuspension

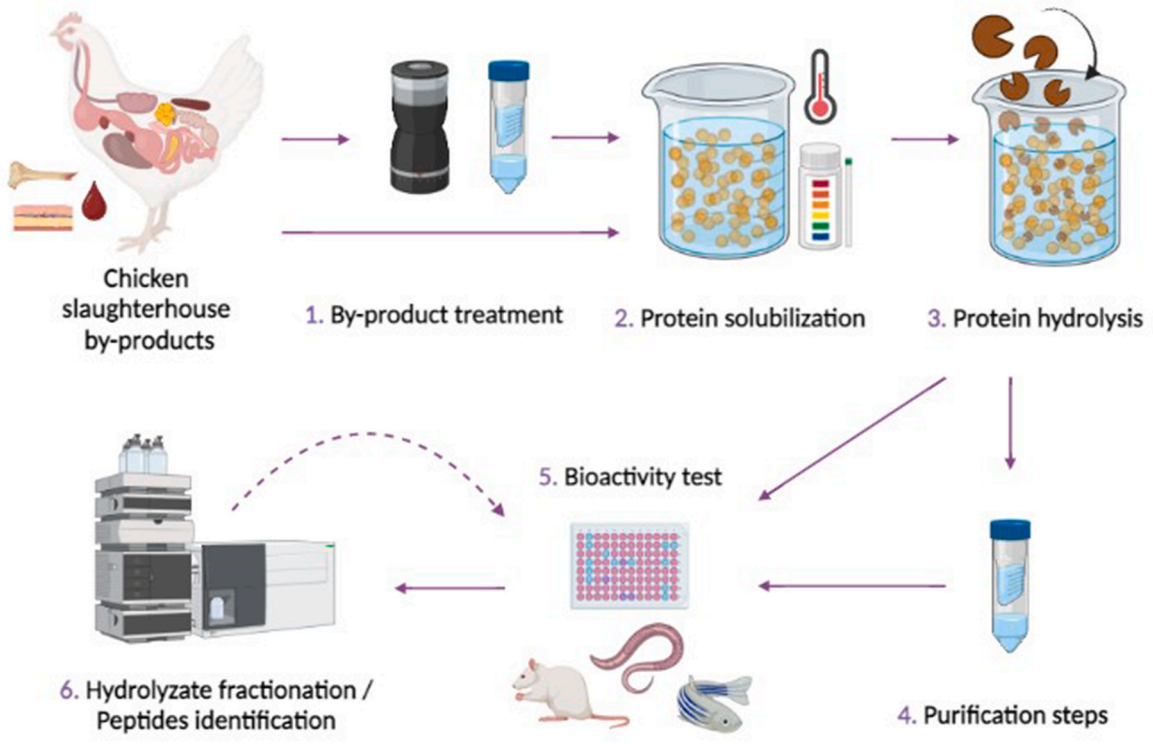

Fig. 2. Schematic representation of the main steps to prepare bioactive hydrolysates from chicken slaughterhouse by-products.Created with BioRender.com.

in water at the desired concentration after freeze-drying. Once the bioactivity was determined, subsequent purification steps, such as ultrafiltration with different molecular weight cutoff membranes followed by reverse-phase HPLC fractionation, were used for the isolation and identification of the bioactive peptides responsible for the bioactivity of the hydrolysate (Bravo, Mas-Capdevila, Margalef, Arola-Arnal, & Muguerza, 2019; Inkanuwat et al., 2019).

4.2. Bioactivity of chicken slaughterhouse by-products

4.2.1. Antioxidant effects

Oxidative stress plays an important role in the onset and/or progression of various non-communicable diseases, including cardiovascular, neurodegenerative, chronic kidney, and chronic obstructive pulmonary diseases, as well as atherosclerosis, cancer, and diabetes (Liguori et al., 2018). Oxidative stress refers to an imbalance between the generation of reactive oxygen and nitrogen species (ROS and RNS, respectively) in cells and the ability of biological systems to eliminate them. These radical and non-radical molecules are by-products generated through different metabolic processes such as the mitochondrial chain, phagocytosis, prostaglandin synthesis, and the cytochrome P450 system, as well as exogenous sources such as tobacco, pollution, radiation, heavy metals, or alcohol (Halliwell & Gutteridge, 2015; Phaniendra, Jestadi, & Periyasamy, 2015). Some examples of biological ROS or compound generators of ROS are the radical superoxide anion ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2), hydroxyl radical ($OH^{\bullet}$), and hypochlorous acid (HOCl), which can damage proteins, lipids, and DNA (Martemucci et al., 2022; Pérez de la Lastra, Juan, Plou, & Pérez-Lebeña, 2022). Moreover, nitric oxide ($NO^{\bullet}$), a RNS, is generated by inducible, endothelial, and neural nitric oxide synthases (iNOS, eNOS and nNOS, respectively), which catalyze the oxidation of L-arginine to L-citrulline, as well as by S-nitrosothiol decomposition or the reaction of L-arginine with H_2O_2 (Forstermann & Sessa, 2012; Nagase et al., 1997; Singh, Hogg, Joseph, & Kalyanaraman, 1996). It is well known that NO is a potent vasodilator; however, when it reacts with $O_2^{\bullet -}$ to produce peroxynitrites ($ONOO^{\bullet}$) (Ibarz-Blanch et al., 2022), the beneficial effect of this molecule disappears. Moreover, peroxynitrites are involved in the oxidation of low-density lipoprotein and amino acids residues, such as tyrosine and methionine and DNA (Bartesaghi & Radi, 2018; Douki & Cadet, 1996; Pérez de la Lastra et al., 2022).

As mentioned above, organisms have endogenous antioxidant mechanisms (enzymatic and non-enzymatic) that contribute to the neutralization of ROS and RNS, thereby avoiding in consequence their prejudicial effects. Thus, $O_2^{\bullet}$ is removed by the enzymes superoxide dismutase (SOD), H_2O_2 by catalase (CAT), glutathione peroxidase (GPx), and peroxiredoxin, whereas peroxide radicals are eliminated by glutathione peroxidases (GPx) (Aoyama & Nakaki, 2015; Wang, Branicky, Noë, & Hekimi, 2018). Moreover, it is worth mentioning the role of reduced glutathione (GSH) against oxidative stress because it contains sulfhydryl groups that can be easily oxidized and reduced back, and is considered as the main endogenous antioxidant. In this regard, $GSSG^{\bullet -}$ (the oxidized form of GSH) is produced when some ROS or GSH-protein mixed disulfides are reduced via GPx or glutathione reductases. The reduction of $GSSG^{\bullet -}$ is catalyzed by GSH reductase (GR) in a NADPH-dependent manner (Aoyama & Nakaki, 2015).

In addition to these endogenous antioxidant mechanisms, other important sources of antioxidant molecules are food compounds such as vitamin C, vitamin E, phenolic compounds, carotenoids, trace elements (Se, Cu, Zn, and Mn), and peptides. They can directly reduce the oxidation of cellular molecules or increase the production and/or activity of endogenous antioxidants (Medina-Vera et al., 2021; Tadesse & Emire, 2020; Wołonciej, Milewska, & Roszkowska-Jakimiec, 2016; Xu et al., 2017). Therefore, given the importance of antioxidant compounds in the prevention of oxidative stress, there is a huge interest in searching new dietary-derived compounds with antioxidant properties. Consequently, different techniques have been also developed to evaluate the *in vitro* antioxidant effects of these compounds. The most commonly used techniques are based on the assessment of the reducing ability or radical-trapping activity of a compound when it reacts with an oxidized metal ion or a known radical, respectively (Zhong & Shahidi, 2015). Related to this, some of the most common antioxidant assays are $DPPH^{\bullet}$ (2,2-diphenyl-1-picryl-hydrazyl-hydrate) radical-scavenging activity, $ABTS^{\bullet +}$ (2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonate) radical-scavenging activity, nitric oxide scavenging activity, total reactive antioxidant potential (TRAP), ferric reducing antioxidant power (FRAP) or cupric ion reducing antioxidant capacity (CUPRAC). Another common assay is the oxygen radical absorbance capacity (ORAC) assay, which measures the ability of a compound to quench peroxyl radicals produced by AAPH (2,2′-azobis(2-methylpropionamidine) dihydrochloride) in presence of oxygen and heat (see Amorati & Valgimigli, 2018; Zhong & Shahidi, 2015 for more detailed information about antioxidant assays).

Antioxidant capacity is one of the main activities studied in hydrolysates obtained from chicken by-products. Specifically, blood, bones, cartilage, a mixture of combs and wattles, feathers, gizzard, liver, mechanically separated meat, skin, viscera, and trachea have been used to generate hydrolysates with antioxidant properties, which were determined by a wide range of assays (Table 1). These bioactive hydrolysates were generated using different methodologies such as fermentation and enzymatic and chemical hydrolysis. The most studied chicken by-products were feathers, which were fermented with different bacterial species (*Pedobacter* sp. *3.14.7, Bacillus pumilus strain A1,* or *Chryseobacteriumsp.kr6*), some of which contain alkaline keratinases, or directly treated with different proteases, including enzymes with keratinolytic activity. For example, the solution obtained from feather fermentation by means of the feather-extracted bacteria *Pedobacter* sp. *3.14.7,* exerted both ABTS and nitric oxide radical-scavenging activities (Bezus et al., 2021). Moreover, KER102 keratinase, a serine protease isolated from *Bacillus* sp.RCM-SSR-102, was used to generate a feather hydrolysate with DPPH and ABTS radical-scavenging activities (Kshetri et al., 2020). In addition, this peptic solution protected the DNA from oxidative damage.

Interestingly, the antioxidant activity of hydrolysates from chicken by-products varied depending on different factors, such as the type of chicken source, the method used to determine the antioxidant capacity, or the hydrolysis conditions (type of enzyme, enzyme/substrate ratio, hydrolysis time, and pH). Moreover, the same by-products from different origins produced hydrolysates with different antioxidant capacities, although the same hydrolysis conditions were applied. In this regard, Onuh et al. (2014) observed that the type of skin (thigh or breast) and enzyme concentration in both DPPH radical-scavenging activity and metal chelation ability, as well as the enzyme type (Alcalase® or Pepsin + Pancreatin) for the metal chelation ability, were key in the generation of antioxidant hydrolysates from chicken skin (Onuh et al., 2014). Furthermore, hydrolysates obtained from thigh (3% Alcalase®) and breast (1% Pepsin + Pancreatin) skins showed strong DPPH radical-scavenging activity and metal chelation activity, and weak hydroxyl and superoxide radical-scavenging activities. Another example of the effects of enzymes and hydrolysis conditions on the generation of antioxidant peptides is the study by Jeampakdee et al. (2020). In this study, Neutrase® was more efficient in generating hydrolysates with DPPH radical-scavenging activity from feather meal or viscera than those generated using Alcalase® or Flavourzyme® (Gonçalves dos Santos Aguilar et al., 2020; Jeampakdee et al., 2020). Furthermore, an enzyme-concentration response for DPPH radical-scavenging activity was observed in feather hydrolysates (Jeampakdee et al., 2020). In contrast, Flavourzyme® was the best enzyme in generating viscera-derived hydrolysates with the highest total antioxidant activity compared to those elaborated with Neutrase® or Alcalase® (Gonçalves dos Santos Aguilar et al., 2020); while Alcalase® was the best enzyme in generating trachea-derived antioxidant hydrolysates in comparison with Flavourzyme®, Protamex® or Papain (Pramualkijja et al., 2021). The hydrolysis time is also an important

Table 1
In vitro antioxidant effects of chicken by-product hydrolysates.

By-product		Enzyme	Amino acid sequence/s	ABTS$^{\bullet+}$-SA	ORAC	DPPH$^{\bullet}$-SA	FRAP/reducing power	Iron/metal chelating activity	$O2^{-}$-SA	•OH-SA	•NO-SA	TEAC	Mo (VI) reduction	β-carotene bleaching inhibition	References
Blood	Meal	Alcalase®		33.0–58.4 μmol TE/g		84.0–86.0 μmol TE/g	2.26–6.2 μmol TE/g								(da Silva Bambirra Alves et al., 2021)
	Red cells	Chlorhydric acid (0.05%)				57% (n.e)									Nikhita and Sachindra (2021)(
	Red cells	Alcalase®				77% (n.e)									Nikhita and Sachindra, 2021)
	Red cells	Pepsin				~1.4 mg/mL									Hamzeh et al. (2019)(Hamzeh et al., 2019)
	Plasma	Pepsin	AMADCCS, YPKAPFS, LLINLIK, DMVECMD, YEGLSKLVK, SPGSLCA, PTATVLG, CGLAGREE, FTVTFENTD, YRDSIVA, HLAVGAS, IEGTSYA, MIGMTPTV, FSYLISKD, DVKDTCM, VWGLASDL, YGTAITS, MQPAMAAI, LSVPLVL, AGSSPI, KIPLNLV, ISVCNSLL, EELPLPL, ALPTGG, DTKSDFH, TKSDFHL, MGTAPMW, ISRDWRGV, GKLGAVL, LRCQCIS, LIVKALMAK			~1.0 mg/mL								
	Corpuscle	Papain + Flavourzyme®	AEDKKLIQ			95% (n.e)	1.8%		53%						Zheng et al. (2018)
	Plasma	Alcalase®				77% (n.e)	0.6%	91%							Cheng et al. (2016)
	Cells	Alcalase®				78% (n.e)	0.3%	86%							(Cheng et al., 2016)
Bones	Carcass	Alcalase®		6988 μmol TE/L	11,683 μmol TE/L										Londoño-Zapata et al. (2022)
		Papain + Neutral protease + Trypsin				~60% (6 mg/mL)	~0.4 (AU) (6 mg/mL)			~25% (10 mg/mL)					Nie et al. (2017)
Cartilage		Trypsin		55.5 mg TE/g		9.8 mg/mL	0.5								Yang et al. (2019)
Combs and Wattles		Alcalase®	GADGAP, GKDLR	~58%		~42% (n.e)	~95%	94%							Bezerra et al. (2020)
Feather		*Bacillus licheniformis.* Fraction <3 kDa				5.0 mg/mL									Alahyaribeik et al. (2021)

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Table 1 (*continued*)

By-product		Enzyme	Amino acid sequence/s	ABTS$^{\bullet+}$-SA	ORAC	DPPH$^{\bullet}$-SA	FRAP/reducing power	Iron/metal chelating activity	$O2^{-}$-SA	•OH-SA	•NO-SA	TEAC	Mo (VI) reduction	β-carotene bleaching inhibition	References
		Pedobacter sp		0.6 g/L			2.2 AU (2 mg/mL)				0.5 g/L	3.6 mTE/g protein			Bezus et al. (2021)
		Bacillus pumilus A1				0.3 mg/mL	~1.6 AU (3 mg/mL)								Fakhfakh et al. (2011)
		Chryseobacteriumsp. kr6		16 mg/mL		83% (n.e)									Fontoura et al. (2014)
		Chryseobacteriumsp. kr6	LPGPILSSFPQ	~10% (3 mg/mL)											Fontoura et al. (2019)
		Bacillus subtilis S1–4.	SNLCRPCG	0.4 mg/mL		0.4 mg/mL		1.9 mg/mL							Wan et al. (2016)
		Sulfuric acid	–			0.5 mg/mL	1.1 AU (5 mg/mL)						60.6 μmol α-TE/mL	~80% (10 mg/mL)	Ben Hamad Bouhamed et al. (2020)
		KER102 keratinase	–	20 μg/mL		1.0 mg/mL									Kshetri et al. (2020)
		Alcalase®	–			90.43% (5 mg/mL)									Alahyaribeik and Ullah (2020)
	Meal	Neutrase®	FDDRGRX, VTLAVTKH, VSEIXSIPIS	9.3 μg/mL		16.5 μg/mL									Jeampakdee et al. (2020)
		Bacillus sp. P45 (fraction <3000 Da)		46.8 μmol TE/g	808.1 μmol TE/g										da Cunha et al. (2023)
Gizzard		*Pediococcus acidilactici* ATCC 8042		19.5 μM TE/g protein		37.5 μM TE/g protein	~40 μM TE/g protein								Ali et al. (2021)
		Bifidobacterium longum B379M				76% (n.e)									Zinina et al. (2022)
Liver		Trypsin				~75% (2 mg/mL)	~0.5 AU (2 mg/mL)			55% (2 mg/mL)					Xiong et al. (2020)
		Alcalase®		7.3 mg		1.74 mg	~0.5 AU (100 μL)		1.4 mg						Chakka, Elias, Jini, Sakhare, and Bhaskar (2015)
Mechanical deboning residues		Alcalase®				4.2 mg/mL									Sbeghen et al. (2022)
Skin		Alcalase® + Freeze dried				47% (n.e)	0.3% (n.e)	92% (n.e)		7% (n.e)					Wan Omar and Sarbon (2016)(
		Alcalase®.+ Vacuum oven dried				38% (n.e)	0.4% (n.e)	86% (n.e)		29% (n.e)					Wan Omar and Sarbon, 2016)
		Alcalase®+ pronase E + collagenase (Fraction)				16.7 mg/mL	~0.03 AU (20 mg/mL)	1.1 mg/mL	8.7 mg/mL						Sarbon, Badii, and Howell (2018)
		Elastase	GAHTGPRKPFKPR, GMPGFDVR, ADASVLPK	1.1 mg/mL		2.8 mg/mL		1.2 mg/mL							Nadalian et al. (2019)
		Alcalase®				61% (n.e)									Safar Razavizadeh, Farmani, and

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Table 1 (*continued*)

By-product		Enzyme	Amino acid sequence/s	$ABTS^{\bullet+}$-SA	ORAC	$DPPH^{\bullet}$-SA	FRAP/reducing power	Iron/metal chelating activity	$O2^{-}$-SA	•OH-SA	•NO-SA	TEAC	Mo (VI) reduction	β-carotene bleaching inhibition	References
															Motamedzadegan (2022a)
	Breast	Pepsin + pancreatin			3180 μM TE/g protein	~32% (1 mg/mL)		~80% (1 mg/mL)							Onuh et al. (2014) (Onuh et al., 2014)
	Thigh	Alcalase®			3497 μM TE/g protein	~34% (1 mg/mL)		~95% (1 mg/mL)							
Trachea		Alcalase®		134.3 μmol TE/mg		4.4 μmol TE/mL	22.5 μmol TE/mg								(Pramualkijja et al., 2021, 2022)
		Alcalase® + Whey proteins + NaCl (1.5%)		181.0 μM/mL		40.0 μM/mL	46.0 μM/mL								Pramualkijja et al. (2022)
Viscera		Flavourzyme® + Alcalase®				71% (n.e)									Gonçalves dos Santos Aguilar et al. (2020)
		Alcalase®				188.1 μmol TE/g	1057.6 μmol TE/g								da Silva and de Castro (2020)

Table shows the most active hydrolysate obtained in each study. ~Data calculated from reported figures (real value were not specified by authors). Numbers in brackets indicate the concentration of protein for testing the antioxidant activity.

Abbreviations: $ABTS^{\bullet+}$ -SA (2,2′-azino-bis-(3-ethylbenzothiazoline-6-sulfonic acid radical scavenging activity), $DPPH^{\bullet}$-SA(2,2-diphenyl-1-picryl-hydrazyl-hydrate radical scavenging activity), FRAP (ferric reducing antioxidant power), n.e (not specified), •NO-SA (nitric oxide scavenging activity), $O2^{-}$-SA(superoxide radical scavenging activity), •OH-SA (hydroxyl radical scavenging activity), ORAC (oxygen radical absorbance capacity), α-TE (α-tocopherol equivalents), TE (Trolox equivalents), TEAC (Trolox equivalent antioxidant activity).

factor in the generation of antioxidant hydrolysates. Thus, the maximum values of activity were found in the aforementioned trachea-derived hydrolysate in the range of 1 and 3 h of hydrolysis for the FRAP method, in the range of 2 and 6 h for the DPPH method, and 6 h for the ABTS method (Pramualkijja et al., 2021). Short hydrolysis times were also better for obtaining the maximum ABTS radical-scavenging activity of red blood cell hydrolysates (1–4 h) (Hamzeh, Wongngam, Kiatsongchai, & Yongsawatdigul, 2019). However, longer hydrolysis periods (18 h) were necessary to obtain the highest ABTS and DPPH radical-scavenging activities in hydrolysates obtained from gizzard fermentation by means of *Pediococcus acidilactici* ATCC 8042 (Ali, Gullo, Rai, & Bavisetty, 2021). The hydrolysate elaborated under these conditions showed strong ABTS and DPPH radical-scavenging activities of 22.8 and 26.3 times, respectively, which were higher than the initial gizzard.

Additionally, technological processes, such as drying, heating, or the matrix conditions in which hydrolysates are incorporated, might change the antioxidant activity of hydrolysates (Table 1). In this regard, a study carried out using an antioxidant skin hydrolysate showed that freeze-dried method was better in conserving its DPPH radical-scavenging and metal-chelating activities than the dried in a vacuum oven; however, hydroxyl radical-scavenging properties were better retained after the vacuum oven drying process than the freeze-drying method (Wan Omar & Sarbon, 2016). Furthermore, the antioxidant stability of thermic processes appears to depend on the hydrolysate itself. Thus, the DPPH radical-scavenging activity of a peptic fraction (<3000 Da) obtained from feather fermentation with *Bacillus licheniformis* was stable after a 30 min of heat treatment (20–100 °C); however, the DPPH radical-scavenging activity of a blood corpuscle hydrolysate was diminished after a 30 min of heat treatment at 80 and 100 °C (Zheng et al., 2018). Moreover, the antioxidant activity of these chicken by-product hydrolysates appears to be affected by pH. In this regard, the aforementioned feather fermented solution was very sensitive to pH, losing its activity at all evaluated pH values (2, 4, 6, and 10) (Alahyaribeik, Seyed, Tabandeh, Honarbakhsh, & Ghazanfari, 2021), whereas the blood corpuscle hydrolysate only lost DPPH radical-scavenging activity at pH higher than 7.0 (Zheng et al., 2018). In addition, another affecting parameter is the protein glycation, which might be produced in the formulation of functional foods using these hydrolysates. There is evidence that the glycation process might increase the antioxidant activity of hydrolysates (Nie et al., 2017; Xiong et al., 2020), although the results depend on the antioxidant assay used (Londoño-Zapata et al., 2022). Londoño-Zapata et al. (2022) observed that glycation with lactose increased the ORAC activity of a bone-derived hydrolysate by 6.57%; however, it decreased the ABTS radical-scavenging activity in the same hydrolysate by 3.73% (Londoño-Zapata et al., 2022). Another example was a bone-protein hydrolysate generated by a mixture of enzymes Papain, Neutral protease and Trypsin. This hydrolysate and its peptic-derived fractions (< and >3000 Da) showed strong DPPH radical-scavenging activity and moderate reducing power; however, both activities, as well as, its hydroxyl radical-scavenging activity significantly increased when proteins and peptides were glycated with galactose (3:1 galactose: hydrolysate, 100 °C, 90 min) (Nie et al., 2017). Moreover, the addition of an Alcalase®-digested trachea hydrolysate to a NaCl solution containing other proteins such as egg white and whey proteins produced changes in the DPPH and ABTS radical-scavenging activities, and ferric reducing ability of the hydrolysate, which depended on the used protein type and concentration. The most active mixture was a combination of 0.5% trachea hydrolysate and whey protein dissolved in 1.5% NaCl (Pramualkijja, Pirak, & Euston, 2022). Furthermore, Sbeghen et al. (2022) observed that ultrafiltration (4000 Da membrane, 2.5 bar at 45 °C) can be a useful technique to improve antioxidant activity in an Alcalase®-digested hydrolysate obtained from mechanically separated chicken meat, as the hydrolysate retentate showed increased DPPH radical-scavenging activity compared to the original hydrolysate (Sbeghen et al., 2022).

Finally, the influence of gastrointestinal digestion on the antioxidant activity of chicken by-product hydrolysates must be considered. In this regard, DPPH radical-scavenging activity seems to be quite stable in this biological process, with an increase in the bioactivity of hydrolysates obtained from blood and isolated red blood cells, and only a reduction of 5% in blood corpuscle hydrolysates after being subjected to Pepsin-Pancreatin digestion (Hamzeh et al., 2019; Zheng et al., 2018).

Even though chicken by-products have been the source of a huge number of hydrolysates with *in vitro* antioxidant effects, the scarce number of hydrolysates that have been evaluated *in vivo* is striking (Table 2). One of the more studied hydrolysates is a Pepsin-digested liver hydrolysate, which has shown *in vitro* DPPH radical-scavenging and ferrous ion chelating abilities (Chou, Wang, Lin, & Chen, 2014). Its antioxidant effects were observed in different oxidative stress animal models, such as mice with D-galactose-induced oxidative stress (Chou et al., 2014), thioacetamide (TAA)-induced fibrotic rat (Chen et al., 2017), streptozotocin (STZ)-induced hyperglycemic mouse (Yeh et al., 2022), mouse with alcoholic liver disease (Lin et al., 2017), and hamsters and mice consuming a high-fat diet (Wu, Lin, et al., 2020; Wu, Lin, Yang, Wang, & Chen, 2021; Yang et al., 2014). For example, the administration of 250 mg/kg body weight (BW) of the Pepsin-derived liver hydrolysate to the D-galactose ROS-induced mouse model for 6 weeks produced a strong antioxidant effect (Chou et al., 2014). Specifically, these animals showed a reduction in thiobarbituric acid reactive species (TBARS) levels and an increase in Trolox equivalent antioxidant capacity (TEAC), GSH levels, and the activity of the antioxidant enzymes SOD, CAT, and GPx in different animal organs, compared to the control D-galactose group (Chou et al., 2014). TBARS assay is an indicator of malondialdehyde (MDA) levels, which is a lipid peroxidation marker (Gaweł, Wardas, Niedworok, & Wardas, 2004), and TEAC assay is commonly used for determining antioxidant capacity in animal tissues. Its effects were attributed to (*i*) the high content of Gly, Cys, Glu, present in the liver-derived hydrolysate, which can be used to produce GSH (Samarasinghe, Munkanatta Godage, VanHecke, & Ahn, 2014); as well as due to the content of the metals Mn and Se, which are cofactors for SOD and GPx, respectively, and (*ii*) its peptic profile (Li & Zhou, 2011; Zoidis, Seremelis, Kontopoulos, & Danezis, 2018). Moreover, chronic administration of this hydrolysate to rats with thioacetamide (TAA)-induced fibrosis (600 mg/kg BW) and to alcoholic mice (320 and 1280 mg/kg BW) also ameliorated the hepatic oxidative state of the animals compared to TAA-induced fibrotic or alcoholic animals, respectively (Chen et al., 2017; Lin et al., 2017). The results were important as the liver-derived hydrolysate counteracted some of the effects of TAA on the liver, such as the activity of SOD and CAT, as well as the TEAC levels, which were similar to those determined in healthy animals. Similarly, oxidative stress induced by the alcoholic diet was counteracted by the consumption of this hydrolysate (TBARS, TEAC, SOD activity, and GPx activity) (Lin et al., 2017).

Moreover, other chicken by-product-derived hydrolysates showed antioxidant effects *in vivo,* although they were not selected based on their *in vitro* antioxidant capacity (Table 2). In this regard, a Protamex®-digested foot hydrolysate with antihypertensive effects, increased hepatic GSH levels in spontaneously hypertensive rats (SHR) compared to the control SHR group (Mas-Capdevila et al., 2019). Moreover, an Alcalase®-digested liver hydrolysate improved serum total antioxidant activity and DPPH radical-scavenging activity in cyclophosphamide-induced anemic mice, although these effects were dependent on the administered concentration and the method used to obtain the hydrolysate (fermentation or enzymatic hydrolysis with Alcalase®) (Chakka et al., 2021).

Antioxidant activity of hydrolysates is attributed to the peptide composition, with the best antioxidant activity for peptides included in fractions of 1 and 3 kDa (Sbeghen et al., 2022). However, contradictory results were found for antioxidant chicken hydrolysates. In this regard, the <3 kDa fraction of a feather meal hydrolysate obtained using *Bacillus* sp. P45 was the most active for peroxyl and ABTS radical-scavenging

Table 2
In vivo antioxidant effects of chicken by-product hydrolysates.

By-product	Hydrolysis conditions	Amino acid sequence/s*	Animal model	Treatment dose and period	Antioxidant effect	Reference
Feather	*Bacillus licheniformis* 5% (v/v), 48 h, 40 °C (F < 3 kDa)		Broiler chicks	50 mg/L for 36 days	↓MDA (thigh muscle)	Alahyaribeik et al. (2021, 2022)
Foot	Protamex® 0.4 AU/g prot, 2 h, 50 °C, pH 7.0		SHR	55 mg/kg BW, 1 day	↑hepatic GSH	Mas-Capdevila et al. (2019)
Liver	Pepsin 1:400, 2 h, 37 °C		57BL/6 mice + d-galactose (1.2 g/BW) subcutaneous injection	50 mg/kg BW for 6 weeks	↓brain and liver TBARS ↑ serum and brain GSH ↑liver and kidney SOD activity ↑heart CAT activity and GPx activity	Chou et al. (2014)
			57BL/6 mice + d-galactose (1.2 g/BW) subcutaneous injection	250 mg/kg BW for 6 weeks	↑liver size ↓TBARS (serum, brain, liver) ↑ brain GSH, TEAC, SOD activity, and CAT activity (↑hepatic GSH, TEAC, SOD activity, and CAT activity ↑kidney GSH, CAT activity and GPx activity ↑heart GPx activity	
			Wistar rats + 100 mg TAA/kg BW (intraperitoneal injection)	200 mg/kg BW for 10 weeks	↓hepatic TBARS ↑hepatic GSH and SOD activity	Chen et al. (2017)
				600 mg/kg bw for 10 weeks	↓hepatic TBARS ↑hepatic TEAC, SOD activity, and CAT activity	
			C57BL/6J (B6) mice + alcoholic diet	80 mg/kg BW for 8 weeks	↑hepatic TEAC and GPx activity	Lin et al. (2017)
				320 mg/kg bw for 8 weeks	↓hepatic TBARS ↑hepatic TEAC, SOD activity, and GPx activity	
				1280 mg/kg BW for 8 weeks	↓hepatic TBARS ↑hepatic TEAC, SOD activity, GPx activity	
			Golden Syrian hamsters + high-fat diet	100 mg/kg bw for 8 weeks	↓serum and hepatic TBARS ↑hepatic GSH, CAT activity, and GPx activity	Yang et al. (2014)
				200 mg/kg BW for 8 weeks	↓serum and hepatic TBARS ↑serum TEAC ↑ hepatic GSH, SOD activity, CAT activity, and GPx activity	
				400 mg/kg BW for 8 weeks (oral)	↓serum and liver TBARS ↑serum TEAC ↑ hepatic GSH, SOD activity, CAT activity, and GPx activity	
			C57BL/6 mice + basal diet	20 weeks	↑hepatic SOD activity	Wu, Korntner, Mullen, and Zeugolis (2021)
			C57BL/6 mice + high-fat diet	~170 mg/kg BW for 20 weeks	↓hepatic TBARS ↑hepatic SOD activity, CAT activity, and GPx activity	
				~510 mg/kg BW for 20 weeks	↓hepatic TBARS ↑hepatic SOD activity and GPx activity	
			C57BL/6 mice + high-fat diet	~170 mg/kg BW for 20 weeks	↓serum TBARS ↑serum TEAC and GSH	Wu, Lau, et al. (2020) Wu, Lau, et al. (2020)
				~510 mg/kg BW for 20 weeks	↓serum TBARS ↑serum TEAC and GSH	

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Table 2 (*continued*)

By-product	Hydrolysis conditions	Amino acid sequence/s*	Animal model	Treatment dose and period	Antioxidant effect	Reference
			Institute of Cancer Research(ICR) mice + STZ (50 mg/kg BW) with nicotinamide (120 mg/kg BW)	409.46 mg mg/kg BW for 9 weeks	↑brain GSH, TEAC, SOD activity, CAT activity, GPx activity	Yeh et al. (2022)
				818.92 mg/kg BW for 9 weeks	↓brain TBARS ↑brain and hepatic TEAC, GSH, SOD activity, CAT activity, and GPx activity	
				1223.38 mg/kg BW for 9 weeks	↓brain TBARS ↑brain and hepatic TEAC, GSH, SOD activity, CAT activity, and GPx activity	
	Alcalase® 1.5%, 150 min, 45 °C		Swiss-albino female mice + basal diet without iron + cyclophosphamide (100 mg/kg BW)	1.5% for 28 days	↑total antioxidant activity in serum. Similar to healthy group	Chakka et al. (2021)
				3% for 28 days	↑DPPH scavenging activity in serum, > healthy group	
				4.5% for 28 days	↓total antioxidant activity in serum ↑DPPH scavenging activity in serum, > healthy group	
	Pediococcus acidilactici N-CIM5368, 10%, 24 h, 37 °C			1.5% for 28 days	↓Total antioxidant activity in serum. ↑DPPH scavenging activity in serum, ≥ healthy group	
				3% for 28 days	↑Total antioxidant activity in serum. Similar to healthy group. ↑DPPH scavenging activity in serum, ≥ healthy group	
				4.5% for 28 days	↑DPPH scavenging activity in serum, ≥ healthy group	

Table shows the most active hydrolysate obtained in each study. ↑ and ↓ indicate an increase or decrease of a parameter, respectively, in comparison with their respective non-treated ill animals.

Abbreviations: BW (body weight), CAT (catalase), DPPH (2,2-diphenyl-1-picryl-hydrazyl-hydrate), GPx (glutathione peroxidase), GSH (reduced glutathione), MDA (malondialdehide), SOD (superoxide dismutase), SHR (spontaneously hypertensive rats), STZ (streptozotocin), TBARS (thiobarbituric acid reactive species), TEAC (trolox equivalent antioxidant capacity).

(*)Amino acid sequences were not reported by the authors in the cited works.

activities (da Cunha, Brandelli, Braga, Sala, & Kalil, 2023), whereas the >4 kDa fraction of an Alcalase®-digested hydrolysate obtained from mechanically separated chicken meat exhibited higher DPPH radical-scavenging activity than the permeate obtained from the hydrolysate ultrafiltration (Sbeghen et al., 2022). Moreover, the highest DPPH and hydroxyl radical-scavenging activities, and ORAC of two chicken skin hydrolysates corresponded to the smallest peptide fraction (<1 kDa) (Onuh et al., 2014). A higher TEAC and reducing power was also observed in the <10 kDa fraction of a Pepsin-digested cartilage hydrolysate in comparison with the original hydrolysate and its >10 kDa fraction (J. Yang et al., 2019). Different antioxidant amino acid sequences have been identified in the antioxidant chicken by-product hydrolysates. In this regard, the amino acid sequence EDKKLIQ was identified in an antioxidant hydrolysate obtained from blood corpuscles, which showed similar radical-scavenging activity (hydroxyl, superoxide, and DPPH) and reducing power as GSH (Zheng et al., 2018). In addition, the peptides LPGPILSSFPQ and SNLCRPCG were also identified in antioxidant feather hydrolysates obtained by fermentation with *Chryseobacteriumsp.kr6* and *Bacillus subtilis* S1–4, respectively, which were capable to scavenge different free radicals or show reducing power (Fontoura et al., 2019; Wan, Dong, Yang, & Feng, 2016). Moreover, peptides from different collagen chains and elastin were identified in an antioxidant hydrolysate obtained from combs and wattles (Bezerra et al., 2020). Some of these peptides were the amino acid sequences GADGAP and GKDGLR, which might exert antioxidant activity according to their specific amino acid sequence (Bezerra et al., 2020). In this regard, the presence of Phe, Ala, Val, Pro and His in peptides have been linked to good radical-scavenging activity (Samaranayaka & Li-Chan, 2011). Moreover, Trp (mainly when it is located at the extreme of a peptide) and Pro seem to act as potent hydrogen donors because of the indole and pyrrolidine rings that they contain, respectively (Fan, He, Zhuang, & Sun, 2012; Girgih et al., 2014). Moreover, the presence of Lys, Glu or Gln in a peptide have been also linked to hydroxyl radical-scavenging and metal binding activities (Shazly et al., 2017). Additionally, Ala and Ile have been associated with the lipid peroxidation inhibitory activity exerted by different dietary peptides (Luo et al., 2020; Zhao et al., 2018) and the presence of polar or charged amino acids (Arg, His or Asp) in a peptide has been associated with iron-binding activity (Sun et al., 2017).

4.2.2. *Effects on cardiovascular related diseases*

Antihypertensive effects have been one of the most researched effects of chicken by-product hydrolysates. The selection of antihypertensive hydrolysates was based on their ability to inhibit ACE *in vitro*. This enzyme is key to BP regulation within the Renin-Angiotensin-Aldosterone system. Its importance lies in the fact that it catalyzes the inactivation of the vasodilator bradykinin, and more importantly, the generation of angiotensin (Ang) II from Ang I. Ang II contributes to increase BP via different pathways. Some of them are i) stimulation of vascular smooth muscle cell contraction, ii) release of endothelial vasoconstrictor factors such as endothelin 1 (ET-1) or ROS, and iii) stimulation of aldosterone release by adrenal glands, producing renal water and sodium reabsorption (Patel, Rauf, Khan, & Abu-Izneid, 2017; Pueyo & Michel, 1997; Touyz et al., 2002). Further details regarding the RAAS can be found in López-Fernández-Sobrino, Torres-Fuentes, Bravo, & Muguerza, 2022.

ACEi activity was observed in hydrolysates derived from a wide range of chicken by-products, including foot, blood, feather, skin, bone, viscera, trachea, comb, and wattle (Bravo et al., 2023). The IC_{50} values of the best ACEi hydrolysates obtained in different studies ranged

between 2.7-2650 μg/mL, although most of them ranged between 130 and 550 μg/mL (Bravo et al., 2023). IC_{50} indicates the minimum amount of hydrolysate required to inhibit 50% of the enzyme. Thus, the lowest value indicates the most active hydrolysate. Alcalase® was the most commonly used cocktail enzyme for generating these bioactive hydrolysates (Chen et al., 2002; Cheng et al., 2008a; Cheng et al., 2008b; Cheng, Liu, Wan, Lin, & Sakata, 2008; Gonçalves dos Santos Aguilar et al., 2020; Huang & Liu, 2010; Nikhita & Sachindra, 2021; Onuh et al., 2013; Onuh, Girgih, Malomo, Aluko, & Aliani, 2015; Pramualkijja et al., 2021; Wongngam et al., 2020). Moreover, studies comparing the effects of different proteases on the generation of ACEi peptides showed that Alcalase® was also the enzyme responsible for releasing the most active peptides in chicken whole blood, blood corpuscle, bone, skin, trachea, and residues, considering the specific test conditions (Chen et al., 2002; Cheng et al., 2008; Huang & Liu, 2010; Onuh et al., 2013; Pramualkijja et al., 2021; Wongngam et al., 2020). However, the best ACEi activity was found in a Protamex®-digested foot hydrolysate (IC_{50} = 27 μg/mL) (Mas-Capdevila et al., 2018), where Alcalase® digestion was not assayed. Furthermore, it was found that the ACEi activity of a specific hydrolysate could be improved through different processes, such as by i) performing gastrointestinal *in vitro* digestion (Saiga et al., 2008); ii) further hydrolysis with other enzymes (Saiga et al., 2008; Yuliatmo, Fitriyanto, Bachruddin, & Erwanto, 2017); and iii) isolating the fraction containing the smallest peptides (Huang & Liu, 2010; Onuh et al., 2013, 2015; Saiga et al., 2008; Wongngam et al., 2020) and iv) by using plastein reaction (Gao et al., 2020). More detailed information about the effects of chicken by-product hydrolysates on the ACEi can be found in Bravo et al. (2023).

In addition to *in vitro* assays, the antihypertensive effects of many of these hydrolysates have been evaluated in hypertensive rats after chronic and/or acute administration (Bravo et al., 2023). Acute administration of these hydrolysates (doses ranging between 50 and 3000 mg/kg BW) to hypertensive rats produced strong reductions in the systolic BP (SBP) (Bravo et al., 2023). The maximum SBP drop ranged from 26 to 60 mm Hg (Chen et al., 2002; Mas-Capdevila et al., 2018; Onuh et al., 2013; Saiga et al., 2008; Wongngam et al., 2020; Zhang, Kouguchi, Shimizu, Ohmori, et al., 2010). Moreover, some of these hydrolysates, such as those obtained from foot, blood, bone, skin, and chicken residues, also produced antihypertensive effects after their long-term administration to hypertensive animals (Chen et al., 2002; Cheng et al., 2008; Cheng et al., 2008b; Mas-Capdevila et al., 2019; Onuh et al., 2016; Saiga et al., 2008; Wongngam et al., 2020; Zhang, Kouguchi, Shimizu, Ohmori, et al., 2010). In addition, these BP-lowering effects could be produced by the action of some of these hydrolysates on ACE, resulting in its partial inhibition (Chen et al., 2002; Mas-Capdevila et al., 2018; Onuh et al., 2016). Consequently, this would lead to a decrease in Ang II production and a reduction in BP levels. Moreover, it was also demonstrated that they could also act on vessels improving hypertension-induced wall thickness (Cheng et al., 2008b), aorta hypertrophy (Zhang, Kouguchi, Shimizu, Ohmori, et al., 2010), and endothelial dysfunction (Mas-Capdevila et al., 2019; Zhang, Kouguchi, Shimizu, Ohmori, et al., 2010). This last hypertension-associated effect is characterized by an imbalance in the proportion of endothelial-derived vasoconstrictor (endothelin 1) and vasodilator factors (NO and prostaglandin), and a reduction in the bioavailability of endothelial NO (Hadi, Carr, & Al Suwaidi, 2005; Yanai et al., 2008), among others. For example, the administration of a Protamex®-digested chicken foot hydrolysate to diet-induced hypertensive rats for 3 weeks resulted in the downregulation of aortic *Edn1* (endothelin 1 gene), upregulation of aortic *Sirt1* (sirtuin 1 gene), as well as an increase in hepatic levels of GSH compared to hypertensive control animals (Mas-Capdevila et al., 2019). Moreover, an improvement in the antioxidant status together with a decrease in BP were observed in cyclophosphamide-induced anemia mice consuming a chicken liver hydrolysate (Chakka et al., 2021). Sirtuin 1 is crucial for the activation of eNOS, stimulates *eNos* transcription (ENOS is responsible for the production of the vasodilator NO), and inhibits NADPH oxidase activity, reducing the production of endothelial ROS by this enzyme (Ibarz-Blanch et al., 2022; Mattagajasingh et al., 2007; Zarzuelo et al., 2013). ROS are involved in the reduction of NO bioavailability, as excessive superoxide anions can scavenge NO, forming peroxynitrite (Rubanyi & Vanhoutte, 1986). Consequently, it would reduce the bioavailability of NO. Another example is the <3 kDa fraction of a chicken leg-derived hydrolysate obtained using *Aspergillus oryzae* proteases and Protease FP, which produced an increase in serum NO levels or a reduction in plasma intercellular adhesion molecule-1 (iCAM-1) levels in NG-nitro-L-arginine-methyl ester (L-NAME)-induced hypertensive rats after its acute or chronic administration, respectively (Zhang, Kouguchi, Shimizu, Ohmori, et al., 2010). iCAM-1 levels, involved in the atherosclerotic-lesions formation and development, have been linked to different cardiovascular diseases and endothelial dysfunction (Gross et al., 2012; Lawson & Wolf, 2009; Springer, 1995). Finally, it is worth mentioning that chicken leg hydrolysates obtained by means of *Aspergillus oryzae* proteases and Protease FP also showed antihypertensive effects in mildly and prehypertensive volunteers after 4 or 12 weeks of consumption (Kouguchi et al., 2013; Saiga-Egusa, Koji, Hayakawa, Takahata, & Morimatsu, 2009). These volunteers, depending on the study, also showed a reduction in plasma renin activity (Saiga-Egusa et al., 2009), which catalyzes the formation of Ang I from angiotensinogen, in brachial-ankle pulse wave velocity (Kouguchi et al., 2013), which is an indicator of arterial stiffness (Tomiyama et al., 2019), and an increase in endothelial progenitor cells colonies (Saiga-Egusa et al., 2009), which are involved in vascular repair (Zhang, Malik, & Rehman, 2014). More detailed information on the antihypertensive effects of chicken by-product hydrolysates can be found in Bravo et al., 2023; Bravo et al., 2023).

In addition to their antihypertensive effects, a mixture of chicken combs and wattles was recently used to generate an Alcalase®-digested hydrolysate with anticoagulant activity, which exerted its effects on the intrinsic pathway (Alencar-Bezerra et al., 2019). Anticoagulants are used to manage several cardiovascular diseases, including thrombotic disorders, acute myocardial infarction, and atrial fibrillation (Larson, German, Shatzel, & DeLoughery, 2019). In addition, liver hydrolysates have shown anti-anemia effects in cyclophosphamide-induced anemia mice (Chakka et al., 2021). In this regard, liver proteins fermented with *Pediococcus acidilactici* N-CIM5368 or hydrolyzed using Alcalase® were administered daily to healthy Swiss-albino female mice fed an iron-deficient diet. After anemia induction for 2 weeks, animals lost BW and their hemoglobin levels decreased; however, both parameters were restored after one week of consuming the hydrolysates in comparison with the control group. Anemia is a published health problem that occurs in 42% of children aged <5 years and 40% of pregnant women (World Health Organization (WHO), n.d.). It is frequent in patients with cardiovascular diseases and can be considered the fifth cardiovascular risk factor (Kaiafa et al., 2015). In addition, other liver hydrolysate administered to C57BL/6 mice consuming a high-fat diet exerted cardioprotective effects (Wu, Lin, et al., 2020). The long-term consumption of this diet by rodents simulates the development of characteristics of human metabolic syndrome, including diabetes, obesity, renal dysfunction, and alterations in lipid homeostasis (Buettner, Schölmerich, & Bollheimer, 2007; Sun et al., 2020). Thus, this Pepsin-digested liver hydrolysate improved the lipid profile and decreased renal lipid deposition, fibrosis, cardiac fibrosis, and inflammation in the treated animals compared with the non-supplemeted group (Wu, Lin, et al., 2020). Finally, an anti-inflammatory Corolase PP® hydrolysate obtained from chicken rest materials, derived from mechanical deboning, showed anti-atherosclerotic effects in apolipoprotein E (ApoE)-deficient ($Apoe^{-/-}$) mice after being consumed for 12 weeks, and this effect was not related to plasma cholesterol-lowering activity (Bjørndal et al., 2020). ApoE is a structural component of most lipoproteins (Hauser, Narayanaswami, & Ryan, 2011). It is a critical ligand for targeting plasmatic apolipoproteins to the liver for metabolism (Mahley & Rall,

2000). Therefore, Apoe$^{-/-}$ mice are unable to properly metabolize lipids, accumulate them in the plasma, and facilitate the atherosclerotic plaque formation via inflammatory cell migration (Lee et al., 2017). Furthermore, a reduction in plasma monocyte chemoattractant protein-1 (MCP-1) protein was also observed in animals consuming the hydrolysate, suggesting that atherosclerosis plaque was reduced because of the decreased chemoattraction of monocytes (Bjørndal et al., 2020).

4.2.3. Antidiabetic effects

Some chicken by-products, such as blood, mechanical chicken deboning residues, feet, and feathers, have also been used to obtain hydrolysates capable of inhibiting DPP-IV enzymes (Table 3) (Casanova-Martí et al., 2019; Fontoura et al., 2014; Hatanaka, Kawakami, & Uraji, 2014; Lima et al., 2019). This protease is an interesting target for the treatment and/or prevention of type 2 Diabetes Mellitus (Green, Flatt, & Bailey, 2006). This chronic disease is the most common type of diabetes and is characterized by impaired insulin secretion and insulin resistance (Shaw, Sicree, & Zimmet, 2010). DPP-IV can hydrolyse different neuropeptides, chemokines, and regulatory peptides, including two incretin hormones: glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1). This serine peptidase/prolyl oligopeptidase acts mainly on the amino acids Pro and Ala located at position 2 of the N-terminus (Mulvihill & Drucker, 2014). Some of the actions of these two incretins are to increase the survival and expansion of mass of pancreatic β-cells and the biosynthesis and the glucose-dependent secretion of insulin as well as to reduce insulin clearance in liver and to exert "insulin-like" effects on hepatic, adipose and skeletal tissues (Green et al., 2006). GLP-1 also inhibits glucagon secretion (Holst, 2007). These functions would result in a reduction in plasma glucose and an increase in cell glucose uptake and metabolism. Thus, inhibition of DPP-IV activity would lengthen the half-life of the active form of these two gut-derived hormones and improve the management of glucose homeostasis in patients with type 2 Diabetes Mellitus.

As mentioned above, DPP-IV inhibitory activity has been observed in hydrolysates obtained from the blood, feet, feathers, and mechanical chicken deboning residues. Table 3 shows the IC_{50} values for these hydrolysates, which ranged from 297.4 to 3570 μg/mL. Studies carried out with mechanical deboning residue hydrolysates using Corolase® and Flavourzyme® showed that DPP-IV inhibitory properties depended on the enzyme (Corolase®>Flavourzyme®) and hydrolysis time (80 min > 240 min) (Lima et al., 2019). The most active DPPV-I inhibitory hydrolysates were those elaborated from chicken feet (Casanova-Martí et al., 2019). Moreover, it is worth mentioning that the antihyperglycemic effect of one of these foot hydrolysates was demonstrated in two animal models of diet- and age-induced glucose intolerance. Specifically, during an oral glucose tolerance test, diet-induced glucose intolerant animals administered an acute dose of a Neutrase®-derived foot hydrolysate showed a lower peak plasma glucose than that observed in untreated rats. Moreover, this hydrolysate tended to normalize the plasma glucose levels of the animals after 120 min of being administered an intragastric glucose load (Casanova-Martí et al., 2019). Additional *in vitro* studies also showed that STC-1 enteroendocrine cells and ileum tissues stimulated by this foot hydrolysate increased active GLP-1 secretion, indicating the potential role of GLP-1 in the antihyperglycemic effect of this hydrolysate (Casanova-Martí et al., 2019). In addition, a Pepsin-digested liver hydrolysate also showed antihyperglycemic effects in STZ-induced diabetes and high-fat diet-induced insulin resistance in mice (Wu, Korntner, et al., 2021; Yeh et al., 2022). Moreover, this hydrolysate also decreased insulin resistance in both animal models as a decrease in the HOMA-IR value (insulin resistance indicator) and the insulin receptor β in the liver and skeletal muscle were observed in STZ-induced diabetes and high-fat diet-induced insulin resistance mice, respectively (Wu, Korntner, et al., 2021; Yeh et al., 2022). In addition, an increase in the protein level of GLUT4, an insulin-stimulated glucose transporter in muscle and fat, was found in different tissues after the consumption of hydrolysate (Wang, Wang, Hu, Huang, & Chen, 2020), indicating that it could be one of the mechanisms underlying its beneficial effects.

Regarding peptides, only five amino acid sequences were identified in different hydrolysates, which corresponded to tri- and dipeptides (Hatanaka et al., 2014; Lima et al., 2019). The IC_{50} values for DPP-IV inhibitory activity ranged from 0.091 mM for LA to >20 mM for GAO (Table 4). Moreover, Carrera-Alvarado et al., 2022 identified three DPP-IV inhibitory peptides (GPF, GGGW, and IGL) resulting from *in silico* gastrointestinal digestion of peptides identified in chicken blood hydrolysates (Carrera-Alvarado et al., 2022). The inhibition of DPP-IV by peptides is strongly influenced by the amino acid profile and position in a manner similar to that of other enzymes. Different studies carried out on peptides from other protein origins have shown that the presence of hydrophobic amino acids in the N-terminal extreme of the peptide exerts a better DPP-IV inhibitory activity (Nongonierma & FitzGerald, 2016; Tulipano, Faggi, Nardone, Cocchi, & Caroli, 2015). Moreover, an increase in this activity was observed when the peptides contained in their N-Terminal extreme: Trp or Met on the last position, Ala or Pro on the second position, and Pro on the second position and it is flanked on both sides by Leu and or Ile (Kęska & Stadnik, 2022; Nongonierma & FitzGerald, 2016; Power, Nongonierma, Jakeman, & FitzGerald, 2014; Tulipano et al., 2015). Good DPP-IV inhibitory activity has been demonstrated when Pro appears at the N-terminal end between the first four amino acid residues and is flanked by Phe, Gly, Leu, Ala and Val (Boots, 2012; Carrera-Alvarado et al., 2022). Moreover, peptides containing Pro and or Hyp have shown a strong inhibitory effect on the DPP-IV activity (Harnedy, O'Keeffe, & FitzGerald, 2015; Lacroix & Li-Chan, 2012). Chicken by-product-derived peptides have not yet been tested in animal models; however, other studies carried out on peptides identified in hydrolysates from different origins have shown that dipeptides containing Leu increased glucose uptake by skeletal muscle cells (Morifuji, Koga, Kawanaka, & Higuchi, 2009).

4.2.4. Effects on biometric parameters and lipid homeostasis

Chicken by-product hydrolysates have also been evaluated for their impact on different biometric parameters, including BW, BW gain, food intake, and tissue weight (Table 5). In addition, the administration of these hydrolysates has shown positive results in the modulation of lipid homeostasis in different animal models (Table 5). In this regard, the administration of the <3 kDa fraction of a feather hydrolysate, obtained by fermentation with *Bacillus licheniformis*, to broiler chicks positively enhanced serum lipidic parameters. Specifically, it decreased the levels of circulating TC, triglycerides (TG), low-density lipoprotein-cholesterol (LDL-C), and very-low-density lipoprotein-cholesterol (vLDL-C) after 10 days of treatment with this hydrolysate. However, these changes were not seen after 26 or 36 days of treatment (Alahyaribeik et al., 2022). Interestingly, consumption of this hydrolysate significantly increased BW gain, which was the desired outcome for this animal model. This increase may be due to an enhancement in the microbiota, as well as in the small intestinal morphology and mucosal immune system due to the ingested peptides (Alahyaribeik et al., 2022). Similar results enhancing the circulating lipid profile were also observed by the consumption of a Pepsin-digested liver hydrolysate by Golden Syrian hamsters and mice fed a high-fat diet for 8 and 20 weeks, respectively (Wu, Lin, et al., 2020, 2021; Yang et al., 2014). In hamsters, decreased levels of serum TG, TC, LDL-C and the LDL-C/HDL-C ratio were observed at all evaluated doses (100, 200 and 400 mg/kg BW). Additionally, an increase in serum HDL-C levels was observed at 200 and 400 mg/kg BW (Yang et al., 2014). All these changes contributed to a better cardiometabolic profile related to the circulating lipid species in the context of an obesogenic diet. In addition, this hydrolysate also decreased BW, BW gain, and liver weight, as well as in the levels of key enzymes, such as alanine transaminase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) in mice fed a high-fat diet (Wu, Korntner, et al., 2021). In the same line, hydrolysates from mixed slaughterhouse by-products

Table 3
Antidiabetic effects of chicken by-product hydrolysates.

By-product	Hydrolysis conditions	Amino acid sequence/s	*In vitro* DPP-IV inhibitory activity		Animal model	Doses	Period	Effects	Mechanisms	References
			%*	Ic_{50} (μg/mL)						
Blood	Alcalase® 2%, 2 h, 55 °C + Protana® Prime 5%, 16 h, 55 °C	GPF, IGL, GGGW	61 (10 mg/mL)							Carrera-Alvarado et al. (2022)
	Alcalase® 2%, 2 h, 55 °C + Protana Prime 5%, Protana UBoost 3%, 16 h, 55 °C	GPF, IGL, GGGW	54 (10 mg/mL)							
Feather	*Chryseobacterium* sp. kr 6, 24 and 48 h, 30 °C, pH 8		42-45 (n.e)							Fontoura et al. (2014)
Foot	Neutrase® 0.4 AU/g prot, 24 h, 50 °C, pH 7.0		100 (20 mg/mL)	297						Casanova-Martí et al. (2019)
	Protamex® 0.4 AU/g prot, 2 h, 50 °C, pH 7		93 (20 mg/mL)	300						
	Neutrase 0.4 AU/g prot, 24 h, 25 °C, pH 7		83 (20 mg/mL)	303	Diet-induced glucose intolerance (Wistar rats)	471.71 mg/kg BW	Acute	↓peak plasma glucose after OGTT		
					STC1 enteroendocrine cells	5 mg/mL		↑active GLP1 secretion		
					Ileum tissue	15 mg/mL		↑active GLP1 secretion		
	Streptomyces collagenase 1%, 17 h, 45 °C, pH 7.5	GAO*, GPA, GPO*		3570						Hatanaka et al. (2014)
Liver	Pepsin 1:400, 2 h, 37 °C				High fat-induced insulin resistance mice	~170 mg/kg BW	Daily 20 weeks	↓fasted glucose ↓peak plasma glucose after OGTT	↑GLUT4 (liver, skeletal muscle and perirenal fat) ↓Irβ (skeletal muscle	Wu, Korntner, et al. (2021)
						~510 mg/kg BW	Daily 20 weeks	↓peak plasma glucose after OGTT	↑GLUT4 (liver, skeletal muscle and peri-renal fat) ↓Irβ (liver and skeletal muscle	
					Streptozotocin-induced diabetic mice	409.46, 818.92, and 1223.38 mg/kg	Daily for 9 weeks	↓HOMA-IR ↓serum glucose, and insulin ↓peak plasma glucose after OGTT	↑GLUT4 (liver, skeletal muscle and brain)	Yeh et al. (2022)
Mechanical deboning residues	Corolase® 80 min, 50 °C	TL, 5-HT, DF, TL, LA, LAD, VEVD, LL, ETGKGEDGE, FL, LFFSMLLML,	60 (1 mg/mL)	919						Lima et al. (2019)
	Corolase® 80 min, 50 °C (Fraction 5)	LF	54 (1 mg/mL)	155	Skeletal muscle cells	1 mg/mL		↑ Glucose uptake		

Table shows the most active hydrolysate obtained in each study.* Numbers in brackets indicate the concentration of protein/dry hydrolysate for testing the DPP-IV inhibitory activity. ↑ and ↓ indicate an increase or decrease of a parameter, respectively, in comparison with their respective non-treated ill animals.
Abbreviations: GLUT4 (insulin-regulated glucose transporter), GLP-1 (glucagon-like peptide 1), Irβ (insulin receptor β), n.e (not specified), OGTT (glucose tolerance test), STC1 (intestinal secretin tumor cell line).(*)'O' indicates 'hydroxyproline'.

Table 4
Dipeptidyl peptidase IV (DPP-IV) inhibitory activity of peptides identified in chicken by-product hydrolysates.

By-product	Hydrolysis conditions	Amino acid sequence*	DPP-IV inhibitory activity (IC_{50})	References
Blood	Alcalase® 2%, 2 h, 55 °C + Protana® Prime 5%, 16 h, 55 °C or hydrolysate using Alcalase® 2%, 2 h, 55 °C + Protana® Prime 5%, Protana® UBoost 3%, 16 h, 55 °C	GPF	0.94 mM	Carrera-Alvarado et al. (2022)
		GGGW	2.73 mM	
		IGL	2.22 mM	
Feet	*Streptomyces* collagenase 1%, 17 h, 45 °C, pH 7.5	GAO	>20 mM	Hatanaka et al. (2014)
		GPA	5.03 mM	
		GPO	2.51 mM	
Mechanical deboning residues	Corolase® 80 min, 50 °C	LA	0.09 mM	Lan et al. (2015); Lima et al. (2019)
		FL	0.40 mM	Lima et al. (2019); Nongonierma and FitzGerald (2013)

(*)'O' indicates 'hydroxyproline'.

(including viscera, heart and blood), obtained by the action of *Bromelia pinguin* and *Bromelia karatas* enzymes, exerted an enhancement in the lipid circulating species and reduced the levels of ALT and AST in Wistar rats fed an obesogenic diet (Romero-Garay et al., 2022). Based on these studies, chicken hydrolysates seems to have potential to ameliorate lipid disorders in the context of an obesogenic diet.

Regarding the mechanisms underlying these effects, an increase in hepatic mitochondrial fatty acid β-oxidation in the liver was observed in high-fat diet-induced obese C57BL/6 mice supplemented for 12 weeks with an Alcalase®- or Corolase PP-derived hydrolysate from chicken meat rest raw materials, resulting from mechanical deboning (Aloysius et al., 2018). In addition, these same hydrolysates administered to ApoE-deficient mice ($Apoe^{-/-}$), which develop hyperlipidemia, increased plasma fatty acid C20:5 n-3 levels and delta-5 desaturase index, while no changes in plasma and hepatic TG and TC were observed (Bjørndal et al., 2020). Moreover, a foot hydrolysate administered to ApoE-deficient C57BL/6.KOR-$ApoE^{shl}$ mice reduced plasma and hepatic TC levels, as well as TG levels, compared to untreated animals (Zhang, Kouguchi, Shimizu, Sato, et al., 2010). Thus, although more studies are needed to elucidate the mechanisms of action, it seems clear that the consumption of these chicken by-product hydrolysates has a direct metabolic effect on the organism.

4.2.5. *Anti-inflammatory effects*

Inflammation is a natural response of an organism to nocuous stimuli or conditions, such as infection, tissue damage, and stress. The inflammatory response can be triggered by both endogenous and exogenous (microbial or non-microbial) inducers (Medzhitov, 2008). The inflammatory process can be regulated by numerous mediators such as cytokines, IL, and enzymes. Due to this fact, inflammation plays a crucial role in the majority of diseases or disorders in organisms, and therefore, the search for compunds capable of counteracting inflammation has gained importance in recent years (Chen et al., 2018). However, chicken by-products have been poorly studied as sources of anti-inflammatory compounds (Table 6). The study of NO levels in lipopolysaccharide (LPS)-activated murine macrophages (RAW 264.7) is frequently used as a preliminary screening method for anti-inflammatory compounds (Han et al., 2022; Liu, Chen, Zheng, Yu, & Wei, 2022; Wang et al., 2018). In addition to the vasodilatory effect of endothelial NO, this molecule is also considered a pro-inflammatory mediator when it is overproduced, with iNOS being one the main NO-producer enzymes. This enzyme is associated with injury-induced NO production and is expressed in many cell types, including macrophages and neutrophils (Kobayashi, 2010).

Regarding chicken by-product hydrolysates, a potent reduction in NO production in LPS-activated murine macrophages was observed when they were treated with a peptidic fraction isolated from a Flavourzyme®-digested feather meal hydrolysate (Inkanuwat et al., 2019). This hydrolysate was previously selected for its good NO scavenging activity *in vitro*. This anti-inflammatory effect was linked to the down-regulation of ciclooxigenase-2 (*Cox2)* and tumor necrosis factor alpha *(Tnf-α)* expression, and a decrease in the mRNA expression and protein levels of iNOS and interleukin (IL)-6 (Inkanuwat et al., 2019). COX-2 is a master regulator enzyme of one of the main inflammatory pathways. More concisely, it synthesizes the pro-inflammatory oxylipin prostaglandine-2 from arachidonic acid and is the target of non-steroideal anti-inflammatory drugs (Ju et al., 2022). Moroever, *Cox2* is an inducible early response gene that can be activated by different factors, including IL-1, TNF-α, or LPS (Gandhi, Khera, Gaur, Paul, & Kaul, 2017). TNF-α and IL-6, together with IL-1 and interferon-γ (IFN-γ), are the most important pro-inflammatory cytokines (Kany, Vollrath, & Relja, 2019). Moreover, the peptide SNPSVAGVR was identified in the hydrolysate fraction, showing a decrease in NO production in the same cell inflammatory model at 30 and 60 mM, which was linked to the downregulation of *Cox2, Tnf-α, iNos,* and *Il6* gene expression (Inkanuwat et al., 2019). In addition to this feather hydrolysate, the *in vitro* anti-inflammatory effect of a chicken feet hydrolysate was also demonstrated in TNF-α-induced inflamed human umbilical vein endothelial cells (HUVEC). A decrease in the levels of several pro-inflammatory proteins, such as soluble (s) ICAM-1 and soluble vascular cell adhesion molecule-1 (sVCAM-1) (Kouguchi et al., 2012); however, anti-inflammatory effects were more potent when the collagen-derived dipeptides PO and PG were tested in TNF-α-induced inflamed HUVECs because these peptides downregulated *iNos* expression, as well as reduced sICAM-1, sVCAM-1 (only for PO sequence), and IL-8 levels compared to the inflamed control HUVECs (Kouguchi et al., 2012). IL-8 is a neutrophil chemotactic factor that exerts proinflammatory effects. Their synthesis by cells such as fibroblasts, epithelial cells, monocytes, neutrophils, tumor cells, endothelial cells, and mesothelial cells, can be stimulated by LPS, TNF-α, and IL-1β (Qazi, Tang, & Qazi, 2011). Circulating ICAM-1 and VCAM-1 are involved in leukocyte-endothelial cell adhesion in different inflammatory diseases, and their expression can be stimulated by IL-1β or TNF-α (Sans et al., 1999). Moreover, some of these anti-inflammatory effects have been confirmed in animals, as plasma sICAM-1 levels, as well as plasma sICAM-1, IL-6, and TNF-α levels were reduced (after the long-term consumption of the fraction <3 kDa of the aforementioned foot hydrolysate) in L-NAME-induced hypertensive rats and ApoE-deficient C57BL/6.KOR-$ApoE^{shl}$ mice, respectively (Y. Zhang, Kouguchi, Shimizu, Sato, et al., 2010; Y. Zhang, Kouguchi, Shimizu, Ohmori, et al., 2010).

Moreover, the *in vivo* anti-inflammatory activity of different hydrolysates obtained from chicken rest raw materials, coming from mechanical meat deboning residues, has been observed in high-fat diet/high sucrose-induced obese C57BL/6 mice. In this sense, obese animals consuming the hydrolysates for 12 weeks showed a reduction in the plasma levels of several pro-inflammatory markers, such as IL-1α, IL-1β, IL-2, IL-6, IL-17, TNF-α, IFN-γ, and MCP-1, when compared with the control group, despite the fact that the levels of the anti-inflammatory cytokine IL-10 were also reduced (Aloysius et al., 2018). Remarkably, MCP-1 facilitates monocytes migration and colonization (Deshmane,

Table 5
Effects of chicken by-product hydrolysates on biometric parameters and lipid metabolism.

By-product	Hydrolysis conditions	Amino acid sequence/s*	Model	Dose	Administration period	Effects	References
Feather	*Bacillus licheniformis* (Fraction <3 kDa)		Broiler chicks	50 mg/L in drinking water	36 days	Treatment of 10 days: ↓serum TC, TG, LDL-C, vLDL-C Treatment of 26 days: ↑ADWG	Alahyaribeik et al. (2022)
Feet	*Aspergillus oryzae* protease (Fraction <3 kDa)		ApoE-deficient C57BL/6. KOR-ApoE^{shl} mice	10%	Daily for 12 weeks	↓plasma and hepatic TC ↓hepatic TG	Zhang, Kouguchi, Shimizu, Sato, et al. (2010)
Liver	Pepsin, 2 h, 37 °C		57BL/6 mice + d-galactose (1.2 g/BW) with subcutaneous injection	250 mg/kg BW	Daily for 6 weeks	↓serum TC	Chou et al. (2014)
			Golden Syrian hamsters + high-fat diet	100 mg/kg BW	Daily for 8 weeks	↓heart, liver and kidney weight ↓serum TG, TC, LDL-C, LDL-C/HDL-C	Yang et al. (2014)
				200 mg/kg BW		↓heart and kidney weight ↓serum TG, TC, LDL-C, LDL-C/HDL-C ↑serum HDL-C	
				400 mg/kg BW		↓heart, liver and kidney weight ↓serum TG, TC, LDL-C, LDL-C/HDL-C ↑serum HDL-C	
			Wistar rats + 100 mg TAA/kg BW (intraperitoneal injection)	200 mg/kg BW 600 mg/kg BW	Daily for 10 weeks	↓food intake and serum ALT ↓food intake, serum AST, and ALT	Chen et al. (2017)
			C57BL/6J (B6) mice + alcoholic diet	80 mg/kg BW	Daily for 8 weeks	↓spleen weight ↓perirenal and epididymal fat ↓serum AST, ALP, TG	Lin et al. (2017)
				320 mg/kg BW		↓spleen weight ↓perirenal and epididymal fat ↓serum AST, ALP, TG	
				1280 mg/kg BW		↓spleen weight ↓perirenal and epididymal fat ↓serum AST, ALP, TG	
			C57BL/6 mice + high-fat diet	~170 mg/kg BW	Daily for 20 weeks	↓heart and liver weight ↓blood AST, LDL-C/HDL-C ↑blood HDL-C	Wu, Lau, et al. (2020)
				~510 mg/kg BW		↓heart and liver weight ↓blood AST, LDL-C/HDL-C ↑blood HDL-C	
			C57BL/6 mice + high-fat diet	~170 mg/kg BW	Daily for 20 weeks	↓final BW, BW gain, and feed efficiency ↓blood TG, ALP, free fatty acids	Wu, Korntner, et al. (2021)
				~510 mg/kg BW		↓final BW, BW gain, feed efficiency ↓liver weight ↓blood TG, ALP, AST, ALT, free fatty acids	
			Institute of Cancer Research(ICR) mice + STZ (50 mg/kg BW) with nicotin-amide (120 mg/kg BW)	409.46 mg mg/kg BW	Daily for 9 weeks	↑hindlimb muscle ↓serum TG, TC, AST, ALT	Yeh et al. (2022)
				818.92 mg/kg BW		↑hindlimb muscle ↓serum TG, TC, AST, ALT	
				1223.38 mg/kg BW		↑hindlimb muscle ↓serum TG, TC, AST, ALT	
Mechanical deboning residues	Alcalase® 0.1%, 1 h, 50 °C		High fat/high sucrose diet-induced obese C57BL/6 mice	9.5 E%	Daily for 12 weeks	↑liver β-oxidation of palmitoyl-Co-A ↑plasma TG ↓plasma NEFA	Aloysius et al. (2018)

(*continued on next page*)

Table 5 (*continued*)

By-product	Hydrolysis conditions	Amino acid sequence/s*	Model	Dose	Administration period	Effects	References
				Casein was replaced by 62.5% of hydrolsate	Daily for 12 weeks	↑plasma long-chain SFAs and MUFAs, C20:5n-3, C18:3n-6, delta 5-desaturase index, C20:5n-3/C18:3n-3 ratio ↓plasma total trans fatty acids	Bjørndal et al. (2020)
	Protamex®, 0.1%, 1 h, 50 °C		High fat/high sucrose diet-induced obese C57BL/6 mice	9.5 E%	Daily for 12 weeks	↓WAT depot	Aloysius et al. (2018)Aloysius et al. (2018)
	Corolase® PP, 0.1%, 1 h, 50 °C		High fat/high sucrose diet-induced obese C57BL/6 mice	9.5 E %	Daily for 12 weeks	↑liver β-oxidation of palmitoyl-Co-A ↓plasma NEFA	
				Casein was replaced by 62.5% of hydrolsate	Daily for 12 weeks	↑plasma long-chain SFAs and MUFAs, C20:5n-3, C18:3n-6, delta 5-desaturase index, C20:5n-3/C18:3n-3 ratio ↓plasma C22:4n-6	Bjørndal et al. (2020)
	Papain + Bromelain, 0.1% (1:1, w/w), 1 h, 50 °C		High fat/high sucrose diet-induced obese C57BL/6 mice	9.5 E%	Daily for 12 weeks	↓WAT depot ↑plasma TG ↓plasma NEFA	Aloysius et al. (2018)
Residues (viscera: 44.5% (w/w), heart: 44.5% (w/w), and blood: 11% (w/w))	*Bromelia pinguin* enzymes, 30 min, 40 °C, pH 6.5 *Bromelia karatas* enzymes, 4 h, 25 °C, pH 6.5 Bromelain, 4 h, 37 °C, pH 7.0.		Wistar rats + hypercaloric diet + STZ	200 mg/kg BW	Daily for 5 weeks	↓serum AL, AST, TC, LDL-C, vLDL-C, TG ↑serum HDL-C ↓serum ALT, AST, TC, LDL-C ↑serum VLDL-C, TG ↓serum ALT, AST, TC, LDL-C	Romero-Garay et al. (2022)

Table shows the most active hydrolysate obtained in each study. ↑ and ↓ indicate an increase or decrease of a parameter, respectively, in comparison with their respective non-treated ill animals.

Abbreviations: ADWG (average daily weight gain), ALP (alkaline phosphatase), ALT (alanine transaminase), Apo E (apolipoprotein E), AST (aspartate aminotransferase), BW (body weight), E (energy), HDL-C (high-density lipoprotein cholesterol), LDL-C (low-density lipoprotein cholesterol), MUFA (monounsaturated fatty acid), NEFA (non-esterified fatty acids), SFA (saturated fatty acid), STZ (streptozotocin), TAA (thioacetamide), TC (total cholesterol), TG (total triglycerides), VLDL-C (very low-density lipoprotein cholesterol), WAT (white adipose tissue). (*)Amino acid sequences were not reported by the authors in the cited works.

Kremlev, Amini, & Sawaya, 2009), and early inflammation is dominated by neutrophils; however in later stages, monocytes become more relevant (Kany et al., 2019). In this sense, the decrease in MCP-1 prevents the progression of the inflammatory process, which combined with the reduction in pro-inflammatory cytokines, suggests an anti-inflammatory potential of these hydrolysates. Their anti-inflammatory effects dependend on the type of hydrolysate consumed, with the most potent of those obtained using Protamex® or Corolase PP® (Aloysius et al., 2018). In addition, an antioxidant chicken liver hydrolysate was also able to decrease several inflammatory markers in high-fat diet animal models (Wu, Lin, et al., 2020, 2021; Yang et al., 2014). Interestingly, supplementation with this liver hydrolysate not only decreased the levels of inflammatory and fibrotic proteins in myocardia of high-fat diet-fed mice, but also attenuated matrix metalloproteinases (MMP2 and MMP9) protein expression (Wu, Lin, et al., 2020). Moreover, the supplementation with the liver-derived hydrolysate attenuated high-fat diet-induced autophagosome accumulation in animals (Wu, Lin, et al., 2020), thereby helping to maintain autophagy homeostasis. Autophagy plays an essential role in the myocardial fibrosis process. In fact, cardiac hypertrophy and lipotoxicicty induced by high-fat diet were associated with an impaired autophagic response, where the accumulation of autophagosomes and an excess of lipids promoted endoplasmic reticulum stress, as well as apoptosis in high-fat diet-fed mice (Che et al., 2018; He et al., 2018). The antiinflammatory effects of the aforementioned liver hydrolysate was also observed in animal models of thioacetamide-induced liver damage (Chen et al., 2017) and in an alcoholic liver disease (Lin et al., 2017) being the lowest tested dose the most effective (80 > 320>1280 mg/kg BW) as it was found in the 80 mg/kg BW dose more pro-inflammatory parameters modified (IL-1β, IL-6 and TNF-α) (Lin et al., 2017). Finally, anti-inflammatory effects were also observed in rats suffering papain-induced osteoarthritis after being administered a Pepsin-digested cartilage hydrolysate for 4 weeks (Yang et al., 2019). These animals showed lower blood levels of TNF-α and IL-1β than control group.

4.2.6. *Neuroprotective effects*

Neurodegenerative diseases, characterized by progressive loss of functional neurons, are another growing disease in our society, especially in the elderly population. It is affected by approximately 50 million people and is expected to double in the next few decades (Hansson, 2021). The prevalence of neurodegenerative diseases is increasing with an increase in the lifespan of the global population. Therefore, new therapies are being investigated to prevent neurological disorders. Recently, it was observed in STZ-induced diabetic mice that the administration of a Pepsin-digested liver hydrolysate improved cognitive dysfunction and behavioral performance of the animals (Yeh et al., 2022). The authors attributed its effects to the reduction of apoptosis in brain cells and amyloid-beta (Aβ) plaques accumulation in the brain with respect to STZ-induced diabetic mice. Apoptosis is characterized by the symptoms of many neurodegenerative diseases and neurological disorders, such Alzheimer's disease or Huntington's disease, and amyotrophic lateral sclerosis (Moujalled, Strasser, & Liddell, 2021). In addition, Aβ plaque accumulation is one of the main histopathological hallmarks of Alzheimer's disease and has been widely

Table 6
Anti-inflammatory effects of chicken by-product hydrolysates.

By-product	Hydrolisis conditions	Amino acid sequence/s	Model	Doses	Administration period	Effect***	References
Cartilage	Trypsin, 10 g/kg by-product, 3 h, 55 °C, pH 7.0	–	Specific pathogen free-grade rats +5% papain solution injected to articular cavity	100 mg/kg BW	Daily for 30 days	↓blood TFN-α, IL-1β, IL-10	Yang et al. (2019)
Feather	Flavourzyme® 10 mg/mL, 4 h, 50 °C, pH 7.0 (F < 0.65 kDa)	SNPSVAGVR, SLFLHTHSIVADK, AVLKKKVTSTFGR, LSPWPVKGV	LPS-activated RAW 264.7	40 μg/mL		↓IL-6 protein and expression ↓iNOS protein and expression ↓*Cox2, Tnf-α*	Inkanuwat et al. (2019)
Feet	*Aspergillus oryzae* protease	PO**, OG**	TNF-α-induced inflamed HUVEC	0.1%		↓sICAM-1 and sVCAM-1	Kouguchi et al. (2012)
	Fraction <3000 Da: *Aspergillus oryzae* protease	–	Hypertensive rats (Wistar Kyoto rats + l-NAME)	2.0 g/kg BW	Daily for 8 weeks	↓plasma siCAM-1 levels	Zhang, Kouguchi, Shimizu,
	Fraction <3000 Da: *Aspergillus oryzae* protease	–	ApoE-deficient C57BL/6. KOR-ApoE^{shl} mice	10%	Daily for 12 weeks	↓plasma IL-6, sICAM-1, and TNF-α	Ohmori, et al. (2010)
Intestine*	Neutrase® +Tripsin (2:1) 0.2%, 4 h, 48.4 °C, pH 7.0	–	Healthy Common carp	25% protein replace	Daily for 8 weeks	↑intestinal *Il-10 and Nf-kB*	Wu et al. (2022)
		–		50% protein replace	Daily for 8 weeks	↓intestinal *Il-1β, Tnf-α* ↑intestinal *Il-10, TGF-β2, and MyD88*	
		–		75% protein replace	Daily for 8 weeks	↓intestinal *Il-8* ↑intestinal *Il-10, TGF-β2, and MyD88*	
		–		100% protein replace	Daily for 8 weeks	↑intestinal *Il-1β, Il-6α, Il-10, Nf-kB, and MyD88*	
Liver	Pepsin 1:400, 2 h, 37 °C	–	Golden Syrian hamsters + high-fat diet	100 mg/kg BW	Daily for 8 weeks	↓liver IL-1β and TNF-α	Yang et al. (2014)
		–		200 mg/kg BW		↓liver TNF-α	
		–		400 mg/kg BW		↓liver TNF-α	
		–	Wistar rats + 100 mg TAA/kg BW (intraperitoneal injection)	200 mg/kg BW	Daily for 10 weeks	↓serum IL-6 and TGF-β	Chen et al. (2017)
		–		600 mg/kg BW	Daily for 10 weeks	↓serum IL-6, TGF-β, and TNF-α	
		–	C57BL/6J (B6) mice + alcoholic diet	80 mg/kg BW		↓liver IL-1β, IL-6, and TNF-α	Lin et al. (2017)
		–		320 mg/kg BW	Daily for 8 weeks	↓liver IL-1β and TNF-α	
		–		1280 mg/kg BW	Daily for 8 weeks	↓liver IL-1β	
		–	C57BL/6 mice + high-fat diet	~170 mg/kg BW	Daily for 20 weeks	↓myocardic IL-1β, IL-6, TNF-α, TGF-β, COX-2, CD36, αSMA, MMP-9, andLC3BII/LC3BI ↑myocardic P62	Wu, Lau, et al. (2020)
		–		~510 mg/kg BW	Daily for 20 weeks	↓myocardic IL-1β, IL-6, TNF-α, TGF-β, COX-2, CD36, αSMA, MMP9, MMP2, LC3BII/LC3BI ↑myocardic P62 and Rab7	
		–	C57BL/6 mice + high-fat diet	~170 mg/kg BW	Daily for 20 weeks	↓liver IL-1β and TNF-α	Wu, Korntner, et al. (2021)
		–		~510 mg/kg BW	Daily for 20 weeks	↓liver IL-1β and TNF-α	
Mechanical deboning residues	Alcalase® 0.1%, 1 h, 50 °C	–	High fat/high sucrose diet-induced obese C57BL/6 mice	9.5 E%	Daily for 12 weeks	↓plasma IL-1β, IL-2, IL-6,IL-10, IFN-γ, TFN-α, MCP-1, and RANTES	Aloysius et al. (2018)
	Alcalase® 0.1%, 1 h, 50 °C	–	ApoE-deficient (Apoe$^{-/-}$) mice + high fat and high sucrose diet	10.6 E%	Daily for 12 weeks	↑plasma IL-2	Bjørndal et al. (2020)
	Protamex®, 0.1%, 1 h, 50 °C	–	High fat/high sucrose diet-induced obese C57BL/6 mice	9.5 E%	Daily for 12 weeks	↓plasma IL-1β, IL-1α, IL-2, IL-6, IL-10,IL-17,	Aloysius et al. (2018)

(*continued on next page*)

Table 6 (*continued*)

By-product	Hydrolisis conditions	Amino acid sequence/s	Model	Doses	Administration period	Effect***	References
						IFN-γ, TFN-α, MCP-1, and GM-CSF	
	Corolase® PP, 0.1%, 1 h, 50 °C	–	High fat/high sucrose diet-induced obese C57BL/6 mice	9.5 E%	Daily for 12 weeks	↓plasma IL-1β, IL-1α, IL-2, IL-6, IL-10, IFN-γ, TFN-α, MCP-1, and GM-CSF	Aloysius et al. (2018)
	Corolase® PP, 0.1%, 1 h, 50 °C	–	ApoE-deficient (Apoe$^{-/-}$) mice + high fat and high sucrose diet	10.6 E%	Daily for 12 weeks	↓plasma MCP-1	Bjørndal et al. (2020)
	Papain + Bromelain, 0.1% (1:1, w/w), 1 h, 50 °C	–	High fat/high sucrose diet-induced obese C57BL/6 mice	9.5 E%	Daily for 12 weeks	↓plasma IL-1β, IFN-γ, TFN-α, MCP-1, and GM-CFS	Aloysius et al. (2018)

Table shows the most active hydrolysate obtained in each study. ↑ and ↓ indicate an increase or decrease of a parameter, respectively, in comparison with their respective non-treated ill animals, except for intestine hydrolysate (*). In this last case, results were compared with those of healthy animals consuming a basic fishmeal.

Abbreviations: αSMA (smooth muscle alpha-actin), Apo E (apolipoprotein E), COX2 (cyclooxigenase-2), E (energy), GM-CSF (granulocyte-macrophage colony-stimulating factor), HUVEC (Human umbilical vein endothelial cells), IL (interleukin), IFN-γ (interferon-gamma), iNOS (inducible nitric oxide synthase), LC3 (microtubule-associated protein 1A/1B-light chain 3), L-NAME (N-nitro L-arginine methyl ester), LPS (lipopolysaccharide), MCP-1 (Monocyte chemoattractant protein-1), MMP-9 (matrix metallopeptidase 9), NF-kB (nuclear factor kB), RANTES (chemokine (C–C motif) ligand 5), sICAM-1 (soluble intercellular adhesion molecule 1), sVCAM-1 (soluble vascular adhesion molecule 1), TAA (thioacetamide), TGF-β (transforming growth factor beta), TNFα (tumor necrosis factor alpha). (**)'O' indicates 'hydroxyproline'. (***) genes are represented by a cursive letter.

studied as a therapeutic target (Ashrafian, Zadeh, & Khan, 2021).

4.2.7. Other effects

Recently, the potential of chicken by-products for osteoarthritis prevention has been highlighted. In this regard, an unspecified hydrolysate obtained from chicken sternal cartilage was administered to female rats with osteoarthritis induced by medial meniscus resection (MMx) and anterior to the medial collateral ligament (ACL) on the left knees, for two weeks (50, 200 and 500 mg/kg BW) before the surgery (Ma et al., 2021). After 12 weeks, in which animals exercised daily for 30 min to induce osteoarthritis, the consumption of the hydrolysate (500 mg/kg BW) prevented the formation of osteophytes in the treated animals and increased the cartilage matrix and collagen content in comparison to control osteoarthritis-induced rats. Moreover, it was observed that hydrolysate-treated animals had repaired the cartilage defects, and the meshwork of collagen fibers was almost intact (Ma et al., 2021). Moreover, a Trypsin-digested cartilage hydrolysate alleviated the effects of osteoarthritis induced by papain injection in male rats, with the <10 kDa fraction being the most effective (Yang et al., 2019).

Using a completely different framework, Lin et al. (2017) observed that pepsin-digested chicken liver hydrolysates ameliorated the development of alcoholic fatty livers in mice. Male C57BL/6J (B6) mice were fed a Lieber-DeCarli regular alcoholic diet containing 5% (v/v) ethanol (35% of the daily caloric intake) and supplemented with chicken hydrolysate for 8 weeks (Lin et al., 2017). The results showed an amelioration of the enlargement of liver and spleen sizes, as well as of the serum AST, ALT, and ALP levels in mice supplemented with the hydrolysate compared to the non-supplemented mice. Furthermore, the antioxidant profile, lipid content, and inflammation status were also reversed by the chicken hydrolysate. The authors suggested that these effects could be attributed to the upregulation of fatty acid β-oxidation, downregulation of fatty acid synthesis, increased antioxidant defenses, and increased alcohol metabolic enzymatic activities (acetaldehyde dehydrogenase).

Finally, the effects of the two chicken by-product hydrolysates on the intestinal function were studied. In this regard, upregulation of intestinal tight junction protein-1 (*Zo-1*) and *Mlck* gene expression was found in common carp fed a chicken intestine hydrolysate (the usual protein fishmeal was replaced by 25, 50, 75, or 100% of the hydrolysate) (Wu et al., 2022). However, their beneficial effects on intestinal barrier function depended on the consumed dose, being the most active when fishmeal protein was replaced by 50% hydrolysate. Moreover, broiler chicks fed a chicken feather hydrolysate had higher muscle layer thickness in several parts of the intestine and lower epithelial thickness in the duodenum and ileum than non-treated animals (Alahyaribeik et al., 2022). These effects suggested that the hydrolysate could increase the intestinal absorptive capacity.

5. Conclusion, current limitations and future perspectives

The study of chicken by-products as a source of bioactive peptides is a very recent activity, with the majority of the studies being carried out in the last decade. Different chicken by-products, including blood, bones, cartilage, combs, feathers, feet, livers, skin, viscera, and wattles have been used to prepare hydrolysates with a wide range of activities. In this regard, the two most searched *in vitro* activities were antioxidant and ACEi activities, although hydrolysates also showed potential effects as DPP-IV inhibitors. Moreover, chicken by-product derived hydrolysates have shown to exert antioxidant, antihypertensive, antidiabetic, anti-hyperglycemic, anti-hypercholesterolemic, anti-inflammatory, anti-coagulant, anti-anemic, hepatoprotective, and neuroprotective effects. Blood, bones, cartilage, combs and wattles, feather, gizzard, liver, skin, trachea, viscera, and residues from mechanical chicken deboning have been useful to obtain antioxidant hydrolysates; blood, feather, foot, liver, and residues from mechanical chicken deboning for antidiabetic hydrolysates; feather, foot, liver, residues from mechanical chicken deboning, viscera, and blood for lipid metabolism management hydrolysates, and cartilage, feather, feet, intestine, liver, residues from mechanical chicken deboning for obtaining anti-inflammatory peptides. Chicken feet stood out as source of antihypertensive peptides and chicken liver as a source of hydrolysates able to exert multiple bioactivities such as antidiabetic, anti-inflammatory and modulator of biometric parameters and lipid metabolism. Although many of the developed hydrolysates have been *in vivo* tested, only one of them has been evaluated in humans, showing antihypertensive effects.

Considering the evidence, chicken by-product hydrolysates have potential applications as functional ingredients; however, many studies are still necessary to achieve this purpose; for instance, studies focus on evaluating the effects of these hydrolysates in clinical trials. Moreover, the design of novel foods or nutraceuticals with specific uses in human health that utilize wastes from poultry farming is still a challenge, since chicken by-products utilization entails several difficulties, such as the limited access to these materials or the lack of environmental education and culture, particularly in developing areas. Thus, efforts must be

carried out to create awareness and motivate industries and workers on poultry leftovers revalorization.

Furthermore, further research is encouraged considering the promising results that have been obtained to date, and some gaps must be addressed, such as analysis of the peptide sequence of the bioactive fractions and other parameters such as molecular weights, as well as allergenicity and immune-reactivity aspects, since novel peptide regions can be exposed after hydrolysis. Besides, most of these hydrolysates are designed to be finally consumed as functional food, so sensory analysis must be an essential part of the future research, since chicken by-products may provide some odd flavors that requires to be eliminated or masked.

In conclusion, the obtaining of bioactive peptides from these by-products could be useful to the valorization of these materials and contribute to drive the development of circular economy principles.

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Declaration of competing interest

The authors declare no conflict of interest.

Data availability

No data was used for the research described in the article.

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