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Hydrolysates and bioactive peptides generated from chicken protein hydrolysis: A systematic review of antihypertensive effects in rats

Hidrolisados e peptídeos bioativos gerados a partir da hidrólise de proteínas de frango: Uma revisão sistemática dos efeitos anti-hipertensivos em ratos

Hidrolizados y péptidos bioactivos generados a partir de la hidrólisis de proteína de pollo: Una revisión sistemática de los efectos antihipertensivos en ratas

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Abstract

In recent years, obtaining protein hydrolysates and peptides from food proteins has been widely studied in order to better understand not only their nutritional and functional properties, but also the possibility of their use as ingredients in functional foods. It is known that many dietary proteins have, in their primary structure, peptide sequences that, when released, can be absorbed by enterocytes and modulate specific physiological functions, in addition to providing essential amino acids and contributing to energy metabolism. Therefore, this review aims to carry out a systematic review to assess the effectiveness of these bioactive compounds in controlling blood pressure in rats. In addition, the methodological quality of the published articles was evaluated. Searches in Scopus, ScienceDirect, ISI Web of Science and PubMed databases were focused on studies on the use of hydrolysates and peptides obtained from the enzymatic hydrolysis of various chicken tissues in rats. It was possible to verify that the positive antihypertensive effects were mainly dependent on the enzymatic conditions and enzymatic hydrolysis and the monitoring of vital

organ functions is essential for the regulation of blood pressure. Due to their effectiveness and low cost, chicken protein hydrolysates could be an interesting alternative for biotechnology applications. Administration of hydrolysates and peptides derived from chicken proteins to spontaneously hypertensive rats (SHR) exhibit potential antihypertensive activity with likely cardiac protective effects against target organ damage.
Keywords: Protein hydrolysates; Bioactive peptides; Chicken protein; Antihypertensive activity; Enzymatic hydrolysis; Spontaneously hypertensive rats.

Resumo

Nos últimos anos, a obtenção de hidrolisados proteicos e peptídeos a partir de proteínas alimentares tem sido amplamente estudada com o intuito de melhor compreender não apenas suas propriedades nutricionais e funcionais, mas também a possibilidade de sua utilização como ingredientes em alimentos funcionais. Sabe-se que muitas proteínas da dieta possuem, em sua estrutura primária, sequências peptídicas que, ao serem liberadas, podem ser absorvidas pelos enterócitos e modular funções fisiológicas específicas, além de fornecer aminoácidos essenciais e contribuir para o metabolismo energético. Portanto, esta revisão tem o objetivo de realizar uma revisão sistemática para avaliar a eficácia desses compostos bioativos no controle da pressão arterial em ratos. Além disso, avaliou-se a qualidade metodológica dos artigos publicados. As buscas nas bases de dados Scopus, ScienceDirect, ISI Web of Science e PubMed foram focadas em estudos sobre o uso de hidrolisados e peptídeos obtidos a partir da hidrólise enzimática de diversos tecidos de frango em ratos. Foi possível verificar que os efeitos anti-hipertensivos positivos foram dependentes principalmente das condições enzimáticas e de hidrólise enzimática e o monitoramento das funções dos órgãos vitais é essencial para a regulação da pressão arterial. Devido à sua eficácia e baixo custo, os hidrolisados de proteína de frango podem ser uma alternativa interessante para aplicações biotecnológicas. A administração de hidrolisados e peptídeos derivados de proteínas de frango a ratos espontaneamente hipertensos (SHR) exibe um potencial atividade anti-hipertensiva com prováveis efeitos protetores cardíacos contra danos em órgãos-alvo.
Palavras-chave: Hidrolisados proteicos; Peptídeos bioativos; Proteína de frango; Atividade anti-hipertensiva; Hidrólise enzimática; Ratos espontaneamente hipertensos.

Resumen

En los últimos años se ha estudiado ampliamente la obtención de hidrolizados de proteínas y péptidos a partir de proteínas alimentarias con el fin de conocer mejor no solo sus propiedades nutricionales y funcionales, sino también la posibilidad de su uso como ingredientes en alimentos funcionales. Se sabe que muchas proteínas de la dieta tienen, en su estructura primaria, secuencias peptídicas que, al ser liberadas, pueden ser absorbidas por los enterocitos y modular funciones fisiológicas específicas, además de aportar aminoácidos esenciales y contribuir al metabolismo energético. Por lo tanto, esta revisión tiene como objetivo realizar una revisión sistemática para evaluar la efectividad de estos compuestos bioactivos en el control de la presión arterial en ratas. Además, se evaluó la calidad metodológica de los artículos publicados. Las búsquedas en las bases de datos Scopus, ScienceDirect, ISI Web of Science y PubMed se centraron en estudios sobre el uso de hidrolizados y péptidos obtenidos de la hidrólisis enzimática de diversos tejidos de pollo en ratas. Fue posible verificar que los efectos antihipertensivos positivos dependían principalmente de las condiciones enzimáticas y de la hidrólisis enzimática y el monitoreo de las funciones de los órganos vitales es esencial para la regulación de la presión arterial. Debido a su efectividad y bajo costo, los hidrolizados de proteína de pollo podrían ser una alternativa interesante para aplicaciones biotecnológicas. La administración de hidrolizados y péptidos derivados de proteínas de pollo a ratas espontáneamente hipertensas (SHR, por sus siglas en inglés) muestra una potencial actividad antihipertensiva con probables efectos protectores cardíacos contra el daño a los órganos diana.
Palabras clave: Hidrolizados de proteína; Péptidos bioactivos; Proteína de pollo; Actividad anti-hipertensiva; Hidrólisis enzimática; Ratas espontáneamente hipertensas.

1. Introduction

Systemic hypertension is a multifactorial clinical condition characterized by high and sustained levels of arterial blood pressure with consequent metabolic alterations in organs such as heart, brain, kidneys and blood vessels (Geleilete et al., 2013). Hypertension is known as a risk factor for cardiovascular diseases, including coronary artery disease, peripheral arterial disease, acute myocardial infarction, heart failure, and stroke; which makes it one of the most important causes of morbidity and mortality worldwide (Jäkälä & Vapaatalo, 2010; Aliani et al., 2015).

The renin-angiotensin system (RAS) plays an important role in the blood pressure control and sodium homeostasis through integrated processes in the kidney, cardiovascular system, and central nervous system (Coffman et al., 2014). In response to a drop in blood pressure, renin cleaves the N-terminus of angiotensinogen, releasing the angiotensin I (Ang I), a 10

amino acid peptide. After the removal of two amino acids from its C-terminus by the angiotensin-converting enzyme (ACE), the Ang I is converted to a potent vasoconstrictor peptide, the angiotensin II (Ang II), which induces several biological responses by binding to specific membrane receptors (Sahay & Sahay, 2012; Sparks et al., 2014). Since RAS plays a critical role in the circulatory homeostasis, the abnormal activation of this system can contribute to the development of cardiovascular disorders like hypertension, heart failure, and hypertrophy (Sparks et al., 2014).

In addition to the pharmacologic therapy, nutritional factors are essential in the prevention and treatment of hypertension, a fact which motivates the search for functional food with antihypertensive properties (Jäkälä & Vapaatalo, 2010). It is known that many food proteins have in their primary structure some peptide sequences easily released after in vivo or in vitro enzymatic proteolysis during gastrointestinal digestion or food processing, that are able to modulate specific physiological functions (Rana et al., 2011). The angiotensin-converting enzyme (ACE) inhibitory peptides (particularly those derived from animal protein) have been extensively studied and the findings have indicated that they are significantly effective in eliminating or reducing the development of hypertension in the spontaneously hypertensive rat (SHR) and human patients (Iwai et al., 2009; Shuib et al., 2013; Liu et al., 2014; Liu et al., 2012).

Due to a high nutritional quality of poultry tissues, obtaining new hydrolysates and peptides from enzymatic hydrolysis of their proteins is of considerable interest for the development of new products, such as nutraceutical compounds. Once ingested they are able to perform basic nutritional functions, as well as trigger beneficial metabolic effects to the human health (Darewicz et al., 2014; Sharma et al., 2012; Hsu et al., 2012; Hubinger et al., 2009).

Different animal models are often used in biomedical research to simulate *in vivo* physiological and pathological conditions in order to improve current practices and technologies. However, it is important that the results obtained with experimental species should be extrapolated to other species that cannot be directly investigated, due to ethical, financial and/or facilities management issues (Fagundes & Taha, 2004; Marquez et al., 2006; Silva et al., 2012). This systematic review was conducted aiming to determine the effectiveness of hydrolysates and peptides derived from chicken protein hydrolysis in reducing and/or maintaining blood pressure in rats.

2. Methodology

2.1 Protocol

This systematic review was conducted in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Moher et., 2009).

2.2 Database search and aim

Electronic searches were carried out on Scopus (http://www.scopus.com/), ScienceDirect (http://www.sciencedirect.com/), ISI Web of Science (http://apps.isiknowledge.com) and PubMed (http://www.ncbi.nlm.nih.gov/pubmed) databases, with recovery time from 2008 to October 2018, using the following keywords: “antihypertensive effect”, “bioactive peptides”, “chicken protein” and “rats” with connector “and”. This present review aimed to provide an overview of the *in vivo* effects of peptides and/or hydrolysates derived from chicken protein enzymatic hydrolysis on rats.

2.3 Selection criteria

No restrictions were made regarding the rat lineage, method for obtaining peptides and/or hydrolysates, dosage, administration form and period. However, only original research papers published in English in peer-reviewed journals and in

the last fifteen years were selected.

The scientific selection criteria were defined to evaluate the inhibitory and protective effects of peptides/hydrolysates on the ACE and the blood pressure, respectively, as well as the methodological quality of the articles. The methodological quality of the published works was assessed according to Greenhalgh (1997) and other systematic reviews (Andrade et al., 2015; Ferreira et al., 2013; Pereira et al., 2011; Silva et al., 2012). The studies were qualitatively categorized on a scale of adequate (score: 2) and unclear/partially adequate (score: 1) and classified by the following criteria: control group, type of control group, dosage, blind assessments, randomized studies, sample size, type of analysis (Table 1).

Table 1. Scientific quality criteria adopted to assess the methodological quality of the published works.

Criteria*	Definition	Score
Control group	Studies that related the use of control group	2
	Papers that did not report the use or did not clearly cited	1
Type of control group	The use of both positive (PC) and negative (NC) control groups	2
	The use of only one control group type, articles that did not clearly mentioned or those ones with score 1 in the "control group" criteria.	1
Administration period	Papers studying the long-term effect of the bioactive compound	2
	A short-term effect study	1
Blind assessments	Papers including double or single-blind assessments	2
	When the blind assessment details were not given in the text	1
Randomized studies	Experiments where the groups were randomized	2
	The absence of randomized experimental design or articles in which randomization was not clearly described	1
Sample size	Papers with 5 or more animals/group	2
	Studies with less than 5 animals/group	1
Type of analysis	Articles that evaluated additional variables, such as other cardiovascular and body weight effects, biochemical parameters	2
	Studies that evaluated only the blood pressure of the animals	1

PC: positive control group; NC: negative control group. *Criteria were adopted according to Greenhalgh (1997) and other systematic reviews (Andrade et al., 2015; Ferreira et al., 2013; Pereira et al., 2011; V. D. O. Silva et al., 2012).
Source: Prepared by the authors.

The maximum score was 14 points (Table 2). Other parameters such as type of bioactive compound administered (protein hydrolysate or bioactive peptide), chicken protein source, dose, administration route, among others, did not score but were taken into consideration to subsequent discussions. Table 3 shows a summary of the selected articles.

Table 2. Scores of the selected articles according to the evaluation criteria.

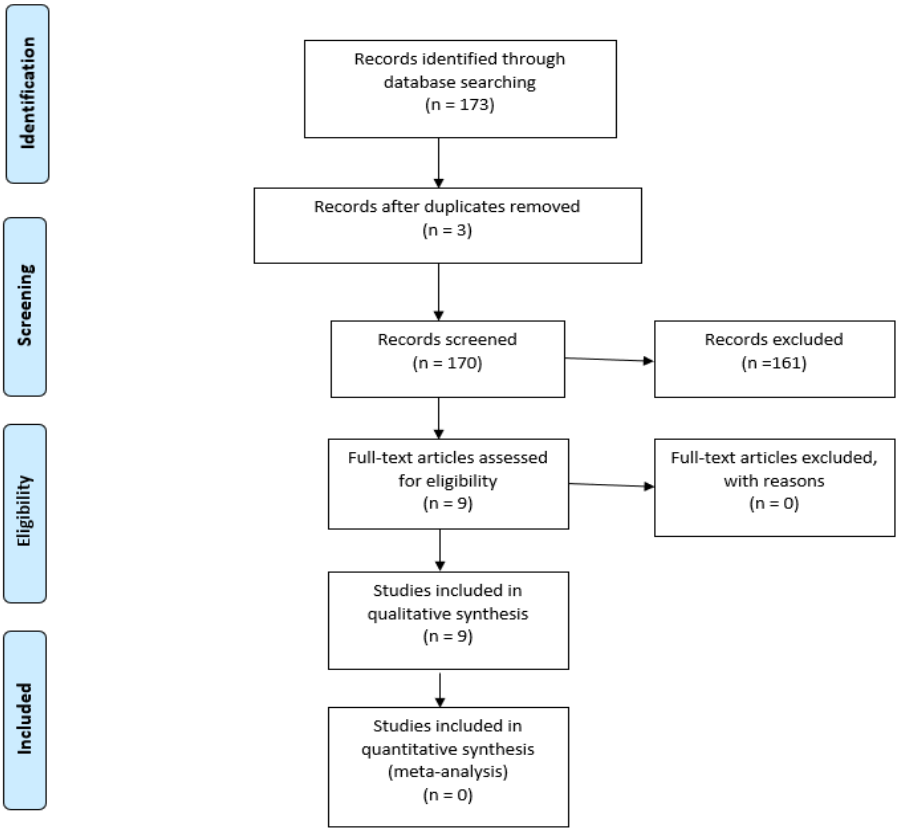
	Published works								
Quality criteria	Cheng et al. (2008)	Mas-Capdevila et al. (2018)	Onuh et al. (2016)	Saiga et al. (2008)	Onuh et al. (2015)	Udenigwe et al. (2017)	Nakade et al. (2008)	Saiga et al. (2006)	Saiga et al. (2003)
Control group*	2	2	2	2	2	2	2	2	2
Type of control group**	1	2	1	1	2	2	2	1	1
Administration period***	2	2	2	2	1	1	1	1	1
Blind evaluation****	1	1	1	1	1	1	1	1	1
Randomization•	2	1	2	1	1	1	1	1	1
Sample size••	2	2	2	2	1	1	1	2	2
Type of analysis•••	2	2	2	2	1	1	1	1	1
Total	*12*	*12*	*12*	*11*	*9*	*9*	*9*	*9*	*9*

*control group (score 2), control group unclear or studies without control group (score 1); **positive and negative controls (score 2), one type of control group, control group type unmentioned, or studies with score 1 in the "control group" parameter (score 1); ***studying long-term effect (score 2), short-term (score 1); ****blind assessments (score 2), unclear or studies without blind assessments (score 1); •randomized studies (score 2), unclear or articles without randomization (score 1); ••Samples groups ≥ 5 animals (score 2); less than 5 animals per group (score 1); •••exclusive SBP measurements (score 1), evaluation of additional *in vivo* variables, such other cardiovascular effects, biochemical parameters, body weight effects, etc. (score 2). Source: Prepared by the authors

3. Results

The overview of the database search and the reasons for the exclusion of some retrieved studies are shown in Figure 1. A search in Scopus found 134 studies, from which 13 were disregarded because they were literature reviews; 7 did not address the use of hydrolysates or bioactive peptides; 92 of them evaluated hydrolysates or peptides derived from sources outside the scope of this study; 13 articles performed only *in vitro* tests, evaluated different biological activities or were not animal studies and 1 article was not written in English. Finally, a total of 8 papers were identified to fit the scope of this review.

Figure 1. Flow diagram for study identification and selection.



Source: Prepared by the authors.

A search in ScienceDirect resulted in 30 studies, 18 of which were previously found in Scopus Database. The remaining studies (12) were not considered because 2 were literature reviews, 9 referred to hydrolysates or peptides derived from a different source (outside the scope of this paper) and 1 paper did not regard hydrolysates or bioactive peptides. The literature survey in the ISI Web of Science database retrieved 5 papers, four of which were duplicates of articles found in Scopus and/or ScienceDirect and 1 was a literature review. In this way, the ISI Web of Science database search did not identify additional papers. The literature search in the PubMed database retrieved 4 papers, three of which were duplicates of articles found in Scopus, ScienceDirect and/or ISI Web of Science databases. Thus, 1 paper was selected for this study. Table 3 shows the experimental design of the 9 selected articles.

Out of the selected articles, 6 (66.70%) reported the use of spontaneous hypertensive rat (SHR) as the animal model and 3 (33.30%) used this lineage in combination with the normotensive Wistar-Kyoto (WKY) rat. The number of animals per group varied in the studies. The smallest sample size comprised 4 animals/group (Nakade et al., 2008; Onuh et al., 2015; Udenigwe et al., 2017), whilst the largest one used 8 animals/group (Cheng et al., 2008) (Table 3).

Table 3. Summary of the selected articles.

	Published works								
Parameters	Cheng et al. (2008)	Mas-Capdevila et al. (2018)	Saiga et al. (2008)	Onuh et al. (2015)	Nakade et al. (2008)	Udenigwe et al. (2017)	Onuh et al. (2016)	Saiga et al. (2006)	Saiga et al. (2003)
Lineage	SHR and WKY	SHR and WKY	SHR	SHR	SHR	SHR	SHR and WKY	SHR	SHR
Sample size	08	06	05	04	04	04	06	05	05
Randomization	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Unclear
Control group	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Type of control group	PC: Captopril	PC: Captopril; NC: Tap water	Unclear	PC: Captopril; NC: PBS	PC: Ile-Pro-Pro; NC: Distilled water	PC: Captopril; NC: Saline	Unclear	Unclear	Unclear
Bioactive compound	Hydrolysate (A4)*	Hydrolysate	Hydrolysate	Hydrolysates (CBS, CBSH, CTS, CTSH)**	Peptide (YYRA)***	Hydrolysate (SPH-P; SPH-PPc)♦	Hydrolysates (CSPH)♦♦	Peptide***	Hydrolysate
Fractionation and/or purification techniques	No	0.45 µm membrane	Ultrafiltration membrane (3 kDa) and HPLC	Ultrafiltration membranes (1; 3, 5 and 10 kDa)	HPLC	No	No	No	Ultrafiltration membrane (1 kDa) and HPLC
Administration period	Short and long-term	Short-term	Short and long-term	Short-term	Short-term	Short-term	Long-term	Short-term	Short-term
Administration route	Intubation	Intubation	Oral	Gavage	Intubation	Gavage	Unclear	Intravenous	Oral
Blind evaluation	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
In vivo analysis	Systolic blood pressure; Total weight gain; heart weight and heart/body weight ratio	Systolic blood pressure; aorta and plasma analysis	Systolic blood pressure; blood components analysis	Systolic blood pressure	Systolic blood pressure	Systolic blood pressure	Systolic blood pressure; plasma analysis; metabolomics studies;	Systolic blood pressure	Systolic blood pressure

*HPLC: High Performance Liquid Chromatography; NC: Negative control; PBS: Phosphate buffered saline; PC: positive control; SHR: Spontaneously hypertensive rats; WKY: Wistar-Kyoto rats. *Hydrolysate obtained after hydrolysis with Alcalase for 4 hours; **CBS: Unhydrolyzed defatted chicken breast skin meal; CBSH: chicken breast skin protein hydrolysate from pepsin + pancreatin digestion; CTS: Unhydrolyzed defatted chicken thigh skin meal and CTSH: chicken thigh skin protein hydrolysate from alcalase digestion; ***YYRA: Tyr-Tyr-Arg-Ala; ♦SPH-P: Spent hen hydrolysate from pepsin digestion and SPH-PPc: Spent hen hydrolysate from pepsin–pancreatin digestion; ♦♦CSPH: chicken skin protein hydrolysate; ♦♦♦Synthesized peptide: Gly-Phe-Hyp-Gly-Thr-Hyp-Gly-Leu-Hyp-Gly-Phe.* Source: Prepared by the authors

Although all articles have reported the presence of control groups in the experiments, 44.44% of the studies mentioned the use of positive and negative controls. In these articles, captopril (Muguerza et al., 2018; Onuh et al., 2015; Udenigwe et al., 2017) and Ile-Pro-Pro (Nakade et al., 2008), a tripeptide with antihypertensive activity, were used as positive control, while phosphate-buffered saline (PBS) (Onuh et al., 2015), distilled water (Nakade et al., 2008), tap water (Mas-Capdevila et al., 2018) and saline (Udenigwe et al., 2017) were used as negative controls. Of the remaining studies, only 1 (11.12%) reported the use of a single type of control group, with the captopril as the positive one (Cheng et al., 2008). Although 4 (44.44%) papers have not informed the type of control group used, casein (Onuh et al., 2016) and saline (Saiga et al., 2003, 2006, 2008) were administered to the animals in the control group (Table 3).

The majority of the retrieved articles (77.8%) evaluated hydrolysates prepared from proteins of various chicken parts such as skins from thigh and breast muscle, collagen, bone legs, breast muscle and chicken feet. The other papers (22.2%) studied peptides obtained from hydrolysis of chicken bone (Tyr-Tyr-Arg-Ala) (Nakade et al., 2008) or synthesized an ACE inhibitory peptide (Gly-Phe-Hyp-Gly-Thr-Hyp-Gly-Leu-Hyp-Gly-Phe) found in the extract digested by gastric enzyme in a previous work (Saiga et al., 2006) (Tables 3 and 4).

Table 4. Effects of administration of chicken protein-derived protein hydrolysates and/or bioactive peptides on short-term and long-term changes in the systolic blood pressure (SBP) of spontaneously hypertensive rats

Protein source	Protease	Dose (mg/kg bw)	SBP maximum reduction (mmHg)[ǂ]	Reference
Leg bones	*Bacillus licheniformis* proteinase	50	- 25 mmHg after 4 h - 20 mmHg after 4 weeks	Cheng et al. (2008)
Feet	Protamex®	85♦	- 30 mmHg after 6h	Mas-Capdevila et al. (2018)
Collagen	*Aspergillus oryzae* protease; a mix of proteases*; pepsin and trypsin/chymotrypsin	3,000	- 40 mmHg after 6 h - 20 mmHg after 2 weeks	Saiga et al. (2008)
Skins from the thigh and breast muscles	*Bacillus licheniformis* alcalase; porcine pepsin with pancreatin	100	CTSH: - 30 mmHg after 3 h CBSH: - 32 mmHg after 5 h	Onuh et al. (2015)
Bone	Pepsin	10	- 20 mmHg after 3 h	Nakade et al. (2008)
Breast muscle	Pepsin + Pancreatin	200	- 40 mmHg after 2 h	Udenigwe et al. (2017)
Skins from the thigh and breast muscles	Alcalase and pepsin + pancreatin	400♦	- 39 mmHg after 6 weeks	Onuh et al. (2016)
-	-	30	- 36 mmHg after 25 min	Saiga et al. (2006)**
Breast muscle	*Aspergillus* protease; trypsin/chymotrypsin; porcine small intestinal juice	1,000	- 45 mmHg after 2 h	Saiga et al. (2003)

bw: body weight; CBSH: chicken breast skin protein hydrolysate from pepsin + pancreatin digestion; CTSH: chicken thigh skin protein hydrolysate from alcalase digestion. ♦*Dose with higher antihypertensive effect;* **Protease FP, protease A amano G, and Protease N;* ***Authors synthesized an ACE inhibitory peptide [Gly- Phe-Hyp-Gly-Thr-Hyp-Gly-Leu-Hyp-Gly-Phe] found in the extract digested by gastric enzyme in a previous work* (Saiga et al., 2003). ǂ*Some values are estimates obtained from graphs in the respective publications.*
Source: Prepared by the authors

The following techniques for the hydrolysate fractionation and peptide purification were used in the papers included in this systematic review: High-Performance Liquid Chromatography (HPLC) (Nakade et al., 2008), ultrafiltration membrane (Onuh et al., 2015) and a 0.45 µm membrane (Mas-Capdevila et al., 2018). A combination of two distinct methods was also used (Saiga et al., 2003, 2008) and in 4 articles no fractionation techniques were applied (Cheng et al., 2008; Onuh et al., 2016; Saiga et al., 2006; Udenigwe et al., 2017) (Table 3).

Of the 9 selected papers, only 2 (22.22%) were randomized experiments (Cheng et al., 2008; Onuh et al., 2016) and none of the studies reported having conduced a blind evaluation (Table 2). There was no consensus about the hydrolysates and/or peptides administration conditions. The lowest dose found was 10 mg/kg bw (body weight), administered once by intubation (Nakade et al., 2008), while the highest one was 3,000 mg/kg bw, single and long-term (four weeks) orally administered (Saiga et al., 2008) (Tables 3 and 4).

All selected articles used the tail-cuff method to measure the systolic blood pressure (SBP) of the rats and made *in vitro* analysis of the ACE inhibitory activity. Other mechanisms involved in the antihypertensive effect of the hydrolysate tested, such plasmatic ACE activity, vascular effects or metabolomics studies were also investigated (Mas-Capdevila et al., 2018; Onuh et al., 2016) (Table 3). Additional parameters analysed in the selected papers included: *in vitro* renin-inhibition analysis (Onuh et al., 2015; Udenigwe et al., 2017), kinetics of enzyme inhibition studies (Mas-Capdevila et al., 2018; Onuh et al., 2015; Saiga et al., 2006), *in vitro* antioxidant capacity (Onuh et al., 2016; Udenigwe et al., 2017), peptide sequence identification (Onuh et al., 2016; Saiga et al., 2006, 2008; Udenigwe et al., 2017), weight gain; heart weight and heart/body weight ratio (Cheng et al., 2008), analysis of the blood components (Saiga et al., 2008), amino acid composition and molecular weight/size determination (Onuh et al., 2015; Udenigwe et al., 2017).

4. Discussion

Reviews provide significant insights into a particular research field as well as suggest the best protocols to assist future studies (Sampaio & Mancini, 2007; Silva et al., 2012). This present study provides an overview of the efficacy of hydrolysates and/or peptides obtained from chicken protein hydrolysis on reducing and/or maintaining blood pressure in rats, focused on targeting which protocols were associated with the most promising results in this species and could be used as a guide to future studies.

According to Huang et al. (2016), hypertension is a threat to human health due to the concomitant risks of cardiovascular and renal diseases. The common drugs prescribed to treat hypertension are mostly “Prils”, such as enalapril, fosinopril and captopril (Deng et al., 2018; Huang et al., 2016). Acting as ACE inhibitors, these synthetic medicines, once ingested, can produce a strong and rapid hypotensive effect (Deng et al., 2018). Cheng et al. (2008), Onuh et al. (2015), Mas-Capdevila et al. (2018) and Udenigwe et al. (2017) reported this powerful antihypertensive effect: the captopril-treated animals showed a rapid significant SBP reduction observed 2 hours after administration (around -30, -25, -15 and -10 mmHg, respectively) and this effect could still be observed during 8 weeks of chronic drug administration (Cheng et al., 2008). Despite its beneficial effects in the blood pressure regulation, the “Prils” drugs can also cause various undesirable side-effects (e.g. dry cough, nausea, rashes and acute renal failure) (Deng et al., 2018; Huang et al., 2016). For this reason, it is growing the scientific efforts to obtain less harmful alternatives (Deng et al., 2018).

It has been reported that through enzymatic proteolysis, *in vitro* chemical hydrolysis, microbial fermentation and gastrointestinal digestion of plants and animals proteins, e.g. winged bean seeds (Saari et al., 2015), egg (Jahandideh et al., 2014), pork (Inoue et al., 2013) and feather (Fontoura et al., 2014), it is possible to obtain hydrolysates and bioactive peptides

which can act like drugs with anti-hypertensive activity by regulating ACE, renin and angiotensin II receptor activities, without or with reduced side-effects to human health (Aluko, 2015; Deng et al., 2018; Jahandideh et al., 2014; Jamdar et al., 2012).

In relation to the proteins of poultry origin, it is known that they are also an excellent source of protein hydrolysates and bioactive peptides. Several of these bioactive compounds have already been reported and, independent of the animal part used, like meat (Fukada et al., 2016; Shahidi et al., 2018; Zhou et al., 2015); viscera (Jamdar et al., 2012; Mane & Jamdar, 2017); feather (Daroit et al., 2018; Fontoura et al., 2014, 2018), skin (Lee et al., 2010, 2012; Howell et al., 2018) and bones (Meng et al., 2017), in all works, the evaluated bioactive compound presented a great antioxidant and/or angiotensin-converting enzyme (ACE) inhibitory capacities.

Although the protein hydrolysates and bioactive peptides with poultry origin could exert their biological activities after direct extraction, a fast method that employ distinct solvents extraction (distilled water, phosphate buffer and aqueous acidic solution), the enzymatic hydrolysis is the method widely-used (Zhang et al., 2016; Wang et al., 2018). This method involves the use of one or more enzymes, usually at the optimum temperature and pH conditions for each protease, that can modify and improve the functional properties of the proteins, enhancing its solubility, without affecting the nutritional value, while converts them into various peptides (Aluko, 2015; Mendoza-Jiménez et al., 2018).

The antihypertensive activity reported to the protein hydrolysates and bioactive peptides studied in the papers retrieved to this systematic review were based on the use of various enzymes and/or proteases, alone (e.g. *Bacillus licheniformis* proteinase; Pepsin), or in combination, (e.g. Alcalase and Pepsin + Pancreatin; Pepsin + Pancreatin; *Bacillus licheniformis* alcalase and porcine Pepsin with pancreatin) (Table 4).

The majority of these proteases are specific, cleaving peptide bonds between specific amino acids (Liu et al., 2016). In this way, the type of protease used in this process, as well the hydrolysis conditions affect the acquisition of antihypertensive hydrolysates and peptides (Bhat et al., 2018; Lee & Hur, 2017; Sánchez & Vázquez, 2017). The hydrolysates should contain peptides with a wide range of chain lengths and composed by distinct amino acids that could influence their nutritional values and biological effectiveness (Aluko, 2015; Iwaniak et al., 2014; Liu et al., 2016). Other hydrolysis parameters which are also known to affect the bioactivity of the hydrolysates and peptides include substrate concentration, enzyme/substrate ratio, incubation time and physicochemical conditions, such as pH and temperature (Mendoza-Jiménez et al., 2018; Silva, 2018; Wang & Shahidi, 2018).

Regarding to the ACE inhibition property, researchers observed that most of the antihypertensive peptides are generally short chains of two to 12 amino acids. Besides that, hydrolysates and peptides with most effective antihypertensive activities likely contain, at the N-terminal position, basic amino acids (such as Lys) or aliphatic amino acids (such as Val and Leu) and, in the C-terminal, hydrophobic amino acids residues (such as Pro, Leu, Phe and Trp) (Huang et al., 2016; Lemes et al., 2016; Yongsawatdigul et al., 2017). For this purpose, the separation of hydrolysates and peptides into groups based on their hydrophobicity, net charge and chain length, and peptide purification by membrane ultrafiltration and chromatography techniques are often applied (Aluko, 2015; Iwaniak et al., 2014).

Although purified peptides and protein hydrolysates with low molecular weight exhibit a strong inhibitory activity, many studies suggest that hydrolysates derived from chicken protein have a longer antihypertensive activity due to the variety of peptides in their composition (Jamdar et al., 2012; Aliani et al., 2013; Terashima et al., 2010). Jamdar et al. (2012), for example, could not improve the ACE inhibitory activity using poultry viscera protein hydrolysates fractionated by ultrafiltration membranes. Onuh et al. (2015) found that peptides present in the CBSH (chicken breast skin protein hydrolysate) and CTSH (chicken thigh skin protein hydrolysate) reduced the inhibitory activity by approximately 50%, probably due to a loss of synergistic functions, which contributes to strong anti-hypertensive properties. Additionally, Cheng et al. (2008) and

Herregods et al. (2011) suggest that the purification of food-derived compounds with ACE inhibitory activity is not profitable and that hydrolysates with high ACE inhibitory activity are preferable in terms of costs and applicability.

Several methods have been devised for estimating potential antihypertensive properties of peptides and the most commons involve *in vitro* ACE or renin activity assays (Aluko, 2015). The method described by Cushman and Cheung (1971) was reported in 5 articles (Cheng et al., 2008; Nakade et al., 2008; Saiga et al., 2003, 2006, 2008) and uses Hippuryl-L-histidyl-L-leucine (HHL) as ACE substrate, with activity estimated by the amount of hippuric acid released from HHL measured by spectrophotometry (Aluko, 2015). Onuh et al. (2015) and Udenigwe et al. (2017) applied the methodology described by Udenigwe et al. (2009) which is based on the use of FAPGG (N-(3-[2-furyl] acryloyl)-phenylalanylglycylglycine) as ACE substrate and estimates. Mas-Capdevila et al. (2018) reported an alternative fluorometric ACE assay, using o-Abz-Gly-p-Phe(NO2)-Pro-OH as substrate and Onuh et al. (2016) determined the plasma ACE activity plasma according to the spectrophotometric method reported by Aluko, (2013).

It is known *in vitro* ACEI activity and *in vivo* antihypertensive effects of protein hydrolysates are not always correlated, due to the bioavailability of the ACE inhibitory peptides after oral administration and the fact that peptides may influence blood pressure by mechanisms other than ACE inhibition (Herregods et al., 2011; Mas-Capdevila et al., 2018). Considering this, *in vivo* assays are performed in order to confirm this bioactivity in an animal model.

Table 4 shows the blood pressure reducing effects of different chicken protein-derived protein hydrolysates and/or bioactive peptides after their administration to SHRs. Although differences were observed to the doses of hydrolysates and bioactive peptides, peptide production method and protein sources, the short and/or long-term administration of all bioactive compounds to spontaneously hypertensive rats led to a reduction in the systolic blood pressure of the animals, with different rates of blood pressure–lowering activity. The tested synthetic peptide (Gly-Phe-Hyp-Gly-Thr-Hyp-Gly-Leu-Hyp-Gly-Phe) (Saiga et al., 2006) and the peptide YYRA (Nakade et al., 2008) produced a maximum decrease within 25 min and 3 h, respectively, whereas the protein hydrolysates obtained from breast muscle (Saiga et al., 2003; Udenigwe et al., 2017), leg bones (Cheng et al., 2008), feet (Mas-Capdevila et al., 2018), collagen (Saiga et al., 2008) and skins from the thigh and breast muscles (Onuh et al., 2016, 2015) took 2-6h and 2-6 weeks after short and long-term administration.

It is known that the use of randomized evaluations and blind assessments improve the reliability of scientific works (Silva et al., 2012). However, only 2 article reported randomization of samples (Cheng et al., 2008; Onuh et al., 2016) and none of the studies reported blind evaluation methods.

5. Conclusion

Administration of chicken protein-derived hydrolysates and peptides to spontaneously hypertensive rats exhibit a potential antihypertensive activity with likely cardiac protective effects against end-organ damage. The degree of the activity depends mainly on the type of enzyme and on the enzymatic hydrolysis conditions. Protein hydrolysates have several advantages when compared with purified chicken peptides. Chicken hydrolysates have a more prolonged antihypertensive activity than purified peptides because of the synergistic effect of their different peptides. The use of hydrolysates reduces the costs with purification and scaling, providing profitability and viability.

New studies in animal models must be carried out to control and establish the measures of administration of hydrolysates with the purpose of possible applications in humans.

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