Food-derived bioactive peptides with antihypertensive activity: A review

Belén Daza-Rodríguez
Corporación Universitaria Rafael Núñez
Angie Rodríguez-Martínez
Corporación Universitaria Rafael Núñez
Albeiro Marrugo-Padilla
University of Cartagena
Johana Márquez-Lazaro (johana.marquez@curnvirtual.edu.co)
Corporación Universitaria Rafael Núñez

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Abstract

Arterial hypertension is a public health problem and one of the most prevalent chronic diseases worldwide, with a considerable impact on the cardiovascular and renal systems, constituting the leading preventable risk factor for premature death and disability worldwide. Modern pharmacological regimens for the treatment of hypertension include the use of Thiazide diuretic, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β-blocker, or calcium channel blockers; Despite the vast therapeutic arsenal that exists, therapeutic failures occur due to a lack of medication adherence, due to the plethora of adverse effects derived from these substances, giving rise to a focus on finding new therapeutic approaches such as bioactive peptides from food. This review aimed to identify the main peptides from foods with antihypertensive activity described in studies published in the last five years (between 2017 to 2021). The review of 23 studies allowed us to identify the peptides with the best antihypertensive potential; these included: RDGGYCC, LRLESF, FHAPWK, and LVLPG from foods of plant origin; LSGYGP, ITT, VISDEDGVTH, ATT, and LWHTH of animal origin; and ALGRV and SPQW derived from fungi.

Introduction

Hypertension is a major global health challenge; its high prevalence and impact on the cardiovascular system, brain, and kidney remain the leading preventable risk factor for premature death and disability worldwide (Ortellado Jose 2017; Oparil et al. 2018; Agüero et al. 2021; Campos-Nonato et al. 2021). This disease is characterized by sustained elevation of blood pressure above 120/80 mm Hg in subjects over 18 years (Oparil et al. 2018). Its etiology is unknown in most cases (85–90%) called primary arterial hypertension (HTN). The remaining 10–15% is secondary to other pathologies such as pheochromocytoma, hyperaldosteronism, alterations in thyroid function, acromegaly, and polycystic kidney disease (Ortellado Jose 2017; Oparil et al. 2018; Campos-Nonato et al. 2021).

H HTN is known to significantly affect cardiovascular conditions, such as heart failure, myocardial infarction, and stroke. Like other diseases, hypertension increases with age, and its prevalence increases from 27% in patients under 60 years of age to 74% in those over 80 years of age (Oliveros et al. 2020).

Modern pharmacological regimens for the treatment of hypertension include the use of Thiazide diuretic (hydrochlorothiazide), angiotensin-converting enzyme inhibitors such as captopril, enalapril, and lisinopril (Lin et al. 2018; Gómez et al. 2019), angiotensin II receptor blocker (Losartan potassium, valsartan), β-blocker (metoprolol, atenolol) or calcium channel blocker (nifedipine, amlodipine, diltiazem) (Joshi et al. 2010). However, these synthetic drugs often cause unwanted side effects such as chronic dry cough, taste disturbances, difficulty swallowing or breathing, headaches, insomnia, diarrhea, allergic reaction, inflammatory responses, angioedema, hyperkalemia, tachycardia, decreased blood pressure, dizziness, ankle swelling, chest discomfort, fatigue, end even leukocytopenia (Joshi et al. 2010; Lin et al. 2018; Gebreyohannes et al. 2019), which increases therapeutic failures due to lack of adherence to the medication, giving rise to a focus on promoting complementary non-pharmacological alternatives such

as physical activity, reduction of alcohol consumption, and a balanced diet in order to mitigate the unwanted effects of antihypertensive drugs (Soto 2018).

Due to the above, the use of natural alternatives for therapeutic purposes has gained great interest in recent years for the control of HTN. Foods such as milk, eggs, meat, corn have presented antihypertensive properties attributed to their major components such as proteins (Ganguly et al. 2019); peptides derived from the metabolism of these proteins are increasingly being studied worldwide, including their biological properties on the modulation of human health (Yang et al. 2021).

Peptides are small isolated protein fragments, usually consisting of 2 to 20 amino acids linked by peptide bonds, whose functionality can provide the necessary nutrients for human growth and development (Yang et al. 2021). Among them, we can find, *bioactive peptides*, or peptides with biological activity produced during gastrointestinal digestion or food processing, could play an important role in metabolic regulation and modulation, suggesting their potential use as nutraceuticals and functional food ingredients to promote health and reduce the risk of diseases.

In recent years, efforts have been made to study the various potential beneficial activities of these bioactive peptides in the body, including their antihypertensive, hypocholesterolemic, antioxidant, antimicrobial, immunomodulatory, and opiate-like activities. Likewise, research is currently being carried out to detect food sources of bioactive peptides, as well as to study their bioavailability, functional properties, and mechanisms of action (Mulero Cánovas et al. 2011).

Bioactive peptides with antihypertensive activity have explicitly been of great interest to the scientific community, as they are one of the most prevalent chronic pathologies worldwide and the leading cause of death in developed countries (Aleixandre et al. 2008; Mills et al. 2020; Zhou et al. 2021). The majority of peptides described in the literature with antihypertensive properties are capable of inhibiting angiotensin-I converting enzyme (ACE-I), a key regulator in the renin-angiotensin system, which leads to the production of angiotensin II; a peptide that acts as a vasoconstrictor agent, implicated in the exacerbation of hypertension (Ganguly et al. 2019).

Due to the above, the objective of this review was to identify the main peptides from foods with antihypertensive activity described in studies published in the last five years (between 2017 to 2021).

Methods

Type of study

A systematic review was carried out following the guidelines of the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (Page et al. 2021).

Search strategy

A systematic electronic search of the literature was carried out in the MEDLINE (via PubMed) and Science direct databases to identify studies evaluating the antihypertensive property of bioactive peptides from food, using the filter from 2017 to 2021. Strategies were used for searches adapted to each database and using the following keywords: ("Antihypertensive Agents"[Mesh]) AND ("Hypertension"[Mesh]) AND (ACE inhibitory) AND (Angiotensin-converting enzyme inhibit*) AND (Antihypertensive activity). The last search was conducted on August 06, 2021 (**Supplementary information Annex 1**).

Studies selection

Studies that met the following inclusion criteria were selected: (**i**) *Type of food from their origin*: meat (chicken, pork, fish, beef, etc.), cereals (rice, soy, corn, etc.), dairy products (milk, cheese), sausages (hams, etc.), eggs, etc. (**ii**) *Evaluation of antihypertensive activity*: we selected bioactive peptides whose antihypertensive activity would have been evaluated in animals or human cells. (**iii**) *Sequence characterization*: we selected bioactive peptides that have their amino acid sequence established in the literature. All articles where peptide activity was not proven, reviews, book chapters, editorials, case reports, and articles where peptide activity was not antihypertensive were excluded.

All reports obtained were stored on the Rayyan platform (Ouzzani et al. 2016), and once duplicates were eliminated; titles and abstracts were examined independently by two reviewers, considering the inclusion and exclusion criteria. Then, the full texts of all relevant articles in the first phase were obtained, reviewed, and determined to meet the eligibility criteria to make a final decision. In case of disagreement between the two reviewers, a third collaborator participated in the selection process until an agreement was reached. For all articles considered relevant for the review and subsequently excluded, the reason for exclusion was clearly stated (**Supplementary information Annex 2**).

Results

Selection of studies

The search in the databases yielded 1,009 studies, two of which were duplicates and were eliminated, obtaining 1,007 articles. When examining the titles and abstracts, 78 studies were selected and subsequently examined in full text, applying the inclusion and exclusion criteria. Finally, 23 studies were obtained to write this review (Fig. 1).

Characteristics of the selected studies

The peptides selected in this review came from animal sources (Cheng et al. 2020; Abdelhedi et al. 2017; Montoro-García et al. 2017; Neves et al. 2017; Chen et al. 2018a, b; Xue et al. 2018; Lin et al. 2019; Liu et al. 2019; Yu et al. 2020; Kang et al. 2020; Oh et al. 2020), plant sources (Cooper et al. 2007; Wang et al. 2017, 2021; Chia-Cheng et al. 2019; Dang et al. 2019; Shih et al. 2019; Vásquez-Villanueva et al. 2019;

Alcaide-Hidalgo et al. 2020; Zhang et al. 2020) and fungi (Manoharan et al. 2017; Amorim et al. 2019) (Table 1).

Table 1
Characteristic of the studies included in the review.

Author	Country	Food	Extraction method	Identification method
(Kang et al. 2020)	Korea	*Styela clava*	Enzymatic hydrolysis (Pepsin, Papain)	HPLC-QTOF-ESI
(Lin et al. 2019)	Taiwan	Marine Cobia Skin	Enzymatic hydrolysis – ultrafiltration - lyophilization.	RP-HPLC-UV
(Liu et al. 2019)	China	Pearl Oyster (*Pinctada fucata martensii*)	Enzymatic hydrolysis with alkaline protease and ultrafiltration.	MALDI-TOF-TOF
(Chen et al. 2020)	China	Lizardfish (*Synodus macrops*) Scale Gelatin	Precipitation and alkaline extraction. Chemical synthesis	HPLC
(Chen et al. 2018a)	China	Big-eyed lizardfish (*Synodus macrops Tanak*a)	Enzymatic hydrolysis with bromelain, alcalase, chymotrypsin, papain, acid protease, trypsin and neutral protease.	Nano-LC-MS/MS
(Oh et al. 2020)	Korea	Olive Flounder (*Paralichthys olivaceus*) Surimi	Acid hydrolysis with hydrochloric acid.	(RP-HPLC) - (ESI)
(Chen et al. 2018b)	China	Ruditapes philippinarum fermented with Bacillus natto	Ultrafiltration	(Nano-RP HPLC-MS / MS).
(Montoro-García et al. 2017)	Spain	Dry cured pork ham.	Chemical degradation with ethanol, centrifugation and lyophilization.	Nano-LC - Q/ToF,
(Abdelhedi et al. 2017)	Tunisia	Smooth - hound viscera protein (*Mustelus mustelus*)	Enzymatic hydrolysis with Esperase.	LC-MS/MS
(Neves et al. 2017)	Ireland	Salmon gelatin	Enzymatic hydrolysis (Alcalase, Flavourzyme).	De novo sequencing

HPLC: high performance liquid chromatography; QTOF: Quadrupole time-of-flight; ESI: Electrospray ionization; MALDI: matrix-assisted laser desorption/ionization; TOF: Time of flight mass spectrometer; LC: Liquid chromatography

Author	Country	Food	Extraction method	Identification method
(Xue et al. 2018)	China	Casein	Enzymatic hydrolysis with pepsin and trypsin.	LC-MC - NSI
(Yu et al. 2020)	China	Egg white	Chemical synthesis	LC-MS
(Wang et al. 2021)	China	Rapeseed meal	Enzymatic hydrolysis with Alcalase.	Spectrophotometric method with FAPGG as substrate.
(Alcaide-Hidalgo et al. 2020)	Spain	Olive Oil	Gel filtration chromatography	Nano-LC-MS/MS
(Vásquez-Villanueva et al. 2019)	Spain	Peach Seed	Enzymatic hydrolysis with thermolysin.	RP-HPLC-MS/MS
(Dang et al. 2019)	China	Broccoli	Enzymatic hydrolysis (chymotrypsin and thermolysin)	HPLC Q-TOF.
(Shih et al. 2019)	Taiwan	Cassia obtusifolia seeds	Enzymatic hydrolysis with four types of proteases, trypsin, α-chymotrypsin, pepsin and thermolysin.	LC-MS/MS - Novo sequencing.
(Li et al. 2019)	Taiwan	corn silk	Centrifugation.	LC-MS/MS
(Wang et al. 2017)	China	Rice bran	Hidrolisis enzimática con tripsina	TOF-Q II - ESI
(Zhang et al. 2019)	China	Glutelin of vinegar-soaked black soybean	Enzymatic hydrolysis with pepsin, trypsin, α-chymotrypsin and alcalase	LC-MS/MS).
(Sonklin et al. 2020)	Canada	Mung bean protein	Enzymatic hydrolysis with bromelain.	MS/MS - ESI
(Manoharan et al. 2017)	Malaysia	*Pleurotus pulmonarius.*	SDS-PAGE.	MALDI-TOF/TOF.

HPLC: high performance liquid chromatography; QTOF: Quadrupole time-of-flight; ESI: Electrospray ionization; MALDI: matrix-assisted laser desorption/ionization; TOF: Time of flight mass spectrometer; LC: Liquid chromatography

Author	Country	Food	Extraction method	Identification method
(Amorim et al. 2019)	Portugal	Spent brewer yeast	Enzymatic autolysis and hydrolysis, membrane filtration fractionation, ultrafiltration, hydrolysis with Cynara cardunculus proteases and nanofiltration.	MALDI-TOF/TOF.

HPLC: high performance liquid chromatography; QTOF: Quadrupole time-of-flight; ESI: Electrospray ionization; MALDI: matrix-assisted laser desorption/ionization; TOF: Time of flight mass spectrometer; LC: Liquid chromatography

Bioactive peptides identified

Bioactive peptides of animal origin

In total, 12 articles were found that studied peptides of animal origin, among which nine came from marine animals (Abdelhedi et al. 2017; Neves et al. 2017; Chen et al. 2018a, b; Lin et al. 2019; Liu et al. 2019; Kang et al. 2020; Oh et al. 2020); one of milk, one of egg, and one of pork (Montoro-García et al. 2017; Yu et al. 2020) (Table 2).

Table 2
Bioactive peptides with hypertensive activity of animal origin.

Food	Peptide sequence	IC_{50}	Main result
Styela clava (Kang et al. 2020)	LWHTH	16,42 – 0,45 μM.	LWHTH strongly inhibited ACE in a concentration-dependent manner. Blood pressure in hypertensive rats decreased and was maintained until 9 h with a clear difference compared to captopril at 9 h. ($p < .01$).
Marine Cobia Skin (Lin et al. 2019)	TAA	118,5 μM	TAA and TL were the most potent ACE inhibitory peptides at in vitro level and had evident antihypertensive activity in vivo when oral doses were administered to hypertensive rats; four hours later, the blood pressure of the experimental group had fallen below controls.
	ATT	9,40 μM	
	ITT	0,50 μM	
	TL	26.8 μM.	
Pearl Oyster (*Pinctada fucata martensii*) (Liu et al. 2019)	HLHT	458,06 ± 3,24 μM.	Peptides HLHT and GWA exhibited high ACE inhibitory activity and competitive and noncompetitive inhibition pathways.
	GWA	109,25 ± 1,45 μM.	
Lizardfish (*Synodus macrops*) Scale Gelatin (Chen et al. 2020)	LSGYGP	2,577 μM	LSGYGP exerted a feasible antihypertensive effect in vitro without cytotoxic concentration; it acts as a mixed non-competitive inhibitor, unlike captopril which is competitive. In vivo tests showed a significant decrease in blood pressure after 6 hours, and good digestive stability was maintained for 4 hours.
Big-eyed lizardfish (*Synodus macrops Tanaka*) (Chen et al. 2018a)	AGPPGSDGQPGAK.	420 ± 20 μM.	AGPPGSDGQPGAK exhibited high ACE inhibitory activity and antihypertensive effect in hypertensive rats at a dose of 2 g kg^{-1}. The decrease in SBP caused by gelatin peptide was greater than that caused by 2 mg/kg captopril.
Olive Flounder (*Paralichthys olivaceus*) (Oh et al. 2020)	IVDR	46900 μM.	IVDR, WYK, and VASVI, all three peptides have high ACE inhibitory activity. However, IVDR exhibited the highest ACE binding energy and negative interaction energy in molecular docking analyses.
	WYK	32970 μM.	
	VSAVI	32660 μM.	

IC_{50}: Half maximal inhibitory concentration; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MAP: Mean arterial pressure; AT1: Angiotensin I, ATII: Angiotensin II.

Food	Peptide sequence	IC_{50}	Main result
Ruditapes philippinarum fermented with Bacillus natto (Chen et al. 2018b)	VISDEDGVTH LDSGDGVT VVVGDGAVGK FAGDDAPRA.	VISDEDGVTH: 8,16 μM.	VISDEDGVTH presented high ACE inhibitory activity, acts as a competitive inhibitor against active sites, is stable against gastrointestinal proteases, also *in vivo* in hypertensive rats, demonstrated an important antihypertensive effect.
Dry cured pork ham (Montoro-García et al. 2017)	KAAAAP AAPLAP AAATP KPVAAP, VPPAK KPGRP PAAPPK.	12,37 – 25,94 μM.	The peptides KAAAAP, AAPLAP, AAATP, KPVAAP, VPPAK, KPGRP, and PAAPPK, demonstrated potent ACE inhibitory activity. A daily intake of 80 g of cured ham did not affect BP or sodium excretion in 24 h.
Smooth - hound viscera protein (*Mustelus mustelus*) (Abdelhedi et al. 2017)	MYPGIADRM MEKIWHHT GDDAPRAVFPS GPAGPRGPA IAGPPGSAGPAG PRGPAGPHGPP VVPFEGAV PLPKREE DSFEGLQQ PTVPKRPSPT EGLQQLR.	571,39–164,56 μg mL^{-1}	All peptides were able to inhibit ACE activity to different degrees. In molecular docking studies, the lowest interaction energy scores were recorded for IAGPPGSAGPAG (-21.076), followed by PLPKREE (-21.143) and PTVPKRPSPT (-21.679), indicating that these peptides could efficiently interact with ACE.
Salmon gelatin (Neves et al. 2017)	PP	1912,46 ± 63,15μM.	PP was the most potent ACE inhibitory peptide, followed by GGPAGPAV. In addition, Salmon gelatin hydrolysates improved SBP, DBP, and MAP in hypertensive rats and reduced heart rate to an extent equivalent to that of Captopril.
	GF	178,14 ± 24,51 μM.	
	GPVA	445,61 ± 6,94 μM.	
	GGPAGPAV	673,16 ± 15,03 μM.	
Casein (Xue et al. 2018)	YQK	15,2 mg mL^{-1}	Of 8 peptides identified, only YQK and INNQFLPYPY showed ACE inhibitory activity. YQK *in vivo* reached a maximal pressure drop in hypertensive rats of 36.8 ± 3.3 mmHg at 4 h in the first dose, and in

IC_{50}: Half maximal inhibitory concentration; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MAP: Mean arterial pressure; AT1: Angiotensin I, ATII: Angiotensin II.

Food	Peptide sequence	IC_{50}	Main result
	INNQFLPYPY	211 mg mL^{-1}	time dose, the pressure remained stable for 4 h.
Egg white (Yu et al. 2020)	TNGIIR	70 μM.	At a 50mg kg^{-1} dose, the TNGIIR peptide showed excellent *in vitro* ACE inhibitory activity. In addition, an excellent inhibitory effect on ACE and AT1 receptor mRNA expression was observed in hypertensive rats, and it also significantly decreased the serum concentration of ATII.
IC_{50}: Half maximal inhibitory concentration; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MAP: Mean arterial pressure; AT1: Angiotensin I, ATII: Angiotensin II.			

Foods of animal origin are highly consumed due to their nutritional contribution, represented in the large number of essential amino acids that have (Quesada and Gómez 2019); They are also more easily digested. During this review, it was found that 52% of the selected studies analyzed peptides of animal origin from foods such as fish (Abdelhedi et al. 2017; Neves et al. 2017; Chen et al. 2018a; Lin et al. 2019; Kang et al. 2020; Oh et al. 2020) pork ham (Montoro-García et al. 2017), milk (Xue et al. 2018) and egg white (Yu et al. 2020).

Most of the animal-derived peptides were obtained from marine sources such as fish, oysters, and clams; interesting fact because these are a good source of protein, and their peptides have shown a wide spectrum of antimicrobial, antiviral, antihypertensive, antidiabetic activities, among others (Cheung et al. 2015), for this reason, they have potential applications in the pharmaceutical and nutritional industry. In the case of the marine invertebrate *Styela clava* (Kang et al. 2020) (67% protein), the **LWHTH** peptide was found to regulate blood pressure in hypertensive rats by strongly inhibiting ACE (IC_{50} = 6.42–0.45 μM). In addition, this peptide was shown to be stable against digestion with gastrointestinal enzymes (pepsin, trypsin, and alpha chymotrypsin) and showed better absorption since it is structurally made up of essential nutrients amino acids, thus favoring its potential use as a natural antihypertensive (Kang et al. 2020).

Other sources such as olive flounder (*P. Olivaceus*) surimi also showed important physiological actions in the regulation of blood pressure (Oh et al. 2020); in which the **IVDR**, **WYK**, and **VASVI** sequences were identified (IC_{50}: 46.90, 32.97 and 32.66 μM, respectively). This study reinforces that evidenced by Ko et al. (2016), where other peptides with antihypertensive activity from the muscle of *P. olivaceus* were identified, including MEVFVP (IC_{50} = 79 μM) and VSQLTR (IC_{50} = 105 μM) (Ko et al. 2016); a fact that demonstrates the potential of this animal as a rich source of bioactive peptides, which are maintained even in preparations such as surimi.

Regarding fish by-products (skin, scales, visors, and bones), it has been found that in addition to obtaining valuable components such as oil, proteins, collagen, enzymes, and minerals, they also have bioactive compounds with antihypertensive action, as reported by Abdelhedi et al. (2017). In this study,

bioactive peptides from fish viscera (IAGPPGSAGPAG, VVPFEGAV, PLPKREE, and PTVPKRPSPT) were identified, which showed in silico inhibitory activity against ACE to different degrees, revealing that they bind to the catalytic site of the enzyme (Abdelhedi et al. 2017). For their part, Chen et al. (2020) found the peptide **LSGYGP** (IC_{50} = 2,577 μM) in tilapia skin, which showed a significant decrease in blood pressure in hypertensive rats as well as good digestive stability (Cheng et al. 2020).

On the other hand, sources derived from animals such as milk and eggs have been subject of much research in terms of bioactive peptides. In this sense, Xue et al. (2018) identified a new ACE-inhibiting peptide derived from bovine casein (**YQK**, IC_{50} = 11.1 μM) and from the YQKFPQYLQY sequence, which was shown to significantly reduce blood pressure systolic blood pressure of hypertensive rats (Xue et al. 2018). Another source of peptides was egg white, of which Yu et al. (2020) found the **TNGIIR** hexapeptide (70 μM), whose activity inhibited the expression of ACE and AT1 receptor mRNA in hypertensive rats and also significantly decreased the serum concentration of ATII (Yu et al. 2020).

Regarding cured meats such as ham, Montoro et al. (2017) showed that the peptides KAAAAP, AAPLAP, AAATP, KPVAAP, VPPAK, KPGRP, and PAAPPK (IC_{50} = 12.37 to 25.94 μM) did not show a decrease in blood pressure of individuals when they were given a daily intake of 80 g of ham (Montoro-García et al. 2017). This shows that their *in vivo* effect may be observed when they are previously digested.

When comparing the inhibitory activities of peptides of animal origin against ACE (Table 2), it was found that the best in decreasing order were: LSGYGP (tilapia skin gelatin), ITT (marine cobia skin), VISDEDGVTH (*Ruditapes philippinarum*), ATT (Cobia Marina skin) and LWHTH (*Styela clava*).

Bioactive peptides of plant origin

A total of 9 articles identified bioactive peptides of plant origin, derived from cereals (Wang et al. 2017, 2021; Chia-Cheng et al. 2019; Shih et al. 2019), legumes (Ciau-Solís et al. 2018; Zhang et al. 2020), fruits (Alcaide-Hidalgo et al. 2020), vegetables (Vásquez-Villanueva et al. 2019), and oils (Dang et al. 2019) (Table 3).

Table 3
Bioactive peptides with hypertensive activity of plant origin.

Food	Peptide sequence	IC_{50}	Main result
Rapeseed meal (Wang et al. 2021)	CI	0,01 – 0,8 mg mL^{-1}	Rapeseed peptides showed antihypertensive activity in hypertensive rats at 25 g kg^{-1} doses, reducing blood pressure after 4-6h. What was highly significant ($p < 0.01$) in SBP, by 21.4 mmHg after 6h of administration, while the Captopril group decreased ($p < 0.01$) by 19.6 mmHg after 4h of oral administration.
	CL		
	VAP		
Olive oil (Alcaide-Hidalgo et al. 2020)	RDGGYCC	0,84 ± 0,02 µM.	Peptides RDGGYCC and CCGNAVPQ produced maximal SBP reductions of 10 and 12% (19 and 23 mmHg), respectively, similar to the reduction produced by Captopril. The antihypertensive effect of the CCGNAVPQ peptide was maintained for 4–8 h and was even significant at 24 h when the Captopril group had returned to baseline levels.
	LEEFCC	–	
	HCGCNTH	–	
	CCGNAVPQ	39,56 ± 2,09 µM	
Peach seeds (Vásquez-Villanueva et al. 2019)	IMAPH	–	IFSPR and IYSPH had a greater inhibitory effect on ACE. Oral administration of the peptide IYSPH at a dose of 1.5 mg kg^{-1} produced a 16% reduction in SBP (about 30 mmHg) after 3–6 h of treatment, compared with captopril at 10 mg kg^{-1}, showed its maximum hypotensive effect 3 hours after administration. Furthermore, there were no statistical differences between the hypotensive effects of captopril and peptides at 6 h after administration ($p > 0.05$).
	ILMH	–	
	IYTPH	–	
	IFSPR	31 ± 2 µg mL^{-1}	
	IYSPH	24 ± 3 µg mL^{-1}	
	VAIP	142 ± 22 µg mL^{-1}	
	ALPDEV	–	
	PILNDE	–	
Broccoli (Dang et al. 2019)	IPPAYTK	–	LVLPGE and LAK exhibit high ACE inhibitory activity; they were found after digestion. LVLPGE peptide at a dose of 10 mg/kg showed a stronger hypotensive effect than Captopril at a dose of 5 mg/kg in hypertensive rats.
	LVLPGE	13,5 µM	
	LAK	48,0 µM.	
	TFQGPPHGIQVER	–	
Cassia obtusifolia Seeds (Shih et al. 2019)	FHAPWK	**FHAPWK**: 6,83 ± 0,90 µM.	FHAPWK was identified as a true competitive inhibitor of ACE; it interacts with several key residues of the enzyme's active site and demonstrated an antihypertensive effect in hypertensive rats.
	LYIPH		

IC_{50}: Half-maximal inhibitory concentration; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MAP: Mean arterial pressure; AT1: Angiotensin I, ATII: Angiotensin II.

Food	Peptide sequence	IC_{50}	Main result
	LYLPH		
	IYIPH		
	IYLPH		
Corn silk (Li et al. 2019)	GLIYPPFSNIR EPFIRPPR MNVPPGPFMAR SKFDNLYGCR AMPTFFLIK	**SKFDNLYGCR**: 44,11 ± 1,04 µM.	SKFDNLYGCR was the most active ACE-inhibiting peptide, lowering SBP by 30 mmHg, while captopril lowered it by 60 mmHg at 2 h; moreover, the decrease by this peptide was persistent for about 6 h.
Rice bran (Wang et al. 2017)	TSL	75,95 µM.	TSL exhibited potent ACE inhibitory activity. Rice bran hydrolysates were administered to hypertensive rats (50 mg kg^{-1}) showing a significant decrease in SBP and DBP of 34–40 mmHg at 6 h, while for the positive control captopril (10 mg kg^{-1}) the SBP decreased 35 mmHg and DBP 30 mmHg at 6 h after administration.
Glutelin of vinegar-soaked black soybean (Zhang et al. 2019)	LSF LAL FGSF IIP ARF.	**FGSF**: 117,11 µM.	FGSF exhibited potent in vitro ACE inhibitory activity and hypotensive effect with the maximal drop of 21.95 mmHg for SBP in hypertensive rats.
Mung bean (Sonklin et al. 2020)	LPRL YADLVE LRLESF HLNVVHEN PGSGCAGTDL	**LRLESF**: 5,4 µM. **LPRL**: 1912 µM.	LRLESF was the most potent ACE inhibitor, and YADLVE was the strongest renin inhibitor with 97% inhibition. Oral administration to Hypertensive Rats revealed strong blood pressure reductions of up to -36 mmHg compared to -15 mmHg for MPH. Furthermore, YADLVE had the most persistent effect after 24 h.

IC_{50}: Half maximal inhibitory concentration; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MAP: Mean arterial pressure; AT1: Angiotensin I, ATII: Angiotensin II.

Plant-based proteins also play an important role in meeting dietary protein needs; 39% of the studies examined peptides from foods such as peaches (Vásquez-Villanueva et al. 2019), broccoli (Shih et al. 2019), corn (Chia-Cheng et al. 2019), rice (Wang et al. 2017) and beans (Sonklin et al. 2020), and olive oil (Alcaide-Hidalgo et al. 2020). Plant-derived peptides have potential ACE inhibitory activities and are also a sustainable option for global consumption (Quesada and Gómez 2019).

Vegetables are a good source of protein despite containing a lower amount of essential amino acids, or in addition to being less accessible to digestive enzymes since they are generally stored in granules, and some plants have inhibitors of these enzymes, for these and other reasons have been widely studied for the extraction of bioactive peptides (Willett et al. 2019).

Among other plant-based foods, we find rice, one of the main cereals that serves as a staple food for almost half of the human population, and its by-product, rice bran, is rich in proteins that are efficient for body growth (Han et al. 2015; Shobako and Ohinata 2020). Wang et al. (2017) isolated a peptide from the rice bran protein, **TSL**, that exhibits potent ACE inhibitory activity (IC_{50} = 75.95 μM); similar to the study reported by Shobako et al. (2018), which identified two peptides, LRA and YY, derived from this protein and which also demonstrated inhibitory activity of the enzyme (IC_{50} = 62 μM and 16.5 μM, respectively) (Wang et al. 2017; Shobako et al. 2018).

Peptides from rapeseed meals reported by Wang et al. (2021) (**CI**, **CL**, and **VAP**, IC_{50} = 0.01 to 0.8 mg mL^{-1}) showed relatively good ACE inhibitory activity *in vitro* and *in vivo* (hypertensive rats) (Wang et al. 2021). Additionally, these authors indicated that when administered concomitantly with captopril, no synergistic effect was observed in the inhibition of the enzyme; however, they found an improvement in nitric oxide levels in hypertensive rats.

Alcaide-Hidalgo et al. (2020) identified olive oil's bioactive peptides RDGGYCC, LEEFCC, HCGCNTH, and CCGNAVPQ. Of these, **RDGGYCC** (IC_{50} = 0.84 ± 0.02 μM) and **CCGNAVPQ** (IC_{50} = 39.56 ± 2.09 μM), showed the highest inhibitory activity against ACE; in addition, their hypotensive effect was similar to that produced by captopril under *in vivo* conditions (Alcaide-Hidalgo et al. 2020).

As for the by-products of food processing, such as peach pits; Vásquez et al. (2019) identified the peptides **IFSPR** (IC_{50} = 31 ± 2 μg mL^{-1}), **IYSPH** (IC_{50} = 24 ± 3 μg mL^{-1}), and **VAIP** (IC_{50} = 142 ± 22 μg mL^{-1}) with antihypertensive activities. **IYSPH** showed the best ACE inhibitory capacity (IC_{50} = 24μg mL^{-1}); it was less susceptible to intestinal peptidases, and its oral administration produced a 16% reduction in its oral administration SBP (around 30 mmHg) in hypertensive rats after 3 to 6 h of treatment (Vásquez-Villanueva et al. 2019). For their part, Shih et al. (2019) identified the peptide **FHAPWK** (IC_{50} = 16.83 ± 0.90 μM) from the seeds of *Cassia obtusifolia*. This peptide proved to be a competitive inhibitor of ACE, whose action managed to reduce at 17 mmHg the SBP of hypertensive rats (Shih et al. 2019). Sonklin et al. (2018) reported five bioactive peptides derived from mung beans, among them, only LRLESF (IC_{50} = 5.4 μM) exhibited significant inhibitory activity against ACE. However, despite not showing *in vitro* inhibitory activity against ACE, the **YADLVE** peptide did show a 97% inhibition of renin; it also reduced the SBP of hypertensive rats between 36 and 15 mmHg, and whose effect was persistent after 24h (Sonklin et al. 2020).

On the other hand, Dang et al. (2019) reported that peptides derived from broccoli, such as **LVLPGE** (IC_{50} = 13.5 μM) and **LAK**: (IC_{50} = 48.0 μM), which showed inhibitory activity against ACE. However, only

LVLPGE exhibited a significant antihypertensive effect against ACE in hypertensive rats (Dang et al. 2019). Li et al. (2019) identified the bioactive peptides GLIYPPFSNIR, EPFIRPPR, MNVPPGPFMAR, SKFDNLYGCR, and AMPTFFLIK from corn silk. However, only **SKFDNLYGCR** (IC_{50} = 44.11 ± 1.04 μM) showed potent *in vivo* activity against ACE (Chia-Cheng et al. 2019). Zhang et al. (2019) reported the bioactive peptides LSF, LAL, FGSF, IIP, and ARF from black soybean glutelin soaked in vinegar. Despite the number of peptides obtained, only **FGSF** (IC_{50} = 117.11 μM) showed a significant hypotensive effect in hypertensive rats (Zhang et al. 2020).

When comparing the inhibitory activities of plant-derived peptides against ACE (Table 3), it was found that the best in decreasing order were: RDGGYCC (olive oil), LRLESF (mung bean), FHAPWK (Cassia obtusifolia seeds) and LVLPGE (broccoli).

Fungus-derived bioactive peptides

Two studies identified bioactive peptides derived from fungi (37, 38), as seen in Table 4.

The fungus has been the subject of recent studies, thanks to its beneficial effects on health (Lau et al. 2013). Although the protein content and quality of mushrooms rank below most animal proteins, they rank above most other foods (Lau et al. 2013; Zhang et al. 2017), making them a good starting material for the production of peptides with bioactive activities, including ACE inhibitory activity.

Manoharan et al. (2017) identified the bioactive peptides ALGVR, VTVGLVVR, VVLRNNK, and ATGNLNPR from the fungus *Pleurotus Pulmonarius*, among this group, only the **ALGVR** pentapeptide (IC_{50} = 55 mg mL^{-1}) was considered a strong competitive ACE inhibitor (Manoharan et al. 2017). Amorim et al. (2019) observed a high percentage (85%) of ACE inhibition in brewer's yeast extracts, which can be easily absorbed due to their size and hydrophobicity (Amorim et al. 2019). The peptides identified in these extracts were: SPQW, PWW, and RYW, of which **SQPW** showed the highest inhibitory activity against ACE (IC_{50} = 12 μM).

Both studies indicated that the peptides with the highest inhibitory activities (ALGVR and SQPW) were resistant to the action of gastrointestinal enzymes, which favors their absorption in the active form, thus potentiating their antihypertensive effect.

Discussion

In order to summarize the available evidence about the antihypertensive activity of bioactive peptides from foods, this systematic review was carried out, in which the currently available evidence of bioactive peptides with antihypertensive activity from foods of plant, animal, and fungi origin was unified.

As mentioned above, ACE inhibition blocks the transformation of angiotensin I into angiotensin II, thus regulating the renin-angiotensin-aldosterone system, preventing an increase in blood pressure. The potency of the peptides to inhibit ACE has been expressed as IC_{50} (half-maximal inhibitory

concentration), which, at a lower value, expresses a greater potential for inhibition of this enzyme, as can be seen in Tables 2 to 4.

Peptides of vegetable origin proved to be more active with IC_{50} from 0.84 μM, standing out RDGGYCC (0.84 ± 0.02 μM) from olive oil and **LRLESF** (5.4 μM) from Mung bean. On the other hand, within the peptides of animal origin, LSGYGP (2.577 μM) from tilapia skin gelatin and **VISDEDGVTH** (8.16 μM) from the clam *Ruditapes philippinarum* stand out. Other foods, such as fungi, showed a marked inhibition of ACE as occurs with **SPQW** (12 ± 3 μM) from brewer's yeast; this is also in contrast to that reported in similar reviews such as the one reported by Ngoh et al. (2018), which identified biologically active peptides from pinto beans with significant ACE inhibitory activity (**PPHMLP** and **PLPTGAGF**) with IC_{50} values of 1.52 and 1.84 μM respectively (Ngoh and Gan 2018). Likewise, peptides with antihypertensive activity have been isolated from many other food sources such as chicken, red meat, wheat gluten, soybeans, sunflower, spinach, etc. Plant sources are mainly attractive for the extraction of these peptides in the industrial sector (food and pharmaceuticals), since they could be included in various food systems and/or medicines to achieve their effect in the body of the final consumer (Aluko 2015; Etemadian et al. 2021).

Several authors attribute the antihypertensive effectiveness of peptides to their structure, which is generally reported to be of low molecular weight (less than 3 kDa), short length (2–20 amino acids), and the presence of hydrophobic residues in their C-segment positively charged terminal have been associated with increased binding affinity with the active site of ACE (Aluko 2015; Amorim et al. 2019). However, Sonklin et al. (2020) found that long peptide chains (**LRLESF**, **PGSGCAGTDL**, and **HLNVVHEN**) had strong ACE inhibitory activity, demonstrating that not only short-chain peptides are active inhibitors of the enzyme.

On the other hand, in addition to demonstrating the ACE inhibitory activity, it is important to study the *in vivo* effect of the peptides to ensure that they can exert their physiological action, since they must overcome the action of proteases present in the gastrointestinal digestion process. For this reason, some studies also show the *in vivo* effect of peptides (Wang et al. 2017, 2021; Chen et al. 2018a; Dang et al. 2019; Lin et al. 2019; Kang et al. 2020), either through an animal model in hypertensive rats, in simulated gastrointestinal digestion, and even in human studies.

In this way, it was found that peptides such as **LWHTH** from the marine invertebrate Styela clava, in addition to presenting powerful ACE inhibitory activity, presented a strong suppressive effect on systolic and diastolic blood pressure in an animal model. Likewise, the peptides (**CI**, **CL**, and **VAP**) from rapeseed meal showed a high inhibition of ACE (IC_{50} = 0.01 and 0.8 mg mL^{-1}) and showed a decrease in blood pressure in hypertensive rats, even higher in a group treated with captopril, a commercial antihypertensive drug.

However, the *in vitro* inhibitory activity does not always correlate at *in vivo* level, as occurs with the mung bean peptide **YADLVE**, which had no detectable ACE inhibitory activity but was found to be a potent

inhibitor of renin activity in 97.06%; when performing *in vivo* studies, this peptide presented the most persistent reductions in blood pressure during a period of 24 h after oral administration in hypertensive rats (Sonklin et al. 2020).

In this sense, the aforementioned makes it clear that there are other mechanisms other than ACE inhibition through which bioactive peptides can act to reduce high blood pressure, such as direct inhibition of the enzyme renin, inhibition of endothelin converting enzyme and antioxidant properties.

Amorim et al. (2019) demonstrated antioxidant activity of spent brewer's yeast peptides and suggest a possible synergistic antihypertensive and antioxidant effect since the deficiency of antioxidant activity has also been involved in the appearance of cardiovascular diseases (Amorim et al. 2019), similar to Neves et al. (2017) in Salmon gelatin (Neves et al. 2017), and Wang et al. (2017) in rice bran (Wang et al. 2017).

Regarding the practical implications, our results contribute to making known to the scientific and health community the potential benefits offered by bioactive peptides from food in the management of hypertension; considering that these promise to be an excellent pharmacological alternative to conventional medications, being able to reduce the side effects that these can cause. Likewise, identifying the presence of bioactive peptides in foods as natural sources of ACE inhibitors makes them functional ingredients applicable both in the food and drug industries to positively reduce the risk of cardiovascular diseases, maintain body health, and disease prevention.

Among the strengths of this review, we highlight that all methods were described in a protocol beforehand. Furthermore, a sensitive search strategy was carried out, so it is unlikely that any relevant evidence was missed. In addition, two reviewers independently performed all selection, methodological quality assessment, and data extraction processes. All of these processes provide reasonable confidence in our results.

Conclusions

Bioactive peptides present in foods have potential health benefits and can be considered a safe and economical option for developing functional products useful in the prevention and treatment of arterial hypertension. Therefore, it is important to continue research to increase knowledge about using bioactive peptides from food as adjuvants in the prevention and treatment of this disease.

Consequently, there has been increased interest in identifying foods that may be natural sources of antihypertensive peptides in recent years. Among the peptides described with the best antihypertensive potential in this review were the sequences RDGGYCC, LRLESF, FHAPWK, and LVLPG from plants, LSGYGP, ITT, VISDEDGVTH, ATT, and LWHTH from animal origin and ALGRV and SPQW derived from fungi, which demonstrated its antihypertensive potential *in vitro* and *in vivo*.

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Table

Table 4 is not available with this version.

Figures

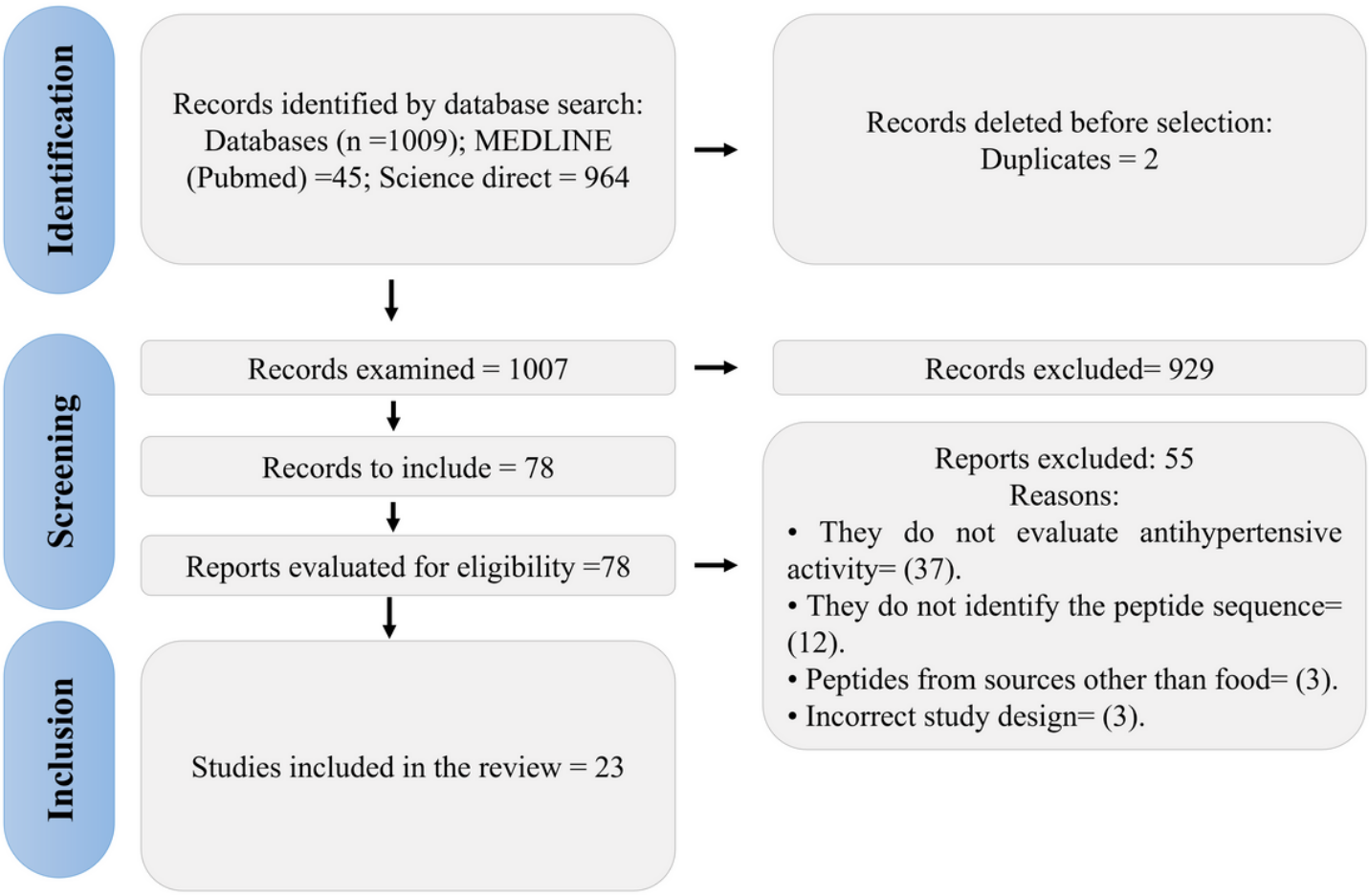

Figure 1

PRISMA flowchart. From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. DOI: 10.1136/BMJ.n71

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