

Food-derived Bioactive Peptides with Angiotensin-Converting Enzyme Inhibiting Effect: A Systematic Review

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Abstract

Objective: To describe the current scientific evidence of food-derived bioactive peptides and their angiotensin-converting enzyme inhibiting effect.

Methods: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) were followed. We searched MEDLINE (through PubMed) and Science Direct databases to identify studies assessing food-derived bioactive peptides and angiotensin-converting enzyme-inhibiting effects. The evidence was organized and presented using tables and narrative synthesis.

Results: We identified 11 peptides with the best antihypertensive potential: RDGGYCC, LRLESF, FHAPWK, and LVLPG from plants; LSGYGP, ITT, VISDEDGVTH, ATT, and LWHTH from animals; and ALGRV and SPQW from fungi, which demonstrated their antihypertensive potential *in vitro* and *in vivo*.

Conclusion: Overall, food-derived bioactive peptides with hypertensive activity were identified, which shows a promising field as a therapeutic alternative to conventional pharmacological treatments.

Keywords

Bioactive peptides, antihypertensive activity, angiotensin-converting enzyme, food

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Introduction

Hypertension (HTN) is a major global health challenge; its prevalence and impact on the cardiovascular system, brain, and kidneys remain the leading preventable risk factors for premature death and disability worldwide.^{1–4} This disease is characterized by sustained elevation of blood pressure above 120/80 mmHg in subjects aged more than 18 years.¹ Its etiology is unknown in most cases (85%–90%), called primary hypertension. The remaining 10%–15% is secondary to other pathologies such as pheochromocytoma, hyperaldosteronism, alterations in thyroid function, acromegaly, and polycystic kidney disease.^{1,3,4}

HTN is known to significantly affect cardiovascular conditions such as heart failure, myocardial infarction, and stroke. Like other diseases, HTN 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.⁵

The current pharmacological regimens for the treatment of HTN include the use of Thiazide diuretics (hydrochlorothiazide) and angiotensin-converting enzyme inhibitors such as captopril, enalapril, and lisinopril, angiotensin II receptor blocker (Losartan potassium and valsartan), β -blockers (metoprolol and atenolol), or calcium channel blockers (nifedipine, amlodipine, and diltiazem).⁶ However, these synthetic drugs often cause

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unwanted side effects such as chronic dry cough, taste disturbances, difficulty in swallowing or breathing, headaches, insomnia, diarrhea, allergic reactions, inflammatory responses, angioedema, hyperkalemia, tachycardia, decreased blood pressure, dizziness, ankle swelling, chest discomfort, fatigue, and even leukocytopenia,^{6–8} which increase 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.⁹

Due to the above, the use of natural alternatives for therapeutic purposes has gained significant interest in recent years for the control of HTN. Foods such as milk, eggs, meat, and corn have presented antihypertensive properties attributed to their significant components, such as proteins;¹⁰ peptides derived from the metabolism of these proteins are increasingly being studied worldwide, including their biological properties on the modulation of human health.¹¹

Peptides are small, isolated protein fragments, usually consisting of 2–20 amino acids linked by peptide bonds, whose functionality can provide the necessary nutrients for human growth and development.¹¹ Among them, we can find bioactive peptides or peptides with biological activity produced during gastrointestinal digestion or food processing. They could play an essential 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.¹²

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.¹³

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.^{14,15} Most peptides described in the literature with antihypertensive properties can inhibit angiotensin-I converting enzyme (ACE-I), a key regulator in the renin-angiotensin system, which leads to the production of angiotensin II, and a peptide that acts as a vasoconstrictor agent implicated in the exacerbation of HTN.¹⁰ Thus, this review describes the current scientific evidence for food-derived bioactive peptides and their angiotensin-converting enzyme-inhibiting effects.

Methods

Type of Study

A systematic review was carried out as per Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA).¹⁶

Search Strategy

A systematic electronic search of the literature was carried out in the MEDLINE (through 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 (“HTN” [Mesh]) AND (ACE inhibitory) AND (Angiotensin-converting enzyme inhibit*) AND (Antihypertensive activity).

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, etc.), sausages (hams, etc.), eggs, and so on. (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 with 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,¹⁷ 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 (Appendix A).

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 (Figure 1).

Characteristics of the Selected Studies

The characteristics of included studies are shown in Table 1. The studies were divided according to origin sources: animal,^{18–29} plant sources,^{30–38} and fungi.^{39,40}

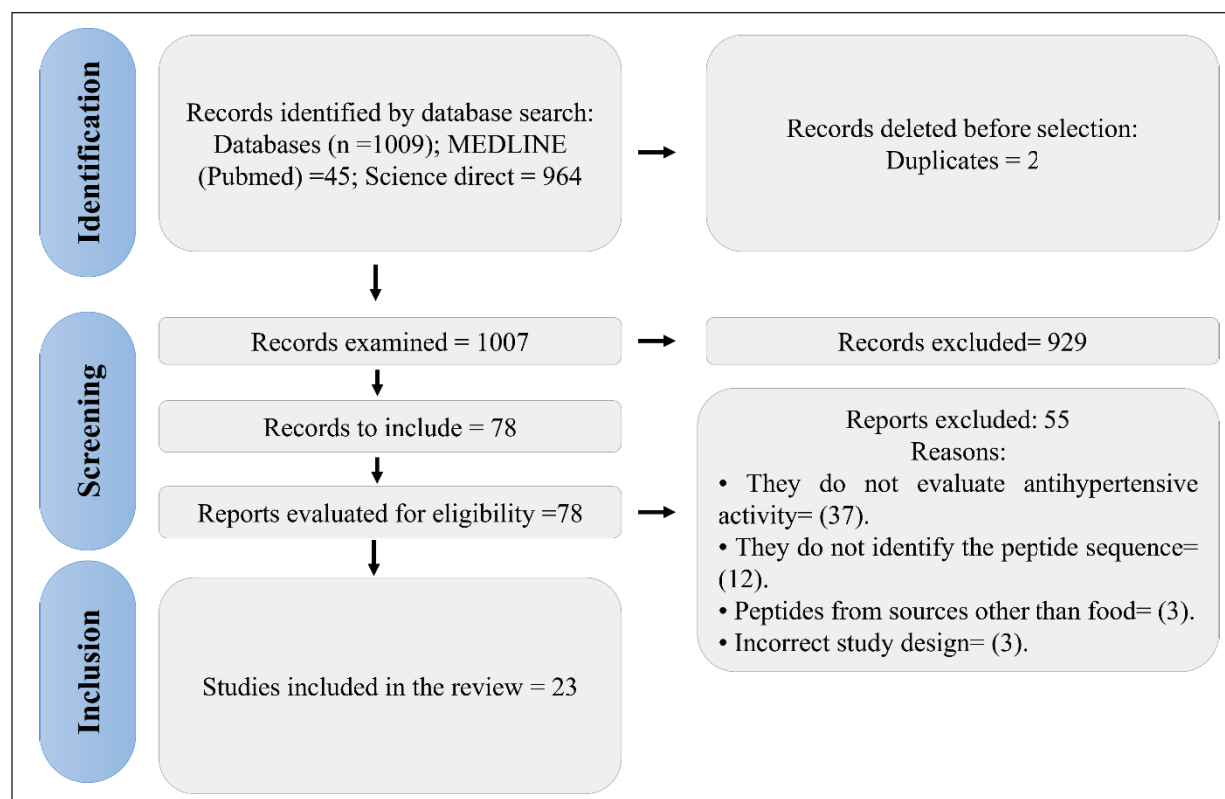


Figure 1. PRISMA Flowchart Describing the Selection of Studies.

Source: Adapted from: Page MJ (2021).¹⁶

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Bioactive Peptides of Animal Origin

There were a total of 12 publications that examined peptides of animal origin, nine of which originated from marine animals,^{18–24,26,27} one from milk, egg, and pork, respectively (Table 2).^{25,28,29}

The substantial contribution of essential amino acids to the diet that comes from the ingestion of proteins like beef, chicken, pork, and even eggs shows how important food of animal origin is to human nutrition.⁴¹ Similar to how they are already commonly used and consumed around the world, these proteins are simple to digest.

In this review, it was found that 52% of the selected studies analyzed peptides of animal origin.^{18–24,26,27} Most of the animal-derived peptides were obtained from marine sources such as fish, oysters, and clams, which is an interesting fact because these are good sources of protein, and their peptides have shown a wide spectrum of antimicrobial, antiviral, antihypertensive, and antidiabetic activities, among others.⁴² For this reason, they have potential applications in the pharmaceutical and nutritional industries. In the case of the marine invertebrate *Styela clava* (67% protein), the LWHTH peptide was found to regulate blood pressure in hypertensive rats by strongly inhibiting ACE ($IC_{50} = 6.42\text{--}0.45\ \mu\text{M}$).¹⁸ In addition, this peptide was stable against digestion with

gastrointestinal enzymes (pepsin, trypsin, and alpha chymotrypsin). It showed better absorption since it is structurally made up of essential nutrients and amino acids, thus favoring its potential use as a natural antihypertensive.¹⁸

Other sources, such as olive flounder (*Paralichthys olivaceus*) surimi, also showed important physiological actions in the regulation of blood pressure, in which the IVDR, WYK, and VASVI sequences were identified (IC_{50} : 46.90, 32.97, and 32.66 μM , respectively).²³ This study reinforces that evidenced by Ko et al. (2016),⁴³ where other peptides with antihypertensive activity from the muscle of *P. olivaceus* were identified, including MEVFVP ($IC_{50} = 79\ \mu\text{M}$) and VSQLTR ($IC_{50} = 105\ \mu\text{M}$), 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.⁴³

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).²⁶ 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.²⁶ In this sense, Chen et al. (2020)²² found the peptide LSGYGP

Table 1. Characteristics of the Studies Included in the Review.

Reference	Country	Food	Extraction Method	Identification Method
(18)	Korea	<i>S. clava</i>	Enzymatic hydrolysis (Pepsin, Papain)	HPLC-QTOF-ESI
(19)	Taiwan	Marine cobia skin	Enzymatic hydrolysis, filtration chromatography.	RP-HPLC
(20)	China	Pearl oyster (<i>Pinctada fucata martensii</i>)	Enzymatic hydrolysis with alkaline protease and ultra-filtration.	MALDI-TOF-TOF
(21)	China	Lizardfish (<i>Synodus macrops</i>) scale gelatin	Precipitation and alkaline extraction. Chemical synthesis	HPLC
(22)	China	Tilapia (<i>Oreochromis niloticus</i>)	Enzymatic hydrolysis with bromelain, alcalase, chymotrypsin, papain, acid protease, trypsin, and neutral protease.	Nano-LC-MS/MS
(23)	Korea	Olive flounder (<i>P. olivaceus</i>) surimi	Acid hydrolysis with hydrochloric acid.	(RP-HPLC) – (ESI)
(24)	China	Ruditapes philippinarum fermented with <i>Bacillus natto</i>	Ultrafiltration	Nano-RP HPLC-MS/MS
(25)	Spain	Dry cured pork ham	Chemical degradation with ethanol, centrifugation, and lyophilization.	Nano-LC – Q/ToF
(26)	Tunisia	Smooth-hound viscera protein (<i>Mustelus mustelus</i>)	Enzymatic hydrolysis with Esperase.	LC-MS/MS
(27)	Ireland	Salmon gelatin	Enzymatic hydrolysis (Alcalase, Flavourzyme).	de novo sequencing
(28)	China	Casein	Enzymatic hydrolysis with pepsin and trypsin.	LC-MC – NSI
(29)	China	Egg white	Chemical synthesis	LC-MS
(30)	China	Rapeseed meal	Enzymatic hydrolysis with Alcalase.	The spectrophotometric method with FAPGG as substrate
(31)	Spain	Olive oil	Gel filtration chromatography	Nano-LC-MS/MS
(32)	Spain	Peach seed	Enzymatic hydrolysis with thermolysin.	RP-HPLC-MS/MS
(33)	China	Broccoli	Enzymatic hydrolysis (chymotrypsin and thermolysin)	HPLC Q-TOF
(34)	Taiwan	<i>C. obtusifolia</i> seeds	Enzymatic hydrolysis with four types: proteases, trypsin, α -chymotrypsin, pepsin, and thermolysin.	LC-MS/MS – Novo sequencing
(35)	Taiwan	Corn silk	Centrifugation.	LC-MS/MS
(36)	China	Rice bran	Hidrolisis enzimática con tripsina	TOF-Q II – ESI
(37)	China	Glutelin of vinegar-soaked black soybean	Enzymatic hydrolysis with pepsin, trypsin, α -chymotrypsin, and alcalase	LC-MS/MS
(38)	Canada	Mung bean protein	Enzymatic hydrolysis with bromelain.	MS/MS – ESI
(39)	Malaysia	<i>Pleurotus pulmonarius</i>	SDS-PAGE.	MALDI-TOF/TOF
(40)	Portugal	Spent brewer yeast	Enzymatic autolysis and hydrolysis, membrane filtration fractionation, ultrafiltration, hydrolysis with <i>Cynara cardunculus</i> proteases, and nanofiltration.	MALDI-TOF/TOF

Abbreviations: 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.

(IC₅₀ = 2.577 μ M) in tilapia skin, which showed a significant decrease in blood pressure in hypertensive rats as well as good digestive stability.²²

On the contrary, sources derived from animals, such as milk and eggs, have been the subject of much research in terms of bioactive peptides. In this sense, Xue et al. (2018)²⁸ identified a new ACE-inhibiting peptide derived from bovine casein (YQK, IC₅₀ = 11.1 μ M) and from the YQKFPQYLQY sequence, which was shown to significantly reduce the systolic blood pressure of hypertensive rats.²⁸ Another source

of peptides was egg white, of which Yu et al. (2020)²⁹ found the TNGIIR hexapeptide (70 μ M), whose activity inhibited the expression of ACE and AT1 receptor mRNA in hypertensive rats and significantly decreased the serum concentration of ATII.²⁹

Regarding cured meats such as ham, Montoro et al. (2017)²⁵ showed that the peptides KAAAAP, AAPLAP, AAATP, KPVAAP, VPPAK, KPGRP, and PAAPPK (IC₅₀ = 12.37 to 25.94 μ M) did not show a decrease in blood pressure in individuals when they were given a daily intake of

Table 2. Bioactive Peptides with the Hypertensive Activity of Animal Origin.

Food	Peptide Sequence	IC ₅₀	Main Result
<i>S. clava</i> ¹⁸	LWHTH	16.42–0.45 μ M	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 ($p < 0.01$).
Marine cobia skin ¹⁹	TAA	118.5 μ M	TAA and TL were the most potent ACE inhibitory peptides at <i>in vitro</i> level and had evident antihypertensive activity <i>in vivo</i> when oral doses were administered to hypertensive rats; 4 h later, the blood pressure of the experimental group had fallen below controls.
	ATT	9.40 μ M	
	ITT	0.50 μ M	
	TL	26.8 μ M	
Pearl oyster (<i>Pinctada fucata martensii</i>) ²⁰	HLHT	458.06 $\pm$ 3.24 μ M	Peptides HLHT and GWA exhibited high ACE inhibitory activity and competitive and noncompetitive inhibition pathways.
	GWA	109.25 $\pm$ 1.45 μ M.	
Tilapia (<i>Oreochromis niloticus</i>) ²²	LSGYGP	2.577 μ M	LSGYGP exerted a feasible antihypertensive effect <i>in vitro</i> without cytotoxic concentration; it acts as a mixed non-competitive inhibitor, unlike captopril, which is competitive. <i>In vivo</i> tests showed a significant decrease in blood pressure after 6 h, and good digestive stability was maintained for 4 h.
Lizardfish (<i>Synodus macrops</i> Tanaka) ²¹	AGPPGSDGQPGAK	420 $\pm$ 20 μ M	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 (<i>P. olivaceus</i>) ²³	IVDR	46,900 μ M	All three peptides, IVDR, WYK, and VASVI, have high ACE inhibitory activity. However, IVDR exhibited the highest ACE binding energy and negative interaction energy in molecular docking analyses.
	WYK	32,970 μ M	
	VSAVI	32660 μ M.	
Ruditapes philippinarum fermented with <i>Bacillus natto</i> ²⁴	VISDEDGVTH LDSDGDGVT VVVG DGAVGK FAGDDAPRA.	VISDEDGVTH: 8.16 μ M	VISDEDGVTH presented high ACE inhibitory activity, acts as a competitive inhibitor against active sites, is stable against gastrointestinal proteases, also <i>in vivo</i> in hypertensive rats, demonstrated an important antihypertensive effect.
Dry cured pork ham ²⁵	KAAAAP	12.37–25.94 μ M	The peptides, such as 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.
	AAPLAP		
	AAATP		
	KPVAAP		
	VPPAK		
	KPGRP		
	PAAPPK.		
Smooth-hound viscera protein (<i>Mustelus mustelus</i>) ²⁶	MYPGIADRM	571.39–164.56 μ g 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.
	MEKIWHHT GDDAPRAVF-		
	PS GPAGPRGPA IAGPPG-		
	SAGPAG PRGPAGPHGPP		
	VVPFEGAV PLPKREE		
	DSFEGQLQQ PTVPKRPSPT		
Salmon gelatin ²⁷	EGLQQLR		
	PP	1912.46 $\pm$ 63.15 μ M	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 Captopril.
	GF	178.14 $\pm$ 24.51 μ M	
	GPVA	445.61 $\pm$ 6.94 μ M	
	GGPAGPAV	673.16 $\pm$ 15.03 μ M	

(Table 2 continued)

(Table 2 continued)

Food	Peptide Sequence	IC ₅₀	Main Result
Casein ²⁸	YQK	15.2 mg mL ⁻¹	Of the 8 peptides identified, only YQK and INNQFLPYPY showed ACE inhibitory activity. YQK <i>in vivo</i> reached a maximal pressure drop in hypertensive rats of 36.8 ± 3.3 mmHg at 4 h in the first dose, and in the second dose, the pressure remained stable for 4 h.
	INNQFLPYPY	211 mg mL ⁻¹	
Egg white ²⁹	TNGIIR	70 µM	At a 50 mg kg ⁻¹ dose, the TNGIIR peptide showed excellent <i>in vitro</i> ACE inhibitory activity. In addition, an excellent inhibitory effect on ACE and ATI receptor mRNA expression was observed in hypertensive rats, and it also significantly decreased the serum concentration of ATII.

Abbreviations: IC₅₀, half maximal inhibitory concentration; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; ATI, angiotensin I, ATII, angiotensin II; ACE, angiotensin converting enzyme.

80 g of ham.²⁵ 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),²² ITT (marine cobia skin),¹⁹ VISDEDGVTH (*Ruditapes philippinarum*),²⁴ ATT (marine cobia skin),¹⁹ and LWHTH (*S. clava*).¹⁸

Bioactive Peptides of Plant Origin

A total of nine articles identified bioactive peptides of plant origin, which were derived from cereals,^{30,35,36} seeds,³⁴ legumes,^{37,38} fruits,³² vegetables,³³ and oils³¹ (Table 3).

Plant-based proteins also play an important role in meeting dietary protein needs; 39% of the studies examined peptides from this source.^{30–38} Plant-derived peptides have potential ACE inhibitory activities and are also a sustainable option for global consumption.⁴¹

Despite having fewer essential amino acids than foods of animal origin and also having reduced digestibility due to their storage in granules that limit the accessibility of proteolytic enzymes, vegetables are regarded as good sources of protein.⁴⁴ One of the reasons why some plants are used as a source for the extraction of bioactive peptides is because they contain enzyme inhibitors.

Among other plant-based foods, we find rice, one of the main cereals that serve 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.^{45,46} Wang et al. (2017)³⁶ isolated a peptide from the rice bran protein, TSL, that exhibits potent ACE inhibitory activity (IC₅₀ = 75.95 µM), like the study reported by Shobako et al. (2018),⁴⁶ which identified two peptides, namely, LRA and YY, derived from this protein and which also demonstrated inhibitory activity of the enzyme (IC₅₀ = 62 and 16.5 µM, respectively).^{36,46}

Peptides from rapeseed meals reported by Wang et al. (2021)³⁰ (CI, CL, and VAP; IC₅₀ = 0.01–0.8 mg mL⁻¹) showed relatively good ACE inhibitory activity *in vitro* and *in vivo* (hypertensive rats).³⁰ 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 as RDGGYCC, LEEFCC, HCGCNTH, and CCGNAVPO. Of these, RDGGYCC (IC₅₀ = 0.84 ± 0.02 µM) and CCGNAVPO (IC₅₀ = 39.56 ± 2.09 µM) showed the highest inhibitory activity against ACE; in addition, their hypotensive effect was like that produced by captopril under *in vivo* conditions.³¹

As for the by-products of food processing, such as peach pits, Vásquez et al. (2019)³² identified the peptides IFSPR (IC₅₀ = 31 ± 2 µg mL⁻¹), IYSPH (IC₅₀ = 24 ± 3 µg mL⁻¹), and VAIP (IC₅₀ = 142 ± 22 µg mL⁻¹) with antihypertensive activities. IYSPH showed the best ACE inhibitory capacity (IC₅₀ = 24 µg 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 3–6 h of treatment.³² Shih et al. (2019)³⁴ identified the peptide FHAPWK (IC₅₀ = 16.83 ± 0.90 µM) from the seeds of *Cassia obtusifolia*.³⁴ This peptide proved to be a competitive inhibitor of ACE, whose action managed to reduce at 17 mmHg the SBP of hypertensive rats.³⁴ Sonklin et al. (2020)³⁸ reported five bioactive peptides derived from mung beans; among them, only LRLESF (IC₅₀ = 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 its effect was persistent after 24 h.³⁸

On the contrary, Dang et al. (2019)³³ reported that peptides derived from broccoli, such as LVLPGE (IC₅₀ = 13.5 µM) and

Table 3. Bioactive Peptides with the Hypertensive Activity of Plant Origin.

Food	Peptide Sequence	IC ₅₀	Main Result
Rapeseed meal ³⁰	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 4–6 h. What was highly significant ($p < 0.01$) in SBP was 21.4 mmHg after 6 h of administration, while the Captopril group decreased ($p < 0.01$) by 19.6 mmHg after 4 h of oral administration.
	CL		
	VAP		
Olive oil ³¹	RDGGYCC	0.84 ± 0.02 µM	Peptides RDGGYCC and CCGNAVPO 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 CCGNAVPO 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	–	
	CCGNAVPO	39.56 ± 2.09 µM	
Peach seeds ³²	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 h 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 ³³	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	–	
<i>C. obtusifolia</i> ³⁴	FHAPWK	FHAPWK: 6.83 ± 0.90 µM	FHAPWK was identified as a true competitive inhibitor of ACE; it interacted with several key residues of the enzyme's active site and demonstrated an antihypertensive effect in hypertensive rats.
	LYIPH		
	LYLPH		
	IYIPH		
	IYLPH		
Corn silk ³⁵	GLIYPPFSNIR	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.
	EPFIRPPR MNVPPG-PFMAR		
	SKFDNLYGCR		
	AMPTFFLIK		
	–		
Rice bran ³⁶	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 ³⁷	LSF	FGSF: 117.11 µM	FGSF exhibited potent <i>in vitro</i> ACE inhibitory activity and hypotensive effect with the maximal drop of 21.95 mmHg for SBP in hypertensive rats.
	LAL		
	FGSF		
	IIP		
	ARF		
Mung bean ³⁸	LPRL	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.
	YADLVE		
	LRLESF		
	HLNVVHEN PGS-GCAGTDL		
	–		

Abbreviations: IC₅₀, half maximal inhibitory concentration; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; AT1, angiotensin I, ATII, angiotensin II; ACE, angiotensin converting enzyme.

LAK: ($IC_{50} = 48.0 \mu M$), showed inhibitory activity against ACE. However, only LVLPGGE exhibited a significant antihypertensive effect against ACE in hypertensive rats.³³ Li et al. (2019)³⁵ identified the bioactive peptides GLIYPPFSNIR, EPFIRPPR, MNVPPGPFMAR, SKFDNLYGCR, and AMPTFFLIK from corn silk. However, only SKFDNLYGCR ($IC_{50} = 44.11 \pm 1.04 \mu M$) showed potent *in vivo* activity against ACE.³⁵ Zhang et al. (2019)³⁷ reported the bioactive peptides such as LSF, LAL, FGSF, IIP, and ARF from black soybean glutelin soaked in vinegar. Despite the number of peptides obtained, only FGSF ($IC_{50} = 117.11 \mu M$) showed a significant hypotensive effect in hypertensive rats.³⁷

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),³¹ LRLESF (mung bean),³⁸ FHAPWK (*C. obtusifolia* seeds),³⁴ and LVLPGGE (broccoli).³³

Fungus-derived Bioactive Peptides

Two studies identified bioactive peptides derived from fungi.^{39,40} The fungus has been the subject of recent studies thanks to its beneficial effects on health.⁴⁷ Although the protein content and quality of mushrooms rank below most animal proteins, they rank above most other foods,^{47,48} making them a good starting material to produce 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 ($IC_{50} = 55 \text{ mg mL}^{-1}$) was considered a strong competitive ACE inhibitor.³⁹ Amorim et al. (2019)⁴⁰ observed a high percentage (85%) of ACE inhibition in brewer's yeast extracts, which can be easily absorbed due to their size and hydrophobicity.³⁸ The peptides identified in these extracts were SPQW, PPWW, and RYW, of which SPQW showed the highest inhibitory activity against ACE ($IC_{50} = 12 \mu M$).⁴⁰

Both studies indicated that the peptides with the highest inhibitory activities (ALGVR and SPQW) were resistant to the action of gastrointestinal enzymes, which favors their absorption in the active form, thus potentiating their antihypertensive effect.^{39,40}

Discussion

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 and 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 (Tables 2 and 3).

Peptides of vegetable origin proved to be more active, with an IC_{50} of $0.84 \mu M$, standing out RDGGYCC ($0.84 \pm 0.02 \mu M$) from olive oil³¹ and LRLESF ($5.4 \mu M$) from mung bean.³⁸ On the contrary, within the peptides of animal origin, LSGYGP ($2.577 \mu M$) from tilapia skin gelatin²² and VISDEDGVTH ($8.16 \mu M$) from the clam *Ruditapes philippinarum* stand out.²⁴ Other foods, such as fungi, showed a marked inhibition of ACE, as occurs with SPQW ($12 \pm 3 \mu M$) from brewer's yeast.⁴⁰ This is also in contrast to that reported in similar reviews, such as the one reported by Ngoh and Gan (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 $1.84 \mu M$, respectively.⁴⁹ Likewise, peptides with antihypertensive activity have been isolated from many other food sources, such as chicken, red meat, wheat gluten, soybeans, sunflower, and spinach. 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 medicines to achieve their effect in the body of the final consumer.^{50,51}

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, which have been associated with increased binding affinity with the active site of ACE.^{40,51} 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.³⁸

On the contrary, 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,^{18,19,21,30,33} either through an animal model in hypertensive rats, in simulated gastrointestinal digestion, or even in human studies.

In this way, it was found that peptides such as LWHTH from the marine invertebrate *S. clava*,¹⁸ 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 the *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% of cases. 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.³⁸

In this sense, it 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 the antioxidant activity of spent brewer's yeast peptides and suggested a possible synergistic antihypertensive and antioxidant effect since the deficiency of antioxidant activity has also been involved in the appearance of cardiovascular diseases,⁴⁰ like Neves et al. (2017) in salmon gelatin²⁷ and Wang et al. (2017) in rice bran.³⁶

Regarding the practical implications, our results contribute to making known to the scientific and health communities about the potential benefits offered by bioactive peptides from food in the management of HTN, considering that these promise to be an excellent pharmacological alternative to conventional medications and 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 prevent disease.

Some limitations of this review are the language barrier due to all the evidence found being published in English, which eliminated the inclusion of available evidence published in any other language. However, it is highlighted that no restrictions about languages were performed. In addition, only some of the selected articles evaluated the safety of peptides. However, this is a window for conducting studies that include this phase.

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 these processes provide reasonable confidence in our results.

Conclusion

Bioactive peptides present in foods have potential health benefits and can be considered an option for developing functional products useful in the prevention and treatment of arterial HTN. Thus, there has been increased interest in identifying foods that may be natural sources of antihypertensive peptides in recent years. Among the peptides described in this

review with the best antihypertensive potential were the sequences RDGGYCC, LRLESF, FHAPWK, and LVLPG from plants; LSGYGP, ITT, VISDEDGVTH, ATT, and LWHTH from animals; and ALGRV and SPQW from fungi, which demonstrated their antihypertensive potential *in vitro* and *in vivo*. However, studies are required to demonstrate the usefulness of these peptides in daily clinical practice in humans.

Abbreviations

ACE-I, angiotensin-I converting enzyme; HTN, Hypertension; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses;

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