Food Chemistry: Molecular Sciences 4 (2022) 100078

Contents lists available at ScienceDirect

Food Chemistry: Molecular Sciences

journal homepage: www.sciencedirect.com/journal/food-chemistry-molecular-sciences

Recent findings on the cellular and molecular mechanisms of action of novel food-derived antihypertensive peptides

Innocent U. Okagu [a,*], Timothy P.C. Ezeorba [a,*], Emmanuel C. Aham [a], Rita N. Aguchem [a], Regina N. Nechi [b]

[a] Department of Biochemistry, University of Nigeria, Nsukka 410001, Nigeria
[b] Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka 410001, Nigeria

ARTICLE INFO

Keywords:
Bioactive peptides
Antihypertensive peptides
Hypertension
ACE-inhibitory peptides
Nutraceuticals
Functional foods

ABSTRACT

Hypertension impacts negatively on the quality of life of sufferers, and complications associated with uncontrolled hypertension are life-threatening. Hence, many research efforts are exploring the antihypertensive properties of bioactive peptides derived from food proteins using *in vitro* ACE-inhibitory assay, experimentally-induced and spontaneous hypertensive rats, normotensive and hypertensive human models. In this study, the cellular and molecular mechanisms of blood pressure-lowering properties of novel peptides reported in recent studies (2015-July 30, 2021) were discussed. In addition to common mechanisms such as the inhibition of angiotensin I-converting enzyme (ACE) and renin activities, recently recognized mechanisms through which bioactive peptides exert their antihypertensive properties including the induction of vasodilation via upregulation of cyclo-oxygenase (COX) and prostaglandin receptor and endothelial nitric oxide synthase expression and L-type Ca^{2+} channel blockade were presented. Similarly, emerging mechanisms of blood pressure-lowering by bioactive peptides such as modulation of inflammation (TNF-α, and other cytokines signaling), oxidative stress (Keap-1/Nrf2/ARE/HO-1 and related signaling pathways), PPAR-γ/caspase3/MAPK signaling pathways and inhibition of lipid accumulation were discussed. The review also highlighted factors that influence the antihypertensive properties of peptides such as method of hydrolysis (type and number of enzymes, and chemical used for hydrolysis, and microbial fermentation), and amino acid sequence and chain length of peptides.

1. Introduction

Hypertension is a medical condition in which an adult has systolic and diastolic blood pressure levels of 140/90 mmHg and above. The number of people living with hypertension (sustained high blood pressure) globally is worrisomely high (WHO, 2021). Despite many efforts in place to reduce this number, the statistics have remained almost the same between 2010 till date due to elevation in alcohol, tobacco and substance use and obesity, which are major risk factors to hypertension (Louca et al., 2020). Hypertension and its co-morbidities are among the leading cause of death accrued to noncommunicable diseases, and although effective, currently-available antihypertensives do not lower blood pressure in some hypertensive patients. In addition, the high cost and side effects such as high serum potassium level and hypotension associated with these drugs also contribute to poor adherence to treatment and increased risk to other chronic diseases associated with unmanaged hypertension such as organ failure and stroke (Leoncini et al., 2020). Hence, the continuous search for more agents that are safe and can effectively normalize blood pressure, which may be the hope of those who do not respond to the currently-available antihypertensives.

In traditional medicine, natural products derived from plants (Verma et al., 2021), and food proteins (Wang et al., 2021) are used in managing cases of hypertension. Plant extracts (especially those rich in polyphenolic compounds) and compounds isolated from them are generating major interest in reducing blood pressure in normotensive, experimentally-induced and spontaneous hypertensive rodents (Kim, Hwang, Kim, Park, & Kim, 2020). Reports of clinical trials on the beneficial effects of dietary proteins on hypertension are accumulating. In POUNT Lost Trials, ingestion of dietary proteins was demonstrated to modify genetic susceptibility to hypertension by significantly reducing the risk of developing hypertension in cohorts receiving high protein diets compared to placebo (Sun, Zhou, Li, Heianza, Liang, Bray, & Qi, 2019). Similarly, a 5-year follow-up of over 13,000 middle-aged Korean men showed that participants who were placed on animal-based

* Corresponding authors.
E-mail addresses: innocent.okagu@unn.edu.ng (I.U. Okagu), timothy.ezeorba@unn.edu.ng (T.P.C. Ezeorba), emmanuel.aham@unn.edu.ng (E.C. Aham).

https://doi.org/10.1016/j.fochms.2022.100078
Received 25 August 2021; Received in revised form 7 January 2022; Accepted 21 January 2022
Available online 25 January 2022

protein-rich diets were more susceptible to hypertension and other metabolic risks compared to participants receiving plant-based protein-rich diets (Chung et al., 2020). A similar result was obtained in participants drawn from Iranian population that consumption of protein-based diets reduces the risk of hypertension (Mehrabani, Asemi, Najafian, Sajjadi, Maghroun, & Mohammadifard, 2017). Upon intestinal hydrolysis, peptides generated from these dietary proteins interact with receptors such as muscarinic and angiotensin II (Ang II) receptors to induce vasorelaxation; the peptides also modulate the renin-angiotensin signaling system (RAS), especially by inhibiting the activities of renin and ACE to lower blood pressure. In addition, some of these intervention agents modify risk factors and co-morbidities of hypertension such as oxidative stress, obesity and diabetes (Metchi Donfack et al., 2021). Furthermore, many dietary proteins reduce blood pressure by increasing nitric oxide availability and inhibiting the formation of advanced glycation end-products and insulin resistance (Ghatage, Goyal, Dhar, & Bhat, 2021). Among the natural products being screened as potential sources of antihypertensive agents, food proteins, their hydrolysates and peptides isolated from them with antihypertensive properties are dominating (Kaur, Kehinde, Sharma, Sharma, & Kaur, 2021; Oh et al., 2020a; Oh et al., 2020b). Generally, the exposure of unique side chains of amino acids in peptides encrypted in proteins during hydrolysis have been shown to increase their biological functionality. The hydrolysis of proteins derived from buffalo and cow milk with papain, pepsin and trypsin were shown to markedly enhance the ACE-inhibitory properties relative to intact proteins (Praveesh, Angayarkanni, & Palaniswamy, 2011). In addition to enzymolysis, it is worthy of note that the release of peptides from proteins are also achieved using chemical hydrolysis and microbial fermentation (Aluko, 2015), discussed briefly later.

Previous review articles discussed antihypertensive protein hydrolysates and their peptides reported up to 2015 (Aluko, 2015; Hernández-Ledesma, Del Mar Contreras, & Recio, 2011; Martínez-Maqueda, Miralles, Recio, & Hernández-Ledesma, 2012). While the first two studies focused more on sources of the peptides, Aluko et al. further discussed methods of preparation of antihypertensive peptides (AHPs) isolated by 2015 and their mode of action, specifically the inhibition ACE and renin activities and blocking of interaction between the vasoconstrictor, Ang II and its receptors. Recently, the inhibitory properties of peptides isolated from proteins originating from Amaranth, fish and microalgae against ACE and renin activities were recently reviewed (Jiang et al., 2021; Nardo, Suárez, Quiroga, & Añón, 2020; Yathisha, Ishani, Iddya, & Mamatha, 2018). It is worthy to mention that the methods of production, isolation, purification and quantification, and bioavailability of the antihypertensive peptides were discussed in previous reviews (Aluko, 2015; Jogi, Yathisha, Bhat, & Mamatha, 2021; Xue, Yin, Howell, & Zhang, 2021). Hence, only some unique steps in peptide isolation with special reference to recently adopted techniques to improve upon some of the challenges associated with peptide isolation, identification and quantification were highlighted in this review. The review further discussed: (I) the ACE-inhibitory and blood pressure-lowering novel peptides isolated from protein hydrolysates of plant and animal origin investigated using *in vivo, in silico*, cell culture, animal and human clinical studies and reported in recent peer-reviewed articles (2015-July 30, 2021), (II) the cellular and molecular mechanisms of blood pressure-lowering potentials of these food protein hydrolysates and peptides due to the induction of vasodilation via upregulation of *cyclo*-oxygenase (COX) and prostaglandin receptor and endothelial nitric oxide synthase expression and L-type Ca^{2+} channel blockade, (III) how the method of preparation (type of microbes used for fermentation and type/number of enzymes used for enzymolysis), amino acid chain length and amino acid sequence influence antihypertensive properties of peptides and (IV) limitations of current research and future research directions. In addition to already demonstrated mechanisms by which food protein hydrolysates and peptides lower blood pressure, we also discussed other potential signaling pathways via which blood pressure can be regulated such as modulation of inflammation (TNF-α, and other cytokines signaling), oxidative stress (Keap-1/Nrf2/ARE/HO-1 and related signaling pathways), PPAR-γ/caspase3/MAPK signaling pathways and inhibition of lipid accumulation. This will encourage researchers to explore these signaling pathways as possible mechanisms of action of AHPs in future studies. Finally, this review aims to project the uniqueness of these novel AHPs mostly sourced from wastes and underutilized natural products such as bones and muscles of marine organisms, plant and animal wastes, and fermentation products of unique microorganisms as excellent candidates for functional food development.

2. Preparation of antihypertensive peptides from food proteins

Dietary proteins are first isolated from its source such as milk, egg, meat, snail, chicken, fish, soybean, rice, lupin, mung bean, and Amaranth. Proteins have been hydrolyzed into peptide units using a variety of ways by basically transferring the proteins into the active site of the proteases to hydrolyze their peptide bonds. Maximum hydrolytic efficiency is achieved by adjusting medium (water or buffer) to optimum temperature and optimum pH of the enzyme (Adjonu, Doran, Torley, & Agboola, 2013). Previously, the use of a single enzyme for protein hydrolysis is common but recently, a combination of two or more enzymes during protein hydrolysis is adopted to increase the yield of shorter chain peptides which are shown exert better bioavailability and bioactivity. Whereas in multiple enzyme digestion method, two or more enzymes are used simultaneously (if they possess same optimal pH and temperature) or consecutively (Aluko, 2015). In many cases, the biological activity (such as antihypertensive activity) of the protein hydrolysates are assayed. This is followed by separation of the protein hydrolysates into fractions based on their molecular weight and the fractions with marked biological activities are selected for separation into their peptides. The peptides in the protein hydrolysate vary in chain length, hydrophobicity, net charge, and activity; these physicochemical properties inform the techniques needed to separate the peptides such as peptide purification, and amino acid sequence identification (Girgih et al., 2015). The most common technique, membrane ultracentrifugation, sort the peptides in protein hydrolysates based on their size/molecular weight/peptide chain length which could be from least to large and vice versa. Other improved techniques such as reverse-phase high-performance liquid chromatography (RP-HPLC) and Fast protein liquid chromatography are currently adopted to improve peptide yield and purity (Franca-Oliveira, Fornari, & Hernández-Ledesma, 2021; Girgih, Udenigwe, & Aluko, 2013; He et al., 2013). Recently, more advanced techniques such as matrix-assisted laser desorption ionization time-of-flight mass spectrophotometer are used for peptide purification while the amino acid sequence of the peptides are recognized using automated techniques such as peptide sequencer (He, Liu, Qiao, Cao, & Song, 2021; Song et al., 2021). This is followed by the confirmation of the antihypertensive activity of the characterized peptide(s) using any of the *in vitro* assays, animal model and human subjects (Fig. 1).

3. Molecular mechanisms of action of food protein-derived antihypertensive peptides

Hypertension is a debilitating condition caused by irregularities with several pathophysiological factors and enzyme systems that play vital roles in maintaining homeostasis between the constriction and dilation of vascular systems. Some of these factors, in addition to RAS, are activities of the various isoform the endothelial nitric oxide synthase (eNOS), serum level of pro-inflammatory cytokines [such as interleukin (IL)-1β, IL-6, IL-8, IL-17, and IL-23, transforming growth factor beta (TGFβ), and tumor necrotic factor alpha (TNFα)], regulation of nuclear factor erythroid 2-like 2 (Nrf2) (Daiber, Steven, Vujacic-Mirski, Kalinovic, Oelze, Lisa, & Münzel, 2020), and possibly, regulation of COX-mediated production of prostanoids and prostacyclins. Many studies have discovered some constitutive bioactive peptides that effectively help in reducing hypertension, by stimulating a balance between the

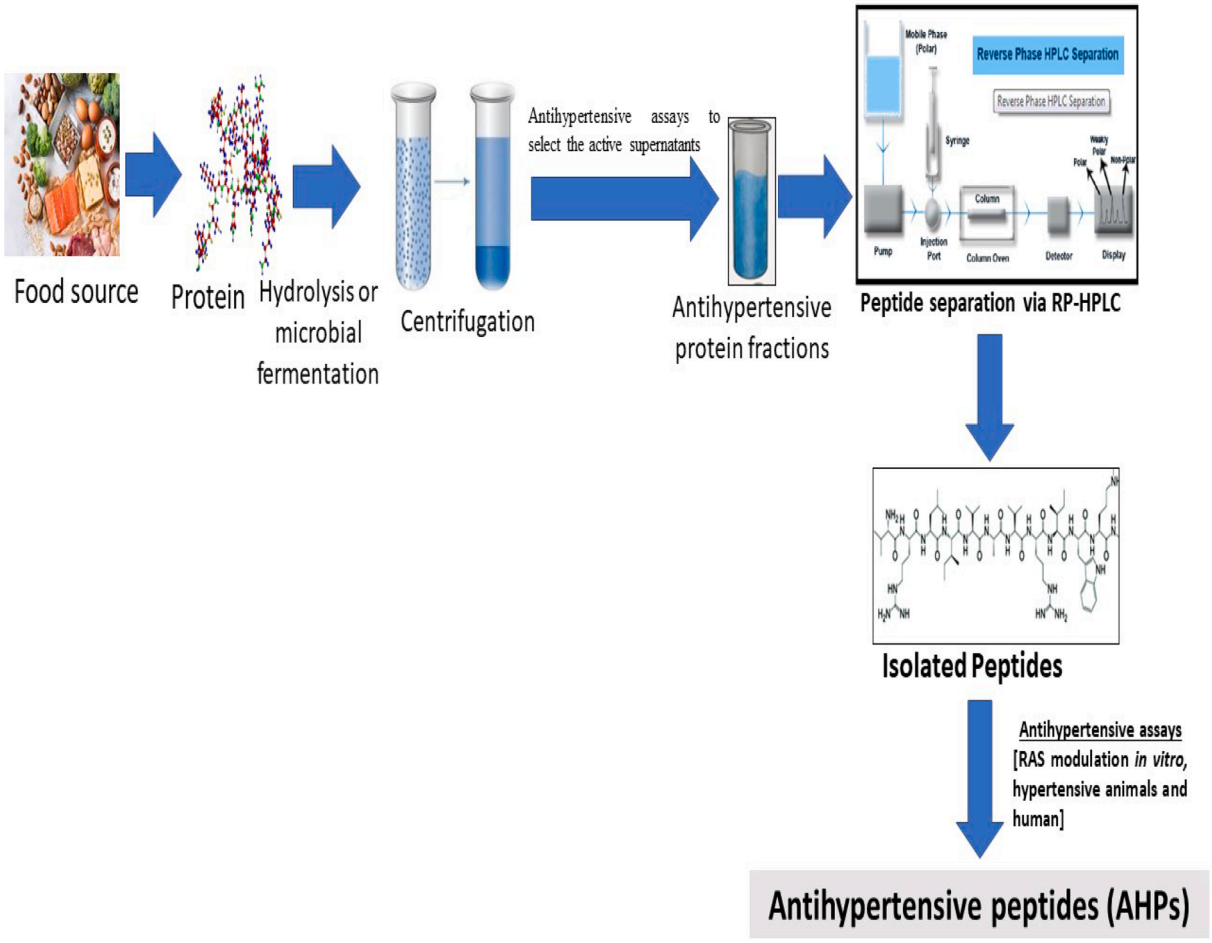

Fig. 1. Key steps in the preparation of antihypertensive peptides.

constriction and dilation events of large blood vessels, especially during vascular injuries and blood clotting. This section provides a brief overview of the different pathways involved in blood pressure regulation and recently isolated antihypertensive peptides modulating these pathways.

4. Previously recognized mechanism of blood pressure lowering by bioactive peptides

Unregulated RAS activity results in elevated blood pressure, modulators of RAS activities such as ACE and renin inhibitors and Ang II receptor blockers are employed to lower blood pressure. These medications are one of the most effective strategies to manage high blood pressure, heart failure, renal failure, and the negative consequences of diabetes (Hanafi, Hashim, Chay, Ebrahimpour, Zarei, Muhammad, & Saari, 2018). Synthetic medicines such as captopril, enalapril, and lisinopril are being used to treat hypertension. These drugs inhibit the ability of ACE to convert Ang I to Ang II, the potent vasoconstrictor; therefore, inhibition of ACE would result in a decrease in blood pressure. However, undesirable side-effects such as angioedema, persistent dry coughs, and fetopathy are common with the use of these synthetic drugs (Hanafi et al., 2018). Unlike synthetic counterparts, natural ACE inhibitors are thought to be a safer option. A number of peptides having *in vitro* ACE inhibitory action have been demonstrated to impact blood pressure in spontaneously hypertensive rats (SHR) and humans in a beneficial way without adverse effects (Hanafi et al., 2018).

From plant-based proteins hydrolysates, a number of novel AHPs with ACE-inhibitory and blood pressure lowering properties have been isolated. For instance, EAQRLLF, PSLRSYLAE, PDRSIHGRQLAE, FITAFR and RGQVLS isolated from alcalase-hydrolyzed green soybean seed protein inhibited ACE activity by 94.19%, 99.31%, 92.92%, 101.51% and 90.40%, respectively (Hanafi et al., 2018). Other plant proteins derived novel peptide with ACE-inhibitory activity include LTFPGSAED from lupin seed in intestinal Caco-2 cells (IC_{50} = 13.7 μM) and in renal HK-2 cells (IC_{50} = 79.6 μM) (Lammi et al., 2020), QTDEYGNPPR, AGFAGDDAPR, IDESLR, IQDKEGIPPDQQR from black tea (IC_{50} values of 210.03, 178.91, 196.31 and 121.11 μmol/L respectively) (Lu et al., 2021), APKIEEV from defatted areca nut kernel globulin (IC_{50} = 550.41 mol/L) (Liu et al., 2021), ALAPE from *Pinctada imbricata fucata* (IC_{50} = 167.5 μM) (Liu et al., 2019) and IW form *Oncorhynchus gorbuscha* (IC_{50} = 1.2 μM) (Abachi, Bazinet, & Beaulieu, 2019).

Similarly, animal protein-derived peptides have been shown to have antihypertensive effects via inhibition of ACE and renin activities. A few examples of these include AEWLHDWKL and MVPYPQR from camel milk (IC_{50} = 30 μM) (Soleymanzadeh, Mirdamadi, Mirzaei, & Kianirad, 2019), and IPP, LIVTQ, IIAE and LVYPFP from whey/milk protein (IC_{50} = values of 1.23, 113, 128 and 97 μg/mL respectively) (Chamata, Watson, & Jauregi, 2020). Generally, these peptides inhibit ACE activity through the formation of H-bonding with the enzyme's active site catalytic residues (Ala 354, Gln 281, His 513, Tyr 520, Lys 511, and Glu 162) (Yu et al., 2020). After demonstrating good ACE-inhibitory activities *in vitro*, Yu et al. (2021) fed two pentapeptides, QIGLF and RVPSL to SHRs for four weeks and recorded strong suppression of SBP. Molecular analysis demonstrated that the peptides elicited their antihypertensive effects by competitively inhibiting ACE activity. Other novel peptides with ACE-inhibitory effects recently isolated are presented in Table 1 while the mechanism of action of the peptides targeting RAS is shown in Fig. 2.

Table 1
Novel ACE-inhibitory peptides isolated recently from food proteins.

Novel peptide	Protein source	Activity (IC_{50} value)	References
LY, LVS, YQ, APSY, and RGGY	Wheat gluten	0.31, 0.60, 2.00, 1.47 and 1.48 mmol/L, respectively	(Liu et al., 2021)
IIAPTPVPAAH	*Bellamya bengalensis* (gastropod snail) muscle meat	8.52 μg/mL	(Dey, Chatterjee, Mandal, Roychoudhury, Paul, Roy, Pateiro, & Dhar, 2021)
SFNLPILR and AFEDGFEWVSKF	Amaranth grains	2.50 and 1.47 mM, respectively	(Nardo et al., 2020)
IVDR, WYK and VASVI	Paralichthys olivaceus (Surimi) myofibrillar	46.90, 32.97 and 32.66 μM, respectively	(Oh et al., 2020a; Oh et al., 2020b)
EKVNELSK, MKP and LLYQEPVLGPVR	Casein hydrolysate	6.0, 0.43 and 5.0 μM, respectively	(Liu et al., 2019; Yuda et al., 2020)
IPP, IIAE, LVYPFP and LIVTQ	Whey/milk protein	1.23, 128, 97 and 113 μg/mL, respectively	(Chamata et al., 2020)
AVKILP, LSGPVKF, AVFQHNCQE, VGKPGARAPMY and QVGPLIGRYCG	Chicken foot	7.1, 80.9, 44.8, 29.7 and 11 μM, respectively	(Bravo et al., 2019)
AVQ and YPQ	Distilled spent grain	181 and 220 μM, respectively	(Wei, Fan, & Xu, 2019)
TNLDWY, RADFY and RVFDGAV	*Ginkgo biloba* (Ginkgo) seeds	1.93, 1.35 and 1.01 mM, respectively	(Ma et al., 2019)
LSGYGP	*Oreochromis niloticus* Linnaeus (tilapia) skin gelatin	2.577 μmol/L	(Chen et al., 2020)
SSYYPFK	*Avena nuda* (Naked oat) globulin	91.82 μM	(Zheng et al., 2020)
WF and FASA	*Euphausia superba* (Antarctic krill)	0.32 and 0.15 mg/ml, respectively	(Zhao, Zhang, Tao, Chi, & Wang, 2019)
EAQRLLF, PSLRSYLAE, PDRSIHGRQLAE, FITAFR and RGQVLS,	*Glycine* max (L) Merr (Green soybean)	878, 532, 1552, 1342 and 993 μM respectively	(Hanafi et al., 2018)
VRP, LKY, VRY, KYKA, and LKYKA,	*Gallus gallus domesticus* (hen)	0.64, 0.81, 5.77, 2.87, and 0.034 μg/ml, respectively	(Fan & Wu, 2020)

5. Recently recognized mechanisms of suppressing blood pressure by bioactive peptides

Up-regulation of angiotensin converting enzyme 2 (ACE2) gene expression and its enzyme activity: An additional mechanism of blood pressure-lowering properties of natural peptides is by up-regulation of gene expression and enzyme activation of ACE2, the enzyme that hydrolyzes the major vasoconstrictor of RAS, Ang II into its less active metabolite, angiotensin-(1–7). For example, IRW, an egg white-isolated peptide was shown to reduce both SBP and DBP in SHR model by enhancing ACE2 mRNA expression (Liao, Chakrabarti, Davidge, & Wu, 2016). Similarly, AKSLSDRFSY from pea protein hydrolysates, a biostable peptide which is resistant to pepsin was shown to upregulate the gene expression of ACE2 in cultured vascular smooth muscle cells (Liao, Fan, Liu, & Wu, 2019). Upon hydrolysis with pancreatin, the two metabolites LSDRFS and SDRFSY identified, where also shown to upregulate the expression of ACE2 in a manner similar to the parent peptide, AKSLSDRFSY, suggesting that these metabolites may be playing major roles in the enhancement of ACE2 gene expression.

Modulation of PPAR-γ/caspase3/MAPK/eNOS signaling pathways: The eNOS is one of the isoforms of nitric oxide synthase (NOS) primarily located in the *peri*-nucleus, Golgi apparatus and caveolae of most endothelial cells (Li, Yon, & Cai, 2015). The eNOS catalyzes the generation of NO from arginine, to help manage oxidative stress or damages caused by endogenously-and exogenously-generated reactive oxygen species (ROS). When released from the endothelial cells, NO causes an increase in the 3′,5′-cyclic-guanosine monophosphate (cGMP), which activates cGMP-dependent kinase, to stimulate vasodilation (Li et al., 2015). Oxidative stress resulting from excessive ROS suppresses gene expression and enzyme activity of eNOS by uncoupling its bound cofactor vital for NO generation (Daiber et al., 2020). Hence, the Apo-eNOS, conversely produces superoxide anion rather than NO, which further worsen the oxidative damage on the cells, exacerbating endothelial dysfunction causing vascular constriction and cardiovascular diseases (Daiber et al., 2020). The activity of eNOS is also regulated by phosphorylation and dephosphorylation of specific amino acid residues in the enzyme. Phosphorylation of Ser-615, 633 and 1177 significantly activates the eNOS whereas phosphorylation of Thr495 inhibits it. Studies have shown that eNOS from patients with cardiovascular diseases have reduced level of the phosphorylated catalytic serine residues and a reduced titer of the kinases known for phosphorylating eNOS (AMP-activated protein kinase (AMPK), protein kinase B (Akt), extracellular signal–regulated protein kinases (ERK-1/2), and calcium-calmodulin kinase II (CaMK-II) (Zippel et al., 2018). On the other hand, the transcription factor, peroxisome proliferator activated receptor (PPAR)-γ potentiates several physiological events including the suppression of oxidative stress, inflammation, and vasoconstriction, and expression of α-smooth muscle actin, RhoA, cleaved caspase-3 whereas action of eNOS and vasodilation were elevated (Stump, Mukohda, Hu, & Sigmund, 2015). Furthermore, the suppression of Ang II-generated hypertension by pharmacological activation of PPAR-γ with its agonist, pioglitazone positions the PPAR-γ as a good target for blood pressure monitoring (Yu, Xue, Wei, Zhang, Beltz, & Guo, 2015).

Intragastric administration of alcalase/protease-hydrolyzed skate skin gelatin for 20 days by spontaneous hypertensive rats (SHRs) was shown to significantly reduce SBP (Ngo et al., 2015). The hydrolysate acted by activating PPAR-γ signaling, leading to the suppression of expression of endothelin-1, α-smooth muscle actin, RhoA, cleaved caspase 3, and MAPK whereas elevation in eNOS action in the lungs. Taken together, the mechanism of action of the hydrolysate is through PPAR-γ/caspase3/MAPK/eNOS signaling pathways. In addition, the potent ACE-inhibitory properties of two peptides isolated from the hydrolysate, LGPLGHQ and MVGSAPGVL (with IC_{50} values of 4.22 and 3.09 μM, respectively) suggest that inhibition of ACE may be an additional mechanism of the blood pressure-lowering effects of the skate skin gelatin hydrolysate. Hence, in addition to ACE inhibitory assay, researchers on AHPs should include the investigation of gene expression profiles of PPAR-γ, MAPK and eNOS in cultured cells to provide more details on the mechanism of action other than ACE inhibition. Low molecular weight peptides bearing proline at the terminal residues and in general, proline-rich peptides have been shown to have antioxidant properties, and are resistant against intestinal hydrolytic enzymes during transepithelial transport (Querobino, Costa, & Alberto-Silva, 2019). Considering the link between oxidative stress and hypertension, many antioxidant agents have been shown to have antihypertensive properties (Ikarashi et al., 2018). An egg white-derived tripeptide (IRW) that hinders oxidative stress, inflammation and migration of vascular smooth muscle cells induced by angiotensin II, was also reported to exhibit antihypertensive effects in SHRs via modulation of endothelial function, suppression of vascular inflammation and enhancement of NO production (Majumder et al., 2015). Increased intracellular NO level in endothelium leads to vasodilation. The ability of IRW to halt angiotensin II-

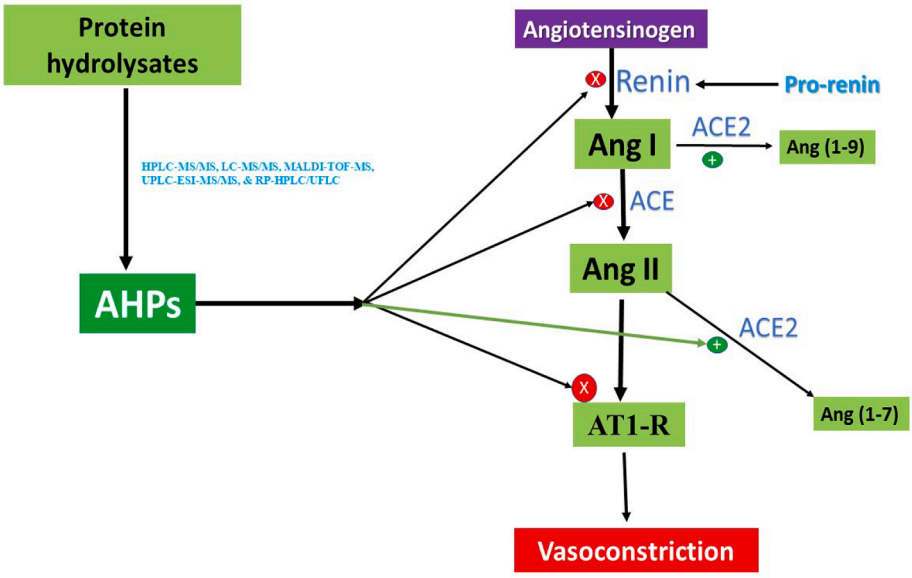

Fig. 2. Mechanism of action of antihypertensive peptides (AHPs) via modulation of renin-angiotensin system (RAS).

induced vascular smooth muscle cells migration was further shown to involve the suppression of matrix metallopeptidase-9 (MMP-9) gene expression and Ang I receptor-dependent inactivation of p38-MAPK signaling. Other tripeptides such as LKP, and IQW derived from egg white protein ovotransferrin were also shown to have blood pressure-lowering in SHRs and permeate intestinal epithelium via passive (TJ-mediated) and active (PepT1-mediated) transport routes (Xu, Fan, Yu, Hong, & Wu, 2017).

Recent studies have revealed several bioactive peptides which manage hypertension and cardiovascular disease through the interaction and regulation of eNOS and its associative kinases, probably showing better biosafety and bioavailability profile than standard small molecule drugs (Cicero, Fogacci, & Colletti, 2017). A recent study conducted by Oh and colleagues investigated for bioactive peptides with antihypertensive and anti-inflammatory activities for from Olive flounder (*Paralichthys olivaceus*) (Oh et al., 2020a; Oh et al., 2020b). Three bioactive peptides, VASVI, IVDR, WYK were found to significantly increase the level of nitric oxide in the HUVECs cell line. More so, there was a significant improvement in the expression of eNOS and protein kinase B (Akt) (Oh et al., 2020a; Oh et al., 2020b). Similarly, another study on Antarctic krill (*Euphausia superba)* reported bioactive peptides (WF, YRK, and FQLFAS) with activities to improve the hypotensive marker– approximately 33% increase in NO and about 50 percent decrease in endothelin-1 (ET-1). Endothelin-1 on its own is a bioactive peptide first isolated from endothelial cells, with activities as vasoconstrictor, pro-inflammatory and proliferative agents. ET-1 is upregulated with a worsening oxidative state or increase in ROS and can serve as a marker for many cardiovascular conditions. Hence, decrease in ET-1 expression implied an improved cardiovascular state. Although many recent studies have investigated antihypertensive properties of protein-based peptides using the ACE/RAS system, the few recent studies on NO titre/eNOS expression for bioactive peptides are summarized in Table 2.

Attenuation of insulin resistance via IP3K/Akt signaling pathway as a mechanism of antihypertensive property: The suppression of blood pressure by the peptides could have resulted from improvement in insulin sensitivity. Insulin resistance and by extension, type-2 diabetes have been shown to positively correlate with hypertension and other cardiovascular diseases (Rojas-Humpire et al., 2021). Interestingly, egg white protein hydrolysates have been demonstrated to reduce blood pressure in SHR models (Jahandideh, Chakrabarti, Davidge, & Wu, 2017) and enhance insulin recognition by its receptor in diet-induced insulin resistance in animal model by activating Akt signaling pathway (Jahandideh et al., 2019). This suggests that peptides in the hydrolysates could have upregulated gene expression and enzyme activity of phosphoinositide-dependent protein kinase 1 (IP3K), the enzyme that activates Akt by phosphorylation to enhance insulin sensitivity and the downstream modulation of metabolism that maintains energy and blood pressure homeostasis (Xing et al., 2019). In addition, the peptides in the hydrolysates could have acted by inducing vasodilation as mediated by activation of Akt to phosphorylate eNOS which produced NO, a potent vasodilator as illustrated in Fig. 3.

Fig. 3: Mechanism of antihypertensive properties of peptides by attenuating insulin resistance via IP3K/Akt signaling pathway. AHPs is proposed to increase the gene expression and enzyme activity of phosphatidylinositiol-3-phosphate kinase (IP3K) through its activator- a

Table 2
Mechanisms of antihypertensive peptides other than ACE inhibition.

Protein sources	Bioactive peptide	Cell line/ Animal Model	Activities	References
Rapeseed and Captopril	CL and VAP	Rat	↑ 12.7% (NO) ↑ 74.1% (eNOS)	(Wang et al., 2021)
Antarctic krill (*Euphausia superba*)	WF, YRK, and FQLFAS	Human umbilical vein endothelial cells	↑ ≈33.3 % (NO) ↓ ≈50.0 % (ET-1)	(Zhao et al., 2019)
Rice Bran Protein hydrosylate		2 K-1C hypertensive rats	↑ ≈37.5 % (NO) ↑ eNOS expression	(Boonla et al., 2015)
Olive flounder (*Paralichthys olivaceus*)	VASVI, IVDR and WYK	Human umbilical vein endothelial cells	↑ ≈10-20 % (NO) ↑ ≈ 500–900% eNOS expression ↑ ≈100 – 300% Akt expression	(Oh et al., 2020a; Oh et al., 2020b)
Mucuna pruriens seeds	Peptide fraction	Human blood	11.11 % ↓ platelet aggregation	(Herrera-Chalé et al., 2016)
Mucuna pruriens seeds	Peptide fraction	*In vitro* analysis	0.47 % ↓ cholesterol micellar solubility	(Herrera-Chalé et al., 2016)

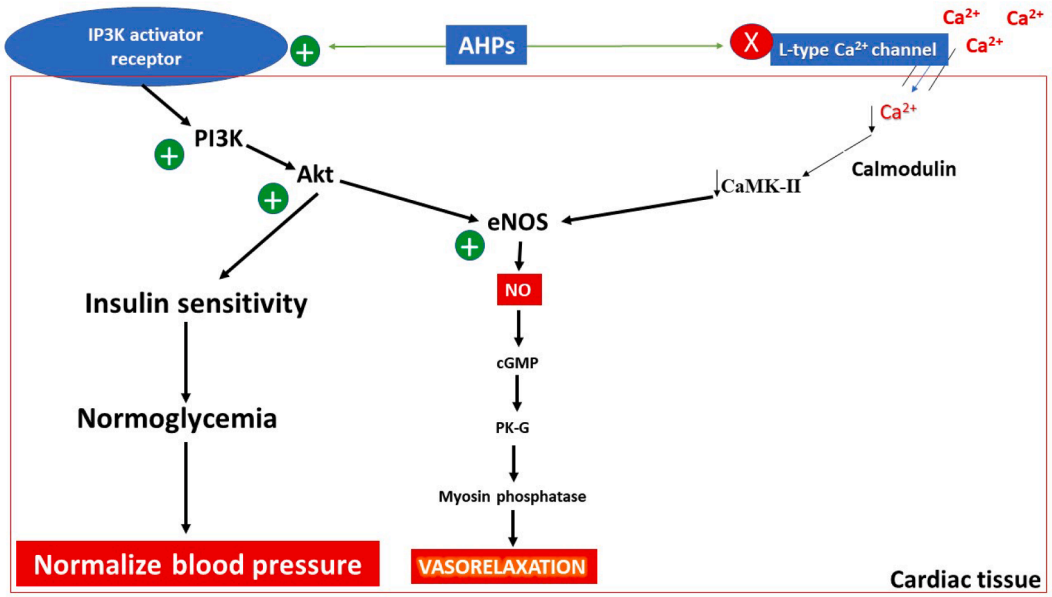

Fig. 3. Mechanism of antihypertensive properties of peptides by attenuating insulin resistance via IP3K/Akt signaling pathway. AHPs is proposed to increase the gene expression and enzyme activity of phosphatidylinositiol-3-phosphate kinase (IP3K) through its activator- a membrane bound G-protein coupled subclass receptor. IP3K activates protein kinase B (Akt) by phosphorylation of Ser^{473} in its catalytic site while Akt activates endothelial nitric oxide synthase (eNOS) by phosphorylation of its catalytic residue (Ser^{1177} or Ser^{1179} depending on the specie). Similarly, the AHPs blocks L-type Ca^{2+} channel which increases intracellular concentration of Ca^{2+} that associates with calmodulin (Cd) to form Ca^{2+}-Cd complex which initiates contraction by depleting NO availability via inhibition of eNOS. Active eNOS synthesizes nitric oxide (NO) from L-arginine, and NO activates soluble guanylyl cyclase to convert guanosine triphosphate (GTP) to 5'-cylic guanosine monophosphate (cGMP). On binding to its site on protein kinase-G (PK-G), cGMP activates PK-G to phosphorylate and activate myosin phosphatase (myosin-P). Activate myosin-P dephosphorylates myosin and induce the relaxation of vascular endothelial smooth muscle, hence, reduction in blood pressure..

membrane bound G-protein coupled subclass receptor. IP3K activates protein kinase B (Akt) by phosphorylation of Ser^{473} in its catalytic site while Akt activates endothelial nitric oxide synthase (eNOS) by phosphorylation of its catalytic residue (Ser^{1177} or Ser^{1179} depending on the specie). Similarly, the AHPs blocks L-type Ca^{2+} channel which increases intracellular concentration of Ca^{2+} that associates with calmodulin (Cd) to form Ca^{2+}-Cd complex which initiates contraction by depleting NO availability via inhibition of eNOS. Active eNOS synthesizes nitric oxide (NO) from L-arginine, and NO activates soluble guanylyl cyclase to convert guanosine triphosphate (GTP) to 5′-cylic guanosine monophosphate (cGMP). On binding to its site on protein kinase-G (PK-G), cGMP activates PK-G to phosphorylate and activate myosin phosphatase (myosin-P). Activate myosin-P dephosphorylates myosin and induce the relaxation of vascular endothelial smooth muscle, hence, reduction in blood pressure.

6. Emerging mechanisms of blood pressure-lowering by bioactive peptides

Considering the hypertension is a multifactorial disease, and that some peptides with *in vitro* ACE inhibitory effects are unable to lower blood pressure *in vivo*, while some peptides with low ACE inhibitory effects significantly lowered blood pressure, we propose here some possible molecular mechanisms through which peptides can mediate their antihypertensive properties.

Antioxidant-mediated antihypertensive properties: Apart from the eNOS regulation, the oxidant/antioxidant balance in the body system are also regulated by a transcription factor called the Nrf2 in association to its promoter bearing the antioxidant response element (ARE) (Pajares et al., 2016). Under normal physiological conditions, Nrf2 which is constitutively expressed in the cytoplasm is sequestered and repressed by the Kelch-like ECH-associated protein 1 (Keap-1). However, when the system is oxidatively-stressed, the Nrf2 from the cytoplasm is translocated to the nucleus, where it binds to the ARE of the gene coding for antioxidant proteins, activating a cascade of reaction which help to curb the oxidative pressure on the cells (Saha, Buttari, Panieri, Profumo, & Saso, 2020). Studies have shown with consensus evidence that decrease in Nrf2 activities invariably contributes to oxidative stress and cardiovascular diseases such as hypertension (Serafini et al., 2020; Zhan, Li, & Zhou, 2021). Considering that some antioxidant peptides also exhibit antihypertensive properties, and that oxidative stress is implicated in hypertension (Griendling et al., 2021), the investigation of Keap-1/Nrf2 signaling pathway (the activation or upregulation the expression and translocation of nuclear Nrf2) and gene expression of antioxidant enzyme activities in peptide-treated SHR is recommended for future studies.

Anti-inflammatory-mediated antihypertensive properties: Inflammation is one common pathology for hypertension and cardiac problems and often result in damage of tissues within the body (Angeli, Reboldi, & Verdecchia, 2021). Inflammatory processes occur due to complex immune reactions involving the different cytokines (IL-1β, IL-6, IL-8, IL-17, IL-23, TGFβ, and TNFα) and other mediators. Several immune cells such as T lymphocytes, dendritic cells and macrophages express constitutive angiotensin 1 receptor (AT1R) (Zhang et al., 2014). During vascular disturbance, angiotensin II binds to AT1R and activates the immune cell differentiation and pro-inflammatory cytokine production – especially IL-6, IFN-γ, and TNFα (Tanase et al., 2019). The pro-inflammatory cytokines IL-6, stimulates the activities of NAD(P)H oxidase, which consequently releases more ROS in the system causing the inhibition of reduced eNOS, endothelial damage, pro-thrombotic recruitment, hypertension and other cardiovascular diseases. Similarly, tumor necrosis factor (TNF)-α stimulates the production of ACE, which invariably also mediates inflammatory and cardiovascular disorder (Mahmudpour, Roozbeh, Keshavarz, Farrokhi, & Nabipour, 2020). When activated, Nrf2 bends to its nuclear receptor, ARE to upregulate the mRNA expression of its target genes, including heme oxygenase-1 (HO-1). This Nrf2-associated upregulation of HO-1 gene expression inhibits TNF-α-induced release of NF-κB and MCP-1, and other pro-inflammatory mediators (Da Costa et al., 2019) while increasing the secretion of anti-inflammatory cytokines (Ahmed, Luo,

Namani, Wang, & Tang, 2017). Based on this, we propose that future research should assess the effects of peptide treatment on Keap-1/Nrf2/ARE/HO-1/NF-κB signaling pathways by assessing the gene expression profiles of Keap-1, Nrf2, HO-1 and NF-κB, and pro-inflammatory cytokine levels in experimental models of hypertension.

Induction of vasodilation via upregulation of COX and prostaglandin receptor: The COX, an enzyme also known as prostaglandin endoperoxide synthase catalyzes the formation of prostaglandin H_2 (PGH_2) from arachidonic acids. The PGH_2 when acted upon different isozymes of synthases and isomerases yields the different prostanoids (PGE_2, PGI_2, PGF_{2a}, and thromboxane A_2 (TXA_2)) (Jang, Kim, & Hwang, 2020). The COX has two membrane-bound iso-enzymes, the COX-1 and COX-2. The cyclooxygenase 1 (COX-1) are constitutively expressed in most human tissues, whereas, COX-2 is triggered by inflammation and damage of the endothelial and vascular tissues (Faki & Er, 2020). Studies have thoroughly described the roles of COX and the different prostanoids in maintaining balance in the vascular system (Mitchell et al., 2021). The TXA_2 and prostacyclin (PGI_2), and to a lesser extent PGE_2 when either upregulated or downregulated effect vasodilation or vasoconstriction (Ozen & Norel, 2017). The platelet, normally recruited at site of injuries or inflammation expresses only COX-1, which catalyzes the formation of TXA_2. The TXA_2.in turn facilitates the aggregation of platelet (prothrombotic activities) leading to further constriction of the blood vessel and then hypertension (Mitchell et al., 2021). On the other hand, $PG1_2$ produced by the activities of COX-2 facilitates vasodilation with anti-thrombotic activities. Moreover, the PGE_2 at different conditions can act as a vasodilator and as well fostering vasoconstriction (Manual-Kollareth, Chang, Zirpoli, & Deckelbaum, 2020). A study exposed human blood to peptide fraction of *Mucuna pruriens* seed protein hydrolysates and observed 1.59–11.11% decrease platelet aggregation compared to control (human blood that was not treated with the protein hydrolysate fraction) (Herrera-Chalé, Ruiz-Ruiz, Betancur-Ancona, & Segura-Campos, 2016). Interestingly, the protein hydrolysate fraction exhibited antioxidant effect, and inhibited cholesterol micellar solubility (0.24%-0.47%) and ACE activity (IC_{50} values range from 2.7 to 6.2 μg/mL). Taken together, the *in vitro* ant-platelet aggregatory, hypocholesterolemic and ACE inhibitory properties suggest that the peptides in the protein hydrolysate fraction may have good antihypertensive properties when ingested intragastrically by hypertensive animal model. Further studies are warranted to isolate the specific peptide (s) and confirm their antihypertensive properties using *in vivo* model by examining the involvement of COX signaling pathway as proposed in Fig. 4.

Blockade of L-type Ca^{2+} channel and inhibition of lipid accumulation: The activation of L-type Ca^{2+} channels have been widely recognized to be involved in the pathogenesis of cardiovascular diseases including hypertension (Fig. 3), making the specific channel blockers target drugs for managing hypertension and related cardiovascular diseases (Medvedev et al., 2021). Based on this, the effect of peptide treatment on experimentally-induced contractility of isolated aortic rings as well as that isolated from hypertensive animal models are recommended in future research.

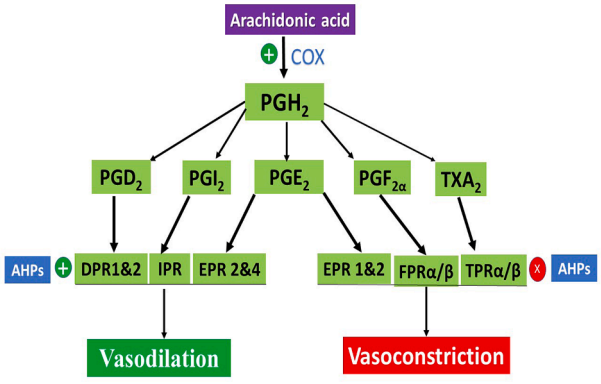

Fig. 4. Proposed mechanism of antihypertensive properties of peptides via COX signaling pathway.

In the same vein, excessive lipid accumulation has been recognized as a risk factor that plays a major role in the pathogenesis of hypertension (Ayoade, Umoh, & Amadi, 2020). Hypolipidemic drugs such as statins that inhibit 3-hydroxy-3-methylglutaryl CoA reductase (HMGCoAR) - the key enzyme of cholesterol biosynthesis are used to prevent and manage hypertension (Wang, Jiang, Feng, Tang, & Kuang, 2020). A good number of peptides isolated from dietary products have been shown to reduce lipid production and accumulation. Notably, the exposure of cultured human hepatic cells with soybean and lupin-originated peptides such as LILPKHSDAD, LTFPGSAED and YDFYPSSTKDQQS demonstrated marked hypocholesterolemic properties by increasing SREBPs-1 and LDLR protein levels which are known to suppress the biosynthesis and accumulation of lipids whereas activating lipid breakdown via the activation of PI3K/Akt/MAPK pathways (Lammi et al., 2019, 2020; Zanoni, Aiello, Arnoldi, & Lammi, 2017). Based on this, the effects of these peptides on hypertensive rats should be investigated in future studies to clarify if the inhibition of lipid accumulation will translate into antihypertensive properties.

7. Factors that influence the antihypertensive properties and nutraceutical applications of food proteins and peptides for managing hypertension

Biostability is an important aspect of assessing the fitness of a potential drug for use in clinical disease management. Considering that several studies assessed the inhibition of ACE and renin activities *in vitro* as indices of antihypertensive properties, it is important that these biological activities reported in *in vitro* environment are confirmed using *in vivo* models such as animal and/or human cases of hypertension. This is because some ACE-inhibitory peptides were shown not to reduce blood pressure when orally ingested, partly due to their susceptibility to hydrolytic activities of intestinal proteases, and serum peptidases prior to reaching their target (Messina et al., 2021). For example, among five ACE-inhibitory peptides isolated from chicken foot protein hydrolysates (AVKILP, LSGPVKF, AVFQHNCQE, VGKPGARAPMY and QVGPLIGRYCG), only AVFQHNCQE and QVGPLIGRYCG significantly lowered blood pressure after 6 h of oral ingestion by SHR at 10 mg/kg body weight (Bravo, Mas-Capdevila, Margalef, Arola-Arnal, & Muguerza, 2019).

In addition, amino acid composition, sequence and chain length are among other factors that influence the antihypertensive properties of peptides. Protein hydrolysates containing proline-rich peptides have been reported to not only inhibit ACE activity *in vitro* but also lower blood pressure *in vivo* (Chamata et al., 2020). The impact of proline could be attributed to conferment of stability due to 'Keil rule' which states that the existence of proline and glutamic acid limits the hydrolytic effects of some proteases such as trypsin on peptides (Udenigwe, Abioye, Okagu, & Obeme-Nmom, 2021). This may explain why short-chain peptides containing arginine, tryptophan, leucine, valine, histidine, and phenylalanine from Chlorella sorokiniana and marine cobia skin protein hydrolysates were reported to exhibit ACE-inhibitory and blood pressure lowering effects (Lin, Chen, Tsai, & Chen, 2019). To further support this observation, several proline-rich peptides have been shown to permeate through the intestinal membrane to elicit their biological response such as cholesterol-lowering and blood pressure-lowering properties (Jiang et al., 2020).

Aside the physicochemical characteristics of peptides such as net charge, amino acid sequence and the chain length, hydrophobicity and molecular weight (Karami & Akbari-adergani, 2019), the interaction between AHPs and other components of food matrix used in delivering the peptides, microbiota activities and mucin content of intestinal epithelium have been suggested to influence their biostability,

bioavailability, bioaccessibility and biological activities (Ozorio et al., 2020). For example, interactions of certain peptides with micronutrient composition of food matrix such as mineral elements have been demonstrated to influence their bioavailability and permeability (Sun, Acquah, Aluko, & Udenigwe, 2020). Another factor that influences peptide biostability and bioactivities is the presence of other peptides, some of which may be additive or counterproductive. In a study, the transepithelial transport of lupin seed-originated peptide, LTFPGSAED and its metabolite, LTFPG was reported to be increased in the presence of YDFYPSSTKDQQS and LILPKHSDAD (Lammi, Zanoni, Arnoldi, & Aiello, 2018). This observation was similar to the report that the rate of transport of LILPKHSDAD which was also enhanced in the presence of YDFYPSSTKDQQS and LTFPGSDAD (Lammi et al., 2021).

The antihypertensive properties of some peptides may have been, partly or totally a result of hydrolytic metabolites of the peptides, and not only the intact ingested parent peptides. This observation was demonstrated in a study where the ingestion of an ACE-inhibitory (IC_{50} value of 25.74 μM) and antioxidant peptide isolated from tilapia skin gelatin, LSGYGP by SHRs suppressed both SBP and DBP (Tianrui, Bingtong, Ling, Liping, & Yongliang, 2019). Further analysis showed that LSGYGP is excellently permeable in Caco-2 cell monolayer with some metabolites such as SGYGP, LSGY, GYGP, LSGYP, LSSGYGP, and LSLSGYGP observed after intestinal transport (Tianrui et al., 2019). One implication of this observation is that the metabolites could have, in part, contributed to the antihypertensive activities recorded after oral consumption of the peptide. For more details on biostability, bioavailability, bioaccessibility and biological activities of bioactive peptides, consult previous reviews (Boegh & Nielsen, 2015; Sun & Udenigwe, 2020; Sun et al., 2020; Udenigwe et al., 2021; Wang & Li, 2018).

The method of preparation of peptides, including the enzymatic system used in hydrolysis, nature of chemicals used, pH and temperature influence their stability, bioavailability and functionality. This was demonstrated in a study where ultrasound treatment of watermelon seed and mung bean proteins prior to enzyme hydrolysis enhanced the hydrophobicity and release of peptides with terminal aromatic amino acids all of which influenced their stability, bioavailability, and bioactivity (such as radical scavenging and antihypertensive properties (Jiang et al., 2021; Wen et al., 2020; Xie et al., 2020). On the other hand, the use of procedures such as microwaves and other thermal techniques for peptide preparation have been shown to affect the functionality of the peptides, by changing the native physicochemical properties of the peptide which affects their stability and bioactivities (Hunsakul, Laokuldilok, Prinyawiwatkul, & Utama-ang, 2021). Considering the better functionality of low molecular weight peptides, a combination of two or more hydrolyzing enzymes is likely to generate shorter chain peptides compared to using one enzyme (Aluko, 2015). For instance, the ACE-inhibitory activities of peptides generated from hard-to-cook bean protein hydrolysate generated with a combination of alcalase and flavourzyme were shown to be higher compared to the use of the enzymes separately (Ruiz-Ruiz, Dávila-Ortíz, Chel-Guerrero, & Betancur-Ancona, 2013). In another study, skimmed buffalo milk protein was hydrolyzed using papain, pepsin or trypsin, and it was observed that hydrolysate-generated with papain exhibited highest ACE-inhibitory and radical scavenging activities (Abdel-Hamid, Otte, De Gobba, Osman, & Hamad, 2017). Similarly, a study hydrolyzed spent hen muscle protein using Protex 26L, pepsin, and thermoase and compared the transepithelial transport and multifunctionality of the hydrolysates and using *in vitro* and *in vivo* models (Fan, Yu, Liao, & Wu, 2020). The hydrolysates generated showed ACE inhibitory, antioxidant, and anti-inflammatory activities; however, only thermoase-generated hydrolysate (TGH) upregulated ACE2 gene expression. Additionally, it is only TGH that resisted hydrolysis in simulation study using Caco-2 cells. Notably, the enhanced ACE2 gene expression, antioxidant and anti-inflammatory activities post-absorption across the caco-2 monolayer suggests the involvement of metabolites of the parent peptides. Furthermore, the intragastric ingestion of all the hydrolysates at 1 g/kg demonstrated that only TGH reduced blood pressure in SHR, indicating that the mechanisms of blood pressure lowering involves the upregulation of ACE2 and inhibition of ACE. Therefore, food protein scientists and nutraceutical developers are advised to adopt protein hydrolysis procedures with minimal effect on the native conformation of the peptide in order to conserve their functionality.

8. Limitations of current research and future research directions

Several studies have been conducted with the aim of uncovering the antihypertensive properties of food protein-based peptides. However, the majority of the studies explored the inhibitory effects of the peptides against ACE and renin activities *in vitro*, while quite a few studies assessed the effects of protein hydrolysates and their peptides on Ang II receptors. In general, a greater number of research efforts in discovering clinically-effective food protein-derived peptides for hypertension focused on RAS. Additionally, among the *in vivo* using experimentally-induced hypertensive and SHR rats, suppression of SBP and/or DBP were recorded without uncovering the molecular mechanisms such as analysis of expression profile of genes that regulate molecular pathways implicated in hypertension.

Future research should not only confirm if all the ACE and renin-inhibitory peptides can lower blood pressure when ingested by normal and experimental models of hypertension, and if active, the molecular mechanism of blood pressure-lowering should be investigated. In addition, the use of multiple enzymes for protein hydrolysis during peptide preparation have been shown to generate low molecular weight peptides which are more biostable and easily permeate the intestinal membrane compared to high molecular weight peptides. Despite the strong scientific evidence on a number of food-based peptides with antihypertensive potentials, quite a few clinical trials on the application of food protein-derived peptides for managing hypertension have been recently reported. Worthy of mention among the bioactive proteins and their peptides under clinical trial are Amaranth hydrolysate-enriched beverages (Valdez-Meza et al., 2019) that was shown to suppress blood pressure after three hours of ingestion. The blood pressure lowering activity was maintained till nine hours post-ingestion, agreeing with the report that Amaranth-derived AHPs are biostable (Espinosa-Hernández et al., 2019). More clinical trials are encouraged especially for peptides sourced from marine organisms, and seeds of soybean and lupin whose multifunctional properties in relation to hypertension have been well characterized.

Finally, the current knowledge on structural-activity relationship of peptides in relation to antihypertensive properties are not well-defined. Mechanistic studies are needed to clarify the structural requirements needed for a peptide to exert antihypertensive properties, especially after oral ingestion. This may involve the use of sequential hydrolysis to determine the specific amino acids and/or amino acid sequence requirements. Additionally, chemical modification of functional group(s) of amino acids in AHPs may underscore the specific functional group(s) involved in antihypertensive activities of the peptides.

9. Conclusions

Hypertension has continued to remain a great burden to global health, and a “silent killer”. Hence, serious research efforts are ongoing to improve the current available strategies for the prevention and management of the diseases. In this study, we have discussed molecular mechanisms of antihypertensive properties of protein hydrolysates and their peptides other than RAS, including induction of vasodilation via upregulation of expression of eNOS, COX and prostaglandin receptor genes. We also have proposed some emerging mechanisms through which these bioactive peptides may have exerted their antihypertensive properties such as modulation of inflammation signaling, Keap-1/Nrf-2 and related antioxidative signaling, and PPAR-γ/caspase3/MAPK signaling pathways, blockade of L-type Ca^{2+} channel and inhibition of

lipid accumulation. We have also briefly discussed factors that influence the biostability, transepithelial transport, bioavailability and activities of AHPs. It is our hope that this review has thrown more light into the current understanding of how newly isolated novel peptides lower blood pressure and by extension, position these AHPs as promising candidates for functional food development for hypertension.

Declaration of Competing Interest

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

References

Abachi, S., Bazinet, L., & Beaulieu, L. (2019). Antihypertensive and Angiotensin-I-Converting Enzyme (ACE)-Inhibitory Peptides from Fish as Potential Cardioprotective Compounds. *Marine Drugs, 17*(11). https://doi.org/10.3390/MD17110613

Abdel-Hamid, M., Otte, J., De Gobba, C., Osman, A., & Hamad, E. (2017). Angiotensin I-converting enzyme inhibitory activity and antioxidant capacity of bioactive peptides derived from enzymatic hydrolysis of buffalo milk proteins. *International Dairy Journal, 66*, 91–98. https://doi.org/10.1016/J.IDAIRYJ.2016.11.006

Adjonu, R., Doran, G., Torley, P., & Agboola, S. (2013). Screening of whey protein isolate hydrolysates for their dual functionality: Influence of heat pre-treatment and enzyme specificity. *Food Chemistry, 136*(3–4), 1435–1443. https://doi.org/10.1016/J.FOODCHEM.2012.09.053

Ahmed, S. M. U., Luo, L., Namani, A., Wang, X. J., & Tang, X. (2017). Nrf2 signaling pathway: Pivotal roles in inflammation. *Biochimica et Biophysica Acta - Molecular Basis of Disease, 1863*(2), 585–597. https://doi.org/10.1016/j.bbadis.2016.11.005

Aluko, R. (2015). Antihypertensive peptides from food proteins. *Annual Review of Food Science and Technology, 6*, 235–262. https://doi.org/10.1146/ANNUREV-FOOD-022814-015520

Angeli, F., Reboldi, G., & Verdecchia, P. (2021). The link between inflammation and hypertension: Unmasking mediators. *American Journal of Hypertension, 34*(7), 683–685. https://doi.org/10.1093/AJH/HPAB034

Ayoade, O. G., Umoh, I., & Amadi, C. (2020). Dyslipidemia and associated risk factors among Nigerians with hypertension. *Dubai Medical Journal, 3*(4), 155–161. https://doi.org/10.1159/000509570

Boegh, M., & Nielsen, H. M. (2015). Mucus as a barrier to drug delivery - Understanding and mimicking the barrier properties. *Basic and Clinical Pharmacology and Toxicology, 116*(3), 179–186. https://doi.org/10.1111/bcpt.12342

Boonla, O., Kukongviriyapan, U., Pakdeechote, P., Kukongviriyapan, V., Pannangpetch, P., & Thawornchinsombut, S. (2015). Peptides-derived from Thai rice bran improves endothelial function in 2K–1C renovascular hypertensive rats. *Nutrients, 7*(7), 5783–5799. https://doi.org/10.3390/nu7075252

Bravo, F. I., Mas-Capdevila, A., Margalef, M., Arola-Arnal, A., & Muguerza, B. (2019). Novel antihypertensive peptides derived from chicken foot proteins. *Molecular Nutrition & Food Research, 63*(12), 1801176. https://doi.org/10.1002/MNFR.201801176

Chamata, Y., Watson, K. A., & Jauregi, P. (2020). Whey-derived peptides interactions with ace by molecular docking as a potential predictive tool of natural ace inhibitors. *International Journal of Molecular Sciences, 21*(3), 1–14. https://doi.org/10.3390/ijms21030864

Chen, J., Ryu, B., Zhang, Y. Y., Liang, P., Li, C., Zhou, C., … Qian, Z. J. (2020). Comparison of an angiotensin-I-converting enzyme inhibitory peptide from tilapia (Oreochromis niloticus) with captopril: Inhibition kinetics, in vivo effect, simulated gastrointestinal digestion and a molecular docking study. *Journal of the Science of Food and Agriculture, 100*(1), 315–324. https://doi.org/10.1002/jsfa.10041

Chung, S., Chung, M., Choi, H., Park, J., Hwang, J., & Joung, H. (2020). Animal protein intake is positively associated with metabolic syndrome risk factors in middle-aged Korean Men. *Nutrients, 12*(11), 1–15. https://doi.org/10.3390/NU12113415

Cicero, A. F. G., Fogacci, F., & Colletti, A. (2017). Potential role of bioactive peptides in prevention and treatment of chronic diseases: A narrative review. *British Journal of Pharmacology, 174*(11), 1378–1394. https://doi.org/10.1111/bph.13608

Da Costa, R. M., Rodrigues, D., Pereira, C. A., Silva, J. F., Alves, J. V., Lobato, N. S., & Tostes, R. C. (2019). Nrf2 as a potential mediator of cardiovascular risk in metabolic diseases. *Frontiers in Pharmacology, 10*(APR), 1–12. https://doi.org/10.3389/fphar.2019.00382

Daiber, A., Steven, S., Vujacic-Mirski, K., Kalinovic, S., Oelze, M., Lisa, F. Di, & Münzel, T. (2020). Regulation of Vascular Function and Inflammation via Cross Talk of Reactive Oxygen and Nitrogen Species from Mitochondria or NADPH Oxidase—Implications for Diabetes Progression. *International Journal of Molecular Sciences 2020, Vol. 21, Page 3405*, *21*(10), 3405. doi:10.3390/IJMS21103405.

Dey, T. K., Chatterjee, R., Mandal, R. S., Roychoudhury, A., Paul, D., Roy, S., Pateiro, M., … Dhar, P. (2021). ACE Inhibitory Peptides from Bellamya bengalensis Protein Hydrolysates: In Vitro and In Silico Molecular Assessment. *Processes 2021, Vol. 9, Page 1316*, *9*(8), 1316. doi:10.3390/PR9081316.

Faki, Y., & Er, A. (2020). Open Access Rambam Maimonides Medical *Journal Different Chemical Structures and Physiological/Pathological Roles of Cyclooxygenases*. doi:10.5041/RMMJ.10426.

Fan, H., & Wu, J. (2020). Purification and identification of novel ACE inhibitory and ACE2 upregulating peptides from spent hen muscle proteins. *Food Chemistry, 345*, Article 128867. https://doi.org/10.1016/j.foodchem.2020.128867

Fan, H., Yu, W., Liao, W., & Wu, J. (2020). Spent hen protein hydrolysate with good gastrointestinal stability and permeability in caco-2 cells shows antihypertensive activity in SHR. *Foods, 9*(10). https://doi.org/10.3390/foods9101384

Franca-Oliveira, G., Fornari, T., & Hernández-Ledesma, B. (2021). A review on the extraction and processing of natural source-derived proteins through eco-innovative approaches. *Processes, 9*(9). https://doi.org/10.3390/pr9091626

Ghatage, T., Goyal, S., Dhar, A., & Bhat, A. (2021). Novel therapeutics for the treatment of hypertension and its associated complications: Peptide- and nonpeptide-based strategies. *Hypertension Research: Official Journal of the Japanese Society of Hypertension, 44*(7), 740–755. https://doi.org/10.1038/S41440-021-00643-Z

Girgih, A. T., Udenigwe, C. C., & Aluko, R. E. (2013). *Reverse-phase HPLC Separation of Hemp Seed (Cannabis sativa L .) Protein Hydrolysate Produced Peptide Fractions with Enhanced Antioxidant Capacity*. doi:10.1007/s11130-013-0340-6.

Girgih, A. T., Nwachukwu, I. D., Hasan, F., Fagbemi, T. N., Gill, T., & Aluko, R. E. (2015). Kinetics of the inhibition of renin and angiotensin I-converting enzyme by cod (Gadus morhua) protein hydrolysates and their antihypertensive effects in spontaneously hypertensive rats. *Food and Nutrition Research, 59*, 29788. https://doi.org/10.3402/fnr.v59.29788

Griendling, K. K., Camargo, L. L., Rios, F. J., Alves-Lopes, R., Montezano, A. C., & Touyz, R. M. (2021). Oxidative stress and hypertension. *Circulation Research, 993–1020*. https://doi.org/10.1161/CIRCRESAHA.121.318063

Hanafi, M. A., Hashim, S. N., Chay, S. Y., Ebrahimpour, A., Zarei, M., Muhammad, K., … Saari, N. (2018). High angiotensin-I converting enzyme (ACE) inhibitory activity of Alcalase-digested green soybean (Glycine max) hydrolysates. *Food Research International*, *106*(September 2017), 589–597. doi:10.1016/j.foodres.2018.01.030.

He, R., Alashi, A., Malomo, S. A., Girgih, A. T., Chao, D., Ju, X., & Aluko, R. E. (2013). Antihypertensive and free radical scavenging properties of enzymatic rapeseed protein hydrolysates. *Food Chemistry, 141*(1), 153–159. https://doi.org/10.1016/J.FOODCHEM.2013.02.087

He, Z., Liu, G., Qiao, Z., Cao, Y., & Song, M. (2021). Novel Angiotensin-I converting enzyme inhibitory peptides isolated from rice wine lees: Purification, characterization, and structure-activity relationship. *Frontiers in Nutrition, 8*, 646. https://doi.org/10.3389/FNUT.2021.746113/BIBTEX

Hernández-Ledesma, B., Del Mar Contreras, M., & Recio, I. (2011). Antihypertensive peptides: Production, bioavailability and incorporation into foods. *Advances in Colloid and Interface Science, 165*(1), 23–35. https://doi.org/10.1016/J.CIS.2010.11.001

Herrera-Chalé, F., Ruiz-Ruiz, J. C., Betancur-Ancona, D., & Segura-Campos, M. R. (2016). Potential therapeutic applications of mucuna pruriens peptide fractions purified by high-performance liquid chromatography as angiotensin-converting enzyme inhibitors, antioxidants, antithrombotic and hypocholesterolemic agents. *Journal of Medicinal Food, 19*(2), 187–195. https://doi.org/10.1089/jmf.2015.0098

Hunsakul, K., Laokuldilok, T., Prinyawiwatkul, W., & Utama-ang, N. (2021). Effects of thermal processing on antioxidant activities, amino acid composition and protein molecular weight distributions of jasmine rice bran protein hydrolysate. *International Journal of Food Science & Technology, 56*(7), 3289–3298. https://doi.org/10.1111/IJFS.15028

Ikarashi, N., Toda, T., Hatakeyama, Y., Kusunoki, Y., Kon, R., Mizukami, N., … Sugiyama, K. (2018). Anti-hypertensive effects of acacia polyphenol in spontaneously hypertensive rats. *International Journal of Molecular Sciences, 19*(3). https://doi.org/10.3390/IJMS19030700

Jahandideh, F., Chakrabarti, S., Davidge, S., & Wu, J. (2017). Egg white hydrolysate shows insulin mimetic and sensitizing effects in 3T3-F442A pre-adipocytes. *PloS One, 12*(10). https://doi.org/10.1371/JOURNAL.PONE.0185653

Jahandideh, F., De Campos Zani, S. C., Son, M., Proctor, S. D., Davidge, S. T., Chan, C. B., & Wu, J. (2019). Egg white hydrolysate enhances insulin sensitivity in high-fat diet-induced insulin-resistant rats via Akt activation. *British Journal of Nutrition, 122*(1), 14–24. https://doi.org/10.1017/S0007114519000837

Jang, Y., Kim, M., & Hwang, S. W. (2020). Molecular mechanisms underlying the actions of arachidonic acid-derived prostaglandins on peripheral nociception. *Journal of Neuroinflammation 2020 17:1*, *17*(1), 1–27. doi:10.1186/S12974-020-1703-1.

Jiang, Q., Chen, Q., Zhang, T., Liu, M., Duan, S., & Sun, X. (2021). The antihypertensive effects and potential molecular mechanism of microalgal angiotensin I-converting enzyme inhibitor-like peptides: A mini review. *International Journal of Molecular Sciences, 22*(8). https://doi.org/10.3390/IJMS22084068

Jiang, X., Pan, D., Zhang, T., Liu, C., Zhang, J., Su, M., … Guo, Y. (2020). Novel milk casein–derived peptides decrease cholesterol micellar solubility and cholesterol intestinal absorption in Caco-2 cells. *Journal of Dairy Science, 103*(5), 3924–3936. https://doi.org/10.3168/JDS.2019-17586

Jogi, N., Yathisha, U. G., Bhat, I., & Mamatha, B. S. (2021). Antihypertensive activity of orally consumed ACE-I inhibitory peptides. doi:10.1080/10408398.2021.1938508.

Karami, Z., & Akbari-adergani, B. (2019). Bioactive food derived peptides: A review on correlation between structure of bioactive peptides and their functional properties. *Journal of Food Science and Technology, 56*(2), 535. https://doi.org/10.1007/S13197-018-3549-4

Kaur, A., Kehinde, B., Sharma, P., Sharma, D., & Kaur, S. (2021). Recently isolated food-derived antihypertensive hydrolysates and peptides: A review. *Food Chemistry, 346*. https://doi.org/10.1016/J.FOODCHEM.2020.128719

Kim, K., Hwang, E., Kim, M., Park, J., & Kim, D. (2020). Antihypertensive Effects of Polyphenolic Extract from Korean Red Pine (Pinus densiflora Sieb. et Zucc.) Bark in Spontaneously Hypertensive Rats. *Antioxidants (Basel, Switzerland), 9*(4). https://doi.org/10.3390/ANTIOX9040333

Lammi, C., Aiello, G., Bollati, C., Li, J., Bartolomei, M., Ranaldi, G., … Arnoldi, A. (2021). Trans-epithelial transport, metabolism and biological activity assessment of the multi-target lupin peptide lilpkhsdad (P5) and its metabolite lpkhsdad (p5-met). *Nutrients, 13*(3), 1–17. https://doi.org/10.3390/nu13030863

Lammi, C., Aiello, G., Dellafiora, L., Bollati, C., Boschin, G., Ranaldi, G., … Arnoldi, A. (2020). Assessment of the Multifunctional Behavior of Lupin Peptide P7 and Its Metabolite Using an Integrated Strategy. *Journal of Agricultural and Food Chemistry, 68*(46), 13179–13188. https://doi.org/10.1021/acs.jafc.0c00130

Lammi, C., Bollati, C., Lecca, D., Abbracchio, M. P., & Arnoldi, A. (2019). Lupin Peptide T9 (GQEQSHQDEGVIVR) Modulates the Mutant PCSK9D374Y Pathway: in vitro Characterization of its Dual Hypocholesterolemic Behavior. *Nutrients 2019, Vol. 11, Page 1665*, *11*(7), 1665. doi:10.3390/NU11071665.

Lammi, C., Zanoni, C., Arnoldi, A., & Aiello, G. (2018). YDFYPSSTKDQQS (P3), a peptide from lupin protein, absorbed by Caco-2 cells, modulates cholesterol metabolism in HepG2 cells via SREBP-1 activation. *Journal of Food Biochemistry, 42*(3), 1–8. https://doi.org/10.1111/jfbc.12524

Leoncini, G., Viazzi, F., De Cosmo, S., Russo, G., Fioretto, P., & Pontremoli, R. (2020). Blood pressure reduction and RAAS inhibition in diabetic kidney disease: Therapeutic potentials and limitations. *Journal of Nephrology, 33*(5), 949–963. https://doi.org/10.1007/S40620-020-00803-3

Li, Q., Yon, J.-Y., & Cai, H. (2015). Mechanisms and Consequences of eNOS Dysfunction in Hypertension. *Journal of Hypertension, 33*(6), 1128. https://doi.org/10.1097/HJH.0000000000000587

Liao, W., Chakrabarti, S., Davidge, S. T., & Wu, J. (2016). Modulatory Effects of Egg White Ovotransferrin-Derived Tripeptide IRW (Ile-Arg-Trp) on Vascular Smooth Muscle Cells against Angiotensin II Stimulation. *Journal of Agricultural and Food Chemistry, 64*(39), 7342–7347. https://doi.org/10.1021/ACS.JAFC.6B03513

Liao, W., Fan, H., Liu, P., & Wu, J. (2019). Identification of angiotensin converting enzyme 2 (ACE2) up-regulating peptides from pea protein hydrolysate. *Journal of Functional Foods, 60*, Article 103395. https://doi.org/10.1016/J.JFF.2019.05.051

Lin, Y., Chen, C., Tsai, J., & Chen, G. (2019). Preparation and Identification of Novel Antihypertensive Peptides from the In Vitro Gastrointestinal Digestion of Marine Cobia Skin Hydrolysates. *Nutrients, 11*(6). https://doi.org/10.3390/NU11061351

Liu, P., Lan, X., Yaseen, M., Wu, S., Feng, X., Zhou, L., … Sun, L. (2019). Purification, Characterization and Evaluation of Inhibitory Mechanism of ACE Inhibitory Peptides from Pearl Oyster (Pinctada fucata martensii) Meat Protein Hydrolysate. *Marine Drugs, 17*(8). https://doi.org/10.3390/md17080463

Liu, X., Li, G., Wang, H., Qin, N., Guo, L., Wang, X., & Shen, S. (2021). Areca Nut Kernel Globulin Hydrolysates. *Molecules, 26*, 3308.

Louca, P., Mompeo, O., Leeming, E., Berry, S., Mangino, M., Spector, T., … Menni, C. (2020). Dietary Influence on Systolic and Diastolic Blood Pressure in the TwinsUK Cohort. *Nutrients, 12*(7), 1–12. https://doi.org/10.3390/NU12072130

Lu, Y., Wang, Y., Huang, D., Bian, Z., Lu, P., Fan, D., & Wang, X. (2021). Inhibitory mechanism of angiotensin-converting enzyme inhibitory peptides from black tea. *Journal of Zhejiang University-SCIENCE B (Biomedical & Biotechnology), 22*(7), 575–589.

Ma, F., Wang, H., Wei, C., Thakur, K., Wei, Z., & Jiang, L. (2019). Three Novel ACE Inhibitory Peptides Isolated From Ginkgo biloba Seeds: Purification, Inhibitory Kinetic and Mechanism. *Frontiers in Pharmacology, 9*, 1579. https://doi.org/10.3389/FPHAR.2018.01579

Mahmudpour, M., Roozbeh, J., Keshavarz, M., Farrokhi, S., & Nabipour, I. (2020). COVID-19 cytokine storm: The anger of inflammation. *Cytokine, 133*, Article 155151. https://doi.org/10.1016/J.CYTO.2020.155151

Majumder, K., Liang, G., Chen, Y., Guan, L., Davidge, S., & Wu, J. (2015). Egg ovotransferrin-derived ACE inhibitory peptide IRW increases ACE2 but decreases proinflammatory genes expression in mesenteric artery of spontaneously hypertensive rats. *Molecular Nutrition & Food Research, 59*(9), 1735–1744. https://doi.org/10.1002/MNFR.201500050

Manual-Kollareth, D. J., Chang, C. L., Zirpoli, H., & Deckelbaum, R. J. (2020). Molecular mechanisms underlying effects of n−3 and n−6 fatty acids in cardiovascular diseases. *Lipid Signaling and Metabolism, 427–453*. https://doi.org/10.1016/B978-0-12-819404-1.00021-X

Martínez-Maqueda, D., Miralles, B., Recio, I., & Hernández-Ledesma, B. (2012). Antihypertensive peptides from food proteins: A review. *Food and Function, 3*(4), 350–361. https://doi.org/10.1039/C2FO10192K

Medvedev, R. Y., Sanchez-Alonso, J. L., Mansfield, C. A., Judina, A., Francis, A. J., Pagiatakis, C., … Gorelik, J. (2021). Local hyperactivation of L-type Ca2+ channels increases spontaneous Ca2+ release activity and cellular hypertrophy in right ventricular myocytes from heart failure rats. *Scientific Reports, 11*(1), 1–9. https://doi.org/10.1038/s41598-021-84275-w

Mehrabani, S., Asemi, M., Najafian, J., Sajjadi, F., Maghroun, M., & Mohammadifard, N. (2017). *Association of Animal and Plant Proteins Intake with Hypertension in Iranian Adult Population : Isfahan Healthy Heart Program*. doi:10.4103/2277-9175.213877.

Messina, C. M., Manuguerra, S., Arena, R., Renda, G., Ficano, G., Randazzo, M., … Santulli, A. (2021). In Vitro Bioactivity of Astaxanthin and Peptides from Hydrolisates of Shrimp (Parapenaeus longirostris) By-Products: From the Extraction Process to Biological Effect Evaluation, as Pilot Actions for the Strategy "From Waste to Profit". *Marine Drugs, 19*(4), 1–18. https://doi.org/10.3390/md19040216

Metchi Donfack, M., Atsamo, A., Temdié Guemmogne, R., Kenfack Ngouateu, O., Dongmo, A., & Dimo, T. (2021). Antihypertensive Effects of the Vitex cienkowskii (Verbenaceae) Stem-Bark Extract on L-NAME-Induced Hypertensive Rats. *Evidence-Based Complementary and Alternative Medicine : ECAM, 2021*. https://doi.org/10.1155/2021/6668919

Mitchell, J. A., Kirkby, N. S., Ahmetaj-Shala, B., Armstrong, P. C., Crescente, M., Ferreira, P., … Warner, T. D. (2021). Cyclooxygenases and the cardiovascular system. *Pharmacology and Therapeutics, 217*. https://doi.org/10.1016/J.PHARMTHERA.2020.107624

Nardo, A. E., Suárez, S., Quiroga, A. V., & Añón, M. C. (2020). Amaranth as a Source of Antihypertensive Peptides. *Frontiers in Plant Science, 11*(September), 1–15. https://doi.org/10.3389/fpls.2020.578631

Ngo, D. H., Kang, K. H., Ryu, B., Vo, T. S., Jung, W. K., Byun, H. G., & Kim, S. K. (2015). Angiotensin-I converting enzyme inhibitory peptides from antihypertensive skate (Okamejei kenojei) skin gelatin hydrolysate in spontaneously hypertensive rats. *Food Chemistry, 174*, 37–43. https://doi.org/10.1016/j.foodchem.2014.11.013

Oh, J. Y., Je, J. G., Lee, H. G., Kim, E. A., Kang, S. I., Lee, J. S., & Jeon, Y. J. (2020a). Anti-hypertensive activity of novel peptides identified from olive flounder (paralichthys olivaceus) surimi. *Foods, 9*(5). https://doi.org/10.3390/foods9050647

Oh, J.-Y., Je, J.-G., Lee, H.-G., Kim, E.-A., Kang, S. I., Lee, J.-S., & Jeon, Y.-J. (2020b). Anti-Hypertensive Activity of Novel Peptides Identified from Olive Flounder (Paralichthys olivaceus) Surimi. *Foods, 9*(5). https://doi.org/10.3390/FOODS9050647

Ozen, G., & Norel, X. (2017). Prostanoids in the pathophysiology of human coronary artery. *Prostaglandins and Other Lipid Mediators, 133*, 20–28. https://doi.org/10.1016/J.PROSTAGLANDINS.2017.03.003

Ozorio, L., Mellinger-Silva, C., Cabral, L. M. C., Jardin, J., Boudry, G., & Dupont, D. (2020). The influence of peptidases in intestinal brush border membranes on the absorption of oligopeptides from whey protein hydrolysate: An ex vivo study using an ussing chamber. *Foods, 9*(10). https://doi.org/10.3390/foods9101415

Pajares, M., Jiménez-Moreno, N., García-Yagüe, A., Escoll, M., de Ceballos, M., Van Leuven, F., … Cuadrado, A. (2016). Transcription factor NFE2L2/NRF2 is a regulator of macroautophagy genes. *Autophagy, 12*(10), 1902–1916. https://doi.org/10.1080/15548627.2016.1208889

Praveesh, B. V., Angayarkanni, J., & Palaniswamy, M. (2011). Antihypertensive and anticancer effect of cow milk fermented by Lactobacillus plantarum and Lactobacillus casei. *International Journal of Pharmacy and Pharmaceutical Sciences, 3* (SUPPL. 5), 452–456.

Querobino, S., Costa, M., & Alberto-Silva, C. (2019). Protective effects of distinct proline-rich oligopeptides from B. jararaca snake venom against oxidative stress-induced neurotoxicity. *Toxicon: Official Journal of the International Society on Toxinology, 167*, 29–37. https://doi.org/10.1016/J.TOXICON.2019.06.012

Rojas-Humpire, R., Olarte-Durand, M., Medina-Ramirez, S., Gutierrez-Ajalcriña, R., Canaza, J. F., & Huancahuire-Vega, S. (2021). Insulin resistance indexes as biomarkers of lifetime cardiovascular risk among adults from Peru. *Journal of Nutrition and Metabolism, 2021*. https://doi.org/10.1155/2021/6633700

Ruiz-Ruiz, J., Dávila-Ortíz, G., Chel-Guerrero, L., & Betancur-Ancona, D. (2013). Angiotensin I-converting enzyme inhibitory and antioxidant peptide fractions from hard-to-cook bean enzymatic hydrolysates. *Journal of Food Biochemistry, 37*(1), 26–35. https://doi.org/10.1111/J.1745-4514.2011.00594.X

Saha, S., Buttari, B., Panieri, E., Profumo, E., & Saso, L. (2020). An Overview of Nrf2 Signaling Pathway and Its Role in Inflammation. *Molecules* 25(22), 5474. doi:10.3390/MOLECULES25225474.

Serafini, M. M., Catanzaro, M., Fagiani, F., Simoni, E., Caporaso, R., Dacrema, M., … Lanni, C. (2020). Modulation of Keap1/Nrf2/ARE signaling pathway by curcuma- And garlic-derived hybrids. *Frontiers in Pharmacology, 10*(January), 1–12. https://doi.org/10.3389/fphar.2019.01597

Soleymanzadeh, N., Mirdamadi, S., Mirzaei, M., & Kianirad, M. (2019). Novel β-casein derived antioxidant and ACE-inhibitory active peptide from camel milk fermented by Leuconostoc lactis PTCC1899: Identification and molecular docking. *International Dairy Journal, 97*, 201–208. https://doi.org/10.1016/j.idairyj.2019.05.012

Song, Y., Yu, J., Song, J., Wang, S., Cao, T., Liu, Z., … Wei, Y. (2021). The antihypertensive effect and mechanisms of bioactive peptides from Ruditapes philippinarum fermented with Bacillus natto in spontaneously hypertensive rats. *Journal of Functional Foods, 79*, Article 104411. https://doi.org/10.1016/J.JFF.2021.104411

Stump, M., Mukohda, M., Hu, C., & Sigmund, C. (2015). PPARγ Regulation in Hypertension and Metabolic Syndrome. *Current Hypertension Reports, 17*(12). https://doi.org/10.1007/S11906-015-0601-X

Sun, D., Zhou, T., Li, X., Heianza, Y., Liang, Z., Bray, G., … Qi, L. (2019). Genetic Susceptibility, Dietary Protein Intake, and Changes of Blood Pressure: The POUNDS Lost Trial. *Hypertension (Dallas, Tex.: 1979)*, *74*(6), 1460–1467. doi:10.1161/HYPERTENSIONAHA.119.13510.

Sun, X., Acquah, C., Aluko, R. E., & Udenigwe, C. C. (2020). Considering food matrix and gastrointestinal effects in enhancing bioactive peptide absorption and bioavailability. *Journal of Functional Foods*, *64*(October 2019), 103680. doi:10.1016/j.jff.2019.103680.

Sun, X., & Udenigwe, C. C. (2020). Chemistry and biofunctional significance of bioactive peptide interactions with food and gut components. *Journal of Agricultural and Food Chemistry, 68*(46), 12972–12977. https://doi.org/10.1021/acs.jafc.9b07559

Tanase, D. M., Gosav, E. M., Radu, S., Ouatu, A., Rezus, C., Ciocoiu, M., … Floria, M. (2019). Arterial hypertension and interleukins: Potential therapeutic target or future diagnostic marker? *International Journal of Hypertension, 2019*. https://doi.org/10.1155/2019/3159283

Tianrui, Z., Bingtong, L., Ling, Y., Liping, S., & Yongliang, Z. (2019). ACE inhibitory activity in vitro and antihypertensive effect in vivo of LSGYGP and its transepithelial transport by Caco-2 cell monolayer. *Journal of Functional Foods, 61*(January), Article 103488. https://doi.org/10.1016/j.jff.2019.103488

Udenigwe, C. C., Abioye, R. O., Okagu, I. U., & Obeme-Nmom, J. I. (2021). Bioaccessibility of bioactive peptides: Recent advances and perspectives. *Current Opinion in Food Science, 39*, 182–189. https://doi.org/10.1016/J.COFS.2021.03.005

Valdez-Meza, E. E., Raymundo, A., Figueroa-Salcido, O. G., Ramírez-Torres, G. I., Fradinho, P., Oliveira, S., … Cabrera-Chávez, F. (2019). Pasta enrichment with an

amaranth hydrolysate affects the overall acceptability while maintaining antihypertensive properties. *Foods, 8*(8), 1–10. https://doi.org/10.3390/foods8080282

Verma, T., Sinha, M., Bansal, N., Yadav, S., Shah, K., & Chauhan, N. (2021). Plants used as antihypertensive. *Natural Products and Bioprospecting, 11*(2), 155–184. https://doi.org/10.1007/S13659-020-00281-X

Wang, Y., Jiang, L., Feng, S.-J., Tang, X.-Y., & Kuang, Z.-M. (2020). Effect of combined statin and antihypertensive therapy in patients with hypertension: A systematic review and meta-analysis. *Cardiology, 145*(12), 802–812. https://doi.org/10.1159/000508280

Wang, B., & Li, B. (2018). Charge and hydrophobicity of casein peptides influence transepithelial transport and bioavailability. *Food Chemistry, 245*(September), 646–652. https://doi.org/10.1016/j.foodchem.2017.09.032

Wang, Y., Li, Y., Ruan, S., Lu, F., Tian, W., & Ma, H. (2021). Antihypertensive effect of rapeseed peptides and their potential in improving the effectiveness of captopril. *Journal of the Science of Food and Agriculture, 101*(7), 3049–3055. https://doi.org/10.1002/JSFA.10939

Wei, D., Fan, W., & Xu, Y. (2019). In vitro production and identification of angiotensin converting enzyme (ACE) inhibitory peptides derived from distilled spent grain prolamin isolate. *Foods, 8*(9). https://doi.org/10.3390/foods8090390

Wen, C., Zhang, J., Zhou, J., Feng, Y., Duan, Y., Zhang, H., & Ma, H. (2020). Slit divergent ultrasound pretreatment assisted watermelon seed protein enzymolysis and the antioxidant activity of its hydrolysates in vitro and in vivo. *Food Chemistry, 328*, Article 127135. https://doi.org/10.1016/j.foodchem.2020.127135

Xie, J., Ye, H., Du, M., Yu, Q., Chen, Y., & Shen, M. (2020). Mung bean protein hydrolysates protect mouse liver cell line Nctc-1469 cell from hydrogen peroxide-induced cell injury. *Foods, 9*(1). https://doi.org/10.3390/foods9010014

Xing, Y., Zhang, J., Wei, H., Zhang, H., Guan, Y., Wang, X., & Tong, X. (2019). Reduction of the PI3K/Akt related signaling activities in skeletal muscle tissues involves insulin resistance in intrauterine growth restriction rats with catch-up growth. *PLOS ONE, 14*(5), Article e0216665. https://doi.org/10.1371/JOURNAL.PONE.0216665

Xu, Q., Fan, H., Yu, W., Hong, H., & Wu, J. (2017). Transport Study of Egg-Derived Antihypertensive Peptides (LKP and IQW) Using Caco-2 and HT29 Coculture Monolayers. *Journal of Agricultural and Food Chemistry, 65*(34), 7406–7414. https://doi.org/10.1021/acs.jafc.7b02176

Xue, L., Yin, R., Howell, K., & Zhang, P. (2021). Activity and bioavailability of food protein-derived angiotensin-I-converting enzyme–inhibitory peptides. *Comprehensive Reviews in Food Science and Food Safety, 20*(2), 1150–1187. https://doi.org/10.1111/1541-4337.12711

Yathisha, U. G., Ishani, B., Iddya, K., & Mamatha, B. S. (2018). Antihypertensive activity of fish protein hydrolysates and its peptides. *59*(15), 2363–2374. doi:10.1080/10408398.2018.1452182.

Yu, Y., Xue, B., Wei, S., Zhang, Z., Beltz, T., Guo, F., AK, J., & RB, F. (2015). Activation of central PPAR-γ attenuates angiotensin II-induced hypertension. *Hypertension (Dallas, Tex.: 1979), 66*(2), 403–411. doi:10.1161/HYPERTENSIONAHA.115.05726.

Yu, X., Su, Q., Shen, T., Chen, Q., Wang, Y., & Jia, W. (2020). Antioxidant peptides from sepia esculenta hydrolyzate attenuate oxidative stress and fat accumulation in caenorhabditis elegans. *Marine Drugs, 18*(10). https://doi.org/10.3390/md18100490

Yu, Z., Wang, L., Wu, S., Zhao, W., Ding, L., & Liu, J. (2021). In vivo anti-hypertensive effect of peptides from egg white and its molecular mechanism with ACE. *International Journal of Food Science and Technology, 56*(2), 1030–1039. https://doi.org/10.1111/ijfs.14756

Yuda, N., Tanaka, M., Yamauchi, K., Abe, F., Kakiuchi, I., Kiyosawa, K., … Nakamura, M. (2020). Effect of the casein-derived peptide met-lys-pro on cognitive function in community-dwelling adults without dementia: A randomized, double-blind, placebo-controlled trial. *Clinical Interventions in Aging, 15*, 743–754. https://doi.org/10.2147/CIA.S253116

Zanoni, C., Aiello, G., Arnoldi, A., & Lammi, C. (2017). Investigations on the hypocholesterolaemic activity of LILPKHSDAD and LTFPGSAED, two peptides from lupin β-conglutin: Focus on LDLR and PCSK9 pathways. *Journal of Functional Foods, 32*, 1–8. https://doi.org/10.1016/j.jff.2017.02.009

Zhan, X., Li, J., & Zhou, T. (2021). Targeting Nrf2-mediated oxidative stress response signaling pathways as new therapeutic strategy for pituitary adenomas. *Frontiers in Pharmacology, 12*. https://doi.org/10.3389/FPHAR.2021.565748

Zhang, J., Patel, M. B., Griffiths, R., Dolber, P. C., Ruiz, P., Sparks, M. A., … Crowley, S. D. (2014). Type 1 angiotensin receptors on macrophages ameliorate IL-1 receptor–mediated kidney fibrosis. *The Journal of Clinical Investigation, 124*(5), 2198. https://doi.org/10.1172/JCI61368

Zhao, Y. Q., Zhang, L., Tao, J., Chi, C. F., & Wang, B. (2019). Eight antihypertensive peptides from the protein hydrolysate of Antarctic krill (Euphausia superba): Isolation, identification, and activity evaluation on human umbilical vein endothelial cells (HUVECs). *Food Research International, 121*(January), 197–204. https://doi.org/10.1016/j.foodres.2019.03.035

Zheng, Y., Wang, X., Zhuang, Y., Li, Y., Shi, P., Tian, H., … Chen, X. (2020). Isolation of novel ACE-inhibitory peptide from naked oat globulin hydrolysates in silico approach: Molecular docking, in vivo antihypertension and effects on renin and intracellular endothelin-1. *Journal of Food Science, 85*(4), 1328–1337. https://doi.org/10.1111/1750-3841.15115

Zippel, N., Loot, A. E., Stingl, H., Randriamboavonjy, V., Fleming, I., & Fisslthaler, B. (2018). Endothelial AMP-Activated Kinase α1 Phosphorylates eNOS on Thr495 and Decreases Endothelial NO Formation. *International Journal of Molecular Sciences, 19*(9). https://doi.org/10.3390/IJMS19092753