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Natural Antihypertensive Peptides: Emerging Therapeutics For Blood Pressure Management

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Hypertension, a primary risk factor for cardiovascular diseases, continues to be a significant global public health challenge. In the pursuit of effective, secure, and sustainable antihypertensive treatments, there has been an increasing emphasis on natural sources, particularly bioactive peptides derived from proteins found in various foods, including milk, fish, and meat. This review delves into advanced bioanalytical methodologies used to quantify and evaluate the pharmacokinetics of emerging antihypertensive peptides obtained from these natural sources. Moreover, this review explores the potential contributions of nanotechnology and bioinformatics in enhancing the delivery and bioavailability of antihypertensive peptides, with the prospect of fostering the development of functional foods and nutraceuticals. Additionally, we underscore the role of biotechnology in facilitating the large-scale production of these peptides while addressing concerns pertaining to their stability and safety. In conclusion, the application of advanced bioanalytical techniques, coupled with a deeper comprehension of pharmacokinetics, offers a promising pathway to unlock the full potential of antihypertensive peptides sourced from natural origins. Ultimately, this endeavour holds the potential to make significant contributions to the management and prevention of hypertension and associated cardiovascular diseases.

Keywords: Antihypertensive Peptides; Advanced Quantification; Hypertension; Natural Sources; Pharmacokinetic parameters.

Hypertension is a medical condition characterized by systolic and diastolic blood pressure (BP) levels of 140/90 mmHg or higher in adults. The global prevalence of hypertension, or sustained high BP, is a matter of concern. Despite numerous initiatives to reduce these figures, the statistics have shown minimal improvement from 2010 to the present day. This lack of progress can be linked to an increase in alcohol, tobacco, and substance use, as well as a rising prevalence of obesity, all of which are significant risk factors for hypertension.[1]

Hypertension and its associated health issues are a leading cause of mortality in the context of non-communicable diseases. Even with the existence of effective antihypertensive medications, some individuals with hypertension do not achieve the desired reduction in BP. Furthermore, the considerable cost and potential adverse effects, like heightened serum potassium levels and decreased BP, associated with these drugs, result in insufficient compliance with treatment. This, in turn, increases the vulnerability

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to other chronic ailments arising from poorly controlled hypertension, e.g., organ dysfunction and stroke.[2] This drives the ongoing pursuit of safer agents that can effectively normalize BP, providing hope for individuals who do not respond favorably to presently available antihypertensive medications.

In traditional medicine, the use of natural products derived from plants[3] and food proteins[4] has been a longstanding approach in the management of hypertension. Plant extracts rich in polyphenols have shown antihypertensive effects in both normotensive and hypertensive rodents.[5] Clinical trials also suggest that high-protein diets can influence hypertension risk. In the POUNT Lost Trials, high-protein intake reduced genetic susceptibility to hypertension.[6] Conversely, a 5-year study of over 13,000 Korean men found that animal-based proteins were linked to a higher hypertension risk than plant-based proteins.[7]

A study in the Iranian population found that protein-based diets are linked to a lower risk of hypertension.[8] Protein-derived peptides, after intestinal hydrolysis, interact with muscarinic and Angiotensin-II receptors, inhibit renin and ACE activity, and modulate the RAS pathway, contributing to BP reduction.[9] Dietary proteins also target hypertension-related factors like oxidative stress, obesity, and diabetes by increasing nitric oxide, reducing advanced glycation end-products, and improving insulin sensitivity.[10]

Food proteins, their hydrolysates, and peptides are key sources of antihypertensive agents. [11] Hydrolysis exposes specific amino acid side chains, enhancing peptide bioactivity. Notably, buffalo and cow milk proteins hydrolyzed with enzymes like papain, pepsin, and trypsin show stronger ACE-inhibitory effects than their native forms.[12]

Biologically active compounds known as Active Hypotensive Peptides (AHPs) exhibit effects similar to those of antihypertensive medications. These peptides are naturally embedded within proteins from numerous sources and may offer additional health advantages, e.g., serving as a valuable source of essential amino acids, thereby enhancing their nutritional value.[13]Diverse techniques are available for the extraction of AHPs and other biopeptides as presented in fig 1 given below: a) Cooking: AHPs and biopeptides can be liberated from protein-rich foods through the process of cooking; b) Chemical Hydrolysis: A chemical approach can be utilized to enzymatically hydrolyze proteins, releasing AHPs; c) Protease Hydrolysis: Enzymes like alcalase, trypsin, pepsin, and flavor enzyme are employed to break down proteins and produce AHPs; d) Fermentation: AHPs and biopeptides can be derived from the fermentation of protein-rich substances using numerous microorganisms, including Lactobacillus and Saccharomyces cerevisiae; e) Recombinant Methods: AHPs can also be generated through recombinant methods. This may include engineering tandem multimers of bioactive peptides by attaching them to carrier proteins or integrating them into food-based proteins such as â-conglycinin, amaranth 11S globulin, or rice glutelins [14]

Active Hypotensive Peptides (AHPs) have been the subject of very few reports in the pharmaceutical literature, with only a small number of investigations involving clinical human trials. Most of these studies, however, have focused on the well-studied tripeptides IPP and VPP, which are frequently present in milk,15 as well as the sardine-derived VY dipeptide.[16]These milk-fermented tripeptides, IPP (Ile-Pro-Pro) and VPP (Val-Pro-Pro), decreased systolic and diastolic blood pressure by 5.0 and 2.3 mm Hg, respectively, when given in doses ranging from 5 to 1000 mg daily.[15] Commercial products such as PeptACETM (LKPNM) and AmealBP® (IPP, VPP) now contain these AHPs.[15]

AHPs in functional foods mainly come from milk, sardines, and bonito. Products include IPP/VPP-fermented milk (Evolus®, Finland), LKPNM soup (Nippon Supplement, Japan), and FV/VY/IY-rich wakame jelly (Riken Vitamin, Japan). Supplements like C12 Peption (DMV International, Netherlands) contain sequences such as FFVAPFPEVFGK. Alternative delivery methods involve AHPs released via gastrointestinal digestion of modified proteins or engineered multimeric proteins in seeds, lactic acid bacteria, or microalgae.[14]

METHODOLOGY

This review is based on a comprehensive selection of relevant peer-reviewed articles sourced

from databases such as PubMed, Scopus, Web of Science, and Google Scholar.

Literature Review

Hypertension and Antihypertensive Peptides (AHP)

Cardiovascular diseases cause around 17 million deaths annually, with hypertension affecting nearly 1 billion people, responsible for up to 9 million of these deaths.[17]In Canada, nearly 6 million individuals, or about one in five adults, have hypertension.[18] Hypertension is often called the silent killer, as it frequently lacks early symptoms and is inadequately managed even when diagnosed early.[19] However, it significantly increases the risk of atherosclerosis and related conditions, e.g., CHD, cerebrovascular disease, and renal disease.[20] Addressing hypertension has significant health and socioeconomic implications. In the USA, the cost of treating hypertension and its associated conditions reached $156 billion in 2011.[21, 22]Many antihypertensive drugs have noticeable side effects, e.g., headaches and dry cough, and patients often have poorly controlled BP despite treatment, increasing the risk of complications.[22,23]Therefore, there's an urgent need for innovative, cost-effective strategies to enhance hypertension management.Diet plays a key role in health, influencing conditions like cardiovascular disease, obesity, and diabetes.[24] The DASH study showed that diets rich in fruits and vegetables help lower BP.[25] Nutrients like sodium and potassium significantly impact BP and vascular health,[29] while macronutrients protein, fat, and carbohydrates also play a crucial role in hypertension management.

The OmniHeart trials showed that replacing carbs with protein or monounsaturated fats can lower BP and heart disease risk.[27] Food proteins contain bioactive peptides released through digestion, fermentation, or processing, offering benefits beyond nutrition.[28] Antihypertensive peptides, especially ACE inhibitors, are promising for managing hypertension [29, 30]. Some also show antioxidant, anti-inflammatory, and opioid-like effects,[31] though in vitro and in vivo results often differ.[32]To develop effective antihypertensive peptides, a comprehensive understanding of hypertension's pathophysiology and potential targets is vital. While previous reviews have explored mechanisms of action for many food-derived antihypertensive peptides,[33] limited information exists on their multifaceted roles in pathways contributing to persistent hypertension. An image (Fig. 2) has been provided highlighting the distribution of antihypertensive peptides in the

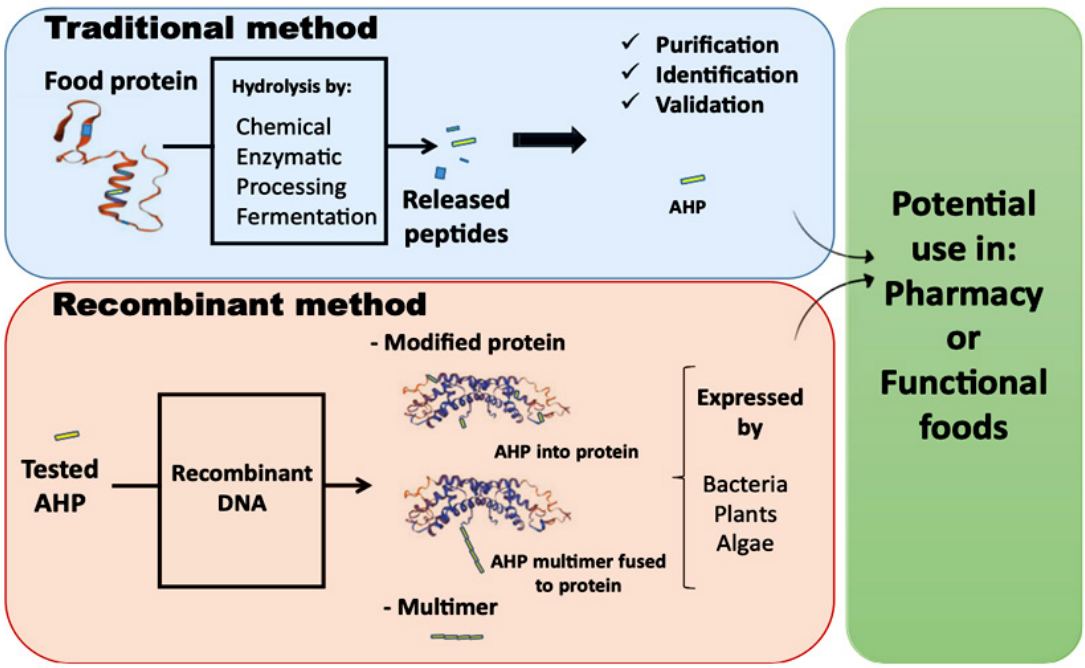

Fig. 1. Techniques of Production of Peptides based on Hypertension

"AHTPDB database (http://crdd.osdd.net/raghava/ahtpdb/) " based on numerous sources.

Hypertension arises from complex genetic and environmental factors, with over 90% of cases having no clear cause.[34] Key contributors include high sympathetic activity, excess sodium and low potassium/calcium intake, altered renin secretion, increased ACE and Ang II levels, reduced nitric oxide, and vascular inflammation.[35] RAS hyperactivity, endothelial dysfunction, sympathetic

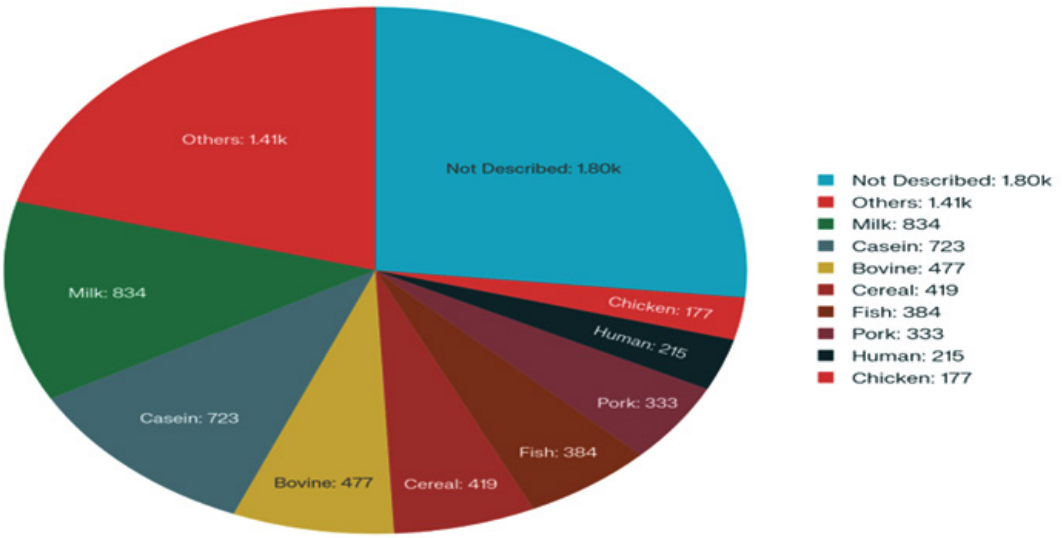

Fig. 2. Dissemination of Peptides based on Hypertension.[95] (Reproduced from cited Sources)

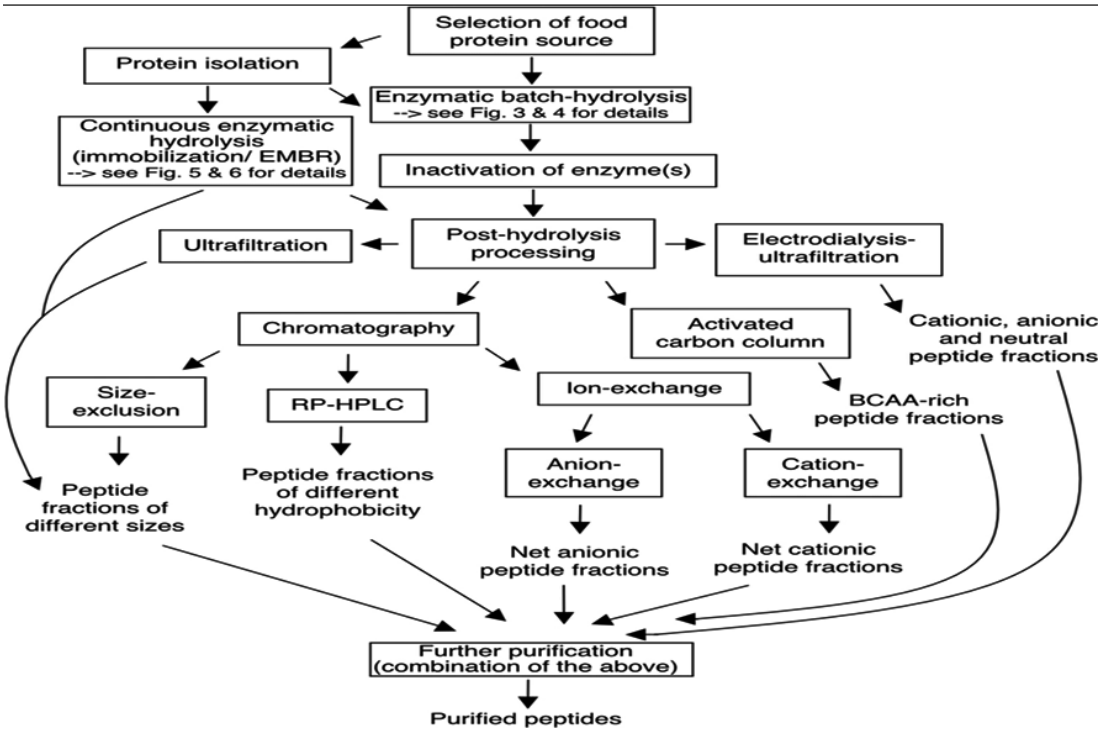

Fig. 3. Production and processing methods based on food protein.[96]

overactivation, and vascular abnormalities are central to its progression.[36]

Production of Antihypertensive Peptides-Food Origin

Clinical trials are essential to assess the efficiency and pharmacokinetics of antihypertensive bioactive peptides. VPP and IPP have shown significant BP reductions in hypertension populations when administered orally in foods like fermented milk and fruit juice in studies from Japan and Finland.[37,38]However, when these same peptides were orally administered to hypertensive individuals in the Netherlands and Denmark, they did not achieve a similar reduction in BP. This observation suggests potential variations in efficiencybetweendiverse human populations.[39]

A meta-analysis of 18 clinical trials confirms that oral VPP and IPP peptides effectively reduce BP in hypertensive individuals, with the most pronounced effects observed in Asian subjects.[40]Boelsma et al. showed that oral IPP significantly reduced BP in Caucasian individuals with stage-1 hypertension.[41]An Alternative study found that milk tripeptides combined with plant sterols lowered systolic BP, total cholesterol, and LDL cholesterol in hypertensive, hypercholesterolemic patients. [42]BP reductions of up to 13/8 mm Hg occur within 1–2 weeks at 3–55 mg/day.

Low doses (2–10.2 mg/day) of VPP and IPP reduced SBP by 4.0 and DBP by 1.9 mm Hg in mildly hypertensive patients [43] Hirota et al. showed these peptides also improved endothelial function.[44] Yoghurt enriched with other casein peptides (RYLGY, AYFYPEL) lowered SBP by 12 mm Hg over 6 weeks.[45] Pea protein hydrolysate

Table 1. Bioactive peptides from numerous animal proteins with antihypertensive action (Bhat et al., 2017)

Protein source	Peptide/sequence
Casein	Phe-Phe-Val-Ala-Pro
	Val-Pro-Pro
	Ile-Pro-Pro
Whey proteins	Tyr-Pro
Porcine skeletal muscle	Ile-Thr-Thr-Asn-Pro
	Thr-Asn-Pro
	Met-Asn-Pro-Pro-Lys
	Ile-Thr-Thr-Asn-Pro
	RMLGQTPT
Chicken	Ile-Lys-Trp
	Leu-Lys-Pro
	Gly-Phe-Hyp-Gly-Thr-Hyp-Gly-Leu-Hyp-Gly-Phe
Beef	Leu-Ala-Gln-Tyr-Lys

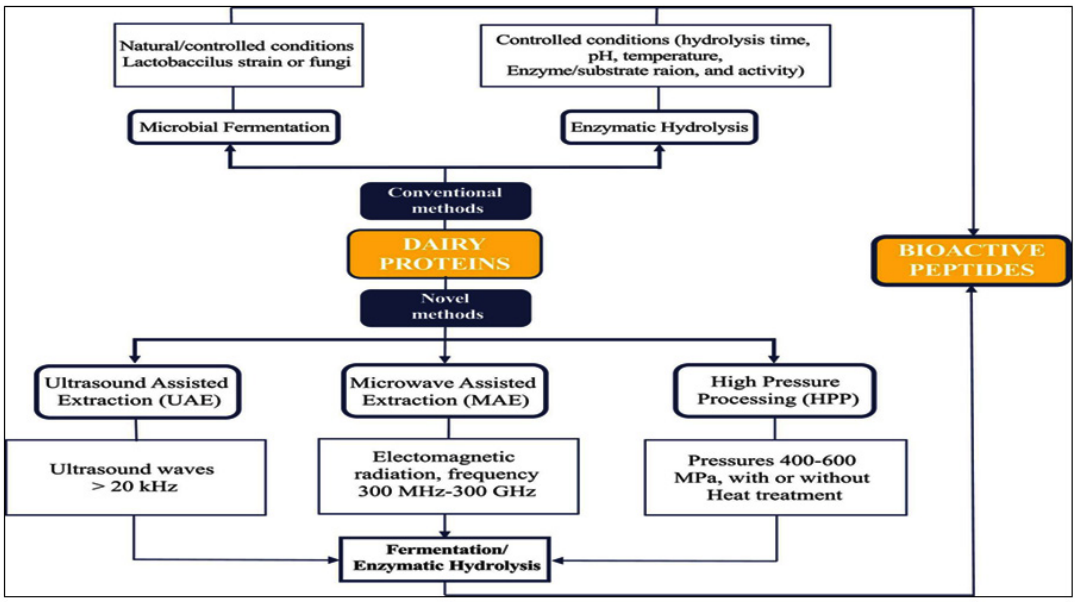

Fig. 4. Novel and conventional methods of bioactive peptides production from dairy proteins.[97]

reduced SBP by 5–7 mm Hg in a small trial, though conclusions are limited because of sample size (n=7).[46] Clinical trials with the sardine-derived dipeptide VY showed mixed results: one small study reported SBP and DBP reductions of 9.3 and 5.2 mm Hg after 4 weeks,[47] while another larger trial found significant BP lowering without side effects.[49] However, a single dose increased plasma VY but did not acutely lower BP, suggesting longer treatment may be needed.[50] The clinical impact remains uncertain because of small, varied samples.[48]

Numerous animal studies have indicated substantial reductions in BP, typically ranging from 20 to 40 mmHg, following the administration of bioactive peptides derived from food proteins.[51] In contrast, human studies have reported more modest reductions, generally falling within the range of 2 to 12 mmHg.[52] It is worth considering that most animal studies focused on specific hypertension models, e.g., spontaneously hypertensive rats (SHR), where all subjects share a common underlying pathophysiology. Conversely, human participants in clinical studies are likely to exhibit diverse etiologies contributing to their hypertension. Animal studies often use specific strains, while human trials include diverse racial and genetic backgrounds, affecting bioactive peptide efficacy.[53] Differences in pharmacokinetics and pharmacodynamics between rodents and humans add complexity. More clinical research across varied ethnic groups is needed to confirm their antihypertensive benefits. A diagram of production and processing methods is shown in Fig. 3.

Production of Antihypertensive Peptides-Animal Origin

There is an emergentimportance in the potential applications of bioactive molecules in the fields of nutrition and healthcare.[54] Meat, being a rich source of protein, has received significant attention for its ability to produce bioactive peptides, especially those with ACE-inhibitory properties. Implementing food-based approaches to manage hypertension offers a promising avenue to enhance overall health, promote well-being, and reduce healthcare costs. ACE-inhibitory peptides have been identified in proteolytic products of animal, plant, and microbial proteins.[55] Enzymatic hydrolysis of muscle proteins like myosin and collagen also yields bioactive peptides.[56] Many studies confirm their in vitro ACE inhibition and BP-lowering effects in animals, with supportive evidence in humans.[55]Arihara et al. identified two ACE-inhibitory peptides from thermolysin-treated porcine muscle that lowered BP in hypertensive rats.[57] Saiga et al. found three potent ACE-inhibitory peptides from chicken breast hydrolysates, with Gly-Phe-Hyp-Gly-Thr-Hyp-Gly-Leu-Hyp-Gly-Phe being the most effective.[58]

Fu-Yuan and their team described the maximum ACE inhibitory action in the hydrolysate acquired from chicken leg bones when using the alkalase enzyme for the hydrolysis process.[61] In separate studies, Jang and Lee, as well as Kazunori and their collaborators, identified powerful ACE inhibitory peptides. Jang and Lee isolated Val-Leu-Ala-Gln-Tyr-Lys from beef protein, and Kazunori et al. identified RMLGQTPT from porcine troponin C; both showed strong ACE inhibition [59,60]

Arihara et al. identified two ACE-inhibitory pentapeptides (myopentapeptides A and B: ITTNP) from thermolysin-digested porcine myosin.[62] Katayama et al. reported an octapeptide VKKVLGNP from pepsin-digested myosin light chain,[63] and a novel antihypertensive peptide M6 (KRVITY) from porcine myosin B hydrolysate.[64] Katayama et al. identified ACE-inhibitory peptides KRQKYDI from porcine troponin T,[65] VKKVLGNP from myosin light chain,[63] and KRVITY (peptide M6) from myosin B of porcine skeletal muscle.[64]

ACE-inhibitory peptides have been found in soluble protein hydrolysates of fish like shellfish, tuna, bonito, salmon, and sardine.[66] Sardine viscera enzymes hydrolyzed sardinelle proteins, yielding low-hydrophobicity peptides (200–600 Da).[67] The sardine-derived dipeptide valyl-tyrosine lowered BP by 7.4–9.7 (SBP) and 4.5–5.2 mm Hg (DBP) in humans.[67] Similar ACE inhibitory activity was found in Pacific Hake after digestion.[68] Fish-derived peptides show promise in pharmaceuticals, e.g., BP-lowering capsules containing Katsuobushi oligopeptide LKPNM from thermolysin-treated dried bonito. This peptide is activated to LKP by digestion. Examples include Vasotensin 120T™ and PeptACE™ Peptides 90.[69]. About 30% of blood from slaughtered animals is used in the food industry, 70%, but safety concerns, religious restrictions, and consumer aversion limit its use. [71,72]

Innovative approaches are needed to better utilize blood components, reducing environmental hazards and tapping into this resource's potential.[72,73]

Studies highlight blood components as promising sources of bioactive peptides, offering value-added use for slaughterhouse blood.[74]Several studies, primarily centred on bovine and porcine blood and conducted over the past decade, have demonstrated the ACE-inhibitory activity of bioactive peptides obtained from blood sources. Food-derived peptides, including blood proteins, inhibit ACE and are milder and safer than synthetic drugs.[75] Moreover, natural peptides with ACE-inhibitory properties often possess additional bioactive functions and are easily absorbed.[76]

Production of Antihypertensive Peptides-Dairy Origin

Epidemiological studies link lower milk and protein intake to higher hypertension risk.[77-80] Garcia-Palmieri et al. found Puerto Rican men who avoided milk had twice the hypertension incidence.[78] Clinical trials further confirm that ACE-inhibitory peptides reduce BP in humans. Milk protein-derived peptides have demonstrated BP-lowering effects in animal models and may benefit vascular health. Though clinical evidence on lactotripeptides is still debated, they provide a valuable non-pharmacological option for managing hypertension(Fig. 4). .[81]Milk-derived ACE inhibitory peptides may be less potent than drugs but are promising, safe, natural agents without side effects. Their effectiveness depends on resistance to degradation by intestinal and plasma peptidases to reach target sites intact.[82]

Bioactive peptides are commonly produced via milk fermentation using traditional dairy starter cultures. Within the end-products, which encompass numerous cheese varieties and fermented kinds of milk, one can find peptides with antihypertensive properties.[83] As a result, when these traditional dairy products are incorporated into one's daily diet, they may confer specific health benefits under certain conditions. Multiple studies have documented the identification and isolation of antihypertensive peptides in numerous cheese varieties. It's important to note that the stability of these peptides, which encompass those with ACE-inhibitory activity,[84] â-casomorphin,[85] and calcium-binding phosphopeptides,[86] is influenced by factors, e.g., pH, salt concentration, and the types of enzymes present during the cheese ripening process.

Muehlenkamp and Warthesen reported â-casomorphin degradation in cheddar cheese,[87] while Gomez-Ruiz et al.[84] found peptides retained ACE-inhibitory activity after simulated digestion. Hernández-Ledesma et al.[88] reported moderate ACE-inhibitory activity in fermented milk and fresh cheeses, which stayed stable or increased after enzymatic digestion. Hernández-Ledesma et al.[89] found infant formulas exhibit ACE-inhibitory activity. Overall, digestion may enhance bioactive peptide release from dairy proteins, with some peptides resisting digestion [90,91]

While the discovery of novel antihypertensive peptides from natural sources has garnered significant attention, their successful therapeutic application hinges on robust bioanalytical and pharmacokinetic evaluation. However, the current literature often overlooks key challenges and methodologies essential for this translation. One critical omission is the detailed discussion of LC-MS/MS quantification strategies, which remain the cornerstone for the accurate detection and quantification of low-abundance peptides in complex biological matrices due to their high sensitivity and selectivity. The bioanalytical evaluation of antihypertensive peptides using LC-MS/MS techniques has become increasingly important due to its high sensitivity and selectivity.[92] These methods face challenges such as signal splitting from multiple charge states, unfavorable fragmentation patterns, and adsorption issues during sample preparation.[93] Strategies to maximize sensitivity and improve quantification limits include optimizing mass spectrometry parameters, chromatography conditions, and sample preparation techniques.[94] Recent advancements in LC-MS technology have enabled the development of highly sensitive methods with lower limits of quantitation in the picomolar range, supporting pharmacokinetic and pharmacodynamic studies. While LC-MS offers advantages over traditional immunoassays, there is still a need for harmonization of regulatory guidelines and further research on matrix effects and co-medications.[95] The integration of artificial intelligence in LC-MS shows promise for revolutionizing bioanalytical methods.[95]

Furthermore, naturally derived peptides

suffer from poor oral bioavailability owing to gastrointestinal degradation, enzymatic hydrolysis, and limited intestinal permeability. These barriers severely limit systemic exposure and must be addressed through formulation and delivery innovations. Oral delivery of peptide drugs faces significant challenges due to poor bioavailability caused by gastrointestinal degradation and limited intestinal permeability.[96,97] These barriers result in oral bioavailability typically under 1% for peptides. To overcome these obstacles, various strategies have been explored, including chemical modifications, incorporation of unnatural amino acids, cyclization, and pro-drug approaches.[98] Advanced delivery systems such as nanoparticles and microemulsions show promise in improving oral peptide bioavailability. Additionally, the use of permeation enhancers has gained renewed interest to increase gut permeability and enhance absorption.[99] Despite decades of research, clinical success remains elusive due to challenges in achieving reproducible efficacy and addressing safety concerns. However, recent advancements in formulation strategies and delivery technologies offer hope for the development of effective oral peptide delivery systems.

The phenomenon of first-pass metabolism, primarily involving hepatic degradation, also significantly impacts peptide pharmacokinetics but is often underreported in early-stage evaluations. The pharmacokinetics of peptide and protein therapeutics are complex, involving various absorption, distribution, and elimination processes.[100] First-pass metabolism, particularly in the liver, significantly impacts peptide pharmacokinetics.[101] Biotransformation studies are crucial for understanding the in vivo stability and potency of biotherapeutics, especially those containing non-native chemical linkers.[102] These studies should be implemented early in development to select stable candidates and appropriate bioanalytical techniques. Renal and hepatic impairment can affect the pharmacokinetics of therapeutic peptides and proteins, often necessitating dose adjustments or risk mitigation strategies.[103] The increasing structural diversity of these therapeutics, including the use of non-natural amino acids and conjugation technologies, suggests a need for reassessing the impact of organ impairment on their pharmacokinetics. Advanced bioanalytical techniques, including mass spectrometry, are essential for efficient and reliable detection of peptide and protein drugs.

In addition, transporter-mediated uptake mechanisms, such as those involving hPEPT1 and OATP1A2, play a crucial role in the intestinal absorption and tissue distribution of bioactive peptides, offering potential targets to enhance peptide delivery. Peptide transporters play a crucial role in the absorption of dietary proteins and peptide-like drugs in the intestine and kidneys. Two main transporters, PEPT1 and PEPT2, have been identified and characterized.[104,105] PEPT1, located in the intestinal brush border membrane, is particularly important for the oral bioavailability of various drugs, including â-lactam antibiotics and antiviral prodrugs.[106] In addition to peptide transporters, organic anion transporting polypeptides (OATPs), such as OATP1A2 and OATP2B1, have been implicated in intestinal drug absorption. These transporters exhibit broader substrate selectivity compared to PEPT1, offering potential for enhanced oral drug delivery. Understanding the structure, function, and regulation of these transporters is crucial for developing novel drug delivery systems and improving the bioavailability of peptide-based therapeutics.

DISCUSSION

The worldwide prevalence of hypertension, a major risk factor for cardiovascular disorders, has attracted a lot of interest in the investigation of natural antihypertensive peptides. Millions of people worldwide suffer from hypertension, which is linked to significant morbidity, mortality, and medical expenses. Even if traditional pharmaceutical treatments, including beta-blockers and ACE inhibitors, successfully reduce blood pressure, prolonged usage of these medications can result in negative side effects, excessive expenses, and non-compliance from patients. Because of this, scientists are now looking into more natural, alternative approaches, especially dietary changes and bioactive peptides that may lower blood pressure.

One of the best-established non-pharmacological strategies for managing hypertension is the DASH (Dietary Approaches

to Stop Hypertension) diet. Adherence to the DASH diet, which is low in saturated fat and cholesterol and high in fruits and vegetables and low in dairy, has been shown to dramatically lower both systolic and diastolic blood pressure[25]. The consumption of naturally occurring bioactive peptides and minerals that regulate vascular function and electrolyte balance is partly responsible for the positive effects of such dietary patterns.

The response of blood pressure to dietary treatments is significantly influenced by genetic predisposition in addition to dietary patterns. Studies have indicated that specific genetic variants impact salt sensitivity, which in turn impacts an individual's hypertensive response to sodium intake in the diet[26]. This highlights the significance of genetic screening and customized nutrition in creating successful hypertension treatments, while also emphasizing that the effectiveness of bioactive peptide interventions may vary based on a person's genetic composition.

Furthermore, it is becoming more well acknowledged that natural protein sources have the capacity to produce peptides that lower blood pressure. For example, bovine blood plasma, which is frequently regarded as a by-product of slaughterhouses, has been used as an economical substrate for the manufacture of probiotics, proving both its economic worth and the viability of producing bioactive peptides with health-promoting qualities[70]. These methods highlight the benefits of using waste materials and producing useful bioactive substances that can control blood pressure.

CONCLUSION

In conclusion, the review underscores the imperative need to explore and harness the potential of antihypertensive peptides derived from natural sources. The thorough examination of bioanalytical methods and pharmacokinetic evaluation techniques within this review significantly enhances our comprehension of the efficacy and safety of these peptides. The implications of this research are extensive, opening the door to innovative non-pharmacological strategies for managing hypertension. As a recommendation for future research, we advocate for ongoing exploration of bioactive peptides, with a specific emphasis on optimization, diverse delivery methods, and the evaluation of their long-term health implications. Such efforts will further propel the practical utilization of these peptides in hypertension management and contribute to the enhancement of public health.

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This research did not involve human participants, animal subjects, or any material that requires ethical approval.

Informed Consent Statement

This study did not involve human participants, and therefore, informed consent was not required.

Clinical Trial Registration

This research does not involve any clinical trials**.**

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Not Applicable.

Author Contributions

Ashvini Trambak Varungase: Conceptualization, Methodology, Writing – Original Draft; Data Collection, Analysis, Writing – Review & Editing; Resources; Nirmala Vikram

Shinde: Visualization, Supervision, Project Administration.

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