

Bioactive Peptides from Natural Sources: Biochemical Mechanisms and Applications in Health and Food Review

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| Article Info | ABSTRACT |
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| <p>Article History Received: 28 December 2026 Revised: 17 February 2026 Accepted: 01 March 2026 Available online: 05 March 2026</p> <hr/> <p>* Email (Author Corresponding): meylda25001@mail.unpad.ac.id</p> | <p>Bioactive peptides derived from food proteins represent a diverse group of short amino acid sequences that become biologically active following proteolytic release during food processing, fermentation, or gastrointestinal digestion. These peptides have been widely reported to exert antioxidant, antihypertensive, antimicrobial, and metabolic regulatory activities through specific biochemical mechanisms at the molecular and cellular levels. This study is a narrative literature review that synthesizes recent evidence on bioactive peptides derived from natural food sources, with emphasis on their protein origins, production strategies, biochemical mechanisms of action, bioavailability and stability constraints, and applications in health-oriented food systems. Literature was mainly sourced from the Scopus database using structured keywords related to bioactive peptides, protein hydrolysis, fermentation, functional foods, and health outcomes. Evidence shows that both animal and plant proteins are key sources of bioactive peptides, but their physiological effects are often limited by gastrointestinal degradation, low intestinal absorption, and interactions with food matrices. Advances in enzymatic processing, fermentation control, and formulation strategies have improved peptide stability and their integration into food products. This review offers a consolidated framework on the current role of food-derived bioactive peptides in functional food and nutrition research.</p> <p>Keywords: Bioactive peptides; Food-derived peptides; Functional foods; Nutraceuticals.</p> |

Introduction

The role of dietary proteins in human health has evolved beyond their traditional nutritional function toward their recognition as sources of biologically active peptide sequences. Recent advances in proteomics, peptidomics, and food biochemistry have demonstrated that food proteins contain encrypted peptides that can be released through controlled proteolysis and subsequently exert measurable physiological effects. This shift in understanding has positioned food-derived bioactive peptides as key molecular mediators linking protein structure, biochemical functionality, and health-oriented food design (Barrero *et al.*, 2023).

Bioactive peptides are typically short amino acid sequences, most commonly ranging from 2 to 20 residues, and remain inactive within intact proteins. Their release occurs during enzymatic hydrolysis, microbial fermentation, or gastrointestinal digestion, generating peptide fractions with defined molecular weights and sequence characteristics. Experimental studies using simulated digestion models and advanced mass spectrometry have shown that peptides below 3 kDa are preferentially generated and are more likely to retain biological activity and

exhibit intestinal transport potential (Liu *et al.*, 2023; Zanutto-Elgui *et al.*, 2019). The biological functionality of these peptides is governed by structure–activity relationships, where amino acid composition, hydrophobicity, net charge, and sequence motifs determine interactions with enzymes, receptors, and cellular membranes (Biparva *et al.*, 2023; Moreno-Montoro *et al.*, 2017).

A broad range of natural protein sources have been identified as reservoirs of bioactive peptides. Proteins derived from milk, eggs, meat, and marine organisms, as well as plant-based proteins from cereals, legumes, oilseeds, and emerging sources such as microalgae, have been shown to generate peptides with defined bioactivities following controlled proteolysis. Recent experimental evidence indicates that enzymatic hydrolysis of these proteins consistently yields peptide fractions enriched in low molecular weight peptides exhibiting enzyme inhibitory, antioxidant, and antimicrobial properties (Baars *et al.*, 2023; de Lima *et al.*, 2018; Sebastián-Nicolas *et al.*, 2021). The increasing focus on plant proteins and food processing by-products reflects sustainability-driven strategies aimed at valorizing underutilized biomass while supporting the development of health-oriented food systems (Romero-Garay *et al.*, 2022).

Functionally, food-derived bioactive peptides have been shown to exhibit a wide spectrum of biological activities relevant to chronic disease prevention and metabolic regulation. These include antihypertensive effects mediated through angiotensin-I-converting enzyme inhibition, antioxidant activity via radical scavenging and modulation of endogenous defense systems, antimicrobial activity through membrane interaction, and metabolic effects such as dipeptidyl peptidase-IV and α -glucosidase inhibition (Bougatef *et al.*, 2024). Such multifunctionality has been demonstrated using enzyme kinetics, molecular docking, cell culture assays, and animal models.

Despite the expanding body of experimental evidence, the translation of bioactive peptides into effective functional ingredients remains influenced by factors related to stability and bioavailability. Peptide susceptibility to gastrointestinal degradation, limited epithelial transport, and interactions with complex food matrices can substantially affect biological efficacy. Recent studies employing standardized digestion protocols and intestinal cell models have highlighted that only a subset of peptides remains intact or bioactive after digestion, emphasizing the importance of peptide characteristics and delivery strategies (Kim & Yoon, 2021; Martini *et al.*, 2019).

This review examines bioactive peptides derived from natural food proteins, with emphasis on their sources and production strategies, biochemical mechanisms underlying biological activities, bioavailability and stability considerations, and applications in health and food systems. The discussion integrates molecular-level findings with technological and nutritional contexts relevant to functional food and nutraceutical development.

A narrative literature review approach was employed to collect and synthesize relevant scientific evidence on bioactive peptides derived from natural food sources, with a particular focus on their production, biochemical mechanisms, bioavailability, and applications in health and food systems. Literature searches were conducted using the Scopus database, which was selected due to its broad coverage of peer-reviewed journals in food science, biochemistry, nutrition, and related disciplines. The search was performed using combinations of keywords related to bioactive peptides, protein hydrolysis, fermentation processes, functional foods, and health benefits.

The following search string was applied to titles, abstracts, and keywords to identify relevant publications: ("bioactive peptides" OR "food-derived peptides") AND ("enzymatic hydrolysis" OR "fermentation" OR "protein hydrolysates") AND ("functional foods" OR

“nutraceutical” OR "health benefits"). The search was limited to articles published in peer-reviewed journals and written in English. No strict publication year restriction was applied in order to capture both foundational and recent advances in the field.

Sources and Production of Bioactive Peptides from Natural Materials

Bioactive peptides are short amino acid sequences encrypted within the primary structure of food proteins and are released through proteolytic processes, yielding peptides with defined molecular weights and quantifiable biological activities. Peptidomic analyses of protein hydrolysates have consistently shown that controlled enzymatic hydrolysis generates peptides predominantly within the molecular weight range of 0.5–3.0 kDa, a fraction commonly associated with higher bioactivity and improved gastrointestinal stability (Martini *et al.*, 2019). In several protein systems, peptide fractions below 1 kDa have accounted for 40–70% of total peptides after optimized hydrolysis, indicating efficient cleavage and enrichment of potentially bioactive sequences. These peptides have been identified from diverse natural protein sources, including animal-derived materials such as milk, eggs, meat, and marine organisms, as well as plant-based sources such as cereals, legumes, oilseed by-products, and microalgae. Together, these findings establish low-molecular-weight peptide fractions from both animal and plant proteins as primary reservoirs of bioactive sequences with enhanced functional potential.

Animal-derived proteins, particularly dairy proteins, represent some of the most extensively characterized precursors of bioactive peptides. Enzymatic hydrolysis of casein and whey proteins using food-grade proteases such as alcalase, pepsin, and trypsin has been reported to produce peptide fractions exhibiting strong angiotensin-I-converting enzyme (ACE) inhibitory activity. Quantitative enzyme inhibition assays have shown IC_{50} values ranging from 0.03 to 0.8 mg/mL for milk-derived peptide fractions, depending on enzyme specificity and degree of hydrolysis (Banic *et al.*, 2024). In fermented dairy systems, milk proteins hydrolyzed by specific *Lactococcus lactis* strains have yielded peptides that reduced cholesterol micellar solubility by up to 35–45% and inhibited platelet aggregation by approximately 30% *in vitro*, demonstrating multifunctional bioactivity relevant to cardiovascular health (Rendón-Rosales *et al.*, 2019). Beyond dairy, egg white protein hydrolysates generated using simulated gastrointestinal enzymes have been shown to reduce plasma oxidative stress markers by more than 25% and improve endothelial function in obese rat models, providing *in vivo* evidence of physiological relevance (Garcés-Rimón *et al.*, 2019). These results highlight animal proteins, especially dairy, as well-validated sources of multifunctional peptides with demonstrated *in vitro* and *in vivo* physiological relevance.

Marine and aquatic protein sources have also received considerable attention due to their high protein digestibility and susceptibility to enzymatic hydrolysis. Proteomic and peptidomic studies of fish and shellfish protein hydrolysates have identified numerous antioxidant and ACE-inhibitory peptides released during alcalase or pepsin hydrolysis, with reported ACE inhibition levels of 50–80% at concentrations below 1 mg/mL (Henriques *et al.*, 2021). These findings support marine proteins as efficient substrates for generating peptides with potential cardiometabolic benefits. Thus, marine proteins represent highly efficient substrates for generating cardioprotective and antioxidant peptides.

Plant-based proteins have emerged as sustainable and versatile sources of bioactive peptides. Enzymatic hydrolysis of rice bran protein using alcalase and flavorzyme has been shown to yield peptide fractions below 1 kDa that retained more than 60% of their ACE inhibitory activity after simulated gastrointestinal digestion, with post-digestion IC_{50} values ranging from 0.6 to 1.2 mg/mL (Mojumder *et al.*, 2024). Similarly, controlled hydrolysis of legume and cereal proteins has generated peptides capable of inhibiting dipeptidyl peptidase-IV (DPP-IV), with reported IC_{50} values between 0.4 and 1.5 mg/mL, suggesting potential applications in glucose metabolism regulation (Bollati *et al.*, 2022). Microalgal proteins, particularly from *Spirulina* species, have also been identified as rich sources of multifunctional peptides. Enzyme-treated *Spirulina* protein hydrolysates have demonstrated dual ACE and DPP-IV inhibitory activities, with enzyme inhibition rates exceeding 60% at concentrations below 1 mg/mL, as confirmed through enzyme kinetics and structure–activity analyses (Aiello *et al.*, 2019). Collectively, plant and microalgal proteins provide sustainable alternatives for producing peptides with cardiometabolic regulatory potential.

Enzymatic hydrolysis remains the primary and most controllable strategy for producing bioactive peptides from natural materials. Original studies have shown that enzyme specificity, degree of hydrolysis (typically ranging from 10–30%), and processing parameters such as pH (6.5–8.5) and temperature (45–60°C) significantly influence peptide yield, molecular weight distribution, and biological activity (Mahmoud & Mahmoud, 2024). Compared with chemical hydrolysis, enzymatic approaches allow selective peptide release while minimizing undesirable by-products and preserving food-grade compatibility. Microbial fermentation provides an alternative and complementary strategy, particularly in dairy and plant-based fermented foods, where endogenous proteolytic systems of starter cultures generate bioactive peptides during processing without the need for external enzymes (Chiacchio *et al.*, 2025; Solieri *et al.*, 2022). Overall, controlled enzymatic hydrolysis and fermentation form the core technological platforms enabling targeted production of functional bioactive peptides from natural proteins.

Biochemical Mechanisms and Biological Activities of Bioactive Peptides

Bioactive peptides exert their biological effects through well-defined biochemical mechanisms that are governed by amino acid composition, sequence length, hydrophobicity, net charge, and three-dimensional conformation. Quantitative experimental studies using enzyme kinetics, molecular docking, cell-based assays, and animal models have demonstrated that these structural parameters directly influence peptide affinity toward molecular targets and, consequently, their biological potency. For instance, peptides with molecular weights below 1 kDa and moderate hydrophobicity generally exhibit stronger enzyme inhibition and cellular activity than larger peptides, highlighting the importance of structure–activity relationships in determining physiological relevance (Mohammadi *et al.*, 2021; Wen *et al.*, 2022).

Antihypertensive activity is one of the most extensively quantified biological functions of food-derived bioactive peptides and is primarily mediated through inhibition of angiotensin-I-converting enzyme (ACE). Enzyme inhibition assays have consistently reported IC_{50} values ranging from 0.05 to 1.5 mg/mL for peptides derived from milk, fish, and plant protein hydrolysates (Jena *et al.*, 2025). Peptides enriched in hydrophobic amino acids, particularly

proline, phenylalanine, leucine, and valine at the C-terminal position, display enhanced binding affinity to the ACE active site. Molecular docking studies have revealed binding energies between -6.0 and -9.5 kcal/mol, supported by hydrogen bonding and hydrophobic interactions with key catalytic residues such as His353 and Glu384 (Ishak *et al.*, 2021). Kinetic analyses further indicate that these peptides may act as competitive or mixed-type inhibitors, depending on sequence length and spatial compatibility with the ACE catalytic pocket.

In addition to antihypertensive effects, bioactive peptides exhibit antioxidant activity through both direct and indirect biochemical mechanisms. Radical scavenging assays, including DPPH, ABTS, and ORAC tests, have shown that peptide fractions below 1 kDa can achieve radical inhibition levels of 40–80% at concentrations between 0.5 and 2.0 mg/mL (Garg *et al.*, 2024). Metal chelation assays have further demonstrated iron-binding capacities exceeding 50% for histidine- and cysteine-rich peptides, contributing to reduced pro-oxidant activity. At the cellular level, treatment with bioactive peptide fractions has resulted in significant reductions in intracellular reactive oxygen species, ranging from 30 to 60%, alongside increases in superoxide dismutase and catalase activities in oxidative stress-induced cell models (Kocazorbaz, 2024). These results indicate that antioxidant peptides function through combined chemical scavenging and biological modulation of endogenous defense systems.

Antimicrobial activity represents another quantitatively characterized function of food-derived bioactive peptides. Minimum inhibitory concentration (MIC) values reported for peptides derived from dairy, fish, and plant proteins typically range from 0.1 to 5.0 mg/mL against Gram-positive bacteria and from 0.5 to 10.0 mg/mL against Gram-negative strains (Akbarmehr *et al.*, 2023). Mechanistic studies using membrane permeability assays and electron microscopy have shown that cationic and amphipathic peptides induce membrane disruption, pore formation, and cytoplasmic leakage, leading to rapid bacterial cell death. Unlike conventional antibiotics, which target specific metabolic pathways, these peptides primarily exert physical membrane damage, a mechanism associated with reduced potential for resistance development (Akbarmehr *et al.*, 2023).

Beyond these well-established activities, growing quantitative evidence supports the role of bioactive peptides in metabolic and immune regulation. Antidiabetic peptides derived from food proteins have demonstrated inhibitory activity against dipeptidyl peptidase-IV (DPP-IV) and α -glucosidase, with reported IC_{50} values ranging from 0.2 to 1.8 mg/mL in enzyme inhibition assays (Fernández-Fernández *et al.*, 2022). Cell-based studies further indicate that these peptides can enhance insulin secretion and reduce glucose uptake rates under hyperglycemic conditions. Immunomodulatory effects have also been quantified, with peptide treatments shown to modulate cytokine secretion profiles by reducing pro-inflammatory mediators such as TNF- α and IL-6 by 20–50% in macrophage models (Villanueva-Lazo *et al.*, 2022). Additionally, hypocholesterolemic peptides have been reported to reduce cholesterol micelle solubility by up to 40% in *in vitro* digestion models, suggesting interference with intestinal cholesterol absorption (Zanoni *et al.*, 2017).

Bioavailability and Stability of Bioactive Peptides

The bioavailability and stability of bioactive peptides critically determine whether their biological activities observed *in vitro* can be translated into physiological effects *in vivo*. Quantitative studies have demonstrated that gastrointestinal digestion, intestinal transport, and food matrix interactions significantly influence peptide integrity and functional potency. As a result, bioavailability assessments increasingly rely on simulated digestion models, intestinal permeability assays, and bioactivity retention measurements rather than qualitative observations alone.

Simulated gastrointestinal digestion studies have revealed substantial variability in peptide stability depending on sequence length and amino acid composition. For instance, rice bran-derived peptides with molecular weights below 1 kDa retained more than 60% of their initial angiotensin-I-converting enzyme inhibitory activity after digestion, whereas larger peptides (>3 kDa) retained less than 30% activity (Mojumder *et al.*, 2024). Similarly, Aiello *et al.* (2019), reported that spirulina protein hydrolysates exhibited a decrease in ACE inhibitory activity from an initial IC₅₀ value of 0.38 mg/mL to 0.62 mg/mL after simulated digestion, indicating partial degradation but preservation of bioactivity. These findings suggest that digestion does not necessarily eliminate functionality but may alter peptide profiles and activity potency.

Intestinal absorption further limits peptide bioavailability, as most food-derived peptides exhibit low transepithelial transport efficiency. Quantitative transport studies using Caco-2 cell monolayers have reported apparent permeability coefficients ranging from 0.2×10^{-6} to 2.5×10^{-6} cm/s for short bioactive peptides, values substantially lower than those of free amino acids but sufficient to allow partial systemic absorption (Liu *et al.*, 2023). Peptides with molecular weights below 500 Da demonstrated up to threefold higher transport rates compared to longer sequences, supporting the preferential absorption of di- and tripeptides via PepT1-mediated mechanisms (Kim & Yoon, 2021). In contrast, peptides with high net charge or bulky side chains showed negligible permeability, indicating that their biological effects are likely localized within the gastrointestinal tract.

Food matrix composition also plays a quantifiable role in peptide bioaccessibility. Hernandez-Sanchez *et al.* (2021), demonstrated that incorporation of milk-derived peptides into fermented dairy matrices resulted in a 25–40% reduction in peptide release during digestion compared to isolated peptide preparations, attributed to protein–protein interactions and matrix entrapment. Conversely, fermentation processes have been shown to enhance peptide bioavailability by producing shorter, digestion-resistant sequences. In fermented spirulina products, peptide fractions below 1 kDa increased by approximately 45% relative to non-fermented controls, correlating with improved post-digestion ACE inhibitory activity (Aiello *et al.*, 2019).

To address bioavailability limitations, encapsulation and delivery strategies have been quantitatively evaluated. Encapsulation of bioactive peptides in lipid-based carriers has been reported to improve peptide recovery after simulated digestion by 1.5- to 2.3-fold compared to non-encapsulated forms (Sarabandi *et al.*, 2024). Additionally, nanoencapsulation approaches increased transepithelial transport efficiency by approximately 30–50% in Caco-2 models,

indicating enhanced absorption potential. These improvements highlight the importance of formulation strategies in bridging the gap between *in vitro* bioactivity and *in vivo* efficacy.

Applications of Bioactive Peptides in Health and Food Systems

Bioactive peptides have attracted major interest in health promotion and food systems due to their biological efficacy, compatibility with food matrices, and favorable safety profiles. Experimental and clinical evidence shows that peptides derived from food proteins can be incorporated into functional foods, nutraceuticals, and dietary supplements at effective intakes ranging from tens of milligrams to several grams per day, depending on peptide type and target activity. Delivery through commonly consumed foods provides a practical strategy for long-term dietary intervention, distinguishing bioactive peptides from conventional pharmacological agents.

In human health applications, bioactive peptides have been most extensively investigated for the management of cardiovascular risk factors, particularly hypertension. Dairy-derived angiotensin-I-converting enzyme (ACE) inhibitory peptides, such as those present in fermented milk products, have been evaluated in both animal models and human trials. Clinical studies have reported reductions in systolic blood pressure of approximately 4–10 mmHg following daily consumption of peptide-enriched dairy products providing 3–10 mg of active peptides over intervention periods of 4–12 weeks (Zheng *et al.*, 2020). These reductions are comparable to those achieved through other dietary interventions and are considered physiologically meaningful at the population level. Importantly, these effects were observed without adverse outcomes, supporting the suitability of food-derived peptides for long-term consumption.

Antioxidant peptides have also been evaluated for their potential to mitigate oxidative stress associated with aging and chronic disease progression. *In vivo* studies have demonstrated that dietary supplementation with peptide-rich protein hydrolysates can reduce biomarkers of lipid peroxidation by 20–40% and enhance endogenous antioxidant enzyme activities, including superoxide dismutase and catalase, in animal models (Kocazorbaz, 2024). These findings support the application of antioxidant peptides in functional foods aimed at supporting cellular redox balance and reducing oxidative damage, particularly in populations exposed to elevated oxidative stress.

Bioactive peptides targeting metabolic health represent another rapidly developing application area. Peptides exhibiting dipeptidyl peptidase-IV (DPP-IV) and α -glucosidase inhibitory activities have been proposed as functional ingredients to modulate postprandial glucose metabolism. Enzyme inhibition studies report IC_{50} values typically ranging from 0.2 to 1.5 mg/mL, while animal studies have demonstrated improvements in glucose tolerance and insulin sensitivity following oral administration of peptide-enriched hydrolysates (Ponce-España *et al.*, 2024). Although clinical evidence remains limited, these data provide a mechanistic basis for incorporating antidiabetic peptides into foods designed for metabolic health management.

Immunomodulatory peptides have also been explored for applications in immune support and inflammation control. Experimental studies indicate that peptide supplementation can reduce pro-inflammatory cytokine levels, such as tumor necrosis factor- α and interleukin-6, by

20–50% in cell and animal models, while enhancing innate immune responses (Villanueva-Lazo *et al.*, 2022). Such effects are particularly relevant for elderly populations and individuals with compromised immune function, positioning bioactive peptides as promising components of preventive nutrition strategies.

From a food systems perspective, bioactive peptides contribute not only health benefits but also technological functionality. Certain peptide fractions exhibit emulsifying activity indices comparable to conventional protein ingredients, with reported improvements in emulsion stability of 15–30% depending on peptide concentration and molecular weight distribution (Mojumder *et al.*, 2024). Peptides derived from protein hydrolysates have also demonstrated foaming capacities and water-holding properties that enhance texture and mouthfeel in formulated foods. In addition, antimicrobial peptides have been shown to inhibit spoilage and pathogenic microorganisms at concentrations between 0.5 and 5.0 mg/mL, leading to shelf-life extensions of 2–5 days in model food systems (Barrero *et al.*, 2023). These properties support the use of bioactive peptides as natural alternatives to synthetic preservatives.

The application of bioactive peptides further aligns with sustainability and circular economy objectives within modern food systems. Protein-rich by-products such as whey, fish skin, fish frames, and plant processing residues have been successfully valorized into peptide-rich hydrolysates, achieving protein recovery yields exceeding 70% in optimized processes (Henriques *et al.*, 2021). Advances in enzymatic hydrolysis optimization and encapsulation technologies have enabled the incorporation of bioactive peptides into diverse food matrices while preserving stability and bioactivity during processing and storage (Hernandez-Sanchez *et al.*, 2021).

Conclusion

Bioactive peptides derived from natural food proteins represent a structurally and functionally diverse group of compounds whose physiological relevance is defined by their origin, sequence characteristics, and mode of release. Evidence discussed in this review indicates that proteins from both animal and plant sources serve as effective precursors, with enzymatic hydrolysis, microbial fermentation, and gastrointestinal digestion governing the generation of peptides with measurable biological activity. The reported functions, particularly enzyme inhibition, antioxidant regulation, antimicrobial action, and modulation of metabolic and immune pathways, are closely associated with peptide length, amino acid composition, and structural conformation.

The extent to which these molecular properties translate into biological effects is constrained by peptide stability and bioavailability. Experimental data consistently show that gastrointestinal digestion and intestinal transport impose selective pressures that limit systemic exposure, while interactions with food matrices and processing conditions further influence peptide integrity. These factors explain the frequent divergence between *in vitro* potency and *in vivo* efficacy and underscore the need to interpret bioactivity data within physiologically relevant contexts.

Within food and nutrition systems, bioactive peptides occupy a dual role as biologically active compounds and functional ingredients. Their production from conventional protein sources, as well as from underutilized raw materials and processing by-products, supports both functional food development and resource-efficient processing strategies. Effective application therefore depends on aligning biochemical activity with technological feasibility, digestive behavior, and regulatory considerations. Framing bioactive peptides within this integrated context is essential for their rational use as functional components in contemporary food and health-related products.

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Conflict of Interest

No conflict of interest.

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