

REVIEW ARTICLE

Pharmacological and toxicological perspectives of bioactive peptides

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Abstract

Bioactive peptides, from dietary and environmental sources, represent a promising front line for developing pharmaceuticals, functional foods, and a new generation of antibiotics. However, their therapeutic application necessitates a comprehensive understanding of their mechanisms of action and toxicological profile. Peptides exhibit effective mechanisms in combating bacterial infections and cancer therapy. However, findings reveal significant toxicological concerns, hemolytic activity, immunogenic reactions, and instability in the cellular environment that can lead to unpredictable metabolic byproducts. Furthermore, the dose and source of peptides are critical determinants of their safety and efficacy. Accordingly, the dual nature of bioactive peptides necessitates a balanced approach to enhance their efficacy while minimizing their potential harm. For these purposes, peptide-specific toxicological screening is essential for translating these natural compounds into safe and effective therapeutic agents. The purpose of this article is to comprehensively review the potential applications of bioactive peptides, their pharmacological mechanisms, and toxicological profiles to elucidate their efficacy and safety for use in food and medicine.

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1. Introduction

Health and a quality of life are the most valuable assets of a society and a productive community. Due to the increasing number of microbial resistances and ineffectiveness of older-generation drugs and antibiotics¹, natural peptides have become an essential source of both nutrition and therapeutic benefits, effectively linking food science with modern medicine.² These biologically active molecules play crucial roles in various physiological processes and offer distinct advantages over synthetic alternatives, due to their high specificity, low toxicity, and a wide range of functional properties.² Sourced from plants, animals, and various microorganisms, natural peptides have

demonstrated an impressive array of biological activities, including antimicrobial, antioxidant, antihypertensive, immunomodulatory, and anticancer effects.³ Their dual function as both food-derived nutraceuticals and clinically approved medications underscores their importance in enhancing health and fighting disease.

One of the most fascinating features of natural peptides is their mode of action, which often involves highly selective interactions with cellular targets such as receptors, enzymes, and signaling molecules. Unlike small-molecule drugs, peptides often have remarkable binding affinity, allowing them to act in the nanomolar range.⁴ This level of precision helps to minimize the chances of adverse reactions. In addition, antimicrobial peptides (AMPs) disrupt bacterial cell membranes with impressive specificity, offering a promising approach to overcome antibiotic resistance.⁵ Likewise, bioactive peptides from food sources, such as lactoferrin and casein-derived fragments, exhibit immunomodulatory and antihypertensive effects by modulating enzymatic pathways or receptor interactions.⁶

On the other hand, natural peptides typically have a favorable safety profile, since they break down into amino acids, which reduces the risk of harmful accumulation. However, challenges regarding their stability, bioavailability, and potential to trigger immune responses remain unresolved.⁷ Furthermore, enzymatic degradation in the gastrointestinal tract may limit the effectiveness of orally administered peptides, necessitating advanced delivery systems, such as encapsulation or nanocarriers.⁸

The early 20th century marked the discovery of groundbreaking bioactive peptides, particularly insulin and adrenocorticotrophic hormone, which were first isolated from natural sources. The discovery and isolation of insulin, a 51-amino-acid peptide, stands out as one of the most transformative breakthroughs in the medical history of peptide science, which was the first peptide drug to be commercialized, saving countless lives.⁹ Therapeutic peptides are a class of pharmaceutical agents composed of carefully arranged sequences of amino acids, typically weighing between 500 and 5,000 Da. The journey into therapeutic peptides began with essential studies of natural human hormones, such as insulin, oxytocin, vasopressin, and gonadotropin-releasing hormone, focusing on their specific roles in the body.¹⁰

Since the groundbreaking synthesis of insulin, the first therapeutic peptide, in 1921, there have been remarkable advances, leading to the approval of over 80 peptide drugs worldwide. As a result, the development of peptide drugs has become one of the most exciting areas in pharmaceutical research. Therapeutic applications of peptides represent a

growing and highly active area of research, as demonstrated by the Food and Drug Administration's approval of 26 peptide drugs between 2016 and 2022, among over 315 new drugs approved in the same period.¹¹ This trend is further supported by a surge in scientific literature and patent filings in recent years, including comprehensive reviews on diverse aspects of the field. Natural peptides can act through diverse mechanisms, often targeting essential physiological processes, depending on the structure, concentration, and biological target.¹² Understanding these mechanisms aids in developing antidotes or therapeutic applications (e.g., peptide-based drugs). The aim of this article is to review the importance of bioactive peptides and to investigate their actions and therapeutic mechanisms from pharmacological and toxicological perspectives.

2. Methods

This narrative review was conducted to comprehensively evaluate the pharmacological activities and toxicological profiles of bioactive peptides reported in the scientific literature. A structured literature search strategy was implemented to ensure the inclusion of relevant and high-quality publications.

2.1. Search strategy and data sources

A systematic search was conducted across major scientific databases, including PubMed, Scopus, Web of Science, and Google Scholar, to identify peer-reviewed articles related to bioactive peptides. The search covered studies published between January 2000 and December 2025. The following keywords and their combinations were used: “bioactive peptides,” “pharmacological activity,” “therapeutic potential,” “toxicity,” “toxicological evaluation,” “safety assessment,” “antioxidant peptides,” “antimicrobial peptides,” “antihypertensive peptides,” and “drug development.” Boolean operators (AND, OR) were applied to refine the search strategy and enhance relevance. Additionally, the reference lists of selected articles were manually screened to identify further relevant studies not captured during the primary database search.

2.2. Inclusion and exclusion criteria

Studies were included if they met the following criteria: published in peer-reviewed scientific journals, written in English, investigated pharmacological effects, mechanisms of action, safety profiles, or toxicological properties of bioactive peptides, and included experimental (*in vitro* or *in vivo*), preclinical, or clinical data. Exclusion criteria were: conference abstracts, editorials, commentaries, and unpublished theses, articles lacking a clear experimental design or toxicological/pharmacological relevance, studies focusing exclusively on peptide synthesis techniques

without biological evaluation, and duplicated records across databases.

2.3. Study selection and data extraction

All retrieved articles were screened based on titles and abstracts for relevance. Full texts of potentially eligible studies were then assessed in detail. Data extracted from selected studies included peptide source, sequence characteristics, biological activity, pharmacological targets, toxicity findings, dosage ranges, and study model (*in vitro*, *in vivo*, or clinical).

The collected data were qualitatively analyzed and categorized according to pharmacological effects (e.g., antimicrobial, antioxidant, antihypertensive, anticancer) and toxicological outcomes (e.g., cytotoxicity, immunogenicity, organ toxicity).

3. Types of peptides

3.1. Natural peptides

Naturally occurring peptides, sourced from diverse biological organisms, exhibited a wide range of biological activities.^{12,13}

3.1.1. Toxic peptides (venoms and defense mechanisms)

Toxic peptides found in venoms play a crucial role in both predation and defense mechanisms across many species, including snakes, spiders, scorpions, and marine animals. These peptides are highly specialized molecules that target vital physiological systems, such as the nervous, cardiovascular, or muscular systems, of their victims. By disrupting ion channels, receptors, or enzymes, they can rapidly immobilize prey or deter predators. In addition to their ecological importance, toxic peptides have gained significant attention in biomedical research for the development of novel drugs, as their specificity and potency make them promising candidates for treating pain, cancer, and neurological disorders.

- Melittin is a cytolytic peptide that is derived from the venom of honeybees. It shows promising anticancer properties across a wide range of cancers. However, its use in therapy is limited due to issues such as non-specific cytotoxicity, instability, and hemolytic effects.^{14,15}
- α -Bungarotoxin (α -BTX) is a key neurotoxin found in the venom of the many-banded krait (*Bungarus multicinctus*). As a powerful member of the three-finger toxin family, α -BTX works by permanently blocking nicotinic acetylcholine receptors. This action can lead to serious consequences, including neuromuscular paralysis and respiratory failure.¹⁶

- Conotoxins are fascinating neurotoxic peptides found in the venom of marine cone snails, specifically from the genus *Conus*. These compounds exhibit an impressive range of pharmacological effects, primarily by influencing voltage- and ligand-gated ion channels. However, the exact mechanisms of numerous conotoxins remain poorly understood.^{17,18}

3.1.2. Antimicrobial peptides

Antimicrobial peptides are small, naturally occurring molecules that play a key role in the innate immune system of many organisms. They exhibit broad-spectrum activity against bacteria, fungi, and viruses by disrupting microbial membranes or interfering with essential cellular processes. Unlike traditional antibiotics, AMPs often act rapidly and reduce the likelihood of resistance development. Due to these properties, they are considered promising alternatives for combating drug-resistant infections and are widely studied in modern biomedical research. Defensins, magainins, and nisin are the most well-known antimicrobial peptides.

- Defensins are tiny, cysteine-rich AMPs that play a crucial role in our innate immune system. They are among the most evolutionarily preserved defense mechanisms we have, showing impressive activity against a wide range of pathogens, including Gram-positive and Gram-negative bacteria, fungi, enveloped viruses, certain parasites, and even some cancer cells. In terms of structure, defensins have both hydrophobic and hydrophilic regions, allowing them to embed themselves into microbial membranes. Their stability and unique three-dimensional shape are derived from six to eight conserved cysteine residues, forming three or four disulfide bonds within the molecule. The way defensins selectively target harmful microbes is mainly due to their electrostatic properties. Being positively charged, they are attracted to the negatively charged elements on microbial surfaces, such as lipopolysaccharide in Gram-negative bacteria or teichoic acids in Gram-positive bacteria. On the other hand, mammalian cell membranes are mostly unaffected because their outer layers are primarily zwitterionic, filled with cholesterol and phospholipids, such as phosphatidylcholine, providing them a neutral charge that reduces defensin binding and insertion.^{19,20}
- When defensins attach to their target membranes, they weave into the lipid bilayer, ultimately compromising the membrane's integrity through various methods, such as forming pores or creating a carpet-like effect, leading to the death of the microbes. This selective targeting, driven by electrostatic interactions, highlights the therapeutic potential of defensins while

safeguarding host tissues.²¹

- Magainins are a class of AMPs first discovered in the 1980s in the skin of the African clawed frog, *Xenopus laevis*. This discovery opened up a new field of research into natural host defense molecules as potential alternatives to conventional antibiotics.²² They are relatively short peptides, typically 21–27 amino acids. The positively charged magainins are strongly attracted to the negatively charged bacterial membrane. In contrast, zwitterionic mammalian cell membranes result in a much weaker attraction.²³ They can selectively lyse cancer cells, which typically have more negatively charged outer membranes compared to healthy mammalian cells, and may also modulate the host immune response, such as promoting wound healing.²⁴ Their imperfectly amphipathic α -helix, with clustered cationic residues on one face, promotes selective electrostatic interaction with anionic bacterial membranes, driving pore formation and high target selectivity over mammalian cells.²²
- Nisin (bacterial origin) is a bacteriocin, a type of AMP produced by certain strains of the bacterium *Lactococcus lactis*, renowned for its potent activity against a range of Gram-positive pathogens.²⁵ Unlike magainins from frog skin, nisin is a lantibiotic, a class of bacteriocins that contain unusual amino acids. It has been used as a natural food preservative for over 50 years and is approved as a food additive (E234) in over 50 countries. The 34-amino acid nisin specifically targets Lipid II, which is a membrane-bound peptidoglycan precursor that is essential for building the bacterial cell wall. The N-terminal rings of nisin bind to the pyrophosphate moiety of Lipid II with high affinity, leading to inhibition of cell wall synthesis.²⁶ Multiple nisin–Lipid II complexes assemble to form a stable pore. This pore causes a rapid efflux of ions, amino acids, and ATP, depleting the cell's energy and leading to a collapse of the proton motive force and ultimately cell death. Nisin stands as a paradigm for the successful application of a natural AMP. Its unique structure, sophisticated dual mechanism of action, and exceptional safety profile have made it an invaluable tool in food safety for decades. While its use in human medicine is limited, it remains a model compound for developing new lantibiotics and antimicrobial strategies to overcome antibiotic resistance.

3.2. Hormonal and signaling peptides

Hormonal and signaling peptides are chains of amino acids that act as chemical messengers, facilitating communication within and between cells. They are secreted by glands, neurons, immune cells, and various other tissues to regulate a diverse array of functions, from

metabolism and growth to behavior and immune response. Unlike classical steroid hormones, which are derived from cholesterol and lipid-soluble, peptides are water-soluble and typically bind to receptors on the surface of target cells, initiating a cascade of intracellular signals.^{27,28}

3.3. Pancreatic and metabolic peptides

These peptides are central to regulating energy balance, appetite, and blood glucose levels²⁹:

- Insulin: Secreted by pancreatic beta cells; lowers blood glucose by promoting its uptake into cells.
- Glucagon: Secreted by pancreatic alpha cells; raises blood glucose by promoting glycogen breakdown and gluconeogenesis in the liver.
- Somatostatin: Secreted by the pancreas (delta cells); inhibits the secretion of both insulin and glucagon.
- Amylin: Co-secreted with insulin; helps suppress appetite and slow gastric emptying.
- Incretins (glucose-dependent insulintropic polypeptide and glucagon-like peptide-1 [GLP-1]): Secreted by the gut in response to food intake; enhance glucose-dependent insulin secretion. GLP-1 receptor agonists (e.g., semaglutide/Ozempic, liraglutide/Victoza) are highly important drugs for the treatment of diabetes and obesity.

3.4. Gastrointestinal peptides

Gastrointestinal peptides are regulatory molecules produced in the digestive tract that coordinate various aspects of digestion and metabolism. Hormones such as gastrin, secretin, and cholecystokinin help control gastric acid secretion, enzyme release, and intestinal motility. These peptides respond to food intake and nutrient composition, ensuring efficient digestion and absorption. Beyond digestion, they also influence appetite, energy balance, and communication between the gut and brain, highlighting their importance in maintaining overall physiological homeostasis. Gastrin, ghrelin, secretin, and motilin are the most well-known peptides of this category.

- Gastrin and cholecystokinin (CCK) are peptide hormones that play a vital role in the digestive process. Gastrin, primarily produced in the stomach, stimulates gastric acid secretion, thereby facilitating the breakdown of ingested food. In contrast, CCK is released from the duodenum in response to the presence of fats and proteins.³⁰ It promotes gallbladder contraction and bile release, as well as stimulating the secretion of pancreatic enzymes.
- Ghrelin, commonly referred to as the “hunger hormone,” is a peptide predominantly produced in the stomach. Its primary function is to stimulate appetite by signaling to the brain, thereby promoting food

intake.³¹

- Secretin is a peptide hormone produced by S cells in the duodenum and plays a crucial role in the regulation of gastrointestinal pH. When the acidic chyme from the stomach makes its way into the duodenum, secretin is released.³² Its function is to stimulate the pancreas to secrete a large volume of bicarbonate-rich fluid, which helps neutralize gastric acid. Additionally, it puts the brakes on gastric acid secretion and encourages the liver to produce bile.
- Motilin is a peptide hormone produced by endocrine cells in the upper small intestine. Its primary function is to regulate gastrointestinal motility during fasting.³³ It stimulates the migrating motor complex, a cyclical, propagating wave of contractions that clears the stomach and small intestine of undigested food residue and bacteria between meals.

3.5. Hypothalamic-pituitary axis peptides

Hypothalamic-pituitary axis peptides are signaling molecules that regulate communication between the brain and endocrine system. The hypothalamus releases factors, such as corticotropin-releasing hormone and gonadotropin-releasing hormone, which act on the pituitary gland to control hormone secretion. In response, the pituitary produces peptides that influence growth, reproduction, and stress adaptation. This tightly controlled axis maintains hormonal balance and allows the body to respond efficiently to internal and external changes. Some of the most important members of this class are as follows:

- Growth hormone-releasing hormone: Stimulates the pituitary to release growth hormone.
- Gonadotropin-releasing hormone: Stimulates the release of luteinizing hormone and follicle-stimulating hormone.
- Thyrotropin-releasing hormone: Stimulates release of thyroid-stimulating hormone (TSH).
- Somatostatin: *Inhibits* the release of growth hormone, TSH, and several other hormones.
- Dopamine (prolactin-inhibiting hormone): Inhibits prolactin release.³⁴

3.6. Peptides from other tissues

Peptides produced in various body tissues play important roles in regulating metabolism and physiological balance. For example, leptin and adiponectin are secreted by adipose tissue and help control appetite, insulin sensitivity, and energy homeostasis. Other tissues also release signaling peptides that influence inflammation, vascular function, and cellular communication. These molecules act locally or systemically, highlighting the diverse roles of tissue-derived peptides in maintaining health and contributing to disease processes.

- Adipokines, also known as adipocytokines, are a fascinating group of active peptides and proteins released by fat tissue.³⁵ Instead of being merely a passive storage site for energy, adipose tissue is now recognized as a vital endocrine organ, with adipokines playing a key role in its communication with the body.
- Leptin is produced by adipose tissue; it acts on the hypothalamus to suppress appetite and increase energy expenditure.³⁶
- Cardiac peptides are a special group of hormones that are mainly produced and released by the heart, making it an essential part of our endocrine system. The distinct member of this group is atrial natriuretic peptide, while brain natriuretic peptide is mostly produced in the heart's ventricles.³⁷ These peptides are released when the heart experiences stretching or volume overload, acting as the body's natural way to balance the renin-angiotensin-aldosterone system.
- Cytokines and chemokines are signaling peptides of the immune system. Cytokines and chemokines are essential players in our immune system, acting as small proteins and peptides that facilitate communication between cells. Although these terms are often mentioned together, they serve different purposes. Cytokines represent a broad category that encompasses various subclasses, including interleukins, interferons, and tumor necrosis factor.³⁸ They play a crucial role in modulating immune and inflammatory responses by up- or downregulating immune cell activity, influencing cell growth, and even mediating fever and acute-phase reactions. Interleukins (IL) (e.g., IL-1, IL-2, IL-6), Interferons (IFN) (e.g., IFN- α , IFN- γ), and tumor necrosis factor-alpha (TNF- α) are powerful cytokines composed of peptides and proteins that essentially orchestrate the immune response. Each of these families has its own unique role, but they often work together in harmony. Interleukins, true to their name, serve as vital communication signals between white blood cells.³⁹

3.7. Peptide drugs

Therapeutic and pharmaceutical peptides come in various types, each defined by its origin, structure, and function.⁴⁰ One of the main ways to classify them is by distinguishing between natural and synthetic peptides. Natural peptides, or their analogs, are designed to mimic the hormones and signaling molecules that our bodies produce. This group includes well-known treatments like insulin for diabetes and calcitonin for bone health. On the other hand, synthetic peptides are crafted entirely in labs, tailored to interact with specific receptors or enzymes that natural peptides might not effectively target. Another important classification is based on molecular size, ranging from tiny

dipeptides to larger, more complex structures resembling small proteins. Cyclic peptides are a notable category in which the amino acid chain forms a ring, providing greater stability against breakdown compared to their linear counterparts.⁴¹ Additionally, peptides can be categorized by their therapeutic actions. For instance, receptor agonists like GLP-1 analogs, such as liraglutide, activate pathways that help manage diabetes and obesity. In contrast, receptor antagonists block specific interactions, making them useful for treating conditions such as cancer and autoimmune diseases. Enzyme-inhibitory peptides, such as those targeting angiotensin-converting enzyme (ACE) for hypertension, are another essential category. Moreover, AMPs play a crucial role as a first line of defense against a wide range of pathogens. The ongoing advancements in peptide engineering also led to the creation of complex hybrid types, such as peptide-drug conjugates that deliver cytotoxic agents directly to cancer cells, and multivalent peptides designed to engage multiple targets at once, boosting therapeutic effectiveness and precision.⁴²

- Fungus-derived cyclosporine is an essential cyclic peptide immunosuppressant that has revolutionized organ transplantation.⁴³ It functions by specifically inhibiting the activation of T-cells, which are crucial players in our immune system, thereby helping prevent the rejection of transplanted organs such as kidneys and hearts. Its application has also expanded to treat serious autoimmune disorders, including psoriasis.
- Glucagon-like peptide-1 analogs (e.g., liraglutide, semaglutide) are natural hormones that are released after food intake.⁴⁴ It plays a crucial role in stimulating insulin secretion in a glucose-dependent manner, suppressing glucagon release, and slowing gastric emptying. Because of these important functions, GLP-1 has become a key target for the management of type 2 diabetes. To mimic this hormone, scientists developed synthetic GLP-1 receptor agonists, such as liraglutide and semaglutide, designed to resist rapid enzymatic breakdown, thereby providing long-lasting control of blood sugar levels and supporting weight loss.
- Bradykinin is a peptide that serves as a signaling molecule, known as a kinin, in our bodies. It is produced from its precursor, kininogen, especially when tissue damage, inflammation, or certain health issues are present.⁴⁵ It acts as a vasodilator, widening blood vessels and increasing their permeability, thereby lowering blood pressure. It also activates pain receptors and plays a role in the inflammatory response, leading to swelling (edema) and redness.

The main role of naturally derived peptide drugs is to serve as precise molecular switches. They either mimic

or block the body's own signaling peptides to create a therapeutic effect.⁴⁶ These drugs work primarily by engaging with specific cell surface receptors in a targeted way, which sets them apart from small molecules that typically inhibit enzymes (Table 1). For instance, the GLP-1 receptor agonists, liraglutide and semaglutide, help manage type 2 diabetes and obesity by binding to and activating GLP-1 receptors on pancreatic beta cells, which in turn stimulates insulin secretion in response to glucose levels. This multi-faceted approach directly tackles the underlying issues of metabolic diseases.

Another important role of naturally derived peptide drugs is hormone replacement, such as insulin. Its main function is to attach to the insulin receptor on cells, initiating a signaling cascade that allows glucose to move from the bloodstream into cells for energy, effectively lowering blood sugar levels. Similarly, Teriparatide, a fragment of parathyroid hormone, acts as an anabolic agent that builds bone. Its unique mechanism stimulates osteoblast activity to create new bone when taken daily, making it a powerful option for treating osteoporosis.⁴⁷

Several peptides also serve as strong enzyme inhibitors. Bivalirudin, which is derived from hirudin in leech saliva, is a direct thrombin inhibitor. It functions by binding directly to thrombin, the crucial enzyme that converts fibrinogen to fibrin in the blood clotting process, making it a highly effective anticoagulant during heart procedures.⁴⁸ Lastly, peptides can act as ion channel blockers for innovative pain management. Ziconotide, a synthetic version of a toxin from cone snails, selectively blocks N-type voltage-gated calcium channels on nerve terminals in the spinal cord.

3.8. Neuropeptides

Neuropeptides are small protein-like molecules used by neurons to communicate with each other. Unlike classic neurotransmitters, they are synthesized in the cell body and released from nerve terminals to modulate synaptic transmission.⁴⁹ Their effects are slower, broader, and longer-lasting. They influence a vast array of brain functions, including pain perception, reward, learning, memory, appetite, and social behaviors. Well-known examples include endorphins (pain relief and pleasure), substance P (pain transmission), and oxytocin (social bonding). The first neuropeptide ever identified was vasopressin, a small peptide made up of nine amino acids released by nerve endings in the neural lobe of the pituitary gland.⁵⁰ This peptide originates from the magnocellular neurons in the hypothalamus, which send their axons to the neurohypophysis, where it is released into the bloodstream in a classic neurosecretory manner. Similar to vasopressin,

Table 1. Selected list of peptide drugs

Drug name (example)	Natural origin/mimic	Primary mechanism of action	Medical use
Insulin lispro (Humalog)	Human insulin hormone	Binds to insulin receptors on cells, promoting cellular uptake of glucose and lowering blood sugar levels.	Diabetes mellitus
Liraglutide (Victoza)	Human GLP-1 hormone	Activates GLP-1 receptors: stimulates insulin release, suppresses glucagon, slows gastric emptying, and promotes satiety.	Type 2 diabetes, obesity
Nesiritide (Natrecor)	Human BNP	Binds to guanylate cyclase receptors, causing vasodilation, natriuresis (sodium loss), and diuresis.	Acute heart failure
Somatropin (Genotropin)	Human GH	Binds to GH receptors, stimulating the production of IGF-1 to promote growth and metabolism.	Growth failure
Teriparatide (Forteo)	PTH fragment	Anabolically stimulates osteoblast activity to increase bone formation and bone mass.	Osteoporosis
Leuprolide (Lupron)	GnRH	Initial: Stimulates pituitary release of LH/FSH; Chronic: Desensitizes GnRH receptors, suppressing LH/FSH and sex hormone production	Prostate cancer, endometriosis
Vasopressin (Vasopressin)	Human vasopressin hormone	Binds to V1 receptors on vascular smooth muscle, causing potent vasoconstriction and increasing blood pressure	Vasodilatory shock
Octreotide (Sandostatin)	Somatostatin hormone	Inhibits the secretion of growth hormone, serotonin, gastrin, vasoactive intestinal peptide, and insulin	Acromegaly, neuroendocrine tumors
Bacitracin (Topical)	<i>Bacillus subtilis</i> bacterium	Inhibits bacterial cell wall synthesis by blocking the dephosphorylation of the lipid carrier bactoprenol	Topical antibiotic
Ziconotide (Prialt)	ω -conotoxin MVIIA (cone snail)	Selectively blocks N-type voltage-gated calcium channels in neurons, preventing the transmission of pain signals	Severe chronic pain

Abbreviations: BNP: B-type natriuretic peptide; FSH: Follicle-stimulating hormone; GH: Growth hormone; GLP-1: Glucagon-like peptide-1; GnRH: Gonadotropin-releasing hormone; IGF-1: Insulin-like growth factor 1; LH: Luteinizing hormone; PTH: Parathyroid hormone.

several gastrointestinal peptides, such as CCK, are present in high concentrations in the nervous system.⁵¹

3.9. Plant-derived peptides

Plant-derived peptides are essentially short chains of amino acids, usually ranging from 2 to 50 amino acids, that either occur naturally or are released from plant proteins through enzymatic processes.⁵² Initially, these peptides are “encrypted” or inactive within the parent protein’s structure and are found in sources such as seeds, grains, and leaves.⁵³ They become active through various methods, such as enzymatic hydrolysis, fermentation, food processing, and gastrointestinal digestion.

- Lunasin is a fascinating peptide made up of 43 amino acids, mainly sourced from soybeans. It is well-known for its role as a chemopreventive agent, selectively inducing cell death in cancer cells. It binds to deacetylated histones, which disrupts the process of cell division. Beyond that, lunasin has impressive anti-inflammatory properties, as it suppresses pro-inflammatory cytokine production and acts as an antioxidant. On top of all this, it may support heart health by managing cholesterol levels. One distinct

feature of lunasin is its ability to remain bioactive even after digestion, which boosts its potential as a therapeutic agent. This makes it a key area of interest in research focused on cancer prevention and functional health.⁵⁴

- Cyclotides are a fascinating group of ultra-stable peptides from plants, mainly found in the Violaceae (violet) and Rubiaceae (coffee) families. What sets them apart is their unique head-to-tail cyclized peptide backbone, held together by three disulfide bonds, forming a knotted structure known as a cyclic cystine knot. This special structure results in high resistance to heat, chemicals, and enzymatic breakdown. In nature, they likely serve as a defense mechanism against insects and pests. Their impressive stability, combined with their highly variable surface loops, makes them an exciting option for drug design.⁵⁵ The cyclic cystine knot architecture of cyclotides, featuring a head-to-tail macrocycle reinforced by three interlocking disulfide bonds, confers exceptional resistance to proteolytic, thermal, and chemical degradation, thereby supporting prolonged *in vivo* stability, while sequence variability in the six inter-cysteine loops governs selective binding to insect or microbial targets.⁵⁶

3.10. Food-derived peptides

Food-derived peptides represent a powerful group of bioactive compounds. Their unique ability to influence human physiology through specific mechanisms makes them essential in creating functional foods, nutraceuticals, and even innovative therapeutic agents aimed at preventing and managing chronic diseases. These peptides are essentially short chains of amino acids, usually made up of 2 to 20 amino acids that are woven into the primary structure of dietary proteins (Tables 2 and 3)⁵⁷⁻⁶¹:

- (i) Antioxidant activity: These peptides work by scavenging free radicals, such as reactive oxygen species, and binding to pro-oxidant metal ions, which helps to lower oxidative stress.
- (ii) Antihypertensive activity: These peptides inhibit ACE, thereby relaxing blood vessels and lowering blood pressure.
- (iii) Anti-diabetic activity: These peptides can inhibit enzymes such as dipeptidyl peptidase-IV and α -glucosidase, which play a role in managing blood glucose levels. They also enhance insulin sensitivity. The protein γ -conglutinin from lupin seeds has shown impressive effects in lowering glucose levels.
- (iv) Anti-microbial activity: These peptides can break down the cell membranes of bacteria, fungi, and viruses, serving as a natural defense mechanism for the plant.
- (v) Anti-inflammatory and immunomodulatory: They can influence the immune response by reducing the production of pro-inflammatory cytokines, such as TNF- α and IL-6.
- (vi) Opioid-like activity: Certain peptides can attach to opioid receptors in the brain, providing calming or pain-relieving effects. These are referred to as exorphins.

4. Discussion

The study of natural peptides as dual resources for enhancing nutrition and serving as therapeutic agents is a rapidly expanding, interdisciplinary field at the interface of food science, biochemistry, and pharmacology. These bioactive peptides, originating from a wide variety of biological sources including plants, animals, microorganisms, and marine organisms, are short chains of amino acids that exert defined physiological effects beyond their conventional role as building blocks of proteins. In recent years, advances in analytical technologies, peptide synthesis, and bioinformatics have accelerated the identification and characterization of these compounds, revealing their immense potential as functional food ingredients and as lead compounds for drug development. Nevertheless, their dual application demands a thorough understanding of

their mechanisms of action, pharmacokinetics, and safety profiles to ensure both efficacy and consumer protection.⁶²

Bioactive peptides exhibit remarkable functional diversity, which underpins their wide-ranging applications. In numerous cases, these peptides are encrypted within the primary structure of larger dietary proteins and are released during gastrointestinal digestion, enzymatic hydrolysis, fermentation, or food processing. Once liberated, they can interact with specific molecular targets and modulate key physiological pathways. Among the most extensively studied activities are the antihypertensive effects mediated through ACE inhibition, which plays a central role in blood pressure regulation. In addition, numerous peptides possess antioxidant properties, acting either by directly scavenging reactive oxygen species or by upregulating endogenous antioxidant defense systems. AMPs represent another important class that can disrupt microbial membranes and provide protection against pathogenic bacteria, fungi, and viruses.²⁵

Beyond these functions, certain peptides exhibit immunomodulatory activity by influencing cytokine production, immune cell proliferation, and inflammatory responses. Others are involved in metabolic regulation, including the modulation of glucose uptake, insulin secretion, and lipid metabolism, highlighting their relevance in managing metabolic disorders such as type 2 diabetes and obesity. For example, the lactotripeptides isoleucine-proline-proline and valine-proline-proline, derived from fermented dairy products, are well-documented ACE inhibitors that contribute to the reduction of hypertension in both experimental and clinical settings. Similarly, marine- and plant-derived peptides are increasingly being explored for their multifunctional bioactivities, including anticancer and neuroprotective effects.

In the pharmaceutical domain, peptides have emerged as highly specific and potent therapeutic agents. Their ability to selectively bind to receptors, enzymes, or ion channels allows them to modulate biological processes with a level of precision that often exceeds that of traditional small-molecule drugs. Classic examples include cyclosporine, a cyclic peptide derived from fungal sources that revolutionized organ transplantation through its immunosuppressive properties, and ziconotide, a peptide derived from cone snail venom that acts as a potent analgesic by targeting voltage-gated calcium channels. More recently, peptide-based drugs such as GLP-1 analogs have transformed the treatment landscape for diabetes and obesity, further demonstrating the clinical relevance of this class of molecules.

Despite these promising attributes, the application of peptides in both food and medicine is accompanied

Table 2. Plant-derived peptides

Plant source	Parent protein	Bioactive peptide examples	Clinical applications
Soybean	Glycinin, β -gonglycinin	Lunasin, soymetide	Anti-inflammatory, antioxidant, ACE-inhibitory (antihypertensive)
Rice	Glutelin, albumin	Oryzatesin	Antihypertensive, immunomodulatory
Pea	Legumin, vicilin	Pea albumin 1b	ACE-inhibitory (antihypertensive), antioxidant
Lupin	γ -conglutin	Lupin peptides	Anti-diabetic (glucose-lowering)
Wheat	Gliadin, glutenin	Gluten exorphins	Opioid-like activity
Corn (maize)	Zein	<i>Zea mays</i> antimicrobial peptide 1	Antimicrobial
Oats	Avenin	Avenin-derived peptides	Antioxidant
Flaxseed	–	Linusin	ACE-inhibitory (antihypertensive)
Mung Bean	–	Mung bean peptide	Antioxidant, anti-fatigue
Hemp Seed	Edestin, albumin	Hemp seed peptides	Antioxidant

Abbreviation: ACE: Angiotensin-I-converting enzyme.

Table 3. Well-known food-derived peptides

Type/bioactivity	Source food	Example peptides	Primary mechanism
Antihypertensive (ACE-inhibitory)	Dairy (milk)	Casokinins (e.g., IPP, VPP)	Inhibits ACE, preventing vasoconstriction
	Soybean	Lunasin	ACE inhibition and anti-inflammatory pathways
	Rice	Oryzatesin	ACE inhibition
	Sardine/fish	Sardine peptide	ACE inhibition
	Egg	Ovokinin	ACE inhibition
Mineral-binding	Dairy (milk)	Caseinophosphopeptides (CPPs)	Bind to minerals (calcium, zinc, iron), enhancing their solubility and absorption
Opioid agonist	Dairy (milk)	Casomorphins, lactorphins	Bind to and activate opioid receptors in the brain and gut
	Wheat	Gluten exorphins	Bind to opioid receptors
Antioxidant	Egg	Ovotransferrin peptides	Scavenge free radicals, chelate pro-oxidant metals
	Rice bran	Rice bran peptides	Free radical scavenging
	Mung bean	Mung bean peptide	Free radical scavenging
	Fish skin	Collagen peptides	Free radical scavenging
Anti-diabetic	Lupin	γ -conglutin	Inhibits DPP-IV enzyme, enhancing insulin secretion
	Whey	Whey protein peptides	May improve insulin sensitivity and inhibit DPP-IV
Antimicrobial	Dairy (milk)	Lactoferricin (from lactoferrin)	Disrupts microbial cell membranes
	Corn	ZmAMP1	Membrane structural disruption
Immunomodulatory	Dairy (milk)	Immunopeptides	Stimulate immune activity or suppress pro-inflammatory cytokines
	Soybean	Lunasin	Suppresses pro-inflammatory cytokines (e.g., NF- κ B)

Abbreviations: ACE: Angiotensin-I-converting enzyme; DPP-IV: Dipeptidyl peptidase IV; IPP: Isoleucine–proline–proline; NF- κ B: Nuclear factor κ B; VPP: Valine–proline–proline; ZmAMP1: *Zea mays* antimicrobial peptide 1.

by important safety considerations. One of the primary concerns is immunogenicity. Peptides may be recognized by the immune system as foreign substances, potentially triggering hypersensitivity reactions ranging from mild allergic responses to severe anaphylaxis. This risk is not limited to pharmaceutical peptides but may also arise from peptide-enriched functional foods, particularly when consumed in concentrated or purified forms. Another safety issue relates to the cytotoxic potential of certain peptides. For instance, while AMPs are effective against pathogens, some may also exhibit hemolytic activity, compromising the integrity of host cell membranes, particularly erythrocytes.^{47,63,64}

Peptide stability represents a further challenge with dual implications. On one hand, natural peptides are often highly susceptible to proteolytic degradation in the gastrointestinal tract and bloodstream, which can limit their bioavailability and therapeutic efficacy. On the other hand, strategies designed to enhance stability, such as cyclization, incorporation of non-natural amino acids, or chemical modifications (polyethylene glycol conjugation), may alter pharmacokinetics and introduce new toxicological concerns. These modifications can affect tissue distribution, metabolic pathways, and elimination, potentially leading to the accumulation of metabolites with unknown or harmful biological effects. Therefore, optimizing peptide stability while maintaining safety remains a critical area of research.^{64,65}

Given these complexities, the successful translation of natural peptides from food sources into validated therapeutic agents requires a comprehensive and systematic toxicological assessment framework. Preclinical evaluation typically begins with *in vitro* studies, including cytotoxicity assays, genotoxicity testing, and assessments of cellular uptake and mechanism of action. These are followed by *in vivo* studies in appropriate animal models to investigate toxicokinetics, dose-response relationships, organ-specific toxicity, and long-term safety under repeated exposure conditions. For peptides intended for pharmaceutical use, adherence to internationally recognized regulatory guidelines is essential to ensure consistency, reproducibility, and safety.⁶⁶

Although food-derived peptides may benefit from a history of safe consumption, their isolation, purification, and administration at pharmacological doses represent a significant shift in exposure that necessitates reevaluation. Regulatory frameworks must therefore distinguish between peptides as components of conventional foods and peptides as active pharmaceutical ingredients. This distinction has important implications for safety assessment, labeling, and approval processes. In this context, the development

of standardized testing protocols and harmonized international guidelines is crucial to facilitate the safe and efficient translation of peptide-based innovations.⁶⁷

5. Conclusion

In conclusion, natural peptides represent a vast and versatile reservoir of bioactive molecules with significant potential in both nutrition and therapeutics. Their diverse mechanisms of action enable targeted modulation of physiological processes, offering promising strategies for disease prevention and treatment. However, the successful integration of these compounds into functional foods and pharmaceutical products requires a careful balance between efficacy and safety. Comprehensive mechanistic studies, advanced delivery systems, and rigorous toxicological evaluations are essential components of this process. Embracing a holistic “from plate to pill” approach, supported by interdisciplinary collaboration and robust regulatory oversight, will be key to unlocking the full potential of natural peptides while ensuring public health and safety.

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