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Review

Bioactive Peptides from Natural Sources: Biological Functions, Therapeutic Potential and Applications

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Abstract

Natural bioactive peptides have emerged as pivotal candidates in modern science due to their multifaceted biological activities and versatile applications across biomedicine, biotechnology, and nutraceuticals. These molecules exhibit a broad pharmacological spectrum including antimicrobial, antiplatelet, antioxidant, antihypertensive, and antitumor properties, positioning them as potent therapeutic agents and essential functional food constituents. Compared to synthetic alternatives, their inherent structural diversity, biocompatibility, and biodegradability offer a superior safety profile by minimizing systemic toxicity and adverse effects. This review provides a comprehensive analysis of the primary natural reservoirs of these peptides, which encompass terrestrial flora and fauna as well as marine organisms and microorganisms, while elucidating their complex mechanisms of action and structure–function relationships. Furthermore, we evaluate contemporary methodologies for peptide identification and optimization, such as high-throughput proteomics, computational modeling, and strategic chemical modifications aimed at enhancing metabolic stability and bioavailability. Although bottlenecks in extraction, scalable production, and proteolytic susceptibility persist, recent breakthroughs in recombinant technology and rational design are facilitating their industrial translation. Finally, we discuss future perspectives focused on the synergy between artificial intelligence, nanotechnology, and sustainable circular economy strategies to maximize the therapeutic accessibility and functional efficacy of natural peptides.

Keywords: bioactive peptides; structural bioinformatics; therapeutic peptides; natural products; proteomics; drug delivery; functional foods; antimicrobial peptides

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1. Introduction

Peptides derived from natural sources have emerged as highly relevant molecules in fields such as biomedicine, biotechnology, and nutrition [1]. These short chains of amino acids, typically ranging between 2 and 50 residues, are defined as bioactive peptides when they exert specific physiological effects that extend beyond their basic nutritional

role [2]. Their biological function is intrinsically linked to their amino acid composition and structural conformation, which may include α-helices, β-sheets, turns, or random coils. These structural arrangements determine their stability, bioavailability, and specificity for molecular targets [3,4]. Furthermore, the presence of disulfide bridges or cyclic motifs often increases their structural rigidity and resistance to enzymatic degradation, enhancing their therapeutic potential [5].

Natural peptides are generally classified into endogenous peptides, which are synthesized by the organism to regulate internal physiological functions, and exogenous peptides, obtained from dietary or environmental sources such as plants, animals, or microorganisms [6]. Endogenous peptides play crucial roles in maintaining homeostasis. For example, angiotensin II, an octapeptide derived from angiotensin I through the action of the angiotensin-converting enzyme (ACE), is a key regulator of blood pressure and fluid balance [7]. Other well-known examples include bradykinin, a vasodilator involved in inflammation; oxytocin and vasopressin, which modulate uterine contraction and water retention; and glucagon, insulin, and endothelin, which regulate metabolism and vascular tone [8–10]. These peptides demonstrate how short amino acid sequences can possess powerful and specific biological activities, thus inspiring the search for similar compounds in alternative natural sources.

From an exogenous perspective, plants, marine organisms, fermented foods, and microorganisms are the main reservoirs of bioactive peptides, each contributing unique structural and functional characteristics. These peptides are typically released from precursor proteins through processes such as enzymatic hydrolysis, fermentation, or gastrointestinal digestion [11,12]. Controlled hydrolysis using enzymes like pepsin, trypsin, alcalase, or flavourzyme can produce short peptides with antioxidant, antihypertensive, antithrombotic, or immunomodulatory properties [13,14]. Similarly, microbial fermentation carried out by lactic acid bacteria or fungi generates peptides with significant health-promoting or preservative capacities [15].

Plant-derived peptides are particularly abundant in seeds, legumes, and cereals. For instance, *Phaseolus vulgaris* (common bean) produces peptides that inhibit ACE activity and reduce blood pressure after in vitro gastrointestinal digestion [16]. Other *Phaseolus vulgaris* derived peptides have shown potent antimicrobial effects against bacteria and fungi [17]. Similarly, peptides derived from soy, such as lunasin, have demonstrated antioxidant and antitumor activity, supporting their role in chronic disease prevention [18]. Cereal proteins, including those from wheat and corn, yield peptides with antioxidant, antihypertensive, anti-inflammatory, and antidiabetic properties [19,20]. Finally, medicinal plants serve as a valuable source of cyclic peptides with immunosuppressive or antidiabetic effects, as evidenced in families such as *Amaranthaceae*, *Caryophyllaceae*, and *Rutaceae* [21].

The marine environment represents another prolific source of peptides characterized by unique biochemical properties. Collagen-derived peptides from fish species, such as salmon or cod, have demonstrated significant antioxidant, anti-inflammatory, and skin-regenerative properties [22,23]. Furthermore, peptides isolated from mussels and crabs exhibit anticoagulant and antiplatelet effects, including the inhibition of platelet aggregation, which suggests potential antithrombotic applications [24]. Marine algae and microalgae, such as *Spirulina*, *Chlorella*, and *Gracilariopsis lemaneiformis*, also produce ACE-inhibitory and antioxidant peptides, capable of reducing blood pressure in hypertensive animal models [25,26]. Recent studies utilizing mass spectrometry have identified novel antimicrobial peptides from *Tetraselmis suecica*, reinforcing the value of marine organisms as reservoirs of bioactive molecules [27].

Fermented foods constitute an equally important dietary source of these molecules. During the fermentation process, microorganisms such as *Lactobacillus* and *Lactococcus*

hydrolyze milk, soy, or cereal proteins, thereby generating peptides with antihypertensive, antioxidant, and anti-inflammatory effects [28,29]. Dairy products, including yogurt and aged cheese, contain specific sequences such as Val-Pro-Pro and Ile-Pro-Pro, which are well-known for inhibiting ACE and promoting vasodilation [30]. Similarly, fermented soy products and kimchi yield peptides that enhance intestinal health, modulate glucose metabolism through DPP-IV inhibition, and reduce systemic oxidative stress [31,32].

Beyond their role in food matrices, microorganisms themselves, including various bacteria and fungi, act as direct producers of bioactive peptides. The most prominent examples are bacteriocins, which are antimicrobial peptides synthesized by bacteria and widely utilized as natural preservatives in the food industry [33]. Among these, nisin, produced by *Lactococcus lactis*, exhibits broad-spectrum antibacterial and antioxidant properties and is currently approved as a safe food additive in multiple countries [34,35]. Additionally, fungal peptides from genera such as *Aspergillus* and *Penicillium* have shown antitumor and antimicrobial effects, while sequences from *Saccharomyces* or marine-derived fungi are being actively explored for advanced biotechnological and pharmacological applications [36,37].

Overall, both endogenous and exogenous peptides represent a diverse and functionally rich family of biomolecules with crucial roles in physiology, health maintenance, and disease prevention. Their structural diversity, combined with high biodegradability, low toxicity, and exceptional specificity, positions them as promising candidates for the development of new therapeutic agents, functional foods, and biotechnological innovations. Current research continues to expand this field by focusing on the identification of novel sources, the optimization of production strategies, and the elucidation of the structure–function relationships that govern their biological activity [38–40].

2. Bioactive Activities, Therapeutic and Biotechnological Applications

Natural peptides display a wide array of pharmacological characteristics that emerge directly from their sequence-encoded physicochemistry, including charge, hydrophobicity, aromatic motifs, and disulfide bonds, as well as the conformations they adopt in membranes or protein targets. This structure–function axis underlies activities that are especially relevant for cardiovascular disease (CVD) and cancer, two areas with a high global burden and the largest volume of translational evidence in the peptide field [41–52]. To visualize the complex relationships between the biological origin of peptides and their functional activities, a bipartite network of connections was generated (Figure 1). This figure centralizes known functions through internal nodes and connects them with their corresponding biological sources represented by peripheral nodes. The thickness of the edges is directly proportional to the number of peptides sharing a specific source–function relationship, providing a clear overview of the current landscape of natural peptide research.

In the context of cardiovascular health, peptides can prevent thrombus formation by inhibiting platelet activation and aggregation or by interfering with coagulation enzymes. Mechanistically, antiplatelet sequences block receptor–ligand interactions, such as the GPIIb/IIIa-fibrinogen complex, modulate intracellular signaling pathways like Ca^{2+} mobilization and PI3K/Akt, or attenuate thrombin activity [41–43,53–57]. For example, marine cysteine-rich peptides and motifs from fish collagen hydrolysates, such as Pro-Gly and Hyp-Gly, inhibit platelet function and reduce experimental thrombosis. Furthermore, in silico analyses suggest that oyster-derived peptides may directly hinder thrombin catalysis [53,55,57]. However, a recurring disadvantage in preclinical research is that although several reports in cowpea, *Hypophthalmichthys molitrix*, and *Pyropia columbina* indicate antithrombotic effects, the lack of explicit sequences limits reproducibility and structure–activity relationship inference, representing an important caveat for the field [54–56].

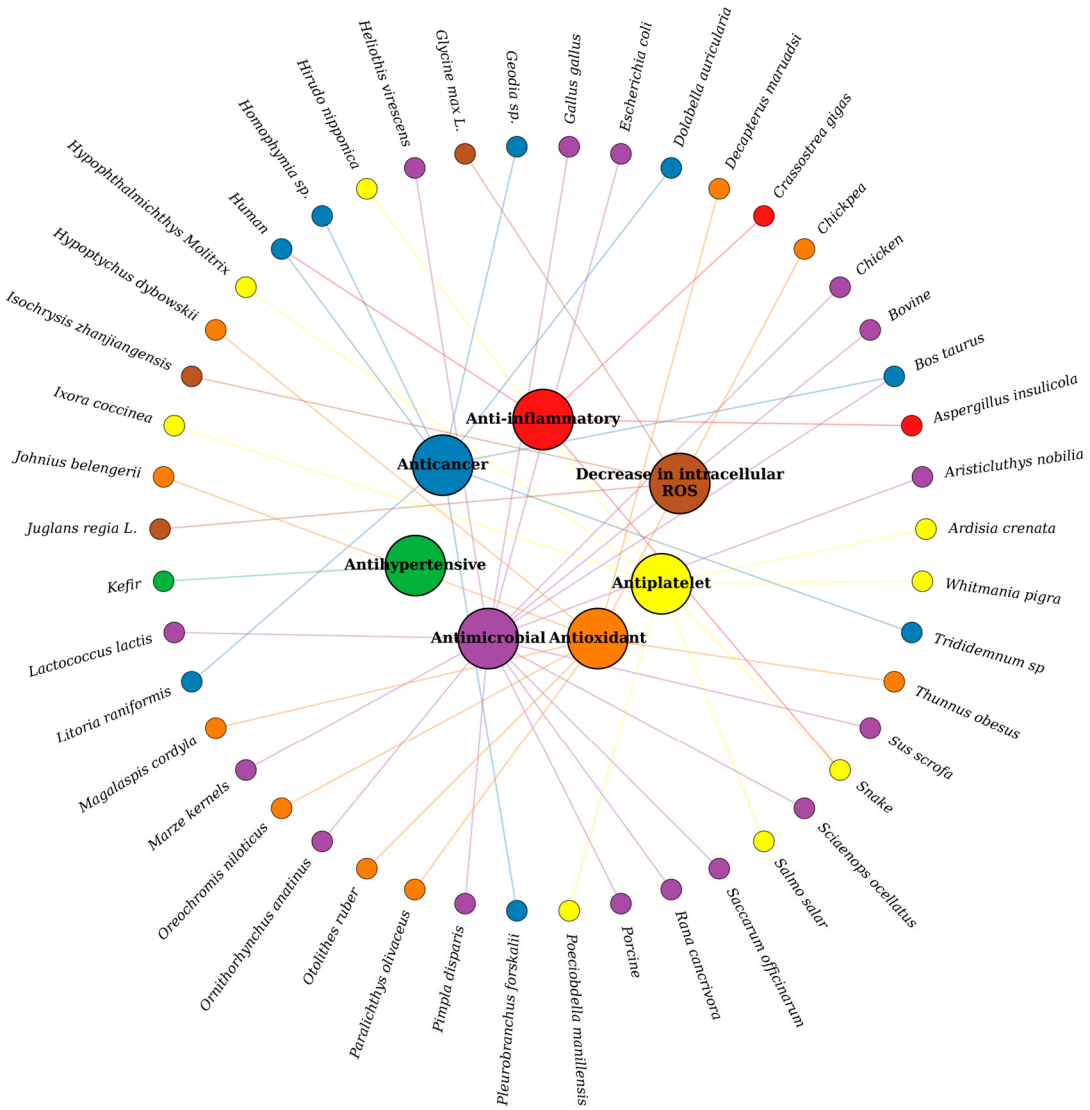


Figure 1. Bipartite network of bioactive peptides: Mapping of sources and functional activities. The central nodes represent the main biological activities. The peripheral nodes indicate the extraction sources. The edges connect the different sources with their biological activity.

Hypertension is another major target, primarily addressed through ACE inhibition to reduce the conversion of angiotensin I to angiotensin II and prevent subsequent vasoconstriction. Food-derived peptides, such as the dairy casein tripeptides Val-Pro-Pro and Ile-Pro-Pro, have been shown to lower blood pressure in both preclinical and human studies [58–74]. A significant advantage of these dietary peptides is their inherent safety profile, stemming from their natural presence in fermented foods, which facilitates their direct incorporation into functional and nutraceutical products. Comparable ACE-inhibitory activity has been reported from orange juice, *Pleurotus* spp., coho salmon, whey, *Vicia faba*, and microalgae, although some sources still lack sequence resolution [62–66]. The clinical translation of these findings is exemplified by GPIIb/IIIa antagonists like eptifibatide and tirofiban, inspired by snake venom peptides, and bivalirudin, a synthetic hirudin analogue that functions as a direct thrombin inhibitor [48–50]. These examples illustrate how natural prototypes can serve as templates for approved drugs and validate peptide mechanisms in CVD management.

Antimicrobial peptides (AMPs) represent a different but equally vital therapeutic category, acting primarily by electrostatically targeting anionic microbial membranes.

By inserting amphipathic α-helices to form pores, these peptides induce cell lysis. This membrane-oriented mechanism gives AMPs a distinct advantage by offering a fast, physical mode of action that significantly reduces the likelihood of microorganisms developing resistance compared to antibiotics that act on intracellular targets. Additional mechanisms include lipopolysaccharide binding and interference with DNA, RNA, or enzymatic processes [75–83]. Magainin, derived from amphibians, serves as a canonical broad-spectrum AMP [79]. While antimicrobial activities have also been reported for extracts from *Didemnum albidum* and *Agrocybe aegerita*, their specific sequences often remain unresolved [84,85]. In applied contexts, nisin, a bacteriocin from *Lactococcus lactis*, is widely used as a natural preservative, and its anti-biofilm effects broaden its potential toward medical uses [86–89]. In addition, several antimicrobial peptides from the microalga *Tetraselmis suecica* were studied using proteomic and bioinformatic approaches, demonstrating enhanced bactericidal activity and highlighting marine microalgae as a promising reservoir of AMPs for biotechnological applications [90]. Altogether, these data support the multifaceted use of peptides across food safety and clinical anti-infective pipelines.

Peptides also play a vital role in modulating oxidative stress and complex metabolic processes. Sequences enriched with residues such as Trp, Tyr, Cys, or His possess the ability to donate electrons and quench reactive oxygen species (ROS), thereby protecting lipids, proteins, and DNA from oxidative damage [91–94]. Hydrolysates derived from fish collagen and soy have demonstrated robust antioxidant effects with potential relevance to aging and degenerative disorders [95,96]. Furthermore, fermented foods yield peptides capable of inhibiting dipeptidyl peptidase IV (DPP-IV), a mechanism that aids in glycemic control; such activity has been identified in products like fermented cheeses and soy [31,32,70]. Beyond direct redox signaling, specific whey-derived di- and tripeptides, including Pro-Glu-Trp and Leu-Leu-Trp, have been reported to ameliorate hyperuricemia and renal injury. These effects are often accompanied by a remodeling of the gut microbiota, highlighting an intricate and promising crosstalk between peptides, the microbiome, and systemic metabolism [97].

In the field of oncology, natural peptides offer a strategic advantage through their ability to preferentially bind to anionic tumor membranes, which are often characterized by exposed phosphatidylserine and sialylated lipids. Upon binding, these peptides can trigger apoptosis, disrupt cell growth, or inhibit angiogenic pathways. This selectivity for malignant membranes over healthy cells represents a significant advantage over traditional cytotoxic treatments, offering the potential for reduced systemic toxicity [14,44,98,99]. Lactoferricin, a milk-derived sequence, serves as a prominent example of such membrane-active oncopeptides [98]. Additionally, marine- and plant-derived peptides contribute both cytotoxic and adjuvant activities [100,101], while the marine compound plitidepsin, originally isolated from *Aplidium albicans*, has successfully advanced to clinical evaluation for hematologic and solid tumors [102]. These developments, supported by mechanistic insights such as caspase activation, mitochondrial depolarization, and VEGF inhibition, justify the continued focus on cancer research within the peptide therapeutic pipeline.

In dermatology and cosmeceuticals, natural peptides are increasingly applied in topical and nutraceutical formulations to counter photoaging, oxidative damage, and to stimulate extracellular matrix remodeling. Natural and AI-predicted sequences, such as pep_RTE62G, show anti-wrinkle activity in preclinical and clinical testing [103]. For instance, *Phaeodactylum*-derived peptides activate fibroblasts to improve wrinkle metrics, whereas nanoliposome delivery systems enhance skin penetration and collagen synthesis. Some sequences even reduce neurotransmitter release at neuromuscular junctions, producing a cosmetic "botox-like" effect [104,105]. Moreover, peptides originating from *Lactobacillus plantarum* fermentation exhibit in vivo antioxidant protection against UV-induced

damage [106]. Clinical studies have shown that marine collagen peptides combined with plant antioxidants improve skin elasticity and dermal ultrasound markers, while elastin hydrolysates from *Katsuwonus pelamis* protect against UVA-induced photoaging [107,108]. Complementing these cosmetic uses, regenerative peptides such as thymosin β-4 promote re-epithelialization and reduce inflammation, underscoring their value in wound-healing models [109,110].

Across these diverse biological contexts, structural parameters fundamentally dictate functional outcomes. Sequence length modulates both diffusion rates and target specificity, while cyclization and the presence of disulfide bonds significantly increase resistance to proteolysis [111–114]. Amphipathic α-helices are recurrent among AMPs, while β-sheets and loop motifs often stabilize receptor-binding epitopes [81–83]. Furthermore, an emerging and highly potent mechanism for natural peptides involves their function as covalent inhibitors of enzymes [115]. Unlike reversible binding, certain peptides can establish stable covalent bonds with target residues in enzymes critical for pathogen survival and cancer progression [116]. This irreversible inhibition provides a prolonged therapeutic effect, allowing for lower dosing and higher efficacy by targeting metabolic pathways essential for disease maintenance.

The biological activity of these molecules is thus intimately linked to the interplay between their primary sequence and their secondary and tertiary structures [111,112]. Hydrophobic residues like leucine and isoleucine facilitate membrane interaction, while charged amino acids such as lysine and arginine enhance electrostatic binding to target sites [117,118]. Cyclization, as observed in cysteine-rich peptides, improves structural stability against proteases and prolongs bioactivity [113]. Targeted amino acid substitutions, for instance, replacing tyrosine with tryptophan, can enhance antioxidant capacity [119], while PEGylation or conjugation to carrier molecules improves solubility and bioavailability [120]. Peptide length also matters: shorter chains generally diffuse more efficiently, whereas longer ones display higher selectivity for complex molecular targets [114]. Structural motifs such as α-helices and β-sheets determine interaction patterns with membranes and receptors [81,82]; amphipathic α-helices, in particular, are common in AMPs and facilitate insertion into bacterial membranes [83].

Polylysines, particularly those derived from marine sources, represent a unique class of cationic bioactive peptides with significant therapeutic interest [18]. These molecules are characterized by their high density of positive charges provided by the ε-amino groups of lysine residues [121]. Beyond their established role as antimicrobial agents, marine polylysines have demonstrated a remarkable ability to interact with non-canonical DNA structures [122]. Specifically, research has shown that these peptides can selectively bind to G-quadruplex DNA, which are secondary structures found in key genomic regions such as telomeres and oncogene promoters [123]. By stabilizing these G-quadruplexes, marine polylysines can interfere with telomerase activity and gene expression, offering a promising strategy for the development of novel anticancer therapies based on DNA-binding mechanisms [124].

Overall, natural peptides exhibit a sophisticated range of mechanisms of action that depend on their precise chemical architecture and specific molecular interactions. Table 1 provides a comprehensive summary of scientific publications detailing various biopeptides and their respective mechanisms. Understanding these structure–function relationships is essential not only for optimizing natural peptide activity but also for informing the rational design of more effective and stable analogues for biomedical, biotechnological, and nutritional applications.

Table 1. Published works on bioactive peptides extracted from different natural resources.

Activity	Sequence	Mechanism	Study Model	Source	Reference
Antioxidant	YFMVLVVMLFHR	Free radical scavenging	*In vitro*	*Hermetiaillucens*	[125]
Antioxidant	APPPLQHQ	Free radical scavenging	*In vitro*	*Izmir Tulum cheeses*	[126]
Antioxidant	LEQQVDDLEGSLEQEKK	Free radical scavenging	*In vitro*, *in silico*	*Hams*	[127]
Antioxidant	GKHQQEEENEGGSI, VNPESQQGSPR, IGINAENNQRN, FVDAQPQQKEEG.	Free radical scavenging	*In vitro*	*Soymilk*	[128]
Antioxidant	AKCAKFQRNMKKVRG-NH2	Free radical scavenging	*In vitro*	*Milk proteins*	[129]
Antioxidant	IVVE	-	*In vitro*	*Chlorella (Chlorellavulgaris)*	[130]
Antioxidant	YWDAW	ROS Scavenging	*In vitro*, *in vivo* (Rat)	*Fish*	[131]
Antioxidant	MVVACVLPEA	Free radical scavenging	*In vitro*	*saltedjellyfish (Rhopilema hispidum)*	[132]
Antioxidant	EMPFPK, PYPQ, PQSV, YFYPE	Free radical scavenging	*In silico*	*Milk*	[133]
Antioxidant	VDPP, SSGE, DGEA, NQDK, WTP	Free radical scavenging	*In vitro*	*Salmo salar*	[134]
Antioxidant	LLGDV, NLDSS	Free radical scavenging	*In vitro*	*Rice wine*	[135]
Antioxidant	LPFR, WGFKPK, PFDLR, FPGEL	Free radical scavenging, tyrosinase inhibitory	*In vitro*, *in silico*	*Camelliaoleifera*	[136]
Antioxidant	FWENHDPTQGMR, SPFEKPGAPGKPTTT, AVGISKPSMPSKPF, SPFEKPGAPGKPTITA, STGISVPGPMGPSGPR, PEEERPKPSRPVVPPLIPPK, HPSDFGADAQAAMSK	Free radical scavenging	*In vitro*	*Freshbeef tripe*	[137]
Antihypertensive	IAE	ACE-inhibitory	*In vitro*	*Spirulina (Arthrospira platensis)*	[130]
Antihypertensive	YPDLPYH	ACE Inhibitory	*In vitro*	*YellowSilkCocoons*	[138]
Antihypertensive	VPP, IPP	ACE inhibitory	*In silico*	*Fermented sour milk*	[133]

Table 1. *Cont.*

Activity	Sequence	Mechanism	Study Model	Source	Reference
Antihypertensive	DPMP, FHPR, FSPR, HPKF	ACE inhibitory	*In silico*	*Nannochloropsis gaditana*	[139]
Antihypertensive	IRDLDYY, AGGTGPMDEYLI, IAGGTGPMDEYL, LGTPGSSVAVG, LIAGGTGPMDEY	ACE inhibitory	*In vitro*, *in silico*	*Arthrospira platensis*	[140]
Antihypertensive	VPPIPP	ACE inhibitory	*In vitro*	*Milk*	[141]
Antihypertensive	EDNSELGQETPTLR	ACE inhibitory	*In vitro*, *in silico*	*Halobatrachus didactylus*	[142]
Antihypertensive	LSMTDTR, NIPVGILR, QAQNVQHY, QEALELIR	ACE inhibitory	*In silico*	*Milk*	[143]
Antihypertensive	GAGAEGGAVGGATGGVGA	ACE inhibitory	*In vitro*, *in silico*	*Vicia faba* L.	[144]
Antihypertensive	PIIAKMY, GGYAMLQS	ACE inhibitory	*In vitro*	*Millet bran*	[145]
Antihypertensive	VFPLK	ACE inhibitory	*In vitro*, *in silico*	*Thunnusmaccoyii*	[146]
Antihypertensive	LCYPR	ACE inhibitory	*In vitro*	*Coregonus*	[147]
Antihypertensive	DAPLPHPNR, GSEDPLPGAK	ACE inhibitory	*In vitro*	*Lentinulaedodes*	[148]
Antihypertensive	LTNVVGGK	ACE inhibitory	*In vitro*	*Silkworm (Bombyx mori)*	[149]
Antihypertensive	RLSFNP	ACE inhibitory	*In vivo* (Rat)	*Wheyprotein*	[150]
Antihypertensive	FAPGG	ACE inhibitory	*In vivo* (Mice)	*Glycinemax*	[151]
Antihypertensive	FPRPFL	ACE inhibitory	*In vitro*, *in silico*	*Highland barley*	[152]
Antihypertensive	FDWLR	ACE inhibitory	*In vivo* (Rat)	*Walnut*	[153]
Antihypertensive	SYRF, GPKLF, SPRPW, FRGF, FERF, FRFQ, WERF, FDRF	ACE inhibitory	*In vitro*, *in silico*	*Cicadachrysalis*	[154]
Antithrombotic	OGEFG, DEGP, PGYV, PGGO, OTGPK, SPGO, QGO	Inhibition of platelet aggregation	*In vitro*, *In vivo*	*Salmo salar*	[155]
Antithrombotic	ALPIDVLANAYR, EFLLAGNNKR, GEEFGAFTPK, QLAQIPR, LQAFEPLR, ALPVDVLANAYR, GEEFDAFTPK, QKEFLLAGNNK, TNPNSMVSHIAGK	Inhibition of platelet aggregation	*In vitro*	*Avena sativa* L., *Hordeum vulgare Linn. var. nudum Hook. f.*, *Fagopyrumesculentum Moench*	[156]

Table 1. *Cont.*

Activity	Sequence	Mechanism	Study Model	Source	Reference
Antithrombotic	ME	Inhibition of platelet aggregation	*In vitro*, *in vivo* (mice)	*Hypophthalmichthysmolitrix*	[157]
Antithrombotic	LTFPRIVFVLG	Inhibition of platelet aggregation	*In vitro*, *in vivo* (mice), *ex vivo*	*Agkistrodonacutus*	[158]
Antithrombotic	FRGCWLKNYSPRGCL-NH2	Inhibition of platelet aggregation	*In vitro*	*Amolopsloloensis*	[159]
Antithrombotic	FAGPPGGDGQPGAK, IAGPAGPRGPSGPA	Inhibition of platelet aggregation	*In vitro*, *in vivo* (mice)	*Salmo salar*	[160]
Antithrombotic	NMEKGSSSVVSSRM	-	*In vitro*	*Nori*	[161]
Antithrombotic	OGEFG	Inhibition of platelet aggregation	*In vitro*, *in vivo* (Rat)	*Salmo salar*	[162]
Antimicrobial	VAGTWY, EQLTK	inhibit Gram-positive and Gram-negative pathogens	*In silico*	*Milk*	[133]
Antimicrobial	YLGYLEQLLRLK	-	*In silico*	*Milk*	[163]
Antimicrobial	SDIPNPIGSENSEK, VLNENLLR, YLEQLLR	-	*In silico*	*Milk*	[164]
Antimicrobial	EDNSELGQETPTLR, DPPNPKNL, PAPPPPPP, VYPFPGPLPN, PFPGPLPN	Growth inhibition	*In vitro*, *in silico*	*Halobatrachusdidactylus*	[142]
Antimicrobial	NINLQTELIAGVTSFFAISYIIVV, KDPFPFVHTNIIGTYT, IKVIAGLVVIILAFLIGRILIQGV	Growth inhibition	*In vitro*	*Lactobacillus plantarum*	[165]
Antimicrobial	FGPKGVGFGMGAGALTMA, GGGGGIGGGIGGGIGGGIGGGIG GGIGGGL, GGGFGGGHGGGGGGGFGGGF, KAAGGGGGIGGGIGGGIGGGIG GGIGGGIGGGL, GDG-GLGGGIGGGHGGGIGGGIGGGIG GGIGGGH, QIPRLLGPGLNKAGKFPGLL	-	*In silico*	*Tenebrio molitor*	[166]

Table 1. *Cont.*

Activity	Sequence	Mechanism	Study Model	Source	Reference
Antidiabetic	AIWGAGGGGLR, FHDPMLR	α-glucosidase inhibitory	*In vitro*	*Sweet potato*	[167]
Antidiabetic	YPDLPYH, NFDLPYH, EFYELAR, VAEASLPR	DPP-IV Inhibitory	*In vitro*	*YellowSilkCocoons*	[138]
Antidiabetic	ACGP, PLMLP, HLPGRG, MFE, QNVLPLH, GPAHCLL	DPP-IV Inhibitory	*In silico*	*Milk*	[133]
Antidiabetic	NRDGIISKDDLRDVLATM, TALEEAEGTLEHEESKILR, AFTIIDQNRDGIISKDDLRDVLATM	DPP-IV inhibitory	*In vitro*	*Clupeaharengus*	[168]
Antidiabetic	EDNSELGQETPTLR, DPPNPKNL, PAPPPPPP, VYPFPGPLPN, PFPGPLPN	α-glucosidase inhibitory	*In vitro*, *in silico*	*Halobatrachusdidactylus*	[142]
Antidiabetic	QTALVELLQ	α-glucosidase inhibitory	*In vitro*	*Kefir*	[169]
Antidiabetic	LLGDV, NLDSS	α-glucosidase inhibitory	*In vitro*	*Rice wine*	[135]
Antidiabetic	DAPLPHPNR, GSEDPLPGAK	DPP-IV inhibitory	*In vitro*	*Lentinulaedodes*	[148]
Antidiabetic	CFA, ACF, RFPS, DEWG, NYCL, CVPR, DACF	DPP-IV inhibitory	*In vitro*	*Pyropiavietnamensis*	[170]
Anticancer	VDPLLSNVALSAPLVR, HALLTSER, APLAYSTPLLK, QSVNHK	Cancer cell elimination	*In vitro*	*Hermetiaillucens*	[125]
Anticancer	LLGDV, NLDSS	Growth inhibition	*In vitro*	*Vigna umbellata*	[135]
Osteoprotective	NAVPITPTL	Suppressing inflammation levels	*In silico*	*Milk*	[133]

3. Identification and Structural Analysis of Bioactive Peptides

The identification, structural characterization, and functional evaluation of bioactive peptides derived from natural sources require an integrative approach that combines chemical, structural, and computational methodologies. Understanding the molecular architecture of these peptides, alongside their conformational behavior, provides the necessary foundation to correlate sequence, structure, and biological activity. The biological behavior of a peptide is strictly determined by its chemical hierarchy. The primary structure defines the physicochemical properties that influence folding; the secondary structure, comprising α-helices, β-sheets, and turns, confers local stability and dictates interactions with cell membranes or receptors; and the tertiary structure defines the final three-dimensional configuration adopted under physiological conditions, governing selectivity and proteolytic resistance [111,112,117].

The specific biomedical activities of natural peptides are strictly governed by their chemical functionalities. For instance, the presence of aromatic rings in residues such as Tyrosine, Phenylalanine, and Tryptophan is crucial for antioxidant activity, as these structures stabilize free radicals through resonance [119,171]. Similarly, sulfur-containing moieties, particularly the thiol groups in Cysteine, are essential for forming disulfide bridges that provide the structural rigidity necessary to resist enzymatic proteolysis and maintain a stable bioactive conformation [172]. Furthermore, the therapeutic efficacy of many antiplatelet and anticancer peptides relies on the strategic distribution of charged amino acids; the cationic nature of Lysine and Arginine facilitates electrostatic attraction to anionic targets, such as bacterial membranes or the phosphatidylserine exposed on tumor cells [173–175]. Connecting these chemical properties with observed bioactivity, as shown in Figure 2, is fundamental for the rational design of new peptide-based drugs.

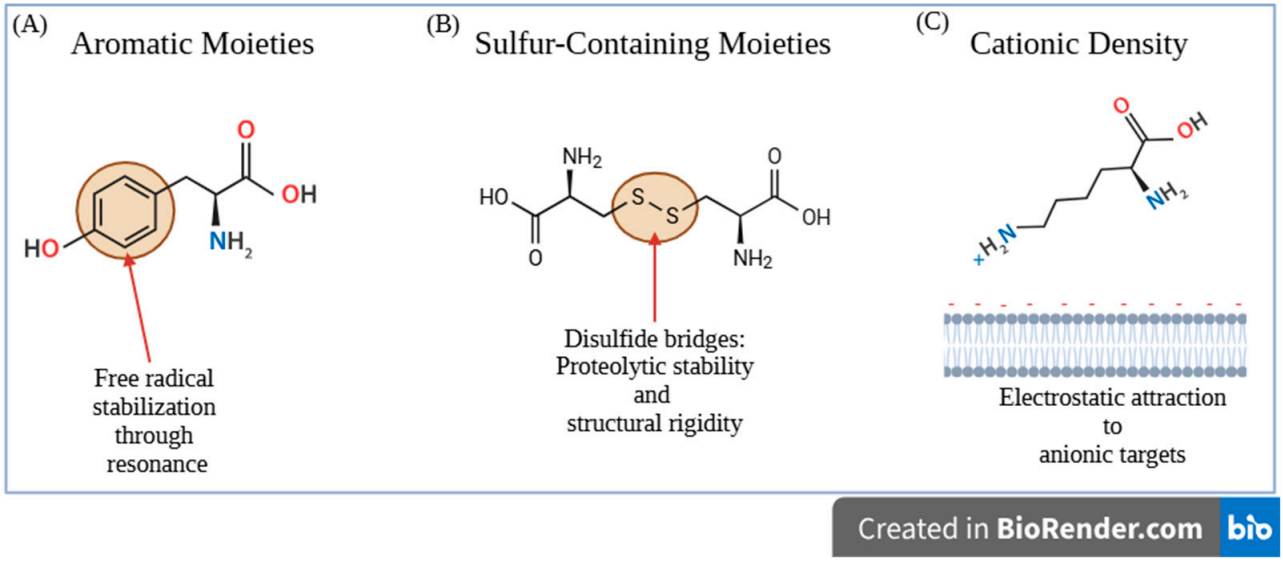


Figure 2. Chemical functionalities and structural motifs governing the bioactivity of natural peptides. (**A**) Aromatic rings stabilize free radicals through resonance; (**B**) Sulfur-containing moieties (disulfide bridges) provide structural stability against enzymatic proteolysis; (**C**) Cationic residues (Lys, Arg) facilitate electrostatic interactions with anionic biological targets. Created with BioRender.com.

From a therapeutic perspective, specific structural motifs are essential for optimizing bioactivity. The presence of amphipathic α-helices is a critical feature for antimicrobial peptides (AMPs), as this conformation allows the hydrophobic face to interact with lipid bilayers while the cationic residues target anionic bacterial membranes [176]. Similarly, the incorporation of disulfide-stabilized loops or cyclic structures provides the necessary rigidity

to fit precisely into receptor pockets, such as the GPIIb/IIIa receptor in antiplatelet therapy, while simultaneously protecting the peptide from rapid systemic degradation [177,178]. The strategic distribution of charged residues like Lys or Arg also dictates the selectivity towards tumor cells by interacting with exposed phosphatidylserine, whereas hydrophobic residues such as Leu and Ile are pivotal for achieving deeper membrane penetration in intracellular targets [117,175].

To elucidate these configurations, a variety of spectroscopic and computational techniques are employed. Nuclear Magnetic Resonance (NMR) and Circular Dichroism (CD) spectroscopy are the primary experimental tools used to identify conformational patterns and secondary motifs in peptides [179,180]. NMR provides atomic level resolution of the peptide backbone and side-chain interactions in solution, while CD allows rapid assessment of α-helical and β-structural content. Furthermore, CD spectroscopy is an essential tool for monitoring peptide aggregation under various physiological conditions and for investigating the binding interactions of peptides with other biomolecules, such as lipids or proteins [181,182]. These techniques have been applied both to naturally isolated and synthetically reproduced peptides to validate their conformation and folding stability [183]. For example, recent studies on the retro-enantiomer peptide Ang (1-9) RE utilized CD and NMR to predict that, although the peptide does not adopt a stable secondary structure in aqueous solution, its side-chain conformation remains similar to that of the natural sequence [184].

Modern proteomic methodologies enable the isolation, purification, and sequencing of peptides from complex biological matrices. Typically, the workflow begins with protein extraction from natural sources, followed by enzymatic hydrolysis using proteases such as trypsin, chymotrypsin, or pepsin to release bioactive fragments [185,186]. While che- mical hydrolysis can also be employed, it is generally less specific and may lead to random cleavage patterns, making enzymatic routes preferable for targeted peptide generation [187].

Once released, peptides are separated according to their specific physicochemical properties. High-performance liquid chromatography (HPLC) remains the gold standard, particularly in its reverse-phase modality (RP-HPLC), which is highly effective for isolating hydrophobic sequences [188–190]. Complementary techniques include size-exclusion chromatography (SEC) for separation by molecular weight and ion-exchange chromato- graphy (IEC) for discrimination based on net charge [191,192]. Additionally, electrokinetic methods such as capillary electrophoresis (CE) are emerging as promising tools for characterizing purity and physicochemical parameters, including Stokes radius and binding constants, of self-assembled peptides in media that mimic biological environments [193]. These integrative approaches ensure the purification of defined fractions necessary for subsequent functional characterization.

Mass spectrometry (MS) is the cornerstone of peptide identification, enabling precise sequencing and quantification even within highly complex mixtures. The MALDI-TOF platform provides rapid mass profiling of peptide extracts [194,195], whereas liquid chromatography–tandem mass spectrometry (LC-MS/MS) affords definitive sequence determination and the detection of post-translational modifications [196]. In a specialized alternative approach, GC-MS studies utilizing derivatization have proven effective for the qualitative and quantitative analysis of γ-glutamyl peptides, such as glutathione (GSH) and its analogs. This two-step methodology involving esterification with HCl/methanol followed by acylation with pentafluoropropionic anhydride (PFPA) reveals the intramolecular conversion of GSH to pyroglutamate (pGlu, 5-oxo-proline) during the esterification phase. The resulting pGlu-methyl ester-PFP derivative can be quantified using electron capture negative ion chemical ionization (ECNICI) mode. This technique leverages the high

electron affinity of fluorinated derivatives to achieve superior analytical sensitivity [197]. Collectively, these platforms form the analytical backbone of contemporary peptide discovery.

Recent methodological innovations also include advancements in solid-phase peptide synthesis (SPPS), such as the use of sustainable "tea bag" supports for Fmoc-based synthesis [198]. SPPS remains the predominant technology for medium-sized peptides (5 to 80 residues), often surpassing solution-phase synthesis in efficiency. Although enzymatic biosynthesis is a less mature route and generally restricted to sequences of fewer than 10 residues, it is increasingly valued for its high specificity and reduced environmental impact [199]. While these approaches originate from synthetic chemistry, they have been adapted to natural peptide research to enable eco-friendly production and the generation of controlled variants for structure–activity analysis. Ultimately, structural identification must be validated through biological assays that confirm physiological relevance. Functional tests are selected based on the hypothesized mechanism of action; for instance, ACE inhibition assays evaluate antihypertensive activity [58], while platelet aggregation assays assess the potential of peptides that interfere with GPIIb/IIIa or thrombin-mediated pathways [200]. These studies establish the essential experimental bridge between molecular architecture and biological function.

Advances in bioinformatics and computational biology have profoundly accelerated the pace of peptide research. Specialized databases, such as BIOPEP, APD (Antimicrobial Peptide Database), and PeptideAtlas, consolidate experimentally validated sequences, structural motifs, and reported biological activities, serving as essential reference points for the scientific community [201–203]. Building upon these data, prediction algorithms like AntiBP and PeptideRanker can estimate potential bioactivity by analyzing physicochemical descriptors, including hydrophobicity, net charge, and chain length [204,205]. Beyond identification, computational tools enable rational design and the prediction of peptide–target interactions. Molecular docking platforms, such as AutoDock and HADDOCK, simulate the binding of peptides to specific enzymes or receptors [206,207], while molecular dynamics (MD) tools like GROMACS analyze conformational flexibility and stability in solution [208]. Furthermore, algorithms such as RosettaDesign facilitate the generation of optimized variants with enhanced stability, solubility, or receptor affinity [209], while predictive software like SwissADME assesses pharmacokinetic parameters crucial for pharmacological development, including gastrointestinal stability and bioavailability [200,210].

The integration of multi-omics data (genomic, transcriptomic, and proteomic) has further expanded the discovery of novel sequences. A prominent example of this synergy is found in the study of *Conus* venoms, where high-throughput sequencing combined with proteomic validation has uncovered hundreds of previously unknown bioactive peptides. Collectively, spectroscopic, chromatographic, proteomic, and computational tools form a methodological continuum that effectively links peptide structure to function, as depicted in the integrative workflow in Figure 3. This holistic approach reveals how structural determination, analytical detection, bioinformatics modeling, and biological assays underpin the rational discovery, optimization, and application of bioactive peptides from natural sources across biomedical, nutritional, and biotechnological contexts.

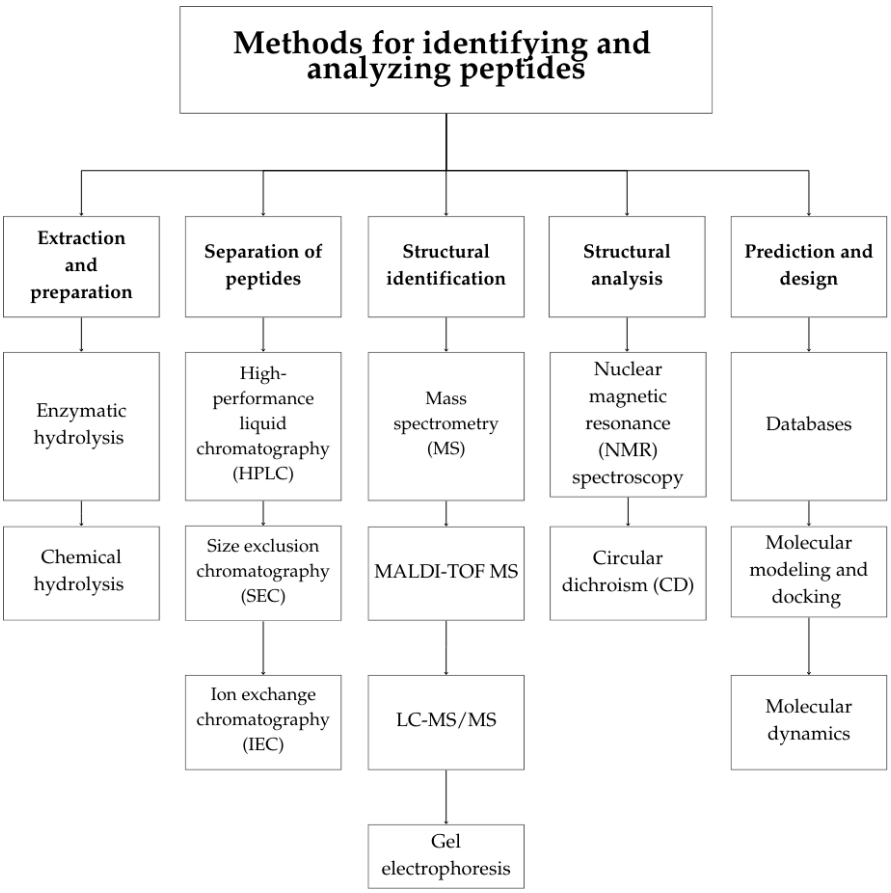


Figure 3. Methods for identifying and analyzing peptides.

4. Challenges and Future Perspectives in the Study and Application of Natural Peptides

The growing scientific and industrial interest in bioactive peptides is driven by their broad spectrum of biological activities and their potential as therapeutic, nutraceutical, and biotechnological tools [185]. However, translating these molecules from the discovery phase to clinical or industrial application continues to pose significant challenges related to large-scale production, metabolic stability, and systemic bioavailability [211]. Despite these hurdles, recent advances in biotechnology, protein engineering, and artificial intelligence (AI) offer promising strategies to overcome these limitations and optimize their utilization across diverse fields [212].

One of the primary obstacles to the industrial exploitation of natural peptides is their limited availability in nature. Many sequences of biomedical interest are isolated from marine organisms, venoms, or rare plants, where collection is not only expensive but may also threaten biodiversity [76,213]. Furthermore, natural peptides typically occur at very low concentrations within complex biological matrices, complicating isolation and purification processes [214]. A major operational disadvantage is that high-resolution chromatographic methods, such as HPLC, while powerful for laboratory scale characterization, are costly and difficult to scale for industrial production [215]. This transition to large-scale manufacturing remains a significant bottleneck, as traditional extraction and microbial fermentation frequently yield insufficient amounts of product to ensure economic feasibility [216,217]. Moreover, maintaining efficiency during purification becomes increasingly complex at larger scales, where methods like RP-HPLC face high operational costs [218]. Although enzymatic hydrolysis offers higher specificity than chemical methods, it requires rigorous control over reaction parameters. Subtle deviations in pH or temperature during large-scale

processing can lead to inconsistent peptide profiles, directly affecting the reproducibility and bioactivity of the final product [219–222]. Consequently, biotechnological alternatives, such as recombinant expression systems or semi-synthetic routes, are being actively developed to enhance production efficiency and sustainability.

In biological environments, peptides are susceptible to rapid degradation by proteolytic enzymes, which drastically shortens their half-life and limits therapeutic efficacy [223,224]. This inherent instability is often compounded by chemical sensitivity to oxidation, hydrolysis, and pH variations, all of which complicate formulation and storage [225,226]. Furthermore, most peptides exhibit poor permeability across biological membranes and the blood–brain barrier (BBB), as well as rapid renal and hepatic clearance. These factors collectively result in low systemic bioavailability, restricting their administration primarily to parenteral routes and hindering their development as oral drugs [227,228].

To address these limitations, diverse protein-engineering and chemical-modification strategies have emerged as viable solutions. Rational peptide design, supported by advanced bioinformatics and structural modeling, enables the optimization of sequences for specific biological activities [229]. A key advantage of peptide engineering is the ability to introduce strategic modifications, such as the incorporation of D-enantiomers or non-natural amino acids, which dramatically increase resistance to proteolysis without altering the conformation required for target binding [225,230]. Similarly, structural modifications like cyclization and disulfide engineering significantly improve metabolic stability [203,231]. Furthermore, chemical conjugation strategies, such as PEGylation, can effectively extend the peptide half-life by reducing renal filtration and minimizing enzymatic degradation [120].

However, these modifications often involve significant trade-offs that must be carefully balanced. For example, while PEGylation effectively increases the hydrodynamic radius of the peptide to reduce renal clearance, the bulky PEG chains can create steric hindrance, potentially reducing the binding affinity for the target receptor [232,233]. Similarly, although the introduction of non-natural amino acids or D-enantiomers enhances proteolytic stability, these changes may alter the native backbone conformation, leading to a loss of biological potency or increased synthetic complexity and cost [231,234,235]. Furthermore, certain chemical conjugations designed to improve solubility may inadvertently increase the risk of immunogenicity, highlighting that every optimization step requires a meticulous evaluation of the balance between stability and pharmacological efficacy [236]. These rational strategies are exemplified by the design of antifungal peptides derived from defensin structural regions, such as SmAPα1-21 and SmAPγ27-44, which displayed potent fungicidal activity against *Candida albicans* through distinct mechanisms [203]. Although synthetically produced, the same conceptual framework applies to optimizing natural peptides for therapeutic use, underscoring the importance of understanding the relationships between sequence, structure, and function.

Large scale recombinant production represents another crucial advance. This approach allows for the sustainable and high-yield production of bioactive peptides, overcoming the scarcity and ethical concerns associated with extraction from natural sources [237]. Genetically engineered bacteria or yeasts can produce bioactive peptides with high efficiency, providing an environmentally friendly alternative to traditional extraction [238]. Enzymatic biosynthesis, in particular, offers high specificity and a lower environmental impact compared with chemical synthesis, as emphasized by Guzmán et al. (2023) [199]. Complementary to these biotechnological routes, combinatorial chemistry enables the creation of extensive peptide libraries for the high-throughput screening of variants with enhanced bioactivity, stability, or multitarget potential [239].

Future progress in peptide research will depend on the convergence of synthetic biology, materials science, and data-driven design. The development of multitarget peptides,

capable of modulating multiple molecular pathways simultaneously, holds significant promise for multifactorial diseases such as cancer and cardiovascular disorders [240]. Simultaneously, the incorporation of machine learning and artificial intelligence (AI) into peptide design pipelines is proving transformative [241]. AI-driven algorithms specifically address the limitations of empirical discovery by enabling high-throughput virtual screening, which identifies physicochemical patterns and predicts receptor interactions with a precision that traditional experimental methods cannot achieve [103,242]. This rational design significantly reduces the time and cost associated with failed laboratory trials while optimizing sequences for specific bioactivities [243].

To resolve the problem of rapid enzymatic degradation, the integration of nanotechnology and targeted delivery systems offers a robust solution. By encapsulating peptides into liposomes, polymeric nanoparticles, or hydrogels, bioactive sequences are physically shielded from proteases in the systemic circulation [114,244,245]. This approach allows for controlled release and improved penetration across biological barriers, such as the blood–brain barrier, transforming natural peptides into viable, targeted therapeutic agents [246]. Finally, the concept of sustainability and the circular economy is gaining traction within the field. The recovery of proteins from agro-industrial by-products and food processing waste offers an eco-friendly source of raw materials for generating bioactive peptides [247]. These strategies not only reduce environmental impact but also improve economic accessibility, facilitating the integration of peptides into functional foods, pharmaceuticals, and cosmetics.

While the study and application of natural peptides face persistent hurdles, including source scarcity, metabolic instability, and limited systemic bioavailability, the convergence of biotechnology, chemical innovation, and computational intelligence is paving the way toward more efficient, sustainable, and targeted peptide-based solutions. The next decade is expected to witness a decisive shift from empirical discovery toward rational and sustainable development. In this evolving landscape, natural peptides are poised to transition from biological curiosities into fully optimized agents, fundamentally transforming human health and industrial applications.

5. Conclusions

Peptides derived from natural sources represent a rich and versatile class of bioactive compounds with vast potential across biomedicine, biotechnology, and nutritional sciences. Their multifaceted ability to exert antimicrobial, antiplatelet, antioxidant, and antitumor effects positions them as indispensable tools in the pursuit of innovative therapies and high-value functional products. Nevertheless, their full-scale exploitation continues to face significant hurdles regarding industrial production, metabolic stability, and systemic bioavailability.

The synergy of technological advancements in proteomics, bioinformatics, chemical synthesis, and recombinant production is effectively transforming these limitations into strategic opportunities. These integrated platforms allow for the precise optimization of peptide activity and safety, facilitating their successful transition into diverse industrial sectors. Furthermore, the implementation of multidisciplinary approaches, including artificial intelligence and nanotechnology, promises to expand their therapeutic reach significantly.

Future research in the field must prioritize the development of sustainable, scaled-up production models and the design of multitarget peptides with enhanced controlled-release systems. Essential to this progress will be the rigorous assessment of in vivo efficacy and safety, alongside the deep integration of multi-omics and AI-driven tools to accelerate discovery and screening pipelines. By addressing these priorities, natural peptides will consolidate their role as fundamental pillars in personalized medicine and functional

nutrition, providing more effective and environmentally friendly alternatives. With a highly promising outlook, these biomolecules continue to lead the way toward a new era of innovation and sustainability in the life sciences.

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Abbreviations

ACE	Angiotensin-converting enzyme
ADME	Absorption, distribution, metabolism, and excretion
AI	Artificial intelligence
Ala (A)	Alanine
AMPs	Antimicrobial peptides
APD	Antimicrobial Peptide Database
Arg (R)	Arginine
Asn (N)	Asparagine
Asp (D)	Aspartic acid
BBB	Blood–brain barrier
CD	Circular Dichroism
CE	Capillary electrophoresis
CVD	Cardiovascular disease
Cys ©	Cysteine
DNA	Deoxyribonucleic Acid
DPP-IV	Dipeptidyl peptidase IV
ECNICI	Electron Capture Negative Chemical Ionization
Fmoc	9-Fluorenylmethoxycarbonyl
GC-MS	Gas chromatographic-mass spectrometric
Gln (Q)	Glutamine
Glu (E)	Glutamic acid
Gly (G)	Glycine

GPIIb/IIIa	Glycoprotein IIb/IIIa
GSH	Glutathione (reduced)
HCl	Hydrochloric Acid
His (H)	Histidine
HPLC	High-performance liquid chromatography
Hyp	Hydroxyprolyl
Ile (I)	Isoleucine
IEC	Ion-exchange chromatography
LC-MS/MS	Liquid chromatography–tandem MS
Leu (L)	Leucine
Lys (K)	Lysine
MALDI-TOF	Matrix-assisted laser desorption/ionization-time of flight
MD	Molecular dynamics
Met (M)	Methionine
MS	Mass spectrometry
NMR	Nuclear Magnetic Resonance
PEG	Polyethylene glycol
PFPA	Pentafluoropropionic anhydride
pGlu	Pyroglutamate (5-oxo-proline)
Phe (F)	Phenylalanine
PI3K/Akt	Phosphatidylinositol 3-kinase/Protein Kinase B
Pro (P)	Proline
RNA	Ribonucleic Acid
ROS	Reactive oxygen species
RP-HPLC	High-performance liquid chromatography reverse-phase
SEC	Size-exclusion chromatography
Ser (S)	Serine
SPPS	Solid-phase peptide synthesis
Thr (T)	Threonine
Trp (W)	Tryptophan
Tyr (Y)	Tyrosine
UV	Ultraviolet
Val (V)	Valine
VEGF	Vascular endothelial growth factor

References

1. Sable, R.; Parajuli, P.; Jois, S. Peptides, Peptidomimetics, and Polypeptides from Marine Sources: A Wealth of Natural Sources for Pharmaceutical Applications. *Mar. Drugs* **2017**, *15*, 124. [CrossRef] [PubMed]
2. Pushpanathan, M.; Gunasekaran, P.; Rajendhran, J. Antimicrobial Peptides: Versatile Biological Properties. *Int. J. Pept.* **2013**, *2013*, 675391. [CrossRef]
3. Zhang, Y.; Li, Y.; Quan, Z.; Xiao, P.; Duan, J. New Insights into Antioxidant Peptides: An Overview of Efficient Screening, Evaluation Models, Molecular Mechanisms, and Applications. *Antioxidants* **2024**, *13*, 203. [CrossRef]
4. Matsui, T.; Matsumoto, K. Antihypertensive Peptides from Natural Resources. *Adv. Phytomed.* **2006**, *2*, 255–271. [CrossRef]
5. Cárdenas, C.; Santana, P.; Álvarez, C.; Mercado, L.; Marshall, S.; Albericio, F.; Guzman, F. Synthetic Peptides as Valuable and Versatile Tools for Research: Our 20 Year Journey in Chile. *Explor. Drug Sci.* **2024**, *2*, 701–718. [CrossRef]
6. Hayashi, M.A.F.; Ducancel, F.; Konno, K. Natural Peptides with Potential Applications in Drug Development, Diagnosis, and/or Biotechnology. *Int. J. Pept.* **2012**, *2012*, 757838. [CrossRef]
7. Jallouk, P.A.; Palekar, U.R.; Pan, H.; Schlesinger, H.P.; Wickline, A.S. Modifications of Natural Peptides for Nanoparticle and Drug Design. *Adv. Protein Chem. Struct. Biol.* **2015**, *98*, 57–91.
8. Ko, J.; Auyeung, K. Identification of Functional Peptides from Natural and Synthetic Products on Their Anticancer Activities by Tumor Targeting. *Curr. Med. Chem.* **2014**, *21*, 2346–2356. [CrossRef] [PubMed]
9. Abdalla, A.M.; McGaw, J.L. Natural Cyclic Peptides as an Attractive Modality for Therapeutics: A Mini Review. *Molecules* **2018**, *23*, 2080. [CrossRef]

10. Prasasty, V.; Radifar, M.; Istyastono, E. Natural Peptides in Drug Discovery Targeting Acetylcholinesterase. *Molecules* **2018**, *23*, 2344. [CrossRef] [PubMed]
11. La Manna, S.; Di Natale, C.; Florio, D.; Marasco, D. Peptides as Therapeutic Agents for Inflammatory-Related Diseases. *Int. J. Mol. Sci.* **2018**, *19*, 2714. [CrossRef]
12. Rutherfurd, J.K.; Gill, S.H. Peptides Affecting Coagulation. *Br. J. Nutr.* **2000**, *84*, 99–102. [CrossRef]
13. Bhutia, K.S.; Maiti, K.T. Targeting Tumors with Peptides from Natural Sources. *Trends Biotechnol.* **2008**, *26*, 210–217. [CrossRef] [PubMed]
14. Bauso, V.L.; La Fauci, V.; Munaò, S.; Bonfiglio, D.; Armeli, A.; Maimone, N.; Longo, C.; Calabrese, G. Biological Activity of Natural and Synthetic Peptides as Anticancer Agents. *Int. J. Mol. Sci.* **2024**, *25*, 7264. [CrossRef]
15. Freuville, L.; Matthys, C.; Quinton, L.; Gillet, J. Venom-Derived Peptides for Breaking through the Glass Ceiling of Drug Development. *Front. Chem.* **2024**, *12*, 1465459. [CrossRef] [PubMed]
16. Rodríguez, A.A.; Otero-González, A.; Ghattas, M.; Ständker, L. Discovery, Optimization, and Clinical Application of Natural Antimicrobial Peptides. *Biomedicines* **2021**, *9*, 1381. [CrossRef] [PubMed]
17. Wang, W.; De Mejia, E.G. A New Frontier in Soy Bioactive Peptides That May Prevent Age-Related Chronic Diseases. *Compr. Rev. Food Sci. Food Saf.* **2005**, *4*, 63–78. [CrossRef]
18. Yeo, J.; Shahidi, F. Bioactive Peptides in Health and Disease: An Overview. *Biol. Act. Pept.* **2021**, *1380*, 1–26.
19. Erdmann, K.; Cheung, W.B.; Schröder, H. The Possible Roles of Food-Derived Bioactive Peptides in Reducing the Risk of Cardiovascular Disease. *J. Nutr. Biochem.* **2008**, *19*, 643–654. [CrossRef]
20. Juárez-Chairez, F.M.; Cid-Gallegos, S.M.; Meza-Márquez, G.O.; Jiménez-Martínez, C. Biological Functions of Peptides from Legumes in Gastrointestinal Health. *J. Food Biochem.* **2022**, *46*, e14308. [CrossRef]
21. Yan, Z.; Gui, Y.; Liu, C.; Zhang, X.; Wen, C.; Olatunji, O.J.; Suttikhana, I.; Ashaolu, T.J. Gastrointestinal Digestion of Food Proteins: Anticancer, Antihypertensive, Anti-Obesity, and Immunomodulatory Mechanisms of the Derived Peptides. *Food Res. Int.* **2024**, *189*, 114573. [CrossRef]
22. Mills, S.; Stanton, C.; Hill, C.; Ross, R. New Developments and Applications of Bacteriocins and Peptides in Foods. *Annu. Rev. Food Sci. Technol.* **2011**, *2*, 299–329. [CrossRef]
23. Daliri, E.; Oh, D.; Lee, B. Bioactive Peptides. *Foods* **2017**, *6*, 32. [CrossRef]
24. Malaguti, M.; Dinelli, G.; Leoncini, E.; Bregola, V.; Bosi, S.; Hrelia, S. Bioactive Peptides in Cereals and Legumes: Agronomical, Biochemical and Clinical Aspects. *Int. J. Mol. Sci.* **2014**, *15*, 21120–21135. [CrossRef]
25. Kiersnowska, K.; Jakubczyk, A. Bioactive Peptides Obtained from Legume Seeds as New Compounds in Metabolic Syndrome Prevention and Diet Therapy. *Foods* **2022**, *11*, 3300. [CrossRef]
26. Zhou, Y.; Xu, Y.; Tian, T.; Xu, Y. Antihypertensive and Antioxidant Effects of Food-derived Bioactive Peptides in Spontaneously Hypertensive Rats. *Food Sci. Nutr.* **2024**, *12*, 8200–8210. [CrossRef] [PubMed]
27. Zhu, B.; He, H.; Hou, T. A Comprehensive Review of Corn Protein-derived Bioactive Peptides: Production, Characterization, Bioactivities, and Transport Pathways. *Compr. Rev. Food Sci. Food Saf.* **2018**, *18*, 329–345. [CrossRef] [PubMed]
28. Cruz-Casas, E.D.; Aguilar, N.C.; Ascacio-Valdés, A.J.; Rodríguez-Herrera, R.; Chávez-González, L.M.; Flores-Gallegos, A.C.; Aguilar, C.N. Enzymatic Hydrolysis and Microbial Fermentation: The Most Favorable Biotechnological Methods for the Release of Bioactive Peptides. *Food Chem. Mol. Sci.* **2021**, *3*, 100047. [CrossRef]
29. Wang, L.; Dong, C.; Li, X.; Han, W.; Su, X. Anticancer Potential of Bioactive Peptides from Animal Sources. *Oncol. Rep.* **2017**, *38*, 637–651. [CrossRef]
30. Ageitos, L.; de Oliveira Torres, T.M.; de la Fuente-Nunez, C. Biologically Active Peptides from Venoms: Applications in Antibiotic Resistance, Cancer, and Beyond. *Int. J. Mol. Sci.* **2022**, *23*, 15437. [CrossRef] [PubMed]
31. Pérez-Peinado, C.; Defaus, S.; Andreu, D. Hitchhiking with Nature: Snake Venom Peptides to Fight Cancer and Superbugs. *Toxins* **2020**, *12*, 255. [CrossRef]
32. Moreno, M.; Giralt, E. Three Valuable Peptides from Bee and Wasp Venoms for Therapeutic and Biotechnological Use: Melittin, Apamin and Mastoparan. *Toxins* **2015**, *7*, 1126–1150. [CrossRef] [PubMed]
33. Cadar, E.; Pesterau, A.; Prasacu, I.; Ionescu, A.; Pascale, C.; Sirbu, R. Marine Antioxidants from Marine Collagen and Collagen Peptides with Nutraceuticals Applications: A Review. *Antioxidants* **2024**, *13*, 919. [CrossRef] [PubMed]
34. Ngo, D.; Vo, T.; Ngo, D.; Wijesekara, I.; Kim, S. Biological Activities and Potential Health Benefits of Bioactive Peptides Derived from Marine Organisms. *Int. J. Biol. Macromol.* **2012**, *51*, 378–383. [CrossRef] [PubMed]
35. Al Hajj, W.; Salla, M.; Krayem, M.; Khaled, S.; Hassan, H.F.; El Khatib, S. Hydrolyzed Collagen: Exploring Its Applications in the Food and Beverage Industries and Assessing Its Impact on Human Health—A Comprehensive Review. *Heliyon* **2024**, *10*, e36433. [CrossRef]
36. Siltari, A.; Vapaatalo, H.; Korpela, R. Milk and Milk-derived Peptides Combat against Hypertension and Vascular Dysfunction: A Review. *Int. J. Food Sci. Technol.* **2019**, *54*, 1920–1929. [CrossRef]

37. Park, W.Y.; Nam, S.M. Bioactive Peptides in Milk and Dairy Products: A Review. *Korean J. Food Sci. Anim. Resour.* **2015**, *35*, 831. [CrossRef]
38. Korhonen, H.; Pihlanto, A. Bioactive Peptides: Production and Functionality. *Int. Dairy. J.* **2006**, *16*, 945–960. [CrossRef]
39. Tagliazucchi, D.; Martini, S.; Solieri, L. Bioprospecting for Bioactive Peptide Production by Lactic Acid Bacteria Isolated from Fermented Dairy Food. *Fermentation* **2019**, *5*, 96. [CrossRef]
40. Saubenova, M.; Oleinikova, Y.; Rapoport, A.; Maksimovich, S.; Yermekbay, Z.; Turmanov, A.; Saubenov, O. Bioactive Peptides Derived from Whey Proteins for Health and Functional Beverages. *Fermentation* **2024**, *10*, 359. [CrossRef]
41. Xiong, J.; Bai, L.; Fang, W.; Fu, J.; Fang, W.; Zheng, L. New Peptide PENW (PGlu-Asn-Trp) Inhibits Platelet Activation by Attenuating Akt Phosphorylation. *Eur. J. Pharm. Sci.* **2012**, *45*, 552–558. [CrossRef]
42. Chiang, T. Recent Development of Peptides from Glycoproteins IIb (αIIβ) and IIIa (β3) That Inhibit Platelet Fibrinogen Binding. *Curr. Med. Chem. Hematol. Agents* **2005**, *3*, 99–103. [CrossRef]
43. Rengasamy, R.K.; Khan, H.; Ahmad, I.; Lobine, D.; Mahomoodally, F.; Suroowan, S.; Hassan, S.T.; Xu, S.; Patel, S.; Daglia, M.; et al. Bioactive Peptides and Proteins as Alternative Antiplatelet Drugs. *Med. Res. Rev.* **2019**, *39*, 2153–2171. [CrossRef]
44. Blanco-Míguez, A.; Gutiérrez-Jácome, A.; Pérez-Pérez, M.; Pérez-Rodríguez, G.; Catalán-García, S.; Fdez-Riverola, F.; Lourenço, A.; Sánchez, B.; Méndez, R.; Boer, H.; et al. From Amino Acid Sequence to Bioactivity: The Biomedical Potential of Antitumor Peptides. *Protein Sci.* **2016**, *25*, 1084–1095. [CrossRef]
45. Wang, L.; Wang, N.; Zhang, W.; Cheng, X.; Yan, Z.; Shao, G.; Wang, X.; Wang, R.; Fu, C. Therapeutic Peptides: Current Applications and Future Directions. *Signal Transduct. Target. Ther.* **2022**, *7*, 48. [CrossRef] [PubMed]
46. Bhat, F.Z.; Kumar, S.; Bhat, F.H. Bioactive Peptides of Animal Origin: A Review. *J. Food Sci. Technol.* **2015**, *52*, 5377–5392. [CrossRef] [PubMed]
47. Cheung, R.; Ng, T.; Wong, J. Marine Peptides: Bioactivities and Applications. *Mar. Drugs* **2015**, *13*, 4006–4043. [CrossRef]
48. Lazarovici, P.; Marcinkiewicz, C.; Lelkes, I.P. From Snake Venom's Disintegrins and C-Type Lectins to Anti-Platelet Drugs. *Toxins* **2019**, *11*, 303. [CrossRef]
49. Marcinkiewicz, C. Functional Characteristic of Snake Venom Disintegrins: Potential Therapeutic Implication. *Curr. Pharm. Des.* **2005**, *11*, 815–827. [CrossRef] [PubMed]
50. Van De Car, D.A.; Rao, V.S.; Ohman, E.M. Bivalirudin: A Review of the Pharmacology and Clinical Application. *Expert Rev. Cardiovasc. Ther.* **2010**, *8*, 1673–1681. [CrossRef]
51. Yamamoto, T.; Takahara, A. Recent Updates of N-Type Calcium Channel Blockers with Therapeutic Potential for Neuropathic Pain and Stroke. *Curr. Top Med. Chem.* **2009**, *9*, 377–395. [CrossRef]
52. Furman, L.B. The Development of Byetta (Exenatide) from the Venom of the Gila Monster as an Anti-Diabetic Agent. *Toxicon* **2010**, *59*, 464–471. [CrossRef]
53. Cheng, S.; Yuan, L.; Li-Gao, R.; Chen, S.; Li, H.; Liu, J. Nutrition and Cardiovascular Disease: The Potential Role of Marine Bioactive Proteins and Peptides in Thrombosis Prevention. *J. Agric. Food Chem.* **2024**, *72*, 6815–6832. [CrossRef] [PubMed]
54. Gerónimo-Alonso, M.; Ortíz-Vázquez, E.; Rodríguez-Canto, W.; Chel-Guerrero, L.; Betancur-Ancona, D. Antithrombotic and Anticariogenic Activity of Peptide Fractions from Cowpea (*Vigna unguiculata*) Protein Hydrolysates. *J. Sci. Food Agric.* **2024**, *105*, 209–217. [CrossRef] [PubMed]
55. Tian, Q.; Li, S.; Li, B. The Pro-Gly or Hyp-Gly Containing Peptides from Absorbates of Fish Skin Collagen Hydrolysates Inhibit Platelet Aggregation and Target P2Y12 Receptor by Molecular Docking. *Foods* **2021**, *10*, 1553. [CrossRef] [PubMed]
56. Cian, E.R.; Garzón, G.A.; Ancona, B.D.; Guerrero, C.L.; Drago, R.S. Hydrolyzates from Pyropia Columbina Seaweed Have Antiplatelet Aggregation, Antioxidant and ACE I Inhibitory Peptides Which Maintain Bioactivity after Simulated Gastrointestinal Digestion. *LWT* **2015**, *64*, 881–888. [CrossRef]
57. Cheng, S.; Tu, M.; Chen, H.; Xu, Z.; Wang, Z.; Liu, G.; Qin, L.; Du, M. Identification and Inhibitory Activity against α-Thrombin of a Novel Anticoagulant Peptide Derived from Oyster (*Crassostrea gigas*) Protein. *Food Funct.* **2018**, *9*, 6391–6400. [CrossRef]
58. Rai, K.A.; Sanjukta, S.; Jeyaram, K. Production of Angiotensin I Converting Enzyme Inhibitory (ACE-I) Peptides during Milk Fermentation and Their Role in Reducing Hypertension. *Crit. Rev. Food Sci. Nutr.* **2015**, *57*, 2789–2800. [CrossRef]
59. Durak, Z.M. Antihypertensive Peptides in Dairy Products. *Am. J. Biomed. Sci. Res.* **2020**, *7*, 191–195. [CrossRef]
60. Jäkälä, P.; Vapaatalo, H. Antihypertensive Peptides from Milk Proteins. *Pharmaceuticals* **2010**, *3*, 251–272. [CrossRef]
61. Mizuno, S.; Matsuura, K.; Gotou, T.; Nishimura, S.; Kajimoto, O.; Yabune, M.; Takeba, Y.; Tano-Debrah, K. Antihypertensive Effect of Casein Hydrolysate in a Placebo-Controlled Study in Subjects with High-Normal Blood Pressure and Mild Hypertension. *Br. J. Nutr.* **2005**, *94*, 84–91. [CrossRef]
62. Wang, K.; Zhu, X.; Liao, X.; Xu, Z. Changes of Low-Abundance Peptides in Frozen Orange Juice before and after Frozen Storage and Pasteurization Processing, and Their Contribution to ACE Inhibition Activity. *Food Res. Int.* **2025**, *202*, 115739. [CrossRef] [PubMed]
63. de Carvalho Cavenaghi, D.F.L.; de Barros, W.M.; de Castro, R.J.S. Antihypertensive Peptides from Hydrolyzed Proteins of *Pleurotus* spp.: Production, in Vitro Digestion and Identification. *Process Biochem.* **2024**, *149*, 1–9. [CrossRef]

64. Barkia, I.; Al-Haj, L.; Hamid, A.A.; Zakaria, M.; Saari, N.; Al-Haj, N.A.; Mohd Ismail, A. Indigenous Marine Diatoms as Novel Sources of Bioactive Peptides with Antihypertensive and Antioxidant Properties. *Int. J. Food Sci. Technol.* **2018**, *54*, 1514–1522. [CrossRef]
65. Herrera-Lavados, C.; Tabilo-Munizaga, G.; Carvajal-Mena, N.; Jara-Quijada, E.; Martínez-Oyanedel, J.; Pérez-Won, M. Obtaining Bioactive Peptides by Enhancing Enzymatic Hydrolysis of Salmon By-Product Proteins through Pulsed Electric Fields (PEF). *Food Res. Int.* **2025**, *208*, 116103. [CrossRef]
66. Krunic, T.; Rakin, M. Combination of Controlled Enzymatic Hydrolysis and Ultrafiltration as the Technique for Bioactive Peptide Production Intended for the Food Industry. *Innov. Food Sci. Emerg. Technol.* **2025**, *102*, 103979. [CrossRef]
67. Nakamura, Y.; Yamamoto, N.; Sakai, K.; Takano, T. Antihypertensive Effect of Sour Milk and Peptides Isolated from It That Are Inhibitors to Angiotensin I-Converting Enzyme. *J. Dairy Sci.* **1995**, *78*, 1253–1257. [CrossRef] [PubMed]
68. Kim, I.; Yang, W.; Kim, C. Beneficial Effects of Soybean-Derived Bioactive Peptides. *Int. J. Mol. Sci.* **2021**, *22*, 8570. [CrossRef]
69. Liu, R.; Kim, H.A.; Kwak, M.; Kang, S. Proline-Based Cyclic Dipeptides from Korean Fermented Vegetable Kimchi and from Leuconostoc Mesenteroides LBP-K06 Have Activities against Multidrug-Resistant Bacteria. *Front. Microbiol.* **2017**, *8*, 761. [CrossRef]
70. Mares-Mares, E.; Barboza-Corona, E.J.; Sosa-Morales, E.M.; Gutiérrez-Chávez, J.A.; Gutiérrez-Vargas, S. Inhibition of Dipeptidyl Peptidase IV by Enzymatic Hydrolysates Derived from Primary and Secondary Whey of Fresh and Oaxaca Cheeses. *Int. J. Dairy Technol.* **2019**, *72*, 626–632. [CrossRef]
71. Giordano, D.; Costantini, M.; Coppola, D.; Lauritano, C.; Nuutinen, J.; Parrilli, E.; Verde, C. Biotechnological Applications of Bioactive Peptides from Marine Sources. *Adv. Microb. Physiol.* **2018**, *73*, 171–220.
72. Ibrahim, R.H.; Ahmed, S.A.; Miyata, T. Novel Angiotensin-Converting Enzyme Inhibitory Peptides from Caseins and Whey Proteins of Goat Milk. *J. Adv. Res.* **2016**, *8*, 63–71. [CrossRef]
73. Chanson-Rolle, A.; Aubin, F.; Braesco, V.; Hamasaki, T.; Kitakaze, M. Influence of the Lactotripeptides Isoleucine–Proline–Proline and Valine–Proline–Proline on Systolic Blood Pressure in Japanese Subjects: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *PLoS ONE* **2015**, *10*, e0142235. [CrossRef] [PubMed]
74. Nakamura, T.; Mizutani, J.; Ohki, K.; Yamada, K.; Yamamoto, N.; Takeshi, M. Casein Hydrolysate Containing Val-Pro-Pro and Ile-Pro-Pro Improves Central Blood Pressure and Arterial Stiffness in Hypertensive Subjects: A Randomized, Double-Blind, Placebo-Controlled Trial. *Atherosclerosis* **2011**, *219*, 298–303. [CrossRef] [PubMed]
75. Robinson, W.M.; Hutchinson, T.A.; Donnelly, S. Antimicrobial Peptides: Utility Players in Innate Immunity. *Front. Immunol.* **2012**, *3*, 325. [CrossRef]
76. Dini, I.; De Biasi, M.G.; Mancusi, A. An Overview of the Potentialities of Antimicrobial Peptides Derived from Natural Sources. *Antibiotics* **2022**, *11*, 1483. [CrossRef]
77. Lei, J.; Sun, L.; Huang, S.; Zhu, C.; Li, P.; Xuan, J.; Li, Y. The Antimicrobial Peptides and Their Potential Clinical Applications. *Am. J. Transl. Res.* **2019**, *11*, 3919–3931.
78. Corrêa, J.A.F.; Evangelista, A.G.; de Melo Nazareth, T.; Luciano, F.B. Fundamentals on the Molecular Mechanism of Action of Antimicrobial Peptides. *Materialia* **2019**, *8*, 10094. [CrossRef]
79. McMillan, K.A.; Coombs, M.R.P. Review: Examining the Natural Role of Amphibian Antimicrobial Peptide Magainin. *Molecules* **2020**, *25*, 5436. [CrossRef] [PubMed]
80. Drayton, M.; Kizhakkedathu, N.J.; Straus, K.S. Towards Robust Delivery of Antimicrobial Peptides to Combat Bacterial Resistance. *Molecules* **2020**, *25*, 3048. [CrossRef]
81. Hong, M. Solid-State NMR Studies of the Structure, Dynamics, and Assembly of β-Sheet Membrane Peptides and α-Helical Membrane Proteins with Antibiotic Activities. *Acc. Chem. Res.* **2006**, *39*, 176–183. [CrossRef] [PubMed]
82. Jin, Y.; Hammer, J.; Pate, M.; Zhang, Y.; Zhu, F.; Zmuda, E.; Blazyk, J.; Smith, J. Antimicrobial Activities and Structures of Two Linear Cationic Peptide Families with Various Amphipathic β-Sheet and α-Helical Potentials. *Antimicrob. Agents Chemother.* **2005**, *49*, 4957–4964. [CrossRef]
83. Velasco-Bolom, J.; Corzo, G.; Garduño-Juárez, R. Molecular Dynamics Simulation of the Membrane Binding and Disruption Mechanisms by Antimicrobial Scorpion Venom-Derived Peptides. *J. Biomol. Struct. Dyn.* **2017**, *36*, 2070–2084. [CrossRef] [PubMed]
84. Kathirvel, I.; Gnanakkan, A.; Ganesan, G.N. Bioactive Antimicrobial Peptides from Didemnum Albidum: An MALDI-TOFMS Analysis. *J. Mol. Struct.* **2024**, *1323*, 140618. [CrossRef]
85. Jadhav, B.P.; Bhosale, J.H.; Mamdapure, V.S.; Jadhav, B.S. Antibacterial and Anti-Breast Cancer Activities, GC–MS Profiling, Molecular Docking and Pharmacokinetic Studies of Nutritious White Kidney Beans. *S. Afr. J. Bot.* **2024**, *177*, 225–236. [CrossRef]
86. Kulkarni, G.R.; Keshavamurthy, M.; Shilpashree, H.P.; Vishwanatha, T. Bacteriocins: Properties and Potential Applications in Food and Pharmaceutical Industry. *Acta Sci. Microbiol.* **2024**, *7*, 66–76. [CrossRef]
87. Małaczewska, J.; Kaczorek-Łukowska, E. Nisin—A Lantibiotic with Immunomodulatory Properties: A Review. *Peptides* **2020**, *137*, 170479. [CrossRef]

88. Zhang, J.; Zhong, J. The Journey of Nisin Development in China, a Natural-Green Food Preservative. *Protein Cell* **2015**, *6*, 709–711. [CrossRef]
89. Shi, Y.; Wen, T.; Zhao, F.; Hu, J. Bacteriostasis of Nisin against Planktonic and Biofilm Bacteria: Its Mechanism and Application. *J. Food Sci.* **2024**, *89*, 1894–1916. [CrossRef]
90. Guzmán, F.; Wong, G.; Román, T.; Cárdenas, C.; Alvárez, C.; Schmitt, P.; Albericio, F.; Rojas, V. Identification of Antimicrobial Peptides from the Microalgae *Tetraselmis suecica* (Kylin) Butcher and Bactericidal Activity Improvement. *Mar. Drugs* **2019**, *17*, 453. [CrossRef]
91. Zhu, Y.; Wang, K.; Jia, X.; Fu, C.; Yu, H.; Zhang, Y.; Wang, L.; Wang, S.; Nie, S.; Xie, M. Antioxidant Peptides, the Guardian of Life from Oxidative Stress. *Med. Res. Rev.* **2023**, *44*, 275–364. [CrossRef]
92. Aguilar-Toalá, E.J.; Liceaga, M.A. Cellular Antioxidant Effect of Bioactive Peptides and Molecular Mechanisms Underlying: Beyond Chemical Properties. *Int. J. Food Sci. Technol.* **2020**, *56*, 2193–2204. [CrossRef]
93. Torres-Fuentes, C.; Contreras, M.M.; Recio, I.; Alaiz, M.; Vioque, J. Identification and Characterization of Antioxidant Peptides from Chickpea Protein Hydrolysates. *Food Chem.* **2015**, *180*, 194–202. [CrossRef]
94. Andrés, C.C.M.; Pérez de la Lastra, J.M.; Andrés Juan, C.; Plou, J.F.; Pérez-Lebeña, E. Impact of Reactive Species on Amino Acids—Biological Relevance in Proteins and Induced Pathologies. *Int. J. Mol. Sci.* **2022**, *23*, 14049. [CrossRef]
95. Venkatesan, J.; Anil, S.; Kim, S.; Shim, M. Marine Fish Proteins and Peptides for Cosmeceuticals: A Review. *Mar. Drugs* **2017**, *15*, 143. [CrossRef]
96. Yamada, S.; Nagaoka, H.; Terajima, M.; Tsuda, N.; Hayashi, Y.; Yamauchi, M. Effects of Fish Collagen Peptides on Collagen Post-Translational Modifications and Mineralization in an Osteoblastic Cell Culture System. *Dent. Mater. J.* **2013**, *32*, 88–95. [CrossRef] [PubMed]
97. Qi, X.; Guan, K.; Liu, C.; Chen, H.; Ma, Y.; Li, X.; Chen, G.; Mao, X. Whey Protein Peptides PEW and LLW Synergistically Ameliorate Hyperuricemia and Modulate Gut Microbiota in Potassium Oxonate and Hypoxanthine-Induced Hyperuricemic Rats. *J. Dairy Sci.* **2023**, *106*, 7367–7381. [CrossRef]
98. Riedl, S.; Leber, R.; Rinner, B.; Schaider, H.; Lohner, K.; Zweytick, D. Human Lactoferricin Derived Di-Peptides Deploying Loop Structures Induce Apoptosis Specifically in Cancer Cells through Targeting Membranous Phosphatidylserine. *Biochim. Biophys. Acta (BBA)-Biomembr.* **2015**, *1848*, 2918–2931. [CrossRef] [PubMed]
99. Cui, H.; Han, W.; Zhang, J.; Zhang, Z.; Su, X. Advances in the Regulatory Effects of Bioactive Peptides on Metabolic Signaling Pathways in Tumor Cells. *J. Cancer* **2019**, *10*, 2425–2433. [CrossRef] [PubMed]
100. Rafieezadeh, D.; Esfandyari, G. Marine Bioactive Peptides with Anticancer Potential, a Narrative Review. *Int. J. Biochem. Mol. Biol.* **2024**, *15*, 118–126. [CrossRef]
101. Kao, H.; Weng, T.; Chen, C.; Chen, Y.; Chi, Y.; Tseng, T. Integrating In Silico and In Vitro Approaches to Identify Natural Peptides with Selective Cytotoxicity against Cancer Cells. *Int. J. Mol. Sci.* **2024**, *25*, 6848. [CrossRef] [PubMed]
102. Alonso-Álvarez, S.; Pardal, E.; Sánchez-Nieto, D.; Navarro, M.; Caballero, D.M.; García-Sanz, R. Plitidepsin: Design, Development, and Potential Place in Therapy. *Drug Des. Dev. Ther.* **2017**, *11*, 253–264. [CrossRef]
103. Kennedy, K.; Cal, R.; Casey, R.; Lopez, C.; Adelfio, A.; O'Sullivan, J.; Conran, M.; Wall, P. The Anti-ageing Effects of a Natural Peptide Discovered by Artificial Intelligence. *Int. J. Cosmet. Sci.* **2020**, *42*, 388–398. [CrossRef]
104. Lourith, N.; Kanlayavattanakul, M. Biopolymeric Agents for Skin Wrinkle Treatment. *J. Cosmet. Laser Ther.* **2016**, *18*, 301–310. [CrossRef]
105. Han, F.; Luo, D.; Qu, W.; Chen, D.; Hong, Y.; He, L. Nanoliposomes Codelivering Bioactive Peptides Produce Enhanced Anti-Aging Effect in Human Skin. *J. Drug Deliv. Sci. Technol.* **2020**, *57*, 101693. [CrossRef]
106. Mo, Q.; You, S.; Fu, H.; Wang, D.; Zhang, J.; Wei, X.; Wu, Z.; Wei, H. Purification and Identification of Antioxidant Peptides from Rice Fermentation of Lactobacillus Plantarum and Their Protective Effects on UVA−Induced Oxidative Stress in Skin. *Antioxidants* **2022**, *11*, 2333. [CrossRef] [PubMed]
107. De Luca, C.; Mikhal'chik, E.V.; Suprun, M.V.; Papacharalambous, M.; Truhanov, A.I.; Korkina, L.G. Skin Antiageing and Systemic Redox Effects of Supplementation with Marine Collagen Peptides and Plant-Derived Antioxidants: A Single-Blind Case-Control Clinical Study. *Oxidative Med. Cell. Longev.* **2016**, *2016*, 4389410. [CrossRef] [PubMed]
108. Amakye, K.W.; Yang, L.; Yao, M.; Yuan, E.; Ren, R.; Ren, J. Skipjack (*Katsuwonus pelamis*) Elastin Hydrolysate-derived Peptides Attenuate UVA Irradiation-induced Cell Damage in Human HaCaT Keratinocytes. *Food Front.* **2021**, *2*, 184–194. [CrossRef]
109. Treadwell, T.; Kleinman, K.H.; Crockford, D.; Hardy, A.M.; Guarnera, T.G.; Kennedy, R.S.; Sosne, G. The Regenerative Peptide Thymosin B4 Accelerates the Rate of Dermal Healing in Preclinical Animal Models and in Patients. *Ann. N. Y. Acad. Sci.* **2012**, *1270*, 37–44. [CrossRef]
110. Fadilah, M.N.I.; Shahabudin, A.N.; Mohd Razif, R.A.; Sanyal, A.; Ghosh, A.; Olatunji, O.J.; Singh, S.; Chuan, T.K. Discovery of Bioactive Peptides as Therapeutic Agents for Skin Wound Repair. *J. Tissue Eng.* **2024**, *15*, 20417314241280359. [CrossRef]
111. Bock, E.J.; Gavenonis, J.; Kritzer, A.J. Getting in Shape: Controlling Peptide Bioactivity and Bioavailability Using Conformational Constraints. *ACS Chem. Biol.* **2012**, *8*, 488–499. [CrossRef]

112. Karami, Z.; Akbari-Adergani, B. Bioactive Food Derived Peptides: A Review on Correlation between Structure of Bioactive Peptides and Their Functional Properties. *J. Food Sci. Technol.* **2019**, *56*, 535–547. [CrossRef]
113. Akcan, M.; Craik, D.J. Discovery and Applications of Cyclotides. In *Peptide Engineering: Methods and Protocols*; Jensen, K.J., Ed.; Royal Society of Chemistry: Cambridge, UK, 2015; pp. 244–271.
114. Acar, H.; Ting, M.J.; Srivastava, S.; LaBelle, L.J.; Tirrell, V.M. Molecular Engineering Solutions for Therapeutic Peptide Delivery. *Chem. Soc. Rev.* **2017**, *46*, 6553–6569. [CrossRef]
115. Konaklieva, I.; Plotkin, B.J.; Roviello, G.N. Nature-Inspired Pathogen and Cancer Protein Covalent Inhibitors: From Plants and Other Natural Sources to Drug Development. *Pathogens* **2025**, *14*, 1153. [CrossRef] [PubMed]
116. Hariri, R.; Saeedi, M.; Akbarzadeh, T. Naturally Occurring and Synthetic Peptides: Efficient Tyrosinase Inhibitors. *J. Pept. Sci.* **2021**, *27*, e3329. [CrossRef]
117. Deber, M.C.; Stone, A.T. Relative Role(s) of Leucine versus Isoleucine in the Folding of Membrane Proteins. *Pept. Sci.* **2018**, *111*, e24075. [CrossRef]
118. Fa, S.; Zhao, Y. Peptide-Binding Nanoparticle Materials with Tailored Recognition Sites for Basic Peptides. *Chem. Mater.* **2017**, *29*, 9284–9291. [CrossRef] [PubMed]
119. Matsui, R.; Honda, R.; Kanome, M.; Hagiwara, A.; Matsuda, Y.; Togitani, T.; Ikemoto, N.; Terashima, M. Designing Antioxidant Peptides Based on the Antioxidant Properties of the Amino Acid Side-Chains. *Food Chem.* **2018**, *245*, 750–755. [CrossRef]
120. Qi, Y.; Chilkoti, A. Protein–Polymer Conjugation—Moving beyond PEGylation. *Curr. Opin. Chem. Biol.* **2015**, *28*, 181–193. [CrossRef] [PubMed]
121. Shi, C.; He, Y.; Feng, X.; Fu, D. ε-Polylysine and next-Generation Dendrigraft Poly-L-Lysine: Chemistry, Activity, and Applications in Biopharmaceuticals. *J. Biomater. Sci. Polym. Ed.* **2015**, *26*, 1343–1356. [CrossRef]
122. Marzano, M.; Falanga, A.P.; Marasco, D.; Borbone, N.; D'Errico, S.; Piccialli, G.; Roviello, G.N.; Oliviero, G. Evaluation of an Analogue of the Marine ε-PLL Peptide as a Ligand of G-Quadruplex DNA Structures. *Mar. Drugs* **2020**, *18*, 49. [CrossRef]
123. Cueny, R.R.; McMillan, S.D.; Keck, J.L. G-Quadruplexes in Bacteria: Insights into the Regulatory Roles and Interacting Proteins of Non-Canonical Nucleic Acid Structures. *Crit. Rev. Biochem. Mol. Biol.* **2022**, *57*, 539–561. [CrossRef]
124. Awadasseid, A.; Ma, X.; Wu, Y.; Zhang, W. G-Quadruplex Stabilization via Small-Molecules as a Potential Anti-Cancer Strategy. *Biomed. Pharmacother.* **2021**, *139*, 111550. [CrossRef]
125. Praseatsook, K.; Vachiraarunwong, A.; Taya, S.; Setthaya, P.; Sato, K.; Jiravanichanun, N. Anticancer and Antioxidant Effects of Bioactive Peptides from Black Soldier Fly Larvae (*Hermetia illucens*). *Nutrients* **2025**, *17*, 645. [CrossRef] [PubMed]
126. Akan, E.; Tok, K.; Kocazorbaz, K.E.; Zihnioglu, F.; Yerlikaya, O. Comparative Biological Evaluation and Identification of Multifunctional Endogenous and Exogenous Bioactive Peptides in Different Matured Izmir Tulum Cheeses. *Int. Dairy J.* **2024**, *161*, 106141. [CrossRef]
127. Correas, H.N.; Martínez, R.A.; Abellán, A.; Pérez-Sánchez, H.; Tejada, L. Curing Strategies and Bioactive Peptide Generation in HAM: In Vitro and in Silico Evaluation. *Food Chem.* **2025**, *484*, 144360. [CrossRef] [PubMed]
128. Fadlillah, N.H.; Nuraida, L.; Sitanggang, B.A.; Palupi, S.N. Antioxidant Peptides Produced by *Pediococcus acidilactici* YKP4 and *Lacticaseibacillus rhamnosus* BD2 in Fermented Soymilk Made from Germinated Soybeans. *Int. J. Food Sci. Technol.* **2025**, *60*, vvae002. [CrossRef]
129. Borges, T.; Coelho, P.; Prudêncio, C.; Gomes, A.; Gomes, P.; Fernandes, R. Bioactive Peptides from Milk Proteins with Antioxidant, Anti-Inflammatory, and Antihypertensive Activities. *Foods* **2025**, *14*, 535. [CrossRef]
130. Guadalupi, S.L.; Bianco, M.; Cataldi, R.T.; Ravnsborg, T.; Jensen, N.O.; Scardino, R.; Quintieri, L.; Larocca, M. Ultrasound-Assisted Protein Extraction for Deep Proteome Analysis of Spirulina and Chlorella Microalgae. *LWT* **2025**, *222*, 117647. [CrossRef]
131. Luo, Q.; Gao, Z.; Bai, L.; Ye, H.; Ye, H.; Wang, X.; Zhang, Y.; Li, J. Bioactive Peptide-Based Composite Hydrogel for Myocardial Infarction Treatment: ROS Scavenging and Angiogenesis Regulation. *Acta Biomater.* **2025**, *197*, 167–183. [CrossRef]
132. Muangrod, P.; Charoenchokpanich, W.; Roytrakul, S.; Rungsardthong, V.; Charoenlappanit, S.; Thumthanaruk, B.; Janyapanich, P.; Jampathong, S. Bioactivity Assessment of Peptides Derived from Salted Jellyfish (*Rhopilema hispidum*) Byproducts. *PLoS ONE* **2025**, *20*, e0318781. [CrossRef]
133. Kashung, P.; Karuthapandian, D. Milk-Derived Bioactive Peptides. *Food Prod. Process. Nutr.* **2025**, *7*, 6. [CrossRef]
134. Liu, Y.; Berrada, H.; Castagnini, M.J.; Barba, J.F. Supercritical Fluid Extraction Prior Pulsed Electric Fields to Improve High-Added-Value Compounds Recovery from Salmon Side Streams: Evaluation of Protein, Bioactive Peptides and Minerals. *Food Chem.* **2024**, *467*, 142283. [CrossRef] [PubMed]
135. Cui, W.; Zheng, X.; Chu, C.; Gui, X.; Cai, S.; Ma, H.; Jia, J.; He, L. Bioactive Peptides from Rice Wine Subjected to a Simulation Digestion: Inhibition of A-Glucosidase and Enhancement of Insulin Sensitivity. *J. Food Biochem.* **2025**, *2025*, 1451387. [CrossRef]
136. Yao, L.; Huang, Q.; Wang, H.; Feng, T.; Yu, C.; Song, S.; Yao, J.; Wang, C. Unlocking Novel Biopeptides Hidden in Camellia Seed Cake Fermented by Bacillus Subtilis through in Silico and Cellular Model Approaches. *Food Chem.* **2025**, *476*, 143342. [CrossRef]
137. Sun, X.; He, Z.; Yang, L.; Li, H. Effect of Cooking Treatment on Protein Digestibility, Peptide Profile and Potential Bioactive Peptides of Beef Tripe during in Vitro Gastrointestinal Digestion. *Food Chem.* **2024**, *470*, 142720. [CrossRef] [PubMed]

138. Sangsawad, P.; Chumee, S.; Laosam, P.; Roytrakul, S.; Katemala, S.; Jaroennonthasit, C.; Jirapakkul, W. Pilot-Scale Production of Sericin-Derived Oligopeptides (SDOs) from Yellow Silk Cocoons: Peptide Characterization and Specifications. *Foods* **2025**, *14*, 500. [CrossRef]
139. Paterson, S.; Alonso-Pintre, L.; Morato-López, E.; de la Fuente, S.G.; Gómez-Cortés, P.; de la Fuente, M.A.; Juárez, M.; Fontecha, J. Microalga Nannochloropsis Gaditana as a Sustainable Source of Bioactive Peptides: A Proteomic and In Silico Approach. *Foods* **2025**, *14*, 252. [CrossRef]
140. Anekthanakul, K.; Senachak, J.; Hongsthong, A.; Charoonratana, T.; Ruengjitchatchawalya, M. Natural ACE Inhibitory Peptides Discovery from Spirulina (*Arthrospira platensis*) Strain C1. *Peptides* **2019**, *18*, 170107. [CrossRef]
141. Haque, E.; Chand, R. Antihypertensive and Antimicrobial Bioactive Peptides from Milk Proteins. *Eur. Food Res. Technol.* **2007**, *227*, 7–15. [CrossRef]
142. Cunha, F.M.; Coscueta, R.E.; Brassesco, E.M.; Almada, F.; Gonçalves, D.; Valente, L.M.P.; Pintado, M.; Teixeira, B. Bioprospecting Bioactive Peptides in *Halobatrachus didactylus* Body Mucus: From In Silico Insights to Essential In Vitro Validation. *Mar. Drugs* **2025**, *23*, 82. [CrossRef] [PubMed]
143. Zhang, W.; Abubaker, A.M.; Li, Z.; He, Y.; Shu, Q.; Mao, X. Bioactive Peptides with Antioxidant and ACE Inhibitory Properties in Goat Milk Protein Hydrolysates: Peptidomics and Molecular Docking Study. *Int. J. Biol. Macromol.* **2025**, *299*, 140286. [CrossRef] [PubMed]
144. Feng, Z.; Morton, D.J.; Maes, E.; Kumar, L.; Serventi, L. Proximate Composition, Peptide Characterization and Bioactive Properties of Faba Bean Blanching Water. *Food Res. Int.* **2024**, *200*, 115426. [CrossRef]
145. Zheng, X.; Ma, J.; Zhang, A.; Zheng, Y.; Song, X.; Shi, S.; Jiang, L.; Li, J. Bioactive Peptides from Millet Bran Glutelin-2: Identification, Virtual Screening, Inhibitory Mechanism towards Angiotensin-I-Converting Enzyme, Stability, Antihypertension, and Ferrous-Transmembrane Absorption. *Food Biosci.* **2024**, *63*, 105595. [CrossRef]
146. Wang, S.; Zhang, L.; Wang, H.; Wu, X.; Tu, Z. Novel Angiotensin-Converting Enzyme Inhibitory Peptides Derived from Tuna (*Thunnus maccoyii*): The Integration of Computer Tools with in Vitro Experiments. *Food Biosci.* **2024**, *63*, 105509. [CrossRef]
147. Wei, Y.; Wang, Z.; Guo, X.; Lei, Y.; Deng, X.; Huang, J. Integrated Network Pharmacology and Experimental Validation to Explore the Mechanisms of Coregonus Peled-Derived Myosin ACE-Inhibiting Peptides for the Treatment of Hypertension. *Int. J. Biol. Macromol.* **2024**, *284*, 138218. [CrossRef] [PubMed]
148. Chen, D.; Shen, X.; Chen, W.; Wu, D.; Zhang, Z.; Wang, S.; Chen, J.; Wang, J. A Screening Strategy for Bioactive Peptides from Enzymolysis Extracts of Lentinula Edodes Based on Molecular Docking and Molecular Dynamics Simulation. *J. Future Foods* **2024**, *5*, 388–397. [CrossRef]
149. Xun, X.; Yan, C.; Yuan, Z.; Zhang, Z.; Herman, A.R.; Li, B.; Wang, J.; Zhao, L. 60Co-γ-Ray-Irradiated Edible Silkworm (*Bombyx mori*) Pupae-Assisted Protease Digestion: A Strategy for Obtaining Low Molecular Weight Bioactive Peptides. *Sustain. Chem. Pharm.* **2025**, *44*, 101941. [CrossRef]
150. Zhao, J.; Guo, J.; Xu, X.; Song, X.; Kong, W.; Zhao, L. Physiological and Hypotensive Effects of Whey Protein-Derived Angiotensin Converting Enzyme Inhibitory Peptides in Spontaneously Hypertensive Rats. *Food Biosci.* **2025**, *68*, 106321. [CrossRef]
151. Cheng, D.; Huang, X.; Shao, B.; Zhang, C.; Li, X.; Chen, G.; Wang, L.; Sun, J. Preventive Efficacy of Sprouting Black Soybean Peptides on High-salt Diet-induced Hypertension in Mice. *J. Food Sci.* **2025**, *90*, e70014. [CrossRef]
152. Bao, X.; Zhang, Y.; Wang, L.; Dai, Z.; Zhu, Y.; Li, X.; Chen, J.; Liu, M. Machine Learning Discovery of Novel Antihypertensive Peptides from Highland Barley Protein Inhibiting Angiotensin I-Converting Enzyme (ACE). *Food Res. Int.* **2025**, *202*, 115689. [CrossRef] [PubMed]
153. Chen, S.; Huan, P.; Ma, T.; Zhong, Y.; Ning, D.; Li, H.; Wang, J.; Zhang, Y. Walnut Peptide Relieves Hypertension and Associated Kidney and Heart Injury by Regulating the Renin–Angiotensin–Aldosterone System and Intestinal Microbiota. *J. Sci. Food Agric.* **2024**, *105*, 1170–1184. [CrossRef] [PubMed]
154. Zhang, Y.; Zhang, Y.; Huang, D.; Chen, S.; Zhu, S. Purification, Characterization, and Bioactivity of Angiotensin-Converting Enzyme Inhibitory Peptides from Enzymatic Hydrolysate Cicada Chrysalis Protein. *Food Biosci.* **2025**, *68*, 106440. [CrossRef]
155. Yang, Y.; Wang, B.; Tian, Q.; Li, B. Purification and Characterization of Novel Collagen Peptides against Platelet Aggregation and Thrombosis from Salmo Salar. *ACS Omega* **2020**, *5*, 19995–20003. [CrossRef]
156. Yu, G.; Wang, F.; Zhang, B.; Fan, J. In Vitro Inhibition of Platelet Aggregation by Peptides Derived from Oat (*Avena sativa* L.), Highland Barley (*Hordeum vulgare* Linn. Var. Nudum Hook. f.), and Buckwheat (*Fagopyrum esculentum* Moench) Proteins. *Food Chem.* **2015**, *194*, 577–586. [CrossRef]
157. Yang, Y.; Song, H.; Wang, B.; Tian, Q.; Li, B. A Novel Di-peptide Met-Glu from Collagen Hydrolysates Inhibits Platelet Aggregation and Thrombus Formation via Regulation of Gq-mediated Signaling. *J. Food Biochem.* **2020**, *44*, e13352. [CrossRef]
158. Chen, M.; Ye, X.; Ming, X.; Chen, Y.; Wang, Y.; Peng, H.; Jiang, Y.; Lu, Y. A Novel Direct Factor Xa Inhibitory Peptide with Anti-Platelet Aggregation Activity from *Agkistrodon acutus* Venom Hydrolysates. *Sci. Rep.* **2015**, *5*, srep10846. [CrossRef]
159. Hao, X.; Tang, X.; Luo, L.; Wang, Y.; Lai, R.; Zhang, Y.; Yang, H. A Novel Ranacyclin-like Peptide with Anti-Platelet Activity Identified from Skin Secretions of the Frog *Amolops loloensis*. *Gene* **2015**, *576*, 171–175. [CrossRef]

160. Liu, H.; Yang, Y.; Liu, Y.; Cui, L.; Fu, L.; Mao, X.; Li, B.; Song, H. Various Bioactive Peptides in Collagen Hydrolysate from Salmo Salar Skin and the Combined Inhibitory Effects on Atherosclerosis in Vitro and in Vivo. *Food Res. Int.* **2022**, *157*, 111281. [CrossRef]
161. Indumathi, P.; Mehta, A. A Novel Anticoagulant Peptide from the Nori Hydrolysate. *J. Funct. Foods* **2015**, *20*, 606–617. [CrossRef]
162. Yang, Y.; Liu, H.; Cui, L.; Liu, Y.; Fu, L.; Mao, X.; Li, B.; Song, H. A Collagen-Derived Oligopeptide from Salmo Salar Collagen Hydrolysates Restrains Atherogenesis in ApoE−/− Mice via Targeting P2Y12 Receptor. *Mol. Nutr. Food Res.* **2022**, *66*, 2200166. [CrossRef]
163. Sansi, S.M.; Iram, D.; Zanab, S.; Vij, S.; Puniya, K.A.; Shandilya, U.K.; Kapila, R.; Kapila, S. Antimicrobial Bioactive Peptides from Goat Milk Proteins: In Silico Prediction and Analysis. *J. Food Biochem.* **2022**, *46*, e14311. [CrossRef]
164. De Fazio, R.; Di Francesco, A.; Di Ciccio, P.A.; Cunsolo, V.; Britti, D.; Muscolo, C.; Salimei, E. Detection of Bioactive Peptides' Signature in Podolica Cow's Milk. *Foods* **2025**, *14*, 877. [CrossRef] [PubMed]
165. Thuluz, M.; Paul, J.P.; Alberto, S.; Dolores, H.; Eliel, R.; Nohemí, G.; Rosalva, M. Antimicrobial Activity and Peptidomic Analysis of Halotolerant *Lactiplantibacillus plantarum* CH. *Probiotics Antimicrob. Proteins* **2025**, *17*, 142–155. Available online: https://link.springer.com/10.1007/s12602-025-10504-7 (accessed on 16 December 2025).
166. Gonzalez-de la Rosa, T.; Marquez-Paradas, E.; Leon, J.M.; Montserrat-de la Paz, S.; Rivero-Pino, F. Exploring *Tenebrio molitor* as a Source of Low-molecular-weight Antimicrobial Peptides Using a n in Silico Approach: Correlation of Molecular Features and Molecular Docking. *J. Sci. Food Agric.* **2024**, *105*, 1711–1736. [CrossRef] [PubMed]
167. Hu, Y.; Sun, H.; Zhang, M.; Mu, T. Production and Characterization of α-Glucosidase Inhibitory Peptides from Sweet Potato Protein by Ultrasound-Assisted Enzymatic Hydrolysis and in Vitro Gastrointestinal Digestion. *Eur. Food Res. Technol.* **2024**, *251*, 257–267. [CrossRef]
168. Aiello, G.; Cropotova, J.; Kvangarsnes, K.; D'Adduzio, L.; Fanzaga, M.; Li, S.; Rustad, T.; Lammi, C. Ultrasonicated Atlantic Herring Side Streams as Source of Multifunctional Bioactive and Bioavailable Peptides. *NPJ Sci. Food* **2025**, *9*, 25. [CrossRef]
169. Akan, E.; Yavaş, A.; Dikme, M. Bioactive Potentials of Paraprobiotic Kefir: Enhanced Protein Hydrolysis and Anticancer Efficacy. *Int. Dairy J.* **2024**, *163*, 106169. [CrossRef]
170. Basri, I.N.; Amin, M.A.; Ahmad, F. Identification and Characterization of Novel Bioactive Peptide From Red Seaweed (*Pyropia vietnamensis*) Proteins. *Qual. Assur. Saf. Crops Foods* **2025**, *17*, 143–162. [CrossRef]
171. Forero-Girón, A.C.; Aliaga, M.E.; López-Alarcón, C. Pyranine as Probe to Assess Antioxidant Activity of Free and Peptide Tryptophan and Tyrosine Residues Towards Peroxyl Radicals. *Appl. Sci.* **2025**, *15*, 4241. [CrossRef]
172. Khoo, K.K.; Norton, R.S. Role of Disulfide Bonds in Peptide and Protein Conformation. *Amino Acids Pept. Proteins Org. Chem.* **2011**, *5*, 395–417. [CrossRef]
173. Deslouches, B.; Di, Y.P.; Deslouches, B.; Peter Di, Y. Antimicrobial Peptides with Selective Antitumor Mechanisms: Prospect for Anticancer Applications. *Oncotarget* **2017**, *8*, 46635–46651. [CrossRef] [PubMed]
174. Schweizer, F. Cationic Amphiphilic Peptides with Cancer-Selective Toxicity. *Eur. J. Pharmacol.* **2009**, *625*, 190–194. [CrossRef]
175. Jobin, M.L.; Alves, I.D. On the Importance of Electrostatic Interactions between Cell Penetrating Peptides and Membranes: A Pathway toward Tumor Cell Selectivity? *Biochimie* **2014**, *107*, 154–159. [CrossRef]
176. Bui Thi Phuong, H.; Doan Ngan, H.; Le Huy, B.; Vu Dinh, H.; Luong Xuan, H. The Amphipathic Design in Helical Antimicrobial Peptides. *ChemMedChem* **2024**, *19*, e202300480. [CrossRef]
177. Bhardwaj, G.; Mulligan, V.K.; Bahl, C.D.; Gilmore, J.M.; Harvey, P.J.; Cheneval, O.; Buchko, G.W.; Pulavarti, S.V.S.R.K.; Kaas, Q.; Eletsky, A.; et al. Accurate de Novo Design of Hyperstable Constrained Peptides. *Nature* **2016**, *538*, 329–335. [CrossRef]
178. O'Neil, K.T.; Hoess, R.H.; Jackson, S.A.; Ramachandran, N.S.; Mousa, S.A.; DeGrado, W.F. Identification of Novel Peptide Antagonists for GPIIb/IIIa from a Conformationally Constrained Phage Peptide Library. *Proteins Struct. Funct. Bioinform.* **1992**, *14*, 509–515. [CrossRef]
179. Mirau, A.P.; Naik, R.R.; Gehring, P. Structure of Peptides on Metal Oxide Surfaces Probed by NMR. *J. Am. Chem. Soc.* **2011**, *133*, 18243–18248. [CrossRef] [PubMed]
180. Ellett, J.L.; Johanssen, A.V. Analysis of Prion Protein Conformation Using Circular Dichroism Spectroscopy. *Methods Mol. Biol.* **2017**, *1658*, 103–115.
181. Pignataro, M.F.; Herrera, M.G.; Dodero, V.I. Evaluation of Peptide/Protein Self-Assembly and Aggregation by Spectroscopic Methods. *Molecules* **2020**, *25*, 4854. [CrossRef]
182. Oyama, T.; Suzuki, S.; Akao, K.I. Circular Dichroism Spectroscopy in Protein Engineering and Pharmaceutical Development: Applications in Structural Characterization and Quality Assessment. *Protein Expr. Purif.* **2026**, *237*, 106826. [CrossRef]
183. Guzmán, F.; Aróstica, M.; Román, T.; Beltrán, D.; Gauna, A.; Albericio, F.; Cárdenas, C. Peptides, Solid-Phase Synthesis and Characterization: Tailor-Made Methodologies. *Electron. J. Biotechnol.* **2023**, *64*, 27–33. [CrossRef]
184. Flores, Y.; Zapata-Torres, G.; Nuñez, A.; Matthies, D.J.; Alemán, L.; Hernández-Fuentes, C.; Sánchez, G.; Araya, E.; Guzman, F.; Pedrozo, Z.; et al. Angiotensin-(1-9) Retro-Enantiomer Peptide with Cardioprotective Activity. *Circulation* **2024**, *150*, 816–820. [CrossRef] [PubMed]

185. Purohit, K.; Reddy, N.; Sunna, A. Exploring the Potential of Bioactive Peptides: From Natural Sources to Therapeutics. *Int. J. Mol. Sci.* **2024**, *25*, 1391. [CrossRef]
186. Aiello, G.; Lammi, C.; Boschin, G.; Zanoni, C.; Arnoldi, A. Exploration of Potentially Bioactive Peptides Generated from the Enzymatic Hydrolysis of Hempseed Proteins. *J. Agric. Food Chem.* **2017**, *65*, 10174–10184. [CrossRef] [PubMed]
187. Yadikar, H.; Johnson, C.; Pafundi, N.; Mouhawasse, E.; Nguyen, L.; Al-Hroub, H.; Shurter, K.; Wang, K.K. Novel Peptidomic Approach for Identification of Low and High Molecular Weight Tauopathy Peptides Following Calpain Digestion, and Primary Culture Neurotoxic Challenges. *Int. J. Mol. Sci.* **2019**, *20*, 5213. [CrossRef]
188. Boysen, I.R.; Hearn, M.T.W. High-Performance Liquid Chromatography of Peptides and Proteins. In *Amino Acids, Peptides and Proteins in Organic Chemistry: Analysis and Structural Characteristics of Amino Acids, Peptides and Proteins*; Hughes, A.B., Ed.; Wiley-VCH: Weinheim, Germany, 2011; Volume 5, pp. 167–210.
189. Aguilar, M. Reversed-Phase High-Performance Liquid Chromatography. In *HPLC of Peptides and Proteins: Methods and Protocols*; Springer: New York, NY, USA, 2004.
190. Kamagata, K.; Chiba, R.; Kawahata, I.; Iwaki, N.; Kanbayashi, S.; Maeda, K.; Takahashi, H.; Hirano, A.; Fukunaga, K.; Ikeda, K.; et al. Characterization of Design Grammar of Peptides for Regulating Liquid Droplets and Aggregates of FUS. *Sci. Rep.* **2021**, *11*, 6643. [CrossRef]
191. Kirkwood, J.K.; Ahmad, Y.; Larance, M.; Lamond, I.A. Characterization of Native Protein Complexes and Protein Isoform Variation Using Size-Fractionation-Based Quantitative Proteomics. *Mol. Cell. Proteom.* **2013**, *12*, 3851–3873. [CrossRef]
192. Xu, B.; Wang, Y.; Zha, L.; Chen, M.; Yu, P.; Zhang, H.; Lin, J.; Dong, C. Novel Antioxidant Peptides from *Volvariella volvacea* Hydrolysed Proteins: Purification, Characterisation and Protective Effects on H_2O_2-Induced Human Skin Fibroblasts. *Food Biosci.* **2025**, *64*, 105825. [CrossRef]
193. D'Orlyé, F.; Trapiella-Alfonso, L.; Lescot, C.; Pinvidic, M.; Doan, B.T.; Varenne, A. Synthesis, Characterization and Evaluation of Peptide Nanostructures for Biomedical Applications. *Molecules* **2021**, *26*, 4587. [CrossRef]
194. Dierig, A.; Frei, R.; Egli, A. The Fast Route to Microbe Identification. *Pediatr. Infect. Dis. J.* **2014**, *34*, 97–99. [CrossRef] [PubMed]
195. Skripnikov, A. Bioassays for Identifying and Characterizing Plant Regulatory Peptides. *Biomolecules* **2023**, *13*, 1795. [CrossRef]
196. van den Broek, I.; Sparidans, W.R.; Schellens, H.J.; Beijnen, H.J. Quantitative Bioanalysis of Peptides by Liquid Chromatography Coupled to (Tandem) Mass Spectrometry. *J. Chromatogr. B* **2008**, *872*, 1–22. [CrossRef]
197. Tzanavaras, D.; Tsiasioti, A.; Bollenbach, A.; Tsikas, D. GC-MS Studies on the Conversion and Derivatization of γ-Glutamyl Peptides to Pyroglutamate (5-Oxo-Proline) Methyl Ester Pentafluoropropione Amide Derivatives. *Molecules* **2022**, *27*, 6020. [CrossRef]
198. Guzmán, F.; Gauna, A.; Roman, T.; Luna, O.; Álvarez, C.; Pareja-Barrueto, C.; Mercado, L.; Albericio, F.; Cárdenas, C. Tea Bags for Fmoc Solid-Phase Peptide Synthesis: An Example of Circular Economy. *Molecules* **2021**, *26*, 5035. [CrossRef]
199. Guzmán, F.; Barberis, S.; Illanes, A. Peptide Synthesis: Chemical or Enzymatic. *Electron. J. Biotechnol.* **2023**, *10*, 279–314. [CrossRef]
200. Golla, K.; Stavropoulos, I.; Shields, C.D.; Moran, N. Peptides Derived from Cadherin Juxtamembrane Region Inhibit Platelet Function. *R. Soc. Open Sci.* **2018**, *5*, 172347. [CrossRef] [PubMed]
201. Minkiewicz, P.; Iwaniak, A.; Darewicz, M. BIOPEP-UWM Database of Bioactive Peptides: Current Opportunities. *Int. J. Mol. Sci.* **2019**, *20*, 5978. [CrossRef]
202. Desiere, F. The PeptideAtlas Project. *Nucleic Acids Res.* **2005**, *34*, D655–D658. [CrossRef]
203. Iturralde, M.; Bracho, J.P.; Valdivia-Pérez, J.A.; Guzmán, F.; Malbrán, I.; Maté, S.M.; Fanani, M.L.; Cavalli, S.V. Antifungal Peptides SmAPα1–21 and SmAPγ27–44 Designed from Different Loops of DefSm2-D Have Distinct Modes of Action. *Antibiotics* **2025**, *14*, 430. [CrossRef]
204. Lata, S.; Sharma, B.; Raghava, G. Analysis and Prediction of Antibacterial Peptides. *BMC Bioinform.* **2007**, *8*, 263. [CrossRef]
205. Mooney, C.; Haslam, J.N.; Pollastri, G.; Shields, C.D. Towards the Improved Discovery and Design of Functional Peptides: Common Features of Diverse Classes Permit Generalized Prediction of Bioactivity. *PLoS ONE* **2012**, *7*, e45124. [CrossRef]
206. Trott, O.; Olson, J.A. AutoDock Vina: Improving the Speed and Accuracy of Docking with a New Scoring Function, Efficient Optimization, and Multithreading. *J. Comput. Chem.* **2009**, *31*, 455–461. [CrossRef]
207. Dominguez, C.; Boelens, R.; Bonvin, A.M.J.J. HADDOCK: A Protein−Protein Docking Approach Based on Biochemical or Biophysical Information. *J. Am. Chem. Soc.* **2003**, *236*, 1731–1737. [CrossRef]
208. Abraham, J.M.; Murtola, T.; Schulz, R.; Páll, S.; Smith, C.J.; Hess, B.; Lindahl, E. GROMACS: High Performance Molecular Simulations through Multi-Level Parallelism from Laptops to Supercomputers. *SoftwareX* **2015**, *1*, 19–25. [CrossRef]
209. Liu, Y.; Kuhlman, B. RosettaDesign Server for Protein Design. *Nucleic Acids Res.* **2006**, *34*, W235–W238. [CrossRef] [PubMed]
210. Daina, A.; Michielin, O.; Zoete, V. SwissADME: A Free Web Tool to Evaluate Pharmacokinetics, Drug-Likeness and Medicinal Chemistry Friendliness of Small Molecules. *Sci. Rep.* **2017**, *7*, 42717. [CrossRef] [PubMed]
211. Pei, J.; Gao, X.; Pan, D.; Hua, Y.; He, J.; Zhou, L.; Wang, Y.; Cao, J. Advances in the Stability Challenges of Bioactive Peptides and Improvement Strategies. *Curr. Res. Food Sci.* **2022**, *5*, 2162–2170. [CrossRef]

212. Alzaydi, A.; Barbhuiya, I.R.; Routray, W.; Elsayed, A.; Singh, A. Bioactive Peptides: Synthesis, Applications, and Associated Challenges. *Food Bioeng.* **2023**, *2*, 273–290. [CrossRef]
213. Pavlicevic, M.; Maestri, E.; Marmiroli, M. Marine Bioactive Peptides—An Overview of Generation, Structure and Application with a Focus on Food Sources. *Mar. Drugs* **2020**, *18*, 424. [CrossRef]
214. Okoye, O.C.; Ezeorba, P.T.; Okeke, S.E.; Okagu, U.I. Recent Findings on the Isolation, Identification and Quantification of Bioactive Peptides. *Appl. Food Res.* **2022**, *2*, 100065. [CrossRef]
215. Alavi, F.; Ciftci, N.O. Purification and Fractionation of Bioactive Peptides through Membrane Filtration: A Critical and Application Review. *Trends Food Sci. Technol.* **2022**, *131*, 118–128. [CrossRef]
216. Gaglione, R.; Pane, K.; Dell'Olmo, E.; Cafaro, V.; Pizzo, E.; Varcamonti, M.; Notomista, F.; Arciello, A. Cost-Effective Production of Recombinant Peptides in Escherichia Coli. *New Biotechnol.* **2019**, *51*, 39–48. [CrossRef] [PubMed]
217. Lou, M.; Ji, S.; Wu, R.; Zhu, Y.; Wu, J.; Zhang, J. Microbial Production Systems and Optimization Strategies of Antimicrobial Peptides: A Review. *World J. Microbiol. Biotechnol.* **2025**, *41*, 66. [CrossRef]
218. Decker, J.S.; Yano, U.; Melgar, R.M.; Lynch, M.D. Precipitation and Extraction Methods for Protein Purification: A Meta-Analysis of Purification Performance and Cost-Effectiveness. *bioRxiv* **2023**. bioRxiv:2023.12.14.571684. [CrossRef]
219. Yang, B.; Dai, Z.; Ding, S.Y.; Wyman, C.E. Enzymatic Hydrolysis of Cellulosic Biomass. *Biofuels* **2011**, *2*, 421–449. [CrossRef]
220. Mohammad, S.S.; da Silva Ferreira, M.V.; Jacintho Barbosa, M.I.; Barbosa, J.L., Jr. Characteristics of Enzymatic Hydrolysis of Protein from Different Food and Potential Separation Techniques. *Curr. Nutr. Food Sci.* **2022**, *19*, 590–601. [CrossRef]
221. Sepahi, M.; Kaghazian, H.; Hadadian, S.; Norouzian, D. Investigation of Purification Process Stresses on Erythropoietin Peptide Mapping Profile. *Adv. Biomed. Res.* **2015**, *4*, 114. [CrossRef]
222. Strasser, L.; Farrell, A.; Ho, J.T.C.; Scheffler, K.; Cook, K.; Pankert, P.; Mowlds, P.; Viner, R.; Karger, B.L.; Bones, J. Proteomic Profiling of IgG1 Producing CHO Cells Using LC/LC-SPS-MS3: The Effects of Bioprocessing Conditions on Productivity and Product Quality. *Front. Bioeng. Biotechnol.* **2021**, *9*, 569045. [CrossRef]
223. Tasdemiroglu, Y.; Gourdie, G.R.; He, J. In Vivo Degradation Forms, Anti-Degradation Strategies, and Clinical Applications of Therapeutic Peptides in Non-Infectious Chronic Diseases. *Eur. J. Pharmacol.* **2022**, *932*, 175192. [CrossRef]
224. Vuong, T.T.; Dupré, A.R.; He, Z.; Minkiewicz, P.; Darewicz, M.; Zhang, H.; Mao, X.; Liu, Y. Cottonseed Vicilin Proteins: Potential Allergen Risk and Source of Bioactive Peptides. *ACS Food Sci. Technol.* **2025**, *5*, 502–511. [CrossRef]
225. Al Musaimi, O.; Lombardi, L.; Williams, D.R.; Albericio, F. Strategies for Improving Peptide Stability and Delivery. *Pharmaceuticals* **2022**, *15*, 1283. [CrossRef]
226. Ashaolu, J.T.; Le, T.; Suttikhana, I. Stability and Bioactivity of Peptides in Food Matrices Based on Processing Conditions. *Food Res. Int.* **2023**, *168*, 112786. [CrossRef] [PubMed]
227. Parrasia, S.; Szabò, I.; Zoratti, M.; Biasutto, L. Peptides as Pharmacological Carriers to the Brain: Promises, Shortcomings and Challenges. *Mol. Pharm.* **2022**, *19*, 3700–3729. [CrossRef]
228. Zhang, Y.; Zhang, H.; Ghosh, D.; Williams, R.O. Just How Prevalent Are Peptide Therapeutic Products? A Critical Review. *Int. J. Pharm.* **2020**, *587*, 119491. [CrossRef]
229. D'Annessa, I.; Di Leva, F.S.; La Teana, A.; Novellino, E.; Limongelli, V.; Di Marino, D. Bioinformatics and Biosimulations as Toolbox for Peptides and Peptidomimetics Design: Where Are We? *Front. Mol. Biosci.* **2020**, *7*, 490836. [CrossRef]
230. Tapeinou, A.; Matsoukas, M.; Simal, C.; Tselios, T. Review Cyclic Peptides on a Merry-go-round; towards Drug Design. *Biopolymers* **2015**, *104*, 453–461. [CrossRef]
231. Lu, J.; Xu, H.; Xia, J.; Ma, J.; Xu, J.; Li, Y.; Wang, Y.; Liu, Y. D- and Unnatural Amino Acid Substituted Antimicrobial Peptides With Improved Proteolytic Resistance and Their Proteolytic Degradation Characteristics. *Front. Microbiol.* **2020**, *11*, 563030. [CrossRef]
232. Reichert, C.; Borchard, G. Noncovalent PEGylation, An Innovative Subchapter in the Field of Protein Modification. *J. Pharm. Sci.* **2016**, *105*, 386–390. [CrossRef]
233. Veronese, F.M.; Mero, A. The Impact of PEGylation on Biological Therapies. *BioDrugs* **2012**, *22*, 315–329. [CrossRef]
234. Werner, H.M.; Cabalteja, C.C.; Horne, W.S. Peptide Backbone Composition and Protease Susceptibility: Impact of Modification Type, Position, and Tandem Substitution. *ChemBioChem* **2016**, *17*, 712–718. [CrossRef]
235. He, M.; Fan Cheng, K.; Vu, A.; Torres, M.D.; Zanos, S.; Mughrabi, I.T.; de la Fuente-Nunez, C.; Al-Abed, Y.; Zucker, B. Atom-Level Backbone Engineering Preserves Peptide Function While Enhancing Stability. *bioRxiv* **2025**. bioRxiv:2025.10.06.678421. [CrossRef]
236. Gonçalves, J.; Caliceti, P. Optimizing Pharmacological and Immunological Properties of Therapeutic Proteins Through PEGylation: Investigating Key Parameters and Their Impact. *Drug Des. Devel Ther.* **2024**, *18*, 5041–5062. [CrossRef] [PubMed]
237. Bhuva, B.; Gawai, K.M.; Singh, B.P.; Sarkar, P.; Hassan, M.Z.; Kovaleva, E.G.; Hati, S. Production, Characterization and Bio-Functional Properties of Multi-Functional Peptides from Fermented Plant-Based Foods: A Review. *Food Biosci.* **2025**, *64*, 105877. [CrossRef]
238. Oliveira, S.A.; Pereira, O.J.; Ferreira, C.; Faustino, M.; Durão, J.; Mendes, R.; Pintado, M.; Carvalho, A.P. Spent Yeast Valorization for Food Applications: Effect of Different Extraction Methodologies. *Foods* **2022**, *11*, 4002. [CrossRef]

239. Bozovičar, K.; Bratkovič, T. Evolving a Peptide: Library Platforms and Diversification Strategies. *Int. J. Mol. Sci.* **2019**, *21*, 215. [CrossRef]
240. Meier-Menches, M.S.; Casini, A. Design Strategies and Medicinal Applications of Metal-Peptidic Bioconjugates. *Bioconjugate Chem.* **2020**, *31*, 1279–1288. [CrossRef] [PubMed]
241. Nissan, N.; Allen, M.C.; Sabatino, D.; Biggar, K.K. Future Perspective: Harnessing the Power of Artificial Intelligence in the Generation of New Peptide Drugs. *Biomolecules* **2024**, *14*, 1303. [CrossRef]
242. Goles, M.; Daza, A.; Cabas-Mora, G.; Sarmiento-Varón, L.; Sepúlveda-Yañez, J.; Echeverría, J.; Camps, I.; Morales-Navarro, S. Peptide-Based Drug Discovery through Artificial Intelligence: Towards an Autonomous Design of Therapeutic Peptides. *Brief. Bioinform.* **2024**, *25*, bbae275. [CrossRef]
243. Giguère, S.; Laviolette, F.; Marchand, M.; Tremblay, D.; Moineau, S.; Liang, X.; Biron, É.; Corbeil, J. Machine Learning Assisted Design of Highly Active Peptides for Drug Discovery. *PLoS Comput. Biol.* **2015**, *11*, e1004074. [CrossRef]
244. Sodhi, H.; Panitch, A. A Tunable Glycosaminoglycan–Peptide Nanoparticle Platform for the Protection of Therapeutic Peptides. *Pharmaceutics* **2024**, *16*, 173. [CrossRef] [PubMed]
245. Haddadzadegan, S.; Dorkoosh, F.; Bernkop-Schnürch, A. Oral Delivery of Therapeutic Peptides and Proteins: Technology Landscape of Lipid-Based Nanocarriers. *Adv. Drug Deliv. Rev.* **2022**, *182*, 114097. [CrossRef] [PubMed]
246. Ghosh, D.; Peng, X.; Leal, J.; Mohanty, R.P. Peptides as Drug Delivery Vehicles across Biological Barriers. *J. Pharm. Investig.* **2017**, *48*, 89–111. [CrossRef]
247. Chavapradit, C.; Visessanguan, W.; Panjanapongchai, S.; Anal, K.A. Techno-Functional Properties and Potential Applications of Peptides from Agro-Industrial Residues. *J. Renew. Mater.* **2025**, *13*, 553–582. [CrossRef]

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