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Review Article

Bioactive Peptides from Industrial Pseudocereal Amaranth and Their Pharmacological Prospects

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Abstract

Bioactive peptides encrypted within food proteins and released by enzymatic hydrolysis or gastrointestinal digestion represent potential functional ingredients. Amaranth is an underutilized pseudocereal with a balanced amino acid profile and a protein composition that may yield peptides with diverse biological activities. However, translation of amaranth-derived peptides remains limited by low or uncertain bioavailability, variable yields, extraction and purification challenges, incomplete sequence identification, insufficient genotype screening, limited understanding of structure-activity relationships, and scarce *in vivo* and clinical validation. This review summarizes current evidence on the production, characterization, and pharmacological potential of amaranth-derived bioactive peptides. Enzymatic hydrolysis, fermentation, gastrointestinal digestion, and protein engineering have generated peptide fractions or sequences with antioxidant, antimicrobial, angiotensin-converting enzyme-inhibitory, dipeptidyl peptidase IV-inhibitory, hypocholesterolemic, anti-inflammatory, antithrombotic, and anticancer activities, primarily in *in silico*, biochemical, cell-based, and animal models. Analytical workflows involving chromatographic separation, mass spectrometry, and bioinformatic prediction have improved peptide discovery, but results remain difficult to compare because processing conditions and activity assays are not standardized. Available evidence suggests that amaranth proteins are promising sources of multifunctional peptides; nevertheless, these findings do not yet establish clinical efficacy. Future work should optimize extraction and identification methods, clarify sequence-structure-activity relationships, evaluate stability and intestinal absorption, compare genotypes and non-seed tissues, and conduct well-designed *in vivo* studies, safety assessments, and clinical trials. Scalable processing and formulation strategies will also be required before amaranth-derived peptides can be developed as reliable functional food, nutraceutical, or pharmaceutical ingredients.

Introduction

Bioactive peptides (BPs) are short protein fragments, generally comprising 2-20 amino acid residues, that exert biological activities beyond their nutritional value.[1,2] They are usually encrypted within parent proteins and become active after proteolytic cleavage. Their amino acid sequence, conformation, and post-translational modifications influence stability, bioactivity, and therapeutic potential. Reported activities include hypocholesterolemic, antihypertensive, immunomodulatory, antioxidant, anti-inflammatory, antidiabetic, antimicrobial, hepatoprotective, and neuroactive effects.[1-3] Some BPs can survive gastrointestinal digestion and reach target tissues, although absorption and systemic bioavailability vary considerably. These properties have prompted interest in their use in functional foods and therapeutic development. Compared with conventional small-molecule drugs, peptide-based agents may offer high target specificity and potency, relatively low toxicity, and limited immunogenicity; however, low oral bioavailability, rapid degradation, and poor metabolic stability remain major limitations. Their pharmacological properties are strongly influenced by amino acid composition and sequence.

Accurate prediction of BP structure-function relationships remains challenging. Activity is influenced by amino acid

Keywords: Amaranth; Bioactive peptides; Protein hydrolysates; Antioxidant activity; Anti-inflammatory activity; Chronic diseases; Pharmacological potential.
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composition, chain length, terminal residues, charge distribution, and hydrophobic-hydrophilic balance. ACE-inhibitory activity is influenced by terminal-residue properties, including hydrophobicity, size, and charge.[4] Any proposed health benefit must also be considered alongside potential toxicity, allergenicity, and mutagenicity.[5] Advances in high-throughput sequencing, structural analysis, mass spectrometry, and bioinformatics have accelerated the detection and molecular characterization of candidate BPs. Plant-derived BPs have shown a range of potentially protective activities in preclinical studies. Their sequences are commonly determined by mass spectrometry, and secondary structures may be investigated using spectroscopic methods. Recent work has also improved understanding of sequence-activity relationships for antioxidant, antimicrobial, and antihypertensive peptides.

Amaranth (family Amaranthaceae) is a nutrient-dense pseudocereal with a balanced protein profile and other nutraceutical attributes, and it has been proposed as an alternate crop. Although *Amaranthus* species have been extensively studied for their protein, amino acid, iron, and dietary fiber contents, their potential as sources of BPs is only beginning to be defined. Interest in grain amaranth as an industrial crop has increased because of its nutritional value and peptide-rich protein fractions. However, most evidence for amaranth-derived BPs comes from *in vitro* or *in silico* studies, and clinical validation is limited. In addition, the contributions of specific sequences and physicochemical properties, including hydrophobicity, to biological potency remain incompletely understood. This review evaluates the nutritional characteristics, production methods, reported bioactivities, and industrial prospects of amaranth-derived BPs. It also identifies research priorities for translating preclinical findings into functional foods, nutraceuticals, natural preservatives, or pharmacological products.

BPs and their properties

Antioxidant peptides

Plant-derived antioxidant peptides may help limit tissue injury caused by excessive reactive oxygen species (ROS) and thereby reduce oxidative stress associated with chronic disease. Uncontrolled ROS production can damage cellular components and contribute to degenerative processes. Antioxidant peptides may act by chelating metal ions, donating protons or electrons,[6] inhibiting lipid peroxidation, and enhancing endogenous antioxidant defenses.[7] Amino acids commonly associated with antioxidant activity include methionine, phenylalanine, histidine, tryptophan, tyrosine, cysteine, lysine, proline, isoleucine, threonine, alanine, and leucine.[8] *In vivo*, ROS can activate signaling pathways such as Kelch-like ECH-associated protein 1-nuclear factor erythroid 2-related factor 2-antioxidant response element, mitogen-activated protein kinase, and nuclear factor-kappa B; plant protein-derived peptides may modulate these pathways.[9] For example, walnut-derived peptides TWLPLPR, KVPPLLY, and YVLLPSPK increased glutathione peroxidase activity and reduced ROS generation in a cell model.[10]

Novel antioxidant peptides have been reported from cereals and legumes, including mung bean, rice bran, cowpea, maize, chickpea, barley, oat, and rye proteins. Other antioxidant proteins and peptides have also been reported from potato,[11] cowpea,[12] amaranth flour and protein isolates,[13] hemp bran protein,[14] and spinach ribulose-1,5-bisphosphate carboxylase/oxygenase.[15] Hemp bran-derived peptides such as LLY, LLR, IR, and TY showed notable free-radical-scavenging activity.[14] Soy-derived peptides may also exhibit greater antioxidant activity than their intact parent proteins.[16] Thus, plant protein-derived peptides may act as natural antioxidants by reducing ROS-mediated and metal ion-mediated cellular damage.

Structure-activity analyses have associated peptide antioxidant activity with residue polarity, steric properties, hydrophobicity, and hydrogen-bonding capacity.[17] The residue adjacent to the C-terminus may be particularly important. Hydrophilic, hydrogen-bonding residues are generally favored at this position, whereas hydrophobic residues may be less favorable. A combination of polar C-terminal residues and hydrophobic N-terminal residues may therefore support antioxidant activity.

Antimicrobial peptides (AMPs)

AMPs are a diverse class of bioactive molecules produced by invertebrates, vertebrates, and plants. Their small size, cationic charge, and amphipathic structure facilitate interaction with and insertion into microbial membranes, which can contribute to antimicrobial activity.[18] AMPs may kill or inhibit bacteria and fungi through membrane disruption or interference with intracellular targets.

AMPs are encoded within natural protein precursors and are typically smaller than 10 kDa. They can also be generated *in vitro* by enzymatic hydrolysis.[19] AMPs are being investigated as alternatives or adjuncts to conventional agents against pathogenic microorganisms,[20] but clinical translation remains constrained by stability, toxicity, delivery, and manufacturing challenges.[21] More than 60 peptide therapeutics have reached the market, and many others are in clinical development, although only a subset are antimicrobial agents.[22]

AMPs are commonly grouped into linear alpha-helical peptides, disulfide-stabilized cyclic or open-chain peptides, and peptides enriched in residues such as proline, glycine, or histidine. Their amphipathic and cationic properties favor selective interactions with negatively charged microbial membranes.[23]

Antimicrobial peptides have been isolated or generated from numerous plant sources. Some plant defensins and antifungal proteins are active against pathogenic yeasts.[24] For example, 12 peptides isolated from soybean meal proteins inhibited Gram-positive and Gram-negative foodborne pathogens.[25] Chymotrypsin hydrolysis of chickpea proteins generated Leg1 and Leg2, which were active against 16 pathogenic, antibiotic-resistant, or spoilage-associated bacterial strains.[26] Similarly, HVLDTPLL, derived from hydrolyzed *Moringa oleifera* seed proteins, inhibited *Staphylococcus aureus*, possibly through interactions with DNA gyrase and dihydrofolate reductase.[27]

Antihypertensive peptides

Hypertension is associated with atherosclerosis, cardiovascular and renal disease, and ischemic stroke.[28] Many antihypertensive agents that act on the renin-angiotensin system lower blood pressure by inhibiting ACE.[29] ACE is a dipeptidyl carboxypeptidase that converts inactive angiotensin I into the vasoconstrictor angiotensin II. Angiotensin II increases blood

pressure through effects on the adrenal glands, vasculature, and sympathetic nervous system.

ACE also degrades bradykinin, an endogenous vasodilator.[30] Through the combined generation of angiotensin II and degradation of bradykinin, ACE has a central role in vascular tone and blood pressure regulation. Consequently, ACE inhibition is an established strategy for lowering blood pressure.

Structure-activity studies of peptide ACE inhibitors indicate that the C-terminal tripeptide sequence contributes substantially to enzyme binding. Gobbetti *et al.*[31] reported that ACE preferentially binds peptides or competitive inhibitors containing hydrophobic residues, particularly aromatic or branched-chain residues, within the three C-terminal positions.

Analysis of the ACE active site suggests that inhibition may involve coordination with the active-site zinc ion, hydrogen bonding with specific subsites, and binding of short proline-containing sequences. These interactions can increase affinity for the enzyme and reduce catalytic activity.[31]

Anticancer peptides

Anticancer peptides are generally 5-50 amino acids long and have shown antitumor activity in experimental models. Compared with some conventional cytotoxic agents, they may offer lower toxicity and greater selectivity for malignant cells. Peptide bioactivity is influenced by physicochemical properties.[32,33] Proposed mechanisms include preferential binding to anionic cancer-cell membranes, membrane disruption, induction of mitochondrial apoptosis, inhibition of angiogenesis, and stimulation of antitumor immune responses.[34] Disulfide-rich cyclotides can disrupt cell membranes.[35,36] Peptides such as lactoferricin B and tachyplesin can activate mitochondrial apoptotic pathways.[37,38] Human neutrophil peptide 1 has also shown immunomodulatory antitumor activity in experimental models.[39] Computational tools such as iDACP have been developed to classify anticancer peptide subtypes based on sequence and physicochemical features.[40] Lunasin is a 43-amino-acid peptide first characterized in soybean and has shown chemopreventive activity in preclinical studies.

Immunomodulatory peptides

Immunomodulatory peptides generally act by modifying host defense pathways rather than directly targeting pathogens. Dietary peptides may influence immune function through interactions with the gastrointestinal immune system.[41] Anti-inflammatory peptides are of interest because chronic inflammation contributes to cardiovascular disease and several cancers.[42] Immunomodulatory activity is influenced by amino acid composition, sequence, net charge, hydrophobicity, and molecular weight. Peptides with immunomodulatory effects often contain relatively high proportions of hydrophobic and positively charged aliphatic or aromatic residues.[43] Hydrophobic regions may facilitate interactions with nonpolar membrane components, whereas positive charge may enable chemokine-like activity, as observed for some defensins.[44]

In one study, 46 of 51 peptides derived from soybean protein hydrolysate showed immunomodulatory activity.[45] Interest in plant-derived anti-inflammatory peptides has increased because inflammation contributes to many chronic disorders. The peptides IIGGAL, FLPPVTSMQ, and PPYLSP were identified from zein hydrolysate after simulated gastrointestinal digestion.[46]

Hypocholesterolemic peptides

Several plant-derived peptides may reduce cholesterol or lipid concentrations. Proposed mechanisms include binding bile acids and cholesterol in the intestine, modulating hormonal signaling and cholesterol receptor activity,[47] and altering hepatic lipid metabolism.[48] Some peptides upregulate low-density lipoprotein receptor expression in hepatocytes.[49] Hydrophobic residues may interact with lipids and the hydrophobic regions of bile acids, whereas hydrophilic peptides may inhibit enzymes involved in lipid biosynthesis. Amaranth protein-derived peptides inhibited pancreatic lipase and cholesterol esterase *in vitro*, suggesting potential cholesterol-lowering activity.[50] Peptide fractions smaller than 3 kDa from chia protein hydrolysate also showed hypocholesterolemic activity.[51]

Sequence analysis of BPs

Considerable effort has been devoted to developing methods for identifying and characterizing BPs. Quantification remains difficult because peptide mixtures are complex and often contain low-abundance analytes.[52] Researchers continue to investigate new sources, extraction strategies, and potential health effects. Modern analytical workflows combine isolation, sequence identification, and functional analysis to improve the characterization of food-derived peptides.[53] A general workflow for BP discovery and evaluation is shown in Figure 1.

Sequence analysis combines experimental and *in silico* approaches. Peptides released by hydrolysis can be identified by mass spectrometry, whereas computational methods can predict bioactivity and structural features. Bioinformatic tools can also screen parent protein sequences for encrypted peptides with potential biological activity.

Bioactive proteins and peptides are commonly isolated by ultrafiltration, membrane separation, precipitation, electrophoresis, and chromatographic methods, including high-performance liquid chromatography (HPLC). Affinity-based methods can provide selective protein purification and peptide enrichment.[54] Mass spectrometry and tandem liquid chromatography-mass spectrometry (LC-MS/MS) can then be used for peptide identification.[55,56] Magnetic separation with fine particles may preserve the structural integrity of large protein complexes that could be disrupted by conventional chromatography.[57] In silico digestion can predict candidate peptide sequences and their potential activities, and bioinformatics can help prioritize the many products generated by protein hydrolysis.[58]

LC-MS/MS is widely used to profile BPs, often with enrichment or other sample-preparation workflows to improve sensitivity and selectivity.[59,60] Ultra-high-performance liquid chromatography coupled with electrospray ionization tandem mass spectrometry (UHPLC-ESI-MS/MS) offers high resolution, specificity, selectivity, low solvent consumption, and targeted ion monitoring through selective fragmentation.[61] Electrospray ionization (ESI) supports the analysis of polypeptide molecular mass, sequence, and structural features in complex samples.[62] ESI is a common interface for LC-MS and can provide high sensitivity at flow rates of approximately 50-300 μL/min.[63]

Reversed-phase HPLC (RP-HPLC) coupled with matrix-assisted laser desorption/ionization time-of-flight tandem mass

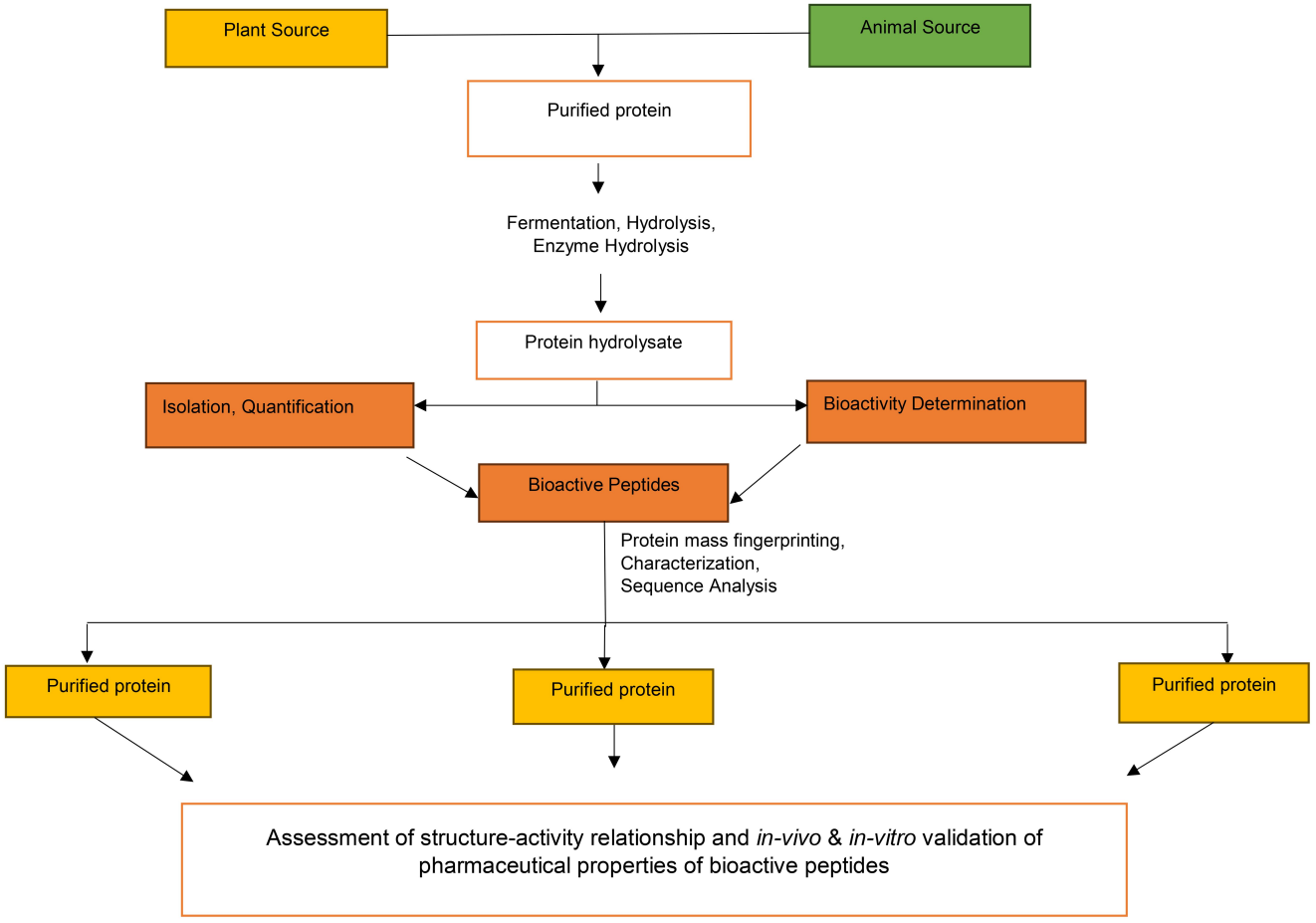

Fig. 1. Workflow for the isolation, characterization, and validation of bioactive peptides.

spectrometry (MALDI-TOF-MS/MS) has been used to investigate ACE-inhibitory and radical-scavenging peptides. However, RP-HPLC may be less effective for resolving some low-molecular-weight peptides.[64] MALDI-TOF commonly produces singly charged ions and is not directly coupled online to LC, which simplifies spectral deconvolution but limits continuous chromatographic analysis.

Seed amaranth as a potential source of BPs

Amaranth contains proteins and other bioactive constituents that may contribute to its potential health effects. Despite its nutritional and functional properties, it remains an underutilized pseudocereal. Grain protein content varies by species and method, typically ranging from approximately 13.1% to 21.5%.[65,66] Amaranth protein has a more balanced essential amino acid profile than many conventional cereals, with relatively high lysine and sulfur-containing amino acid contents.[67] Plant proteins are commonly classified by solubility as albumins, globulins, glutelins, and prolamins, or by structural and functional roles.[68] Unlike maize, rice, and soybean, in which much of the protein is located in the endosperm, approximately 65% of amaranth grain protein is localized in the embryo and 35% in the perisperm.[69] Reported fractions include albumins (approximately 46-65%), globulins (approximately 20%), and glutelins (up to approximately 42.5-46.5%), although values vary among species and extraction methods.[67,70] Amaranth globulins are commonly divided into 7S and 11S fractions, with 11S globulin, also called amarantin or proamaranthin, being the predominant globulin.[71]

Beyond their conventional nutritional value, amaranth proteins can release BPs containing 2-20 amino acids and generally having molecular masses below 6 kDa.[72] These peptides may act locally or systemically as signaling molecules, growth regulators, or neurotransmitter-like agents.[73] Bioactive sequences are inactive while encrypted within the parent protein and may be released by enzymatic hydrolysis, gastrointestinal digestion, or microbial fermentation.[74,75] Each process cleaves peptide bonds and generates fractions with different molecular masses, as shown in Figure 2.[76] Enzymatic hydrolysis is widely used because it is rapid, controllable, and generally produces few unwanted by-products. Proteases of microbial, plant, or animal origin can be selected to tailor peptide release, and biotechnological processes may further improve production efficiency.[77]

Among grain amaranths, *Amaranthus hypochondriacus L.* is

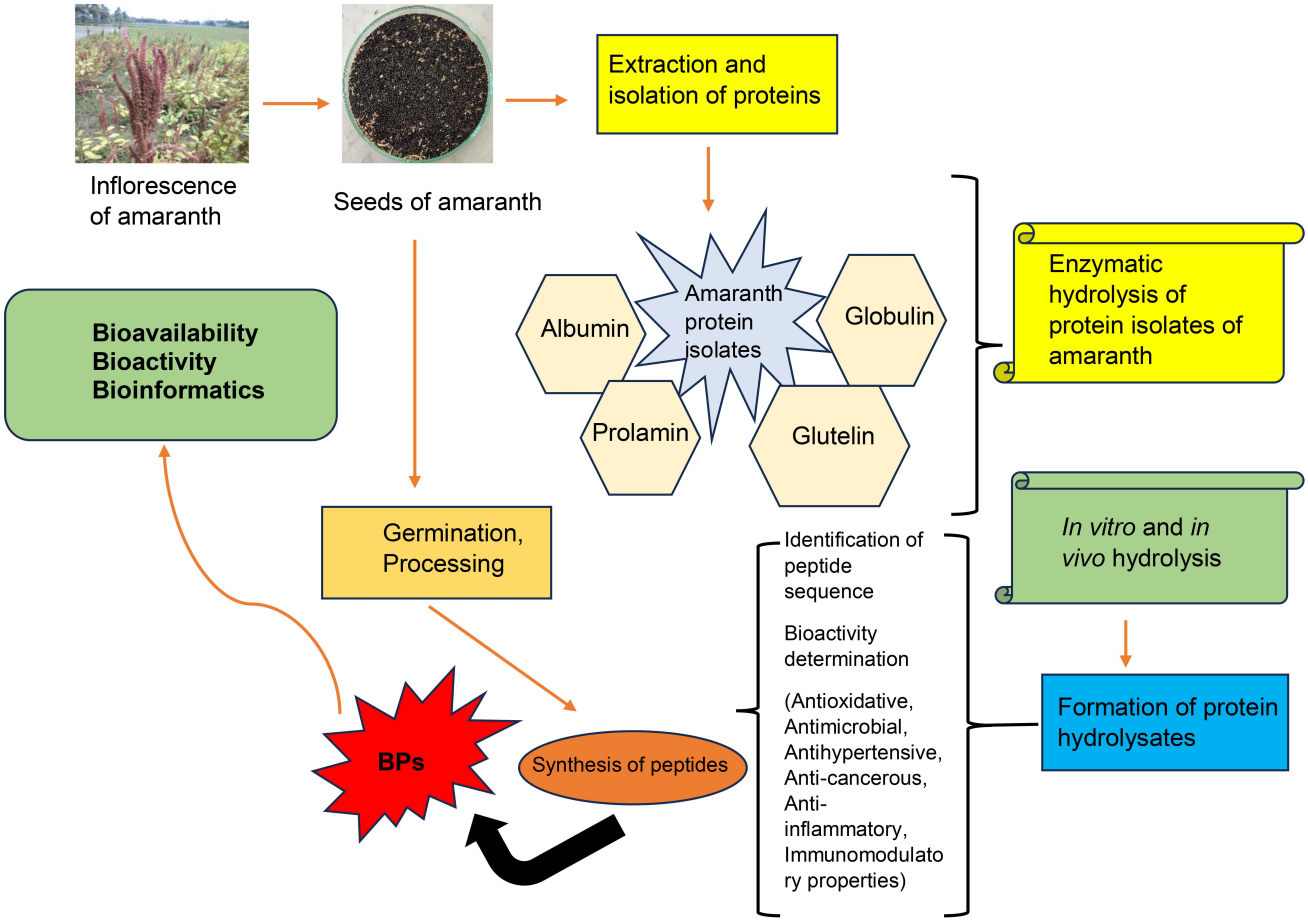

Fig. 2. Production and characterization of bioactive peptides from amaranth seeds. BPs, bioactive peptides.

the most extensively studied species as a source of BPs. Its seed glutelins and globulins contain multiple encrypted peptide sequences and have therefore attracted interest in functional food research.[3,68] These peptides can be released during gastrointestinal digestion or food processing. Preclinical studies have reported ACE-inhibitory, antioxidant, anti-inflammatory, antidiabetic, and anticancer activities, but the strength of evidence varies and clinical efficacy has not been established. Lunasin-like peptides isolated from *A. hypochondriacus* grains have also shown anticarcinogenic activity in cell-based studies.[78]

Enzymatic hydrolysis and production of BPs in amaranth

Tironi and Añón reported that several enzymatic hydrolysate fractions from *Amaranthus mantegazzianus* seeds scavenged free radicals, with the strongest activity in the fraction containing peptides smaller than 0.5 kDa.[79] The fraction smaller than 0.25 kDa showed lower radical-scavenging activity but inhibited linoleic acid oxidation. Peptide release and bioactivity depend on the enzyme, pH, temperature, reaction time, enzyme-to-substrate ratio, and protein pretreatment.[80]

Silva-Sánchez *et al.*[81] isolated a glutelin fraction from *Amaranthus hypochondriacus* seeds and hydrolyzed it with trypsin; the resulting digest induced apoptosis in HeLa cells. The authors also predicted that amaranth globulins could contain ACE-inhibitory peptides. Asao and Watanabe reported radical-scavenging and antihypertensive activities in amaranth-derived products.[82] Montoya-Rodríguez *et al.*[83] extruded *A. hypochondriacus* flour before protein fractionation and *in vitro* digestion. The hydrolysates showed antioxidant and ACE-inhibitory activity and reduced proinflammatory cytokine production in human THP-1 and murine RAW 264.7 macrophages.[83] In Amaranthus cruentus, in vitro digestion generated the tri- and tetrapeptides GGV, IVG, LVG, VGVI, and VGVL, which inhibited 3-hydroxy-3-methyl-glutaryl coenzyme A reductase in vitro. Plant-derived peptides may also influence hyperlipidemia through pathways that include cholesterol metabolism.[84,85]

Fermentation-mediated production of BPs in amaranth

Fermentation is another approach to BP production and uses microbial proteolytic systems.[86] Microorganisms secrete proteases that hydrolyze proteins into peptides and amino acids, which can support microbial nitrogen requirements during growth. Rizzello *et al.*[87] reported production of lunasin, a 43-amino-acid peptide with reported anticancer potential, during lactic acid fermentation of amaranth flour. The process used five peptidase-active lactic acid bacterial *strains—Lactobacillus plantarum* 3DM, *L. pentosus*

12H6, *L. brevis* AM7, *L. rossiae* CD76, and *L. curvatus* SAL33—incubated for 16 h at 30°C with an initial cell density of 8.0 log CFU/g.

Gastrointestinal digestion and production of BPs in amaranth

Several studies have evaluated ACE-inhibitory peptides released during simulated gastrointestinal digestion. Tiengo *et al.*[88] subjected heated and unheated *Amaranthus cruentus* protein concentrates and their Alcalase-derived hydrolysates to pepsin-trypsin digestion. Protein denaturation did not significantly alter susceptibility to Alcalase, and some released peptides remained resistant to gastrointestinal proteases. Vilcacundo *et al.*[89] applied the standardized method of Minekus *et al.*[90] to an *Amaranthus caudatus* protein concentrate and evaluated the multifunctional activity of peptides released at different digestion stages.

Genetically engineered BPs in amaranth

Amarantin, the principal seed storage protein of *Amaranthus hypochondriacus*, has been engineered to generate ACE-inhibitory peptides. Luna-Suárez *et al.*[91] modified the acidic subunit of amarantin in *Escherichia coli* by site-directed mutagenesis, inserting four tandem repeats of the ACE-inhibitory peptide VY into the third hypervariable region. The recombinant protein was termed bioamarantin. The same group subsequently inserted RIPP or IPP into the fourth hypervariable region.[92,93] All modified subunits showed greater ACE-inhibitory activity than the native protein.

Chemistry and bioactivity of peptides isolated from amaranth

Silva-Sánchez *et al.*[81] initiated systematic identification of amaranth BPs by examining 36 *Amaranthus* protein sequences available in the National Center for Biotechnology Information database. Comparison with peptides in the BIOPEP database predicted multiple potential activities.[94] Amaranth proteins were predicted to contain sequences with antihypertensive, antithrombotic, immunomodulatory, opioid, antioxidant, ligand-binding, protease-inhibitory, and other regulatory activities.[68] In the same study, the glutelin fraction of *Amaranthus hypochondriacus* was digested with trypsin, and the resulting sequences were identified by LC-MS/MS and searched against the MASCOT database. Comparison with BIOPEP predicted 508 peptides with diverse potential activities, most commonly hypoglycemic and antihypertensive effects.[81]

Amaranth grains are therefore promising sources of BPs that may be developed as functional food or nutraceutical ingredients, although most reported activities require further validation (Table 1).[81,84,89,95-103]

Amaranth-derived peptides have been investigated for possible roles in the prevention or management of chronic conditions, including cancer, obesity, type 2 diabetes, and cardiovascular disease.[104] Their high protein content and diverse peptide profiles may contribute to pharmacological effects relevant to these diseases (Fig. 3).

Industrial and pharmacological potential of amaranth bioactive peptide

ACE is central to blood pressure control through the renin-angiotensin system, and several amaranth-derived peptides inhibit ACE *in vitro*.[105] ACE generates the vasoconstrictor angiotensin II and degrades the vasodilator bradykinin; angiotensin II also promotes aldosterone-mediated sodium and fluid retention.[106] Accordingly, ACE inhibition is an established antihypertensive strategy. Protein fractions from amaranth grain have shown competitive or uncompetitive ACE inhibition. An amaranth protein hydrolysate retained ACE-inhibitory activity after incorporation into a pasta matrix.[107] Similar activity was reported after Alcalase hydrolysis and simulated gastrointestinal digestion of *Amaranthus cruentus* protein concentrates.[88] The lack of further activity enhancement after digestion suggests that some peptides resist gastrointestinal proteolysis. Tryptic digests of amaranth glutelin inhibited ACE and increased endothelial nitric oxide production *in vitro*.[108] Endothelial nitric oxide regulates vascular tone and inhibits platelet aggregation and smooth-muscle contraction. The 7S globulin fraction also showed ACE-inhibitory activity comparable to that of the 11S fraction.[109]

Amaranth and other pseudocereals have antioxidant capacities comparable to those of rice and soybean. Polyphenols are major contributors, but proteins and peptides can also scavenge radicals.[110] Peptides may neutralize free radicals by donating electrons and may chelate metal ions, thereby reducing oxidative damage to lipids, proteins, and DNA.[111] Hydrolysis of albumin, globulin, and glutelin fractions from *Amaranthus mantegazzianus* with Alcalase generated peptides that scavenged ABTS radicals and inhibited linoleic acid oxidation.[79] Alcalase hydrolysates of albumin-1 and globulin from *Amaranthus hypochondriacus* also scavenged DPPH and ABTS radicals. In ferric reducing antioxidant power assays, these fractions showed low copper-chelating activity, strong iron-chelating activity, and reducing capacity.[112]

Dipeptidyl peptidase IV (DPP-IV) is a serine protease expressed on endothelial and epithelial cells and contributes to glucose homeostasis by inactivating the incretin hormones glucagon-like peptide 1 and glucose-dependent insulinotropic polypeptide (GIP).[113] Incretins account for a substantial proportion of postprandial insulin secretion, but their circulating half-lives are short because of rapid DPP-IV-mediated cleavage. Inhibiting DPP-IV prolongs incretin activity, increases insulin secretion, and reduces postprandial glycemia.[114] Velarde-Salcedo *et al.*[115] investigated DPP-IV-inhibitory peptides from *Amaranthus hypochondriacus* albumin, globulin, and glutelin hydrolysates smaller than 10 kDa. Glutelin-derived fractions showed the greatest inhibition, which increased with concentration and reached approximately 60-80% after tryptic hydrolysis. Simulated gastrointestinal digestion of glutelin fractions from raw and popped grain generated peptides with similar inhibitory activity; fractions from raw flour were more active than those from popped flour, possibly because heating reduced peptide availability or altered peptide structure.[115] The peptides appeared to act competitively at the DPP-IV active site. In streptozotocin-induced diabetic mice, orally administered glutelin-derived peptides reduced blood glucose and glucagon concentrations and increased insulin concentrations, with effects reported as comparable to those of sitagliptin.[116] These animal findings require confirmation in humans.

Lunasin is a relatively large, 43-amino-acid peptide reported in

Table 1. Amaranth-derived bioactive peptides and their reported activities

Amaranth species	Peptide sequence or protein hydrolysate	IC_{50} value	Reported bioactivity	Reference
A. hypochondriacus	HGSEPFGPR; RDGPFPWPWYSH; RPRYPWRYT	11.5 µM; > 50 µM; 17.3 µM	LOX-1 inhibition	Montoya-Rodríguez and González de Mejía, 2015[95]
Amaranthus sp.	SSEDIKE	Not determined	Anti-inflammatory activity	Moronta *et al.*, 2016[96]
A. hypochondriacus	ALEP and VIKP (tetrapeptides from 11S globulin); GKP, LF, YL, RF, and HY (tripeptide and dipeptides)	6.32 mM (ALEP) and 175 µM (VIKP)	ACE inhibition (ALEP and VIKP) and antihypertensive potential predicted using BIOPEP-UWM (GKP, LF, YL, RF, and HY)	Vecchi and Añón, 2009[97] (ALEP and VIKP); Silva-Sánchez *et al.*, 2008[81] (GKP, LF, YL, RF, and HY)
A. hypochondriacus	LPP, LRP, VPP, and YP (glutelin fraction)	Not determined	ACE-inhibitory activity	Silva-Sánchez *et al.*, 2008[81]
A. mantegazzianus	Alcalase protein hydrolysate	Not determined	ACE-inhibitory activity	Fritz *et al.*, 2011[98]
A. hypochondriacus	Protein isolates hydrolyzed with Alcalase and Flavourzyme; NIDMLRL, LVRW, VRWS, VR, and CIHNIVY	Not determined	Antioxidant, antithrombotic, and antihypertensive activities	Ayala-Niño *et al.*, 2019[99]
A. hypochondriacus	QAFEDGFEWVSFK, AFEDGFEWVSFK, SFNLPILR, FNLPILR, SFNLPIL, and VNVDDPSKA	0.6 mg/mL	Renin-inhibitory activity	Quiroga *et al.*, 2017[100]
A. caudatus	Peptide fractions F1 and F2; FLISCLL, SVFDEELS, and DFIILE identified in F2	Not determined	Antioxidant activity and inhibition of alpha-amylase and ACE	Vilcacundo *et al.*, 2019[89]
A. caudatus	HVIKPPS	Not determined	Antioxidant activity and alpha-amylase inhibition in the F2 fraction	Vilcacundo *et al.*, 2019[89]
A. caudatus	FLISCLL, SVFDEELS, DFIILE, NRPET, and HVIKPPS	Not determined	Antioxidant activity and inhibition of alpha-amylase and ACE	Park *et al.*, 2020[102]
A. mantegazzianus (mainly 11S-globulin-derived peptides)	IR, EL, TY, HL, YL, LH, KP, VY, LK, PHG, PEL, RHL, LHV, AWEEREQGSR, YLAGKPQQEH, IYIEQGNGITGM, and TEVWDSNEQ	Not determined	Antioxidant activity	Orsini Delgado *et al.*, 2016[101]
A. cruentus	Tri- and tetrapeptides GGV, IVG, LVG, VGVI, and VGVL	Not determined	Hypocholesterolemic activity	Soares *et al.*, 2015[84]
A. hypochondriacus	Trypsin-digested glutelin fraction	Not determined	Induction of apoptosis in HeLa cells	Silva-Sánchez *et al.*, 2008[81]
Amaranthus sp.	FPFPPTLGY and FPFPR generated with bromelain	Not determined	Binding to multiple active-site hotspots of DPP-IV and alpha-glucosidase	Kamal *et al.*, 2021[103]
A. caudatus	FLISCLL, SVFDEELS, and DFIILE released by *in vitro* gastrointestinal digestion	Not determined	Antioxidant activity and inhibition of ACE and alpha-amylase	Vilcacundo *et al.*, 2019[89]

ACE, angiotensin-converting enzyme; BIOPEP-UWM, bioactive peptide database of the University of Warmia and Mazury; DPP-IV, dipeptidyl peptidase IV; IC_{50}, half-maximal inhibitory concentration; LOX-1, lectin-like oxidized low-density lipoprotein receptor 1.

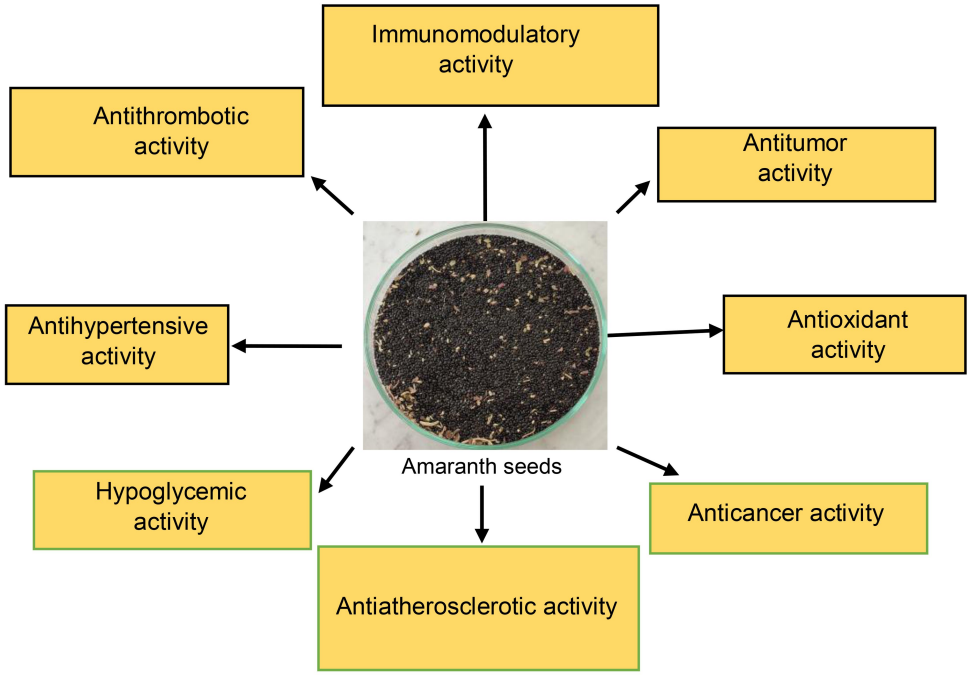

Fig. 3. Reported pharmacological activities of bioactive peptides derived from amaranth seeds.

Amaranthus hypochondriacus grain. It has been detected in albumin, globulin, glutelin, and prolamin fractions, with the highest concentration reported in glutelin. A tryptic digest of the glutelin fraction induced apoptosis in HeLa cells.[81] *Amaranthus mantegazzianus protein isolate and digestion-derived peptides also inhibited HT-29 cell proliferation and induced apoptosis, suggesting antiproliferative activity.*[117]

Thrombosis involves formation of blood clots within the heart or blood vessels. Peptides with sequence similarity to the fibrinogen gamma-chain can bind platelet receptors and may inhibit platelet aggregation.[118] In vitro, enzymatically hydrolyzed albumin, globulin, and glutelin fractions from *Amaranthus mantegazzianus* inhibited thrombus formation, possibly by interacting with thrombin and reducing conversion of fibrinogen to fibrin.[119]

Peptides may modulate immune responses by influencing antibody production, cytokine signaling, and lymphocyte proliferation *in vitro* and *in vivo*.[73] Protein isolates from *Amaranthus hypochondriacus* released anti-inflammatory peptides after enzymatic hydrolysis or simulated gastrointestinal digestion. In human and murine macrophage models, these peptides reduced inflammatory responses by inhibiting nuclear factor-kappa B signaling and did not show appreciable cytotoxicity under the tested conditions.[83]

Atherosclerosis is characterized by plaque formation and reduced arterial blood flow and can lead to myocardial infarction, stroke, or peripheral vascular disease.[120] Vasoactive peptides may influence endothelial function, ventricular remodeling, and expression of inflammation-related genes. Montoya-Rodríguez and González de Mejía reported that the pure *Amaranthus hypochondriacus* peptides showed antiatherosclerotic activity *in vitro*.[95] In lipopolysaccharide-stimulated THP-1 macrophage-like cells, the peptides HGSEPFGPR, RDGPFPWPWYSH, and RPRYPWRYT reduced expression of lectin-like oxidized low-density lipoprotein receptor 1, intercellular adhesion molecule 1, and matrix metalloproteinase 9.[95]

Enzymatic hydrolysis of *Amaranthus cruentus* grain proteins generated peptides that inhibited 3-hydroxy-3-methylglutaryl coenzyme A reductase, a rate-limiting enzyme in cholesterol biosynthesis, by approximately 40-45%.[84] These findings suggest that amaranth-derived peptides may provide leads for managing hypercholesterolemia, but their efficacy and safety require *in vivo* and clinical evaluation.

Limitations

Despite progress in characterizing BPs from grain amaranths, important limitations remain. High-throughput methods for peptide purification and recovery are not standardized, and the formation, stability, intestinal absorption, and metabolic fate of these peptides are poorly understood. Most evidence reviewed here derives from *in silico* prediction, simulated gastrointestinal digestion, biochemical assays, or cell lines, animal studies are limited, and robust clinical trials evaluating efficacy, dose, safety,

and long-term outcomes are scarce. Data are also insufficient on resistance to enterocyte peptidases, transport across the intestinal epithelium, and interactions with complex food matrices during processing. Research has focused mainly on seeds, whereas leaves, stems, and other tissues remain understudied. In addition, genotype-dependent differences in peptide yield, composition, and bioavailability have rarely been evaluated. These limitations restrict direct translation of laboratory findings into evidence-based functional foods, nutraceuticals, or pharmaceutical products.

Future directions

Future studies should integrate optimized extraction, purification, and quantitative proteomic methods with rigorous structural and functional validation. Comparative screening of *Amaranthus* species and genotypes could identify lines with high peptide yield and desirable activity. In silico prediction and molecular dynamics simulations may help prioritize candidate sequences, but findings should be confirmed by biochemical assays, cell models, and well-designed animal studies. Particular priorities include defining sequence-structure-activity relationships, tracking peptide stability and absorption *in vivo*, establishing dose-response relationships, evaluating allergenicity and toxicity, and determining interactions with food matrices. Standardized processing and scalable manufacturing will be essential for reproducible production. Ultimately, randomized clinical trials are needed to establish efficacy, safety, and appropriate use in humans.

Conclusions

Amaranth is a climate-resilient, gluten-free pseudocereal with protein fractions that can release peptides showing antioxidant, ACE-inhibitory, DPP-IV-inhibitory, anti-inflammatory, antimicrobial, antithrombotic, hypocholesterolemic, and anticancer activities in preclinical models. These findings support its potential as a source of functional food, nutraceutical, or pharmaceutical ingredients. However, the current evidence does not establish clinical benefit, and amaranth-derived BPs are unlikely to replace established therapies in the near term. Their practical development will depend on improved extraction and identification methods, clearer structure-activity characterization, *in vivo* validation, clinical trials, safety assessment, and scalable industrial processing.

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Conflict of interest

The authors have no conflicts of interest related to this publication.

Author contributions

Conceptualization of the review (SB); drafting the manuscript (SB, AD, SG); critical revision of the manuscript (SB). All authors have approved the final version and publication of the manuscript.

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