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Food-Derived Bioactive Peptides: Computational Discovery, Molecular Mechanisms, and Therapeutic Applications

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ABSTRACT: The bioactive peptides derived from food have proven to be of great potential as natural therapeutic agents for the prevention of chronic diseases and for health maintenance. The field of computational biology, which is evolving at an astounding pace, has transformed the peptide discovery process and brought together the tools of bioinformatics, artificial intelligence (AI) and machine learning (ML) into a streamlined in silico pipeline, alongside molecular docking, molecular dynamics (MD) simulations and prediction of ADMET properties. They can be used to rapidly identify, screen, optimize, and characterise bioactive peptides derived from a wide range of food proteins and can reduce the time, cost, and experimental effort, compared to laboratory methods. Bioactive peptides from foods possess different biological roles, including antioxidant, anti-inflammatory, antimicrobial, antihypertensive, antidiabetic, immunomodulatory, and anticancer activities, which are associated with several molecular targets and signaling pathways. They have been shown to regulate oxidative stress, inflammation, immune response, glucose metabolism, and cellular homeostasis, which highlights their therapeutic potential in various diseases, including cardiovascular diseases, cancer, metabolic disorders, neurodegenerative diseases, gastrointestinal diseases, etc.

Also, structure–activity relationship (SAR) analysis and AI-assisted molecular optimization can be applied to enhance the stability, specificity, and bioavailability of peptides, thereby paving the way for functional foods, nutraceuticals, and peptide-based therapeutics. Although considerable advances have been made, there are still issues of peptide stability, oral bioavailability, large-scale production, regulatory approval, and clinical validation. The application of multi-omics, generative AI, precision nutrition, and improved food delivery systems will likely lead to increased advances in food bioactive peptide research into personalized medicine and new therapeutic options.

1. INTRODUCTION

Bioactive peptides are short protein sequences (usually 2-20 residues) produced by the enzymatic digestion of food proteins, food processing, and/or microbial fermentation with properties unrelated to nutrition. These are classified into antihypertensive, antioxidant, antimicrobial, anti-inflammatory, antidiabetic, immunomodulatory, anticancer, opioid, mineral-binding, and cholesterol-lowering peptides, and are reported to have substantial health-promoting properties, which can be utilized in the development of functional food and nutraceuticals (1). Bioactive peptides are short sequences of amino acids that become active only in response to proteolytic processing and that occur naturally in milk and dairy products, eggs, fish and meat, soybeans and legumes, cereals, marine organisms, and some protein sources in plants. The advent of proteomics, peptidomics, bioinformatics, and computational biology, along with the application of these techniques in the field of enzymatic hydrolysis, microbial fermentation, gastrointestinal digestion, recombinant protein technology, and new bioprocessing technologies, has led to the discovery of novel peptide candidates with high biological activity and stability in record time. The biological activity of food-derived bioactive peptides is based on their ability to modulate various intracellular and molecular mechanisms by interacting with enzymes, receptors, transcription factors, and signaling molecules that are related to oxidative stress, inflammation, metabolism, and immune function. The peptides have been demonstrated to exhibit antioxidant, anti-inflammatory, antimicrobial, antihypertensive, hypoglycemic, hypolipidemic, and immunomodulatory properties, such as angiotensin-converting enzyme (ACE) inhibition, free radical scavenging, regulation of cytokines, modulation of gut microbiota, improvement in insulin sensitivity, and regulation of lipid metabolism, which play a role in the prevention and management of various chronic diseases (3). The evidence for them being therapeutic in cardiovascular diseases, diabetes mellitus, obesity, cancer, neurodegenerative disorders, gastrointestinal disorders, and even immune-related diseases is due to their high target specificity, low toxicity, ease of biocompatibility, and natural origin when compared to many synthetic drugs (4). Furthermore, the advancements in the field of AI, machine learning, molecular docking, molecular dynamics simulation, and multi-omics technologies provided a new approach to speedy virtual screening, computational prediction of peptide–target interactions, and prediction of pharmacokinetic and toxicity properties of bioactive peptides before experimental studies. With these computational integration tools, peptide-based drug discovery and precision nutrition have been significantly reduced, and thereby, food-derived bioactive peptides are excellent candidates for the development of next-generation functional foods, nutraceuticals, and personalized therapeutic interventions (5).

2. COMPUTATIONAL DISCOVERY AND CHARACTERIZATION OF FOOD-DERIVED BIOACTIVE PEPTIDES

The computational discovery and characterization of food-derived bioactive peptides drastically changed the research of peptides by enabling the identification, screening, and optimization of biologically active peptide sequences from a range of food proteins that were not experimentally validated before. The discovery process usually starts with the in silico recognition of protein sequences from public databases such as UniProt, NCBI, BIOPEP-UWM, PeptideAtlas, and other peptide repositories, proceeding to the virtual enzymatic digestion of these protein sequences with proteases such as pepsin, trypsin, chymotrypsin, alcalase, and papain, from which a library of potential bioactive peptides is generated. Bioinformatic analysis of these peptide sequences, sequence alignment, motif analysis, quantitative structure–activity relationship (QSAR) models, and prediction of physicochemical properties select candidates with desirable biological activities (6). The latest developments in AI and machine learning have also greatly expedited the peptide discovery process by predicting antioxidant, antimicrobial, antihypertensive, anticancer, anti-inflammatory, immunomodulatory, and antidiabetic effects of peptides with high levels of accuracy by scanning large peptide databases. The deep learning algorithms, support vector machines, random forests, transformer-based models, and neural networks can recognize the complex sequence–function relationships, optimize peptide structures, and predict stability, solubility, and target specificity with drastically lower time and cost spent on the conventional time-consuming experimental screening (7).

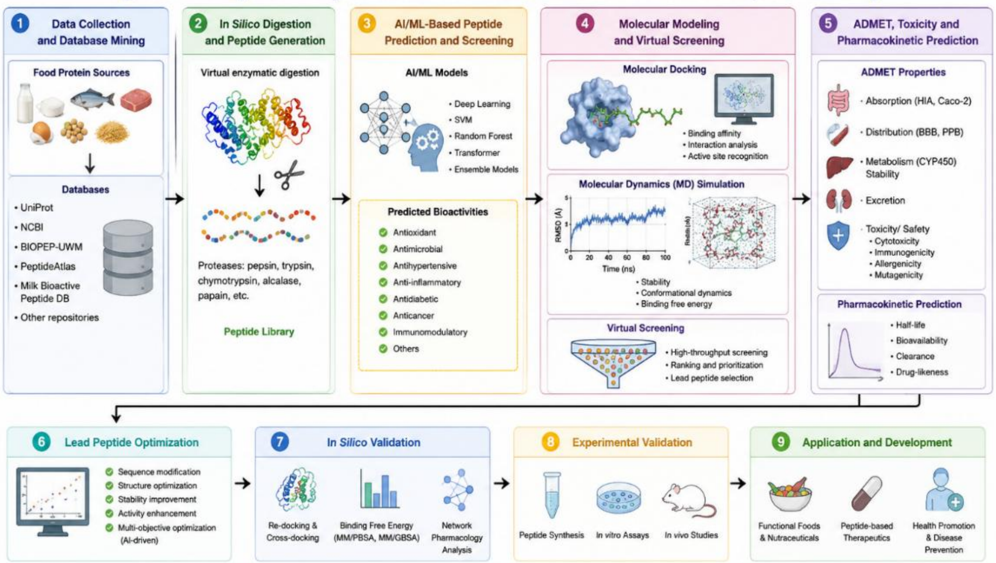

Figure 1. AI-Integrated Computational Workflow for Food-Derived Bioactive Peptide Discovery

After computational prediction, molecular docking is used for the evaluation of the interactions of peptides with disease-associated proteins using binding affinity, estimation of hydrogen bonding, electrostatic interaction, and active-site recognition, and molecular dynamics (MD) simulations are used to assess the structural stability and conformational flexibility of peptide-protein complexes under physiological conditions. Concurrently, virtual screening can be used to rapidly prioritize thousands of peptide candidates based on predicted biological activity and binding strength to help build an efficient workflow for selecting lead peptides for lab validation, as shown in Figure 1 (8). In addition, computational prediction of absorption, distribution, metabolism, excretion and toxicity (ADMET) properties is an essential part of peptide development as it assesses intestinal absorption, membrane permeability, plasma protein binding, metabolic stability, blood–brain barrier penetration, allergenicity, immunogenicity, cytotoxicity and overall pharmacokinetic behavior. Early evaluation of these parameters can aid in the identification of peptides with desirable safety profiles and drug-like properties and minimize failures in later preclinical and clinical studies (9). In summary, the combination of database mining, AI, molecular docking, molecular dynamics simulation, virtual screening, and the prediction of ADMET properties has created a comprehensive computational pipeline that can drive the discovery and optimization of bioactive peptides derived from food, leading to the development of next-generation food-derived functional foods, nutraceuticals, and peptide-based therapeutics with improved efficacy, specificity, and clinical potential (10).

3. MOLECULAR MECHANISMS OF FOOD-DERIVED BIOACTIVE PEPTIDES

The biological activities of food-derived bioactive peptides are mediated by highly selective interaction with cellular receptors, enzymes, ion channels, transcription factors and intracellular signaling molecules which control a variety of biological processes. After being absorbed, these peptides interact with molecular targets, such as angiotensin-converting enzyme (ACE), dipeptidyl peptidase-IV (DPP-IV), cyclooxygenase-2 (COX-2), nuclear factor-kappa B (NF-κB), mitogen-activated protein kinases (MAPKs), phosphoinositide-3 kinase/protein kinase B (PI3K/Akt), nuclear factor erythroid 2-related factor 2 (Nrf2), and Toll-like receptors (TLRs), and modulate gene expression, enzyme activity, inflammatory responses, oxidative stress, apoptosis, and metabolic homeostasis (11). The main mechanisms include antioxidant activity, in which antioxidant peptides directly neutralize the reactive oxygen species (ROS); chelation of transition metal ions; inhibition of lipid peroxidation; and activation of antioxidant defense systems through the Nrf2/ARE pathway, leading to higher expression of antioxidant enzymes like superoxide dismutase, catalase, and glutathione peroxidase (12). Its anti-inflammatory properties are mainly attributed to its ability to inhibit NF-κB and MAPK signaling pathways, which result in the decreased secretion of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6), and also to the increased production of anti-inflammatory molecules, which play a role in the regulation of immune homeostasis and protection of tissues (13). The antimicrobial activity of most food-derived peptides is also related to their capacity to disrupt microbial cell membranes, increase the permeability of the cell membrane, interfere with the intracellular metabolism, and inhibit the formation of bacterial, fungal, and some viral biofilms. In addition, immunomodulatory peptides have the ability to regulate innate and adaptive immune defense systems by modulating the activation and maturation of macrophages, maturation and proliferation of dendritic cells, proliferation of lymphocytes, production of antibodies, and secretion of cytokines, without producing immune system over-activation (14). Peptide length, the amino acid composition, hydrophobicity, net charge, molecular weight, sequence orientation, and secondary structure all contribute to the biological activity. The structure–activity relationship (SAR) is used to determine this. The optimization of peptide sequences is becoming more and more crucial and is facilitated by a variety of computational methods such as molecular docking, molecular dynamics simulation, artificial intelligence peptide engineering, or quantitative structure–activity relationship (QSAR) modeling. These molecular optimization approaches have proven to be highly effective for the rational design of multifunctional food-derived bioactive peptides that are applied to functional foods, nutraceuticals, and peptide-based therapeutics for cardiovascular disease, diabetes, cancer, neurodegenerative disease, inflammatory disease, and infectious diseases (15).

Table 1. Food-Derived Bioactive Peptides, Molecular Targets, Biological Activities, and Therapeutic Applications

Food Source	Representative Bioactive Peptide	Major Molecular Target	Primary Biological Activity	Potential Therapeutic Application
Milk (Casein)	Val-Pro-Pro (VPP), Ile-Pro-Pro (IPP)	ACE	Antihypertensive	Hypertension, cardiovascular diseases
Soybean	Lunasin	Integrins, Histones	Anticancer, Anti-inflammatory	Cancer prevention, chronic inflammation
Egg White	Ovokinin	ACE	Blood pressure regulation	Hypertension
Fish Protein	Fish collagen peptides	Nrf2, MAPK	Antioxidant	Oxidative stress, tissue protection
Marine Proteins	Marine antimicrobial peptides	Microbial cell membrane	Antimicrobial	Bacterial and fungal infections
Rice Bran	Rice bioactive peptides	DPP-IV	Antidiabetic	Type 2 diabetes mellitus
Wheat Protein	Gluten-derived peptides	Immune signaling pathways	Immunomodulatory	Immune regulation
Soy Protein	Soy peptides	NF-κB	Anti-inflammatory	Chronic inflammatory diseases
Egg Protein	Egg-derived peptides	PI3K/Akt	Antioxidant, Cytoprotective	Metabolic disorders
Milk Whey	Lactoferricin	Bacterial membrane, TLRs	Antimicrobial, Immunomodulatory	Infectious diseases, immune support
Hemp Seed	Hemp peptides	AMPK	Lipid metabolism regulation	Obesity, metabolic syndrome
Corn Protein	Zein peptides	COX-2	Anti-inflammatory	Arthritis and inflammatory disorders

Pea Protein	Pea peptides	ACE, DPP-IV	Antihypertensive, Antidiabetic	Cardiometabolic diseases
Marine Algae	Algal peptides	ROS signaling pathways	Antioxidant	Healthy aging, neuroprotection
Mixed Food Proteins	AI-optimized multifunctional peptides	Multiple therapeutic targets	Multi-target bioactivity	Precision nutrition and peptide therapeutics

4. THERAPEUTIC APPLICATIONS OF FOOD-DERIVED BIOACTIVE PEPTIDES

Given these properties, food derived bioactive peptides are emerging as potential therapeutic agents, having the ability to modulate several molecular targets that are implicated in the pathogenesis of chronic diseases, in addition to being highly biocompatible, non-toxic and nutritious. Many peptides obtained from milk protein, soy protein, fish, egg and plant protein have been demonstrated to possess high antihypertensive and cardioprotective properties, such as inhibition of the activity of Angiotensin-converting enzyme (ACE), stimulation of nitric oxide production by endothelial cells, reduction of the oxidative stress and modulation of the renin–angiotensin–aldosterone system (RAAS) in cardiovascular diseases. The mechanisms include blood pressure regulation, vascular function, reducing inflammation and reducing atherosclerosis and heart failure risk (16). Additionally, the peptides derived from food have substantial anticancer and anti-inflammatory effects, in part by modulating cell proliferation, apoptosis, autophagy, angiogenesis and immune surveillance. They can inhibit nuclear factor-kappa B (NF-κB), phosphoinositide-3 kinase/protein kinase B (PI3K/Akt), mitogen-activated protein kinase (MAPK), and signal transducer and activator of transcription (STAT), which play a role in suppressing tumor growth, inflammatory cytokine production, oxidative damage, and progression of metastasis, and promoting antioxidant defense mechanisms (17).The bioactive peptides have anti-diabetic activity by inhibiting dipeptidyl peptidase-IV (DPP-IV), α-glucosidase, α-amylase and enhancing insulin secretion and sensitivity, regulating AMP-activated protein kinase (AMPK) signaling and improving lipid metabolism in diabetes mellitus and metabolic syndrome. In doing so, it will lead to improved glycemic control, reduced insulin resistance, reduced obesity-related inflammation and improved metabolic health (18). Food-derived peptide also has a neuroprotective effect because of their ability to cross or act on the blood–brain barrier, reduce oxidative stress, inhibit neuroinflammation, suppress the aggregation of amyloid-β, regulate cholinesterase activity, and protect neuronal cells from apoptosis, among other properties, which may be useful in the treatment of Alzheimer's disease, Parkinson's disease, and other neurodegenerative disorders (19). The food derived bioactive peptides are also known to play a crucial role in gastrointestinal health and immune modulation by enhancing intestinal barrier integrity, promoting growth of beneficial gut microbiota, inhibiting pathogenic microorganisms, lowering levels of cytokines, and triggering innate and adaptive immune responses. These activities contribute to better digestion, a better immune system and less inflammation in the intestine, as well as keeping the immune system in check. The diversity of molecular mechanisms responsible of these disease-specific therapeutic activities, as well as their cross-talk with several cell pathways, is summarized in Figure 2, showing how peptides, derived from food, target various pathways, which is a cornerstone of precision nutrition, functional food development and next-generation peptide-based therapeutics (20).

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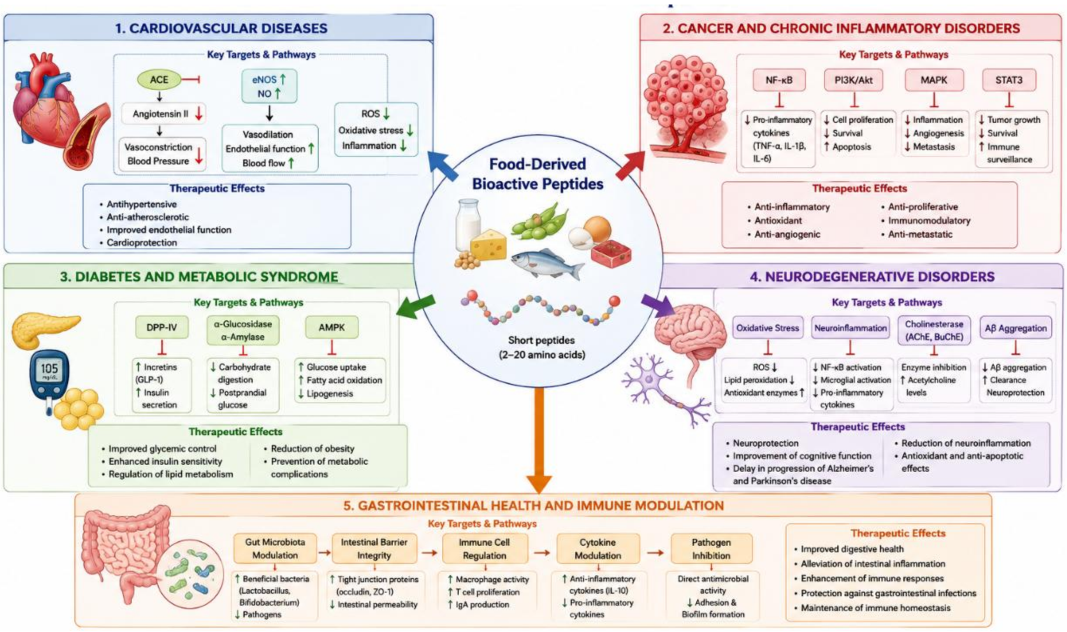

Figure 2. Molecular Mechanisms and Disease-Specific Therapeutic Applications of Food-Derived Bioactive Peptides

5. CHALLENGES

Although there have been tremendous progress in computational peptide discovery, there are still a number of challenges that hinder the clinical translation of food derived bioactive peptides. Therapeutic effect is diminished by peptide instability during food processing and gastrointestinal digestion, low oral bioavailability, and rapid enzymatic degradation, along with low membrane permeability. The variability of the protein source and the different extraction procedures can also cause differences in peptide reproducibility and standardization. Moreover, it takes a huge amount of in vitro, in vivo and clinical validation prior to the commercialization of computational prediction. Other challenges include regulatory approval, large-scale manufacturing, quality control and cost-efficient production. These limitations can be overcome with better peptide engineering, delivery systems and standardized evaluation testing to aid in successful therapeutic development.

6. FUTURE PERSPECTIVES

For the future, the use of AI, ML, multi-omics and high performance computing for the discovery and optimization of bioactive peptides from food will become increasingly common. Generative AI and Deep Learning models should discover more than a single peptide with a variety of functions and enhanced stability, bioavailability, and targeting. Precision nutrition, personalized medicine, and peptide delivery systems using nanotechnology and digital health will continue to enhance the effectiveness of peptides and their clinical usefulness. Experimental validation, Systems biology, real data from clinical trials and computational prediction will expand the applications of peptide therapeutics in functional foods, nutraceuticals and precision healthcare and will help develop safer and more effective therapeutics.

7. CONCLUSION

Bioactive peptides are naturally occurring therapeutic molecules with wide range of applications in disease prevention and treatment, which are derived from food. Artificial intelligence, molecular docking, molecular dynamics simulation and ADMET prediction are just a few examples of computational methods that have revolutionized the discovery of peptides by enhancing the efficiency of the screening process and lowering development costs. These peptides have a wide array of biological properties that can affect multiple molecular targets associated with cardiovascular, cancer, diabetes, neurodegenerative diseases and immune regulation. Meanwhile, the development of novel peptide-based functional foods, nutraceuticals and precision therapeutics for the future healthcare can be further accelerated by continued integration of computational biology with experimental validation and clinical research.

DECLARATIONS

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Ethical Approval: Not applicable, as this study is based solely on published literature.

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