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Bioactive Peptides and Polyphenols as Next-Generation Nutraceuticals: Mechanisms, Bioavailability, and Clinical Prospects

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ABSTRACT: Bioactive peptides and polyphenols are compounds found in food that have complementary molecular actions that could participate in the prevention or in the complementary treatment of chronic pathologies. The peptides derived from the proteins in dairy, marine, egg, plant, and meat products can alter the activity of angiotensin-converting enzyme, redox homeostasis, glucose metabolism, immune signalling, and satiety, while polyphenols are known to regulate antioxidant-response pathways, inflammatory mediators, cellular metabolism, vascular function, and gut microbial ecology. They have been limited in their translation to effective nutraceuticals, however, due to inconsistent compositions, gastrointestinal degradation, restricted intestinal permeability, fast metabolism, unknown tissue exposure, and inconsistent clinical trials. This critical integration of evidence brings together sources, structure–activity relationships, production, molecular mechanisms, pharmacokinetics, formulation technologies, clinical applications, safety and regulation information in the context of this narrative review. Literature was retrieved from PubMed/MEDLINE, Scopus, Web of Science and Google Scholar by employing various combinations of the keywords bioactive peptides, polyphenols, nutraceuticals, bioavailability, nanoencapsulation, mechanisms and clinical trials. There is current evidence for biologically plausible effects on antioxidant, anti-inflammatory, cardiometabolic, neuroprotective, and microbiota-

mediated effects, but results in purified systems or animal models do not necessarily translate to human exposures.

Apparent bioavailability and stability may be improved by encapsulation, lipid-based carriers, protein–polysaccharide complexes, cyclodextrins, and co-delivery systems, but there is limited comparative human data. Future developments should focus on chemically standardized preparations, validation of dose-response biomarkers, dose-ranging studies, interaction testing and sufficiently sized studies based on diet, microbiome, metabolic phenotype and medication use. Bioactive peptides and polyphenols are next-generation nutraceutical ingredients, but with clinically credible products, there needs to be a change from general antioxidant claims to evidence that is specifically linked to the mechanism, formulated to a specific product, and compliant with regulatory standards.

1. INTRODUCTION

1.1 Chronic Diseases, Functional Foods, and Nutraceuticals

Chronic diseases of cardiovascular, respiratory, neurodegenerative, diabetes, and cancer, represent a significant burden of disability and mortality. Interactions among genetic susceptibility, ageing, diet, physical inactivity, the environment, adiposity, and social determinants are all involved in their development. Comparative risk assessment indicates that sub-optimal diet is a key driver of death and disability-adjusted life-years (DALYs), reinforcing the interest in foods and ingredients that offer more than just nutritional benefits [1]. Functional foods and nutraceuticals fall in this space between nutrition and health. Functional foods are typically eaten as part of a regular diet, but nutraceuticals are often in concentrated, standardized, or capsule, powder, or liquid forms that are targeted at a specific food function. The difference isn't consistent in all parts of the world, and neither group should be considered equal to a registered drug.

Consumer interest in self-care, healthy ageing and prevention is key to the commercialization of nutraceuticals. Market size does not, however, prove effectiveness. Food derived compounds are present in complex matrices, have variable concentrations, and are extensively processed and metabolized. Therefore, the biological activity of a whole food does not necessarily reflect the activity of a single molecule and an effect that can be proven from high doses of a purified compound cannot be assumed from the normal diet. To be scientifically credible, the development of a nutraceutical should include compositional characterization, plausible mechanisms, exposure data, safety evaluation, and clinical outcomes relevant to the intended claim.

1.2 Importance of Bioactive Peptides and Polyphenols

Bioactive peptides are short chains of amino-acids that can be released from parent proteins during digestion, fermentation, enzymatic hydrolysis or food processing. Selected sequences can affect enzymes after release, bind receptors, modify transport function, inhibit reactive species or affect intracellular signalling [2,3]. They are activity dependent on sequence, length, charge, hydrophobicity, terminal residues, conformation, dose and resistance to gastrointestinal and brush-border peptidases. Polyphenols are a large group of plant secondary metabolites, such as flavonoids, phenolic acids, stilbenes, lignans and tannins. They are found in fruits, vegetables, cereals, legumes, tea, coffee, cocoa, herbs and spices, nuts, seeds, wine and olive products. These impacts are not only due to their direct chemical antioxidant properties, but also result from their ability to regulate enzymes, transcription factors, inflammatory mediators, vascular signalling and the metabolism of the host and microbes [4,5].

The combination of peptides and polyphenols is of special interest as a nutraceutical platform. Peptides can offer enzyme inhibition, carrier and matrix functions, and polyphenols can modulate redox-sensitive and inflammatory networks. The interactions between protein and polyphenols could either enhance or diminish their solubility, stability, digestibility, sensory properties and intestinal release depending on the strength of the interaction and the formulation conditions. Therefore, synergy can occur, but not presumed, as can antagonism, precipitation, modified proteolysis, and decreased absorption.

1.3 Knowledge Gaps and Review Objectives

The main translational barrier to consider is the difference between mechanistic potency and clinically achievable exposure. Lots of studies have been performed with peptides which have not been digested or with concentrations that are not likely to be attained in target tissues, after oral administration. Product heterogeneity, lack of reporting of the chemical composition, limited sample size, limited intervention time, and inconsistent result make comparison even more limited. The classification, sources, production, biological mechanisms, bioavailability, delivery strategies, clinical applications, safety, and regulatory status of bioactive peptides and polyphenols, are therefore reviewed. It highlights evidence boundaries and provides an outline of the requirements needed to make molecules derived from food systems into reproducible and clinically credible nutraceuticals.

2. LITERATURE SEARCH STRATEGY

2.1 Databases and Search Terms

A structured narrative search was designed with reference to transparent review-reporting principles [6]. PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar were searched for English-language literature published primarily from January 2005 to June 2026, while seminal earlier articles were retained when essential. Search combinations included "bioactive peptide," "food-derived peptide," "polyphenol," "flavonoid," "phenolic acid," "nutraceutical," "functional food," "structure activity," "gastrointestinal digestion," "bioavailability," "pharmacokinetics," "microbiota," "nanoencapsulation," "liposome," "clinical trial," "toxicity," and "regulation." Reference lists of relevant articles were screened to identify additional foundational and human-intervention studies.

2.2 Eligibility and Study Selection

Experimental studies and human trials as well as systematic or authoritative reviews, pharmacokinetic studies and official regulatory documents on food derived peptides and polyphenols were eligible for inclusion. Studies were prioritized when they were reported to have a clearly defined source, extraction or production method, chemical characterization, dose, model, comparator, outcome or exposure measurement. Articles focused on exclusively synthetic therapeutic peptides that are not associated with food, poorly characterized mixtures, non-retrievable articles, conference abstracts without sufficient data and promotional claims without scientific basis were not included. As this was not a new meta-analysis, inclusion of studies did not depend on pooled effect estimation but instead on relevance, methodological quality and coverage of the domains of interest pre-defined in the research protocol.

2.3 Data Extraction and Evidence Assessment

The following information was extracted: compound/peptide identity, food source, production method, biological target, experimental model, dose, formulation, pharmacokinetic behaviour, clinical outcome, and safety finding. Clinical and pharmacokinetic data from humans took precedence in the translation to other evidence-based data (animal studies, cell studies, chemical assays). Special consideration was given to the following: whether it was the parent substance ingested orally per se, a digestive product or a circulating microbial or phase-II metabolite. Mechanistic claims were considered tentative if there was no exposure at the desired target level.

3. BIOACTIVE PEPTIDES

3.1 Classification and Structure–Activity Relationships

The bioactive peptides in food typically consist of 2-20 amino acids, but longer peptides can be bioactive. They can be divided according to origin, production route or function such as antihypertensive, antioxidant, antimicrobial, immunomodulatory, opioid, mineral-binding, antidiabetic, satiety-regulating, and antithrombotic peptides [2,3]. Activity is significantly influenced by structure. Hydrophobic or aromatic residues close to the C-terminus are common in angiotensin-converting enzyme (ACE)-inhibitory peptides, with a preference to interact with the ACE active site. Histidine, cysteine, methionine, tyrosine, hydrophobic residues which can donate electrons, chelate metals or position the peptide at the lipid–water interface are often present in antioxidant peptides [7]. Cationic and amphipathic sequences can interact with microbial membranes while proline-rich sequences can exhibit increased protease resistance.

Activity prediction can be carried out using the sequence; this is very helpful for screening purposes but should not be used as a substitute for experimental testing. Accessibility is affected by peptide conformation, food matrix, aggregation, degree of

hydrolysis and co-existing salts and lipids. Furthermore, an active sequence needs to endure processing and digestion, cross or signal through the intestinal barrier and achieve a meaningful concentration. The same hydrolysate may thus exhibit a high activity in an enzyme test but a weak activity in humans.

3.2 Dairy, Marine, Egg, Plant, and Meat Sources

Milk proteins are one of the most-studied precursors. During digestion or fermentation of caseins or whey proteins, sequences are released that exhibit ACE-inhibitory, opioid, mineral-binding, antimicrobial, and immunomodulatory properties. Proline rich sequences as small as Val-Pro-Pro and Ile-Pro-Pro can be added to fermented milk products, the effect on blood pressure depends on the population and study design [8]. The peptides extracted from marine proteins of fish muscle, skin, frames, collagen, shellfish, and processing wastes have antioxidant, antihypertensive, antidiabetic, and antimicrobial properties. They are also developed to facilitate circular use of side streams from food industries in the case of such products, control needs to be exercised over the allergenicity of the product, contaminants, oxidation, and sensory quality.

Egg proteins provide peptides of ovalbumin, ovotransferrin, lysozyme and yolk protein. These can have ACE inhibitory, antioxidant, antimicrobial and immune modulatory properties. The use of plant proteins from soy, pea, lentil, chickpea, lupin, cereal, rice, hemp and oilseed meal is gaining in significance due to sustainability and plant-based nutrition. Antinutritional factors and incomplete protein digestion may impact release and absorption of legume-derived peptides, which have been studied for lipid regulation, glucose metabolism, inflammation and satiety [9]. Meat proteins and collagen can yield peptides with a variety of beneficial properties, including ACE-inhibitory, antioxidant, antithrombotic and connective-tissue-related. When selecting a source, potency should not be the only criterion used as other factors such as reproducibility, cultural acceptance, cost, amino-acid composition, allergens, and environmental impact should be taken into account.

3.3 Production, Isolation, and Purification

The controlled production methods are predominantly enzymatic hydrolysis. Proteases: Can break down proteins depending on the accessibility of the substrate and the specificity of the enzyme, e.g., alcalase, flavourzyme, pepsin, trypsin, chymotrypsin, papain and microbial enzymes. Peptide distribution is determined by the temperature, pH, enzyme-to-substrate ratio, time, and degree of hydrolysis and can cause bitterness from the exposure of the hydrophobic residues. Gastrointestinal enzymes are of benefit in simulating digestive release, while food grade microbial proteases may be more economical for the production. Lactic-acid bacteria, yeasts or other microorganisms are used to hydrolyse proteins during fermentation, and the fermentation modifies the acidity, flavour, and microbial stability. Strain selection is important as there are significant differences among the proteolytic systems.

Hydrolysates are enriched by molecular size ranges using membrane ultrafiltration and are further enriched by nanofiltration, ion-exchange, gel-filtration and reversed-phase chromatography. The use of chromatography and mass spectrometry can facilitate the identification of the sequence, and peptidomics and in-silico digestion can speed up the discovery process [10]. However, large scale purification may be impractical commercially. A standardised active hydrolysate may sometimes be more practical than an individual peptide, where composition, marker peptides, activity, contaminants and batch variability are controlled. Targeted sequences are allowed in recombinant or microbial production; however, there are further regulatory and processing considerations to take into account.

3.4 Principal Biological Activities

In addition to its cardiovascular activity, ACE inhibition can encompass other beneficial effects on renin, endothelial NO signalling, lipid oxidation, bile-acid binding, dipeptidyl-peptidase-4 inhibition, α-glucosidase inhibition, glucose uptake and satiety-hormone release. Antioxidant peptides can inhibit the formation of radicals, chelate pro-oxidant metals, inhibit lipid peroxidation and activate endogenous defence mechanisms. Immunomodulatory peptides can modulate the activation of macrophages, cytokine production, the function of lymphocytes or the integrity of the epithelial barrier. Antimicrobial sequences may affect the membrane or interfere with the activity of microbes within the cell. The anticancer activity has been reported by membrane disruption, apoptosis, cell-cycle arrest, and antiangiogenic signalling, however most of the evidence has been found in the preclinical stage and cannot justify therapeutic claims [11]. The best development pathway would then be to correlate a chemically defined peptide preparation with a measurable physiological target and then validate that target engagement in humans.

4. POLYPHENOLS

4.1 Classification and Structure–Activity Relationships

Polyphenols have 1 or more hydroxyl groups on their aromatic rings. Flavonoids are a group of compounds which contains flavonols, flavones, flavanones, flavan-3-ols, anthocyanins, isoflavones. Phenolic acids are hydroxybenzoic and hydroxycinnamic acids, stilbenes are resveratrol, lignans are secoisolariciresinol and tannins are hydrolysable and condensed [12]. Chemical reactivity, solubility, metabolism, and biological activity are determined by number and position of hydroxyl groups, conjugation, glycosylation, methylation, polymerization, and interactions with proteins or lipids. Glycosides can be broken down by enzymes or micro-organisms; large proanthocyanidins are poorly absorbed as such and may have gastrointestinal tract or microbial metabolite effects.

The previous concept of polyphenols having an exclusive direct systemic antioxidant action is insufficient. Concentrations of most parent compounds in circulation are low and parent compounds are quickly conjugated. At nutritional exposures the more likely actions are modulation of redox-sensitive enzymes and transcription factors, mild electrophilic or xenobiotic signalling, effects on membrane and receptor function, inhibition of digestive enzymes and production of bioactive microbial metabolites [13].

4.2 Dietary and Botanical Sources

Polyphenols are found in a variety of foods including berries, grapes, apples, citrus fruits, pomegranate, onions, leafy vegetables, legumes, cocoa, tea, coffee, whole grains, herbs, spices, nuts, flaxseed and olives. Content will differ depending on cultivar, climate, maturity, storage, processing and analytical methods. Catechins or theaflavins are contained in tea, flavan-3-ols are found in cocoa, anthocyanins in berries, flavanones in citrus, isoflavones in soy, chlorogenic acid in coffee, stilbenes in grapes, some berries and lignan precursors in flaxseed. Whole foods provide mixtures that may modify the absorption and biological responses of other food components such as fibre, vitamins, minerals, lipids and proteins. Plant-based alternatives can offer higher concentrations, but with a greater variation in concentration and potential contamination or interaction.

4.3 Extraction and Purification Technologies

Conventional extraction involves the use of aqueous alcohols, acetone, ethyl acetate or water at controlled pH, time and temperature. The solvent should have a similar polarity as the target compounds, and should be kept away from oxygen, light, heat, and metals. The ultrasound-assisted, microwave-assisted, pressurized-liquid, supercritical-fluid, enzyme-assisted, and deep-eutectic-solvent methods reduce time and/or solvent consumption and enhance the recovery [14]. Enrichment with adsorption resins, preparative chromatography, liquid–liquid partitioning and membrane processes. The appeal of green extraction is overlooked – yield is not the only factor to consider: energy considered; scale-up potential; degradation products; co-extraction of toxins; residual solvent. The required parameters should be defined by standardization, namely botanical plant, plant part, extraction ratio, solvent, marker compounds, chromatographic fingerprint, moisture, microbial quality, pesticides, mycotoxins, heavy metals as well as stability.

4.4 Principal Biological Activities

Polyphenols can affect excessive inflammatory signalling, improvement of endothelial nitric-oxide availability, change the signalling of the insulin receptor, influence the activation of platelets, alter the digestion of carbohydrates and lipids, and reshape microbial communities, all of which reduce oxidative injury. They can also impact on cell cycle regulation, cell death, angiogenesis, plasticity of synapses and neuroinflammation. Activity, however, is dependent on the actual molecules present where activity is occurring. Phenolic acids arising from gut metabolism (phenolic acids and phase II conjugates) could be more important than the parent compound in a cell culture experiment [15]. This is crucial to rational dose selection and biomarker development.

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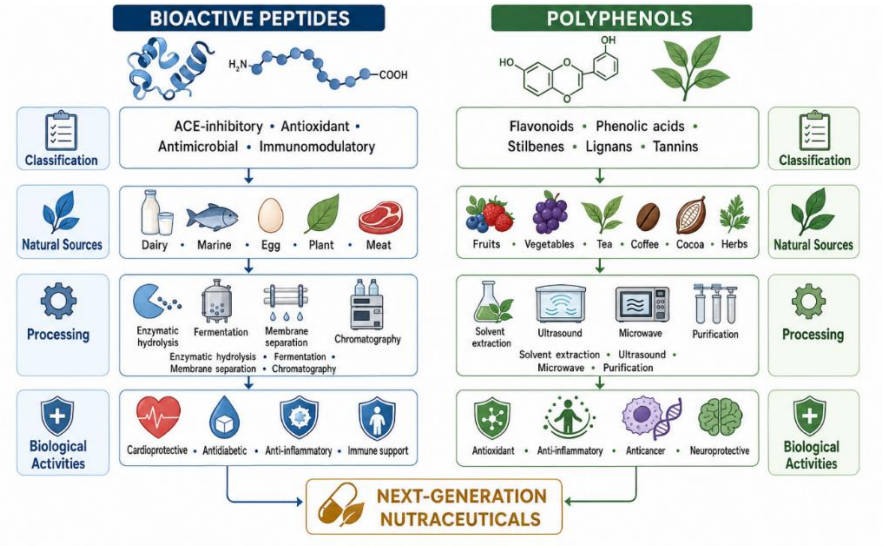

Figure 1. Comparative classification, natural sources, production or extraction methods, and principal biological activities of bioactive peptides and polyphenols.

5. MOLECULAR MECHANISMS OF ACTION

5.1 Antioxidant and Anti-inflammatory Mechanisms

Peptides may donate protons and/or electrons, chelate iron and copper, inhibit lipid oxidation and reduce reactive oxygen species at interfaces. The direct quenching of reactive species in chemical systems is another potential mode of action for polyphenols, though their potential in-vivo role is more likely to be via regulation of endogenous defence mechanisms. Nuclear factor erythroid 2–related factor 2 (Nrf2) activation leads to upregulation of heme oxygenase-1, NAD(P)H quinone dehydrogenase 1, glutathione-related enzymes and other cytoprotective proteins. Further redox imbalance can be reduced by modulating NADPH oxidases, mitochondrial function and/or nitric-oxide bioavailability [13,16]. The effects are context dependent and hormetic, meaning that high concentrations are pro-oxidant or disrupt the normal redox signalling.

Chronic low-grade inflammation is linked with atherosclerosis, insulin resistance, fatty liver disease, cancer progression and neurodegeneration. The peptides and polyphenols selected inhibit activation of the nuclear factor-ϰB, mitogen-activated protein kinases, cyclooxygenase-2, inducible nitric-oxide synthase, and tumour necrosis factor-α, interleukin-1β, and interleukin-6 production. There are some compounds that affect the activation of the NLRP3 inflammasome and macrophage polarization. However, general pathway diagrams do not imply that all compounds have an impact on all targets. To fulfil mechanistic validity, concentration–response relationships, adequate controls, metabolite testing and confirmation at physiologically relevant exposure are needed.

5.2 Immunomodulation and Gut Microbiota Regulation

The intestine wall (mucosa) is target and mediator of nutraceutics action. Peptides can bind to epithelial receptors, modify tight junction proteins, affect mucin production and affect innate or adaptive immune cells. Polyphenols and their metabolites have been seen to influence the redox state of the epithelial cells, inflammatory responses and microbial growth. A large proportion of polyphenols ingested in food are absorbed by bacteria in the colon and these smaller phenolic metabolites have different absorption and activity. In contrast, polyphenols can promote or suppress specific taxa, alter the production of short-chain-fatty-acids and affect bile-acid metabolism [17].

A person's baseline diet, microbial genes, medications, intestinal transit and host physiology are factors that can influence microbial effects in individuals. The idea of "metabotypes" is thus desirable: people can metabolize the same precursor into different metabolites and the clinical effects of these metabolites may differ. Microbial degradation of peptides is also known, but less investigated than polyphenol degradation. Future trials need to incorporate metagenomic or targeted microbial analysis with plasma and urinary metabolomics, and not just taxonomic shifts.

5.3 Antidiabetic and Cardioprotective Effects

The antidiabetic effects are mediated through inhibition of α-amylase, α-glucosidase and dipeptidyl-peptidase-4; stimulation of insulin signalling; activation of AMP-activated protein kinase; modulation of glucose transporters; preservation of pancreatic β-cells and inhibition of hepatic gluconeogenesis. Peptides can affect satiety and postprandial metabolism and polyphenols can affect incretin response and carbohydrate digestion. Human evidence reviews indicate potential to improve glycaemia and insulin sensitivity for some preparations but there is variability in effect size and certainty, as the compounds, doses, background diets, and participant phenotypes vary [18].

ACE and renin inhibition, enhanced endothelial nitric-oxide production, reduced oxidative modification of lipoproteins, cholesterol handling modulation, antiplatelet and reduced vascular inflammation are all cardioprotective mechanisms. Cocoa flavanols, tea catechins, olive polyphenols, anthocyanins, and certain dairy peptides have been demonstrated to have positive effects on intermediate outcomes in specific trials. These outcomes do not necessarily equate to hard cardiovascular events for which evidence is less strong and more likely to be associated with overall dietary patterns instead of an individual nutraceutical [19].

5.4 Anticancer and Neuroprotective Effects

Peptides and polyphenols are able to modulate apoptosis, proliferation, DNA-damage responses, angiogenesis, invasion and immune surveillance in experimental cancer models. Some polyphenols can interact with the pathways related to phosphatidylinositol-3-kinase/Akt, MAPK, p53, Wnt/β-catenin and epigenetic regulators, and some peptides alter tumour-cell membranes or possess cytotoxic sequences [11,20]. However, the concentrations used in cell culture may be higher than those that can be found in human plasma and antioxidants can interact with redox-dependent anticancer interventions. Nutraceuticals should thus be explored as specific preventative or adjunctive approaches, but not as alternatives to oncology therapy.

Actions that may be protective include reducing neuroinflammation, reducing oxidative stress, protecting the mitochondria, modulating protein aggregation, regulating cerebral blood flow and affecting synaptic signalling. Metabolites might be more readily transported than parent polyphenols across the blood–brain barrier. While a vast number of preclinical studies have been performed, human cognitive trials have varied widely in compound selection, length of trial, pre-existing cognitive function, and outcome measure [21]. Central exposure and selection of prespecified cognitive and imaging endpoints are priorities.

5.5 Synergistic Peptide–Polyphenol Actions

Peptide–polyphenol interactions can produce synergistic antioxidant, enzyme-inhibitory, emulsifying and barrier supporting properties. Hydrogen bonding, hydrophobic interaction, ionic force and covalent reaction following oxidation can all occur between polyphenols and proteins and peptides. Polyphenols can be preserved during processing from their degradation by binding, the binding can help to cover up the bitterness, the binding could be used for controlled release, or for stabilising emulsions. It may also impair digestibility of protein, form complexes, mask active peptide sequences or hinder polyphenol accessibility [22]. Synergy should therefore be determined through factorial designs, comparing each component with the combination, and digestion, transport and human exposure studies. Evidence specific to the formulation conveys more information than the belief that two active ingredients working on their own will be better when used simultaneously.

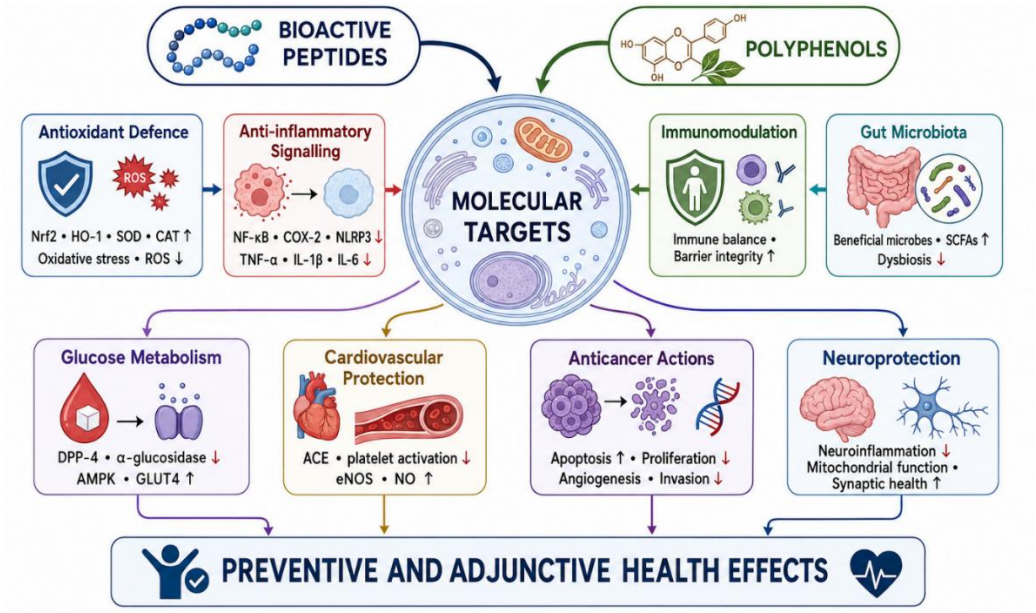

Figure 2. Molecular mechanisms through which bioactive peptides and polyphenols may regulate oxidative stress, inflammation, immune responses, gut microbiota, glucose and lipid metabolism, vascular dysfunction, neurodegeneration, and cancer-related pathways.

6. BIOAVAILABILITY AND PHARMACOKINETICS

6.1 Gastrointestinal Digestion and Stability

Oral efficacy starts with survival during processing and storage, gastric acidity and digestive enzymes, bile salts, and intestinal conditions. In addition to the ability to be broken down into inactive peptides, peptides can also be cleaved to release an active peptide sequence, though the opposite is not always true. Tripeptides and oligopeptides with a higher proline content are generally more resistant, and longer ones are more susceptible. Polyphenols can be degraded to their aglycones, oxidized, hydrolyzed or bound by proteins and fibre. The food matrix and if the food is the original molecule, a conjugate, or a microbial metabolite, therefore, affect stability.

6.2 Absorption, Metabolism, Distribution, and Elimination

Di- and tripeptides can be absorbed via peptide transporter 1 while some sequences can be absorbed via paracellular routes, transcytosis or receptor mediated. Large peptides are poorly permeable, and are likely to act locally in the gut. At present, there is limited evidence for the bioavailability of food peptides via the oral route and it is challenging to measure these in the presence of endogenous peptides, the rapid degradation of peptides, and analytical sensitivity. Time-dependent and sequence-specific mass spectrometry are needed for reliable studies.

There is a wide absorption variability for polyphenols. Glycosides may need to be hydrolyzed to aglycones, which are then able to cross enterocytes via a passive or transporter-mediated pathway. Faster generation of glucuronidated, sulfated and methylated conjugates by enterocytes and liver. Non-absorbed compounds reach the colon where they are further metabolized by the microbes to yield smaller phenolics that can be absorbed into the circulation. Albumin binding, tissue perfusion and deconjugation at inflammatory sites all effect distribution. It may take hours to be eliminated from the body, either in urine or in bile, but subsequent ingestion can keep metabolites present in the body [4,24].

6.3 Factors Affecting Bioavailability

Dose, chemical form, particle size, solubility, formulation, meal timing, lipid content, protein and fibre interactions, intestinal transit, age, sex, genotype, microbiome, disease state, and medication use all influence exposure. Food processing can either enhance release or accelerate degradation. The term “bioavailability” should not be restricted to the percentage of parent

compound detected in plasma; for compounds acting in the gut, local availability may be more relevant, while for systemic claims, active metabolites and tissue exposure must be considered. Consensus approaches recommend measuring multiple metabolites, using validated analytical methods, reporting the food matrix, and relating exposure to function [25].

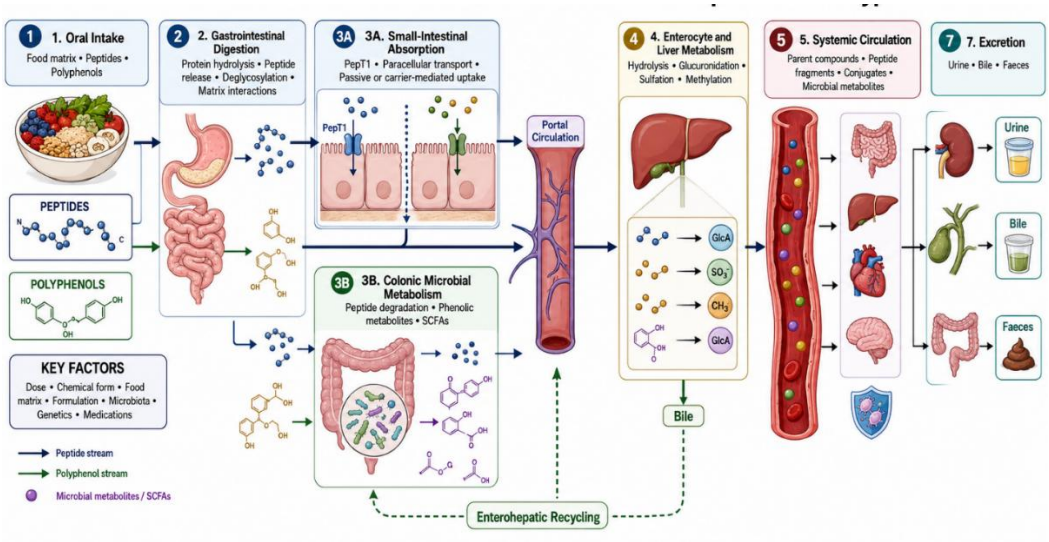

Figure 3. Gastrointestinal fate and pharmacokinetic pathways of bioactive peptides and polyphenols, including release from the food matrix, digestion, intestinal and microbial transformation, absorption, conjugation, distribution, target interaction, and excretion.

7. BIOAVAILABILITY-ENHANCEMENT STRATEGIES

7.1 Nanoencapsulation, Liposomes and Nanoemulsions

Encapsulation can provide protection from oxygen, light, acidity, enzymes, enhance dispersibility, mask undesirable taste and alter intestinal release. Nanoemulsions are capable of enhancing the apparent solubility of the lipophilic polyphenols, and they lead to an increase in the interfacial area. Liposomes offer both a hydrophilic and a lipidic compartment for incorporation of peptides and polyphenols that are hydrophilic and hydrophobic, respectively. They are affected by the composition, size, charge, lamellarity, oxidation stability, digestion, and reproducibility of manufacture of the phospholipids. No simple correlation between increased plasma exposure and clinical benefit is to be accepted and the nanocarriers have to be evaluated in terms of the potential for carrier-related toxicity and changes in tissue distribution [26].

7.2 Polymeric and Protein-based Nanocarriers.

There are controlled release and mucoadhesion properties in biodegradable polymers, polysaccharides, protein nanoparticles, hydrogels and complex coacervates. Chitosan can increase adhesion of the epithelium and alginate can encase and provide protection to the cargo in the stomach, which has a lower pH, and release it at a higher pH in the intestines. Nanoparticles or fibrils of whey, casein, gelatin, zein, and plant proteins can be formed which are able to bind polyphenols and protect peptides. The use of protein-based systems is nutritionally compatible, but can contain allergens, digestive variability, or competitive binding. In vitro simulated digestion, intestinal transport models, and stability testing should be performed prior to animal/human evaluation to optimize formulations.

7.3 Cyclodextrin, Co-delivery, and Targeted Systems

Because cyclodextrins are able to contain hydrophobic regions within a molecular cavity they have a beneficial effect on the dispersibility in an aqueous medium. Phenolics may be protected from degradation and enhance sensory properties by inclusion complexes, but the stability of the complex must allow the release of phenolics. Bioactive peptides and polyphenols can be used in combination in co-delivery systems, or a bioactive can be co-delivered with a lipid or a phospholipid or piperine or other absorption modifier. These methods need to be approached in a different manner to account for metabolic and drug interactions. The intestine or colon might be the target of stimuli-responsive carriers that are activated by pH, enzymes,

oxidative conditions, or microbial activity. Although laboratory results were favourable, the ability to manufacture in large quantities, shelf life, food grade, cost and regulatory approval are critical issues that must be addressed.

8. CLINICAL APPLICATIONS

8.1 Cardiovascular and Metabolic Diseases

Fermented milk products such as peptide-containing fermented milk, fish hydrolysates, soy peptides, cocoa flavanols, tea catechins, anthocyanins, resveratrol and olive polyphenols have been studied in humans with inconsistent findings regarding blood pressure, endothelial function, lipids, glucose control, or inflammatory biomarkers. Signals from a meta-analysis can be statistically significant but are often small, and the products can't be substituted. Response can be modified by baseline risk, medications, Na intake, habitual diet, dose, duration and geographic population. Nutraceuticals can be used in conjunction with, but not as a substitute for, dietary modifications and recommended treatment for hypertension or dyslipidaemia. Trials should provide details of adverse events and medications changes and should not overestimate surrogate endpoints as a prevention of clinical events.

Polyphenols from foods and extracts may positively affect certain parameters of glycaemia, insulin sensitivity, oxidative stress or lipid metabolism, whereas peptides may have an inhibitory effect on digestive enzymes or DPP-4 and affect satiety in diabetes and metabolic syndrome. But the evidence is not consistent, and some preparations include bioactives such as carbohydrates, caffeine, fats or other compounds that are difficult to assign to the product. Results may be more sensitive than fasting glucose alone with longer trials using controlled formulations and more frequent glucose measurements (continuous or postprandial).

8.2 Cancer and Neurodegenerative Disorders

There is not enough evidence from a clinical trial to show that the treatment is more effective than standard treatment. These can be roles of risk reduction in a healthy diet, symptom management in the context of treatment, or carefully managed adjunctive use. The effects of chemotherapy, radiotherapy, anticoagulants and liver enzymes should be taken into account. The action of high dose extracts is different than polyphenol containing foods. The same applies to neurodegenerative applications, which are promising but not confirmed. Studies of flavanols in cocoa, anthocyanins in berries, tea, curcumin supplements, and resveratrol supplements have yielded inconsistent results for cognition and/or biomarkers. There are many sources of variation, such as stage of the disease, exposure of the BBB, length of the trials, learning effects, and bioavailability of the formulation.

8.3 Gastrointestinal, Immune, and Inflammatory Disorders

In gastrointestinal applications, local acting compounds might have a benefit, due to the fact that not all the time a systemic action is required. Peptides can be involved in barrier function or immune signaling and polyphenols could regulate modulation of microbial metabolism or mucosal inflammation. Functional bowel symptoms, inflammatory states and restoration of microbial ecology after disturbance of the diet are examples of candidate applications, but causality is hard to establish. Alterations in relative abundance of microorganisms should be paralleled by functional metabolites, barrier markers, signs and symptoms, and clinically relevant outcomes. The broad endpoints associated with immune health claims are particularly sensitive to undefined endpoints; future immune health trials should specify the desired outcome, such as improved vaccine response, faster recovery from infection, changes in inflammatory status, or some other measurable function of immune health.

8.4 Evidence from Human Clinical Trials

The strongest human evidence is collected by a trial that includes a chemically characterized product, a dose that is justified, an appropriate comparator, an adequate duration, preregistered outcomes, assessment of adherence, and biomarkers of exposure or target engagement. There are several trials that do not have all these properties. There is significant interindividual response and average effects may mask subgroups of responders. However, post-hoc subgrouping can result in a false positive result. Ideally, it would be preferable to stratify the patients beforehand based on their baseline diet, microbiome, genotype, metabolic state, or medication use. Clinical prospects are therefore best in the narrower indications with reasonable mechanisms and logically clinically intermediate measurable outcomes, and then larger trials to examine long-term clinical efficacy.

9. SAFETY AND REGULATORY CONSIDERATIONS

9.1 Toxicity, Allergenicity, and Recommended Intake

Concentrated doses of food are not safe when coming from any source. Peptide products may contain allergenic sequences or contamination from marine, egg, milk, soy or other sources. Hydrolysis can decrease or sometimes reveal allergenic epitopes. Polyphenol extracts can lead to gastrointestinal problems, liver damage in susceptible individuals, pro-oxidant effects, thyroid or iron-related toxicity or toxicity due to contamination. As an example, green-tea catechins highlight the importance of differentiating customized beverage intake from concentrated extracts. Identity, impurities, dose, duration, vulnerable population, reproductive consideration, organ-function monitoring and post-market surveillance should be included in the assessment for safety.

9.2 Drug–Nutraceutical Interactions

Polyphenols can affect cytochrome P450 enzymes, glucuronidation, efflux and uptake transporters, platelet function, and mineral absorption. Peptides or protein hydrolysates may influence blood pressure or glucose and thereby add to medication effects. Clinically relevant interactions are preparation- and dose-specific; in-vitro inhibition alone is not sufficient evidence, but it should guide targeted testing. Patients receiving anticoagulants, antiplatelet agents, antihypertensives, glucose-lowering drugs, immunosuppressants, or anticancer therapy should seek professional advice before using concentrated products.

9.3 FDA, EFSA, and FSSAI Frameworks

In the United States, dietary supplements are regulated under a framework distinct from conventional foods and drugs; firms are responsible for product safety and truthful labelling, and disease-treatment claims are not permitted without drug authorization [27]. The European Food Safety Authority evaluates scientific substantiation of nutrition and health claims under European legislation, with attention to characterization of the food or constituent, claimed effect, and causal evidence [28]. In India, the Food Safety and Standards Authority of India regulates health supplements, nutraceuticals, foods for special dietary use, and related categories through notified standards and labelling requirements [29]. Developers must determine the intended category early because ingredient permissibility, dose, claims, manufacturing, and evidence expectations differ among jurisdictions.

10. CHALLENGES AND FUTURE PERSPECTIVES

10.1 Stability, Standardization, and Quality Control

The field must move beyond naming a source such as “marine peptides” or “grape polyphenols.” Reproducibility requires marker compounds or sequences, molecular-weight distribution, chromatographic fingerprints, degree of hydrolysis, extraction conditions, contaminant limits, and stability-indicating assays. Processing-induced oxidation, peptide aggregation, polyphenol polymerization, moisture uptake, and packaging interactions can change activity over shelf life. Reference materials and interlaboratory analytical validation are therefore essential.

10.2 Preclinical-to-Clinical Translation

Experimental models should reflect digestion, metabolism, and human exposure. Cell studies should test physiologically plausible parent compounds and metabolites. Animal studies should report formulation, route, dose equivalence, and exposure, while acknowledging species differences. Early human studies should establish tolerability, pharmacokinetics, and target engagement before large efficacy trials. Null findings should be published because they refine dose selection and prevent repetition. Core outcome sets would improve comparability across trials.

10.3 AI-Driven Discovery and Personalized Nutrition

Machine learning can be used to predict the probability that a protein will be cleaved, what activity motifs it contains, whether it is toxic, allergenic, and what are its physicochemical properties. It can also incorporate polyphenol structure, metabolomics, microbial pathways, and formulation data to help prioritize candidates. The quality of the prediction depends on the representativeness of the training data set and on the strict external validation of the models; models trained on small and redundant peptide data sets can overestimate the performance. Explainable models are preferred when used to inform ingredient selection or safety decisions. Personalised nutrition would involve algorithms to integrate diet, genotype, microbiome, exposure to metabolites, and clinical phenotype, but prospective studies are required to demonstrate that personalisation is superior to generic recommendations in terms of outcomes [30].

10.4 Future Clinical Trial Requirements

Standardized products, preregistration, sufficient sample size, clinically relevant doses, active-comparator or placebo controls, and reporting of adverse events should be used in future trials. Conjugates and microbial metabolites should be quantified in the pharmacokinetic substudy designs. The interaction between peptide and polyphenol compounds can be studied by factorial trials to identify additivity, synergy and antagonism. Adaptive dose-ranging can provide efficient identification of exposure thresholds and decentralised monitoring can provide adherence and diet. Overall, there is a need for a greater number of well-defined translational programs in the field that tie together the links between chemistry, digestion, exposure, mechanism and clinical effect.

11. CONCLUSIONS

Bioactive peptides and polyphenols are versatile building blocks for new generation nutritional supplements as they can act on complementary targets such as oxidative stress, inflammation, vascular function, metabolism, intestinal ecology, and cellular resilience. They have significant restrictions in stability, absorption, metabolism, standardization, dose selection and clinical evidence. What is actually consumed by the organism could be an intestinal fragment, conjugate, or a microbial metabolite of the ingredient on the label. While formulation technologies can help improve stability and exposure, they must be proven in man to be effective and must be taken into account from a safety, manufacturing and regulatory point of view. The progress will rely on chemically-defined preparations, realistic mechanistic studies, validated biomarkers, interaction assessment and well-designed clinical trials. In this scenario, peptide- and polyphenol-based products can be considered as possible candidates which can be used as effective supplements to healthy diet and existing healthcare rather than potentially offered to a wide audience as alternatives to healthy diet.

The same is true for existing syntheses of cardiovascular peptides, dietary phenolics, and resveratrol trials, which reiterate the point that there is strong biological plausibility, but product-specific human evidence is needed to decide clinical use [31-33].

Abbreviations

ACE, angiotensin-converting enzyme; AI, artificial intelligence; DPP-4, dipeptidyl-peptidase-4; EFSA, European Food Safety Authority; FDA, Food and Drug Administration; FSSAI, Food Safety and Standards Authority of India; MAPK, mitogen-activated protein kinase; NF-ϰB, nuclear factor kappa B; Nrf2, nuclear factor erythroid 2–related factor 2; NLRP3, NOD-like receptor protein 3.

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