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Narrative review of bioactive peptides from plants

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ABSTRACT

Bioactive peptides (BPs) are short amino acid sequences with significant health-promoting properties. Increasing evidence highlights plant-derived peptides as sustainable and safe alternatives to synthetic drugs and animal-based peptides, given their wide distribution in legumes, cereals, pseudocereals, fruits, vegetables, herbs, and spices. These peptides exhibit diverse bioactivities, including antioxidant, antihypertensive, antimicrobial, anti-inflammatory, hypocholesterolemic, and immunomodulatory effects. Their functionality is largely determined by amino acid composition, sequence, and structure, with hydrophobic and aromatic residues playing central roles. Extraction and characterization techniques such as enzymatic hydrolysis, fermentation, and advanced analytical tools have facilitated their identification and application. However, commercialization is challenged by issues of stability, bioavailability, high production costs, and limited clinical validation. Regulatory frameworks, particularly those established by the EFSA and FDA, demand rigorous safety and efficacy data, further slowing product development. Despite these limitations, plant-derived bioactive peptides represent a promising frontier in functional foods, nutraceuticals, and therapeutic innovations. This review synthesizes current knowledge on their sources, extraction methods, health benefits, challenges, and regulatory considerations, while highlighting the future potential of these biomolecules in promoting human health.
Keywords: Bioactive peptides, Plant-derived compounds, Functional foods, Nutraceuticals, and Therapeutic potential.

INTRODUCTION

Bioactive peptides are specific protein fragments with a beneficial influence on body functions or conditions and may ultimately impact health. The scientific community is interested in these peptides because they translate into a wide range of bioactivities, such as antioxidant, angiotensin-converting enzyme (ACE) inhibitory, anti-inflammatory, or hypocholesterolemic properties [1, 2]. These biomolecules usually contain a mixture of hydrophobic (predominantly aromatic) and basic (e.g., arginine or lysine) amino acid residues, linking the basic concepts of bioactive peptides to the classification of sources and investigation of their health effects.

Definition and Classification of Bioactive Peptides

Bioactive peptides are sequences of amino acids consisting of fewer than 50 residues [1]. BPs fall into two groups based on their origin: Endogenous peptides are synthesized within cells, such as those produced by neural and immune cells, whereas exogenous peptides are acquired from external sources like food and dietary supplements. Bioactive peptides exhibit a range of biological activities and contribute to the regulation of various physiological functions in the body [1]. Their physiological effects depend on the specific type of peptide, as well as the sequence and properties of their constituent amino acids. Peptides offer several advantages over intact proteins from a nutritional standpoint, as they typically possess higher bioavailability and lower allergenic potential, rendering them well-suited for applications such as infant formulas [2]. Therapeutically, bioactive peptides provide distinct benefits, including targeted activity at low effective doses, minimal toxicity, and efficient excretion from the body [3]. This contrasts with many conventional pharmaceutical agents, which often exhibit broader mechanisms of action, accumulate in different tissues, and can lead to increased toxicity and environmental concerns. During the past decade, research focusing on the biological, physiological, and biochemical properties of bioactive peptides has rapidly advanced, underscoring their potential across various fields such as medicine, pharmacology, and nutrition. Thousands of bioactive peptides have been identified across diverse groups of organisms, including both plants and animals. Dietary peptides are present in a wide array of foods, with prominent sources spanning both animal- and plant-based categories [2]. Plant-derived peptides are isolated from legumes, cereals and pseudocereals, fruits and nuts, as well as herbs and spices.

Sources of Plant-Derived Bioactive Peptides

Plant-derived bioactive peptides are essential components in plants, with mixtures often totaling up to 10% of the total nitrogen content [3]. Main sources of bioactive peptides include legumes, cereals, fruits and vegetables, as well as herbs and spices [2]. Legumes offer proteins with excellent nutritional value and well-balanced amino acid compositions. Cereals and pseudocereals such as amaranth, quinoa, millet, and sorghum, which are staple foods in many parts of the world, contain many promising protein sources. Protein recovery from fruits and vegetables usually involves loading the material's residues onto an ion exchange column. Usually, the bioactive peptides from these proteins present antioxidant and antihypertensive properties. Similarly, herbs and spices like cardamom, cinnamon, clove, coriander, nutmeg, and oregano possess high medicinal, antimicrobial, and antioxidant properties. Peptides from this source generally possess antioxidant, antihypertensive, cholesterolemic, and antimicrobial properties [2].

Legumes

The development of novel prophylactic and therapeutic agents for common disorders, such as diabetes, cardiovascular diseases, cancer, and obesity, is a critical research focus [2]. It is well established that consuming pulses such as beans, peas, lentils, and chickpeas reduces plasma cholesterol levels in humans. Peptides derived from pulses exhibit various health-promoting properties, including antioxidant, anti-inflammatory, antihypertensive, antidiabetic, immunomodulatory, anticancer, and antimicrobial effects. Several investigations into the angiotensin I-converting enzyme-inhibitory (ACE-I) activity of lupin protein hydrolysates and lupin-derived peptides have been conducted, given the establishment of a plant-based antihypertensive drug market. Tan et al. reported that a protein hydrolysate generated by enzymatic hydrolysis using alcalase and flavourzyme exhibited promising antihypertensive effects in spontaneously hypertensive rats [5]. Proteins from green peas have also been utilized for antihypertensive activities [6]. Many ACE-I inhibitory peptides originate from thermolysin-treated Phaseolus vulgaris seed globulin proteins, with Pro–Leu–Val–Leu–Tyr–Pro peptide identified as the most potent inhibitor. Soybean-derived bioactive peptides possess immunomodulatory, anticancer, antidiabetic, and antimicrobial properties. Luo et al. extracted a proline-rich antimicrobial peptide from broad beans that interacts with the negatively charged lipopolysaccharide components of Gram-negative Salmonella membranes. More recent research has focused on the antioxidant properties of Phaseolus lunatus seed protein hydrolysate and green pea protein [7].

Cereals

Cereal grains stand among the world's most widely consumed staple foods, constituting a primary source of dietary plant proteins that supply essential amino acids. Recent research underscores the potential of bioactive peptides derived from these crops to impact human health positively. Cereals and legumes form the cornerstone of a healthy diet, a fact widely reflected in various international nutritional guidelines and food selection strategies. Mounting evidence confirms that peptides naturally present or released in cereals and legumes, either by enzymatic hydrolysis or during gastrointestinal digestion or fermentation, may promote health through diverse activities [2, 3]. These include antimicrobial effects; inhibition of the angiotensin-converting enzyme involved in blood pressure regulation; cholesterol-lowering and antioxidant activities; improved mineral absorption; and immunomodulatory phenomena [4]. The correspondence of these bioactivities in humans remains limited by physiological aspects that preclude the delivery of peptides to target tissues at effective concentrations after their absorption in the gastrointestinal tract. The bioactive potential of seed storage proteins evidences an evolutionary path that extends well beyond their nutritional role. The health benefits attributed to the plant seeds stem from studies employing enzymatic hydrolysis, natural occurrence in the intact storage protein, or gut digestive proteolysis [5]. These findings suggest opportunities for the development of supplementary, complementary, or pharmaceutical tools for integrated, preventive, or curative health care and the possible use of naturally derived portfolios of peptides as functional food ingredients. Peptides identified in cereals possess a broad range of activities and potential health benefits that may underlie the positive effects associated with whole grain products.

Fruits

A fruit is the mature ovary of a flowering plant, usually consisting of a seed and its envelope, although in some cases the seed may be absent. Fruit can be divided into two types, fleshy fruit and dry fruit, based on the structure of the ovary wall (pericarp). Examples of fleshy fruits include citrus, berries, melons, mangoes, and bananas, and common dry fruits include wheat, oats, chickpeas, mustard, and flaxseed [5]. Fruits are an essential part of a healthy diet and represent one of the most critical sources of micronutrients and natural antioxidants, including antioxidant bioactive peptides. A bioactive peptide is a specific protein fraction that has a physiological cardioprotective effect and has antioxidant, antimicrobial, cytotoxic, and anticancer properties. Antioxidant peptides are also important because they are involved in many pathological processes of disease and aging. They act as phytochemicals, scavenging free radicals and protecting cells from oxidative stress [6]. Adenanthera pavonina is a deciduous, medium-sized tree found in Asia, Africa, Australia, and several Pacific islands, including Fiji. The seeds can be used to source bioactive peptides that show antioxidative, reddish brown, apricot-like aroma, and antityrosinase activity, which are important for human nutrition. 7S globulin, an IP of A. pavonina seeds, demonstrates enhancement of hydroxyl radical scavenging activity. Citrus fruits are one of the most commercially important fruit crops globally and an excellent source of fiber, vitamins, carotenoids, and minerals. Extraction of bioactive peptides from citrus fruit may provide natural ingredients for hypoglycemic activities and the development of food with antidiabetic activity [7]. Depolymerized pectin from citrus peel by acid-extraction, which has suppressive effects on obesity, can be used as a new and natural biomaterial for anti-obesity treatments. The pseudocereals amaranth and quinoa are considered complete nutritional sources, which provide essential fatty acids and a high-quality protein source with a balanced amino acid composition. Bioactive peptides from amaranth grain can be used as a safe source to mitigate Alzheimer's pathology and promote healthy brain aging. Bioactive peptides obtained from quinoa that exhibit good cholesterol-lowering activity in a high-fat diet could be useful in the control of cardiovascular diseases. Other methods for loading the antioxidant bioactive peptides into natural substances include heating, enzyme, and fermentation to be used as natural antioxidants with potential as substitutes for synthetic antioxidants [5, 6, 7].

Vegetables

Vegetables have been popular as functional foods for a long time across all cultures. Bioactive peptides are water-soluble and thus can be easily liberated from vegetables. Apart from anti-obesity, anti-cancer, anti-inflammatory, and cardiovascular protective activities, vegetable-derived peptides have been reported for their antioxidant, anti-hypertensive, and anti-proliferative properties [4, 5]. The limited number of studies reported to date suggests that this category of bioactive peptides deserves deeper research. Recent studies have also indicated that the production of bioactive peptides from fruit and vegetable proteins should find an increasingly important role in the near future. These observations have opened new perspectives for the utilization of peptides and hydrolysates from fruits and vegetables. In the human diet, vegetables are of primary importance as sources of peptides and proteins. Only in the last few years, however, has the true potential of this protein source been investigated. Proteins derived from broccoli, cauliflower, and radish have been considered as prospective sources of bioactive peptides [5]. Membrane cleavage of Bryophyllum proteins is another technology with recognised potential [4]. The antioxidant, antihypertensive, and anti-proliferative properties demonstrated for broccoli- and cauliflower-based peptides suggest, in particular, the apparent potential for deriving anti-cancer compounds from vegetable proteins.

Herbs and Spices

Herbs and spices are a broad category of plant materials that impart characteristic colour and flavour to food and beverages [5]. They represent a very diverse group from an ethnopharmacological and phytochemical viewpoint 6. Bioactive peptides isolated from several of these have been reported in the last decade [6]. In a study designed to characterise the bioactive potential of culinary and medicinal herbs and spices, those whose extracts exhibited the broadest and most potent bioactivities were Ocimum sanctum, Andrographis paniculata, and Curcuma longa. The latter was particularly effective as an antioxidant. Peptides present in Curcuma longa exhibited a wide spectrum of antioxidant activity against free radical scavenging, ferric-reducing, lipid peroxidation inhibiting, metal ion-chelating, and other activities. It was suggested that these peptides may be useful nutraceutically [5].

Extraction Methods for Bioactive Peptides

Plant-derived bioactive peptides represent a promising category of secondary metabolites. Therefore, experimental methods aimed at extracting these peptides prior to structural and functional characterization are of special interest. Peptides are usually extracted from their natural sources by enzymatic hydrolysis, chemical extraction, or fermentation processes [6]. Enzymatic hydrolysis, the method of choice, involves incubating the raw materials with a suitable proteolytic enzyme to obtain partial or complete hydrolysis of proteins and generation of bioactive peptides. Using chemical extraction approaches, peptides can be recovered from biological materials using heat, acid, or alkali treatments [8]. Such treatments, however, lead to protein denaturation or conversion of all peptides to amino acids, so that acid or alkali hydrolysis is mainly suitable for amino acid extraction. A diversified methodology of fermentation can remove antinutritional factors and improve the nutritional quality and functional characteristics of plant proteins and peptides because of the hydrolysis of the nutritive molecules. Each method of peptide extraction has its advantages and disadvantages, and the choice mainly depends on the source and nature of the desired peptides [5]. However, attempts have also been undertaken to optimize the conditions for enzymatic hydrolysis, and new technologies are often combined with enzymatic digestion to ensure the maximal yield during the extraction of the peptides. In recent years, methods such as microwave-assisted extraction, ultrasonic-assisted extraction, reverse micelles extraction, membrane extraction, ion exchange chromatography, gel permeation chromatography, and immobilized metal affinity chromatography have also found application in the extraction of bioactive peptides [7].

Enzymatic Hydrolysis

Bioactive peptides are conventionally isolated by chemical or enzymatic hydrolysis and fermentation 6. Enzymatic hydrolysis is the most commonly used method for the generation of bioactive peptides from protein sources. Enzymatic hydrolysis produces hydrolysates with a wide range of compounds. The protein is usually hydrolyzed by proteases from animal, plant, and microbial sources [8]. Proteases from animal sources, such as trypsin and pepsin, have been widely used for the generation of bioactive peptides. Examples of proteases from microbial sources are papain, Alcalase, and Neutrase. Plant proteases can be obtained from plant latex and fruits and are considered safe for use in the food industry because some of them are considered GRAS (Generally Recognized as Safe) [8].

Chemical Extraction

Chemical extraction is a direct alkaline or acid hydrolysis method in which plant-derived protein sources are first treated with an acid or alkaline solution to hydrolyze them and then neutralized and purified to obtain plant-derived BPs [9]. This method requires a much longer extraction time (approximately 16–24 h) than enzymatic hydrolysis and produces a high yield. Alkaline extraction and acid precipitation methods are often used for soybean, rapeseed, and corn proteins, but this method is not preferred for the extraction of peptides with specific bioactive functions 5. Acid hydrolysis of protein raw materials can be another method, and peptides can be extracted by HCl (3 mol/L) hydrolysis for 1–3 days and then neutralized and purified [10]. Chemical extraction is also used as the first extraction step for various plant species. Chemical methods like acid and alkaline extraction are used at the first step, mainly in the extraction of protein from plant biomass that is rich in cellulose, lignin, and hemicellulose. For example, alkaline extraction using 1 M NaOH (pH 13) can be an effective way to extract proteins from rice residue to obtain bioactive peptides [9].

Fermentation Techniques

The oldest method for producing bioactive peptides is microbial fermentation, in which proteolytic enzymes break down proteins into peptides and amino acids [2]. The proteolytic ability of microorganisms has been extensively used for centuries in coagulated milk products and fermented products, such as soy sauce, fish sauce, wine, and vinegar. Hydrolysis can be catalyzed by microbial enzymes during microorganism growth or by certain added commercial proteases in a secondary hydrolysis step. LAB species, such as Lactobacillus, Leuconostoc, Pediococcus, Streptococcus, and Enterococcus, possess high proteolytic activity [5]. In fermentation, microbial strains, substrates, media compositions, and controlling parameters such as pH, temperature, and time must be carefully chosen [3]. Liu et al. successfully produced bioactive peptides by hydrolyzing pea protein using yogurt and marsh grape juice fermented with Lactobacillus and yeast strains. Similarly, Luo et al. developed antioxidative peptides from cottonseed protein fermented with Bacillus species, and Arunachalam et al. obtained antihypertensive peptides from black gram using Lactococcus lactis. A proteolytic-deficient mutant strain of Propionibacterium freudenreichii was also employed to produce anti-inflammatory peptides from raw milk, illustrating the versatility of fermentation in generating functional peptides from diverse protein sources [13].

Characterization of Bioactive Peptides

The characterization of plant-derived bioactive peptides encompasses the determination of amino acid composition, sequence, and analytical techniques that shed light on their physical and chemical characteristics. Chemical and spectroscopic methods quantify amino acid content, while mass spectrometry establishes molecular weight and elucidates sequence [2, 6]. X-ray diffraction and nuclear magnetic resonance further reveal molecular structure, and chromatographic methods aid purification and characterization. Understanding these distinctive attributes is vital because the biological action of bioactive peptides closely depends on gastrointestinal stability, absorption capability, and enzymatic resistance 6. Bioactive peptides typically consist of 2 to 20 amino acids with molecular masses ranging from 0.4 to 2 kDa, holding promise for functional foods and nutraceuticals aimed at preventing or managing chronic diseases. High-throughput peptidomics of crop proteomic datasets reveal that more than 6000 plant proteins potentially contain bioactive peptides [5]. The elucidation of structure–activity relationships plays a pivotal role in advancing the design of bioactive peptides to enhance their efficacy as functional ingredients [2].

Amino Acid Composition

The amino acid composition of peptides is a major factor influencing the bioactivity of plant-derived peptides. Peptide chains commonly feature leucine (L), isoleucine (I), valine (V), glutamine (Q), alanine (A), proline (P), glycine (G), or tryptophan (W). Aromatic and acidic amino acids are present in many bioactive peptides, though it remains unclear whether they serve as functional or structural components [5]. Active peptide sequences generally comprise 2–20 amino acids; although length does not define activity, shorter chains exhibit greater resistance to degradation by the proteolytic enzymes in the digestive system, thereby offering enhanced functionality, patentability, and broader applications [5].

Molecular Weight Determination

Bioactive peptides typically contain 2-20 amino acid residues and have molecular masses ranging from 0.4 to 2 kDa. The magnitude of their biological activities is strongly correlated with structure, composition, and especially molecular weight [4]. Research results provided clear evidence that smaller peptides are more potent antioxidants than larger ones. Mass spectrometry is commonly used to determine the molecular weight of bioactive peptides. The amino acid polarity distribution influences antioxidant capacity in a way that smaller peptides with equal or lesser antioxidant capacity have, in general, fewer polar residues except when one of the aromatic amino acids Tyr or Phe is found in their sequence [5].

Structural Analysis

The structural attributes of bioactive peptides significantly influence their physiological roles and potential applications. Characterizing these structures involves determining the amino acid composition, peptide and protein sequence, homology, molecular weight, and crystallinity [5]. Structural analysis employs techniques such as Fourier-transform infrared spectroscopy, nuclear magnetic resonance, circular dichroism, X-ray crystallography, and molecular dynamics simulations [6]. Nuclear magnetic resonance and X-ray crystallography provide atomic-scale resolution essential for understanding interactions between peptides and larger biomolecules. Circular dichroism spectroscopy is commonly used to investigate secondary structures of peptides and proteins. The structural properties are pivotal for assessing the biological activity of peptides; various domains correspond to different biological functions, including antimicrobial, antiviral, antioxidant, and antihypertensive activities [8].

Health Benefits of Plant Bioactive Peptides

Plant bioactive peptides exhibit various biological activities, such as antioxidant, antihypertensive, antimicrobial, anti-inflammatory, and immunomodulatory, and serve as precursors of active amino acids and minerals. The applications of bioactive plant peptides in functional food production highlight their key role as health-promoting ingredients [2].

Antioxidant Activity

Reactive oxygen species (ROS) such as hydroxyl radical, superoxide anion radical, and singlet oxygen are highly reactive molecules that are capable of attacking cell components such as lipids, proteins, membranes, and DNA molecules. A chain reaction mediated by ROS, leading to oxidative stress, may damage cells and organ tissues and has been implicated in cardiovascular diseases, cancers, dementia, and Alzheimer's. Sotiroudis et al. presented the mechanisms through which antioxidants neutralize ROS [1]. These include free radical scavenging by electron donation, metal chelation, and lipid peroxidation prevention. Products containing antioxidants that are capable of counterbalancing ROS and interfering with the oxidation chain reaction through these mechanisms can inhibit excessive damage to cells suffering from oxidative stress [2]. They discussed that the antioxidant activity of these products can be measured using various assays, including lipid peroxidation inhibition, ferric-reducing power, DPPH scavenging, and metal-ion chelating activities [9]. It is not unusual to receive multiple antioxidant values for the same product using multiple methods, because different products may act through different antioxidant mechanisms. Antioxidant peptides have been successfully isolated from a large number of bioresources, including plants, fish skin, and meat. Plant sources include seeds of Sesamum indicum, rice bran, quinoa, chickpea, and oat. The antioxidative capacity of some pea-protein isolates has been investigated [9]. Most of these plant proteins are from a legume or cereal source. Linked to their antioxidant properties, a number of these peptides have been shown to be heat-stable and pH-tolerant and to provide protective effects in the prevention of lipid peroxidation. Most also contain hydrophobic residues, although positively charged residues (Arg) have also been found in a few hydrolysates [11]. The length of these peptides varies considerably from 2 to 20 residues. Shi et al. discussed that bulky hydrophobic residues such as Pro, His, and Trp also contribute to antioxidant activity. The mechanisms through which peptides exert their antioxidant effects are proposed to be related to the presence and position of aromatic and hydrophobic amino acids in the sequence. Both aromatic and hydrophobic amino acids are also implicated in metal-ion chelating activity and radical scavenging [1].

Antihypertensive Effects

Hypertension is considered a syndrome triggered by the body's inability to control blood pressure. It is defined as a persistent elevation of the systolic and diastolic arterial pressures higher than 140 mmHg and 90 mmHg, respectively, and can be classified as primary or secondary [2]. High blood pressure is one of the major risk factors related to the development of kidney, heart, and brain diseases, including myocardial infarction, stroke, atheroma, arteriosclerosis, kidney failure, and blindness [3]. Natural antihypertensive agents have gained considerable attention because they do not possess the side effects associated with synthetic chemical drugs. The enzyme angiotensin-converting enzyme (ACE) plays a major role in blood pressure regulation. Substances able to efficiently inhibit this enzyme are considered capable of controlling hypertension. ACE catalyzes two crucial reactions: it converts angiotensin I into angiotensin II, a potent vasoconstrictor capable of constricting blood vessels and increasing blood pressure; and it inhibits the release of bradykinin, a strong vasodilator that dilates blood vessels and lowers blood pressure. Bioactive peptides able to inhibit ACE act by blocking these pathways, thereby reducing blood pressure. Plant-derived peptides have been proven to be potent ACE inhibitors, exhibiting antihypertensive properties [5].

Antimicrobial Properties

Plant-derived peptides have demonstrated significant antimicrobial potential against a broad range of pathogens 10. In the last two decades, eighteen plant-derived peptide protease inhibitors (PPIs) with antimicrobial activity have been identified [1, 2]. Several PPIs exhibit broad-spectrum efficacy against bacteria, fungi, and viruses, including Kunitz and Trypsin type inhibitors from species belonging to the Solanaceae, Fabaceae, and Moringaceae families [7]. These peptides are promising candidates for novel antibacterial and antifungal agents, and their mechanisms of action and efficacy continue to be the subject of active research. Antimicrobial peptides (AMPs) constitute a diverse group of small molecules synthesized by many living organisms, including plants. Due to their antimicrobial and immunomodulatory capacities, AMPs feature in numerous clinical and preclinical development programmes [6].

Anti-inflammatory Effects

Inflammation is the body's defence mechanism against harmful stimuli or irritation. It consists of four phases: induction, detection, production of mediators, and target tissue response [10, 11]. When kept under control, inflammation helps counteract injury or infection, promote repair, and restore the normal physiological state of the tissue. However, long-lasting or aberrant inflammatory stimuli can lead to chronic inflammation, which has been involved in atherosclerosis, diabetes, cancer, and ageing [11]. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most prescribed anti-inflammatory drugs; however, they present severe side effects. The search for new, safe, and effective drugs has focused on food-derived bioactive compounds able to reduce pro-inflammatory mediators. Peptides from fish- or shellfish proteins show relevant anti-inflammatory effects, able to reduce the production of inflammatory mediators like NO, IL-6, and IL-1β and to increase antioxidant activity [11]. The MAPK pathway is partially involved in the activity. Several peptides also modulate the immune response by regulating immune-related genes.

Immunomodulatory Effects

Immunomodulatory peptides regulate the immune response, either by stimulation or suppression. They have attracted increasing interest in recent years due to the crucial role the immune system plays in achieving good health [4, 5]. Among the most investigated bioactivities of plant-derived bioactive peptides are their antioxidant, antihypertensive, antimicrobial, and anti-inflammatory properties, yet few studies focus on their immunomodulatory effects [2, 3]. Positive immunostimulatory properties can be evidenced through humoral and cell-mediated immune responses, which manifest as antibody production, activation of phagocytic macrophages, promotion of cytokine expression, and stimulation of proliferation or function of T and B cells. A summary of immune-stimulating peptides isolated from different plants reveals a rather heterogeneous group, differing in origin, amino acid sequence, and peptide length [5, 8]. Seeds of Phaseolus vulgaris L. (common bean) are an important source of protein, constituting about 10.44% of the dry weight. An immunomodulatory peptide was isolated and purified from raw red beans after simulated gastro-duodenal digestion. Human peripheral blood mononuclear cells (PBMCs) were treated in vitro with the purified peptide, and the production of pro-inflammatory cytokines, tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6) was quantified by ELISA. At a concentration of 200 μg/mL, the peptide enhanced TNF-α release more than threefold and IL-6 production approximately fourfold compared to the untreated control. The increasing interest in food-derived immunomodulatory peptides is not surprising, since they might represent a useful intervention tool in supporting a depressed immune function, either associated with certain physiological conditions, such as aging, or with cellular responses induced by pathological conditions [1, 2].

Bioactive Peptides in Functional Foods

Adding bioactive peptides to foods to produce products with enhanced nutritional value is of practical interest to the food industry. Plant peptides possessing attractive physiological features or health-promoting properties may be incorporated into widely consumed food products such as baked goods, breakfast cereals, snacks, bars, soups, sauces, and beverages as functional ingredients. As a viable alternative to conventional drugs, bioactive peptides can be used commercially as ingredients in functional foods, nutraceuticals, pharmaceuticals, and dietary supplements [9]. Bioactive peptides from plant sources play an important role as functional ingredients for supplementation and fortification of various food products designed to impart specific health benefits. Understanding the isolation, purification, and sequencing of bioactive peptides is essential for their commercial use in nutraceutical products; an overview of the different techniques available is therefore provided [8]. Bioactive peptides in functional foods exert physiological effects and regulate mechanisms associated with immunity, inflammation, infection, hypertension, hypercholesterolemia, diabetes, cancer, and neurological problems. Because they are often degradation products of more abundant proteins, bioactive peptides derived from plant proteins such as soybean and rice can provide natural sources of bioactive components in functional foods. Delivering bioactive peptides through food, therefore, represents an attractive alternative strategy to synthetic drugs, since peptides can bind selectively to receptors without the potential toxicity of chemical products. The medicinal use of bioactive peptides is still limited, however, due to scant information on their mechanisms of action. Models that establish structure–activity relationships are needed to predict their biological activity and to screen and design synthetic peptides for specific applications [6]. Hydrolysates are often easier and cheaper to produce than purified peptides, and their manufacture from food-processing by-products offers an additional cost advantage. The biological activities of plant protein hydrolysates indicate that the corresponding peptides may be employed in the development of functional foods with beneficial health effects. Strict regulatory requirements regarding the efficacy and safety of health claims represent a barrier to the commercialization of authentic nutraceuticals, since the necessary clinical evidence is both expensive and time-consuming to collect. Furthermore, the bioavailability of hydrolysed peptides in the human organism is still largely unexplored [5]. The detailed mechanisms of absorption, distribution, metabolism, and excretion of those peptides remain unclear, as it is still unknown whether their effects develop directly in the gut or only after translocation into the bloodstream. The role of the gut microflora is also largely unexplored [12].

Challenges in Bioactive Peptide Research

Plant bioactive peptides hold promising potential in food, agriculture, and pharmaceutical industries. Nevertheless, to proactively advance research and fully realize their therapeutic promise, numerous challenges must be addressed [4]. The peptide properties, such as amino acid composition, sequence, and molecular weight, along with environmental factors, influence the stability of bioactive peptides throughout food processing, digestion, and storage, thus affecting their bioactivities. Effective delivery of bioactive peptides depends on maintaining their in vivo target tissue activities. Unlike their synthetic counterparts, natural bioactive peptides generally exhibit poor bioavailability, susceptibility to enzymatic degradation, and limited absorption from gastrointestinal fluids, which hinders the desired pharmacological response [5]. Systematic understanding of the mechanism of disintegration and the mode of transportation of bioactive peptides within the human gastrointestinal tract remains insufficient. Therefore, further studies on gastrointestinal stability, bioavailability, and transport mechanisms are essential. Peptides derived from enzymatic hydrolysates, fermentation, and other plant-based hydrolysates can significantly impact consumer health and may serve as potential new drug sources. Continued research into the absorption, bioavailability, and mechanisms of action of these peptides is crucial to unlock their full medicinal capabilities [1]. A major obstacle in the clinical application of active peptides is their instability under listed storage conditions, with many bioactive peptides being highly unstable. Most peptide drug preparations lack definitive data on pharmacological safety, efficacy, and [3]. Obtaining clinical trial certificates is typically a lengthy and costly process. Regulatory and legislative restrictions delay product registration and launch. Consumers often harbor doubts regarding the efficacy of plant-based peptide products, while many regulatory authorities impose stringent regulations on such products. Additionally, manufacturing costs remain a significant barrier to commercialization, and the eventual retrieval of bioactive peptide products from the market due to safety concerns imposes additional burdens on manufacturers [2].

Stability and Bioavailability

In addition to discussions on their health benefits and applications, the stability and bioavailability of plant-derived bioactive peptides present significant challenges. Peptides may experience decomposition during storage as a result of oxidation, enzymolysis, temperature fluctuations, variations in heat treatment, and ultraviolet light exposure [5]. Furthermore, their resistance to gastric digestion is limited during oral administration. The bioavailability of a specific physiologically bioactive peptide typically hinges on its absorption and potential metabolic transformations occurring along the gastrointestinal tract [7]. The low bioavailability of plant peptides poses a considerable obstacle to their utilization. Upon entering the bloodstream, plant peptides exhibit poor stability and a short residence time, thereby affecting their therapeutic efficacy. Chemical modifications of peptides, such as targeted terminal alteration, incorporation of unusual amino acids, and modulation of amino acid composition, serve to extend plasma half-life, enhance oral absorption, facilitate blood-brain barrier penetration, and improve resistance to enzymatic degradation. In light of these factors, the oral availability of plant peptides emerges as a crucial concern in their development and application [8].

Regulatory Issues

Numerous reports about the beneficial effects of bioactive peptides have promoted interest in developing food as well as pharmaceutical products. Although dietary supplements, formulated with bioactive peptides, are already being marketed, they are integrated within the regulatory framework for food or pharmaceuticals in different countries [5]. However, in order for these products to be approved, specific regulations should be taken into account, and strong scientific evidence must be provided on their safety and efficacy. Moreover, information about the possible risks and benefits must be clearly described in labelling in order for the consumer to make an informed decision about intake as well as risk [7]. However, it is often the case that the suggested use, doses, and PBPs benefit information included on food products do not correspond to scientifically proven results. Therefore, these products should be regulated so that consumers are protected. Regulatory bodies, such as the European Food Safety Authority (EFSA) and the Food and Drug Administration (FDA), prescribe certain criteria for preparing structure/function claims, which include a description of the effects of substances on the growth, development, and normal functioning of the body. There is a growing global interest in the use of natural alternatives to synthetic ingredients for therapeutic purposes [10]. In spite of the numerous beneficial properties attributed to PBPs, only a small number of products have been commercialized so far, due to concerns about their safety and efficacy. The main reasons for these concerns include a lack of sufficient preclinical randomized clinical trials involving humans and failures in postmarket product surveillance and monitoring, highlighting the need for considerable strengthening of the existing regulatory framework. The bioavailability of PBPs, as well as their stability during and after oral administration, are other key aspects constraining their use as therapeutic agents and, consequently, should be carefully considered when preparing structure/function claims [11].

Consumer Acceptance

Acceptance of plant-derived bioactive peptides by consumers is an important facet of research. Several factors can affect consumer responses toward these peptides, most of which are based on the nature and processing of the bioactive peptides. Sensory attributes such as flavor, odor, texture, appearance, and the resultant taste of plant-based bioactive peptides influence consumer acceptance [2]. Other concerns include awareness about the preparation and consumption of these peptides, informed knowledge about where these peptides can be sourced, and the availability of various plant-based extracts. A study exploring the market acceptability of plant-based food supplements revealed that the primary reason for the widespread usage of the bioactive ingredients in such preparations is the minimal reports of side effects based on public consensus. On the contrary, plant bioactive peptide medications are yet to receive widespread acceptance [5]. A survey involving many respondents on the appearance of bioactive peptides, without disclosure of their names, indicated a marked preference for medicinally available bioactive peptides extracted from plants rather than from animals. To achieve higher consumer acceptability of plant-based bioactive peptides, variable shades of brown, ranging from pale brown to dark brown, in the preparatory forms of the peptides have been found to be beneficial [6].

Future Perspectives in Bioactive Peptide Research

Diverse plants have been identified as sources of various bioactive peptides having antioxidant, antihypertensive, antimicrobial, anti-inflammatory, and immunomodulatory properties. The interaction of bioactive components with peptide chains is also vital to the expression of beneficial effects. Effective use of bioactive peptides requires careful consideration of their stability, bioavailability, safety, and other regulatory concerns [9]. Earlier studies primarily employed enzyme hydrolysis and chemical extraction for the isolation of bioactive peptides. However, these methods have limitations such as low yield and impaired biological activity arising from intense processing conditions that alter the peptide structure and final activity. To overcome these limitations, advanced technologies like microwave-assisted extraction (MAE), ultrasound-assisted extraction (UAE), supercritical fluid extraction (SFE), and subcritical water extraction (SWE) are currently being utilized [10]. These innovative techniques offer advantages in yield and preservation of bioactivity. Additionally, biotechnological approaches can be employed to increase yield and enhance the functionality of bioactive peptides, presenting promising avenues for future research. Furthermore, the application of bioactive peptides as active pharmaceutical ingredients in medicine will significantly impact human health in the coming years.

Innovative Extraction Techniques

Bioactive peptides are usually obtained through enzymatic hydrolysis, chemical treatment, and fermentation. In plants, protein hydrolysates obtained through the enzymatic activity of fungal proteases and of edible mushrooms are important sources of novel peptides with potent bioactive properties [7]. This bioactivity may be improved by separating proteases and peptides through ultrafiltration techniques, although a large quantity of waste production may negatively affect the environment [6]. Waste management is likewise a concern for the chemical method of peptide extraction, which can use alkaline, acidic, or organic reagents. Considerable attention has been focused on the use of autolytic plant enzymes to replace costly and/or hazardous exogenous agents. Additional peptide sources may be found in organic solid-state fermentation of plant materials with proteolytic fungi, whose enzymes indirectly carry out the bioconversion [8]. However, these systems are often complex in nature, and the production of several secondary metabolites during fermentation can adversely affect the peptide dioxide crosslinking. Recent trends in both analytical chemistry and biochemistry have produced several novel techniques to reduce peptide extraction times, enhance peptide yield, and minimize the use of chemicals. These novel methods allow for precise targeting of bonds within the protein structure [9].

Biotechnological Advances

Enzymatic hydrolysis, chemical treatment, and fermentation are the most promising approaches for the synthesis of bioactive peptides from plant sources [5]. Agro-food wastes were also recognized as an interesting source for the generation of biopeptides with various biological activities [6]. A variety of biotechnological approaches (e.g., enzymatic hydrolysis, fermentation, in vitro proteolysis, in silico analysis, and genetic engineering) were also proposed to enhance the production capacity and biological activity of plant-derived bioactive peptides [13]. In recent years, the design and synthesis of peptides with minimal active structures required for biological activity has been the focus of intense research. Various extraction methods are described for the recovery of bioactive peptides from different food matrices, as well as the measurement of antioxidant capacity by different analytical methods. However, large-scale production of antioxidant peptides and commercial manufacture of antioxidant products remain problematic [6]. Further investigations on the structural characteristics and molecular mechanisms of antioxidant activity are necessary. In addition, new experimental and theoretical methods under development may further improve the application of plant-derived antioxidant peptides in the functional food industry. Therapeutic applications based on nanotechnology are expected to boost the effectiveness of existing nutritional peptides [12].

Potential Applications in Medicine

Plant-derived peptides may form the basis for innovative and inspiring lead compounds in the development of novel medicinal products. In drug discovery, their inherent and varying degrees of bioavailability, enzymatic stability, structural diversity, and mechanism of action enable the design of tailor-made leads to meet the numerous challenges that human disease presents [3] The successful introduction of orally active, small-molecule protease inhibitors into the pharmaceutical market has invigorated interest in the structural mimicry of bioactive peptides, as therapeutic agents often need to inhibit disease-causing enzymes. The design of radio-theranostic probes, inspired by peptide-cancer cell receptor interactions, has advanced the field, contributing to the development of agents displaying tumor localization [5]. The detailed structural and dynamic understanding of peptide-receptor interactions is crucial for tailoring compounds for therapeutic efficacy. Plant-derived bioactive peptides exhibit a broad spectrum of physiological modulatory functions, including antioxidative, antihypertensive, antithrombotic, cholesterol-lowering, antibacterial, immunomodulatory, and opioid-like activities [5]. These properties render them candidates for the treatment of chronic conditions such as oxidative stress, hypertension, and inflammatory and immunomodulatory disorders. Products based on plant-derived peptides have thus gained attention within the functional food and pharmaceutical industries [14-16].

CONCLUSION

Plant-derived bioactive peptides hold immense promise as multifunctional compounds capable of contributing to disease prevention and overall wellness. Their wide distribution in commonly consumed plants positions them as cost-effective, sustainable, and safe alternatives to synthetic agents. Advances in extraction and characterization techniques have deepened understanding of their structural features and mechanisms of action. However, critical challenges remain, particularly in overcoming stability and bioavailability barriers, ensuring cost-effective large-scale production, and providing robust clinical evidence to support health claims. Furthermore, regulatory requirements for safety and efficacy must be met to foster consumer confidence and industry growth. Looking forward, integrated research efforts involving biotechnology, food science, and clinical trials will be essential for unlocking the full potential of plant-derived peptides. If these challenges are addressed, bioactive peptides may become a cornerstone of next-generation functional foods, nutraceuticals, and therapeutic strategies aimed at enhancing global health outcomes.

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