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REVIEW PAPER

Bioactive peptides from traditional homemade fermented foods as an alternative for treatment

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Abstract: Bioactive peptides in fermented foods are attracting scientific interest due to their prospective applications as nutraceutical and functional foods. Conventional fermented foods are naturally processed at home through the action of lactic acid bacteria (LAB). These bacteria break down food components and generate lactic acid, various organic acids, hydrogen peroxide, carbon dioxide, and short-chain peptides, which offer numerous health benefits. The bioactive peptides formed during fermentation exhibit diverse biological functions influenced by their structural compositions. Following enzymatic hydrolysis, peptides initially inactive within the native protein matrix are released and exhibit biological activity. This review aims to comprehensively examine the functional properties of bioactive peptides derived from the fermentation of traditional foods, with a particular emphasis on their therapeutic potential, including antidiabetic, antihypertensive, and anticarcinogenic activities. This review examines the health benefits of various bioactive peptides produced by lactic acid bacteria during the fermentation of traditional foods. Microbial bioactivity during the fermentation process can produce hydrolytic enzymes that break down macromolecules in food into smaller compounds, such as bioactive peptides. A wide range of peptides have been identified as improving insulin uptake, decreasing blood glucose concentrations, and inhibiting key enzymes involved in the pathogenesis of diabetes. Specific peptides exert antihypertensive effects by acting as angiotensin-converting enzyme (ACE) inhibitors, thereby preventing the transformation of angiotensin I into angiotensin II. Moreover, some bioactive peptides demonstrate immunomodulatory properties by enhancing immune responses and inducing apoptosis in cancer cells. This article provides a comprehensive overview of the therapeutic and health-promoting potentials of bioactive peptides derived from fermented foods.

Keywords: Fermented foods, bioactive peptides, anti-hypertension, antidiabetic, anticancer

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INTRODUCTION

These days, consumers and experts are paying close attention to fermented foods, which are gaining increasing significance in terms of food safety and sustainability. Fermented foods are beneficial for the human digestive tract (GIT) and can have a positive impact on overall health. Furthermore, because fermented foods contain probiotics, bioactive chemicals, and nutraceuticals with no adverse side effects, they can help prevent or lower the risk of disease [1]. Various digestive and microbial fermentation enzymes can hydrolyze

proteins present in fermented foods, releasing substantial quantities of free amino acids (AAs) and peptides [2]. Tasdemir et al. (2020) [3] noted that fermentation is a metabolic pathway characterized by anaerobic microbial activity that converts carbohydrates into end products such as carbon dioxide and ethanol. Microbial activity during fermentation can alter the food's physical, chemical, and biological properties. Fermentation facilitates the biological generation of bioactive peptides through the action of proteolytic enzymes that hydrolyze proteins during food processing steps such as heating, fermentation, and maturation [4]. This hydrolytic process cleaves peptide bonds, releasing peptide fragments of varying lengths and properties, which are influenced by the specific amino acid composition of each peptide [5].

Covalent peptide bonds between amino acids form bioactive peptides, which are chemical compounds. Most bioactive peptides are produced following enzymatic processing and are inactive in the primary protein. Chemical synthesis is another method for creating bioactive proteins [6]. As described by Li-Chan (2015) [7], bioactive peptides are specific fragments of proteins that can exert a wide range of beneficial physiological effects depending on their structural configuration, composition, and amino acid sequence. A diverse array of bioactive peptides encoded within the primary structure of plant- and animal-derived proteins has been identified [8] [9]. Recent research highlights that naturally occurring peptides from dietary plant and animal proteins are generally more biocompatible, less toxic, and more readily absorbed than those produced through chemical synthesis [10]. The most often utilized animal proteins are meat, eggs, and Milk (casein and whey). Familiar plant-derived sources of bioactive peptides include soybeans, wheat, legumes such as chickpeas, peas, lentils, canola, oats, flaxseed, and hemp seeds. Marine organisms such as fish, squid, salmon, sea urchins, oysters, seahorses, and snow crabs have been explored as protein sources for peptide extraction [11]. Notably, a single protein source can generate multiple peptide variants with unique amino acid sequences, structural features, and biological functions, depending on the processing methods employed [12].

Bioactive peptides derived from microbial activity can be generated through three main approaches: enzymatic hydrolysis, microbial fermentation, and genetic engineering involving bacteria and yeast [12][13][14][15]. Protein fermentation using microbes is the most popular food processing method for producing biogenic proteins, as it can be purified without further hydrolysis and is less costly than enzymatic methods. Protein hydrolysis during the fermentation process is a result of a combination of enzymes, and the peptides produced are influenced by the fermentation time and depend on the type of bacteria or yeast used [16].

Bioactive peptides generally consist of short chains comprising 2 to 20 amino acids. They are known to exhibit a broad spectrum of biological functions, such as antihypertensive, antimicrobial, anti-inflammatory, antithrombotic, antioxidant, antidiabetic, anticancer, antiadhesive, dipeptidyl-peptidase IV (DPP-IV) inhibitory, opioid-like, immunomodulatory, and mineral-chelating activities [2][17]. Furthermore, multiple studies have confirmed the therapeutic potential of peptides resulting from protein hydrolysis, particularly their anti-inflammatory, antihypertensive, antithrombotic, immunoregulatory, and antidiabetic properties [18].

Bioactive peptides can act as angiotensin-converting enzyme (ACE) inhibitors, which are key physiological targets in the clinical management of hypertension. These peptides influence the renin-angiotensin system and the kinin–nitric oxide pathway [19][20]. Unlike synthetic ACE inhibitors, the antihypertensive effects of bioactive peptides offer a natural and effective alternative for controlling elevated blood pressure [21]. Side effects from synthetic ACE inhibitors include the possibility of allergic reactions, kidney problems, and coughing [22]. The hydrolysate of the protein from the jellyfish Rhopilema esculentum, which was produced with papain and pepsin for ACE inhibitor activity and antihypertensive effects, yielded biogenic peptides for Liu et al. (2013)[23].

Fermented camel milk has been identified as a source of peptides with ACE inhibitory activity, as Moslehishad et al. (2013) [24] and Alhaj et al. (2017) [22] reported. *Lactobacillus rhamnosus* was reported to exhibit ACE-I action when added to camel milk. Modulation of the ACE system benefits various metabolic conditions, such as diabetes, obesity, and chronic kidney disease. This system can be targeted using two types of pharmacological agents: angiotensin receptor blockers (ARBs), which inhibit the AT1 receptor, and ACE inhibitors (ACEIs), which block the enzymatic conversion of angiotensin I to angiotensin II

[25]. Notably, bioactive peptides such as LHLPLP and HLPLP, generated through the fermentation of Milk by *Enterococcus faecalis*, have demonstrated antihypertensive effects in rat models [26].

Antidiabetic bioactive peptides exert their effects by inhibiting the enzymatic activities of α-amylase and β-glucosidase, two key enzymes responsible for carbohydrate digestion. These peptides also influence the activity of dipeptidyl peptidase-4 and glucagon-like peptides, which regulate blood glucose and glycemic levels in response to carbohydrate intake [27]. Spinach contains several chemicals that have anticancer activity, stimulate the immune system, reduce blood glucose levels, lower plasma cholesterol levels, and improve symptoms of anaemia and hypertension [28].
Therefore, the creation of biogenic proteins from different dietary sources that undergo microbial fermentation and their impact on diabetes, hypercholesterolemia, and anticancer are the main topics of this review. Fermented foods include bioactive peptides that show promise in treating various illnesses. Peptides derived from common beans, chickpeas, wheat germ, and mung beans have demonstrated cytotoxic and antiproliferative effects against cancer cells by promoting apoptosis and inducing cell cycle arrest. However, marine-derived peptides have shown the ability to prevent tumour growth and metastasis [29].

By emphasizing the potential of bioactive peptide sources from traditionally fermented, home-grown foods that have not been thoroughly investigated as alternative natural remedies, this study presents a fresh perspective. The production of specific bioactive peptides with pharmacological activities, including antihypertensive, antioxidant, anti-inflammatory, and antidiabetic properties, is made possible through the cultivation of traditional fermentation, which combines natural processes with indigenous microbes. To increase the evidence of the biological activity of peptides and close the gap between fundamental research and clinical application, this study also combines in vitro, in vivo, and clinical methodologies. It is advantageous in contrast to earlier research, which frequently concentrated on a particular raw ingredient or the fermentation industry. The outcomes of local fermentation research that yield bioactive peptides with various health benefits, as well as the use of a combination strategy in contemporary bioactive study methodologies, are references pertinent to this novelty.

RESEARCH METHODS

The methodology of this research involved conducting a comprehensive literature review using reputable sources, including Google Scholar, Scopus, and PubMed. The primary aim was to explore the health-related functions of bioactive peptides synthesized by lactic acid bacteria during the fermentation of traditional foods. Keywords like "bioactive peptides", fermented foods", and "health benefits," specifically linked to diseases such as diabetes, hypertension, and cancer, were employed during the search process. Through a systematic screening, the initial large pool of publications was narrowed down to 112 relevant studies. Articles are taken from publications from 2000 to 2025. To give the results a more thorough overview and greater validity, a mix of in vitro, in vivo, and clinical research was carried out. The abstracts and conclusions of each study were reviewed to ensure relevance and alignment with current scientific discussions. The gathered data were then summarized through descriptive analysis to convey the research findings in a clear and accessible manner.

RESULTS AND DISCUSSION

Microorganisms in Traditional Fermented Foods

Microorganisms in traditional fermented spices (such as yeast, fungi, and bacteria) differ from their original environment. During the fermentation process, these microbes break down the components of the raw materials, boosting the product's nutritional and bioactive value and preserving its quality [1]. Lactose ferments throughout the fermentation process, releasing oxygen and reducing the pH, which makes the food acidic [30]. Compared to enzymatic hydrolysis, fermentation employing these microbes has the benefit of producing bioactive peptides more cheaply and efficiently. Moreover, natural substrates may be effective growth media for lactic acid bacteria [31].

These bacteria are generally characterized as non-spore-forming, Gram-positive, catalase-negative, lacking cytochromes, either anaerobic or aerotolerant, nutritionally fastidious, acid-tolerant, and highly fermentative [1][32][33]. The functional roles of lactic acid bacteria (LAB) in food systems can be categorized into three main applications: as starter cultures in fermentation processes, as natural preservatives, and as essential components in probiotic formulations [34]. LAB genera commonly isolated from fermented food products include *Lactobacillus*, *Pediococcus*,

Enterococcus, *Lactococcus*, *Oenococcus*, *Streptococcus*, and *Weissella* [1].

One of the microorganisms that may be utilized as a probiotic is LAB. Probiotics are "live microorganisms" that have the potential to improve health when taken in adequate amounts. Probiotic organisms are frequently present in fermented foods and benefit consumers' health [33]. They exhibit a wide range of functional properties, including antioxidant, antidiabetic, anti-obesity, antiallergenic, cholesterol-lowering, anti-inflammatory, and anticancer activities, all of which contribute to improving host health [1].

Fermented bioactive peptides have several physiological benefits, including antioxidant, antihypertensive, and immunomodulatory effects. Fermentation is a low-cost and effective technique for manufacturing these peptides, which are commonly found in Indonesian fermented foods such as tempeh and dadih. Their use has the potential to reduce the risk of noncommunicable diseases while also enhancing public health.

Bioactive peptides in fermented foods

Fermented foods are recognized as a source of bioactive peptides, which are predominantly produced by lactic acid bacteria (LAB) during fermentation. The most popular LAB genera for producing bioactive peptides are *Lactobacillus* and *Bifidobacterium*. The production of bioactive peptides can be modulated to some extent by manipulating the growth conditions of the microorganisms involved [35]. The stability of these peptides is affected by a combination of intrinsic and extrinsic factors, including surface hydrophobicity, the presence of reducing sugars, moisture content, pH, and the extent of protein hydrolysis, as well as environmental influences such as light exposure, oxygen availability, packaging properties, temperature, and relative humidity [36].

Bioactive peptides are embedded within the primary structure of both animal- and plant-derived proteins. They generally consist of short sequences containing two to twenty amino acid residues and are often abundant in hydrophobic amino acids. Proteolysis is necessary to liberate bioactive peptides from precursor proteins [7][11][26][37]. These peptides exert their biological effects after being released through food fermentation, enzymatic protein hydrolysis, or degradation by digestive enzymes within the gastrointestinal tract [35]. Hydrolysates derived from fermented dietary proteins and peptides have been reported to exhibit antihypertensive activity and may influence inflammatory responses, oxidative stress, and the composition of gut microbiota [38]. Furthermore, bioactive peptides are recognized for their diverse functional roles, including antioxidant, anticancer, anti-inflammatory, antimicrobial, and immunomodulatory activities [1].

The biological compounds known as bioactive peptides, which are created when dietary proteins undergo proteolytic cleavage or maturation, have numerous advantageous and favourable impacts on human health. One of the products that contains a lot of bioactive peptides is Milk. Milk is a rich source of high-quality protein, particularly casein, and provides essential nutrients such as calcium, vitamin D, vitamin B12, vitamin A, riboflavin, potassium, and phosphorus. Bioactive peptides in Milk can be liberated through various processes, including food processing, enzymatic or microbial fermentation, and gastrointestinal digestion. These peptides exhibit several beneficial effects, including lowering cholesterol, reducing blood pressure, enhancing immunity, reducing inflammation, and preventing thrombosis [14]. Yan Jin and colleagues identified several bioactive compounds in yoghurt, including immunomodulatory agents, antioxidants, and peptides with angiotensin-converting enzyme (ACE) inhibitory activity [39]. ACE-inhibitory peptides are the most commonly observed among the various bioactive peptides found in fermented Milk [19]. Sevim et al. (2023) [40] reported that traditional kefir fermentation produces a range of metabolites, including lactic acid, carbon dioxide, ethanol (in concentrations below 0.5%), peptides, exopolysaccharides, antibiotics, and numerous bacteriocins. Table 1 provides an overview of food-derived bioactive peptides and their associated health benefits.

Fermented foods have high levels of bioactive peptides, which are predominantly produced by lactic acid bacteria, particularly Lactobacillus and Bifidobacterium. The generation and stability of these peptides are affected by a variety of intrinsic and extrinsic factors. At the same time, their release through fermentation or enzymatic hydrolysis provides multiple health benefits, including antioxidant, anti-inflammatory, and antihypertensive properties. These peptides highlight the potential of fermented foods as functional foods for promoting health and preventing disease.

Antidiabetic

Diabetes mellitus is currently recognized as one of the most significant global public health challenges, contributing to reduced life expectancy and elevated mortality rates [1][15]. According to the World Health Organization (WHO), diabetes ranks among the top ten leading causes of death worldwide, with diabetes-related mortality increasing by approximately 70% between the years 2000 and 2019 [5][15]. Insulin resistance or insufficient insulin production are hallmarks of diabetes, a noncommunicable metabolic disease that impairs glucose homeostasis regulation [55]. Persistent hyperglycemia and several metabolic dysfunctions are hallmarks of diabetes mellitus, a chronic metabolic disease [56]. Chronic hyperglycemia can harm the neurological system and other organs, such as the skin, kidneys, heart, and eyes, among other issues [57]. Numerous variables, including sedentary lifestyles, ageing, growing urbanization, bad diets, and a general increase in body mass index, are linked to the rising prevalence of diabetes [15].

Diabetes mellitus is characterized by impaired insulin sensitivity or inadequate insulin secretion, which results in elevated blood glucose concentrations [27][57]. It makes people with diabetes mellitus permanently reliant on medications that lower blood sugar levels. Diabetes mellitus is generally categorized into three main types: type 1, type 2, and gestational diabetes. Among these, type 1 diabetes (T1D) accounts for approximately 5–7% of cases, type 2 diabetes (T2D) comprises around 90%, and gestational diabetes (GD) represents about 2–3% [57]. Type 1 diabetes, also known as insulin-dependent diabetes mellitus, is an autoimmune disorder that destroys pancreatic β-cells, resulting in minimal or absent insulin production [57][58]. In contrast, type 2 diabetes mellitus (T2DM), also known as non-insulin-dependent diabetes, is primarily associated with insulin resistance and impaired insulin function. Insulin secretion and blood sugar absorption are out of balance in this form of diabetes. Type 2 diabetes mellitus (T2DM) is caused by insulin resistance and a progressive decline in pancreatic cell insulin production. Insulin resistance disrupts the normal metabolism of carbohydrates, proteins, and lipids, leading to elevated blood glucose levels and postprandial hyperglycemia. This condition is a significant contributing factor to the development of neurological and cardiovascular disorders, as well as complications such as blindness, renal failure, and lower limb amputations [58].

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Table 1. Health benefits associated with bioactive peptides originating from food sources.

Source	Peptides produced	Effect	Limis	Ref.
Camel Milk Fermentation	ACE-inhibitory and antioxidant	Antihypertensive Effect	Additional research is required to validate the pesticide's efficacy both in vitro and in vivo.	[40]
Dromedary Fermented Camel Milk	ACE inhibitory	Antihypertensive Effect	The mechanism of action of peptides in the body, as well as additional in vitro and in vivo studies, is required.	[22]
Fermented Cow Milk	ACE inhibitory	Antihypertensive Effect	Restricted to bioinformatics methods and in vitro study, without peptide function being validated in vivo.	[41]
Rainbow Trout Skin (*Oncorhynchus Mykiss*)	antioxidant properties and cytotoxic properties	Inhibit The Growth Of Cancer Cells	To confirm the safety and therapeutic efficacy of these peptides in vivo, further investigation is required.	[[37]
Kluyveromyces marxianus Protein Hydrolysates	ACE-inhibitory and antioxidant	Antihypertensive Effect: Atherosclerosis, Cancer, And Diabetes	Both in vitro and in vivo testing are required for validation.	[26]

Seaweed	ACE inhibitory, antioxidant, and antidiabetic.	Antihypertensive, Antioxidant, And Antidiabetic	For additional validation, more in vitro and in vivo studies are required.	[42]
Fermented Milk	ACE inhibitory	Peptida Antihipertensi	Additional clinical or in vivo testing is required.	[43]
Fermented Milk	Antioxidant	Anticancer	Effectiveness in biological systems must be confirmed through in vivo testing.	[44]
Bamboo Fermentation	Antidiabetic	Antidiabetic	Without being backed up by experimental testing, the majority of the results are based on surveys of the literature and in silico research	[1]
Kefir	ACE inhibitory	Antihypertensive	To validate the therapeutic potential of these peptides, further in vivo investigations and toxicological analyses are required.	[45]
Fermented Quinoa	ACE inhibitory	Antihypertensive	Clinical trials or in vivo studies are required..	[46]
Fermented Soybeans	ACE inhibitory	Antihypertensive	Additional research incorporating clinical trials is required.	[47]
Fermented Beef	ACE inhibitor	Antihypertensive	Clinical trials involving humans are required.	[31]
Fermented Milk	ACE inhibitory	Antihypertensive	Tests for biological and in vivo activities must be validated.	[48]
Fermented Bitter Melon Juice	Alpha-glucosidase inhibitor	Diabetes Type 2	Mechanistic analysis and human clinical studies are required.	[49]
Tempe	ACE inhibitory	Antihypertensive	More research on stability and bioactivity is required.	[50]
Milk Fermented	ACE inhibitory	Antihypertensive	Clinical trials involving humans are required.	[51]
Ruditapes Philippinarum Fermented	ACE inhibitory	Antihypertensive	Clinical trials and mechanistic investigations are required for additional research.	[52]
Cordyceps Militaris (L.) Fr. Fermentation	ACE inhibitory	Antihypertensive	Clinical trials and in vivo testing are required.	[53]
Sarobuong	Antibacterial	Antibacterial	Only concentrate on identifying and isolating lactic acid bacteria; in vitro, in vivo, and clinical studies are required.	[54]

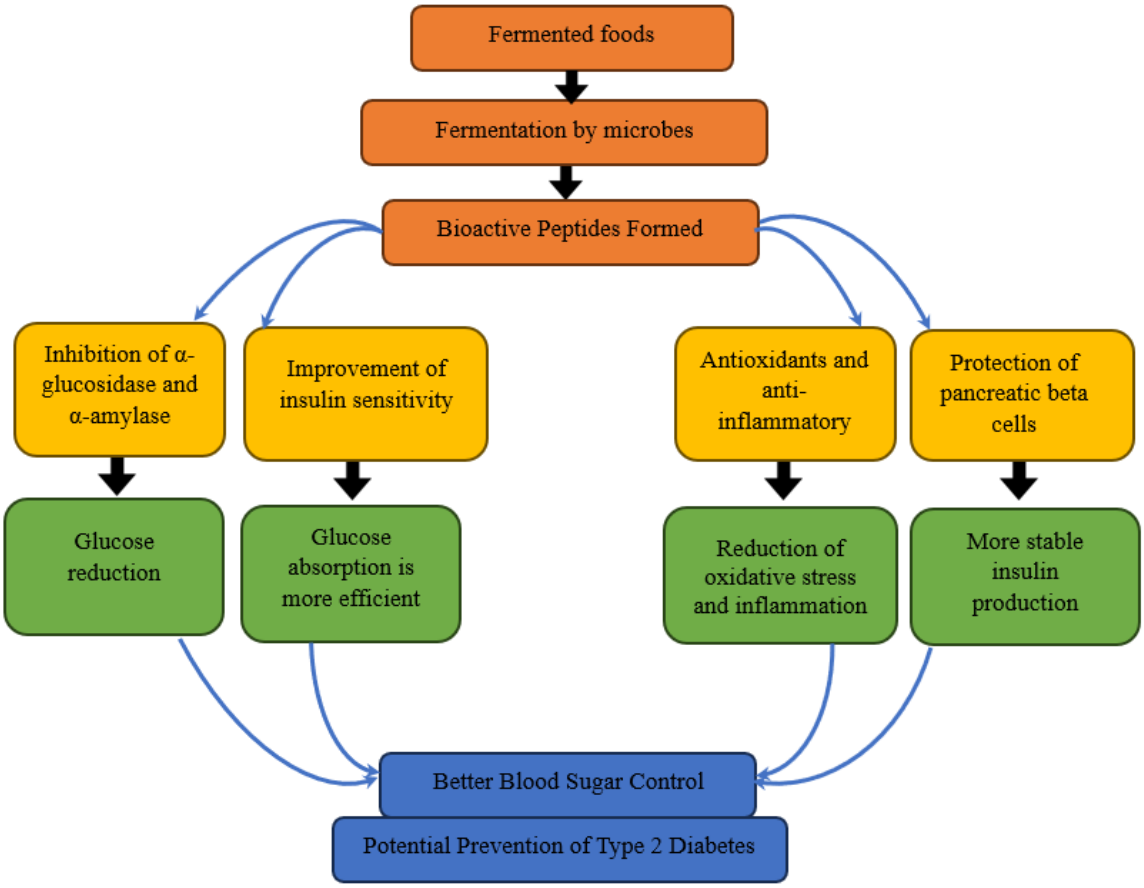

Figure 2. Mechanism of Action of Bioactive Peptides on Diabetes

Synthetic drugs identified to cure T2D by lowering glucose levels may lead to lifelong dependence [57]. In addition, diabetes therapy using synthetic drugs can cause side effects and increase the risk of obesity, gastrointestinal disorders, pancreatitis, intolerance, and other metabolic disorders [59]. Various pharmacological agents are available to reduce blood glucose levels, each targeting different metabolic pathways. These include biguanides, which suppress hepatic gluconeogenesis and improve insulin sensitivity; thiazolidinediones, which also enhance insulin responsiveness; and drugs that stimulate insulin secretion, such as sulfonylureas, meglitinides, GLP-1 receptor agonists, and DPP-4 inhibitors. Additionally, alpha-glucosidase inhibitors reduce the intestinal absorption of sucrose and starch, while GLP-1 receptor agonists and DPP-4 inhibitors delay gastric emptying. Sodium-glucose co-transporter 2 (SGLT-2) inhibitors facilitate increased urinary glucose excretion [60]. In addition to using synthetic medications, blood glucose levels can typically be lowered by consuming fewer carbohydrate-rich foods and engaging in more exercise.

Furthermore, it is thought to be safer and lower blood sugar levels to utilize fermented foods, particularly plant-based foods and drinks made by fermenting fruits, vegetables, grains, nuts, and legumes. Fermented foods generally have reduced fat content, are cholesterol-free, and are enriched with polyphenols, antioxidants, and microbiota-accessible carbohydrates, including dietary fibre. For individuals with diabetes, plant-based fermented foods or beverages are considered more effective than fermented dairy products in preventing and managing metabolic syndrome (MetS), its components, and type 2 diabetes mellitus (T2DM) [61]. Additionally, certain bioactive compounds produced during fermentation, such as gamma-aminobutyric acid (GABA) and polyphenols, have enhanced hepatic insulin sensitivity by activating insulin signalling pathways [1].

Antidiabetic Peptide Action Mechanism

Bioactive peptides contribute to the reduction of blood glucose levels in individuals with type 2 diabetes through multiple mechanisms, including the inhibition of α-glucosidase and α-amylase, enhancement of

insulin sensitivity, antioxidant and anti-inflammatory actions, and protection of pancreatic β-cells (Figure 2). This process begins upon ingestion, as bioactive proteins and peptides enter the gastrointestinal tract. During digestion, enzymatic activity modifies their structural configuration, influencing their biological function [62]. The physiological roles of the resulting peptides can differ—some exert their effects locally within the digestive tract. In contrast, others act systemically after being absorbed, distributed, and transported to target tissues. The digestive system can absorb di and tripeptides undamaged [36]. Food-derived bioactive peptides have been shown to inhibit key metabolic enzymes, including α-amylase, α-glucosidase, and dipeptidyl peptidase IV (DPP-4). By interfering with these enzymatic activities—particularly through DPP-4 inhibition—these peptides can attenuate carbohydrate digestion and reduce glucose absorption, thereby helping to lower postprandial blood glucose levels [16][63]. Differently, bioactive peptides can prevent pancreatic β-cells from dying by stimulating their insulin production [64]. Through the cAMP/PKA and PI3K/Akt signalling pathways, these peptides will activate GLP-1 receptors (including GLP-1 analogues), boost glucose-dependent insulin production, encourage β-cell proliferation, and decrease β-cell death [65]. In addition, bioactive peptides can enhance insulin sensitivity and promote glucose uptake—particularly in muscle and adipose tissues by stimulating the PI3K/Akt signalling pathway, which facilitates the translocation of the GLUT4 transporter to the cell membrane [66]. Numerous bioactive peptides are also recognized for their hypolipidemic and antioxidant effects. For instance, in diabetic animal models, the PRDA peptide has been shown to reduce oxidative stress markers, elevate the activity of antioxidant enzymes, and lower circulating lipid levels [64].

The enzymes α-amylase and α-glucosidase play a central role in initiating carbohydrate digestion. In contrast, glucagon-like peptide-1 (GLP-1) helps regulate postprandial blood glucose fluctuations by enhancing insulin secretion in a glucose-dependent manner. Gastric inhibitory polypeptide (GIP), a 42-amino acid peptide (GIP 1-42), is derived from the precursor proGIP, while GLP-1 is generated from proglucagon through translational processing, producing two biologically active isoforms: GLP-1 (7-36) amide and GLP-1 (7-37) glycine-extended [67]. Inhibitors targeting α-amylase and α-glucosidase enzymes contribute to regulating glucose homeostasis by modulating carbohydrate digestion. The pancreas and salivary glands emit peptides that block α-amylase, which causes polysaccharide hydrolysis and the release of oligosaccharides that can be further hydrolyzed by intestinal wall-resident α-glucosidase [68]. Over 95% of inactive GLP-1 is expected to be released during a meal when DPP-4 is present [67].

Bioactive peptides generated during the fermentation process possess antidiabetic properties, including the ability to lower blood glucose levels, enhance insulin uptake, and inhibit the enzymatic activities of α-amylase and α-glucosidase, key enzymes implicated in the development and progression of diabetes [1]. The regulation of glycemic response following carbohydrate consumption is significantly affected by the inhibitory effects of these peptides on α-amylase and α-glucosidase [68]. Bioactive peptides have shown antidiabetic potential by inhibiting dipeptidyl peptidase-4 (DPP-4) as well as key carbohydrate-metabolizing enzymes, including α-amylase and α-glucosidase [69]. Although it does not stop the breakdown of exogenous GLP-1 in pigs under anaesthesia, DPP-4 is a key mechanism linked to improved insulinotropic and antihyperglycemic effects after intravenous glucose delivery [59]. Peptides that inhibit dipeptidyl peptidase-4 (DPP-4) typically feature branched-chain amino acids such as leucine, isoleucine, or valine, or aromatic residues with polar side chains—particularly tryptophan—positioned at the N-terminal region [68]. Previous studies have shown that peptides such as AKSPLF, ATNPLF, FEELN, and LSVSVL, derived from hydrolyzed black bean proteins, possess inhibitory activity against sodium-dependent glucose transporter-1 (SGLT-1) and glucose transporter-2 (GLUT-2). Kwon et al. reported that genistein and daidzein enhanced glucagon-like peptide-1 (GLP-1) secretion in enteroendocrine NCI-H716 cells, exerting insulinotropic effects. Their findings indicated that genistein and kimchi-derived peptides significantly increased glucose-induced insulin secretion in rat insulinoma cells [70]. Moreover, peptides LPIIDI and APGPAGP, isolated from silver carp protein hydrolysate, also exhibited vigorous DPP-4 inhibitory activity [69].

Therefore, through several mechanisms, such as increased insulin sensitivity, reduced blood glucose levels, and the action of the enzymes α-amylase, α-glucosidase, and DPP-4, which are crucial in

regulating carbohydrate metabolism and glycemic response, bioactive peptides produced during fermentation have significant antidiabetic potential. This inhibitory action is significantly enhanced by the presence of specific amino acids, such as branched-chain and aromatic residues. The activity of glucose transporters and increased GLP-1 secretion, which intensifies insulinotropic action, are also supported by several studies. Therefore, bioactive peptides derived from fermented foods represent a potential therapeutic option for type 2 diabetes.

Antidiabetic Peptides' Mode of Action in Type 2 Diabetes

The regulation of glucose metabolism is primarily governed by the interplay between insulin-responsive tissues—such as the liver, skeletal muscle, and adipose tissue—and pancreatic β-cells. Insulin is synthesized by β-cells in the form of its precursor, pre-proinsulin [71]. Located within the islets of Langerhans, these β-cells mediate postprandial blood glucose reduction through glucose-stimulated insulin secretion [57]. Various proteins within the endoplasmic reticulum (ER) facilitate the proper folding of pre-proinsulin into proinsulin. This proinsulin is then transported to the Golgi apparatus, where it is packaged into immature secretory granules and subsequently processed into active insulin and C-peptide [71].

Insulin facilitates energy storage by promoting the uptake and conversion of glucose, fatty acids, and amino acids in insulin-sensitive tissues such as the liver, skeletal muscles, and adipose tissue. However, under conditions of insulin resistance, these tissues lose their ability to utilize glucose efficiently. Consequently, higher insulin levels are required to maintain normal glucose homeostasis, potentially leading to β-cell dysfunction and excessive secretory burden on the pancreatic islets. Type 2 diabetes or hyperglycemia develops due to inadequate insulin production caused by β-cell malfunction [57].

A key therapeutic strategy in managing type 2 diabetes involves inhibiting α-glucosidase and dipeptidyl peptidase IV (DPP-IV) enzymes [72]. In response to nutrient ingestion, the gut releases the incretin hormones GLP-1 and GIP, which function as signaling molecules to regulate hormone secretion from pancreatic α- and β-cells, facilitating efficient nutrient metabolism [73]. GLP-1, a peptide derived from proglucagon, is primarily secreted by enteroendocrine L cells in the distal small intestine [74]. In healthy individuals and those with type 2 diabetes, GIP and GLP-1 together account for approximately 50–70% of the insulin secretion following a meal [73]. However, active GLP-1 is rapidly degraded by DPP-IV through cleavage of the N-terminal dipeptide (His–Ala), resulting in the formation of inactive GLP-1 (9–36 amide) [74].

Glucose transporter 2 (GLUT2), a member of the solute carrier protein family, functions not only to facilitate glucose uptake into pancreatic β-cells but also serves as a glucose sensor in response to elevated blood glucose levels [71]. Upon glucose entry into the cell, its metabolism increases the intracellular ATP/ADP ratio, resulting in the closure of ATP-sensitive potassium (K^+) channels on the plasma membrane. It initiates membrane depolarization and the subsequent opening of voltage-gated calcium (Ca^{2+}) channels. The ensuing rise in intracellular Ca^{2+} concentration promotes the priming and fusion of insulin-containing secretory granules with the plasma membrane, ultimately triggering the exocytosis of insulin [71]. A summary of antidiabetic peptides relevant to type 2 diabetes is presented in Table 2.

In conclusion, inhibiting the α-glucosidase and DPP-IV enzymes, which regulate the secretion of incretin hormones such as GLP-1 and GIP, is crucial for the effective management of type 2 diabetes. Through a complicated process involving the GLUT2 glucose sensor and increased intracellular calcium concentration, these hormones accurately regulate glucose metabolism and boost glucose-dependent insulin production from pancreatic β-cells. Therefore, the development of more targeted and efficient antidiabetic treatments depends on a comprehensive understanding of the function and interplay of incretin hormones and their enzyme targets.

Antihypertensive

Hypertension is a prominent chronic condition characterized by elevated arterial blood pressure. Individuals with hypertension typically exhibit sustained blood pressure levels exceeding 140/90 mm Hg [81]. In cases of treatment-resistant hypertension, patients may develop dysautonomia and chronic low-grade inflammation, which can lead to persistent hypertension and progressive organ damage [47]. If left unmanaged, hypertension significantly increases the risk of stroke and mortality due to compromised blood flow to vital

organs. The regulation of blood pressure in humans is primarily mediated by the renin-angiotensin system (RAS), involving two key proteolytic enzymes: renin and angiotensin-converting enzyme (ACE) [82]. ACE (EC 3.4.15.1), which plays a central role in converting angiotensin I to the vasoconstrictor angiotensin II, is commonly targeted by synthetic ACE inhibitors—though these pharmacological agents may produce adverse side effects [83]. When blood pressure decreases, the zymogen prorenin is converted into its active form, renin, triggering the RAS pathway in the kidney. The decapeptide angiotensin (AT)-I is subsequently released into the bloodstream by renin at the N-terminal of angiotensinogen [84].

Table 2. Bioactive peptides with antidiabetic potential for the management of type 2 diabetes mellitus (T2DM)

Bioactive peptide	Origin	Function	References
NNDDRDS,LSSTEAQQS,NAENNQRN, QQQQQGGSQSQ,EEPQQPQQ,IKSQSES	Germinated soybean	Inhibits DPP-4, α-amylase, and α-glucosidase	[14]
PPL	Meat protein	Inhibits DPP-4	[75]
SDIPNPIGSE, NPWDQVKR, SLSSSEESITH, QEPVLGPVRGPFP	Goat milk	Inhibits DPP-4	[76]
KDLWDDFKGL, MPSKPPLL	Camel milk protein	Inhibits DPP-4	[77]
MHQPPQPL, SPTVMFPPQSLV, VMFPPQSVL, INNQFLPYPY, AWPQYL	Goat Milk Casein	Inhibits DPP-4	[69]
LPIIDI, APGPAGP, AGPPGPSG, ALAPSTM	Dorsal muscle	Inhibits DPP-4	[78]
PGVGGPLGPIGPCYE, CAYQWQRPVDRIR, PACGGFWISGRPG	Tuna	Inhibits DPP-4	[79]
PHPATSGGGL, YVDGSGTPLT,	Chickpea	Inhibits DPP-4	[80]

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The renin–angiotensin system (RAS), a key regulator of blood pressure and vascular homeostasis, is initiated in the kidneys through the enzymatic cleavage of angiotensinogen by renin to form angiotensin I (Ang I). This inactive decapeptide is subsequently converted into the potent vasoconstrictor angiotensin II (Ang II), an octapeptide, by the catalytic action of angiotensin-converting enzyme (ACE) [48][81]. Effective regulation of blood pressure involves inhibiting ACE activity, as this enzyme facilitates the transformation of Ang I to Ang II and degrades bradykinin, a vasodilatory peptide [27]. In pathological conditions, heightened renin and/or ACE activity leads to elevated circulating levels of angiotensin II (Ang II), contributing to excessive vasoconstriction and impaired vasodilation [82].

Angiotensin-converting enzyme (ACE) plays a vital role in the human body's complex physiological system that regulates blood pressure [85]. This enzyme influences both the renin-angiotensin system (RAS) and the kinin–nitric oxide system (QNOS), which are critical pathways involved in maintaining vascular tone and cardiovascular homeostasis [86]. Because the binding channel is too small to accommodate large peptides, the peptide's size and sequence significantly impact its affinity for the ACE active site [87]. Studies have indicated that peptides derived from fermented food products—including fermented dromedary camel milk exhibit angiotensin-converting enzyme (ACE) inhibitory activity [22]. Several studies have also demonstrated this, including the fermentation of quinoa (a pseudo-cereal) by Li-chan (2015) [7], which yielded five angiotensin-converting enzyme (ACE) inhibitor peptides. Mirdhayati et al. (2024) [31] carried out fermentation of fermented beef (Cangkuk) and successfully identified peptides with angiotensin-converting enzyme (ACE) inhibitory activity. Two peptide sequences were characterized as ACE inhibitors: IVG, with an IC_{50} value of 97.3 µmol/L, and EAPLNPKANR, with an IC_{50} value of 44.6 µmol/L [31]. Beyond dairy sources, peptides derived from fish proteins have also demonstrated antihypertensive properties

through ACE inhibition. Specifically, three peptides, LKP, IKP, and IWH, isolated from dried bonito hydrolysate, were reported to significantly lower systolic blood pressure (SBP) in spontaneously hypertensive rats (SHR) [81].

Mechanism of Bioactive Peptides in Reducing Hypertension

The antihypertensive effects of bioactive peptides can be mediated through multiple pathways, primarily targeting the renin-angiotensin system (RAS) and modulating vascular function [88][89][90]. It works because, firstly, the bioactive peptide will work as an ACE inhibitor. This ACE inhibitor prevents the conversion of angiotensin I to angiotensin II. As reported by Lee et al. (2023)[91], angiotensin-converting enzyme (ACE) inhibitors reduce the formation of angiotensin II while simultaneously preventing the degradation of bradykinin—a vasodilator produced by the kallikrein-kinin system. This dual action promotes vasodilation through enhanced nitric oxide (NO) production, ultimately reducing blood pressure. The RPYL peptide, derived from lactoferrin, exerts its antihypertensive effect by antagonizing angiotensin II receptors. Additionally, the pentapeptide HLPLP and its five analogues have been shown to inhibit angiotensin I-induced vasoconstriction in isolated aortic rings [89].

Within the RAS, renin (EC 3.4.23.25), an enzyme secreted by juxtaglomerular cells of the kidney, catalyzes the cleavage of angiotensinogen (AGT)—a glycoprotein prohormone synthesized by the liver with the amino acid sequence DRVYIHPFHLVI—into angiotensin I (ANG I), a decapeptide with the sequence DRVYIHPFHL [12]. Due to spatial constraints, large peptides generally cannot bind effectively to the active site of ACE. In contrast, ACE-inhibitory peptides are short, typically composed of 2 to 12 amino acid residues [97]. Moreover, peptides rich in acidic residues such as aspartic acid (Asp) and glutamic acid (Glu) often carry a net negative charge, which allows them to chelate the zinc ion critical for ACE catalytic activity through direct interactions [97][100]. The presence of positively charged amino acids at the C-terminal end of a peptide is also known to enhance ACE-inhibitory potential. However, the removal of arginine at this position has been reported as essential for optimizing inhibitory effects [97][100].

In pathological conditions, elevated renin and/or ACE activity leads to abnormally high circulating levels of angiotensin II, resulting in excessive vasoconstriction and impaired vasodilation [16][82]. Angiotensin II primarily exerts its effects via two receptor subtypes: angiotensin type 1 (AT1) and type 2 (AT2) receptors [81]. Ang II is implicated in various physiological and pathological processes, notably in the pathogenesis of hypertension. As Anna et al. (2020) [94] reported, ACE inhibition effectively reduces blood pressure by limiting the conversion of angiotensin I to angiotensin II. The ACE enzyme catalyzes the removal of a dipeptide from the C-terminal end of angiotensin I to form Ang II, a potent vasopressor, which subsequently stimulates aldosterone secretion. It promotes sodium kidney retention, increasing blood volume and elevated blood pressure [20].

Another mechanism involves ACE2, which converts angiotensin II into angiotensin (1–7) by cleaving the C-terminal phenylalanine. Angiotensin (1–7) then interacts with the MAS1 receptor, counteracting the vasoconstrictive effects of angiotensin II [92]. Moreover, ACE2 also hydrolyzes angiotensin I into angiotensin (1–9), which can subsequently be converted into angiotensin (1–7) by ACE [89].

Unlike synthetic ACE inhibitors such as enalapril, captopril, and benazepril, which are often associated with side effects like headache, fatigue, insomnia, and hyperkalemia, natural ACE inhibitors are increasingly utilized due to their greater stability and lower risk of adverse effects [88]. Bioactive peptides exhibiting ACE-inhibitory activity have been successfully isolated from animal- and plant-based protein-rich foods [88][89]. The efficacy of ACE inhibitors is influenced by the structural properties of the peptide, including its chain length, content, and sequencing [97]. As outlined by Jianping et al. (2006) [98], the structural composition of ACE-inhibitory tetrapeptides typically includes Tyr or Cys at the first position, followed by residues such as His, Trp, or Met in the second position; Ile, Leu, Val, or Met at the third; and Trp at the fourth position. Additionally, common motifs found in ACE-inhibitory peptides include specific amino acid sequences such as Tyr-Pro-Val-Glu-Pro-Phe-Thr-Glu and Glu-Met-Pro-Phe-Pro-Lys [35]. ACE plays a crucial role in regulating blood pressure through its direct action on blood vessels, sympathetic nerves, and adrenal glands [99].

Peptides that possess dicarboxylic amino acids such as glutamic acid (E) and

aspartic acid (D) at their C-terminal end are known to exhibit low binding affinity toward the angiotensin-converting enzyme (ACE) [22]. According to Iwaniak et al. (2014) [93], longer-chain peptides have inhibitory effects associated with the C-terminal amino acids. According to Iwaniak et al. (2014) [93], long-chain peptides have an inhibitory effect related to the C-terminal amino acid. As explained by Brunswick et al. (1971) [101], ACE consists of two distinct domains, namely the N-terminal and C-terminal domains, each of which contains an active site responsible for coordinating zinc ions essential for catalytic activity. ACE is important in hypertension and belongs to the M2 metallopeptidase family. Bioactive proteins from fermented foods can produce ACE [102].

To summarize, bioactive peptides exert antihypertensive effects primarily by blocking the angiotensin-converting enzyme (ACE), thereby reducing the synthesis of angiotensin II and enhancing vasodilation through increased nitric oxide generation. Additional methods include angiotensin II receptor antagonism and regulation of the ACE2 pathway. Natural peptides offer greater stability and fewer side effects than synthetic ACE inhibitors, making them promising candidates for safer antihypertensive medications derived from both animal and plant sources.

Anticancer Peptides

Cancer is a malignant tumour caused by gene mutations in normal cells [54]. Cancer occurs when normal cells transform into tumour cells that grow uncontrollably and exceed their normal limits, invading surrounding tissues and organs through metastasis [3]. In cancer treatment, bioactive peptides derived from fermented foods offer several advantages, including enhanced target specificity, reduced toxicity toward healthy tissues, and the ability to modulate various biochemical pathways involved in cancer development [6]. These food-derived peptides may also serve as preventive agents by inhibiting both the initiation and progression of cancer [35]. It is because bioactive peptides can readily enter or damage cell membranes, resulting in necrosis or apoptosis due to their molecular weight of approximately 102–103 Da and their composition of 2–50 amino acid residues [103]. Dietary proteins contain peptides that may inhibit cancer at several stages, including initiation, promotion, and progression. Bioactive peptides have little to no adverse effects and perform various biological tasks, including regulating the immune system and exhibiting anti-tumour activities. Anticancer peptides, such as antimicrobial peptides, possess cytotoxic properties that kill cancer cells by inducing necrosis and cell death through membrane lysis or pore formation [104]. Food-derived anticancer peptides exhibiting potent anticancer activity are predominantly characterized by low molecular weight and a high content of hydrophobic amino acid residues [105].

Bioactive peptides derived from fermented foods contribute to robust immune protection against infections and cancer by enhancing the activation and proliferation of immune cells, as well as cytokine production. Furthermore, bioactive peptides can prevent cell migration by altering the mechanisms of tissue turnover, chemotaxis, and cell adhesion [6]. The short anticancer peptide ACP harms cancer cells and contains amino acid sequences. Due to its high selectivity, high penetration, and ease of modification, ACP is a more effective therapeutic choice than antibodies and small molecules [106]. Anticancer peptides (ACPs), originating from natural and modified peptide sources, have recently gained significant interest as emerging therapeutic and diagnostic agents in cancer treatment, owing to their numerous advantages over conventional treatment approaches [3].

Numerous ACP species have been identified in various organisms across different categories. The most widely used classification technique is structural, as the type, quantity, and structure of the amino acids that comprise ACPs significantly influence their activity. According to this classification, ACPs fall into four groups: cyclic, random coil, β-pleated sheet, and α-helical [106]. Peptides' primary benefits as medications include their high biological activity, lower cost of care, and minimal adverse effects due to their low toxicity [37]. Numerous studies have demonstrated kefir's possible anticancer effects against malignant T cells, colorectal cancer, and breast cancer.

Bioactive peptides derived from fermented foods have strong potential as anticancer medicines due to their specific and selective modes of action, which include inducing apoptosis and suppressing cancer cell proliferation. In addition to having few adverse effects, these peptides can stimulate the immune system, making them a viable and safe treatment option. To develop successful health products, further study is needed on

using locally fermented foods as a source of bioactive peptides.

Bioactive peptides and cancer cells

The immune system may be strengthened by bioactive peptides found in cancer cells, which are naturally created during food digestion. It may impact cell function and immunological responses [36]. These peptides significantly contribute to the regulation of immune responses by modulating key interleukins—such as IL-4 and IL-10, known for their anti-inflammatory effects; IL-1β and IL-2, which exhibit pro-inflammatory activity; and IL-6, which can function in both anti- and pro-inflammatory roles—as well as cytokines like tumour necrosis factor-alpha (TNF-α) [107]. Antimicrobial peptides are a type of peptide used to treat cancer. Through various processes, including apoptosis, necrosis, destruction of cell membranes, suppression of angiogenesis, and immune system activation, antimicrobial peptides can combat cancer cells [36][108]. Antimicrobial peptides, a class of bioactive proteins, play a vital role in the innate immune system, the body's primary defense against diverse infections [109]. These peptides can suppress pathogen proliferation either directly by interfering with microbial adhesion and invasion mechanisms or indirectly by enhancing the growth of beneficial gut microbiota [108]. It can also prevent pathogen growth by denying them the nutrients necessary for bacterial growth. Anticancer peptides (ACPs) will target cancer cell membranes due to their high phospholipid content. Specific peptides enhance anti-tumour immunity by activating antigen-presenting cells (APCs) and inducing cytokine release [6][105]. Anticancer peptides (ACPs) induce programmed cell death via the mitochondrial apoptotic pathway by elevating reactive oxygen species (ROS) levels and activating pro-apoptotic proteins such as Bad and caspase-3 while simultaneously downregulating the anti-apoptotic protein Bcl-2 [105]. Moreover, bioactive peptides can exert their anticancer effects by modulating cellular signalling pathways, including the inhibition of survival pathways such as Akt/GSK-3β/β-catenin and the upregulation of tumour suppressor proteins, such as p53 [105].

Bioactive peptides, naturally produced during food digestion, play a crucial role in strengthening the immune system and preventing cancer by influencing key interleukins and cytokines. Antimicrobial peptides, in particular, can induce cancer cell death and inhibit growth through various mechanisms, including activation of the immune system and induction of apoptosis pathways. Bioactive peptides from fermented foods have considerable potential as natural anticancer medicines due to their ability to target cancer cell membranes and regulate cellular communication cascades selectively.

Immunomodulatory dan Anti-inflammatory

Bioactive peptides produced through hydrolysis exhibit immunomodulatory properties, including the enhancement of phagocytosis and the promotion of immune cell maturation, as well as the maturation of lymphocytes, antibodies, and cytotoxic T cells [35]. The biological activities of these peptides, particularly their ability to inhibit cell proliferation or induce cancer cell death, are influenced by several structural parameters, including amino acid composition, peptide length, isoelectric point, molecular weight, net charge, hydrophobicity, amphiphilicity, secondary structure, and spatial configuration [106]. Peptides have also garnered considerable interest in the development of anticancer drugs [110]. Previous studies have demonstrated that germination enhances the anticancer potential of soy protein-derived peptides against breast and cervical cancer cell lines. Additionally, peptide fractions separated from soy protein hydrolysates after six days of hydrolysis—classified into >10 kDa, 5–10 kDa, and <5 kDa via ultrafiltration—exhibited antioxidant and antiproliferative effects [111]. According to Yaghoubzadeh et al. (2019) [37], peptides derived from rainbow trout possess bioactive properties and display anticancer activity against HCT116 colon cancer cells in vitro, indicating their potential application as natural dietary antioxidants.

According to Gutierrez et al (2015) [112], medications used to treat and control different types of cancer are mostly unsuccessful and have adverse consequences, including gonadotoxicity, nephrotoxicity, neurotoxicity, and cardiotoxicity. Immunomodulatory peptides derived from fermented foods have been shown to enhance immune function by promoting the differentiation and proliferation of immune cells, including human lymphocytes, and stimulating the activation and expansion of T lymphocytes and natural killer (NK) cells. These peptides also support the synthesis of antibodies and increase macrophage phagocytic activity [35]. In addition to their immunomodulatory effects, bioactive peptides possess anti-inflammatory

properties. Inflammation, which represents the vascular response to various stimuli—including sublethal injury—is characterized by increased endothelial permeability, protein-rich fluid exudation, and the infiltration of leukocytes into surrounding extravascular tissues [35]. The body's resistance to infection depends on this mechanism. However, if the response is out of control, the risk of tissue damage from the overproduction of oxidants and enzymes can increase. This can result in issues like cancer, atherosclerosis, myocardial infarction, stroke, and chronic disease.

Overall, hydrolyzed bioactive peptides have immunomodulatory qualities that can improve immune system function and demonstrate anticancer action depending on their structure. Soybeans and fish have been shown to produce peptides with antioxidant and antiproliferative properties, making them potential candidates for the development of natural therapies that are safer than conventional drugs while also helping to control chronic inflammation and degenerative diseases.

Research Gaps and Challenges on Bioactive Peptides from Traditional Fermented Products

Several research gaps still need to be filled, despite the identification and demonstration of the potential bioactive peptides in traditional fermented foods such as tempeh, dadih, rusip, and shrimp paste, which have been shown to have therapeutic effects. Without extensive testing in vivo models or clinical trials to validate their health advantages, a large number of studies continue to concentrate on in vitro and bioinformatics tests. Understanding the production mechanisms and optimizing fermentation is essential, as the quantity and consistency of bioactive peptide production are also influenced by the variety of bacteria and non-standardized traditional fermentation conditions. The safety and consistency of bioactive peptide products are also threatened by sanitation and quality control problems in small and medium-sized businesses that produce conventional fermented foods. To encourage the development of locally produced functional food products that are safe, efficient, and generally well-received by customers, this gap creates numerous opportunities for further study in the areas of standardizing fermentation techniques, peptide characterization, and integrative bioactivity testing.

CONCLUSION

In conclusion, probiotic microorganisms in various fermented foods offer numerous health advantages. Compared to enzymatic meals, fermented foods are recognized to contain more affordable and cost-effective bioactive components. Large quantities of biogenic proteins can be released during fermentation through enzymatic hydrolysis, which offers advantages for cancer treatment, the prevention and treatment of metabolic illnesses, including anti-obesity and antidiabetic effects. Biologically active proteins have potential applications as therapeutic agents and functional food additives for preventing and managing various diseases and health conditions, including diabetes, hypercholesterolemia, and cancer.

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