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REVIEW

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Bioactive peptides from fermented foods and their relevance in COVID-19 mitigation

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Abstract

Bioactive peptides are unique, low molecular weight peptide sequences generally consisting of 2–20 amino acid residues. These peptide sequences are inactive within the parent protein but they become physiologically active once released from the native polypeptide sequence via hydrolysis. There are multiple methods for producing bioactive peptides from precursor protein molecules, with microbial fermentation of various dietary matrices indubitably being a novel method to produce peptides with specialized bioactivity. Fermented foods especially fermented dairy products, legumes, cereals, meat and marine life as a source of bioactive peptides have been well documented. These peptides have gained scientific attention owing to their biofunctional attributes. The food-derived bioactive peptides have the potential to serve as valuable ingredients in functional foods and nutraceutical products to promote health. Bioactive peptides are known to possess various health-promoting properties including anti-carcinogenic, anti-hypertensive, anti-microbial, antioxidant, anti-diabetic, and immunomodulatory effects. The COVID-19 pandemic has put the world's health, economy, and social stability in jeopardy. The SARS-CoV-2 infection contributes to severe conditions and higher mortality in COVID-19 patients with comorbidities. The viral infection not only causes severe respiratory infection but also causes malfunctioning of the Renin-Angiotensin system (RAS), resulting in the downregulation of Angiotensin-converting enzyme II(ACE-II) and subsequent accumulation of Angiotensin II. Several synthetic ACE inhibitory medications are being used to minimize the severity of Angiotensin II adverse effects such as hypertension. The growing concern about the side effects associated with these pharmaceuticals has prompted researchers to look for alternatives in the form of foods and nutraceuticals with health-promoting features. Biologically active peptides have the potential to be used as a new-generation pharmaceutical product for various diseases including COVID-19. The multi-functional food-derived peptides could be a promising approach against COVID-19 infection in patients with chronic complications through their therapeutic actions. However, more in vitro and in vivo studies are required to validate their efficacy in enhancing the survivability and viability of COVID-19 patients. Although many peptides have demonstrated their positive effects via biochemical assays, cell culture, and animal models, the translation of these findings into practical application is limited. This might be related to the bioavailability issues, which influence the correlation of in vitro results with in vivo functions of peptides. To exert a health-promoting impact, these peptides need to withstand severe gastrointestinal conditions and the action of digestive enzymes to reach the target site in an active state. Therefore it is critical to thoroughly investigate the gastrointestinal stability and transport of these biopeptides and devise strategies to improve their absorption and bioavailability.

Keywords Bioactive peptides, Fermentation, COVID-19, Angiotensin-converting enzyme, Anti-hypertensive

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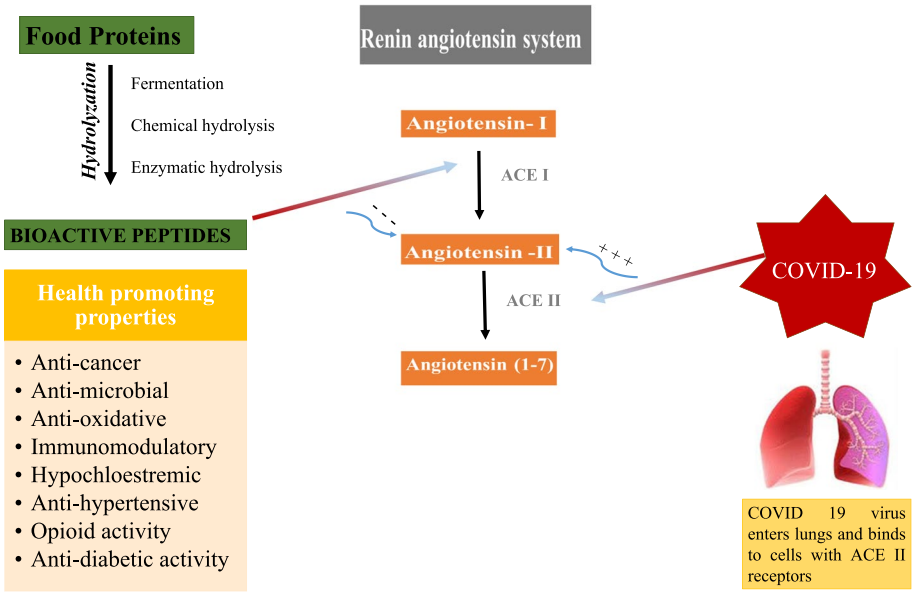
Graphical Abstract



Introduction

Numerous research studies have been conducted over the years to assess the novelty of various food ingredients, particularly phytochemical compounds, and proteins. There is sufficient evidence to demonstrate that dietary proteins of both plant and animal origin not only serve as a valuable source of nutrients but also perform some physiologically important functions which are attributed to the specific sequences of amino acids embedded within the protein molecule. The bioactive peptides have been known to have a positive impact on human body functions which have a consequential influence on health in addition to providing basic nutrition. These protein fragments generally comprise 2 to 20 amino acid molecules joined together by peptide bonds (Sánchez & Vázquez 2017). However, some bioactive peptides such as Lunasin, a soy-derived peptide have been known to have more than 20 amino acid residues (Ďúranová et al. 2019). When present within the parent protein molecule, these bioactive peptides are practically inactive; however, once released from the parent matrix, they exhibit hormone or drug-like activity. They modulate physiological functions within the body by binding with receptors on target cells responsible for specific physiological responses. The bioactive peptides are released from the protein matrix either by chemical or enzymatic hydrolysis of proteins, digestion process taking place in the gastrointestinal tract, or during the processing of food such as fermentation of food using proteolytic starter cultures. Bioactive peptides can also be produced during the protein hydrolysate manufacturing process (Daliri et al. 2017; Walther & Sieber 2011). The degree of hydrolysis during biopeptide production is known to be improved by the use of novel technologies such as high-pressure processing, ohmic heating, supercritical water extraction, and pulsed electric fields (Ulug et al. 2021). Furthermore, many scientists have used in-silico proteolysis and molecular docking analysis to identify potential bioactive peptides and understand the mechanism behind the functioning of these peptides. This method is entirely dependent on the information available in the various databases containing information about previously identified peptides. BIOPEP-UWMTM, formerly known as BIOPEP, is a well-known database (Mada et al. 2020). Bioactive peptides are recognized as a new generation of bio-regulators due to their biological activity that can be used to manage a wide range of physiological conditions. Various in vitro and in vivo studies show that bioactive peptides have a wide range of health-promoting activities, including mineral-binding, immunomodulatory, antimicrobial, antioxidative, anticancer, hypocholesterolemic, anti-diabetic, anti-tumor, anti-hypertensive, antithrombotic and anti-inflammatory properties (Karami & Akbari-adergani 2019). New research studies are directed toward the conception of bioactive peptide-based functional foods and nutraceuticals to improve people's quality of life. As a result, there has been a lot of

interest in researching the various sources, production methods, and mechanisms of action of bioactive peptides (Bhandari et al. 2020; Sánchez & Vázquez 2017). Food proteins have been recognized as the primary source of bioactive peptides. So far, the majority of bioactive peptides discovered have been of animal origin, specifically milk and egg (Sánchez & Vázquez 2017). Plant-derived proteins are a viable substitute for animal proteins. Identification of bioactive peptides from vegetable sources, in particular, is gaining popularity within scientific society, and the public's growing interest in vegetarian and vegan foods has turned it into a thriving research topic. Cereals and legumes provide the vegetarian population with the protein they require, and because of their rich protein profile, they can also be used to obtain bioactive peptides. Tubers, garlic, broccoli, spinach, pseudocereals, peanuts, and cocoa beans have all been found to contain bioactive peptides (Rizzello et al. 2016). So far the key research investigations regarding the bioavailability of bioactive peptides have been done by using in-vitro cell models. There is a lack of research data based on in-vitro and in-vivo experiments that would evaluate the bioavailability of the bioactive peptides, their concentration in plasma, their pharmacokinetics, and their health-promoting effects (Xu et al. 2019). Coronavirus disease- 19 (COVID-19), an acute respiratory syndrome has emerged as a global threat in last 2 years (Sanders et al. 2020).The viral infection has been linked to the suppression of renin-angiotensin system (RAS) mediated by angiotensin converting enzyme II (ACE II), which is a physiological system associated with maintaining hemodynamic stability of the body by regulating blood pressure, fluid volume and electrolyte balance (Muñoz-Durango et al. 2016). This pandemic continues to cause mortality worldwide due to lack of proper medication. In absence of the effective antivirals, the treatment of COVID-19 infection mainly focuses on respiratory and symptomatic support. Although vaccination has been developed there still prevails an urgent need to develop effective theurapetic agents against this viral infection.The bioactive peptides especially those with anti-hypertensive effect possess the potential to be used as novel theurapetic agent for COVID-19 and other chronic ailments linked to malfunctioning of RAS system.This review focuses on fermented foods as a source of bioactive peptides and their potential to treat various pathological conditions particularly those influenced by the RAS system.

The functionality of bioactive peptides

Bioactive peptides exhibit various biological activities such as ACE-inhibitory, antidiabetic, cholesterol-lowering, antimicrobial, and Immunomodulatory activities that can be used to treat and manage numerous diseases. The following are some of the important functions that various bioactive peptides perform.

ACE inhibitory activity

The inhibition of the angiotensin-converting enzyme (ACE) is one of the most notable functions of bioactive peptides. ACE is an exopeptidase that catalyzes the conversion of angiotensin I into angiotensin II, a powerful vasoconstrictor, as well as the degradation of bradykinin, a vasodilator, both of which are required for blood pressure regulation. Excessive ACE activity results in increased angiotensin II production and, as a result, an increase in blood pressure. Angiotensin II contributes to the development of several physiological and pathophysiological conditions, including hypertension. Inhibiting ACE reduces the conversion of angiotensin I to angiotensin II, resulting in lower overall blood pressure (Jakubczyk et al. 2020). The first ever reported mitigation of hypertension by oral administration of food-derived ACE inhibitory peptides has been reported by Yokoyama and Chiba in 1992 (Yokoyama et al. 1992).

Antioxidative activity

Peptides with antioxidative activity are capable of minimizing oxidative stress caused by an overwhelming accumulation of reactive oxygen species in cells and tissues because of various environmental stress factors such as pollutants, ultra-violet (UV) rays, excessive calorie intake, heavy metals, and high-fat diets. A significant increase in the level of reactive oxygen species can cause cell and tissue damage, which in turn contributes to aging and the development of neurological disorders. Antioxidative peptides prevent reactive oxygen species from causing damage by acting as direct radical scavengers, and metal chelators, and by removing radical compound precursors (Pessione & Cirrincione 2016).

Antimicrobial activity

Bioactive peptides with antimicrobial activity have been identified as small oligopeptides with about 1–100 amino acid residues and an amphipathic structure. These peptides have a broad spectrum of action showing an inhibitory effect on microorganisms such as bacteria, molds, yeasts, parasites, and some viruses. The positively charged bioactive peptides interact electrostatically with negatively charged molecules in the microbial cell, resulting in the formation of channels or pores within the cellular membrane of microorganisms, impairing their normal cellular processes. Various physicochemical properties (size, charge, solubility, amphipathicity, and hydrophobicity), type and number of amino acid residues influence the antimicrobial property of peptides (Lei et al. 2019; Pushpanathan et al. 2013).

Anti-cancer activity

Numerous bioactive peptides have been studied for their anticancer potential, with lower molecular weight peptides fitting well in this category. Because of their antioxidant, anti-proliferation, and anti-mutated properties, these peptides have the potential to prevent various stages of cancer. The anticancer peptides induce cell death via various mechanisms such as apoptosis, anti-proliferation, and cytotoxicity. The cationic nature of peptides allows them to interact with negatively charged molecules associated with the cell membrane of cancer cells causing destabilization of the membrane. Moreover, these bioactive peptides exert antitumor activity by enhancing the expression of tumor-associated antigens in cancer cells, stimulating the immune response by triggering the release of danger signals from cancer cells, or by increasing the predisposition of tumor cells to be recognized and killed by the immune system (Díaz-Gómez et al. 2017; Yaghoubzadeh et al. 2020).

Hypochloestremic activity

The human body requires a significant amount of cholesterol for the biosynthesis of vitamin D, bile acids, and certain steroid hormones. However excess levels of these compounds lead to hypercholesterolemia causing arteriosclerosis, hypertension, and cardiovascular diseases. Several bioactive peptides with anticholesterogenic activity have been discovered. These peptides inhibit dietary cholesterol absorption in the intestines by targeting cholesterol metabolism. Certain peptides are known to bind to bile acids, preventing reabsorption and stimulating cholesterol transformation in blood plasma (Boachie et al. 2018). Hypochloestremic peptides inhibit a key enzyme- 3-hydroxy-3-methylglutaryl CoA reductase (HMGCoAR) linked with cholesterol synthesis. Expression of proteins namely proprotein convertase subtilisin/kexin type 9 (PCSK9), sterol regulatory element-binding protein 2 (SREBP2), hepatocyte nuclear factor (HNF)-1a, and low-density lipoprotein receptor (LDLR) involved in cholesterol metabolism is also targeted by these peptides (Lammi et al. 2015).

Opioid activity

Peptides with an affinity for opioid receptors present in the nervous, immune, and endocrine systems of mammals exhibiting morphine-like activity are termed opioid peptides. These peptides have a structural similarity to endorphins and enkephalins which explains their affinity to the relevant receptors (Mora et al. 2015).

Immunomodulatory activity

Bioactive peptides with immunomodulatory properties facilitate the host's defense system. These peptides not only have an impact on the immune system but also influence the proliferation of cells. Immunomodulatory peptides promote immune cell proliferation and maturation, induce "natural killer cell" (NK cell) activity and macrophage phagocytosis, increase antibody synthesis, and inactivate inflammatory compounds (Maestri et al. 2016; Mora et al. 2015).

Anti-diabetic activity

A highly prevalent, complex metabolic disorder, Diabetes mellitus has been associated with significantly high levels of blood glucose characterized by inadequate insulin production or insulin resistance. Many anti-diabetic peptide sequences have been identified, and these peptides can be used to implement various health management strategies based on the use of bioactive compounds as ingredients in drugs and functional foods for diabetes patients. These anti-diabetic peptides function by inhibiting the functioning of key enzymes (α-amylase and β-glucosidase) associated with carbohydrate digestion. These peptides also influence the functioning of glucagon-like peptides and dipeptidyl peptidase-IV that participate in glycaemic level control from the intake of carbohydrates to blood glucose regulation (Mada et al. 2020; Yan et al. 2019).

Production of bioactive peptides

There are several methods for producing bioactive peptides from precursor protein molecules. Enzymatic hydrolysis of proteins, digestion of food proteins in the gastrointestinal tract and microbial fermentation of proteins using proteolytic strains are all common processes. If the sequence of a bioactive peptide is known, it can be synthesized using one of three methods: chemical synthesis, enzymatic synthesis, or recombinant DNA technology. Enzymatic hydrolysis and fermentation are two of the most commonly utilized methods for producing bioactive peptides.

Several innovative technologies, such as high-pressure processing, ultrasound, and pulsed electric field are being employed to enhance proteolytic hydrolysis during the production of biopeptides (Mada et al. 2020; Ulug et al. 2021). Figure 1 presents a summarization of the various methods for the production of bioactive peptides.

Enzymatic hydrolysis, the most widely used conventional method for peptide production involves the cleavage of the parent protein molecule by proteolytic enzymes to release the biologically active amino acid sequence under mild process conditions, allowing the production of a peptide with well-defined characteristics. Various proteolytic enzymes (trypsin, pepsin, chymotrypsin, and elastase) and enzyme preparations (savinase, flavourzyme, thermolysin, and pancreatin) can be employed to break the peptide bonds in the protein

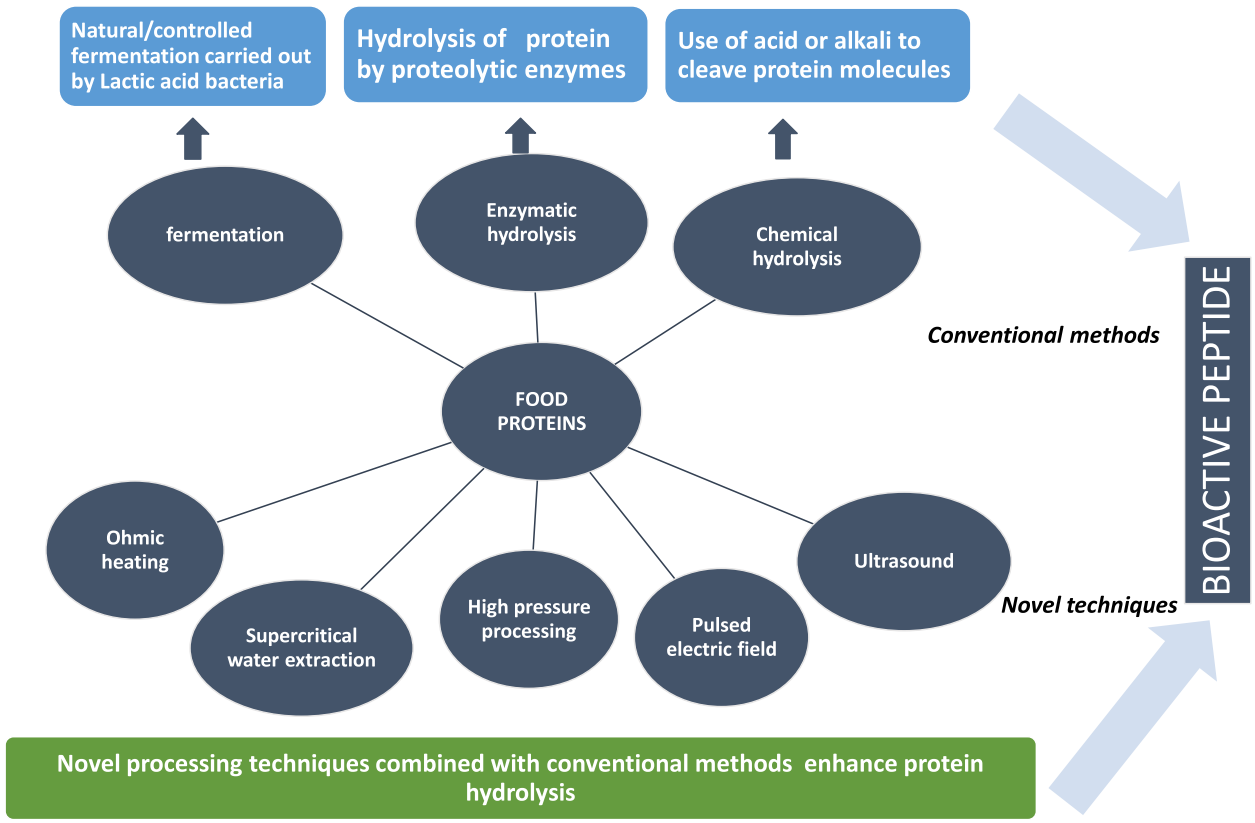


Fig. 1 conventional and novel methods used for the production of bioactive peptides

structure either individually or in combination when enzymes have a similar optimum working condition. The enzyme-to-substrate ratio has been identified as a significant factor influencing the degree of hydrolysis. Furthermore, the peptide sequence produced and their biological activity may differ depending on the type of enzyme utilized for hydrolysis. Though this method is preferred for being less time-consuming, and with good predictability, it cannot be employed as the best alternative on a commercial scale owing to the high cost of enzymes and a significantly low production rate. Also, this process needs strict control over process parameters such as pH and temperature to ensure desired results (Daliri et al. 2017; Zambrowicz et al. 2013). The action of digestive enzymes such as pepsin, trypsin, chymotrypsin, and peptidases within the human gastrointestinal tract can result in the release of some biologically active peptides from food proteins. The action of hydrochloric acid in the stomach causes the denaturation of food proteins. Pepsin and other digestive enzymes are activated by hydrochloric acid, which hydrolyzes proteins into smaller fragments (Mohanty et al. 2016). Using strong chemicals especially sulphuric acid, hydrochloric acid, and phosphoric acid to break the peptide bonds to release the active peptide is being employed widely as an alternative to the enzymatic process because of being relatively simple and less expensive. However, the use of chemicals has been associated with several limitations, such as the difficulty of controlling a chemical process and the possibility of modifying amino acid sequences, which can have a significant impact on functional properties (Wang et al. 2017). The two approaches to the chemical synthesis of peptides are synthesis in solution and solid-phase synthesis. In the former approach, the protein to be hydrolyzed, the chemical being used as a hydrolyzing agent, and the peptides generated are all dissolved in a medium whereas, in the case of the solid-phase synthesis process, the peptides remain insoluble in the medium as they are produced on a solid matrix (Chauhan & Kanwar 2019). Microbial fermentation is regarded as a low-cost, traditional method for producing peptides due to the proteolytic nature of many starter cultures, which can result in the hydrolysis of food proteins, resulting in the generation of peptide sequences with biological properties. The type and activity of the bioactive peptides are determined by the microorganism used (Mada et al. 2020). It is considered to be an ideal process suitable for commercial-scale as it is economical and eco-friendly. Apart from the production of

bioactive peptides it also enhances the physiochemical and organoleptic quality of food. Using novel processing methods such as pulsed electric fields, high-pressure processing, and ultrasound as assisting techniques, the degree of hydrolysis of proteins can be increased. Emerging processing methods have been considered to overcome the limitations associated with traditional methods (Tadesse & Emire 2020). Recombinant DNA technology has recently gained prominence as a technique that can be explored and used for the generation of bioactive peptides, providing a cost-effective solution for scaled-up commercial production. This method of production entails creating a peptide's coding region and cloning it into a prokaryotic cell for expression, allowing for the simultaneous production of multiple peptides (Chauhan & Kanwar 2019). After production is complete, the bioactive peptides are subjected to various purification processes after washing and centrifugation. Ion exchange chromatography, size exclusion chromatography, reverse phase high-performance liquid chromatography, and electrophoresis are employed to get rid of any unwanted residues associated with the crude bioactive peptide. On an industrial level, membrane technology processes including reverse osmosis, ultra-filtration, nano-filtration and microfiltration are also being employed for this purpose. The purity of the peptide is confirmed after the purification process by using different types of mass spectrometry (Mada et al. 2020). Figure 2 presents a schematic representation of production, purification and characterization of bioactive peptides.

Fermentation as a novel bioactive peptide production process

Fermentation is one of the well-known biological processes. It uses microorganisms to improve the quality and nutritional profile of foods by transforming dietary components into valuable products such as organic acids, enzymes, and other biotechnological compounds. Based on the fermentation processes, the specific microorganism is used to carry out the process which may last for a few hours to several days. Lactic acid bacteria (LAB), is one of the most pervasive, heterogeneous, gram-positive bacterial groups consisting of six families namely *Aerococcaceae, Carnobacteriaceae, Enterococcaceae, Lactobacillaceae, Leuconostocaceae,* and *Streptococcaceae*, has been associated with fermentation of food since time immemorial. Lactic fermentation, an anaerobic process, has been employed as a food preservation technique globally owing to the production of various metabolites of antimicrobial nature such as organic acids, particularly lactic acid, diacetyl, hydrogen peroxide, and antimicrobial peptide molecules termed bacteriocins. The lactic acid bacteria produce lactic acid as a prime end product of their anaerobic cellular metabolism along with synthesizing a diverse range of metabolites that have a favorable effect on the nutritional, sensorial, and technological properties of fermented food products. Though yeasts and fungi are also used as starters for various fermentation processes, LAB is always preferred because they have GRAS (generally recognized as safe) status with the highest number of GRAS species belonging to the family

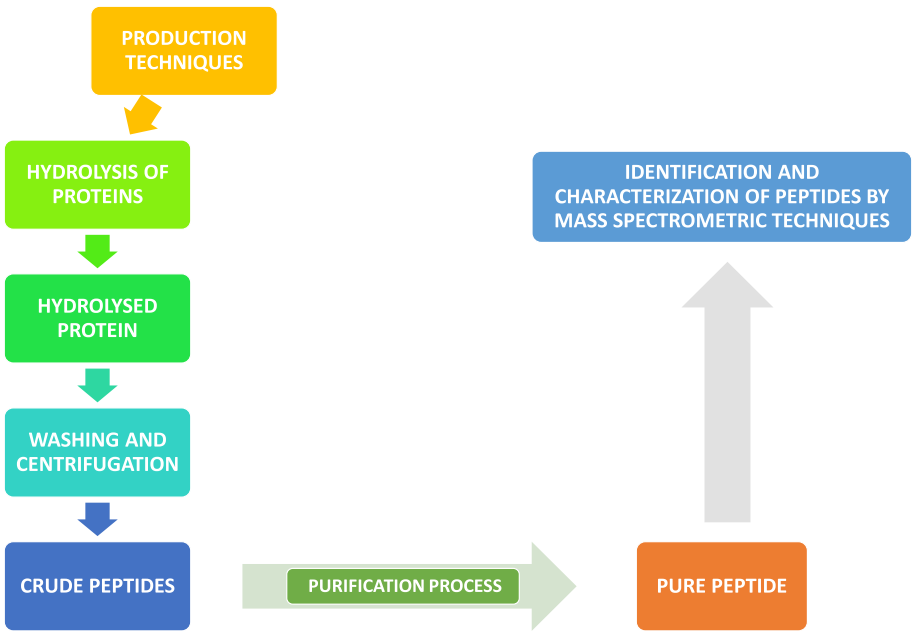


Fig. 2 Schematic representation of production, purification and characterization of bioactive peptides

Lactobacillaceae (Felis et al. 2015; Ruiz Rodríguez et al. 2019). During the fermentation process, the microorganism either present naturally as the indigenous microflora of food or is added to it as a starter culture, producing enzymes including those of proteolytic nature. These enzymes hydrolyze the dietary proteins into amino acids and small amino acid sequences termed peptides which may have some sort of beneficial effect owing to diverse pharmacological properties (Yarlina et al. 2020).

LAB proteolytic system

Lactic acid bacteria are not capable to synthesize various amino acids such as glutamic acid, glycine, leucine, isoleucine, histidine, methionine, and valine, which are essential for growth. They use an external source of protein to fill in the need for amino acids. Through the action of a well-defined proteolytic system (Fig. 3), the lactic acid bacteria hydrolyze the proteins present in the fermentation medium into amino acids which serve as nitrogen sources essential for their growth and proliferation, resulting in the release of various peptide sequences during the process. The proteolytic system of lactic acid bacteria (LAB), especially *Lactococcus lactis, Lactobacillus helveticus,* and *Lactobacillus delbrueckii subsp. bulgaricus* is well characterized and consists of three basic components: cell envelope proteinase (CEP), peptide transporters, and intracellular peptidases. CEPs also known as cell wall-bound proteinases, cell envelope–bound proteinases, cell-surface proteinases, and cell envelope–associated proteinases, form the most important component of the proteolytic system of LAB.They initiate the degradation of proteins, cleaving the protein molecules into peptides consisting of 4 to 30 amino acid residues. About six different types of CEPs have been identified in the LAB to date: i) PrtP, the first to be characterized in *Lactobacillus paracasei subsp. paracasei, Lactococcus lactis subsp. cremoris* and *Lactococcus lactis subsp. lactis;* ii) PrtB found in *Lactobacillus delbrueckii subsp. Bulgaricus*, iii)PrtH found in *Lactobacillus helveticus*; (iv) PrtS found in *Streptococcus thermophilus*; (v) PrtR found in L*actobacillus rhamnosus* and (vi) PrtL found in *Lactobacillus delbrueckii subsp. lactis*. A few CEPs have also been identified in *Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus plantarum,* and *Lactobacillus sanfrancisco* (Ji et al. 2021). In general, the lactic acid bacteria are known to possess only one unique CEP. However, the presence of two and four CEPs in *Lactobacillus bulgaricus* and *Lactobacillus helveticus* respectively have been reported in the literature (Jensen et al. 2009; Sadat-Mekmene et al. 2011; Stefanitsi et al. 1995). *Lactobacillus helveticus* is the most proteolytic species of the genus *Lactobacillus* with the potential to generate diverse bioactive peptides owing to the presence of four CEPs with different specificities (Raveschot et al. 2018). The peptides formed by the cleaving action of CEP are released into the extracellular environment wherefrom they are transported into the cells. the transport is carried out by three transporting systems namely

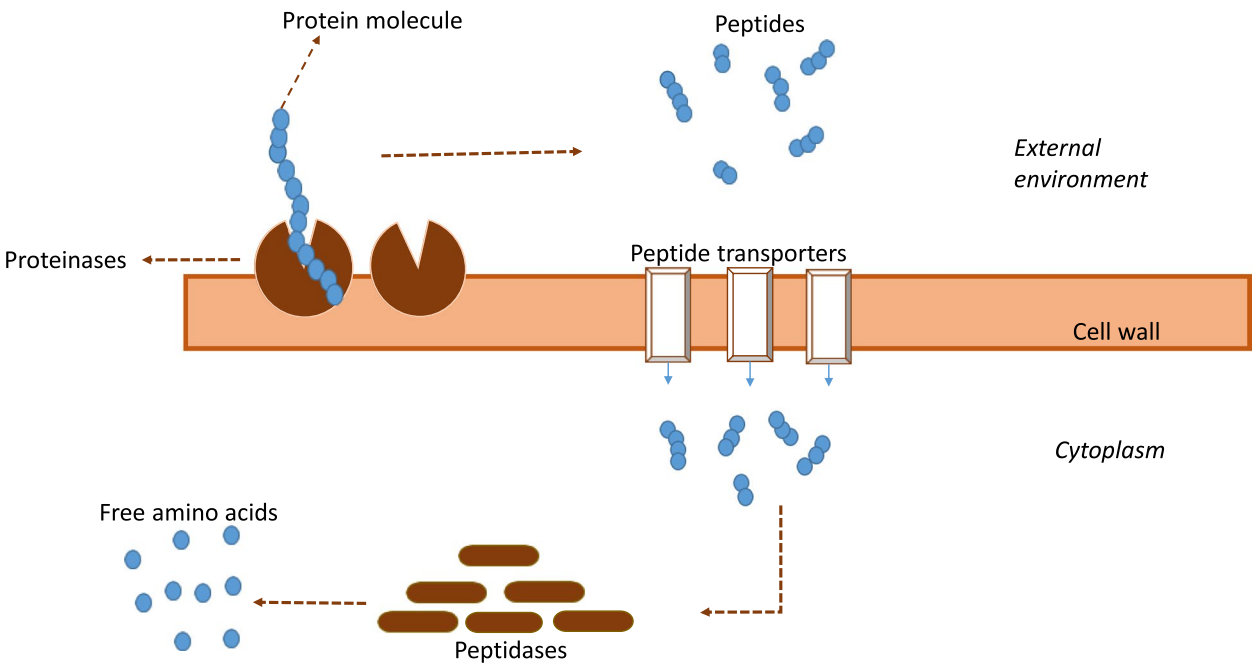


Fig. 3 Proteolytic system of Lactic acid bacteria

oligopeptide permease (Opp)-an ATP-driven active transport system, the ion-linked transporter (DtpT) -driven by proton motive force, and the ABC transporter (Dpp). Within the cell, these peptides are further degraded into amino acids, the final product of hydrolysis, by a combined action of various peptidases such as endopeptidases, aminopeptidases, tripeptidases and dipeptidases with different or slightly similar and overlapping specificities (Savijoki et al. 2006). Endopeptidases break down the intracellular bonds in peptides, while aminopeptidases remove amino acids from the N- and C-terminal of peptides. The breakdown products formed by the action of endopeptidases and aminopeptidases act as substrates for di- and tripeptidases. The final hydrolysis products are free amino acids, which are a rich source of nitrogen and are used by lactic acid bacteria for their metabolic process (Kieliszek et al. 2021).The peptides produced at the end of the fermentation process can be used directly by consuming the fermented food product or it can be easily collected after being subjected to a purification process (Rizzello et al. 2016). Bacteriocins, which are peptides in nature, are produced by LAB, but differently than the other biopeptides found in fermented foods. Bacteriocins are produced within bacterial cells during growth and then released into the environment, whereas other peptides are produced from protein substrates in extracellular space by the action of bacterial proteases (Venegas-Ortega et al. 2019). Apart from lactic acid bacteria, fungi associated with food fermentation are also known to generate bioactive peptides by the action of proteinases belonging to four families namely serine proteases, cysteine proteinases, aspartic proteinases, and metalloproteinases. It has been known that lactic acid bacteria are capable of regulating their gene expression in response to changing environmental conditions. The availability of nitrogen in the growth environment influences the regulation of proteolytic system activity and synthesis of proteolytic enzymes within the microbial cells to ensure nitrogen balance. The presence of any sort of energy source in the growth medium other than proteins leads to catabolic repression of nitrogen, which includes the inhibition of the biosynthesis of protein-degrading enzymes (Kieliszek et al. 2021). It has been reported that in *Lactococcus lactis*, the di and tripeptides with hydrophobic residues act as effector molecules in transcriptional regulation of peptide transport system-Opp, impacting the proteolytic system. Repression of around 5 to 150 folds has been noted in the expression of six transcriptional units in a protein-rich growth medium. However, upon encountering the nitrogen-limiting conditions, the expression of these transcriptional factors was relieved (Guédon et al. 2001). The synthesis of cell envelope proteinase in *Lactobacillus helveticus* is influenced by the peptide concentration in the growth medium, which causes about 32-fold repression of CEP activity. Similar to the composition of the growth medium, physiological conditions such as pH, temperature, and oxygen concentration are also known to impact the regulatory process associated with the proteolytic system (Hebert et al. 2000).

Bioactive peptides in fermented foods

Foods with modified physical, chemical, and biological characteristics as a result of microbial activity are termed fermented foods. These foods are known to contain a diverse range of metabolites including bioactive peptides, which have been the subject of research over the years owing to their health-promoting activities (Martinez-Villaluenga et al. 2017; Matar et al. 2000). Biologically active peptides derived from fermented dairy products, legumes, cereals, meat, and marine life have been extensively studied to date, some of which are listed in Table 1.

Bioactive peptides in fermented milk and milk products

Milk, a highly nutritious food encompasses a wide range of nutrients, especially calcium, vitamin D, proteins, vitamin B12, vitamin A, riboflavin, potassium, and phosphorus. Milk is known to be a rich source of quality proteins namely casein, constituting about 80% of the total milk proteins and whey. These proteins act as precursors for the generation of a wide range of bioactive peptides possessing various physiological roles (Davoodi et al. 2016). Fermentation of milk has been associated with the production of biologically active compounds particularly peptides encrypted on milk proteins. Lactic acid bacteria act as prime catalysts for the production of bioactive peptides from milk, hydrolyzing the milk proteins and releasing peptides into the medium. Although the majority of the generated peptides are used by the microbe for its growth, a significant amount is still present in the final fermented product (Chai et al. 2020). Certain bacterial species namely *Lactobacillus helveticus, Lactobacillus delbrueckii, Lactococcus lactis, Streptococcus thermophilus,* and *Enterococcus faecalis* have exhibited the excellent potential to hydrolyze milk proteins and release bioactive peptides in fermented milk. Tripeptides, IPP and VPP have been noted to have excellent anti-hypertensive activity along with an array of other biological activities such as anti-inflammatory, antiadipogenic, antiatherosclerotic, and antiosteoporotic activities (Martinez-Villaluenga et al. 2017). Milk fermented with *Lactobacillus helveticus CP790* contained about 3% peptides at the end of fermentation with amino acid sequence Asp-Glu-Leu-GIn-Asp-Lys-Ile-HisPro-Phe-Ala-Gln-Thr-Gln-Ser-Leu-Val-TyrPro-Phe-Pro-Gly-Pro-Ile-Pro-Asn-Ser exhibited ACE inhibitory activity in spontaneously hypertensive

Table 1 Biologically active peptides derived from fermented foods

Fermented Food	Microorganism involved	Bioactive Peptides	Bioactivity	Reference
Fermented milk	*L. helveticus CP790*	AGLGALIHPPAGTGSLVTPPPGPIPAS	ACE inhibitory	(Yamamoto et al. 1994)
	Lactobacillus jensenii	LVTPPPGPIHASLPGA and LVTPPPGPIH	ACE inhibitory	(Pihlanto et al. 2010)
	Bifidobacterium bifidum MF 20/5	LVYPFP	ACE inhibitory	(Gonzalez-Gonzalez et al. 2013)
	L. helveticus MTCC5463	IPP and VPP	Antihypertensive and antioxidative	(Hati et al. 2017)
	Lactobacillus helveticus KLDS.31 and Lactobacillus casei KLDS.105	LPAGAP, LAALSGM, LLAAMAM and LAHVPGGAA	ACE inhibitory	(Li et al. 2019)
	Lactobacillus fermentum M4	YIPIQYVLSR and HPHPHLSFMAIPPK	Antioxidative	(Panchal et al. 2020)
Koumiss (fermented mare's milk)	*LAB*	YQDPRLGPTGELDPATQPIVAVHNPVIV, PKDLREN, LLLAHLL, and NHRNRM-MDHVH	ACE inhibitory	(Chen et al. 2010)
Kefir	*Lactococcus Lactis, Leuconostoc ssp., St. thermophilus, Lactobacillus ssp. and kefir yeast or kefir grain microflora*	VYPFPGPIPN, NLHLPLP, VLNENLLR, KIEKFQSEEQQQTS7	ACE inhibitory, anti-microbial, antioxidative, mineral binding	(Ebner et al. 2015)
Yogurt	*Lactobacillus delbrueckii subsp. Bulgaricus,Streptococcus thermophilus and Lactobacillus paracasei subsp. paracasei DC412*	YPVEPFTE	antihypertensive and opioid activities	(Papadimitriou et al. 2007)
	Lactobacillus acidophilus L. casei and L. paracasei spp. paracasei	YQEPVLGPVRGPFPIIV and SLPQNIP-PLTQTPVVVPPF	Anti-proliferative	(Sah et al. 2016)
Dahi	*L. delbrueckii ssp. bulgaricus, S. thermophilus, and Lactococcus lactis ssp. lactis biovar. Diacetylactis*	SKVYP	ACE inhibitory	(Mann et al. 2017)
Cheddar cheese	*Lactobacillus casei*	RPKHPIK, RPKHPI, FVAPFPEVFGK YQEPVLGPVRGPFPIIV and RPKHPIKHQ	ACE inhibitory	(Ong et al. 2007)
Natto	*B. subtilis O9516*	Not identified	ACE inhibitory	(Ibe et al. 2009)
Cheonggukjang(fermented soya bean)	*Bacillus licheniformis-67*	LE, EW, SP, VE, VL, VT, and EF	Antidiabetic	(Choi et al. 2016; HJ et al. 2013)
Fermented soymilk	*Lactobacillus paracasei ssp. paracasei NTU and Lactobacillus plantarum NTU*	Not identified	Antiosteoporotic	(Chiang et al. 2012)
Sourdough (fermented soy flour)	*Lactobacillus curvatus SAL33 and Lactobacillus brevis AM7*	Lunasin	Cancer preventive, antioxidative	(Rizzello et al. 2012)
Boza(fermented cereal based beverage)	*yeast and LAB*	Not identified	ACE inhibitory	(Kancabaş & Karakaya 2013)
Huang Jiu(Chinese rice wine)	*Aspergillus, Rhizopus, Mucor, Monascus, acetic acid bacteria and LAB*	VY,YW, LLPHH and YPR	ACEinhibitory,antioxidative, and hypocholesterolemic	(Han & Xu 2011)
Fermented Bitter bean	*Lactobacillus fermentum ATCC9338*	EAKPSFYLK, PVNNNAWAYATNFVPGK and AIGIFVKPDTAV	Antioxidative and antibacterial	(Muhialdin et al. 2020)
Fermented pea	*Lactobacillus plantarum 299v*	KEDDEEEEQGEEE	ACE inhibitory	(Jakubczyk et al. 2013)
Fermented navy bean milk	*L. plantarum 70,810, L. plantarum B1-6 and L. bulgaricus*	Not identified	ACE inhibitory	(Rui et al. 2015)

Table 1 (continued)

Fermented Food	Microorganism involved	Bioactive Peptides	Bioactivity	Reference
Cucumber pickle	*Lactobacillus pentosus*	IPP, LPP, VPP, KP and RY	ACE inhibitory	(Fideler et al. 2019)
Red wine (fermented grapes)	*Not specified*	AWPF, SWSF, YYAPF, WVPSVY, LIPPGVPY, and YYAPFDGIL	ACE inhibitory	(Takayanagi & Yokotsuka 1999)
Budu (fermented fish sauce)	*Not specified*	LDDPVFIH and VAAGRTDAGVH	Antioxidative	(Najafian & Babji 2019)
Pekasam (fermented fish)	*Not specified*	AIPPHPYP and IAEVFLITDPK	Antioxidative	(Najafian & Babji 2018)
Sausages	*Lactobacillus sakei and L. curvatus*	Not identified	Antioxidative and antihypertensive	(Takeda et al. 2017)

rats (Yamamoto et al. 1994). A research study based on the fermentation of milk using *Lactobacillus delbrueckii subsp. bulgaricus and Lactococcus lactis ssp. cremoris* reported the production of ACE inhibitory peptides in fermented milk after 72 h of fermentation (Gobbetti et al. 2000). Peptides having amino acid sequences YQDPRL-GPTGELDPATQPIVAVHNPVIV, PKDLREN, LLLAHLL, and NHRNRMMDHVH, with ACE inhibitory activity have also been identified in traditionally fermented mare's milk- koumiss (Chen et al. 2010). LVYPFP, a novel peptide sequence with ACE inhibition capacity has been isolated from fermented milk produced by the action of *Bifidobacterium bifidum MF 20/5* (Gonzalez-Gonzalez et al. 2013). β-casein-derived ACE inhibitory peptides with amino acid sequences Leu-Val-Try-Pro-Phe-Pro-Gly-Pro-Ile-His-Asn-Ser-Leu-Pro-Gln-Asn and Leu-Val-Try-Pro-Phe-Pro-Gly-Pro-Ile-His were identified in milk fermented by *Lactobacillus jensenii* (Anne Pihlanto et al. 2010). Ebner et al. (2015) reported the identification of about 236 multifunctional peptide sequences like VYPFPGPIPN, KIEKFQSEEQQQT, VLNENLLR, and NLHLPLP in kefir, a carbonated, alcoholic milk-based beverage. As reported by Hati et al. (2017), *Lactobacillus helveticus MTCC5463* fermented honey-based milk contained peptides with amino acid sequences IPP and VPP with antihypertensive and antioxidative activity. Peptides sequences with ACE inhibitory activity in the order Lys-Pro-Ala-Gly-Asp-Phe > Lys-Ala-Ala-Leu-Ser-Gly-Met > Lys-Lys-Ala-Ala-Met-Ala-Met > Leu-Asp-His-Val-Pro-Gly-Gly-Ala-Arg have been produced in milk fermented by *Lactobacillus helveticus KLDS.31* and *Lactobacillus casei KLDS.105* with a fermentation and storage temperature of 37 °C (Li et al. 2019). Two peptides with the sequence having antihypertensive properties have been isolated from milk fermented by *E. faecalis CECT 5727*. Panchal et al. (2020) reported the production of peptides with antioxidant potential in goat milk fermented by *Lactobacillus fermentum M4*. Peptide sequences (YIPIQYVLSR and HPHPHLSFMAIPPK) identified in fermented goat milk matched with an antioxidant fraction of IPIQYVL and HPHPHLSFM on bioactive peptide database –BIOPEP. Moreover, yeast species namely *Clavispora lusitaine, Galactomyces geotrichum, Pichia kudriavzevii, S. cerevisiae,* and *Candida parapsilosis* are known to produce ACE-inhibitory peptides in fermented milk (Martinez-Villaluenga et al. 2017). A multifunctional peptide YPVEPFTE displaying antihypertensive and opioid activities has been reported in yogurt prepared from sheep milk (Papadimitriou et al. 2007). SKVYP, an ACE inhibitory peptide has also been isolated from Dahi, a traditional counterpart of yogurt produced by fermentation of milk with *L. delbrueckii ssp. bulgaricus, S. thermophilus,* and *Lactococcus lactis ssp. Lactis biovar. diacetylactis* (Mann et al. 2017). Peptides- LQDKIHP, VLPVPQK, KIHPFAQTQ, and VYPF-PGPIPK, identified in different yogurt samples have been observed to possess antioxidant properties (Ahmed et al. 2015; De Gobba et al. 2014). β-casein-derived peptides, YQEPVLGPVRGPFPIIV and SLPQNIPPLTQT-PVVVPPF isolated from probiotic yogurt supplemented with pineapple peel powder exhibited antiproliferation action on HT29 cancer cells (Sah et al. 2016). Beside the above mentioned bioactive peptides, presence of immunomodulatory and opioid peptide sequences have also been reported in fermented milk products.Various antihypertensive peptide sequences such as IPP, VPP, RPKH-PIKHQGLPQEV and EVLNENLLRF have also been identified in different fermented cheeses namely Gouda, Festivo, Cheddar, Fresco and some Swiss cheese varieties as a result of proteolysis during cheese ripening process (A. Pihlanto & Korhonen 2014). Probiotic proteolytic strains of *Lactobacillus casei* were reported to increase the production of bioactive peptides (RPKHPIKHQ, RPKHPIK, RPKHPI, FVAPFPEVFGK and YQEPVLG-PVRGPFPIIV) with consequent increase in ACE inhibitory activity in Cheddar cheese (Ong et al. 2007).

Bioactive peptides in fermented cereals and legumes

Soybean (*Glycine max*) having a protein content of about 35–40% on a dry weight basis, has been recognized as the chief protein source in a vegetarian diet containing all essential amino acids. Soybean forms a part of the global diet either in an unfermented form or in a fermented form. The fermented products made from soya beans such as natto, miso, tofu, tempeh, tungrymbai, hawaijar, and meju are widely consumed in Asian countries. Being rich in high-quality protein, soybean serves as a potent source of bioactive peptides. Consumption of soybean and its products have been linked to the modulation of physiological functions and prevention of various chronic conditions owing to the presence of bioactive peptides (Chatterjee et al. 2018; Mojica et al. 2014). Fermentation of soybean has been reported to release many small bioactive peptide sequences with therapeutic properties by microbial proteinases. ACE inhibitory peptides are generated by the degradation of glycinin and β-conglycinin protein fraction of soybean. Ibe et al. (2009) reported the presence of antihypertensive peptides in natto, a Japanese fermented soybean product, fermented by *Bacillus subtilis O9516*. Both in vivo and in vitro studies confirmed the antihypertensive activity of the peptide. Peptides with amino acid sequences Ile-Phe-Leu and Trp-Leu isolated from tofu extracts also exhibited ACE inhibitory properties. Peptides LIVTQ, LIVT, WL, IFL, and HHL isolated from fermented soya products namely douche, tofu, and soybean paste have exhibited ACE inhibitory activity

in vitro (Martinez-Villaluenga et al. 2017). Insulin-sensitizing dipeptides (LE, EW, SP, VE, VL, VT, and EF) have been generated in Cheonggukjang, fermented by *Bacillus licheniformis-67* (Choi et al. 2016). Similar, observations have also been reported by HJ et al. (2013). Being rich in bioactive peptides Chungkookjang has also been linked to anti-inflammatory effects on breast cancer cells MCF7 by downregulation of cytokine/chemokines expression and activation of transforming growth factor (TGF)-beta signaling (Hwang et al. 2011). Chiang et al. (2012) suggested that soymilk fermented by *Lactobacillus paracasei ssp. paracasei NTU* and *Lactobacillus plantarum NTU* exhibited antiosteoporotic activity attributed to the presence of bioactive peptides along with other bioactive compounds. A multifunctional peptide, lunasin having 43 amino acid residues in its sequence is present in high concentration in sourdough prepared by soya flour fermented by *Lactobacillus curvatus SAL33* and *Lactobacillus brevis AM7*. Lunasin has been identified as a novel soybean peptide noted to exhibit antioxidant, anti-inflammatory, antitumor, and hypocholesterolemic properties as shown by various scientific research. Lunasin (0.09 to 0.10 mg/g of dough), has also been isolated from sourdough prepared from amaranth flour (Lule et al. 2015; Rizzello et al. 2012). A well-known traditional Turkish beverage, Boza, prepared from rice, corn, wheat, and maize flour by the action of yeast and LAB, exhibited ACE inhibitory activity however the responsible peptide sequences have not been identified so far (Kancabaş & Karakaya 2013). Huang Jiu (Chinese rice wine) has been reported to have a high peptide content of around 500 peptides with ACE inhibitory, antioxidant, and hypocholesterolemic activities (Han & Xu 2011). Bitter bean (*Parkia speciosa*) fermented by *Lactobacillus fermentum ATCC9338* exhibited antioxidative and antibacterial activities owing to the presence of peptide sequences- EAKPSFYLK, PVNNNAWA YATNFVPGK, and AIGIFVKPDTAV. These peptide sequences demonstrated antibacterial effects at different concentrations against pathogenic microbes namely *Escherichia coli, Salmonella typhimurium, Staphylococcus aureus,* and *Listeria monocytogene* (Muhialdin et al. 2020). Peptide KEDDEEEEQGEEE isolated from pea after fermentation using *Lactobacillus plantarum 299v* possessed Anti-ACE properties (Jakubczyk et al. 2013). Navy bean (*Phaseolus vulgaris*) milk fermented by *Lactobacillus plantarum 70,810, Lactobacillus plantarum B1-6* and *Lactobacillus bulgaricus* exhibited ACE inhibitory properties though the responsible peptide sequences have not been identified (Rui et al. 2015).

Bioactive peptides in fermented vegetables and fruits

Cucumber pickle is a lactic acid fermented vegetable product widely consumed in the United States. The commonly associated microorganisms responsible for fermentation are *Lactobacillus plantarum, Lactobacillus pentosus, Lactobacillus brevis, Enterococcus faecalis, Leuconostoc mesenteroides,* and *Pediococcus cerevisiae*. Fideler et al. (2019) identified ACE inhibitory bioactive peptides IPP, LPP, VPP, KP, and RY in cucumber fermented by *Lactobacillus pentosus strain LA0445*. Peptide sequences AWPF, SWSF, YYAPF, WVPSVY, LIPPGVPY, and YYAPFDGIL with ACE inhibitory activity have been identified in red wine prepared from Grapes (Takayanagi & Yokotsuka 1999).

Bioactive peptides in fermented fish and meat products

Fish sauce forms one of the widely derived products from fish fermentation constituting an important part of the diet of people especially the lower-income group of the population of south-east Asian countries. Budu, a fermented fish sauce prepared on the east coast of west Malaysian states has been evaluated for its bioactive peptide content and two peptide sequences, LDDPVFIH and VAAGRTDAGVH with 8–11 amino acid residues have been identified as having antioxidant potential attributed to the presence of histidine for its imidazole characteristics that indicate proton-donation capability which contributes to antioxidant potential (Najafian & Babji 2019). Najafian and Babji (2018) reported the presence of two novel peptide sequences AIPPHPYP (Ala-Ile-Pro-Pro-His-Pro-Tyr-Pro) and IAEVFLITDPK (Ile-Ala-Glu-Val-Phe-Leu-Ile-Tre-Asp-Pro-Lys) in fermented fish-pekasam, exhibiting high antioxidant potential possibly due to the presence of hydrophobic and basic amino acids namely lysine, proline, alanine and isoleucine in the peptide sequences. Proteolysis of meat proteins is one of the important processes that occur during the preservation of meat by fermentation. During the fermentation of meat into fermented products such as dry-cured ham and fermented sausages, proteolytic degradation certainly results in the generation of bioactive peptides. To date, few research studies have reported the presence of low and medium-weight peptides, oligopeptides, and free amino acids in protein extracts from crude meat and fermented sausages. These peptides are produced by the action of endogenous muscle enzymes and exhibit in vitro antioxidant and antihypertensive effects (Escudero et al. 2013; Stadnik & Keska 2015). Castellano et al. (2013) reported the generation of bioactive peptides, especially FISNHAY with notable ACE inhibitory activity from porcine skeletal muscle proteins, generated by the proteolytic action of meat-borne *Lactobacillus sakei CRL1862* and *Lactobacillus curvatus CRL705*. Yu et al. (2020) demonstrated the generation of bioactive peptides from sarcoplasmic and myofibrillar protein degradation carried out by *Lactobacillus plantarum CD101* and

Staphylococcus simulans NJ201.KPVSPLL, KPVSPLLL, KPVSPL, THLDT, VLLFH, and VKVG were some of the identified peptide sequences having the potential for antioxidant capacity. Takeda et al. (2017) suggested high antioxidant and antihypertensive activities in sausages fermented by *Lactobacillus sakei* and *L. curvatus*, attributed to the generation of bioactive compounds, especially bioactive peptides.

Food-derived bioactive peptides and their relevance in the COVID-19 pandemic

COVID-19 and RAS system

Coronaviruses are a large and diversified group of viruses capable of infecting various animals and humans, resulting in mild to severe respiratory ailments. Two coronaviruses of zoonotic origin, namely, severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), infected humans. Because these viruses produced serious respiratory infections, coronaviruses were identified as a new and growing public health problem in the twenty-first century (Hu et al. 2020). In 2019 a novel form of SARS-CoV, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified in Wuhan, China. Being highly transmissible, this viral strain soon spread to different parts of the world causing coronavirus disease (COVID-19), which is an acute respiratory ailment. Since its initiation in Wuhan, China, this disease has become a worldwide pandemic, raising enormous global concern. It poses a continuous threat to world health, social stability, and the global economy (Phan et al. 2020). The clinical trials related to the disease severity in the patients suggest that patients with underlying ailments including hypertension, diabetes, cardiovascular diseases, pulmonary diseases, and kidney injuries exhibit higher mortality and morbidity. Moreover, the statistical data reveal that higher mortality of COVID-19 patients was associated with coronary heat disease, followed by diabetes mellitus and hypertension (Mahamud et al. 2021). The renin-angiotensin system (RAS), is a complex hormone network playing a key role in maintaining blood pressure as well as electrolyte and fluid balance, affecting the functioning of many organs, including the heart and kidneys. The dysfunctioning of this system plays a key role in the pathophysiology of various chronic diseases. The RAS system primarily comprises Angiotensin-converting enzyme I (ACE-I), Angiotensin-converting enzyme II(ACE-II), and their receptors namely angiotensin type 1 receptor (AT1R), angiotensin type 2 receptor (AT2R) and Mas receptor (MasR) (McKinney et al. 2014). Typically, renin secreted by the juxtaglomerular cells of the kidney cleaves the substrate angiotensinogen, mainly released by the liver to form angiotensin I (Ang-I), a decapeptide that undergoes removal of two amino acids by the action of ACE at the carboxyl terminus to generate Angiotensin-II (Ang-II). Among the three identified angiotensin II receptors, angiotensin type 1 receptor (AT1R) binds to Ang-II, resulting in vasoconstriction, cell proliferation, inflammatory responses, blood coagulation, and extracellular matrix remodeling, AT2R counteracts the above-mentioned effects mediated by AT1R.

The imbalance between ACE-I and ACE-II leads to the dysregulation of RAS, which inturn results in the accumulation of Ang-II, a representative bioactive peptide in the RAS, taking part in the progression of many physiological dysfunctions that lead to hypertension, myocardial infarction, heart failure, kidney injury, lung failure, and diabetes. As the data suggests that the deaths related to COVID-19 are mainly due to the association between the SARS-CoV-2 viral infection and several comorbidities. Many clinical studies also have linked COVID-19 deaths with comorbidities. The comorbidities such as hypertension, renal failure, and diabetes are all connected by RAS and there exists a link between COVID infection and these chronic complications. The start of SARS-CoV-2 infection within the human body is marked by the entry of viral pathogens into the host cells. Coronavirus is known to possess a spike glycoprotein on its envelope which is capable of binding to specific receptors on the host cell's membrane (Ni et al. 2020). Recent research works suggested that angiotensin-converting enzyme II (ACE-II) is a specific receptor for coronavirus. Digging deep into the entry mechanism it has been noted that Transmembrane serine protease 2 (TMPRSS2), a cell surface protein is required for successful priming of the viral spike protein. Upon binding with the ACE receptor, the viral spike protein undergoes conformational changes leading to proteolytic activation by TMPRSS2 which results in the fusion of the cellular membrane with the virus (Hoffmann et al. 2020). It has been confirmed that SARS-CoV-2 enters cells with ACE-II expression (P. Zhou et al. 2020). There is a varying degree of ACE-II expression in all human cells, including type II alveolar epithelial cells of the lungs as revealed by single-cell RNA-sequencing analysis indicating that the lungs are the primary target of SARS-CoV-2. ACE-II is also weakly expressed on the surface of epithelial cells in the oral and nasal mucosa and nasopharynx. It has also been noted that ACE-II is highly expressed in myocardial cells, proximal tubule cells of the kidney, and bladder urothelial cells, and is abundantly expressed in the enterocytes of the small intestine, especially in the ileum. Moreover, the cell-free and macrophage phagocytosis-associated virus can spread to other body organs from the lungs via

blood circulation (Ni et al. 2020) (Fig. 4). The coronavirus contributes to RAS dysfunction by downregulating the ACE-II expression leading to the accumulation of Ang-II. The profound amount of this compound leads to multiple organ disorders and chronic comorbidities in COVID-19 patients. The accumulation of Ang-II in the plasma contributes to pulmonary vasoconstriction which leads to hypoxia, fibrosis, pulmonary edema, and enhanced vascular permeability. This facilitates the entry of the SARS-CoV-2 virus into the lung cells, pulmonary hypertension, and pulmonary tissue modeling that results in accelerated lung injury in the infected patients (Mahamud et al. 2021). Moreover, due to vasoconstriction properties, elevated levels of Ang-II lead to high blood pressure by constricting the blood vessels, which inturn reduces the blood flow thereby inducing arterial inflammation, aldosterone secretion,s and sodium reabsorption resulting in hypertension, hypertension-induced renal diseases, and cardiovascular diseases (Szczepanska-Sadowska et al. 2018). The dysregulation of RAS may also provoke perivascular inflammation by inducing the synthesis of reactive oxygen species and pro-inflammatory substances, activating the bradykinin receptor. This may lead to hypertension, diabetes, lung injury, renal injury, and cardiovascular damage in infected patients (Chawla et al. 2010; Kreutz et al. 2020). Due to the presence of RAS in the pancreas, Coronavirus infection can also worsen the condition of diabetic patients by damaging islets cells which may dysregulate glucose metabolism (Maddaloni & Buzzetti 2020). The elevated levels of Ang-II influence the secretion of pancreatic regulatory hormones such ad cholecystokinin, pancreatic polypeptide, and somatostatin (Tikellis et al. 2006). Moreover, it may also inhibit insulin signaling and increase insulin resistance (M. S. Zhou et al. 2012). Thus, the pathophysiological role of RAS contributes to many chronic diseases which lead to higher morbidity and mortality in COVID-infected patients. Based on this concept, many researchers have suggested targeting the RAS, blocking or inhibiting RAS components and their functional pathways to reduce the severity of COVID-19 infection.

Therapeutic agents currently used for COVID-19 treatment and prospects of food-derived ACE inhibitory bioactive peptides in its mitigation

The world is facing a health emergency in the form of the COVID-19 pandemic. Even though the vaccines that have been developed against this virus show efficiency,

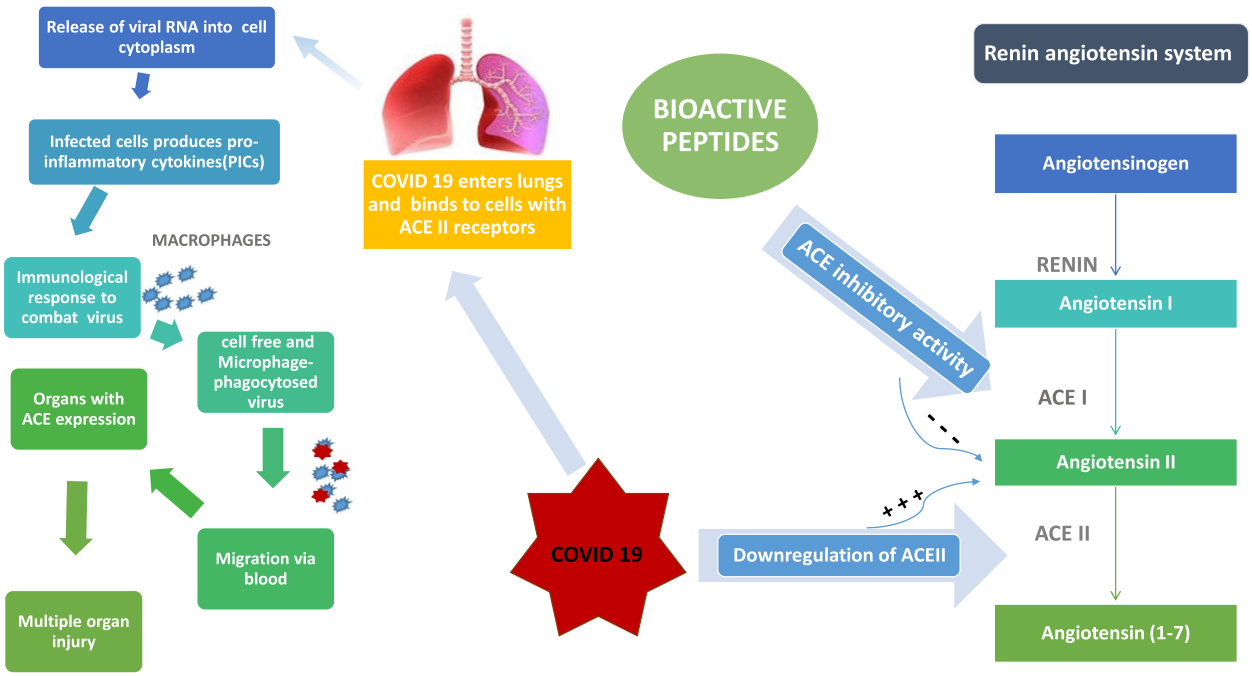


Fig. 4 A representation of the process of SARS-CoV-2 entry into host cells via lungs, migration to other organs, its pathological consequences on RAS system and presumed activity of ACE inhibitory peptides. COVID-19 virus enters the body via lungs, where the virus binds to ACE2 receptors on cells. The infected cells produce pro-inflammatory cytokines (PICs), activating immunological reactions to combat the viruses. Cell-free and macrophage-phagocytosed viruses migrate to different organs via blood. Infection with SAR-COV-2 leads to downregulation of ACE-II which results in accumulation of vasoconstrictive peptide Angiotensin II, leading to hypertension. The bioactive peptides with ACE inhibitory activity can regulate the functioning of RAS system by inhibiting the activity of ACE-I thereby preventing the formation of Angiotensin II from Angiotensin I

it requires more time to ascertain the long-term impact of these vaccines. Moreover, several approved vaccines exhibit low efficacy against the new variants of coronavirus which is acting as a hurdle in ending this health emergency (Mahamud et al. 2021; Wouters et al. 2021). The vaccines may provide a certain level of protection against the viral infection, but the inadequacy of existing therapeutic medicines to treat this fatal viral infection and its post-infection complications necessitates the development of novel ideas and concepts to find and create therapeutic compounds capable of fighting this infection and manage the post-infection complications in the recovered patients (Guan et al. 2020). Due to a link between SARS-CoV-2 infection and RAS, targeting this system can be an effective strategy to minimize the severity and fatality in infected patients. The potential of using RAS to treat COVID-19 patients is due to its dual nature. The RAS can be targeted either by ACE-I inhibition or upregulation of ACE-II to decrease the overall production of Ang-II. Many therapeutic agents have been widely investigated for their potential to manage and treat hypertension and are hence commonly termed antihypertensive drugs. These drugs include ACE inhibitors, Angiotensin receptor blockers (ARB), direct renin inhibitors (DRIs), and calcium channel blockers (CCBs) (Gheblawi et al. 2020). Targeting RAS by using antihypertensive drugs to treat COVID-19 patients has been advocated by many scientific studies. It has been noted that upregulation of ACE-II expression reduces the virus and induces lung injury in COVID-19 patients by counteracting the deteriorating effects of Ang-II in the lungs. Moreover, the ARB could prevent viral entry by stabilizing the ACE-II – AT1R interactions which inhibit the interaction between viral spike protein and ACE-II receptor and hence can be a potential therapeutics for COVID-19 patients before any serious lung injury develops. This has resulted in a notion within the scientific society, that discontinuation of antihypertensive drugs might accelerate the severity of the chronic disease and cause higher mortality among COVID-19 patients. Moreover, the administration of ACE inhibitors and ARBs has been approved in the management of various chronic diseases.Although ACE inhibitors and ARBs have shown significant efficiency in chronic disease management, several adverse effects such as hypotension, hyperkalemia, persistent cough, skin rashes, renal dysfunction, fetal abnormalities, etc. have also been associated with them in many cases. Therefore in-depth investigations are needed to ensure the safe administration of these drugs. WHO has approved the trial of dexamethasone in critically ill COVID-19 patients in order to reduce the pro-inflammatory responses induced by SARS-CoV-2 infection, resulting in a noteworthy reduction of mortality in patients. However, corticosteroids have adverse effects on health such as hyperglycemia, hypokalemia, and risk of secondary infections. Furthermore, it has been seen that corticosteroids delay the clearance of the virus during the SARS outbreak and have shown an association with higher mortality in COVID patients. Taking into account these side effects of the above-mentioned drugs and a prevailing need to develop effective therapeutic agents to support current covid-19 treatment, bioactive peptides derived from foods present an excellent research opportunity to explore their application for possible mitigation of infection by SARS-CoV-2 and chronic disease complication associated with it. (Bhullar et al. 2021). Food protein-derived ACE inhibitory peptides represent a suitable group of natural compounds that could serve as alternative ACE inhibitory agents or work as disease prophylactic agents to support the covid-19 treatment based on drug therapy with fewer negative side effects (Xue et al. 2021). These peptides derived from foods, especially fermented food appear to be potential therapeutic agents for use in COVID-19 patients. The various peptides derived from fermented food sources such as yogurt, fermented milk, fermented soya products, etc. have been noted to have ACE-inhibitory activity (Table 1) and hence can work effectively in counteracting COVID-19 pathogenesis and its negative effects on health. Various identified peptides sequences such as VPP, IPP, SKVYP, SWSF, and VY can modulate the renin-angiotensin system (RAS) by lowering the activities of renin and angiotensin-converting enzyme (ACE), the two main enzymes that are associated with regulation of blood pressure. These peptides are also capable of increasing the level of nitric oxide within vascular walls by enhancing the endothelial nitric oxide synthase (eNOS) pathway leading to vasodilation. Moreover, these peptides can also block the interactions between angiotensin II and angiotensin receptors, which can contribute to reduced blood pressure. The mode of action of these peptides is similar to most of the antihypertensive drugs used (Aluko 2015).Rathod et al. (2020) put forward promising results regarding the use of peptides as therapeutic agents for COVID-19 infection. Based on modeling and screening of peptides it is hypothesized that bioactive peptides could be pursued as one of the possible treatment options for coronavirus infection as they deflect ACE-II from their actual binding mode which prevents the binding of the virus to host cells. Moreover, instead of direct inhibition of ACE, TMPRSS 2 inhibition can also be exploited for the prevention of entry of virus within the host cells. TMPRSS2 has a strong preference for substrates with arginine, leucine and isoleucine. Therefore the bioactive peptides with the above-mentioned amino acids can serve as a rational approach to further research to evaluate their potential

to inhibit TMPRSS 2 activity (Bhullar et al. 2021). However, these bioactive peptides with ACE inhibitory action or possible TMPRSS inhibitory action require detailed epidemiological investigation and clinical trials to evaluate their exact effect on the manifestation of COVID-19 (Gouda et al. 2021).

Other possible effects of food-derived bioactive peptides aginst COVID-19

It has been noted that SARS-CoV-2 infection is responsible for immune dysfunction and inflammation which leads to autoimmune disease in COVID-19 patients. It has also been reported that COVID-19 infection also leads to abnormalities in cellular and humoral immunity. There occurs a reduction in immunomodulatory spleen cells and anti-inflammatory components and an increase in pro-inflammatory compounds such as cytokines that results in severe illness and higher mortality in COVID-19 patients. Therefore, prevention of the immune dysfunction and inflammatory responses and the improvement of the immune system is crucial for COVID-19 patients. Many food-derived peptides have immunomodulatory effects that stimulate the immune system by accelerating macrophage phagocytosis, enhancement of natural killer cell functions, modulation of the inflammatory responses, stimulation of T and B lymphocyte production, activation of transcription nuclear factor NF-Kβ dependent pathways, cytotoxicity of spleen cells (CD4+, CD8+, CD11b+, and CD56+); and IgA producing mucosal cells of the gut (Chalamaiah et al. 2018; Mahamud et al. 2021). Through these various mechanisms, the immunostimulating food-derived peptides enhance immune functions and prevent inflammation which may protect COVID-19 patients from autoimmune diseases and autoinflammation. Apart from the immunostimulatory effect, the food peptides also have other functions such as anti-inflammatory, antioxidative, anti-diabetic, anti-microbial, and cholesterol-lowering contributing to the overall development of the strong immune system to survive against several chronic and infectious diseases (Mahamud et al. 2021). Considering all the beneficial effects of food-derived peptides, it is assumed that these peptides may enhance the survivability and vitality of COVID-19 patients with underlying chronic diseases, exhibiting the potential to be used in the mitigation of COVID-19 patients.

Bioavailability of bioactive peptides

The in vitro bioactivity of various peptides is often not translated into in vivo pharmacological effects due to concerns associated with its absorption, bioavailability, and susceptibility to breakdown when in contact with physiological enzymes. For food-derived biopeptides to exert their bioactivity they must show resistance to breakdown caused by the gastrointestinal protein degrading enzymes. The amino acid sequence of the peptide influences its ability to resist the attack of digestive enzymes within the gastrointestinal tract. In general, the peptides having proline and hydroxyproline in their sequence are resistant to attack by digestive enzymes. The intact peptides, after surviving the digestion process reach the intestines where they undergo absorption via intestinal absorptive cells termed enterocytes into the bloodstream without being broken down by serum peptidases, ensuring that bioactive peptide is delivered to target sites in intact form, capable of exerting health-promoting effect (Segura-Campos et al. 2011). The bioavailability of peptides is also influenced by the physicochemical properties of the concerned peptides which include charge, solubility, molecular weight, and lipophilicity. It has been noted that the smaller peptide sequences are easily transported through enterocytes via peptide transporters while the oligopeptides are absorbed by a passive transport system through hydrophobic regions of the membrane (Aluko 2015; Bhandari et al. 2020). The long-chain peptides are susceptible to breakdown by peptidases associated with enterocytes (Bouglé & Bouhallab 2016). It has been reported that the peptides with neutral amino acids are recognized easily by the peptide transporters as they have an affinity towards neutral peptide molecules as compared to charged ones (Balvinder S. Vig et al. 2006). Several other factors have been reported to influence the absorption and bioavailability of food-derived peptides. It has been noted that food processing can lead to undesirable interactions between peptides and other compounds present in the food matrix that can limit the absorption of peptides. Interaction between free radicals formed by phenolic compounds of food and peptides via oxidation reactions and nucleophilic moieties can result in the formation of new peptide derivatives that modify their bioavailability. The breakdown of peptides including ACE inhibitory peptides depends on the presence of cleavage sites for digestive enzymes and whether these sites are exposed for enzymes to act upon them. Many in-vitro digestion studies have been carried out, mimicking human digestion process to evaluate the resistance of ACE inhibitory peptides to gastrointestinal enzymes (Xue et al. 2021).Small intestines act as the main organ for the absorption of peptides, where the surviving or newly formed peptides from digestion are transported into the blood stream. Many in-vitro and in-vivo models have been used to investigate the absorption of peptides in the intestines. The three mechanisms that have been investigated for the transportation of peptides through small intestines include carrier-mediated (Pep T1-mediated)

transport, paracellular transport, and transcytosis (Xue et al. 2021). However, before their uptake into the bloodstream, these peptides may further be hydrolyzed into small fragments and amino acids by several proteases and peptidases released in small intestines. Once the peptides enter the bloodstream their stability is reduced greatly due to the presence of large amounts of peptidases in blood. The concentration of bioactive peptides in the bloodstream depends on the number of peptides being absorbed in the intestines and their residence time in the bloodstream and accumulation within the organs. The maximum plasma concentration and elimination half-life of bioactive peptides has been presented in Table 2, validating the fact that these peptides are absorbed in vivo in animals and humans. It has been seen that some peptides such as YAEERYPIL and RADHPFL are susceptible to proteolytic degradation there by decreasing or losing their ACE inhibitory activity. The ACE inhibitory activity of these peptides dropped 100 folds in-vitro after digestion with pepsin and pancreatic extract (Miguel et al. 2006). On the other hand, it has also been seen that gastrointestinal digestion may enhance the ACE inhibitory activity of some peptides such as DLAIPVNRPGQLQSF due to fragmentation. The IC50 value of this peptide decreased from 500 to 11.4 ± 0.78 μM (García-Mora et al. 2017). The in silico digestion of LVYPFP from fermented milk suggested that this peptide could undergo hydrolysis under gastrointestinal conditions into fragments that have a higher potency than the parent compound enhancing the antihypertensive activity of the *Bifidobacterium bifidum MF 20/5* fermented milk (Gonzalez-Gonzalez et al. 2013). LVYPFP showed pepsin cleavage sites resulting in the release of L, VYPFP, L, VY, LVY, and PFP as sub-fragments. Out of these fragments, VY has been reported to reduce blood pressure in hypertensive rats (Matsufuji et al. 1995). Peptides LPAGAP, LAALSGM, LLAAMAM, and LAHVPGGAA obtained from *Lactobacillus helveticus KLDS.31 and Lactobacillus casei KLDS.105 fermented milk* exhibited no effect on the ACE inhibitory activity upon pepsin hydrolysis. However, it has been noted that trypsin digestion caused a 3.91% decrease in the ACE inhibitory activity, suggesting that these peptides from ferm, ented milk retain their original ACE inhibitory activity after gastrointestinal digestion indicating a possibility that oral administration of these peptides can retain the bioactivity of these peptide fragments (Li et al. 2019). IPP and VPP, two tripeptides present in *Lactobacillus helveticus* fermented milk were found to have a blood pressure-lowering effect in hypertensive humans. Upon consumption of fermented milk at a dose of 150 ml per day for 21 weeks, it was observed that there was a mean difference of 0.7 ± 3.0 mm Hg in systolic blood pressure and 3.6 ± 1.9 mm Hg in diastolic blood pressure between the test subjects and control (Seppo et al. 2003). VPP AND IPP have been known to exert antihypertensive effect in spontaneously hypertensive rats upon oral administration of Calpis sour milk containing these bioactive peptides.The oral administration of sour milk at a dose rate of 5 ml per kg body weight had a significant decrease of systolic blood pressure from 6 to 8 h after administration (Nakamura et al. 1995) A study based on evaluation of ACE inhibitory activity of

Table 2 Maximum plasma concentrations and elimination half-lives of bioactive peptides administered to animals and humans

Peptide sequence	Administration dose	Test subject	Maximum plasma concentration	Half life	Reference
WH	Oral 10 mg/kg body weight	Rats	19 nM	37 min	(Hanh et al., 2017)
LPP	oral 12.3 μg/kg body weight	Pigs	21 nM	42 min	(Ten Have et al., 2015)
VPP	oral 12.8 μg/kg body weight	Pigs	21 nM	23 min	(Ten Have et al., 2015)
HLPLP	Intravenous 4 mg/kg body weight	Rats	120 ng/ml	8 min	(Sánchez-Rivera et al., 2014)
PG	167 mg/kg body weight	Humans	18 μM	~2 h	(Shigemura et al., 2012)
VY	Oral 30 mg/kg body weight	Rats	1.1 ng//ml	4.1 h	(Nakashima et al., 2011)
YPFVEPI, YPFPGPI	Oral milk	Infants	0.3 μM	Not determined	(Kost et al., 2009)
IPP, LPP, AW, IW, LW, VY, FY	Oral yoghurt	Humans	0.1-3 nM	~30 min	(Foltz et al., 2007)
VY	Oral 12 mg	Humans	1.9 μM	3.1 h	(Matsui et al., 2002)
MAIPPKKNQDK	Oral milk or yoghurt	Newborn infants	21 μg/ml	At least 1 h	(Chabance et al., 1995)
IAIPPKKIQDK	Oral milk or yoghurt	Newborn infants	16 μg/ml	At least 1 h	(Chabance et al., 1995)

fermented colostrum extracts reported that the ACE inhibitory activity ranged between 72.85% to 78.52% which was not much lower than that exerted by Captopril 5 ng/ml (96.48%) indicating their potency (Gaspar-Pintiliescu et al. 2020). An IC50 value of 64.04 µg/ml for ACE inhibitory activity was obtained for the peptide fraction KEDDEEEEQGEEE obtained after fermentation and digestion of pea protein (Jakubczyk et al. 2013).

The prime challenge associated with bioactive peptides is their bioavailability and gastrointestinal absorption within the human body and it needs to be explored and understood properly through in-depth research based on ex vivo and in vivo experiments (Xu et al. 2019). Elaborate peptidomics and transcriptomics studies that are focused on the bioavailability and bioaccessibility of bioactive peptides present in complex food matrices and the development of strategies to enhance their stability would eliminate the need for purification of protein hydrolysates. Moreover, it has been reported that non-dietary factors also affect the bioavailability of food-derived bioactive peptides. Therefore those factors also need to be taken into consideration while interpreting data from in-vivo bioavailability studies of these peptides. The strategies to improve the bioavailability of food bioactive peptides should focus on reducing any detrimental impact of food processing on the bioactivity of biopeptides, promoting desirable interaction between bioactive peptides and other food matrix components, reducing the undesirable interactions, protecting the bioactive peptides from gastrointestinal conditions and action of digestive enzymes, promoting sustained and targeted release of peptides and improving the transport of these peptides across the intestinal epithelium and cells (Amigo & Hernández-Ledesma 2020). Various strategies such as the use of permeation enhancers, microencapsulation, enzyme inhibitors, nano and micro-sized particles, nanocarriers, emulsions, liposomes, hydrogels, site-specific delivery, targeting the membrane transport, chemical modification and cell-penetrating peptides have been explored to enhance the stability, bioavailability, and absorption of bioactive peptides (Nwachukwu & Ekezie 2021).

Conclusion

Food fermentation is undoubtedly a potential alternate method of producing bioactive peptides from various dietary sources of animal or plant origin. Fermenting foods with diverse microorganisms and fermentation conditions can yield a wide spectrum of peptides with particular bioactivities. Despite tremendous progress and advancement in the isolation and purification of bioactive peptides, the research studies on bioactive peptides produced by microbial fermentation are few in comparison to those produced by other methods. As a result, much more research is required to uncover possibly new peptide sequences from fermented foods. The research on bioactive peptides from fermented foods has mostly been confined to the laboratory scale and must be scaled up to develop health-promoting bioactive peptide-based products. This could help commercialize fermented foods. Furthermore, more in-depth studies are needed to confirm that these peptides are as beneficial to human health as claimed, as the existing literature has limited validity when it comes to extrapolation to humans. The world is facing a health emergency in the form of the COVID-19 pandemic, and the inadequacy of existing therapeutic medicines to treat this fatal viral infection necessitates the development of novel ideas and concepts to find and create therapeutic compounds capable of fighting this infection. Because of their health-promoting qualities, particularly their ACE inhibitory impact, bioactive peptides have a great potential to be used to reduce pathological problems associated with SARS-CoV-2 infection, with the Renin-Angiotensin System (RAS) as a possible target. However, epidemiological research examining the precise effect of food-derived ACE inhibitory bioactive peptides on the severity of COVID-19 complications, particularly hypertension induced by RAS dysfunction, is urgently needed. Apart from ACE-inhibitory peptides, other multifunctional peptides also present a promising approach to enhance the survivability of COVID-19 patients with chronic comorbidities. Extensive research is needed to fully understand the gastrointestinal stability and transport of food-derived peptides. Stimulated gastrointestinal conditions and cell culture mimicking the intestinal absorptive environment can be optimized and therefore can be used as a valuable strategy to validate the beneficial role of peptides on health at physiologically relevant doses. Most of the food-derived peptides have been noted to possess low bioavailability therefore efforts need to be channelized to design such strategies that will enhance their resistance to gastrointestinal conditions and digestive enzymes and also allow a sustained and targeted release of peptides. Among the explored strategies use of permeation enhancers, microencapsulation, enzyme inhibitors, nano and micro-sized particles, nanocarriers, emulsions, liposomes, hydrogels, site-specific delivery, targeting the membrane transport and chemical modification have proven to be promising. Although significant progress has been made in the field of food-derived bioactive peptides, there is still room for further in-vitro and in-vivo research to transform these active compounds into new pharmaceutical medicines to improve human health and wellness.

Abbreviations

ACE	Angiotensin converting enzyme
ACE-I	Angiotensin-converting enzyme I
ACE-II	Angiotensin-converting enzyme II
AT1R	Angiotensin type 1 receptor
AT2R	Angiotensin type 2 receptor
ARB	Angiotensin receptor blocker
Ang-I	Angiotensin I
Ang- II	Angiotensin II
COVID-19	Coronavirus disease
CCB	Calcium channel blocker
CEP	Cell envelope proteinase
DRI	Direct renin inhibitor
eNOS	Endothelial nitric oxide synthase
GRAS	Generally recognized as safe
HMGCoAR	3-Hydroxy-3-methylglutaryl CoA reductase
HNF	Hepatocyte nuclear factor
LDLR	Low density lipoprotein receptor
LAB	Lactic acid bacteria
MERS-COV	Middle East Respiratory syndrome coronavirus
MasR	Mass receptor
NK cells	Natural killer cells
PCSK9	Proprotein convertase subtilisin/kexin type 9
RAS	Renin angiotensin system
SREBP2	Sterol regulatory element binding protein 2
SARS-CoV	Severe acute respiratory syndrome coronavirus
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
TMPRSS2	Transmembrane serine protease 2
UV	Ultra-violet

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