



## Review

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# Food-derived bioactive peptides: health benefits, structure–activity relationships, and translational prospects

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**Abstract:** Food-derived bioactive peptides (FBPs), particularly those with ten or fewer amino acid residues and a molecular weight below 1300 Da, have gained increasing attention for their safe, diverse structures and specific biological activities. The development of FBP-based functional foods and potential medications depends on understanding their structure–activity relationships (SARs), stability, and bioavailability properties. In this review, we provide an in-depth overview of the roles of FBPs in treating various diseases, including Alzheimer’s disease, hypertension, type 2 diabetes mellitus, liver diseases, and inflammatory bowel diseases, based on the literature from July 2017 to Mar. 2023. Subsequently, attention is directed toward elucidating the associations between the bioactivities and structural characteristics (e.g., molecular weight and the presence of specific amino acids within sequences and compositions) of FBPs. We also discuss *in silico* approaches for FBP screening and their limitations. Finally, we summarize recent advancements in formulation techniques to improve the bioavailability of FBPs in the food industry, thereby contributing to healthcare applications.

**Key words:** Functional foods; Biological compound; *In silico* prediction; Bioavailability; Oral delivery; Absorption

## 1 Introduction

Bioactive peptides (BPs) are usually short chains of 2–20 natural amino acids. Most BPs with specific physiological functions are typically low in molecular weight. These peptides are encrypted within food proteins. They are usually produced via protein hydrolysis, fermentation, or food processing (Kang et al., 2022). Peptides with low molecular weight are easier to digest and absorb than larger peptides and intact proteins (Wang and Li, 2017). Moreover, they are frequently preferred in solid-phase synthesis (Hamley, 2017). Due to

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their diverse activities, small food-derived BPs (FBPs) are among the most popular research topics in the field. This review covers FBPs with a molecular weight of less than 1300 Da and no more than ten amino acid residues.

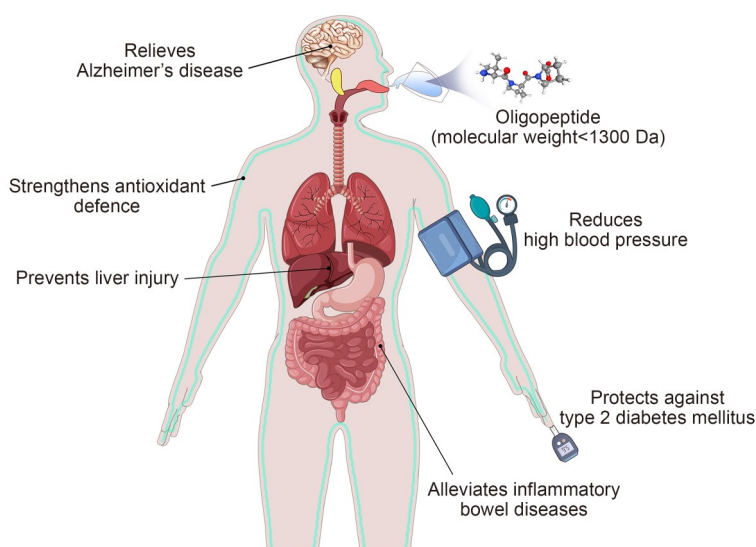
While traditional absorption theory suggests the complete degradation of proteins into free amino acids for absorption, discoveries since the 1960s have shown that proteins can be absorbed by intestinal mucosal cells in the form of peptides following digestion. Various BPs, notably hepatoprotective glutathione (Masubuchi et al., 2011), antioxidant carnosine (Vistoli et al., 2012), and anticancer tyroservatide (Jia et al., 2005), have been incorporated into nonpharmacological therapeutic approaches. Meanwhile, the U.S. Food and Drug Administration (FDA) has approved numerous peptide drugs for medical purposes (Erak et al., 2018), demonstrating their efficacy in treating metabolic disorders, such as obesity, diabetes, hypertension, infection, and inflammation (Fosgerau and Hoffmann, 2015).

FBPs exhibit high biological activity and minimal side effects beyond their nutritional value (Duffuler et al., 2022). However, the current methods for FBP discovery, which depend on structure–activity relationships (SARs) using *in silico* approaches combined with bioinformatics and biomolecular simulations, are hindered by a limited understanding of the actual SARs of these peptides (Gu et al., 2011; Daliri et al., 2017a). Therefore, there is an urgent need to elucidate the explicit relationships between the biological activities and structural characteristics of FBPs.

Although FBPs have potential uses for disease prevention, their bioactivity *in vitro* does not easily translate into pharmacological effects *in vivo* due to obstacles such as mucus and digestive enzymes in the gastrointestinal tract (GIT). These factors can disrupt the stability, bioavailability, and oral absorption of BPs (Sun and Udenigwe, 2020). As oral agents, the palatability of BPs with high oral bioavailability is essential to ensure patient compliance. Ensuring palatability is one of the greatest challenges to consumer acceptance (Jakubczyk et al., 2020). This review focuses on the potential pharmacological intervention of FBPs in chronic diseases (Fig. 1) based on the literature from July 2017 to Mar. 2023. To facilitate and broaden the possible applications of FBPs as functional foods and potential medications, we also introduce advanced formulation techniques of FBPs and their application prospects. An in-depth understanding of the biological activities, mechanisms, and obstacles of intestinal absorption will broaden the potential preventive applications of FBPs.

## 2 Bioactivity and preventive potential of FBPs in chronic diseases

Certain FBPs demonstrate antioxidant, anti-hypertensive, antidiabetic, hepatoprotective, and anti-inflammatory activities, contributing to the multi-preventive potential of FBPs in different chronic



**Fig. 1** Illustration of the potential medical applications of food-derived bioactive peptides (FBPs) in various chronic diseases, highlighting their roles in antioxidant defense, oral route tolerance, and gastrointestinal absorption.

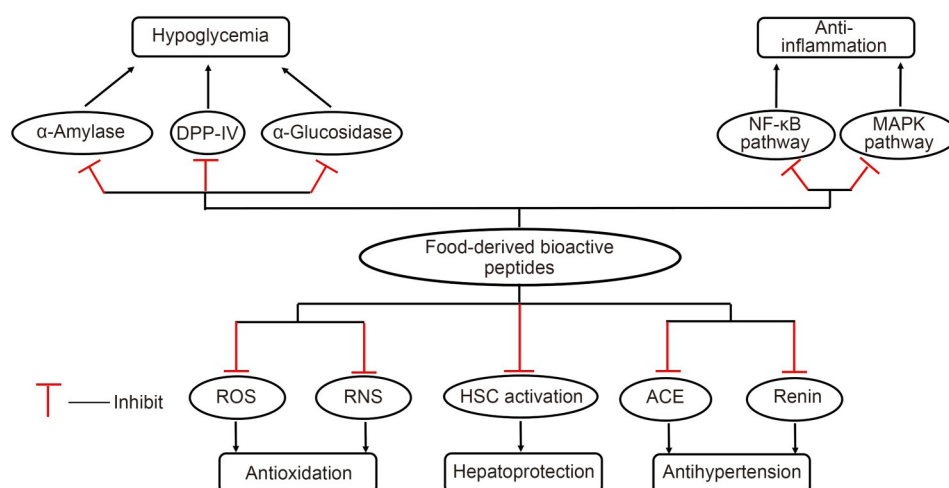
diseases. Antioxidant FBPs inhibit reactive oxygen species (ROS) or reactive nitrogen species (RNS). Suppressing the activation of hepatic stellate cells (HSCs) by FBPs is a key strategy for liver protection, as HSC activation leads to liver fibrosis and potentially cirrhosis or even hepatocellular carcinoma. Anti-hypertensive peptides target mainly angiotensin-converting enzyme (ACE) and renin, while antidiabetic FBPs usually inhibit  $\alpha$ -amylase,  $\alpha$ -glucosidase, or dipeptidyl peptidase-IV (DPP-IV). Furthermore, anti-inflammatory FBPs act predominantly by suppressing the nuclear factor- $\kappa$ B (NF- $\kappa$ B) or mitogen-activated protein kinase (MAPK) pathway, and anticancer FBPs work by promoting immune defense and apoptosis while inhibiting tumor cell proliferation (Fig. 2). Using FBPs for pharmacological intervention against chronic diseases offers significant advantages, such as safe sources, low cost, and additional nutritional benefits. Generally, FBPs not only provide essential amino acids but also offer benefits for preventing and treating chronic diseases (Udenigwe and Aluko, 2012). As novel functional foods, FBPs have become promising sources for drug discovery (Pavlicevic et al., 2022). However, the preventive or therapeutic use of FBPs is still limited, possibly due to low bioavailability or indirect relationships between administered FBPs and their actual effects, leading to misconceptions and incorrect assumptions regarding their mechanisms of action. This section summarizes the bioactivities of some FBPs in specific chronic diseases,

with a particular focus on disease-related mechanisms of action (Table 1).

## 2.1 Alzheimer's disease

Alzheimer's disease (AD) is characterized by the accumulation of amyloid- $\beta$  (A $\beta$ ) peptides, dystrophic neurites, and neurofibrillary tangles (Martins et al., 2018), which are considered hallmarks of the disease. Despite uncertainties in the pathogenesis of AD, elevated levels of various biomarkers, including lipid peroxidation, 4-hydroxy-2-nonenal, 3-nitrotyrosine, and 8-hydroxy-deoxyguanosine, have been found in AD brains, indicating oxidative or nitrosative damage (di Domenico et al., 2017). Research thus points to oxidative stress as a crucial factor in the pathogenesis and development of AD (Butterfield and Boyd-Kimball, 2018; Butterfield and Halliwell, 2019).

Oxidative stress refers to the disequilibrium between the production of ROS/RNS and the efficacy of antioxidant defense. The ROS group includes superoxide, hydroxyl radicals, hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), and singlet oxygen and consists of highly reactive molecules/radicals formed through O<sub>2</sub> oxidation. These species are integral to cellular metabolism under aerobic conditions and play a significant role in cellular signaling pathways (Jakubczyk et al., 2020). Therefore, antioxidant supplements have been suggested as potential pharmacological interventions to mitigate AD progression by neutralizing excess ROS and RNS (Butterfield and Halliwell, 2019).



**Fig. 2** Diagram depicting the biological activities of food-derived bioactive peptides (FBPs) and their therapeutic targets, including their roles in combating oxidative stress, liver fibrosis, hypertension, diabetes, inflammation, and cancer. ACE: angiotensin-converting enzyme; DPP-IV: dipeptidyl peptidase-IV; HSC: hepatic stellate cell; MAPK: mitogen-activated protein kinase; NF- $\kappa$ B: nuclear factor- $\kappa$ B; RNS: reactive nitrogen species; ROS: reactive oxygen species.

Table 1 Food-derived bioactive peptides with different activities and corresponding mechanisms

Sequence	Activity	Source	Function	Target	Reference
Gln-Gln-Arg-Gln-Gln-Gly-Leu (QQRQQQL)	Antioxidative	Defatted walnut meal	In vitro: protection on H <sub>2</sub> O <sub>2</sub> -injured SH-SY5Y cells	ROS	Sheng et al., 2019
Tyr-Val-Leu-Pro-Ser-Pro-Lys (YVLLPSPK)	Antioxidative, anti-Alzheimer	Walnut	In vivo: alleviating learning and memory impairments in scopolamine-treated mice	NRF2/KEAP1/HO-1 pathway	Zhao et al., 2021
Tyr-Trp (YW)	Anti-Alzheimer	Soybean	In vivo: increasing spatial working memory	Catecholamine synthesis and metabolism	Ichinose et al., 2020
Tyr-Pro (YP)	Anti-Alzheimer	Soybean	In vivo: increasing working and fear-conditioning memory; enhancing choline acetyltransferase protein expression	Cholinergic neurotransmission pathway	Tanaka et al., 2020
Lys-Glu-Leu-Glu-Glu-Lys (KELEEK); Arg-Asp-Pro-Glu-Glu-Arg (RDPEER); Leu-Asp-Asp-Gly-Arg (LDDDDGR); Gly-Phe-Ala-Gly-Asp-Asp-Ala-Pro-Arg-Ala (GFAGDDAPRA); Asp-Ala-Ala-Gly-Arg-Leu-Gln-Glu (DAAGRLEQ)	Antioxidative	Watermelon seed	In vitro: cytoprotecting H <sub>2</sub> O <sub>2</sub> -injured HepG2 cells	ROS	Wen et al., 2020
Gln-Met-Asp-Asp-Gln (QMDDQ); Lys-Met-Asp-Asp-Lys (KMDDK); Lys-Met-Asp-Gln (KMDDQ); Gln-Met-Asp-Lys (QMDDK); Met-Thr-Thr-Asn-Ile (MTTNI); Met-Thr-Thr-Asn-Leu (MTTNL)	Antioxidative	Shrimp meat	In vitro: increasing the viability of PC12; inhibiting apoptosis	ROS	Wu et al., 2019
Arg-Asp-Arg-His-Gln-Lys-Ile-Gly (RDRHQKIG); Thr-Asp-Arg-His-Gln-Lys-Leu-Arg (TDRHQKLR); Met-Asn-Asp-Arg-Val-Asn-Gln-Gly-Glu (MNDRVNQGE); Arg-Glu-Asn-Ile-Asp-Lys-Pro-Ser-Arg-Ala (RENIDKPSRA); Ser-Tyr-Pro-Thr-Glu-Cys-Arg-Met-Arg (SYPTECMR)	Antioxidative	Sesame ( <i>Sesamum indicum</i> L.)	In vitro: radical-scavenging effect	ROS	Lu et al., 2019
Ser-Phe (SF); Gln-Tyr (QY)	Antioxidative	<i>Moringa oleifera</i> seeds	In vitro: increasing activity of superoxide dismutase and catalase	ROS	Liang et al., 2020
Tyr-Leu-Val-Asn (YLVN); Gln-Glu-His-Leu-Cys-Phe-Arg (EEHLCFR); Thr-Phe-Tyr (TFY)	Antioxidative	Pea protein hydrolysates	In vitro: radical-scavenging effect; In silico: inhibiting the activation of the KEAP1-NRF2 pathway	ROS	Zhao and Liu, 2023
Val-Tyr-Pro-Phe-Pro-Gly-Pro-Ile-Pro-Asn (VYFPFGPIP)	Antioxidative, anti-Alzheimer	Brazilian kefir	In vitro: radical-scavenging effect; In silico: interacting with $\beta$ -amyloid plaque; neutralizing the negative effects of $\beta$ -amyloid plaque aggregation	ROS, $\beta$ -amyloid plaque	Malta et al., 2022

To be continued

Table 1 (continued)

Sequence	Activity	Source	Function	Target	Reference
Se-Met-Pro-Ser (Se-MPS)	Antioxidative	Se-rich brown rice	In vitro: inhibiting lipid peroxidation; transferring hydrogen atom	ROS	Liu KL et al., 2019
Leu-Ile-Val-Gly-Ile-Ile-Arg-Cys-Val (LIVGHIRCV)	Antihypertensive	Beef myofibrillar proteins	In vitro: ACE inhibitory activity; In vivo: antihypertensive effect in spontaneously hypertensive rats	ACE	Lee and Hur, 2019
Leu-Pro-Gly-Pro-Gly-Pro (LPGPGP); Glu-Tyr-Phe-Arg (EYFR)	Antihypertensive	<i>Channa striatus</i>	In vitro: ACE inhibitory activity	ACE	Ma et al., 2021
Ile-Phe (IF)	Antihypertensive, antioxidative	Potato	In vitro: ACE inhibitory activity; In vivo: renal-protective effects	ACE, ROS	Tsai et al., 2020
Leu-Tyr (LY); Arg-Ala-Leu-Pro (RALP); Gly-His-Ser (GHS)	Antioxidative, antihypertensive, anti-inflammatory	Rapeseed	In vivo: lipid peroxidation inhibition; inhibiting the secretion of proinflammatory cytokines; improving cell damage; decreasing the systolic blood pressure	ROS, ACE, renin	He et al., 2019a, 2019b
Tyr-Val (YV)	Antihypertensive	Ostrich ( <i>Struthio camelus</i> ) egg white ovalbumin	In vitro: ACE inhibitory activity	ACE	Khueychai et al., 2018
Tyr-Ala-Cys-Ser-Val-Arg (YACSVR); Cys-Ala-Glu-Ala-Gly-His (CAEAGH)	Antidiabetic	<i>Sardine pilchardus</i>	In vitro: DPP-IV inhibitory activity	DPP-IV	Rivero-Pino et al., 2020
Leu-Pro-Leu-Leu-Arg (LPLLR)	Antidiabetic	Walnut	In vitro: promoting glycogen synthesis; improving glucose uptake; suppressing improved glucose uptake; activating IRS-1/PI3K/Akt and AMPK signaling pathway (in insulin resistance HepG2 cell)	$\alpha$ -Glucosidase and $\alpha$ -amylase, IRS-1/PI3K/Akt and AMPK pathway	Wang et al., 2020
Gly-Ser-Arg (GSR); Glu-Ala-Lys (EAK)	Antidiabetic	Soybean	In vitro: $\alpha$ -glucosidase inhibitory activity; In vivo: hypoglycemic efficacy in mice with alloxan-induced diabetes	$\alpha$ -Glucosidase	Jiang et al., 2018
Gly-Arg-Val-Ser-Asn-Cys-Ala-Ala (GRVSNCAA); Thr-Tyr-Leu-Pro-Val-His (TYLPPVH)	Antihypertensive, antidiabetic	<i>Ruditapes philippinarum</i>	In vitro: ACE and DPP-IV inhibitory activity; In vivo: promoting NO secretion and reducing ET-1 secretion to lower blood pressure; exerting hypoglycemic activity by increasing the PK and HK levels	ACE, DPP-IV	Zhang Y et al., 2021
Ile-Pro-Ile-Pro-Ala-Thr-Lys-Thr (IPIPATKT)	Antihypertensive, antidiabetic	Sanhuang chicken	In vitro: ACE and DPP-IV inhibitory activity; In vivo: promoting NO secretion and reducing ET-1 secretion to lower blood pressure; exerting hypoglycemic activity by increasing the PK and HK levels	ACE, DPP-IV	Chen et al., 2021

To be continued

Table 1 (continued)

Sequence	Activity	Source	Function	Target	Reference
Asp-Ile-Lys-Thr-Asn-Lys-Pro-Val-Ile-Phe (DIKTNKPVIF)	Antidiabetic	Potato ( <i>Solanum tuberosum</i> L.)	In vivo: regulating blood glucose; retaining insulin levels; efficient immunomodulatory effects	NF- $\kappa$ B-associated iNOS	Marthandam Asokan et al., 2019
Leu-Pro-Thr-Gly-Trp-Leu-Met (LPTGWLM); Met-Phe-Glu (MFE); Gly-Pro-Ala-His-Cys-Leu-Leu (GPAHCLL); His-Leu-Pro-Gly-Arg-Gly (HLPGRG); Gln-Asn-Val-Leu-Pro-Leu-His (QNVLPLH); Pro-Leu-Met-Leu-Pro (PLMLP)	Antidiabetic	Camel and bovine casein	In vitro: $\alpha$ -glucosidase and DPP-IV inhibitory activity	$\alpha$ -Glucosidase, DPP-IV	Mudgil et al., 2021
Lys-Asp-Leu-Trp-Asp-Phe-Lys-Gly-Leu (KDLWDDFKGL); Met-Pro-Ser-Lys-Pro-Pro-Leu-Leu (MPSKPPLL)	Antidiabetic	Camel milk	In vitro: $\alpha$ -amylase inhibitory activity	$\alpha$ -Amylase	Mudgil et al., 2018
Phe-Pro-Val-Gly (FPVG); Leu-Pro-Val-Leu (LPVL); Val-Pro-Phe-Pro (VPPF); Ile-Pro-Leu (IPL)	Antidiabetic	<i>Oncorhynchus keta</i> (chum salmon) milt	In vitro: DPP-IV inhibitory activity	DPP-IV	Takahashi et al., 2021
Tyr-Pro-Leu-Pro (YPLP); Leu-Pro-Tyr-Pro (LPYP)	Hepatoprotective, antioxidant	<i>Corbicula fluminea</i>	In vitro: radical-scavenging effect; protection on ethanol-injured LO2 cells	ROS, CYP2E1	Ren et al., 2021
Asp-His-Asn-Asn-Pro-Gln-Ile-Arg (DHNNPQIR)	Hepatoprotective, antioxidant	Rapeseed	In vivo: suppressing fibrosis-associated genes in models of high-fat diet-induced and CCl <sub>4</sub> -induced liver injury	Cell cycle, ROS	Zhao et al., 2019
Leu-Asp-Ala-Pro-Gly-His-Arg (LDAPGHR)	Anti-inflammatory	Hazelnut	In vitro: inhibiting release of proinflammatory cytokines; inhibiting the NF- $\kappa$ B and MAPK pathway activation	NF- $\kappa$ B and MAPK pathways	Ren et al., 2018
Leu-Ser-Trp (LSW)	Anti-inflammatory	Soybean	In vitro: decreasing phosphorylation of Src, ERK1/2, and nuclear transcription factor p50	NF- $\kappa$ B pathway	Lin et al., 2017
Tyr-Phe-Tyr-Pro-Gln-Leu (YFYFQL)	Anti-inflammatory, antioxidative	Buffalo casein	In vitro: suppressing the secretion of IFN- $\gamma$ ; promoting the secretion of IL-10	ROS	Sowmya et al., 2019
Trp-Phe-Asn-Asn-Ala-Gly-Pro (WFENNAGP)	Anti-inflammatory, antioxidative	<i>Tricholoma matsutake</i>	In vivo: inhibiting myeloperoxidase and proinflammatory cytokine expression; protecting the barrier function by promoting the expression of occludin and ZO-1 in the colon	NF- $\kappa$ B pathway	Li et al., 2021
Gly-Pro-Ala-Gly-Pro-Leu (GPAGPL); Gly-Pro-Pro-Gly-Ala-Pro (GPPGAP)	Anti-inflammatory	Dry-cured ham	In vitro: inhibiting the secretion of NO, IL-6, and TNF- $\alpha$ in LPS-induced RAW264.7 cells	PI3K/Akt signaling pathway	Fu et al., 2021

ACE: angiotensin converting enzyme; Akt: protein kinase B; AMPK: AMP-activated protein kinase; CCl<sub>4</sub>: carbon tetrachloride; CYP2E1: cytochrome P450 2E1; DPP-IV: dipeptidyl peptidase-IV; EPK1/2: extracellular signal-regulated kinase 1/2; ET-1: endothelin-1; HK: hexokinase; HO-1: heme oxygenase-1; IFN- $\gamma$ : interferon- $\gamma$ ; IL: interleukin; iNOS: inducible nitric oxide synthase; IRS-1: insulin receptor substrate-1; KEAP1: Kelch-like ECH-associated protein 1; LPS: lipopolysaccharide; MAPK: mitogen-activated protein kinase; NF- $\kappa$ B: nuclear factor- $\kappa$ B; NO: nitric oxide; NRP2: nuclear factor erythroid 2-related factor 2; PI3K: phosphoinositide 3-kinase; PK: pyruvate kinase; ROS: reactive oxygen species; Src: proto-oncogene tyrosine-protein kinase Src; TNF- $\alpha$ : tumor necrosis factor- $\alpha$ ; ZO-1: zonula occludens-1.

FBPs exhibit antioxidant characteristics (He et al., 2019a; Lu et al., 2019; Qu et al., 2020), including radical-scavenging effects, metal chelation, inhibition of lipid oxidation, and ferric-reducing capability, thereby effectively scavenging ROS. Some enzymatic hydrolysates obtained from walnut and soybean proteins exhibited memory-enhancing effects in animal models (Katayama et al., 2021). Tyr-Val-Leu-Leu-Pro-Ser-Pro-Lys (YVLLPSPK), derived from walnut, increases spatial learning memory ability, suppresses oxidative stress and mitochondrial damage, and activates phosphatase and tensin homolog (PTEN)-induced putative kinase 1 (PINK1) via the nuclear factor erythroid 2-related factor 2 (NRF2)/Kelch-like ECH-associated protein 1 (KEAP1)/heme oxygenase-1 (HO-1) pathway (Zhao et al., 2021). The brain-transportable soy dipeptides, Tyr-Trp (YW) (Ichinose et al., 2020) and Tyr-Pro (YP) (Tanaka et al., 2020), alleviate amyloid beta peptide (25–35 residues)-induced memory impairment in mice. In cellular model tests, recent research has indicated that the defatted walnut meal hydrolysate-derived peptide Gln-Gln-Arg-Gln-Gln-Gly-Leu (QQRQQGL) exhibits potent antioxidant activity by neutralizing hydroxyl radicals and eliminating ROS to protect SH-SY5Y cells from H<sub>2</sub>O<sub>2</sub>-induced oxidative stress-induced harm (Sheng et al., 2019). Purified watermelon seed protein hydrolysates, Asp-Ala-Ala-Gly-Arg-Leu-Gln-Glu (DAAGRLQE), Arg-Asp-Pro-Glu-Glu-Arg (RDPEER), Gly-Phe-Ala-Gly-Asp-Asp-Ala-Pro-Arg-Ala (GFAGDDAPRA), Leu-Asp-Asp-Asp-Gly-Arg (LDDDGR), and Lys-Glu-Leu-Glu-Glu-Lys (KELEEK), also protect against H<sub>2</sub>O<sub>2</sub>-induced cell damage (Wen et al., 2020). Molecular docking results demonstrated that Tyr-Leu-Val-Asn (YLVN), Glu-Glu-His-Leu-Cys-Phe-Arg (EEHLCFR), and Thr-Phe-Tyr (TFY) derived from pea protein hydrolysates might inhibit the activation of the KEAP1-NRF2 pathway by occupying the KEAP1-NRF2-binding site (Zhao and Liu, 2023). Another major source, animal meat, contains peptides such as Gln-Met-Asp-Asp-Gln (QMDDQ), Lys-Met-Asp-Asp-Lys (KMDDK), Lys-Met-Asp-Asp-Gln (KMDDQ), Gln-Met-Asp-Asp-Lys (QMDDK), Met-Thr-Thr-Asn-Ile (MTTNI), and Met-Thr-Thr-Asn-Leu (MTTNL) found in shrimp meat, which shield PC12 cells from oxidative damage through the inhibition of the apoptotic pathway (Wu et al., 2019). Val-Tyr-Pro-Phe-Pro-Gly-Pro-Ile-Pro-Asn (VYPPFGPIP), screened in the “milk and bovine” database, was observed to interact with amyloid plaques based on molecular

docking analysis (Malta et al., 2022). The consequent conformational changes might reduce the toxicity of  $\beta$ -amyloid plaques and therefore attenuate the effects of AD. Overall, ROS scavengers demonstrate the potential for augmenting antioxidant defense.

## 2.2 Hypertension

Hypertension is a prominent risk factor for heart disease and stroke, with its prevalence escalating rapidly, especially in East Asia, Southeast Asia, South Asia, and Oceania (NCD Risk Factor Collaboration, 2017). Several physiological systems regulate blood pressure, including the renin-angiotensin system (RAS), renin-angiotensin-aldosterone system (RAAS), kallikrein-kinin system (KKS), and nitric oxide system (NOS), with renin and ACE playing critical roles (Daliri et al., 2017b). ACE promotes the conversion of angiotensin I (Ang-I) to Ang-II, which negatively impacts vasodilation, leading to sustained vasoconstriction and limiting blood pressure reduction by degrading the antihypertensive agent bradykinin (Wu et al., 2017). Furthermore, excessive accumulation of Ang-II retards vasodilation and contributes to increased blood pressure. Renin initiates the conversion of angiotensinogen to Ang-I, marking the first and rate-limiting step in the RAS. Chymotrypsin can bypass the typical ACE pathway by facilitating the conversion of Ang-I to Ang-II, thus directly inhibiting renin, offering a greater potent antihypertensive effect than ACE inhibition (Wu et al., 2017).

Some FBPs with antihypertensive potential have greater tissue affinity and fewer side effects than chemically synthesized antihypertensive drugs (Daliri et al., 2017b; Duffuler et al., 2022). Milk is the most abundant source of antihypertensive BPs (Kaur et al., 2021), such as the well-known antihypertensive peptides Val-Pro-Pro (VPP) and Ile-Pro-Pro (IPP) (Li et al., 2019). Seafood, eggs, and certain plants also serve as rich FBP sources. The hydrolysis of ostrich egg white protein using pepsin, pancreatin, or alkaline hydrolysis yields Trp-Glu-Ser-Leu-Ser-Arg-Leu-Leu-Gly (WESLSRLLG) and Tyr-Val (YV), which exhibit ACE inhibition (Khueychai et al., 2018; Kaur et al., 2021). *In silico* analysis determined that Asp-Asn-Arg-Tyr-Tyr (DNRYYY), a low-molecular-weight pentapeptide purified from the hydrolysate of velvet antler, can interact with ACE (Im and Lee, 2023). *In vivo* analysis also demonstrated that DNRYYY significantly reduced blood pressure in

spontaneously hypertensive rats following oral administration. FBP inhibition mechanisms, particularly for ACE inhibitors, are categorized mainly into competitive, non-competitive, and anticompetitive types. For example, Val-Tyr (VY) competitively inhibits ACE; Val-Pro (VP), Ile-Tyr (IY), and Leu-Trp (LW) non-competitively inhibit ACE; Ala-Trp (AW), Phe-Tyr (FY), and Ile-Trp (IW) reduce enzyme activity by binding to the intermediate formed by ACE and its substrate (Sato et al., 2002). Lastly, Leu-Tyr (LY), Arg-Ala-Leu-Pro (RALP), and Gly-His-Ser (GHS), which are purified from rapeseed, exhibit strong anti-hypertensive effects by inhibiting renin (He et al., 2019b).

### 2.3 Type 2 diabetes mellitus

The latest report by the International Diabetes Federation indicated that in 2019, about 463 million adults aged 20–79 years had diabetes worldwide. It was predicted that the number of people with diabetes will rise to 578.4 million by 2030 and 700.2 million by 2045, which shows that diabetes is reaching epidemic levels (IDA, 2019). Diabetes mellitus (DM) is a chronic, progressive metabolic disease whose pathogenesis remains partially understood. Hyperglycemia results from an imbalance between glucose absorption and insulin secretion (Chaudhury et al., 2017). DM manifests in two forms: type 1 (T1DM) and type 2 (T2DM). T1DM is triggered by an autoimmune reaction leading to a pancreatic attack, which reduces or halts insulin production. T2DM is closely linked to obesity, age, and genetic factors, defined by insufficient insulin production or insulin resistance (Yan et al., 2019). The pathogenesis of T2DM is more complex than that of T1DM (IDA, 2019).

For these reasons, the development of hypoglycemic drugs for the treatment of T2DM is a major focus of clinical research. Normally, chemically synthesized hypoglycemic drugs are associated with pancreatitis, hypoglycemia, weight gain, and other unfavorable effects (Daliri et al., 2017a). Strategies to design hypoglycemic drugs aim to prevent excessive blood glucose levels and improve insulin sensitivity in patients. One approach involves identifying FBPs for compounds that can inhibit the activity of enzymes such as  $\alpha$ -amylase and/or  $\alpha$ -glucosidase, which are responsible for digesting polysaccharides into glucose (Yan et al., 2019). Additionally, food digestion releases

insulin-secreting hormones called incretins, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which act to maintain stable blood glucose levels (Campbell and Drucker, 2013). The inhibition of DPP-IV, which rapidly hydrolyzes GLP-1 and GIP, is another strategy to reduce blood glucose levels.

Vegetables (Chan-Zapata et al., 2020), dairy products, and marine sources are excellent sources of anti-diabetic peptides. Asp-Ile-Lys-Thr-Asn-Lys-Pro-Val-Ile-Phe (DIKTNKPVIF) (derived from potato protein hydrolysate) (Marthandam Asokan et al., 2019), Leu-Pro-Thr-Gly-Trp-Leu-Met (LPTGWLM), Met-Phe-Glu (MFE), Gly-Pro-Ala-His-Cys-Leu-Leu (GPAHCLL), His-Leu-Pro-Gly-Arg-Gly (HLPGRG), Gln-Asn-Val-Leu-Pro-Leu-His (QNVLPLH), Pro-Leu-Met-Leu-Pro (PLMLP) (derived from camel and bovine casein hydrolysates) (Mudgil et al., 2021), Lys-Asp-Leu-Trp-Asp-Asp-Phe-Lys-Gly-Leu (KDLWDDFKGL), Met-Pro-Ser-Lys-Pro-Pro-Leu-Leu (MPSKPPLL) (derived from camel milk protein hydrolysates) (Mudgil et al., 2018), Phe-Pro-Val-Gly (FPVG), Leu-Pro-Val-Leu (LPVL), Val-Pro-Phe-Pro (VPPF), Ile-Pro-Leu (IPL) (derived from salmon milt) (Takahashi et al., 2021), Cys-Ala-Glu-Ala-Gly-His (CAEAGH), and Tyr-Ala-Cys-Ser-Val-Arg (YACSVR) (derived from discarded *Sardine pilchardus* protein) (Rivero-Pino et al., 2020) have shown potential antidiabetic activities. Zhang Y et al. (2021) found that Gly-Arg-Val-Ser-Asn-Cys-Ala-Ala (GRVSNCAA) and Thr-Tyr-Leu-Pro-Val-His (TYLPVH), which are derived from *Ruditapes philippinarum*, have both antihypertensive and antidiabetic activities by promoting nitric oxide (NO) secretion, reducing endothelin-1 secretion, and increasing hexokinase and pyruvate kinase levels. Another umami peptide, Ile-Pro-Ile-Pro-Ala-Thr-Lys-Thr (IPIPATKT), exhibits strong dual hypertensive and antidiabetic effects both in vitro and in vivo (Chen et al., 2021). Furthermore, the peptides Gly-Ser-Arg (GSR) and Glu-Ala-Lys (EAK), obtained after the hydrolysis of soybean protein with trypsin, effectively suppress  $\alpha$ -glucosidase activity (Jiang et al., 2018), while the walnut peptide Leu-Pro-Leu-Leu-Arg (LPLLR) inhibits  $\alpha$ -amylase and  $\alpha$ -glucosidase (Wang et al., 2020). YACSVR and CAEAGH, recognized for their potent DPP-IV inhibitory activities, appear to be viable alternatives to traditional antidiabetic medications (Rivero-Pino et al., 2020). Although most studies have demonstrated the

antidiabetic properties of FBPs in vitro, their efficacy in vivo remains less clear (Liu R et al., 2019), which has limited the translation of many antidiabetic FBPs into commercial antidiabetic medications (Buckley et al., 2018).

## 2.4 Liver diseases

In recent decades, non-alcoholic steatohepatitis has emerged as the most prevalent chronic liver disease in developed regions. It is often accompanied by progressive collagen deposition and vascular remodeling, resulting in liver fibrosis and cirrhosis (Abdelmalek, 2021). In addition, acute hepatitis can be caused by excessive alcohol intake (Xiao et al., 2019), leading to ongoing liver damage and eventually liver fibrosis. Liver fibrosis, a precursor to cirrhosis and potentially hepatocellular carcinoma, results from an imbalance between hepatic parenchymal cells and the accumulation of the extracellular matrix (ECM) (Tsochatzis, 2022). The regulation of ECM generation and degradation is generally accomplished by matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) (Yoshiji et al., 2002; Atta et al., 2014), while HSCs are crucial to the development of liver fibrosis and ECM remodeling. Unfortunately, specific antifibrotic drugs that can effectively control HSC activation or liver fibrosis are lacking, with existing drugs showing limited efficacy and adverse effects (Bataller and Brenner, 2005; Tsuchida and Friedman, 2017). Active ingredients extracted from food may have significant potential in the development of healthcare supplements to address liver diseases worldwide.

Several food-derived substances that exhibit hepatoprotective effects, including FBPs and polysaccharides, have been found in a variety of sources, such as corn, soybean, wheat, fruit, and marine animals (Yamaguchi et al., 1997; Liu et al., 2018; Jiang et al., 2020; Qu et al., 2020). For instance, Ren et al. (2021) found that Tyr-Pro-Leu-Pro (YPLP) and Leu-Pro-Tyr-Pro (LPYP) derived from *Corbicula fluminea* provide strong protection for LO2 cells against ethanol-induced damage because of their antioxidant activity and inhibition of cytochrome P450 2E1. Asp-His-Asn-Asn-Pro-Gln-Ile-Arg (DHNNPQIR), a natural FBP derived from rapeseed, has been shown to improve insulin resistance and directly suppress fibrosis-associated genes in models of high-fat diet-induced and carbon tetrachloride (CCl<sub>4</sub>)-induced liver injury (Zhao et al., 2019).

Note that leucine and alanine alone do not have any hepatoprotective properties, but corn peptides consisting of these amino acids (either alone or in combination) aid in alcohol metabolism (Yamaguchi et al., 1997).

## 2.5 Inflammatory bowel diseases

Effective immunomodulation is essential for maintaining immune function and promoting human health through the suppression or stimulation of immune responses. When immune responses become dysregulated or excessively active, both acute and chronic inflammation can occur (Majumder et al., 2016). Inflammatory bowel diseases (IBDs) are chronic inflammatory diseases that pose a significant health burden and are becoming increasingly prevalent in many developing countries (Høivik et al., 2013). They are characterized by gastrointestinal disorders, and the extravasation of numerous inflammatory cells in patients with IBDs is caused by complex interactions. Numerous studies suggest that oxidative stress increases during chronic intestinal inflammation (Pereira et al., 2015). However, the mechanisms by which factors initiate and perpetuate inflammation and disrupt intestinal homeostasis remain unclear. Certain FBPs, including Tyr-Phe-Tyr-Pro-Gln-Leu (YFYPQL), exhibit both anti-inflammatory and antioxidant properties and may serve as effective interventions for IBDs (Sowmya et al., 2019).

Anti-inflammatory FBPs exert their effects mainly by modulating the MAPK and NF- $\kappa$ B pathways. Additionally, downregulation of cyclooxygenase-2 (COX-2), reduction in tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), histamine release, and NO production play essential roles in anti-inflammatory activities (Chakrabarti et al., 2014; Majumder et al., 2016; Guha and Majumder, 2019). Overall, most modulatory effects target proinflammatory or inflammatory cytokines.

Leu-Asp-Ala-Pro-Gly-His-Arg (LDAPGHR), a peptide derived from hazelnut protein, can regulate both the NF- $\kappa$ B and MAPK pathways by inhibiting the phosphorylation of inhibitor of NF- $\kappa$ B $\alpha$  (I $\kappa$ B $\alpha$ ), extracellular signal-regulated kinase 1/2 (ERK1/2), p38, and c-Jun N-terminus kinase (JNK) and the nuclear translocation of p65. This action results in the suppression of COX-2, NO, and inflammatory cytokines (TNF- $\alpha$ , interleukin-1 $\beta$  (IL-1 $\beta$ ), and IL-6). Thus, LDAPGHR produces a strong anti-inflammatory effect (Ren et al., 2018). The *Tricholoma matsutake*-derived peptide Trp-Phe-Asn-Asn-Ala-Gly-Pro (WFNNAGP) significantly ameliorates dextran sodium sulfate-induced

oxidative damage by downregulating NF- $\kappa$ B expression and inhibiting the formation and activation of NOD-like receptor family, pyrin domain-containing protein 3 (NLRP3) and caspase-1 (Li et al., 2021). Gly-Pro-Ala-Gly-Pro-Leu (GPAGPL) and Gly-Pro-Pro-Gly-Ala-Pro (GPPGAP) derived from dry-cured ham showed anti-inflammatory capacity by decreasing the secretion of NO and IL-6 (Fu et al., 2021). Moreover, some peptides modulate cytokines to exert anti-inflammatory effects. For instance, YFYFQL, an anti-inflammatory hexapeptide isolated from buffalo casein, suppressed the secretion of the proinflammatory cytokine interferon- $\gamma$  (IFN- $\gamma$ ) and induced the secretion of the anti-inflammatory cytokine IL-10 in a Caco-2 cell model under attack by H<sub>2</sub>O<sub>2</sub> (Sowmya et al., 2019).

Natural antimicrobial peptides consist of 10–100 but usually fewer than 50 amino acid residues (Maróti et al., 2011) and have significant potential value in medicine. Some antimicrobial peptides also have anti-inflammatory bioactivity (Luo and Song, 2021), such as Leu-Ile-Lys-Lys-Ile-Tyr-Arg-Lys-Trp-Lys-Arg-Trp (LIKKIYRKWKRW) and Leu-Trp-Lys-Lys-Ile-Tyr-Arg-Lys-Trp-Lys-Arg-Trp (LWKKIYRKWKRW), which are derived from duck cathelicidin (Kumar and Shin, 2020). The antimicrobial activity of these peptides is positively correlated with chain length (Liu et al., 2007). However, most antimicrobial peptides do not belong to FBPs because of their excessive number of amino acid residues. The screening approaches and

SARs of antimicrobial peptides have been summarized in recent reviews (Bin Hafeez et al., 2021; Luo and Song, 2021).

### 3 Relationships between the bioactivity and structure of FBPs

All the functions of FBPs are tightly related to their structure. The structural characteristics of FBPs found both in silico and in trials are summarized in Table 2. The following section highlights the molecular weights, specific amino acid sequences, and spatial structures of different FBPs to summarize the SARs of FBPs.

#### 3.1 Molecular weight

Although the relationships between the FBP structure and related bioactivity are still not fully elucidated, considerable evidence has highlighted that molecular weight plays a crucial role in antioxidant, antihypertensive, antidiabetic, and anti-inflammatory effects (Guha and Majumder, 2019; Nwachukwu and Aluko, 2019; Yan et al., 2019; Jakubczyk et al., 2020; Hu et al., 2023). Compared with other biofunctional peptides, FBPs have improved molecular mobility and diffusivity due to their low molecular weights. Therefore, FBPs can penetrate the intestinal barrier more easily than traditional large peptides and terminate free radical chain

**Table 2 Structural characteristics of food-derived bioactive peptides**

Activity	Structure characteristics	Example	Reference
Antioxidative	Low molecular weight; hydrophobic amino acids; aromatic amino acids; basic amino acids; Arg at C-terminal; Cys, Tyr, and Trp at N-terminal	Ile-Tyr (IY), Gln-Tyr (QY)	Nwachukwu and Aluko, 2019; Wu et al., 2019; Jakubczyk et al., 2020; Liang et al., 2020
Antihypertensive	Hydrophobic amino acids, aliphatic or aromatic amino acids at the C-terminal; hydrophobic amino acids at the N-terminal and bulky amino acids at the C-terminal	Ile-Trp (IW)	Udenigwe et al., 2012; Lee and Hur, 2019
Antidiabetic	Tri- to hexa-peptides containing hydroxyl or other basic side chains at the N-terminal, Pro at the penultimate C-terminal, and Ala or Met as the C-terminal residue	Leu-Pro-Leu-Leu-Arg (LPLLR)	Ibrahim et al., 2018; Wang et al., 2020
Hepatoprotective	Hydrophobic amino acids	Tyr-Pro-Leu-Pro (YPLP), Leu-Pro-Tyr-Pro (LPYP)	Ren et al., 2021
Anti-inflammatory	Hydrophobic amino acids at N-terminal; charged amino acids; low molecular weight with glycine	Leu-Asp-Ala-Pro-Gly-His-Arg (LDAPGHR)	Tang and Skibsted, 2016; Ren et al., 2018; Guha and Majumder, 2019

reactions to exhibit antioxidant activities (Chi et al., 2015; Pan et al., 2019). Meanwhile, crystallographic studies of ACE-inhibitory peptides have shown that large peptides cannot bind to the active sites of ACE, which limits their antihypertensive activity (Natlesh et al., 2003). However, these findings do not imply that low-molecular-weight FBP exert better bioactivity. Jahanbani et al. (2016) found that the antioxidant activities of fractions with lower molecular weight were not superior to those of whole hydrolysates.

### 3.2 Specific amino acid sequence and composition

The bioactivities of most FBPs may hinge more on the presence of specific amino acids rather than peptide length. Recent reviews have summarized the specific amino acid residues that contribute to effective antioxidant activities, including hydrophobic amino acids (Ala, Ile, Leu, Val, Met, and Pro), aromatic amino acids (Phe, Trp, and Tyr), acidic amino acids (Asp and Glu), and basic amino acid (His) (Nwachukwu and Aluko, 2019; Jakubczyk et al., 2020). Metal-chelating amino acid residues (e.g., Gln and Lys) within FBPs lead to strong radical scavenging potential by inhibiting the prooxidant activity of superior  $Fe^{2+}$  and/or charged groups (Xia et al., 2012). Most hydrophobic amino acid residues can interact with free radicals (Sila and Bougatef, 2016), whereas the enrichment of hydrophobic residues in FBPs does not directly correlate with antioxidant activities. For example, IY, with two hydrophobic amino acid residues, has a weaker free radical-scavenging ability than Gln-Tyr (QY), which contains only one (Liang et al., 2020). The location and repetitive units of specific amino acids can be critical factors for antioxidant capacity, as in LDDDGR and Tyr-Pro-Gln-Leu-Leu-Pro-Asn-Glu (YPQLLPNE) (Siow and Gan, 2013; Jin et al., 2016; Wen et al., 2020). Moreover, amino acids involved in both terminals of FBPs are also vital to antioxidant activities, such as the C-(Arg) and N-(Cys, Tyr, and Trp) terminals, which may be attributed to carboxyl- and amino-active hydrogen atoms serving as active sites (Wu et al., 2019).

Similarly, hydrophobic amino acids are crucial for antihypertensive activity and constitute a high proportion of the amino acids in antihypertensive FBPs. Meanwhile, acidic amino acids (Asp and Gln) in the sequence of FBPs may chelate zinc atoms essential for enzyme activity (e.g., ACE) (Aluko, 2015). Additionally, Wu et al. (2006a, 2006b) suggested SARs for

antihypertensive dipeptides, tripeptides, and tetrapeptides, identifying specific structural prerequisites for each peptide type that contribute to their antihypertensive efficacy. Such dipeptides contained amino acids with hydrophobic and bulky side chains; tripeptides had an aromatic amino acid at the C-terminal, a hydrophobic residue at the N-terminal, and a positively charged amino acid in the middle; in the case of tetrapeptides, the preferred amino acids at the C-terminal were Cys and Tyr, with Trp, His, or Met in the second position, Met, Val, Leu, or Ile in the third position, and Trp at the N-terminal. Notably, the modulation of hypertension by identified antihypertensive FBPs encompasses ACE inhibition and renin suppression, with the amino acid composition at the C-terminal significantly influencing ACE-inhibitory activity (Daliri et al., 2017b). Higher ACE-binding affinity is observed when the C-terminal of antihypertensive FBPs is composed of aliphatic (Gly, Ala, Val, Leu, and Ile) or aromatic amino acids (Trp, Tyr, and Phe) or other hydrophobic residues rather than hydrophilic groups (Lee and Hur, 2019). Likewise, for renin inhibition, dipeptides exhibiting bulky side chains and hydrophobic amino acids at the C- and N-terminal, respectively, demonstrate potent renin suppression. For instance, enzymatic inhibition assays have shown that the dipeptides IW and LW effectively inhibit renin, whereas AW and Val-Trp (VW) are inactive under the same conditions (Udenigwe et al., 2012).

In antidiabetic FBPs, Pro at the penultimate C-terminal and Ala or Met at the C-terminal enhance  $\alpha$ -glucosidase inhibitory activity, whereas a negative charge diminishes it (Ibrahim et al., 2018). The hydrophobicity and isoelectric points are less predictive of  $\alpha$ -glucosidase inhibition.

Anti-inflammatory FBPs that contain glycine were found to have a high affinity for calcium binding and to disrupt  $Ca^{2+}$  signaling through glycine-gated chloride channels (Tang and Skibsted, 2016). Charged amino acids and hydrophobic amino acids also participate in hepatoprotective and anti-inflammatory FBPs. FBPs containing either positively or negatively charged amino acids, such as Lys, Arg, and Gln, also exhibit strong anti-inflammatory effects (Ren et al., 2018). These effects can be further enhanced by hydrophobic amino acids clustering at the N-terminal (Lin et al., 2017), probably due to enhanced peptide–cell membrane interactions. A high proportion of hydrophobic amino

acids are usually found in hepatoprotective food hydrolysates (Yu et al., 2017; Chen et al., 2020; Ren et al., 2021).

The existing findings offer plenty of clues for screening appropriate FBPs. However, these scattered clues still need systematic organization, which depends on *in silico* tools.

#### 4 *In silico* methods used in FBP screening

To identify the specific biological activities of FBPs, the development of suitable screening methods is necessary. Methods commonly used to screen for FBP activity include bioassays, kinetic analysis, and computational docking simulation (Nong and Hsu, 2022). Bioassays and kinetic analysis use a variety of instruments, including spectrophotometers and fluorescence spectrophotometers (Lahogue et al., 2010), to study the impact of BPs on a target enzyme. During the testing of antihypertensive BPs, the standard substrate *N*- $\alpha$ -hippuryl-L-histidyl-L-leucine is commonly used to form hydrolysis products (hippuric acid and histidyl-leucine), which are monitored at 228 nm. Similarly, the screening process for hypoglycemic peptides involves observing changes in the fluorescence signal generated by the tested BPs resulting from the cleavage of the fluorescent substrate Gly-Pro-7-amino-4-methylcoumarin (AMC) hydrobromide. Zhou et al. (2021) used this method to discover a DPP-IV inhibitory peptide Val-Pro-Leu-Val-Met (VPLVM) derived from broccoli. Nevertheless, these methods can ascertain only the relative potency of the test peptides when compared to a standard and thus are not suitable for high-throughput screening of BPs. Using an *in silico* approach for screening provides an efficient solution to this issue.

The use of computer-aided approaches has hastened the discovery of FBPs. Such approaches use diverse databases and associated algorithms to model the pharmacological and structural characteristics of these peptides. These *in silico* methods involve mainly bioinformatics and biomolecular simulations. Bioinformatic methods use extensive databases to provide robust statistics and classification based on factors including bioactivity, absorption, distribution, metabolism, excretion, and toxicity of FBPs (Agyei et al., 2018; Shakya et al., 2020). Online *in silico* tools such

as bioactive peptide database (BIOPEP), predictor of anti-inflammatory peptides (PreAIP), the scoring card method (SCM) for modeling the bioactivity of DPP-IV inhibitory peptides (iDPPIV-SCM), and antihypertensive peptide inhibitor database (AHTPIN) facilitate the rapid screening of FBPs (Kumar et al., 2015; Khatun et al., 2019; Minkiewicz et al., 2019; Charoenkwan et al., 2020), including anti-inflammatory, hypoglycemic, and antihypertensive peptides (Kumar et al., 2015; Khatun et al., 2019; Charoenkwan et al., 2020). Different machine-learning models are essential for successful bioactivity prediction. However, two limiting steps hinder model performance: model selection and peptide representation (Du et al., 2023b). Recently, a screening model for antihypertensive peptide discovery has been released that uses a protein language model with evolutionary scale modeling embeddings that are refined through training on experimental datasets (Du et al., 2024). Using confidence learning theory for BP dataset cleaning and a pretrained language model for peptide embedding, this model exhibited superior performance in precise bioactivity prediction compared with the twelve traditional embedding methods. Understanding protein–peptide interactions is as vital as bioactivity prediction. Computational methods commonly used for analyzing the binding sites and affinity effects of FBPs include qualitative structure–activity relationship (QSAR) and structure–property relationship (QSPR) analyses, molecular docking, and molecular dynamics simulations (MDSs). Pei et al. (2022b) validated the robust binding affinity between the DPP-IV enzyme and VPLVM through MDSs. Meanwhile, it is necessary to obtain the three-dimensional (3D) structure of the targeted protein, which is used for binding analysis (Du et al., 2023a). In the last five years, AlphaFold2 and cryo-electron microscopy have been useful for circumventing the limitations of traditional X-ray crystallography and nuclear magnetic resonance (NMR) spectroscopy (Callaway, 2020; Jumper et al., 2021).

Although molecular docking and MDS have enhanced the understanding of the SARs of FBPs, their potential limitations often translate into discrepancies with experimental data. Molecular docking approximations of real molecular interactions suffer from fluctuations in the body's environment and sampling method limitations (e.g., solvent and pH), which restrict prediction accuracy (Trott and Olson, 2010).

Predicting the time evolution of a system that comprises particles (i.e., atoms and molecules) and external factors (i.e., temperature and electric field) is a complex challenge for biomolecular simulations. To handle such a complex system, researchers often rely on MDS simulations to solve the equations of motion of particles interacting within the system. However, the computational demands and extended processing time limit the practicality of these simulations by using force field equations in modeling systems (Vidal-Limon et al., 2022). Unfortunately, most FBPs are characterized by unknown pharmacokinetics, a short half-life ( $t_{1/2}$ ), and rapid elimination by peptidases in the body (e.g., pepsin and trypsin), thereby limiting their potential development as oral supplements or drugs (Pei et al., 2022a). For example, casein-derived peptide Val-Pro-Tyr-Pro-Gln (VPYPQ) and its fragments VP, Val-Pro-Tyr-Pro (VPYP), Tyr-Pro-Gln (YPQ), and Val-Pro-Tyr (VPY) exhibited DPP-IV inhibitory bioactivity in vitro, with VPYPQ administration lowering blood glucose levels in vivo. However, their  $t_{1/2}$  was less than 20 min (Zheng et al., 2019), highlighting the insufficiencies of current research methodologies.

## 5 Oral delivery of FBPs

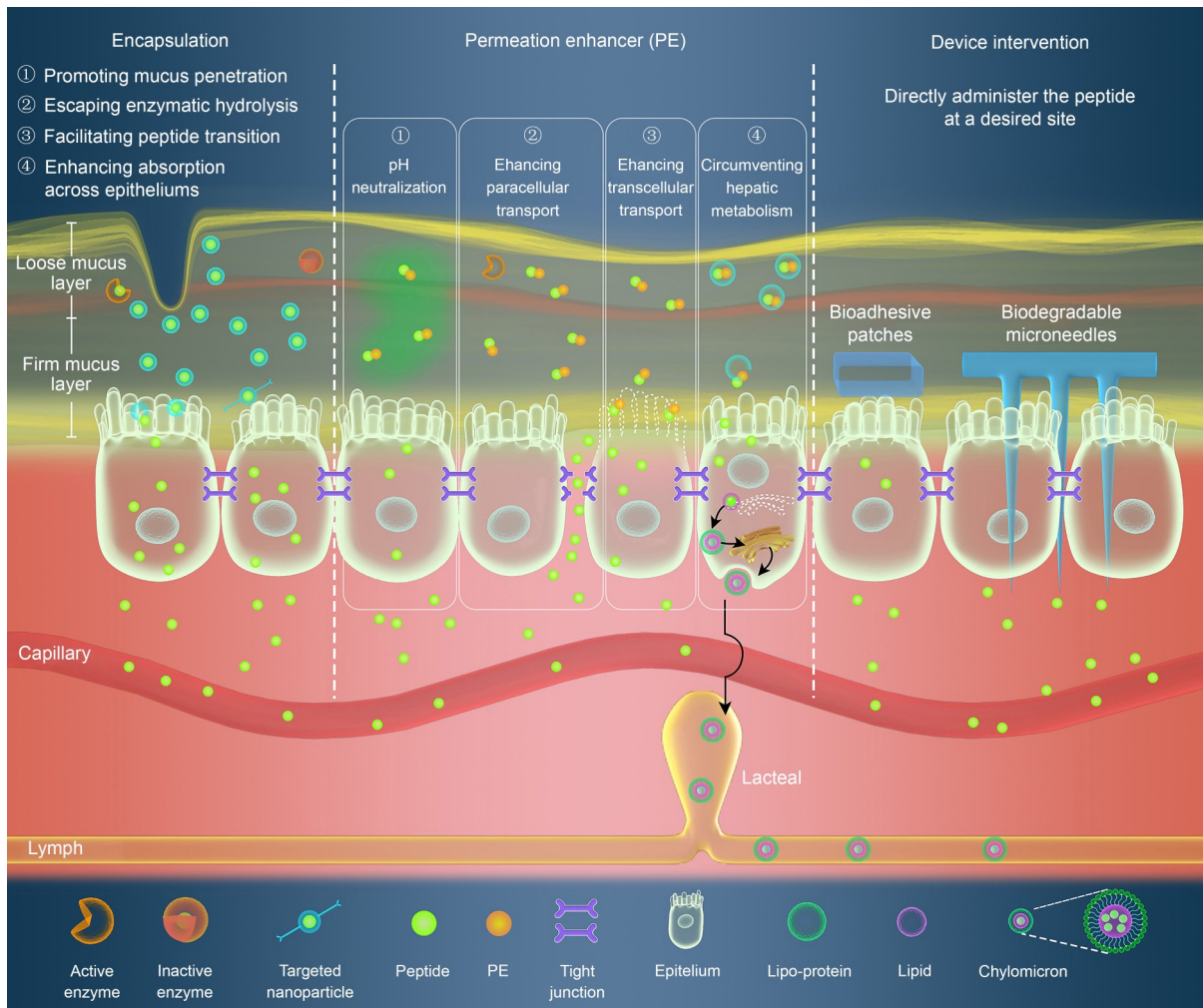
The oral administration of FBPs is the most favorable and expedient route. While low-molecular-weight FBPs exhibit tolerance to hydrolases in the GIT (Udenigwe and Aluko, 2012), recent studies have demonstrated that oral administration of FBPs may lead to their degradation, thereby reducing their bioactivity or causing deactivation. Deactivation of orally administered FBPs is influenced by proteases in the GIT, peptidases in epithelial cells, and transepithelial peptide transport. Brush-border peptidases regulate the degradation and bioavailability of orally administered FBPs by breaking them down into smaller peptides (Wang and Li, 2017). Peptide transportation across the intestine is facilitated by three vital factors: peptide transporter 1, responsible for the transfer of di- and tripeptides; a paracellular transporter, facilitating the movement of hydrophilic, low-molecular-weight peptides; and transcytosis, involving endocytic uptake and subsequent basolateral release (Shimizu et al., 1997; Daniel, 2004; Regazzo et al., 2010). Regrettably, the oral bioavailability of most FBPs is typically less than 1%, significantly limiting their development as promising oral drugs.

### 5.1 Barriers to oral delivery

The absorption of FBPs through the GIT faces three major obstacles, namely, the biochemical environment, mucus, and epithelial lining (Brown et al., 2020). The bioavailability of FBPs may be affected by active biochemical barriers, including pH and enzymes (e.g., brush border and cytosol peptidases) (Allen and Carroll, 1985). The pH gradient from the stomach (pH 1.0–2.0) to the intestine (pH 4.0–7.5), along with gastrointestinal motility and abundant digestive enzymes, heavily impacts the absorption of oral FBPs (Brown et al., 2020). The coating of the GIT, comprising a firm mucus layer bound to the epithelial lining and a loose mucus layer adherent to the lumen, acts as an efficient physical barrier that frequently limits the diffusion of oral FBPs (Brown et al., 2020; Drucker, 2020). The epithelial lining, which includes enterocytes, heavily influences the absorption process by inhibiting their transport from the GIT to the bloodstream. Furthermore, tight junctions between the epithelium, enterocytes, and active efflux pumps (e.g., P-glycoprotein) directly impact the bioavailability of oral FBPs by regulating the paracellular and transcellular pathways (Brayden et al., 2020; Brown et al., 2020). Once absorbed, FBPs undergo hepatic first-pass metabolism, which significantly shortens their elimination  $t_{1/2}$ .

### 5.2 Approaches to overcome oral barriers

Despite being a relatively new field (under 40 years old), there have been significant efforts to develop strategies that enable the clinical translation of orally delivered medical FBPs. Common strategies that have been used to enhance BP absorption include promoting penetration, impeding enzyme hydrolysis, and promoting mucus adhesion, as well as physical insertion. Several strategies for enhancing the stability and absorption of oral BPs in the GIT have been outlined (Fig. 3). These include encapsulation methods to protect FBPs from hydrolysis and promote their penetration and absorption, permeation enhancers that stabilize peptides by neutralizing pH, and device interventions such as bioadhesive patches and biodegradable microneedles, which facilitate direct transportation of FBPs to target sites, bypassing biochemical barriers, mucus, and the epithelial lining (Brayden et al., 2020; Brown et al., 2020; Drucker, 2020). For instance, semaglutide, a GLP-1 receptor agonist that is used in



**Fig. 3** Schematic representation of strategies to enhance the bioavailability of oral food-derived bioactive peptides (FBPs) in the gastrointestinal tract, including encapsulation, permeation enhancer, and device intervention.

T2DM treatment (Mosenzon et al., 2020), is successfully delivered orally when co-formulated with the absorption enhancer sodium *N*-[8-(2-hydroxybenzoyl)aminocaprylate] (SNAC) (Buckley et al., 2018). SNAC inhibits enzyme hydrolysis, neutralizes acidic pH, and enhances transcellular transport, thereby improving the oral bioavailability of BPs (Buckley et al., 2018; Brayden et al., 2020). In addition, Chiasma Pharmaceuticals (MA, USA) developed transient permeation enhancement (TPE) technology, an oily suspension technique used to increase the transcellular transport of octreotide, a cyclic octapeptide (Brayden et al., 2020). Using TPE technology, the oral formulation of octreotide involves sodium caprylate, a medium-chain fatty acid (as a permeation enhancer), and oil-based excipients, which generate a lipophilic suspension of hydrophilic particles in a hydrophobic environment

(Tuvia et al., 2014). Other strategies used to facilitate oral absorption include microneedle-pill and enhancing paracellular transport (Vecchio and Stroud, 2019; Brayden et al., 2020). For metabolically fragile peptides, the absorption risk could be overcome by exploring lymphatic transport as an alternative route. This route includes the chylomicron and microfold cell pathways, which bypass hepatic first-pass metabolism (Zhang Z et al., 2021).

Encapsulation is a technology used to safeguard bioactive compounds from unfavorable conditions in the GIT environment. Currently, nanoencapsulation (ranging from 10 to 1000 nm) and microencapsulation (ranging from 1 to 1000  $\mu\text{m}$ ) are at the forefront of enhancing the stability and bioavailability of orally administered FBPs (Witika et al., 2020; Cian et al., 2022). Whereas Val-Leu-Pro-Val-Pro (VLPVP) is vulnerable

to degradation in the GIT, it remains active in simulated GI fluids because of the deployment of Shirasu porous glass membrane emulsification technology (Huang et al., 2017). However, poor absorption and low tolerance in the GIT still constrain the development of oral delivery systems for bioactive compounds (Nur and Vasiljevic, 2017). Core-shell nanoparticles with a thiolated hyaluronic acid coating for the encapsulation of insulin have achieved high mucus penetration ability and high oral bioavailability (11.3%) in type 1 diabetic rats (Tian et al., 2018). Electrospinning, an adaptable encapsulation method that uses micro- and nanosized fibers to protect bioactive compounds from deactivation and increase bioavailability prospects, has shown great potential in improving the bioavailability of FBPs (Wen et al., 2017).

### 5.3 Challenges and solutions for taste and odor

The taste and odor of FBPs are critical determinants of their palatability, particularly in forms like suspensions, powders, and granules. Most bioactive compounds, included in FBPs, have a bitter or astringent taste that negatively impacts patient adherence (Perry and McClements, 2020). Therefore, it is crucial to mask these unpleasant flavors to enhance patient acceptability. Taste masking is achieved through diverse methods, including the addition of sweeteners and encapsulation (Nasr et al., 2022). For example, Zhao et al. (2020) used oxidized starch hydrogel microencapsulation to mask the astringency of proanthocyanidins in beverages. Encapsulating gluten-derived peptides using water-in-oil high internal phase emulsions has been effective in improving gastrointestinal stability and reducing bitterness (Gao et al., 2022). While direct applications of taste masking for FBPs are infrequent, they offer a spectrum of possibilities for the development of FBP-based products.

## 6 Conclusions and perspectives

Food protein serves not only as a source of nutrients but also as a reservoir of FBPs with multifunctional activities, offering potential therapeutic benefits. Despite the growing body of evidence indicating their health-promoting bioactivities, few FBP-related products have been approved for clinical applications. The following research avenues could facilitate the

application of FBPs as functional foods or potential medications:

(1) Therapeutic targets and mechanistic studies: The activities of FBPs have been extensively studied in multiple diseases, such as AD, hypertension, T2DM, liver diseases, and IBD. However, the therapeutic targets of most BPs are not clear, and their mechanisms of action remain to be elucidated. There are known targets for each disease, such as A $\beta$  and tau for AD, ACE and angiotensin receptor for hypertension,  $\alpha$ -amylase and DPP-IV for T2DM, ECM and TIMPs for liver diseases, and NF- $\kappa$ B and COX-2 for IBD, which can be used as screening tools to identify novel BPs for metabolic diseases and, in turn, reveal the underlying mechanisms of action. Furthermore, the use of biotin-labeled BPs may open a new path for specific receptor identification and is also conducive to elucidating pharmacological mechanisms, especially direct evidence for target binding by cryo-electron microscopy, X-ray crystallography, or nuclear magnetic resonance techniques.

(2) Pharmacological potential of FBPs: Given the pharmacological functions and SARs of FBPs, their development into potential active ingredients for disease prevention and treatment is vital. Recently, studies of FBPs have focused on the relationship between their regular pattern of structure and activities, which provides a structural basis for the design of new FBPs. Modification of the peptide backbone, such as replacing L-amino acids with D-amino acids or substituting amino acid residues, will improve the bioavailability and potency of FBPs for potential pharmacological applications.

(3) Stability and pharmacokinetics of FBPs: In silico analysis has expanded the scope of methods available for screening bioactivity and exploring the SARs of FBPs. This approach assumes that FBPs are stable in vivo. However, most FBPs have a short  $t_{1/2}$ , which requires confirmation of their stability and pharmacokinetics before proceeding with in silico analysis. Combining plasma stability assays with ultrahigh-performance liquid chromatography-tandem mass spectrometry (UHPLC-MS/MS) could be instrumental in discovering new FBPs.

(4) Bioavailability improvement: FBPs usually exhibit low water solubility, poor stability in the GIT, and unacceptable taste, which can potentially limit their bioavailability. The drug delivery system can help

overcome these barriers. For example, the side chains of BPs carry a variety of active functional groups, such as carboxyl, hydroxyl, amino, and thiol groups, which can be modified to overcome the physiological barriers of oral delivery, such as water solubility, hydrolysis through the digestive tract, permeability through the gastrointestinal mucus and epithelial lining, and first-pass metabolism. Moreover, the introduction of functional peptides (i.e., targeting, cell-penetrating, responsive, and self-assembling peptides) provides a new strategy to enhance the targeting, stability, taste, and bioactivity properties, which may provide new insight for the precise treatment of diseases.

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### Author contributions

Hongda CHEN: conceptualization, writing – original draft, and visualization. Jiabei SUN: writing – original draft. Haolie FANG: conceptualization and visualization. Yuanyuan LIN, Han WU, Dongqiang LIN, Zhijian YANG, Bingxiang ZHAO, Tianhua ZHOU, Jianping WU, and Shanshan LI: writing – review & editing. Quan ZHOU and Xiangrui LIU: funding acquisition and writing – review & editing. All authors have read and approved the final version.

### Compliance with ethics guidelines

Hongda CHEN, Jiabei SUN, Haolie FANG, Yuanyuan LIN, Han WU, Dongqiang LIN, Zhijian YANG, Quan ZHOU, Bingxiang ZHAO, Tianhua ZHOU, Jianping WU, Shanshan LI, and Xiangrui LIU declare that they have no conflicts of interest.

This review does not contain any studies with human or animal subjects performed by any of the authors.

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