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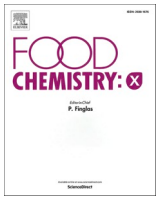

Preparation, design, identification and application of self-assembly peptides from seafood: A review

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ABSTRACT

Hydrogels formed by self-assembling peptides with low toxicity and high biocompatibility have been widely used in food and biomedical fields. Seafood contains rich protein resources and is also one of the important sources of natural bioactive peptides. The self-assembled peptides in seafood have good functional activity and are very beneficial to human health. In this review, the sequence of seafood self-assembly peptide was introduced, and the preparation, screening, identification and characterization. The rule of self-assembled peptides was elucidated from amino acid sequence composition, amino acid properties (hydrophilic, hydrophobic and electric), secondary structure, interaction and peptide properties (hydrophilic and hydrophobic). It was introduced that the application of hydrogels formed by self-assembled peptides, which lays a theoretical foundation for the development of seafood self-assembled peptides in functional foods and the application of biological materials.

1. Introduction

Peptide self-assembly is the spontaneous formation of ordered structures by individual molecules in response to non-covalent interactions, driven by thermodynamics and kinetics(Pugliese & Gelain, 2017). Non-covalent interactions such as hydrogen bonding, electrostatic interactions, hydrophobic interactions, etc. (Fig. 1A)(Wang et al., 2016). The peptides are self-assembled to form nanofibrous hydrogels, which are further wound to form a three-dimensional structure. The special spatial structure gives the hydrogel special properties. With high water content and high drug-carrying capacity, hydrogels are widely used in biomedical fields. During the assembly process of peptides, the molecules may fluctuate due to reversible non-covalent interactions. The molecules will spontaneously reach the minimum free energy state, in which the self-assembling sequences are highly ordered and well-defined in structure. Self-assembling peptide-based hydrogels can be made to reach different sub-stable states and obtain ordered nanostructures by varying the kinetic parameters (Fichman et al., 2016) (Fig. 1B).

The formed self-assembling peptide-based hydrogels are easily metabolised into amino acids. Therefore, they are biocompatible, safe, non-toxic, and easy to use. It has better mechanical properties and biological functions than protein hydrogels(Liu et al., 2024). They are widely used in biomedical applications such as controlled drug release, tissue engineering scaffolds, and immunomodulatory and antibacterial drugs (Hu et al., 2020; Liu et al., 2019; Singh & Peppas, 2014; Yadav et al., 2020). They are used in nanotechnology for biosensors, semiconductors, photosensitizers, and so on (Tao et al., 2017). In the food industry, to bring more benefits to consumers, self-assembling peptides can also be used to improve the functionality and quality of products. However, there are fewer studies on self-assembling peptides from seafood. There is not enough research on the mechanism of self-assembly, design and screening of self-assembling peptides.

Therefore, this paper reviews the latest research progress on self-assembling peptides from seafood. The mechanism and design of self-assembly were introduced, and how to design self-assembling peptides to meet the requirements was discussed. Screening and identification techniques, peptidyomics techniques, molecular dynamics simulations,

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and some instrumental characterization methods were introduced. Finally, applications and potential uses of self-assembling peptide-based hydrogels in food are highlighted. Shortcomings in existing applications are summarised and solutions are proposed. This review provides a theoretical basis for the wide application of self-assembled peptide hydrogels.

2. Sources and preparation of self-assembling peptides

2.1. Sources of self-assembling peptides

Seafood is abundantly available on Earth and most seafood is rich in amino acids and proteins, making it a good source of self-assembling peptides (Chen, Chen, et al., 2022; Chen, Zhang, et al., 2022). Yu et al. obtained a self-assembling peptide from an oyster using an enzymatic digestion technique. In Table 1, the peptides was demonstrated to have antioxidant activity and could promote coagulation and epidermal cell proliferation (Yu et al., 2023). The self-assembling peptide APATPAAPALLPLWL of sturgeon skin mucus showed good antibacterial activity after mutation (Yang et al., 2024). Coiled-coil scallops (*Chlamys farreri*) peptide IEELEEELEAER can be self-assembled to form hydrogels for use in the food industry (Wu et al., 2024). Natural self-assembling hydrogels are suitable for commercial 3D scaffolds. Mildenberger et al. extracted self-assembling peptides from sea cucumber and studied their cytotoxicity, and gelation, and indicated hydrophobicity (Mildenberger et al., 2021). Oral administration of peptides is a very favorable route of drug delivery. Yang et al. extracted self-assembling peptides from marine shellfish species using controlled enzymatic digestion technology and explored the functional mechanism of self-assembling peptides through in vivo and in vitro experiments. The study showed that oral administration of natural self-assembling peptides can inhibit inflammation, promote cell proliferation, and accelerate skin repair (Theodoroula et al., 2022). In recent years, increasing antioxidant peptide activity has gained popularity as a research area. Ma et al. investigated self-assembly as a new method to enhance the antioxidant activity of peptides. Compared with sea cucumber peptide VLLY and pine nut peptide KDHCH, the synthesized self-assembly peptide VLLYKDHCH showed higher antioxidant activity by increasing random crimp secondary structure and exposing active hydrogen.(Ma et al., 2020). As shown in Fig. 2, peptides from seafood can be made into self-assembling peptide hydrogels (Majura et al., 2022) that are widely used in the food industry.

Table 1
Sequence of self-assembling peptides from Seafood.

Source	Sequence	Formula	Ref.
Coiled-coil scallops (*Chlamys farreri*)	Ac-IEELEEELEAER-NH_2	ABCB ABAC	(Wu et al., 2024)
Sturgeon	Ac-APATPAAPALLPLWLL-NH_2	ABCB ABAC	(Yang et al., 2024)
Oysters (*Crassostrea gigas*)	Ac-DELEDNLEREKK-NH_2	ABCB ABAC	(Yu et al., 2023)
Oysters (*Crassostrea gigas*)	Ac-ISIEDVEESRNK-NH_2	ABAC	(Yu et al., 2023)
Oysters (*Crassostrea gigas*)	Ac-HGDSDLQLE-NH_2	ABCB ABAC	(Yu et al., 2023)
Oysters (*Crassostrea gigas*)	Ac-LDELEDNLERES-NH_2	ABCB ABAC	(Yu et al., 2023)
Oysters (*Crassostrea gigas*)	Ac-IEEDAGLGNGGLGR-NH_2	ABCB ABAC	(Yu et al., 2023)

2.2. Preparation

2.2.1. Enzymatic hydrolysis

As shown in Fig. 2, these are conventional methods for preparing bioactive peptides such as enzymatic hydrolysis, fermentation, chemical methods, microbial recombinant peptides, etc. In general, bioactive peptides can be enzymatically hydrolyzed by directly applying different enzymes to naturally extracted proteins (Lacou et al., 2016). Enzymatic hydrolysis is low-cost and has been widely used. Screening suitable enzymes is a key step in peptide production. Several commercial enzymes have been found to have good bond cleavage specificity, such as pepsin, trypsin, alkaline protease, etc (Chalamaiah et al., 2018). Enzymatic hydrolysis is widely used in the extraction of marine protein, animal protein, and plant protein. Alkaline protease, papain, and pepsin are widely used in the production of proliferative peptides because of their specificity for peptide sequence length and hydrophobic amino acids (Shaik & Sarbon, 2020). The carbo-terminal peptide hydrolyzed by alkaline protease can improve the anti-cancer, ACE inhibition, and antioxidant activities of the peptide. Pepsin and trypsin are widely used in mimics of gastrointestinal digestion to assess the effect on the release of bioactive peptides (Ulug et al., 2021). Before hydrolysis, the type and quantity of peptide fragments produced after enzymatic treatment can be predicted by computer. The protease hydrolysate obtained by hydrolysis can be separated and purified according to peptide properties such as molecular weight, electric capacity, hydrophilicity, polarity and so on to obtain the required peptide components.

Enzymatic digestion is effective in improving protein quality by breaking down proteins into more soluble and smaller molecular weight

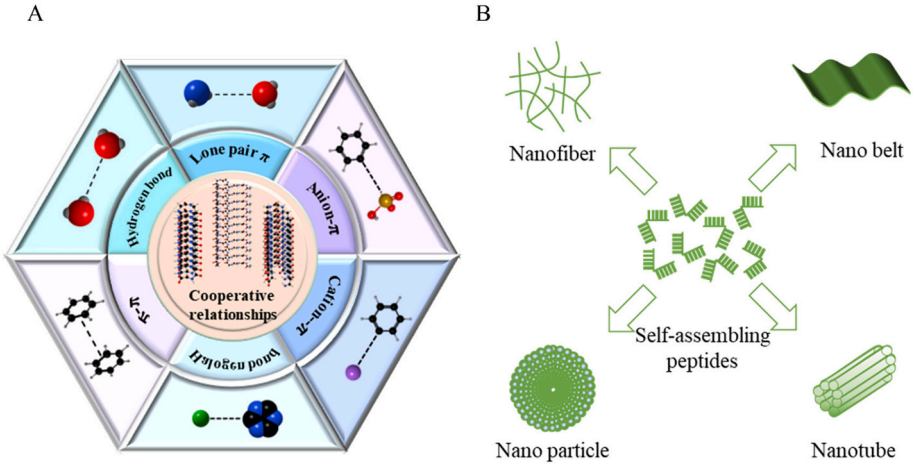

Fig. 1. Self-assembly forces and the types of structures formed. A: Major non-covalent interactions controlling the self-assembly of short peptides. B: Nanostructures that can be formed by self-assembly of peptide molecules.

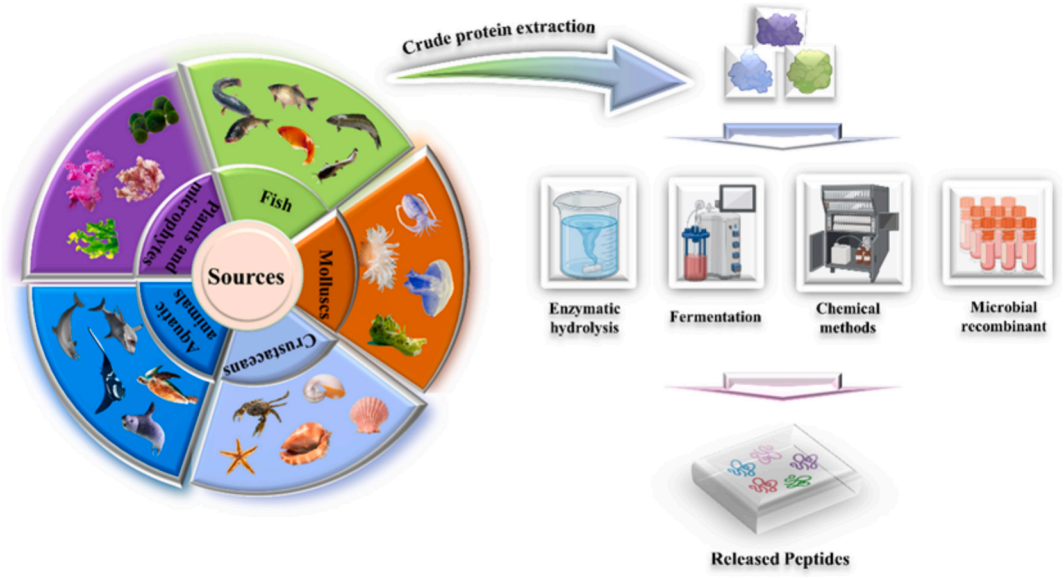

Fig. 2. Sources and preparation of peptides.

fractions. No harmful compounds or organic solvents are contained in the final product (Singh et al., 2022).

2.2.2. *Fermentation*

Microorganisms use their intracellular enzymes to hydrolyze proteins into different sequences of polypeptide fragments, which is called fermentation (Cruz-Casas et al., 2021). Microbial fermentation of proteins is a new method for producing bioactive peptides, which is less expensive than enzymatic hydrolysis, and the bioactive peptides produced by microbial fermentation can be obtained as pure peptides without further hydrolysis (Chai, Adzahan, et al., 2019a; Chai, Adzahan, et al., 2019b; Chai, Chang, et al., 2019). Most microbial proteases are expressed on cell membranes, so harvesting and purification is simple and cheap. And the microorganisms are less expensive to cultivate (Singh et al., 2022). It has been widely used to improve the nutritional composition of foods, reduce the antibiotic content, and increase the diversity of foods (Tamang et al., 2020; Tan et al., 2020a; Tan et al., 2020b).

Microbial fermentation allows the synthesis of a wider range of proteases to produce different protein hydrolysates by using different types of microorganisms and fermentation conditions. Different protein sequences can be decoded by studying the proteases produced by different fermenters (bacteria, yeast, and fungi), understanding the enzyme specificity, and the possible N-terminal and C-terminal amino acid sequences produced by each enzyme. The optimal parameters for fermentation can also be determined with the help of computer simulations (Chai et al., 2020).

Many naturally occurring bioactive peptides are found in traditional fermented foods and are released into the intestinal tract through enzymatic reactions after the ingestion of foods containing protein precursors. Nutraceuticals and functional foods are the subject of growing amounts of research now being conducted. Bioactive peptides can be added to products by changing production parameters or by using fermentation cultures (Hartmann & Meisel, 2007). The addition of bioactive peptides to infant formulas, probiotic beverages, and functional beverages is a popular product in the functional food industry (Manzoor et al., 2022).

2.2.3. *Chemical methods*

Liquid phase synthesis: Early peptides are synthesized in solution, and the operation is complex. It is an alternative method for the synthesis of polymerized peptides and is limited to short sequences because each step requires the separation and characterization of intermediates (Isidro-Llobet et al., 2019).

Solid-phase synthesis: Peptides less than 35 amino acids in length are usually prepared by solid-phase synthesis, in which a peptide chain is constructed using protected amino acids and then attached to a solid polymeric support. Solid-phase synthesis of peptides is an automated process, and the protected peptide fragments are attached to a solid support, simplifying the purification steps and removing non-ethers in the solvent simply and efficiently. While the chemical synthesis of peptides makes it easier to analyze peptide function throughout the design and testing stages, its high cost, low yield, and toxicity from the use of hazardous materials and organic solvents during the synthesis process make it unsuitable for large-scale production (Behrendt et al., 2016; Mukherjee et al., 2016; Winkler & Tian, 2015).

Other methods: Flow chemistry is a green chemical synthesis method, which can rapidly heat transfer, reduce reaction time and energy consumption, and reduce the influence of the environment on reaction (Ahmed, 2018; Gordon, 2018). The green label-assisted liquid phase synthesis method can reduce the amount of reagent, and remove by-products and reagents through precipitation or crystallization (Takahashi et al., 2017). Enzymic peptide ligation has the characteristics of high specificity and mild reaction conditions. The peptide fragment can be protected by using various ligases to connect with peptide (Schmidt et al., 2017; Schmidt et al., 2018). Mechanochemistry promotes the reaction between solids by inducing mechanical energy. It is a kind of green chemistry with a high yield and low isomerization degree of peptides (Bolm & Hernandez, 2018).

2.2.4. *Microbial recombinant peptides*

Microbial recombinant peptides are a sustainable and productive method for the production of long peptide sequences greater than 50 amino acids (Wegmueller & Schmid, 2014). Because peptides are produced from safe organisms, safety concerns are reduced. However, recombinant peptides are limited to the production of natural amino acid peptide sequences (Kyle et al., 2009). A successful example of recombinant technology in the preparation of peptide hydrogels is the production of QQRFEWEFQQ in *E. coli* strains by fusing peptide sequences into recoverable inclusion bodies and then recovering the peptides from the inclusion bodies by washing lysis and releasing the peptides from the proteins by hydrogen bromide cleavage (Riley et al., 2009). Microorganisms can be used for the delivery of drugs to produce bioactive peptides that have antihypertensive, antiviral, and antibacterial effects

(Markakiou et al., 2020; Mejia-Pitta et al., 2021; Zhou et al., 2020; Zou & Chen, 2020; Zuo et al., 2020). Probiotics as a type of microorganism, can be applied in milk and fermented dairy products, and lacto-streptococci can improve peptide production and enhance the sterilization effect (Plavec & Berlec, 2020).

3. Self-assembling peptides sequences and regularities

3.1. Self-assembling peptides sequences

For self-assembling peptides in general, their self-assembly process is concentration-dependent and graded by concentration. Reduced peptide concentrations result in the formation of dimers, which in turn combine to create oligomers over time, which in turn develop to form micelles or vesicles. This self-assembly process gradually forms higher-order aggregates (like nanotubes or nanofibers) at higher concentrations, which bind together and elongate in one-dimensional, two-dimensional, and three-dimensional space. These higher-order aggregates are then further entangled to form hydrogel networks (Fig. 3A).

3.2. The law of peptide sequence

(1) Table 2 shows that the self-assembling peptides contain amino acid sequences of the form ABAB (the first and third positions of the peptide sequence are the same, the second and fourth positions are the same)/ABAC (the first and third positions of the peptide sequence are the same, the second and fourth positions are different)/ABCB (the first and third positions of the peptide sequence are different, the second and fourth positions are the same). Some also contain amino acids with specific functions(such as glycine as a linker to avoid interference between bioactive motifs and self-assembling backbones, cysteine is oxidized to disulfide bonds for intermolecular cross-linking) (Hao et al., 2022; Mikamori et al., 2022; Pugliese et al., 2022) (Fig. 3B、3C). (2) Amino acids with alternating hydrophobic and hydrophilic properties,

Table 2
Sequence of self-assembling peptides.

Name	Sequence	Formula	Ref.
RADA-16	Ac-RADARADARADARADA-NH_2	ABCB	(Paradis-Bas et al., 2013)
EAK16-II	Ac-AEAEAKAKAEAEAKAK-NH_2	ABAB	(Forte et al., 2018)
KLDL12-I	Ac-KLDLKLDLKLDL-NH_2	ABCB	(Sun & Zheng, 2009)
SPG-178	Ac-RLDLRLALRLDLR-NH_2	ABCB	(Mikamori et al., 2022)
FEFK8-II	Ac-FEFEFKFK-NH_2	ABAB	(Cai et al., 2022)
FEFK8-I	Ac-FEFKFEFK-NH_2	ABAC	(Wychowaniec et al., 2020)
KVW10	Ac-WKVKVKVKVK-NH_2	ABCB ABAB	(Sathaye et al., 2014)
LKLK12	Ac-LKLKLKLKLKLK-NH_2	ABAB	(Pugliese et al., 2022)
LDLD12	Ac-LDLDLDLDLDLD-NH_2	ABAB	(Raspa et al., 2014)
(LE)8	Ac-LELELELELELELELE-NH_2	ABAB	(Nonoyama et al., 2012)
PFD-5	Ac-PDFDFDFDFDP-NH_2	ABAB	(Hao et al., 2022)
K2(SL)6K2	Ac-KKSLSLSLSLSLSLKK–NH_2	ABAB	(Lee et al., 2011)
E(SL)6E	Ac-ESLSLSLSLSLSLE-NH_2	ABAB	(Hao et al., 2022)
KW+	Ac-KKFEWEFEKK-NH_2	ABCB	(Hao et al., 2022)
KW-	Ac-EEFKWKFKEE-NH_2	ABCB	(Hao et al., 2022)
MAX1	Ac-VKVKVKVKV^{D}PPTKVKVKVKV-NH_2	ABAB	(Sathaye et al., 2014)
MAX8	Ac-VKVKVKVKV^{D}PPTEVKVKVKV-NH_2	ABAB	(Lindsey et al., 2015)
MAX1/8	Ac-IKIKIKIKV^{D}PPTKIKIKIKI-NH_2	ABAB	(Wu et al., 2015)
HLT2	Ac-VLTKVKTKV^{D}PPTEVKVKVLV-NH_2	ABCB	(Sinthuvanich et al., 2012)
P11–2	Ac-QQRFQWQFEQQ-NH_2	ABCB	(Hao et al., 2022)
P11–4	Ac-QQRFEWEFEQQ-NH_2	ABCB	(Dawasaz et al., 2022)
P11–13	Ac-EQEFEWEFEQE-NH_2	ABAC	(Hao et al., 2022)

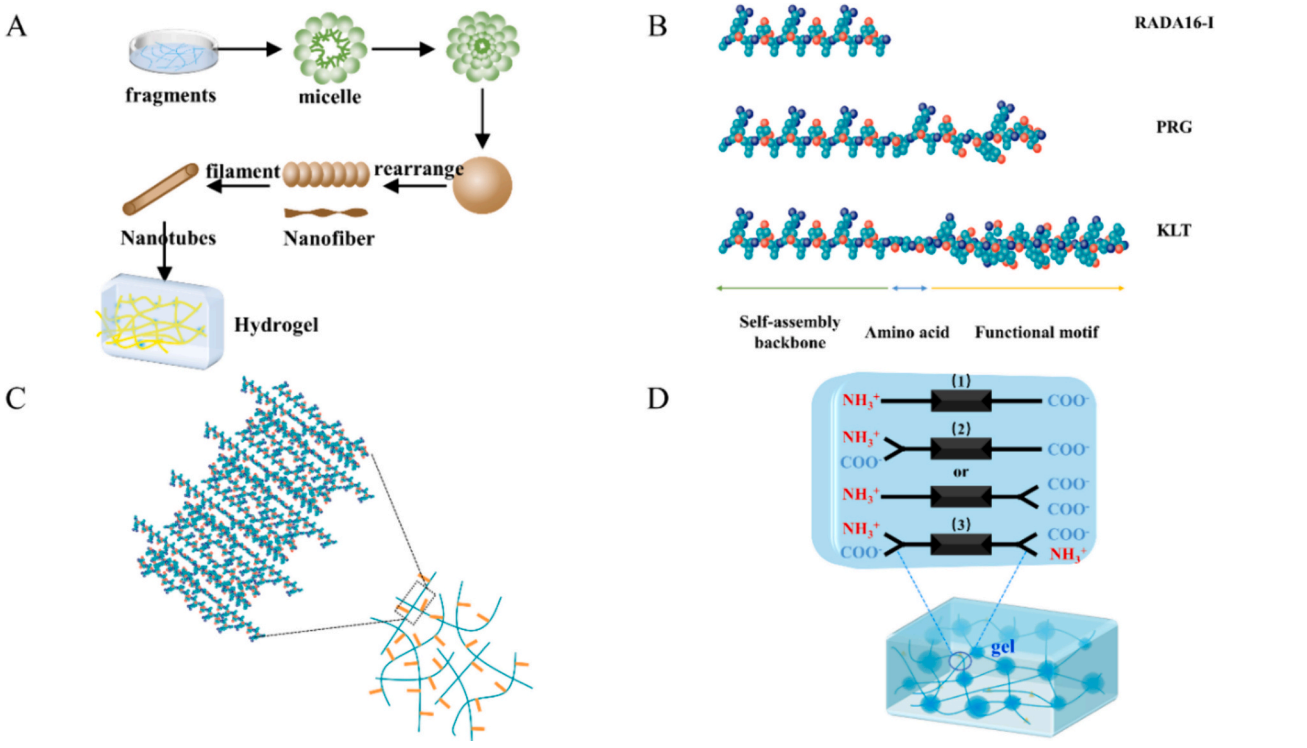

Fig. 3. Self-assembly process and rules. A: Schematic diagram of the self-assembly process. B: Design of molecular models for self-assembling peptides and active groups. C: Schematic diagram of self-assembling peptides and functional groups mixed to form self-assembling peptides nanofibers. D: Summary of gelation rules for ionization of peptide side groups occurring.

and the self-assembled peptide FEFEFKFK, phenylalanine is a hydrophobic amino acid, while glutamic acid is a hydrophilic amino acid (Cai et al., 2022; Forte et al., 2018; Wychowaniec et al., 2020). (3) Positively or negatively charged amino acids alternate with uncharged amino acids, in the peptide RADARADARADARADA, arginine is positively charged, aspartic acid is negatively charged, and alanine is uncharged. (Lee et al., 2011; Paradis-Bas et al., 2013; Sathaye et al., 2014). (4) With a β-fold structure, regardless of its terminal charge, the β-chain has the organization of anti-parallel direction. β-fold in which the peptide AEAEAKAKAEAEAKAK segments are arranged in parallel, and the peptide chain direction can be the same or opposite. β-fold has two kinds of parallel and anti-parallel, and the anti-parallel is more stable (Forte et al., 2018; Lee et al., 2011; Sun & Zheng, 2009). (5) The phenomenon of self-assembly consists of many weak non-covalent interactions: hydrogen bonding, aromatic stacking, electrostatic interactions, van der Waals force interactions, and hydrophobic interactions, the presence of higher arginine in VKVKVKVKV^{D}PPTKVKVKVKV leads to stable salt Bridges and hydrogen bonding (Hao et al., 2022; Liu et al., 2019; Sathaye et al., 2014). (6) Amphiphilicity: Amphiphilic peptides have hydrophobic and hydrophilic regions in their sequences, and the incompatibility between hydrophilic and lipophilic chain segments causes microphase separation to occur, allowing amphiphilic polymers to exhibit self-assembly properties in selective solvents, ontologies, and surface and interfacial structures. The peptide FEFEFKFK has a hydrophilic amino acid group on one side and a hydrophobic amino acid group on the other that makes the peptide amphiphilic. (Cai et al., 2022; Wang et al., 2020).

4. Design of self-assembling peptides

Rational design of amino acid sequence: design the amino acid sequence in the form of ABAB/ABAC/ABCB and then add other amino acids with specific functions. The positions of amino acids are designed to facilitate self-assembly. For example, aromatic amino acids are placed in the middle or C terminus of the tripeptide, and positively charged amino acids are placed in the N or C terminus. However, this result is limited to the study of tripeptide, and whether it is effective for long peptide needs further exploration (Frederix et al., 2011; Frederix et al., 2015).

Rational design of hydrophilic and hydrophobic amino acid number and arrangement: self-assembling peptide-based hydrogels can be further classified into four forms based on secondary structure: α-helix, β-fold, β-turn and irregular curl. β-folded is the most widely studied, which is an arrangement of adjacent parallel or antiparallel chains driven by hydrogen bonds. The β-fold has alternating sequences of hydrophilic and hydrophobic amino acids, which makes amino acids amphiphilic and is the most important group of structural forms. The most common type of peptide design is to use the amphiphilic nature of the peptide to induce self-assembly (Chen, 2005; Shah et al., 2018; Yang et al., 2020). As the self-assembled peptide RADARADARADARADA hydrophilic amino acids are arginine and aspartic acid, and hydrophobic amino acids are alanine (Paradis-Bas et al., 2013). Almost all self-assembling peptides retain a significant amount of water to form various hydrogels. The hydrophilic residue side chains interact directly with water, and the water molecules form inclusion complexes to surround the hydrophobic residue side chains. Too many hydrophobic residues of the peptide and the peptide will precipitate out insoluble in water. If there are too many hydrophilic residues, the peptide will be highly soluble in water and cannot form hydrogels. When designing the amino acid sequence of a peptide, the number of hydrophobic and hydrophilic amino acids should be reasonable. The number of hydrophilic and hydrophobic amino acids can be altered to promote hydrogenation and improve mechanical properties, shorten the peptide's length, and cut costs when alanine is substituted with more hydrophobic residues. This increases the peptide's assembly tendency and mechanical strength (Isidro-Llobet et al., 2019; Liu et al., 2019; Tsai et al., 2018).

Rational design of molecular structure: the geometry of the molecule also plays an important role in self-assembly, where amino acid sequences, amino acid chiral changes, and appropriate amino acid substitutions in peptides can alter one or more non-covalent interactions and facilitate the formation of β-fold conformations (Cui et al., 2014; Han et al., 2011; Wang, Mao, et al., 2017; Wang, Zhou, et al., 2017). During peptide structure design, bioactive motifs and bioactive factors can also be adsorbed onto self-assembling peptide-based hydrogels to confer different physiological functions according to physiological and pharmacological needs. Self-assembly of peptides can also be regulated by changing pH, temperature, ionic strength, etc. The process of self-assembly can also be influenced by the peptide's length and the presence of proteins. The antioxidant activity of the self-assembled peptide VLLYKDHCH was promoted by the increase of the random curled secondary structure due to the difference in the length of the peptide (Ma et al., 2020). Self-assembly of short peptides can be induced using enzymes. In general, various factors, including their effectiveness and practicality, should be considered when designing self-assembling peptide-based hydrogels for different applications, which also require a more individualized design.

Alternating arrangement of positive and negative groups: when designing short peptides, the following rules are followed: the α-NH_2 and α-COOH groups at the N′ and C′ termini are charged simultaneously; if only one side chain group of the terminal amino acid is charged, it should be negatively charged; when both side chain groups of both terminal amino acids are charged, they must have a charge opposite to the COO^{-} or NH^{3+} group (Chen, Chen, et al., 2022; Chen, Zhang, et al., 2022; Hao et al., 2022; Pugliese et al., 2022) (Fig. 3D).

Equilibrium of non-covalent interactions: due to the balance of attraction and repulsion between non-covalent interactions, peptides can form different self-assembly modes such as nanotubes and protofibrils. This equilibrium can be controlled by kinetic parameters. Besides the peptide concentration and sequence, the kinetic parameters are also the key factors to determine the self-assembly process. When designing the self-assembly process of peptides, the kinetic parameters should be precisely controlled. Such as temperature, ionic strength, pH, etc. Among them, the aggregation of self-assembling peptide IEELEEELEAER and the hydrophilic and hydrophobic interaction between helices were regulated by zinc ion strength to make the hydrogels stronger (Wu et al., 2024).The pH value change can deprotonate or protonate the charged amino acids and can control the balance between electrostatic interaction attraction and repulsion, which is very important for the final assembly results (Mendes, Baran, Reis, & Azevedo, 2013; Vahedifar and Wu, 2022).

5. Isolation and purification of self-assembling peptides

The traditional line of research to obtain peptides from food-derived protein hydrolysates is to purify the hydrolysates in a step-by-step separation supplemented by activity tracking, both through a multi-step chromatographic separation step to obtain a single-component peptide fraction, followed by the structural identification of the peptide sequences therein by mass spectrometry (Tu et al., 2018). The usual chromatographic separation methods used for peptide purification are hydroxyapatite chromatography (HAC), immobilized metal affinity chromatography (IMAC), gel permeation chromatography (GPC), molecular exclusion chromatography (SEC), ion exchange chromatography (IEC), and reversed-phase high-performance liquid chromatography (RP-HPLC) (Guo et al., 2014). The separation principles of HAC and IMAC are somewhat similar and are usually used as the first step in the separation of food-derived protein hydrolysates; GPC, SEC, and IEC are used to separate samples based on molecular weight and charge properties and are generally used as intermediate steps in peptide purification; RP-HPLC is usually used for the final step of peptide purification.

In recent years, the development trend of self-assembled peptide separation and purification is the combination of multiple methods.

Although it is possible to achieve complementary advantages and hierarchical separation, so as to obtain highly pure peptide components and carry out structural analysis, the process is cumbersome and complicated, the recovery rate is low, and the effect is not ideal for the separation of peptides with specific functions. Therefore, the search for more efficient and rapid peptide separation methods will bring broader development space for peptide functional research and utilization. The efficiency of traditional screening and preparation of self-assembled peptides can be improved by mastering the rules and characteristics of self-assembled peptides.

6. Screening identification

6.1. Peptidomics technology

The main method currently used for peptide structure identification is mass spectrometry. Among them, electrospray time-of-flight tandem mass spectrometry (ESI-QTOF-MS/MS) and matrix-assisted laser-resolved ionization time-of-flight mass spectrometry (MALDI-TOF-MS/MS) are methods that have been used more often in recent years (Guo et al., 2014; Wu, Pan, Zhen, & Cao, 2013). The structural identification of peptide sequences presupposes the availability of peptide fractions with a single composition. Traditional separation and purification methods usually require multiple purification steps to obtain very few target products, which on the one hand is a large workload and inefficient; on the other hand, some peptide fragments that may have self-assembly ability will be inevitably missed during the activity tracking process.

Emerging bioinformatics methods can effectively overcome the problems of long experimental cycles, high packing costs, tedious activity tracking process, and easy omission of peptide information in the traditional bioactive peptide isolation and purification process, making it possible to characterize bioactive peptides in a large-scale, rapid and efficient manner (Tu et al., 2018). Using bioinformatics analysis methods, proteomics, transcriptomics, and metabolomics can be integrated and analyzed for better application in food research. Peptidomics, which is a branch of proteomics, is a discipline that focuses on the structural identification, optimization of hydrolysis conditions, and prediction of the structure and function of active peptides and their precursor proteinsc (Carrasco-Castilla et al., 2012).

In recent years, with the development of mass spectrometry and proteomics, peptidomics has become an emerging technology for the identification of food-derived bioactive peptide sequences (Yu et al., 2017). Wu et al. identified five angiotensin converting enzyme (ACE) -inhibiting peptides from soy protein hydrolysates by liquid chromatography-mass spectrometry (LC-MS/MS) coupled with a quantitative conformational database search (Gu & Wu, 2013). Liu et al. identified 19 active peptide sequences from egg white enzymatic digests with the help of peptidomic techniques and successfully obtained peptides with antidiabetic effects as well as ACE inhibitory activity through subsequent activity screening experiments (Liu et al., 2010; Yu et al., 2011). Similarly, Yu et al. successfully identified 966 peptides from Philippine heterochromatic clam trypsin hydrolysates by ultra-performance liquid chromatography-electrospray time of flight tandem mass spectrometry (UPLC-ESI-Q-TOF-MS/MS) matched with a peptidomics database search and demonstrated that this approach could efficiently identify additional active peptide sequences from the protein database (Yu et al., 2017). A total of 302 peptides in mussel protease hydrolysate were identified by NanoLC-Q-TOF, and 10,088 peptides in large yellow croaker were identified by UPLC-Q Exactive™ HF-X (Xu et al., 2019; Xu et al., 2023). Large-scale, rapid, and efficient screening of peptides from food-derived protein hydrolysates with the help of peptidomics technology would be a proven strategy to obtain more sequence information on food-derived peptides.

6.2. Molecular dynamics simulations

Computer predictions have been invoked in food science, and the use of these methods before the start of experiments can be effective in reducing time and costs. For self-assembling peptide analysis, several stand-alone web-server-based software packages are available and computer studies can be performed using molecular dynamics simulations to predict the final self-assembling structure. Self-assembly simulations of peptides are performed using the MARTINI force field, kinetic simulations are performed using the Gromacs program, and Virtual Molecular Dynamics (VMD) watches structures and trajectories. After the simulations, the assembly structure was examined using VMD, and a simple analysis of the assembly structure was performed using the analysis program that comes with Gromacs (Vahedifar & Wu, 2022).

In general, tools for predicting amyloid proteins are divided into structure-based algorithms and sequence-based algorithms. The structure-based algorithm takes into account the three-dimensional structure of the protein as opposed to the sequence-based algorithm. According to sequence-based algorithms, it is concluded that the roommate sequence controls the aggregation tendency of self-assembling peptides. There are four main types of sequence-based algorithms: phenomenological approaches, which identify the determinants of aggregation by collecting experimental data from the core regions of amyloid proteins of various protein sources; computational approaches, which do theoretical evaluation of several physicochemical properties associated with aggregation (e.g., stacking density of proteins, high hydrophobicity, etc.); machine learning approaches, which use neural networks to determine the sequence properties associated with self-assembling peptides aggregation; and Consensus predictors, which calculate their resultant output by weighting a combination of other methods (Santos et al., 2020). On the basis of molecular docking to simulate the binding mode of small molecule ligand and receptor, the interaction between metal ion and self-assembled shellfish peptide IEELEEELEAER and sea cucumber peptide EDLAALEK was predicted (Cui et al., 2019; Wu et al., 2024; Xu et al., 2022).

6.3. Characterization techniques

Peptides that have undergone self-assembly can also be characterized by instrumental methods such as Fourier transform infrared spectroscopy (FTIR), far-UV circular dichroism (CD), thioflavin T-spectroscopy (ThT), oscillatory stress rheology (OSR), and atomic force microscopy (AFM) to characterize the secondary structure, biomechanics, and nanostructure morphology of peptide hydrogels. Super-resolution microscopy combined with modern image analysis has been used to quantify the structure and dynamics of peptide hydrogels, while small-angle neutron scattering (SANS) and solid-state nuclear magnetic resonance (SSNMR) can provide complementary information about length-scale structures.

Characterization of peptide secondary structures: The occurrence of self-assembly behavior of polypeptides is usually accompanied by changes in the secondary structure of the polypeptide. CD spectroscopy is commonly used to study secondary structure changes in proteins or peptides(Ranjbar & Gill, 2009; Zhang et al., 2019). If the spectrum shows a negative peak at around 215 nm and a positive peak at around 195 nm, it proves the existence of a β-fold structure. The β-fold structure is a typical feature of self-assembling peptides. The change of peaks at 1600 cm^{-1} (amide I band) and 1500 cm^{-1} (amide II band) in FTIR spectra also proved that mainly the β-fold structure was changed (Monti et al., 2021; Pansieri et al., 2019). ThT is a cationic dye with enhanced fluorescence intensity upon binding to amyloid in tissue sections. Peptides were mixed with thioflavin T solution and used to assess the presence of amyloid protofibril structures. The more β-folding, the higher the fluorescence intensity(Pugliese & Gelain, 2020, 2022). The secondary structure changes of Coiled coil scallops (*Chlamys farreri*) self-assembled peptide IEELEEELEAER during the formation of

hydrocolloids were characterized based on CD and FTIR (Wu et al., 2024). SSNMR was used to complement CD and FTIR to determine the molecular stacking of self-assembling short peptide aggregates (Draper & Adams, 2018; Wallace et al., 2017).

Morphological structure: Details of the nano-supramolecular structure (e.g., length and cross-section of nanometers) can be observed by imaging techniques such as Transmission Electron Microscope (TEM), Atomic Force Microscope (AFM), X-ray diffraction (XRD), and small angle X-ray scattering (SAXS). Vijay Kumar Pal used AFM to understand the changes in nanoparticle morphology after pH-switching. To further understand the structural differences between peptide nanoparticles and nanofibers, the scattering distribution of both was performed by small-angle X-ray scattering (Pal & Roy, 2022). Stochastic optical reconstruction microscopy (STORM) is a promising super-resolution fluorescence microscopy technique, self-assembling peptides are labeled with fluorescent dyes, and the dye molecules are activated by laser light to induce fluorescence. The technique can precisely determine the position of each dye molecule and then construct super-resolution images by combining all the localizations together. The combination of STORM and AFM allows us to see the dynamic process of self-assembly and to differentiate between peptides with different dye markers (Beun et al., 2016; Cox et al., 2018; Cox et al., 2019). SANS can measure the intensity of the scattered neutron beam from the peptide solution, and the scattered intensity distribution can indicate information about the nanostructures formed by the self-assembly of short peptides. SANS is able to reveal the detailed structure of short peptide self-assembly beyond the resolution of conventional imaging techniques. ANS is highly complementary to TEM and AFM imaging techniques in revealing detailed structural features (Hu et al., 2019; Zhao et al., 2018).

Some high-resolution spectroscopic methods also have promising applications, such as nonlinear Raman, nitrogen-vacancy single-molecule nuclear magnetic resonance spectroscopy, two-dimensional infrared vibrational echo spectroscopy (2D IR), and frequency comb infrared spectrometer (Hu et al., 2020).

7. Applications in food

7.1. Low-calorie foods

Excessive intake of high-calorie foods can have many adverse effects on the body, such as increased lipid content in blood vessels and sticky blood. People are also aware of the link between high-calorie foods and health, so low-calorie foods that are slow-glycemic and satiating have become popular products in the food industry. (Hoefkens et al., 2011b). The morphological diversity of the self-assembly provides a range of interfacial properties that make it an excellent emulsifier for different purposes. The fibrous structure is attractive for stabilizing emulsions and foams due to unique interfacial properties such as a high aspect ratio, fast adsorption to the interface, and surface activity (Vahedifar & Wu, 2022; Wan et al., 2018). Many emulsifiers are high in calories, but reducing the fat content of emulsion products affects the taste of the product, etc., because fat droplets have an important role in the appearance and flavor of foods (Hoefkens et al., 2011a). Cheryl Chung et al filled hydrogel particles with a mixture of fat droplets, sodium caseinate, and high methoxylated pectin as ingredients (Chung et al., 2013). Hydrogels increase the viscosity of aqueous solutions and can replace starch granules or fat droplets in low-calorie foods. Hydrogel particles can also modulate the sensory quality of the product, so hydrogel particles have great potential in the formulation of low-calorie foods.

7.2. Carriers of bioactive ingredients

At this stage, people are paying more and more attention to a healthy diet to prevent the development of some chronic diseases. Incorporating bioactive substances into foods makes it easier to design foods that meet the needs of the human body. These bioactive substances should be able to mix with the food and be digested and absorbed in the gastrointestinal tract. However, the poor stability of many bioactive ingredients limits their use in food products (Mao et al., 2020). Anthocyanins are active substances with antioxidant capacity and can be used as functional food additives, but anthocyanins are unstable under acidic conditions and their activity is easily destroyed in the gastrointestinal environment. Michael Betz et al. have developed a microencapsulation system for encapsulating anthocyanins, and this technique uses whey protein hydrogel as a matrix material to maintain the biological activity of phenol (Betz & Kulozik, 2011). Huimin Chen designed and prepared a pH-responsive amphiphilic pentapeptide for encapsulation of curcumin, which improved the thermal and photostability of curcumin (Chen, Chen, et al., 2022; Chen, Zhang, et al., 2022).

7.3. Functional foods

Bioactive peptides can modulate human metabolism and physiological functions and are considered to be valuable components in the composition of dietary supplements and functional foods, but food-derived peptides have low stability and bioavailability in the gastrointestinal tract. Carmen Lamm encapsulated hemp seed hydrolysate into RADA16 peptide hydrogels to improve the stability and antidiabetic properties of hemp seed hydrolysate, and this study provides bioactive hydrolysates and self-assembling peptide-based hydrogels made into nanomedicines provide new ideas for the formulation of nanomedicines to prevent diabetes and other metabolic diseases (Lammi et al., 2018). Most inorganic or organic calcium preparations currently available on the market form precipitates in the weak alkaline environment of the small intestine after ingestion, reducing their utilization. Recent studies have found that food-derived calcium-binding peptides can promote the absorption of calcium ions by the body and are more acceptable. Cui et al. extracted a novel octapeptide EDLALLEK from sea cucumber ovum trypsin hydrolysate, and the peptide and calcium ions could chelate to form self-assembling peptides-calcium nanocomplexes (Cui et al., 2019). This experiment showed that the sea cucumber egg-derived peptide has the potential to act as an efficient nanocarrier to transport calcium through the gastrointestinal tract, promote calcium absorption in vivo, and prevent osteoporosis.

7.4. Treatment

Metabolic syndrome is a major risk for the development of chronic diseases, leading to diabetes, cardiovascular disease, and obesity. Traditional treatments are medically monitored complex, expensive and have side effects. Self-assembling peptide formulations hold promise as an alternative for the treatment of metabolic syndrome, particularly self-assembling peptide-based hydrogels. It can combine growth factors, drug molecules, and cells to form a self-assembling product (Fig. 4A). It is important in the prevention and restoration of normoglycemia as well as in the control of cardiovascular disease and obesity (Arhire et al., 2019; Hutchinson et al., 2018; Ichihara et al., 2018).

Caliskan, O showed the importance of the spatial structure of bioactive groups in nanofiber systems, introducing a scaffold for the production of brown adipocytes from mesenchymal stem cells (Caliskan et al., 2017). Lee, W investigated the effect of self-assembling hyaluronic acid nanoparticles (HA-NP) on adipogenesis in vitro and in vivo, confirming that HA-NP inhibits adipogenesis by suppressing CD44 (Lee et al., 2020). Castillo-Díaz, L. A. showed that self-assembling peptides can be effective in the treatment of diabetes and obesity by encapsulating drugs and organs and that self-assembling peptides bioactive patches can be developed to reduce the risk of cardiovascular disease (Castillo-Diaz et al., 2020). Self-assembling of peptides and starch into resistant starch through non-covalent interactions, which has become a potential additive for the treatment of diseases related to metabolic syndrome or a substrate with high nutritional value.

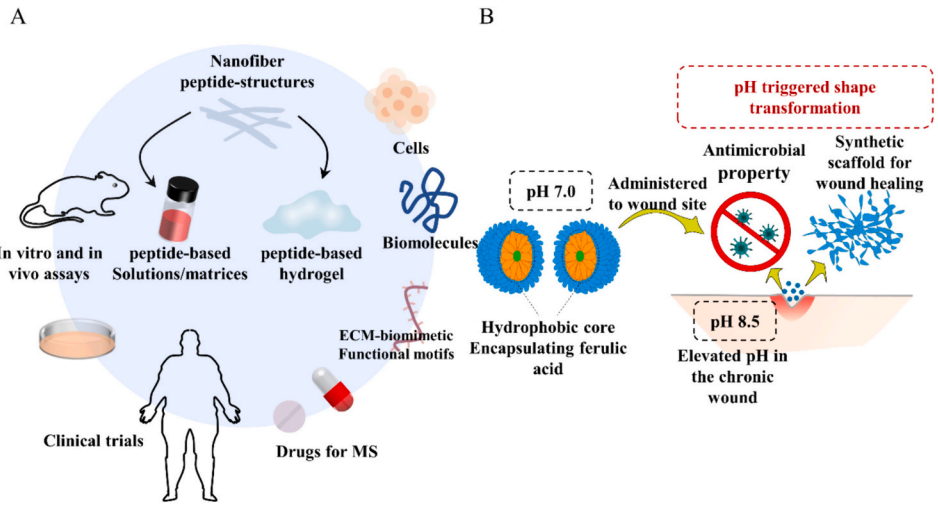

Fig. 4. Application of self-assembling peptides. A: Overview of self-assembling peptides for the treatment of metabolic syndrome and related complications. B: Applications in mouth healing.

The hydrogel material has good properties of water retention and water absorption, which can provide a moist environment for wound healing and also absorb exudate from the skin to prevent wound adhesion, thus hydrogel materials have a wide range of applications for the field of wound repair (Ito, Yoshida and Murakami, 2013; Jaipan, Nguyen and Narayan, 2017; Lih et al., 2012). Vijay Kumar Pal reports on the fabrication of bio-nanostructures with dual functionality and environmental tunability, offering advances for wound healing applications (Pal & Roy, 2022) (Fig. 4B).

Self-assembling peptide-based hydrogels are inherently pharmacologically active as therapeutic materials. Since self-assembling peptides can carry drugs, they should also be used as carriers of nutrients to develop healthy foods or medicinal diets.

7.5. Food preservatives

Food spoilage due to microbial proliferation is a problem in the food industry. It was found that the stability and antimicrobial activity of antimicrobial peptides could be improved by self-assembly (Guyon et al., 2018; Rodrigues de Almeida et al., 2019). After self-assembly, the antimicrobial peptide can increase its own positive charge density and mass. Moreover, the self-assembling nanostructures have a larger surface area, which increases the contact area between the particles and the bacterial surface. Therefore, many self-assembling peptides with antimicrobial properties have been designed as novel antimicrobial agents (Guo et al., 2021; Sha et al., 2020).

Because of its excellent antibacterial properties, it has a broad application prospect in food preservatives and preservation agents. Wang et al prepared biodegradable polymeric Polycaprolactone (PCL) substrates with antimicrobial properties in a facile way, which can be used for food packaging (Wang, Mao, et al., 2017; Wang, Zhou, et al., 2017). Shwaiki et al extracted Snakin-1 from potato tubers can inhibit spoilage of food caused by yeast, which can be used as a potential new food preservative. The development of more natural and safer preservatives has broad application prospects (Shwaiki et al., 2020).

7.6. Biosensors

Traditional food testing techniques include chromatography and enzyme-linked immunosorbent assay, etc. These techniques usually require expensive equipment and materials, which are time-consuming and costly (Bilal et al., 2020; Ong et al., 2021). Advances in biosensing technology in various fields have drawn the attention of researchers to biosensors (Charoenkitamorn et al., 2020), in which the recognition of specific toxins by corresponding antibodies allows rapid, reliable, and sensitive detection of mycotoxins in food (Liu et al., 2020). Cell-based biosensors are promising new tools for food safety risk assessment and monitoring.

Ochratoxins are a group of fungal toxins that are produced as secondary metabolites of fungi and can contaminate a wide range of food and feed commodities. Due to its teratogenic and carcinogenic properties, ochratoxin poses a serious risk to human and animal health. Yuan established a surface plasmon resonance biosensor for the detection of ochratoxin in cereals and beverages using Au and protein by self-assembly. It provides a powerful tool for the rapid and sensitive quantitative determination of ochratoxin in food matrices (Yuan et al., 2009). Ruchika developed a label-free immunosensor based on an electrochemical quartz crystal microbalance for the quantitative detection of aflatoxin in peanuts. In peptide amphiphiles, positively charged arginine can excite the ordered self-assembly of gold nanocomposites (Chauhan et al., 2015). Mao et al used five arginine residues as hydrophilic chains and myristic acid as hydrophobic chains to form peptide amphiphiles that excite AuNPs to form AuNPs (rasAuNPs) (Mao et al., 2022). Self-assembly of peptides and metals can be used to improve the sensitivity of electrochemical sensors. This method can be easily applied to detect other small molecule compounds for food safety purposes.

7.7. Other applications

Some animal foods can cause allergies, and self-assembling peptides can encapsulate these allergenic ingredients, thereby reducing the risk of allergies. (Bechaux et al., 2019). Self-assembling nanofibre structures of peptides can be used to design allergen vaccines with reduced overreaction. Self-assembling peptides can also be used as additives in meat products in the form of thickeners and gelling agents to reduce cooking losses and increase water retention.(Lacou et al., 2016). Building blocks are used to design and develop food-grade micro- and nano-network structures, thus serving as thickeners or fat substitutes or nutritional nanocarriers. It can also be used as a source of protein nutrients and protein stabilizer (Suwal et al., 2019). Electroactive self-assembled hydrogels can be electrically stimulated to change transparency to visible light, and the integration of hydrogels into flexible semiconductor polymer substrates can be used as switching elements in flexible displays with high efficiency and low cost.

8. Outlook

Self-assembled peptide hydrogels have the advantages of increased

bioavailability of active substances, accurate delivery and reduced risk of allergies. This hydrogel can be further developed into edible films, coatings, functional food and biomedical materials such as nano/microgel particles/microbeads. However, screening and large-scale preparation of self-assembled peptides are the main problems that limit their application. By elucidating the law of self-assembly peptide sequence, the screening cost can be reduced. Based on the characteristics of these self-assembled peptides, such as the separation of charge and hydrophilicity can be carried out, which lays a foundation for large-scale preparation of self-assembled peptides.

Seafood is rich in protein and is also an important source of bioactive peptides. Currently, some seafood self-assembly peptides have been screened for good activity, but their specific mechanisms still need to be further explored. With the cooperation of various disciplines, the screening, characterization and application of seafood self-assembly peptides will gradually increase. In the future, with the gradual clarification for the mechanism of self-assembled peptide, the preparation cost of seafood self-assembled peptide will be reduced. The amino acid composition of self-assembled peptides can be designed and mutated according to the desired function, and the application range of seafood self-assembled peptide hydrogels will be more and more widely.

CRediT authorship contribution statement

Zhe Xu: Writing – review & editing, Writing – original draft, Project administration, Funding acquisition, Formal analysis. **Shiying Han:** Writing – original draft, Methodology, Data curation. **Shuang Guan:** Formal analysis, Data curation. **Rui Zhang:** Writing – review & editing, Software. **Hongrui Chen:** Writing – review & editing, Methodology. **Lijuan Zhang:** Writing – review & editing, Methodology, Formal analysis. **Lingyu Han:** Writing – review & editing, Data curation. **Zhijian Tan:** Writing – review & editing, Methodology. **Ming Du:** Writing – review & editing, Project administration. **Tingting Li:** Writing – review & editing, Funding acquisition, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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