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Review Article

Peptides as carriers of active ingredients: A review

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ABSTRACT

Bioactive compounds are highly valuable in the fields of food and medicine, but their application is limited due to easy deterioration after oral or skin administration. In recent years, the use of peptides as delivery systems for bioactive compounds has been intensively researched because of their special physicochemical characteristics. Peptides can be assembled using various preparation methods and can form several composite materials such as hydrogels, micelles, emulsions and particles. The composite material properties are determined by peptides, bioactive compounds and the construction methods employed. Herein, this paper provides a comprehensive review of the peptides used for active ingredients delivery, fabrication methods for creating delivery systems, structures, targeting characteristics, functional activities and mechanism of delivery systems, as well as their absorption and metabolism, which provided theoretical basis and reference for further research and development of functional composites.

1. Introduction

Bioactive compounds usually refer to plant secondary metabolites and their degradation products, low molecular peptides, low molecular carbohydrates, vitamins, nucleotides, minerals and so on. Most of these compounds possessed significant biological activities, such as antioxidant activity (Deghima et al., 2020), anti-inflammatory activity (Singh et al., 2020b), antibacterial activity (Kim et al., 2018), inhibition of cancer cell growth (Li et al., 2021a,b). As a result, they have promising prospects for development as functional healthy foods and drugs. However, some bioactive compounds exhibited poor water solubility, stability and bioavailability (Anand et al., 2007; Fracassetti et al., 2013; Israeli-Lev and Livney, 2014; Ochoa et al., 2001), which restricted their widespread use in healthy foods and drugs. Using delivery systems to transport could solve these problems (Chen et al., 2017; Loira-Pastoriza et al., 2021; Wang et al., 2020). In recent years, more edible polymers such as lipids, carbohydrates and proteins have been used as carriers of bioactive compounds. In particular, peptides attract more attention because of their nutritional value and their ability to modify other macromolecular structure. Peptides (or protein hydrolysates) were easily absorbed by the body and have good water solubility. They possessed various physiological effects, such as antioxidant and antibacterial activities, and played a role in regulating immune function regulation (Hu et al., 2021; Taniguchi et al., 2017; Zhu et al., 2021). Various properties of peptide-based materials could be significantly influenced by physical conditions such as heat, pH, or metal ions. In addition, another method to modify the physicochemical properties was through self-assembly or combining peptides with other natural polymers like polysaccharides and lipids (Garcia-Moreno et al., 2020; Li et al., 2020). Therefore, some novel materials with improved functions were created by this way. Relevant reports have shown that certain amphiphilic peptides had great potential as transport carriers, primarily because of their self-assembly property (Gong et al., 2019b; Yao et al., 2016). Among them, hydrolysates of α-lactalbumin was one of the typical examples that could be prepared to form a variety of nanostructures (Bao et al., 2020; Du et al., 2019a; Jiang et al., 2018). Furthermore, peptide-based delivery systems are formed through chemical reactions or non-covalent interactions, including hydrogen

Abbreviations: DOX, doxorubicin; SSPS, soybean soluble polysaccharide; CPP, cell penetrating peptide; FTIR, fourier transform infrared spectroscopy; SEM, scanning electron microscopy; LNV, lopinavir; EPR, enhanced permeability and retention effect; SOD, superoxide dismutase; GSH-PX, glutathione peroxidase; CAT, catalase; MDA, malondialdehyde; ROS, reactive oxygen species; ACPP, activatable cell penetrating peptide.

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bonding, van der Waals forces, π-π stacking, host-guest and hydrophobic interactions. Some peptides with hydrophobic groups could bind to other bioactive compounds, particularly hydrophobic substances, and formed stable architectures such as gels, liposomes, emulsions, micelles, and nanoparticles (Altunbas and Pochan, 2012; Du et al., 2019b; Liu et al., 2021; Wang et al., 2016). The sizes of these particles could be adjusted from nanometric to micrometric scale by manipulating reaction conditions.

In recent years, there has been an increase in researches on peptides as delivery systems due to their superior absorption capabilities. However, it is important to mention that there is currently no comprehensive review available on the various properties of peptide-based materials. Therefore, this article provides a summary of recent advancements in peptides used for active ingredients delivery, construction methods, structural characterization, absorption and metabolism, functional activities and targeting properties of composite materials, so as to broaden the application of peptide in functional food, drug and cosmetics industries.

2. Peptides used for active ingredients delivery

Peptides, which are composed of various amino acids, play a crucial role in the development and maintenance of the body. They also serve as a valuable resource for developing biocompatible materials. Peptides used for delivering active ingredients could be obtained from three sources: animals (Bao et al., 2020; Zhao et al., 2020), plants (Li and Yao, 2020) and artificial synthesis (Wang et al., 2014). Besides, peptide-based delivery structure can also be produced from multicomponent interactions, such as interactions between peptides of different origin, peptides and polysaccharides, or even peptides and lipids.

2.1. Animal peptides

Among animal peptides, milk-derived peptides are extensively studied for developing delivery systems of active ingredients. Whey proteins, such as α-lactalbumin and β-lactoglobulin, made up approximately 20% of the total protein in milk. They were known for their excellent nutritional value due to their well-balanced amino acid composition (Adjonu et al., 2014). Whey proteins contained hydrophobic residues that were buried within their rigid, globular structures, which could potentially affect their functionality. However, smaller enzymatic peptides of whey proteins, especially α-lactalbumin peptides, had partially exposed hydrophobic cores. These peptides are highly valued as raw materials for micelles or emulsifiers due to their amphiphilicity, which means they have both hydrophilic and hydrophobic groups. These properties allow whey peptides to become potential nanoemulsifying agents. They orderly arranged themselves on the surface of oil droplets, thereby stabilizing the newly generated emulsion. For example, β-carotene nanoemulsions developed using whey protein isolate hydrolysates showed smaller droplet sizes compared to those formed by soy protein and whey protein (Chu et al., 2007). Besides, curcumin and anthocyanin were loaded into α-lactalbumin peptides to improve stability and water solubility (Jiang et al., 2018). Egg derived peptides are another important raw material to deliver active ingredients. Egg white and yolk proteins constitute the main parts of egg proteins, and the former one is widely studied due to their high nutritional value, digestibility and amphiphilic properties. Recently, more and more studies have reported that chelating egg white protein peptides with metal ions could serve as a potential trace element supplement. For instance, iron delivery system could be obtained from chelates of ferrous and desalinated duck egg white, and calcium also had a similar delivery system constructed using liposomes or chelates (Shi et al., 2021; Zhao et al., 2020). Some food-derived egg yolk peptides have also gradually attracted attention as edible particulate emulsifiers due to their amphiphilic properties. A new Pickering nanoemulsion made by egg yolk micellar nanoparticles was stable, monodisperse, and controllable. This nanoemulsion had the potential to deliver fat-soluble active ingredients (Du et al., 2019b). Some studies have also focused on the delivery system assembled by peptide derived from sea cucumber ovum. Calcium could trigger the self-assembly of these peptides, leading to the formation of nanocomposites that dissociated and self-assembled during digestion (Cui et al., 2019). Moreover, silk fibroin peptides showed promise as delivery materials (Li et al., 2021a,b).

2.2. Plant peptides

Peptides derived from corn and soybean protein are actually two widely studied delivery matrices. Zein is the main storage protein in corn endosperm, and its structure has been investigated thoroughly using different techniques, revealing its remarkable amphiphilicity. In addition to better absorption, zein hydrolysates also have the same self-assembly and other excellent properties like emulsification as protein, which makes it an ideal delivery material for active ingredients, drugs, oils and other food ingredients. According to Liu et al., zein peptides combined with oils as stabilizers, then these composite carriers encapsulated lutein, and developed into three types of nanocarriers (Liu et al., 2021). Moreover, small molecule containing sufficient hydroxyls and carboxyls could effectively stabilize peptide-based nanoemulsion through non-covalent interactions. For example, tannic acid loaded zein hydrolysate possessed remarkable emulsifying activity and high antioxidative property, thus, emulsions stabilized by these complexes showed improved physical stability (Wang et al., 2016). Currently, insoluble peptide derived from soybeans is another developing material for the delivery of active ingredients with poor bioavailability or water solubility. Pepsin resistant soybean peptide based nanoparticles could assemble with curcumin to develop core-shell structure under ultrasonic condition (Zhang et al., 2018). Also, the assembly of soybean peptide into functional nanoparticles might be triggered by pH changes (Zhang et al., 2021b). These researches provided new strategies to improve the value of these peptide byproducts and expand their application fields.

2.3. Synthetic peptides

Synthetic peptides have been extensively studied and have more applications compared to natural peptides because of their well-defined amino acid sequences. Nowadays, researchers focus on constructing peptide drug delivery systems. Several reports have summarized the types of these systems, the structures they formed through self-assembly, and their applications in medicine. Peptides of different types and structures, such as α-helical and β-sheet peptides, cyclic and linear peptides could self-assemble into various nanostructures, such as nanofibers, nanotubes, nanospheres and nanocapsules (Tesauro et al., 2019). In addition, construction conditions such as pH, ionic strength and temperature are important factors affecting the self-assembly of these peptides. It is worth noting that peptide-based molecular self-assembly has a broad application prospect in nano biomaterials, skin care and cosmetic products, drug delivery and release, and tissue engineering scaffold materials. This is due to its strong self-assembly driving force, unique self-assembly nanostructures, special self-assembly functions, and excellent biocompatibility. The hydrogels based on the short homodipeptide phenylalanine-phenylalanine demonstrated good biocompatibility *in vitro* within 2 days. They also exhibited good stability and slow drug release, making them suitable for delivering two complementary anticancer drugs (Mao et al., 2012). Additionally, lipopeptides crosslinked by disulfide linkages were used to form self-assembled micelles through nanoprecipitation methods. Subsequently, doxorubicin (DOX) and RNA were encapsulated into micelles by hydrophobic interactions (Yao et al., 2016).

3. Preparation methods of peptide-based delivery system

There are various methods to produce peptide-based delivery system. Chemical-based methods employ chemical additives like ethanol to promote complex formation, while physical-based techniques rely on physical elements like heat or pressure to construct complexes. Among the chemical-based approaches, solvent volatilization, ionic gel and self-assembly are the widely utilized methods. The physical-based methods such as ultrasonic, stirring and anti-solvent, will be discussed later. In what follows, a general review is provided of the methodologies, raw materials and mechanistic fundamentals of each classical method for the preparation of peptide-based delivery system (Fig. 1).

3.1. Solvent volatilization method

Solvent volatilization is commonly used to prepare microspheres through emulsification technology. The hydrophilicity or hydrophobicity of the active ingredients determines the solvent evaporation technique that will result in an effective active ingredient encapsulation. The hydrophilicity or hydrophobicity of the active ingredients determines the appropriate solvent evaporation technique for effective encapsulation. The most common oil-in-water (o/w) technique is widely employed for poorly water-soluble cargos. The process involves four main steps: (1) Peptide-containing organic solvents are used to dissolve the hydrophobic cargos. (2) The organic phase (dispersed phase) is emulsified in an aqueous phase (continuous phase). (3) The continuous phase extracts the solvent from the dispersed phase and solvent is evaporated, which results in solidification of the droplets of the dispersion phase. (4) The microspheres are recovered and dried to eliminate residual solvents (Mora-Huertas et al., 2010). Due to their poor solubility in organic solvent and diffusion into the continuous phase during emulsion, the aforementioned approach is inappropriate for the encapsulation of highly hydrophilic cargos. There are four other alternative techniques for encapsulating the hydrophilic cargos, including w/o/w double emulsion, o/w co-solvent, o/w dispersion, and o/o non-aqueous solvent evaporation method. For example, hydrophobic camptothecin and curcumin were embedded in amphiphilic peptide-based membrane through o/w solvent volatilization method (Li et al., 2017; Soukasene et al., 2011). Similarly, PLGA-PEG nanoparticles loaded peptide and hydrophilic DOX through double emulsion solvent evaporation (Nejabat et al., 2020).

3.2. Ionic gel method

The preparation of peptide-based nanoparticles by ionic gel technology relies on electrostatic interactions. Peptide acts as a crosslinking agent, binding its negative charge to the positive charge carried by some polysaccharides in acidic conditions. Due to a gentle preparation process, the molecular structures and activities of the active ingredients will not be compromised. The particle size of nanoparticles can be controlled by adjusting the preparation conditions. More importantly, the application of reversible physical electrostatic interactions instead of chemical crosslinking agents can eliminate potential toxicity and other adverse effects. Stable catechin loaded chitosan-casein phosphopeptide nanoparticles with higher encapsulation efficiency were prepared using the ionic gel method (Hu et al., 2012). The slower and more controllable

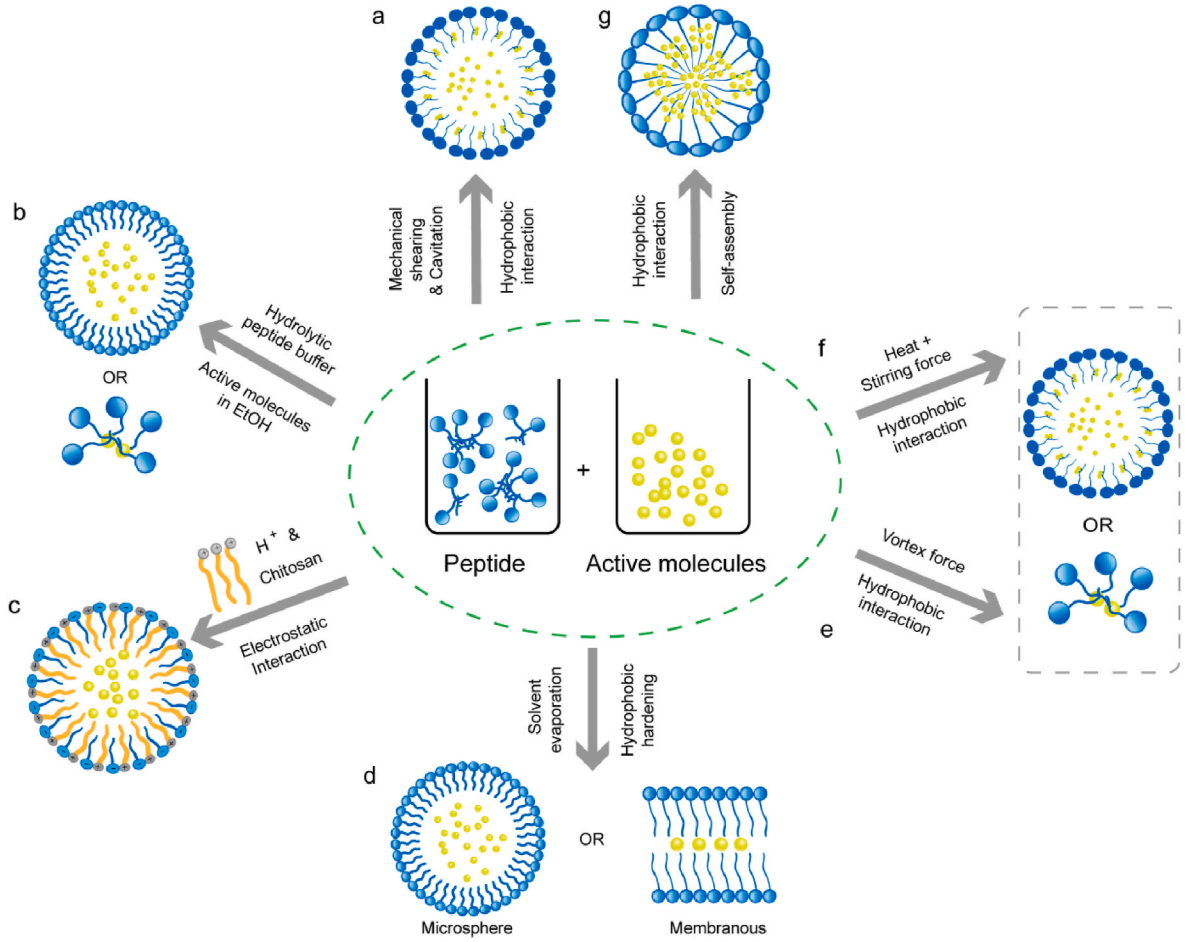

Fig. 1. Construction process of peptide-based delivery system through different methods. *Note:* a. Ultrasonic method; b. Anti-solvent method; c. Ionic gel method d. Solvent volatilization method; e. Vortexing method; f. Magnetic stirring method; g. Self-assembly.

release process of catechin in chitosan casein peptide nanoparticles was primarily attributed to the strong binding between catechin and casein phosphopeptide.

3.3. Self-assembly

Self-assembly technology commonly utilizes the special structural of peptides or modifies their surface with functional groups to spontaneously form ordered periodic structures spontaneously. The self-assembly is based on non-covalent interactions including hydrogen bonding, hydrophobic interactions, and electrostatic interactions. The amphiphilic peptide has been focused on as a hotspot for peptide self-assembly. Deamidated zein peptide and α-lactalbumin peptide are most common amphiphilic peptides from food. Bioactive compounds were incorporated into amphiphilic peptides via hydrophobic and electrostatic interactions, leading to form a composite with good redispersibility (Li and Yao, 2020). Similar composites also enhanced the thermal stability (Jiang et al., 2018) and water solubility of the active ingredients (Du et al., 2019a; Jiang et al., 2018). Besides, the curcumin bioavailability was higher in simulated digestive solution (Jiang et al., 2018).

3.4. Ultrasonic method

Ultrasonic method belongs to physical methods to construct peptide-based delivery system using ultrasonic mechanical shear and cavitation. Cavitation in a liquid can generate bubbles and produce high temperatures instantaneously, which is the underlying principle of the ultrasonic method. The bubble collapse shows a strong mechanical effect, leading to the destruction of peptide structures and the exposure of hydrophobic groups. This, in turn, enhances the combination between peptides and active ingredients. DOX was embedded in LKR peptide through an ultrasonic method, resulting in the formation of spherical nanocomposites (Gong et al., 2021). These nanocomposites could expand, rupture, and quickly release DOX under acidic conditions. Likewise, RGD motifs, tripeptides consisting of arginine, glycine and aspartic acids, have been found to bind specifically with certain integrin, causing superior tumor targeting property and better antitumor activity *in vivo*. Liang et al.'s research also showed that ultrasound treatment could induce smaller and more tightly structured peptide/polysaccharide nanoparticles, resulting in higher quercetin encapsulation efficiency, environmental stability, and antioxidant activity (Liang et al., 2021). Due to simple equipment, mild conditions and short reaction time, sonochemical method is efficient and popular nowadays, so it has been applied in many studies.

3.5. Anti-solvent method

The anti-solvent method involves the use of both a solvent, typically an organic medium, and an anti-solvent phase, usually water. By changing the polarity of the solution, the solutes are able to aggregate after the two phases are mixed (Mora-Huertas et al., 2010). According to existing literatures, anti-solvent method is commonly used to construct peptide-based delivery system. The properties of obtained composites are influenced by the mixing ratio, speed and solution concentration. Nanoparticles were constructed by dropping curcumin ethanol solution into the phosphate buffer of zein hydrolysates (Wang et al., 2015). Zein hydrolysates greatly improved the solubility and stability of curcumin, with more than 90% of curcumin remaining intact for at least two weeks. Another nanocomposite was prepared using soybean soluble polysaccharide (SSPS), nisin and curcumin through anti-solvent method (Luo et al., 2021). Due to excellent surface activity of raw materials, more hydrophobic environment was produced by electrostatic binding of nisin and SSPS, which significantly increased the encapsulation efficiency of curcumin.

3.6. Stirring method

There are two main types of stirring methods, eddy current stirring and magnetic stirring, and these methods have similar principles. The peptide chain is stretched and exposes more hydrophobic regions because of eccentric or magnetic field rotation, facilitating more sufficient combination. Both of these methods are known for their gentle and non-destructive nature, although they require longer processing time. Anthocyanin and silk fibroin peptide were mixed by vortexing to prepare stable composites. The physicochemical stability of anthocyanin was significantly improved under the alkaline condition, heat and metal ions (Li et al., 2021a,b). The formation of ellipticine loaded histidine fatty peptides were promoted by deprotonating histidine in peptides (Zhang et al., 2019). The complex structures altered with changes of pH value, making pH-responsive disassembly and release promising strategies for delivering active ingredients. Another complex was obtained by magnetic stirring of anthocyanin and C6M1, an amphiphilic octadecapeptide (Yao et al., 2021).

In addition to the construction methods summarized above, peptides could also bind with other micelles as modification groups, allowing for the construction of a stable delivery system through membrane hydration (Zhan et al., 2010). To date, numerous have focused on the construction methods of peptide-based delivery systems. However, there are still certain cases where the reproducibility of encapsulation efficiency may be slightly limited. As a result, exploring more diverse, efficient, stable peptide-based delivery systems is still promising in the future.

4. Behaviors of peptide-based delivery systems

The following section of this review will focus on the behaviors of peptide-based delivery systems in relation to their size, zeta-potential, interaction force, encapsulation efficiency, stability and drug release. These factors can serve as references for selection of the appropriate preparation method (Table 1). These properties have been selected because they are those most frequently explored.

4.1. Particle size

The mean particle sizes of peptide-based delivery systems varied widely, typically ranging from 10 to 500 nm. Table 1 summarizes research on the impact of composition parameter changes on sizes. As can be seen, the nature size of the peptides or cargos, pH and the ratio of cargos/peptides were essential factors in determining sizes of delivery systems. Besides, peptides were sometimes combined with polysaccharides to form carrier, hence the ratio of peptides to polysaccharides had non-ignorable effects on composite size (Luo et al., 2021).

In comparison with single peptides or active ingredients, their composites usually exert larger sizes. Likewise, the sizes of the composites also increased based on the growing size of their constituent components. However, another research has reported different result, that is, a further shrinkage of the curcumin loaded peptide micelles when combined with anthocyanin. This result was attributed to the electrostatic interaction between the micelles and the released anthocyanin counterions, which caused the micelles to undergo osmotic deswelling (Li et al., 2021a,b). The change in size as pH increases was due to the alteration of electrostatic attraction between peptide and polysaccharide, the elongation of polysaccharide chains and the reduction in peptide solubility (Luo et al., 2021). It was worth noting that a high rate of active ingredients/peptides induced small size, while a low rate caused opposite effect (Bawa et al., 2012). Also, excessive peptide or polysaccharide resulted in larger particle size (Luo et al., 2021). It was possible to obtain low mean particle sizes by using ultrasound in the initial steps of the procedure (Zhang et al., 2018).

Table 1
Behaviors of peptide-based delivery systems.

Peptides	Active molecules	Work conditions	Mean size range (nm)	Zeta-Potential (mV)	Technology	Interaction force	Binding group in peptides	Work conditions	Encapsulation efficiency (%)	Stability conditions	Stability (Loss)	References
Soy peptide	curcumin	Variable	103.95–489.70	−26.95	/	/	/	Peptide type (Soy peptide)	62.76%	/	/	Zhang et al. (2018)
Heat soy peptide	curcumin	Variable	106.00–506.55	−24.3	/	/	/	Peptide type (Heat soy peptide)	76.68%	/	/	Zhang et al. (2018)
Zein hydrolysate	curcumin	Variable	20~100- < 50	−45	FTIR, Fluorescence emission spectrum	Hydrophobic interaction	Glutamine, Tyrosine, proline	Peptide concentration (More than 2.5 mg/mL)	90%	Ambient conditions, 72 h 4 °C, light resistant conditions, 15 d	Storage stability (Less than 40%) Storage stability (Less than 10%)	Wang et al. (2015)
AAP8 peptide	ellipticine	Variable	16.86–36.6	36.6	/	/	/	/	/	/	/	Sadatmousavi et al. (2012)
AAP8-DEG	ellipticine	Variable	10.2–30.46	30.46	/	/	/	/	/	/	/	Sadatmousavi et al. (2012)
DEG-AAP8-DEG	ellipticine	Variable	8.21–30.86	30.86	/	/	/	/	/	/	/	Sadatmousavi et al. (2012)
Silk fibroin peptide	cyaniding -3-O- glucoside	Variable	51.34–102.77	24.43	Fluorescence emission spectrum	/	Tyrosine	Peptide type (Silk fibroin peptide)	48.43%	0.8 μL NaOH 0.1 M Cu^{2+} 6 h-12 h	pH stability (No shift in absorption peak) metal stability (2.07%–13.55%)	Li et al. (2021a,b)
Histidine fatty peptide	ellipticine	Variable	19.43–34.43	37.9	/	/	/	/	/	/	/	Zhang et al. (2019)
α-Lactalbumn peptides	curcumin	Variable	19–23	−20.8	/	/	/	/	/	/	/	Jiang et al. (2018)
α-Lactalbumn peptides	curcumin and anthocyanins	Variable	19–21	−5.29	/	/	/	/	/	60 °C, 24 h UV, 24 h	Heat stability (Curcumin 50%, anthocyanins 40%) Photostability (Curcumin 40%, anthocyanins 24%)	Jiang et al. (2018)
Nisin-soy soluble polysaccharide	curcumin	pH (2.0-4.0-7.0)	~155-~120-~245	/	/	/	/	Ratio of SSPS/ Nisin (3:1) pH (4.0) Curcumin concentration (1–4 mg/mL)	91.66% 90.44% 90%–69.71%	80 °C, 0.5 h-2.5 h	Heat stability (20%–37%)	Luo et al. (2021)
EAK16-II peptide	ellipticine	ratio of peptides active/ molecules (5:1–0.5:1)	40~300–900~3000	/	/	/	/	/	/	/	/	Bawa et al. (2012)
Nisin-soy soluble polysaccharide	curcumin	(ratio of peptides/ polysaccharide) s 1:1–3:1–5:1	~150-~120-~160	/	/	/	/	/	/	/	/	Luo et al. (2021)
Deamidated zein peptide	Curcumin	/	/	/	FTIR, Fluorescence emission spectrum	Hydrogen bond, hydrophobic interaction	Tyrosine	/	/	/	/	Li and Yao (2020)
C6M1 peptide	Anthocyanin	/	/	/	Fluorescence emission spectrum	/	Tryptophan	/	/	/	/	Yao et al. (2021)

4.2. Zeta-potential

It was widely believed that a stable nanosuspension could be maintained with an absolute zeta potential of 20 mV. However, no clear trend regarding the zeta potential behavior of peptide-based delivery systems has been revealed. The absolute zeta-potential values of particular peptide carriers can typically be increased or maintained as shown in Table 1, indicating their excellent stability. Numerous studies have demonstrated that the zeta-potential is primarily affected by the pH of the medium and chemical nature of the peptides and active ingredients. For example, when ellipticine was protonated under the effect of acidic peptide, the resulting complex exhibited a positive zeta potential (Sadatmousavi et al., 2012). Also, the zeta potential of a cargo loaded complex with positively charged arginine outward peptides as carrier was found to be positive (Zhang et al., 2019). In contrast, α-lactalbumin micelles possessed a negative zeta-potential due to their negative surface charge (Jiang et al., 2018).

4.3. Interaction force between peptides and active molecules

As is well known, the structure of a substance is closely related to its internal force interactions. Hydrophilic and hydrophobic cargos were loaded into peptides including silk fibroin peptide (Li et al., 2021a,b), histidine fatty peptide (Zhang et al., 2019) and bis(pyrene)-cationic dipeptide, to prepare nanoparticles. Their scanning electron microscopy (SEM) results revealed spherical (Nejabat et al., 2020; Sun et al., 2017a), smooth surface and uniform distribution (Das et al., 2020). However, some papers reported the contradictory conclusions. The flufenamic acid loaded diphenylalanine peptide displayed a rough surface, indicating that combination of cargos and peptides changed the morphology and formed incomplete nanotubes. The reasons for this phenomenon might be attributed to the spontaneous assembly of flufenamic acid in both inner and outer nanotubes (Zohrabi et al., 2016). In addition, internal force could also significantly influence stability. Diethylene glycol modified peptide could inhibit the aggregation of AAP8 and ellipticine due to a more hydrophilic environment. It effectively stabilized the ellipticine effectively through good hydrophobic interaction between active ingredients and phenylalanine (Sadatmousavi et al., 2012).

Common technologies of exploring interaction forces include infrared spectroscopy and fluorescence emission spectrum. Table 1 summarizes research on the interaction force between peptides and active ingredients using the aforementioned technology. Based on existing literatures, the binding between peptides and cargos generally depends on hydrophobic forces, and some bindings also involve hydrogen bonds. Meanwhile, tyrosine played a crucial role in combining and stabilizing of active ingredients (Li et al., 2021a,b). Summarizing previous reports (Fig. 2), it was found that free active ingredients especially hydrophobic molecules mostly appeared in crystalline, and transformed into amorphous state after binding with peptide (Li and Yao, 2020; Zhang et al., 2018) due to suppression of crystallization by the interaction between active ingredients and peptides. Additionally, for hydrophobic molecules embedded in peptides, there was a blue shift in the peak maximum, indicating that the binding of hydrophobic molecules with peptides occurred in a hydrophobic environment.

4.4. Encapsulation efficiency

The encapsulation efficiency of cargo is determined by the active chemical nature of cargo or peptide, particularly their polarity. The ratio of peptides and other substances like polysaccharides can also affect the encapsulation efficiency through variation in structure and polarity. Besides, pH in environment can change polarity of peptide-based delivery systems. The concentration of peptides and cargos influenced

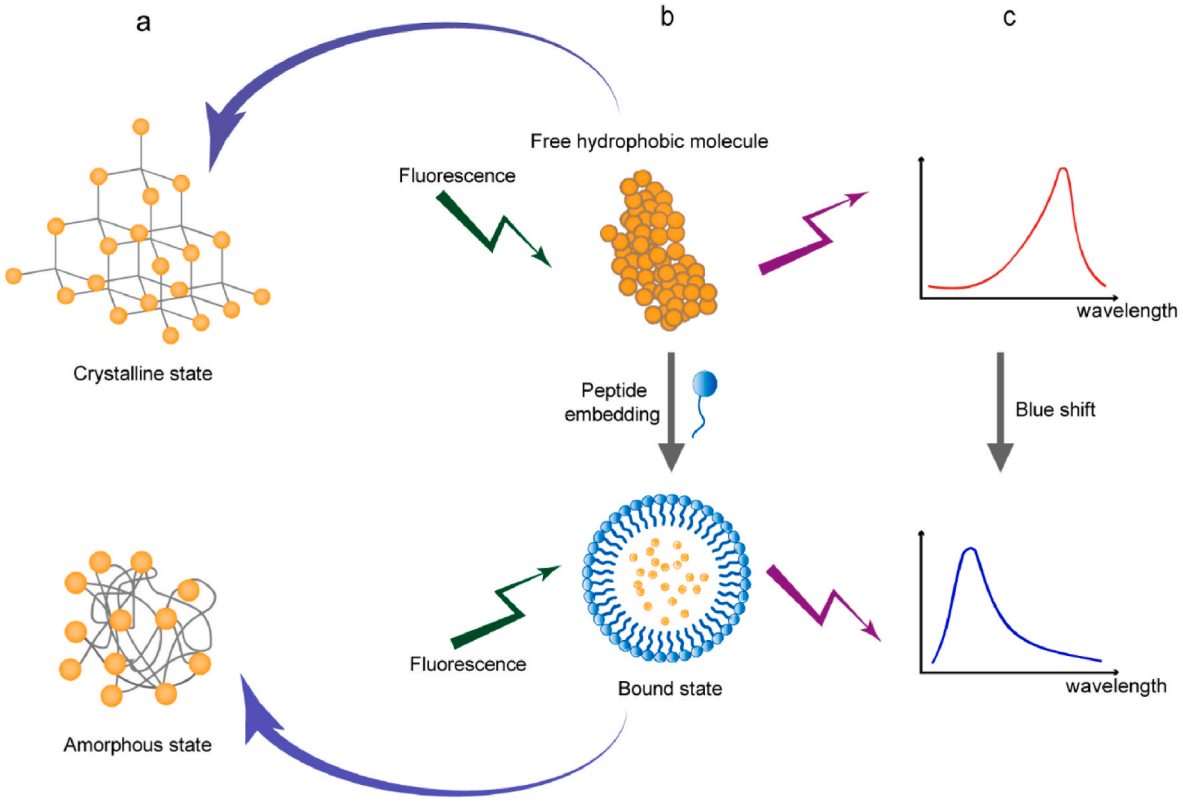

Fig. 2. Structures of peptide-based delivery system *Note:* a. Crystal and amorphous structure of hydrophobic molecules; b. The illustration of hydrophobic molecules and peptides that loaded hydrophobic molecules; c. Fluorescence emission spectrum results.

encapsulation efficiency, because too high concentration of active ingredients could produce peptide saturation. Table 1 showed the effect of different parameters on the encapsulation efficiency.

4.5. Stability

Natural active ingredients are unstable when exposed to challenging processing or storage conditions, such as high temperatures or strong light. However, once loaded in peptides, their photostability, pH stability, thermal stability, and storage stability had been significantly improved. Furthermore, they had been shown to maintain their integrity in the gastrointestinal tract (Li et al., 2021a,b). The fundamental reason was that the binding of active ingredients with peptides immobilized them, thus reducing their fluidity and consequently decreasing their chemical reactivity. In addition, the peptide layer might be employed as a physical barrier to resist oxidation, ultraviolet rays, and other forms of penetration. At the molecular level, the groups of active ingredients had strong interaction with the amino acids of peptides, and peptide groups operated as buffers by initially combining with acids, bases, and metal ions to ensure stability. Table 1 summarizes different kinds of stability. In addition to high active ingredients residue rate, stable diameter could reflect the excellent storage stability (Luo et al., 2021; Zhang et al., 2018).

4.6. Active ingredients release of peptide-based delivery system

A drug release model with three phases has been proposed: an initial burst release, a plateau phase for a certain period caused by drug diffusion in the polymer matrix, finally, a constant sustained release of the drug due to drug diffusion through the polymer wall and erosion of the polymer. (Mora-Huertas et al., 2010). The *in vitro* release curve of active ingredients showed a rapid release rate in the first 4 h, known as the initial burst stage, which was likely attributed to the loss of active molecules weakly adsorbed on the peptide matrix near the particle surface (Luo et al., 2021). In general, being loaded in peptides promoted the sustained-release of active substances. It was worth noting that release of hydrophobic substances was rarely affected by pH, while the release of hydrophilic substances was strongly pH dependent due to the change of dominant force (Jiang et al., 2018). This helped prevent premature release and degradation of encapsulated components in gastric conditions.

4.7. The relationship between structure and self-assembly of peptides

The internal factors that influence peptide self-assembly include the sequence, quantity, hydrophilicity, and hydrophobicity of amino acids, as well as the secondary structure of peptides. Common self-assembled peptide structures include nanofibers, nanoribbons, and nanotubes. The various self-assembly forms arise from the different interactions between the side chains of amino acid residues, including electrostatic, hydrophilic, and hydrophobic interactions. The properties of amino acid side chains are crucial in the self-assembly of peptides. Hydrophobic amino acids can significantly impact the mechanical properties and self-assembly speed of materials. Therefore, the reasonable selection and design of peptide sequences are essential for studying peptide self-assembly. Extensive research has shown that diphenylalanine and its analogues could self-assemble into ordered nanotubes, while diphenylglycine peptides formed spherical nanostructures. The absence of methylene in the side chains of phenylglycine made it harder than the side chains of phenylalanine. The enhanced lateral growth ability caused the structure to resemble the long axis direction, resulting in the transformation of the original tubular structure into a spherical shape (Reches and Gazit, 2003; 2004). The arrangement order of amino acids affected the self-assembly ability and morphology of peptides with similar overall hydrophobicity and charge. Lee et al. compared several peptides with similar amino acid compositions but varying sequences of intermediate amino acids. They discovered that certain peptides could self-assemble into β-sheet nanoribbons under acidic conditions, while others failed (Lee et al., 2013).

The hydrophilic and hydrophobic properties of amino acids, as well as their quantity, greatly influence the self-assembly behavior and morphology of peptides. Meng et al. found that replacing lipophilic amino acids, like glycine, with more hydrophobic ones increased the hydrophobicity of peptides. This change in hydrophobicity led to a transition in the self-assembled nanostructures from vesicles to tubes and bands (Meng et al., 2012). The morphology of self-assembled nanostructures could be altered by changing the peptide sequence. Wang et al. observed the dynamic self-assembly of A6K and A9K peptides (Wang et al., 2009). At a neutral pH, A6K self-assembled into small spherical sediments that fused together to form large peptide nanoaggregates. These aggregates served as the building blocks for short nanofibers. In contrast, the self-assembly kinetics of A9K were faster compared to other substances. It formed small nano aggregates and then transformed into nanorods that were approximately 3–4 nm in diameter and less than 100 nm in length. This difference could be attributed to the longer tail length of hydrophobic peptides, which increased entropy gain and electrostatic interactions, while reducing the critical aggregation concentration.

On the other hand, the secondary structures of peptides that tend to self-assemble include α-helices, β-sheets, and β-hairpins. The α-helix is the primary secondary structure in proteins, but it is thermodynamically unstable. Linear peptides with helical structures are prone to losing their helical conformation. The stability of the helix is essential for initiating peptide self-assembly. The methods of spiral stabilization include side chain cross coupling, hydrogen bond substitutes, metal coordination, and salt bridge formation. The 17-peptide fragment designed by Mihara et al., was stabilized into an α-helix structure and further self-assembled into stable nanostructures (Sakamoto et al., 1998). Lee et al. demonstrated that β-sheet could effectively stabilize α-helices, thus enabling peptides to self-assemble into nanostructures in aqueous solutions (Lim et al., 2009). The β-sheet is important secondary structures in peptide molecules. Lego peptide could form hydrophilic and hydrophobic surfaces through hydrogen bonding in aqueous solutions, resulting in a β-sheet structure. In water, the tail of the aliphatic group induced the formation of β-sheet and hydrophobic collapse, leading to the assembly of molecules into one-dimensional nanostructures. These nanostructures were typically cylindrical or banded nanofibers (Hendricks et al., 2017). Yokoi et al. designed a peptide consisting of alanine, aspartic acid and arginine (Yokoi et al., 2005). In an aqueous solution, hydrophobic alanine residues aggregated to minimize energy within the system, while aspartic acid and arginine residues were attracted to each other through electrostatic interactions and were positioned on the outer layer of the component. Alanine residues could laterally slide to reduce their contact with water molecules, allowing the hydrophobic surface of the peptide chain to form a regular β-sheet structure and self-assemble into nanofibers. Peptides could form nanofibers as well as self-assemble into β-sheet secondary structures to create nanotubes, vesicles, and other assemblies. β-Hairpin is a type of β-turn derivative that requires peptide segments with amino acid sequences capable of bending. These peptides typically consist of alternating sequences of hydrophilic lysine residues and hydrophobic valine amino groups. By adjusting the pH or ion concentration of a solution, peptides could be formed with lysine residues on the inner surface and valine residues on the outer surface. This hairpin structure was then used for hydrophobic self-assembly, resulting in the formation of nanofibers (Schneider et al., 2002).

4.8. The relationship between structure of peptides and encapsulation of active ingredients

Current research indicates that the ability of peptides to encapsulate may be influenced by certain structural characteristics, including molecular weight, amino acid composition and sequence, specific amino

acid groups, and secondary structures.

The molecular weight of peptides significantly affects the encapsulation of active substances and their stability post-encapsulation. Low molecular weight peptides generally exhibit strong metal chelating activity. For instance, Torres Fuentes et al. studied the enzymatic hydrolysis of chickpea protein to obtain iron chelating peptides, and found that small molecular weight peptides exhibit greater iron chelating activity compared to high molecular weight peptides (Torres-Fuentes et al., 2012). Similarly, Huang et al. purified a calcium chelating peptide with a molecular weight of 359 Da from shrimp (Huang et al., 2011). Additionally, Guo et al. identified an iron chelating peptide Ser-Cys-His with a molecular weight of only 345 Da from the skin of Alaskan finned fish (Guo et al., 2013). After being digested by flavor enzymes, corn gliadin was hydrolyzed into small peptide fragments with a molecular weight primarily ranging from 93 to 1385 Da. When digested by trypsin, the molecular weight was mainly distributed between 91 and 692 Da. Peptides with low molecular weights were more likely to diffuse and adsorb onto the oil-water interface. This promoted the diffusion of zein soluble peptides hydrolyzed by trypsin towards the oil-water interface, resulting in improved interfacial activity and enhanced storage stability (Liu et al., 2021).

The amino acid composition and sequence of peptides, along with their molecular weight, are important factors that influence the encapsulation of active substances. Research has shown that peptides with metal chelating activity typically contain amino acids such as histidine, cysteine, glutamic acid, and aspartic acid in their composition. The metal chelation sites in proteins typically involve the carboxyl groups of aspartic acid and glutamic acid, the imidazole group of histidine, and the oxygen, nitrogen, and sulfur atoms on the neighboring thiol groups of cysteine. Bao et al.'s research suggested that certain amino acid sequences, like aspartic acid-cysteine-serine, exhibited strong chelating activity (Bao et al., 2008). In addition, a suitable amino acid composition played a crucial role in enhancing the stability of peptide aggregates, leading to an increased loading rate of active substances (Li and Yao, 2020). Corn gliadin peptides produced through alkaline hydrolysis underwent a deamidation reaction, resulting in an increased presence of glutamic acid and aspartic acid residues, or more carboxyl groups, compared to corn gliadin and corn gliadin peptides produced using internal proteases such as alkaline enzymes and trypsin. Therefore, the hydrophilicity/hydrophobicity of deamidated zein peptides were determined by both the molecular fragments and the degree of deamidation of asparagine and glutamine residues, as well as the pH of the solution. The deamidated corn protein peptide and curcumin were dissolved in a simple alkaline solution. The hydrophobicity of deamidated zein peptides and curcumin increased under acidification conditions with a pH range of 5.5–7.0, due to the protonation of carboxyl and hydroxyl groups. The electrostatic repulsion on the carboxyl group of deamidated zein peptides prevented macroscopic precipitation and formed negatively charged composite nanoparticles through hydrogen bonding and hydrophobic interactions. These nanoparticles had a loading capacity of 31.9% (w/w), which was significantly higher than values reported in the literature (Yallapu et al., 2015). Compared to flavor enzyme hydrolysis, peptides obtained from trypsin hydrolysis exhibited increased hydrophobicity and had a greater ability to bind with lipid fatty acid chains in lipid carriers, leading to improved storage stability (Liu et al., 2021).

After cyanidin-3-O-glucoside and silk fibroin peptide formed nanocomposites, the secondary structure of them remained unchanged (Li et al., 2021a). This was due to the interaction between tyrosine and the 3-phenylbenzopyran ring structure. The combination of cyanidin-3-O-glucoside and silk fibroin peptide was primarily driven by molecular forces, suggesting a direct binding process between the two rather than encapsulation through co-assembly methods (Yao et al., 2021). Their encapsulation efficiency is reported to be 48.43 ± 1.48%. The co-assembly mechanism involved the encapsulation of cyanidin-3-O-glucoside by C6M1 amphiphilic peptides, which contained four tryptophan aromatic rings and conjugated groups (Yao et al., 2021). By binding cyanidin-3-O-glucoside to the tryptophan of the amphiphilic peptide, the secondary structure of the peptide changed from an α-helix to a β-sheet dominated structure. The size of C6M1 peptide nanocomposites that encapsulated cyanidin-3-O-glucoside were less than 100 nm, with an encapsulation efficiency of 77.06%. The maximum load-bearing mass exceeded 600 wt% (w/w). By comparing the difference in the encapsulation efficiency of two peptides loading cyanidin-3-O-glucoside, it is speculated that self-assembly might enhance the encapsulation efficiency of active ingredients. Self-assembly was also closely linked to the secondary structure. The secondary structure might also impact the encapsulation of the substance. However, the specific relationship between secondary structures and the encapsulation of active ingredients is currently unclear and requires further research.

4.9. Advantages of peptide-based delivery systems

Compared to synthetic polymers, many natural biopolymers used in the preparation of nanocarriers were derived from food, and they exhibited excellent biocompatibility and minimal toxicity. Peptides, unlike polysaccharides, contained both hydrophilic and hydrophobic amino acids, rendering them prone to self-assembly. This property of peptides facilitated their efficacy in encapsulating hydrophobic compounds. Protein-based nanoparticles typically had limited loading capacity for hydrophobic compounds when compared to peptides. This was because the hydrophobic amino acid residues of proteins were usually buried within protein molecules and/or aggregates (Kazlauskas, 2018). Organic solvents and/or high-energy processes were commonly used (Galazka et al., 2000; Luo and Wang, 2014) to expose hydrophobic amino acid residues and enhance protein binding to hydrophobic compounds, thereby increasing their loading capacity (Ding and Yao, 2013; Liang et al., 2018; Luo and Wang, 2014). The anti-solvent method was used to prepare alcohol-soluble protein nanoparticles that loaded hydrophobic substances. It was found that, because of the hydrophobicity of alcohol-soluble proteins, protein nanoparticles tended to aggregate in aqueous solutions without any stabilizers (Patel et al., 2010). This presents a significant challenge for future applications such as beverage additives. However, peptides had a small molecular weight and good solubility, allowing the prepared composite particles to have smaller sizes. These particles could be uniformly dispersed without stabilizers, effectively improve the water solubility of hydrophobic substances, and the preparation process was easy to operate. Peptides also had lower allergenicity, making them a preferable delivery system for patients with protein allergies. From a production perspective, utilizing insoluble peptide aggregates as byproducts in the preparation of bioactive peptides could save costs and provide new strategies for the high-value application of low value protein resources. Unlike other biological macromolecules, peptide molecules composed of amino acids could be easily obtained through chemical synthesis, which is feasible for future large-scale industrial production. The relatively weak non-covalent interactions among peptide molecules facilitated the process of assembling or disassembling peptide monomers under specific conditions. Peptide-based delivery systems provided targeted delivery and stimulus response capabilities. The reversible ability of peptide assembly expanded the potential applications of peptide nanomaterials.

5. Absorption and metabolism of peptide-based delivery system

From the current researches, peptide-based delivery system not only possessed various physiological activities and good drug sustained-release effects, but also improved the biological accessibility and stability of active ingredients. Nowadays, the application of peptide-based delivery system mainly focused on the delivery of anticancer drugs *in vivo*, the encapsulation and release of active ingredients in health food, and the sealing of bitter, peculiar and odor substances, which reflected

that complexes had great economic benefits in the drug and health food industries. However, compared to other natural substances (proteins, polysaccharides.) as carriers (Devi et al., 2017; Zhang et al., 2021a), the current application of peptide-based delivery system was still not wide enough, and there were few reports on their effective release of natural components as an additive in cosmetics and skin care products. In this section, we summarize the factors affecting the absorption of peptide-based delivery systems. We also discuss their absorption and metabolism to provide a theoretical basis for the application of complexes in food, drug and skin care industry. The absorption and metabolism of peptide-based delivery system in the gastrointestinal tract, airway and skin are displayed in Fig. 3.

5.1. Factors affecting the absorption of peptide-based delivery system

In general, delivery system could improve the bioavailability of cargos, which should be explained from the properties of their compositions (Semenova et al., 2021). It meaned that molecular size, surface properties, charge, structure, organization and hydrophilicity/hydrophobicity of cargos and peptides could significantly affect the bioavailability, metabolism and absorption of peptide-based delivery system.

Particle size played a crucial role in the release rate, biological distribution, adhesion, uptake and diffusion of peptide-based delivery system. The size of the particles was directly determined by the size of peptides and cargos. It had been proved that small drugs loaded peptides penetrated faster, while large drugs loaded peptides transported through slower vesicles (Tuennemann et al., 2006). Simultaneously, it was found that the particle size could influence the release performance of the drug, thus affecting its absorption. In addition, significant differences were found in the surface properties of peptide-based delivery system prepared by different cargos and peptides. These differences had a significant impact on the bioavailability of cargos. It had been reported that certain bioactive peptides with protective films on their surface, would not be susceptible to secondary hydrolysis by pepsin, trypsin and other enzymes in the human body (Kim et al., 2018). Therefore, these peptides directly entered the small intestine in a basically complete form, were subsequently absorbed by small intestine, and finally entered the human circulatory system to perform their function. This process facilitated the absorption of the active ingredients.

The changes of delivery system structure also significantly influenced the transport of active ingredients. For example, cell uptake and absorption could be enhanced by transforming peptides into cyclic peptides (Panigrahi et al., 2018), dendrimers (Kozhikhova et al., 2018) or transforming their side chains (Tesei et al., 2017). Besides, adding trifluoromethylquinoline moiety (Andaloussi et al., 2011) or substituting certain residues with histidine had been a commonly employed strategy for developing cell penetrating peptides (CPP).

Nowadays, passive diffusion, carrier-mediated transport, receptor-mediated transport, and efflux pump mechanisms were the four mechanisms used to transfer cargos through small intestinal epithelial cells (Bao et al., 2019). To improve mucosal permeability and facilitate drug absorption, drugs must have the proper hydrophilicity/lipophilicity. On the one hand, it is well known that most hydrophobic substances were absorbed through passive diffusion and receptor-mediated transport without high efficiency (Gambini et al., 2015). Additionally, the digestive tract contained many drug efflux pumps, predominantly P-glycoprotein (Li et al., 2015), which exhibited an affinity for hydrophobic (lipophilic) molecules. If drug molecules were highly lipophilic, they could be expelled by efflux pumps. On the other hand, hydrophilic substances usually diffused passively through the paracellular pathway (tightly connected cell gap), but they rarely opened the zonula occluden, which was one of the main factors hindering cargos delivery. When drugs bound to a target, they commonly interacted with a hydrophobic binding pocket, so excessively hydrophilic drugs were unable to effectively bind to their intended target. However, the transport pathway of numerous natural organic compounds like peptides, involved carrier-mediated transport, which exhibited high efficiency and prevents their expulsion from intestinal epithelial cells. Therefore, it is necessary to use amphiphilic peptides or specialized peptides to modulate the hydrophilicity/lipophilicity and absorption pathways of cargos. In fact, stability is also a significant factor in absorption. The stable combination of cargo and peptides was mainly achieved through different intermolecular forces. Therefore, the choice of carrier should depend on the type of drug transported. Selecting appropriate carrier peptides for active ingredients laid a solid foundation for obtaining complexes with high absorption and stability.

5.2. Absorption

Peptide-based delivery systems can enter the human body through various pathways, including oral administration, inhalation and skin absorption.

5.2.1. Absorption in gastrointestinal tract

Peptide-based delivery systems could improve the release and absorption of active ingredients in gastrointestinal tract. They could also prevent premature disassembly of complexes in gastric acid and protect active ingredients, leading to improved bioavailability (Jiang et al., 2018; Li and Yao, 2020). Caco-2 cells are typical model for analyzing the transportation of cargos into the small intestine. It was found that a peptide carrier based on α-lactalbumin could effectively deliver curcumin and anthocyanin through Caco-2 cells due to higher cellular absorption efficiency (Du et al., 2019a), which was related to improved water solubility of cargos through encapsulation of amphiphilic peptides.

The complexes could deliver cargos through Caco-2 cells effectively for the following reasons. Firstly, certain peptides such as α-lactalbumin peptide possessed active cellular absorption (Du et al., 2019a; Jiang et al., 2018). Besides, some peptides were not recognition substances of glycoprotein, so they were not expelled from intestinal epithelial cells through the “multidrug resistance” mechanism (Jiang et al., 2018). These studies have also shown that some peptides could cross zonula occludens and promote paracellular transport (Du et al., 2019a; Jiang et al., 2018).

However, the low absorption rates of some peptide complexes after oral administration were induced by their easy decomposition by gastric acid and enzymes (Lundquist and Artursson, 2016). And the low absorption rate of nanoparticles can be attributed to their short retention time in the intestinal, which is caused by their low affinity for mucus and the blockage of the mucus barrier. Therefore, Mao et al. prepared a functionalized peptide delivery carrier, it was complete until absorbed by intestinal epithelial cells and remained in the small intestine for subsequent absorption (Mao et al., 2019). When sulfhydrylated polymer of carrier entered mucus, it gradually separated from the surface of composites. Subsequently, the cell penetrating peptide facilitated high cell absorption, allowing drugs to enter the interior of the intestinal myenteric membrane through the surface of the intestinal villi. After loading lopinavir (LNV) in peptides, higher LNV level was also detected in blood for three reasons. (1) The solubility of LNV was improved because of its uniform dispersion and amorphous form. (2) The sulfhydryl polymer enhanced the mucus affinity and mucosal permeability of LNV particles. (3) In addition, cell penetrating peptide could directly penetrate epithelial cells and enter the bloodstream without encountering any barriers. It should be noted that transport carriers were designed according to the actual transport conditions, because cell types, properties of drugs and penetrating peptides all had effects on cell absorption (Habault and Poyet, 2019).5.2.2 Absorption in respiratory system.

Airway drug administration is an increasingly interesting topic for research and development in the pharmaceutical field. Recently, peptide-based delivery systems penetrating the mucus of human cystic

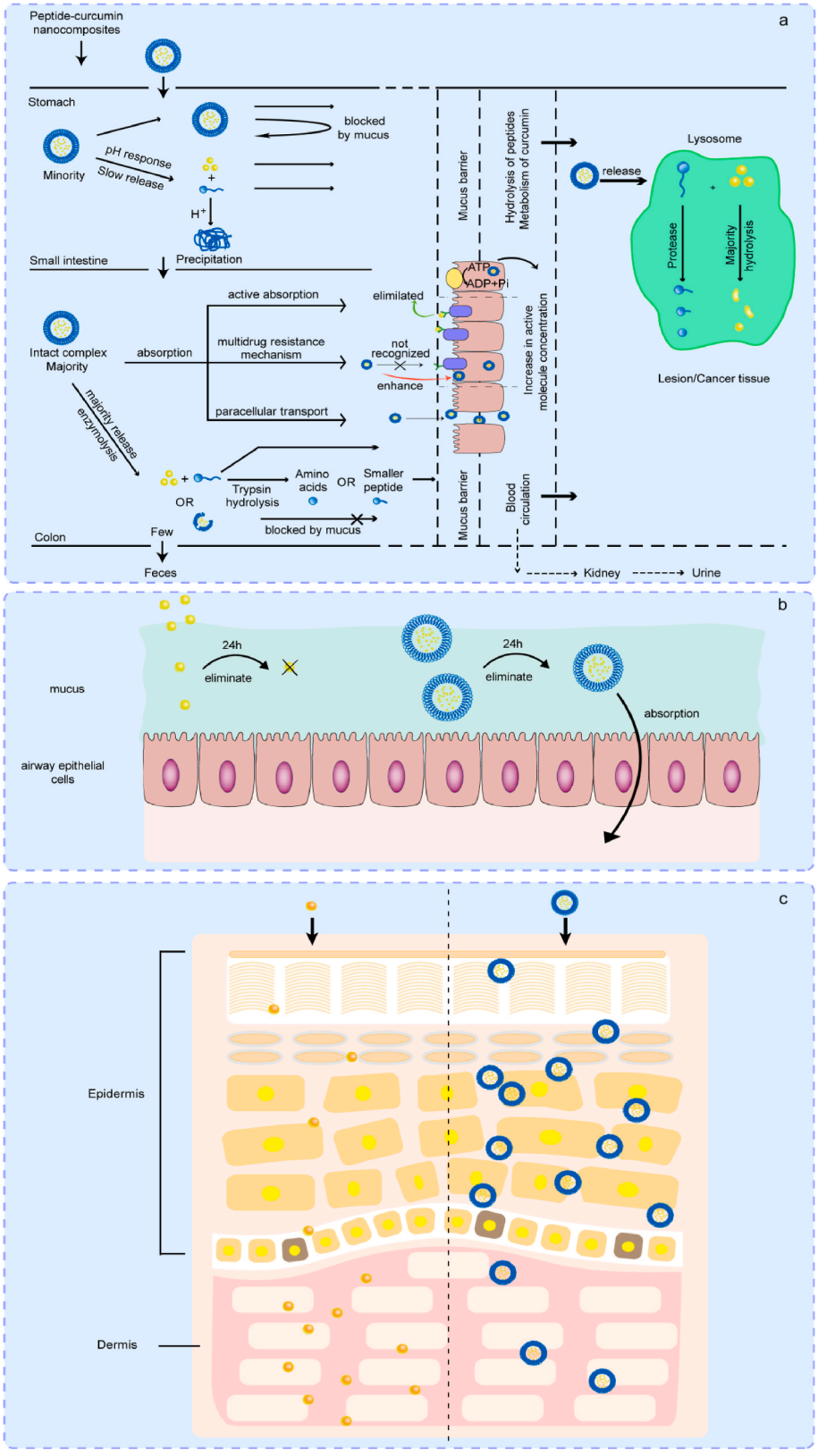

Fig. 3. Absorption and metabolism of peptide-based delivery system Note: a. Absorption and metabolism of peptide-based delivery system in gastrointestinal tract; b. Absorption of peptide-based delivery system in airway; c. Absorption of peptide-based delivery system in skin.

fibrosis were designed (Leal et al., 2020). After addition of peptide coating, complexes exhibited higher absorption in lung epithelial cells. Moreover, they showed more uniform disperse and longer retention time in lung airway of mice. After intratracheal administration of peptide-based delivery system, a half hour later, the complexes with peptide coatings exhibited uniform dispersion in lung airway, while the major unwrapped complexes were accumulated. One day after administration, the evenly distributed peptide particles remained in the airway and relatively complete, while about a half of complexes without peptide coating was removed. These results suggested that complexes without peptides coating in the lung airway could be easily and rapidly eliminated through the steady-state mechanism of mucus.

5.2.2. Absorption in skin

Peptide-based delivery systems applied to the skin penetrate the epidermis and dermis. The main barrier in the absorption process is the shallowest layer of the epidermis, known as the stratum corneum. After combination of corticosterone and space™ peptide, the conjugate demonstrated improved penetration of the epidermis and localization effect (Kumar et al., 2015). The complexes also enhanced the total skin penetration and epidermal deposition of corticosterone, while the permeability of corticosterone in dermis and receptor compartment decreased obviously. In comparison with the hydrocortisone alone, the accumulation of hydrocortisone in the skin and epidermis increased, while the accumulation in the dermis and receptor compartment significantly decreased. However, the accumulation of triamcinolone acetonide in epidermis, dermis, receiver and skin did not have obvious changes when binding with SPACE™ peptide. The experimental results in mice also showed that the accumulation of hydrocortisone in the application skin increased after the addition of SPACE™ peptide, and there was no significant increase in the drug accumulation in most organs except the heart and spleen.

5.3. Metabolism

A peptide-based delivery system consists of peptides and active ingredients. Due to peptidase in human gastrointestinal tract and plasma, many peptides could not reach their targets to exert biological activities (Xu et al., 2019). For example, the β-casomorphin derived from bovine casein were enzymatically degraded in the gastrointestinal tract and plasma of rabbits (Mahe et al., 1989; Petrilli et al., 1984). Then, the loaded active ingredients would be released, enter into various tissues with the circulation of body fluid, and participate in different metabolism. In addition to stomach and small intestine digestion, peptides could also be further digested into small peptides and amino acids by endopeptidases of the brush border membrane. However, many studies had shown that biological peptides derived from food proteins, appeared completely in the human circulation (Nongonierma and FitzGerald, 2015; Righard et al., 2014). Some peptides could resist proteases in the intestinal membrane, survive degradation in the gastrointestinal tract and plasma, enter the human circulation, and reach their target organs without being broken down. They could be found in various organs such as the plasma, heart, liver and kidney. Of course, after reaching the target organ, some peptide-based delivery systems entered the cell and underwent decomposition in the lysosome. For example, Al-azzawi et al. combined flurbiprofen and apolipoprotein E-derived peptides in simulated lysosomal acidic conditions. Most peptides were hydrolyzed into amino acid residues and smaller peptides, and the drug was further hydrolyzed by acid after being released in free state (Al-azzawi et al., 2020). When daunorubicin peptide complexes were mixed evenly with lysosomal homogenate, the peptides were similarly hydrolyzed. However, daunorubicin was not released, because the final product was related to the amino acid sequence of the peptide segment (Dokus et al., 2020). Also, some undigested and/or unabsorbed peptides might also reach the large intestine, where they could be metabolized by the gut microbiota. With the continuous decomposition of peptides, active ingredients were released, and various metabolites were also produced in the gastrointestinal tract. Taking active ingredients polyphenols as an example, 48% of the ingested polyphenols were degraded in the small intestine, 42% in the large intestine, and 10% were undigested (Tarko et al., 2013). Besides, some flavonoids were chemically hydrolyzed in stomach, and their further reactions (glucuronidation, methylation, deglycosylation, sulfonation and hydroxylation) occurred in the small intestine. However, the metabolism of peptide-based delivery systems is currently only clarified at the cellular or animal level, and further exploration is needed to understand the actual metabolic process in the human body.

6. Functional activities

Peptide are substances composed of peptide bonds formed through dehydration and condensation of several amino acids. They have various benefits, including reducing blood lipid levels (Nagaoka et al., 2021), enhancing immunity (Yimit et al., 2012), improving muscle atrophy (Zhao et al., 2018), regulating the intestinal environment (Shang et al., 2021), and protecting the liver (Kawakami et al., 2017). In recent years, whether peptide-based delivery system can enhance the bioactivities or produce new physiological activities is also a research hotspot.6.1 Antioxidant activity.

Many natural active ingredients and peptides possessed antioxidant properties, and their combination often had a synergistic effect. Soybean protein hydrolysate that loaded curcumin could effectively protected against oxidative damage induced by glutamate, with a stronger protective effect compared to soybean protein hydrolysate alone (Zhang et al., 2018). The bioavailability of curcumin loaded deamidated zein peptide constructed by Li et al. was 75%, which possessed remarkable antioxidant activity in animal experiments (Li and Yao, 2020). Besides, the encapsulation of anthocyanin by C6M1 peptides could maintain the antioxidant capacity of anthocyanin in a stable state (Yao et al., 2021). Also, it was found that curcumin and anthocyanin loaded peptide complexes exhibited a stronger antioxidant effect in cells when compared to the individual active ingredients alone (Jiang et al., 2018). Similar results were also reported by Du et al., but the micelle alone did not decrease the fluorescence intensity of 2′,7′-dichlorofluorescein, which indicated that the enhanced antioxidant capacity might be due to the accelerated cell absorption of β-carotene (Du et al., 2019a).

6.1. Antitumor activity

Some complexes not only exhibited antioxidant activity but also showed improved antitumor activities. It has been found that anticancer drugs loaded peptides were more cytotoxic (Sadatmousavi et al., 2012; Soukasene et al., 2011; Zhan et al., 2010) and had enhanced transport efficiency through the caveolae-dependent endocytosis mechanism (Bawa et al., 2012). Of course, antitumor activity can be influenced by pH and charge. The ellipticine loaded NP1 peptides (an externally positively charged peptide) interacted with the negatively charged cell membrane to directly translocate complexes, thereby inhibiting the activities of cancer cells. The transformation of composite structures at different pH levels affected loading and accumulation active ingredients at the lesion, resulting in improved tumor inhibition in larger cylindrical structures through the enhanced permeability and retention effect (EPR) (Moyer et al., 2014). Moreover, peptide carriers had been used to load and release various cargos, including hydrophilic and hydrophobic drugs, leading to the inhibition of tumor cells (Das et al., 2020; Li et al., 2017). According to Guo et al., multiple drugs jointly promoted the accumulation at the targeting sites via co-delivery systems, resulting in an effective anti-tumor effect (Guo et al., 2021). Besides, antitumor activity could also be generated or enhanced through other methods such as two-photon activated photodynamic therapy, peptide modification targeting. 6.3 Antibacterial activity.

Antibacterial activity is also an important characteristic of peptide

complexes. The combination of polymyxin B and peptides relied on electrostatic interactions (Xu et al., 2020). More importantly, the hydrogels formed after their binding had good control-release performance and remarkable antibacterial activity. Some positively charged peptides disrupted the cell membrane of bacteria. After combining this peptide with traditional antibiotics, the complexes could synergistically inhibit bacteria growth (de Almeida et al., 2019). A unique self-assembled peptide could change its shape in the presence of H_2S after loading drugs, resulting in the inhibition of highly drug-resistant bacteria (Singh et al., 2020a). DOX could enter the hydrophobic core of self-assembled amphiphilic peptides and bound to peptides via non-covalent forces, which resulted in the inhibitory effect of bacteria (Gong et al., 2019a).

6.2. Other activities

Self-assembling peptides could load and sequentially release multiple drugs, leading to various effects such as alleviating inflammation and inhibiting the growth of diseased cells (Liu et al., 2020). Antibodies and cell growth factor were successfully delivered to the inflammatory area using self-assembling peptides. As a result, drugs loaded peptides could relieve kidney inflammation and down-regulate various inflammation-related molecules in mice. The hypoglycemic effect is another important application of peptide-based delivery system. The modified cell penetrating peptide was used as a carrier insulin delivery, and the carrier was more closely bound with insulin through hydrophobic interaction in complexes, resulting in more stable insulin (Zhu et al., 2014). Gene therapy was a promising treatment strategy for severe cell damage or congenital diseases. However, there is a need to improve the efficiency of gene localization and transportation. Chen et al. developed a polypeptide delivery system that effectively delivered the IL-22 gene to the targeted lesion, demonstrating strong anti-hepatitis activity (Chen et al., 2018). Diseases of the nervous system can be challenging to treat due to the blood-brain barrier, which is the barrier between brain cells and blood plasma produced by the capillary walls and glial cells, as well as the barrier between the blood plasma and cerebrospinal fluid formed by the choroid plexus, and can prevent certain substances (mostly harmful ones) from entering the brain tissue. Cell penetrating peptides were very promising as carriers to deliver drugs in the nervous system (Vlieghe and Khrestchatisky, 2010; Zou et al., 2013). Therefore, the combination of RGD modified exosomes and curcumin could alleviate the inflammation and apoptosis in the lesion, suggesting that these complexes might be beneficial for treating nervous system diseases (Tian et al., 2018). Besides, curcumin loaded α-lactalbumin peptide had shown promising therapeutic effects on DSS-induced ulcerative colitis in mice by inhibiting the inflammation in the affected area (Bao et al., 2020).

7. Mechanism of enhancing the efficacy of peptide-based delivery system

The activity of a peptide-based delivery system is mostly consistent with the active ingredients it carries. For example, paclitaxel has antitumor activity, and complexes still shows the ability to inhibit tumor growth after paclitaxel is embedded with peptides. However, what we want to explain here is the mechanism behind why a peptide-based delivery system produces stronger efficacy. According the past literatures and aforementioned summary, the activity of raw materials (including active ingredients and peptides), the improved absorption, more stable and complete active ingredients had synergistically improved the biological activity. Figs. 4 and 5 show partial mechanisms of enhanced antioxidant activity and anti-tumor activity, respectively.

7.1. Natural activities of both active ingredients and peptides

Firstly, active ingredients themselves play a crucial role in activities, but some peptides also have similar efficacy, which may lead to the synergy between the drug and the carrier and enhanced activity. Curcumin displayed the ability to scavenge free radicals, and soy peptide based nanoparticle exerted good antioxidant ability as well due to the exposure of antioxidant amino acid residues (cysteine and tryptophan, etc.) during ultrasonic treatment. They synergistically improved the activity levels of glutathione peroxidase (GSH-PX), superoxide dismutase (SOD) and catalase (CAT), reduced lipid peroxidation products,

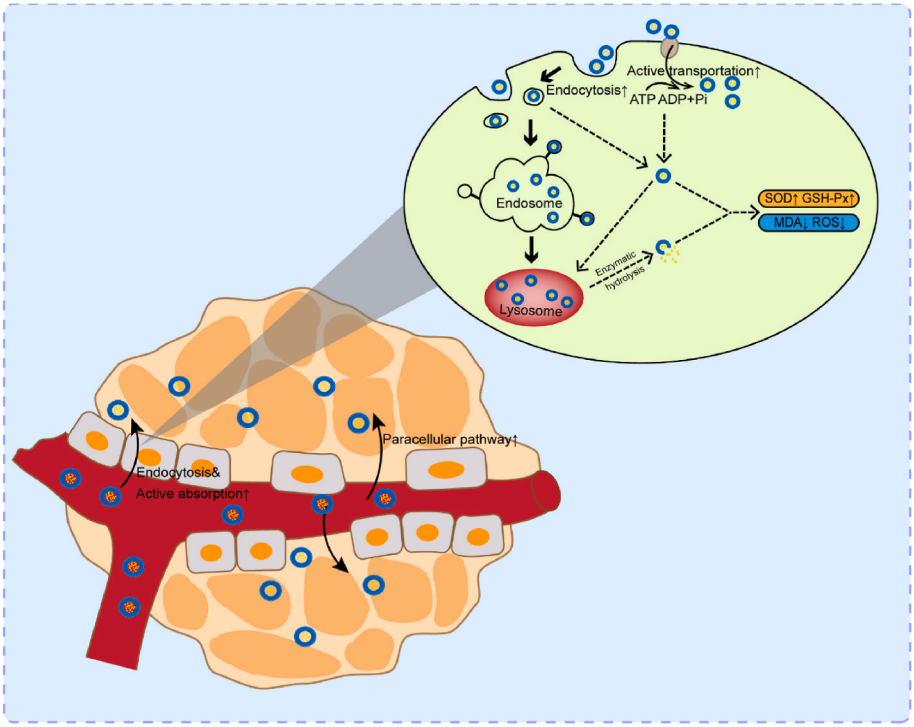

Fig. 4. Mechanism of enhancing the antioxidant activity of peptide-based delivery system.

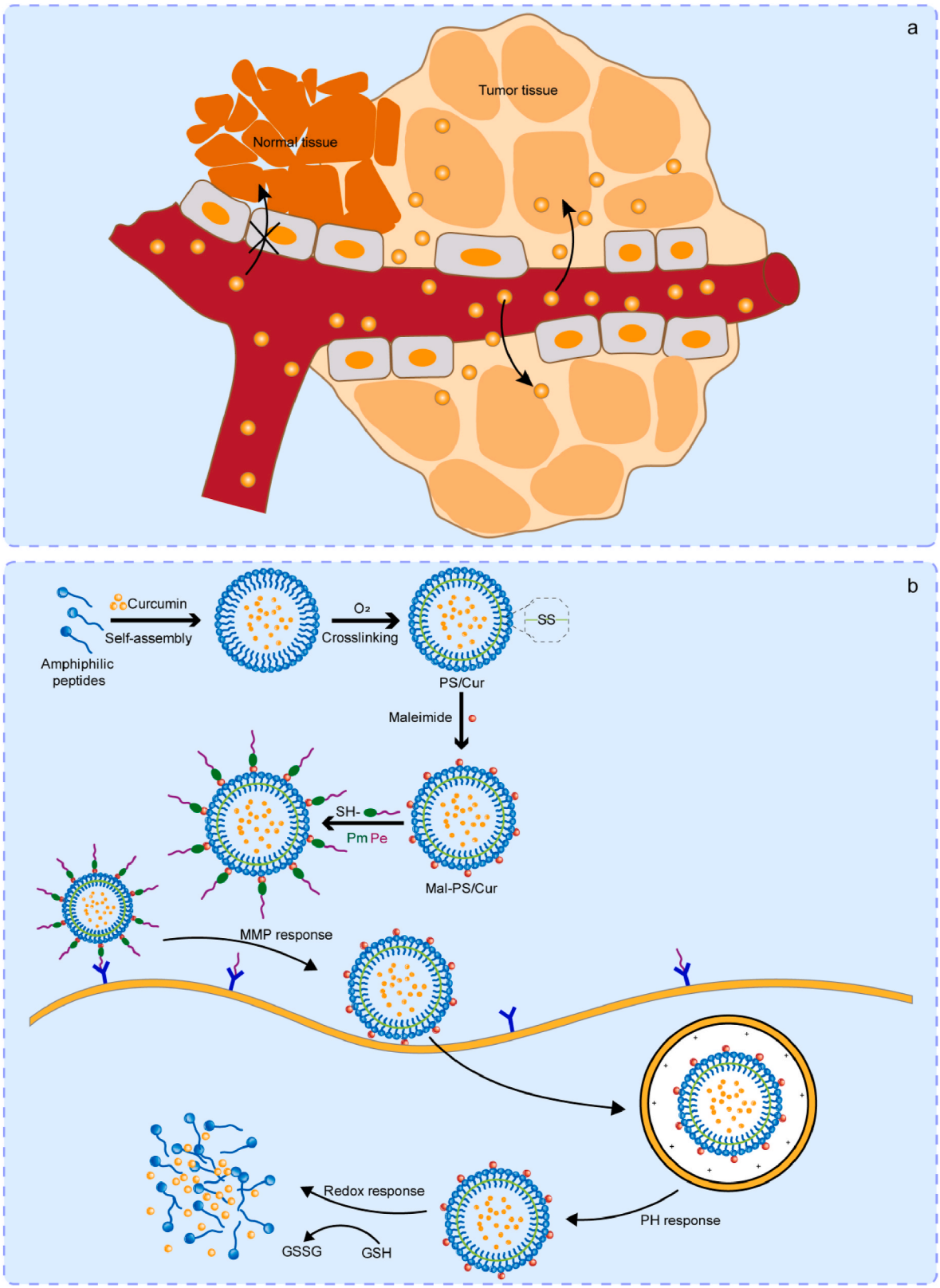

Fig. 5. Mechanisms of enhancing the antitumor activity of peptide-based delivery system. Note: a. EPR mechanism of enhancing the antitumor activity; b. Programmed stimulation mechanism of enhancing the antitumor activity.

inhibited cell aggregation, membrane foaming and contraction, and ultimately reduced apoptosis to play an antioxidant effect (Fig. 4) (Zhang et al., 2018). Also, compared to single active ingredient loaded peptide, the cellular antioxidant activity of two types of cargos was better on account of synergistic antioxidant effects (Jiang et al., 2018). The loaded substance is responsible for the anti-tumor activity of the peptide-based delivery system. Occasionally, peptides might demonstrate functional properties such as antibacterial activity, in addition to

their primary function as carriers. The outer surface of Gram-positive bacteria and Gram-negative bacteria contained negatively charged lipopolysaccharide, which made the cationic antimicrobial peptide have initial electrostatic attraction. After the initial electrostatic and hydrophobic interactions, antimicrobial peptides aggregated on the surface and self-assembled on the bacterial membrane after reaching a certain concentration, resulting in the formation of pores on the cell membrane and, finally the disintegration of the cell membrane. When antimicrobial peptides were combined with antibiotics, the perforation characteristics of antimicrobial peptides might promote antibiotics to enter bacterial cells and act on intracellular targets to produce drug synergistic activity.

7.2. Improved absorption

Another possible reason for the increased activity could be better cell absorption. It is widely recognized that cells can more easily absorb nanocomposites with small diameters. The diameter of peptide-based delivery systems mentioned above were in nano-scale and evenly dispersed. Peptides entered cells through more efficient pathway, while small cargos were absorbed by passive diffusion (Jiang et al., 2018), thus resulting in stronger antioxidant activity. For instance, peptide-based delivery systems entered cells through active absorption that requires energy consumption. Additionally, they also entered cells in the form of endosomes via endocytosis, and subsequently enzymatically hydrolyzed by lysosomes. Furthermore, paracellular pathway was a nonnegligible and rapid pathway. The peptide-based delivery systems mentioned above could release active ingredients due to pH changes or enzymatic hydrolysis (Fig. 4). The EPR effect accelerated drug absorption, leading to the accumulation of the drug in tumor tissue (Fig. 5a). The anti-inflammatory mechanism might be related to the growth of blood vessels in the inflammatory tissue, leading to the occurrence of the EPR effect. In inflammation or other lesions, the permeability of tissue vascular wall was enhanced, which selectively allowed macromolecular delivery systems to stay near tumor tissue and achieve targeted distribution. Besides, caveolae-dependent endocytosis mechanism enhanced cytotoxicity and cell uptake (Fig. 6). The caveolae-dependent endocytosis involved the formation of 60–80 nm invaginations in the cell membrane and the uptake of extracellular fluid components. Peptide-based nanocarriers bound to receptors and formed caveolar vesicles. Multiple caveolar vesicles merged to create caveosomes, which then fused bidirectionally with early endosomes. Then early endosomes developed into late endosomes, which merged with lysosomes and underwent hydrolysis by enzymes. Peptide-based delivery systems bound to the receptor protein on the surface of cell membrane through specific amino acid sequence on the peptide. This binding triggered a series of signal transduction, induced the formation and separation of cell membrane invagination and endocytic vesicles, so this system could successfully enter tumor cells. Electrostatic interactions between peptides and cell membranes facilitated uptake. For example, the presence of Arginine on the NP1 peptide resulted in a positive charge for the peptide, whereas the cell membrane was negatively charged. Therefore, NP1 could transport loaded ellipticine more directly through electrostatic interactions with the cell membrane, which had higher transport efficiency and better inhibitory effect on cancer cells than the endocytosis of common compounds (Zhang et al., 2019). Additionally, the active ingredients could be encapsulated by specially designed peptides. These peptides on the surface could bind to the receptors on the cell membrane at some lesion tissues, promoting targeted localization and enhancing the efficiency of the active ingredients. The programmed stimulation mechanism is based on targeted localization principle. After accumulating the peptosome in the lesion, the intermediate peptide connecting drug peptide and amphiphilic peptide was hydrolyzed by enzymes. As a result, drug peptide occupied ErbB-2 receptor on the surface of tumor cells. In addition, the positive charge of the remaining parts promoted their internalization, and then the pH response caused the remaining parts to escape from the lysosome. Finally, the peptosome was decomposed and the curcumin was released after redox reaction in the cytoplasm (Fig. 5b) (Li et al., 2017). The anti-hepatitis activity was achieved through targeted gene expression therapy, which activated liver repair pathways, eliminated reactive oxygen species, and promoted hepatocyte growth. Moreover, the targeted effect of RGD allowed the drugs to act more completely and efficiently on the problem nerve, so it was beneficial for treating nervous system diseases.

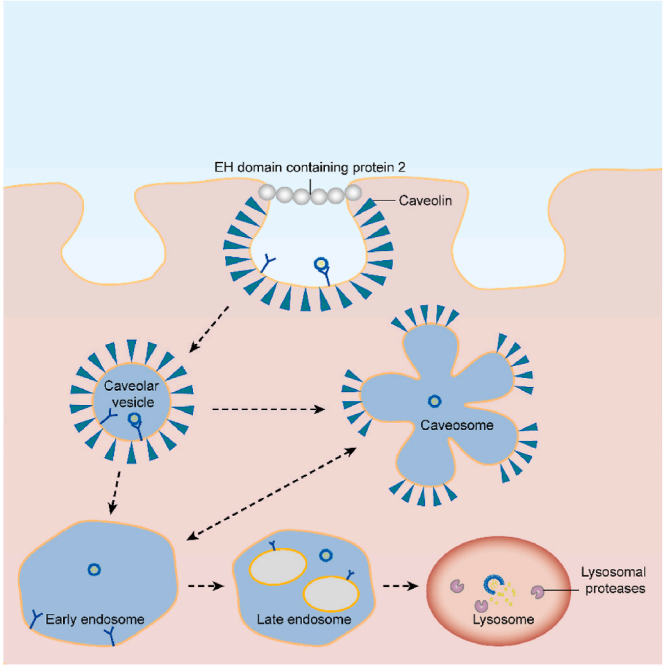

Fig. 6. Caveolae-dependent endocytosis mechanism.

7.3. More stable and complete active ingredients

Some active ingredients, like anthocyanin, can bind to peptides through non-covalent interactions such as hydrogen bonding and hydrophobicity, which causes that peptides exhibit more regular β-sheet structure. This phenomenon improved the encapsulation of the active substance by peptides, resulting in increased stability and prolonged antioxidant activity (Li et al., 2021a,b). Besides, the enhanced hypoglycemic effect was attributed to the stabilization of insulin, which reduced hydrolysis and enzymatic hydrolysis sites. This stabilization increased the hydrophobic effect, allowing insulin to maintain its biological activity in the human body and thus improve its hypoglycemic effect (Zhu et al., 2014). Other drugs were easily blocked by the blood-brain barrier, but cell penetrating peptides could pass through it and enter the nerve area, which caused active molecules loaded penetrating peptides could better treat nervous system diseases. However, many activity mechanisms have not been thoroughly studied and require further research.

8. Targeted transport

Peptides could specifically bind to receptors on the surface of tissues and cells in the human body through various amino acid sequences and advanced structures. At present, targeted transport is widely used in cancer treatment. However, traditional targeted chemotherapy not only affects cancer cells, but also impacts normal cells that are actively dividing and proliferating, such as bone marrow, hair, gastrointestinal mucosa, and germ cells. In order to reduce non-selective side effects, specific peptide sequences can be used in chemotherapy. Besides, peptides can be modified to increase receptors and combined with active molecules or drugs, which has more specific targeted transport ability.

The most direct method for cancer cells to gain specificity is to utilize tumor homing CPP. RGD was a special sequence that could specifically bind to various integrins (Pasqualini et al., 1995). Previous studies have shown that DOX loaded and RGD peptide modified nanomedicines had a low toxicity and increased therapeutic effect on breast cancer (Sun et al., 2017b). Moreover, some researches had attempted to combine more molecules on CPP modified nanomaterials for enhanced specificity. A targeted drug loaded transport complex was fabricated according to combination of CPP and certain copolymer with tumor targeted characteristic through EPR effect (Xiang et al., 2018). Thus, DOX loaded complexes exhibited higher specificity and anti-cancer activity.

Another strategy to improve specificity is the use of activatable cell penetrating peptide (ACPP), which differs from CPPs by having certain peptides that cover the cell penetrating function of CPPs. The peptides were digested by proteases upon entering the lesion location, activating the cell penetration effect of CPPs (Jafari et al., 2015). ACPP had been proved to exhibit significant tumor inhibition effect (Cheng et al., 2015). The cell penetration of CPP were inhibited using some shielding groups at approximately neutral environment, while the function of CPP to guide drugs into cells were activated due to positive and negative charge change from the hydrolysis of shielding groups.

Intracellular specific passive targeting could also be achieved by the specific mechanisms of tumor cells. A cyclic CPP combined DOX through disulfide bond to build an intelligent cargo transport system. It was found that glutathione exhibited higher activity in tumor tissues. Therefore, disulfide bond could improve the antitumor activity of complexes because of being cleaved by glutathione. The data showed that the cytotoxicity of complexes on cancer cells increased (Darwish et al., 2019).

Finally, peptides could be modified to enhance specificity. The peptides were modified with RGD, resulting in conjugates that bound more tightly to integrin. This increased the targeting effect of the active molecule (Sadatmousavi et al., 2011). In addition, DOX loaded cyclic RGD had good anticancer effect and inhibited cancer cell metastasis (Murphy et al., 2008). LyP-1 was a localization peptide that could be modified on the surface of a drug delivery system, and it could recognize lymphatic metastasis and possessed cytotoxicity. Besides, Lyp-1 modified nanocomposites obtained better targeting property to cancer cells and higher cellular absorption (Luo et al., 2010).

9. Conclusion and perspective

Peptide-based delivery systems have been greatly developed and have broad application prospects. Although some complexes had high yields and were easily operated, the scarce product types limited their applications. The preparation of active ingredients loaded peptide microcapsules through drying technology is expected to be a future research focus. Simultaneously, the structural characterization of peptide-based delivery system had also been widely studied. The particle sizes of the complexes were mostly in the nano scale with various shapes, and the binding between peptides and active ingredients depended on hydrophobic force. However, the relationship between properties like encapsulation efficiency and structures (amino acid composition, primary and secondary structures) of delivery systems were unclear and needed to be further explored. In addition, peptide-based delivery system could enhance the absorption of active ingredients and improve bioavailability. There were few reports about important metabolic process of peptide-based delivery systems *in vivo*, thus it is a considerable challenge to clarify their metabolites after absorption in gastrointestinal tract or skin. Furthermore, peptide-based delivery system could produce or enhance a variety of biological activities as a potential drug carrier. In the meanwhile, the activity of raw materials (including active ingredients and peptides), the improved absorption, more stable and complete active ingredients have synergistically improved the biological activity. Further mechanisms of these activities had not been reported in detail, which is an urgent problem to be solved. Ultimately, peptide-based delivery system had good targeting property, which could deliver active ingredients by tumor homing penetrating peptides, activating cell penetrating peptides, tumor cell specific cellular mechanisms, modified protein peptides. It seemed to be an effective strategy for minimizing the side effects of some drugs, but the danger of miss-targeting effect and the influence of drug resistance mechanism were still controversial. Therefore, more researches are expected to provide further evidence to support the targeting stability of peptide complexes.

Author contributions

Qian Li conceived, edited, and corrected the portions of the manuscript. Qunyu Gao corrected the portions, review and editing the manuscript. Congyi Nie wrote the original draft, Yuxiao Zou and Sentai Liao review and editing the review.

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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