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REVIEW ARTICLE

How do various encapsulation techniques improve the oral delivery of food protein hydrolysates?

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Abstract

The development of bioformulations based on food protein hydrolysates (FPHs) has gained significant traction in the food and pharmaceutical sectors due to their biophysical and biochemical properties, including health-promoting effects, biocompatibility, and biodegradability. However, the oral delivery of FPHs presents notable technical challenges, largely due to their inherent limitations such as (bio)stability, permeability, bioavailability, and molecular size. This review provides a comprehensive overview of FPHs, including their structural characteristics, origins, methods of preparation, and associated health benefits. Additionally, it highlights the challenges related to their oral delivery. Recent advancements in the formulation and delivery of FPHs through biopolymeric controlled release systems—such as micro- and nanoparticles, hydrogels, biofunctional films and composites, and electrospun fibers—are discussed. We also explore lipid-based delivery platforms, including liposomes, chitosomes, emulsions, Pickering emulsions, nanostructured lipid carriers, solid lipid nanoparticles, and surfactant-based carriers. Furthermore, this article emphasizes the importance of controlled delivery and targeted release of FPHs following oral administration. The challenges in designing effective lipid/biopolymer-based carriers for FPHs, along with future prospects and opportunities in this growing field, are also thoroughly examined.

KEYWORDS
controlled release, encapsulation, food protein hydrolysates, improved oral bioavailability, peptides

1 | INTRODUCTION

The field of encapsulation has long aimed to optimize the stability, bioavailability, and efficacy of food bioactives and drugs (Liu, Chai, et al., 2022; Nadendla et al., 2018). In this context, biological molecules, such as food protein hydrolysates (FPHs), have occupied a prominent place due to their biological activities—such as antimicrobial, antioxidant, antihypertensive, anti-inflammatory, osteoprotective, immunomodulatory, and opioid-like effects—as well as their role in providing essential amino acids (AAs) and energy (Ndayishimiye et al., 2020; Zhu et al., 2021). Although FPHs are found in proteins in an inactive form, they can be released through enzymatic hydrolysis, fermentation, or food processing (Kurz & Seifert, 2021).

Despite their numerous beneficial properties, why do many FPHs have limited applicability in food and pharmaceutical contexts? The answer lies primarily in their large size, complex molecular structure, poor permeability, and low bioavailability (Luo et al., 2022). Additionally, delivering these bioactives via oral administration is challenging due to their bitter taste and susceptibility to acid and enzymatic degradation in the gastrointestinal (GI) tract, as well as harsh food processing conditions, all of which diminish their activity (Falsafi et al., 2022; Rostamabadi, Falsafi et al., 2020; Zhang, Su, et al.,2021 ; Zhang, Zuo, et al., 2021).

As a result, the scientific community has dedicated significant effort to designing efficient delivery vehicles aimed at overcoming the barriers that limit the pharmaceutical and food applications of FPHs. Encapsulation strategies using advanced lipid- and biopolymer-based carriers have proven to be an effective formulation approach, enhancing the in vitro and in vivo performance of FPHs while protecting them from chemical and enzymatic degradation following oral administration (Liu et al., 2022). Moreover, by employing such potent delivery vehicles, this can be achieved without altering the chemical structure of FPHs, thus preserving their biological potency. Additionally, these carriers can mask the unpleasant taste of peptides while improving their oral permeability, bioavailability, and ability to cross biological barriers (McClements, 2018).

In this review, we will first focus on FPHs and the challenges associated with their oral delivery. The second major section will explore encapsulation approaches using various lipid- and biopolymer-based delivery vehicles with potential for the oral delivery of FPHs. The final section will address the prospects and challenges in this field. Altogether, this review aims to provide readers with a fresh perspective on the encapsulation and oral delivery of FPHs.

2 | FOOD PROTEIN HYDROLYSATES

FPHs are specific fragments of proteins (parent proteins) that positively impact body functions and may influence health. They are composed of AAs linked by amide or peptide bonds (Ling et al., 2020). The majority of known FPHs are embedded within the structure of parent proteins found in various raw materials and food products. To date, over 3000 different FPHs and bioactive peptides have been cataloged in the BIOPEP-UMW database (Iwaniak et al., 2014). Research has identified numerous types of FPHs, including antithrombotic, antihypertensive, antioxidant, immunomodulatory, and antimicrobial peptides. These FPHs are primarily released from the parent proteins through enzymatic processes, although some can also be found in their free form in natural sources. For food and biomedical applications, FPHs can be produced using traditional methods such as microbial, chemical, or enzymatic synthesis, as well as innovative techniques like pulsed electric field or microwave-assisted extraction (Zhang et al., 2021).

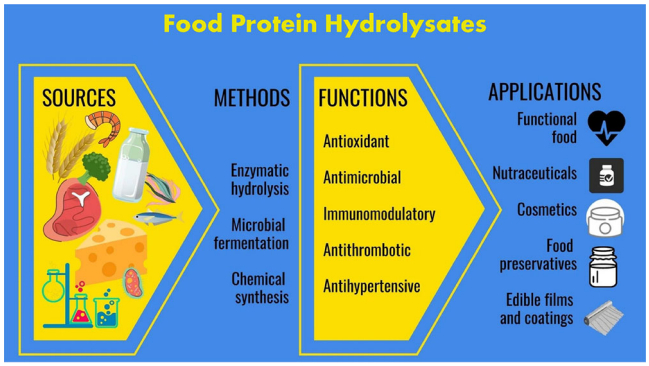

FIGURE 1 An overview on the sources, production methods, functions, and applications of food protein hydrolysates.

The low toxicity, thermostability, and high specificity of FPHs, combined with the growing demand for safe antimicrobial, antioxidant, and bioactive compounds for food fortification, make these molecules highly appealing to the food industry. It is also important to note that FPHs not only provide health benefits to consumers but can also have positive effects on food products themselves. They can be incorporated directly into food, sprayed onto surfaces as bacteriostatic or antioxidant agents, or used as bioactive components in edible films and coatings (Cunha et al., 2014). Figure 1 provides an overview of the sources, production methods, functions, and applications of FPHs.

2.1 | Health-promoting activities

FPHs are regarded as a new generation of biologically active regulators, exhibiting a broad range of physiological effects on the cardiovascular, immune, nervous, digestive, endocrine, and GI systems. As a result, they hold promise for improving the treatment of various diseases and disorders. Many FPHs are multifunctional, with multiple modes of action, enabling them to exert more than one physiological effect (Mehra et al., 2021). Recent studies have highlighted the correlation between the health benefits of peptides and their AA composition and sequences (Iwaniak et al., 2014). For instance, cyclic peptides with low molecular weights (e.g., 3–5 kDa) have been shown to possess anticancer and antiproliferative properties. Hydrophobic and cationic peptides with molecular masses below 25 kDa often display antimicrobial activity. Additionally, the presence of hydrophobic

and certain aromatic AAs can contribute to the antioxidant capacity of FPHs (Korhonen & Pihlanto, 2006).

The type of protein source and substrate used plays a crucial role in producing FPHs with specific functions. For instance, among milk protein hydrolysates, the most extensively studied property is their angiotensin-converting enzyme inhibitory activity. Their antioxidant properties have also been investigated, with research linking these effects to the chelation of transition metal ions, free radical scavenging, and inhibition of lipid peroxidation. According to Cunha et al. (2014), the predominant bioactivities observed in marine FPHs are antihypertensive and antioxidant effects. In contrast, a limited number of anticancer and antimicrobial peptides have been isolated from algae. Antimicrobial and anti-inflammatory peptides are more frequently derived from mollusks than from other sources. Additionally, various microbial species, including lactic acid bacteria, produce bacteriocins—low molecular weight, heat-stable peptides with antimicrobial properties against foodborne pathogens and certain fungi.

2.2 | Structure–function relationship

FPHs are low molecular weight protein fragments (<6000 Da), typically composed of 3–20 AA residues, which exhibit a wide range of beneficial physiological properties in vivo. Structurally, they possess specific N- and C-terminal AA residues, and these structural properties can significantly influence their biological functions. For instance, the antioxidant potential of FPHs is closely related to their AA composition, and enzymatic hydrolysis of the parent proteins disrupts their tertiary structure, thereby increasing the solvent accessibility of oxidatively sensitive AA residues. Additionally, as demonstrated by Mor (2000), antimicrobial FPHs possess an amphipathic structure, which facilitates their attachment to microbial cytoplasmic membranes and the subsequent formation of pores.

2.2.1 | Antioxidant properties

Numerous studies have highlighted the radical scavenging activity of FPHs through mechanisms such as single electron transfer, hydrogen atom transfer (HAT), ferric reducing capacity, and inhibition of linoleic acid oxidation. Particle size is a key factor influencing the antioxidant activity of FPHs. Fractions of FPHs smaller than 3 kDa, typically composed of fewer than ten AA residues, have been shown to possess superior antioxidant function. Indeed, smaller FPHs exhibit greater accessibility to oxidant molecules (Zhang et al., 2021). In addition to particle size, the antioxidant properties of FPHs are determined by their peptide sequences and individual AA residues. AAs, such as Tyr, Met, Lys, Cys, and His, are commonly found in antioxidant FPHs (Hu et al., 2020).

Although the overall sequence of AAs in the peptide chain is important, it is believed that the N- and C-terminal residues play a more dominant role in determining antioxidant activity. Hydrophobic peptides, for instance, can more easily dissolve in lipids and interact more effectively with hydrophobic radicals and lipids compared to hydrophilic FPHs. The pyrrolidine ring of proline also contributes to quenching singlet oxygen due to its low ionization capacity and its ability to increase the flexibility of FPHs through interaction with the peptide's secondary structure. Furthermore, aromatic AAs, like Phe, Tyr, and Trp, enhance the radical scavenging activity of FPHs by donating electrons to radicals and promoting metal ion chelation. Histidine, with its imidazole group, and cysteine, with its thiol group, act as scavengers of hydroxyl radicals, further improving the antioxidant properties of FPHs. Additionally, the indole group in tryptophan (Trp) is crucial for scavenging hydroxyl radicals, enhancing the antioxidant capacity of FPHs (Mignone et al., 2015; Zhu et al., 2021). For example, a functionalized rice husk biochar was produced for enriching antioxidant FPHs. Various antioxidant peptides (AOPs) (including LKFL, QLLF, WLAYG, and HFCGG) were identified (Tao et al., 2025). It was revealed that HFCGG possessed comparable antioxidant capacity to glutathione. Sun et al. (2024) identified and investigated molecular mechanism five of novel AOPs from fish sauce using a combined quantum chemistry and molecular simulation. ALA510 and GLY509 were main binding sites of Keap1-peptides. Hydrogen linkages and van der Waals force were the key binding forces for Keap1-peptides.

2.2.2 | Bactericide properties

The bactericidal function of FPHs is influenced by various factors such as charge, size, sequence, hydrophobicity, and degree of helicity. Based on their secondary structures, bactericidal FPHs can be categorized into four main groups: α-helix, β-sheet, loop, and extended peptides, with α-helical and β-sheet structures being the most common. β-Sheet FPHs typically have cyclic architectures stabilized by disulfide bonds and often contain cysteine residues (Yokoyama et al., 2016; Zhang et al., 2014, 2015). In β-pleated sheets, two or more segments of a peptide chain align side by side, forming a sheet-like structure held together by hydrogen bonds. These bonds form between the carbonyl (C = O) and amino hydrogen (N–H) groups of the peptide backbone, whereas the R groups extend above and below the plane of the sheet. The strands of a β-pleated sheet may be parallel or antiparallel.

In contrast, α-helical FPHs are free of cysteine, are typically shorter than 40 AAs, and contain around 50% hydrophobic residues. In aqueous environments, these peptides exist in a linear configuration but transition into an amphipathic helical structure upon contact with bacterial membranes. In an α-helix, the carbonyl group of one AA forms a hydrogen bond with the amino group of another AA four residues down the chain. This bonding pattern pulls the peptide chain into a helical structure, with each turn of the helix comprising 3.6 AAs. The R groups extend outward from the helix, allowing interaction with their environment. Hydrogen bonds are critical to maintaining the integrity of both α-helices and β-sheets and are thus essential for stabilizing secondary structures.

Certain AAs are more or less likely to be found in either α-helices or β-pleated sheets. For example, proline is known as a "helix breaker" due to its unique R group, which forms a ring structure that disrupts

the helical formation, often leading to bends or unstructured regions between secondary structures. On the other hand, AAs like Trp, tyrosine (Tyr), and phenylalanine (Phe), which have large ring structures in their R groups, are commonly found in β-pleated sheets, which provide ample space for these bulky side chains.

Many bactericidal FPHs are positively charged, enabling them to target the anionic cell walls and plasma membranes of bacteria. Conversely, most anionic FPHs are involved in the antibacterial mechanisms of yeast. Divalent metal cations (e.g., Mn^{2+}, Fe^{2+}, or Mg^{2+}) can enhance the bactericidal activity of anionic FPHs by promoting their binding to negatively charged components of the cell membrane. The majority of antibacterial FPHs contain around 50% hydrophobic residues, and their degree of hydrophobicity significantly impacts their ability to penetrate the lipid bilayer of the cell membrane (Zhao et al., 2022; Zhong et al., 2019).

Bhatnagar et al. (2024) assessed antibacterial activity (against *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa*), hemotoxicity, and efficacy of peptides via an explainable machine learning framework. The authors demonstrated that physicochemical attributes as well as the occurrence of certain AAs had the most important effect in determining antibacterial performance, efficacy, and hemolytic properties of the resulting peptides.

2.2.3 | Angiotensin-converting enzyme inhibitory (ACE-I) function

Angiotensin-converting enzyme (ACE) exists in two forms: somatic ACE and testicular ACE. Somatic ACE, which serves as the principal model, is a single polypeptide chain that contains a C-terminal cytosolic domain, a heavily glycosylated extracellular domain, and a hydrophobic transmembrane domain. The extracellular domain consists of two homologous regions, the C and N domains, which have 600 and 612 residues, respectively. Both domains contain an active catalytic site at their center, characterized by a zinc-binding motif (HEXXH, where X is any AA residue). In the body, the C-terminal domain serves as the primary active site for the cleavage of angiotensin I. The hydrophobic sequence in the C domain allows the enzyme to anchor to the cell membrane (Mirzaei et al., 2021; Xue et al., 2021).

The presence of aromatic residues such as Trp, Phe, and Tyr, along with branched aliphatic hydrophobic residues like glycine (Gly), valine (Val), leucine (Leu), and isoleucine (Ile) in ACE-inhibitory FPHs, particularly at the C domain, strongly influences peptide–enzyme interactions. Additionally, amino groups from lysine (Lys), histidine (His), or arginine (Arg) contribute to the ACE-I function by forming chelate complexes with Zn^{2+} cations (Pihlanto-Leppälä, 2000).

2.3 | Various origins

FPHs have been derived from a wide variety of food sources, including animal products (e.g., milk, eggs, cheese, beef, pork, bovine blood, gelatin, and chicken), plant-based materials (e.g., rice, maize, pumpkin, corn, soy and its derivatives, wheat, barley, broccoli, pulse crops, and amaranth), and marine origins such as fish, microalgae, mollusks, and crustaceans. Among these, milk proteins—specifically casein and whey—are some of the most prominent sources of FPHs (FitzGerald & Meisel, 2000). Thus, dairy products are considered a rich source of FPHs, with peptides being generated through the hydrolysis of milk proteins by the proteolytic enzymes of starter bacteria. Although many peptides are assimilated by bacteria for growth, a significant amount remains and accumulates during fermentation (Worsztynowicz et al., 2020).

Currently, an important trend in FPH production is the use of food and agricultural waste and by-products. For example, the industrial production of fruit, vegetable, olive oil, meat, and cheese generates substantial by-products and waste. Enzymatic hydrolysis and other methods can be applied to protein-rich waste, converting them into valuable FPHs. This has been demonstrated with materials such as olive seeds and pulp (Prados et al., 2020), fruit stones (García et al., 2016), trimmings (Neves et al., 2017), collagen (Liu et al., 2022), blood (Mora et al., 2014), skin (Chotphruethipong et al., 2020), and microalgae waste (Moaveni et al., 2022).

2.4 | Preparation approaches

Recent advancements in the applications of FPHs have driven the development of production methods aimed at enhancing their desired properties and quality. These peptides can be obtained through various processes, including in vitro enzymatic hydrolysis, microbial fermentation, or chemical synthesis, as outlined below.

2.4.1 | In vitro enzymatic hydrolysis

Enzymatic hydrolysis is the primary method for producing FPHs due to its advantages of avoiding residues of chemical solvents or toxic substances in the final peptides. This method is also relatively straightforward to scale up and predict, with generally shorter reaction times compared to microbial fermentation (Mora & Toldrá, 2022). In vitro proteolysis employs commercial enzymes of microbial, plant, or animal origin. Commonly used enzymes at the industrial scale include trypsin, papain, pepsin, bromelain, and alkaline phosphatase. The process involves hydrolyzing parent proteins with food-grade enzymes under controlled pH and temperature conditions to release the desired FPHs.

The in vitro production of FPHs includes several stages: protein selection, enzymatic hydrolysis, separation, and purification. Following these steps, the biological activity, peptide sequences, peptide structure, and functional properties of the peptides are assessed (Coscueta et al., 2019; Iwaniak et al., 2014). Key factors influencing the specific molecular size, AA sequence, and functional properties of FPHs include temperature, pH, reaction time, and enzyme-to-protein ratio. After hydrolysis, the peptides are separated from the reaction mixture through centrifugation, as they are found in the supernatant. Recovery

of these bioactive compounds can be achieved using various methods, including column chromatography, membrane ultrafiltration, freeze-drying, cross-flow membrane filtration, and gel filtration (Abdel-Hamid et al., 2017).

2.4.2 | Microbial fermentation

Microorganisms can hydrolyze protein structures into shorter peptide sequences using their enzymes. To initiate the process, microorganisms are added to an inoculum containing glucose and distilled water during their exponential growth phase. Key parameters influencing the degree of hydrolysis include fermentation time, microbial strain, and the origin of the parent protein. Generally, *Lactobacillus* species are the most commonly used microorganisms for FPH production, as they are classified as generally recognized as safe (Rivero-Pino, 2022).

2.4.3 | Chemical synthesis

The goal of chemical synthesis methods for FPHs is to produce bioactive peptides through a bottom-up approach. This technique involves using various chemical reagents to activate the carboxylic acid (RCOOH) groups in the parent protein molecules, which facilitates the formation of peptide bonds by freeing the acyl group (R–CO–). There are two primary types of chemical synthesis for FPHs: (i) traditional synthesis in solution and (ii) solid-phase peptide synthesis (SPPS).

The traditional synthesis method involves all reagents being present in the solution. Although this approach can be effective, it often requires extended synthesis times and generates significant chemical waste. In contrast, SPPS involves attaching the parent protein to a solid support that is insoluble in the reaction medium (Akbarian et al., 2022). SPPS is widely favored for its simplicity and is applied on an industrial scale. However, it has limitations, such as the potential for peptide folding or aggregation, which can reduce product yield. Recent advancements in SPPS have incorporated the use of fluorenylmethoxycarbonyl as a protective group for AA side chains. This modification allows for better control of the reaction by selectively protecting certain groups from the reaction process.

Although FPHs synthesized chemically are not typically used in food-grade formulations, they are commonly employed in the pharmaceutical and diagnostic fields. Although chemical synthesis often yields high-purity compounds, it is associated with high costs, low product yield, and environmental concerns due to hazardous reagents (Shaji & Patole, 2008; Shazly et al., 2017; Sosalagere et al., 2022).

3 | CHALLENGES TO ORAL DELIVERY OF FPHS

To achieve the desired physiological effects in vivo, FPHs must reach their target tissues—such as the brain, kidneys, intestine, or vascular endothelium—intact. This requires resistance to hydrolysis by digestive, plasma, and liver enzymes, as well as successful transport across intestinal barriers. Several factors influence the oral delivery of FPHs, including their physicochemical properties and interactions with the physiological environment of the GI tract.

One of the primary challenges to the oral bioavailability of FPHs is their large molecular size, which impedes diffusion across the mucous membrane, leading to poor absorption by epithelial cells and consequently, low bioavailability (Tyagi et al., 2021). Additionally, FPHs often have a bitter taste, a high tendency to aggregate, and are susceptible to enzymatic and chemical degradation, further limiting their oral bioavailability (Chan & Stewart, 1996). The key limitations associated with the oral delivery of FPHs are discussed in the following sections.

3.1 | GI instability

The broad pH range within the GI tract—from the highly acidic conditions in the stomach to the neutral and slightly basic environment in the intestinal lumen—presents a significant challenge for the successful oral delivery of FPHs. In very acidic conditions (pH < 4), bioactive FPHs are fully ionized, which may lead to intrinsic electrostatic repulsions and potential conformational changes, resulting in a loss of biological activity. Additionally, the GI transit time, which averages around 3–4 h in the small intestine but varies widely in the large intestine, can affect the stability of FPHs. The varying pH levels can cause oxidation, deamination, and acid- or base-catalyzed hydrolysis of FPHs, leading to a reduction in health-promoting activities before reaching their intended target (Sood & Panchagnula, 2001; Zhu et al., 2021).

Beyond pH-related issues, the oral delivery of certain FPHs—especially linear peptides—faces the challenge of sensitivity to enzymatic degradation. The GI tract contains a diverse array of metabolic and hydrolytic enzymes, including luminal enzymes (such as pepsin, trypsin, and α-chymotrypsin), mucosal enzymes, and cytosolic enzymes (e.g., dipeptidases and aminotripeptidases) within the epithelial cells. Pepsinogen is secreted in the stomach and converted to pepsin, an aspartic peptidase that cleaves links between hydrophobic AAs and facilitates the action of proteases in the small intestine. Various enzymes (e.g., endopeptidase 24.11, dipeptidyl peptidase IV, endopeptidase-2, aminopeptidase A, and aminopeptidase N) are also present in the enterocytes of the brush border region of the apical intestinal membrane. Consequently, the presence of these enzymes makes bioactive peptides, such as FPHs, particularly vulnerable to degradation following oral administration (Santos-Hernández et al., 2018).

3.2 | Mucosal and epithelial barriers in the intestine

Although FPHs may escape pH- and enzyme-induced degradation in the GI tract, the intestinal mucus layer presents another obstacle by limiting the interaction between peptides and enterocytes required for absorption (Faller & Ertl, 2007; Hidalgo et al., 1991; Turner, 2009). The thickness of the mucus membrane varies, being approximately 180 μm

TABLE 1 Transport routes of some food protein hydrolysates across Caco-2 cell monolayers.

FPH	Origin	Bioactive properties	Transport route	Reference
Val–Tyr and Ser–Phe–Leu–Leu–Arg	Soy-fermented douchi	Hhypoglycemic	Tight junctions, PepT1	Yu et al. (2023)
Lys–Tyr–Ile–Pro–Ile–Gln	Yak milk casein	Antihypertensive	Tight junctions	Lin et al. (2020)
Lunasin and Arg–Lys–Gln–Leu–Gln–Gly–Val–Asn	Soy protein	Chemoprevention	Tight junctions	Fernández-Tomé et al. (2018)
Leu–Ser–Trp	Soy protein	Antihypertensive	Tight junctions, PepT1	Lin et al. (2017)
Arg–Leu–Ser–Phe–Asn–Pro	Whey protein	Antihypertensive	Tight junctions	Guo et al. (2018)
Tyr–Phe–Cys–Leu–Thr and Gly–Leu–Leu–Leu–Pro–His	Corn gluten	Antioxidative	Transcytosis and tight junctions	Ding et al. (2018)
Leu–Lys–Pro and Ile–Pro–Pro	Bovine milk β-casein and bonito fish muscle	Antihypertensive	Tight junctions, PepT1	Gleeson et al. (2017)
Leu–Lys–Pro and Ile–Gln–Trp	Egg white ovotransferrin, bonito, or chicken protein	Antihypertensive	Tight junctions, PepT1	Xu et al. (2017)
Val–Leu–Pro–Val–Pro–Gln–Lys	Bovine milk casein	Antioxidative and antihypertensive	Transcytosis	Vij et al. (2016)

in the stomach, 15–450 μm in the small intestine, and 100–2000 μm in the colon, depending on GI activity and diet (Liu et al., 2018; Lundquist & Artursson, 2016). This mucus layer consists of crosslinked mucin fibers, a diverse microbiome, and various components such as antibodies, lipids, carbohydrates, proteins, cellular debris, and salts. This complex environment can trap and impede FPHs from reaching the absorptive epithelial cells (Lundquist & Artursson, 2016).

If FPHs manage to survive the degradative enzymes and acidic conditions in the GI tract and traverse the mucus layer, they must then penetrate the intestinal epithelial membrane, which serves as a major absorption barrier for proteins and peptides before entering the bloodstream. The intestinal epithelium is composed of two main cell types: absorptive and secretory cells (Banan et al., 2005). Enterocytes, the absorptive cells, make up approximately 90% of the small intestinal epithelium and feature microvilli that significantly increase the surface area for absorption to about 300–400 m^2 (Helander & Fändriks, 2014). The remaining secretory cells include Paneth, goblet, tuft, and enteroendocrine (Cheng & Leblond, 1974). Understanding the various transport mechanisms across the GI epithelial barrier is crucial for developing strategies to improve the oral delivery of FPHs (Figure 2).

3.3 | Structural complexity

Not only transcellular transport but also paracellular routes are challenged by the molecular attributes of FPHs. The properties of FPHs that pose problems for these transport pathways are summarized in Table 1. FPHs often exhibit poor permeability due to their large size or high polarity. This hinders their ability to penetrate tight junctions required for passive paracellular transport and affects their partitioning into cellular membranes necessary for passive transcellular transport (Park et al., 2011; Renukuntla et al., 2013; Yun et al., 2013).

In practice, permeation is generally less of an issue for bioactives with molecular weights below 500–700 Da; however, it decreases significantly when the molecular mass exceeds this range. Specifically, when the molecular mass of FPHs exceeds 1000 Da, their permeability through these mechanisms is considerably reduced. Additionally, the bioavailability of FPHs is largely independent of molecular mass if it is below 700 Da. However, once the molecular mass surpasses this threshold, bioavailability tends to decrease (Goldberg & Gomez-Orellana, 2003).

Bioactive agents must exhibit appropriate lipophilicity to adhere to cell layers of enterocytes and be absorbed transcellularly through passive diffusion (Camenisch et al., 1998). However, most FPHs are highly hydrophilic, carrying multiple positive charges, which poses a challenge for their bioavailability. The lipophilic nature of biological membranes restricts the spontaneous entry of macromolecular FPHs into cells. Without a degree of lipophilicity, passive transcellular absorption is unlikely, and the paracellular pathway is not a viable alternative for FPHs (Goldberg & Gomez-Orellana, 2003).

Although active (carrier-mediated) transport can be an alternative absorption route, it is limited because FPHs with more than four AA residues typically cannot be absorbed through this mechanism. Additionally, although transcytosis might facilitate the transport of large protein hydrolysates and peptides across cells, most internalized bioactives are often degraded. Endocytosed molecules are frequently routed to lysosomes, where they are broken down (Heyman et al., 1990; Neutra et al., 1987).

4 | ENCAPSULATION APPROACHES FOR ORAL DELIVERY OF FPHS

Oral delivery of FPH faces multiple physiological and physicochemical bottlenecks. To solve those limitations, an efficient vehicle (Figure 3) for oral delivery of high molecular weight FPHs should be engineered to (i) offer a notable shield from the proteolytic/chemical breakdown in the GI tract, (ii) promote penetration/permeation across the

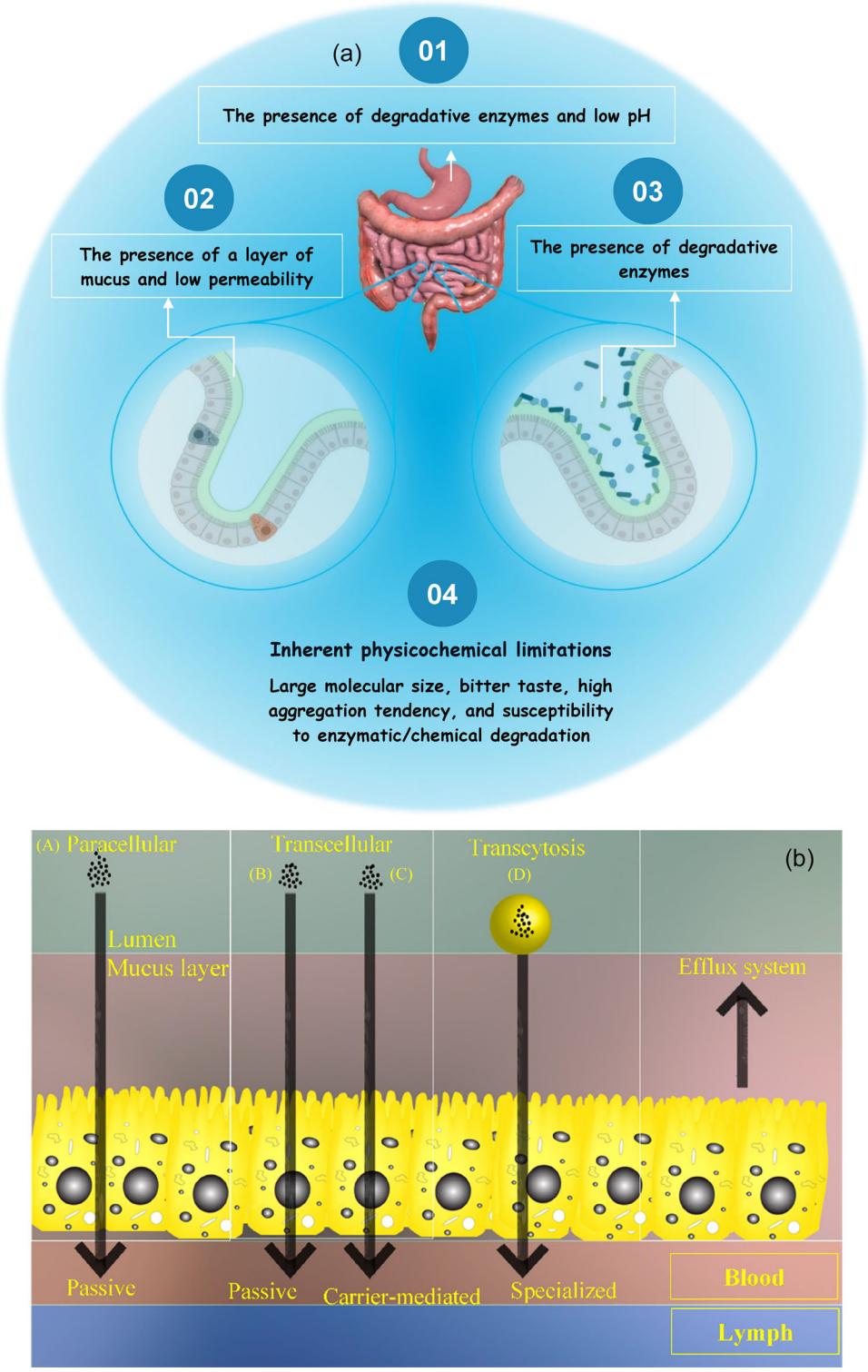

FIGURE 2 **(a)** Schematic illustration of the dilemmas relevant to oral delivery of food protein hydrolysates in gastrointestinal tract. These barriers can selectively limit the permeability of food protein hydrolysates either owing to their chemical attributes or their molecular weight. **(b)** Different mechanisms related to the transport of FPHs across the intestinal epithelium layer. In the paracellular pathway, hydrophilic small-sized food protein hydrolysates pass in between adjacent cells via passive diffusion (A). The transcellular pathway applies by enterocyte cells through passive diffusion (B). Moreover, carrier-mediated transcellular (C) and transcellular transport through transcytosis (D) are other mechanism of transport for food protein hydrolysates.

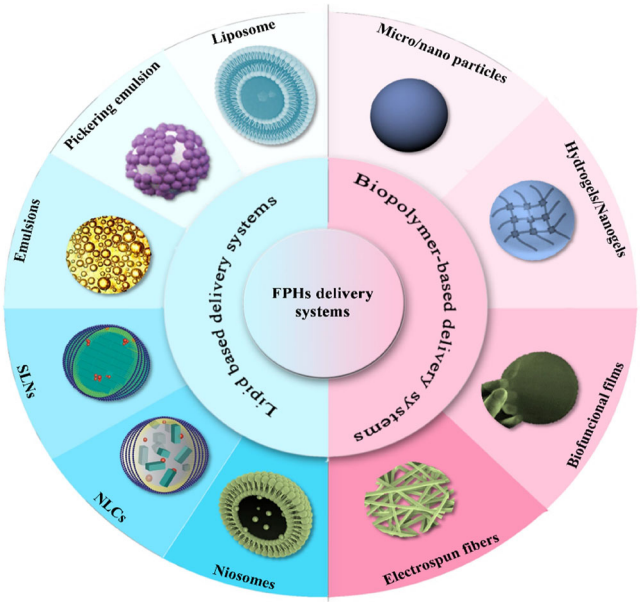

FIGURE 3 Scheme of food protein hydrolysate–loaded biopolymer- and lipid-based delivery systems.

mucosal and epithelial barriers, and (iii) mask bitter taste and improve other peptide characteristics (Wagner et al., 2018). The parameters that affect GI absorption, such as size, size distribution, consistency, hydrophobicity, and surface qualities of colloidal carriers, are still a source of debate. Bioadhesive vehicles can help delivery matrix contact absorptive cells for longer periods. In a second step, particle absorption would be followed by bioadhesion. To ensure stability and bioavailability, biomaterials with adhesive and protective qualities may be desirable for oral delivery of FPHs (Chakrabarti et al., 2018; Mackie et al., 2020; Ozorio et al., 2020). This section discusses the recent studies where encapsulation technologies using biopolymer and lipid-based vehicles have been exploited to enhance permeability and (bio)stability of FPHs.

4.1 | Lipid-based delivery systems

4.1.1 | Liposomes and chitosomes

To endow their beneficial properties following oral administration, FPHs must be absorbed into the blood circulatory system so they can be delivered to the intended locus. Nevertheless, it is more difficult for most of the oligopeptides to be absorbed intact, as they are highly vulnerable to enzymatic hydrolysis upon GI digestion. In this line, liposomal vectors are the most widely utilized vehicles to enhance the (bio)stability and bioavailability of entrapped FPHs due to their nontoxicity, biodegradability/biocompatibility, and peptide-controlled release. Liposomes comprise a phospholipid bilayer (like cell membranes) and render a physical barrier to shield FPHs against stresses. These peptide delivery systems also can improve the inclusion of hydrosoluble, liposoluble, and amphiphilic ingredients, given the amphiphilic character of phospholipids (Falsafi et al., 2022).

Zhang, Su et al. (2019), for example, investigated the transepithelial transport pathway and encapsulation process of milk-derived ACE-inhibitory peptides (Arg–Leu–Ser–Phe–Asn–Pro) using liposomal vehicles. The transepithelial transport mechanism was evaluated via transport inhibitors in human intestinal Caco-2 cell monolayers. The FPHs had no cytotoxicity effect on Caco-2 cells. The cell monolayer had a transepithelial electrical resistance value of 335 Ω cm^2 following 21 days of cell growth, showing its suitability for the transport experiment. Gly–Pro that is a substrate for the transport PepT1 displayed no considerable influence on the transport flux of the peptides as opposed to the control sample, implying that PepT1 is not involved in peptide transport through the Caco-2 cell monolayer (Figure 4c). Additionally, the presence of paracellular transport promoter sodium deoxycholate slightly affected on the bioactive peptide permeability. On the other hand, sodium azide and wortmannin considerably lowered the permeability of FPHs, implying the effect of energy-dependent transcytosis in the transport of hexapeptides through Caco-2 cells (Figure 4a, b, c, and d). The liposomes loaded with FPHs can be absorbed across Caco-2 cells, with an improved intestinal bioavailability and sustained bioactive release compared to the bioactives alone (Figure 4e,f).

Jiang et al. also described the design of a novel liposomal nanocarrier decorated with self-assembled *Lactobacillus acidophilus* S-layer protein to promote the absorption of cholesterol-lowering peptide Leu–Gln–Pro–Glu across the intestinal epithelium (Jiang et al., 2021). FPH-loaded nanoliposomes not only exhibited superior sustained release manner and GI tolerance in vitro but also enhanced the retention time in mice intestine. Furthermore, the transshipment of FPHs promoted dramatically following being entrapped by vehicles and decorated with the S-layer protein.

In another study, a nanopeptide delivery material based on milk polar lipid liposome coated with S-layer proteins was engineered to deliver ACE-inhibitory peptide Arg–Leu–Ser–Phe–Asn–Pro (Zhang et al., 2021). Surface decoration of the ordinary liposome bilayers with the S-layer protein promoted the antioxidant activity and ACE-inhibitory activity of the hydrolysate-loaded liposomes, enhanced their resistance to harsh GI conditions (Figure 5), alongside the promoted absorption and delayed release. This may be due to the good biocompatibility of liposomes with cell membranes, promoting the permeability of oral FPHs in intestinal epithelial cells (Figure 5a–j). Moreover, liposomes could properly adhere to the small intestinal epithelial cells, extending the intestinal absorption time of FPHs and ensuring a sustained/controlled release to prolong the duration of the bioactive peptides. Liposomal delivery systems could not only shield FPHs from being hydrolyzed/depredated by the GI tract, but their repairing influence on the GI environment could also critically lower the side effects of the FPHs in vivo.

Recently, Chen et al.'s (2021) group studied interactions between liposomes and FPHs obtained from soybean protein isolate (SPI) during oxidation and demonstrated the inhibited lipid peroxidation by the hydrolysates in a dose-dependent manner. The prepared FPHs

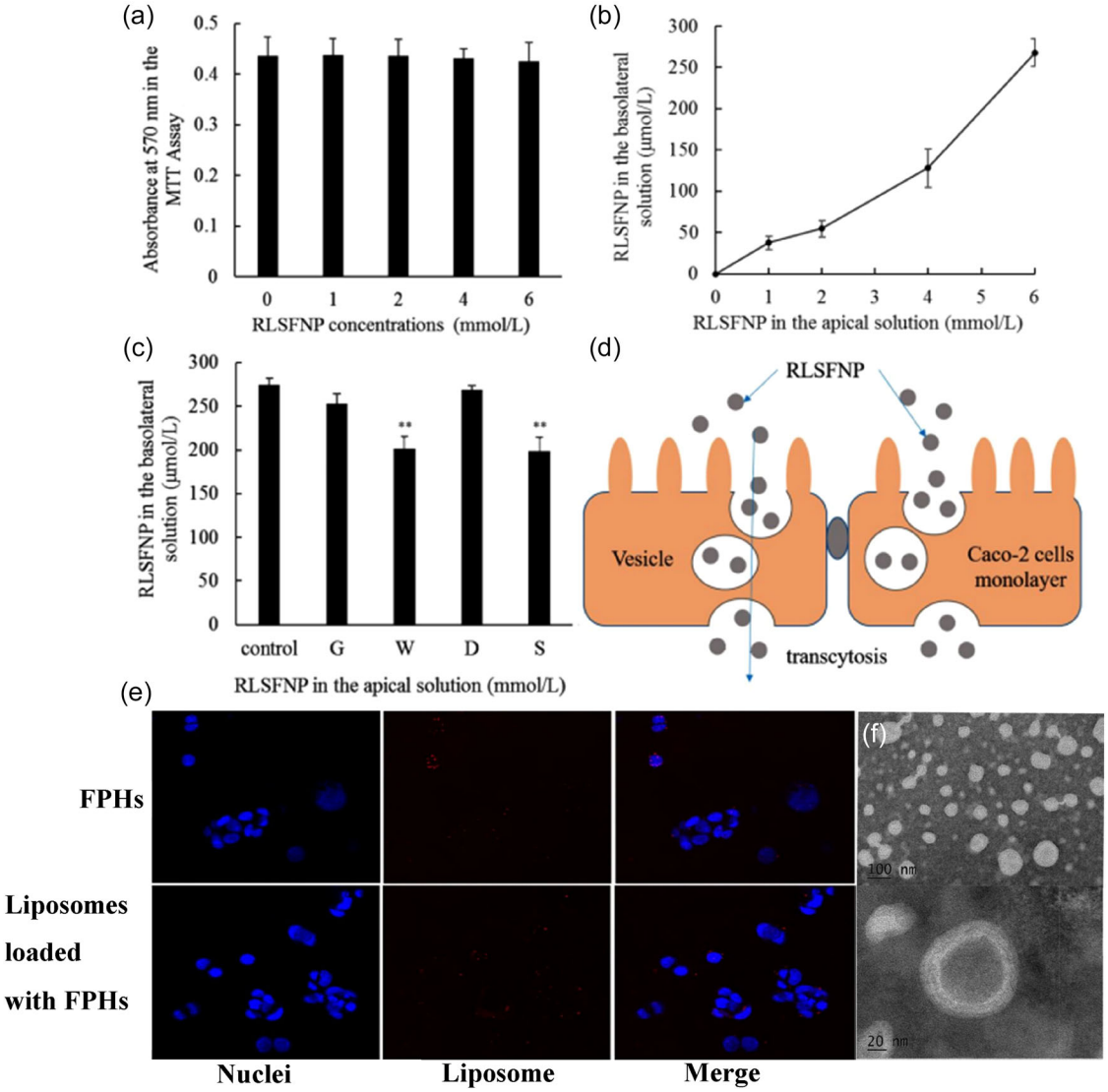

FIGURE 4 (**a**) Cytotoxicity of food protein hydrolysates in Caco-2 cells; (**b**) concentration influence of food protein hydrolysates transport through Caco-2 cell monolayers (measuring hydrolysate concentration in the basolateral side solution following 2 h incubation); (**c**) transport pathway of the food protein hydrolysates; influence of Gly–Pro (**G**), wortmannin (**W**), sodium deoxycholate (**d**), and sodium azide (**S**) on transepithelial transport of food protein hydrolysates; (**e**) confocal laser scanning microscopy (CLSM) images of food protein hydrolysates and liposomes loaded with food protein hydrolysates in Caco-2 cells following 2 h incubation (the Caco-2 cells were labeled blue to attain cell locations. Food protein hydrolysates and food protein hydrolysates entrapped in liposomes show red fluorescence that reveals cellular uptake); (**f**) transmission electron microscopy (TEM) images of the peptide-loaded liposomes at scale bars 100 and 20 nm (Zhang et al., 2019).

interacted with liposomes through electrostatic forces, H_2 bonding, and hydrophobic effects, inducing the increased liposomal rigidity. It was revealed that both antioxidative and hydrophobic AAs (Trp and Tyr) in FPHs played a pivotal role in stabilizing liposomes against oxidation process. The FPH–liposome interaction and lipid peroxidation favored high hydrophobicity, β-structure (β-helices, β-sheet, and β-turn), and disordered configuration. Given the benefits of such systems, SPI-based FPHs as an effective antioxidant and stabilizer can be applied in liposome-containing food systems and different bioactive vehicles. In this line, Table 2 represents recent studies on the oral delivery of FPHs using liposomal delivery systems.

4.1.2 | Emulsion and Pickering emulsion-based delivery systems

For applications in bioactive delivery, emulsion-based vehicles have been proven to offer numerous significant benefits. Colloidal bioactive vehicles based on oil-in-water (O/W), water-in-oil (W/O), water-in-oil-in-water (W/O/W), or oil-in-water-in-oil (O/W/O) double emulsions are well established. The viscoelastic and soft attributes of the emulsions allow them to create superior interaction with tissue cell membranes. Indeed, such viscoelastic structures can considerably deform/squeeze through micropores, conform well to the microscale topography of

TABLE 2 Recent studies on the oral delivery of food protein hydrolysates using various encapsulation approaches.

Liposomal delivery systems					
Sources	**FPHs**	**Delivery system**	**GI model**	**Key outcomes**	**Reference**
Tilapia viscera	Antioxidant peptides	Liposomes formulated by soy lecithin, rapeseed lecithin, and soy-rapeseed lecithin	N/A	I. Lower particle size and polydispersity index (PDI) of soy lecithin liposomes II. Higher antioxidant activity of rapeseed lecithin III. The higher the hydrolysate concentration, the lower the encapsulation efficiency (EE%)	Sepúlveda, Zapata et al. (2021)
Fish protein	Antioxidant peptides	Crosslinked chitosan-coated liposomes	In vitro	I. Improved thermal stability of the peptide-encapsulated liposomes after coating and crosslinking II. Enhanced antioxidant activity of the peptidic fraction due to the three-dimensional structure of the liposomal delivery system	Ramezanzade et al. (2021)
Tilapia viscera	Antioxidant peptides	Spray dried soy-rapeseed lecithin/trehalose liposomes	In vitro	I. Formation of liposomal fine powder via spray-drying using trehalose II. Enhanced antioxidant capacity and liposomal storage stability after hydrolysate-loading III. More structural variations upon storage at high temperature/humidity IV. High biological activity of the formulation after GI digestion	Sepúlveda, Alemán et al. (2021)
Orange seed protein	Antioxidant peptides	Chitosan-coated nanoliposomes	N/A	I. Improved stability and diminished release rate of the FPHs after coating process II. Instability of the liposomal structure to freeze–thaw stress III. Settling the FPHs in polar-regions and bilayer membrane of the spherical nanoliposomes	Mazloomi et al. (2020)
SPI	Antioxidant peptides	Liposome	In vitro	I. Higher antioxidant activity of the peptide fractions smaller than 1 kDa II. Significant effect of the combination hydrolysis strategy on antioxidant capacity III. Discrepancies in antioxidant capacities induced by different peptide–liposome interactions IV. The higher the FPHs, the higher the stability of the liposomes	Chen et al. (2020)
Whey proteins	Anionic and cationic FPHs	Liposome	N/A	I. EE of over 85% II. Dependency of the liposome size and EE% to the peptide net charge III. No effect of the peptide charge on the location of the bioactives within the delivery system	Mohan et al. (2018)
Defatted Asian sea bass skin	Hydrolyzed collagen	Liposome	In vitro	I. High EE% in cholesterol-containing liposomes II. -High antioxidant activity and in vitro stability of the formulation upon storage and in GI conditions	Chotphruethipong et al. (2020)

(Continues)

TABLE 2 (Continued)

Liposomal delivery systems					
Sources	**FPHs**	**Delivery system**	**GI model**	**Key outcomes**	**Reference**
Food-grade emulsions and pickering emulsions					
Rice protein	Antioxidant peptides	Pickering emulsion	In vitro	I. Ultrasonication as an effective strategy to generate FPHs of excellent antioxidant properties II. Fast absorption and appropriate wetting properties of FPHs at the O–W interface	Zhang et al. (2021)
Whey protein	Antioxidant peptides	O/W emulsion	In vitro	I. Glycation between FPHs and dextrin II. Increased β-sheet content of whey protein hydrolysate (WPH) following glycation III. Higher iron chelating activity and 2,2-diphenyl-1-picrylhydrazyl (DPPH) scavenging ability of the conjugates IV. Superior stability by proper steric hindrance	Du et al. (2021)
Egg white gel	Antioxidant peptides	O/W emulsion	In vitro	I. Decreased surface hydrophobicity of FPHs after hydrolysis II. Emulsion of stable ionic, temperature, and storage stability III. Enhanced antioxidant activity following digestion	Ling et al. (2020)
β-Lactoglobulin	Antioxidant peptides	W/O/W emulsion	In vitro	I. Release rate of FPHs in the order mineral oil $<$ linseed oil $<$ jojoba oil. II. The lower the oil phase viscosity and the higher the peptide hydrophobicity, the higher the release rate III. The lower release in gastric phase than in intestinal medium. IV. Controling the peptide release by the oil digestibility and lipolytic degradation of the emulsion	Giroux et al. (2019)
Zein	Antioxidant peptides	O/W emulsion	In vitro	I. Electrostatic interactions between sage (*Salvia officinalis*) extract and FPHs II. Enhanced emulsifying/antioxidative properties	Li et al. (2019)
Porcine bone protein	Antioxidant peptides	O/W emulsion	In vitro	I. Maillard conjugation of FPHs and rutin II. Formation of a self-assembled structure on the O/W interface III. Improved stability	Liu et al. (2019)

(Continues)

TABLE 2 (Continued)

Liposomal delivery systems					
Sources	**FPHs**	**Delivery system**	**GI model**	**Key outcomes**	**Reference**
Biopolymer micro and NPs					
Rice protein	Antioxidant peptides	Wheat starch NPs	In vitro	I. Great potential of FPHs in regulating starch digestion to formulate low-glycemic index foods II. Enhanced gelatinization temperature, while dropping the gelatinization enthalpy and recrystallization of starch molecules III. Variations in water distribution followed by influencing the interactions between starch molecular chains, resulting in changes in the gel network	Lin et al. (2022)
Feather keratin	Antioxidant peptides	Spray-dried maltodextrin	In vitro	I. Efficient hydrolysis of feathers by *Bacillus* sp. B4 in low mass peptides II. Formulation of a new biotechnological product using FPH-loaded particles III. High stability, proper solubility, and low moisture content of the formulation	Sironi et al. (2022)
Rice husk	Antioxidant and anticancer peptides	Chitosan NPs produced via ionic gelation	In vitro	I. EE of around 89% II. Around a 65% bioactive release at the end of 6 days III. The lowest cell viabilities with A549 and MCF7 cells IV. Anticancer activity of FPHs ranging from 10 kDa to more than 180 kDa	Ilhan-Ayisigi et al. (2021)
Flaxseed protein	Antioxidant peptides	Spray-dried maltodextrin	In vitro	I. Improved antioxidant properties of FPHs II. High hydrolysis degree (~38%), hydrophobic AAs (255 mg/g), and antioxidant properties (126 mg/g) of the alcalase-produced peptides III. Generation of shrunk and irregular particles of diverse particle sizes and matrix-type configurations	Akbarbaglu et al. (2019)
Whey proteins	Antihypertensive peptides	Alginate–collagen, alginate–gum arabic, and alginate–gelatin particles	In vitro	I. The highest EE (95%) of FPHs using alginate–gum arabic particles II. Increased ACE activity (85%) of the peptides after loading	Alvarado et al. (2019)
Hydrogels and nanogels					
Bovine serum albumin (BSA), whey protein isolate, insulin, and casein	Antioxidant peptides	Chitosan and polyphosphoric acid particles	In vitro	I. Major influence of the polyphosphoric acid concentration on both entrapment and release of the bioactives II. Protective effect of the formulation in simulated gastric phase III. Inhibited/gradual release of the bioactives in simulated intestinal phase	Yuan et al. (2018)

(Continues)

TABLE 2 (Continued)

Liposomal delivery systems					
Sources	**FPHs**	**Delivery system**	**GI model**	**Key outcomes**	**Reference**
SPI	Antioxidant peptides	SPI hydrogels produced by acid-induced gelation	In vitro	I. Mitigated gel properties after incorporation of FPHs II. Reduced the adverse effects of FPHs on the formation of the protein gel via the glycosylation mechanism III. Lower stiffness of the glycosylated hydrolysate-incorporated gel as compared to the protein gel	Li et al. (2021)
Nisin	Antioxidat and antibacterial properties	Chitosan–gallic acid coating	In vitro	I. Production of a hurdle biofunctional packaging for preserving fresh pork II. Enhanced bactericidal effects if nisin and gallic acid–loaded chitosan films III. Reduced rate of protein and lipid oxidation by the prepared films	Cao et al. (2019)
Jackfruit leaves (Pep-P)	Antibacterial peptides	Edible pectin film	In vitro	I. Higher inhibitory effect of peptide-loaded films against *Colletotrichum gloeosporioides* than control pectin film II. Controlling anthracnose in tropical fruits by the developed biofunctional films	Brion-Espinoza et al. (2021)
Casein phosphopeptides (CPP)	Antioxidant peptides	Gelatin edible films	In vitro	I. Inhibitory activity of the films against *Bacillus cereus* and *Staphylococcus aureus* II. Strong antioxidant activity of the films	Khedri et al. (2021)
Phaseolus vulgaris beans	N/A	Polyvinyl alcohol and starch nanocomposite	In vitro/in vivo	I. Suitability of the fabricated nanocomposites for oral administration of the peptides to overpass GI barriers	Rodrigues et al., 2022
Collagen	ACE-inhibitory peptides	Carboxymethyl cellulose (CMC)	In vitro	I. Any adverse effect of glycerol on ACE-inhibitory properties of hydrolysate collagen-encapsulated nanoliposomes II. Improved ACE-inhibitory ability of hydrolysate collagen-encapsulated liposomes after in vitro GI digestion III. No need to additional plasticizer by the presence of glycerol-comprising liposomes IV. Superior stability of the glycerol-comprising liposomes following film drying and in vitro digestion	Marín-Peñalver et al. (2019)

Abbreviation: **GI**, gastrointestinal.

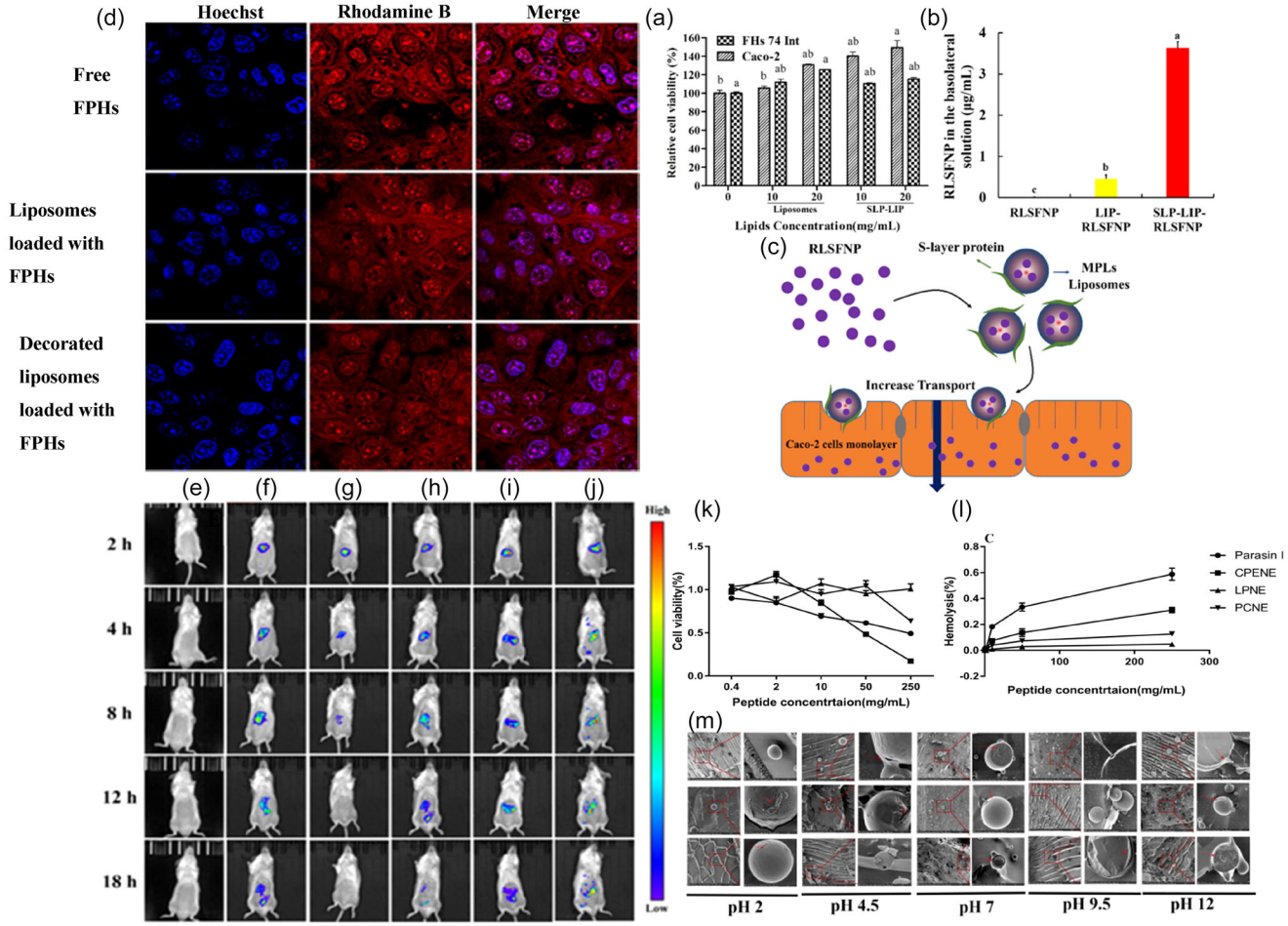

FIGURE 5 (**a**) Cytotoxicity studies of liposomes and peptide-loaded liposomes in food protein hydrolysates 74 Int cells and Caco-2 cells (evaluated by MTT assay); (**b**) transmembrane transport of unloaded FPHs, liposomes loaded with food protein hydrolysates, and peptide-loaded decorated liposomes; (**c**) schematic diagram of the transport of peptide-loaded decorated liposomes through Caco-2 cells; (**d**) confocal laser scanning microscopy of unloaded food protein hydrolysates, liposomes loaded with food protein hydrolysates, and peptide-loaded decorated liposomes in Caco-2 cells following 2 h of incubation; in vivo fluorescence images of (**e**) control group; (**f**) rhodamine B; (**g**) FITC; (**h**) unloaded food protein hydrolysates; (i) liposomes loaded with food protein hydrolysates; (**j**) peptide-loaded decorated liposomes (Zhang et al., 2021); (**k**) cytotoxicity and (**l**) hemolysis curves of parasin I, chitosan peptide-encapsulated nanoparticles (NPs) Whey Protein Hydrolysate emulsion (CPENE), lipid/peptide NPs emulsion (LPNE), and parasin I-conjugated chitosan NPs emulsion (PCNE); (**m**) cryo-SEM of CPENE (first row), LPNE (second row), and PCNE (third row) (Cai et al., 2020).

the cell surface when they come into contact, and burst after contact, enabling effective delivery of the active payload to the cells through diffusion. Different hydrophilic and hydrophobic FPHs can be encapsulated within emulsion-based carriers and protected against detrimental circumstances. Emulsions are neutrally biodegradable, buoyant, and biocompatible, essential features for food/pharma applications (Singh et al., 2017).

Recently, Suárez and Añón (2019) assessed the possibility of using amaranth protein emulsions as delivery system of ACE-inhibitory peptides in vitro and showed the susceptibility of the emulsions to aggregation/coalescence phenomenon, probably due to the chaotropic action of the bile salt on the interface and the lipolytic and proteolytic action of lipase and pancreatin, respectively. Moreover, it was found that the protein-stabilized emulsions had higher resistibility to gastric conditions compared to duodenal digestion. Following the in vitro GI digestion, the inhibition of ACE (IC_{50} of ~0.13 mg/mL) was maintained potently, indicating the protective influence of the emulsions on bioavailability of the FPHs. This could result from their participation in the formation of the interfacial film and/or their participation in the network of formed flocs. Tamm et al. (2016) evaluated functional attributes of pea protein hydrolysates in emulsions and corresponding spray-dried microcapsules. Relying on the enzyme employed to generate FPHs, the dilatational moduli enhanced and the phase angle diminished, implying the formation of more elastic and stronger interfacial layers. Both the intact protein isolate- and trypsin-derived FPH-comprising emulsions exhibited a high stability during atomization/drying, providing a high encapsulation efficiency (EE) (~95%). Additionally, trypsin-produced FPHs possessed a greater capability than the intact protein to lower lipid oxidation of emulsions upon storage. This behavior may be mainly ascribed to the modified

physical features of the interfacial film and the antioxidative potential of the FPHs.

In another attempt, the in vitro controlled release of casein-derived FPHs in the GI environment by encapsulation in W/O/W double emulsions was investigated by Giroux et al. (2016). It was demonstrated that the release rate of the FPHs was highly affected by the hydrophobicity as well as the composition of oil phase. Relying on molecular weight of the FPHs, the kinetics of release was controllable through fine-tuning the oil phase composition.

Pickering emulsions possess a great capability to safely deliver FPHs and improve their defects. Nonetheless, there are limited lectures to try to utilize these vehicles for the encapsulation purposes. Very recently, Cai et al. (2020) applied a slow-release and nontoxic Pickering emulsion platform to encapsulate and protect FPHs. The parasin I (an antimicrobial FPH derived from the skin of the catfish) interacted/conjugated with lecithin/chitosan and designed NPs entrapped by Pickering emulsions (Figure 5m). The deprotonation or protonation of amino groups in parasin I and chitosan resulted in formation of NPs in different aggregate states and notably affected the emulsion stability. The prepared nanoformulation induced a severe bacterial agglomeration on Gram-positive/negative bacteria via the membrane disintegration mechanism. Additionally, the Pickering emulsions were potently able to alleviate the cytotoxicity of human liver cells and hemolytic activity in rat blood cells (Figure 5k,l). In combination with the lack of acute cytotoxicity in Kunming mice and milder, more effective anti-inflammatory effect in peritonitis demonstrated for these Pickering emulsions, a potential role in combating multidrug-resistant bacteria in biomedical applications. Du, Li et al. (2019) designed a novel Pickering nanoemulsion with high stability, monodispersity, and controllability via spherical NPs, self-assembled from the amphiphilic egg yolk peptides (EYPs). The EYPs had a small particle diameter, high surface activity, intermediate wettability, and deformability at the interface, facilitating the development of stable Pickering nanoemulsions (<200 nm) versatile for various oil phases of diverse polarities. The natural edible nano-Pickering emulsions were highly applicable to design stable food Pickering nanoemulsions with the qualities of versatility, simplicity, low cost, and the possibility of mass production, rendering them viable systems for various sustainable applications.

A pH switchable food-grade Pickering emulsion using soy β-conglycinin peptides decorated calcium phosphate particles (CaP) was developed by Ruan et al. (2017). The FPHs characterized with a large amount of carboxyl AAs (i.e., Glu and Asp) and showed high affinity to CaP particles. The functionalization of CaP particles with FPHs increased their electrodynamic properties and hydrophobic wettability at the same time. Therefore, the surface modification of CaP particles could develop an interfacial crystal layer, resulting in the formation of stable Pickering emulsions. Finally, the pH switchable feature of the emulsions was recognized relying on the pH-dependent dissolution-recrystallization transition of CaP particles. Table 2 summarizes the previous work utilizing emulsions and Pickering emulsions to promote FPH characteristics.

4.1.3 | Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs)

Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) have already been identified as having multiple benefits in facilitating the delivery of hydrophilic/hydrophobic FPHs. These lipid-based NPs possess low toxicity and higher stability as compared to liposomal delivery systems and can efficiently control the bioactive release in vivo (Sadegh Malvajerd et al., 2019; Wibel et al., 2021).

In a very recent report, Su et al. (2020) investigated the effects of SLNs on the stability of two fractions of oat globulin-derived peptides (MW < 3 kDa and MW = 3–10 kDa) in simulated GI fluids. SLNs improved the stability of oat peptides against GI tract. Furthermore, both peptide fractions inhibited dipeptidyl peptidase IV in simulated GI fluids. García-Fuentes et al. (2003) reported that both pancreatic enzymes of intestinal medium and low pH of the gastric environment were responsible for the wide aggregation and degradation of the non-coated lipid nanoparticles (80% degradation in 4 h). This effect could be explained with the PEG brush around the particles that decreased the attachment of the enzymes and further degradation of the triglycerides core. On the other hand, PEG-stearate coating layer totally prevented aggregation and significantly alleviated pancreatin-induced degradation (approximately 40% in 4 h). It was noteworthy that the release behavior of peptides was greatly influenced by the composition as well as the hydrophobicity of the oil phase (Giroux et al., 2016).

4.1.4 | Niosomes

Niosomal delivery systems are one of the evolutionary vehicles, which have been actively utilized to improve the biostability and bioavailability of numerous agents. Architecturally, niosomes are nonionic surfactant vesicles with a bilayer configuration generated by self-assembly of hydrated surfactant monomers (Rostamabadi, Falsafi et al., 2020). They are nontoxic, stable, biodegradable, biocompatible, non-immunogenic, and osmotically active vehicles that can enhance the efficacy of embedded bioactives. By virtue of the amphiphilic structure of niosomal systems, both hydrophobic and hydrophilic FPHs can be loaded by these carriers.

More recently, Mor et al. (2021) prepared a niosomal formulation (via high shear homogenization) to deliver milk protein hydrolysates (i.e., casein peptides) with potential for promoted peptide bioavailability. The FPH-entrapped niosomes (~38 nm and −23 mV) could provide a high EE (approximately 67%) and controlled/sustained release of FPHs upon simulated GI environment. Furthermore, the antioxidant capacity of the FPHs was not influenced following their entrapment into niosomes.

In year 2019, Rezvani et al. (2019) investigated the efficiency and potential application of both niosomal and liposomal vehicle systems for fortification of functional beverages with FPHs (i.e., Ile–Pro–Pro). Vesicles were designed by various synthesis approaches (i.e., ethanol injection–microchannel method, thin film hydration, and probe

sonication) via phospholipid and nonionic surfactants. Utilized in functional beverage, the FPH-loaded niosomal vesicles exhibited superior palatability, physicochemical attributes, and biological properties during long-term storage compared to liposomal ones. Besides, niosomes entrapped with FPHs showed more bioactive sustained release in simulated blood fluid than liposome vehicles.

Very recently, Du et al. (2022) synthesized nanoscaled niosomes as effective vehicles to enhance the bioaccessibility and (bio)stability of FPHs derived goat milk whey protein. The papain-based enzymatic hydrolysis was performed to produce FPHs, and the ultrafiltration was used to obtain a low molecular weight peptide (<3 kDa) of potent hypoglycemic function. The FPH-embedded β-sitosterol niosomes possessed a higher peptide EE (~90%) and a smaller particle size (~92 nm) as compared to liposomes. Nanosized niosomal systems could considerably improve the bioaccessibility and long-term storage stability of the encapsulated FPHs.

4.2 | Biopolymer-based vehicles

Biopolymers have significantly contributed to the pharmaceutical and food sectors in multiple dimensions for the protective delivery of FPHs due to their diverse structures, distinctive physiological applications, biodegradability, safety, renewability, durability, and low toxicity (Udayakumar et al., 2021). A wide range of biopolymer-based vehicles has been used for the encapsulation, protection, and release of FPHs, improving their (bio)stability and bioavailability. In this context, biopolymer carriers with little or no reactivity with FPHs are desirable for the use in functional foods or biofunctional packaging (Sun et al., 2020). Generally, the selection of delivery system utilized for the delivery of bioactive molecules is dependent on encapsulation purpose, nature of FPHs, and food formulation type (Sarabandi et al., 2020).

Biopolymers naturally derived from biomass are either polysaccharides or proteins. The polysaccharides used for the delivery of FPHs mainly include maltodextrin, chitosan, alginate, cellulose and its derivatives, starch, pectin, and gums. The biopolymers from plant- and animal-derived proteins employed as a delivery vehicle of FPHs are mainly zein, gelatin, collagen, and milk proteins. Protein as a delivery system has also several advantages in the food industry, such as solubility, emulsification, gelation capacity, foaming capacity, and viscoelastic film formation ability. Besides polysaccharides and proteins, microbiologically produced biopolymers, such as bacterial cellulose, dextran, and xanthan, can also be used in the field of encapsulation for oral delivery of FPHs (Sarabandi et al., 2020).

Notwithstanding the application of traditional biopolymer systems, the binary systems of different biopolymers, especially proteins and polysaccharides, are among the interesting systems for the delivery of FPHs. Examples of some micro- and nanosized biopolymer-based vehicles for the encapsulation of FPHs are presented in Table 2.

4.2.1 | Microscopic/nanosized particles

Encapsulation of FPHs using microscopic/nanosized particles protects them from harsh gastric milieu and degradation in the GI tract and enhances their intestinal absorption. The micro and NPs utilized to deliver FPHs are commonly produced through spray-drying, coacervation, ultrasonic atomization, microfluidic, pore-closing, and electrospraying techniques. To fabricate a micro/NP-based delivery vehicle for the encapsulation of FPHs, physical properties, like zeta-potential, particle size, polydispersity index, and drug loading parameters, should be precisely controlled and optimized.

Among different biologically active peptides, nisin is a well-known bioactive molecule extensively employed in food industries with exceptional antibacterial activity against Gram-positive bacteria (Xiong et al., 2020). The antimicrobial activity of nisin has been shown to increase by encapsulation within biopolymer-based micro- or NPs. For instance, Calderón-Oliver et al. (2017) performed a study to examine the potentiality of complex coacervates based on collagen–pectin and collagen–alginate particles for the encapsulation and protection of nisin. The authors found that multiple factors could be developed that suit varied applications of loaded nisin in food industry. Recently, Salama et al. (2020) successfully grafted soy protein bioactive peptides to the cellulose nanofibril bodies and pointed out the improved bioactivity of cellulose fibers following the amidation of carboxylic groups. In vitro assessments on human mesenchymal stem cells also corroborated the biocompatibility of grafted materials, representing the potential of the formulation for the repair and/or the regeneration of hard tissues. In another study, Luo et al. (2022) investigated the encapsulation of rice selenium-containing peptide TSeMMM within zein–gum arabic NPs through ultrasound treatment to promote its bioavailability and bioactivity in vitro/in vivo. It has been revealed that the cumulative release rate of the active small molecular peptides from biopolymer NPs reached a maximum of ~81% following 6 h. Moreover, the designed NPs dramatically affected the levels of tissue glutathione and enhanced oral bioavailability of the FPHs.

Cow's milk allergy is a common diagnosis in infants and children. Liu, Thijssen et al. (2022) investigated the oral delivery of 18-AA β-lactoglobulin-derived peptides loaded within poly (lactic-co-glycolic acid) (PLGA) NPs against cow milk allergy. Mice pre-treated with high-dose of β-lactoglobulin-derived peptides loaded PLGA NPs represented significantly less acute allergic skin response, revealing the significant protective effect of encapsulation. In addition, the high-dose peptide-loaded NPs' pre-treatment prevented ex vivo whey-stimulated pro-inflammatory cytokine TNF-α release by splenocytes. Table 2 summarizes more examples of micro- and nanosized delivery systems used for delivering FPHs for different purposes. Many different research studies thus have been performed to protect, increase stability and bioavailability, and maintain biological activity of FPHs in varied biopolymer micro and NPs.

4.2.2 | Hydrogels and nanogels

Hydrogel is a polymeric material made from polysaccharides, proteins, or their compounds with a three-dimensional network that can encapsulate and protect FPHs from external environments such as heat, light, oxygen, acids, and enzymes. The physicochemical stability, water solubility, and bioavailability of FPHs are improved by loading them in a polymeric hydrogel (Liu et al., 2021). The gel structure of these vehicles could be customized at different conditions, making them control the release of bioactive compounds with different release mechanisms to targeted sites. Moreover, pH-sensitive hydrogels show typically enhanced stability in gastric conditions but are unstable under intestinal conditions. Such hydrogels can increase the uptake and utilization of FPHs by protecting them from degradation in the stomach and releasing them in the small intestine.

In recent years, the hydrogels synthesized from biopolymers have gained wide recognition in functional foods owing to their edibility, biodegradability, biocompatibility, low toxicity, affordability, and enhanced stability and bioavailability of FPHs. Hydrogels can be developed from a broad range of polysaccharides and proteins, and the majorly employed hydrogel fabrication methods for delivering FPHs comprise acid-induced gelation, self-assembly, emulsion templating, injection–gelation, antisolvent precipitation, and thermodynamic incompatibility methods (Perry & McClements, 2020). Careful determination and customization of composition, dimension, morphology, and interfacial attributes of biopolymer hydrogels governs the functional performance of hydrogels for particular applications.

FPHs are incorporated in hydrogels by either loading them after hydrogel preparation, or by blending them with biopolymers prior to hydrogel preparation (McClements, 2018). Among these two methods, loading FPHs after hydrogel formation exhibits higher loading efficiency attributed than liposomes or emulsions (Perry & McClements, 2020).

Nanogels are nanometer-sized polymeric hydrogels (1–1000 nm), which are also known as hydrogel NPs. Nanogels are swollen networks made of hydrophilic or amphiphilic polyionic polymers that show potential as delivery systems owing to their unique properties. Nanogels possess tunable physical and chemical structures, large surface area for multivalent conjugation, high loading capacity, high water content, immunomodulatory properties, and ability to target specific cell compartments and specific cells. The nanogels have been designed by various approaches that can be categorized into crosslinking of preformed polymers, self-assembly of interactive polymers, template-assisted nanofabrication, and physical polymerization of monomers in a micro- or nanoscale heterogeneous environment or in a homogeneous phase (Ferreira et al., 2013).

Owing to the ability of hydrogels and nanogels to encapsulate a high amount of bioactive ingredients and protect them from degradation, they have been widely explored for the delivery of FPHs (Table 2). For example, Pugliese et al. (2019) introduced a simple and harmless nanotechnological technique as a key step in developing innovative nanomaterials for encapsulation of FPHs. The authors utilized a supramolecular technique to design soybean and lupin peptide-loaded nanogels (via a solvent-triggered method) with enhanced stability and antidiabetic properties. The nanogels self-aggregated into stable cross-β structures exhibited superior stability against enzymatic hydrolysis and improved the bioavailability of FPHs based on the in situ studies on Caco-2 cells. In another study, whey protein concentrate hydrolysate (WPCH) was loaded into hydrogels prepared from gelatin and chitosan, and the effect of microencapsulation on the protection and stability of peptides against lactic acid fermentation during the manufacturing of yoghurt was examined. The study revealed that peptide-loaded chitosan hydrogels showed an improved stability during lactic acid fermentation compared to those encapsulated in gelatin hydrogels. However, only 5 out of 21 fermentation-susceptible peptides were guarded by chitosan hydrogels (Gómez-Mascaraque et al., 2016).

A noticeable limitation of hydrogel beads is that the FPHs might leak out of the beads during storage in aqueous solutions (Zhang et al., 2016). Consequently, further research is required for fabricating hydrogels economically from food-grade ingredients that are better capable of retaining the FPHs and at the same time maintaining their activity. Moreover, research is highly encouraged for determining the efficacy of hydrogels and nanogels at ameliorating the bioavailability of FPHs via oral administration in in vivo studies involving human and animal feeding experiments.

4.2.3 | Biofunctional films/composites

Biofunctional food packaging systems are effective platform to functional foods for providing health benefits other than essential nutrients (Tkaczewska, 2020). Biopolymer composites are prepared by various methods like solvent casting, film stacking, extrusion, molding, melt blending, grafting, phase separation, intercalation, electrospinning, filament winding, and laser printing. FPHs can be incorporated as active ingredients in food packaging systems for shelf life extension in packed or coated foods. For instance, microbial contamination of foods chiefly betides on the surfaces, and the application of biofunctional films or coatings with antimicrobial peptides effectively protects foods from contamination by continuous release of peptides from the packaging material to the food surfaces. Development of biofunctional films and composites with FPHs is manufactured either by coating peptides on the polymeric surfaces, or by direct addition of peptides into the polymer matrices, or by peptide immobilization in the polymer (Udayakumar et al., 2021).

Furthermore, FPHs are utilized in combination with other natural additives for developing biofunctional films and composites with improved antimicrobial activity (Cao et al., 2019). The biofunctional films, coatings, and composites prepared as a delivery vehicle for FPHs are summarized in Table 2. To date, no regulation has been acknowledged with regard to the permitted amount of FPHs that should be released to foods from packaging systems. Nisin, designated as E234, is the only approved bacteriocin by the European

Community that can be used as a safe preservative in food contact surfaces (Tkaczewska, 2020). Future studies should explore the potentiality and release of FPHs from food packaging systems other than nisin.

4.2.4 | Electrospun fibers

Electrospun fibers are polymer fibers with high surface porosity, large surface area to volume ratio, and great EE% fabricated by electrospinning technique (Rostamabadi, Assadpour et al., 2020; Rostamabadi et al., 2021). There are few studies depicting the delivery of FPHs in electrospun micro- and nanofibers. For example, Hosseini et al. (2019) encapsulated fish-purified AOP into electrospun chitosan/poly(vinyl alcohol) (PVA) nanofibrous mats (~181–279 nm) for food biopackaging purposes. Thermal/mechanical properties and hydrophobicity of the ternary mat (around threefold) improved in the presence of the bioactive peptide, whereas the water vapor permeability decreased considerably. Importantly, the engineered fibers showed high EE (around 94%) and good cytocompatibility, while enabling a sustained release of the bioactive through the polymer mat. Stephansen et al. (2014) prepared nano-microfibers from cod (*Gadus morhua*) sarcoplasmic proteins (FSP) via electrospinning technique and loaded with a dipeptide (Ala–Trp). The release properties of FSP fibers were determined in gastric and intestinal buffers. The release profile exhibited an initial burst property, where 30% of the dipeptide was released during the first minute, and another 40% was released within next 30 and 15 min in gastric and intestinal buffers, respectively. The remaining 30% was retained in the time span of the experiment. In another study, He et al. (2017) developed a hierarchically structured delivery system for FPHs that undertakes structural changes for triggering multiple functions by a sequence of stimuli. The system comprises NPs in nanofibers configuration, where both NPs and nanofibers are biocompatible as well as pH-responsive. A model peptide was successfully loaded into the nanocarriers, and they were then subjected to electrospinning with a pH-responsive mucoadhesive polymer. The study concluded that nanoparticles were released from the nanofibers, and subsequently, the peptides were released from nanoparticles in a pH-responsive manner. Furthermore, a food biopackaging was successfully prepared by the encapsulation of fish-purified AOP in an electrospun chitosan/PVA nanofibrous mat. The chitosan/PVA/AOP ternary fibers showed an enhanced EE (> 94%) and had a sustained release profile of AOP by retaining its antioxidant activity in electrospun fibers. Besides, the in vitro cell toxicity experiment revealed good cytocompatibility of nanofibers encapsulating AOP (Hosseini et al., 2019). The research provided an uncomplicated approach to fabricate a fiber-based bioactive food packaging material. Although all ingredients employed in these studies were not acceptable for food application and consumption, it is likable to develop delivery systems employing food-grade ingredients. In-depth investigation involving in vivo experiments in this area is necessary to promote the commercialization of electrospun micro- and nanofibers in food products.

5 | FUNCTIONALITY OF LIPID/BIOPOLYMER-BASED CARRIERS FOR ORAL DELIVERY OF FPHS

To eliminate formulations that are dangerous for human or animal usage, preclinical and toxicological studies must be conducted according to FDA requirements to determine whether an oral carrier, such as biodegradable NPs or microspheres, is efficaciously safe. Any oral formulation that seeks FDA approval must take into account the existence of residual solvents and polymers that may persist after delivery, as well as preclinical and toxicological investigations. All biopolymeric materials used in oral delivery applications must be tested for safety and biocompatibility before being employed (Gheorghita et al., 2021; Rusu et al., 2020). The tests required to determine safety will vary depending on the device, the bioactive to be given, and the intended use. Biopolymeric materials should be tested in vivo and in vitro to explore polymer mucosal interface reactions, impacts on subsurface tissue, and systemic effects (Sharma et al., 2021).

FPHs as an additive for food can be produced via artificial synthesis of the desired section or by enzymatic hydrolysis. In the latter case, adding an enzyme solution to the selected protein and then purifying the peptides is possible. However, there is a risk that the enzyme undergoes hydrolysis. In addition to the peptide sections of the protein, there are also peptide sections of the enzyme or enzymes in the hydrolysate. One solution to this problem would be immobilizing the corresponding enzymes (Akbarian et al., 2022).

The ability of bioactive peptide drugs to cure disorders would be greatly enhanced if they were administered orally. So far, two systems have been successfully designed and proven to improve oral peptide bioavailability, namely, NLCs and SLNs. NLCs exhibit good solubility and bioavailability. NLCs are advanced nanoscale active systems with a lipid core and a water-soluble shell. They have high stability, protect the active biomolecules from degradation, and provide sustained drug release (Almeida & Souto, 2007; Su et al., 2020; Talegaonkar & Bhattacharyya, 2019).

The lipid–biopolymer hybrid NPs are one of the most recently developed nanoscale delivery systems. These hybrid systems utilize solid lipid as the core matrix to increase encapsulation and sustained release features. On the other hand, proteins and polysaccharides are used as emulsifiers/stabilizers and surface coatings in the formulation to increase overall colloidal stability during storage and digestion. The size of lipid–biopolymer hybrid nanoparticles is larger than that of corresponding nanoparticles without a lipid core, similar to that of biopolymer ternary complex nanoparticles. However, due to the thick hydrophilic coating, this hybrid combination may overcome two long-standing historical problems of SLNs such as severe and irreversible aggregation upon drying or poor GI stability. Pretreatment of the protein–polysaccharide matrix with nontoxic chemical reactions (such as the Maillard reaction and oxidation) increased the stability of the hybrid nanoparticles while also significantly reducing their particle size and thus increasing the bioactivity of encapsulated bioactive compounds.

Hydrophilic biopolymers can self-assemble into nanoparticles when combined with hydrophobic lipid molecules (Khan et al., 2019). Oral delivery is improved by combining the biopolymer and lipid into a single system. Functionalization of lipids with biopolymers (e.g., starch, protein, and chitosan) is a revolutionary concept and potential area for advancements in different applications. Lipids impart positive qualities to biopolymers, and biopolymers enhance the properties of lipids, resulting in the functionalization of the composite for improved performance. This is not only for biopolymers but also for synthetic polymers. The use of biopolymers to conjugate lipids and lipid-based systems can help overcome some disadvantages such as low stability, low production feasibility, lack of hydrophilic characteristics, poor mechanical strength, and expensive processing costs (Basim et al., 2021). Starch esterification with fatty acids has been researched and succeeded, resulting in high hydrophobicity, flexibility with a low glass transition temperature, and film formability even without plasticizers. The starch characteristics are adjusted by mixing with lipids. Various ratios of lipid and chitosan have been researched to produce hybrid nanoparticles by the single-step ionic gelation method based on ionic interaction of positively charged chitosan and negatively charged lipid. Because of their excellent biocompatibility and biodegradability, chitosan and phospholipid are perfect candidates. On the other side, biopolymers have emulsifying properties, and emulsion stability can be improved. According to Pereda et al. (2012), chitosan can be added to oil emulsion films to produce stable olive oil emulsions with homogeneous, thin, and translucent films.

The future success of oral delivery of FPHs will depend on the commitment of researchers to develop new strategies for efficient and cost-effective systems. The potential of newly created lipid–biopolymer hybrid nanoparticles for oral administration of bioactive substances has been successfully established, but because their exact absorption methods and uptake pathways may differ significantly from their separate components, still little is known about the biological fate of hybrid nanoparticles (Taoran Wang & Yangchao Luo, 2019).

6 | CONCLUSIONS, CHALLENGES, AND PROSPECT VIEW

This review highlights the functionality and versatility of biopolymer- and lipid-based delivery systems for FPHs. These nature-derived carriers offer exceptional biodegradability, biocompatibility, scalability, and low toxicity. Crucially, they are highly customizable, allowing their physicochemical and biological properties to be tailored for specific applications. This customization enables researchers to precisely control the (bio)stability and release profiles of FPH formulations. With the implementation of these vehicles, the permeability, bioavailability, and stability of FPHs can be significantly enhanced. Moreover, the sophisticated design of biopolymer- and lipid-based carriers can modulate the release kinetics of FPHs, facilitating controlled or prolonged release profiles.

A basic tree diagram for selecting the most suitable delivery for FPHs is depicted in Figure 6. Although FPHs have shown promising

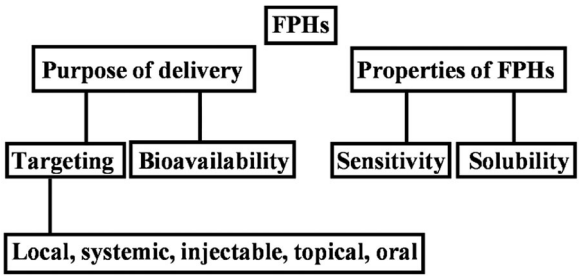

FIGURE 6 A basic tree diagram for selecting the most suitable delivery for food protein hydrolysates (FPHs).

potential, their development, unlike other bioactive agents that have undergone a century of research, is still relatively recent. As such, the effective encapsulation and delivery of FPHs is as critical as the discovery of novel FPH sequences. Nanoformulation of FPHs includes creating nanosized carriers to promote their stability, bioavailability, and functionality. Some common shortcomings relevant to this process are listed as follows:

- Stability issues: FPHs can be sensitive to environmental factors such as extreme pH, high temperatures, or oxidation. Nanoformulations must be designed to shield these agents from degradation.
- Encapsulation efficiency (EE): Achieving high EE is vital. Incomplete encapsulation can lead to leakage of FPHs, reducing their effectiveness.
- Controlled release: Developing nanoformulations that ensure controlled and targeted release of FPHs is challenging. The release profile must be optimized to match the desired therapeutic or functional outcomes.
- Compatibility: Ensuring that FPHs are compatible with the materials used in the nanoformulation (e.g., polymers or lipids) is important. Any incompatibility can affect the stability and performance of the formulation.
- Size and distribution: Maintaining uniform size and distribution of nanoparticles is critical for consistent performance. Variability can lead to inconsistent release rates and bioavailability.
- Scalability: Scaling up the production of nanoformulations from lab scale to industrial scale while maintaining quality and efficacy can be challenging.
- Regulatory issues: Meeting regulatory requirements for nanoformulations, including safety and toxicity assessments, can be complex and time-consuming.
- Cost: The development and production of nanoformulations can be expensive due to the need for specialized equipment and materials.
- Addressing these challenges often involves a combination of careful material selection, optimization of formulation parameters, and rigorous testing.

Despite the significant advancements in this field, FPH-based bioformulations have seen limited in vivo studies. Key gaps remain regarding peptide encapsulation, controlled release mechanisms, and the interactions of FPH-loaded lipid/biopolymer carriers with the GI

environment. Consequently, the low in vivo bioactivity and stability of these formulations are often due to a lack of understanding in designing biomaterials that can withstand the harsh GI conditions while maintaining their functional integrity.

Although extensive research has focused on the physicochemical properties of these delivery systems, the characterization of FPH-loaded lipid/biopolymer formulations at the cellular level remains a major challenge. Progress in cellular studies will be a significant breakthrough in the field, opening new avenues for the application of these advanced delivery systems.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

ETHICS STATEMENT

This work is a narrative review paper with ethical code of IR.MUI.RESEARCH.REC.1400.457.

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