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Introduction

Peptides and proteins are macromolecules that are the backbone of living organisms. Peptides comprise many amino acids (short chains of amino acids that range from two to fifty) linked by peptide bonds. The combination of these peptides (chains with more than 50 amino acids) are proteins (1). The FDA approved cyclosporine as the first oral peptide in 1983 and continued to approve many PPs as therapeutic agents and an alternative to tiny molecular medicines in treating many diseases due to their excellent selectivity, effectiveness, and minimal toxicity (Figure. 1).

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Review Article

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Oral Peptides And Proteins Delivery

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Abstract

Peptides and Proteins (PPs) have been used as therapeutic agents in treating many diseases. Therefore, the current review intends to focus on oral peptides and protein and different strategies for enhancing their oral absorption and permeation. Although the oral route is the preferred route of drug administration, it is challenging for PPs. Many biological barriers, such as pH, mucus, and enzymes, may restrict the absorption of PPs. Therefore, many approaches are used to overcome these difficulties, prove absorption, and enhance the bioavailability of PPs such as enzyme inhibitors, mucoadhesive, nanoparticles, active targeting, and many other techniques.

Each approach is needed to obtain a good PP oral delivery; hence, multiple formulation techniques may be combined into one.

In conclusion, this review display the important aspects of Peptides and Proteins, and the different approaches for enhancing their oral absorption and permeation.

Keywords: Diseases, nanoparticles, oral delivery , PPs.



The global market for therapeutic peptides, valued at a staggering 26.98 billion \$US in 2019, is projected to nearly double to about 51.24 billion \$US by 2027. This exponential growth rate of 8.7% annually from 2020 to 2027 (2) underscores the immense potential and growing demand for PPs, making them a highly promising area of research and development in the pharmaceutical industry.

While oral delivery is the most appealing, safe, and compliant route of administration, it poses significant challenges for PPs. These challenges have prompted numerous efforts to overcome them (Table 1) and develop alternative delivery methods. The parenteral route, despite its limitations in terms of oral bioavailability, is often preferred. However, factors such as pain, injection phobia, needle size concerns, injection site irritation, and long-term injection requirements can significantly hinder medication compliance (3).

The biological barriers are the main difficulties that restrict PP absorption, and it is critical to comprehend the biological and preparation variables to overcome these problems concerning the administration of PPs. These variables involve enzymes, pH, mucus, and the epithelial permeability of the stomach and intestines, which all affect the bioavailability of PPs after oral administration. This review involved different strategies for enhancing the absorption and permeation of oral PPs.

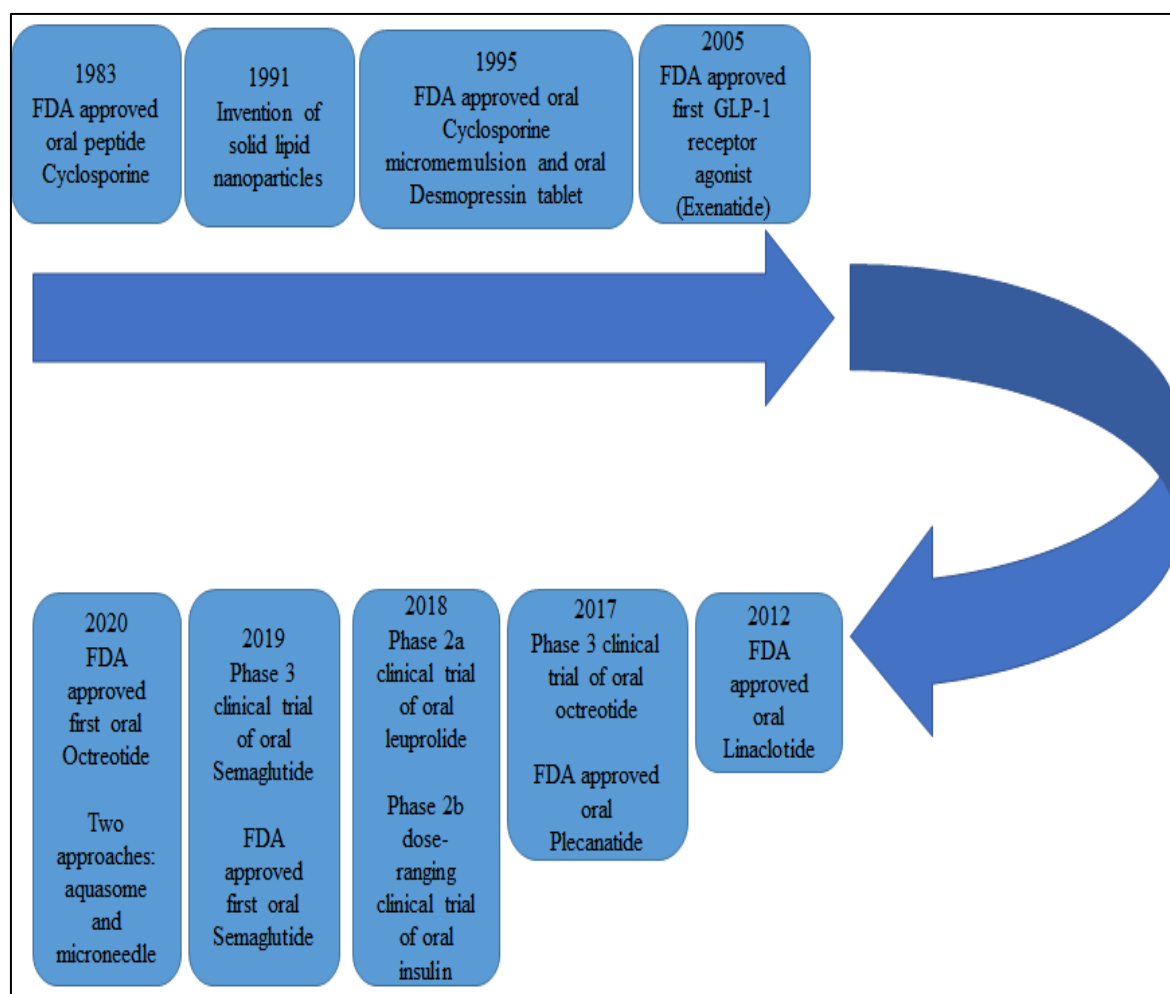


Figure.1: Development of PPs (modified from: Chen *et al.*, 2022 (4))

Table. 1:The barriers for oral administration of PPs

Absorption barriers	The effect
pH gradient	Conformational alteration of PPs leading to low therapeutic efficacy (5)
Proteolysis Enzymes	Many proteins degraded in gastric fluids rapidly (6)
Mucus	Reduce the PPs diffusion through mucus affects their residence time in the small intestine (7)
Epithelial barriers	Restricted towards oral protein drug delivery and a gatekeeper to macromolecules (8)

Approaches to Enhance the Oral PP Formulations

Different approaches are used to overcome the difficulties of biological barriers and improve the solubility, permeability, and stability of macromolecules, such as absorption enhancers, cell-penetrating peptides, and proteolytic enzyme inhibitors (Figure 2).

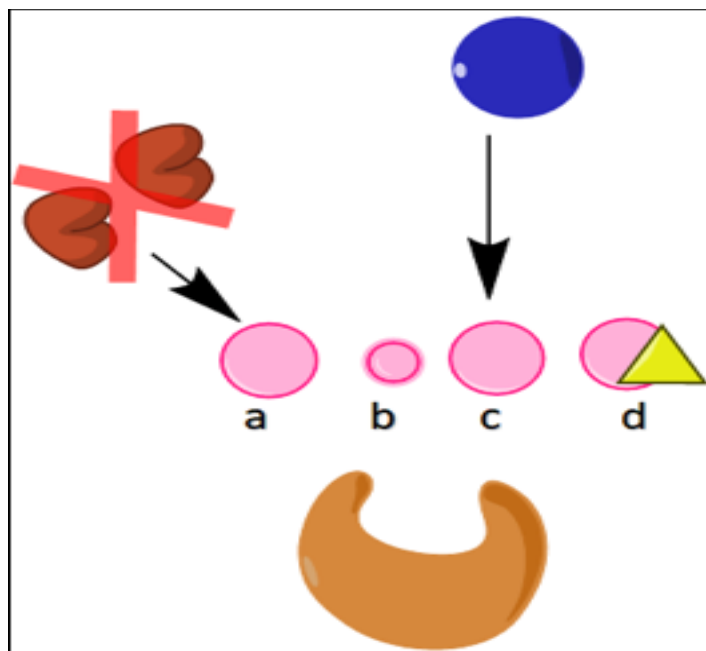


Figure. 2 Different approaches to improve oral PPs(a, enzyme inhibitor; b, nanoparticle; c, chemical modification; d, absorption enhancer)

One of the significant approaches to enhance the absorption of PP is to use the natural products that the body needs and allow for penetration as a carrier system, for instance, vitamin B12

(vitamin 12), which is absorbed by an active transporter. Chalasani et al. have harnessed the combination effect of both nanoparticles (NPs) and the active transporter for VB12 for the enhancement of insulin oral absorption. These dextran NPs – Vit B12 conjugates target the systemic circulation via VB12-IF-IFR (intrinsic factor receptor) ligand-mediated endocytosis which is ligand responsible for the absorption of vitamin B12 from the GIT. These conjugates were tested in diabetic rats, they show a profound blood glucose lowering effect and prolonged antidiabetic effect(9).

PE Glation, a technique that links the desired PPs covalently with Poly ethylene glycol moiety, has practical implications in enhancing the solubility, blood distribution, and reducing immunogenicity of PPs. Nojima et al. has successfully used this technique for the delivery of lactoferrin, an iron-binding glycoprotein with numerous pharmacological effects such as immunomodulation, antimicrobial, anti-inflammatory and lipid metabolism. The lactoferrin-PEG conjugates were examined in vitro and in vivo for their pharmacological and pharmacokinetic properties. Resistance to proteolytic enzymes was enhanced, which was examined when the half-life increased 6 folds of the conjugate compared with the original drug. This suggests that this modification enhances the bioavailability of lactoferrin(10).

Del Curto et al. prepared an oral formulation of insulin with camostat mesylate and sodium glycocholate, assayed by high-performance liquid chromatography (HPLC), and then stored them at four °C for 12 months. There was no significant increase in the degradation product or decrease in the content or percentage of the protein (11). The formulation involved the active ingredient insulin (a peptide hormone) and excipients to improve its oral delivery: camostat mesylate (protease inhibitor) and sodium glycocholate (absorption enhancer). Then, the overall formulation showed a great insulin release in the body.

Although it is preferred to use one or more than one approach to enhance the oral bioavailability of PPs, as discussed previously, incorporating nanoparticles plays a significant role in facilitating its penetration and enhancing the blood circulation time inside the body according to the different compositions of the nanoparticles.

Su et al. encapsulated NPs with Diethylene triamine penta-acetic acid (DTPA) and γ PGA-DTPA. The developed NP insulin system swelled and disintegrated with a pH greater than 7, resulting in reduced blood glucose levels with a maximum concentration at 4 hours and a relative bioavailability of about 20% following the treatment (12). This nano-formulation insulin with (DTPA) (a chelator) and a γ PGA-DTPA (protease enzyme inhibitor) improved intestinal oral insulin because of the ability of the chelator to inhibit intestinal proteases and break up intestinal tight junctions in a pH-sensitive medium.

Gradauer et al., (2013) (13) used liposomes to enhance salmon calcitonin's absorption as a model drug through the gastrointestinal tract. These liposomes were coated with a mucoadhesive polymer (chitosan -thioglycolic acid). This coat will keep the particles in contact with the intestinal mucosa for a prolonged time, allowing permeation enhancement. The preparation method was thin film hydration to obtain liposomes, and then the drug was loaded into the formulated liposomes. The excellent stability is related to particle size reaching 500 nm and a zeta potential near ± 40 . The permeation of the liposomes was enhanced by about 3.8 folds in ex vivo experiments. At the same time, the in vivo study, after allowing the rats to ingest orally prepared formulations and measuring the blood level of calcium, showed an 8.2-fold increment in the area under the curve. These results encouraged further development in the oral delivery of PPs using NPs (13).

Conclusion

In conclusion, this review displayed the proposed novel approaches to enhance the oral delivery and absorption of proteins and polypeptides, which are crucial for their pharmacological effects. While the oral route is the most preferred, numerous barriers hinder the PPs absorption and permeation. Therefore, a variety of techniques have been used to enhance the PPs oral delivery such as nanotechnology, enzyme inhibitors, mucoadhesive, active targeting and others. It is important to note that no single technique is sufficient to establish a good oral bioavailability of proteins and polypeptides, hence the suggestion to combine multiple approaches in a single formulation.

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Competing interests statement

The authors declared that they have no conflict of interest.

Ethics statement

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to.

Author contributions

Author 1 provided the concepts, data analysis, and writing of the manuscript; Author 2 worked with data analysis and writing of the manuscript; Author 3 worked with data analysis; Author 4 revised the manuscript.

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