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[Review Article] Nanocarriers for Protein and Peptide Drug Delivery

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Abstract

Background: Protein and peptide drugs offer significant promise as therapeutic agents due to their superior efficacy and reduced toxicity compared to conventional chemical drugs. Nevertheless, difficulties with medication delivery techniques impede their practical deployment. Poor absorption limits non-invasive delivery methods such as nasal, pulmonary, and transdermal distribution, whereas oral administration suffers from low bioavailability and stability problems. Parenteral administration involves certain difficulties, such as low patient compliance and pain, but it also shows promise as a protein-based drug delivery method.

Aim: This review article aims to explore the development of structure-based nanocarriers designed for drug delivery, which have shown potential to address the limitations associated with protein and peptide drug delivery.

Materials and Methods: A complete literature review was undertaken utilizing Google Scholar and other trustworthy scientific sources to acquire relevant material for this study. Keywords included in the search were “Nanocarriers”, “bioavailability”, “absorption”, “peptide”, “protein drug delivery”, and “permeability”. This review investigated peer-reviewed publications, research papers, and reviews relating to the issue of inclusion.

Results: The review highlights the advancements in structure-based nanocarriers for protein and peptide drug delivery. These nanocarriers have demonstrated reduced side effects and improved therapeutic efficacy compared to free drug molecules. The ability of new and advanced nanocarriers to facilitate targeted drug delivery, overcome physiological barriers, and enable controlled drug release within the body is discussed.

Conclusion: By developing structure-based nanocarriers, the problems with conventional drug delivery techniques may be addressed, and protein and peptide medication delivery can be improved. Potential benefits of these nanocarriers include enhanced absorption, tailored drug administration, and greater bioavailability, which might result in safer and more successful treatment results for a range of illnesses.

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Introduction

Peptides and proteins are essential for contemporary biomolecular applications, particularly in the diagnostic domain. Many proteins and peptides, including insulin, antibodies, recombinant proteins, and vaccinations, show great promise. However, owing to their short half-life in bodily fluids and quick breakdown in the gastrointestinal system, oral use of these drugs is frequently restricted. As a result, most protein-based medications are typically delivered through intravenous as well as dermal routes to ensure their efficacy and therapeutic effectiveness [1]. Skin barriers, local allergies, and permeability are some of their disadvantages. Applications in medicine have shown considerable potential for nanotechnology. Numerous nanomedicines are being studied in clinical settings, and several have been authorized for use in medicine. The size of the nanoparticles and a high surface-to-volume ratio are two physical and chemical characteristics that often set apart drug delivery methods at the nanoscale [2]. These attributes have a major impact on the properties of nanocarriers, especially when it comes to passive targeting techniques [3]. Nanoparticles of diameters ranging from 10 to 150 nm, including inorganic nanomaterials, micelles, polymer nanoparticles, and liposomes, provide considerable benefits as drug carriers. The use of nanoparticle technology in protein delivery can be applied to the following: I extending the half-life of proteins with poor pharmacokinetic properties in vivo; ii) protecting proteins from premature degradation or denaturation in biological environments; iii) facilitating controlled and sustained release of optimum drug concentrations, and iv) targeting sick tissue, cells, and subcellular sections, hence increasing biologic therapies' safety and effectiveness [4][5].

A variety of materials are used to create different nanostructure delivery systems. Polymeric nanoparticles have been widely employed in the development of controlled-release and targeted medication delivery systems. However, synthetic polymers may pose toxicity concerns and lack sufficient biocompatibility. As an alternative, natural biodegradable polymers, including proteins, offer more desirable characteristics in terms of safety and biocompatibility. Thus, for biological treatment, natural protein-based nanoparticles are becoming more and more popular [6][7].

Potential Nanocarriers Approaches

To increase the activity of peptides and proteins, colloidal particle carriers have been widely used in pharmaceutical formulations. Exciting techniques include mucoadhesive polymers, microspheres, nanoparticles, nanoemulsion, and nanoemulsion [8]. The following are effective methods for delivering proteins and peptides utilizing different carrier systems.

I) Microsphere

The microspheres are made of biodegradable polymers, are readily injected subcutaneously as a parenteral depot, and have an acceptable size range of 1 μm to 100 μm [9]. Although it is also possible to deliver them orally, the oral bioavailability of this medication is very low due to its poor absorption, but the release of its active ingredients in the gastric tract after the effect of several degradative enzymes. Because the subcutaneous administration approach provides regulated medication release and does away with the necessity for frequent invasive dosage, it is highly sought after [10]. The crucial factor in microsphere formulation lies in the selection of the appropriate polymer. Both natural and synthetic polymers are utilized based on their distinct release profiles. The release of drugs from microspheres depends on two main mechanisms: first, diffusion of the bioactive substance and polymer degradation. Polyester stands out as the most commonly employed polymer among all for this purpose [11]. Polyester microspheres can be prepared using different techniques, including double emulsification, spray drying, and phase separation-coacervation. These microspheres exhibit higher physical and chemical stability compared to liposomes and are valuable carriers for protein drug delivery in pulmonary administration [12][13]. Several dosage forms in pharmacies composed of protein-based drugs using biodegradable microspheres are available [14]. See Table 1.

Table 1. Pharmaceutical Drugs and their Trade Names, Companies, Routes, and Applications

Drug	Trade Name	Company	Route	Application
Leuprolide acetate	Lupron	Takeda- Abbott	3-month depot suspension	Prostate Cancer
Goserelin acetate	Zoladex	I.CI.	S/c implant	Prostate cancer
Octreotide acetate	Sandostatin	Novartis	Injectable s/c suspension	GH suppression anticancer
Triptorelin recombinant bovine somatropin	Posilac	Monsanto	Oil-based injection	To increase milk production in cattle
Minocycline	Arestin	Orapharma	Unit dose cartridge	Nill
Buserelin	Suprecur	Sanofi- Aventis	Nill	Nill

II) Microemulsion

The microemulsion is transparent, with several characteristics such as thermodynamic stability, isotropy, and a composition mainly consisting of surfactant, water, and oil. The water-in-oil type of microemulsions has special benefits. Because of their inherent water solubility, proteins and peptides may pack more information into their hydrophilic cores [15]. By doing this, the protein is shielded from peptide breakdown and external denaturation. A lipophilic environment that resembles the skin's outer layer surrounds the outer phase and facilitates the simple absorption of

bioactive compounds via the skin [16][17]. Microemulsions are a good choice for topical treatment on the skin's surface because of this resemblance. This microemulsion composition has particles that are 0.15 µm in size. A very promising drug delivery technique, insulin encapsulation, was used to further investigate the W/O/W approach of numerous emulsions [18][19].

III) Nanoemulsion

Nanoemulsion is a thermodynamically stable, isotropic, transparent or translucent particle with a particle size of 1 to 100 nm formed spontaneously from water, oil, surfactants, and co-surfactants. It is a homogeneous dispersion system. Generally speaking, nanoemulsions are divided into three types, namely oil-in-water nanoemulsion (O/W), water-in-oil nanoemulsion (W/O), and bicontinuous nanoemulsion (B.C). This dispersion system was first discovered and reported by Hoar and Schulman in 1943. It was not until 1959 that Schulman proposed the concept of "Nanoemulsion" [20][21]. Since then, theoretical and applied research on nanoemulsions has developed rapidly. Nanoemulsification technology has penetrated the fields of daily chemicals, fine chemicals, petrochemicals, materials science, biotechnology, and environmental science; it has become a research field with huge application potential in the world today [22].

Nanoemulsion has many advantages that are unparalleled by other preparations: ① It is an isotropic transparent liquid, a thermodynamically stable system, and cannot stratify even after autoclaving or centrifugation; ② The process is simple, and no special equipment is required for the preparation process. It can form spontaneously, and the particle size of nanoemulsion is generally 1 to 100 nm; ③ low viscosity, which can reduce pain during injection; ④ has sustained release and targeting effects; ⑤ improves the solubility of the drug, reduces the enzymatic hydrolysis of the drug in the body, and can form a protective impact on drugs and improve the absorption of drugs in the gastrointestinal tract, improving the bioavailability of drugs [20]. Therefore, nanoemulsion has received widespread attention as a drug carrier. Nanoemulsions are essential in the preparation of oral and topical dosage forms that enable optimum transport of proteins and peptides. The latest research in the field of nanoemulsion showed that it has the best pharmacokinetic and biopharmaceutical properties as compared to routinely designed dosage forms of drugs [23].

IV) Nanoparticles

The rapid progress in nanotechnology offers a groundbreaking approach to designing drug delivery systems utilizing nanoparticles. These nanoparticles serve to protect proteins and facilitate their targeted delivery to specific locations within the body. Nanoparticles have found wide applications as carriers for delivering both chemical compounds and biomolecular drugs, including anticancer medications and therapeutic proteins [24][25]. In nanoparticle formulation, natural biomolecules like proteins are gaining popularity as a safer alternative to synthetic polymers. Various approaches are employed to formulate nanoparticles and ensure their targeted delivery to specific sites [26].

Several substances can form these systems. Nanoparticles, depending on their properties, can be made of lipids, such as liposomes and micelles, solid lipid nanoparticles, protein-based nanoparticles, as well as inorganic and polymer-based nanoparticles (both synthetic and natural). These nanoparticles are employed for protein distribution [27]. In general,

protein nanoparticles exhibit numerous benefits, including biocompatibility, biodegradability, and versatility compared to other nanosystems. More specifically, because of their remarkable biocompatibility, stability, rigid structure, well-defined pore structure, programmable shape, and customizable surface chemistry, mesoporous silica nanoparticles (MSNs) have attracted a lot of interest in protein delivery [27].

a) Liposomes

A liposome refers to a spherical-shaped nanoparticle made of either one or several phospholipid bilayers, resembling the structure of cell membranes [28][29]. These liposomes have proven to be valuable medical delivery systems owing to their capacity to encapsulate both hydrophilic and lipophilic medications. To address these issues, researchers are employing various strategies, including coating the vesicles [30][31].

Liposomes have been thoroughly researched as potential delivery systems for proteins and peptides, with a specific focus on their suitability for oral administration. One of the key advantages of liposomes in oral delivery is their capability to protect proteins (e.g., Insulin, Lactoferrin) from hydrolytic processes by gastric enzymes (GIT). Lactoferrin, in particular, has garnered significant attention due to its essential role in the immune system and its antioxidant, anti-inflammatory, anti-viral, and anti-bacterial properties [32]. However, its oral bioavailability is limited by susceptibility to gastrointestinal enzyme hydrolysis. To overcome this limitation, researchers have investigated the encapsulation of lactoferrin in liposomes [33]. Moreover, certain studies have reported successful dermal delivery of proteins, including superoxide dismutase, tissue growth factors, and interferons, using liposomes as carriers [34][35].

b) Protein-based nanoparticles

Protein nanoparticles have gained significant attention in research due to their biologically safe properties and ability to be metabolized and biodegraded. Their high affinity for drug encapsulation capacity and solubility characteristics make them particularly favourable as nanocarriers [36][37]. Protein nanoparticles encompass several nanomedicine classes, wherein drugs are either linked to proteins as carriers or the active therapeutic agents themselves are recombinant proteins [38]. These nanoparticles can be formulated using both animal-based and plant-based proteins. Animal proteins come from seafood, egg yolks, milk, and other tissues that animals produce, whereas plant-based ones come from plant sources [19][39]. Figure 1 illustrates the frequently utilized animal proteins, while Figure 2 displays the commonly employed plant proteins concerning the delivery of bioactive molecules.

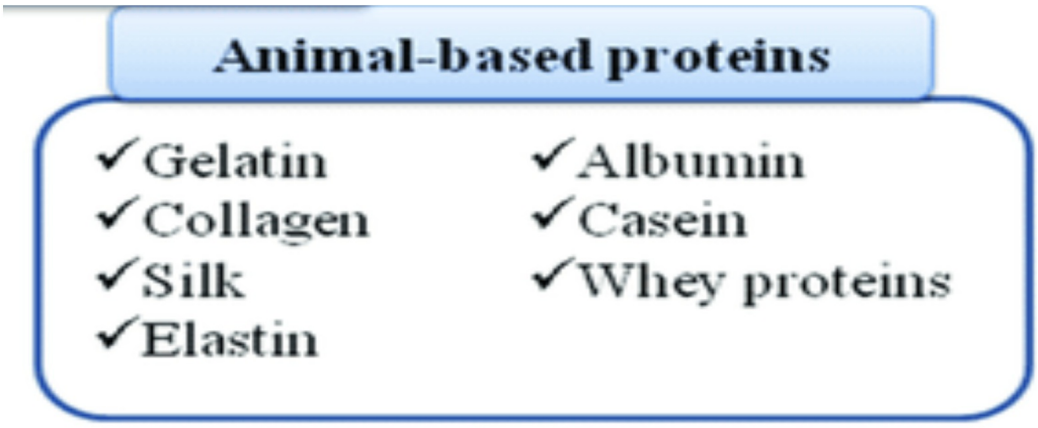

Figure: 1. Animal Proteins

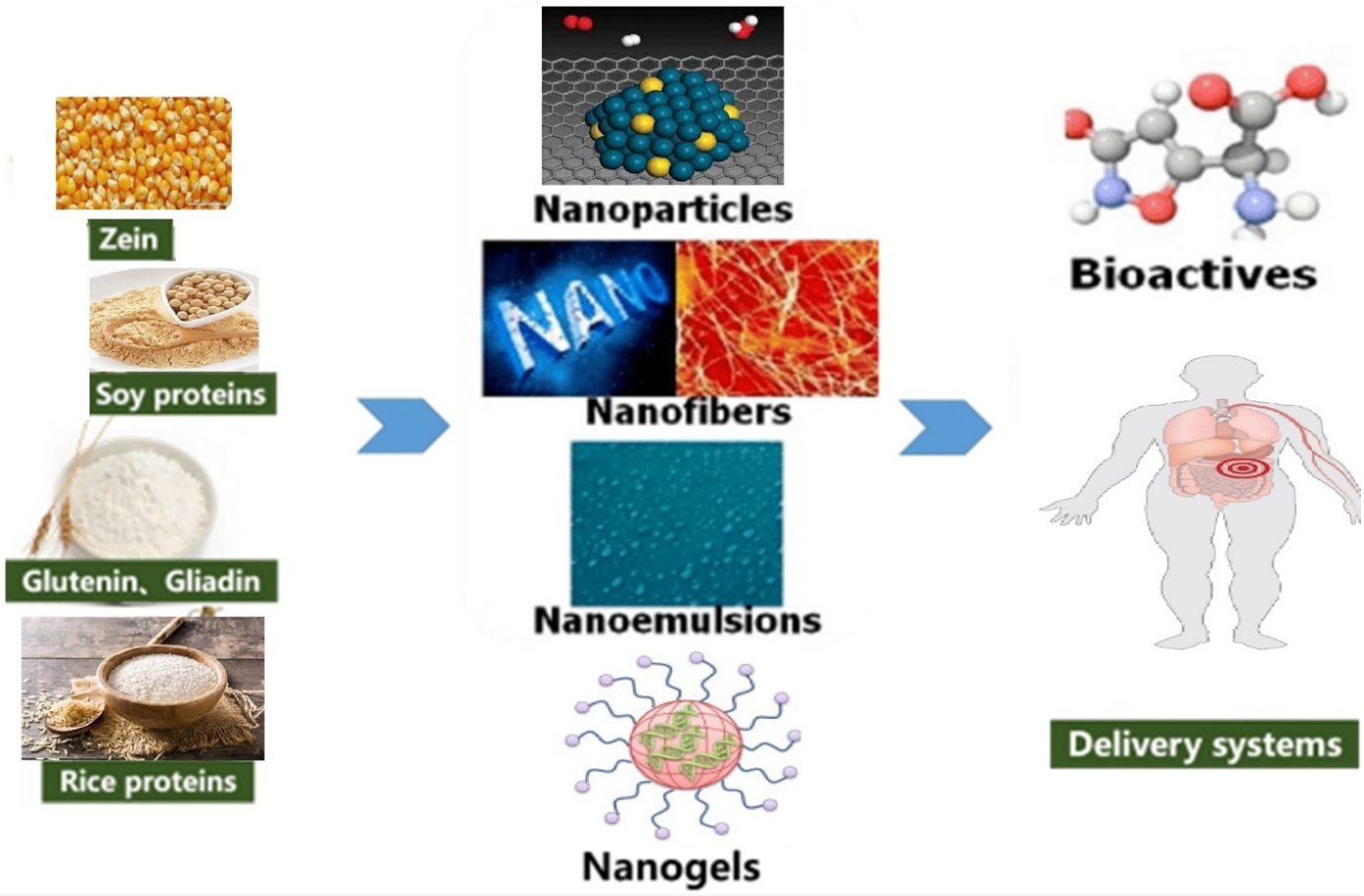

Figure 2. Plant Protein Sources

c) Polymeric Nanoparticles

Therapeutic proteins may be delivered to a precise location using polymeric nanocarriers, which also shield the body from any physiological alterations brought upon by outside stimulation. The capacity of charged surface nanoparticles to provide mild protection through electrostatic interactions makes them desirable for a variety of applications [38].

Different techniques are used to prepare natural and synthetic polymers into polymeric nanoparticles. The following table

lists some of the frequently used natural and man-made biodegradable polymers. Different techniques are used to prepare natural and synthetic polymers into polymeric nanoparticles. The following table lists some of the synthetic biodegradable polymers and natural polymers that are often employed [40].

Table 2. Polymeric Nanoparticles for Targeted Drug Delivery (Both Natural and Synthetic Polymers)

Natural Polymers	Synthetic Polymers
Cyclodextrins	Albumin
Xanthan Gum	Silk
Polysaccharides	Protein-based polymers
Chitosan	Fibrin
Alginate	Gelatin
Dextran	Elastin
Hyaluronic Acid	Corn Zein
Pectin	Keratin

Several considerations play a crucial role in selecting the suitable polymer for formulating polymeric nanoparticles, including factors like biocompatibility, safety, and immunogenicity [40]. Figure 3 illustrates the fundamental conventional method of protein-conjugated polymeric nanoparticles.

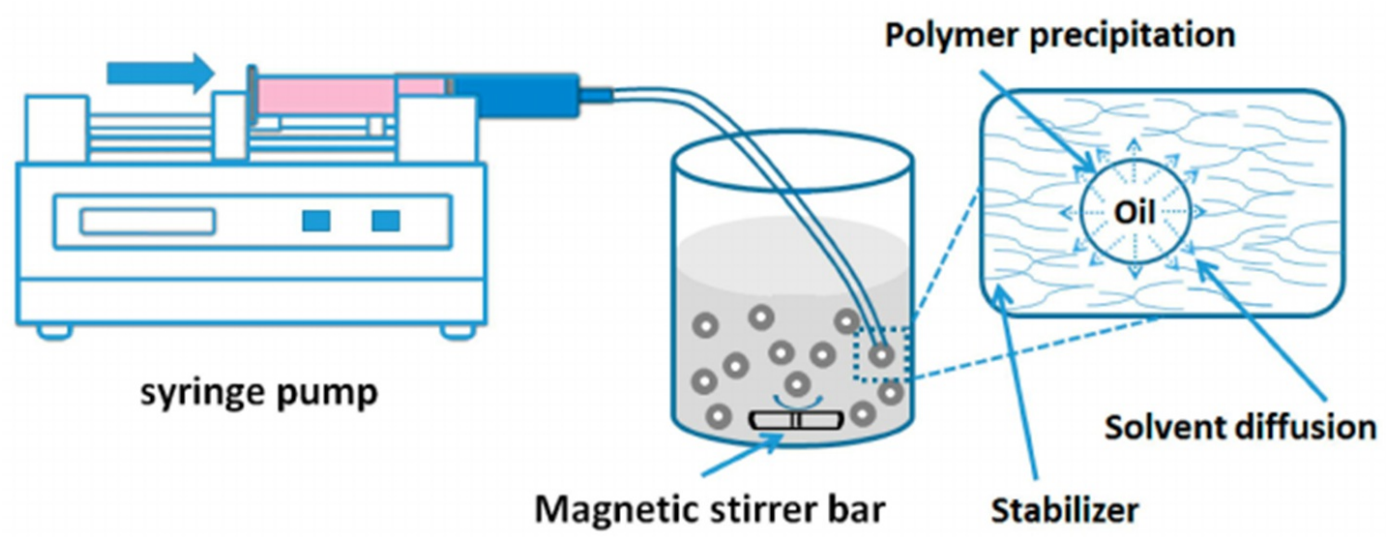

Figure 3. Diagram illustrating the classical method for polymeric nanoparticles.

d) Inorganic Nanoparticles

Inorganic nanoparticles have garnered increasing interest as carriers for proteins or peptides due to their specific

properties. These macromolecules can be encapsulated inside the nanoparticles, providing protection against enzymatic degradation. Porous inorganic nanoparticles are appealing for API (Active Pharmaceutical Ingredient) delivery as they allow loading of the API within their structure, offering additional control over drug release kinetics. Several properties regulate the rate and the release of bioactive substance, including the size of particles, and the pores' related surface shape. Pore capping or filling strategies can be tailored to regulate the release of bioactive molecules from these nanoparticles. Gold nanoparticles, carbon nanotubes, quantum dots, calcium, porous silicon, and mesoporous silica nanoparticles are examples of inorganic nanomaterials [41]. Among these, mesoporous silica nanoparticles have been extensively employed due to their inert, non-immunogenic nature and their capacity to efficiently load therapeutic agents, facilitated by their large surface area and pore volume [6].

The unique properties of inorganic nanoparticles have sparked interest among researchers in incorporating them into biomaterials, leading to the creation of multifunctional hybrid materials that provide enhanced control over API release. In a study by Kane et al., the effective intracellular delivery of antibodies was demonstrated using silica nanoparticles. These nanoparticles were loaded with proteins and antibodies after being surface-modified using n-octadecyltrimethoxysilane (n-ODMS) [42].

e) Solid Lipid based Nanoparticles

To overcome the drawbacks of liposomal drug administration, solid lipid nanoparticles were introduced in 1990 as an alternative to liposomes and emulsions [41]. These nanoparticles have proven to be efficient in drug delivery through various routes, including dermal, ocular, rectal, and pulmonary, offering controlled release, enhanced drug stability, and improved safety [43]. Solid lipid nanoparticles are made of a solid lipid matrix, whereas the matrix of nanostructured lipid carriers is made up of a combination of liquid and solid lipids [43]. These carriers have a surfactant coating on their surface that stabilizes their hydrophobic core, which stays solid at body temperature. Waxes, acyl-glycerol mixes, and pure tri-acyl-glycerol complexes are the most often utilized lipids in these systems [44]. The two primary methods of manufacture are the microemulsion-based technology and high-pressure homogenization. Under the brand name NanoRepair™, Dr. Rimpler's topical version of SLN has already been commercialized [44].

V) Mucoadhesive Polymeric Systems

Protein distribution using mucoadhesive polymeric systems is a highly creative technique that makes use of the bioadhesive qualities of polymeric materials and the mucosal surface. After hydration, the polymers with certain structural characteristics stick to the mucus layer [45]. This adhesion's longer residence duration results in a greater concentration of the medicinal compounds. Different polymer types included in the formulation result in different adhesion mechanisms [46].

Table 3 lists a few potential interaction theories along with their processes.

Methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, and thiol groups are examples of mucoadhesive nanocarriers for protein delivery [47]. Polyacrylic acid derivatives like carbopol and polyacrylate are other polymers that are employed. Some of the newest polymers, including cationic chitosan and anionic alginate, gain their superior adhesive

characteristics over unmodified polymers through strong disulphide bonding with the mucus layer [47].

Table 3. Interaction Theories and Mechanisms of Mucoadhesive Polymeric Systems for Protein Delivery

Theory	Mechanism
Electronic	Electrons transfer between mucus and polymer, forming a double layer of electrical charge.
Adsorption	Van der Waals interaction and hydrogen bonding
Wetting	Polymers' ability to swell and spread over mucous layers.
Diffusion	The mucoadhesive polymer interpenetrates and physically entangles with the mucus layer.

Conclusion and Future Trends

In conclusion, the utilization of nanocarriers for protein and peptide drug delivery represents a pivotal advancement in therapeutic modalities. This review has elucidated the various nanocarrier systems available, their mechanisms of action, and their potential in enhancing the bioavailability, stability, and targeted delivery of protein and peptide drugs. Nanocarriers have successfully addressed some of the inherent challenges associated with protein and peptide therapeutics, such as degradation by enzymatic processes and poor membrane permeability. However, while significant progress has been made, the translation from laboratory research to clinical practice faces considerable hurdles, including scalability of production, reproducibility of therapeutic effects, and stringent regulatory challenges.

Proteins are essential medicinal substances that are employed in the management of several illnesses. Consequently, for the therapeutic effect, their distribution to the biological location is essential. It is quite difficult to get these molecules to the site because of their vast size, high molecular weight, and extremely complicated structure. Their application has been restricted by their unfavorable physicochemical characteristics, which include hydrophilicity, stability, and macro size. Numerous nanocarriers have been created to address these issues. The safe, simple, and effective distribution of the target proteins and peptides was the subject of several of the strategies covered in this article. The problems associated with peptide/protein-based medication delivery in the contemporary period may be effectively resolved by combining the two methods. It would be very helpful to create a safe and effective nanocarrier system that can transport and preserve the systemic stability of different proteins and peptides in the near future.

Future research should focus on the optimization of nanocarrier design to improve targeting specificity and payload release control. Innovative strategies for crossing biological barriers and reaching intracellular targets need to be explored to expand the therapeutic potential of protein and peptide drugs. Additionally, long-term in vivo studies are essential to understand the biodistribution, biodegradation, and potential immunogenicity of nanocarriers. From a technological standpoint, the development of scalable manufacturing processes that comply with regulatory standards is critical for the commercial viability of nanocarrier systems. Furthermore, interdisciplinary collaboration among nanotechnologists, biologists, chemists, and clinicians is paramount to the development of next-generation nanocarrier systems that are safe,

effective, and patient-friendly. Lastly, ethical considerations and patient-centric approaches in the development of nanocarrier-based therapeutics will be integral to their success and acceptance in mainstream healthcare.

Statements and Declarations

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Author contribution

All Authors contributed equally to this review.

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