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Protein Nanoparticles in Therapeutic Drug Delivery

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Abstract

Protein-based nanoparticles have emerged as a highly promising class of nanocarriers for drug delivery, offering unique advantages in terms of biocompatibility, biodegradability, and functional versatility. These nanoscale systems, derived from natural or engineered proteins, enable precise control over particle size, surface properties, and drug release kinetics—critical parameters for achieving targeted and efficient therapeutic outcomes. This review presents a comprehensive overview of the development, fabrication methods, and biomedical applications of protein-based nanoparticles. We discuss various types of proteins utilized in nanoparticle construction, including albumin, gelatin, chitin, silk fibroin, ferritin, and virus-like particles, highlighting their structural properties and suitability for different delivery contexts. Special emphasis is placed on recent advances in dynamic and stimuli-responsive protein nanoparticles, which can disassemble or activate in response to specific physiological conditions, enabling controlled drug release and enhanced cellular uptake. Additionally, we examine current challenges in clinical translation, such as scalability, immunogenicity, and regulatory considerations. Overall, this review aims to provide an in-depth understanding of the design principles, functionalities, and future directions of protein-based nanocarriers in drug delivery and related biomedical applications.

Keywords: protein nanoparticle, drug delivery, biocompatible, biodegradable, controlled release.

1. Introduction

Drug delivery systems are engineered to transport therapeutic agents to specific sites within the body, enhancing efficacy while minimizing systemic toxicity. These systems improve pharmacokinetics, enable controlled or sustained release, and facilitate localized drug delivery [1]. Effective therapy requires maintaining drug concentrations within a therapeutic window and ensuring consistent release rates of bioactive compounds. Consequently, the development of advanced drug delivery platforms has gained significant attention.

Historically, protein-based delivery systems trace back to the 1970s, when albumin microparticles were introduced for circulatory diagnostics in nuclear medicine [2], soon followed by therapeutic applications [3]. These early platforms employed preparation methods such as emulsification [4], chemical crosslinking [5], and desolvation [6]. A pivotal shift occurred in the late 2000s with the development of gentle formulation techniques that preserved protein function and structure [7], facilitating the use of diverse functional proteins and enzymes in delivery systems. These advances laid the groundwork for multifunctional protein nanoparticles used in theranostic imaging [8] and enzymatic nanoreactors [9].

Nanomaterials such as liposomes [10,11], synthetic polymers [12,13], dendrimers [14,15], and magnetic nanoparticles [16,17] have been extensively explored as drug carriers. Among these, nanoparticle-based formulations are particularly suited for poorly soluble drugs, as their small size enhances dissolution in physiological fluids and promotes cellular or tissue-specific targeting.

Artificially assembling proteins into nanostructures offers significant therapeutic advantages over free proteins, including enhanced circulation times, improved cellular uptake, and the spatial arrangement of multiple functional domains—beneficial for drug delivery and multistep catalytic processes [18,19].Recently, biopolymer-based nanoparticles, particularly those derived from proteins, have emerged as promising alternatives due to their biocompatibility, low immunogenicity, and biodegradability [20]. Proteins are highly ordered biopolymers composed of linear peptide chains that fold into intricate three-dimensional conformations, conferring diverse biological functions. They are involved in processes ranging from molecular transport to structural support and cellular signalling. Their well-defined structures, specific receptor interactions, and biological relevance render them ideal for biomedical use.

More recently, attention has turned to dynamic protein nanoparticles that respond to environmental stimuli. These systems are designed to disassemble into native protein building blocks upon cellular uptake, enabling controlled release and intracellular delivery of functional proteins—an approach with growing promise in protein-based therapeutics [21].

Protein nanoparticles offer several inherent advantages, including ease of size control, surface modifiability, and protection of cargo from enzymatic degradation and renal clearance, which extends half-life and bioactivity [22]. Their small size facilitates uptake via endocytosis [23], and their generally non-antigenic nature allows them to be used in applications ranging from pulmonary delivery [24] and cancer therapy [25] to tumor targeting [26] and vaccination [27]. Moreover, optimizing parameters such as particle size, surface properties, and drug loading remains critical to tailoring pharmacological responses and site-specific delivery [28].

This review highlights the proteins most commonly employed in nanoparticle fabrication, the diverse methods of their assembly, and provides a comparative analysis of their respective strengths and limitations in drug delivery applications.

2. Types of protein for nanoparticle preparation

Table1. Comprehensive Table of Protein Nanoparticles

Protein (source / class)	Typical particle features	Typical drugs / uses	Prep methods	Key advantages / limitations	Zeta potential & EE%
Albumin (HSA, rHSA)	Spherical; ~50–200 nm (Abraxane ≈130 nm)	Paclitaxel (Abraxane), hydrophobic drugs; cancer	Nab, desolvation, self-assembly	Clinically proven, biocompatible; recombinant forms improve uniformity but cost more	Zeta: −5.6 to −26.8 mV; EE: 82–98%
Gelatin (animal)	Smooth spherical; ~100–300 nm (tunable)	DOX, antibiotics, vaccines, small molecules	Desolvation/coacervation, emulsification, crosslinking	Biodegradable, cell-adhesive; may need crosslinkers (toxicity risk)	Zeta: −40 mV; EE: 53.7–65.1%
Silk fibroin	Spherical / irregular; 50–400 nm; slow degradation	Curcumin, DOX, antibiotics, growth factors	Desolvation, nanoprecipitation, electrospray	Mechanically robust; sustained release; controllable by β-sheet content	Zeta: negative (pH-dependent); EE: up to 98%

Zein (plant prolamin) & glycosylated composites	Hydrophobic NPs, ~50–300 nm; good hydrophobic cargo entrapment	Hydrophobic drugs, nutraceuticals; oral delivery	Antisolvent precipitation, emulsification, spray drying	Good oral stability, long-term release; plant origin reduces zoonotic risk	Zeta: +21.6 to +23.5 mV; EE: >98.5%
Casein (milk protein)	Micellar / self-assembled NPs, ~50–200 nm	Hydrophobic drugs, vitamins, nutraceuticals; oral delivery	Self-assembly, desolvation, spray drying	Food-grade, amphiphilic pockets for hydrophobic drugs	Zeta: −8 to −40 mV; EE: 85–95%
Ferritin & protein cages (viral capsids, engineered cages)	Uniform hollow cages (inner ≈8–12 nm)	Small drugs, metal ions, contrast agents, enzymes; theranostics	Recombinant expression, disassembly/reassembly loading	Very uniform; modifiable; limited cargo volume	Zeta: around −20 mV; EE: varies, often low unless optimized
Elastin-like polypeptides (ELPs) / recombinant polypeptides	Tunable (10s–200s nm), stimuli-responsive	Small drugs, peptides, proteins; depot/tumour targeting	Recombinant expression → self-assembly, coacervation	Precise sequence control; cost & scale challenges	Varies; formulation-specific
Lipoprotein / apolipoprotein mimetics (HDL-like)	Discoidal / spherical, ~8–30 nm	Lipophilic drugs, siRNA, imaging agents	Reconstitution with phospholipids + apoproteins	Natural tropism; complex formulation	Varies; depends on system
Lactoferrin (Lf; iron-binding glycoprotein)	Spherical, ~60–250 nm; slightly positive surface charge	Doxorubicin, paclitaxel, rifampicin, peptides, nucleic acids; brain targeting	Desolvation, ionic gelation, nanoprecipitation	Receptor-mediated uptake; excellent biocompatibility; protects drug from enzymes	Zeta: −10.4 mV; EE: 28.9–97%

2.1 Human Serum Albumin Nanoparticles for Targeted Drug and Gene Delivery

Human serum albumin (HSA) is a globular, non-glycosylated plasma protein composed of approximately 585 amino acids, corresponding to a molecular weight of ~66 kDa [19]. Structurally, HSA comprises three homologous domains (I–III), each divided into subdomains A and B, with two major drug-binding regions known as Sudlow's sites I and II located in subdomains IIA and IIIA, respectively [29]. Owing to its abundant availability and intrinsic ligand-binding capacity, HSA serves as a natural carrier that enhances the solubility and systemic transport of hydrophobic molecules. HSA exhibits exceptional physicochemical stability, remaining functional over a pH range of 4–9 and resistant to heat denaturation up to 60 °C for prolonged periods [30–32]. Its biodegradability, non-immunogenicity, and aqueous solubility further contribute to its wide biomedical applicability.

HSA nanoparticles (HSANPs) have emerged as versatile carriers for drugs, peptides, and nucleic acids. The presence of surface amino, carboxyl, and thiol groups allows covalent coupling of targeting ligands and functional moieties [33-34]. Typically fabricated via the desolvation method, the physicochemical characteristics of HSANPs—including size, polydispersity, and zeta potential—are governed by protein concentration, solvent composition, ethanol addition rate, and choice of crosslinker [29]. Jahanban-Esfahlan et al. reported that increasing salt concentration or rapid ethanol addition produced larger particles, whereas optimal conditions (50–60 mg/mL protein, low ethanol rate) yielded uniform nanoparticles. Similarly, Langer et al. [19]

demonstrated that higher pH values favour smaller particles and more negative surface potentials.

HSANPs are inherently biocompatible and non-toxic, exhibiting high drug-binding capacity through both covalent and non-covalent interactions [40–42]. Saleh et al. [43] formulated curcumin-loaded HSANPs (246 ± 15 nm, $\zeta = -25 \pm 3$ mV) with 71 % encapsulation efficiency, resulting in enhanced solubility, stability, and cellular uptake in HER2-positive breast cancer cells. Clinically, albumin–paclitaxel nanoparticles (Abraxane) have demonstrated significant antitumor efficacy and manageable safety profiles in advanced pancreatic and triple-negative breast cancers [44-46]. Beyond small-molecule delivery, HSA nanoparticles have shown promise as platforms for gene and antibody transport. Mesken et al. [47] developed cell-penetrating peptide (CPP)-modified HSANPs for plasmid delivery to HEK 293T cells (size ≈ 210 nm; $\zeta \approx -45$ mV), achieving a plasmid loading efficiency of ~78 % and up to 50 % transfection efficiency with minimal cytotoxicity. Similarly, Redín et al. [48] fabricated bevacizumab-loaded HSANPs (~300 nm, $\zeta \approx -15$ mV) via desolvation, achieving a biphasic release profile with an initial burst followed by sustained release over 24 h and excellent in vivo tolerance.

Collectively, HSA-based nanoparticles represent a clinically validated, highly adaptable platform for targeted drug, gene, and antibody delivery. Their favourable stability, biocompatibility, and tuneable surface chemistry position them as one of the most advanced and translationally promising protein-nanoparticle systems in current nanomedicine research.

2.2 Gelatin Nanoparticles as Biopolymer-Based Drug Delivery Systems

Gelatin, a denatured form of collagen, is a natural, water-soluble polymer obtained through thermal, enzymatic, or hydrolytic degradation of collagen in acidic or alkaline conditions [49]. It was one of the first proteinaceous materials employed for nanoparticle fabrication. The molecular weight of gelatin ranges from 20 to 220 kDa, and it remains soluble in water above 35–40 °C [50]. Depending on the method of collagen hydrolysis, two major commercial types are available: type A (cationic, isoelectric point 7–9), derived from partial acid hydrolysis of porcine skin collagen, and type B (anionic, IEP 4.8–5), obtained from alkaline-treated bovine collagen [51-53]. Structurally, gelatin retains a partial triple-helix conformation composed of three α-polypeptide chains enriched in glycine, proline, and alanine, conferring high structural stability [54, 55]. The presence of reactive amino and carboxyl groups allows facile chemical modification and covalent attachment of drugs or targeting ligands either within the polymer matrix or on the nanoparticle surface [56]. Gelatin's biodegradability, biocompatibility, and Food and Drug Administration (FDA)-approved status make it an attractive candidate for biomedical applications [57]. Gelatin nanoparticles (GNPs) have been used to encapsulate nucleic acids, growth factors, and proteins, including DNA, RNA, bovine serum albumin (BSA), bone morphogenetic protein 2 (BMP-2), and basic fibroblast growth factor (bFGF). However, gelatin's low mechanical strength and rapid solubility necessitate crosslinking to enhance nanoparticle stability. Chemical crosslinkers such as glutaraldehyde (GA) and carbodiimide, or biological and physical methods, are typically employed to improve mechanical integrity and modulate degradation kinetics [1].

Wang *et al.* [58] demonstrated that BMP-2 and bFGF-loaded GNPs, prepared via desolvation and crosslinked with varying GA concentrations, exhibited tunable degradation and release profiles. Higher crosslinking density reduced solubility and prolonged drug release, while lower densities facilitated faster degradation. Combined delivery of the two growth factors enhanced osteogenic activity and bone regeneration *in vivo*, underscoring the potential of crosslink-density modulation for controlled release applications.

Surface functionalization further expands gelatin's versatility as a carrier for proteins and nucleic acids. Cationizedgelatin derivatives are commonly synthesized by introducing amine residues through reagents such as polyethyleneimine (PEI), cholamine, ethylenediamine, spermidine, or spermine [59–63]. These modifications enhance electrostatic interactions with negatively charged biomolecules, enabling efficient gene or protein complexation. Chou *et al.* [64] prepared PEI-modified GNPs via desolvation, achieving particles of approximately 135 nm with a positive zeta potential (~ +60 mV). The nanoparticles displayed high protein-loading efficiency, excellent colloidal stability across physiological pH and temperature ranges, and negligible cytotoxicity, while promoting efficient cellular uptake and intracellular protein delivery.

In addition to their biocompatibility and tunability, GNPs exhibit preferential accumulation in macrophage-rich tissues and the ability to traverse the blood–brain barrier, making them valuable for targeted delivery of anticancer agents, genetic material, and therapeutic biopolymers. Overall, gelatin nanoparticles represent a safe, FDA-approved, and chemically versatile platform for controlled and targeted delivery of biologics and small-molecule therapeutics.

2.3 Silk Fibroin Nanoparticles in Drug Delivery Systems

Silk fibroin is the dominant structural protein in *Bombyx mori* silk fibers, comprising approximately 65–85% of the total silk protein content [65]. It is obtained by degumming raw silk with sodium carbonate (Na_2CO_3) to remove the sericin coating, followed by solubilization in lithium bromide (LiBr) or calcium chloride ($CaCl_2$) to yield a regenerative fibroin solution [66]. The purified fibroin consists of a semi-crystalline structure formed by a heavy and a light chain [67-69]. The heavy chain, rich in glycine, alanine, and serine, contains repeating hydrophobic motifs (Gly-Ala-Gly-Ala-Gly-Ser) that assemble into β-sheet crystals through hydrogen bonding and van der Waals forces, conferring high tensile strength and mechanical stability. The light chain, more hydrophilic, contributes to elasticity. Fibroin exhibits an isoelectric point near pH 7 and a molecular weight of ~83 kDa, though processing conditions can alter these values [67-69].

The unique combination of mechanical robustness, flexibility, biodegradability, biocompatibility, and low immunogenicity makes fibroin an ideal material for nanoparticle (FNP) fabrication [70-72]. FNPs generally carry a negative surface charge but can be rendered cationic via coating or crosslinking with polyethyleneimine (PEI), chitosan, or carbodiimide reagents (e.g., EDC). Particle size, zeta potential, encapsulation efficiency, and release kinetics are influenced by fibroin molecular weight, crystallinity, solvent choice, and drug physicochemical properties.

Polar protic solvents such as ethanol, methanol, and acetone promote spherical nanoparticle formation, whereas acetonitrile induces amorphous aggregation [73]. Higher fibroin concentrations and fibroin-to-solvent ratios yield larger, more polydisperse particles. Crystallinity, controlled by salt concentration, solvent polarity, and temperature, dictates drug loading and release behavior: increased β-sheet content enhances structural rigidity and sustains release, while reduced crystallinity accelerates diffusion. Storage at 4 °C preserves nanoparticle stability, whereas elevated temperatures favor aggregation; colloidal stability also depends on surface charge magnitude ($|\zeta| > 30$ mV preferred) [70,71].

Fibroin nanoparticles effectively enhance the therapeutic performance of hydrophobic or labile drugs by improving solubility, reducing degradation, and enabling controlled release. For instance, Pham *et al.* [70] produced α-mangostin-loaded FNPs (≈ 300 nm) crosslinked with EDC or PEI, achieving adjustable surface charges (−15 to +30 mV), ≈ 70 % encapsulation efficiency, and prolonged release over 72 h with markedly reduced hematopoietic toxicity. Similarly, quercetin-loaded FNPs exhibited up to 70 % encapsulation efficiency and retained antioxidant activity post-release [28]. Resveratrol-loaded FNPs improved anti-inflammatory efficacy in a rat colitis model, partly through suppression of macrophage-mediated nitric oxide production [74].

Fibroin's tunable chemistry has also been exploited for enzyme and gene delivery. Kim *et al.* [75] developed fibroin–lipid hybrid nanoparticles to deliver Pin1 isomerase, restoring osteogenic signaling in deficient cells. Song *et al.* [16] reported fibroin-PEI–magnetic hybrid nanoparticles that achieved magnetically guided transfection of anti-sense oligonucleotides with enhanced efficiency and reduced cytotoxicity. Chitosan-fibroin nanoparticles further demonstrated improved siRNA stability in serum, albeit with moderate gene-silencing efficiency [76].

2.4 Casein Nanoparticles as Natural Protein-Based Drug Delivery Systems

Casein, the predominant protein in milk, has emerged as a promising natural biomaterial for nanoparticle-based drug delivery owing to its abundance, low cost, high stability, and biocompatibility [77,78]. Unlike globular whey proteins, caseins exhibit exceptional thermal stability and remain structurally intact even above 70 °C, making them suitable for diverse pharmaceutical formulations [79-81]. Their unique physicochemical attributes—ion- and ligand-binding capacity, surface activity, emulsification ability, and water-binding and gel-forming behaviour—enable the development of versatile delivery systems. Additionally, casein films possess high tensile strength, supporting their use as tablet coatings and protective encapsulants.

Casein exhibits inherent photoprotective properties, absorbing ultraviolet radiation within the 200–300 nm range and thereby safeguarding sensitive bioactive molecules from photooxidative degradation [82-84]. These multifunctional characteristics support the design of advanced nanocarriers such as casein nanomicelles and "nano-camel" systems for encapsulating hydrophobic drugs and nutraceuticals. Nevertheless, certain limitations exist, including potential allergenicity and immunogenicity upon parenteral administration, as well as possible immunosuppressive effects, which must be considered for clinical applications [85-87].

Structural Features and Self-Assembly

Milk casein is a phosphoprotein complex composed of ~94% protein and 6% colloidal calcium phosphate. Casein subunits, with molecular weights of 19–25 kDa and an isoelectric point of pH 4.6–4.8, possess both hydrophilic and hydrophobic domains, enabling spontaneous self-assembly into micellar structures ranging from 50 to 500 nm in diameter (average ~250 nm) [88]. These micelles feature a hydrophobic core encased by a κ-casein-rich hydrophilic shell, stabilized by electrostatic and steric repulsion forces [89-92]. Functionally, casein micelles in milk serve as natural nanocarriers for amino acids and calcium phosphate transport, offering a biological precedent for drug delivery design.

Applications in Drug Delivery

Owing to their amphiphilic nature, casein micelles can encapsulate and protect hydrophobic bioactives such as vitamin D, omega-3 fatty acids, and β-carotene from oxidative and photolytic degradation [93]. Casein nanoparticles have also demonstrated efficacy in delivering anticancer agents including curcumin, mitoxantrone, vinblastine, docetaxel, and paclitaxel [94]. For instance, β-casein nanoparticles show selective gastric tumor targeting through enzyme-mediated degradation by pepsin in the stomach, enabling controlled drug release and enhanced therapeutic efficacy. The micellar shell protects encapsulated drugs from premature release and mitigates cytotoxicity in the upper gastrointestinal tract, while pH-sensitive gelation behaviour supports the design of intelligent, site-specific delivery systems. Additionally, casein nanoparticles exhibit excellent lyophilization stability and can be freeze-dried without cryoprotectants, facilitating long-term storage and ease of reconstitution [93,94]. Together, these features establish casein as a robust, multifunctional protein platform for developing next-generation nanocarriers capable of protecting, stabilizing, and delivering a wide range of therapeutic molecules.

2.5 Ferritin Nanocages as Bioinspired Nanoplatforms for Targeted Drug Delivery

Ferritin, first identified by Laufberger in 1937, is a ubiquitous iron-storage protein found across microorganisms, plants, and animals [95]. It forms a hollow, spherical nanocage with a molecular weight of approximately 474 kDa, composed of 24 self-assembled subunits that enclose a 6-nm core of hydrated ferric oxide (ferrihydrite) within a protein shell known as apoferritin. Mammalian ferritin consists of two functionally distinct but complementary subunits, heavy (H) and light (L), which cooperate in iron oxidation and mineralization processes [96]. The H subunit contains a dinuclear ferroxidase center that catalyzes Fe^{2+} oxidation by molecular oxygen, while the L subunit, lacking this active site, facilitates Fe^{3+} nucleation and turnover through glutamate-rich residues on its inner surface [97,98].

Ferritin's quaternary architecture—24 subunits arranged with octahedral symmetry—creates an internal cavity (~8 nm in diameter) accessible through eight hydrophilic channels that regulate ion transport and molecular exchange. This dual-interface design allows independent chemical modification of the outer surface for targeting ligand attachment and the inner cavity for drug or metal loading [99,100]. The protein exhibits exception

2.6 Elastin and Elastin-Like Polypeptides as Tuneable Biopolymers for Nanomedical Applications

Elastin is the principal structural protein in the extracellular matrix of elastic tissues such as arterial walls, lungs, skin, and ligaments, where it imparts resilience and elasticity in response to mechanical stress and cyclic deformation [101,102]. In vivo, elastin is synthesized as a soluble monomeric precursor, tropoelastin, which undergoes enzymatic crosslinking to form insoluble elastic fibers. The resulting network provides long-term mechanical stability and flexibility critical to vascular and tissue function.

Advances in genetic and protein engineering have enabled the synthesis of **elastin-like polypeptides (ELPs)**—recombinant biopolymers that mimic the repetitive pentapeptide motifs (e.g., Val-Pro-Gly-X-Gly, where X is any amino acid except Pro) found in native elastin [103,104]. Through precise sequence control, these polymers can be designed to exhibit tailored physicochemical and biological properties. Incorporation of functional peptide domains or bioactive motifs allows ELPs to respond to specific stimuli, self-assemble into nanostructures, or interact selectively with biological targets.

Because of their structural homology to native elastin, ELPs display **excellent biocompatibility and minimal immunogenicity**, allowing them to evade immune detection [138]. Their recombinant production confers several additional advantages: monodisperse molecular weight distribution, reproducible architecture, and tunable pharmacokinetics. ELPs can be engineered to conjugate multiple therapeutic agents or targeting ligands, enabling the development of multifunctional and site-specific drug delivery systems [105-108].

A defining feature of ELPs is their **stimuli-responsive behavior**, particularly their reversible phase transition in response to temperature. Above a characteristic transition temperature (T_t), the polymers undergo hydrophobic collapse and self-assemble into nanoparticles or coacervates. This property enables thermally triggered drug release and tissue-specific delivery, particularly in hyperthermic tumor microenvironments.

Collectively, the modularity, biocompatibility, and environmental responsiveness of ELPs make them a powerful class of genetically engineered biomaterials. Their capacity for precise molecular design and adaptive behavior positions them at the forefront of next-generation nanotherapeutic and regenerative medicine platforms.

2.7 Lipoprotein Nanoparticles as Natural Biomimetic Carriers for Therapeutic Delivery

Lipoproteins are naturally occurring nanoparticles responsible for the systemic transport of lipids throughout the body [109]. Their distinctive amphiphilic architecture—comprising a hydrophobic core of triglycerides and cholesterol esters surrounded by a phospholipid monolayer embedded with apolipoproteins—enables efficient solubilization and trafficking of otherwise insoluble lipids [110]. Based on their size, density, and composition, lipoproteins are classified into five major subclasses: high-density lipoproteins (HDL, 7–13 nm), low-density lipoproteins (LDL, 22–27 nm), intermediate-density lipoproteins (IDL, 27–30 nm), very low-density lipoproteins (VLDL, 35–80 nm), and chylomicrons (80–1200 nm) [90]. Each class performs distinct biological functions, reflecting differences in apolipoprotein composition, lipid content, and receptor affinity. Lipoprotein nanoparticles are typically isolated from plasma via density-gradient ultracentrifugation [111].

As **natural, biodegradable, and non-immunogenic nanocarriers**, lipoprotein-based nanoparticles have emerged as promising alternatives to synthetic delivery systems. Their intrinsic biocompatibility, prolonged circulation half-life (48–72 h), and innate receptor-mediated targeting capacity make them ideal for therapeutic applications [112,113]. Lipoproteins can encapsulate or associate with diverse cargos—including small-molecule drugs [114] and nucleic acids [115]—while surface conjugation of targeting ligands further enhances tissue specificity [116]. These features have been exploited for the treatment of several diseases, including neurodegenerative and cardiovascular disorders, as well as cancer [117].

Biomedical and Therapeutic Applications

Lipoproteins play critical roles in lipid homeostasis and are intimately linked to cardiovascular pathophysiology. Elevated plasma levels of LDL-cholesterol are positively correlated with the risk of coronary artery disease, whereas HDL-cholesterol levels exhibit an inverse relationship [118,119]. Pharmacological reduction of LDL levels using statins or anti-PCSK9 monoclonal antibodies has demonstrated significant clinical benefit in lowering cardiovascular risk [`120,121].

In oncology, LDL nanoparticles have gained attention as targeted carriers since many cancer cells overexpress the LDL receptor (LDLR), internalizing LDL at rates up to 50-fold higher than normal cells [122]. This receptor-mediated endocytosis has been harnessed to selectively deliver chemotherapeutic agents to tumor sites, minimizing systemic toxicity. Similarly, HDL nanoparticles exploit the scavenger receptor class B type I (SR-BI), which is abundantly expressed in hepatic, adrenal, and macrophage tissues, as well as in certain tumors [103,104]. HDL-based nanocarriers functionalized with apolipoprotein A-I (apoA-I) or its mutant variant apoA-I Milano have shown promise in both cardiovascular and cancer therapeutics. Clinical trials have demonstrated that weekly administration of apoA-I Milano/phospholipid complexes over five weeks markedly reduced coronary atherosclerotic burden, underscoring their therapeutic efficacy [123,124].

Collectively, lipoprotein nanoparticles represent an elegant example of **nature-inspired nanomedicine**, combining intrinsic biological compatibility with programmable functionality. Their structural versatility, receptor-specific targeting, and ability to encapsulate hydrophobic or genetic cargos position them as a next-generation platform for precision drug delivery and cardiovascular therapy.

2.8 Lactoferrin Nanoparticles as Carriers for Therapeutic Delivery

Lactoferrin (Lf), a multifunctional iron-binding glycoprotein, has emerged as a highly promising carrier in nanoparticle-based drug delivery owing to its intrinsic receptor-mediated uptake, biocompatibility and versatility[125].

As a drug-delivery platform, Lf nanoparticles offer several key advantages: (i) natural affinity for receptors on tumour, brain and immune cells; (ii) the ability to encapsulate hydrophobic and hydrophilic therapeutics; (iii) intrinsic bioactivities (antimicrobial, immunomodulatory) that may synergise with delivered drugs. Recent studies demonstrate Lf nanoparticles loaded with chemotherapeutics or nucleic acids achieving enhanced cellular uptake, improved biodistribution and superior therapeutic indices compared to non-targeted systems. For example, in brain-delivery models, Lf–drug nanosystems exhibit enhanced transcytosis across the blood-brain barrier and improved therapeutic efficacy [126].

Moreover, Lf carriers have been engineered for oral or mucosal administration to protect cargo through the gastrointestinal tract and target inflammatory bowel disease, colon cancer or macrophage-rich tissues [127]. They also offer a modular platform for surface functionalization, stimuli-responsive release, and combination therapies. Challenges remain, including detailed mechanistic understanding of in-vivo biodistribution, scale-up reproducibility and long-term toxicity, but the convergence of ligand-mediated targeting and nanoparticle design positions Lf nanoparticles as a next-generation class of biopolymer carriers for targeted oncology, neurotherapeutics and immunomodulation.

Disadvantages of protein nanoparticles:

Despite their numerous advantages in drug delivery and tissue engineering, protein-based nanoparticles face several limitations that restrict their widespread application in the pharmaceutical and medical industries. Since proteins are natural polymers, they often exist as heterogeneous mixtures of varying sizes and molecular weights, resulting in challenges related to reproducibility and batch-to-batch consistency during large-scale production. To address this issue, recombinant proteins produced through genetic engineering have been developed, offering uniform molecular weights and allowing for precise structural modification—such as attaching targeting ligands or controlling drug release rates. Examples include engineered elastin-like polypeptides (ELPs), recombinant human serum albumin (rHSA), and recombinant gelatin, though these methods increase production costs [128]. Another challenge is immunogenicity, as foreign proteins can provoke immune responses; however, studies have shown minimal reactions to intravenously administered nanoparticles made from albumin, gelatin, casein, and zein. Additionally, achieving controlled and sustained drug release remains difficult due to the hydrophilic nature of most proteins, which causes nanoparticle swelling and rapid drug diffusion in biological environments. To stabilize these structures, toxic chemical cross-linkers like formaldehyde and glutaraldehyde are often employed, prompting ongoing research into safer, biocompatible alternatives. Notably, hydrophobic plant proteins have demonstrated potential for creating nanocarriers capable of prolonged drug release. A further concern involves the risk of transmitting animal-borne diseases, such as bovine spongiform encephalopathy, when animal-derived proteins are used in nanoparticle fabrication.

Conclusions

Protein-based nanoparticles have emerged as a promising class of biocompatible carriers for the controlled delivery of therapeutic agents, including anticancer drugs, genetic materials, peptide hormones, growth factors, and nucleic acids (DNA and RNA). Compared with other colloidal systems, protein nanoparticles offer several distinct advantages: they are inherently biodegradable, exhibit high structural stability, and can be synthesized via straightforward, cost-effective, and environmentally sustainable processes that minimize the use of toxic reagents. Their physicochemical versatility allows precise control over particle size, surface charge, and morphology, thereby enabling tunable pharmacokinetic behavior and drug-release kinetics in vivo.

A wide range of proteins—derived from both animal and plant sources—have been explored for nanoparticle fabrication, with **albumin** and **silk fibroin** representing the most extensively investigated materials. In parallel, increasing attention has been directed toward **legumin** and other plant-derived proteins as renewable and non-immunogenic alternatives, though optimization of their structural stability and reproducibility remains a key challenge. Nanoparticle synthesis methods such as **desolvation**, **complex coacervation**, and emerging physical techniques like **nano-spray drying** have demonstrated strong potential for scalable production. However, limitations such as low throughput, surfactant dependency, and process heterogeneity must be addressed through continued technological refinement. The performance of protein nanoparticles—particularly in drug loading, release profiles, and targeting efficiency—is governed by the interplay of formulation parameters and the physicochemical properties of the encapsulated molecules.

While substantial progress has been made, **comparative in vivo data** between protein-based systems and conventional nanocarriers remain limited. Future research should focus on systematic evaluation of material–process relationships to optimize nanoparticle design for specific therapeutic applications. The case-by-case selection of protein source and fabrication technique will be critical for developing efficient, safe, and clinically translatable protein nanoparticle systems

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