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Original Research Article

Protein Nanoparticles in Drug Delivery: Biocompatibility, Functionalization, and Therapeutic Applications

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Abstract

Due to being biocompatible and biodegradable with a wide variety of structural characteristics, protein nanoparticles (PNPs) can act as novel drug delivery vehicles. PNPs can be constructed from the natural proteins: albumin, gelatin, silk fibroin, casein, and ferritin, thus providing several advantages compared to organic polymers and inorganic materials. PNPs can encapsulate a number of types of therapeutic agents (designed to prevent degradation and premature clearance), like proteins, peptides, nucleic acids and small molecules. Moreover, they have a unique surface chemistry that permits functionalizing with other polymers, ligands for targeting, or biomimetic coatings to achieve enhanced circulation time, tissue specificity and uptake. Finally, some of the many attributes of PNPs include: pharmacokinetic and pharmacodynamics profiles that increase the efficacy of therapeutic treatments while decreasing levels of toxicity to healthy tissues. Current fabrication techniques allow for precise regulation of the size, morphology and release kinetics of the PNPs. Protein nanocarriers have demonstrated potential as delivery systems for genes and vaccines, as well as for antimicrobial treatment, cancer treatment, and regenerative medicine. While protein nanocarriers have many advantages, there are still challenges related to lot-to-lot reproducibility, stability, and large-scale manufacturing of the carrier system. This review highlights recent advancements made in regard to the design of protein nanoparticles, their biocompatibility, their functionalization methods, and their therapeutic uses; these advancements demonstrate that protein nanoparticles could potentially serve as safe, efficient, and readily translatable drug delivery systems in the future.

Keywords: Protein Nanoparticles; Drug Delivery Systems; Biocompatibility; Surface Functionalization; Targeted Therapy; Nanomedicine.

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Introduction

Drug delivery systems are among the biggest concerns of pharmaceutical companies today. Traditional forms of medicine tend to exceed safe dosage limits, are unstable and degrade quickly, don't absorb well into the blood, are insoluble and don't distribute properly throughout the body. These issues become even more significant when drugs such as proteins, peptides, nucleic acids, or anticancer are introduced into the body. Nanotechnology-based drug delivery systems have proven to be valuable tools to address these issues by enhancing the therapeutic advantages of these types of drugs while reducing their side effects.[1]The different types of nanocarrier systems that have been investigated and have unique biological and physicochemical properties include protein nanoparticles (PNPs), which have garnered greater interest than liposomes, polymeric nanoparticles, dendrimers, and inorganic nanoparticles. Protein nanoparticles are colloidal systems made of natural or recombinant proteins that usually range in size from 10 to 500 nm. Proteins are widely used in biomedical applications because they are naturally biocompatible, biodegradable, and non-toxic. Protein-based systems, in contrast to many synthetic carriers, can be metabolized into amino acids that the body can readily eliminate or reuse, lowering the risks of long-term accumulation and toxicity. Furthermore, proteins have a variety of functional groups that enable surface functionalization and chemical modification, including amino, carboxyl, and thiol moieties.[2] Because of these characteristics, protein nanoparticles can be used as flexible platforms to deliver a variety of therapeutic agents. Over the past decade, a whole lot of proteins had been investigated for nanoparticle formula, such as albumin, gelatin, silk fibroin, casein, collagen, ferritin, and zein. Among those, albumin-primarily based nanoparticles have done enormous medical success, exemplified by means of the FDA-permitted system Abraxane®, which includes paclitaxel certain to human serum albumin. The Protein Nanoparticle Capacity Milestone has evaluated the bio-related capacity of protein nanoparticles and continues to improve research into alternative protein-based delivery systems (for example, protein nanoparticles) as well as demonstrate proof of the capability of protein nanoparticles to improve drug solubilisation, improve pharmacokinetic profiles (the movement of a drug through the body), and reduce (decrease) toxicity that may occur with the use of solvent.

One important advantage of protein nanoparticles is their ability to encapsulate and protect therapeutically sensitive compounds. Proteins and peptides, in particular, are subject to enzymatic degradation as well as membrane permeability problems when delivered by the standard route. Encapsulating these compounds in protein nanoparticles protects them from extreme physiological conditions, increases time to diffusion and allows for controlled or prolonged drug release.[3] Additionally, by optimizing particle length and surface properties, protein nanoparticles can utilize a number of biological processes, including enhanced permeability and retention (EPR), for passive targeting, especially in tumor tissue.

Aside from using passive targeting, protein nanoparticles can be actively targeted by surface functionalization. The many reactive functional groups on protein surfaces can be used to couple with ligands (like antibodies, peptides, aptamers and small molecules) which will then bind to any cells that are over-expressing particular receptors on the cell surface. This ability to deliver drugs to a specific site will help reduce the incidence of off-target delivery of medications. Surface-modifying methodologies (e.g., PEGylation, etc.) will also help to make protein nanoparticles more stable and enhance their circulation times by reducing opsonization and immune recognition. As a result of these surface functionalization methodologies, the use of protein nanoparticles as delivery vehicles for medications has been greatly increased through multiple therapeutic areas.[4]

As fabrication and characterization technologies develop more, more and more people are interested in using protein nanparticles. The development of fabrication and characterization technologies as they continue to advance is having a great impact in terms of generating increased interest in the use of protein nanoparticles.

Methods along with desolvation, emulsification, coacervation, self-assembly, and electrospraying permit particular manage over particle length, morphology, drug loading, and launch kinetics. These strategies are generally carried out beneath slight situations, retaining the structural integrity and biological interest of each the protein service and the encapsulated drug. As a end result, protein nanoparticles are mainly appealing for the delivery of biologics and gene-primarily based therapeutics.

Protein nanoparticles have proven promising outcomes in a extensive range of healing programs, such as most cancers therapy, antimicrobial treatment, gene transport, vaccine improvement, and regenerative medication. In oncology, protein-based totally nanocarriers had been shown to beautify intracellular drug accumulation, triumph over multidrug resistance, and decrease systemic toxicity. In antimicrobial remedy, protein nanoparticles enable managed drug release and stepped forward penetration into biofilms, addressing the growing project of antibiotic resistance. Moreover, their immunogenic residences may be harnessed for vaccine shipping, in which protein nanoparticles serve each as providers and adjuvants. Protein nanoparticles have several advantages, but they are not without challenges. To contribute to the successful clinical translation of protein nanoparticles, several challenges must be addressed, including batch-to-batch variability, storage stability, large-scale manufacture, and immunogenicity. In addition, there are also regulatory challenges and reproducibility challenges facing the commercialization of protein nanoparticles. However, continued research related to recombinant protein engineering, advanced stabilisation technology, and scalable production technology continues to mitigate these challenges.[5]

Due to the rapid advances in nanotech and pharmaceutical sciences, protein-based nanoparticles offer an exciting new class of targeted and personalised drug delivery systems. They will also serve as critical components for the next generation of targeted and individualised medicines due to their unique combination of organic compatibility, functional versatility, and therapeutic versatility. This review article provides a detailed evaluation of protein nanocarriers for drug delivery with an emphasis on biocompatibility and modification strategies and also discusses current challenges and future prospects for this rapidly evolving area of research.

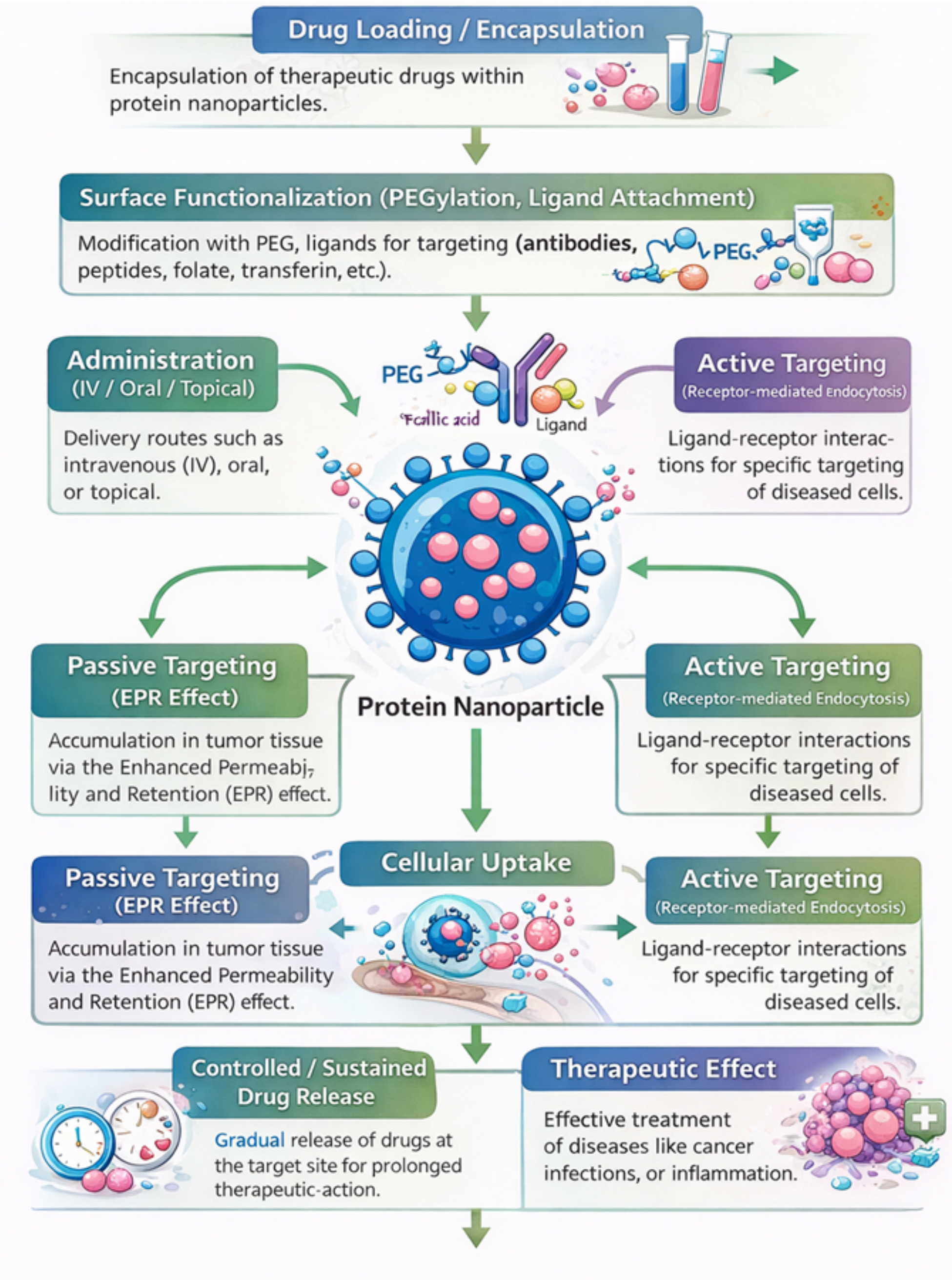

Figure 1: Mechanism of Action of Protein Nanoparticles

Biocompatibility of Protein Nanoparticles: Biocompatibility has become an essential criterion for any drug delivery system destined for clinical use and due to their completely natural sources, protein nanoparticles (PNPs) meet this requirement because of their similarity to macromolecules found in nature.

The proteins used to make PNPs consist of all the most common proteins in humans, including but not limited to: albumin, gelatin, silk fibroin, casein, collagen, and ferritin. Additionally, most of the proteins used to create PNPs have either been derived from human beings (endogenously) or from a biocompatible source. The result is that the formation of the protein nanoparticles themselves leads to low immunogenicity, minimal cytotoxicity, and very good tolerance when administered through any route. Furthermore, the final products formed through the degradation of PNPs include free amino acids and short chains of amino acids (peptides), both of which can be readily metabolized and reused in various metabolic pathways, therefore significantly reducing the potential for long-term accumulation within the body and the associated risk of chronic toxicity.[6] Unlike inorganic or synthetic polymeric nanoparticles, protein-primarily based vendors intently mimic endogenous biomolecules, allowing efficient cell uptake via receptor-mediated endocytosis or passive diffusion. This organic compatibility minimizes damage to healthful tissues and reduces inflammatory responses.

Additionally, protein nanoparticles display decreased hemolytic pastime and limited interference with normal cellular features, making them suitable for systemic management. Studies have demonstrated that albumin- and gelatin-based nanoparticles exhibit outstanding blood compatibility and do no longer notably activate complement pathways, that is essential for intravenous drug transport.

Immunogenicity is an important factor of biocompatibility, and protein nanoparticles usually exhibit low immunogenic ability whilst derived from human or highly purified sources. Human serum albumin nanoparticles, specially, are well tolerated and had been effectively translated into clinically authorised formulations. However, proteins of animal or plant origin may also elicit immune responses if no longer nicely purified or modified. To address this, strategies including PEGylation, surface shielding, and using recombinant or humanized proteins had been hired to in addition reduce immune recognition and beautify flow time. Studies conducted to analyze the biological compatibility of proteins in vitro show that protein nanoparticles are highly compatible with living cells and tissues, as evidenced by a high percentage of viable cell numbers remaining even at very high concentrations. The in vivo studies also provide additional evidence for the high biocompatibility of these protein nanoparticles since there was little evidence of organ toxicity, little evidence of inflammation, and positive biodistribution profiles. By tailoring the length, floor fee, and hydrophobicity of protein nanoparticles, researchers can optimize protein nanoparticles for specific applications, fewer off-target interactions, and fewer detrimental consequences.

Despite their commonly favorable biocompatibility profile, sure elements can influence the organic behavior of protein nanoparticles. These encompass the kind of protein used, technique of nanoparticle instruction, degree of move-linking, floor change, and direction of administration. Excessive chemical go-linking or residual solvents may additionally compromise biocompatibility and have to be cautiously controlled all through components. Therefore, thorough physicochemical characterization and biocompatibility evaluation are critical throughout the development of protein-based totally nanocarriers.

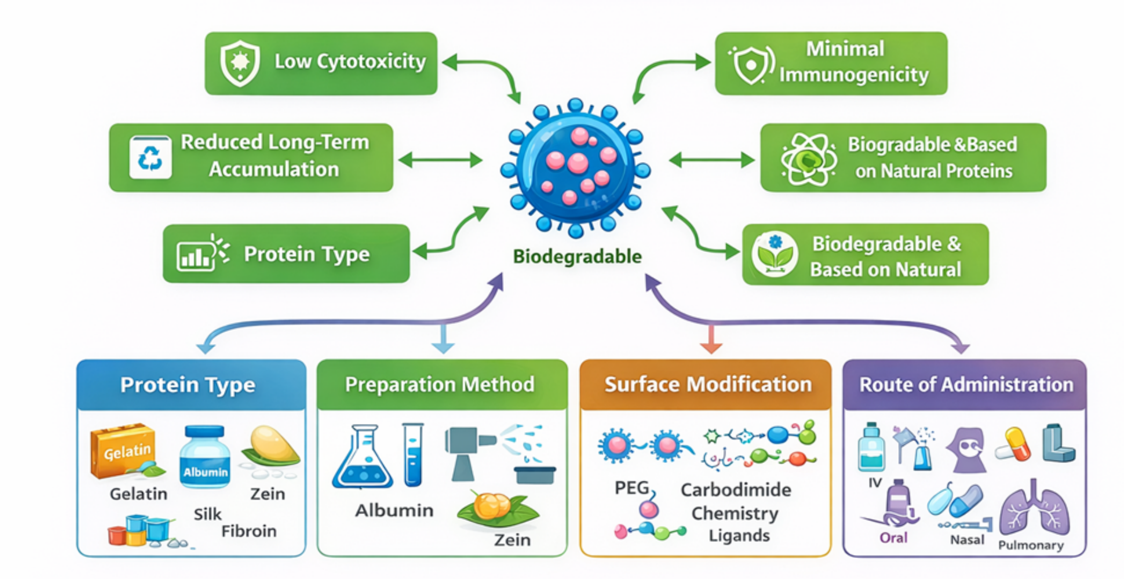

Figure 2: Biocompatibility of Protein Nanoparticles

Preparation and Functionalization Techniques: Protein nanoparticles (PNPs) are prepared the usage of numerous physicochemical and biological strategies that allow particular manage over particle length, morphology, drug loading, and launch conduct. The desire of practise and functionalization method depends at the sort of protein, nature of the therapeutic agent, supposed direction of administration, and preferred targeting profile.

Recent advances in fabrication and surface engineering have considerably stronger the overall performance and applicability of protein-based nanocarriers.

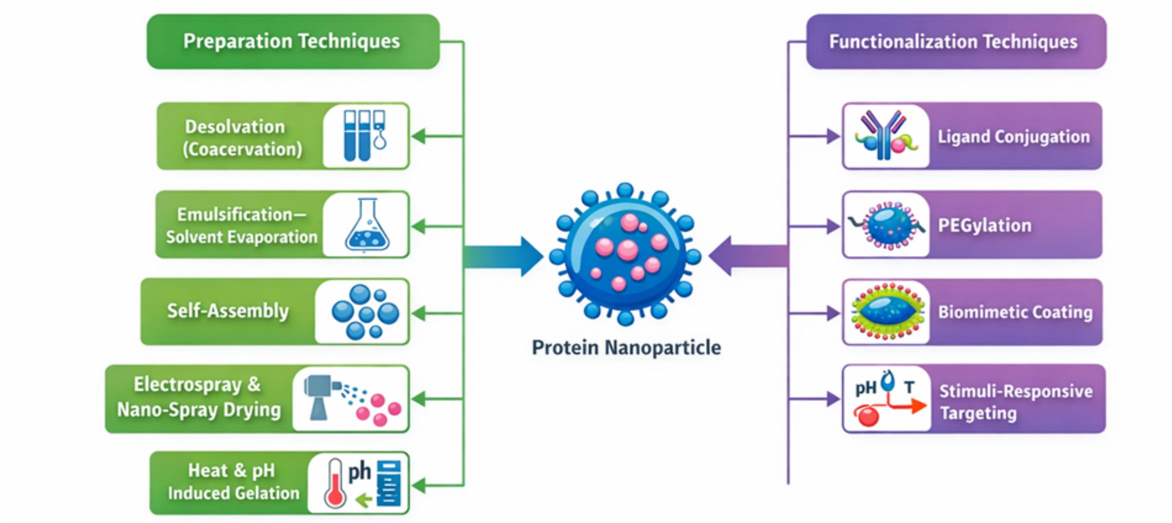

Figure 3: Preparation and Functionalization Techniques

Preparation Techniques of Protein Nanoparticles [2, 5]

Desolvation (Coacervation) Method: The desolvation approach is one of the maximum widely used strategies for making ready protein nanoparticles, in particular albumin and gelatin nanoparticles. In this system, a desolvating agent which include ethanol or acetone is progressively delivered to an aqueous protein answer below regular stirring.

The reduction in solvent polarity ends in managed aggregation of protein molecules, ensuing in nanoparticle formation. Cross-linking agents inclusive of glutaraldehyde or genipin may be used to stabilize the nanoparticles and improve their mechanical strength. Desolvation techniques are preferred for their ease of use, efficiency of encapsulating drugs, and by maintaining moderate processing conditions which keep the biological nature intact on the surface area of the capsule.

Emulsification–Solvent Evaporation Method: An emulsification technique can be used to emulsify a liquid preparation of active ingredient as an aqueous protein solution into a liquid organic phase using surfactants to form an emulsion of aqueous solution inside the organic solvent. To obtain particles made of protein, the active ingredient contains protein nanoparticles, by evaporating the organic solvent during the emulsification process.

Emulsification using surfactants to form W/O and W/O/W emulsions allows for great control of the size of the nanoparticles and is beneficial for the encapsulation of both hydrophilic and hydrophobic tablet forms. Natural or synthetic surfactants /solvents may have toxicity considerations that may require additional levels of purification.

Self-Assembly Method: Many specific types of proteins have natural compartments that allow for spontaneous nanostructure creation, depending on physical conditions like temperature, ionic strength and pH. Ferritin, viral-like particles and silk fibroin are examples of proteins that show self-assembly characteristics and create extremely regular and stable nano-particles through self-assembly. The use of self-assembly techniques offers the benefits of avoiding harsh chemical treatments, as well as increasing control of the final product structure. Self-assembled nano-structures may have applications in targeted delivery and imaging; however, limitations exist on the type of protein that may be used for such purposes.[3]

Electrospray and Nano-Spray Drying: Electrospray techniques make use of high-voltage electric powered fields to generate first-rate droplets from protein solutions, which swiftly dry to form nanoparticles.

This method enables the manufacturing of uniform nanoparticles with slender size distribution and high drug-loading efficiency. Nano-spray drying is also used for large-scale production and offers stepped forward stability of protein formulations. These strategies are in particular beneficial for pulmonary and nasal delivery structures however require specialized equipment and cautious process optimization.[4]

Heat-Induced and pH-Induced Gelation: Heat-triggered or pH-brought on denaturation of proteins can lead to managed aggregation and nanoparticle formation. In these methods, adjustments in temperature or pH adjust protein conformation, selling intermolecular interactions and nanoparticle formation. These approaches are simple and solvent-unfastened but may not be appropriate for warmth-sensitive tablets or proteins.

Drug Loading Strategies: Ways to incorporate drugs into protein-based nanoparticles include encapsulation, adsorption, or covalent attachment. During nanoparticle production, encapsulation has the highest rate of drug loading and can offer sustained release of drugs, while surface adsorption allows for the addition of drugs after the initial formulation. Conversely, covalent attachment results in very stable and strong drug-carrier interactions, but this attachment should be carefully considered to prevent the loss of drug activity after loading onto the nanoparticle surface. When choosing a loading method, both drug release kinetics and drug efficacy will be greatly impacted by how to load the drug onto the protein nanoparticles.[5]

Functionalization of Protein Nanoparticles: The ability of protein nanoparticles to target specific places, remain stable, and perform therapeutically has all been improved by functionalizing them. Surface modifications can be accomplished by physical, chemical or biological means.

Ligand Conjugation for Targeted Delivery: Antibodies, peptides, aptamers, folic acid and sugars are examples of ligands that can be attached to protein nanoparticles. These ligands will interact with specific receptors that are greatly overexpressed by the target cells, thus allowing for targeted active delivery and increased cellular uptake of the nanoparticles. Ligands can be chemically bound to the protein nanoparticle using chemistry techniques of carbodiimide or ‘click’ reactions.[6]

PEGylation and Surface Shielding: The process known as 'PEGylation' entails the adding of polyethylene glycol (PEG) chains to the surface of a nanoparticle in order to improve colloidal stability and extend their circulation time in vivo. By having PEG chains attached to their surfaces, colloidal nanoparticles may have lower degrees of opsonisation and immune recognition thus improving their overall bioavailability. Additional surface-shielding polymers (including polysaccharides and zwitterionic materials) are also being studied to address some of the limitations of PEGylation.

Biomimetic and Stimuli-Responsive Functionalization: Biomimetic functionalization refers to the coating of protein nanoparticles with components of cell membranes (or biological molecules) in order that the resulting construct will be able to imitate normal cells and provide the means for immune evasion, as well as improved targeting. In addition, functionalization responsive to stimuli (i.e., pH, enzymes, temperature, and redox) enables the programmed release of drugs from nanoparticles when certain trigger conditions are present, e.g., cancers or inflammatory diseases.[7]

Genetic and Recombinant Functionalization: Genetic engineering advancements allow us to genetically engineer proteins not only by enabling the introduction of novel functional domains or targeting sequences but also by allowing us to engineer response to stimuli in those proteins. By making use of recombinant protein nanoparticles, we can precisely control both the physical structure of the protein and its target function, while at the same time minimizing variations from one batch to another. This method would be useful for gene delivery and vaccines.[8]

Advantages and Challenges of Preparation and Functionalization: With regards to preparation and functionalization methodologies, advancements in the applicability of protein nanoparticles have been tremendous; however, issues concerning scalability, reproducibility, stability, and regulatory compliance still exist. Future research will be directed at creating standardised, scalable and environmentally benign manufacturing methods, as well as developing multifunctional protein nanoparticles with improved targeting capabilities and regulated release profiles.[9]

Therapeutic Applications: Because they exhibit good compatibility with biological tissues, break down in the body, and can be designed specifically for drug delivery and control, proteins in the form of nanoparticles are of great interest as new methods of delivering drugs to patients. Due to the high amount of flexibility in the structure of protein nanoparticles and the fact that modifications can be made to the surface of the particles for different types of therapeutic agents, including but not limited to small molecules, proteins and peptides, DNA and RNA (nucleic acids), it will be described in the following pages what the most important therapeutic uses of proteins as nanoparticles are.

Cancer Therapy: Protein nanoparticles have been widely studied as vehicles for delivering cancer therapies (drug delivery vehicles). Many standard chemotherapeutic agents have poor solubility, high levels of non-specific distribution, short time of delivery in the body, and have severe, dose-limited toxicity. Protein nanoparticles can help improve these problems by making them more soluble in a liquid suspension that will be used for injection (increasing the amount of drug that can be delivered), improve how much of the drug accumulates in a tumor (targeting the drug to a diseased area), and to decrease the amount of side effects produced when being injected into the body (making them safer). One of the best examples is albumin-bound paclitaxel (Abraxane®), which has been shown to have better efficacy and less toxicity than solvent-based formulations of paclitaxel.[10]

Through their ability to utilize the enhanced permeability and retention (EPR) effect, protein nanoparticles can achieve passive targeting to tumors and have a preference for accumulating in the tumor tissue. Furthermore, protein nanoparticles can be modified to possess various targeting ligands, such as folic acid, peptides, antibodies or transferrin, that allow for active targeting of tumor-specific receptors, thereby enhancing the amount of drug taken up by the tumor cell(s). They have also been used to deliver multiple types of chemotherapeutic drugs and/or sensitizers or imaging agents (theranostics) at the same time, allowing them to be used in combination therapy approaches.[11]

Antimicrobial and Antifungal Therapy: Antimicrobial resistance has created a demand to develop new avenues for drug administration in order to increase the effectiveness of previously established antifungal and antibacterial drugs. One way to assist in this area would be to utilize protein molecules in the form of protein based nanoparticles as they have many qualities that can assist with this goal, such as increasing the stability of the antimicrobial agent from chemical degradation and allowing for controlled release of the drug, as well as providing enhanced ability to penetrate into infected tissues and biofilm infections.

In addition to the above-mentioned advantages, studies have shown that various types of protein based nanoparticles (such as those made from casein, albumin and gelatin) have demonstrated effective encapsulation of antifungal and antibacterial agents, ultimately improving the overall therapeutic efficacy, and reducing the number of doses that an individual may need to take.[12]

The use of protein nanoparticles will also allow for the targeted delivery of the drug to the site of infection, thus reducing the potential for off-target effects, and lessening the risk of systemic toxicity caused by the delivery of high concentrations of drug to non-target tissues. In addition, the local delivery system is ideally suited for the treatment of skin and soft tissue infections, since the topically applied protein-based nanocarriers will retain greater amounts of drug at the site of application when compared to delivering the drug alone by topical administration.

Gene and Nucleic Acid Delivery: Nucleic acids like DNA, small interfering RNA (siRNA) and messenger RNA (mRNA) are challenging to deliver due to their large size and intrinsic instability, as well as their tendency to undergo enzymatic degradation. Because of their low toxicity as compared to viral delivery vehicles, protein-based nanoparticles are emerging as promising non-viral gene delivery vehicles. Nucleic acids can be electrostatically bound to proteins. Proteins such as albumin, histones, and recombinant protein-based nanoparticles can form stable complexes with nucleic acids that shield them from degradation by nucleases. The addition of cell-penetrating peptides or targeting ligands enhances the cellular uptake and transfection efficiencies of protein-based nanoparticles. Protein-based nanoparticles have been utilized for gene silencing, gene replacement therapy, and mRNA-based therapeutics, representing their potential use in the treatment of cancer, genetic diseases, and viral infections. The potential for repeated administration because of their biodegradability and lower immunogenicity is an additional attraction to their use.[13]

Vaccine Delivery and Immunotherapy: Nanoparticles composed of proteins have become more significant as delivery methods regarding the generation of new vaccines and immunotherapy due to their ability to imitate the properties of structures that have been associated with pathogens and can elicit a type of immune response. In regard to vaccines, protein-based nanoparticles serve not only as delivery systems (carriers) but also as adjuvants (helping provide greater stability and presentation of antigens), enhancing the uptake of the antigen by antigen-presenting cells (APCs). Engineer protein nanoparticles can display (exposed) and provide a prolonged duration of stimulation through the prolonged release of an antigen either by appearing on the surface or being encapsulated in the matrix of the nanoparticle, enabling an immune response over time. Research studies concerning the use of protein nanoparticles have been conducted for delivery of subunit vaccines, peptide antigens, and nucleic acid-based vaccines to induce a specified immune response for various diseases.[14]In addition to their applications as a vaccine carrier, protein nanoparticles have also been investigated for use as delivery systems for immune-modulating substances such as cytokines and checkpoint inhibitors to enhance the antitumor immune response while reducing the occurrence of adverse events (i.e., systemic toxicity). The tunable size and surface properties of protein nanoparticles also enable targeted delivery to lymphoid tissue, thereby enhancing the efficacy of the vaccine.

Delivery of Proteins, Peptides, and Biologics: Biologically derived medicines like peptides and proteins are very effective treatments; however, they often have some issues, such as having an insufficiently long half-life, low stability, and low bioavailability (i.e., the amount of the drug that actually reaches the circulation). The use of protein nanostructures to deliver these types of medications protects proteins and peptides from being destroyed by enzymes and provides a way to provide a sustained or controlled release of the therapeutic agent. Encapsulation of therapeutic proteins into a protein-based carrier increases their stability and can extend the time that the proteins remain in circulation.[15]

Protein nanostructures have been examined for use in oral, nasal, pulmonary, and injection delivery of biological agents; therefore, they can solve many of the issues associated with traditional forms of medication. This is particularly pertinent when providing an appropriate dosage of hormone, enzyme, or growth factor therapy because of the need for precise dosing and timed exposure.

Regenerative Medicine and Wound Healing: Protein nanoparticles are being used in regenerative medicine for the delivery of growth factors, cytokines and other bioactive molecules that are needed for tissue repair and regeneration. As they are biocompatible, provide localized and sustained release of the active agents, protein nanoparticles are suitable for use in the applications of wound healing, bone regeneration and tissue engineering.[16]

By using protein nanoparticles in combination with hydrogels, scaffolds and/or dressings, the amount of time a cell can proliferate, undergo angiogenesis and remodel can be enhanced. The use of protein-based nanoparticles as nanocarriers in the treatment of wounds results in improved drug retention at the wound site, decreased chances of infection and an accelerated rate of healing. The versatility and safety profile of protein nanoparticles give them great potential as advanced materials in regenerative therapies.[17]

Table 1: Therapeutic Applications of Protein Nanoparticles in Drug Delivery [19,18]

Therapeutic Area	**Type of Protein Nanoparticles**	**Delivered Therapeutic Agents**	**Mechanism / Role of Protein Nanoparticles**	**Key Advantages**
Cancer Therapy	Albumin, Ferritin, Gelatin, Silk fibroin	Anticancer drugs (paclitaxel, doxorubicin, cisplatin), imaging agents	Passive (EPR effect) and active targeting, controlled release, intracellular delivery	Enhanced tumor accumulation, reduced systemic toxicity, improved bioavailability
Antimicrobial Therapy	Albumin, Casein, Gelatin	Antibiotics, antifungal agents	Improved stability, sustained release, enhanced penetration into infected tissues and biofilms	Reduced dosing frequency, improved efficacy against resistant strains
Gene & Nucleic Acid Delivery	Albumin, Histone-based, Recombinant proteins	DNA, siRNA, mRNA	Protection from enzymatic degradation, enhanced cellular uptake, non-viral transfection	Low immunogenicity, safer alternative to viral vectors
Vaccine Delivery	Ferritin, Albumin, Virus-like proteins	Protein antigens, peptide antigens, mRNA	Antigen protection, enhanced antigen presentation, immune stimulation	Prolonged immune response, improved vaccine efficacy
Immunotherapy	Albumin, Engineered proteins	Cytokines, immune modulators, checkpoint inhibitors	Targeted delivery to immune cells, controlled immune activation	Reduced systemic toxicity, enhanced therapeutic response
Protein & Peptide Delivery	Albumin, Gelatin, Silk fibroin	Hormones, enzymes, therapeutic peptides	Protection from degradation, sustained release	Improved stability, prolonged circulation time
Wound Healing	Collagen, Gelatin, Silk fibroin	Growth factors, antimicrobials	Localized delivery, sustained release, tissue regeneration	Accelerated healing, reduced infection
Regenerative Medicine	Collagen, Albumin, Silk fibroin	Growth factors, stem cell regulators	Controlled release, scaffold integration	Enhanced tissue regeneration and repair
Pulmonary & Nasal Delivery	Albumin, Gelatin	Antiasthmatic drugs, vaccines	Enhanced mucosal adhesion, deep lung deposition	Improved absorption, non-invasive administration
Theranostics	Albumin, Ferritin	Drugs + imaging agents	Combined diagnosis and therapy	Real-time monitoring, personalized treatment

Conclusions and Future Perspectives: Due to their excellent biocompatibility, biodegradability and versatility, protein nanoparticles are an exciting and rapidly developing group of systems for delivering drugs. Because protein nanoparticles are constructed from naturally occurring proteins that are broken down into amino acids, they are metabolically safe and do not pose long-term toxicity risks. As a result, protein nanoparticles are well-suited for repeat or chronic dosing. In addition, the wide variety of structures possible with proteins and the presence of numerous reactive groups provide the capability to encapsulate drugs, control their release from the protein nanoparticle and functionalize the protein nanoparticle surface with either targeting ligands or stealthy coatings. These advantages have significantly improved the pharmacokinetic and pharmacodynamic properties of the therapeutics delivered by protein nanoparticles, improving the efficacy of these agents while reducing their systemic side effects. There is broad applicability of protein-nanoparticle-based formulations across numerous therapeutic areas, including; cancer therapy; antimicrobial therapy; gene and vaccine delivery; and regenerative medicine. Therapeutic agents manufactured as protein-nanoparticle-based formulations have been clinically approved (e.g., albumin-bound paclitaxel) and provide confidence that the use of protein nanoparticles in clinical practice will continue to increase. Despite their many advantages, there are still multiple challenges to be overcome prior to wider acceptance of protein-nanoparticle-based formulations for clinical and commercial use, including large-scale manufacturing; batch-to-batch consistency; long-term storage stability; and the possibility of immunogenic responses associated with the protein source used to create the nanoparticle. Furthermore, limited regulatory guidance and a lack of standardized characterization criteria are further complicating the development and approval of protein-nanoparticle-based formulations for use in clinical practice.

Going forward, future investigators need to optimize scalable production methods of protein-based drugs; improve their stability during formulation/distribution/storage; continue developing recombinant/engineered versions of the drug to reduce the likelihood of unintended effects due to varying patient responses; integrate advanced therapeutic methods such as responsive delivery systems; develop precise targeting methods; and utilize personalized medicine principles with these products to substantially increase their therapeutic potential. Through ongoing interdisciplinary collaboration among researchers; and ongoing development of innovative technologies, protein-based drugs delivered via nanoscale delivery systems will likely form a cornerstone of future drug delivery systems by improving safety, efficacy, and targeting to individual patients.

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