

Review Article

Preparation of Drug-Loaded Albumin Nanoparticles and Its Application in Cancer Therapy

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Albumin is derived from plasma and it is the most abundant protein in plasma, which is an ideal material for the preparation of nanoparticles because of its good biocompatibility, noncytotoxicity, nonimmunogenicity, biodegradability, and so on. Besides, albumin can enhance the targeting of drugs, reduce the toxicity of free drugs, and enhance the water solubility of hydrophobic drugs, etc. Drug delivery systems based on albumin nanoparticles are widely used in the medical field. At present, the main methods of preparing albumin nanoparticles are desolvation, self-assembly, thermal gelation, spray-drying, double emulsification, emulsification, Nab-technology, pH coacervation, and so on. Due to the differences of principle and preparation conditions, these methods show different advantages and disadvantages. This review systematically summarizes the latest research progress of albumin nanoparticles about its methods of preparation in past five years, and it also introduces the latest applications in cancer therapy, existing difficulties. Thus, this review can fill the two gaps that few articles focus comprehensively on the application of albumin nanoparticles in tumor therapy and no article clearly points out the difficulties faced in current research of albumin nanoparticles.

1. Introduction

In recent years, new tumor treatment strategies have attracted increasingly researchers' attention. However, most of antitumor drugs are hydrophobic drugs, with side effects and poor targeting, and all the above problems lead to the limited use of antitumor drugs. Thus, it is necessary to develop new therapeutic strategies that can improve drug solubility, targeting, and reduce side effects. Nanoparticles are widely used in the biomedical fields; for example, metal oxide nanoparticles can exhibit better antibacterial or antioxidant potency, such as copper nanoparticles [1], silver nanoparticles [2–4], and zirconium nanoparticles [5]. Meanwhile, protein-based nanoparticles are widely used as drug carriers to deliver relevant substances. Such as natural or chemical drugs, nucleic acids, peptides, and small-molecule protein can be delivered through protein-based nanoparticles. Nanoparticles with appropriate size can enrich in tumor tissue, improve the bioavailability of drugs, and

reduce the toxic and side effects of free drugs. Protein-based nanoparticles target tumor mainly by enhancing permeability and retention effect (EPR effect) or receptor-mediated pathways; among these protein-based nanoparticles, albumin nanoparticles are a typical representative. In 2005, the FDA approves Abraxane[®] for marketing, which is a kind of nanoparticles based on albumin. This kind of albumin nanoparticles with targeting properties has attracted extensive attention. Albumin is the most abundant protein in plasma (30–50 g/L, human serum), and it has many advantages, such as good biocompatibility, noncytotoxicity, nonimmunogenicity, and biodegradability, so albumin is an ideal material for the preparation of nanoparticles. In addition, albumin-binding glycoprotein 60 (gp60) on the surface of vascular endothelial cells and secreted proteins acidic and rich in cysteine (SPARC) overexpressed on the surface of a variety of tumor cells can efficiently bind to albumin and promote the aggregation of nanoparticles loaded with drugs in the stroma of tumor cells (Figure 1).

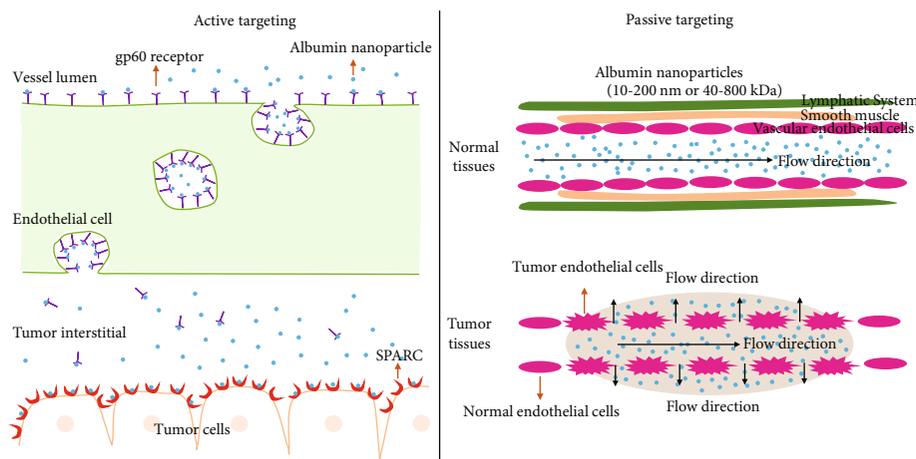


FIGURE 1: Schematic diagram of the mechanism of albumin nanoparticles targeting tumor tissue. Arrows indicate the flow direction of nanoparticles.

Based on the above advantages and characteristics of albumin, more and more researchers turn their attention to the study of albumin nanoparticles, and albumin nanoparticles have become one hot topic for research in biomedical field, especially in cancer therapy.

2. Types of Albumin

2.1. Ovalbumin. Ovalbumin is the most abundant protein in egg white, which accounts for 54-69% of total protein in egg white [6]. The isoelectric point of ovalbumin is 4.5, which is composed of 385 amino acid residues, and more than half of the amino acids are hydrophobic amino acids. Ovalbumin is a typical kind of globulin, and it is also the only protein containing free sulfhydryl groups buried in the hydrophobic core in egg white. Ovalbumin is a monomer and globular phosphoglycoprotein, whose molecular weight is about 45 kDa. Ovalbumin contains A1, A2, and A3 domains, whose difference lies in the number of phosphate groups. Glycosylation sites accounted for 3.5% in ovalbumin; 4 free sulfhydryl groups and 1 disulfide bond were buried in the hydrophobic center. In the crystal structure of natural ovalbumin, α -helix protrudes from the reaction center and 5 β -pleated sheets parallel to the long axis of the molecule. Disulfide bonds and sulfhydryl groups in the structure have a great influence on the aggregation structure of ovalbumin. Main functional characteristics of ovalbumin are emulsifying properties [7], foaming properties, water holding capacity, and film forming properties, which can be used as emulsifiers, moisturizer, edible packaging film, gel, and drug carriers [8-10]. It can improve food taste and texture, enhancing product stability and prolonging shelf life [11, 12]. Xiong et al. constructed lipid-soluble nutrient delivery vehicles based on ovalbumin [13]. Ovalbumin nanoparticles also were used to enhance efficiency of antigen uptake [14]. Self-assembled ovalbumin nanoparticles can deliver polyunsaturated fatty acids [15]. Rao et al. fabricated ovalbumin-carvacrol gel nanoparticles which show physicochemical and antibacterial properties [16]. Ovalbumin complex nanoparticles exhibit good encapsulation efficiency [17].

2.2. Bovine Serum Albumin. Bovine serum albumin (BSA) is a globulin in bovine serum, which contains 583 amino acid residues, whose molecular weight is 66.43 kDa and isoelectric point is 4.7. BSA is widely used in biochemical experiments [18]. For example, as a blocking agent in Western blot, BSA was added into restriction endonuclease reaction buffer to protect enzymes by increasing the concentration of protein in solution, and the specific principle is that BSA can block the degradation of enzymes and nonspecific adsorption, and it also can reduce the denaturation of enzymes caused by some adverse environmental factors such as heating, surface tension, and chemical factors. BSA comes from bovine plasma and is very cheap, which is often used to prepare nanoparticles as well as HSA. Chang et al. constructed a kind of complex nanoparticles based on BSA, and it shows high stability, good cell penetrating ability, and potential anticancer activity [19]. Cu^{2+} -BSA complex nanoparticles show better antibacteria activity [20]. BSA complex nanoparticles can be used as biocompatible nanoprobes for super resolution imaging [21]. BSA nanoparticles modified by N-Acetylcysteine can improve its stability [22], and BSA nanoparticles are often used as drug carriers to control the release of drug [23].

2.3. Human Serum Albumin. Human serum albumin (HSA) is the most abundant protein in human plasma, accounting for about 50% of total plasma protein. Its concentration in human plasma is about 30-50 g/L, and human liver can synthesize 12-20 g HSA every day. HSA consists of 585 amino acid residues with a molecular weight of about 67 kDa, whose single-molecule conformation likes a heart-shaped structure [24]. HSA is mainly divided into three domains, I, II, and III, respectively. Each domain is further divided into two substructures, namely, IA and IB, IIA and IIB, and IIIA and IIIB. Because albumin is derived from human plasma, it has good biocompatibility [25, 26]. Because of its good biodegradability, high biological stability, noncytotoxicity, and more drug-binding sites, it is widely used in medicine [27-29], biochemistry [30], and other fields [31, 32]; especially, the development and application of albumin

TABLE 1: Basic information of four types of albumin.

Types of albumin	Structure	Length (amino acid)	Molecular weight	Half-life	Organism	Main functions	References
Ovalbumin		385	~45 kDa	19 days	Egg white	Noninhibitory serpin, storage protein of egg white	[38–41]
Bovine serum albumin		583	~66.43 kDa	19 days	Bovine serum	Binds water, metal ions, fatty acids, hormones, bilirubin, and drugs and regulates the colloidal osmotic pressure of blood.	[40, 42]
Human serum albumin		585	~67 kDa	14 days	Human serum	Binds water, metal ions, fatty acids, hormones, bilirubin, and drugs and regulates the colloidal osmotic pressure of blood	[40, 43]
Mouse serum albumin or rat serum albumin	Crystal structures of MSA and RSA have not yet been clarified, and the predicted structure is similar to that of human serum albumin or bovine serum albumin by alphafold2	608	68.693 kDa, 68.731 kDa	Not clear	Serum of mice or rats	The same as the functions of serum albumin in bovine and human	[44–47]

drugs-carrier have attracted increasingly researchers' attention. Diethylenetriaminepentaacetic acid- (DTPA-) loaded HSA nanoparticles were used to treat generalized arterial calcification of infancy and pseudoxanthoma elasticum [33]. HSA-functionalized nanoparticles can deliver antitumor drug to HER-2-positive breast cancer cells [34], and HSA-functionalized nanoparticles can also be used as an MRI contrast agent and a potential luminescent probe to detect Fe^{3+} , Cr^{3+} , and Cu^{2+} in water [35]. Voicescu et al. constructed silver-HSA complex nanoparticles which can carry riboflavin [36].

2.4. Mouse Serum Albumin and Rat Serum Albumin. Mouse or rat serum albumin is composed of 608 amino acid residues with a molecular weight of about 68.7 kDa. Its structure is similar to that of other serum protein, and it can be divided into mouse serum albumin (MSA) and rat serum albumin (RSA) according to its source. However, crystal structures of both have not been determined [37], and the predicted structures can be obtained by alphafold2. So far, mouse serum protein is mainly used as a carrier to couple haptens in the process of antibody preparation, and there is no research report on its application in drug delivery.

Table 1 summarizes the basic information of four types of albumin.

3. Main Methods to Prepare Albumin Nanoparticles

3.1. Desolvation Method. A desolvation method means using a dehydrating agent such as ethanol to remove the hydrated membrane of albumin under stirring conditions, so its hydrophobic region is exposed and the solubility of albumin can be reduced; eventually, albumin will precipitate into

nanoparticles. Stable albumin nanoparticles can be formed by thermal denaturation or chemical crosslinking and glutaraldehyde is often used as a crosslinking agent. Finally, the residual crosslinking agent and organic solvent were removed to obtain purified albumin nanoparticles. A desolvation method has many advantages such as simple preparation process, rapid reaction, and no need to add surfactants. It is suitable for the encapsulation of a variety of hydrophobic drugs, and it is also the most widely used method for the preparation of albumin nanoparticles at present. Whose disadvantage is that residual crosslinking agents such as glutaraldehyde have certain toxic and side effects on organisms.

The process of traditional desolvation method also has the following disadvantages, such as unstable stirring speed, low efficiency, and friction with bottom of the reaction vessel, which limits its large-scale application. Wacker et al. realized large-scale preparation of albumin nanoparticles by using a two propeller stirring system [48]. Particle size of nanoparticles is in the range of 234.1–251.2 nm, and the polydispersity index (PDI) is lower than 0.2. Nanoparticles can be stored for a long time after freeze-drying, and the resuspended nanoparticles can be further treated, such as adsorbing drugs or covalently modifying targeted ligands on the particle surface. In recent years, nanoparticles prepared by the desolvation method have been studied widely in antitumor applications. Doxorubicin-loaded human serum albumin nanoparticles prepared by the desolvation method show good antitumor activity [49]. Ziaaddini et al. constructed a kind of BSA nanoparticles with the desolvation method which can enhance the efficacy and reduce cytotoxicity of anticancer drug [50]. Folate-decorated HSA nanoparticles acquired by desolvation can target breast cancer cells [51].

TABLE 2: Advantages and disadvantages of various methods for preparing albumin nanoparticles.

Methods	Main advantages	Main disadvantages	References
Desolvation method	Simple preparation process, rapid reaction, no need to add surfactants and repeatability	Having certain toxic and side effects due to the usage of crosslinking agents, unstable stirring speed, low efficiency, friction with bottom of the reaction vessel	[59]
Self-assembly	No inducer is added	Chemical modification may be needed to increase the self-assembly force	[60, 61]
Thermal gelation	Easy operation, no need to add crosslinking agents, good stability of products	Not suitable for heat-sensitive drug	[62]
Spray-drying	Easy operation, fast speed of production and good dispersion	Denaturation and inactivation of proteins because of high temperature	[62, 63]
Emulsification	Experimental conditions are relatively mild and experimental process is simple	Albumin nanoparticles may be destroyed and degraded because of mechanical shear force and ultrasonic action, and emulsification also has poor efficiency of encapsulation of hydrophilic drugs	[64, 65]
Double emulsification	Efficiency of encapsulation of hydrophilic drugs is improved, and the experimental conditions are relatively mild.	Albumin nanoparticles may be destroyed and degraded because of mechanical shear force and ultrasonic action	[66–68]
Nab-technology	Decreasing the usage of surfactants, simple and safe process	Needing to add toxic solvents such as chloroform and dichloromethane	[69, 70]
pH coacervation	Simple preparation process and repeatability	Crosslinking agents needed to be used, such as glutaraldehyde, which may have potential toxic and side effects	[71, 72]

3.2. Self-Assembly. Increasing the hydrophobicity of albumin molecules can make it self-assemble by certain methods, such as reducing the internal disulfide bond of albumin molecules, heating treatment, or adding denaturants. Then, drug molecules combine with the hydrophobic domains of albumin to mediate self-assembly of albumin into nanoparticles. Common reducing agents include β -mercaptoethanol, dithiothreitol, and cysteine. Some steps of self-assembly method are very similar to that of desolvation. Albumin nanoparticles obtained by self-assembly method can better retain functions of the protein, so which have active targeting properties. For example, Cai et al. constructed a kind of nanoparticles by self-assembly which can target neurons [52].

3.3. Thermal Gelation. Thermal gelation is a continuous process involving protein interactions (such as hydrogen bonding, electrostatic, and hydrophobic interaction) and thermal induced unfolding. Advantages of this method are that it is easy to operate and does not need to use crosslinking agents; the albumin nanoparticles prepared by this method have good stability. However, the disadvantage is that they are not suitable for heat-sensitive drugs. Albumin nanoparticles prepared by thermal gelation are relatively stable, so which often have good mechanical properties. Hughes et al. constructed nanoscale hydrogels based on albumin by thermal gelation, and it exhibits well mechanical properties [53].

3.4. Spray-Drying. Spray-drying is the process of changing the material from liquid to powdery. The typical spray-drying process consists of 4 steps, that is, atomization of materials, drying through gas, particle formation, and collecting particles. Spray-drying has some advantages, for example, the process of production is simple, the speed of

drying is fast, and the dispersion of products is well. Thus, it is widely used in medicine, detergents, dairy products, and other fields. However, the traditional spray-drying device is difficult to capture particles whose size is less than $2\ \mu\text{m}$, and the hot air drying process is easy to denature and inactivate albumin, so it is not suitable for the preparation of albumin nanoparticles. Steps of spray-drying are relatively simple, and albumin nanoparticles prepared by this method often have high drug loading. Chow et al. utilized spray-drying method to prepare high siRNA loading powders based on HSA [54].

3.5. Emulsification. An emulsification method is aimed at mixing aqueous solution of albumin with the oil containing drugs and emulsifiers, and emulsifying can be achieved by stirring, ultrasonic or high-pressure homogenization; oil in water (W/O) emulsion would be obtained. Albumin bound to drugs is distributed in aqueous droplets of internal phase, and then, the droplets are solidified by thermal denaturation or chemical crosslinking. Finally, albumin nanoparticles are obtained after the organic agents are removed. Size of albumin nanoparticles is affected by shear force, the nature and concentration of emulsifier, and so on. Albumin nanoparticles loaded with hydrophobic drugs can be acquired effectively by emulsification, but its deficiency is that mechanical shear force and ultrasonic action in the process of emulsification may destroy the stability of albumin and degrade albumin. Uppal et al. constructed a kind of albumin nanoparticles using emulsification, and it can deliver benzyl isothiocyanate efficiently [55].

3.6. Double Emulsification. Hydrophobic drugs can be encapsulated effectively by nanoparticles prepared by the emulsification method, but this method has poor efficiency

TABLE 3: Application of albumin nanoparticles in the diagnosis and therapy of cancer in the last five years (Excerpt).

Title	The preparation method of nanoparticles	Aims	Types of cancer	References
VE-Albumin Core-Shell Nanoparticles for Paclitaxel Delivery to Treat MDR Breast Cancer	Desolvation	Therapy	Breast cancer	[86]
HA/HSA Co-Modified Erlotinib-Albumin Nanoparticles for Lung Cancer Treatment	Desolvation	Therapy	Lung cancer	[87]
Preoperative Albumin-Bilirubin Grade as a Useful Prognostic Indicator in Patients with Pancreatic Cancer	N/A	Diagnosis	Pancreatic cancer	[88]
Preparation and Evaluation of Cabazitaxel-Loaded Bovine Serum Albumin Nanoparticles for Prostate Cancer	Biom mineralization	Therapy	Prostate cancer	[89]
In Vivo Efficacy of Bevacizumab-Loaded Albumin Nanoparticles in the Treatment of Colorectal Cancer	Coacervation	Therapy	Colorectal cancer	[90]
Self-Assembled PEGylated Albumin Nanoparticles (SPAN) as a Platform for Cancer Chemotherapy and Imaging	Self-assembly	Therapy	Breast cancer	[91]
pH-Responsive Allochroic Nanoparticles for the Multicolor Detection of Breast Cancer Biomarkers	Self-assembly	Diagnosis	Breast cancer	[92]
Triple-Functional Albumin-Based Nanoparticles for Combined Chemotherapy and Photodynamic Therapy of Pancreatic Cancer with Lymphatic Metastases	Nab-technology	Therapy	Pancreatic cancer	[93]
Precise Cancer Anti-Acid Therapy Monitoring Using pH-Sensitive MnO ₂ @BSA Nanoparticles by Magnetic Resonance Imaging	pH coacervation	Therapy	Lung cancer	[94]
A Phase II Study of nab-Paclitaxel in combination with Ramucirumab in Patients with Previously Treated Advanced Gastric Cancer	Nab-technology	Therapy	Gastric cancer	[95]
Beta-Carotene-Bound Albumin Nanoparticles Modified with Chlorin e6 for Breast Tumor Ablation Based on Photodynamic Therapy	Nab-technology	Therapy	Breast cancer	[96]
RGD-Conjugated Resveratrol HSA Nanoparticles as a Novel Delivery System in Ovarian Cancer Therapy	Emulsification	Therapy	Ovarian cancer	[97]
Albumin Nanoparticle of Paclitaxel (Abraxane) Decreases While Taxol Increases Breast Cancer Stem Cells in Treatment of Triple Negative Breast Cancer	Nab-technology	Therapy	Triple negative breast cancer	[98]
Nanoparticle Albumin-Bound Paclitaxel Plus Carboplatin Induction Followed by Nanoparticle Albumin-Bound Paclitaxel Maintenance in Squamous Non-Small-Cell Lung Cancer (ABOUND.sqm): A Phase III Randomized Clinical Trial	Nab-technology	Therapy	Lung cancer	[99]
Interstitial Lung Disease Associated with Nanoparticle Albumin-Bound Paclitaxel Treatment in Patients with Lung Cancer	Nab-technology	Therapy	Lung cancer	[100]
Enzyme-Sensitive Gemcitabine Conjugated Albumin Nanoparticles as a Versatile Theranostic Nanoplatfor m for Pancreatic Cancer Treatment	Conjugation	Therapy	Pancreatic cancer	[101]
Investigation of Different Targeting Decorations Effect on the Radiosensitizing Efficacy of Albumin-Stabilized Gold Nanoparticles for Breast Cancer Radiation Therapy	Chemical reduction	Therapy	Breast cancer	[102]
Tumor Progression of Non-Small Cell Lung Cancer Controlled by Albumin and Micellar Nanoparticles of Itraconazole, a Multitarget Angiogenesis Inhibitor	Gelation	Therapy	Non-small-cell lung cancer	[103]
EGFR Targeted Cetuximab-Valine-Citrulline (vc)-Doxorubicin Immunoconjugates-Loaded Bovine Serum Albumin (BSA) Nanoparticles for Colorectal Tumor Therapy	Desolvation	Therapy	Colorectal tumor	[104]
Efficacy and Safety of Nanoparticle Albumin-Bound Paclitaxel as Neoadjuvant Chemotherapy in HER2-Negative Breast Cancer	Nab-technology	Therapy	HER2-negative breast cancer	[105]
Nanoparticle Albumin-Bound Paclitaxel in Elder Patients with Advanced Squamous Non-Small-Cell Lung Cancer: A Retrospective Study	Nab-technology	Therapy	Non-small-cell lung cancer	[106]

TABLE 3: Continued.

Title	The preparation method of nanoparticles	Aims	Types of cancer	References
Albumin-Based Nanoparticles Loaded with Hydrophobic Gadolinium Chelates as T 1-T 2 Dual-Mode Contrast Agents for Accurate Liver Tumor Imaging	Coacervation	Diagnosis	Liver tumor	[107]
Doughnut-Shaped Bovine Serum Albumin Nanoparticles Loaded with Doxorubicin for Overcoming Multidrug-Resistant in Cancer Cells	Desolvation	Therapy	Lymphoblastic leukemia	[108]

TABLE 4: Summary of review papers about albumin nanoparticles in the last decade.

Title of review	Main scope	Year	References
Targeted Delivery of Albumin Nanoparticles for Breast Cancer: A Review	The using of albumin nanoparticles in the therapy of breast cancer	2022	[109]
Hyaluronic Acid and Albumin Based Nanoparticles for Drug Delivery	Preparation of hyaluronic acid and albumin-based nanoparticles and its application in tumors, skin tissue, joints, and vitreum	2021	[29]
Anticancer Nano-Delivery Systems Based on Bovine Serum Albumin Nanoparticles: A Critical Review	Bovine serum albumin nanoparticles for anticancer drug delivery	2021	[110]
Navigating Albumin-Based Nanoparticles through Various Drug Delivery Routes	Discussing various drug delivery routes of albumin nanoparticles and exploring their possibilities in other administration routes	2018	[28]
Treatment Innovations for Metastatic Breast Cancer: Nanoparticle Albumin-Bound (NAB) Technology Targeted to Tumors	Mechanism of action, efficacy, and safety of albumin nanoparticles loaded with paclitaxel	2014	[111]
Challenges, Expectations and Limits for Nanoparticles-Based Therapeutics in Cancer: A Focus on Nano-Albumin-Bound Drugs	Components, characteristics, limits, and clinical efficacy of nanoalbumin-bound drugs	2013	[112]
Albumin-Based Nanoparticles as Potential Controlled Release Drug Delivery Systems	Albumin nanoparticles as controlled release drug delivery systems and methods of surface modification of albumin nanoparticles	2012	[27]
Management of Breast Cancer with Nanoparticle Albumin-Bound (nab)-Paclitaxel Combination Regimens: A Clinical Review	The application of albumin-bound (nab)-paclitaxel nanoparticles in the clinical treatment of breast cancer	2011	[113]

of encapsulation for hydrophilic drugs. To improve the efficiency of encapsulation, a double emulsification method was proposed to prepare albumin nanoparticles containing hydrophilic drugs. Main steps are as follows. First, albumin was dissolved in deionized water and hydrophilic drugs were mixed with the oil containing surfactant to form a primary W/O emulsion. Albumin and medicine are dispersed in the internal water phase, and a surfactant is distributed on surface of the emulsion to stabilize. Then, the primary emulsion was dispersed into the water phase added with another surfactant, and the water/oil/water (W/O/W) composite emulsion was obtained. After evaporation of the intermediate oil phase, nanoparticles with uniform particle size were obtained. Zhang et al. constructed a kind of BSA complex nanoparticles by double emulsification, which can control drug release [56].

3.7. Nab-Technology. Nab-technology (NABTM) developed by American Bioscience is a unique method for preparing hydrophobic drug-loaded albumin nanoparticles. The technology uses albumin as a substrate and stabilizer, mixing nonpolar solvents containing hydrophobic drugs (chloro-

form, dichloromethane, etc.) and water containing albumin to obtain nanosize emulsions under high shear force (ultrasonic treatment, high pressure homogenization, etc.). After evaporation of nonpolar solvents, albumin nanoparticles loaded with drugs are obtained and particle size is usually the range of 100-200 nm. Compared with traditional preparation methods, NABTM technology does not need to use other surfactants, which avoids the use of glutaraldehyde that is toxic to the human body. It is a relatively simple and safe method to prepare drug-loaded albumin nanoparticles. The disadvantage is that toxic solvents such as chloroform and dichloromethane still need to be used. Abraxane[®] (it is also known as NAB-PTX) is the first chemotherapy drug prepared by Nab-technology and approved by the FDA for the first-line tumor therapy, which can effectively treat multiple types of cancer including metastatic breast cancer and non-small-cell lung cancer. In addition, the combined use of this product and gemcitabine has been approved to treat metastatic pancreatic cancer by FDA. Luo et al. used Nab-technology to construct albumin nanoparticles which exhibited antitumor efficacy, good pharmacokinetics, and better drug-safety [57].

3.8. pH Coacervation. Changing pH of the solution can effectively adjust the solubility and ionization of albumin in water. Based on this finding, adding organic solvents such as ethanol can promote the precipitation of albumin into nanoparticles, which is equivalent to an improved desolvation method. Disadvantages of this method are similar to the desolvation method. It also needs to use crosslinking agents such as glutaraldehyde, which may have potential toxic and side effects. Advantages of this method are simple preparation, good repeatability, and mechanical properties. Albumin-based nanoparticles acquired by pH coacervation showed good mechanical features [58].

Various methods for the preparation of albumin nanoparticles have their own advantages and disadvantages, which are summarized in detail in Table 2.

4. Applications in the Diagnosis and Therapy of Cancer

Albumin and its nanoparticles can be used in the diagnosis and therapy of various diseases, such as various kinds of cancer [73–75], diabetes [76, 77], kidney inflammation [78–80], liver diseases [81, 82] and so on [83–85]. In this section, we focus on the application of albumin nanoparticles in the diagnosis and treatment of cancer in recent five years, and specific information can be seen in Table 3.

In the past ten years, there are some reviews that summarize the applications of albumin nanoparticles in cancer therapy (Table 4). However, these reviews rarely summarize the preparation methods of albumin nanoparticles in detail, and this review makes up for some deficiencies to some extent.

5. Challenges

Albumin has good biocompatibility, nontoxicity, and non-immunogenicity, and its application in novel drug carriers is increasing. Especially for tumor therapy, albumin nanoparticles have shown some unique advantages. However, the development of albumin nanoparticles still faces the following challenges:

- (1) In recent years, there are increasingly researchers focusing on albumin nanoparticles, and there are also many articles reporting about various albumin nanoparticles, but few of them are effectively transformed into clinical applications. How to make more research about albumin nanoparticles transform into clinical application, which is still a big challenge to scientists
- (2) Organic reagents are almost used in the preparation of albumin nanoparticles nowadays, and albumin has been denatured during the preparation of albumin nanoparticles. If albumin is denatured and inactivated, some of its functions will be lost. Therefore, how to acquire albumin nanoparticles without organic reagents, which is also a challenge to researchers

- (3) Although albumin nanoparticles have advantages such as better biocompatibility, nontoxicity, and nonimmunogenicity, there are still some shortcomings in delivering drugs. For example, albumin may react with protein in blood leading to a decrease in number of nanoparticles entering the tumor tissue [114]
- (4) Albumin is not sufficiently stable due to its structural properties and the complex environment of the body containing various enzymes and proteins [115]. Appropriate modifications to albumin are still needed to enhance its stability

6. Conclusions

Currently, there are many methods to prepare albumin nanoparticles, and all of these methods have their own advantages. However, these methods have one common disadvantage, which is that albumin nanoparticles will be denatured during the preparation. Proposing a new method to prepare nondenatured albumin nanoparticles, so these nanoparticles will have more biological functions of natural albumin, which is a challenge that scientists should face. Besides, researchers also need to think how to make more albumin nanoparticles available for clinical use and not just limited to research.

Conflicts of Interest

All authors declare that there are no conflicts of interest regarding the publication of this paper.

Authors' Contributions

RM wrote the original manuscript and contributed to the draft design and conception. HZ revised the manuscript. ZW collected some references. SH and BW revised the manuscript and contributed to the draft conception. All authors agree to the final submission of the manuscript.

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