Kiarashi and Yasamineh
BioMedical Engineering OnLine (2024) 23:122
https://doi.org/10.1186/s12938-024-01318-9

BioMedical Engineering OnLine

REVIEW Open Access

Albumin nanoparticles are a promising drug delivery system in dentistry

Mohammad Kiarashi[1] and Saman Yasamineh[2*]

*Correspondence:
yassaman124@gmail.com

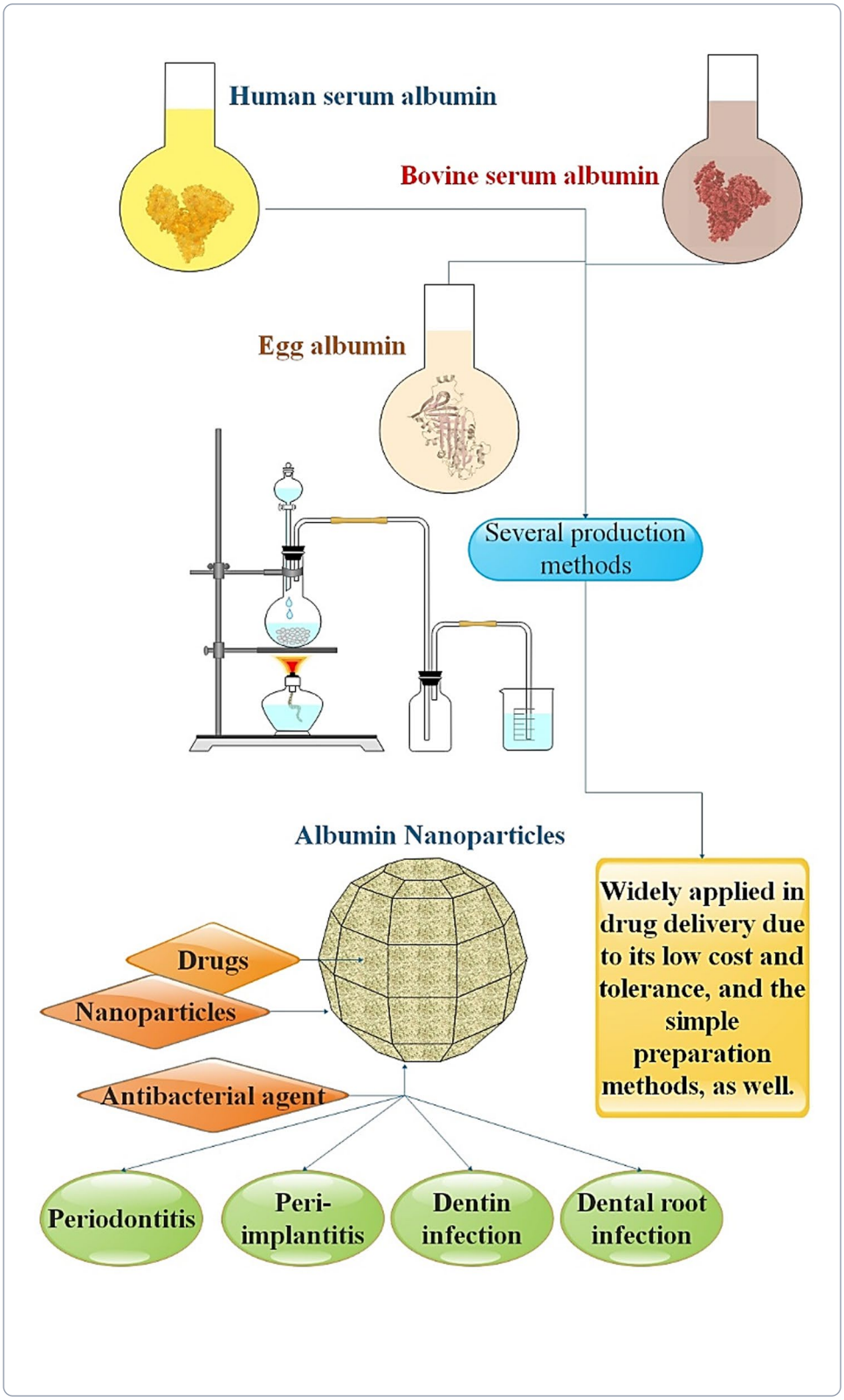
[1] College of Dentistry, Lorestan University of Medical Sciences, Khorramabad, Iran
[2] Young Researchers and Elite Club, Tabriz Branch, Islamic Azad University, Tabriz, Iran

Abstract

Periodontal infection is a long-lasting inflammatory condition caused by the growth and development of an abnormal and harmful community of microorganisms. This destructive illness leads to the loss of the tissues that support the teeth, degradation of the bone surrounding the teeth, and eventually tooth loss. To treat oral infections, it is necessary to use nonsurgical methods such as antibiotics. However, the indiscriminate and incorrect use of antibiotics results in drug resistance. Among these alternate therapeutic options, using nanoparticles to treat infectious dental disease was particularly significant. Consequently, researchers have worked to develop an effective and satisfactory drug delivery method for treating periodontal and dental illnesses. Albumin nanoparticles serve a considerable function as carriers in the drug delivery of chemical and biomolecular medications, such as anticancer treatments; they have several advantages, including biocompatibility and biodegradability, and they are well-tolerated with no adverse effects. Albumin nanoparticles have several benefits over other nanomaterials. Protein nanocarriers provide advantages such as biocompatibility, biodegradability, reduced immunogenicity, and lower cytotoxicity. Furthermore, this nanoparticle demonstrated significant intrinsic antibacterial properties without being loaded with antibiotic medicines. As a medication and antibacterial nanoparticle delivery method, albumin nanoparticles have substantial applications in periodontal and dental infectious disorders such as periodontal infection, apical periodontitis, and peri-implantitis. As a result, in this article, we studied the usage of albumin nanoparticles in dental disorders.

Keywords: Albumin nanoparticles, Periodontitis, Peri-implantitis, Dentin and canal root infections, Drug delivery system

Graphical Abstract


Human serum albumin
Bovine serum albumin
Egg albumin
Several production methods
Albumin Nanoparticles
Drugs
Nanoparticles
Antibacterial agent
Widely applied in drug delivery due to its low cost and tolerance, and the simple preparation methods, as well.
Periodontitis
Peri-implantitis
Dentin infection
Dental root infection

Introduction

Plaque biofilm, a complex community of bacteria or fungi, significantly contributes to dental illnesses such as caries and periodontitis. It acts as a protective shield for harmful germs against drugs and also avoids the body's defense mechanisms [1]. The pulp chamber and root canal system, constantly exposed to mechanical and chemical harm, should be protected from pathogens and commensal microorganisms in the oral cavity. The oral microbiome plays a substantial role in causing this harm. When cavities, fissures, or injuries impair the dentinal barriers, opportunistic and pathogenic microorganisms can enter these sites, which should typically be inaccessible. This could lead to harmful consequences, such as inflammation, death of the dental pulp, and periodontitis [2]. Gingivitis and periodontitis are inflammatory disorders caused by an excessive growth of bacteria. It has been recognized that bacteria are the primary cause of these diseases; however, the presence of certain bacteria does not ensure that a disease will progress to periodontitis. Periodontitis is a multifactorial condition; certain bacteria are linked to the disease but may not be the focus of treatment [3].

Osseointegrated dental implants are advanced tools used in reconstructive dentistry to replace missing teeth and restore functionality such as chewing, biting, and appearance. The oral component of dental implants, like the texture of natural teeth, offers a pristine, non-shedding surface that facilitates the attachment of bacteria and the development of biofilms, a process facilitated by the salivary pellicle. The bacterial communities in the early phases of colonization exhibit reduced diversity and closely mirror those found in healthy periodontal sites. Hence, it is crucial to understand the ecological factors that cause microbial pathogenesis in peri-implantitis to create efficient strategies for prevention, diagnosis, and treatment, given that the peri-implant tissues are very vulnerable to oral infections originating from within the body [4].

Although numerous studies have focused on the creation of antimicrobial substances to tackle this issue, most of these efforts have not yielded the desired outcomes due to the quick deterioration and release of antibacterial agents, leading to low effectiveness and safety concerns [5]. Using nanomaterials, cutting-edge clinical instruments, and devices, nanotechnology has completely changed the dental field and has the potential to provide comprehensive oral health care. By utilizing nanomaterials' atomic or molecular properties, new materials with superior properties can be developed [6].

In addition, nanotechnology has greatly revolutionized the healthcare sector, with its utilization extending to biomedical and dental treatment. Currently, it is being applied in multiple areas of diagnosing, preventing, and treating oral disorders [7]. The field of dentistry has incorporated the use of advanced technology to manufacture nanoparticles (NPs). The uses of these materials are diverse and encompass caries inhibitors, biomembranes, scaffolds, and targeted medication transfer [8]. These emerging technologies have the potential to advance dental research significantly. Nanomaterials additionally transport oral fluid or medications, averting and treating certain oral diseases and preserving oral health [9]. NPs can avoid dental materials, tools, processes, and drug restrictions [10]. NPs may offer an innovative method for preventing and managing dental infections. NPs exhibit higher antimicrobial activity due to their high charge density and extensive surface area, facilitating their interaction with bacteria's negatively charged

surfaces. It was also found that NPs deposited onto biomaterial surfaces or mixed with polymers exhibited superior antibacterial properties in the oral cavity [11].

For instance, researchers demonstrated that the antibacterial activity of Cu–ZrO_2 NPs was significantly lower than that of ZrO_2 NPs when tested against both Gram-positive (*Lactobacillus* sp.) and Gram-negative (*Pseudomonas aeruginosa*) bacteria [12]. Moreover, NPs have unique therapeutic features that make them helpful in treating periodontitis. These attributes include remarkable antibacterial, anti-inflammatory, and antioxidant capabilities, immunomodulatory capacities, and the capacity to promote bone regeneration [13]. Recent developments in nanotechnology have enabled the delivery of anti-inflammatory biomolecules and pharmaceuticals to specific locations inside the mouth, such as periodontal tissues, inflammatory cells, and pathogens. These areas may be reached in combination with NPs. Further investigation into the effectiveness of NP-based local drug delivery medications in managing clinical periodontal disease is strongly advised [14–16].

Nanomaterials may be engineered to target delivery and interact with biological systems. While there is no official survey on the size of therapeutic nanomaterials or nanomedicines, it is customary for drug delivery nanomaterials to have a diameter of 40–400 nm. Nanomaterials have a very high surface-area-to-volume because of their nanoscale size constraints, making them excellent transporters for various therapies to the targeted cells [16]. Biomaterials in dental implants: by providing the required strength, biocompatibility, and tissue integration, biomaterials are essential to the success of dental implants. Therapeutic substances may be released locally and continuously using nano-based drug delivery devices. With regulated release just at the implant site, this may be very helpful in the oral environment. Drug release kinetics may be precisely controlled using nanoformulations, increasing therapeutic effectiveness and reducing adverse effects. Implant surface nanocoatings may lessen the chance of infection and inhibit microbial adherence. Implant surfaces coated with nanostructured materials may improve osseointegration via improved contact with neighboring bone tissues. Developing biomaterials to distribute anti-inflammatory medications to reduce inflammation related to the implantation procedure is possible [17].

An improvement in biocompatibility, the ability to focus medications on particular organs, and a decrease in toxicity effects are just a few of the many benefits of using NPs as drug delivery vehicles. In targeted drug delivery, NPs can potentially be used in treating cancer, osteoporosis, bone disorders, and periodontitis, among other oral conditions. To effectively use them as medication delivery agents, one must thoroughly understand the NPs' composition, properties, manufacture, and drug attachment characteristics. Magnetic NPs' behavior and magnetic properties may be affected by their size, shape, core–shell designs, and magnetic qualities, among other attributes. Researchers informed several revisions to the procedures used to create these NPs, creating composite systems for administering therapies. These systems have also improved and adapted their magnetic properties, shell–core designs, particle size, and nanosystem features [18].

Albumin comprises 585 amino acids and has a low molecular weight of 66/5 kDa. It is a single-chain protein. There are hydrophobic patches and voids, and it does not include any prosthetic groups; it is a simple protein, not glycosylated. There are three

structurally similar domains that make up albumin. The structure has three domains: domain I, which spans residues 1–195; domain II, which spans residues 196–383; and domain III, which spans residues 384–585. Every domain has two identical subunits, denoted A and B, sequentially composed of four and six α-helices. X-ray crystallography showed that human albumin is a tertiary structure with 17 pairs of disulfide bridges and a heart shape. Albumin has a single unpaired cysteine (Cys34) in its structure. It is about 68% α-helix (any β-sheet) and has dimensions of $80\times80\times30$ Å [19]. In addition, albumin's inherent qualities, such as its biodegradability and biocompatibility, make it a widely used macromolecule [20]. Making albumin nanoparticles (ABNPs) is a viable method for improving drug solubility and creating efficient carriers for regulated drug delivery [21]. ABNP carrier systems are an appealing technique because the albumin molecule contains numerous drug-binding sites, which allow for the incorporation of a substantial amount of drug into the particle matrix [22].

ABNPs possess a high concentration of charged amino acids, such as lysine, and have a well-defined fundamental structure. As a result, these NPs may easily attract and bind molecules with positive or negative charges through electrostatic adsorption without requiring additional chemicals [23]. Clinical conditions involving the accumulation of albumin in affected tissues, such as cancer, infections, and immunological disorders, are characterized by cachexia. This complex illness leads to significant weight loss and muscle wasting. Abraxane was confirmed via the Food and Drug Administration (FDA) in 2005, partly due to the rapid advancement of NP albumin-bound (NAB) methods. This technology is a proven and valuable method of delivering drugs, allowing low solubility in water-active pharmaceutical ingredients (API) to be entrapped in NPs. It has demonstrated several advantages, including avoiding using solvents/solubilizers in the preparation procedure, enabling a high tolerable dose, prolonging the drug's presence in the tumor, reducing infusion time, and minimizing the risk of adverse events [24]. Levemir®, Tresiba®, and Victoza® are examples of market-approved medications that are fatty acid derivatives of human insulin or the glucagon-like-1 peptide, which physically bind to the corresponding binding sites of human serum albumin (HSA) to prolong their half-lives. Abraxane®, a paclitaxel ABNP, is authorized for the treatment of advanced pancreatic cancer, non-small cell lung cancer (NSCLC), and metastatic breast cancer. Aldoxorubicin, the doxorubicin prodrug that binds covalently to the cysteine-34 position of circulating albumin, is now undergoing advanced clinical studies. A phase 3 registration study for soft tissue sarcoma was started in Q1 2014 [25]. Furthermore, researchers demonstrated that the microtubule inhibitor NAB paclitaxel, or nap-paclitaxel, has shown clinical benefit, whether used alone or in combination, to treat advanced NSCLC. Nap-paclitaxel was created to lessen the toxicities connected to solvent-bound paclitaxel (sb-paclitaxel) [26].

Furthermore, albumin is an extraordinary extracellular antioxidant that provides a strong defense against free radical attack. Finally, albumin can undergo structural changes to evade lysosomes and low-pH endosomes, resulting in the efficient discharge of drugs into the cellular environment. The proteolytic degradation of albumins accompanies this process. Combining these properties has made albumin a desirable carrier in drug-carrying nanotechnology [27]. BSA, a protein that dissolves in water and can hold many drugs, has been used to transport medicines at a nanoscale level. This system

has several advantages, including breaking down naturally, being compatible with living organisms, having a simple manufacturing process, and producing consistent results. Bovine serum albumin (BSA)-NPs, which have a large surface area, have the potential to release drugs slowly over a long period [28].

Generally, amoxicillin, ciprofloxacin, gentamicin, and tobramycin are among the antibiotics delivered using ABNP in various illnesses [28–30]. ABNP is applied to address multiple dental and periodontal diseases. For instance, HSA NPs were used as a drug delivery system (DDS) to build a functional dental adhesive resin structure that featured antibacterial qualities. A desolvation procedure was applied to make HSA NPs laden with Peridex (chlorhexidine (CHX)) diacetate, a model antibacterial drug. The commercial methyl methacrylate (MMA)-based resin was mixed with the Peridex-loaded HSA NPs, forming a resulting mixture. The resin matrix containing the HSA NPs displayed persistent Peridex release over a 4-week immersion test, but there were no early release surges. The resin matrix containing the Peridex-loaded HSA NPs displayed a larger zone of suppression against *Streptococcus mutans* in the agar diffusion test than the resin matrix employed alone. Investigators suggested that the delivery system successfully imparts antibacterial action to the resins. These outcomes further reveal that Peridex, which prevents the multiplication of oral bacteria, can be powerfully integrated into the MMA-based resin matrix by employing HSA NPs [21].

In this study, we explore the types of significant properties and the production technique of ABNPs. We then examine their usage in various dental and gum illnesses such as periodontitis, peri-implantitis, and other dental disorders.

Albumin nanoparticles characterization

Serum albumins (SABs) are the most prevalent globular proteins in the albumin family [31]. The process is initiated by albumin binding to the 60-kDa glycoprotein (Gp60) receptor on the surface of endothelial cells. Afterward, Gp60 attaches to an internal protein called caveolin-1 and causes the cell membrane to fold inward, forming transcytotic vesicles known as caveolae [32]. Moreover, ABNPs possess functional chemicals, such as amino and carboxylic groups, which can be utilized to alter the surface [33]. The zeta sizer analysis revealed that the average size of ABNPs was 225.1, 223.5, 226.3, and 228.7 nm. This indicates that the ratio of drug to polymer did not have a notable effect on the particle size [34]. In 2005, Nab-paclitaxel was licensed and marketed as the first pharmaceutical product based on serum ABNPs. Consequently, albumin can enhance the transcytosis of unbound and albumin-bound plasma components into the extravascular environment through the endothelium [35].

ABNPs have gained popularity in pharmaceutical research due to their prolonged half-life, compatibility with biological systems, and larger surface area. In recent years, many drugs have been successfully incorporated into albumin matrices. The intrinsic features of albumin make it an ideal material for developing nano-sized drug-delivery vehicles [36]. Furthermore, albumin is a fascinating transporter in the field of nanomedicine because of its distinctive characteristics. These include its capacity to be linked to various receptor ligands, which improve the targeted delivery of medications to specific areas. Albumin is also the most prevalent protein in plasma [37]. Second, albumin's chemical structure and conformation allow interaction with many different medications,

perhaps shielding them from removal and metabolism in vivo, thereby increasing their pharmacokinetic qualities [38].

Furthermore, albumin can bind to receptors that are excessively expressed in various diseased tissues and cells, allowing for precise targeting of the disease site without requiring specific ligands in the nanocarrier. As a result, albumin, with a serum half-life of around 19 days, can enhance targeted drug delivery and prolong the duration of action [39]. Albumin's potential for application in medicine and disease therapy is attributed to its essential activities in the human body. In recent years, albumin has been applied in diagnosing and treating numerous disorders [40]. Nanocarriers, such as albumin, have the potential to address the limitations of therapeutic medications, including their limited solubility, shallow absorption, and numerous side effects. Researchers have investigated the possibility of albumin as an NP to reduce therapeutic side effects and enhance its stability [41, 42].

It possesses desirable characteristics such as biodegradability, not toxic to cells, non-immunogenicity, and excellent biocompatibility, making it an ideal material for producing NPs. Moreover, albumin can enhance drug targeting, decrease the toxicity of unbound drugs, and improve the water solubility of hydrophobic drugs, among other advantages [43]. The medical field makes considerable use of drug-delivery devices based on ABNPs. Currently, the most frequent procedures to prepare ABNPs are desolvation, self-assembly, thermal gelation, spray drying, double emulsification, emulsification, Nab technology, pH coacervation, etc. These procedures have varied benefits and downsides due to variances in the underlying principles and conditions of preparation [44]. Nevertheless, the clinical implementation of albumin-based therapy is still relatively new, with only a few products available for clinical use. This is even though the treatment has clear potential and many scientific reports to support it [45]. SAB, a primary protein in the circulatory system, is a globular protein with a molecular weight of 66 kDa. It has a heart-shaped structure and comprises around 585 amino acids. Albumin increases the ability of hydrophobic chemicals to dissolve in the bloodstream and acts as a DDS for several molecules [46].

Because NPs shield the active ingredient and facilitate delivery to damaged tissue, local medication concentrations may be raised, and adverse effects can be minimized. Additionally, targeting ligands may modify the surface of NPs for more site-specific targeting. Therefore, using particle DDSs rather than a traditional solution to provide the medication is a strong and promising substitute. For instance, the unique interaction between lectins and cellular carbohydrates may improve absorption, similar to the uropathogenic bacteria's FimH-dependent bacterial adhesin invasion process. Researchers present a novel drug-delivery vehicle that includes wheat germ agglutinin (WGA) to promote cellular internalization, trimethoprim, rifampicin as API, and HSA as the NP shell and core component. Cell binding tests showed that the cell-binding potential increased by up to 60% when WGA was inserted into the proteinaceous particle shell. Furthermore, NPs demonstrated excellent efficiency against both Gram-positive and Gram-negative bacteria [47].

Two main approaches were taken to increase the accumulation of drug-loaded NPs in tumor locations, decrease the therapy's adverse effects, and increase its efficacy. Passive targeting produces high permeability and accumulation by treating aberrant tumor

blood vessel cells and inadequate lymphatic drainage. The increased permeability and retention (EPR) effect, which describes how molecules of specific sizes tend to concentrate in tumor tissue much more than in normal tissues, is the foundation of the passive targeting technique. The alternative approach, active targeting, directs medications to certain cells and facilitates the drug's specific absorption and retention by the targeted disease cells by using affinity ligands. Various ligands have been used to target anticancer therapies, including transferrin, folic acid, and monoclonal antibodies (mAb) [48].

In recent years, albumin has become a very effective macromolecular carrier for therapeutic and diagnostic medical applications. Anderson et al. examined its function in binding to the neonatal Fc receptor (FcRn) and elucidated its pH-dependent binding mode. There are at least three key reasons why using SAB in medicine is beneficial. It may accumulate in inflammatory and malignant tissues because its molecular weight is over the renal threshold and its circulation duration is prolonged. Second, albumin is transcytosis by endothelial cells via the Gp60 receptor, which helps move the protein into the tumor despite the efflux by solid tumors' interstitial fluid pressure. Not only does the FcRn bind IgGs, but it also gives the protein in the body a lengthy half-life. Thirdly, the abundance and variety of binding sites found in albumin help enhance the pharmacokinetic characteristics of small-sized antibody moieties or therapeutically active peptides [49, 50].

Since albumin typically has a pH of 7 (PI = 4.7), it may carry a variety of chemotherapeutic medications. Even though ABNPs lessen the adverse effects of drugs and enhance their curative effects, they are quickly recognized and consumed by the mononuclear macrophage system due to antibody targeting or protein adsorption in plasma. As a result, the NPs are eliminated from the body through the bloodstream. Much potential exists for ABNPs to be readily coated with various polymers or ligands due to their high content of carboxyl and amine groups and different binding sites. This can be achieved through covalent coupling to modify surface properties (e.g., PEG modification to improve hydrophilic, avoid macrophage phagocytosis), binding with ligands (e.g., folic acid modification of tumor cells with rich folate receptors targeting), immune antibody interacts with antigen (antibody-mediated system), and other measures to realize the active target of drugs. Furthermore, via increased penetration and retention (EPR), circulating ABNPs may passively collect in tumor tissue. To achieve tissue-specific targeting, NPs may alter their characteristics by changing their surface coating, particle size, and ligand binding. These methods allow HSA NPs to escape absorbing macrophages primarily found in the liver's reticuloendothelial system (RES) [24, 51–53].

ABNPs are an excellent example of protein-based NPs that target tumors via receptor-mediated pathways or the enhanced permeability and retention effect (EPR effect). Abraxane®, a class of ABNPs, was approved for commercialization by the FDA in 2005. There has been a lot of interest in ABNPs with targeting capabilities. With several desirable properties, including excellent biocompatibility, noncytotoxicity, nonimmunogenicity, and biodegradability, albumin is a perfect building block for NPs. Albumin is the most abundant protein in plasma (30–50 g/L, human blood). Furthermore, vascular endothelial cell surface albumin-binding Gp60 and tumor cell surface acidic and cysteine-rich secreted proteins (SPARC) can bind to albumin efficiently and promote drug-loaded NP aggregation in tumor cell stroma [54].

While designing NPs to facilitate clearance would help reduce their toxicity, a quick clearance would further impair their therapeutic efficacy and targeting. Thus, it is evident that striking a balance is necessary to create safe, effective, and translatable nanomedicines. The hepatic and renal systems are the two primary routes by which NPs are eliminated from the body. NPs enter the liver and spleen by the hepatic pathway, where they are taken up by tissue-resident phagocytes or the mononuclear phagocyte system (MPS). NPs are then eliminated via the biliary system and eliminated through the feces. NPs are immediately removed from the renal route by renal filtration and are discharged in the urine [55].

Binding sites I and II are two important non-covalent binding sites in HSA that may bind various exogenous pharmacological molecules, such as benzodiazepines, antibiotics, and anti-inflammatory medications. The therapeutic effectiveness of these medications is extended when they are linked to albumin, which has an average circulation half-life of *19 days. This increases their circulating lifetime. Because of its enormous size, near-absence of filtration in the glomerulus (pore size: 5–6 nm), and very low immunogenicity, albumin undergoes relatively little metabolism in blood. This physical or chemical interaction may enhance the subpar pharmacokinetic profiles of several medications with albumin. Hydrophobic medications are the only ones that can bind non-covalently to albumin; hydrophilic chemical pharmaceuticals and peptide/protein drugs have much fewer binding sites and cannot bind albumin molecules in circulation for an extended period. Since the half-life extension effect was most noticeable for tiny peptides, researchers have been trying to associate them with albumin artificially [56].

Different types of albumin

Researchers looked at several albumin production and transportation techniques and several kinds of albumin, including HSA, BSA, and egg albumin [23].

Ovalbumin

Ovalbumin (OVA) is the critical protein in egg whites, making up 54–69% of the total protein content. It is a globular phosphoglycoprotein that exists as a single unit and has a molecular weight of around 45 kDa. OVA is the only egg white protein with hidden sulfhydryl groups within its hydrophobic core. It is a commonly found globulin. OVA contains 385 amino acid residues, over half being hydrophobic [57]. OVA comprises three domains, A1, A2, and A3, which differ in their number of phosphate groups. The hydrophobic center of OVA hides four free sulfhydryl groups and one disulfide bond. OVA has 3.5% of its sites available for glycosylation. Disulfide bonds and sulfhydryl groups significantly influence OVA's aggregation structure. The primary functional properties of OVA include emulsification, foaming, water-holding capacity, and film-forming properties. These properties make it suitable for use as emulsifiers, moisturizers, drug carriers, and consumable packaging film. OVA NPs were also employed to improve [54].

Researchers examined OVA-carvacrol NPs' physicochemical and bactericidal characteristics (OCGns). The NPs were produced using a gel embedding technique at different pH values (2, 5, 7, and 9). Encapsulation was successfully performed at pH 2 and pH 9 with encapsulation efficiencies of 89.34% and 91.86%, respectively. However, studies that suppressed activity showed that the lowest dosage at which OCGn-2 inhibited the

growth of Gram-positive *Bacillus cereus* and Salmonella was lower than that of OCGn-9 (0.28 mg mL^{-1}) (0.08 and 0.16 mg mL^{-1}, respectively). In addition, OCGn-2 demonstrated a superior thick gel structure, increased stability, encapsulation rate, and antibacterial activity. The pH influences the encapsulation efficiency (EE) and bacteriostatic characteristics of the produced NPs [58].

Bovine serum albumin (BSA)

BSA is a globular protein present in cattle serum. The molecule has a mass of 66.43 kDa, 583 amino acid units, and an isoelectric point of 4.7. BSA is commonly utilized in biological studies [59, 60]. BSA was used in the restriction endonuclease reaction buffer as a blocking agent in Western blotting to protect enzymes by elevating the protein concentration in the solution. BSA can inhibit enzyme degradation and non-specific adsorption. It also helps to minimize enzyme denaturation induced by unfavorable environmental conditions such as heat, surface tension, and chemical variables. BSA is an economical option that is obtained from cow plasma. NP synthesis is a typical application of this technique [61, 62]. The scientists employed citrus lemon extract-assisted green synthesis to produce zinc oxide NPs (ZnO NPs) with an average diameter of around 11 nm. The interaction between BSA and ZnO NPs was observed by measuring changes in BSA's natural fluorescence emission characteristics and the constituent fluorophores' synchronized emission spectra. ZnO NPs produced using lemon fruit extract perform better when comparing binding constants to similar experiments. The molecular docking studies provided insights into the mode of interaction and binding models. Negative values in the binding models indicate a meaningful and viable interaction. The antibacterial activity of ZnO NPs was investigated against *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Escherichia coli*, and *Proteus mirabilis*. The generated ZnO NPs exhibit bacterial killing activity versus the tested diseases [63].

Human serum albumin (HSA)

HSA is the most plentiful protein in human plasma, making up approximately 50% of the whole plasma protein. The human liver can produce 12 to 20 g of HSA daily, and its concentration in human plasma ranges from 30 to 50 g per liter. HSA has a molecular weight of approximately 67 kDa and is made up of 585 amino acid residues. Its structure is similar to that of a heart [64]. It is widely employed in biochemistry, medicine, and other sectors due to its high biological stability, strong biodegradability, lack of cytotoxicity, and abundance of drug-binding sites; in particular, the creation and usage of albumin drug carriers have drawn the interest of researchers more and more [65]. Numerous sources of naturally occurring antimicrobial peptides (AMPs) have been identified. They have a cationic, hydrophobic amphipathic structure and range in length from 10 to 50 amino acid residues. Even antibiotic-resistant bacteria can have their membrane integrity disrupted by them in minutes, and they do not tend to cause drug resistance. With 70–76% identity, the amino acid sequences of human, bovine, and mouse albumins are highly similar. It has seven fatty acid-binding sites and two drug-binding sites. Over 90% of the antipyretic drug ibuprofen and the anticoagulant medication warfarin were attached to human albumin's sites II and I, respectively. HSA (90–94%) binding and inhibiting the lipopeptide antibiotic daptomycin and several short AMPs is prominent at site II [66].

Albumin nanoparticles preparation

ABNPs can be generated via three primary mechanisms: desolvation, emulsification, and thermal gelation. Recently, nano-spray drying, Nab-technology, and self-assembly approaches have been utilized [67]. ABNPs can be produced using either chemical or physical processes. Chemical approaches utilize chemical additives, such as ethanol, cottonseed oil, or β-mercaptoethanol, to stimulate the creation of NPs. Conversely, physical approaches utilize physical variables like heat or pressure to produce NPs [68]. Self-assembly, emulsification, and desolvation are the most frequently employed chemical-based techniques [69].

Desolvation (coacervation)

The desolvation or coacervation operation is a widely used and direct method for producing ABNPs. Desolvation is a frequently used method for generating ABNPs. The process involves gradually adding a desolvating substance, such as ethanol or acetone, to a stirred aqueous albumin solution until the solution becomes turbid [70]. In this procedure, a desolvation agent, such as acetone or ethanol, is supplied to the aqueous albumin solution under a continuous agitation condition using a magnet. The process is maintained until the solution achieves a turbidity [71]. The flow velocity and volume of the desolvating chemical are crucial factors in producing ABNPs of the desired size. After adding the desolvation agent, it is necessary to introduce a cross-linker, such as a glutaraldehyde solution, to stabilize the inherently unstable particles. The produced suspension should be continuously stirred overnight to guarantee complete crosslinking of all amino acid residues in the protein [72]. The amino groups in the arginine residues and the guanidino side chains in the lysine residues of albumin are chemically linked together through a condensation reaction with the glutaraldehyde aldehyde group. During the purification process of the NPs, centrifugation is utilized to eliminate any surplus cross-linking agent, ethanol, and unreacted albumins [73]. The nanosuspension obtained is subjected to freeze-drying, producing a fine powder consisting of NPs. This powder contains 5% mannitol, a cryoprotectant [74]. A tubing pump is an essential instrument for precisely regulating the flow rate of the desolvation agent's addition. The manual addition of ethanol using a syringe has also been documented in the literature; however, using a pump is challenging and has drawbacks, as the addition of ethanol cannot be precisely controlled. Consequently, in the present study, a simple apparatus was developed to precisely control the flow rate and the addition of ethanol, rather than relying on a pump or syringe. Additionally, EDC was employed to cross-link the produced ABNPs, which reduced the overnight duration of the preparation process to three hours [75]. Glutaraldehyde, although present in the structure of the NPs, has adverse effects. On the other hand, EDC is a cross-linker that creates peptide bonds between carboxyl and amide groups of amino acids in the stabilized NPs. Urea, a by-product of the reaction, can be easily eliminated by centrifugation. This research aims to develop a simple and effective procedure that aligns with the desolvation method to produce future protein-based NPs with smaller particle sizes [76]. The desolvating agents gradually alter the tertiary structure of albumin, resulting in phase separation and protein aggregation. The homogeneous solution is divided into two phases: one predominantly composed of

solvent and the other formed by albumin, which forms submicronic aggregates [67]. The parameters of the method, such as pH, protein concentration, cross-linker concentration, desolvating agent level, ionic strength, and stirring speed, define the features of the final formulation. Typically, the formulation obtained is not stable enough. Therefore, a cross-linker, such as glutaraldehyde, is needed to enhance and stabilize the morphology of the NPs [77].

The emulsion-solvent evaporation (ESE) technique

The ESE technique is a more reliable and amplification-potential method appropriate for producing NPs with smaller dimensions and lower polydispersity index than the pH-condensation or microfluidic techniques. It is less complex, takes time, and needs fewer chemicals. To create a rudimentary emulsion, a non-aqueous solution (oily phase) comprising a suitable quantity of emulsifier is stirred with an albumin solution (aqueous phase) [78]. Although this technique is appropriate for hydrophobic medication entrapment via connecting with hydrophobic cavities on HSA molecules, it is primarily restricted by using toxic organic solvents (such as dichloromethane or chloroform) in the oil phase. The emulsion can be homogenized through homogenization or ultrasonic treatment, and the emulsion particles can subsequently be solidified through chemical crosslinking or heating deformation. Ultimately, the ABNPs are collected by removing the residual organic solvent [79]. Additionally, surfactants are necessary for the stabilization of emulsions. Researchers utilized double emulsion solvent evaporation to create NPs that encapsulated BSA and model antigens. Additionally, the presence of chitosan (CS) hydrochloride in the outer phase of the lotion solvent resulted in the formation of a hybrid cation of CHL NPs, which subsequently adsorbs the NP's surface [80].

Nab technology

Among these methods, Nab technology is a technique for preparing ABNPs that employs albumin as a matrix and stabilizer. First, the substance is dissolved in a solid organic solvent (usually dichloromethane or chloroform) to make an oil phase. Next, albumin is dissolved in water to make an aqueous phase. Finally, an O/W emulsion is made by mixing an oil phase with an insoluble drug in water and an aqueous phase with albumin under shear solid forces. The drug contains no common surfactant or polymer core [81]. The oil and water phases are homogenized under high pressure, and the solvent is rapidly evaporated under vacuum to produce a colloidal dispersion system composed of ultra-fine NPs. A disulfide bond is formed when the unbound sulfhydryl group of albumin cross-links during cavitation. The physiological properties of HSA are preserved by the substance enclosed within the NP [82]. Nab technology differs from conventional preparation methods because it does not necessitate special infusion equipment, typical surfactants, or polymer cores. Additionally, albumin is a lyophilization agent, eliminating the necessity for the other traditional freeze-dried protection ingredient. He et al. conducted a study on various types of primary solid organ cancers to compare the risk of adverse events related to nab-PTX with that of typical taxanes. The study found that nab-PTX increases the likelihood of experiencing general hematological and non-hematological adverse events. However, it significantly reduces the occurrence of allergic reactions and makes neurotoxicity easier to manage. Furthermore, administering lower

doses of nab-PTX every week showed better tolerance than standard PTX [83]. Despite ocular adverse effects, nab-PTX treatment patients exhibited a substantially reduced visual acuity. In clinical settings, topical dorzolamide or steroidal treatment is an effective alternative when the patient's general condition precludes the treatment from being discontinued [39].

Self-assembly method

In aqueous environments, albumin self-assembles and forms NPs by reducing primary amine groups with a lipophilic compound or disrupting disulfide bonds with β-mercaptoethanol [84]. Self-assembly technique improves the hydrophobicity of albumin by using denaturants (such as β-mercaptoethanol, dithiothreitol, and cysteine) to reduce disulfide bonds and lipophilic medicines to reduce primary amine groups on protein surfaces [84]. The primary process of self-assembly technology is the non-covalent contact between molecules, which creates a stable and transparent structure. When subjected to turbulent conditions, the drug molecules can bind with the hydrophobic area of albumin, resulting in the creation of ABNPs [85]. Glutathione (GSH) can be used as a reducing agent in the self-assembly process to create redox-sensitive ABNPs. GSH cleaves disulfide bonds within albumin molecules, exposing hydrophobic cavities and subsequent interaction with hydrophobic medicines. These medications later undergo re-oxidation to form disulfide bonds. However, this approach is restricted to drugs soluble in lipids and faces difficulties expanding its application. Furthermore, there are cases where the inclusion of reducing agents can lead to potential toxicity [86].

Thermal gelation

Thermal gelation is displayed, which comprises the structural alterations and unfolding of proteins generated by heat. Protein–protein interactions, such as hydrogen bonds, electrostatic interactions, hydrophobic contacts, and disulfide-sulfhydryl exchange events follow this [87]. To summarize, heating the albumin solution can cause alterations in the protein's structure and unfold it. Ultimately, this leads to the aggregation of albumin particles [88]. This approach avoids the potential toxicity related to the introduction of organic solvents. The process conditions' pH, protein content, and ionic strength determine the NPs' properties. However, this approach is unsuitable for drugs that are sensitive to heat [89].

Nanospray drying

Nanospray drying is a highly adaptable technology that transforms a liquid phase into a dried powder. One of its main benefits is the ability to produce and dry particles continuously and efficiently. The release of droplets from a liquid solution is the defining characteristic of this process [90]. The liquid feedstock is transformed into a fine mist of particles and subjected to a drying gas at a sufficiently elevated temperature to cause the moisture to evaporate. The process consists of multiple stages, including the interaction between the spray and the air, the evaporation of the spray, and the isolation of the dried product from the drying air [91]. The interaction occurs within a drying chamber that houses an aqueous albumin solution. During evaporation, the water content transforms into solid particles, which are then gathered using an electrostatic particle collector. By

manipulating the settings of the nanospray drying process, it is possible to optimize the properties of the NPs to meet the requirements of individual applications [92].

Spray drying

Spray drying is an established technique for converting liquid phases into dry powder, commonly employed in the pharmaceutical sector. This approach has the advantage of combined particle generation and drying. Particle production takes place in a continuous and single-step process [93]. Furthermore, the desirable characteristics of particles, such as their size, flow behavior, and density, can be altered by manipulating process parameters or making configuration adjustments. The solid products generated through this technique exhibit superior physicochemical properties and stability compared to liquid formulations [94]. Hence, nanospray drying holds promise as an economical and versatile technique for manufacturing peptide and protein drugs. The standard spray drying technique involves the following steps: atomization transforms the liquid raw materials into tiny spray droplets. These droplets are subsequently subjected to a high temperature, hot, dry gas to facilitate the evaporation of water. The solid product is formed due to water evaporation from the droplet, and the powder is collected from the dry gas [95].

The pH-condensation method

The pH-condensation approach involves dissolving the medication in a solution of HSA at room temperature, adjusting the pH, and letting it remain in the dark. Agitating or sonicating the solution speeds up the process of albumin coagulation, which is then followed by crosslinking with glutaraldehyde. Afterward, the solution is centrifugated, washed, and freeze-drying to produce HSA NPs. Nevertheless, controlling the pH value is more complex than adjusting the salt content or including other organic solvents to achieve spherical NPs and a consistent particle size [96].

Microfluidic mixing

Microfluidic technology provides a more advanced option for producing serum, polymeric, and lipid ABNPs. However, it has not garnered as much attention as other alternatives [97]. This technique utilizes a regulated preparation procedure to produce particles with an adjustable size and a limited size distribution. Moreover, it offers a distinct chance for the mechanized manufacturing of pharmaceuticals on a significant magnitude [98]. Research about the production of ABNPs under conditions of minimal flow is scarce in the literature. In an investigation focused on synthesizing drug-loaded core–shell-based ABNPs. The study produced positive outcomes [99]. The stabilizer PAA HCl (poly(allylamine hydrochloride)) was introduced into channel 1 (v1) of the initial syringe pump, while the solution containing the medication and carrier (BSA/KYNA) was placed in channel 2 (v2). After passing through the syringe pumps, the two solutions were merged in the 250 μL μ-mixer cell using a pressure regulator machine. The sample was then collected at predetermined intervals [39] (Fig. 1).

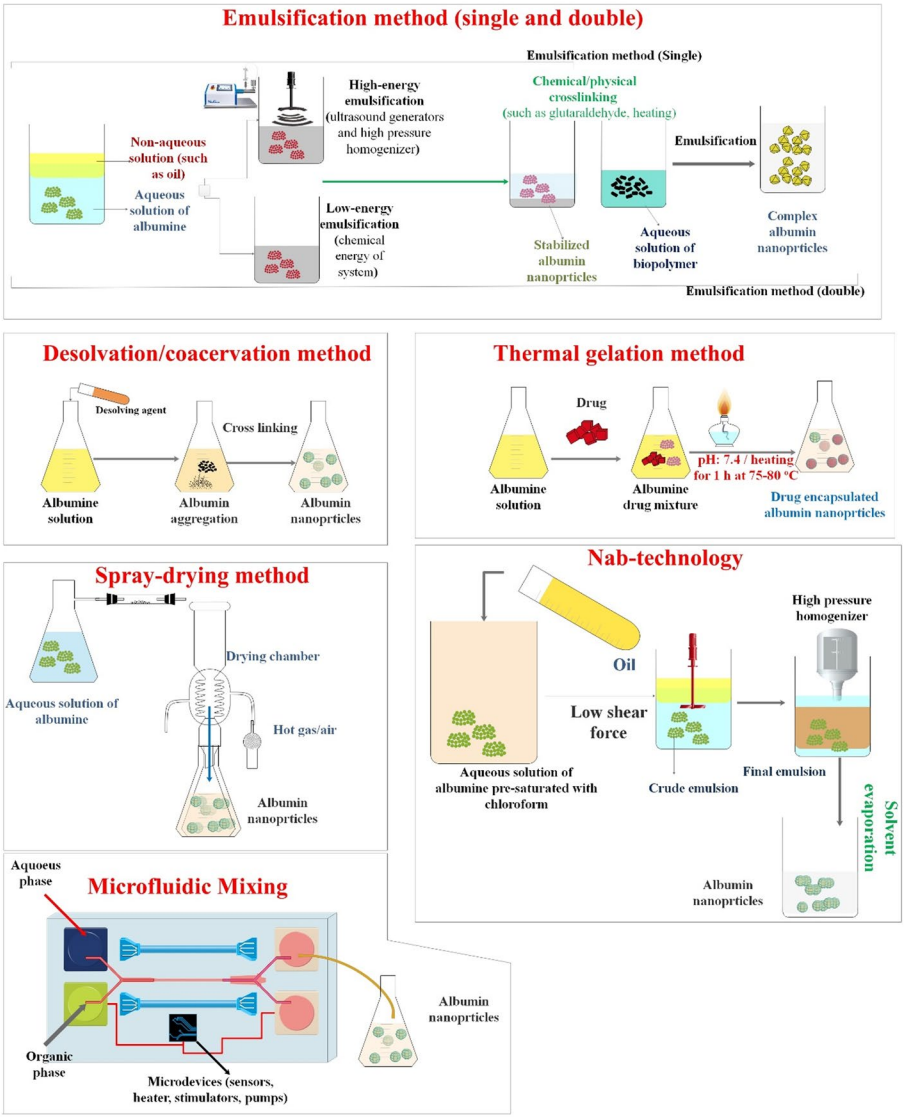


Fig. 1 This figure shows the different methods of producing ABNPs and the procedures of these production methods. ABNPs can be created with a simple and inexpensive method so that they can be instrumental in the treatment of dental diseases [39]

Albumin nanoparticles as drug delivery system

ABNPs are highly appealing due to their tolerability and absence of adverse reactions. They exhibit a significant affinity for various drugs, regardless of their physicochemical and structural characteristics [100]. ABNPs appear to be a viable carrier for multiple treatments due to their capacity to target specific cells [101]. Because the multiple drug-binding sites found in albumin molecules enable a considerable quantity of drug to be absorbed into the particle matrix, ABNP carrier systems offer an appealing approach [102]. ABNPs are suitable for the electrostatic adsorption of positively charged molecules (such as ganciclovir) or negatively charged molecules (such as oligonucleotides) because of the distinctive primary structure of albumin and its

high lysine content. This is accomplished without the requirement of supplementary compounds [103].

Furthermore, ABNPs can be easily synthesized using gentle methods such as coacervation, controlled desolvation, or emulsion formation. NPs have a narrower size range of 50 to 300 nm, making them smaller than microparticles. In general, NPs have more precise control over substance release than liposomes. This improved control can potentially increase patient acceptance and compliance [104]. The three-dimensional structure of albumin, consisting of hydrophilic and hydrophobic domains and charged amino acids, allows it to transport drugs with diverse physicochemical properties effectively. Albumin exhibits robust biological activity under diverse situations, such as pH levels ranging from 4 to 9, exposure to 40% ethanol, and heating at 60 °C for 10 h. Additionally, it possesses a relative molecular weight of 66,500 Da [39].

Albumin has been used for drug administration for a long time, with records reaching back to the 1960s, first as a diagnostic agent. The development of albumin as a drug carrier occurred in the 1970s and 1980s, with the introduction of nano-sized albumin carriers [105]. ABNPs are highly preferred in many disease treatments because they are strongly attracted to protein medications, specific sites on cells for binding, and the necessary chemical groups for modification. These characteristics make it easier to create nano-complexes. Albumin shows potential as a carrier for drug delivery due to its excellent biocompatibility and enhanced targeting ability, among other factors [106]. Albumin has attracted growing attention from the pharmaceutical sector as a possible drug transporter, in addition to its physiological roles. This statement holds especially true with the endorsement of the initial albumin formulation, paclitaxel-albumin-stabilized NPs (Abraxane®) [76]. The emergence of albumin as an effective drug carrier results from the development of nanotechnology, which facilitates such applications and certain intrinsic qualities of the protein. Initially, it is immune-suppressive, biodegradable, and biocompatible due to its endogenous nature [107]. Albumin's high water solubility allows it to transport less water-soluble medications across aqueous compartments and to their pharmacological objectives, thereby preventing harm from unfavorable immunoreactions. Additionally, the albumin structure is composed of three homologous domains (designated I, II, and III), each of which has two smaller subdomains (A and B) that are capable of negotiating a unique ligand binding [108].

Additionally, albumin has a unique capacity for active targeting, improving cellular uptake. Lastly, albumin can undergo a conformational shift to escape from low-pH lysosomes and endosomes following cellular absorption. This conformational change, in concert with the proteolytic destruction of albumin, facilitates the efficient release of therapeutic payloads into the cellular milieu. Consequently, the loaded drugs or target gene can elude endocytic recycling and fast enzymatic breakdown in late endosomes for regulated release [109]. Nanotechnology has long been used to deliver drugs and/or imaging agents to prevent, diagnose, and treat different diseases [110]. Albumin is an extensively studied protein for its role in pharmacokinetics and therapeutic applications, which makes it a highly versatile colloidal drug carrier system [111]. NPs are highly interesting as large molecule carriers since they can hold a lot of drugs, break down naturally, and are well-tolerated without causing any adverse effects. Furthermore, they function as a storage and transporter for several types of molecules, successfully

attaching to a wide range of drugs [111]. Abraxane (paclitaxel-ABNPs) has been proven to have clinical benefits. This innovative nanomedicine product utilizes HSA, the most abundant protein in the human bloodstream, as a carrier [112]. HSA NPs, formed by dissolving and subsequently crosslinking the protein, show great potential as a vehicle for drug delivery. Researchers have analyzed the particle size distribution and shape of HSA NPs in water by utilizing electron microscopy (EM) to investigate negatively stained samples and sedimentation velocity analysis in an analytical ultracentrifuge. The computer application SEDFIT was used to calculate the sedimentation coefficient distribution, $g^*(s)$, to characterize the size distribution of the particles. The sedimentation of the particles was assessed to be impeccable and to exhibit minimal diffusion. The results demonstrated significant variability, with the values within a single preparation differing by approximately 5. Moreover, depending on the preparation, the distributions' maximum values exhibited a range of 5,000–20,000 S. The sedimentation coefficients can be transformed into radius distributions using EM, confirming that the particles have a spherical shape. The peaks of these distributions are observed to fall within the 85 to 160 nm range. One can obtain precise charts showing the relationship between relative concentration and particle radius by adjusting the vertical values in the distributions for Mie light scattering. Preparative sucrose density gradient centrifugation can separate the significant distributions into smaller distributions. These isolated fractions could be valuable for investigating the relationship between the biological activity and size of the HSA carriers. Moreover, the procedure described for analyzing the size distribution of the HSA NPs could improve the preparation approach [113].

Researchers investigated the advancement of new hydrogels as potential carriers for proteins in controlled-release formulations. The hydrophilic protein BSA was chosen as the representative protein enclosed within the hydrogel of xanthan gum (XG) and poly(N-vinyl imidazole). The collected data showed that the drug loading percentage (DL%) and EE% increased with longer gelation duration and higher BSA concentration. Conversely, the drug DL% and EE decreased with higher polymer concentration. The maximum values for %DL and %EE were 59.50% and 99.17%, respectively. The results of the BSA release in phosphate-buffered saline (PBS) in an in vitro setting showed that the release of BSA was enhanced with increasing concentrations of the polymers XG and PVI. An unconventional and advanced transport mechanism, known as non-Fickian and case II, was discovered during the study of the release of BSA from the XG/PVI/BSA matrix in a laboratory setting. Furthermore, the cytotoxicity data demonstrated that this innovative hydrogel is compatible with living cells. The encapsulation or release conditions had no impact on the structural integrity of BSA, as shown by SDS-PAGE analysis. Thus, this new hydrogel can effectively serve as a carrier for BSA protein [114] (Fig. 2).

Albumin nanoparticles in dentistry

The researchers created a dental adhesive resin system that can eliminate bacteria by employing HSA NPs as a carrier for drug delivery. HSA NPs were produced by a desolvation technique and filled with CHX diacetate, which acts as a representative antibacterial medication. The CHX-loaded human serum ABNPs were mixed with a commercially accessible methyl methacrylate-based resin. The NPs displayed a size distribution from 50 to 300 nm and were evenly disseminated inside the resin matrix.

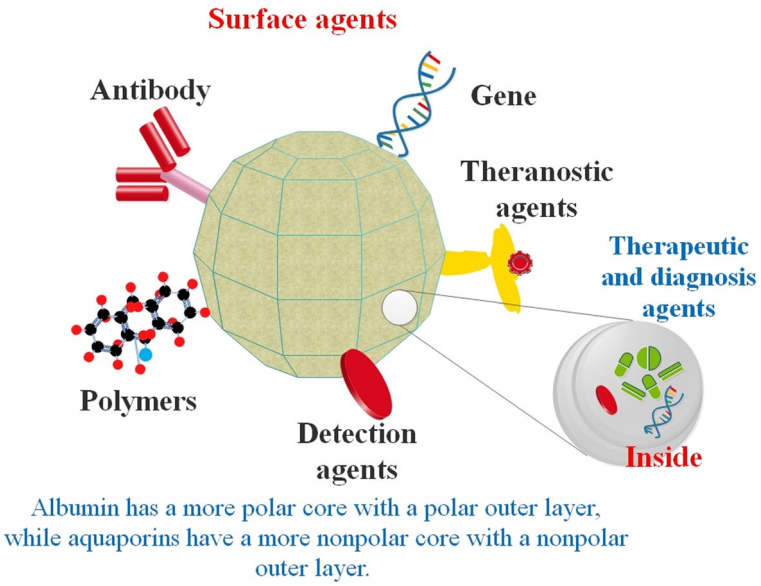


Fig. 2 Albumin nanoparticles (NPs) as drug delivery systems (DDSs). This NP is used to treat various diseases as a powerful DDS for delivering therapeutic molecules, diagnostic agents, drugs, antibodies, genes, NPs, and theranostics agents [115]

The HSA NPs containing CHX demonstrated an initial release of approximately 20% of the total CHX on the fifth day, followed by a continuous release of the remaining CHX over the next 20 days. Nevertheless, a 4-week immersion study demonstrated that the resin matrix containing HSA NPs steadily discharged CHX without any abrupt initial release. The agar diffusion test showed that the resin matrix with CHX-loaded HSA NPs exhibited a significantly greater zone of growth inhibition against Streptococcus mutans than the resin matrix without NPs. This suggests that the delivery mechanism effectively delivers antibacterial properties to the resins. The results indicate that CHX, a compound that inhibits the proliferation of oral bacteria, may be effectively integrated into the MMA-based resin matrix utilizing HSA NPs [21].

A separate study focused on creating antimicrobial drugs to combat the growing occurrence of drug-resistant diseases. Nevertheless, controlling and regulating the germs accountable for these diseases continue to pose a significant difficulty. Researchers synthesized silver NPs (AgNPs) with CS and BSA coatings utilizing an aqueous reduction process. The approach was distinguished by temperature analysis, transmission electron microscopy (TEM), and dispersion light scattering. The microdilution test and scanning electron microscopy (SEM) assessed the antibacterial activity of seven oral and non-oral microorganisms. Six unique sizes and arrangements of coated single nucleotide polymorphisms (SNPs) were produced and used. The characterization analysis indicated the existence of coatings on the surfaces of the AgNP and the presence of spherical and pseudospherical shapes. Furthermore, the particles were found to have a restricted size and displayed exceptional dispersion. The AgNPs samples and samples with smaller sizes demonstrated the most potent inhibitory effects, but other samples displayed antibacterial activity. Gram-positive bacteria displayed the highest degree of microbial resistance. The effectiveness of coated AgNPs depends on the specific bacterium, although BSA and CS-coated AgNPs could be advantageous for treating drug-resistant diseases [116].

A separate study utilized individuals carrying ABNP to create a straightforward, highly efficient method of delivering substances from titanium (Ti) surfaces. A metal implant was created using a Ti disc coated with a resorbable blasting media on its surface. This implant incorporates a localized DDS. HSA NPs were impregnated with the model drug CHX diacetate salt hydrate using a desolvation technique. The HSA NPs containing CHX were crosslinked using glutaraldehyde (GA). The NPs were coated with positively charged polyethylenimine (PEI) molecules and then attached to the negatively charged surface of a Ti disc through electrical interactions. Researchers indicated that the PEI–CHX–HSA NPs, loaded with CHX and coated with PEI, were evenly and efficiently spread throughout the surfaces of the Ti discs. The Ti surface treated with PEI–CHX–HSA NPs in the agar diffusion test showed a more expansive growth inhibition zone against *Streptococcus mutans* than the untreated Ti surface. This indicates that the Ti surface exhibits substantial antibacterial effectiveness due to this novel delivery strategy. Hence, the incorporation of CHX, which hinders the growth of oral infections, into Ti surfaces can be accomplished by employing HSA NPs [117].

According to another study, antibiotics are commonly employed to prevent bacterial infections after orthopedic or dental implant surgery. However, drug-resistant bacteria can increase the likelihood of diseases that lead to hospitalization, failure of implants, and even death. Therefore, it is necessary to develop antibacterial frameworks to combat bacterial infections associated with implants. CHX was loaded onto NPs made of HAS. These NPs were then attached to the surface of a novel antibacterial hydroxyapatite (HAp) scaffold using polyethylenimine (PEI) through surface charge interaction. The CHX-loaded HSA NPs were formed using a desolvation process. Subsequently, the PEI molecules (PEI–CHX–HSA) were applied as a coating and securely attached to the scaffold surface by charge interaction. The PEI–CHX–HSA NPs exhibited a uniform distribution on the scaffold surface. The NPs immobilized the scaffold, resulting in a visible inhibitory zone against *Streptococcus mutans*, as shown by the agar diffusion test. The examination of *Streptococcus mutans* adherence utilized fluorescence and SEM to determine the antibacterial activity of the scaffold. The results suggest that the PEI–CHX–HSA NPs, immobilized in the HAp scaffold, effectively released drugs and exhibited antibacterial solid effects against *Streptococcus mutans*. An investigation explored a direct binding method that utilizes the surface charge interaction between the HAp scaffold surface and CHX–HSA NPs coated with PEI. The objective was to develop an antibacterial HAp scaffold [118].

Controlling the distribution of bioactive molecules is crucial for regulating the production of stem cells, as indicated by an alternative study. Researchers investigated the ability of stem cells from the apical papilla (SCAP) to regulate alkaline phosphatase activity (ALP) by releasing BSA from CSnp at a predetermined period. To achieve the desired controlled release of BSA, researchers synthesized BSA-loaded CSnp using two distinct methods: (1) the encapsulation approach (BSA-CSnpI) and (2) the adsorption technique (BSA-CSnpII). After determining the size, charge, and release kinetics, the NPs loaded with bioactive molecules were introduced into SCAP cells. To assess the impact of these NPs, which release bioactive molecules, on cytotoxicity and differentiation potential, researchers evaluated the vitality of SCAP cells at 1, 7, 14, 21, and 28 days. Additionally, researchers examined ALP activity every 7 days up to 21 days. BSA-CSnpI

and BSA-CSnpII exhibited different release patterns of BSA in a regulated manner in a laboratory setting. BSA-CSnpI and BSA-CSnpII significantly improved cell viability over time compared to BSA-nonloaded CSnp. BSA-CSnpI showed a substantial increase in ALP activity after three weeks compared to BSA-CSnpII alone. Researchers synthesized and characterized CSnps that were loaded with BSA. The interaction between BSA and CSnp, either by encapsulation or surface adsorption, altered the ALP activity of SCAP in a laboratory setting or led to varying release patterns over time. This study highlighted the potential of utilizing temporally regulated bioactive chemical release technology to induce stem cell differentiation for dentin pulp regeneration [119].

Many dental products use NPs to improve oral health. Mouth paint is a liquid solution used for oral care that is applied directly to the mouth. It aims to treat oral health issues such as bad breath, irritation, and bacterial infections [120]. The present study examined the antimicrobial, anti-inflammatory, and cytotoxic properties of a mouth paint prepared using titanium dioxide NPs (TiO_2NPs) in an aqueous formulation of dried ginger and lemongrass. The antimicrobial effects of TiO_2NPs are achieved through the direct interaction with microbial cells and the production of reactive oxygen species. A mouth paint was developed and evaluated for potential applications by synthesizing TiO_2NPs with ginger and lemongrass. The antimicrobial activity of the prepared TiO_2NPs-mediated mouth paint at different concentrations (25, 50, and 100 µL) against oral pathogens (*Streptococcus mutans*, *Enterococcus faecalis*, *Staphylococcus aureus*, and *Candida albicans*) was evaluated using the agar well diffusion method. The mouth paint's anti-inflammatory activity was assessed using an egg albumin denaturation assay and a BSA denaturation assay. The cytotoxic effect of the mouth paint that was produced was evaluated through a brine shrimp lethality experiment. Green TiO_2NPs exhibited a potent antibacterial effect against the tested oral pathogens, with a zone of inhibition of 11 mm on a Petri plate against *Staphylococcus aureus* and *Candida albicans* at 100 µL. When using a volume of 50 µL, the mouth paint containing NPs effectively prevents the denaturation of BSA by 74%, indicating a solid anti-inflammatory impact. The egg albumin denaturation experiments showed an inhibition of 80% when 50 µL was used. After 48 h, the lowest dosage of 5 µL of the lip paint created resulted in 90% viability of the brine shrimp nauplii (egg-to-larvae stage). Researchers demonstrated that the mouthwash produced utilizing TiO_2NPs synthesized with lemongrass and dried ginger formulations displayed a notable antibacterial impact and a promising anti-inflammatory impact [121].

Streptococcus mutans is the primary pathogen that causes tooth cavities. Specific serotypes of *Streptococcus mutans* (c, e, f, and k) have also been linked to systemic illnesses. Studies have shown that AgNPs have antibacterial solid effects against *Streptococcus mutans.* As a result, only a few research studies have examined biofunctionalized AgNPs' effectiveness in killing *Streptococcus mutans* serotypes. Researchers assessed the antibacterial efficacy of AgNPs in clinical isolates of *Streptococcus mutans* strains and serotypes to produce and characterize coated AgNPs utilizing two different organic components. An evaluation was conducted to analyze the physical, chemical, and microbiological properties of AgNPs coated with either BSA or CS. Both versions of coated AgNPs exhibited their ability to kill *Streptococcus mutans* bacteria and serotypes effectively. The presence of BSA coatings and smaller particles increased the level

of inhibition. However, there were no notable variations between serotypes, suggesting they all had comparable sensitivity to the coated AgNPs. Investigators indicated that AgNPs coated with BSA and CS had potent antibacterial effects against *Streptococcus mutans* strains, including all four serotypes. Researchers extensively proposed utilizing AgNPs as an antibacterial agent to inhibit *Streptococcus mutans* bacteria [122].

Azithromycin-incorporated bovine serum ABNPs coated with biocompatible polymers were tested for enhanced antibacterial efficacy against human pathogenic microorganisms in a different investigation. Phosphorus, the ratio of ethanol to BSA, cross-linking duration, and other parameters were investigated to optimize BSA NPs. An antibacterial investigation was conducted using the nano-conjugate against clinical isolates of the human pathogenic bacteria Pseudomonas aeruginosa and *Staphylococcus aureus* using the excellent diffusion assay. Using the broth dilution method, the minimal inhibitory concentration was investigated. It was discovered that the ideal pH was 8.0, the ideal ethanol-to-albumin ratio was 4:1, and the ideal cross-linking time was 8 h, all of which contributed to the increased yield of BSA NPs. By utilizing a scanning electron microscope to characterize the nanospheres that were so created, it was discovered that their particle size ranged from 145 nm. *Pseudomonas aeruginosa* and *Staphylococcus aureus*, two clinical isolates of human pathogenic bacteria, were the subjects of an antibacterial study using the nano-conjugate. The antibacterial activity was enhanced by a minimum of 10 to a maximum of 20 mm of the zone of inhibition, and all tested bacteria were susceptible to the testing concentration of the nano-drug conjugate. There is a significant increase in the antibacterial activity of the polymer-coated BSA nano-drug conjugate against human pathogenic bacteria, which suggests that azithromycin-incorporated polymer-coated BSA NPs may be effective against pathogenic bacteria [123].

Oral cancer is among the most common cancers in the world. The hydrophobic medication DTX may be effectively loaded into a biocompatible tumor-targeted nanoformulation that the researchers created by conjugating HSA to poly(lactide) at various HSA:PLA ratios (1:1, 2, 3). Surface tension analysis, UV, IR, NMR, GPC, and pyrene incorporation were used to study the physicochemical properties of the HSA-(PLA)1–3 conjugates. The desolvation-self-assembly method was then used to create the DTX-loaded DTX@HSA-(PLA)1–3 NPs, further optimized by DOE. To evaluate cellular uptake, the degree of cell survival, and apoptosis induction after NPs treatment, monolayers/multicellular spheroids were created using the mouse and human oral cancer cell lines, MOC2 and FaDu. DTX@HSA-(PLA)1–3 NPs had a size range of about 149–212 nm, drug entrapment of around 75–96%, and loading efficiency of approximately 21–27%. Compared to HSA NPs, the chosen DTX@HSA-(PLA)2 NPs demonstrated time-dependently better targetability towards cancer cells, demonstrating the advantage of HSA polymerization in NPs internalization. 48 h after treatment, a time-dependent reduction in cell viability was seen for both cell lines, with IC50 values for the FaDu and MOC2 cell lines being 7.12 ± 1.84 and 6.38 ± 1.63 μg/mL, respectively. Compared to free DTX and DTX@HSA NPs, the DTX@ HSA-(PLA)2 NPs treatment caused more significant apoptotic marker expressions, cell-cycle arrest in the G2/M-phase, DNA damage, and mitochondrial depolarization. Moreover, compared to DTX and DTX@HSA NPs, DTX@HSA-(PLA)2 NPs demonstrated significantly lower plasma clearance and volume of distribution. As a result, the created polyprotein NPs have a longer half-life, better cell

internalization, and stable drug incorporation, all of which indicate their potential as a powerful nanomedicine for treating oral cancer [124].

Researchers created a new DDS termed HSA-indocyanine green-cisplatin NPs (HSA–ICG–DDP NPs) to assure site-specific drug delivery/release in tumor cells and cancer-associated fibroblasts (CAFs) and lessen the systemic toxicity of chemotherapy. By demonstrating synergistic effects with PDT, PTT, and chemotherapy, researchers could describe this system both in vitro and in vivo. As a result, this system may dramatically enhance therapeutic effectiveness compared to cancer monotherapy. Researchers also validated the high expression of SPARC in CAFs and oral squamous cell carcinoma (OSCC). Investigators also discovered that SPARC-mediated endocytosis may increase the cellular absorption of HSA–ICG–DDP NPs in tumor cells and CAFs. It is possible to precisely control the release of cisplatin (DDP) from the NPs at the tumor site by cleaving the coordination link of ICG–DDP by a NIR-induced photothermal action of ICG. HSA–ICG–DDP NP treatment increased ROS production and cytotoxicity in tumors and CAFs with high SPARC expression. Upon in vivo administration, HSA–ICG–DDP NPs were concentrated in the tumor tissue, demonstrating more potent anticancer effects than ICG, HSA-ICG, and DDP therapy. Because of the synergistic effects of chemotherapy and PTT/PDT, this innovative NIR-triggered drug release method shows promise for improving OSCC treatment [125].

Albumin nanoparticles in periodontitis

Periodontitis is an inflammatory condition that causes harm to the tissues that provide support to the periodontium. The condition results from an immunological response of the gums to plaque, leading to the breakdown of periodontal attachment structures [126]. Periodontitis is a widely acknowledged dental ailment that greatly contributes to the loss of permanent teeth in adults. Scaling and root planing are essential treatments for chronic periodontitis [127]. Periodontitis, if left untreated, can harm the bone that supports your teeth, causing them to loosen or even fall out [128].

However, merely depending on mechanical interventions such as extractions, root planning, and periodontal surgery is insufficient to prevent the disease from worsening. Some researchers are working to find alternative antibiotics to address bacterial resistance [129]. Furthermore, some researchers concentrate on developing novel materials that can support osteogenic repair and create a strong milieu for periodontal tissue regeneration. NPs can effectively cure periodontitis because they possess distinctive therapeutic attributes, such as exceptional antibacterial, anti-inflammatory, and antioxidant activities, immunomodulatory capacity, and the ability to stimulate bone regeneration [130].

Although frequent, periodontitis is typically preventable. The cause of periodontal disease is complex. The bacterial biofilm that accumulates on the surfaces of teeth is the primary cause of periodontitis. The host response, in conjunction with local factors such as calculus and plaque, genetics, environmental factors, the patient's overall health, lifestyle choices, and various social determinants, all influence how the illness progresses [131]. The harmful impacts of periodontopathogens extend beyond the periodontium and manifest as detrimental effects on the patient's overall health. Advanced cases of periodontitis result in loss of teeth and a decline in life quality. Periodontitis

has a complex etiology [132]. The irreversible devastation of the periodontium, which encompasses the alveolar bone and periodontal ligament, is the ultimate consequence of an inflammatory and immunological response induced by subgingival dental biofilm in a vulnerable host [133]. Accurate diagnosis, elimination of root causes, and reduction of modifiable risk factors play a crucial role in preventing and treating periodontitis [134].

The essential components of early nonsurgical periodontal therapy are scaling, root planing, and a home maintenance review. During the periodontal re-evaluation, either new regenerative or conventional surgical treatment can be used to treat the remaining areas with active periodontitis. The success of the treatment and the long-term retention of teeth depends on how often periodontal maintenance therapy is performed and how regularly follow-up appointments are scheduled [134] (Fig. 3).

Based on this study, periodontal disease is a complex problem that often correlates with many hazardous systemic disorders. However, a viable clinical treatment has not yet been created. The present investigation focused on formulating and integrating SAB microspheres containing minocycline and ZnO NPs into a Carbopol 940® hydrogel. Compared to Perio®, a 2% minocycline ointment, the hydrogel has shown clear therapeutic advantages and the capacity to repair gingival tissue autonomously. The SAB microspheres, which consisted of 0.06% minocycline and 0.025% ZnO NPs, had an average size of 139 ± 0.42 nm. This site was evaluated by electrophoretic light scattering, with three measurements taken. The particles exhibited a consistent spherical shape, as demonstrated by the TEM photomicrographs. The minocycline exhibited a pH-dependent slow-release profile lasting more than 72 h, with an encapsulating effectiveness of

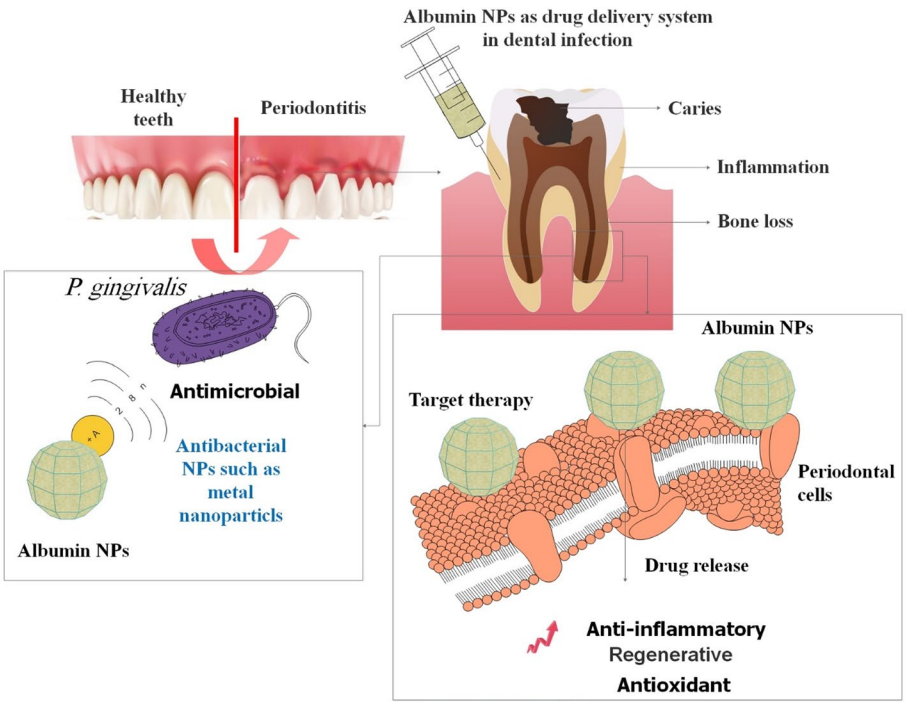


Fig. 3 The antibacterial and anti-inflammatory properties of ABNPs and the property of having very low toxicity can be of great use in the administration and treatment of gingival infections such as periodontitis. It can also deliver other antibacterial NPs to the diseased tissue and kill the diseased bacteria

99.99%. The most tremendously significant bioadhesive force observed in the in vitro skin adhesion experiment was measured to be 0.35 N. In addition, the hydrogel exhibited potent antibacterial and wide-ranging antimicrobial characteristics when the concentration of ZnO NPs exceeded 0.2 μg/mL. Investigators demonstrated the robust security and minimal toxicity of ZnO NPs, as indicated by cell survival rates surpassing 85% at doses lower than 0.8 mg/L [135].

According to a different study, the critical cells needed for regenerating periodontal bone deficits are a diverse group of human periodontal ligament cells (hPDLCs) and nanomaterials used in ring techniques for periodontal bone regeneration. Utilizing BSA to manufacture cerium-based NPs proved to be a viable, environmentally friendly, and efficient approach. CeO_2@BSA significantly enhanced osteogenesis in hPDLCs via the TGF-β signaling pathway at reduced doses, as evidenced by the results of in vitro tests. Nevertheless, this capacity was diminished at high concentrations, potentially due to an overabundance of autophagic activation. Notably, the osteogenic potential of hPDLCs was reduced by the inhibition of autophagy. Developing tissue-engineered membranes in Sprague–Dawley (SD) rodents confirmed that CeO_2@BSA facilitated the regeneration of periodontal bone deficiencies. The use of CeO_2@BSA in the treatment of illness was substantially increased by the discovery of its practical therapeutic effects in the repair of periodontal bone defects and osteogenic differentiation by researchers [136].

A separate investigation concluded that the successful implementation of RNA interference (RNAi) technology in medical practice depends on the reduction of the toxicity, immunogenicity, and cost of carrier materials for small interfering RNAs (siRNA). Calcium ions (Ca^{2+}) are currently being studied as a substitute for delivering siRNA to cells. However, the utilization of Ca^{2+} in living organisms is limited due to the differing sensitivity of cell types to its concentration. BSA can form a complex with Ca^{2+} by chelation. Moreover, BSA is an ideal choice for coating NPs because of its outstanding biocompatibility. Researchers have shown that covering Ca^{2+-}siRNA with BSA helps reduce the harmful effects of Ca^{2+} toxicity in living organisms. Combining BSA with Ca^{2+-}siRNA can generate a stable nanoscale complex with a diameter of around 140 nm. The nano-complexes can gradually release siRNA for over one week in a neutral PBS solution while inducing fast disintegration in an acidic PBS solution with a pH of 5.0. The cells primarily internalized the NPs through macropinocytosis and then released them intracellularly via endosome/lysosome acidification. The BSA–Ca^{2+} carrier demonstrated remarkable biocompatibility and effective transfection in the laboratory and living organisms. To highlight the therapeutic capabilities of BSA coating-optimized Ca^{2+}–siRNA technology, Researchers found that BSA–Ca^{2+}–siWWP1 complexes significantly improved the process of bone formation in inflammatory PDLSCs and showed promise in treating periodontitis [137].

A solution-based reduction method was used to create AgNP with coatings made of BSA and CS. The antibacterial efficacy of the AgNP was assessed through dispersion light scattering, TEM, and thermal analysis on seven oral and non-oral microorganisms. SEM and a microdilution test were also employed to evaluate the antibacterial activity. Seven bacterial strains were tested, including *Streptococcus salivarius*, *Staphylococcus aureus*, *Escherichia coli*, *Streptococcus mutans*, and *Streptococcus salivarius* strains. Six different sizes and forms of coated AgNPs were created and used. The characterization

technique determined that the particles were both tiny and evenly distributed. They exhibited spherical and pseudospherical shapes and had coatings on the surfaces of the AgNP. All samples demonstrated antibacterial activity; however, the inhibitory effects were particularly prominent in CS samples at smaller sizes. Gram-positive bacteria demonstrated the most elevated levels of microbial resistance. Although the efficacy of coated AgNPs varies by bacterium, BSA and CS-coated AgNPs could be used to treat drug-resistant infectious diseases. *Staphylococcus aureus* and *Enterococcus faecalis* had the highest resistance to AgNPs, followed by *Streptococcus salivarius*, *Staphylococcus aureus*, *Escherichia coli*, *Streptococcus mutans*, and *Streptococcus salivarius* strains. The principal Gram-positive (*Staphylococcus aureus* and *Enterococcus faecalis*) and Gram-negative (*Escherichia coli*) bacteria that cause multidrug-resistant illnesses had different MIC findings. Gram-positive bacteria *Staphylococcus aureus* and *Enterococcus faecalis* had upper MIC values (852 ± 260 μg/mL) compared to *Escherichia coli* (746 ± 353 μg/mL). Gram-positive bacteria demonstrated the most robust microbiological resistance to AgNPs. However, *Escherichia coli* bacteria can offer stronger antimicrobial inhibitory resistance than *Staphylococcus aureus* strains in identical circumstances [116].

Researchers utilized ABNP carriers to develop a direct and highly efficient method for transferring compounds from Ti surfaces. The metal implant consisted of a Ti disc with a surface made of resorbable blasting media, and it also had a framework for delivering drugs in a specific area. The CHX diacetate salt hydrate was incorporated into NPs of HSA using a desolvation process. The HSA NPs loaded with CHX underwent crosslinking using glutaraldehyde (GA). The NPs were first covered with cationic polyethylenimine (PEI) molecules and then attached to the anionic Ti disc surface through electrostatic interactions. Investigators demonstrated that the PEI-coated HSA NPs, which were loaded with CHX (PEI–CHX–HSA), were successfully integrated and evenly spread across the surfaces of the Ti discs. The agar diffusion test on the Ti surface coated with PEI–CHX–HSA NPs demonstrated a significantly greater zone of growth inhibition for *Streptococcus mutans* than the control Ti surface. This indicates that the surface of Ti possesses antibacterial solid properties due to the use of this unique delivery platform. As a result, HSA NPs may efficiently include CHX, which hinders the growth of oral bacteria onto titanium surfaces [117].

A new HAp scaffold with antibacterial properties was created by attaching CHX-loaded HSA NPs to its surface using polyethylenimine (PEI) through surface charge interaction. The CHX-loaded HSA NPs were made using a desolvation method. Then, they were enclosed with PEI molecules (PEI–CHX–HSA) and attached to the scaffold surface through electrostatic attraction. The scaffold surface exhibited a homogeneous distribution of PEI–CHX–HSA NPs. The agar diffusion test revealed a well-defined inhibitory zone of *Streptococcus mutans* surrounding the scaffold immobilized with NPs. The efficacy of the scaffold's antibacterial properties was confirmed by examining *Streptococcus mutans* adherence using fluorescence microscopy and SEM. Investigators indicated that the HAp scaffold, which has PEI–CHX–HSA NPs fixed, demonstrated strong antibacterial effectiveness against *Streptococcus mutans* and displayed efficient drug release characteristics [118].

Porphyromonas gingivalis, a bacterium linked to active chronic periodontal diseases, releases several proteolytic enzymes. It is suspected that these enzymes play a

role in host colonization, disruption of the immune system, and destruction of tissues. Researchers evaluated the role of Arg- and Lys-gingipains, enzymes generated by *Porphyromonas gingivalis*, in promoting its growth. *Porphyromonas gingivalis* destroyed all the proteins that were studied. However, when transferred repeatedly, only HSA and transferrin allowed for growth and multiplication in a chemically defined medium (CDM). Disabling both gingipains stops growth, while disabling either Arg- or Lys-gingipain activity prolongs the doubling periods to 33 or 13 h, respectively, compared to 9 h for the original strain. These findings come from growth experiments conducted with genetically modified mutants of *Porphyromonas gingivalis* lacking specific gingipains. The mutants and the original strain exhibited comparable growth patterns when the CDM was enriched with a protein hydrolysate as a substitute for HSA. The inactive *Porphyromonas gingivalis* ATCC 33277 cells were exposed to albumin tagged with a fluorescent dye, revealing that the bacterial cells took in the broken-down protein fragments produced by the gingipains. The internalization of fluorophore-labeled albumin fragments was either wholly blocked or decreased in proteinase-deficient mutants. Low-molecular-mass albumin fragments were present in gingival crevicular fluid samples obtained from diseased periodontal sites but not in samples from healthy sites. The pivotal function of proteinases in the propagation of *Porphyromonas gingivalis* was further examined by employing selective Arg- and Lys-gingipain inhibitors. Upon the addition of inhibitors to CDM with albumin, it was shown that leupeptin, an inhibitor of Arg-gingipain A and B, exhibited a more inhibitory effect on growth compared to cathepsin B inhibitor II, which is an inhibitor of Lys-gingipain. The researchers have found that in a specific environment where a human protein is the only source of carbon and nitrogen, the growth of *Porphyromonas gingivalis* relies on the presence of Arg-gingipains and, to a lesser extent, Lys-gingipain [138].

Ag-Pt alloy NPs were produced by capping proteins in situ using BSA foams. An analysis was conducted to determine the cytotoxicity and rate of proliferation of human gingival fibroblasts (HGFs) when exposed to the previously synthesized alloy NPs in a controlled laboratory environment. The expression profile of metallothionein (MT), a protein involved in detoxification, was quantified using enzyme-linked immunosorbent assay (ELISA), and the levels of mRNA transcripts were determined using reverse transcription polymerase chain reaction (RT-PCR). The cytotoxicity findings indicate that protein-capped nano-alloys have the potential to be considered viable options for implants and prosthetic materials. MT in cells treated with alloy NPs was confirmed using RT-PCR and ELISA. SEM research demonstrated that cells exposed to alloy NPs retained an undamaged morphology [139].

Researchers showed that AgNPs' effectiveness is reduced in the presence of blood serum proteins despite their common use as antibacterial chemicals that release ions in medical devices. The presence of proteins, such as BSA, can affect the antibacterial or cytotoxic effects of AgNPs. It has been shown that BSA can bind silver (Ag) and Ag ions, even when they are embedded in a solid agar hydrogel matrix. Researchers utilized laser ablation to produce AgNPs without ligands in a water medium. This process yielded aqueous solutions with Ag mass concentrations varying from 0.5% to 7.1%. Agar was utilized to submerge AgNPs at a concentration ranging from 5 to 70 $\mu g\ mL^{-1}$. Researchers assessed the toxic effects of colloidal AgNP on fibroblasts in the presence

and absence of 1% BSA. Additionally, investigators evaluated the antibacterial properties of the NPs on four medically significant bacterial strains using a hydrogel matrix containing 1% BSA. The inclusion of BSA dramatically diminished the antibacterial efficacy of hydrogel-immobilized AgNPs. The cytotoxicity was seen when the concentration of colloidal AgNP reached 35 μg ml^{-1}. However, the presence of BSA greatly reduced the adverse effects on both cell survival and morphology. Overall, the presence of BSA significantly reduced the antibacterial and cytotoxic properties of AgNPs. Significantly, the lack of BSA was the only requirement for identifying a therapeutic AgNP range, which requires a precise dosage to hinder the proliferation of harmful bacteria while preserving the vitality of fibroblasts. The addition of BSA reduces the antibacterial action of AgNP, leading to a lack of considerable reduction of *Staphylococcus aureus* growth. Nevertheless, the cytotoxic effects of HGFib continue to exist. The presence of a considerable blood serum protein greatly reduces the antibacterial activity of AgNPs on various dangerous bacteria, even when the NPs are fixed within an agar hydrogel substrate [140] (Table 1).

Albumin nanoparticles in peri- implantitis and peri-implant diseases

Peri-implantitis is a pathological disorder that affects the tissues around a dental implant. It is characterized by [141]. Mechanical debridement and antiseptics are noninvasive therapies for peri-implantitis, a disorder characterized by progressive degradation of the bone surrounding a dental implant and inflammation of the adjacent soft tissues. Eliminating bacteria from dental implants is challenging due to the complex structure [142]. Peri-implant mucositis is a condition that primarily impacts the soft tissues surrounding the implant without producing any bone loss during the early phases of recovery [143]. After dental implantation, peri-implantitis is a common problem that can cause progressive degradation of both soft and complex structures, ultimately resulting in implant failure [144]. Common causes of peri-implantitis, which are often acknowledged, include occlusal stress, bacterial biofilms, insufficient primary stability after implant insertion, pain, neuropathy, and smoking [145]. It is the main factor responsible for peri-implantitis. The primary goal in treating peri-implantitis is to decrease the total presence of bacteria in the area surrounding the implant [146].

Scientists evaluated the impact of a new hydrogel, which includes ZnO-loaded and minocycline serum ABNPs (Mino-ZnO@Alb NPs), on mouse models of peri-implantitis. Mino-ZnO@Alb NPs were synthesized, as previously documented. Rats were used to create the peri-implantitis model and were randomly divided into three groups: the untreated group, the minocycline group, or the Mino-ZnO@Alb NPs (Mino-ZnO) group. The model was successfully established. After four weeks, clinical and radiographic assessments were conducted to measure the degree of soft tissue inflammation and bone resorption. Histologic examination was used to quantify the amount of supporting bone tissue (SBT) that remains near the implants. The amounts of the anti-inflammatory factor tumor necrosis factor-alpha (TNF-α) and the inflammatory factor interleukin-1-beta (IL-1β) near the implants were measured using ELISA testing. After one month, the Mino-ZnO group demonstrated superior performance compared to the other two groups in probing pocket depth, bleeding index, gingival index, and bleeding on probing. The subgingival bleeding tendency

Table 1 Description of the potential use of albumin NPs in treating periodontitis

Type of albumin NPs	Type therapeutic agents	Production methods	Explanation	Ref.
Albumin microspheres	Minocycline and ZnO NPs into a Carbopol 940® hydrogel	Emulsification cross-linking approach	Minocycline exhibited a 99.99% encapsulation efficiency and a pH-sensitive slow-release duration lasting more than 72 h. The hydrogel known as mino-ZnO@Alb increases bioavailability reduces the minocycline dosage, mitigates side effects, and boosts patient adherence	[135]
Bovine serum albumin (BSA)	CeO_2	BSA incubation method	High temperatures and pressures are unnecessary because the synthesis process only uses three raw ingredients. The synthesis technique can be scaled up for large-scale manufacturing. The BSA incubation approach satisfies the conditions above. CeO_2@BSA activated autophagy and the TGF-β signaling pathway to promote periodontal bone defect regeneration	[136]
BSA	Ca^{2+}-siRNA	New self-assembly method through thermal-driven to prepare BSA NPs	The pH-responsive activity of BSA-Ca^{2+}-siRNA achieves effective and long-lasting gene silencing, facilitating the release of siRNA into the cytoplasm. As a result, BSA-Ca^{2+} NPs are highly biocompatible for intravenously administered medications and might serve as a platform to introduce siRNA into the cytoplasm for various gene targets	[137]
Human serum albumin (HSA)	CHX-loaded HSA	Desolvation technique	The zeta potential data showed that the PEI coating effectively reversed the negative charges of the HSA or CHX–HSA NPs. A CHX molecule possesses a positive charge and highly cationic characteristics. As a result, it may attach easily to negatively charged spots on the bacterial cell wall, ultimately preventing the bacterium from growing	[118]

(SBT) in the areas next to the implants was notably reduced in the Mino-ZnO group compared to the other two groups, as evidenced by the X-ray findings. The Mino-ZnO group exhibited fewer osteoclasts in the peri-implant tissues compared to the minocycline and untreated groups. The Mino-ZnO group had lower levels of IL-1β compared to the other two groups. The level of TNF-α exhibited an inverse relationship. Mino-ZnO@Alb NPs can function as a product since they have demonstrated efficacy in treating peri-implantitis and facilitating soft tissue regeneration [147].

A separate study examined the possibility of protein release from plasma electrolytic oxidation coatings applied on commercially pure Ti infused with BSA. The study examined four different types of coatings: graded porosity, roughness, content, and thicknesses of 5 and 15 μm. The TiO_2 coatings exhibited enhanced levels of calcium (3.7–11.1 at. %) and phosphorus (1.5–6.5 at.%). The evaluation of albumin transport capacity over a 48-h timeframe seems to rely more on the composition of the coating rather than the porosity of the volume. The coating with a calcium-to-phosphorus ratio 4.0 and without crystalline calcium phosphate compounds released BSA faster than the non-coated Ti control in the initial 12-h period. Furthermore, it completely released the entire BSA load within 48 h. Over the same time frame, the coatings with a Ca/P ratio ranging from 1.5 to 2.0 discharged 15% of the load, regardless of the volume and porosity of the surface. The binding to the surface and subsequent retention have been linked to the interaction between albumin calcium and phosphorus in the coatings. PEO coatings can confine and release chemicals like antibiotics, growth hormones, and anti-inflammatory medicines. This approach can decrease the occurrence of disorders linked to dental implants in the biomedical domain [148].

For implants to maintain stability over a prolonged period, it is crucial to have effective sealing of the transmucosal soft tissue. Studies have demonstrated that human gingival fibroblasts (HGFs) exhibit enhanced adhesion to implant surfaces treated with hydrogenated titanium nanotubes (H2-TNTs). These nanotubes are commonly employed as carriers for drug delivery purposes. BSA, the most abundant albumin in body fluid, is widely recognized as a standard-loading protein and plays a crucial role in cell adhesion. Albumin is the initial protein that comes into contact with the implant's surface, and it plays a vital role in the early attachment of soft tissue cells. It also serves as a general transporter, loading and conveying a range of naturally occurring and externally derived substances, like ions, drugs, and other minuscule molecules. The present work examined the capability of BSA-loaded H2-TNTs to promote the first attachment of HGFs. H2-TNTs were produced through heat treatment of hydrogenated anodized TNTs, and BSA was then loaded into the nanotubes using vacuum drying. Researchers demonstrated that the high affinity for water exhibited by H2-TNTs enhanced the ability to load BSA. Both hydrogenated and non-H2-TNTs demonstrated an initial fast release within the first hour, followed by a subsequent phase of gradual and uninterrupted release. Nevertheless, the presence of BSA hindered the initial attachment of HGFs to the material, while H2-TNTs exhibited the highest ability to facilitate cell adhesion. Following 4 h, BSA was discharged, reducing its suppressive impact on cell adhesion [149].

Albumin nanoparticles in dentin infections and apical periodontitis

Apical periodontitis may exhibit a dentinal tubule infection in around 50–80% of affected teeth [150]. The necrotic pulp tissue within a root canal acts as a location for colonization and offers bacteria a moist, warm, nutritious, and anaerobic habitat. The lack of active blood circulation in the necrotic tissue protects this milieu from the host's immune system [151]. Endodontic infections are categorized based on the anatomical site (intra-radicular or extraarticular infection) and the duration of bacterial infiltration into the root canal (initial, secondary, or permanent infection) [152]. Bacteria are the primary pathogens found in endodontic infections. However, rare instances have revealed the presence of unique microbes. To successfully treat apical periodontitis, it is necessary to eliminate or effectively control the pathogenic microbiota. This condition is an infectious disease caused by a bacterial infection in the root canal system. An infection in the dental root canal system is the leading cause of apical periodontitis [153].

Researchers evaluated the effectiveness of a new photosensitizer called rose bengal (RB) functionalized chitosan NPs (CSRBnp) in killing bacteria. This assessment will involve various root canal ingredients that decrease root canal disinfectants' ability to kill bacteria. The use of antimicrobial NPs to enhance root canal cleansing has gained considerable attention in recent months. The synthesized CSRBnp was assessed for its dimensions, electrical charge, and singlet oxygen emission. The antibacterial effect of CSRBnp was examined using planktonic *Enterococcus faecalis* and various inhibitory substances, such as dentin, dentin-matrix, pulp tissue, bacterial lipopolysaccharides, and BSA, with and without pretreatment. The viability of bacteria was evaluated over time. The bactericidal properties of CSRBnp, a positively charged photosensitizer (methylene blue), and a negatively charged photosensitizer (RB) were additionally assessed in the presence of inhibitors after photodynamic activation. The diameter of CSRBnp was measured to be 60 ± 20 nm, and it exhibited a decreased rate of singlet oxygen release compared to methylene blue and RB. The antimicrobial efficacy of CSRBnp was substantially reduced by cellulose and BSA, even after a 24-h contact without photoactivation. In the context of photodynamic therapy, both the pulp and BSA substantially diminished the bactericidal activity of all three photosensitizers. CSRBnp demonstrated a persistent impact and eliminated the bacteria after a 24-h interaction with the organism following photodynamic therapy. CSRBnp can provide strong antibacterial effectiveness, even when tissue inhibitors are present in root canals. This is due to the combined production of singlet oxygen when RB is activated by light and the natural antibacterial properties of polycationic CS NPs [154].

The effectiveness of chemical irrigants in fighting bacteria is affected by the amount of organic matter in the root canals. Researchers assessed the antibacterial efficacy of several intracanal irrigants of BSA, an organic material. The bactericidal action of NaOCl 5.25%, cetrimide 0.5%, and Smear Clear was observed quickly after incubation. The BSA did not hinder the bactericidal activity of these three medicines. When BSA was present, CHX eradicated all bacterial cells within 10 min; in its absence, it took just five minutes. EDTA and citric acid exhibited the lowest efficacy as antibacterial agents. Compared to EDTA 17% and citric acid 10%, NaOCl 5.25%, cetrimide 0.5%, and Smear Clear showed much greater effectiveness against *Enterococcus faecalis*, regardless of the presence or absence of BSA. In addition, the ability of CHX 0.2% to kill bacteria was much higher

than that of EDTA when BSA was present after 10 and 30 min of contact time. EDTA and citric acid demonstrated the lowest level of bactericidal action [155] (Table 2).

Advantages and disadvantages

Albumin has attracted the interest of many researchers in recent years as a drug-delivery vehicle due to its biocompatibility, biodegradability, nonimmunogenicity, and nontoxicity. It is the predominant protein in the plasma, enhancing its attractiveness. Additionally, the immune system does not recognize it as a foreign substance; therefore, it is not rejected. The strong attraction of hydrophobic drugs, the ability to modify the surface, and the ability to hold many drugs help us overcome the challenges posed by many compounds currently on the market. It is a multifunctional drug carrier that can be utilized for gene therapy, imaging, and drug transportation. The albumin-based formulation's active targeting and exact recognition of the target location are facilitated by its strong affinity for particular receptors on the surface of endothelial cells and other cells in diseased organs. This feature sets albumin apart from other nanocarriers and is the most crucial and distinctive attribute. This characteristic may have influenced the decision to use albumin as a pre-made corona instead of other nano-delivery systems. Currently, there are ongoing clinical trials for various formulations based on albumin. Among these, the Abraxane formulation, which has already received approval, has shown remarkable outcomes in patients with cancer. Therefore, albumin nano-based formulations provide a secure and possibly efficient method for formulating a wide range of established and new medications, resulting in an improved therapeutic index [39].

OVA, BSA, and HSA are commonly utilized in biophysical and biochemical research, and they may all be readily obtained from commercial sources. Albumin is obtained from various sources, such as eggs (OVA, BSA, HSA), rat serum, soy, milk, and cereals [156]. Albumin possesses chemical attractiveness due to its disulfide bonds and sulfhydryl groups, which facilitate its interaction with organic and inorganic ligands. It exhibits the characteristics and benefits of OVA, BSA, and HSA, such as exceptional stability, compatibility with living organisms, resistance to changes in pH, and insensitivity to low temperatures [157].

BSA is one of the most extensively used and recognized among them in research due to its affordability, ease of access, and purification capacity. However, among other foods, milk, soy, and legumes offer a novel albumin basis that has lately made "green preparation" possible [158]. Despite its well-known biological roles, such as providing nutrition for stem cells in culture, albumin remains an underutilized biomaterial in regenerative medicine. It is a constitutional plasma protein [159]. Sutures and bone grafts are two examples of implants whose biocompatibility can be improved with albumin coating. However, albumin is generally thought of as an anti-attachment protein, its application to implantable surfaces has the opposite effect, increasing stem cell adherence and proliferation [160]. Albumin possesses anticoagulant, antibacterial, and anti-inflammatory characteristics that aid in precisely regulating the biological response to implantable tissue-engineering constructions [161]. Recent material breakthroughs have enabled the electrospinning of the globular albumin protein, opening up new possibilities for creating albumin-based scaffolds for cell treatment.

Table 2 Albumin NPs as drug delivery system in peri-implant diseases, peri-implantitis, and root canal infection

Type of albumin NPs	Type therapeutic agents	Dental diseases	Production methods	Explanation	Ref.
Albumin microspheres	Mino-ZnO@Alb NPs	Peri-implantitis	Emulsification cross-linking method	Mino-ZnO@Alb NPs decreased the number of osteoclasts and prevented neutrophil infiltration around the implant. To improve soft tissue healing in patients with peri-implantitis, mino-ZnO@Alb NPs decreased the IL-1β level but increased the TNF-α level in the gingiva around the implants	[147]
BSA	Titanium that had been infused with BSA	Peri-implant diseases	Desolvation	The majority of the supplied albumin forms a film on the coated surface. Given that the pore volume is negligible compared to the loaded volume, there is no relationship between the coating porosity and albumin release rate. Coating B-15 with a composition that has an over stoichiometric Ca/P ratio of 4.0 releases the whole BSA load in 48 h, which is 4 h quicker than the control Ti CP	[148]
BSA	H2-TNTs	Peri-implant diseases	Desolvation	Although BSA-loaded H2-TNTs possessed a highly hydrophilic surface and nanoscale roughness, their abrupt burst release at the early stage caused HGFs to exhibit early adhesiveness to be inhibited. With the release of BSA, the inhibitory impact of BSA-loaded H2-TNTs progressively decreased over four hours	[149]

Table 2 (continued)

Type of albumin NPs	Type therapeutic agents	Dental diseases	Production methods	Explanation	Ref.
BSA	CHX 0.2% and BSA	Root canals infection	-	After five minutes of contact, CHX 0.2% eradicated every *Enterococcus faecalis* cell; however, BSA slowed down the solution's antibacterial activity by ten minutes. In both the presence and absence of BSA, NaOCl 5.25%, cetrimide 0.5%, and Smear Clear showed considerably higher efficacy against *Enterococcus faecalis* when juxtaposed with EDTA 17% and citric acid 10%	[155]

Some described approaches have already progressed to the clinical phase, utilizing SAB's biological solid, regulatory, manufacturing, and clinical characteristics [162].

The albumin coating possesses supplementary antimicrobial characteristics. Albumin is widely used in the biomedical area because of its regenerative solid qualities, easy availability, and inexpensive production costs. The protein is well-recognized as one of the most famous [163]. On one side, its inherent antithrombotic, anti-inflammatory, and antibacterial capabilities make it a protein that can neutralize or prevent the formation of blood clots, reduce inflammation, and fight against bacterial infections when applied to non-reactive substances [164]. On the other hand, when the structure of albumin is altered or mixed with other biomaterials, it promotes cell adhesion, tissue growth, and healing. Researchers believe incorporating albumin-based biomaterials and medicines into regenerative medicine treatments can benefit patients. This integration can help minimize the occurrence of adverse side effects and lead to better clinical results [165].

To determine whether periodontitis is present and how severe it is, serum and salivary albumin can be employed as prognostic and diagnostic biomarkers, especially in the early stages of the illness. Although this interaction's precise nature and degree are unknown, there appears to be a connection between dental caries and albumin levels. Furthermore, the SAB level is a helpful indicator of the nutritional and systemic impacts of oral function in older age groups. Moreover, the SAB level is a reliable measure of the relationship between nutritional status and dental health. According to the published research, SAB values indicate a bidirectional relationship between tooth loss and malnutrition. Salivary indicators, such as albumin levels, can be utilized as additional tools in diagnosing diabetes to evaluate a patient's overall metabolic state. Finally, there is enough data to conclude that blood albumin levels can predict a cancer patient's prognosis. Salivary albumin may be a useful diagnostic tool for separating oral premalignant cases from malignant ones [166].

Based on the latest advancements, albumin is expected to be used in new regenerative medicine solutions. This is supported by a large amount of scientific evidence that shows its excellent ability to work well with living tissues and promote regeneration. The albumin protein, known for its modest nature, is increasingly acknowledged as regenerative medicine progresses and findings are translated from the laboratory to the patient's bedside. There is a growing body of research focused on examining the intricate connections between albumin and other substances, as well as finding ways to overcome the main obstacle to using albumin as a biomaterial, which is its relatively fast breakdown rate [167]. ABNPs are biodegradable and non-toxic because they are made of protein albumin. These substances can undergo metabolism through a straightforward process called coacervation or desolvation. Additionally, their physical properties, such as size and degradation time, can be controlled by adjusting the process parameters [168]. Nanomaterials exert many impacts on human health, with the primary concern being their chemical composition, which may inadvertently interact with our physiological systems [169]. However, the therapeutic use of albumin-based therapy is still relatively new despite its apparent potential and the many scientific studies on the subject. Very few products are currently being used in clinical settings [139].

Nanotechnology involves the application of elemental NPs as a potent antibacterial ingredient in dental materials [170]. Plaque bacteria, namely acid-producing bacteria like *Streptococcus mutans* and *Lactobacilli*, are the main reason for restoration failure. These bacteria flourish when fermentable carbohydrates are present. To ensure the durability of restorations, it is advisable to utilize antibacterial materials [171]. Additionally, the potential applications of NPs in managing oral infections and as topically applied agents within dental materials are addressed [172]. Albumin is a promising drug delivery option because of its superior biocompatibility and improved ability to target specific areas [173]. ABNPs are highly preferred in the treatment of various dental infections, such as peri-implantitis, periodontitis, and dentin infection, due to their ability to be modified with suitable chemical groups, possess cell-binding sites for cell adhesion, and exhibit affinity to protein medicines, enabling the creation of effective nano-complexes [21].

Protein-based NPs are an essential class of accessible potential colloidal drug carrier systems encompassing the indicated size range. Three basic preparation techniques have been developed based on emulsion generation, desolvation, or coacervation. The most common starting materials for the formulations were gelatin and SAB from various sources. It was discovered that the particle size of the HSA solution decreased as the pH value rose. This is likely because the HSA (isoelectric point pI = 5.3) is more ionized, which causes the HSA molecules to repel one another and form aggregates during particle formation. HSA NPs in the 90 to 250 nm size range were produced by varying the pH and the quantity of additional acetone. Although the NPs reported had a spherical form, TEM analysis showed a wide range of sizes. No more information was provided on the polydispersity of the NPs produced under various circumstances. The research's main flaw is that the pH was adjusted without adding salt, even though it is well recognized that under these circumstances, pH measurements using glass electrodes—as is often done—are not very reliable, especially when large protein concentrations are present [32].

The albumin raises the dielectric constant, lowering the zeta potential and permitting the red blood cells to approach. Because albumin is a dipolar protein, it may waste energy during rotation, which thins the ionic cloud surrounding each cell. Using a zeta sizer, albumin NPs revealed typical sizes of around 225.1, 223.5, 226.3, and 228.7 nm, respectively. Therefore, it may be concluded that the drug–polymer ratio has no appreciable impact on particle size. Moreover, variations in surface charge throughout formulations and the durability of NPs may also be inferred using zeta potential [174].

Although protein NPs offer unique inherent benefits, their ex vivo colloidal stability in biological conditions has not yet been well investigated. It was discovered that the stability of BSA NPs was comparatively more excellent in glucose, distilled water, and NaCl than in PBS and Dulbecco's Modified Eagle Medium (DMEM). After 48 h of incubation in various biological media, researchers noticed a slight change in the hydrodynamic diameter of BSA NPs. However, a notable increase in hydrodynamic diameter was seen for the particles suspended in DMEM. Atomic force microscopy and TEM demonstrate the semi-spherical shape and size of the BSA NPs, which are found to be between 50 and 150 nm in length. The structural alterations of the BSA NPs were thoroughly examined, confirming the conformational stability of the NPs suspended in various biological environments. Zeta potential measurements were used to investigate the physical strength of the NPs, and the results indicated that they were highly stable. It has been predicted that the suitable biological media would increase colloidal and conformational stability, suggesting the possibility of using BSA NPs as an efficient drug carrier [175].

For instance, researchers have created a tiny BSA-NP exhibiting antibacterial activity using BSA molecules without any chemical alteration. The bottom-up technique was used to develop BSA NPs, created by dissolving BSA in Tris buffer containing urea for 60 min at 60 °C. The BSA solution was then dialyzed against distilled water to produce NPs. Dynamic light scattering (DLS), field emission surface electron microscopy (FESEM), SDS-PAGE, Fourier transform infrared spectroscopy (FTIR), and ultraviolet (UV) spectrophotometry have all been used to analyze the resulting BSA-NP. Utilizing the minimum inhibitory concentration (MIC) approach, the antibacterial activity of BSA-NP against *Pseudomonas aeruginosa* and *Staphylococcus aureus* was assessed. According to the DLS method findings, BSA molecules are self-assembled into tiny aggregates with a hydrodynamic diameter of 23.23 ± 2.1 nm. The spherical homogeneity of the NPs was excellent, with a minimal polydispersity index. The NPs are relatively straightforward and comprise a single protein molecule (BSA). Both *Pseudomonas aeruginosa* and *Staphylococcus aureus* saw a reduction in cell proliferation due to the BSA NPs. They also demonstrated a bacteriostatic impact ($MIC = 112 \times 10^{-5}$ μM) against *Pseudomonas aeruginosa*. Using a green synthesis technique, scientists could create consistent, minuscule BSA NPs without changing the chemical makeup of BSA molecules. Furthermore, it has bacteriostatic qualities against *Pseudomonas aeruginosa*. Thus, the BSA NPs developed by researchers may work well as a novel strategy to fight antibiotic resistance [27]. Therefore, paying attention to ABNP size and Zeta potential is crucial when designing and developing an appropriate, successful, focused therapy strategy for infectious dental illnesses.

Conclusion

Dental infections are relatively frequent and possibly deadly if underestimated. In endodontic surgeries, the vitality of the tooth is typically lost as the root cannot be exposed to diseases, and there is a risk of bacteria spreading throughout the body. Disinfectant rinses, which are cytotoxic at effective bactericidal concentrations, are one of the current therapy methods. Albumin is a desirable protein when creating NPs with possible medicinal uses. Many specialized delivery systems have been developed in response to growing knowledge about periodontal disease and medication administration techniques, which have helped eradicate antibiotics' systemic adverse effects. Targeting a broad spectrum of molecular mediators of tissue degradation, DDSs aim to halt the progression of periodontal disease. The finest delivery systems for medication release and other potential biomedical uses were considered BSA-coated NPs. HSA as a drug carrier is a new technique for regulated medication delivery. There have been reports on its application as a conjugation with medicinal molecules or as a polymeric particulate system. Numerous studies have demonstrated the ability of ABNPs to act as a drug carrier, delivering a wide range of medications and metallic NPs, including gold, Ag, zinc, and Ti, to the diseased and inflamed gum and tooth tissue to eradicate the pathogen. This NP's antibacterial and anti-inflammatory qualities have made it appealing and practical for medication administration and medical treatments. However, there is very little research on treating disorders such as periodontitis and peri-implantitis, as well as dentin and root infections. Future research indicates that this NP may be utilized in clinical settings. Thus, in nano-dentistry, researchers ought to take note of ABNPs superior medication delivery capabilities.

Acknowledgements
We try to create a beautiful smile for you.

Author contributions
M.K., S.Y., Writing—original draft. M.K., S.Y., conceptualization, Investigation. S.Y., Figure design. S.Y., Corresponding authors and Project administration. M.K., S.Y., reviewed and edited the revision. All authors have read and agreed to the published version of the manuscript.

Funding
There is no funding.

Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
All authors consent to publication.

Competing interests
The authors declare no competing interests.

Received: 10 September 2024 Accepted: 19 November 2024
Published online: 27 November 2024

References

1. Cao W, et al. Development of a novel resin-based dental material with dual biocidal modes and sustained release of Ag+ ions based on photocurable core-shell AgBr/cationic polymer nanocomposites. J Mater Sci - Mater Med. 2017;28:1–11.
2. Sobieszczański J, et al. Root canal infection and its impact on the oral cavity microenvironment in the context of immune system disorders in selected diseases: a narrative review. J Clin Med. 2023;12(12):4102.
3. Bartold PM, Van Dyke TE. An appraisal of the role of specific bacteria in the initial pathogenesis of periodontitis. USA: Wiley Online Library; 2019.
4. Belibasakis G, Manoil D. Microbial community-driven etiopathogenesis of peri-implantitis. J Dent Res. 2021;100(1):21–8.
5. Sabatini C, et al. Incorporation of bactericidal poly-acrylic acid modified copper iodide particles into adhesive resins. J Dent. 2015;43(5):546–55.
6. Kanaparthy R, Kanaparthy A. The changing face of dentistry: nanotechnology. Int J Nanomed. 2011;2799:2804.
7. Vasiliu S, et al. The benefits of smart nanoparticles in dental applications. Int J Mol Sci. 2021;22(5):2585.
8. Yazdanian M, et al. The potential application of green-synthesized metal nanoparticles in dentistry: a comprehensive review. Bioinorg Chem Appl. 2022;2022(1):2311910.
9. Marica A, et al. Current use of nanoparticles in endodontics: a systematic review. Romanian J Oral Rehabil. 2022;14:3.
10. Kasraei S, et al. Antibacterial properties of composite resins incorporating silver and zinc oxide nanoparticles on streptococcus mutans and Lactobacillus. Restorative Dent Endod. 2014;39(2):109–14.
11. Yue S, et al. Novel dental adhesive resin with crack self-healing, antimicrobial and remineralization properties. J Dent. 2018;75:48–57.
12. Nishakavya S, et al. Size attenuated copper doped zirconia nanoparticles enhances in vitro antimicrobial properties. Appl Biochem Biotechnol. 2022;194(8):3435–52.
13. Wang D, et al. Nanoparticles in periodontitis therapy: a review of the current situation. Int J Nanomed. 2024;6857:6893.
14. Kiarashi M, et al. Spotlight on therapeutic efficiency of green synthesis metals and their oxide nanoparticles in periodontitis. J Nanobiotechnol. 2024;22(1):21.
15. Nasiri K, et al. Recent advances in metal nanoparticles to treat periodontitis. J Nanobiotechnol. 2023;21(1):283.
16. Girigoswami K, Pallavi P, Girigoswami A. Crafting porous nanoscaled architecture as a potential frontier for drug delivery. Mol Syst Des Eng. 2024. https://doi.org/10.1039/D4ME00098F.
17. Hakim LK, et al. The current applications of nano and biomaterials in drug delivery of dental implant. BMC Oral Health. 2024;24(1):126.
18. Higino T, França R. Drug-delivery nanoparticles for bone-tissue and dental applications. Biomed Phys Eng Express. 2022;8(4): 042001.
19. Raoufinia R, et al. Overview of albumin and its purification methods. Adv Pharm Bull. 2016;6(4):495–507.
20. Park K-H, Dhayal M. Simultaneous growth of rutile TiO2 as 1D/3D nanorod/nanoflower on FTO in one-step process enhances electrochemical response of photoanode in DSSC. Electrochem Commun. 2014;49:47–50.
21. Kim H-J, et al. Long-term release of chlorhexidine from dental adhesive resin system using human serum albumin nanoparticles. Polym Bull. 2014;71:875–86.
22. Butrón-Téllez Girón C, et al. Effectiveness of a combined silver nanoparticles/fluoride varnish in dental remineralization in children: in vivo study. Superficies y vacío. 2017;30(2):21–4.
23. Montesarchio, E., *Multifunctional nanoparticles for dental applications*. Politecnico di Torino. 2020
24. Qu N, et al. Albumin nanoparticle-based drug delivery systems. Int J Nanomed. 2024;6945:6980.
25. Kratz F. A clinical update of using albumin as a drug vehicle—a commentary. J Control Release. 2014;190:331–6.
26. Adrianzen Herrera D, et al. Nanoparticle albumin bound-paclitaxel for treatment of advanced non-small cell lung cancer: an evaluation of the clinical evidence. Expert Opin Pharmacother. 2019;20(1):95–102.
27. Sheikh Hosseini M, Moosavi-Nejad Z, Mohammadi P. A new nanobiotic: synthesis and characterization of an albumin nanoparticle with intrinsic antibiotic activity. Iran J Microbiol. 2023;15(5):697–704.
28. Mardikasari SA, et al. Quality by design-based optimization of in situ ionic-sensitive gels of amoxicillin-loaded bovine serum albumin nanoparticles for enhanced local nasal delivery. Int J Pharm. 2023;645: 123435.
29. Bobrowska K, et al. Bovine serum albumin–hydroxyapatite nanoflowers as potential local drug delivery system of ciprofloxacin. Int J Nanomed. 2023;6449:6467.
30. Bi S, et al. A sensitive surface-enhanced Raman spectroscopy detection for gentamicin and tobramycin using γ-Al2O3-modified silver nanoparticles coated with bovine serum albumin as substrate. Talanta. 2023;260: 124635.
31. Belinskaia DA, et al. Serum albumin. Encyclopedia. 2020;1(1):65–75.
32. Langer K, et al. Optimization of the preparation process for human serum albumin (HSA) nanoparticles. Int J Pharm. 2003;257(1–2):169–80.
33. Li C, et al. Preparation and characterization of galactosylated bovine serum albumin nanoparticles for liver-targeted delivery of oridonin. Int J Pharm. 2013;448(1):79–86.
34. Ray B, et al. Neuroprotective and neurorescue effects of a novel polymeric nanoparticle formulation of curcumin (NanoCurc™) in the neuronal cell culture and animal model: implications for Alzheimer's disease. J Alzheimers Dis. 2011;23(1):61–77.
35. Gao S, et al. Preparation, characterization and pharmacokinetic studies of tacrolimus-dimethyl-β-cyclodextrin inclusion complex-loaded albumin nanoparticles. Int J Pharm. 2012;427(2):410–6.
36. Larsen MT, et al. Albumin-based drug delivery: harnessing nature to cure disease. Mol Cell Therap. 2016;4:1–12.
37. Carvalho JR, Machado MV. New insights about albumin and liver disease. Ann Hepatol. 2018;17(4):547–60.
38. Lv L, et al. Structural and functional properties of ovalbumin glycated by dry-heating in the presence of maltodextrin. Int J Food Prop. 2015;18(6):1326–33.
39. Spada A, et al. The uniqueness of albumin as a carrier in nanodrug delivery. Mol Pharm. 2021;18(5):1862–94.

40. Lee HJ, et al. Enzyme delivery using the 30Kc19 protein and human serum albumin nanoparticles. Biomaterials. 2014;35(5):1696–704.
41. Nosrati H, et al. Bovine serum albumin: an efficient biomacromolecule nanocarrier for improving the therapeutic efficacy of chrysin. J Mol Liq. 2018;271:639–46.
42. Divsalar A, et al. Characterization and side effect analysis of a newly designed nanoemulsion targeting human serum albumin for drug delivery. Colloids Surf, B. 2012;98:80–4.
43. Zou W, et al. Phase separation behavior and characterization of ovalbumin and propylene glycol alginate complex coacervates. Food Hydrocolloids. 2020;108: 105978.
44. Yao Y, et al. Molecular modelling, thermal, adsorption and biological studies of conjugate Cu2+-BSA nanoparticles. J Mol Liq. 2021;331: 115732.
45. Crommelin DJ, van Hoogevest P, Storm G. The role of liposomes in clinical nanomedicine development. what now? now what? J Cont Rel. 2020;318:256–63.
46. Elsadek B, Kratz F. Impact of albumin on drug delivery—New applications on the horizon. J Control Release. 2012;157(1):4–28.
47. Skoll K, et al. Human serum albumin nanoparticles as a versatile vehicle for targeted delivery of antibiotics to combat bacterial infections. Nanomed Nanotechnol Biol Med. 2023;50: 102685.
48. Mohammadian M, et al. Targeted albumin nanoparticles for the enhancement of gemcitabine toxicity on cancerous cells. J Drug Deliv Sci Technol. 2020;56: 101503.
49. Hornok V. Serum albumin nanoparticles: problems and prospects. Polymers. 2021;13(21):3759.
50. Pressacco J, Papas K. Gadofosveset-enhanced magnetic resonance angiography as a means of evaluating pulmonary arteriovenous malformation: a case report. Magn Reson Imaging. 2012;30(6):886–8.
51. Mohammad-Beigi H, et al. Strong interactions with polyethylenimine-coated human serum albumin nanoparticles (PEI-HSA NPs) alter α-synuclein conformation and aggregation kinetics. Nanoscale. 2015;7(46):19627–40.
52. Jahanban-Esfahlan A, et al. Recent developments in the detection of bovine serum albumin. Int J Biol Macromol. 2019;138:602–17.
53. Kunde SS, Wairkar S. Targeted delivery of albumin nanoparticles for breast cancer: a review. Colloids Surf, B. 2022;213: 112422.
54. Meng R, et al. Preparation of drug-loaded albumin nanoparticles and its application in cancer therapy. J Nanomater. 2022;2022(1):3052175.
55. Zhu GH, Gray AB, Patra HK. Nanomedicine: controlling nanoparticle clearance for translational success. Trends Pharmacol Sci. 2022;43(9):709–11.
56. Lee ES, Youn YS. Albumin-based potential drugs: focus on half-life extension and nanoparticle preparation. J Pharm Investig. 2016;46:305–15.
57. Turner PJ, et al. Safety of live attenuated influenza vaccine in atopic children with egg allergy. J Allergy Clin Immunol. 2015;136(2):376–81.
58. Rao S-Q, et al. Physicochemical and antibacterial properties of fabricated ovalbumin–carvacrol gel nanoparticles. Food Funct. 2020;11(6):5133–41.
59. Dantas M, et al. Interactions of tetracyclines with ovalbumin, the main allergen protein from egg white: spectroscopic and electrophoretic studies. Int J Biol Macromol. 2017;102:505–14.
60. Shin SY, et al. Polyphenols bearing cinnamaldehyde scaffold showing cell growth inhibitory effects on the cisplatin-resistant A2780/Cis ovarian cancer cells. Bioorg Med Chem. 2014;22(6):1809–20.
61. Stănciuc N, et al. pH and heat induced structural changes of chicken ovalbumin in relation with antigenic properties. Int J Biol Macromol. 2016;93:572–81.
62. Shreaz S, et al. Cinnamaldehyde and its derivatives, a novel class of antifungal agents. Fitoterapia. 2016;112:116–31.
63. Prasad AR, et al. Investigation on bovine serum albumin (BSA) binding efficiency and antibacterial activity of ZnO nanoparticles. Mater Chem Phys. 2020;240: 122115.
64. Hekmat A, Salavati F, Hesami Tackallou S. The effects of paclitaxel in the combination of diamond nanoparticles on the structure of human serum albumin (HSA) and their antiproliferative role on MDA-MB-231cells. Protein J. 2020;39:268–83.
65. Rabbani G, Ahn SN. Structure, enzymatic activities, glycation and therapeutic potential of human serum albumin: a natural cargo. Int J Biol Macromol. 2019;123:979–90.
66. Tang W-H, Wang C-F, Liao Y-D. Fetal bovine serum albumin inhibits antimicrobial peptide activity and binds drug only in complex with α1-antitrypsin. Sci Rep. 2021;11(1):1267.
67. Wilson B, et al. Albumin nanoparticles for the delivery of gabapentin: preparation, characterization and pharmacodynamic studies. Int J Pharm. 2014;473(1–2):73–9.
68. Cheng Z, et al. Multifunctional nanoparticles: cost versus benefit of adding targeting and imaging capabilities. Science. 2012;338(6109):903–10.
69. Lee D-E, et al. Multifunctional nanoparticles for multimodal imaging and theragnosis. Chem Soc Rev. 2012;41(7):2656–72.
70. Von Storp B, et al. Albumin nanoparticles with predictable size by desolvation procedure. J Microencapsul. 2012;29(2):138–46.
71. Chompunut L, et al. Synthesis of copper nanoparticles from the aqueous extract of Cynodon dactylon and evaluation of its antimicrobial and photocatalytic properties. Food Chem Toxicol. 2022;166: 113245.
72. Chi NTL, et al. Fabrication, characterization, anti-inflammatory, and anti-diabetic activity of silver nanoparticles synthesized from Azadirachta indica kernel aqueous extract. Environ Res. 2022;208: 112684.
73. Sheng Y, et al. In vitro and in vivo efficacy of green synthesized AgNPs against Gram negative and Gram positive bacterial pathogens. Process Biochem. 2022;112:241–7.
74. Karami K, et al. BSA nanoparticles as controlled release carriers for isophethalaldoxime palladacycle complex; synthesis, characterization, in vitro evaluation, cytotoxicity and release kinetics analysis. New J Chem. 2020;44(11):4394–405.

75. Medina-Navarro R, et al. Lysosomal dysfunction induced by changes in albumin's tertiary structure: potential key factor in protein toxicity during diabetic nephropathy. Life Sci. 2019;230:197–207.
76. Elzoghby AO, Samy WM, Elgindy NA. Albumin-based nanoparticles as potential controlled release drug delivery systems. J Control Release. 2012;157(2):168–82.
77. Hermann B, Seidenberg M, Jones J. The neurobehavioural comorbidities of epilepsy: can a natural history be developed? Lancet Neurol. 2008;7(2):151–60.
78. Verma ML, et al. Carbohydrate and protein based biopolymeric nanoparticles: current status and biotechnological applications. Int J Biol Macromol. 2020;154:390–412.
79. Alfagih IM, et al. In vitro characterization of inhalable cationic hybrid nanoparticles as potential vaccine carriers. Pharmaceuticals. 2021;14(2):164.
80. Wan X, et al. Incorporation of lapatinib into human serum albumin nanoparticles with enhanced anti-tumor effects in HER2-positive breast cancer. Colloids Surf, B. 2015;136:817–27.
81. Di Pippo M, et al. Nab-Paclitaxel related cystoid macular edema. Clin Ter. 2022;173:4.
82. He F, et al. Adverse event profile for nanoparticle albumin-bound paclitaxel compared with solvent-based taxanes in solid-organ tumors: a systematic review and meta-analysis of randomized clinical trials. Ann Pharmacother. 2022;56(8):898–909.
83. Füredi P, et al. Development and characterization of voriconazole loaded nanoparticles for parenteral delivery. Int J Pharm. 2016;510(1):159–63.
84. Abolhassani H, Shojaosadati SA. A comparative and systematic approach to desolvation and self-assembly methods for synthesis of piperine-loaded human serum albumin nanoparticles. Colloids Surf, B. 2019;184: 110534.
85. Saleh T, Soudi T, Shojaosadati SA. Redox responsive curcumin-loaded human serum albumin nanoparticles: Preparation, characterization and in vitro evaluation. Int J Biol Macromol. 2018;114:759–66.
86. Curcio M, et al. Functional albumin nanoformulations to fight adrenocortical carcinoma: a redox-responsive approach. Pharm Res. 2020;37:1–10.
87. Boye JI, Alli I, Ismail AA. Interactions involved in the gelation of bovine serum albumin. J Agric Food Chem. 1996;44(4):996–1004.
88. Li F, et al. A novel thermal-driven self-assembly method to prepare albumin nanoparticles: formation kinetics, degradation behavior and formation mechanism. AAPS PharmSciTech. 2022;23(7):250.
89. Pulakkat S, et al. Surface engineered protein nanoparticles with hyaluronic acid based multilayers for targeted delivery of anticancer agents. ACS Appl Mater Interfaces. 2016;8(36):23437–49.
90. Faheem A, Haggag Y. Evaluation of nano spray drying as a method for drying and formulation of therapeutic peptides and proteins. Front Pharmacol. 2015;6:140.
91. Lee SH, et al. Nano spray drying: a novel method for preparing protein nanoparticles for protein therapy. Int J Pharm. 2011;403(1–2):192–200.
92. Abdel-Mageed HM, et al. Optimization of nano spray drying parameters for production of α-amylase nanopowder for biotherapeutic applications using factorial design. Drying Technol. 2019. https://doi.org/10.1080/07373937.2019.1565576.
93. Vehring R. Pharmaceutical particle engineering via spray drying. Pharm Res. 2008;25(5):999–1022.
94. Almansour K, et al. Particle engineering by nano spray drying: optimization of process parameters with hydroethanolic versus aqueous solutions. Pharmaceutics. 2022;14(4):800.
95. Heng D, et al. The nano spray dryer B-90. Expert Opin Drug Deliv. 2011;8(7):965–72.
96. Lin W, et al. Preparation of sub-100 nm human serum albumin nanospheres using a pH-coacervation method. J Drug Target. 1993;1(3):237–43.
97. Shrimal P, Jadeja G, Patel S. A review on novel methodologies for drug nanoparticle preparation: microfluidic approach. Chem Eng Res Des. 2020;153:728–56.
98. Belliveau NM, et al. Microfluidic synthesis of highly potent limit-size lipid nanoparticles for in vivo delivery of siRNA. Mol Therapy-Nucleic Acids. 2012;1: e37.
99. Liu D, et al. Microfluidic-assisted fabrication of carriers for controlled drug delivery. Lab Chip. 2017;17(11):1856–83.
100. Esim O, Hascicek C. Albumin-based nanoparticles as promising drug delivery systems for cancer treatment. Curr Pharm Anal. 2021;17(3):346–59.
101. Tan YL, Ho HK. Navigating albumin-based nanoparticles through various drug delivery routes. Drug Disc Today. 2018;23(5):1108–14.
102. Irache J, et al. Albumin nanoparticles for the intravitreal delivery of anticytomegaloviral drugs. Mini Rev Med Chem. 2005;5(3):293–305.
103. Chen H, et al. Preparation and blood compatibility of carbon/TiO2 nanocomposite. Diam Relat Mater. 2013;38:52–8.
104. Reinhart SA, Schulzki T, Reinhart WH. Albumin reverses the echinocytic shape transformation of stored erythrocytes. Clin Hemorheol Microcirc. 2015;60(4):437–49.
105. Ezhilarasan D, Lakshmi T, Mallineni SK. Nano-based targeted drug delivery for lung cancer: therapeutic avenues and challenges. Nanomedicine. 2022;17(24):1855–69.
106. Raghav A, et al. New insights into non-enzymatic glycation of human serum albumin biopolymer: a study to unveil its impaired structure and function. Int J Biol Macromol. 2017;101:84–99.
107. Chen Q, et al. Albumin-NIR dye self-assembled nanoparticles for photoacoustic pH imaging and pH-responsive photothermal therapy effective for large tumors. Biomaterials. 2016;98:23–30.
108. Woods A, et al. In vivo biocompatibility, clearance, and biodistribution of albumin vehicles for pulmonary drug delivery. J Control Release. 2015;210:1–9.
109. Seo J, et al. Therapeutic advantage of inhaled tacrolimus-bound albumin nanoparticles in a bleomycin-induced pulmonary fibrosis mouse model. Pulm Pharmacol Ther. 2016;36:53–61.
110. Bhushan B, et al. Bionanotherapeutics: niclosamide encapsulated albumin nanoparticles as a novel drug delivery system for cancer therapy. RSC Adv. 2015;5(16):12078–86.

111. Sun S, et al. Roles of alcohol desolvating agents on the size control of bovine serum albumin nanoparticles in drug delivery system. J Drug Del Sci Technol. 2018;47:193–9.
112. Lin T, et al. Blood–brain-barrier-penetrating albumin nanoparticles for biomimetic drug delivery via albumin-binding protein pathways for antiglioma therapy. ACS Nano. 2016;10(11):9999–10012.
113. Vogel V, et al. Characterization of serum albumin nanoparticles by sedimentation velocity analysis and electron microscopy. Cham: Springer; 2002.
114. Sabaa MW, et al. Encapsulation of bovine serum albumin within novel xanthan gum based hydrogel for protein delivery. Mater Sci Eng, C. 2019;94:1044–55.
115. Karami E, Behdani M, Kazemi-Lomedasht F. Albumin nanoparticles as nanocarriers for drug delivery: Focusing on antibody and nanobody delivery and albumin-based drugs. J Drug Delivery Sci Technol. 2020;55: 101471.
116. Espinosa-Cristóbal LF, et al. Bovine serum albumin and chitosan coated silver nanoparticles and its antimicrobial activity against oral and nonoral bacteria. J Nanomater. 2015;2015(1): 420853.
117. Kim DH, et al. Antibacterial releasing titanium surface using albumin nanoparticle carriers. J Nanosci Nanotechnol. 2014;14(11):8422–6.
118. Kim DH, Son JS, Kwon T-Y. Antimicrobial effect of chlorhexidine-releasing porous hydroxyapatite scaffold incorporated with human serum albumin nanoparticles. Mater Lett. 2020;266: 127479.
119. Shrestha S, Diogenes A, Kishen A. Temporal-controlled release of bovine serum albumin from chitosan nanoparticles: effect on the regulation of alkaline phosphatase activity in stem cells from apical papilla. J Endod. 2014;40(9):1349–54.
120. Wang L, Hu C, Shao L. The antimicrobial activity of nanoparticles: present situation and prospects for the future. Int J Nanomed. 2017;1227:1249.
121. Rifaath M, et al. Preparation of herbal nano-formulation-assisted mouth paint using titanium dioxide nanoparticles and its biomedical applications. Cureus. 2023;15:11.
122. Martínez-Robles ÁM, et al. Antimicrobial properties of biofunctionalized silver nanoparticles on clinical isolates of Streptococcus mutans and its serotypes. Nanomaterials. 2016;6(7):136.
123. Namasivayam SKR, et al. Biocompatible polymer gum acacia coated bovine serum albumin (BSA) nanoparticles incorporated azithromycin (P-BSA NP-AZ) preparation for the improved anti bacterial activity against human pathogenic bacteria. World J Pharm Sci. 2013;2:3094–106.
124. Kumbham S, et al. Human serum albumin-poly (Lactide)-conjugated self-assembly NPs for targeted docetaxel delivery and improved therapeutic efficacy in oral cancer. Int J Biol Macromol. 2022;222:1287–303.
125. Wang Y, et al. A near infrared light-triggered human serum albumin drug delivery system with coordination bonding of indocyanine green and cisplatin for targeting photochemistry therapy against oral squamous cell cancer. Biomater Sci. 2019;7(12):5270–82.
126. Mohd-Said, S., et al. *Validation of a simplified digital periodontal health screening module for general dental practitioners*. 2022.
127. Herrera D, et al. Association between periodontal diseases and cardiovascular diseases, diabetes and respiratory diseases: consensus report of the joint workshop by the European federation of periodontology (EFP) and the European arm of the world organization of family doctors (WONCA Europe). J Clin Periodontol. 2023;50(6):819–41.
128. Kwon T, Lamster IB, Levin L. Current concepts in the management of periodontitis. Int Dent J. 2021;71(6):462–76.
129. Kang Y, et al. Dental plaque microbial resistomes of periodontal health and disease and their changes after scaling and root planing therapy. Msphere. 2021. https://doi.org/10.1128/msphere.
130. Norouzi M, et al. Recent advances on nanomaterials-based fluorimetric approaches for microRNAs detection. Mater Sci Eng, C. 2019;104: 110007.
131. Preshaw PM, Bissett SM. Periodontitis and diabetes. Br Dent J. 2019;227(7):577–84.
132. Papapanou, P.N. and C. Susin, *Periodontitis epidemiology: is periodontitis under-recognized, over-diagnosed, or both?* Periodontology 2000, 2017. **75**(1): p. 45–51.
133. Preshaw PM, et al. Periodontitis and diabetes: a two-way relationship. Diabetologia. 2012;55:21–31.
134. Meyle J, Chapple I. Molecular aspects of the pathogenesis of periodontitis. Periodontolog. 2015;69(1):7–17.
135. Mou J, et al. Hydrogel containing minocycline and zinc oxide-loaded serum albumin nanoparticle for periodontitis application: preparation, characterization and evaluation. Drug Delivery. 2019;26(1):179–87.
136. Meng X, et al. Bovine serum albumin-coated ceria nanoparticles activate the TGF-β signaling pathway for periodontal bone regeneration. ACS Appl Nano Mater. 2023;6(7):5623–34.
137. Wang Y, et al. Calcium-siRNA nanocomplexes optimized by bovine serum albumin coating can achieve convenient and efficient siRNA delivery for periodontitis therapy. Int J Nanomed. 2020;9241:9253.
138. Grenier D, et al. Role of gingipains in growth of Porphyromonas gingivalis in the presence of human serum albumin. Infect Immun. 2001;69(8):5166–72.
139. Singh A, et al. Synthesis of Ag–Pt alloy nanoparticles in aqueous bovine serum albumin foam and their cytocompatibility against human gingival fibroblasts. Colloids Surf, B. 2009;69(2):239–45.
140. Grade S, et al. Serum albumin reduces the antibacterial and cytotoxic effects of hydrogel-embedded colloidal silver nanoparticles. RSC Adv. 2012;2(18):7190–6.
141. Klinge B, Hultin M, Berglundh T. Peri-implantitis. Dental Clinics. 2005;49(3):661–76.
142. Heitz-Mayfield LJ, Mombelli A. The therapy of peri-implantitis: a systematic review. Int J Oral Maxillofacial Implants. 2014;29:325–45.
143. Boccia G, et al. Local and systemic antibiotics in peri-implantitis management: an umbrella review. Antibiotics. 2023;12(1):114.
144. Javed F, et al. Clinical efficacy of antibiotics in the treatment of peri-implantitis. Int Dent J. 2013;63(4):169–76.
145. Renvert S, Quirynen M. Risk indicators for peri-implantitis. A narrative review. Clin Oral Implants Res. 2015;26:15–44.
146. Thoma DS, et al. Effects of soft tissue augmentation procedures on peri-implant health or disease: a systematic review and meta-analysis. Clin Oral Implant Res. 2018;29:32–49.
147. Li X, et al. The efficacy of hydrogel containing zinc oxide-loaded and minocycline serum albumin nanoparticle in the treatment of peri-implantitis. Med Oral Patol Oral Cir Bucal. 2023;28(5): e487.

148. Campos EM, et al. Albumin loaded PEO coatings on Ti—potential as drug eluting systems. Surf Coat Technol. 2015;283:44–51.
149. Sun Y, et al. The early adhesion effects of human gingival fibroblasts on bovine serum albumin loaded hydrogenated titanium nanotube surface. Molecules. 2021;26(17):5229.
150. Gomes B, Herrera DR. Etiologic role of root canal infection in apical periodontitis and its relationship with clinical symptomatology. Brazilian oral Res. 2018;32(1): e69.
151. Ørstavik D. Apical periodontitis: microbial infection and host responses. Essential Endodontol Prev Treat Apical Period. 2019;1:10.
152. Nair PR. Apical periodontitis: a dynamic encounter between root canal infection and host response. Periodontol. 2000;13(1):121–48.
153. Bouillaguet S, et al. Root microbiota in primary and secondary apical periodontitis. Front Microbiol. 2018;9:2374.
154. Shrestha A, Kishen A. Antibacterial efficacy of photosensitizer functionalized biopolymeric nanoparticles in the presence of tissue inhibitors in root canal. J Endod. 2014;40(4):566–70.
155. Khedmat S, Aligholi M, Sadeghi S. Influence of bovine serum albumin on the antibacterial activity of endodontic irrigants against Enterococcus faecalis. Iran Endod J. 2009;4(4):139–43.
156. Kelly KL, et al. The optical properties of metal nanoparticles: the influence of size, shape, and dielectric environment. Washington, D.C: ACS Publications; 2003.
157. Commisso C, et al. Macropinocytosis of protein is an amino acid supply route in Ras-transformed cells. Nature. 2013;497(7451):633–7.
158. Elzoghby AO, Samy WM, Elgindy NA. Protein-based nanocarriers as promising drug and gene delivery systems. J Control Release. 2012;161(1):38–49.
159. Preston TJ, et al. Modified surface coatings and their effect on drug adsorption within the extracorporeal life support circuit. J ExtraCorporeal Technol. 2010;42(3):199–202.
160. Mariani E, et al. Biomaterials: foreign bodies or tuners for the immune response? Int J Mol Sci. 2019;20(3):636.
161. Mijiritsky E, et al. Albumin-impregnated bone granules modulate the interactions between mesenchymal stem cells and monocytes under in vitro inflammatory conditions. Mater Sci Eng, C. 2020;110: 110678.
162. Schandl K, et al. Bone-Albumin filling decreases donor site morbidity and enhances bone formation after anterior cruciate ligament reconstruction with bone-patellar tendon-bone autografts. Int Orthop. 2016;40:2097–104.
163. Hermawan H, Ramdan D, Djuansjah JR. Metals for biomedical applications. Biomed Eng Theory Applic. 2011;1:411–30.
164. Mylne JS, Hara-Nishimura I, Rosengren KJ. Seed storage albumins: biosynthesis, trafficking and structures. Funct Plant Biol. 2014;41(7):671–7.
165. Yang J, et al. Rethinking plant protein extraction: Albumin—From side stream to an excellent foaming ingredient. Food Struct. 2022;31: 100254.
166. Mahmood MK, et al. Implication of serum and salivary albumin tests in the recent oral health related epidemiological studies: a narrative review. Saudi Dental J. 2024. https://doi.org/10.1016/j.sdentj.2024.02.019.
167. Layman DK, Lönnerdal B, Fernstrom JD. Applications for α-lactalbumin in human nutrition. Nutr Rev. 2018;76(6):444–60.
168. Pawar N, Bohidar H. Anisotropic domain growth and complex coacervation in nanoclay-polyelectrolyte solutions. Adv Coll Interface Sci. 2011;167(1–2):12–23.
169. Tafti F, et al. Hazards associated with nanotechnology in clinical dentistry. Cureus. 2023;15:10.
170. Dastjerdi R, Montazer M. A review on the application of inorganic nano-structured materials in the modification of textiles: focus on anti-microbial properties. Colloids Surf, B. 2010;79(1):5–18.
171. Emmanuel R, et al. Antimicrobial efficacy of green synthesized drug blended silver nanoparticles against dental caries and periodontal disease causing microorganisms. Mater Sci Eng, C. 2015;56:374–9.
172. Zannella C, et al. Antibacterial activity of indolicidin-coated silver nanoparticles in oral disease. Appl Sci. 2020;10(5):1837.
173. Arias CA, Murray BE. The rise of the Enterococcus: beyond vancomycin resistance. Nat Rev Microbiol. 2012;10(4):266–78.
174. Jithan A, et al. Preparation and characterization of albumin nanoparticles encapsulating curcumin intended for the treatment of breast cancer. Int J Pharm Investig. 2011;1(2):119–25.
175. Rohiwal S, et al. Preparation and evaluation of bovine serum albumin nanoparticles for ex vivo colloidal stability in biological media. Colloids Surf, A. 2015;480:28–37.

Publisher's Note