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Tripathi, A., Pandey, V.K., Rustagi, S. et al. (2 more authors) (2025) Alginate-based NPs for targeted ovarian cancer therapy: Navigating current progress and biomedical applications. International Journal of Biological Macromolecules, 319 (Pt 3). 145365. ISSN: 0141-8130

https://doi.org/10.1016/j.ijbiomac.2025.145365

Title
Alginate-based NPs for targeted ovarian cancer therapy: Navigating current progress and biomedical applications

Abstract
Ovarian cancer continues to be one of the most lethal gynecological malignancies, with earlier symptoms that are frequently subtle, resulting in detection at late stages. Although there are several traditional treatments, patients do not respond well to them owing to serious side effects. Alginate, a polysaccharide extracted from brown seaweed (a natural polymer), has gained significant attention as an ideal biopolymer for developing drug delivery systems because of its nontoxicity, biodegradability, and ease of manipulation. Alginate-based NPs (ABNPs) represent a new strategy for the targeted treatment of ovarian cancer, increasing the efficacy of chemotherapeutic agents in tumor cells while reducing systemic toxicity. Current strategies to exploit ABNPs relate to their capability to encapsulate different types of payloads, including small-molecule drugs, proteins, and genetic materials. Functionalization with targeting peptides, antibodies, or FA imparts selective affinity for ovarian cancer cells, and hence, a targeted chemotherapeutic approach. Alginate NPs are a versatile and potent platform for the targeted treatment of ovarian cancer, integrating drug delivery into diagnostics, as well as gene therapy. This review presents the latest research trends and an understanding of the characteristic features and functions of ABNPs in targeted delivery against ovarian cancer.

1. Introduction

Ovarian cancer is among the deadliest gynecological malignancies because of its late-stage diagnosis. It is also known as the “silent killer,” as it bears nonspecific symptoms of abdominal distension, pelvic pain and urinary incontinence that can be confused with benign pathologies. Approximately 70 % of cases are detected at an advanced stage, when the cancer has spread beyond the ovaries. Conventional treatment for ovarian cancer is a combination of surgery and chemotherapy [1]. Surgery is the main treatment for debulking (partial or complete removal of tumors), with the remaining cancer cell population eliminated by chemotherapy, which is generally mediated by platinum-based drugs such as cisplatin, carboplatin, and taxane paclitaxel. Although the first response to chemotherapy is generally good, recurrence occurs in most patients and chemoresistance is very frequent. This resistance eventually limits the effectiveness of further treatment and is a major obstacle to long-term remission. Toxicity caused by traditional chemotherapeutic drugs can lead to nephrotoxicity, neurotoxicity, and myelosuppression. The variety of challenges in this environment has created a critical and ongoing need for better, more specific treatments that can remove cancer cells without affecting normal tissues. Addressing these challenges together with long-term outcomes, DDSs, immunotherapy, and personalized medicine under innovations have been actively investigated to extend survival rates and minimize therapeutic adverse effects [2].

Alginate, a naturally derived polysaccharide from brown seaweed, has become a central biomaterial for biomedical applications, particularly for the development of DDSs. Its biocompatibility, biodegradability, and gel-forming ability in the presence of divalent

cations such as Ca2+ make it an ideal candidate for the encapsulation and delivery of medicinal agents. Alginate-based NPs have been specifically designed to increase the delivery and efficiency of drugs. These NPs allow for the encapsulation of a variety of therapeutic agents, such as small-molecule drugs, proteins, and nucleic acids. During the encapsulation process, therapeutic agents are protected from degradation, stabilization, and release by controlled and sustained processes [3]. The ability of alginate to form gels is particularly beneficial for preparing NPs suitable for the sustained release of drugs, which enhances therapeutic level maintenance over long periods. In addition, alginate NPs can carry targeting ligands, such as antibodies, peptides, or FA. This functionalization allows the NPs to attach only to the preferred type of cells (e.g., cancer/negative) instead of normal/positive cells. This increases the targeting efficiency and reduces the off-target effects. This is particularly desirable in cancer therapy, where the drug needs to be delivered to the tumor site without eliciting systemic toxicity. In addition to the unique features of controlled drug release, they are well prepared for different administration routes (ranging from oral and intravenous routes to the nasal route), so that alginate NPs can be used in diverse therapeutic applications. Since they can be crosslinked and form hydrogels, this offers possibilities for controlled-release applications of drugs, especially where drug release must be localized or mitigated from the rest of the systemic circulation [4].

ABNPs have been extensively studied for the targeted therapy of ovarian cancer. These design able further study the advantages of tailoring ABNP size, charge, and surface modifications for improved tumor-specific delivery [5]. Functionalization of ABNPs with targeting ligands, such as FA, antibodies, or peptides that recognize overexpressed receptors on ovarian cancer cells is one of the most widely adopted approaches. This promoted intracellular drug accumulation through receptor-mediated endocytosis. ABNPs can be designed for dual or multidrug delivery to combine chemotherapy and gene therapy, allowing the circumvention of drug resistance mechanisms [6]. ABNPs respond to external stimuli, related to pH, enzymes, or temperature changes in the tumor microenvironment and improve therapeutic accuracy. ABNPs have also been investigated as carriers for a wide range of therapeutics, such as immunotherapies and RNA-based therapeutics (siRNA and mRNA) to silence oncogenes and modulate immune responses [7].

Targeted therapy uses drugs or other substances to identify and attack specific elements in molecular pathways that cancer cells need to live through. While traditional chemotherapy kills both cancerous and normal cells, targeted therapies provide the opportunity to limit harm to non-cancerous tissues, mitigating side effects in patients. This is achieved by targeting certain molecular markers or genetic mutations that are overexpressed in ovarian cancer cells. The development of PARP inhibitors represents a breakthrough in the targeted therapy of ovarian cancer. The actions of these drugs on defective DNA repair, particularly in cells with BRCA1 or BRCA2 mutations in ovarian cancer, through which they cause selective cancer cell death while sparing normal cells, are well characterized [8]. PARP inhibitors have been shown to prolong progression-free survival in ovarian cancer relapse in clinical trials. One promising strategy is to use drugs known as angiogenesis inhibitors (e.g., bevacizumab) that attack the blood vessels and provide nutrition to tumors. This effectively cuts off the supply lines of nutrients and

oxygen from the tumor, reducing its growth and limiting metastasis. Immunotherapy, using the body's immune system to target and kill cancer cells, has emerged as a promising approach for ovarian cancer treatment. Clinical trials with immune checkpoint inhibitors (used to block proteins that protect the body (immune system) from attacking cancer cells) are under investigation and show promise but lack close monitoring [9]. The primary focus of this review is to present the emerging potential of ABNPs for targeted drug delivery in ovarian cancer. This review article aims to highlight the development and optimization of alginate-based DDSs for targeted ovarian cancer therapy. It presents the physical and chemical properties of alginate, different formulations of NPs, and novel methods of functionalization to improve therapeutic efficacy and selectivity.

2. Alginate-based nanoparticles: composition and properties

Edward Stanford, a researcher, initiated the use of alginates in 1883, with the commercial development of the substance beginning in 1927. Currently, the annual global production of alginates is approximately 40,000 t. Alginates are widely utilized in the pharmaceutical, cosmetic, dental, and food [10]. In the following sections, we delineate the major properties and compositions of the ABNPs.

2.1. Alginate as a natural polymer

Commercially available alginate is produced from brown algae derived from seaweeds including Laminaria digitata, Laminaria hyperborea, Macrocystis pyrifera, Ascophyllum nodosum, and Laminaria japonica. Alginates are typically insoluble. To produce the water-soluble sodium/potassium salt of alginic acid, they must be treated with a basic solution, specifically NaOH or KOH, after being rinsed, pulverized, dried, and powdered. Alginates, specifically sodium alginate or alginic acid sodium salt, are commercially available [10]. Alginates are considered favorable biodegradable biopolymeric materials for biomedical applications owing to their acidic characteristics. Gel formation occurs rapidly in alginates owing to the high acid content and the presence of the guluronic acid (G) monomer, particularly in the presence of Ca^{2+} ions. The gelling property of alginate enables its utilization for a variety of purposes, including the encapsulation of diverse fragments or cells within the alginate matrix, all with minimal adverse effects. Because the carboxylic groups in alginates are highly effective, they can be modified to suit specific requirements and find numerous applications [11]. Azotobacter and Pseudomonas are examples of bacteria capable of producing alginate as an exopolysaccharide. It is possible that these bacterial alginate producers could generate alginates with specific monomer formulations and, using genetic and protein engineering, could produce “tailored” bacterial alginates [12]. The molecular weights of the alginates collected from various seabed locations ranged from 50 to 500 kDa. The alginate solution exhibited a pH-dependent increase and decrease in viscosity; the solution reached a pH below 3.5, owing to the protonation and formation of hydrogen bonds by carboxylate groups in guluronic acid that are present in the alginate structure [10]. The molecular weight of alginates can vary depending on whether they are utilized to independently monitor the viscosity of the pre-gel solution or the strength distribution after gelling. To modify the viscosity of the solution, a combination of alginate polymers with high and low molecular weights was used [12].

Alginates have gained major acceptance in the pharmaceutical and dermatology sectors for their utilization in scaffolds, controlled drug delivery, wound healing, and biocompatibility [13,14] (natural disintegration, gel formation, and non-toxicity, respectively) illustrated in Fig. 1A. Alginates, a type of natural material, possess several advantages over synthetic polymers, including the ability to form hydrogels, cost-effectiveness, and ease of accessibility. In addition, alginate gels can be orally administered subcutaneously (Fig. 1B), allowing for a vast array of pharmaceutical applications. As potential biomaterials for tissue engineering and cell transplantation, alginate gels can substitute organs or tissues in patients who have failed or are lost [10].

2.2. Drug delivery properties of alginate-based nanoparticles

The anticancer efficacy of these NPs is highly dependent on their diverse physical properties, such as particle size, zeta potential, surface functionalization, crosslinking density, and drug-loading capacity, as discussed in the table below. These factors are important in the design of nanoparticle-based DDSs with improved bioavailability, stability, and therapeutic activity. Alginate NPs are ideal candidates for polysaccharide-based NPs utilized for various biomedical applications. Alginate NPs are of special interest because of their excellent biocompatibility, low cytotoxicity, and good biodegradability, which make them ideal for drug delivery, tissue engineering, and wound healing. Alginate NPs can be crosslinked ionically with divalent cations such as calcium (Ca^{2+}), which is advantageous over other polysaccharides used in NP design, such as agarose and collagen, to improve integrity and control release properties [15].

Alginate NPs possess another interesting feature that has the potential to be utilized for therapeutic purposes and can interact with immune cells. For instance, it has been demonstrated that in calcium alginate hydrogels, pro-inflammatory cytokines, such as IL-1β, are upregulated (compared to agarose and collagen-based materials) and a more robust immune response is observed. This property is especially useful in in vaccine delivery and cancer immunotherapy, where controlled immune activation is advantageous. Alginate NPs provide a more conducive microenvironment for encapsulated cells, allowing for better retention of cell viability and function than certain polysaccharide-based materials [16].

According to a study by Si et al. [17], by displaying advantages over free melittin, the potential use of alginate NPs, especially SAMNs, as a targeted therapy for ovarian cancer, is highly promising. Melittin (M), a bee venom-derived cytotoxic peptide with potent anticancer activity, exhibits severe off-target effects and is unstable in its free form. Enhanced stability reduced nonspecific toxicity, and targeted delivery of melittin to ovarian cancer cells (SKOV3) were achieved by encapsulation with alginate NPs. A significant advancement of this study was that alginate lyase degrades alginate and triggers a controlled, dose-dependent release of melittin. This regulated release improves therapeutic efficiency and reduces damage to normal cells.

Alginate microparticles simultaneously loaded with disulfiram (an off-label anticancer agent) and SPIOs were created in this study using an electrospray system. The study revealed that these disc-shaped particles exhibited high drug encapsulation efficiency (98.89 %) and promoted dual-function therapy through chemotherapy and magnetically

induced hyperthermia. The in vivo study indicated that disulfiram/SPIO/alginate microparticles resulted in a 55.9 % tumor volume reduction compared to the free form disulfiram treatment group (48.2 %) as well as cisplatin administration based on some parameters. In addition, the magnetic SPIOs could be activated externally, generating localized hyperthermia (approximately 42–45 °C), which worked synergistically to improve anticancer efficacy, but at lower dosages of disulfiram, thus reducing their systemic toxicity. In vitro and in vivo evaluations demonstrated that these alginate carriers effectively targeted ovarian cancer cells with limited off-target effects [18] (Table 1). The optimization of these properties is important for drug delivery, as they control the pharmacokinetics and therapeutic efficacy of alginate NPs.

In addition to above mentioned properties, the mucoadhesive properties and injectability of these nanostructures render them highly suitable for target-specific drug delivery applications. Considerable research has been devoted to the use of alginate microspheres and NPs in the oral delivery of nutraceuticals and pharmaceuticals. Oral administration continues to be the preferred method of drug delivery owing to its cost-effectiveness, noninvasive nature, and convenience. Nevertheless, transportation of bioactive and labile pharmaceuticals into the gastrointestinal (GI) tract is complicated by enzymatic barriers and extreme pH conditions [21]. Alginate-based micro/NPs offer a potentially effective strategy for safeguarding encapsulated cargo and attaining controlled release kinetics that are specifically designed for gastrointestinal transit. ABNPs have been the subject of extensive research on oral drug delivery. Manatunga et al. [22] used a co-precipitation method to produce ABNPs loaded with curcumin. Sustained release of curcumin from the NPs was observed in in vitro analyses, in contrast to free curcumin. When encapsulated curcumin was administered orally to rodents, its bioavailability increased by a factor of five compared with that of unbound curcumin. This study highlights the capacity of ABNPs to augment the bioavailability of pharmaceuticals with low solubility, such as curcumin. Selenium was incorporated into alginate microspheres by Cavalu et al. [23] via a process involving ionotropic gelation and crosslinking. The in vitro release profiles of selenium in simulated gastric fluid were found to be negligible, whereas the release was sustained in the intestinal fluid. These findings suggest that the use of alginate microspheres for targeted intestinal delivery is feasible. Furthermore, the safety and effectiveness of selenium-loaded microspheres as dietary selenium supplements have been demonstrated by oral administration in rodents. ABNPs have been used to deliver chemotherapeutic agents in a targeted manner. Curcumin-loaded NPs were synthesized by Saralkar and Dash [24] via emulsification and crosslinking. The cytotoxicity and cellular absorption of the NPs against prostate cancer cells were significantly enhanced. Zhang et al. [25] utilized freeze-drying to produce ABNPs loaded with 5-fluorouracil. Drug toxicity in rodents was diminished, and colon-specific drug release was observed. For combination drug delivery, alginate nanoformulations have been the subject of numerous investigations. Song et al. [26] utilized co-precipitation to generate ABNPs loaded with curcumin. Sustained release and enhanced cytotoxicity were observed in NPs when applied to breast cancer cells [27,28]. Alginate nanogels loaded with 5-fluorouracil were produced by Hosseinifar et al. [29] via emulsification and crosslinking. The nanogels exhibited a high degree of cytotoxicity towards colon cancer cells, rapid cellular absorption, and colon-specific drug release.

2.3. Methods of preparing alginate-based nanoparticles

Several preparation methods have been utilized to produce ABNPs, including controlled gelation with Ca2+ ions, the generation of polyionic complexes via ionotropic gelation facilitated by intermolecular interactions, spray drying, self-assembly techniques, electrospinning/electro-spraying, thermally induced phase separation, and microfluidic-assisted polyelectrolyte complexation.

2.3.1. Ionic gelation and emulsification

One of the most conventional techniques for generating ABNPs is ionic gelation [30]. The process begins with the ascertainment of an aqueous resolution of alginate, a polysaccharide extracted from seaweed, and an admixture of the divalent cation CaCl2. Calcium ions, which are positively charged, interact with negatively charged alginate polymer chains to create a gel network, which in turn results in the development of ABNPs. The proportions and characteristics of the particles may be systematically influenced by tweaking solution parameters, such as alginate and calcium ion concentrations, biocompatibility, pH, and temperature. Another common method for creating ABNPs is emulsification. An organic solvent such as ethyl acetate or dichloromethane dissolves alginate to create a homogenous solution. This solution was emulsified in an aqueous phase comprising a surfactant, causing the generation and dissemination of alginate droplets throughout the aqueous phase. Emulsification/gelation is the process by which emulsion particles form an oil-phase-dispersed alginate solution gel [31]. This method is generally straight forward and economical compared with nozzle-based approaches. The two main stages of this procedure are creating an alginate-in-oil (w/o) emulsion and gelling alginate emulsion particles using a covalent or ionic crosslinker. Internal and external gelation are the two standard procedures. To facilitate external gelation, crosslinkers such as CaCl2 diffuse from the exterior phase into the interior core of the alginate emulsion particles. They reacted expeditiously with the carboxylic groups of L-guluronic acid at that location. The customary procedure following the crosslinker-induced gelation of alginate emulsion particles (Fig. 2A and B) was to demix the emulsion. Emulsification and external gelation generate micro/nanospheres characterized by a rigid outer matrix and flexible interior.

However, the internal gelation method is predicated on the discharge of cations from the central area of particles comprising the alginate emulsion. Prior to emulsification, alginate is fundamentally combined with a water-insoluble calcium salt such as CaCO3 [32]. When the solubility of the calcium source was increased and/or the pH of the emulsion was reduced from 7.5 to 6.5, alginate gelation was initiated. As shown in Eqs. (1), (2), calcium ion migration from the interior to the exterior of the particles commences at this pH. In contrast to external gelation, internal gelation yields symmetrical micro/nanospheres characterized by substantial pore size and diminished matrix density [33].

The solvent evaporation method is another prevalent technique in which hydrophobic drugs and polymers are dissolved in a volatile organic solvent using this method. An emulsion (o/w) is generated through the addition of an organic solution (oil phase) to an aqueous solution of a surfactant such as ethyl acetate, dichloromethane, or chloroform. This process was performed using ultrasonication or rapid homogenization.

Subsequently, the organic solvent was evaporated using either a high temperature, reduced pressure, or continuous stirring. Following the removal of surplus solvent, the NPs were gathered via ultracentrifugation; any remaining drug and surfactant were subsequently eliminated via rinsing with distilled water (Fig. 2B1) [34]. Zein NPs were synthesized through the solvent evaporation method in a study by Dai et al. using Pickering emulsions of zein and PGA. The ethanol was evaporated using a rotary evaporator, and the resulting solid zein-PGA NPs were freeze-dried for three days. Initially, PGA was combined with an ethanolic zein solution at mass ratios of 1:1, 5:1, 10:1, 20:1, and 40:1. The results indicated that the nanoparticle size was considerably reduced at a 10:1 mass ratio. Additionally, sample stability was improved by a higher PGA concentration because of the strong electrostatic repulsion between particles, which facilitated the production of stable Pickering emulsions [35]. However, the process of encapsulating hydrophilic molecules, including vaccine antigens, peptides, and proteins, generally employs the double emulsion (w/o/w) method. This process entails the continuous churning of an oil phase containing a polymer and volatile solvent with an aqueous drug phase, with the objective of generating a stable emulsion (w/o). A double emulsion (w/o/w) was formed when the resulting emulsion was subsequently transferred to the aqueous phase of the surfactant under the same conditions, as shown in Fig. 2B [36].

Calcium-loaded alginate NPs can influence cell functions by altering calcium homeostasis. The secondary messenger calcium is involved in cell signaling, apoptosis, and inflammation. Excessive calcium release from alginate NPs may induce oxidative stress, mitochondrial dysfunction, and immune activation, which can cause cytotoxicity, but also provide an avenue for promoting targeted cancer therapy [16]. As per the study of Bai et al. (2022), calcium can induce mitochondrial dysfunction, oxidative stress, and cell death (“calcicoptosis”), that is applicable for cancer therapy. However, this is still consistent with the concept of disrupting intracellular calcium homeostasis using calcium from Ca-Alg NPs, leading to cytotoxic effects. Chan & Mooney (2013) demonstrated that Ca2+ released from calcium alginate gels influence immunological cells through IL-1β secretion and dendritic cell maturation. Their studies confirmed that calcium in alginate NPs is not biochemically inert and can elicit cellular responses, including immune activation and inflammation [15].

Although ABNPs show promising potential for drug delivery and cancer treatment, several technical issues remain. Batch-to-batch variability continues to be a significant concern, particularly for ionic gelation methods, owing to their sensitivity to solution parameters including alginate and calcium ion concentrations, pH, and temperature [21]. Minor changes in these factors can cause variability in the particle size, shape, and drug encapsulation efficiency, contributing to the irreproducibility of therapeutic results. Alginate NPs, particularly those prepared through an external gelation pathway, exhibit a hard outer shell and softer inner core, which can induce swelling, burst release, or gelatinization under physiological conditions. While internal gelation methods provide more uniform structures with larger pore sizes, they may compromise matrix integrity over time to an even greater extent [19].

2.3.2. Layer-by-layer

LBL is a bottom-up coating technique that generates a core-shell system from which the film is formed by employing construction layers of micrometric or nanometric thickness. By exploiting the electrostatic interactions between oppositely charged polyelectrolytes, this method permits the alternating adsorption of anionic and cationic multilayer polymers onto planar substrates. Furthermore, this methodology facilitates the integration of the drug between the layers, thereby enhancing the efficiency of encapsulation and the ability to regulate drug release according to the physicochemical characteristics of the polymeric carrier employed [33]. The LBL process is susceptible to several variables, including the type of matrix and core employed, pH of the medium, saturation adsorption time, polyelectrolyte concentration, adsorption temperature, and salt concentration of the polyelectrolyte solutions [37]. One predominant method for producing micro-and NPs is spray drying, in which a liquid is atomized into droplets and subsequently dried using hot gas. Percy obtained the first patent in 1872 for a spray-drying method that had been improved in terms of efficiency and safety. The spray-drying process to produce NPs relies on the elimination of moisture from moist droplets that are sprayed through the utilization of a heated atmosphere. The operation of a spray dryer involves four essential processes: (i) dispersing, emulsifying, or dissolving the drug in the solvent; (ii) atomizing the solution to create a spray via a specialized nozzle; (iii) utilizing drying gas to dry the sprayed droplets; and (iv) gathering the completed product. Dehydrating gas was introduced into the chamber via an air dispenser located in the upper portion of the chamber. The feed solution was atomized within the dehydrating gas chamber by maintaining a constant flow rate and appropriate temperature [38]. Within this chamber, moisture vaporization was utilized to dry the moist fine droplets. An electrostatic particle collector is utilized to gather dry particles by imbuing the particle surface with charge and deflecting it with an electric field. The collector consisted of a rounded stainless-steel tube linked to a high-voltage source (anode) and a grounded star electrode (cathode) within the tube. Finally, an outlet filter was applied to the exhaust gas to capture free particles.

2.3.3. Electrospray method

The electrospray method is highly advantageous for producing micro-and NPs, owing to its user-friendly one-step procedure, particle size control, low solvent consumption, and yield regulation. The utilization of this method is thriving in both academic and industrial sectors because of its capacity to generate monodisperse droplets ranging in size from nanometers to hundreds of micrometers, contingent upon processing parameters. Numerous scientists have effectively utilized this methodology to encapsulate macromolecular bioactive substances including nucleic acids, proteins, and cells. The liquid was initially pumped at a constant rate through a thin metal needle using a syringe pump. Subsequently, a substantial voltage was supplied to the needle to enhance the velocity of the liquid as it escaped from the needle and surmounted the droplet surface tension. Subsequently, the droplets originating from the needle tip undergo transformation into a spray of nano/micro-scale dimensions, culminating in the formation of a cone known as the Taylor cone (Fig. 2C) [39]. The regulation of the final particle size can be achieved through the manipulation of formulation parameters, including crosslinkers, surfactants, and material concentration, as well as processing parameters, including flow rate, voltage, needle size, and the distance between the needle and collector's surface. This method offers numerous benefits, including the

ability to obtain a high yield of NPs from small input materials, thereby preventing the waste of costly substances, as well as a single continuous one-step process [40].

2.3.4. Electrospinning

Electrospinning is a straightforward method for extracting ultrafine fibers from a polymer solution or melt by using electric fields to generate nanofibers. Achieving precise control over the properties of the formed fibers, including their shape, size, and porosity, has garnered significant interest in tissue engineering, industrial sectors, and regenerative medicine. Furthermore, nanofibers have been applied in DDSs to facilitate the transportation of antibiotics, proteins, DNA, RNA, growth factors, and living cells. This is because of their exceptional surface-to-volume ratio and capacity to regulate the loading and release profiles of drugs. Standard electrospinning equipment involves a collector, high-voltage power supply, and syringe pump that are spaced apart by a specified distance [41]. The electrospinning process is commonly regarded as an offshoot of the electrospray method, as shown in Fig. 2D. The primary distinction between the two methods lies in the polymer concentration. Electrospinning can achieve a more stable jet using a high concentration of polymer, whereas elongation occurs via a whipping instability mechanism. The morphology and diameter of the electrospun nanofibers are notably affected by a number of critical parameters, including the needle diameter, flow rate, solvent volatility, and applied voltage [42].

2.4. Comparative analysis of different methods for alginate based nanoparticles synthesis

There are several different approaches to making ABNPs, as stated above, yet each has its own benefits and disadvantages. From the existing literature, Table 2 provides a comparative analysis of the most common methods of ABNPs synthesis and their applications.

2.5. Factors affecting performance of sodium alginate based nanoparticles

2.5.1. Polymer concentration

The viscosity of the solution varies with the concentration of sodium alginate and leads to changes in nanoparticle size and drug loading efficiency. Generally, higher concentrations yield bigger NPs owing to immersive intermolecular interactions, which can improve drug encapsulation. In contrast, much lower grades lead to smaller NPs, which may have a lower drug-loading efficiency. The use of appropriate polymer concentrations modulates the nanoparticle dimensions and prolongs the drug release timeline [49].

2.5.2. Crosslinking agent type and concentration

$CaCl_2$, which forms ionic bridges with alginate carboxyl groups (thereby enhancing the stability of the NPs), is the most frequently used crosslinker. The rigidity of the NPs and the kinetics of the released drug were highly sensitive to $CaCl_2$ concentrations. It was shown that crosslinker concentrations can yield compact NPs with slower drug release activity, but excessive crosslinking can cause aggregation/instability. Alternatively, oxide crosslinkers, such as barium chloride or zinc sulfate, can be utilized based on specific requirements for drug delivery [50].

2.5.3. pH of the solution

Changing the pH of the medium influences the ionization property of alginate, which directly impacts the properties of drug loading and controlled release of particles. Alginate is negatively charged and promotes stable interactions with crosslinkers at neutral and basic pH. Under acidic conditions, protonation of carboxyl groups decreases crosslinking efficiency, contributing to the weakness of the nanoparticle structure. pH-sensitive drug release can be used for targeted delivery owing to different physiological settings, such as the gastric and intestinal regions [51].

2.5.4. Stirring speed and homogenization

The temperature influences the viscosity of the algae solution and the formation kinetics of NPs. Higher temperatures can reduce the viscosity of the solution, resulting in smaller NPs, whereas lower temperatures can increase the particle size. Ensuring the stability of both the polymer and drug prevents any loss of therapeutic capabilities when stored. Various parameters, such as polymer concentration, crosslinker type, pH, stirring speed, and temperature, have a profound influence on the performance of sodium alginate NPs in drug delivery. SA-NPs can improve drug stability and bioavailability and enable controlled release by optimizing these parameters; thus, they can be a novel tool for improved and targeted drug delivery [52].

2.5.5. Degradation kinetics and long-term safety

Several factors, including molecular weight, crosslinking density, pH, and enzymatic activity, determine the degradation kinetics of sodium alginate NPs. Under physiological conditions, sodium alginate NPs are slowly degraded through hydrolysis and enzymatic cleavage (mainly by alginate lyases), resulting in controlled drug release over time [17]. The rate of decomposition can be adjusted by varying the level of crosslinking or introducing further stabilizing agents. The long-term safety of sodium alginate NPs is an important concern for their clinical application. Therapies with low toxicity and low immune response are due to the hydrophilic nature and natural origin of these therapies. In vivo studies demonstrated the safety and biocompatibility of sodium alginate NPs through low major organ bioaccumulation (e.g., the liver and kidney). They are mostly eliminated by renal clearance and biodegraded to nic-toxic oligomers. However, the safety profile of NPs is dependent on formulation parameters such as nanoparticle size, surface charge, and drug loading efficiency [53].

Knowledge of the nature of ABNPs and the method of their synthesis enables the development of successful strategies for targeted drug delivery. This section describes specific strategies with the aim of enhancing the selectivity and therapeutic effectiveness against ovarian cancer cells, exploiting the multimodalities of the versatile strategy reported above.

3. Targeting strategies for ovarian cancer therapy

3.1. Targeting mechanisms for drug delivery to ovarian cancer cells

Ovarian cancer is a challenging subject for therapy because the disease is too aggressive and, unfortunately, is detected at later stages in most cases. Therefore, targeted mechanisms of drug delivery have become a promising strategy to achieve better outcomes due to the minimization of off-target effects and improved specificity and

efficiency. Drug delivery strategies that target cancer can be classified into three categories: active targeting, stimulus-responsive release, and passive targeting (Fig. 3). Passive targeting, also referred to as the enhanced permeability and retention (EPR) effect, enables the targeted distribution of nano-sized carriers at high concentrations within the tumor, facilitating their more efficient uptake by cells. Active targeting is the process by which DDSs are conjugated with ligand-receptor, antigen-antibody, or other forms of molecular recognition to transport substances to cells, tissues, or organs. Stimulus-responsive DDSs typically undergo a phase transition when cancer cells are exposed to changes in their microenvironment, including temperature, pH, or particular ions [54]. Drug release can be initiated by external non-invasive physical triggering signals, including light, heat, ultrasound, and magnetic fields. Once drug carriers accumulate passively within tumors, stimuli-responsive release and active targeting processes initiate [55]. This passive accumulation is typically accomplished by nano-sized carriers through the EPR effect. As a result, nanoscale DDSs are frequently used in cancer-targeted therapy [56]. The former category is predicated on the enhanced permeability and retention effect that arises from the suppression of lymphatic drainage and the enlargement of permeable vasculature [56].

The use of NPs is crucial because of their size and characteristics, which allow them to accumulate in living tissues, specifically in tumors. Current studies have used NPs 100–200 nm in diameter to ensure targeted and optimal accumulation of the substance in ovarian tumors with permeable vasculature for regulated release [57]. Targeted drug delivery has potential, but the current field of ovarian cancer treatment still has some challenges, as the specificity of targeting is significantly limited due to extensive tumor heterogeneity because different parts of the tumor have different drug uptake and response. There are several types of ovarian cancer, such as clear cell carcinoma and high-grade serous carcinoma, which create a challenge for drug targeting approaches. The response to treatment and the effectiveness of targeted therapy is currently individual and depends on the unique characteristics of the tumor, including genetic mutations and resistance to drugs, which dictates the necessity of specific and individual approaches to therapy. Recent advances in targeted therapy have focused on the development of DDSs based on nanostructures, that is, polymeric NPs and liposomes [56]. The use of liposomes is critical because they are lipid colloidal vesicles used to enhance the solubility, stability, and bioavailability of hydrophobic drugs by incorporating encapsulation. The functionalization of nanostructures with molecules, which are ligands to tumor cells, makes them more specific to malignant cells and minimizes off-target effects. Likewise, polymeric NPs enable the encapsulation of the drug substance and regularize the release of the drug, maintain passive release, and prolong the probability of drug exposure to the targeted living tissue. These NPs use a certain biomarker to boost targeted delivery and diagnostic accuracy. In the work of Ding et al. [58], CA-125 biomarker detection was performed using graphene nanosensors to enable label-free detection after polyaniline surface precipitation and conjugation with anti-CA 125 antibodies. The developed nanosensor was the most sensitive detector for CA-125, with a detection limit of 0.92 ng/uL. Aptamer-nanoparticle conjugates target the inhibitor of apoptosis protein survivin (Baculoviral IAP Repeat-5), which then prevents survivin activity and inhibits tumor proliferation [59]. The use of nanotechnology allows scientists

to propose new systems and modes of drug delivery to overcome the above-mentioned challenges of treatment in the field of ovarian cancer [60].

3.2. Ligand-mediated targeting using alginate-based nanoparticles

Alginates, which have been introduced as polymers featuring an abundance of free hydroxyl and carboxyl groups dispersed along the backbone of the chain, are amenable to modification with ligands or specific functional groups to acquire cancer-targeting properties. By leveraging the benefits of biodegradability, biocompatibility, and non-toxicity associated with alginate-based systems, it is possible to implement photothermal, photodynamic, and chemodynamic cancer therapies in addition to targeted and site-specific anticancer drug delivery [61]. The researchers employed a hybrid pre-gel and co-precipitation method to produce core-shell nanostructures in their investigation. Alginate forms the exterior of these nanostructures, which are encased in inorganic Fe3O4 nanomaterials (core). The outer surface was attached to cell-targeting ligands (d-galactosamine). The nanosystem, which exhibited enhanced cellular uptake, validated exceptional hyperthermic efficacy against human hepatocellular carcinoma (HepG2) cell lines; thus, it offers the possibility of employing DDSs that are specifically designed for in vivo targeted cancer therapy. To augment the therapeutic potential of nanosystems targeting cancer, the surface of graphene oxide-based platforms was surface-modified using natural peptide protamine sulfate and sodium alginate via the LBL self-assembly.

DOX-loaded nanocomposites showed a significant drug release profile that was sensitive to pH. They exhibited enhanced stability and dispersibility at physiological pH levels, which are favorable attributes for targeted cancer therapy. The advancement of core-shell phytosterol-Alg NPs (FPA NPs) is mediated by folate for the targeted intracellular delivery of anticancer agents [5]. Folate, being a ligand specific to cancer, enables the specialized targeting of cancer cells that overexpress the folate receptor. Dialysis was used to insert DOX into the FPA NPs with an encapsulation proficiency of 75 %. Additionally, the viability of KB cells was assessed to be 52.4 % when free folate (500 mg/l) was present, but declined to 20.2 % when it was absent. It was hypothesized that free folate molecules could inhibit the cellular assimilation of DOX/FPA NPs by competitively binding to folate receptors located on KB cells. The folate-receptor-mediated endocytosis mechanism has been identified using CLSM as a potential means for the internalization of FPA NPs by KB cells [51]. As a result, it has the potential to serve as a nanocarrier for drug delivery, given its ability to inhibit the proliferation of KB cells and its lack of cytotoxicity compared to empty FPA NPs [62]. FA is a ligand with specific affinity for folate receptors, which are significantly upregulated in colorectal malignancies. Sodium alginate is NH2-linked to NPs, which are subsequently transported to the colon via a pH-sensitive hydrogel [63]. Numerous biopolymer DDSs employ FA as a ligand to achieve specificity against malignancy. Research utilizing alginate/chitosan and FA systems is particularly attractive because of the simplified conjugation of FA and comparatively reduced expense.

ASGPR receptor-based targeting is predominantly localized in hepatocytes and employs clathrin-mediated endocytosis to facilitate internalization. It demonstrates a notable preference for carbohydrates, particularly galactose, N-glucose and

acetylgalactosamine [64]. ASGPR in hepatoma cells can bind specifically to ligands containing N-acetylgalactosamine and β-D-galactose residues; therefore, galactosyl moieties have the potential to be employed as functionalization agents in hepatocyte-targeted delivery systems. Galactosylated alginate-based carriers are anticipated to facilitate ASGPR-mediated endocytosis-mediated uptake of therapeutic agents by hepatocellular carcinoma cells. On the other hand, the EGFR tyrosine kinase family comprises the HER1, HER2, HER3, and HER4 proteins. In general, these proteins activate an intricate network of signal transduction pathways that regulate cellular processes such as proliferation, differentiation, adhesion, and apoptosis. Significant disparities in the quantity of receptor molecules present on the surfaces of malignant and healthy cells result from the high expression levels observed in numerous epithelial tumors. Diverse mechanisms induce aberrant EGFR activation, which is linked to the formation of numerous types of tumors [65]. Cisplatin-alginate conjugate (CS) liposomes that were EGF-modified to deliver them specifically to EGFR-positive ovarian cancer cells were developed. Hence, alginate-based platforms modified with EGFR ligands have the potential to selectively target tumors that express EGFR through receptor-mediated endocytosis, thereby enhancing the effectiveness of anticancer agents. Receptor-based biotin-targeting biotin, also known as vitamin H, exhibits tumor-targeting properties because of the upregulation of its receptors in numerous types of cancerous cells, including those found in the ovary, colon, lungs, kidney, and breast. In contrast, expression of the biotin receptor is infrequent in healthy cells, and biotin is a vital micronutrient; expeditiously proliferating malignant cells necessitate additional biotin receptors to fulfil their biotin uptake demands [66]. Table 3 summarizes the different ligands, along with their specific carrier-utilizing cancers.

3.3. Passive targeting mechanisms and their role in improving drug accumulation in tumors

Passive targeting mechanisms are based on the principle of increasing drug accumulation in tumor tissues and are a versatile approach, as they utilize the unique features of the tumor microenvironment. This method is centered on the enhanced permeability and retention effect, which is observed in a variety of malignancies owing to defective lymphatic drainage and leaky vasculature. NPs preferentially accumulate in tumor tissues after systemic administration by exploiting vascular abnormalities caused by their size and surface characteristics [77]. The EPR effect allows NPs to extravasate into the tumor interstitium from leaky blood vessels and prevents their removal via lymphatic drainage. NPsAs a result, NPs remain within the tumor microenvironment for extended periods. Additional factors NPs, such as size, shape, and surface alteration, affect the extravasation and penetration of NPs into tumor tissues. The ability to target NPs passively, leveraging their physical qualities and limiting them to tumor tropism, allows for higher concentrations of drugs to be delivered to malignant lesions [78].

Passive targeting involves the delivery of medications into the tumor mesenchyme or cells via the interstices of the tumor capillary apertures via passive diffusion or convection. This mechanism is illustrated in Fig. 3. Convection refers to the migration of molecules within a fluid. When the net filtration rate reached zero, convection emerged as the predominant mode of transport for most macromolecules passing through the vascular pore spaces. Conversely, oxygen and other low-molecular-weight compounds

are transported primarily through diffusion. The process by which molecules are conveyed across the cell membrane in the absence of cellular energy expenditure is characterized by diffusion, as indicated by the concentration gradient. Nevertheless, due to the restricted convection across the tumor mesenchyme induced by heightened interstitial pressure, diffusion has emerged as the predominant method of drug delivery. As a physiological phenomenon exclusive to solid tumors, the passive strategy consists of particle-mediated EPR effects with a wavelength of <150 nm. This phenomenon is distinguished by the increased permeability of capillaries encircling solid tumors in comparison to healthy tissues, as well as the lack of functional lymphatic vessels. This physiological process facilitates the transportation of NPs (approximately 250 nm in size) from the blood to the tumor site via passive diffusion or convection through the capillary pores of the tumor [79]. Over time, NPs accumulate in the tumor tissues and progressively infiltrate the tumor mesenchyme and intracellular compartments. The theoretical underpinning of the passive localization of nanodrugs in diverse tumors has been established by this phenomenon. Numerous studies have demonstrated that the traditional EPR effect is applicable to rapidly proliferating solid tumors [80]. Table 4 provides a summary of the components of passively targeting DDSs, which include metal oxide NPs, silicon dioxide NPs, and polymeric NPs. This methodology not only improves the therapeutic value of drugs but also reduces their systemic adverse effects. Therefore, there is an impending need to revolutionize cancer treatment as well as the practice of personalized medicine within the realm of oncology.

The focus of the targeted delivery strategies summarized above highlights the importance of selectively delivering therapeutic agents to ovarian cancer cells, thereby improving specificity and reducing off-target systemic toxicity. Exploiting these strategies, the next section critically appraises recent progress and experimental findings in the context of the effectiveness and safety of alginate nanoparticle formulations that are important for clinical translation.

4. Current progress in alginate-based nanoparticles for ovarian cancer therapy

4.1. Evaluation of efficacy and safety profiles of alginate nanoparticle formulations

ABNPs exhibited comparable effectiveness to NPs composed of chitosan and starch. The ability of ABNPs to target tumors and enhance cellular absorption is noteworthy. Alginate microspheres, which are generated via ionic gelation or spray drying, can deliver medications orally, while protecting the colon. It has been suggested that oxaliplatin-enriched ABNPs encapsulated with folate-conjugated HA could enhance the antitumor and apoptotic activity of the drug in colorectal cancer cells compared to the free drug formulation [92].

Alginates have applications in microencapsulation to regulate drug release in the context of cancer therapy. This study illustrates how a system composed of alginates can improve the targeting capabilities, bioavailability, pharmacokinetic profile, and bio-clearance of the active ingredient while maintaining a low toxicity profile and high efficacy. Alginate-based nanogels have been shown to enhance the apoptosis-inducing and cell-growth-inhibiting properties of Artemisia ciniformis extract in comparison to the free extract. As stated in, the use of alginate microbeads loaded with peppermint oil potentially augments drug delivery while ensuring the absence of adverse effects. According to this

study, it is also possible to achieve sustained release of DOX in the form of alginate-based nanohybrids with a pH-sensitive encapsulation efficacy of approximately 80 %. Theophylline was also administered under control through the development of calcium-ion-crosslinked alginate microspheres [80]. Selenium was incorporated into alginate microspheres via a process involving ionotropic gelation and crosslinking. The in vitro release profiles of selenium in simulated gastric fluid were found to be negligible, whereas the release was sustained in the intestinal fluid. These findings suggest that the use of alginate microspheres for targeted intestinal delivery is feasible. The safety and efficacy of selenium-loaded microspheres as dietary selenium supplements have been demonstrated by oral administration in rodents. Lai et al. [21] used solution casting after mechanically merging alginate and chitosan to produce films laden with curcumin. The composite films exhibited significant dose-dependent anticancer properties against oral cancer cells in vitro, suggesting that the curcumin release was sustained. Mucoadhesion testing confirmed that the porcine oral mucosa adhered optimally for 30–36 min under simulated salivary conditions. This demonstrates the potential of these films for use in the treatment of lesions and tumors via localized oral medication delivery. Additional in vivo evaluation is necessary to determine the safety and therapeutic efficacy of these composite films [93]. Although numerous studies on their safety and toxicity have been conducted, alginate microparticles and NPs have been deemed safe. As an illustration, the utilization of ABNPs as a nontoxic vehicle for administering miltefosine (MFS) to treat candidiasis and cryptococcosis was examined. The toxicity of the ABNPs generated via external emulsification/gelation was evaluated in red blood cells and Galleria mellonella larvae. The presence of MFS in ABNPs did not induce hemolysis or toxicity in G. mellonella larvae. The results of this study indicated that drug-delivery systems based on alginate can effectively regulate fungal infections in an in vivo model of G. mellonella without causing toxicity. The improved effectiveness and safety of sodium alginate in drug or protein delivery systems are illustrated by modifications in the physicochemical properties of drugs or proteins [94].

4.2. Comparison with other nanoparticle-based drug delivery systems

To enhance ovarian cancer therapeutic outcomes, comparisons between ABNPs and other nanoparticle-based DDSs are necessary. ABNPs, composed of an alginate polymer matrix, are biocompatible with tunable characteristics, and therefore have potential for targeted drug delivery. Folate receptor-targeted ABNPs offer a tailored approach for the treatment of ovarian cancer. Conversely, other nanoparticle-based DDSs are composed of various polymers or materials with unique characteristics. Folate receptor targeted or HER2 targeted these nanoparticle systems offer specific drug delivery to ovarian cancer cells. In addition, ABNPs offer moderate to high drug loading capacity; other nanoparticle DDSs offer variability in drug loading capacity depending on the polymer material, size, and formulation method [95]. Physiochemical characteristics such as size, surface charge, stability, controlled release, cellular uptake, and clinical translation of these nanoparticle DDSs vary between formulations. Table 5 provides a few important comparisons based on specific characteristics.

Although the therapeutic efficacy and safety of alginate-based NPs have been recently shown in ovarian cancer models, the biomedical application of these NPs may not be limited to their use as carriers. The next section further discusses the wider applications

of these NPs in imaging, diagnosis, and theranostics, along with their multifunctionality in contemporary oncological applications.

5. Biomedical applications of alginate-based nanoparticles

5.1. Applications in imaging, diagnosis, and theranostic

ABNPs exhibit efficacy as contrast agents across various imaging modalities such as MRI, CT, and ultrasound. The possibility of encapsulating contrast agents, such as gadolinium for MRI and gold for CT in alginate NPs can improve contrast in the images and allow for clear detection of pathological lesions and tissues [102]. Encapsulating gadolinium in alginate NPs has great potential to increase the signal intensity in MRI, thus enabling the imaging of anatomical structures with more distinctive and intricate images. According to the study of Do et al. [103], studied biomedical applications facilitated by Fe3O4/Cur@ALG NPs, which exhibit minimal acute toxicity towards rodents. However, it is necessary to ascertain its long-term impact on the structure and function of the liver. Fe3O4/Cur@ALG NPs have also been utilized for MRI and cancer treatment in in vitro and in vivo models [104]. By working in conjunction with chemotherapy and thermal therapy, these NPs can improve the MRI contrast, eliminate cancer cells, and impede tumor growth, as illustrated in Fig. 4.

Gold NPs added to alginate-based contrast agents in CT enhance X-ray attenuation; hence, they have a similar contribution to tissue boundary demarcation. ABNPs can be engineered to target specific tissues or sites of disease. In the diagnostic application of ABNPs, these are important for targeted delivery of diagnostic agents. The surface of NPs is modified using targeting ligand enzymes that can be specific, such as antibodies or peptides, and allow the NPs to attach only to disease biomarkers. This approach allows the diagnosis to be highly sensitive and specific [105]. One application of ABNPs is conjugation with a fluorescent dye and attachment to the cancer biomarker, which permits the identification and early diagnosis of malignant lesions. These NPs can be used as vehicles because of their biocompatibility and biodegradability. Interest in ABNPs has grown significantly as a possible mechanism for theranostic applications. These applications allow for the combination of therapy and diagnostics into a single framework. There has been a significant advance in the real-time monitoring of therapeutic delivery and response by fusing imaging agents and therapeutic agents in the same nanoparticle. Therefore, it is particularly important to develop a personalized approach to improve treatment outcomes. For example, alginate NPs loaded with fluorescent imaging agents and the chemotherapy drug Pearl can be administered to cancer patients. Hence, after this treatment, MR or fluorescence imaging can show drug deposits in tumors, and the effectiveness of therapy can be assessed. The modification of alginate NPs enables the design of NPs that can only enter the desired site. This improves the therapeutic efficacy of the NPs and leads to better patient outcomes [105].

5.2. Potential for combination therapy

A considerable number of patients experience chemotherapy relapse because of the development of drug resistance. Multiple mechanisms contribute to drug resistance, including drug efflux, mutation or loss of drug targets, drug inactivation through detoxification or compartmentalization, DNA repair, inhibition of cell death, and modification of apoptotic pathways. Angiogenesis and tumor heterogeneity are two

additional factors that should be considered [106]. It has been observed that ovarian cancer cells can develop resistance to numerous drugs such as paclitaxel, carboplatin, and cisplatin [107]. The potential for an enhanced curative effect exists when chemotherapy and immunotherapy are combined owing to their respective capabilities: immunotherapy can counterbalance the transient immunosuppression induced by chemotherapy and prevent immunological degradation; chemotherapy can stimulate anticancer immunity and produce antigenic molecules; and immunotherapy can prevent immunological degradation. Nevertheless, immunotherapeutic agents encounter the same challenges as chemotherapy, including instability, immune-related adverse effects, and ineffective drug delivery. Moreover, in addition to the combination of PDT and chemotherapy, it has been demonstrated that chemotherapy combined with ultrasound or tumor-treating fields can enhance the prognosis of ovarian cancer treatment [108]. Baghbani et al. [52] provided evidence that the use of ultrasound irradiation in conjunction with DOX and curcumin-loaded alginate/perfluorohexane nanodroplets resulted in cytotoxicity and rapid enhancement of drug internalization in DOX-resistant A2780/DOX ovarian cancer cells compared to the non-sonicated group. The findings of an in vivo investigation indicated that co-loading curcumin and DOX into nanodroplets completely eradicated DOX-resistant A2780/DOX ovarian tumors. In contrast, the non-ultrasound irradiation group experienced only partial inhibition of tumor growth. By combining these medications with NPs for the treatment of ovarian cancer, several obstacles can be circumvented. By incorporating pharmaceuticals into NPs, toxicity can be reduced and solubility can be enhanced. Sequential drug delivery can be facilitated by controlled drug release from NPs, allowing for greater pharmacokinetic control. Levit et al. [106] conducted a comprehensive analysis of solid lipid polymer-based platforms, micelles, dendrimers, and polymer-based NPs (as illustrated in Fig. 5A) that are utilized in conjunction with platinum or taxanes to deliver drugs simultaneously or sequentially to ovarian cancer. Our focus was on quantitatively assessing the impact of nanoparticle formulations on drug synergy [106]. Combination therapy offers numerous benefits, such as the ability to decrease drug dosage to minimize toxicity, obstruct cancer activity by targeting multiple molecular targets, and surmount drug resistance mechanisms (Fig. 5B and C) [106]. At present, the prevailing approach entails the utilization of a two-drug combination therapy consisting of paclitaxel and platinum agents. Certain therapeutic approaches have transitioned to employing platinum agents with reduced toxicity, such as carboplatin, in lieu of cisplatin.

Ovarian cancer, classified into histological subtypes, high-grade serous (HGSOC), low-grade serous (LGSOC), endometrioid, clear cell, and mucinous carcinomas, has diverse molecular features and therapeutic responses. High-grade serous ovarian cancer (HGSOC) is the most common subtype (approximately 70 %) and is often associated with mutations in BRCA1/2 and homologous recombination repair deficiency. These tumors are highly sensitive to PARP inhibitors (e.g., olaparib and niraparib), which act via synthetic lethality in DNA-repair-deficient cells. Clinical trials have demonstrated substantial PFS benefits in patients with BRCA mutations (up to 70 % risk reduction in the progression of disease in the PAOLA-1 trial) [109].

Low-grade serous ovarian cancer (LGSOC) is also chemoresistant and commonly harbors mutations in KRAS or BRAF. Nonetheless, it is sensitive to MEK inhibitors (e.g.,

trametinib), with a known 26 % response rate and longer median PFS compared than chemotherapy (GOG-281 trial). Endometrioid and clear cell subtypes associated with PIK3CA, ARID1A, and mismatch repair deficiencies are likely candidates for PI3K/AKT/mTOR and immune checkpoint inhibitors. The merged results show small advantages, especially in mismatched restore deficient tumors. Mucinous ovarian cancers, which are often resistant to platinum-based therapy and carry HER2 amplification, have demonstrated potential sensitivity to HER2-targeted agents, including trastuzumab; however, data are limited [110].

5.3. Clinical studies

Si et al. [17] reported a novel approach for treating a highly lethal gynecologic malignancy that is often diagnosed at late stages and is resistant to conventional therapies. Melittin, an oncotoxin from bee venom, has demonstrated antitumor activity, but is constrained by its inherent instability and off-target cytotoxicity. To address these issues, the present study constructed SiO2–alginate–melittin nano-conjugates (SAMNs) that include alginate lyase to promote the sustained release of melittin but minimize its side effects. In this study, we synthesized SAMNs and investigated their effects on SKOV3 ovarian cancer cells using viability, invasion and migration assays, and mitochondrial function tests. The results revealed that SAMNs dramatically inhibited cancer cell proliferation, invasion, and migration, and reduced mitochondrial damage compared to free melittin. Moreover, alginate lyase mediates the controlled release of melittin to minimize off-target cytotoxicity. Our study shows that SAMNs can be a general nanoparticle-based delivery system that can enhance therapeutic efficacy while reducing the side effects of melittin, which is an important strategy for ovarian cancer therapy. Alginate-based systems induce reactive oxygen species (ROS) production downstream of cancer cell apoptosis and promote chemodynamic therapy. Although significant progress has been made, issues such as stability, scale-up, and clinical translation remain. Further studies are required for novel DDSs, synthesis optimization, and clinical validation to ensure the safety and efficacy of cancer therapies [51].

6. Clinical translation and regulatory challenges

Although ABNPs can be beneficial for targeted therapy in ovarian cancer, the regulatory and translational challenges are large. These can be generally classified into formulation consistency, safety and toxicity, scalability, and clinical validation. Nanoparticle formulations must be characterized more comprehensively and reproducibly to meet the expectations of regulatory agencies, including the FDA and EMA. As alginates are derived from different sources (e.g., M/G ratio, molecular weight, and degree of acetylation), their biochemical properties can alter the stability, drug-release kinetics, and targeting efficiency of ABNPs. If batch-to-batch consistency is not achieved, then regulatory approval cannot be achieved. Alginate is considered biocompatible overall; however, contaminants (e.g., endotoxins, proteins, and heavy metals) gained during extraction from brown algae or bacterial sources may cause inconsistent immunogenic reactions. Preclinical toxicology studies under GLP conditions, including long-term biodistribution, clearance, and systemic toxicity, are required by relevant regulatory bodies. Alginate-based systems are often susceptible to standard sterilization techniques (e.g., autoclaving and gamma irradiation), which can modify the structure of NPs and the integrity of the drug payload. Regulatory prescriptions require sterile, stable formulations

with defined shelf-lives and thus present a significant formulation challenge for ABNPs [58,111].

Alginate NPs can certainly be functionalized for targeted delivery, but their in vivo performance is often limited by biological barriers, such as the mononuclear phagocyte system (MPS), renal clearance, and variability in the enhanced permeability and retention (EPR) effect in human tumors. Adding complexity to this is the need to overcome these issues with a clinical grade targeting ligands and surface modifications. Owing to limitations in predictive validity, the current in vitro and murine models frequently used to study human ovarian tumors do not adequately recapitulate the heterogeneity and microenvironment associated with human disease. Bridging this translational gap necessitates investing in improved models that have not yet been optimized for use by regulatory agencies. Scaling up from laboratory-scale synthesis to GMP-compliant large-scale manufacturing is a non-trivial exercise. These key steps (alginate crosslinking, nanoparticle size control, and ligand conjugation) should be optimized and standardized. Establishing rigorous, reproducible processes that adhere to GMP and ICH guidelines is challenging. Targeted therapy with ABNPs requires biomarker-driven patient stratification, which indicates response. Companion diagnostics that have been validated and clearly defined endpoints are often required when approaching regulatory bodies [59,112].

7. Future research and development

Continued progress in nanotechnology, materials science, and cancer biology is likely to allow the development of ABNPs for use in the treatment of ovarian cancer. In the future, there are important areas for development and innovation that could improve both the efficacy and applicability of these NPs. A promising approach is to increase the targeting specificity. Narrow down based on more specific biomarkers of ovarian cancer might allow for the development of NPs with better targeting efficacy in the future. This could include designing the ligand to be multifunctional or engineering new molecular recognition elements, such as aptamers, which have strong binding affinity to certain cancer cell receptors. Moreover, the formulation and manufacturing processes for ABNPs must be advanced. Methods such as microfluidics and 3D printing can be used to generate NPs of consistent sizes. Furthermore, with later technologies, NP production is more scalable, and thus, clinically accessible. In addition, the coupling of ABNPs with other therapeutic strategies holds promise. The NPs might also serve as synergistic theranostics when combined with immunotherapy agents or could be incorporated into CRISPR/Cas9 gene-editing elements, which would improve the remedy effectiveness. The integration of drug delivery with diagnostic functionality (theranostics) further supports the potential of real-time assessment of therapeutic responses and disease activity.

8. Conclusion

ABNPs engineered for targeted ovarian cancer therapy offer great potential to revolutionize current therapeutic regimens into more efficient and less toxic strategies for treating this formidable disease. Late diagnosis and high relapse rates of ovarian cancer highlight the necessity for innovative therapeutic approaches that can overcome the limitations of current modalities. Alginate, a naturally derived biopolymer, has been

widely used in the design of NPs for drug delivery because of its ability to be functionalized and because it is also non-cytotoxic/immunogenic. The matrix of NPs can accommodate a broad variety of therapeutic agents (e.g., chemotherapeutics, proteins, or nucleic acids) in nanoscale compartments, providing protection from degradation and stability improvements. Sufficiently moderate drug release control and accommodation to surface functionalization allow for the direct targeting of specific cancer cells, thereby increasing therapeutic efficiency while reducing systemic toxicity. FA, antibodies, and peptides are ligands that can direct drugs from ovarian cancer cells to improve the effect of treatment on target organs and reduce side effects. Owing to their potential integration with functional DDSs, ABNPs are applicable in diagnostics and imaging. These NPs can be used simultaneously for the treatment and diagnosis of ovarian tumors, as they can detect the tumor earlier, in addition to acting as contrast agents. In summary, this study demonstrated the potential of ABNPs for ovarian cancer therapy.

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