ISSN 2959-409X

Nanoparticles in breast cancer therapy

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Abstract:

Nanoparticles have been popular as therapeutic agents for breast cancer due to their distinct properties and wide range of applications. Nanoparticles, which are extremely small and have a high surface area-to-volume ratio, have several benefits, including improved drug solubility, precise delivery to specific targets, and longer circulation in the body. Their targeted drug delivery systems minimize exposure to neighboring healthy cells, reducing potential side effects. Encapsulation of drugs within nanoparticles improves efficacy and stability while protecting them from premature metabolism and degradation. Additionally, nanoparticles facilitate combination therapy by carrying multiple therapeutic agents simultaneously, targeting different aspects of cancer progression. Lipid-based, polymer-based, inorganic, and hybrid nanoparticles are prominent types of nanoparticles utilized in clinical breast cancer treatment. Nanoparticle-based cancer therapy utilizes nanoparticles to deliver therapeutic agents directly to the tumor site, maximizing the therapeutic effect. This article provides a thorough examination of various nanoparticle varieties and their therapeutic applications in the treatment of breast cancer.

Keywords: Nanotechnology; Nanoparticles; Breast Cancer therapy.

1. Introduction

Breast cancer (B.C.) is the most diagnosed cancer in females and is one of the top three prevalent malignancies globally, along with lung and colon cancer. In 2020, B.C. has emerged as the most frequently diagnosed cancer worldwide, with a steadily rising annual death rate. Nearly seven million fatalities have been documented globally [1]. B.C. is a heterogeneous disease characterized by molecular heterogeneity. The presence of B.C. is linked to several risk factors, with age being a primary one. These risk factors include genetic and inherited predispositions, as well as obesity, physical inactivity, and alcohol use [2].

Locoregional therapy and systemic therapy are the two main types of treatment for B.C. The molecular characteristics of the cancer play an essential role in determining the most effective treatment strategy. Based on both molecular and histological evidence, B.C. can be divided into three subtypes: triple-negative breast cancer (T.N.B.C.), B.C. expressing human epidermal growth factor receptor 2 (HER2+), and B.C. expressing estrogen receptor (ER+), progesterone receptor (PR+) [3]. The hormone receptor-expressing type is the most prevalent kind of B.C., commonly observed in women who have not yet reached menopause. Although there have been notable progressions in the treatment of B.C., there are still obstacles to overcome, particularly with the emergence of drug resistance as a key issue [4]. Most advanced B.C. patients inevitably develop drug resistance due to gene mutations, amplifications, and other mechanisms, compromising treatment efficacy and resulting in disease relapse and recurrence [5]. Traditional cancer treatments, while effective, often come with substantial toxicities that can significantly impair life quality [6]. Hormone therapy often causes hot flashes, and tamoxifen is recognized as a particularly potent trigger. Aromatase inhibitors also induce joint pain, vaginal dryness, and dyspareunia. Chemotherapy, a commonly employed method, is linked to symptoms such as nausea, exhaustion, infertility, and cognitive impairment. Nanomedicine, utilizing nanoparticles, has emerged as the most encouraging strategy for targeted drug delivery in response to these obstacles [7]. Recent advancements in nanotechnology have spurred significant enhancements in the treatment of various forms of B.C., instilling renewed hope among both patients and clinicians [5]. Nanotechnology is the field of science that deals with materials and devices at the nanoscale, typically between 1 and 100 nanometers in size. Nanomedicine is the application of nanotechnology in medicine, focusing on utilizing nanoparticles for the diagnosis, prevention, detection, and treatment of diseases [8]. Nanoparticles can trigger apoptosis in cancer cells through diverse mechanisms, such as generating reactive oxygen species (R.O.S.), altering protein expression, immune system interventions,

site-specific cytotoxicity, and so on [9]. Meanwhile, to maximize therapeutic effects, nanoparticle-based cancer therapy utilizes nanoparticles as carriers to deliver therapeutic drugs directly to the tumor [10]. Nanoparticles can reduce unwanted side effects, shield the medicine from breaking down quickly, and increase the concentration of the drug in the target tissues in a drug delivery system. Various types of nanoparticles have been synthesized for drug delivery, encompassing lipid-based nanoparticles, polymer-based nanoparticles, inorganic nanoparticles, and hybrid nanoparticles, among others (Figure 1) [8]. Different types of nanoparticles used in B.C. therapy will be covered in this review, along with their potential as formidable tools and cutting-edge therapeutic interventions.

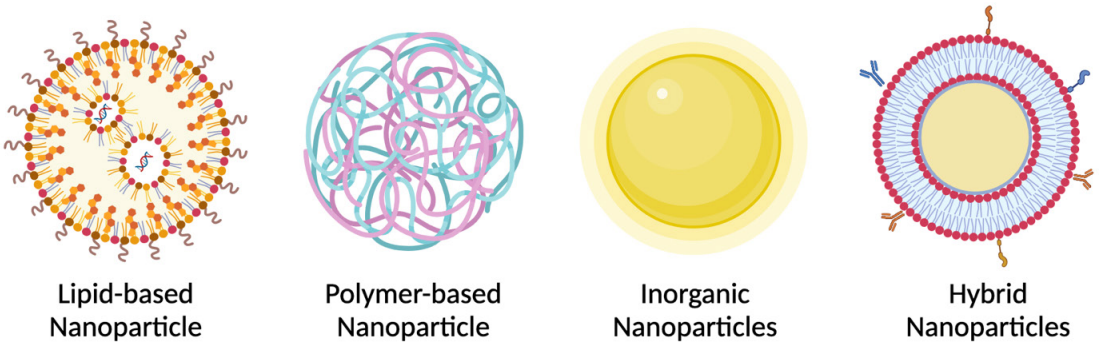

Figure 1. The structures of different types of nanoparticles.

2. Lipid-based Nanoparticles

Lipid-based nanoparticles (L.B.N.P.s) have garnered significant interest as an optimal vehicle for nucleic acids due to their exceptional biocompatibility, biodegradability, and efficacy in trapping nucleic acids. The bottom-up self-assembly technique is used for fabricating lipid-based nanomedicines. There are several common categories of L.B.N.P.s used for drug delivery, which include liposomes, solid lipid nanoparticles (S.L.N.s), micelles, and nanostructured lipid carriers [11]. While liposomes and S.L.N.s may have diverse internal structures, most L.B.N.P.s have a spherical form and consist of ionizable lipids that include tertiary or quaternary amines. These lipids are used to encapsulate anionic payloads. Low-biodegradable nanoporous materials (L.B.N.P.s) have the potential to carry both water-repelling and water-attracting molecules. They are not harmful to living organisms, can increase the ability of substances to pass through barriers, and can prolong the time that drugs remain effective by releasing them in a controlled manner.

Solid lipid nanoparticles (S.L.N.s) are a notable type of L.B.N.P.s that serve as a recently developed colloidal drug delivery technology. It remains chemically unchanged in its solid state at both typical room temperature and body temperature [12]. S.L.N.s have a size range of 50 to 10000 nm and are composed of completely crystalline lipid components [11]. Due to their diminutive size, they can effortlessly circulate in the bloodstream and avoid being eliminated by macrophages. S.L.N.s provide a flexible method for delivering medications, allowing for targeted distribution and regulated release of both lipophilic and hydrophilic pharmaceuticals. They are also easy to make. S.L.N.s have been widely utilized in the field of anticancer therapy due to their capacity to enhance the absorption of oral medications, protect unstable pharmaceuticals, and minimize negative effects by accurately targeting specific areas. This enables the use of lower doses at the desired site of action [12]. The potential of solid lipid nanoparticles (S.L.N.s) in B.C. treatment rests in their capacity to surpass existing constraints in chemotherapy and multidrug resistance. This is due to their successful targeting of tumor cells, utilizing the passive targeting properties of the enhanced permeability and retention (E.P.R.) effect. The study of paclitaxel-loaded solid lipid nanoparticles (S.L.N.s) has demonstrated improved stability and consistency, highlighting their potential in B.C. therapy. Furthermore, data suggest that S.L.N.s are highly suitable for encapsulating anticancer medicines. The utilization of niclosamide-loaded solid lipid nanoparticles (S.L.N.s) has been found to promote cellular absorption and demonstrate enhanced effectiveness in treating triple-negative breast cancer (T.N.B.C.). Similarly, incorporating talazoparib into S.L.N.s has been shown to improve its therapeutic index against T.N.B.C. [13, 14].

Niosomes, which are lipid-based nanoparticles, have gained considerable interest in the field of B.C. treatment. They have led to the advancement of several delivery systems for chemicals such as gingerol, tamoxifen citrate, and lawsone [12]. A notable example is the use of niosome calcium alginate as a drug delivery vehicle for curcumin, demonstrating a unique technique with encouraging results. This novel approach in the treatment of B.C. has shown the capacity to increase cancer cell death and

trigger apoptotic effects, highlighting the potential of niosomes in fighting this disease.

3. Polymer-based Nanoparticles

Polymeric nanoparticles (PNPs) have been extensively utilized in various biomedical applications and have been developed to serve as nanocarriers for hydrophobic chemotherapeutics and hormone regulators. PNPs are colloidal particles ranging in size from 1 to 1000nm, synthesized from biodegradable and biocompatible raw materials. Various methods can be utilized for particle production, depending on the drug type intended for loading into PNPs and the specific requirements of the administration route. Generally, production methods include solvent evaporation, emulsification, reverse salting-out, and nanoprecipitation. These methods facilitate the loading of chemotherapy drugs through encapsulation or conjugation [15]. PNPs play a crucial role in the drug delivery system because they meet the targeted delivery requirement by encapsulating active compounds and delivering them to their intended site [16]. PNPs are broadly used as nanocarriers due to their good biodegradability, biocompatibility, and high drug-loading capacity. They encompass various forms, such as polymeric spheres, capsules, dendrimers, and nanohydrogels. Nanohydrogels exhibit higher strength and elasticity compared to traditional PNPs, especially in the field of cancer theranostics. Nanohydrogels, characterized by their cross-linked hydrophilic nanoparticles forming a polymeric network, possess the ability to retain water within the spaces between the polymer chains [17]. After removing a tumor, locoregional B.C. recurrence can be very difficult to treat, and most standard therapies used after surgery are linked to serious side effects that affect the whole body. Nanohydrogels have shown outstanding performance as an ideal platform for BC-localized therapeutic approaches [16].

In recent years, significant advancements have been made in the development of polymeric nanoparticle systems utilized in B.C. therapy techniques for precise and targeted drug delivery. Several research investigations examine the use of polymeric nanoparticle drug delivery systems to treat B.C. by loading them with chemotherapeutic medicines, phytoconstituents, or a combination of both. Recently, there has been substantial progress in the advancement of polymeric nanoparticle systems for precise and targeted drug administration in B.C. therapy techniques [18].

4. Inorganic Nanoparticles

Inorganic nanoparticles (I.N.P.s), crafted from carbon-free inorganic materials, are the most extensively produced and utilized nanoparticles in commercial applications, owing to their diminutive dimensions and high surface-to-volume ratio [19]. Nanoparticles offer numerous advantages, including non-toxicity, hydrophobicity, ease of surface functionalization, and excellent biocompatibility. I.N.P.s, which are typically made of metals or metal oxides, are a diverse group of materials that include metals (such as gold, silver, and zinc), metalloids (like silicon), semiconductors (such as quantum dots), carbon nanotubes, and oxides (like iron oxide). They have been extensively studied in the field of oncology, primarily for their potential in diagnostic and therapeutic applications [20]. Furthermore, as compared to organic nanoparticles, inorganic nanoparticles (I.N.P.s) exhibit greater stability and possess distinctive characteristics that render them superior for applications such as imaging and drug administration [19, 20].

Nanogold refers to a fluid containing gold particles that are smaller than one millimeter in size. Gold nanoparticles (AuNPs) are advantageous substitutes for conventional inorganic nanoparticles employed in drug delivery and chemotherapy owing to their non-reactivity, minimal toxicity, chemical durability, favorable optical characteristics, convenient synthesis, and surface modification capabilities [19]. Surface-functionalized AuNPs, when utilized, exploit their inert gold core to enhance drug accumulation and overcome treatment resistance in malignancies. AuNPs have exceptional properties for photodynamic therapy (PDT) in cancer therapies due to their surface plasmon resonance (S.P.R.) characteristics and high photothermal conversion efficiency [21]. AuNPs are able to efficiently transform light energy from the near-infrared region (NIR) into heat energy through electron-phonon and phonon-phonon interactions. As a result, they can effectively cause localized cell damage. This was shown by exposing antibody-conjugated nanoparticles to shorter laser pulses, which presents a hopeful approach for eradicating cancer cells [22]. Near-infrared (NIR) lasers and gold nanoparticles (AuNPs) have been shown to be effective in thermal therapy for B.C. cell lines.

Photodynamic therapy (PDT) involves the administration of photosensitizers, either locally or systemically, followed by the targeted exposure of tissues to light of a specified wavelength that is appropriate for the photosensitizers. This method effectively avoids the buildup of photosensitizers in the nuclei, hence eliminating the potential for cancer formation [23]. A commonly employed approach to enhance the anticancer effects is the combination of chemotherapy with photodynamic treatment (PDT). Photodynamic therapy (PDT) employs light, a photosensitizer, and molecular oxygen to trigger cellular apoptosis. Upon exposure to light of a suitable wavelength, the photosensitizer undergoes excitation and generates reactive oxygen

species (R.O.S.) [24]. PDT functions as an adjuvant to enhance the effects of other therapies, enabling targeted and localized destruction of tumors and the blood vessels around them. This procedure depends on the activation of a harmless photosensitizer using appropriate light in order to eradicate cancer cells efficiently.

5. Hybrid Nanoparticles

Despite prolonged and thorough research endeavors over numerous years, the treatment of B.C. continues to pose a substantial challenge due to its diverse nature and tendency to spread to other bodily locations. Non-specific drug delivery and multidrug resistance are two interrelated problems that hinder the effectiveness of B.C. chemotherapy. To address these issues, scientists have recently concentrated on developing lipid-polymer hybrid nanoparticles (LPHNPs-DTX) that encapsulate docetaxel (D.T.X.). These nanoparticles are designed to provide controlled and prolonged drug administration, with the goal of resolving non-specific drug delivery problems in the treatment of BC [25]. The enclosing process of D.T.X. within L.P.H.N.P.s has demonstrated greater efficacy compared to its unbound state. LPHNPs-DTX exhibits heightened efficacy in the treatment of B.C. by directly suppressing the growth of cancer cells, impeding the synthesis of microtubules, and activating apoptotic pathways [25]. Furthermore, research evidence substantiates the idea that the novel L.P.H.N.P.s system improves the ability of doxorubicin (DOX) to kill cancer cells, hence overcoming resistance to several drugs in B.C. therapy. By integrating DOX with lipid and polymer components within a single nanoparticle (DOX-SLN), the medication can efficiently counteract various drug resistances in comparison to separate administration. DOX-SLN demonstrates markedly greater cytotoxicity against cell lines that overexpress P-glycoprotein in vitro, as compared to free DOX solutions. This highlights the crucial role of incorporating drug, polymer, and lipid components into nanoparticle form to promote cytotoxicity, drug uptake, and retention [26].

6. Summary

Overall, the range of nanoparticle-based drug delivery systems for B.C. treatment is varied and encouraging. Several categories of nanoparticles, such as lipid-based nanoparticles (L.B.N.P.s), polymeric nanoparticles (PNPs), and inorganic nanoparticles (I.N.P.s), are gaining recognition for their substantial potential. L.B.N.P.s, including solid lipid nanoparticles (S.L.N.s), demonstrate exceptional biocompatibility and adaptability, exhibiting potential for improving drug bioavailability and effectiveness. Polynucleotide polymers (PNPs), renowned for their ability to naturally break down and carry a large number of drugs, offer a versatile framework for delivering drugs to specific targets, especially in combination treatments to address drug resistance. Indium nanoparticles (I.N.P.s), particularly gold nanoparticles (AuNPs), possess remarkable characteristics that make them very suitable for photothermal therapy and photodynamic therapy. These capabilities offer novel strategies for targeted cancer treatment.

The emergence of hybrid nanoparticles, such as L.P.H.N.P.s, emphasizes the significance of collaborative drug delivery systems in tackling issues including indiscriminate drug administration and resistance to multiple drugs in B.C. treatment. Given the progress made in research and the growing knowledge of the tumor microenvironment and molecular pathways in B.C., there is hope for the creation of improved and focused treatments in the future. Nanoparticle-based drug delivery systems are becoming important in precision medicine, namely in tailoring treatments to particular patient subtypes. By utilizing the unique advantages of nanotechnology, B.C. treatment can be improved in terms of efficacy, specificity, and customization. In the end, this can greatly improve patient results and quality of life.

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