Review Article

Nanoparticle-Based Drug Delivery Systems for Cancer Therapy

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Received: 03-03-2025; **Revised:** 26-05-2025; **Accepted:** 08-06-2025; **Published online:** 15-06-2025.

ABSTRACT

Cancer remains one of the most significant global health challenges, with millions of new cases diagnosed annually. Conventional cancer treatments, such as chemotherapy, radiotherapy, and surgery, have limitations, including non-specific cytotoxicity and multi-drug resistance. Nanoparticle-based drug delivery systems (NPDDS) have emerged as a promising approach to overcome these challenges. This review highlights the potential of NPDDS in cancer therapy, focusing on various types of nanoparticles, including liposomes, polymeric nanoparticles, metal nanoparticles, dendrimers, and micelles. These nanoparticles can be engineered to target specific cancer cells, improving therapeutic efficacy and reducing side effects. The review also discusses the design and development of NPDDS, including targeting strategies, functionalization, and modification techniques. By leveraging the unique properties of nanoparticles, NPDDS can enhance the delivery of therapeutic molecules, improving cancer treatment outcomes. Nanoparticle-based drug delivery systems (NPDDS) have shown significant potential in cancer therapy, offering targeted and efficient delivery of therapeutic agents. Various applications of NPDDS include chemotherapy, immunotherapy, targeted therapy, gene therapy, and combination therapy. Despite the benefits, challenges such as toxicity, clinical translation, and off-target effects need to be addressed.

Keywords: Nanoparticles, Cancer Therapy, Targeted Therapy, Drug Delivery Systems, chemotherapy.

1. INTRODUCTION

Cancer is a condition that results in an abnormality in the cell's structure as a result of genetic changes. It is one of the most common causes of death worldwide [1]. Cancer remained one of the most significant global health challenges, with millions of new cases diagnosed annually. Despite considerable progress in oncology, conventional treatment modalities, chemotherapy, radiotherapy and surgery, continue to dominate clinical practice [2].

The United States alone is expected to see 610,000 cancer-related deaths and about 1.7 million new cancer diagnoses in 2018. Conventional first line cancer therapies consist of radiation, chemotherapy, surgery, or a mix of these. All of these therapies have disadvantages in cases of severe disease; relapses can lower the 5-year survival rate by more than 50%. When cancer is still in its early stages, before metastases have formed, tumour excision is most beneficial [3]. Globally, cancer is regarded as a new public health concern in the 21 century [4]. Cancer is an anomaly that arises from genetic alterations in the cell's structure. The three main approaches to cancer treatment are surgical excision, chemotherapy, and radiation [1]. Immunotherapy is becoming a cutting edge cancer treatment option. The development of immunotherapeutic regimens and combination treatments for cancer has significantly advanced thanks to drug delivery systems (DDSs). The utilization of nano, micro, and macroscale DDSs for the co-delivery of various immunostimulatory agents to rewire the immune system to fight cancer is the main topic of this thorough analysis. Additionally, our viewpoint on the advancement of next-generation cancer immunotherapy based on drug delivery system [5].

The delicate interaction between cancer and the immune system, which Daniel S. Chen and Ira Mellman dubbed the "famous cancer-immunity cycle" in 2013, should be well understood in respect to cancer immunotherapy. The importance of T-cell immunity for anticancer action is now widely recognized. The start of an anticancer T-cell immune response often consists of a sequence of sequential events. (Fig. 1) [6].

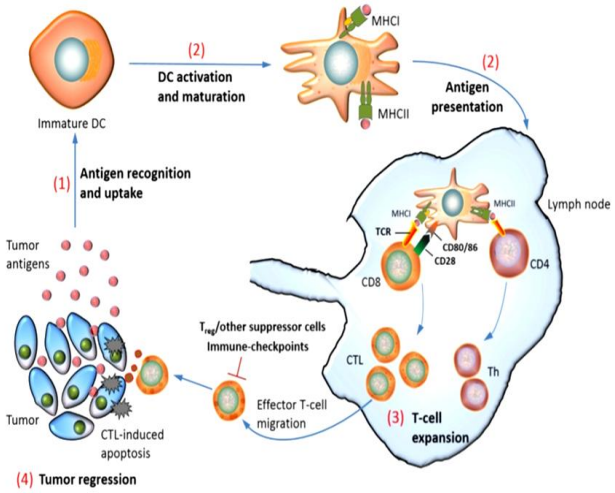

Figure 1: A schematic diagram of cancer-immunity cycle.

Generally, professional antigen-presenting cells (APCs) such as dendritic cells (DCs) recognize and uptake tumor antigens and process them, during which DCs become mature. Then, DCs present antigen fragments to T cells, stimulating T-cell immunity, and effector T cells infiltrate to tumors and kill cancer, during which immune checkpoints and regulatory T cells may down-regulate the antitumor response.

Chemotherapy side effects are very important concerns since traditional chemotherapeutic agents, e.g. small anticancer drugs, have non-specific cytotoxicity. These side effects may include severe systemic toxicity, low levels of drug uptake and also the development of multi drug resistance (MDR). MDR is the principal mechanism by which many cancers develop resistance to chemotherapy drugs. These unsatisfactory effects can also be caused by specific properties of anticancer drugs, such as low solubility, poor stability, and rapid metabolism. To overcome these drawbacks, drug delivery systems (DDS) have been designed to transport chemotherapeutic molecules to the tumor site to achieve better therapeutic efficiency (Fig. 2). Since new technological platforms have demonstrated better cancer therapy outcomes, nanotechnology is playing a bigger role in the development of DDS. The administration of numerous therapeutic agents, such as drug–drug, drug–gene, and gene–gene co-administration, is another strategy to improve cancer treatment [7].

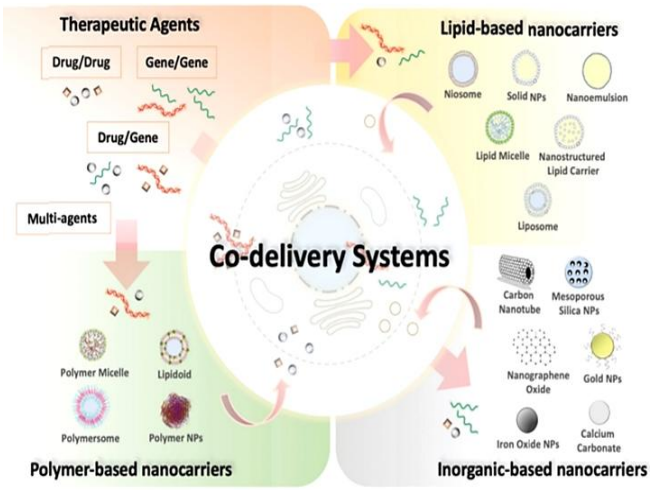

Figure 2: Schematic illustration of different inorganic, polymeric, and lipid-based nanoparticles and possible co-delivery approaches [7].

2. NANOPARTICLE-BASED DRUG DELIVERY SYSTEMS (NPDDS) FOR CANCER THERAPY

Given their distinct physical, chemical, and biological characteristics such as the small-size effect, surface effect, and quantum size effect nanoparticles which are described as nanoscale particles with diameters ranging from 1 to 100 nm are unquestionably one of the current hotspots in medical materials research. Because of their various sizes, shapes, and architectures, nanoparticles can be altered or encapsulated to enhance their targeting and biocompatibility. Their flexibility is demonstrated by the variety of designs, preparations, and applications. Nanoparticles scalability and functional benefits have shown great promise in improving medication delivery efficiency, developing diagnostic techniques, and accurately diagnosing diseases. Because of this potential, they can be used to create more specialised and efficient medical treatments [8].

3. TYPES OF CANCER

3.1. Breast cancer

Breast cancer has the highest incidence in the USA, according to the American Cancer Society. It was estimated that in 2023, approximately 298 thousand women and 3 thousand men were diagnosed with invasive breast cancer, resulting in 43,700 deaths [9]. Due to variables like weight gain after the age of 18, physical inactivity, and hormone therapy during menopause, the incidence of breast cancer in women has increased by 0.5% since 2020. Furthermore, a history of ductile carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS), high breast tissue density, inherited genetic mutations (BRCA1 or BRCA2 genes), and high-dose radiation to the chest before the age of 30 are risk factors for the development of breast cancer [10].

In figure no.3 shows that a 1 mm fiber laser with a 1 cm diffuser tip of 690 nm and 150 m W/cm power was used to irradiate the tumor. Complete tumoral necrosis resulted from a dose of 50 J.

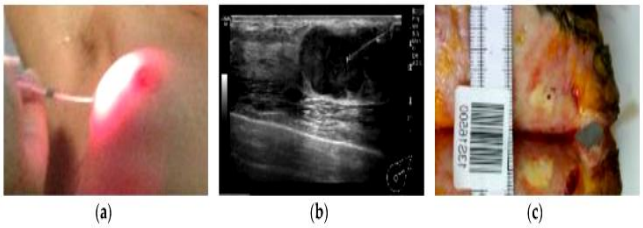

Figure 3: (a) Laser fiber inserted into the tumor (under the armpit); (b) Ultrasound image of the laser fiber into the tumor; (c) Fiber track under microscope as a uniform, pale patch of PDT-induced necrosis in the resected tissue that has been sliced perpendicular to the needle track. The bottom uniform, pale region is on the cut's opposite side [11].

3.2. Prostate cancer

These types of cancer have most common cause of cancer-related death among males worldwide. Although PDT exhibits potential as a treatment for prostate cancer, it is still classified as an experimental or investigational therapy. Scientific investigations and clinical trials are currently underway to assess the efficacy and safety of PDT. Generally, prostate cancer is managed through surgery or radiotherapy [10].

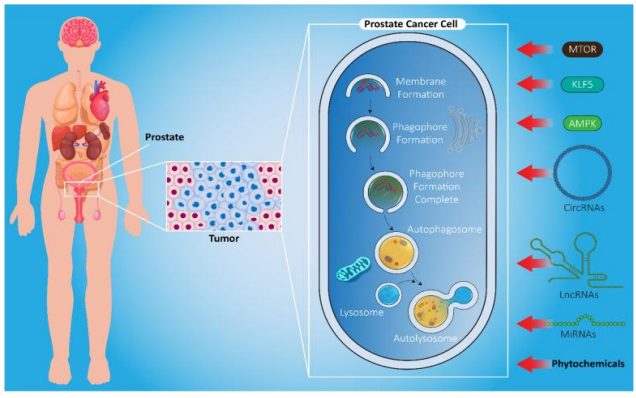

Figure 4: Diagrammatic representation of prostate cancer[12].

3.3. Skin Cancer

According to WHO estimates, 132,000 melanoma skin cancers and 2 to 3 million non-melanoma skin cancers are diagnosed globally each year. The most deadly type of skin cancer is melanoma. If it is not identified and treated very away, it is more likely to spread to other body parts. According to the American Cancer Society, there were approximately 1,06,110 new cases of melanoma and 7,180 fatalities from the disease in the United States in 2023. These skin cancers have a high cure rate and are typically less aggressive than melanoma [10].

3.4. Gynecological cancers

One of the most common gynecological cancers to be diagnosed is uterine corpus cancer. Human papillomavirus (HPV) infection is linked to this cancer, which ranks sixth among cancers diagnosed in women. Women's cervix, vulva, vagina, perineum, and anus can all be impacted by this virus [10].

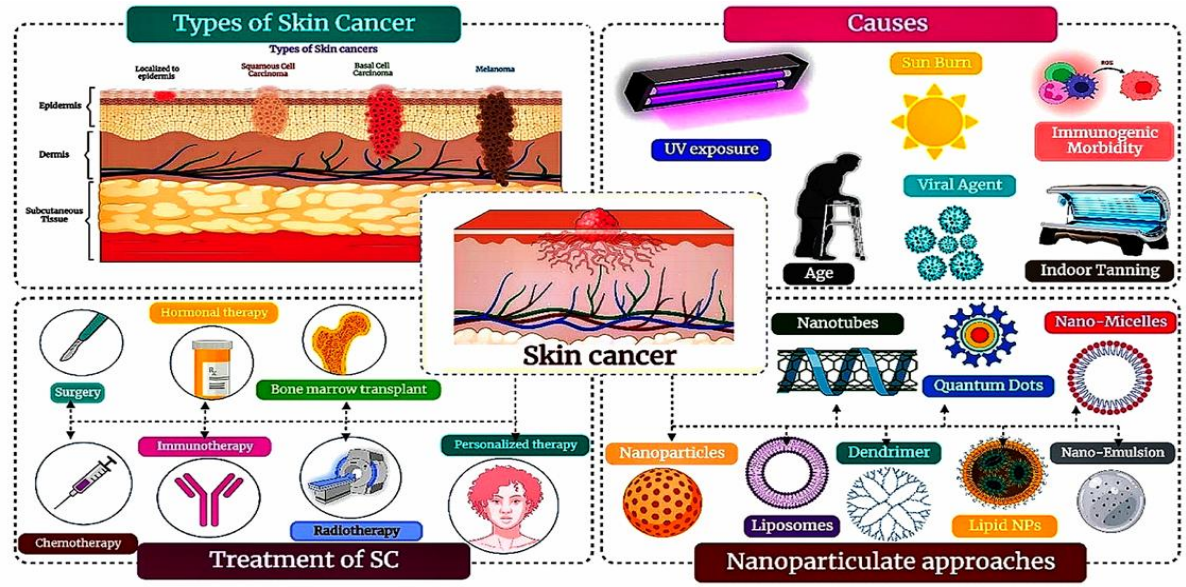

Figure 5: Diagrammatic representation of skin cancer [13].

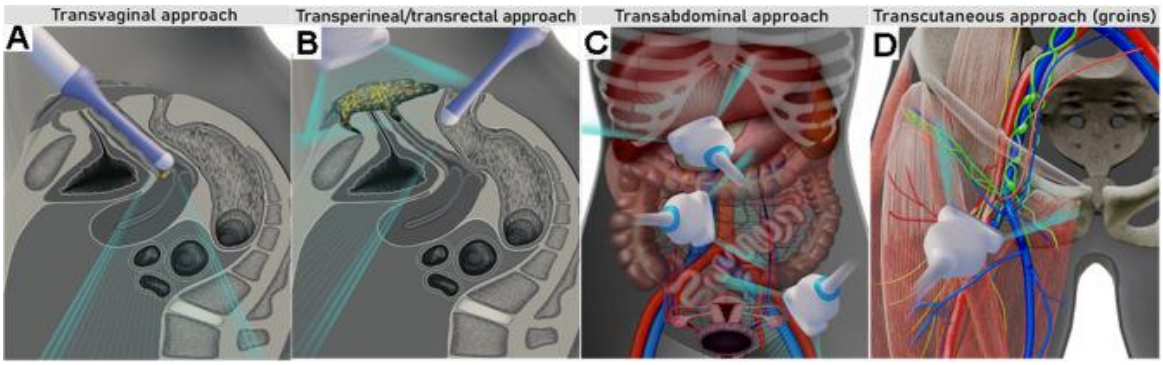

Figure 6: Ultrasound approaches for gynecological cancer staging: transvaginal (A) and transperineal in combination with transrectal (B) approach for local staging; transabdominal approach using a convex array probe for evaluation of abdominal infiltrated visceral and retroperitoneal lymph nodes, peritoneal, or parenchymal metastases (C); transcutaneous approach with linear array probe for evaluation of inguinofemoral lymph nodes (D) [14].

3.5. Head and neck cancer

About 4% of all new cancer cases are head and neck malignancies, making it the sixth most frequent malignancy worldwide [8]. To treat head and neck cancer holistically, PDT is frequently combined with other therapies including chemotherapy, radiation therapy, or surgery. It can be applied to tumors in their early stages or, in more advanced cases, as a palliative measure to alleviate symptoms [10].

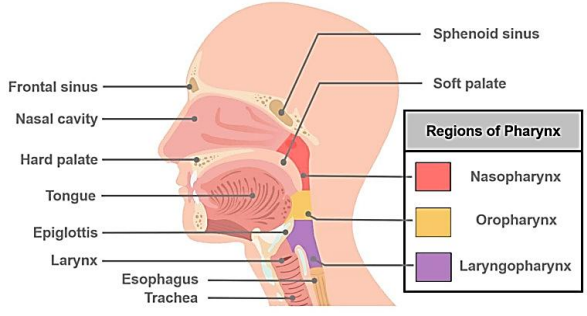

Figure 7: Schematic diagram of major sites of cancers of head and neck. Head and neck cancer (HNC) is a general

term that describes many different types of cancer and involves multiple organs and tissues within the head and neck region. HNCs generally occur in the oral cavity, oropharynx, hypopharynx, nasopharynx, larynx, and nasal cavity [15].

4. NANOPARTICLE-BASED DELIVERY SYSTEMS

4.1. liposomes

Liposomes are round sac phospholipid molecules. It encloses a water droplet especially as form artificially to carry drug into tissue membrane [16]. Liposomes provide numerous advantages as carriers, including a cell-like membrane structure, high biocompatibility, low immunogenicity, protection of the active ingredient or drug, extended half-life, reduced toxicity, increased effectiveness, and more. These carriers are essential to the efficient administration and effectiveness of treatment [17]. Liposomes are tiny vesicles of lipid that range in size from 50 to 1000 nm. Liposomes have been thoroughly researched as drug carriers, especially for cancer therapy, due to their distinct advantages over conventional drug therapy, which include their capacity to shield the drugs from degradation, target the drug to the site of action, and lessen the toxicity and side effects of such drugs. Liposomes can be divided into three groups based on their size and number of bilayers: small uni-lamellar vesicles (SUV), large uni-lamellar vesicles (LUV), and multi-lamellar vesicles (MLV) [18].

Liposomes are biocompatible and non-toxic. They are composed of a lipid outer layer enclosing an aqueous core. Both hydrophilic and lipophilic drugs can be integrated into liposomes. Liposomes are a viable option for DDS because of their special qualities. These characteristics include scalability, affordability, biocompatibility, and high drug entrapment efficiency [19].

4.2. Polymeric nanoparticles

It has been demonstrated that using polymeric nanoparticles (NPs) to transport medications is beneficial when treating cancer. These nanoparticles, which range in size from 10 to 1000 nm, are composed of biocompatible and biodegradable polymers [19]. Polymeric nanoparticles can be developed with many materials, including carbon nanotubes, lipids, polymers, and ceramics. Polymer materials, compared to other compositions, exhibit a suitable combination of features [20]. Promoting the potential of RNA delivery for cancer treatment through the use of polymeric nanoparticles [21]. Targeted vincristine delivery system and carbon dot-based imaging probe that can improve hepatocellular cancer diagnosis and treatment. A twofold emulsion process can be used to encapsulate vincristine sulphate and c-dots within biodegradable polymeric nanoparticles. According to scanning electron microscopy, spherical PCL nanoparticles were successfully produced and characterized, with a typical particle size of about 200 nm [22].

4.3. Metal nanoparticles (Gold and Silver)

Most attempts to translate drug-carrying nanoparticles for human cancer therapy have been thwarted by challenges with formulation, characterisation, and scale-up. However, nanotechnology offers the potential to improve the effectiveness and decrease off-target toxicity of small-molecule drugs used as proteotoxic stress inducers. The fundamental technologies of clinically approved nanotherapeutics have remained essentially unaltered. Metal-based nanoparticles, such as gold, silver, iron, and gadolinium, have been explored for imaging and therapeutic uses in pre-clinical cancer models, but their translation has been constrained by concerns about toxicity[23].

i) Gold nanoparticles

Gold nanoparticles (AuNP) are the most popular and have been the go for the choice in many studies. Their physicochemical characteristics, minimal cytotoxicity, enzymatic stability, and chemical resistivity are the most important ones [24]. AuNPs range in size from 1 nm to 1000 nm and are wine-red substances having antioxidant qualities. It comes in a variety of morphologies, including irregular, spherical, sub-octahedral, nanorod, nanotriangle, and more. Because of its abundance, ease of handling, ease of production, ease of modification, corrosive resistance, chemical stability, biocompatibility, etc., Au is a nonreactive chemical element that finds extensive use. Because of their small size, stability, low toxicity, optical characteristics, bioimaging, and vast surface area, AuNPs have several uses in the biomedical industry [15]. Gold nanoparticles can be used for the identification of many cancer cell types, including breast, lung, and prostate cancers [25]. Cancer cells are destroyed by the heat produced when AuNPs absorb incident photons and transform them into heat. Au-nanorods, Au-nanostars, and Au-nanocages are among the several forms of AuNPs [15].

ii) Silver nanoparticles

Silver Nanoparticles (AgNPs) are characterized as nanomaterials with dimensions ranging from 1 to 100 nm. Silver nanoparticles, or AgNPs, have been utilized across various sectors, including medicinal and consumer items, due to advancements in nanotechnology [26]. Silver nanoparticles have been used as antibacterial agents and in detectionand diagnosis platforms, tissue repair materials and personal healthcare products due to their outstanding antimicrobial and wound healing characteristics. Silver nanoparticles, however, have recently entered the area of plasmonic photothermal therapy (PTT) for cancer treatment. Their use is attributed to their higher heat conductivity compared to other metals, low toxicity, ease of synthesis, metabolic nature, and tunable SPR band. In general, silver nanoparticles used in biomedicine have a plasmon resonance of 410 nm and are spherical, which make them unsuitable for deep-penetrated PTT. However, the plasmon resonance can possibly be precisely modified to the NIR domain by creating anisotropic silver

nanoparticles like silvernanospheres, nanotriangles, and nanocages. The capability to synthesize MNPs with specific sizes and shapes using several process parameters is crucial to comprehending and predicting their characteristics and behavior under various circumstances [24].

4.4. Dendrimers

Dendrimers are a unique category of polymeric substances. Dendrimers are typically defined as monodisperse macromolecules with a highly three-dimensional structure, which imparts significant surface activity and an extensive range of functionalities [27]. There are two main methods for chemically synthesising dendrimers: divergent and convergent. The divergent technique synthesises dendrimers in a stepwise manner from an initiator core, which serves as a starting point, to the periphery. However, especially in higher generations, the many alternative techniques need long chromatographic separation and excessive monomer loading. The divergent method's shortcomings were addressed by the convergent technique. This method involves growing dendrimer surface units independently and then coupling them to the dendrimer's central core in the last stages [28]. The formation of subsequent generations will follow the same pattern, with two monomers joined to the monomer from the preceding generation. With every extra generation, the dendrimer's molecular weight almost doubles. Additionally, terminal groups can be altered to achieve a hydrophilic or lipophilic function in addition to a charged one for the intended biological and drug transport application [18].

4.5. Micelles

Micelles, magnetic micelles and drug-loaded micelles can be prepared by a solvent evaporation method [29]. Amphiphilic di-block, tri-block, or grafted co polymers self-assemble in aqueous solutions to create polymeric micelles [30]. The polymeric micelles deliver the drug payload to the cancer cells via two processes. The therapeutic agents may reach the cancer cell as free medications following their release from the micelles or be internalized as drugs encapsulated within the micelles for further release within the cell [31]. They develop spontaneously as a result of a reduction in free energy resulting from the aggregation of the hydrophobic components of the aqueous environment and the formation of a micelle core that is stabilized by hydrophilic fragments that are exposed to water [32].

5. DESIGN AND DEVELOPMENT OF NPDDS FOR CANCER THERAPY

By improving the precise delivery of therapeutic molecules for the diagnosis and treatment of cancer, nanotechnology is transforming the field of cancer treatment. Because of their special qualities, NPs are being used more and more in different cancer treatments. These have significant benefits over traditional drugs, such as better tumor targeting, increased stability, improved biocompatibility, and improved pharmacokinetics. Additionally, NPs offer a versatile platform for integrating various therapies, which can greatly improve therapy results. The efficiency of several NP types, including polymeric, metallic, and hybrid NPs, in improving drug delivery has been demonstrated by recent studies. Scientists must fully comprehend the characteristics of these nano-platforms as well as the unique qualities of the medications they carry[33].

5.1. Targeting strategies

Target infectious cells to improve therapeutic effect compared to normal cells [34]. Because of the pathophysiologic features of tumour blood vessels, the majority of nanoparticles are predicted to aggregate in tumours. When the volume of an actively growing tumour exceeds 2 mm, the delivery of nutrients becomes diffusion-limited, necessitating the development of new blood vessels to deliver oxygen and nutrients [35].

5.1.1 Passive Targeting

Chitosan Nanoparticles (CS-NPs) passively diffuse via leaky blood vessels (immature vasculature) that supply cancer tissue through a process known as passive targeting. The penetrated CS-NPs maintained in tumour tissues for prolonged periods of time due to aberrant lymphatic drainage in those tissues. The "Enhanced Permeation and Retention (EPR)" effect is the name given to this phenomenon. By adjusting different formulation ingredients and fabrication procedures, the physicochemical properties of CS-NPs, such as particle size, shape, and surface charge, can be optimised as they have a substantial impact on the EPR effect. Furthermore, because of their special properties, CS-NPs can be functionalised to increase the duration of plasma circulation and the passive penetration of chemotherapy drugs into tumour tissues [36].

It has been observed that there is an abnormally high porosity in the vasculature of cancer cells due to the excessive production of various vascular mediators and cytokines, such as bradykinin and vascular endothelial growth factor (VEGF) in cancer cells. This causes nanoparticles and macromolecular anticancer agents to preferentially accumulate more in cancer cells than normal cells and hence exert their cytotoxic effect with higher specificity. This mechanism is referred to as the EPR effect[37].

5.1.2 Active Targeting

Active targeting is the most selective strategy among the several targeting mechanisms for optimizing therapeutic efficacy while reducing off-target effects. It describes the process of delivering a diagnostic or chemotherapeutic payload to particular cells while preventing it from building up in non-target cells. This method involves conjugating CS-NPs with certain targeting ligands (such as folic acid, hyaluronic acid, transferrin, antibodies, peptides, and aptamers) to identify particular antigens or receptors (such as CD44, FA, and transferrin receptors) on cancer cells. Chemotherapeutics are more effective when ligand-functionalized NPs bind to cancer cells specifically. Because of their abundance of hydroxyl and amino groups, CS-NPs have a great deal of potential for functionalisation with

various targeting ligands to enable the selective targeting of various types [36].

Nano-conjugated hypocrellin not only benefited from passive accumulation but also surface engineering that allowed it to target cancer cells preferentially. A high degree of accuracy can be attained by incorporating certain ligands, such as small molecules, peptides, and antibodies, onto the NPs' surface. These ligands have been carefully chosen to accurately target and detect overexpressed receptors on the surface of cancer cells, allowing for precision targeting and absorption of the NPs into the malignant cells. This active targeting approach reduces off-target effects on healthy cells while optimising treatment efficacy by improving the selectivity of drug delivery to malignant areas[37].

Membrane is one of the greatest examples of NPs success in cancer treatment to yet. Membrane, the first NP medication ever approved by the US FDA, was released in 2005 and comprises nanoformulated paclitaxel in a human serum albumin (HSA) shell. Lung, pancreatic, and breast malignancies are among its indications. Additionally, compared to conventional chemotherapy techniques, NP albumin-bound paclitaxel delivers paclitaxel to tumour cells more efficiently and with fewer adverse effects, according to published research. Clinical trials demonstrated that paclitaxel nanoformulations had decreased systematic toxicity; nonetheless, these investigations frequently lacked appropriate research design [38].

5.2. Functionalization and Modification Strategies-

Customising the characteristics of ZnO-based nanomaterials for targeted oral cancer therapy requires surface functionalisation and modification. Researchers can improve ZnO nanoparticles biocompatibility, stability, dispersibility, and targeting specificity by altering their surface chemistry. This will increase the therapeutic efficacy of the particles while reducing off-target effects. This section examines the many surface functionalisation and modification techniques used to maximise ZnO nanoparticles for applications related to oral cancer [39].

1. Ligand Conjugation

2. Polymer Coating

3. Surface Charge Modification

4. Bioconjugation Techniques

5.3. Drug loading and release mechanism

In recent years, the application of nanoparticles (NPs) as drug delivery vehicles has drawn a lot of interest in the context of cancer treatment. By using passive or active targeting techniques, NPs can enhance the pharmacokinetics of hydrophobic medications that are poorly soluble and enable cancer-specific drug delivery. This can encourage the preferential accumulation of these pharmaceuticals in tumour tissues. Nanocarriers are distinguished by their high surface area and nanometric size (less than 1000 nm). For the transport of Dtx, multifunctional liposomes have been created and modified with gold nanorods (GNRs), PEG, and RLT (low-density lipoprotein receptor (LDLR)-binding peptide). These liposomes can be applied to cancer using photothermal treatment (PTT) in conjunction with chemotherapy [40]. This work will concentrate on the comprehensive properties of AuNPs in drug administration, despite their numerous applications in clinical chemistry, biosensors, genomics, and cellular-level optical bioimaging [41].

5.4. Nanoparticles size, shape and surface charge

Drug delivery methods utilizing nanoparticles have demonstrated potential for efficiently administering treatments in natural settings, such as the intricate environment of the human body. NPs face a number of physiological difficulties in this natural setting, including interactions with blood components, immunological reactions, and tissue-specific barriers [42].

i) Size

The size of NPs is one of the dominant factors that has a key role in protein adsorption, conformational changes, and PC composition, and thereby biological interactions. Typically, larger NPs exhibit a greater ability to adsorb proteins compared to their smaller counterparts due to their higher curvature suppressing protein adsorption [33]. Technology that interacts with objects nanotechnology enables objects as small as nanometres. Nanotechnology is expected to develop in a number of ways, beginning with materials, devices and systems. In terms of both commercial applications and scientific understanding, nanomaterials are currently at the most advanced stage. Nanoparticles were studied ten years ago because of their size-dependent characteristics and chemical makeup. They are currently in the process of commercial investigation [43].

ii) Shape

The size, shape, and surface characteristics of various nanoparticles, as well as their clearly unique physiochemical characteristics, impact how they are absorbed, distributed, metabolized, and removed from the human body and within cells. The absorption, distribution, metabolism, and elimination receptors are the names given to these mechanisms [44].

6. APPLICATION OF NPDDS IN CANCER THERAPY

Nanotechnology has demonstrated previously unheard-of potential in the field of cancer diagnostics as medical technology develops, particularly in the early detection and precise diagnosis of colorectal cancer. Blood tests (such as the CEA test), digital rectal examination, computed tomography (CT), magnetic resonance imaging (MRI), colonoscopy, and other conventional techniques are currently used for screening, identifying, and diagnosing colorectal cancer (CRC).

1. Capturing antigens shed from tumors following radiotherapy.

2. Designing nanoparticle-based vaccines to raise T cell responses.
3. In situ vaccination with artificial antigen presenting cells or immune depots placed near tumors. By increasing sensitivity, specificity, and the ability to detect many markers at once, nanoparticles can be used to create highly sensitive and specific biomarker detection platforms [8].

6.1. Chemotherapy

A few decades ago, the first chemotherapeutic medication to be clinically approved for melanoma was dacarbazine (DTIC; 1970s), an alkylating agent with cytostatic action. Since temozolomide, an analogue of DTIC that is approved for glioblastoma multiforme, is taken orally, enters the central nervous system, and has a favourable toxicity profile, it is frequently utilized in patients with advanced melanoma. However, because they are not selective to tumour sites and melanoma cells frequently develop resistance to alkylating agents, these drugs do not demonstrate significant therapeutic benefits and instead cause side effects [45].

6.2. Cancer Immunotherapy

By triggering the immune system to attack and destroy cancer cells, cancer immunotherapy may stop the disease from spreading and recurring. One of the most important mechanisms of action in cancer immunotherapy is the Cancer Immunity Cycle (CI cycle). Anti-PD-1 immune checkpoint drugs are also being used to treat cancers to boost the immune system's defences against mutations or viral gene expression. Even though immunotherapy techniques have advanced significantly, many patients do not benefit from these treatments [46].

T cells then identify antigens on Major Histocompatibility Complex I (MHCI) and MHCII molecules produced by dendritic cells, which triggers an antitumor T cell response and starts and activates effector T cells for a particular reaction against the neoantigens [47].

6.3. Targeted Therapy

As the pharmaceutical industry developed, targeted medicines emerged as a viable area of study. For example, all mammalian cells growth, proliferation, differentiation, migration, and survival are regulated by the mitogen-activated protein kinase/extracellular signal-related kinase (MAPK/ERK) signalling pathway [46]. Drugs are packaged into tiny particles and delivered to target cells using nanodelivery, which lessens harm to healthy cells and boosts the drug's effectiveness [48].

6.4. Gene therapy

The latter comprises gene therapy, mechanical stability devices, and tissue engineering techniques that combine autologous or allogeneic grafts and substitutes with mesenchymal stem cells [49]. According to the animal results, the mice treated with PEDF-PLGA nanoparticles appeared to have more apoptotic CT26s than the group treated with normal saline (NS). For the treatment of primary colorectal cancer, using PEDF gene and PLGA nanoparticles is a safe and efficient gene delivery method [50].

6.5. Combination therapy

Even though MSN-based human trials have started, there is still a long way to go before true therapeutic therapy is possible. To optimise and measure the advantages of combination therapy, further fundamental research on MSN–immune cell interactions is required to develop new delivery systems and actively control the immunological response [46].

7. CHALLENGES AND LIMITATIONS OF NPDDS IN CANCER THERAPY

Although epigenetic drugs show promise in cancer therapy due to their capacity to alter gene expression, safety, and off-target repercussions remain a problem. Numerous diseases and functions can be impacted by the malfunctioning of mitochondria. Some of these disorders have been linked to the emergence of mutations or deletions in mitochondrial DNA (mt-DNA) [51].

These drugs, which include EZH2 inhibitors (like tazemetostat), HDAC inhibitors (like vorinostat and romidepsin), and DNA methylation inhibitors (like azacitidine, decitabine), could unintentionally affect non-target genes or pathways, which can have adverse effects Off-target impacts may result in altered gene expression and disruption of normal cellular functions. The risks that need to be considered include haematologic toxicity (like cytoplasmic), gastrointestinal toxicity (like nausea and vomiting), neurological toxicity (like peripheral neuropathy), cardiovascular toxicity (like hypertension), and immune system impacts (like immune-related adverse effects). Careful dosing and monitoring, supportive care to limit side effects, continued research to uncover biomarkers and improve drug design, and combination techniques to boost therapeutic efficacy are all examples of mitigation methods [52].

7.1. Toxicity

Given that NPs are used in tissue repair, medication administration, food packaging, and related derivative fields, toxicity is a crucial consideration. The toxicity is influenced by the base material, and its mechanism is comparable to that of the application area. An NP's toxicity is influenced by its administration concentration, stability, bioavailability, and propensity to accumulate in a tissue or organ. The material and type of NP, as well as its size and surface characteristics, affect each of these variables. ROS (reactive oxygen species) production can cause NPs to be hazardous regardless of the substance [53]. Despite their enormous advantages, little is known about the short- and long-term health effects of nanoparticles on living things and the environment. Safety concerns have been brought up due to the nanomaterials' known toxicity and possible hazards [54].

7.2 Clinical translation

Only a few treatments are now approved for reducing the risk of cancer due to significant obstacles that have hampered the development process. One of the greatest hurdles to successful clinical translation of potential preventative medicines is a lack of pharmacodynamic biomarkers to provide an early read out of biological activity in humans and for adjusting doses to take into large scale randomised clinical trials [55]. It must be overlooked that a very small number of novel products have advanced to human usage, despite the potential for significant clinical benefits and ongoing research work in the development of oral drug delivery systems based on nanotechnology. Additionally, all oral nanomedicines used in clinical therapy today are SDNs, and their goal is to increase the rate at which poorly soluble medications dissolve [56].

7.3 Future direction

Even with significant progress in cancer treatment, most cancers still do not respond to standard treatment methods. Compared to alternative drug delivery methods, the science of employing nanoparticles as anti-cancer agents and drug resistance modulators has several benefits [57].

Experiments on a tumour model of B16F10 lung metastases demonstrated the combination's encouraging and noteworthy synergistic effects, opening the door for potential future clinical use [58]. Combining small molecule inhibitors like (Enhancer of Zeste Homolog 2) EZH2 or (Heikin Ashi Delta Candle) HDAC inhibitors with advances in clustered regularly interspaced short palindromic repeat (CRISPR) and their associated protein (Cas9)-based epigenetic editing enables precise gene and epigenetic regulation, potentially leading to treatments for genetic disorders and cancer [52]. Small medications typically target particular molecular targets that are essential for angiogenesis, metastasis, and the proliferation of cancer cells [59]. With a primary focus on Pancreatic Ductal Adenocarcinoma (PDAC), this review attempts to present a thorough examination of the current methods and potential future directions in the use of therapeutic radiopharmaceuticals for the treatment of pancreatic cancer. It also explores the changing field of radio pharmaceutical therapy, emphasising its potential advantages, drawbacks, and new developments [60].

8. ADVANCE THERAPEUTIC APPROACHES

8.1. Combination Therapies

The development of cancer and its capacity to elude immune monitoring and, consequently, anti-tumor immunity are significantly influenced by immune checkpoint proteins. Immunocheckpoint inhibitors (ICIs), such as pembrolizumab and nivolumab, have revolutionised the treatment of cancer [61].

8.2. Targeting cell

Targeted therapy refers to the specific combination of drugs with specific carcinogenic sites on cells through biological, physical or chemical means to kill cancer cells and avoid damage to normal cells, which has gradually become the mainstream method of leukemia treatment. In the treatment of leukemia, a combination of multiple drugs is usually used in order to achieve synergistic effect and improve the therapeutic effect [62]. The development of nano-vehicles that can safely and securely carry a range of genetic materials to the same target is motivated by the challenge of gene transfer [7]. By eliminating the NPs from the bloodstream, the liver and kidney offer an additional barrier for drug delivery to the target location in systemic applications of nanomedicine for the treatment of skin cancer [46].

8.3. Immune Checkpoint Inhibition

Even if a large number of medications have been approved by the FDA and entered clinical trials, there are still numerous obstacles to overcome in the fight against cancer. One of the most difficult problems is the immunosuppressive tumour microenvironment (TME), which is a significant obstacle to cancer immunity. Antigen-presenting cells (APCs) phagocytosed, processed, and presented the many cancer antigens generated during tumour progression via the major histocompatibility complex. Dendritic cells (DCs) and other APCs move to draining lymph nodes, where T cells can recognise the given antigen through their T cell receptor and start the activation process [63].

It's highly interesting to consider using immunotherapy using IC inhibitors (ICIs) to treat upper tract urothelial carcinoma (UTUC). In fact, UTUC is still a difficult tumour to treat for a number of reasons [64]. Immune checkpoints are signal pathways on the surface of T-cells that inhibit activation of T-cells and hence actively participate in immune responses. If the immunencheckpoint is activated, it suppresses the immune cells. To avoid the attack of the immune system, cancer cells generally activate immune checkpoints to inhibit the immune system from attacking them. In addition, if the activation of immune checkpoints by cancer cells is prevented, the immune system can maintain normal functions of attacking and killing cancer cells [65].

CONCLUSION

Nanoparticle-based drug delivery systems (NPDDS) have shown potential in cancer therapy by providing targeted and efficient delivery of therapeutic agents. Various types of nanoparticles, such as liposomes, polymeric nanoparticles, metal nanoparticles, dendrimers, and micelles, have shown promise in improving treatment outcomes. The design and development of NPDDS involve targeting strategies, functionalization, and modification to enhance efficacy and reduce off-target effects. Despite challenges like toxicity and clinical translation, ongoing research and advancements in NPDDS are expected to overcome these hurdles.

Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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