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A Review of Nanoparticles as Drug Delivery Systems in Cancer Therapy

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ABSTRACT: Nanoparticles have emerged as promising tools in modern medicine due to their unique physicochemical properties, including small size, large surface area, and enhanced drug-loading capacity. In cancer therapy, nanoparticle-based drug delivery systems have gained significant attention for their ability to improve the targeted delivery of anticancer agents while reducing systemic toxicity and adverse side effects associated with conventional chemotherapy. Various types of nanoparticles, such as liposomes, polymeric nanoparticles, metallic nanoparticles, and dendrimers, have been extensively investigated for their therapeutic applications. These systems can enhance drug stability, bioavailability, and controlled release, thereby increasing treatment efficiency. Despite these advantages, several challenges remain, including potential toxicity, immune responses, limited clinical translation, and high production costs. Recent advances in nanotechnology and targeted therapy continue to improve the safety and effectiveness of nanoparticle-mediated drug delivery. Overall, nanoparticle-based drug delivery systems represent a promising approach in cancer treatment and hold substantial potential for future clinical applications and personalized medicine.

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Keywords: *Nanoparticles, Drug Delivery Systems, Cancer Therapy, Nanomedicine, Targeted Drug Delivery, Anticancer Agents*

Introduction

Cancer remains one of the leading causes of morbidity and mortality worldwide, and despite decades of intensive research, substantial challenges persist in improving patient outcomes. Cancer research evaluation in the United States shows that despite decades of effort focused mainly on treatment, cancer mortality continued to rise slowly from 1950 onward. An updated analysis extending to 1994 also examines the influence of the National Cancer Act of 1971, which significantly increased research activity. Earlier interpretations were challenged on the basis that new scientific findings had not yet been fully implemented in clinical practice. Additional criticism focused on methodological issues, including the use of combined cancer data and age-adjusted mortality rates, which may mask important differences across cancer types and age groups [1].As scientific understanding has advanced, cancer is now recognized as a highly complex biological system in which tumor development and progression are driven not only by genetic alterations but also by dynamic interactions with the surrounding microenvironment. The tumor microenvironment contains various cellular and extracellular components that actively participate in tumor growth, immune regulation, angiogenesis, and metastasis. Different cell populations within this environment may either inhibit or promote cancer progression depending on tumor type, stage, and physiological conditions. Therefore, the tumor microenvironment has become an important focus in cancer research and a potential target for novel therapeutic strategies [2]. To combat this complexity, systemic chemotherapy emerged as one of the earliest and most widely used treatment modalities. Chemotherapy began in the 1940s with nitrogen mustard, whose toxic effects on the lymphatic system led to its first successful use in lymphoma. Although responses were temporary, this marked the start of modern cancer chemotherapy. Since then, many cytotoxic drugs have been developed, with increased approvals in later decades. Early agents acted mainly through DNA alkylation, followed by antimetabolites such as methotrexate and 5-fluorouracil based on advances in cellular biochemistry. The 1960s–70s introduced natural product drugs like doxorubicin and vinca alkaloids. A major breakthrough was cisplatin in the late 1970s, which significantly improved outcomes in

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several cancers, especially testicular cancer [3]. Further progress in chemotherapy demonstrated that combining agents with different mechanisms of action could significantly enhance treatment efficacy. Modern chemotherapy emerged in the 1950s with antileukemic agents such as 6-mercaptopurine, which inhibited DNA/RNA synthesis. Vinca alkaloids were later found to block cell division by interfering with microtubules. A key breakthrough in 1965 showed that combination therapy (POMP regimen) using drugs with different mechanisms could produce long-term remission in childhood ALL, establishing the principle that multi-drug regimens are more effective than single agents [4]. Despite these advances, conventional chemotherapy remains limited by poor selectivity and significant systemic toxicity, creating a strong need for more precise therapeutic approaches. Targeted drug delivery is a strategy designed to direct medications specifically to desired tissues or receptors, increasing drug concentration at the site of action while minimizing exposure to non-target tissues. This selective distribution enhances therapeutic effectiveness and reduces systemic side effects and toxicity. The approach improves the drug's therapeutic index by ensuring stronger interaction with target sites and limited interaction with healthy tissues. Overall, site-specific drug delivery is an important method for improving treatment efficiency and safety [5]. Several strategies have been developed to achieve targeted drug delivery. Although invasive methods such as direct injection or catheter-based administration can improve localization, they are often limited by cost and patient discomfort. Modern approaches instead use chemical and biological modifications or carrier systems to improve targeting. These include optimizing drug properties for better tissue penetration, using prodrugs activated at the target site, and attaching targeting ligands such as antibodies or folic acid to enhance specificity and reduce systemic toxicity [6]. Among these emerging carrier systems, nanoparticle-based drug delivery platforms have attracted considerable attention because of their ability to improve drug stability, prolong circulation time, facilitate controlled release, and enhance tumor-specific accumulation. Accordingly, this review aims to summarize current advances in nanoparticle-based drug delivery for cancer therapy, with emphasis on their role in improving targeted delivery and reducing systemic toxicity. It also highlights key challenges in clinical translation and discusses future perspectives for more effective and safer cancer treatment strategies.

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Basics of Nanoparticles in Medicine

Nanotechnology is a multidisciplinary field that integrates physics, chemistry, engineering, and biology to develop nanoscale materials and devices. It has shown great potential in improving human and veterinary health and in treating severe diseases. However, concerns remain regarding nanoparticle-related health risks, as exposure to nanoparticles may induce inflammation, oxidative stress, toxicity, apoptosis, and pulmonary disorders, while also affecting organs such as the heart, liver, and brain [9]. Nanoparticles in medicine are nanoscale materials with unique physicochemical properties that enhance their interaction with biological systems. Their small size and modifiable surfaces allow improved penetration, targeting, and controlled behavior in the body. They are widely used for sensitive disease detection and targeted drug delivery, especially in cancer therapy, reducing off-target effects. Different types, including inorganic, organic, liposomal, and hybrid nanoparticles, share the ability to be engineered for specific biomedical functions. Overall, nanoparticles provide a multifunctional platform for integrated diagnosis and therapy in modern nanomedicine [7]. Nanoparticle-based therapeutics have increased rapidly in recent decades, with liposomal drugs and polymer–drug conjugates becoming the dominant clinical nanomedicine products. Liposomes are lipid vesicles capable of carrying both hydrophilic and hydrophobic drugs, protecting them from degradation, and enabling targeted and biocompatible drug delivery [8]. Nanomaterials are widely applied in fields such as medicine, energy, agriculture, and water treatment due to their unique physicochemical properties. Their behavior differs from bulk materials mainly because of surface and quantum effects. High surface area, increased surface atom proportion, and reduced atomic coordination enhance their mechanical, optical, catalytic, magnetic, and electronic properties. In addition, quantum confinement at the nanoscale leads to size-dependent characteristics that are not observed in larger materials. These properties increase the reactivity and biomedical potential of nanomaterials, although aggregation can influence their stability and performance Nanomaterials can also be classified according to their dimensional structure, including zero-dimensional, one-dimensional, two-dimensional, and three-dimensional nanomaterials. [Figure 1] [10].

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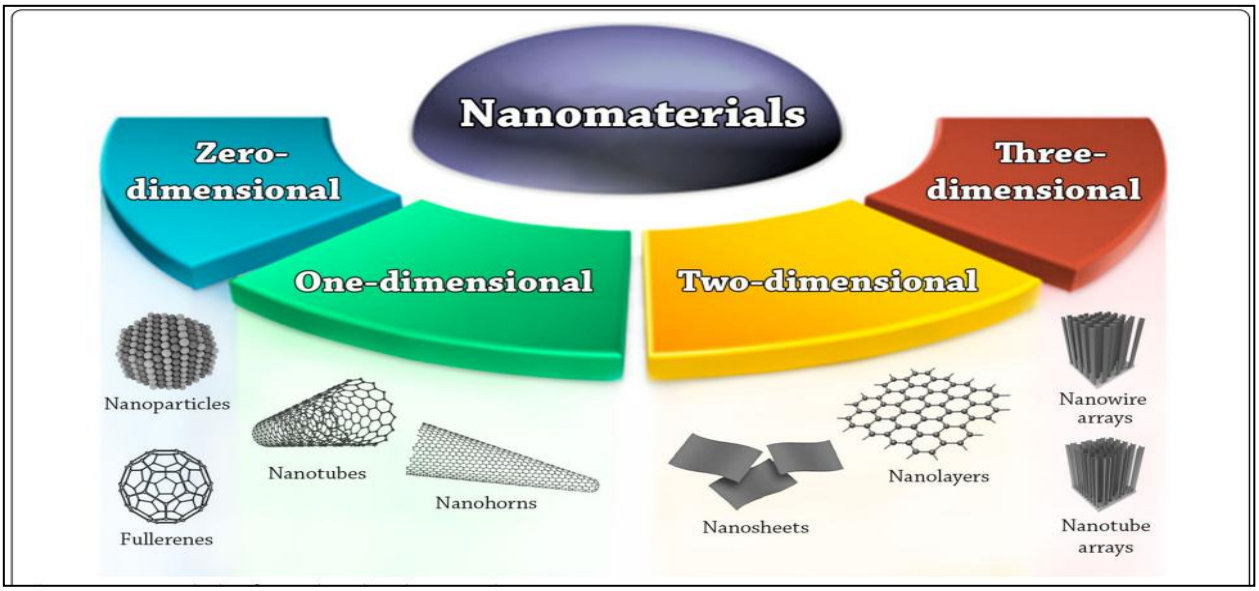

Figure 1. Classification of Nanomaterials According to Their Dimensional Structure

Particle size, surface charge, and shape are key physicochemical factors that strongly influence nanoparticle behavior in biological systems. Size determines cellular uptake and biodistribution, where smaller particles are generally favored by non-phagocytic cells, while larger particles are more efficiently taken up by macrophages. Surface charge affects interactions with cell membranes, with positively charged nanoparticles showing higher cellular internalization due to electrostatic attraction. Shape also plays a role in cellular interaction and circulation behavior, influencing uptake mechanisms and in vivo distribution. Overall, these properties are critical for optimizing nanoparticle performance in drug delivery systems [11,12]. Drug loading in nanoparticles occurs mainly through physical encapsulation, adsorption, or chemical conjugation, depending on the carrier system. In polymeric nanoparticles, drugs are entrapped within or adsorbed onto the polymer matrix, enabling controlled release. In liposomes, hydrophilic drugs are loaded into the aqueous core while lipophilic drugs are incorporated into the lipid bilayer, although stability and leakage can be limiting factors. Solid lipid nanoparticles embed drugs within a solid lipid matrix, offering improved stability and sustained release. Overall, drug loading efficiency is influenced by nanoparticle composition, drug properties, and preparation methods [Figure 2 [13,14].

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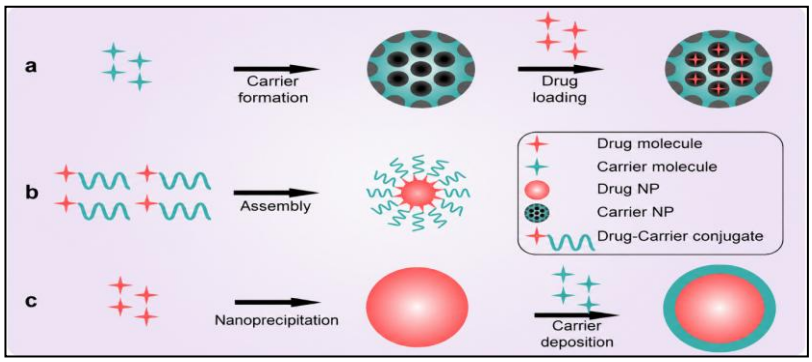

Figure 2. Three representative strategies for making high drug-loading nanoparticles. a, Post loading. b, Co-loading. c, Pre-loading.

Types of Nanoparticles Used in Cancer Therapy

Nanoparticles are nanoscale materials with sizes ranging from 1–100 nm that possess unique biological and physicochemical properties. In cancer therapy, different types of nanoparticles such as silver, gold, alloy, and metal oxide nanoparticles are widely used because of their ability to improve drug delivery, enhance targeting efficiency, and support cancer diagnosis. Silver nanoparticles exhibit strong antimicrobial and biomedical properties, while gold nanoparticles are especially important in cancer diagnostics and detection of cancer stem cells due to their excellent biocompatibility and optical characteristics. Additionally, biologically synthesized nanoparticles produced by microorganisms, fungi, algae, and plant extracts have gained significant attention because they provide eco-friendly and less toxic alternatives to chemical synthesis methods. These nanomaterials play an important role in modern oncology by increasing therapeutic effectiveness and reducing adverse effects on healthy tissues [15,16].

1. Lipid-Based Nanoparticles

Lipid-based nanoparticles are important nanocarriers widely used in cancer therapy and drug delivery systems due to their high biocompatibility, low toxicity, and ability to improve therapeutic efficiency. These systems are mainly composed of natural or synthetic lipids that self-assemble into stable nanostructures capable of encapsulating drugs, genes, or imaging agents. Among the most studied forms are liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and bolaamphiphile-based nanoparticles. Liposomes consist of phospholipid bilayers with an aqueous core and are extensively used for delivering anticancer drugs such as doxorubicin, helping to reduce side effects and

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improve targeting. Advanced formulations like PEGylated and thermosensitive liposomes allow longer circulation time and controlled drug release at tumor sites [Figure 3] [17,18].

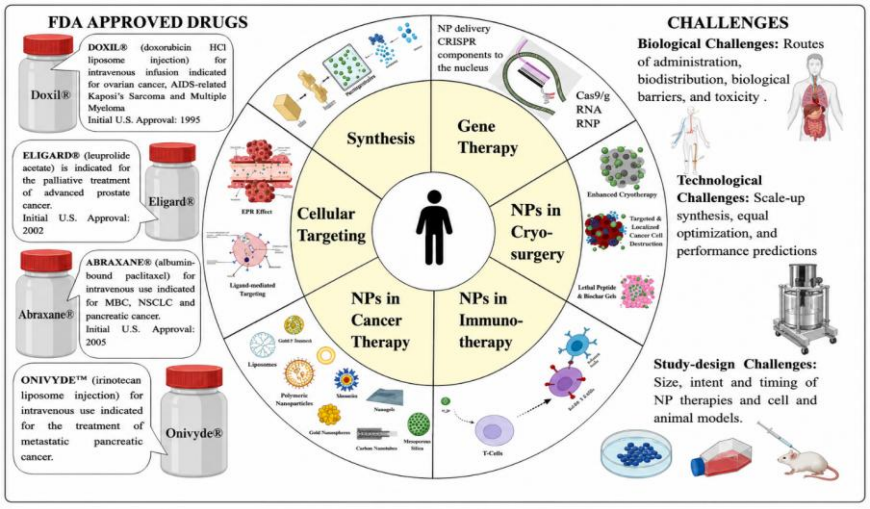

Figure 3. Schematic representation of Solid Lipid Nanoparticles (SLN) and Nanostructured Lipid Carriers (NLC)

2. Polymeric Nanoparticles

Solid lipid nanoparticles and nanostructured lipid carriers offer improved stability and higher drug-loading capacity compared to traditional systems. Overall, lipid-based nanoparticles play a key role in modern cancer therapy by enhancing drug delivery, reducing toxicity, and enabling targeted and controlled treatment strategies [Figure 4] [19]

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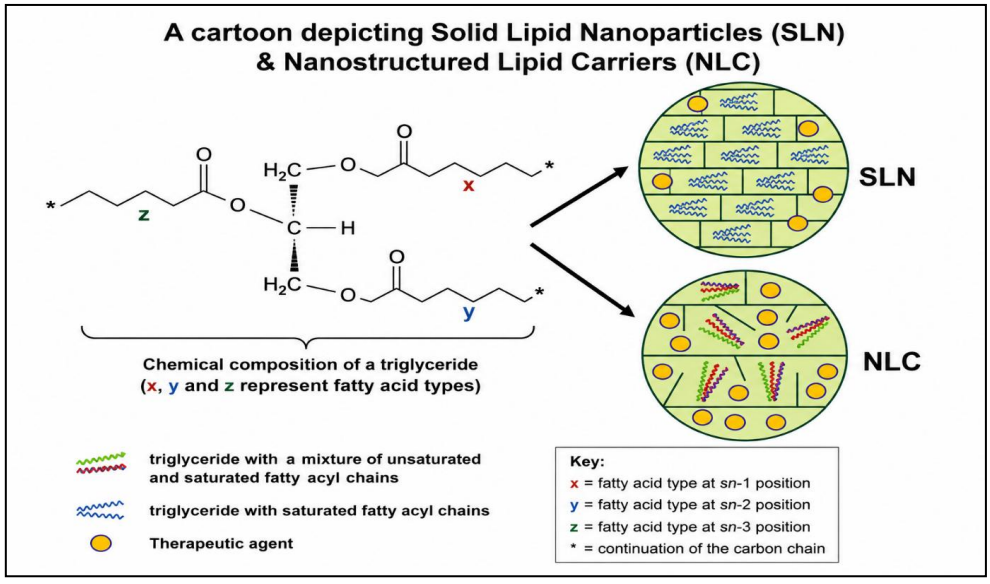

Figure 4. Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC)

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Polymeric nanoparticles (PNPs) are biodegradable and biocompatible nanocarriers (10–1000 nm) used for drug delivery. They load drugs by dissolution, encapsulation, or adsorption within a polymer matrix. They are classified into nanospheres (matrix type) and nanocapsules (core–shell type). PNPs are widely used in medicine and biotechnology to improve drug stability, bioavailability, and targeted delivery, especially in cancer therapy and controlled release systems. Common polymers include natural (chitosan, gelatin, alginate, albumin) and synthetic (PLA, PGA, PLGA, PCL, PEG, PVA) polymers. Drug release occurs via diffusion from swelling, enzymatic degradation, or desorption. Main preparation methods include solvent evaporation and nanoprecipitation, which control particle size and drug loading [Figure 5] [20,21].

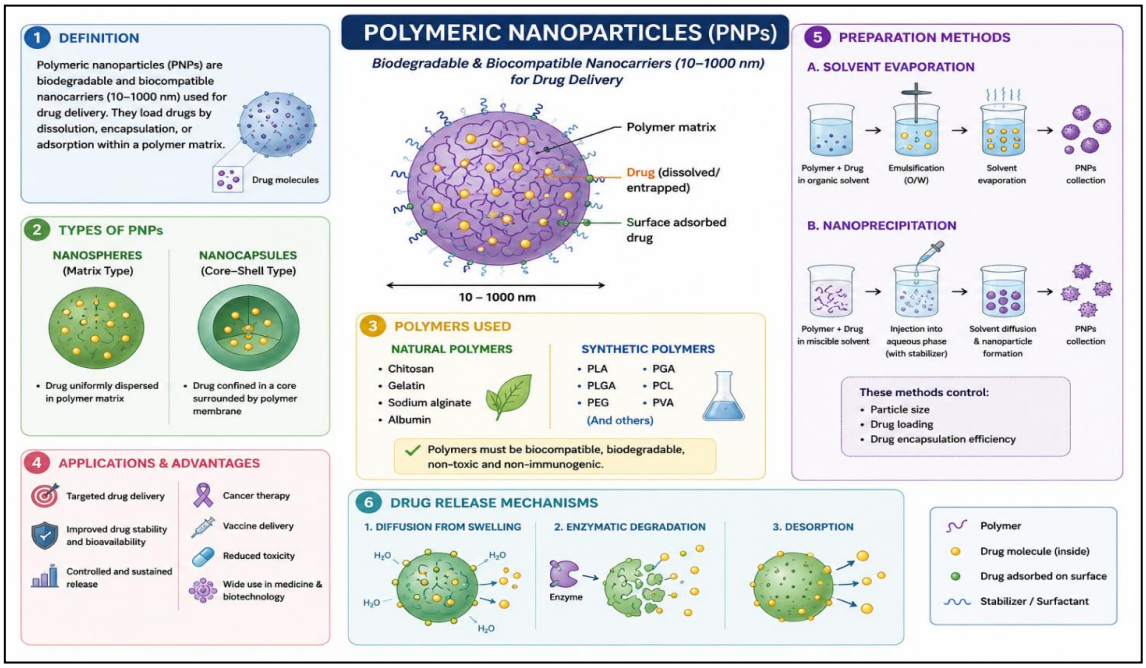

Figure 5. Schematic overview of polymeric nanoparticles (PNPs) as biodegradable drug delivery systems showing types, preparation methods, and drug release mechanisms.

3. Metallic Nanoparticles

Metallic nanoparticles are nanoscale materials (10–500 nm) with unique physicochemical properties arising from their high surface-to-volume ratio. They include iron oxide (Fe_3O_4), gold, silver nanoparticles, nano shells, and nanocages, which can be functionalized with ligands, antibodies, or drugs for biomedical use. These nanoparticles are widely applied in targeted drug and gene delivery, cancer therapy, magnetic separation, and molecular imaging [22]. They serve as contrast agents in imaging techniques such as MRI, CT, PET,

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ultrasound, optical imaging, and SERS. Among them, superparamagnetic iron oxide nanoparticles (SPIONs) are especially important in MRI due to their ability to enhance T1 and T2 relaxation contrast. Metallic nanoparticles can be synthesized using methods such as coprecipitation, microemulsion, sol–gel, hydrothermal, and thermal decomposition techniques, and their surface modification improves stability, targeting ability, and circulation time for theragnostic applications [Figure 6] [23].

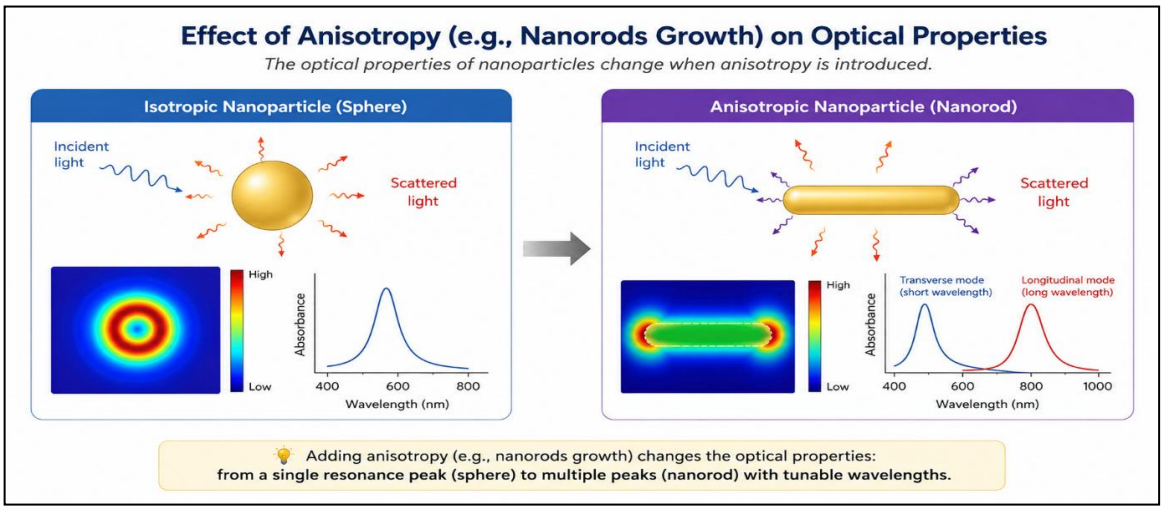

Figure 6. The optical properties of the nanoparticles changes, when anisotropy is added to the nanoparticle, changes such as nanorods growth.

4. Dendrimers

Dendrimers are highly branched, well-defined synthetic polymers widely used in nanotechnology and drug delivery. Common dendrimers include poly(amidoamine) (PAMAM) and poly(propylene imine) (PPI). Due to their three-dimensional structure and internal cavities, dendrimers can encapsulate metal ions and nanoparticles within their interior. They help control nanoparticle size, improve stability, and prevent particle agglomeration [Figure 7] [24].

Metal ions such as Cu^{2+}, Pt^{2+}, Pd^{2+}, and Au^{3+} can bind to the internal functional groups of dendrimers and form stable nanoclusters after chemical reduction. The outer surface groups of dendrimers can also be modified to adjust solubility and targeting properties. Dendrimer-encapsulated nanoparticles are usually very small (less than 5 nm), nearly monodisperse, and highly stable. Because of these properties, dendrimers are important in

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catalysis, molecular imaging, sensing, nanomedicine, and targeted drug delivery applications [25].

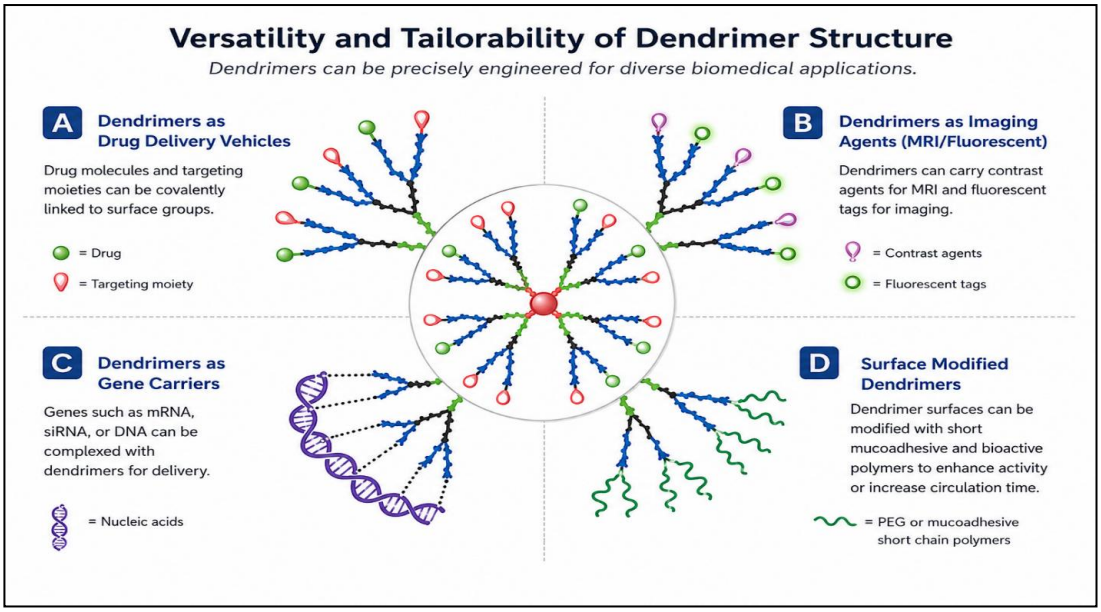

FIG. 7. A diagrammatic representation of the versatility of the dendrimer structure that enables tailorability. (A) Dendrimers as drug delivery vehicles where drug molecules and targeting moieties can be covalently linked to surface groups. (B) Dendrimers as carriers of contrast agents for MRI and fluorescent imaging. (C) Dendrimers as gene delivery vehicles where genes such as mRNA, siRNA, or DNA can be complexed. (D) A surface modification of the dendrimer surface with short mucoadhesive and bioactive polymers to enhance their activity or to increase their circulation time.

5. Carbon-Based Nanoparticles

Carbon-based nanoparticles such as carbon nanotubes (CNTs), fullerenes, and graphene oxide (GO) exhibit strong antimicrobial activity and are considered promising alternatives against antibiotic-resistant microorganisms. Their antibacterial effects mainly result from direct interaction with bacterial cell membranes, causing membrane damage, oxidative stress, and cell death. Factors such as nanoparticle size, surface area, and surface modification significantly influence their activity. Functionalized carbon nanomaterials and metal-carbon nanocomposites (e.g., CNT-Ag and GO-Ag) show enhanced antimicrobial efficiency and potential applications in drug delivery and nanomedicine[Table 1] [26,27].

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Table 1. Types of carbon-based nanoparticles as antimicrobial agent, their mechanisms of action and characteristics

Type of nanoparticles	Proposed mechanism of antimicrobial action	Main characteristics as antimicrobial agent	The main factors that influence antimicrobial activity	References
Fullerenes	Inhibit bacterial growth by impairing the respiratory chain; inhibition of energy metabolism.	Stability; Photodynamic therapy activity; high ability to functionalization; high surface/volume ratio; large inner volume.	Particle size; type of functional group; surface charge.	31, 33, 37, 51
SWNTs	Physical interaction with cell membrane; formation of cell CNTs aggregates; induction the cell membrane disruption.	Stability; high ability to functionalization; high surface/volume ratio; large inner volume.	Particle size; particle length; type of functional group; type of buffer; concentration; surface charge.	37, 43, 51, 52
GO	Physical interaction with cell membrane; formation of cell-GO aggregates; induction the cell membrane disruption.	Stability; high ability to functionalization; high surface/volume ratio; sharp edges of nanosheets.	Particle size; type of functional group.	31, 33, 51, 61, 68

Mechanisms of Drug Delivery

Drug delivery systems are designed to transport therapeutic agents to target tissues while improving efficacy and reducing side effects. Nanocarriers offer significant advantages due to their small size, large surface area, and tunable properties. Successful drug delivery depends on the ability of nanoparticles to accumulate at the target site, recognize specific cells, release drugs in a controlled manner, and enter cells efficiently. Therefore, understanding passive targeting, active targeting, controlled drug release, and cellular uptake mechanisms is essential for the development of effective nanomedicine systems [28,29].

I. **Passive Targeting (EPR effect):** Passive targeting is primarily based on the enhanced permeability and retention (EPR) effect, which enables nanoparticles to accumulate preferentially in tumor tissues through leaky vasculature and impaired lymphatic drainage. This phenomenon increases local drug concentration while minimizing systemic side effects. The extent of EPR-mediated delivery depends on factors such as nanoparticle size, shape, and circulation time. Nevertheless, tumor heterogeneity, abnormal extracellular matrix composition, and elevated interstitial fluid pressure often limit nanoparticle penetration. Advances in nanocarrier engineering are therefore being developed to enhance EPR efficiency and improve therapeutic outcomes in cancer treatment [Fig. 8] [30,31].

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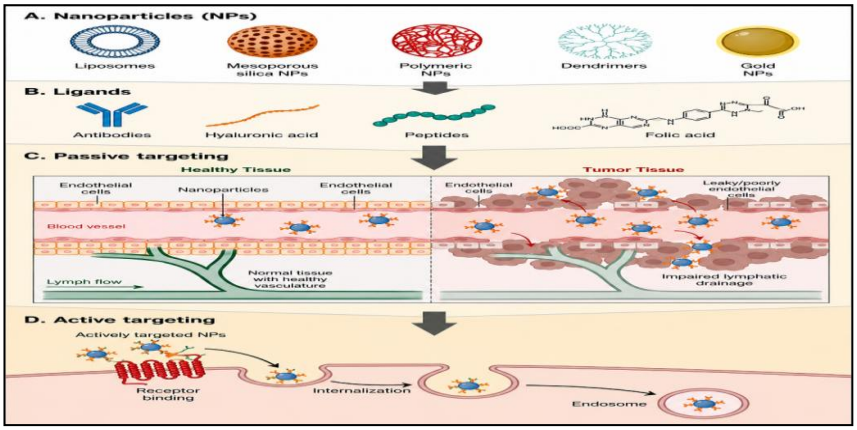

Figure 8. Schematic illustration of the different types of nanoparticles used for passive and active tumor targeting through the EPR effect (created with BioRender.com)

II. Active Targeting: Active targeting enhances drug delivery by functionalizing nanoparticles with specific ligands such as antibodies, peptides, aptamers, or small molecules that selectively bind to overexpressed receptors on cancer cells. Unlike passive accumulation through the EPR effect, this strategy promotes receptor-mediated recognition and cellular uptake, increasing treatment precision and therapeutic efficacy. Common targets include folate receptors, transferrin receptors, HER2, and EGFR, which are highly expressed in many tumor types. Active targeting also improves intracellular drug delivery while reducing off-target toxicity and minimizing damage to healthy tissues. When combined with optimized nanocarriers and favorable tumor microenvironment conditions, it represents a promising approach for overcoming the limitations of passive targeting and advancing precision cancer therapy [32,33].

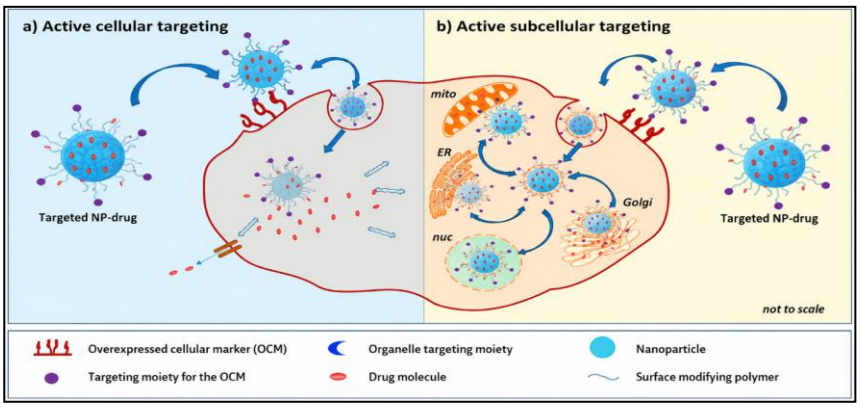

Figure.9. Schematic representation of active cellular and subcellular targeting by nanoparticle (NP) drug delivery systems. Ligand-functionalized nanoparticles bind to specific cell receptors, undergo endocytosis, and deliver drugs either to the cytoplasm or directly to intracellular organelles such as the nucleus or mitochondria, improving targeting specificity and therapeutic efficacy.

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III. Controlled Drug Release

Controlled drug release systems are designed to deliver therapeutic agents at a predetermined rate, concentration, and duration, thereby improving treatment efficacy while minimizing systemic toxicity. Biodegradable polymeric nanoparticles, particularly those based on materials such as PLGA and PEG, enable sustained and site-specific drug delivery by gradually releasing encapsulated drugs through diffusion, polymer degradation, or stimulus-responsive mechanisms [34]. In addition to conventional release pathways, changes in the tumor microenvironment—such as acidic pH, enzymatic activity, or oxidative stress can be exploited to trigger drug release selectively at the target site. These strategies enhance drug bioavailability, prolong therapeutic action, and provide greater spatiotemporal control over anticancer therapy [35].

Applications in Cancer Therapy

Nanoparticles improve cancer therapy by enabling targeted drug delivery with reduced toxicity to healthy tissues. Systems such as polymeric nanoparticles, liposomes, dendrimers, and magnetic nanoparticles deliver drugs and genes mainly through the EPR effect and active targeting. They are widely used in breast, lung, liver, brain cancers, and leukemia, where they enhance drug accumulation, improve treatment efficiency, and support imaging and gene delivery [36].

Breast cancer: In breast cancer therapy, nanoparticles have significantly improved targeted treatment and drug delivery. By recognizing tumor-specific biomarkers such as ER, PR, and HER2, they enhance therapeutic precision while reducing toxicity to normal tissues [table 2] [37]. In addition, nanoparticle-based systems such as liposomal doxorubicin and albumin-bound paclitaxel have demonstrated improved efficacy and safety, highlighting their important role in advancing personalized breast cancer management [38].

Table 2: Clinical applications of organic nanoparticles in breast cancer

	Structure	Applications
Liposomes	Self-assembled closed colloid structures composed of lipid layers	Drug delivery: anthracyclines, taxanes, vinca alkaloids, platinums, camphothecins; immunoliposomes: antiERBB2 conjugates
Dendrimers	Globular macromolecules for which all bonds emerge radially from a central focal point with regular branching pattern and repeated units	Drug delivery: fluorouracil, methotrexate, doxorubicin, oestrogen; MRI; gene delivery
Carbon nanoparticles	Carbon-containing nanotubes	Drug delivery; sentinel-node visualisation

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Lung cancer:

Nanoparticles have shown considerable potential in lung cancer therapy by enhancing targeted drug delivery and improving treatment efficacy while reducing systemic toxicity. Various nanocarriers, including liposomes, micelles, dendrimers, carbon nanotubes, and quantum dots, protect anticancer agents from degradation and facilitate site-specific delivery to tumor cells. Moreover, nanoparticle-based platforms can be combined with immunotherapy and gene-silencing strategies, offering promising approaches for precision treatment and improved therapeutic outcomes in lung cancer [Figure 10] [39,40].

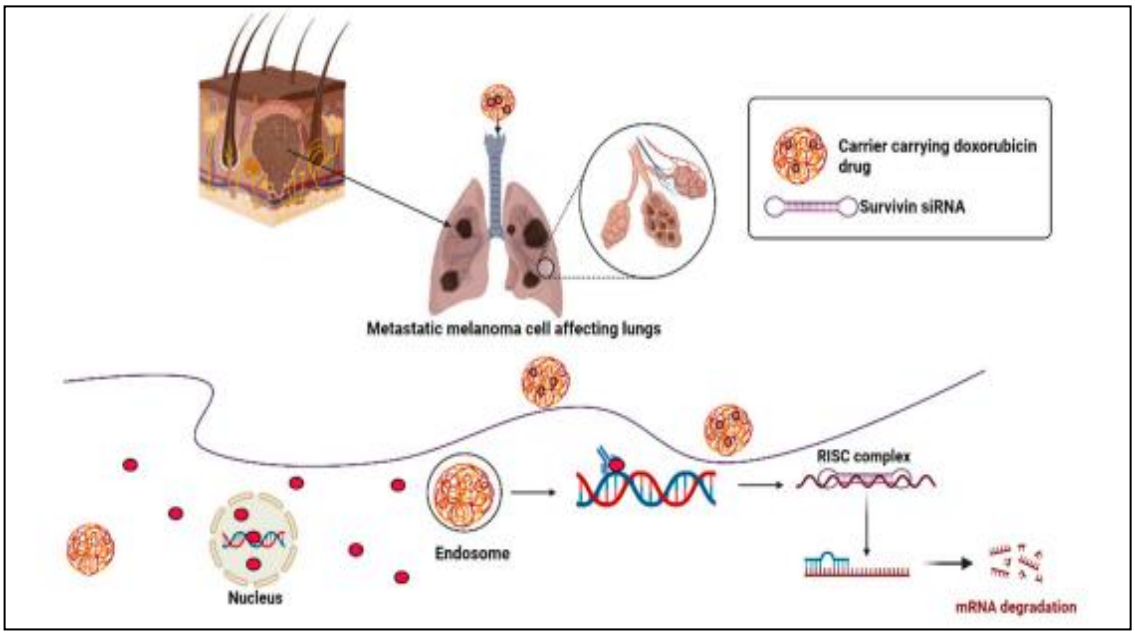

Figure. 10. Nanopolymer-based co-delivery of doxorubicin and Survivin siRNA into lung cancer cells, leading to RISC-mediated mRNA degradation.

Liver cancer: Nanoparticles have become valuable tools in the management of liver cancer, particularly hepatocellular carcinoma (HCC), by improving early diagnosis and targeted therapy. Their unique physicochemical properties enable enhanced accumulation in liver tissue and facilitate the delivery of imaging agents and therapeutics. Gold nanoparticles and superparamagnetic iron oxide nanoparticles (SPIONs) have shown particular promise as contrast agents for CT and MRI, enhancing tumor visualization and supporting more accurate detection and monitoring of liver malignancies [Table 3][41].

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Table.3. Summary of some types of nanoparticles available for liver imaging.

Nanoparticles	Size	Properties	Application	Other
SPION	> 50 nm	- High transverse relaxation - Rapid detection of some pathogens	Liver and spleen imaging at MRI, hyperthermia, cell labeling	Negative contrast agent
USPIO	< 50 nm	- Short T2 time - Less uptake in liver than SPIO	MRI of liver	Positive contrast agent
SPIO+ QD(Ag_2S)		- Noninvasive - Great luminescence - Good response to magnetic field - Correct diagnosis and anatomical information - SPIO is effective probe as contrast agent	Molecular imaging	Mixed procedures
IONPs	10–30 nm	Large size = high r^2 = effective agent	MRI of liver	There are 4 type and SHP-30 is good contrast agent
AuNPs	Smaller or larger than 25 nm (almost 99 nm)	- Unique optical and electronic property - Effective device - Cost-effective - Greater contrast agent for imaging	For diagnosis of different cancers, liver imaging with micro-CT, CT imaging, spectroscopy	Negative contrast agent
Iodinated-based (exiA-160)	55–100 nm	- Common accessible - Low energy of k-edge - Not good formulation	Micro CT imaging	-
Non-iodinated (alkaline earth, ExiTron-6000, ExiTron-12000)	-	- Low clearance - Long-term contrast - Biocompatible	Micro CT imaging	ExiTron-12000 is the highest contrast enhancement

Brain tumors: Nanoparticles, particularly magnetic nanoparticles (MNPs), have emerged as promising tools in the treatment and imaging of brain tumors such as glioblastoma (GBM). Due to the presence of the blood–brain barrier (BBB), conventional drug delivery is limited; however, MNPs can be engineered for targeted delivery across or directly into tumor sites [42]. They improve MRI imaging as contrast agents by enhancing tumor visualization and enabling detection of tumor progression or recurrence. In addition, MNPs can be used for hyperthermia-based therapy, where an alternating magnetic field induces localized heat, leading to selective tumor cell death while minimizing damage to healthy brain tissue [Figure 11][43].

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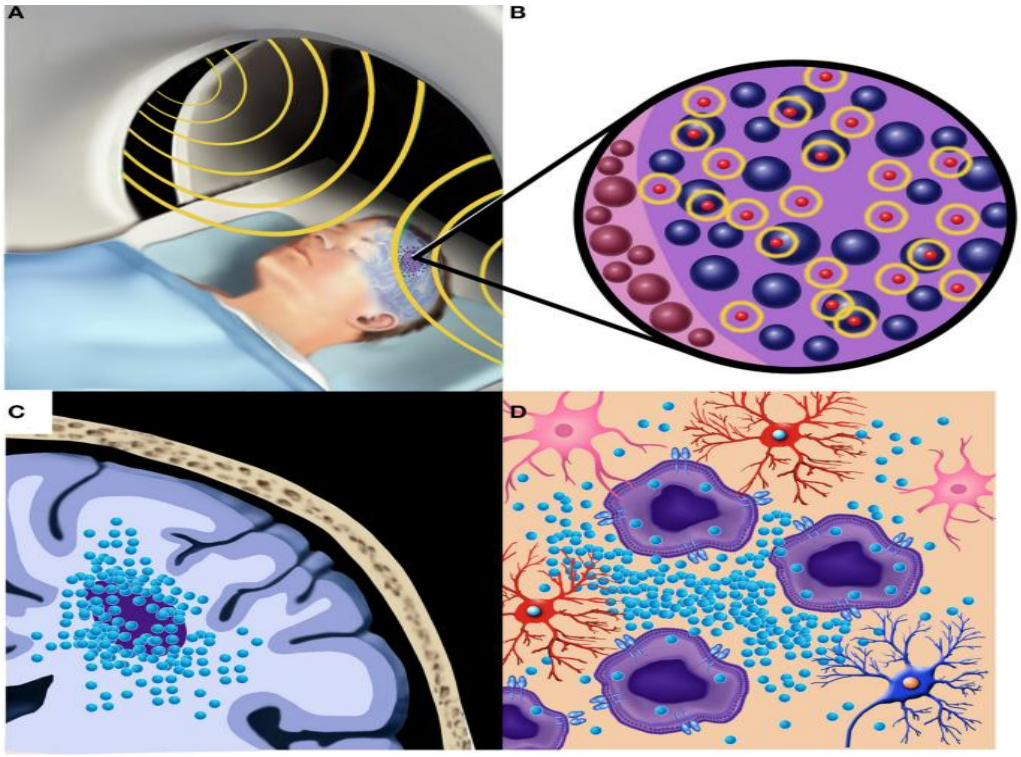

Figure .11. FIGURE 1 | Local hyperthermia therapy in a brain tumor patient after MNP implantation. (A) An alternating magnetic field (AMF) session (yellow) is applied to generate localized heat at the tumor site. (B) Oscillation of MNPs within and around tumor cells produces the therapeutic hyperthermia effect. (C) Direct implantation of MNPs enables targeted treatment of the brain tumor. (D) Infiltrating tumor cells in normal brain tissue may be more sensitive to hyperthermia due to increased MNP uptake and temperature susceptibility.

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